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HYGIENE  
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**The safety of influenza vaccination in pregnancy:  
Examining major congenital malformations as potential adverse  
outcomes using UK electronic health records**

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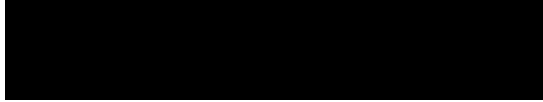
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## **Declaration**

I, Maria Peppia, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.



Maria Peppia (26/03/2020)

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*‘Επιστήμη χωριζομένη δικαιοσύνης και της άλλης αρετής, πανουργία ου σοφία φαίνεται’*

– Plato

## Abstract

The aim of this thesis was to examine the safety of maternal influenza vaccination with respect to major congenital malformations in live-born infants. UK electronic health records from the Clinical Practice Research Datalink were used and work was conducted using linked primary care, hospitalisation and mortality data.

The first study systematically reviewed existing methods for identifying congenital malformations in UK electronic health records, and the results of any validation studies. Studies relied on stand-alone primary care or hospitalisation data to identify congenital malformations; none examined linkage between these. Overall, congenital malformations recorded in primary care data had a high positive predictive value (80-100%) but the validity in hospitalisation data was not explored.

Methods from these studies informed the development of a comprehensive algorithm to identify major malformations in live-born infants. Using linked primary care, hospitalisation and mortality data, the second study in this thesis demonstrated that just 20% (95% CI, 19-21) of infants with a major malformation had evidence of their condition in both primary care and hospitalisation data. Almost 65% (95% CI, 64-66) only had evidence in hospitalisation data.

The third study demonstrated that the overall prevalence of major malformations established in primary care data using this algorithm was slightly higher than published estimates from other studies using UK primary care records (Prevalence ratio, 1.2; 95% CI, 1.2-1.3).

Comparisons of linked data with population-based registry data demonstrated a four-fold higher prevalence for major malformations overall in the linked electronic health records (Prevalence ratio, 4.3; 95% CI, 4.1-4.5). This was primarily driven by the high prevalence of some of these conditions in hospitalisation data, which could potentially be explained by non-specific codes used to record certain malformations that could have related to either major or minor conditions.

The fourth study examined the association between the trivalent seasonal inactivated influenza vaccine and major malformations. Among 78,150 live-birth pregnancies, 6,872 (8.8%) were vaccinated in the first trimester whilst 46,669 (59.7%) were unvaccinated throughout pregnancy. There was no evidence to suggest an association between first-trimester vaccination and major malformations recorded in first year of infant life in models adjusted for confounding (HR, 1.06; 99% CI, 0.94-1.19; p=0.23). The fifth study, which examined the safety of the monovalent pandemic inactivated influenza vaccine, showed similar results (HR, 1.02; 99% CI, 0.72-1.46; p=0.86). However, although these vaccine safety studies did not find evidence for an association between vaccination and major malformations, terminations due to foetal anomaly were not included. Therefore, the possibility of an increased risk of the specific subtypes of major malformations typically detected during antenatal scans and subsequently terminated could not be discounted.

These results provide additional evidence on the safety of maternal influenza vaccination but highlight the need for further explorations of major malformations among pregnancies that do not result in live-births. The component of this work relating to the methods used to identify major malformations highlights the potential to increase ascertainment through the use of linked data whilst underscoring the need for further studies, particularly in hospitalisation data, to establish the validity of codes used to record these conditions.

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# Contents

<b>1. Background</b> .....	<b>19</b>
1.1 Synopsis.....	19
1.1.1 Influenza virus and vaccines .....	19
1.1.2 Use and safety of influenza vaccines in pregnant women.....	20
1.1.3 Research presented in this thesis .....	21
1.2 Risks associated with influenza infection in pregnancy and early infancy .....	22
1.2.1 Risks pertaining to pregnant women .....	22
1.2.2 Risks pertaining to the foetus .....	22
1.2.3 Risks pertaining to newborn infants .....	23
1.3 Effectiveness of maternal influenza vaccination .....	23
1.3.1 Influenza vaccine effectiveness in pregnant women .....	23
1.3.2 Influenza vaccine effectiveness in newborn infants .....	24
1.4 Maternal determinants of influenza vaccine uptake during pregnancy.....	26
1.5. Maternal influenza vaccination in the UK.....	27
1.5.1 Influenza vaccination policy for pregnant women in the UK.....	27
1.5.2 Influenza vaccines recommended for pregnant women in the UK .....	28
1.5.3 Uptake of the influenza vaccine by pregnant women in the UK .....	31
1.6 Maternal influenza vaccination safety and major congenital malformations.....	32
1.6.1 The aetiology and importance of congenital malformations .....	32
1.6.2 Current safety evidence for maternal influenza vaccination and congenital malformations.....	34
1.7 Methodological considerations for safety studies examining major congenital malformations.....	39
1.7.1 Available UK data sources.....	39
1.7.2 Potential maternal risk factors for congenital malformations .....	44
1.8 Thesis rationale, aims and objectives .....	51
1.8.1 Rationale .....	51
1.8.2 Aims and Objectives.....	52
<b>2. The identification and validity of congenital malformation diagnoses in UK electronic health records: A systematic review</b> .....	<b>54</b>
2.1 Introduction .....	54
2.2 Paper 1: The identification and validity of congenital malformation diagnoses in UK electronic health records: A systematic review.....	57
2.3 Summary and conclusions .....	105
<b>3. Data Sources</b> .....	<b>107</b>
3.1 CPRD.....	107
3.1.1 Data collection and structure.....	108

3.1.2 Data quality and completeness.....	110
3.1.3 Linkage to other patient data .....	112
3.2 The Mother-Baby link .....	113
3.3 The CPRD/LSHTM Pregnancy Register .....	114
3.4 HES .....	116
3.4.1 Data collection and structure.....	116
3.4.2 Data quality and completeness.....	117
3.5 ONS Mortality Data .....	118
3.5.1 Data collection and structure.....	118
3.5.2 Data quality and completeness.....	119
3.6 ONS Deprivation data .....	119
3.6.1 Data collection and structure.....	119
3.6.2 Data quality and completeness.....	120
3.7 Data management .....	120
3.8 Ethics .....	121
3.9 Chapter Summary .....	121
<b>4. Identifying eligible pregnancies and defining study populations.....</b>	<b>122</b>
4.1 Introduction .....	122
4.2 Identifying potentially eligible pregnancies.....	124
4.2.1 Criteria for potentially eligible pregnancies.....	124
4.2.2 Data extraction for potentially eligible pregnancies.....	124
4.3 Pregnancy-related exclusion criteria .....	126
4.3.1 Multiple pregnancies .....	127
4.3.2 Live-birth pregnancies with a discrepancy between the delivery date and infant month/year of birth .....	127
4.3.3 Stillbirth pregnancies linked to live-born infant records .....	129
4.3.4 Pregnancies with implausible duration.....	130
4.3.5 Overlapping pregnancies .....	131
4.3.6 Pregnancies with unknown outcomes.....	131
4.3.7 Ectopic, molar and blighted ovum pregnancies.....	132
4.3.8 Pregnancy losses, terminations, live-birth deliveries without linked infant records and other pregnancy outcomes.....	133
4.4 Congenital malformation exclusion criteria.....	135
4.4.1 Malformations with known causes .....	135
4.4.2 Congenital infections .....	136
4.5 Additional study-specific exclusion criteria .....	137
4.6 Defining potential confounders in the study population .....	139



4.7 Chapter Summary .....	143
<b>5. Developing an algorithm to identify major congenital malformations .....</b>	<b>144</b>
5.1 Introduction .....	144
5.2 Recapitulation of the methods used in other studies to identify congenital malformations in UK electronic health records.....	145
5.3 Use of EUROCAT guidelines to develop initial code lists .....	146
5.3.1 Defining congenital malformations and anatomical subgroups using EUROCAT ....	147
5.3.2 Developing Read code lists .....	149
5.3.2 Developing ICD-10 code lists.....	150
5.3.4 Developing OPCS-4 code lists.....	151
5.4 Refining code lists .....	151
5.4.1 Codes that could relate to non-congenital conditions. ....	152
5.4.2 Codes that could relate to minor or potentially minor malformations .....	154
5.4.4 Codes relating to major malformations with known causes .....	155
5.5 Use of code lists to identify congenital malformations in live-born infants.....	155
5.6 Identifying antenatal diagnoses of MCMs .....	157
5.7 Chapter Summary .....	158
<b>6. Identifying the influenza vaccination status of pregnant women.....</b>	<b>159</b>
6.1 Introduction .....	159
6.2 Annual availability of the influenza vaccine.....	159
6.3 Evidence of vaccination in primary care records .....	160
6.4 Exclusion criteria for pregnancies with uncertainty in vaccination timing.....	164
6.5 Exclusion criteria for pregnancies with uncertain vaccine type .....	168
6.6 Summary of vaccination exclusion criteria .....	171
<b>7. The ascertainment of major congenital malformations in linked UK electronic health records .....</b>	<b>173</b>
7.1 Introduction .....	173
7.2 Deriving the eligible study population .....	174
7.3 Paper 2: Identifying major congenital malformations in anonymised UK electronic health records: the value of primary care, hospital admissions and mortality data. ....	177
7.4 External validation of MCMs identified in CPRD with published THIN data.....	202
7.4.1 Results of prevalence comparisons between CPRD & THIN .....	202
7.4.2 Could differences in Read code lists used to identify MCMs explain the higher prevalence of limb, digestive, urinary and eye malformations in CPRD compared to THIN? .....	203
7.4.3 Could Read codes used to identify MCMs in the THIN study but not in CPRD explain the lower prevalence of nervous system malformations in CPRD?.....	206
7.4.4 Could differences in the study periods explain differences in the prevalence rates between CPRD & THIN? .....	206

7.4.5 Could differences in the criteria used to define study populations explain differences in the prevalence rates between CPRD & THIN? .....	207
7.5 External validation of MCMs identified in CPRD, HES and linked data with data from English EUROCAT registries.....	207
7.5.1 Results of prevalence comparisons with English EUROCAT registries.....	209
7.5.2 Could limited follow-up in some English registries explain differences in prevalence rates? .....	211
7.5.3 Could limitations of clinical coding systems and practices in UK electronic health records explain differences in prevalence rates? .....	212
7.6 Chapter summary and conclusions.....	214
<b>8. Examining seasonal influenza vaccination during pregnancy and major congenital malformations .....</b>	<b>215</b>
8.1 Introduction .....	215
8.2 Deriving the final study population for analyses on SIV safety .....	215
8.3 Submitted Paper: Seasonal influenza vaccination during pregnancy and the risk of major congenital malformations in live-born infants .....	219
8.4 The prevalence of system-specific major congenital malformations by vaccination status .....	250
8.5 Why did the analysis examine the safety of vaccination in the second and third trimesters as well as the first trimester? .....	255
8.6 Why were analyses restricted to live-births? .....	256
8.6.1 MCMs are under-recorded in the antenatal period .....	258
8.6.2 MCMs recorded antenatally have poor validity .....	259
8.6.3 Vaccine uptake is low among miscarriages and terminations.....	261
8.6.4 Summary of exploration of antenatally-recorded MCMs.....	262
8.7 Could the exclusion of terminations due to foetal anomalies have biased results? .....	262
8.8 Could the exclusion of live-births without linked infant records have biased results?..	264
8.9 Chapter summary and conclusions.....	266
<b>9. Examining the association between pandemic influenza vaccination during pregnancy and major congenital malformations.....</b>	<b>267</b>
9.1 Introduction .....	267
9.2 Deriving the final study population for analyses on PIV safety .....	267
9.3 Characteristics of the eligible study cohort .....	269
9.4 Primary and secondary analyses.....	273
9.5 Sensitivity analyses .....	273
9.6 Chapter summary and conclusions.....	276
<b>10. Discussion I: Key results and strengths of the research.....</b>	<b>278</b>
10.1 Recapitulation of the aims and objectives of the thesis.....	278
10.2 Summary of main results .....	279

10.2.1	The identification and validity of congenital malformation diagnoses in UK EHR	279
10.2.2	The value of primary care, hospital admissions and mortality data in identifying major congenital malformations in anonymised UK EHR	281
10.2.3	Prevalence comparisons of major malformations identified in UK EHR data sources and in registries	282
10.2.4	The safety of influenza vaccination during pregnancy and major congenital malformations	283
10.3	Strengths	285
10.3.1	The use of large, multiply-linked EHR databases	285
10.3.2	The use of the newly-developed CPRD/LSHTM Pregnancy Register	287
10.3.3	Development and use of a novel algorithm for identifying congenital malformations	288
10.3.4	Careful approach in determining exposed and unexposed cohorts	289
<b>11.</b>	<b>Discussion II : Challenges in using UK electronic health records for safety studies concerning major congenital malformations.</b>	<b>290</b>
11.1	Validity of MCMs recorded in UK electronic health records: limitations of clinical coding systems and practices	291
11.1.1	Non-specific codes outside of the dedicated congenital malformation chapters	292
11.1.2	Non-specific codes within chapters dedicated to congenital malformations	294
11.1.3	Coding thresholds	298
11.1.4	Tentative diagnoses	298
11.1.5	Temporal changes in coding practices	298
11.1.6	Summary of the key factors that may have increased the prevalence of MCMs	299
11.1.7	Alternative approaches	299
11.2	Other misclassification	300
11.2.1	Misclassification of influenza vaccination status and its timing within pregnancy	300
11.2.2	Misclassification of potential confounders	301
11.2.3	Further approaches to explore the impact of misclassification	302
11.3	Limited ability to examine terminations due to foetal anomaly	303
11.4	Limited ability to examine major malformation subgroups	304
11.5	Other selection bias	305
11.6	Residual confounding	305
11.7	Generalisability	306
<b>12.</b>	<b>Interpretation, recommendations for future work and conclusions</b>	<b>308</b>
12.1	Interpretation	308
12.2	Recommendations for further research	310
12.3	Conclusions	312
	<b>References</b>	<b>313</b>

Appendix 1 – Systematic review search strategy .....	331
Appendix 2 – Code lists for identifying major congenital malformations .....	335
Read codes .....	335
ICD-10 codes .....	397
OPCS-4 codes .....	408
Appendix 3 – Code lists for antenatal diagnoses of major congenital malformations.....	416
Read codes for use in pregnant women .....	416
ICD-10 codes for use in pregnant women .....	417
Appendix 4 – Code lists for malformations with known causes .....	418
Read codes for antenatal diagnoses .....	418
Read codes for postnatal diagnoses .....	418
ICD-10 codes for antenatal diagnoses .....	430
ICD-10 codes for postnatal diagnoses.....	431
Appendix 5 – Code lists for congenital infections.....	435
Read codes for use in pregnant women .....	435
Read codes for use in infants .....	438
ICD-10 codes for use in infants .....	438
Appendix 6 – Code lists used for influenza vaccination.....	441
Read codes .....	441
Immunisation codes.....	446
Product codes .....	446
Appendix 7 – Read codes used in the published THIN study.....	449

## List of Figures

Figure 1.1 - Availability of seasonal and pandemic influenza vaccines for pregnant women in the UK.	28
Figure 1.2 - Influenza vaccine uptake in the UK and England among pregnant women by season.	31
Figure 1.3 - Aetiology of congenital malformations.	33
Figure 3.1 - Linkage of CPRD data to other datasets.	112
Figure 3.2 - Spells and episodes of care in HES data.	116
Figure 4.1 - Identification of potentially eligible pregnancies.	125
Figure 4.2 - Potentially eligible pregnancies after the application of pregnancy-related exclusion criteria.	126
Figure 4.3 – An example of the potential misclassification of vaccination and MCMs among pregnancies with a delivery date preceding the infant’s month of birth.	128
Figure 4.4 – Summary of the criteria used to define study populations for the objectives of the thesis.	138
Figure 4.5 – Conceptual framework used to identify potential confounders for vaccine safety analyses.	139
Figure 6.1 – Scenarios for pregnancies overlapping with two vaccination periods, with vaccination receipt records in both.	167
Figure 6.2 – Additional exclusion criteria for pregnancies that overlapped with both the 2009/10 and 2010/11 seasons.	170
Figure 7.1 - Deriving the study population to assess the ascertainment of MCMs in different data sources.	174
Figure 7.2 - Distribution of codes used to identify MCMs in the CPRD study and published THIN study.	203

Figure 7.3 - Derivation of pregnancies included in the comparison of MCM prevalence rates with English EUROCAT data.	208
--	-----

Figure 8.1 – Deriving the study population for seasonal influenza vaccine safety analyses.	216
--	-----

Figure 9.1 – Deriving the study population for pandemic vaccine safety analyses.	268
--	-----

## List of Tables

Table 1.1 – Effectiveness of maternal influenza vaccination against maternal laboratory-confirmed influenza illness or hospitalisation.	25
---	----

Table 1.2 - Effectiveness of maternal influenza vaccination against laboratory-confirmed influenza illness or hospitalisation in newborn infants.	25
---	----

Table 1.3 - Seasonal influenza vaccines recently introduced in the UK.	29
--	----

Table 1.4– Seasonal and pandemic influenza vaccines available for use in pregnant women between 2009 and 2016.	30
--	----

Table 1.5 - Available safety evidence on maternal seasonal or pandemic influenza vaccination and congenital malformations.	38
--	----

Table 1.6 – Characteristics of English congenital malformation registries.	42
--	----

Table 1.7 – Examples of electronic primary care databases available in the UK.	44
--	----

Table 1.8 - Thesis Objectives.	53
--------------------------------	----

Table 3.1 - Overview of the data included in CPRD files.	109
--	-----

Table 3.2 – Pregnancy outcomes recorded in the CPRD/LSHTM Pregnancy Register.	115
---	-----

Table 3.3 - Overview of the data included in HES files.	117
---	-----

Table 4.1 – Potential reasons for incomplete linkage between mothers and infants in the Mother-Baby Link.	134
Table 5.1 – Congenital malformation case definitions in EUROCAT and in the initial code-lists developed for this thesis.	148
Table 5.2 - Defining search terms for Read codes based on EUROCAT BPA ICD-10 codes.	150
Table 5.3 - Identifying ICD-10 codes based on EUROCAT BPA-modified ICD-10 codes.	151
Table 6.1 - Source of vaccination receipt evidence for each woman and vaccination period.	161
Table 6.2 - Read terms used among women whose only evidence of vaccination receipt across a vaccination period came from the clinical file.	161
Table 6.3 – Scenarios of conflicting influenza vaccination receipt records in pregnant women, within a single vaccination period.	162
Table 6.4 - Source of the earliest evidence of vaccine receipt among women with evidence of receipt from multiple files.	163
Table 6.5: Read terms used among women with evidence of vaccination in the immunisation and clinical file but whose earliest evidence of vaccination receipt came from the clinical file.	164
Table 7.1 - Prevalence of MCMs in stand-alone CPRD and published THIN data in the year after delivery.	202
Table 7.2 - Number of infants whose only evidence of an MCM was from a CPRD-only code by subgroup.	205
Table 7.3 - The prevalence of MCMs in stand-alone CPRD, stand-alone HES, linked CPRD-HES-ONS and English EUROCAT registries.	210
Table 8.1 – Prevalence of system-specific major congenital malformations in the first year of life per 10,000 live-births, by vaccination status.	253

Table 8.2 - Potential bias in the hazard ratios for MCMs, by pregnancy outcome	257
Table 8.3 - Number and proportion of pregnancies with an antenatal MCM record, by pregnancy outcome.	258
Table 8.4 - Most specific available antenatal evidence of MCM, by pregnancy outcome.	259
Table 8.5 - Antenatal codes used among all pregnancy outcomes.	260
Table 8.6 - Positive predictive values of antenatal codes used among live-birth pregnancies with a linked infant.	261
Table 8.7 - Vaccine uptake by pregnancy outcome.	261
Table 8.8 - Most common non-chromosomal major congenital malformations among terminations due to foetal anomalies in UK EUROCAT registries between 2010-2013.	263
Table 9.1 - Follow-up time among infants included in the PIIV safety analysis.	269
Table 9.2- Receipt of PIIV in pregnancy, by characteristics.	271
Table 9.3 - Major malformations among those eligible for the PIIV safety analysis, by characteristics.	272
Table 9.4 - Examining the association between pandemic influenza vaccination in pregnancy and MCMs.	274
Table 9.5 - Examining the association between first trimester vaccination with pandemic influenza vaccine and MCMs in sensitivity analyses.	275



## List of Abbreviations

WHO	World Health Organization
SIIV	Seasonal Inactivated Influenza Vaccines
PIIV	Pandemic inactivated influenza vaccines
CM	Congenital Malformations
MCM	Major congenital Malformations
RCT	Randomized control trials
CI	Confidence Interval
BMI	Body-mass Index
GP	General practitioner
OR	Odds Ratio
EUROCAT	European Concerted Action on Congenital Anomalies and Twins programme
EMSYCAR	East Midlands and South Yorkshire Congenital Anomaly Register
NorCAS	Northern Congenital Abnormality Survey
SWCAR	South West Congenital Anomaly Register
CAROBB	Congenital Anomaly Register for Oxfordshire, Berkshire & Buckinghamshire
WANDA	Wessex Antenatally Detected Anomalies Register
WMCAR	West Midlands Congenital Anomaly Register
YHCAR	Yorkshire and the Humber Congenital Anomalies Register
NHS	National Health Service
CPRD	Clinical Practice Research Datalink GOLD
THIN	The Health Improvement Network
HES	Hospital Episode Statistics
ONS	Office for National Statistics
QOF	Quality and Outcomes Framework
ICD-10	International Classification of Diseases, 10th Revision
OPCS-4	Classification of Surgical Operations and Procedures, 4th Revision
EHR	Electronic health records
ACE	Angiotensin-converting-enzyme
OXMIS	Oxford Medical Information System
PPV	Positive predictive value
QUADAS-2	Quality Assessment of Diagnostic Studies tool
PR	Prevalence ratio
LSOA	Lower-layer super output areas
BPA	British Paediatric Association
MBL	Mother-Baby Link
IQR	Interquartile range
IMD	Index of Multiple Deprivation
HR	Hazard Ratio

## Background Section

This thesis examines the safety of maternal influenza vaccination during pregnancy with respect to major congenital malformations using multiply-linked, routinely-collected UK electronic health records.

The background to this work is described in two chapters:

**Chapter 1** begins with a synopsis of influenza vaccines, their safety during pregnancy, and the research covered by this thesis. **Sections 1.2-1.4** summarize the rationale for maternal influenza vaccination and the determinants of vaccine uptake in pregnant women. **Section 1.5** provides details of maternal influenza vaccination in the UK. **Section 1.6** describes the available evidence on maternal influenza vaccination safety with respect to congenital malformations; **Section 1.7** describes methodological considerations when carrying out safety assessments with congenital malformations as an outcome of interest and **Section 1.8** sets out the research aims and objectives of this PhD.

**Chapter 2** presents a systematic review of the methods used by other researchers to identify and validate congenital malformations in UK electronic health records, and the results of these validation studies. This was used to inform the identification of major congenital malformations in the research described here.

# 1. Background

## 1.1 Synopsis

### 1.1.1 Influenza virus and vaccines

Influenza is a viral respiratory illness whose clinical manifestations range from mild to severe.<sup>1</sup> Although most individuals recover on their own, infection-related complications can result in hospital admission and death. Newborn infants and young children, pregnant women, the elderly and those with underlying health conditions are considered to be the most vulnerable to such complications.<sup>1</sup>

Annual influenza epidemics of varying severity occur as a result of influenza A and B viruses evading immunity in the population through antigenic drift, a process by which minor mutations cause changes in the surface proteins of the virus.<sup>2,3</sup> In the UK, these epidemics last eight to ten weeks and peak between December and February.<sup>4</sup> Seasonal influenza vaccines can provide protection against influenza and related complications but must be reformulated frequently to mitigate antigenic drift.<sup>5</sup> The World Health Organization (WHO) carries out surveillance of circulating strains and makes annual recommendations on the seed strains to be used in the vaccine.<sup>5</sup>

Seasonal influenza vaccines are commonly: inactivated (i.e. there is no potential for viral replication), non-adjuvanted (i.e. do not contain substances used to enhance the immune response to the vaccine) and either trivalent or quadrivalent (i.e. protecting against two influenza A strains and either one or two influenza B strains).<sup>5</sup> Henceforth, these will be referred to as **seasonal inactivated influenza vaccines (SIIVs)**. Live-attenuated and adjuvanted seasonal influenza vaccines are available but will not be discussed in detail as they are not recommended for use in pregnant women in the UK.

On rare occasions, a novel influenza A virus for which there is very little or no population immunity emerges through antigenic shift, a process by which major mutations result in new

surface proteins on the virus, and causes a pandemic which may result in high levels of mortality and morbidity, including in pregnancy.<sup>2, 6</sup> The most recent pandemic occurred in 2009/10 following the circulation of a new H1N1 subtype of the influenza A virus.<sup>6</sup> In the prior century there were three pandemics: one in 1918/19, one in 1957/58 and one in 1968/69.<sup>2, 6</sup> Pandemic influenza vaccines can only be manufactured once the novel virus has been isolated and characterized. In the UK, two pandemic influenza vaccines were available in 2009/10: Pandemrix and Celvapan. Both were inactivated and monovalent, but only Pandemrix contained an adjuvant.<sup>7</sup> Henceforth, these two vaccines will be referred to as **pandemic inactivated influenza vaccines (PIIVs)**.

### 1.1.2 Use and safety of influenza vaccines in pregnant women

In 2005, the WHO recommended maternal seasonal influenza vaccination in any trimester to protect both women and, through passive immunity, newborn infants.<sup>8</sup> Despite this, vaccination policies between countries were largely inconsistent prior to the 2009/10 pandemic. For example, the USA recommended vaccination for all pregnant women in any trimester whilst the UK restricted recommendations to pregnant women with underlying conditions and Germany made no recommendations at all.<sup>9, 10</sup> Although the UK and other countries began to expand recommendations to include all pregnant women in any trimester after the pandemic, some continued to restrict vaccination to the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters or to pregnant women with underlying conditions.<sup>11-14</sup>

Many factors have been shown to influence the uptake of influenza vaccine by pregnant women but one of the most consistently reported factors is concern for the foetus.<sup>15-17</sup> A large number of post-licensure observational studies have demonstrated good safety profiles for SIVs and PIIVs with respect to adverse pregnancy outcomes such as preterm delivery, low birth weight, small size for gestational age and foetal death.<sup>18-24</sup>

A number of observational studies have also been carried out to examine the safety of SIVs and PIIVs with respect to congenital malformations (CMs). Whilst these have not raised

concerns, at the time of this work there were calls for further evidence to address the limitations of existing studies, particularly for SIVs.<sup>20, 23</sup> Limitations included low numbers of pregnant women vaccinated in the first trimester (the critical period for organogenesis), short infant follow-up resulting in the under-ascertainment of CMs, inadequate adjustment for confounders and a need to assess safety in a setting other than the US where most studies were conducted.<sup>20, 23</sup>

### 1.1.3 Research presented in this thesis

The aim of this PhD was to address some of the limitations in the available literature by using UK electronic health records to assess the safety of SIVs and PIVs received during pregnancy with respect to major congenital malformations (MCMs). The objectives to achieve this were:

1. To systematically review the methods used by other researchers to identify and validate congenital malformations in UK electronic health records and the results of any such validations (**Chapter 2**).
2. To use the findings from the systematic review to inform the development of a detailed and comprehensive algorithm to identify MCMs in live-born infants using linked primary care records, hospital admissions and mortality data (**Chapter 5**).
3. To establish the value of these different data sources in identifying infants with MCMs, and their agreement (**Chapter 7**).
4. To compare the rates of MCMs in stand-alone and linked data with rates from the available literature and national surveillance data (**Chapter 7**).
5. To examine the association between maternal vaccination with SIVs and MCMs in live-born infants, stratified by trimester of vaccination (**Chapter 8**).
6. To examine the association between maternal vaccination with PIVs and MCMs in live-born infants, stratified by trimester of vaccination (**Chapter 9**).

## 1.2 Risks associated with influenza infection in pregnancy and early infancy

### 1.2.1 Risks pertaining to pregnant women

The increased risk of mortality among pregnant women during influenza pandemics has been well-documented. During the 1918/19 pandemic, for example, the case fatality rate for influenza-related pneumonia in the USA was 50% in pregnant women compared to 33% in the general population.<sup>25, 26</sup> The risk of mortality and of adverse pregnancy outcomes such as premature deliveries increased with gestational age and were highest in the third trimester.<sup>26</sup> A systematic review of observational studies during the recent 2009/10 pandemic noted an increased risk of hospitalisation (n=3 studies), intensive care admission (n=7 studies) and mortality (n=8 studies) in pregnant women compared to non-pregnant women.<sup>27</sup> However, for intensive care admission and mortality, risks varied considerably between individual studies and, in some, evidence was weak or absent.<sup>28-36</sup> The review also noted that evidence was limited due to low numbers of women, infrequent laboratory confirmation of infection and a tendency to group pregnant and post-partum women together.<sup>27</sup>

Seasonal influenza epidemics do not generate the levels of morbidity and mortality seen in pandemics but can still be serious for pregnant women. Influenza-related hospitalisation rates during seasonal epidemics have been shown to be higher among pregnant women compared to those in the post-partum period or those not pregnant, with rates increasing with gestational age.<sup>37, 38</sup> Pregnant women are also thought to be at increased risk of mortality during severe seasonal epidemics.<sup>37</sup> A report on maternal mortality in the UK between 2009-2012 (which included the 2009/10 pandemic and subsequent seasonal epidemics) noted that influenza accounted for 1 in 11 maternal deaths and stressed the importance of vaccination in this population.<sup>39</sup>

### 1.2.2 Risks pertaining to the foetus

Evidence regarding adverse foetal outcomes following maternal influenza infection is inconsistent, with high-quality evidence generally limited to the 2009/10 pandemic.<sup>40, 41</sup>

In a systematic review of 16 observational studies examining preterm birth following maternal infection, just four demonstrated an increased risk (two examining seasonal influenza and two examining pandemic influenza). The remaining studies showed no evidence for an association in either direction.<sup>40</sup> However, of these four studies, only the two examining pandemic influenza were assessed as “good quality”. The methodological quality across most of the 16 studies was judged to be “very low”.<sup>40</sup>

The same review also examined the risk of foetal death following maternal infection. Out of nine such studies, four demonstrated an increased risk (two examining seasonal influenza and two examining pandemic influenza).<sup>40</sup> The review authors stressed that conclusions regarding foetal death were difficult to draw due to low numbers of outcome events and variable foetal death definitions.<sup>40</sup>

### 1.2.3 Risks pertaining to newborn infants

Although evidence on adverse foetal outcomes is limited, influenza has been shown to pose considerable morbidity burden to infants under six months of age who are not eligible for vaccination.<sup>42-44</sup> Infants under six months old experience 104 excess hospitalisations for cardiorespiratory disease per 10,000 infants during an influenza season (95% CI, 89-119), compared to hospitalisations during the rest of the year.<sup>42</sup> This is more than double the excess number of hospitalisations in any other age group.<sup>42</sup>

## 1.3 Effectiveness of maternal influenza vaccination

### 1.3.1 Influenza vaccine effectiveness in pregnant women

Although pregnant women are usually excluded from clinical trials, evidence from randomized control trials (RCTs) in low- and middle-income countries suggests that SIV reduces laboratory-confirmed influenza illness in pregnant women (**Table 1.1**). In Mali and South Africa, SIV was shown to have an efficacy of 70% (95% CI, 42-86) and 50% (95% CI, 15-71), respectively.<sup>45, 46</sup> In Nepal, however, there was no evidence to suggest protective efficacy from the vaccine (31%;

95% CI, -10-56).<sup>47</sup> An RCT in Bangladesh did not examine laboratory-confirmed influenza illness as an outcome but demonstrated a 36% reduction in maternal respiratory illness with fever (95% CI, 4-57).<sup>48</sup>

Evidence from observational studies conducted in high-income countries was often of low quality; studies were frequently underpowered or did not confirm influenza infection using laboratory techniques.<sup>49-52</sup> Among those that examined laboratory-confirmed influenza illness or hospitalisation as the outcome, vaccine effectiveness ranged from 31-70% (**Table 1.1**).<sup>45, 46, 53-58</sup> Based on evidence from RCTs and observational studies, it appears influenza vaccination is moderately effective at protecting against influenza in pregnant women and is not dissimilar to the effectiveness seen in adults aged 18-65 years.<sup>59</sup>

### 1.3.2 Influenza vaccine effectiveness in newborn infants

RCTs in Mali, South Africa, Nepal and Bangladesh all concluded that SIIV receipt during the 2<sup>nd</sup> or 3<sup>rd</sup> trimester was associated with a reduction in laboratory-confirmed influenza illness in newborn infants (**Table 1.2**).<sup>45, 46, 48, 56</sup> The efficacy did, however, vary between countries. It was lowest in Mali (33%; 95% CI, 4-54) and Nepal (30%; 95% CI, 5-48), but higher in South Africa (49%; 95% CI, 12-70) and Bangladesh (63%; 95% CI, 5-85).<sup>45, 46, 48, 56</sup>

Observational studies from high-income countries were limited for the same reasons as described in the previous section. Among those examining laboratory-confirmed influenza illness or hospitalisation as the outcome, vaccine effectiveness ranged from 30% to 92% (**Table 1.2**).<sup>54, 60-64</sup> Based on evidence from RCTs and observational studies, influenza vaccination during pregnancy appears to provide moderate to good protection against influenza in the first few months of the infant's life.



**Table 1.1 - Effectiveness of maternal influenza vaccination against maternal laboratory-confirmed influenza illness or hospitalisation.**

Author	Period	Vaccine	Study Design	Country	Total number of pregnant women (no. vaccinated)	Trimester vaccinated	Outcome	Vaccine efficacy or effectiveness (95% CI)
Tapia <sup>46</sup>	2011-2014	SIIV	RCT	Mali	4,193 (2,108)	3 <sup>rd</sup>	LCI-illness	70 (42-86)
Madhi <sup>45</sup>	2011-2012	SIIV	RCT	South Africa	2,116 (1,062)	2 <sup>nd</sup> , 3 <sup>rd</sup>	LCI-illness	50 (15-71)
Steinhoff <sup>56</sup>	2011-2013	SIIV	RCT	Nepal	3,693 (1,847)	2 <sup>nd</sup> , 3 <sup>rd</sup>	LCI-illness	31 (-10-56)
Mølgaard-Nielsen <sup>54</sup>	2010-2017	SIIV	Test-negative	Denmark	626 (50)	Any	LCI-illness	64 (29-82)
Thompson <sup>57</sup>	2010-2016	SIIV	Test-negative	Canada, Israel, Australia, USA	1,030 (169)	Any	LCI-hospitalisations	40 (12-59)
Thompson <sup>58</sup>	2010-2012	SIIV	Case-control	USA	292 (154)	Any	LCI-illness	44 (5-67)
Haberg <sup>53</sup>	2009-2010	PIIV	Retrospective cohort	Norway	113,331 (59,266)	Any	LCI-illness or clinical diagnosis	70 (66-75)
Richards <sup>55</sup>	2009-2010	PIIV	Retrospective cohort	USA	3,367 (1,165)	3 <sup>rd</sup>	LCI-illness or clinical diagnosis	61 (16-83)

RCT, Randomized control trial; LCI, lab-confirmed influenza; CI, confidence interval; SIIV, seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine.

**Table 1.2 - Effectiveness of maternal influenza vaccination against laboratory-confirmed influenza illness or hospitalisation in newborn infants.**

Author	Period	Vaccine	Study Design	Country	Total number of live-born infants (no. of maternal vaccinations)	Trimester vaccinated	Outcome	Vaccine efficacy or effectiveness (95% CI)
Tapia <sup>46</sup>	2011-2013	SIIV	RCT	Mali	4,105 (2,064)	3 <sup>rd</sup>	LCI-illness	33 (4-54)
Madhi <sup>45</sup>	2011-2012	SIIV	RCT	South Africa	2,049 (1,026)	2 <sup>nd</sup> , 3 <sup>rd</sup>	LCI-illness	49 (12-70)
Steinhoff <sup>56</sup>	2011-2013	SIIV	RCT	Nepal	3,520 (1,757)	2 <sup>nd</sup> , 3 <sup>rd</sup>	LCI-illness	30 (5-48)
Zaman <sup>48</sup>	2004-2005	SIIV	RCT	Bangladesh	316 (159)	3 <sup>rd</sup>	LCI-illness	63 (5-85)
Mølgaard-Nielsen <sup>54</sup>	2010-2017	SIIV	Test-negative	Denmark	920 (75)	Any	LCI-illness	57 (25-75)
Dabrera <sup>63</sup>	2013-2014	SIIV	Case-only	UK	37 (5)	Any	LCI-illness	71 (24-89)
	2013-2014	SIIV	Case-only	UK	32 (5)	Any	LCI-hospitalisations	64 (6-86)
Shakib <sup>64</sup>	2005-2014	SIIV/PIIV	Retrospective cohort	USA	658 (20)	Any	LCI-illness	67 (48-79)
	2005-2014	SIIV/PIIV	Retrospective cohort	USA	151 (3)	Any	LCI-hospitalisations	83 (45-95)
Benowitz <sup>60</sup>	2000-2009	SIIV	Case-control	USA	247 (33)	2 <sup>nd</sup> , 3 <sup>rd</sup>	LCI-hospitalisations	92 (62-98)
Eick <sup>61</sup>	2002-2005	SIIV	Prospective cohort	USA	1,160 (573)	2 <sup>nd</sup> , 3 <sup>rd</sup>	LCI-illness	41 (7-63)
Poehling <sup>62</sup>	2002-2009	SIIV	Case-control	USA	1,510 (294)	Any	LCI-hospitalisations	45 (5-68)
Walker <sup>65</sup>	2013-2014	SIIV	Case-only	UK	37 (7)	2 <sup>nd</sup> , 3 <sup>rd</sup>	LCI-hospitalisations	66 (18-84)
	2014-2015	SIIV	Case-only	UK	81 (19)	2 <sup>nd</sup> , 3 <sup>rd</sup>	LCI-hospitalisations	50 (11-72)

RCT, Randomized control trial; LCI, lab-confirmed influenza; CI, confidence interval; SIIV, seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine.

## 1.4 Maternal determinants of influenza vaccine uptake during pregnancy

Understanding vaccine confidence and barriers to vaccination is a complex task and a field in its own right. A detailed review of the maternal determinants of influenza vaccination will not be attempted here. Instead, a comprehensive overview of the salient points will be given.

Studies have converged upon three key factors related to vaccine confidence among pregnant women. The first appears to be a lack of knowledge about the effectiveness of the vaccine and the protection it provides against serious disease.<sup>17, 66-68</sup> The second, and perhaps most frequently reported factor, is a widespread concern about safety of influenza vaccine for the foetus.<sup>16, 17, 66-69</sup> In the UK, an online survey of pregnant women and mothers found that 95% of women cited the safety of their child as their primary concern when considering vaccination in pregnancy.<sup>15</sup> A lack of recommendation of the vaccine by health-care workers is the third key factor.<sup>17, 66-68</sup> Pregnant women have been shown to be more likely to accept vaccination if it is recommended by a health-care worker such as a midwife.<sup>17, 66-68</sup> Evidence has, however, emerged to suggest that a large proportion of health-care workers in the UK do not feel confident providing advice about vaccination in pregnancy and are concerned about a perceived lack of safety studies in pregnant women.<sup>16, 67</sup> Providing further good evidence of vaccine safety is therefore key in addressing the concerns of pregnant women, increasing confidence among health-care workers, and ultimately in sustaining and increasing vaccination uptake.

In addition to the above, a number of sociodemographic maternal factors are thought to be associated with vaccine uptake. Young pregnant women have consistently been shown to be less likely to receive the vaccine than older women.<sup>17, 66, 67</sup> A number of studies have also shown lower vaccine uptake among ethnic minorities.<sup>17, 67, 68</sup> Reasons for this are inadequately described in the literature and whilst it is possible that variation in knowledge of benefits, social norms and cultural beliefs may play a role, it is also well-recognized that there are barriers in access to health services for these groups.<sup>70</sup> Distal factors such as greater socio-

economic deprivation, measured by numerous indicators including education level, employment, income and insurance, have also been associated with low vaccine uptake.<sup>17, 67</sup> More proximal reproductive factors have not been widely explored although there is evidence to suggest that primiparous women are more likely to be vaccinated than multiparous women.<sup>17</sup>

Health status and lifestyle factors have been infrequently examined but there is evidence to suggest that some may be associated with vaccine uptake. Pregnant women without underlying health conditions are, unsurprisingly, less likely to receive the vaccine.<sup>17, 67</sup> Whilst the evidence on alcohol consumption doesn't point to a clear relationship with vaccination, there is evidence that pregnant smokers are less likely to be vaccinated.<sup>17, 66, 67</sup> In the UK, obesity was recently classified as a clinical risk group for which vaccination was recommended, suggesting that uptake among pregnant women in this group is likely to rise.<sup>5</sup> Evidence on the association between body-mass index (BMI) at the start of pregnancy and vaccine uptake is limited, although in the general population there is evidence that low BMI is associated with lower uptake of the vaccine.<sup>66</sup> It is possible that such a relationship persists in pregnancy.

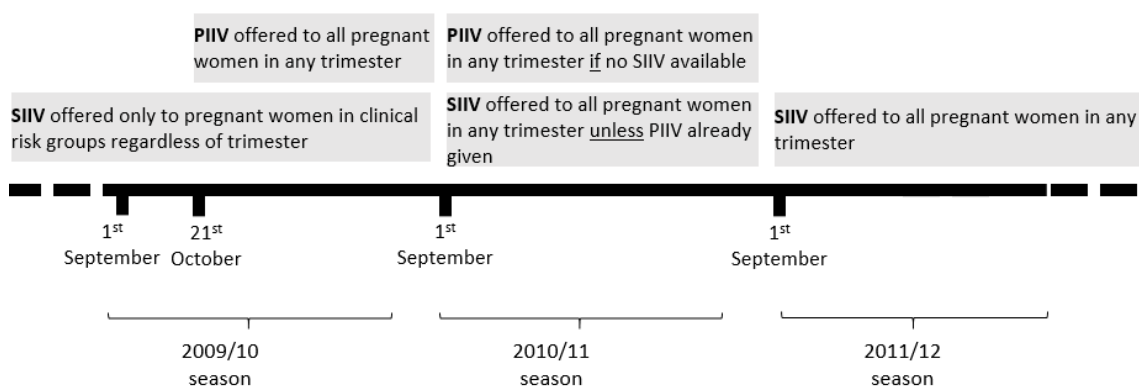
## 1.5. Maternal influenza vaccination in the UK

### 1.5.1 Influenza vaccination policy for pregnant women in the UK

Prior to the 2009/10 pandemic, pregnant women in the UK were offered SIV in any trimester if they were part of a clinical risk group (**Figure 1.1**).<sup>13</sup> This included those vulnerable to influenza-related complications due to chronic respiratory, heart, renal, liver or neurological diseases, diabetes or immunosuppression.

During the 2009/10 pandemic, SIV continued to be offered only to those pregnant women in clinical risk groups at any time in their pregnancy. Conversely, PIV was offered to all pregnant women in any trimester, regardless of clinical risk group status, once it became available on October 21, 2009 (**Figure 1.1**).<sup>12</sup>

Guidelines for the subsequent 2010/11 influenza season recommended that pregnant women in any trimester should be offered SIIV regardless of clinical risk group - unless they had already received PIIV (**Figure 1.1**).<sup>13</sup> During this season, PIIV was also available for use in case of a depletion of SIIV stocks. From 2011/12 onwards, SIIV has continued to be offered to pregnant women in any trimester regardless of clinical risk group status (**Figure 1.1**).<sup>4, 13</sup>



**Figure 1.1 - Availability of seasonal and pandemic influenza vaccines for pregnant women in the UK**

Currently, the UK maternal influenza vaccination programme is delivered primarily through general practice although vaccinations can be given in pharmacies and a small number of antenatal care services have introduced vaccinations by midwives in recent years.<sup>4, 71, 72</sup> It is, however, a contractual requirement for general practitioners (GPs) to document vaccinations occurring outside of the practice.<sup>73</sup>

## 1.5.2 Influenza vaccines recommended for pregnant women in the UK

### Seasonal influenza vaccines

In the UK, SIIVs are available as early as September and vaccination can continue into March.<sup>73</sup> Until recently, all SIIVs in the UK were trivalent, inactivated and un-adjuvanted. In 2013/14, a quadrivalent SIIV became available (**Table 1.3**).<sup>74</sup>

Live-attenuated and adjuvanted seasonal influenza vaccines have also been introduced over the course of the last decade (**Table 1.3**). In 2012, live-attenuated vaccines were

recommended only for those aged two to less than 17 years and a phased rollout was initiated the following year.<sup>74</sup> Whilst the ages of cohorts eligible to receive live-attenuated vaccines differ between the devolved administrations, the latest cohort to be eligible in England during the 2019/20 influenza season was children aged two to 10 years. Therefore, during the period that the work in this thesis was conducted, no pregnant individual would have received the live-attenuated vaccine. Adjuvanted vaccines are only recommended for elderly populations and were also unavailable during the time the work described in this thesis was conducted (**Table 1.3**). SIVs that could have been received by pregnant women during the time this work was carried out are shown in **Table 1.4**.

**Table 1.3 - Seasonal influenza vaccines recently introduced in the UK.**

Influenza vaccine Type	Season introduced	Recommended/Target Population
Live-attenuated trivalent vaccine <sup>a</sup>	2012/13	Phased rollout among children aged 2-17 years with no contraindications <sup>b</sup>
Egg-based quadrivalent inactivated vaccine <sup>a</sup>	2013/14	At risk <sup>c</sup> adults aged 18-64 years <b>including pregnant women</b> At risk <sup>c</sup> children aged 6 months – 2 years Children aged 2-17 years unable to receive the live vaccine
Live-attenuated quadrivalent vaccine <sup>a</sup>	2014/15	Phased rollout among children aged 2-17 years with no contraindications <sup>b</sup>
Adjuvanted trivalent inactivated vaccine	2018/19	Adults aged ≥65 years
Cell-based quadrivalent inactivated vaccine <sup>a</sup>	2019/20	At risk <sup>c</sup> adults aged 18-64 years <b>including pregnant women</b> Adults aged ≥65 years

<sup>a</sup>Do not contain an adjuvant, <sup>b</sup>E.g. immunodeficiency, <sup>c</sup>Those with conditions for which there is an increased risk of morbidity and mortality associated with influenza infection.

### **Pandemic influenza vaccines**

The influenza strain responsible for the 2009/10 pandemic was not included in SIVs prepared for the 2009/10 influenza season and was manufactured at a later date. PIIVs were available in the UK from October 21, 2009.<sup>12</sup> In the UK there were two PIIVs, Pandemrix and Celvapan, of which just Pandemrix was adjuvanted (**Table 1.4**).<sup>7</sup> Due to the absence of an adjuvant, two doses of Celvapan were required three weeks apart to provide a sufficient immune response. Pandemrix was the recommended vaccine for pregnant women as a single dose conferred protection. Though both of these PIIVs could be used, the overwhelming majority of individuals vaccinated received Pandemrix.<sup>75</sup>

**Table 1.4– Seasonal and pandemic influenza vaccines available for use in pregnant women between 2009 and 2016.**

Product Name (Supplier)	Vaccine Type	Formulation	Influenza season in which the specified vaccine was available						
			2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
Agrippal (Novartis/MASTA)	Trivalent SIIV	Surface antigen	✓	✓	✓	✓	✓	✓	✓
Begrivac (Novartis)	Trivalent SIIV	Split virion	✓	✓					
CSL inactivated influenza vaccine (Pfizer/Wyeth)	Trivalent SIIV	Split virion	✓	✓	✓	✓	✓	✓	✓
Enzira (Pfizer/MASTA/Wyeth)	Trivalent SIIV	Split virion	✓	✓	✓	✓	✓	✓	✓
Fluarix (GlaxoSmithKline/MASTA)	Trivalent SIIV	Split virion	✓	✓	✓	✓	✓		
Fluarix Tetra (GlaxoSmithKline)	Quadrivalent SIIV	Split virion					✓	✓	✓
Fluvirin (Novartis)	Trivalent SIIV	Surface antigen	✓	✓	✓	✓	✓		
Inactivated influenza vaccine BP (Sanofi Pasteur MSD/MASTA)	Trivalent SIIV	Split virion				✓	✓	✓	✓
Imuvac (Abbott/MASTA)	Trivalent SIIV	Surface antigen	✓	✓	✓	✓	✓	✓	✓
Inflexal (Crucell/Janssen-Cilag)	Trivalent SIIV	Surface antigen				✓	✓		
Influvac (Abbott)	Trivalent SIIV	Surface antigen	✓	✓	✓	✓	✓	✓	✓
Intanza (Sanofi Pasteur MSD)	Trivalent SIIV	Split virion		✓	✓	✓	✓	✓	✓
Optaflu (Novartis)	Trivalent SIIV	Surface antigen	✓			✓	✓	✓	✓
Preflucl (Baxter)	Trivalent SIIV	Split virion			✓				
Viroflu (Sanofi Pasteur MSD/Crucell/Janssen-Cilag)	Trivalent SIIV	Surface antigen	✓		✓	✓	✓		
Pandemrix (GlaxoSmithKline)	Monovalent PIIV	Split virion, adjuvanted	✓	✓					
Celvapan (Baxter)	Monovalent PIIV	Whole virion	✓	✓					

Abbreviations: SIIV, Seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine.

### 1.5.3 Uptake of the influenza vaccine by pregnant women in the UK

GPs submit data on influenza vaccine uptake among target groups at their practice to the Department of Health 'ImmForm' website. Public Health England subsequently publish aggregated data for the UK and the devolved administrations. Based on these data, influenza vaccine uptake among pregnant women in the UK is thought to have increased since its introduction, with an uptake of 52% for the 2018/19 influenza season compared to 40% in 2011/12 (Figure 1.2).<sup>76,77</sup>

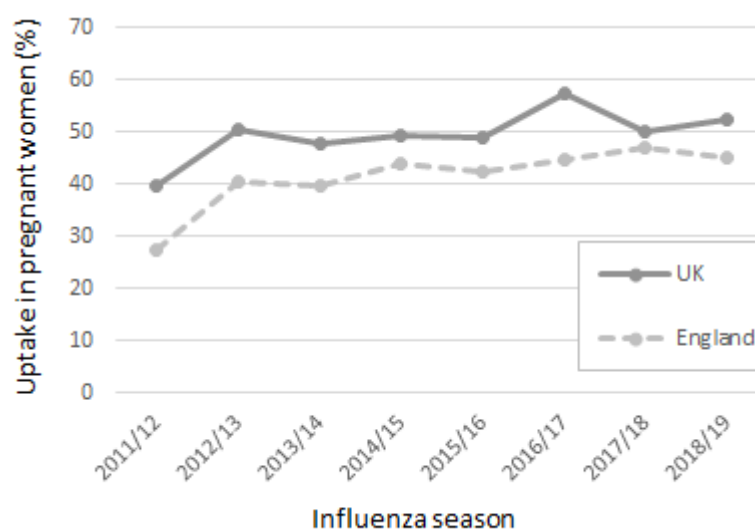


Figure 1.2 - Influenza vaccine uptake in the UK and England among pregnant women, by season. Data are based on Public Health England national surveillance through the 'ImmForm' system.<sup>76,77</sup>

Although this is similar to or higher than the uptake seen in other countries, it is below a 75% coverage target aimed at by the WHO.<sup>78</sup> There is also considerable variation in uptake by region. In 2018/19, for example, uptake at the level of clinical commissioning groups ranged from 29% in Enfield to 69% in Stockport.<sup>77</sup> These uptake rates should, however, be interpreted with caution as identifying pregnant women and non-pregnant women accurately over the course of each influenza season is challenging and may introduce uncertainty in the denominators.<sup>4,72</sup>

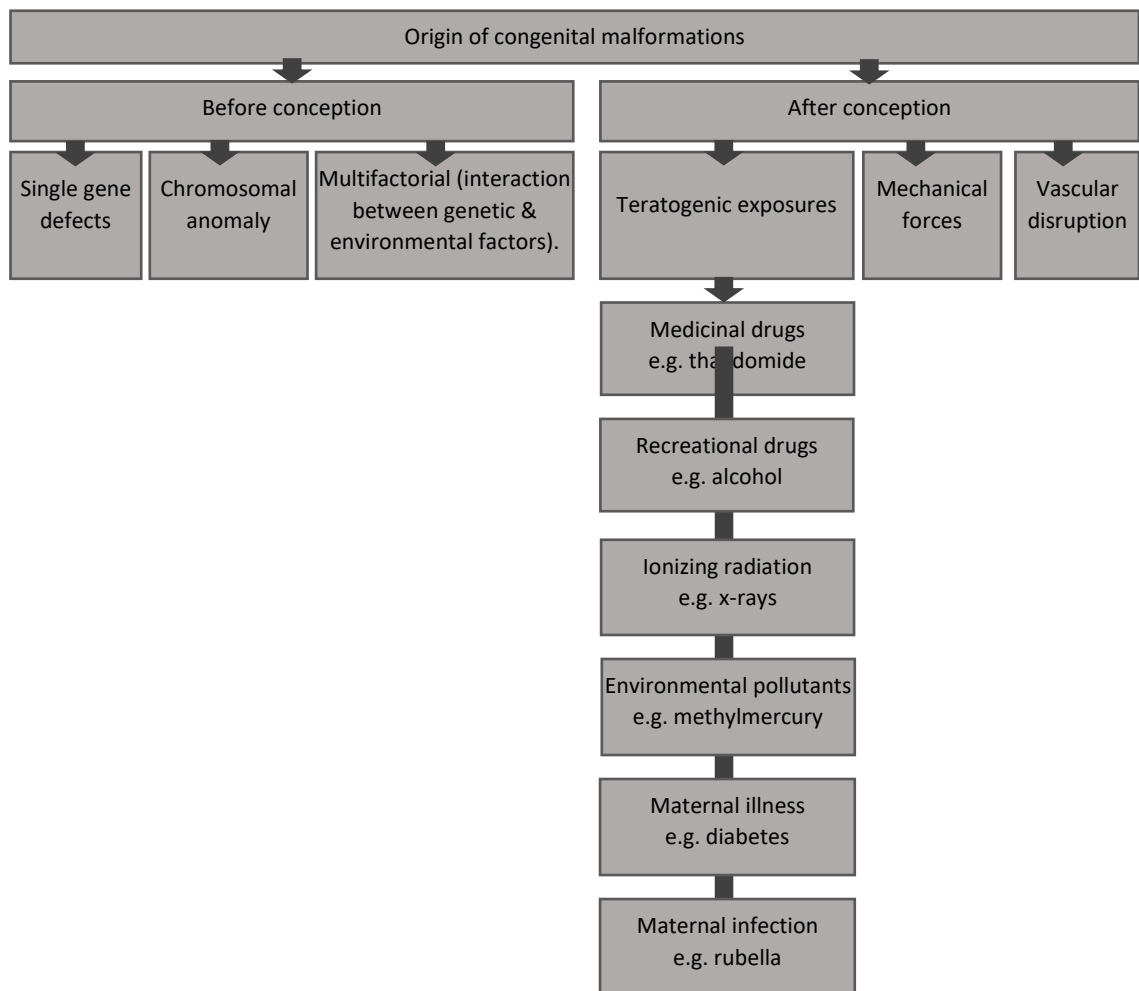
## 1.6 Maternal influenza vaccination safety and major congenital malformations

### 1.6.1 The aetiology and importance of congenital malformations

Congenital malformations are defined as structural or functional defects that arise *in utero* and are present at birth.<sup>79</sup> Globally, they are estimated to affect 2-6% of viable pregnancies and are a leading cause of infant mortality and morbidity.<sup>80-83</sup> In the UK and other high-income countries, congenital malformations are responsible for up to 25% of neonatal deaths and those who survive are likely to have disabilities resulting in considerable health and social care needs over their lifespan.<sup>83,84</sup> This is particularly true of those with major congenital malformations (MCMs) which represent severe conditions and are, therefore, of particular public health importance.<sup>85</sup> Conversely, minor malformations are those not associated with serious medical needs or functional impairment of individuals and have limited cosmetic importance.<sup>86</sup>

The causes of congenital malformations can be divided into those that occur prior to conception and those that occur after (**Figure 1.3**).<sup>81</sup> Pre-conception causes of congenital malformations include genetic abnormalities such as single gene defects and chromosomal aberrations that may be inherited or may occur spontaneously without any prior family history.<sup>81</sup> After conception, congenital malformations are thought to arise chiefly through *in utero* exposure to mechanical forces, vascular disruptions or teratogens which disturb the normal development of the foetus. Teratogenic agents include maternal infections that can be transmitted across the placenta to infect the foetus (e.g. rubella), certain drugs or chemicals (e.g. thalidomide) and radiation (e.g. x-rays). A third of congenital malformations are known to be multifactorial, occurring as a result of an interaction between genetic abnormalities that have occurred before conception and environmental exposures.<sup>81</sup> Despite the large amount of research carried out to determine the above, up to half of congenital malformation cases have no known aetiology.<sup>81</sup>





**Figure 1.3 - Aetiology of congenital malformations.**

Based on the 'Global Report on Birth Defects' by Christianson *et al.*<sup>81</sup>

Congenital malformations received global attention in the 1960s following the thalidomide disaster.<sup>87</sup> Thalidomide was widely prescribed to pregnant women as an anti-emetic for morning sickness but was eventually found to be a teratogen responsible for congenital malformations in 10,000 live-born infants worldwide.<sup>87</sup> This disaster resulted in changes to legislation around drug regulation as well as an understanding of the need for post-marketing drug surveillance.<sup>88</sup> The latter is of particular importance for pregnant women who are often not included in RCTs carried out as part of the drug licensing process. As vaccination during pregnancy has been increasingly recommended to prevent illness in pregnant women and/or their infants, congenital malformations have become an important outcome of interest in post-marketing vaccine safety studies. This is particularly the case for first-trimester vaccination as this is when most organogenesis occurs.

The theoretical mechanisms by which vaccines could cause congenital malformations depend on the formulation of the vaccine.<sup>89</sup> Live-attenuated vaccines are often contraindicated in pregnancy due to the theoretical risk of the virus infecting the foetus after crossing the placenta.<sup>89</sup> This is not a concern for inactivated vaccines but other mechanisms may still pose a risk. Ingredients added to the vaccine such as adjuvants (especially those that are novel and for which safety data is lacking), preservatives, emulsifiers, stabilisers or those that are part of the manufacturing process could theoretically act as teratogens.<sup>89</sup> The available evidence on the safety of maternal influenza vaccination with respect to congenital malformations is described below.

### 1.6.2 Current safety evidence for maternal influenza vaccination and congenital malformations

The majority of evidence on maternal influenza vaccination safety has been obtained from observational studies. Whilst the RCTs described in **Section 1.3** did not produce any safety signals of concern, they were not powered to detect rare outcomes. Since 2015, five systematic reviews have examined evidence on the safety of maternal influenza vaccination with respect to congenital malformations from available observational studies and all have concluded that there is no evidence for an association.<sup>20-24</sup> **Table 1.5** summarizes all 20 observational studies included across the five systematic reviews.

Before the work conducted in this thesis began, the largest available systematic review was by Polyzos *et al.* and included 15 studies with more than 36,000 vaccinated pregnant women in total (>4,700 vaccinated in the first trimester).<sup>23</sup> Only two of these studies assessed SIIV, the remaining studies focused on PIIV. Authors pooled effect estimates from all 15 studies and found no evidence of an association between maternal influenza vaccination and congenital malformations (Odds Ratio (OR), 0.96; 95% CI, 0.86-1.07). Similar results were found when restricting to the eight studies that examined first-trimester vaccination (OR, 1.03; 95% CI, 0.91-1.18) and the seven of these which assessed MCMs (OR, 0.98; 95% CI, 0.83-1.16).<sup>23</sup> A sub-

analysis of adjuvanted and unadjuvanted inactivated vaccines also showed no evidence for an association. A systematic review by McMillan *et al.* covered a subset of the studies examined by Polyzos *et al.* and demonstrated similar results.<sup>20, 23</sup>

**Limitations of the available safety evidence for major congenital malformations:**

Despite finding no evidence for an increased risk, these two systematic reviews that included a total of 15 studies highlighted the limitations of existing research. These included:

1. A focus on PIIV, with limited evidence on SIIVs. Of the 15 primary studies, just two examined SIIVs alone<sup>50, 90</sup> and one examined PIIV alongside SIIV.<sup>91</sup>
2. A limited number of studies examining vaccination in the first trimester despite this being the critical period for organogenesis. Of the 15 primary studies, seven examined first-trimester vaccination and MCMs<sup>90-96</sup> and only one of these examined SIIV alone.<sup>90</sup>
3. Small sample sizes in the context of the rarity of congenital malformations, especially in the studies examining vaccination in the first trimester. The single study examining SIIV in the first trimester had fewer than 500 vaccinated pregnant women.<sup>90</sup> Only one study examining the safety of PIIV in the first trimester included more than 1,000 pregnant women.<sup>94</sup>
4. Limited infant follow-up, precluding the identification of diagnoses made later in childhood. Follow-up time among the 15 studies was generally short; just one study examining PIIV identified congenital malformations up until the first birthday.<sup>96</sup> The majority identified congenital malformations at the time of delivery or shortly after.
5. Inadequate adjustment for confounders in several studies, particularly among those that focused on first-trimester vaccination. Among the 15 studies, seven did not adjust for any factors.<sup>90, 91, 93, 97-100</sup>

6. Inconsistent definitions of congenital malformations and inconsistent handling of hereditary disorders across studies. Furthermore, studies often did not examine malformation subgroups and tended to focus on malformations as aggregate outcomes.<sup>20</sup> Associations of vaccination with specific types of malformations were therefore less likely to be detected and the totality of evidence for any particular malformation subgroup was limited.

After the work described in this thesis began, a further five primary studies were published.<sup>101-</sup>

<sup>105</sup> Two examined PIIV, with one including over 14,000 first-trimester vaccinated pregnancies and following infants up for a year.<sup>102, 105</sup> Neither of these found evidence of an association with aggregate congenital malformations although one study did find evidence to suggest an association with oral cleft when comparing vaccination in the first eight weeks of pregnancy with vaccination after eight weeks (OR, 1.6; 95% CI, 1.01-2.65; p value not reported).<sup>105</sup>

However, as the lower confidence interval is close to the null, these results should be interpreted with caution.

The other three studies examined the safety of SIIV receipt, including in the first trimester.<sup>101,</sup>

<sup>103, 104</sup> None of these studies found evidence of an association with congenital malformations.

One of these studies, conducted by Kharbanda *et al.*, is the largest safety study examining SIIV received in the first trimester to date.<sup>103</sup> Using the Vaccine Safety Datalink, which collects

vaccination data from several different sites in the US and links these to other healthcare data

(e.g. inpatient, outpatient and emergency admissions to hospital), almost 53,000 infants

whose mothers received SIIV in the first trimester were followed-up for a year and compared

to those unexposed in the first trimester and those unexposed throughout pregnancy. The

adjusted prevalence ratio for MCMs was the same in both analyses (1.02; 95% CI, 0.94-1.10).<sup>103</sup>

MCM subgroups were also examined but none of these showed an association with

vaccination.

In the time since the work for this thesis began, three further systematic reviews were published in addition to the five primary studies described above.<sup>21, 22, 24</sup> The largest of these included 19 of the 20 known observational studies (**Table 1.5**), including the five most recently published primary studies. There was no evidence to suggest an association between maternal influenza vaccination during pregnancy and congenital malformations, even after adjusting for the gestational age at vaccination.<sup>24</sup> Results from the other two most recent systematic reviews were consistent with this.<sup>21, 22, 24</sup>

Although results from studies so far are reassuring, further investigations in different settings can increase confidence in the available evidence. Whilst the recent study by Kharbanda *et al.* assessed the safety of first-trimester SIIV in a large study population and ascertained MCMs in the first year of life, the study relied on the Vaccine Safety Datalink which requires participants to be insured. The health-seeking behaviour of participants may therefore differ from the general population.<sup>106</sup> Indeed, vaccine coverage rates among participants have been shown to be higher than the national average for some vaccines.<sup>106</sup> If those included in the Vaccine Safety Datalink are more likely to be vaccinated than those not included, and if they also differ in their underlying risk factors for MCMs, this may mean that results are not generalizable to those outside of the Vaccine Safety Datalink. This can be addressed by confirming evidence of safety in different settings and with different methods.

No large safety studies of maternal influenza vaccination and MCMs have been carried out in the UK and all studies of SIIV have been carried out in North America. The generalizability of results to the UK could be affected by differences in healthcare systems (universal coverage vs insurance-based care), vaccine confidence, antenatal screening for congenital malformations and terminations, as well as possible differences in the available influenza vaccines for pregnant women. Assessing safety in the UK provides an opportunity to address some of the limitations in the available literature whilst also establishing whether results can be replicated elsewhere.

**Table 1.5 - Available safety evidence on maternal seasonal or pandemic influenza vaccination and congenital malformations.**

Author	Study Period	Country	Study Design	Total no. of vaccinated pregnancies (No. vaccinated in 1 <sup>st</sup> trimester)	Follow-up from delivery	Outcome Examined					Calculated measures of effect for 1 <sup>st</sup> trimester vaccination?	Were any associations with vaccination detected?
						Any CM	Any MCM	MCM subgroups	Limb defects	Heart defects		
<b>SIIV</b>												
Munoz <sup>50</sup>	1998-2003	US	Cohort (R)	252 (0)	Around delivery <sup>a</sup>	✓						No
Sheffield <sup>90</sup>	2003-2008	US	Cohort (R)	10,225 (439)	Around delivery <sup>a</sup>		✓				✓	No
Chambers <sup>101</sup>	2010-2014	US, Canada	Cohort (P)	1,263 (457)	1 year		✓				✓	No
Kharbanda <sup>103</sup>	2004-2013	US	Cohort (R)	52,856 (52,856)	1 year		✓	✓	✓	✓	✓	No
Louik <sup>104</sup>	2011-2014	US	Case-control	711 (711)	6 months		✓	✓		✓	✓	No
<b>PIIV</b>												
Trotta <sup>107</sup>	2009-2010	Italy	Cohort (R)	6,246 (0)	Around delivery <sup>a</sup>		✓	✓	✓	✓		No
Rubinstein <sup>100</sup>	2010-2011	Argentina	Cross-section	7,293 (2,874)	1 week	✓						No
Launay <sup>98</sup>	2009-2010	France	Cohort (P)	320 (0)	Around delivery	✓ <sup>b</sup>						No
Lin <sup>108</sup>	2009-2010	Taiwan	Cohort (R)	198 (10)	8 weeks	✓ <sup>b</sup>						No
Fabiani <sup>102</sup>	2009-2010	Italy	Cohort (R)	2,003 (0)	Delivery; 6 months	✓	✓	✓	✓	✓		No
Cleary <sup>93</sup>	2008-2010	Ireland	Cohort (R)	2,996 (246)	Around delivery <sup>a</sup>	✓					✓	No
Kallen <sup>94</sup>	2009-2010	Sweden	Cohort (R)	18,612 (3,197)	Unclear	✓	✓	✓		✓	✓	No
Heikkinen <sup>109</sup>	2009-2010	Netherlands, Italy, Argentina	Cohort (P)	2,295 (92)	3 months		✓					No
Pasternak <sup>96</sup>	2009-2010	Denmark	Cohort (R)	6,989 (345)	1 year		✓				✓	No
Oppermann <sup>95</sup>	2009-2010	Germany	Cohort (P)	323 (55)	8 weeks	✓	✓				✓	No
Mackenzie <sup>99</sup>	2009-2010	UK	Cohort (P)	97 (10)	Delivery	✓						No
Ludvigsson <sup>105</sup>	2009-2011	Sweden	Cohort (R)	40,983 (14,385)	1 year	✓ <sup>c</sup>		✓	✓	✓	✓	Yes <sup>d</sup>
Deinard <sup>e,97</sup>	1976-1977	US	Cohort (P)	189 (NS)	8 weeks	✓					-	No
<b>PIIV or SIIV</b>												
Chambers <sup>f,92</sup>	2009-2012	US, Canada	Cohort (P)	841 (328)	Around delivery <sup>a</sup>		✓				✓	No
Louik <sup>91</sup>	2009-2011	US	Case-control	1,524 (NS)	Unclear		✓	✓			✓	Yes <sup>g</sup>

<sup>a</sup>Follow-up not specified but conditions identified around time of birth; <sup>b</sup>CMs not specified but no exclusions mentioned; <sup>c</sup>Excluded hip dislocation, undescended testes, ear malformations, tongue tie, neoplastic naevus, pyloric stenosis, patent ductus arteriosus; <sup>d</sup>OR<sub>adj</sub> for oral cleft following maternal vaccination in the first 8 weeks versus vaccination after 8 weeks: 1.6 (95% CI, 1.0–2.7); <sup>e</sup>Restricted access to full-text; <sup>f</sup>Adjusted for SIIV exposure; <sup>g</sup>OR<sub>adj</sub> for specified eye malformations following 1<sup>st</sup> trimester vaccination: 8.7 (95% CI 1.1-68.5). Abbreviations: CM, congenital malformation; MCM, major congenital malformation; NS, not specified; CI, confidence interval; SIIV, seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine; OR<sub>adj</sub>, Adjusted odds ratio; R, retrospective; P, prospective.

## 1.7 Methodological considerations for safety studies examining major congenital malformations

### 1.7.1 Available UK data sources

In the UK, the following data sources have been used to carry out post-licensure safety assessments of medications used in pregnancy with CMs as the outcome of interest:

1. Pregnancy exposure registries.
2. Population-based surveillance registries.
3. Electronic health records.

#### **Pregnancy exposure registries**

Pregnancy exposure registries enrol pregnant volunteers into prospective cohort studies to examine the association between drugs or vaccines given in pregnancy and adverse foetal outcomes such as MCMs.<sup>110</sup> Some may examine a broad range of medications, as is the case with the UK Teratology Information Service.<sup>111</sup> Others, such as the UK Epilepsy & Pregnancy Register, may enrol only those on specific treatments.<sup>112, 113</sup> Typically, information about the drug or vaccine used is collected as well as basic clinical, obstetric and demographic data.

Outcomes are usually ascertained by standardized questionnaires sent to GPs shortly after the estimated delivery date.<sup>114</sup>

Pregnancy exposure registries are particularly limited in their scope due to their reliance on the voluntary enrolment of women. Due to low levels of enrolment, these registries are typically only able to detect major teratogenicity. Furthermore, voluntary enrolment can introduce concerns around selection bias and generalizability. Vaccine safety studies using such registries could be vulnerable to these concerns if those choosing to receive the vaccine were more likely to enrol and have lower or higher risk of the outcome. Finally, such registries typically identify outcomes around the time of delivery and collect minimal information on potential confounders.

### Population-based surveillance registries

Population-based surveillance registries aim to identify individuals with particular conditions, such as MCMs, within a defined population. By collecting additional data on medications received during pregnancy, post-licensure safety assessments can be conducted.<sup>115</sup> At the time of this work, there were seven regional registries in England collecting data on MCMs among live-births, stillbirths, spontaneous abortions and pregnancy terminations due to foetal anomaly (**Table 1.6**).<sup>116,117</sup> These were the:

- East Midlands and South Yorkshire Congenital Anomaly Register (EMSYCAR),
- Northern Congenital Abnormality Survey (NorCAS),
- South West Congenital Anomaly Register (SWCAR),
- Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB),
- Wessex Antenatally Detected Anomalies Register (WANDA),
- West Midlands Congenital Anomaly Register (WMCAR), and the
- Yorkshire and the Humber Congenital Anomalies Register (YHCAR).

Registries employ both active and passive ascertainment procedures to identify MCMs.<sup>118</sup> They receive notifications of congenital malformations from multiple sources, some of which include: maternity units, neonatal units, child health systems, paediatricians, cardiologists, midwives, ultrasonographers, geneticists and surgeons.<sup>119</sup> Over the years, registries have developed close working relationships with local health services: setting up regular multi-disciplinary meetings to link hospitals with other services (e.g. cytogenetics services) and performing cross-validations of cases using available data sources.<sup>120-122</sup> Registries that have established close links with regional cytogenetics centres and tertiary care centres (e.g. cardiology units) also receive case lists from these routinely.<sup>117, 120, 121</sup> Increasingly, registries are also receiving electronic data on congenital malformations from NHS Trusts – with over 500 NHS providers sharing data with registries as of 2015.<sup>123</sup> Population-based registries are not limited by issues around voluntary enrolment and are generally better-placed for post-



marketing safety assessments than pregnancy exposure registries. However, the availability of resources can impact the potential for active case finding and long-term follow-up, with some registries under-ascertaining conditions in the postnatal period despite high levels of ascertainment in the antenatal period.<sup>120, 121, 124</sup>

Several registries contribute data to the 'European Concerted Action on Congenital Anomalies and Twins' programme (EUROCAT) which is a consortium of population-based registries covering over 30% of the European birth population that has been used for the post-marketing surveillance of medications in pregnancy.<sup>86</sup> Data submitted to EUROCAT by registries are standardized; registries must follow EUROCAT guidelines to code MCMs and must also collect and submit additional data on the infant (e.g. birth weight, sex), obstetric characteristics (e.g. gestational length, type of outcome) and maternal characteristics (e.g. maternal age).

Registries can opt to collect data on drug exposures during pregnancy, maternal illness before and during pregnancy, family medical history and sociodemographic information on an ongoing basis. However, as resources for this are often limited, these data may instead be collected in an ad-hoc way for specific studies.

On 1<sup>st</sup> April 2015, these regional registries were incorporated into the new National Congenital Anomaly and Rare Disease Registration Service, overseen by Public Health England.<sup>116</sup> As part of this change, a single data management system was established and paper notifications were ceased in favour of electronic notifications.<sup>123</sup> Until recently, no registries covered the highly populated areas of London and South East England, nor the East of England or North West regions. Three new reporting regions have been created for these and the first national coverage data are expected.

In addition to the above UK registries, there are also malformation-specific population-based registries. An example of such a registry is the Cleft Registry and Audit Network, which receives information on children born with a cleft lip and/or cleft palate from 15 hospitals across England, Wales and Northern Ireland.<sup>125</sup>

**Table 1.6 – Characteristics of English congenital malformation registries.**

Name of Registry	EUROCAT member?	Year Established	Geographic coverage	Annual births	Upper age limit for diagnoses	Source of denominator data since 2005	Are any exposure data recorded?
East Midlands & South Yorkshire Congenital Anomaly Register (EMSYCAR)	Yes	1997	South Yorkshire, Derbyshire, Nottinghamshire, Lincolnshire, Leicestershire, Rutland and Northamptonshire	74,000	None	ONS	Type of data collected not specified <sup>a</sup>
Northern Congenital Anomaly Survey (NorCAS)	Yes	1985	North East England, North Cumbria, Northumberland, Newcastle upon Tyne, North Tyneside, Gateshead, South Tyneside, County Durham, Darlington and Tees	33,000	12 years	ONS	Maternal diabetes, maternal medications, maternal smoking, major maternal medical problems, maternal weight and height <sup>a</sup>
South West Congenital Anomaly Register (SWCAR)	Yes	2002	South West Strategic Health Authority	60,000	18 years	ONS	Maternal age, maternal medications, maternal smoking, maternal deprivation status
Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB) <sup>b</sup>	Yes	1991	Local authority regions for Oxfordshire, Berkshire and Buckinghamshire	31,000	1 year	ONS	Maternal chronic illness, details of assisted conception, invasive tests in pregnancy and maternal alcohol abuse <sup>a</sup>
Wessex Antenatally Detected Anomalies Register (WANDA) <sup>c</sup>	Yes	1994	Old 'Wessex' region, Jersey and Guernsey	31,000	None <sup>d</sup>	Hospital labour wards	Maternal chronic illness, details of assisted conception, invasive tests in pregnancy and maternal alcohol abuse <sup>a</sup>
West Midlands Congenital Anomaly Register (WMCAR)	No	1995	West Midlands Strategic Health Authority	72,500	2 years	ONS	Maternal age and ethnicity
Yorkshire and the Humber Congenital Anomalies Register (YHCAR)	No	2011	No available information	45,000	No available information	No available information	No available information

<sup>a</sup>Recorded if available; <sup>b</sup>Also known as the Thames Valley Register; <sup>c</sup>Merged with SWCAR in 2015; <sup>d</sup>Despite no upper age limit, data are considered unreliable after the neonatal period.

## Electronic health records

In the UK, healthcare is provided by the National Health Service (NHS) and is free at the point of delivery.<sup>126</sup> The first point of contact with the health service for most individuals in the UK is the general practice, with almost 99% of the population registered with one.<sup>126</sup> General practitioners provide patients with primary care services but also act as the gatekeeper for access to further services. Therefore, a patient's general practice record will contain details of any consultations with practice staff as well as information on referrals and feedback from secondary or tertiary care services.<sup>127</sup> As general practitioners use clinical management software to record consultations, prescriptions and other clinical data, general practice records are digitized and can be used for research purposes.<sup>128</sup>

At the time this work began, three UK-wide electronic primary care databases were available: The Clinical Practice Research Datalink GOLD database (henceforth referred to as 'CPRD'), The Health Improvement Network (THIN) and the Q-Research database (**Table 1.7**). Although none of these databases provide investigators with access to the primary care records of the entire UK population, records are available for a large enough proportion of the population that the examination of rare outcomes such as MCMs is possible.<sup>127</sup> Primary care data can also be linked to other data including hospital admissions from the Hospital Episode Statistics database (HES) and Office for National Statistics (ONS) mortality data, thus providing a rich source of information on patients. This potential was further improved following the introduction of the Quality and Outcomes Framework (QOF) in 2004 which financially incentivized the recording of a number of diagnoses and other key variables in primary care.<sup>126</sup>

Based on the above, UK electronic primary care data have considerable potential for use in pharmaco-epidemiological research and are increasingly used in post-licensure studies examining the association between drug or vaccine exposures during pregnancy and congenital malformations.

**Table 1.7 – Examples of electronic primary care databases available in the UK**

Database	Established	No. active <sup>a</sup> patients in data	No. general practices contributing <sup>b</sup>	Data collection	Information collected
Clinical Practice Research Datalink GOLD	1987	4.4 million	685	During or after an appointment at a contributing general practice using <b>Vision</b> software.	Demographics, Diagnoses, Prescriptions, Referrals, Test results.
The Health Improvement Network	2002 <sup>c</sup>	3.7 million	587	During or after an appointment at a contributing general practice using <b>Vision</b> software.	Demographics, Diagnoses, Prescriptions, Referrals, Test results.
Q-research	2003 <sup>c</sup>	5.1 million	950	During or after an appointment at a contributing general practice using <b>EMIS</b> software.	Demographics, Diagnoses, Prescriptions, Referrals, Test results.
Clinical Practice Research Datalink Aurum <sup>d</sup>	2017 <sup>c</sup>	7 million	738	During or after an appointment at a contributing general practice using <b>EMIS</b> software.	Demographics, Diagnoses, Prescriptions, Referrals, Test results.

<sup>a</sup>Active patients are those alive and registered at a practice. <sup>b</sup>Some practices contribute to multiple databases. <sup>c</sup>For some practices, data may be available prior to the year the database was established. <sup>d</sup>Aurum became available after the work described in this thesis started.

### 1.7.2 Potential maternal risk factors for congenital malformations

In order to identify potential confounders for vaccine safety analyses, it is helpful to consider risk factors for MCMs that may also be associated with vaccine uptake. Extensive research has been carried out to elucidate risk factors for MCMs but the relationship is not always consistent between studies, regions and among major malformation subgroups. Below, potential risk factors for MCMs that were later considered to be potential confounders are described.

#### Age

The association between advanced maternal age and malformations resulting from chromosomal anomalies is well-established. However, the relationship between maternal age and non-chromosomal MCMs is less clear.<sup>129-131</sup> A number of studies have suggested an increased risk of MCMs in young mothers (<20 years), particularly for gastroschisis and anencephaly.<sup>130, 132-134</sup> Others have suggested an association between advanced maternal age

(≥35 years) and MCMs such as congenital heart defects, though this too has been inconsistent.<sup>129, 133, 135-138</sup>

A study using data from population-based MCM registries across 15 European countries found that the relationship between maternal age and non-chromosomal MCMs varied by country.<sup>130</sup> This suggested that maternal age itself may not be a risk factor, but rather that age is associated with other demographic, social or behavioural risk factors that differ across countries.<sup>130</sup>

### **Ethnicity**

Ethnicity may be associated with MCMs as a result of varying socioeconomic, cultural or genetic factors. In a cohort study from Bradford in the UK, infants born to Pakistani mothers were shown to be at greater risk of having an MCM compared to infants of white British mothers or other ethnicities.<sup>139</sup> Education was found to have a protective effect but adjustment for deprivation did not make a difference. The latter findings contradicted those from another UK study that demonstrated an increased risk of congenital heart defects in Asian and Black infants and an increased likelihood of these populations living in more deprived areas than white infants.<sup>140</sup> Consanguinity was reported to account for a third of MCMs in infants of Pakistani ethnicity in the cohort study in Bradford.<sup>139</sup> However, this was inconsistent with other studies that have assigned consanguinity a much smaller role in the development of MCMs. A meta-analysis of 17 studies across six countries estimated that the excess risk of MCMs attributable to consanguinity was just 3%.<sup>141</sup> The Bradford study did not explore other factors that are likely to contribute to the increased risk seen in this population, such as language barriers and inequalities in access to healthcare. Conflicting results in the literature highlight the difficulty in teasing apart the relationship between ethnicity and MCMs and the potential usefulness of ethnicity as a proxy for other risk factors that may be hard to define.

### **Socioeconomic status**

Socioeconomic status is thought to be associated with adverse infant outcomes and, although not extensively reported in the literature, is likely to be associated with MCMs.<sup>142, 143</sup> A study using data from four UK population-based registries for MCMs demonstrated increased risk with increasing deprivation as measured by the Carstairs deprivation index.<sup>144</sup> An increased risk was also seen for heart and digestive malformation subgroups but not for others. Studies in the US which have used parental education, occupation, income and insurance status to define socioeconomic status have also found associations with MCMs although not always for the same subgroups.<sup>145, 146</sup> A meta-analysis of 33 observational studies in the USA, Europe, Asia and Africa found an increased incidence of congenital heart defects among the most socioeconomically deprived groups, regardless of whether this was measured by education, income or occupation.<sup>147</sup> However, only the association with income persisted when meta-analyses were restricted to studies in North America and none of the associations persisted when meta-analyses were restricted to studies in Europe.

### **Geographic region**

The prevalence of MCMs has been shown to differ by geographic region when comparing data from population-based registries in different parts of the UK as well as when comparing hospital catchment areas.<sup>148, 149</sup> These differences have been shown to persist after adjusting for factors such as maternal age and deprivation.<sup>149</sup> Ascertainment bias caused by differences in diagnostic expertise, availability of relevant specialist units for diagnosis, recording practices, prenatal screening or uptake of termination could explain regional variation. It has been suggested that studies examining MCMs should adjust for region to account for differential case ascertainment.

### **Alcohol consumption**

Exposure to alcohol in pregnancy, especially if excessive, can result in foetal alcohol spectrum disorders which can affect organogenesis and impair physical and mental development.<sup>81</sup>

Outside of this, the association between alcohol consumption and MCMs is unclear. A meta-analysis of seven observational studies suggested that prenatal binge-drinking was associated with congenital heart defects.<sup>150</sup> Whilst most studies have not shown an association between low to moderate alcohol consumption and MCMs overall, others have suggested an increased risk for particular conditions such as neural tube defects and specified congenital heart defects.<sup>150-152</sup> Available evidence has generally been limited by methodological weaknesses including recall bias, inconsistent definitions of congenital malformations and lack of adjustment for confounders.

### **Smoking**

Smoking during pregnancy is known to be associated with adverse pregnancy outcomes, likely as a result of vascular disruption. Most studies have not found evidence of an association between smoking during pregnancy and congenital malformations overall; a meta-analysis of 38 studies that included almost 70,000 cases of malformations did not detect an association and these results were further supported by a more recent population-based study in Denmark that included more than 800,000 live-born singletons.<sup>153, 154</sup>

However, both the systematic review and Danish study showed associations between smoking and particular malformation subgroups. Whilst there was some variation between studies in the subgroups associated with smoking, both studies observed an increased risk of congenital heart defects, orofacial and gastrointestinal malformations. Although it was not possible to control for alcohol use in the Danish study, the authors were able to show a dose-response relationship between the daily number of cigarettes smoked and the risk of malformation subgroups, strengthening the evidence for an association.<sup>154</sup> In the systematic review, associations with malformation subgroups persisted after restricting to studies that identified smoking status prospectively and those that adjusted for potential confounders.<sup>153</sup>

## **Infections**

Some maternal infections can cross the placenta and act as teratogens, affecting the development of the foetus. These are known as congenital infections and are thought to account for up to 3% of all congenital malformations.<sup>155</sup> They include: rubella, toxoplasmosis, syphilis, HIV, varicella-zoster, herpes simplex virus, parvovirus, and cytomegalovirus.<sup>155</sup>

For others infections, such as influenza, the association with congenital malformations is uncertain. A systematic review which included a meta-analysis of 22 observational studies suggested an association between maternal influenza-like illness (with or without serological confirmation) in the first trimester and the risk of particular malformation subgroups including neural tube defects and congenital heart defects.<sup>156</sup> Results were consistent with evidence from another systematic review that suggested an association between hyperthermia and neural tube defects.<sup>157</sup> However, the authors cautioned that many primary studies did not adjust for confounding and that the risk of ascertainment bias or publication bias could not be discounted. Furthermore, it was not clear what role medication taken for influenza infection could have played.

## **Chronic illness**

There is strong evidence that some chronic maternal illnesses are associated with congenital malformations. Pre-gestational diabetes and associated hyperglycaemia are well-established risk factors for congenital malformations and have been shown to increase the risk of congenital heart defects and neural tube defects.<sup>158, 159</sup> Other conditions, such as epilepsy, have been found to increase the risk of MCMs primarily as a result of the medications used for treatment.<sup>160</sup>

Relationships between other chronic illnesses, the drugs used to treat them and congenital malformations are less well-understood but are important to consider. For instance there is a suggestion that asthma, a common condition that is likely to affect a substantial proportion of pregnant women, may be a risk factor for congenital malformations.<sup>161</sup> A meta-analysis of 14



cohort studies found evidence of an association between asthma and congenital malformations, which persisted after restricting to those studies that adjusted for confounders, as well as evidence of an association with orofacial malformations. Overall, the evidence from the systematic review did not suggest a large role for asthma medications in this association.

Chronic pre-gestational hypertension is becoming increasingly common in pregnant women and is frequently treated with angiotensin-converting-enzyme (ACE) inhibitors which have been associated with the development of MCMs.<sup>162-164</sup> Recently, two large cohort studies from the US have suggested that the underlying hypertension may have a role in this association. The first cohort study demonstrated an increased risk of congenital heart defects among pregnancies exposed to ACE inhibitors compared to those without hypertension or any hypertensive treatment.<sup>165</sup> The increased risk among those using ACE inhibitors disappeared when compared to those with hypertension but no treatment.<sup>165</sup> In the second study, normotensive individuals were compared to treated and untreated individuals with chronic hypertension; the risk of heart defects was similarly increased in both the treated and untreated groups.<sup>166</sup>

### **Obesity**

Nutritional deficiency during pregnancy has long been recognized as a determinant of MCMs, with folate deficiency in particular being associated with neural tube defects. More recently, evidence has started to emerge that BMI at the start of pregnancy may also be associated with MCMs. Potential mechanisms for this include reduced folate levels, underlying hyperglycaemia or reduced sensitivity of ultrasound scanning. A meta-analysis of 18 studies found that obesity was associated with an increased risk of neural tube defects, congenital heart defects, limb reduction defects, and orofacial defects.<sup>167</sup> A recent Swedish cohort study using registry data on over 1 million singleton live-births supported these findings and showed an increasing risk of congenital heart defects, nervous system and limb malformations with increasing BMI.<sup>168</sup>

Results from both the meta-analysis and Swedish study were robust to the exclusion of women with gestational diabetes which is known to be associated with MCMs and increased BMI.

Whilst most studies have focused on maternal obesity, some studies have also shown maternal underweight to be associated with an increased risk of congenital malformations. A study using registry data from the UK found that obesity was associated with congenital malformations as previously suggested, but that maternal underweight was also a risk factor for some malformations including atrial septal defects.<sup>169</sup> Two additional studies have supported the latter.<sup>170, 171</sup>

### **Parity**

Some studies have suggested an association between increasing parity and MCMs. A meta-analysis of 14 observational studies found evidence to suggest an increased risk of congenital heart disease with increasing maternal parity, independently of maternal age, and demonstrated a dose-response relationship.<sup>172</sup> Mechanisms suggested to explain this include a greater risk of nutrient depletion among non-nulliparous women, the exposure of the developing foetus to viruses carried by other children in the household, changes in the uterine environment and increased maternal stress with increasing parity.<sup>172</sup>

Conversely, others have demonstrated a relationship in the opposite direction. A study using a UK population-based surveillance registry demonstrated a lower prevalence of MCMs in second pregnancies compared to first pregnancies.<sup>173</sup> This supported results from a multi-site case-control study of almost 18,000 cases that found certain MCMs such as hydrocephaly and limb reduction defects to be more likely to occur among nulliparous women compared to primiparous women.<sup>174</sup> A history of MCMs in pregnancy may affect family planning decisions which may explain these findings.

## 1.8 Thesis rationale, aims and objectives

### 1.8.1 Rationale

Although several studies have examined the safety of influenza vaccination in pregnancy with respect to MCMs, there have been calls for additional work to assess the safety of SIIV given during the first trimester. To date, only one large cohort study has examined MCMs following first-trimester vaccination with SIIV and this was conducted in the US between 2004 and 2013 within a population selected on the basis of health insurance. The safety of PIIV has been examined more frequently, including when given in the first trimester. However, no such study has been carried out using UK data. In addition to limited power, available safety evidence has been further limited by inconsistent definitions for MCMs, inadequate adjustment for potential confounders and short-term infant follow-up. Most studies examined outcomes around the time of delivery only, and although some studies attempted to ascertain outcomes in the first year of life, none extended this to capture those diagnosed later in childhood.

Whilst registries have been important in monitoring the safety of newly-authorized medications, population-based electronic health records are increasingly being used for this purpose. These data cover large populations and are collected routinely, allowing for the examination of rare outcomes and reducing the potential for under-ascertainment and selection bias. Ascertainment can be further maximized by linkage of primary care records to hospital admissions and mortality data and long-term follow-up. Finally, because data collection occurs routinely, electronic health records have the potential to provide information on risk factors for MCMs that can then be adjusted for in analyses.

The overarching aim of this work was to use UK electronic health records to assess the safety of maternal influenza vaccination with respect to MCMs which are of particular public health importance. Although both PIIV and SIIV were examined, the emphasis was on first-trimester receipt of SIIV. As part of addressing this aim, the work carried out here included a considerable methodological component that may serve to inform future safety studies. This

work offered the opportunity to: explore the way MCMs have been identified in other studies, develop methods to define MCMs using electronic health records, and assess the value of linked data and long-term follow-up in the ascertainment of these conditions. This work also provided the opportunity to capitalize on a newly-developed Pregnancy Register (which identifies pregnancy episodes in electronic health records and enables the identification of individual trimesters) and explore its use in safety studies.

### 1.8.2 Aims and Objectives

The principal aim of this research was to evaluate the safety of SIV and PIV administration during pregnancy and stratified by trimester with respect to MCMs. The objectives to achieve this were:

**Objective 1.** To systematically review the literature on the methods used to identify and validate congenital malformations in UK electronic health records and the results from any validation studies.

**Objective 2.** To develop a comprehensive algorithm to identify MCMs recorded in linked Clinical Practice Research Datalink primary care records, hospital admission data from Hospital Episode Statistics and Office for National Statistics mortality data.

**Objective 3.** To establish the value of each of the above data sources in identifying infants with MCMs and the agreement between them.

**Objective 4.** To compare the prevalence of MCMs in stand-alone and linked data sources with published prevalence estimates from other electronic health record databases and with national surveillance data from EUROCAT registries.

**Objective 5.** To use linked data to examine the association between maternal vaccination with SIVs and MCMs in live-born singletons, stratified by trimester.

**Objective 6.** To use linked data to examine the association between maternal vaccination with PIVs and MCMs in live-born singletons, stratified by trimester.

**Table 1.8 - Thesis Objectives**

Objective	Study Design	Population	Exposure	Outcomes	Effect measures	Relevant chapter
1. Systematically review the methods used to identify CMs in UK electronic health records and results from any related validation studies	Systematic review and meta-analysis	Individuals of any age with any type of CM identified in primary or secondary care data in the UK	-	1. Methods used to develop code lists 2. Results of validation studies 3. Results of CM prevalence rate comparisons with external data sources	Positive predictive values; Prevalence ratios	2
2. Develop an algorithm to identify MCMs recorded in CPRD, HES and ONS mortality data.	Methodological	-	-	1. Develop Read code lists to identify MCMs recorded in CPRD 2. Develop ICD-10 code lists to identify diagnoses and causes of death recorded in HES and ONS mortality data, respectively. 3. Develop OPCS-4 code lists to identify procedures for the treatment of MCMs recorded in HES.	-	5
3. Assess the value of stand-alone CPRD, HES and ONS and linked data in identifying individuals with MCMs.	Cohort	Live-born singletons	-	1. Comparison of prevalence rates between stand-alone CPRD, HES and linked data. 2. Comparison of proportion of infants with MCM recordings in single and multiple data sources.	Prevalence ratios	7
4. Compare rates of MCMs in stand-alone and linked CPRD, HES and ONS mortality data with rates from THIN and UK EUROCAT data.	Cohort	Live-born singletons	-	1. Comparison of MCM prevalence rates in the first year of life with THIN data. 2. Comparison of MCM prevalence rates in the first year of life with UK EUROCAT data.	Prevalence ratios	7
5. Examine the association between maternal vaccination with SIIV and MCMs.	Cohort	Live-born singletons delivered during a period when all pregnant women were eligible for seasonal influenza vaccination and had an opportunity of at least one week to be vaccinated.	SIIV received in pregnancy, stratified by trimester	<b>Primary:</b> 1. Any MCM recorded in the first year of life <b>Secondary:</b> 1. Any MCM recorded between delivery and the end of the study period 2. Any major congenital heart defect recorded between delivery and the end of the study period 3. Any major limb defect recorded between delivery and the end of the study period	Odds ratios; Hazard ratios	8
6. Examine the association between maternal vaccination with PIIV and MCMs	Cohort	Live-born singletons delivered during a period when all pregnant women were eligible for pandemic influenza vaccination and had an opportunity of at least one week to be vaccinated.	PIIV received in pregnancy, stratified by trimester	<b>Primary:</b> Any MCM recorded in the first year of life <b>Secondary:</b> Any MCM recorded between delivery and the end of the study period	Odds ratios; Hazard ratios	9

Abbreviations: CM, Congenital malformation; MCM, Major congenital malformation; THIN, The Health Improvement Network; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics; SIIV, Seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine; ICD-10, International Classification of Diseases (10<sup>th</sup> Revision); OPCS-4, Classification of Surgical Operations and Procedures (4<sup>th</sup> Revision).

## 2. The identification and validity of congenital malformation diagnoses in UK electronic health records: A systematic review

### 2.1 Introduction

This chapter presents a systematic review of the methods used by other researchers to identify and validate congenital malformations in UK electronic health records (**Objective 1**). Results from any validation studies are also presented. Results from the systematic review informed the development of a comprehensive algorithm to identify MCMs in linked primary care, hospital admission and mortality data (**Objective 2; Chapter 5**). This chapter is presented in the form of a research paper prepared for submission.

## RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

### SECTION A – Student Details

Student ID Number	1300677	Title	Miss
First Name(s)	Maria		
Surname/Family Name	Peppa		
Thesis Title	The safety of influenza vaccination in pregnancy: Examining major congenital malformations as potential adverse outcomes using UK electronic health records		
Primary Supervisor	Professor Punam Mangtani		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

### SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

\*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

### SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Pharmacoepidemiology & Drug Safety
Please list the paper's authors in the intended authorship order:	Maria Peppa, Punam Mangtani, Caroline Minassian, Sara L Thomas

Stage of publication	<b>Not yet submitted</b>
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#### **SECTION D – Multi-authored work**

<p>For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)</p>	<p>The scope of the systematic review was decided by P Mangtani, S Thomas and myself. I developed the search strategy (including the search terms) and the eligibility criteria used following detailed discussions with P Mangtani and S Thomas. I screened abstracts and full-text publications and a random sample of abstracts were also screened by P Mangtani and S Thomas to check consistency. With the exception of quality assessments, which were carried out jointly with S Thomas to ensure agreement and consistency, I conducted all analyses. I drafted the initial manuscript and revised it based on comments by co-authors.</p>
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#### **SECTION E**

<b>Student Signature</b>	Maria Peppa
<b>Date</b>	19.03.2020

<b>Supervisor Signature</b>	Punam Mangtani
<b>Date</b>	20.03.2020



## 2.2 Paper 1: The identification and validity of congenital malformation diagnoses in UK electronic health records: A systematic review.

**Authors:** Maria Peppas<sup>\*a</sup>, Punam Mangtani<sup>a</sup>, Caroline Minassian<sup>a</sup>, Sara L Thomas<sup>a</sup>.

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## **Abstract**

### **Purpose**

To describe the methods used to identify and validate congenital malformations recorded in UK electronic health records, and the results of any such validation studies.

### **Methods**

Medline and Embase were searched for publications that involved the identification of congenital malformations in UK electronic health records using diagnostic codes between 1987 and 2019. Retrieved publications, reviews and bibliographies of UK electronic health record databases were searched to identify additional studies. The methods and code lists used to identify congenital malformations were examined, as well as the methods and results of any validation studies.

### **Results**

We identified 54 eligible studies; 36 used primary care records to identify congenital malformations and 18 used secondary care data alone or in combination with birth and/or death records. Studies using primary care data were frequently found to use Read codes outside of the 'P' chapter dedicated to congenital malformation diagnoses. Conversely, studies using secondary care data relied on the 'Q' chapter for congenital malformations in ICD-10. Eight studies attempted to validate congenital malformations identified in primary care data, with most using GP questionnaires or a mixture of further information from primary care. Congenital malformations overall, major malformations and heart defects had a high positive predictive value (80-100%) whilst this was lower for neural tube defects (71%) and developmental dysplasia of the hip (56%). Although the positive predictive value was high for most conditions, the validity of the reference standard used was often uncertain.

### **Conclusions**

Studies using primary care data to identify congenital malformations provide limited details about the identification methods used, whilst studies using secondary care data have not attempted to validate diagnostic codes. Studies using primary care data frequently use non-'P'

chapter codes which can increase the ascertainment of congenital malformations in these data. However, the validity of these codes has not been explored. Further assessments of validity in both data sources and of further malformation subgroups should be considered.

## Introduction

Post-licensure safety studies of drugs and vaccines given in pregnancy increasingly rely on the use of large databases of anonymised, routinely-collected electronic health records (EHR).<sup>175,</sup>  
<sup>176</sup> UK EHR used for safety research include primary care databases, such as the Clinical Practice Research Datalink (CPRD), which contain information recorded in general practice for a representative sample of the population.<sup>126</sup> Secondary care databases, such as the Hospital Episode Statistics Admitted Patient Care (HES-APC) database, capture information on all patients admitted to NHS hospitals in England and are also available for research.<sup>177</sup> Data from primary and secondary care databases, as well as data from other sources such as death certificates, can be provided to researchers pre-linked, thus maximizing the ascertainment of important but rare safety outcomes.<sup>126, 177</sup>

Congenital malformations are important outcomes in post-licensure safety studies of drugs or vaccines given in pregnancy. The methods developed for their identification in EHR are therefore of particular interest. In primary care, clinical data including diagnoses and procedures are currently coded using the hierarchical Read coding system (some databases previously used Oxford Medical Information System (OXMIS) codes).<sup>126</sup> Secondary care databases include diagnoses and procedures coded using the 10<sup>th</sup> Revision of the International Classification of Diseases (ICD-10) and the 4<sup>th</sup> Revision of the Classification of Interventions and Procedures (OPCS-4), respectively.<sup>177</sup> Underlying and contributing causes of death on death certificates are also coded using ICD-10.<sup>178</sup>

Chapters 'P' in Read and 'Q' in ICD-10 are dedicated to congenital malformation codes. However, clinical coders in primary and secondary care may choose to code a congenital malformation with a code from outside these chapters. For example, an individual with a congenital pulmonary valve malformation could have their condition recorded using the code for '*pulmonary valve anomalies*' from the Read 'P' chapter on congenital malformations or the

code for '*pulmonary valve disorders*' from the 'G' chapter on circulatory system diseases (which may not be congenital in origin).

Researchers who want to identify individuals with a specific congenital malformation in EHR data have to develop a list of relevant diagnostic and procedural codes ('code lists') that can then be used to search patient records.<sup>179</sup> To aid code list development, researchers may refer to published guidelines which define the codes for particular conditions or provide an idea of relevant key terms which can be used to identify equivalent codes. For example, the European Network of Population-based Registries for Congenital Malformations (EUROCAT) publishes the guidelines used by individual registries to code and classify congenital malformations using modified ICD-10 codes.<sup>86</sup> Such guidelines are not used by clinical coders in primary and secondary care to encode congenital malformations. Researchers therefore need to consider that a wider range of codes may be used in routine clinical practice.

When developing code lists, the inclusion of broad-ranging codes from outside the dedicated chapters enables more complete capture of congenital malformations in EHR but also increases the risk of including some conditions that are not congenital in nature. The wide array of congenital malformations and the lack of a standardized algorithm for their identification complicate their ascertainment and may result in a variety of approaches, affecting replicability across studies and the validity of the findings. Previous reviews have highlighted that the validity of diagnostic codes in UK EHR is good in general.<sup>180, 181</sup> However, to date, no study has systematically assessed the validity of code lists developed and used to identify congenital malformations in these data.

This systematic review aimed to inform future safety studies by describing the methods used to identify individuals with congenital malformations from UK electronic health records and by summarizing the results of any associated validations.

## Methods

We carried out a systematic review of studies that involved the identification of congenital malformations in UK EHR. The systematic review was registered with PROSPERO (registration number: CRD42017037168).

### Eligibility criteria

Studies were included if they involved the use of diagnostic codes to identify congenital malformations in UK EHR and were published after 1987 (the year the first database, CPRD, was established).<sup>126</sup> As the main objective of this study was to review the methods used to identify congenital malformations from large electronic datasets, case series and case reports were excluded but all other study designs were permitted. We excluded studies if the population examined was sourced from a tertiary care setting or a specialist registry as we considered that the differences in case mix and coding practices in these settings would seriously limit the generalizability of results. Studies restricted to congenital malformations with known causes that are frequently excluded from safety studies (for example, chromosomal abnormalities and single gene defects) were not included. Conference abstracts were also excluded as they did not contain sufficient methodological detail to meet the objectives of this review.

Validations of diagnostic codes for congenital malformations, reported within the EHR studies identified as eligible, were included if they used any of the following methods: manual review of the entire patient record (including anonymised free-text when available), additional information from GPs (e.g. via questionnaires or provision of hospital letters or death certificate data), comparison with records in an external database, or comparison of prevalence with that derived from external population-based data (providing this was a study objective and not simply referred to in the discussion section to provide context to the study results). Validation studies also needed to report  $\geq 1$  validity measurement (sensitivity,

specificity, positive predictive value or negative predictive value), or provide data that allowed their calculation.

### **Search strategy and study selection**

The search for this review was a component of a wider search strategy for studies examining congenital malformations or pervasive developmental disorders using UK or US health data. Medline and Embase were searched up to 20 September 2019 for English-language publications using keywords and subject headings for ‘congenital malformations’ and ‘electronic health records’ (**Appendix 1**). This was supplemented with a manual search of the bibliographies of three of the main UK primary care EHR databases (CPRD, The Health Improvement Network (THIN) and Q-Research) and the Boston Collaborative Drug Surveillance Programme.<sup>182-185</sup> Reference lists of relevant reviews and eligible studies were subsequently hand-searched for further studies.

The titles and abstracts of studies identified in the search were screened by one author (MP) to determine those eligible for full-text review. A sample of abstracts was also screened by ST and PM to establish consistency, with any differences resolved through discussion.

### **Data extraction**

Details of the methods used to identify congenital malformations were extracted using a standardized form. The key data extracted from each study included: the congenital malformations identified and any exclusions or subsequent classification into subgroups, the use of any externally-developed guidelines to inform case definitions, details of the identification process (including whether code lists for malformations were developed and the methods used to develop them, whether a computerized search using pre-prepared code lists was conducted versus a manual review of infant records to identify possible malformations) and any published code lists or algorithms. Code lists that were not included in published papers but were publicly available elsewhere (e.g. in a report or thesis) were identified or were requested from authors.

When studies examined the diagnostic validity of recorded congenital malformations, the following data were also extracted: the main conditions validated, the methods used (e.g. the information used to validate diagnoses, the proportion of identified diagnoses that authors chose to validate and the rationale for their selection, the response rate for any information requests authors made and the reasons for non-responses, and the reported results. When validation comprised prevalence comparisons with external data sources, we extracted information about the external data-source, the period of comparison and any results.

### **Quality assessment**

A modified version of the Quality Assessment of Diagnostic Studies tool (QUADAS-2) was used to assess the quality of studies performing validations.<sup>186</sup> Six areas from the tool considered to be applicable to EHR were adapted for use, relating to: enrolment of patients, patient exclusions, blinding to the reference standard results, the validity of the reference standard, consistent use of the reference standard, and inclusion of patients in the analysis (see

**Supplementary Table 1**).

### **Data synthesis and analysis**

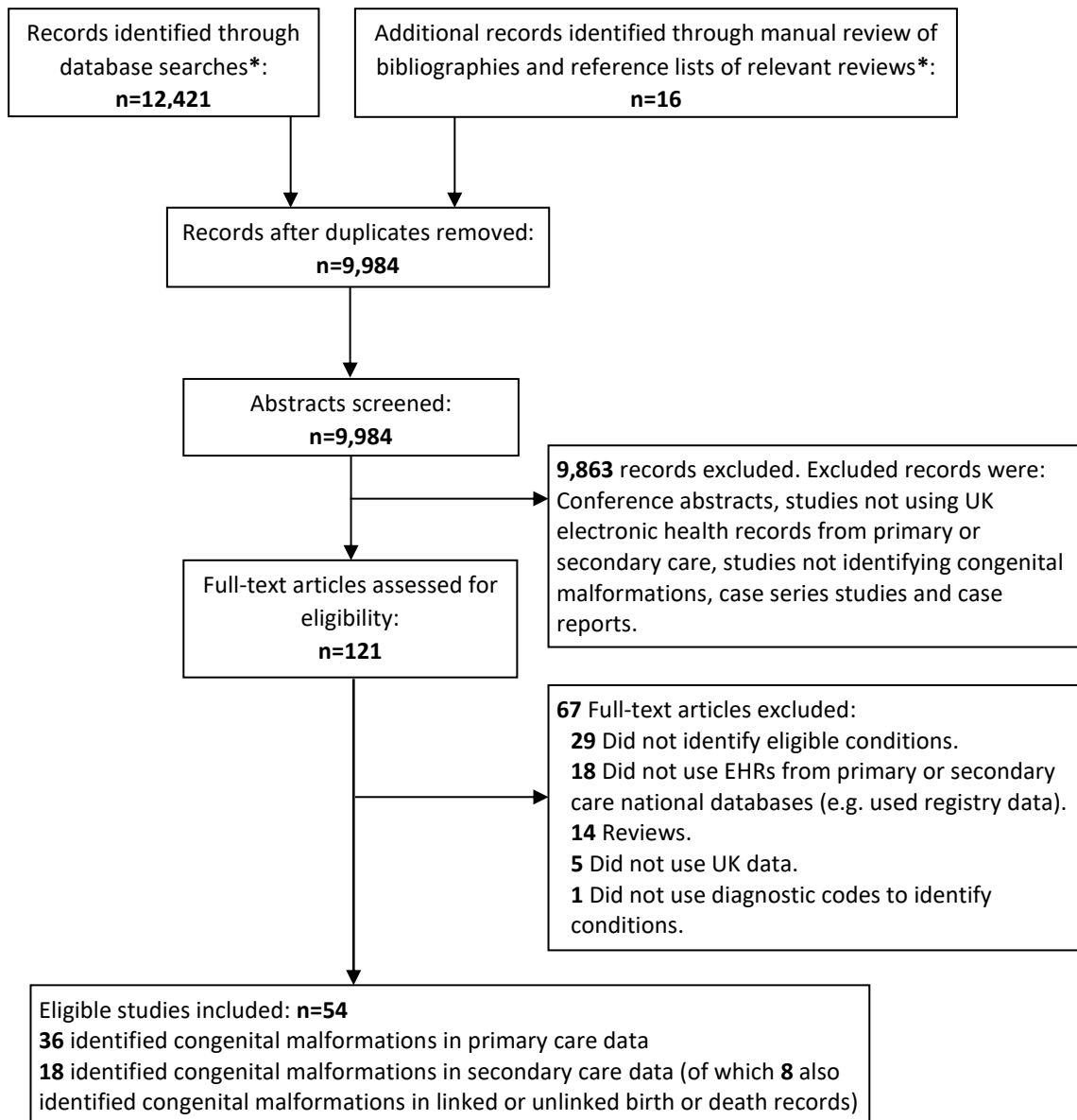
Studies were stratified according to whether congenital malformations were identified in primary or secondary care. The methods used to identify individuals with congenital malformations and the methods and results of any validation studies, were summarized for each group and by type of congenital malformation when possible. When validation studies presented a validation measure without 95% confidence intervals (CIs), these were calculated using the Wilson method. As only a very small number of studies performed validations, with a diversity of methods after stratifying by malformation subtype, summary estimates of validation measures were not attempted. Between-study heterogeneity in validity estimates within strata was investigated using  $\chi^2$  tests.



## Results

We retrieved 54 eligible studies that identified congenital malformations from UK EHR (**Figure 1**). Individuals with congenital malformations were identified from primary care data in 36 studies, most of which aimed to assess drug safety during pregnancy.<sup>187-222</sup> More than half of these 36 studies used stand-alone CPRD (n=21) and major malformations were the most frequently identified condition (n=19). Only one study used primary care records linked to HES. This study identified congenital malformations in CPRD and subsequently validated identified diagnoses using HES data.<sup>222</sup>

The remaining 18 studies used secondary care data to identify individuals with congenital malformations and typically aimed to assess health service delivery, surgical outcomes and disease trends.<sup>223-240</sup> Almost all these studies used HES (n=16) and the most commonly identified congenital malformations were heart and orofacial defects (n=4). Eight of the secondary care studies also used linked (n=6)<sup>223-227, 237</sup> or unlinked (n=1)<sup>228</sup> death certificate data or linked birth data (n=2).<sup>237, 238</sup>



**Figure 1 - Identification of eligible studies.** \*This was part of a larger search strategy that included studies identifying pervasive developmental disorders and studies using electronic health records in the US, neither of which were considered here.

## Defining and identifying congenital malformations in primary care data

The 36 studies using primary care data often relied on published guidelines to develop case definitions for the congenital malformations of interest, especially when identifying a wide array of conditions that required the exclusion of minor diagnoses or further classification of diagnoses into malformation subgroups (**Table 1**). Of the 22 studies that identified ‘any’ or ‘major’ malformations, 91% (n=20) referred to guidelines, the majority using EUROCAT (n=16).<sup>187, 189-202, 206</sup> Four studies indicated that they sought clinical input alongside the guidelines to define and further classify conditions of interest (**Table 1**).<sup>189-191, 218</sup>

Once defined, the methods used to identify the congenital malformations of interest within the data were rarely detailed in publications. Just three studies specified the use of a computerized search.<sup>203-205</sup> Feedback from authors clarified that a manual review of the data was conducted in another three studies<sup>189, 192, 207</sup> of which two did not refer to pre-prepared code lists of malformations when reviewing recorded events in their study populations.<sup>189, 192</sup>

The majority of the other 34 studies were known to use code lists because they were publicly available (n=11)<sup>195-202, 206, 219, 222</sup> or could be obtained from authors (n=12)<sup>193, 194, 203-205, 207, 208, 210, 213, 218, 220, 221</sup> and another three were thought likely to have used them based on our communication with authors and the nature of the studies (**Table 2**).<sup>209, 215, 216</sup> The use of a code list was therefore uncertain for the remaining 8 studies.<sup>187, 188, 190, 191, 211, 212, 214, 217</sup>

A small number of studies examined additional data for evidence of congenital malformations. Three studies described manually reviewing anonymised free-text in maternal records to identify evidence of congenital malformations among pregnancies that did not result in a live-born infant (e.g. terminations, stillbirths, miscarriages) (**Table 1**).<sup>188, 192, 193</sup> Another two requested and reviewed complete paper records (n=2) and anonymised free-text (n=1) to inform the classification of identified congenital malformations as major or minor.<sup>190, 191</sup>

Methods used to develop code lists were described briefly in 17 studies (**Table 1**). In almost all studies, code list development relied on relating relevant ICD codes to equivalent Read/OXMIS codes (n=16) (**Table 1**).<sup>193-205, 207, 208, 218</sup> Few studies described how this mapping was achieved

(n=3)<sup>193, 194, 218</sup> but two approaches were identified. In the first approach, search terms were created using ICD code descriptions and applied to Read/OXMIS dictionaries to identify relevant codes (and potentially closely related codes in the Read/OXMIS hierarchy).<sup>193, 194</sup> Alternatively, potential Read/OXMIS codes of interest were identified by examining all codes in the patient's records and those thought to correspond to relevant ICD codes were included.<sup>218</sup> Reference ICD codes were often determined using published guidelines (n=14), with EUROCAT guidelines again being the most frequently referred to (n=11) (**Table 1**).<sup>193-206, 218</sup> We examined the codes used to identify congenital malformations in the 24 studies known or thought likely to have used Read code lists (two of the studies known to use code lists only used OXMIS codes and were not explored).<sup>193-206, 209, 210, 213, 215, 216, 218-222</sup> For 16 of these, the level of detail was sub-optimal and only broad code lists were available which included some codes that were not part of the final congenital malformation case definition but were not marked as such (**Table 2**).<sup>193-206, 210, 218</sup> Another 3 only provided the subset of codes identified in the study population rather than all possible malformation codes.<sup>209, 215, 216</sup> Specific detailed code lists were available for just 5 studies (**Table 2**).<sup>213, 219-222</sup>

All 24 studies considered 'P' chapter Read codes when identifying congenital malformations. However, most studies also considered codes from other chapters, although this was rarely described in the published methods. The most frequently considered codes from other chapters were those related to procedures (n=20) (e.g. *'repair of cleft lip operations'*) and diagnostic codes (n=19) (e.g. *'mitral stenosis'* from the 'G' chapter on diseases of the circulatory system) (**Table 2**). Studies also frequently considered codes indicating that an individual had a history of a congenital malformation (n=14) (e.g. *'personal history of congenital malformations'*) and administrative codes relating to transfers of care, monitoring or counselling of individuals with malformations (n=12) (e.g. *'transfer of care from paediatric congenital heart services'*). Codes relating to testing or screening for malformations (e.g. *'screening for congenital eye anomaly'*) or observations of conditions made on examination (e.g. *'observed on examination – pigeon chest'*) were least frequent (n=2).

**Table 1 - Studies identifying congenital malformations using primary care data.**

Author	Study Aim	Data Source	Identification Period <sup>a</sup>	Population	Methods used to identify evidence of malformations	Classifications used for malformations and exclusions	Guidelines used to define, classify or exclude malformations	Code list development described?
<b>Any congenital malformation</b>								
Cea-Soriano 2018 <sup>187</sup>	Assess the safety of non-insulin antidiabetic drugs in pregnancy	THIN	1995-2013	Live-born infants	<b>Read codes</b> were identified in infant records anytime in the identification period. Maternal records were also searched for codes during pregnancy (methods not described).	<b>Classified</b> into subgroups. <b>Excluded</b> minor and genetic conditions and birth marks in safety assessments.	EUROCAT	No
Baril 2015 <sup>188</sup>	Assess the safety of the human papillomavirus vaccine in pregnancy	CPRD	2008-2011	Live-born infants Terminations Miscarriages Stillbirths	<b>Medcodes<sup>b</sup></b> were identified in infant clinical or referral files in the first 12 weeks of life and entity types were examined. <b>Free-text</b> in the maternal record was examined for other pregnancy outcomes.	<b>Classified</b> as major or minor.	Metropolitan Atlanta Congenital Defects Program Report	No
Ruigomez 1999 <sup>189</sup>	Assess the safety of antacids in pregnancy	CPRD	1991-1997	Live-born infants Terminations Stillbirths	<b>Manual review</b> of infant records in the first year of life by two physicians. Maternal records were also thought to be examined (methods not described).	<b>Classified</b> as major or minor and into subgroups. <b>Excluded</b> genetic conditions.	EUROCAT, with physician input <sup>c</sup>	N/A (Authors communicated that no code list was developed)
<b>Major congenital malformations</b>								
Petersen 2017 <sup>190</sup>	Assess anticonvulsant safety in pregnancy.	THIN	1995-2014	Live-born infants	<b>Read codes from the 'P Chapter'</b> were identified in infant records.	<b>Excluded</b> minor conditions.	EUROCAT, with GP input.	Only identified 'P' codes, unclear if code list used.
Petersen 2016 <sup>191</sup>	Assess the safety of antipsychotics in pregnancy.	CPRD & THIN	1995-2012	Live-born singletons	<b>Read codes from the 'P Chapter'</b> were identified in infant records during the first year of life. Codes were also identified from maternal records during pregnancy.	<b>Excluded</b> minor conditions and Down syndrome.	EUROCAT, with GP input <sup>d</sup>	Only identified 'P' codes in the infant records, unclear if code list used.
Charlton 2015 <sup>192</sup>	Assess the safety of inhaled corticosteroids in pregnancy.	CPRD	2000-2010	Live-born singletons Terminations Stillbirths	<b>Manual review</b> of clinical, referral and test files of infants during the identification period to identify Read codes. <b>Free-text</b> in the maternal record that was associated with other pregnancy outcomes was searched for evidence.	<b>Classified</b> into subgroups. <b>Excluded</b> minor conditions & syndrome-related defects in infants with syndromes.	EUROCAT.	N/A (Authors communicated that no code list was developed)
Charlton 2011 <sup>193</sup>	Assess the safety of anticonvulsants in pregnancy.	CPRD	1990-2006	Live-born infants Terminations Stillbirths Neonatal deaths	<b>Read and OXMIS</b> codes were identified in clinical, referral and test files of infants during the identification period. <b>Free-text</b> in the maternal record was searched. It was examined from 2 months before until 4 months after a termination or 6 months after a stillbirth or neonatal death.	<b>Classified</b> into subgroups. <b>Excluded</b> minor conditions, genetic conditions & those not plausibly drug-induced.	EUROCAT.	Created search terms using ICD-9 codes 740-759. Read codes containing the terms were identified
Charlton 2010 <sup>194</sup>	Assess the identification of major malformations in CPRD	CPRD	1990-2006	Live-born infants	<b>Read and OXMIS</b> codes were identified in clinical, referral and test files of infants during the identification period.	<b>Classified</b> into subgroups. <b>Excluded</b> minor conditions.	EUROCAT.	Created search terms using ICD-9 codes 740-759. Read codes containing the terms were identified

Author	Study Aim	Data Source	Identification Period <sup>a</sup>	Population	Methods used to identify evidence of malformations	Classifications used for malformations and exclusions	Guidelines used to define, classify or exclude malformations	Code list development described?
Dhalwani 2015 <sup>195</sup>	Assess nicotine replacement therapy in pregnancy.	THIN	2001-2012	Live-born infants	<u>Read codes</u> were identified in the medical file of infants during the identification period.	<b>Classified</b> into subgroups. <b>Excluded</b> minor defects and those due to known teratogens	EUROCAT.	Relevant ICD-10 codes were used to identify equivalent Read codes.
Ban, 2014a <sup>196</sup> 2014b <sup>197</sup> 2014c <sup>198</sup> 2015a <sup>199</sup> 2015b <sup>200</sup>	Assess the risks in pregnancy of: 1) depression & therapy 2) inflammatory bowel disease & therapy 3) anxiolytics/hypnotics 4) anti-epileptics & 5) coeliac disease	THIN	1990-2009 1990-2010 1990-2010 1990-2013 1990-2013	Live-born singletons	<u>Read codes</u> were identified from infant records during the identification period.	<b>Classified</b> into subgroups. <b>Excluded</b> minor and genetic conditions and those due to known teratogens.	EUROCAT.	Relevant ICD-10 codes were used to identify equivalent Read codes.
Sokal 2013 <sup>201</sup> 2014 <sup>202</sup>	Compare prevalence of MCMs in THIN with: 1) EUROCAT, 2) other population-based data.	THIN	1990-2010	Live-born singletons	<u>Read codes</u> were identified in infant records during the identification period.	<b>Classified</b> into subgroups. <b>Excluded</b> minor conditions.	EUROCAT.	Relevant ICD-10 codes were used to identify equivalent Read codes.
Vasilakis-Scaramozza 2013a <sup>203</sup> 2013b <sup>204</sup> 2013c <sup>205</sup>	Assess the risk of: 1) asthma treatment, 2) depression, & 3) hypertension in pregnancy.	CPRD	1991-2002	Live-born singletons Terminations Stillbirths	<u>Read codes</u> were identified in infant records during the identification period. <u>Cause of death</u> for stillbirths and terminations was checked for evidence. <sup>e</sup>	<b>Classified</b> into subgroups. <b>Excluded</b> minor and genetic conditions and those associated with prematurity among preterm births.	Centers for Disease Control & Prevention guidelines.	ICD-9 codes 740-7599 were used to identify equivalent Read codes.
Tata 2008 <sup>206</sup>	Assess asthma and treatment in pregnancy.	THIN	1988-2004	Live-born infants	<u>Read codes</u> were identified in infant records during the identification period.	<b>Classified</b> into subgroups. <b>Excluded</b> minor conditions.	EUROCAT.	No
Jick 1999 <sup>207</sup>	Assess the safety of antifungals in pregnancy	CPRD	Not specified	Live-born infants	<u>Manual review</u> of infant records for evidence at birth. If a malformation was suspected, relevant paper records were requested from the GP for further information.	<b>Classified</b> into subgroups.	Defined as those needing surgery or treatment.	ICD-8 codes 7400-7590 were used to identify equivalent OXMIS codes <sup>f</sup>

Author	Study Aim	Data Source	Identification Period <sup>a</sup>	Population	Methods used to identify evidence of malformations	Classifications used for malformations and exclusions	Guidelines used to define, classify or exclude malformations	Code list development described?
Jick 1997 <sup>208</sup>	Assess the safety of anticonvulsants in pregnancy.	CPRD	1988-1993	Live-born infants	<b>OXMIS codes</b> were identified in infant records around the time of birth.	<b>Excluded</b> minor conditions, hypospadias, hernias, & those that could not be drug-induced.	N/S	ICD-8 codes 7400-7590 were used to identify equivalent OXMIS codes
<b>Neural Tube Defects</b>								
Devine 2008 <sup>209</sup>	Examine the validity of neural tube defects recorded in CPRD.	CPRD	1987-2004	Live-born infants Terminations Stillbirths Miscarriages	<b>Read and OXMIS codes</b> for anencephaly, encephalocele, spina bifida & meningocele were identified in infant records in the 1 <sup>st</sup> year of life. The 1 <sup>st</sup> code was included. Codes on January 1 <sup>st</sup> were excluded unless within 30 days of birth. <b>Read and OXMIS codes</b> within 210 days of a pregnancy record were identified in maternal data. The 1 <sup>st</sup> code was included. Codes were excluded if: within 60 days of the 1 <sup>st</sup> code, if on January 1 <sup>st</sup> and not within 30 days of a pregnancy record, or, if within 180 days of a code in the infant.	<b>Classified</b> anencephaly, cephaloceles, meningoceles and spina bifida separately for some analyses.	N/S	No
Tata 2005 <sup>210</sup>	Assess the risks of celiac disease in pregnancy.	CPRD	1987-2002	Live-born infants	<b>Read codes</b> for meningocele, meningomyelocele, spina bifida and hydrocephalus were identified in infant records during the identification period.	None described	N/S	No
Lawrenson 2001 <sup>211</sup>	Estimate prevalence and incidence of renal failure and replacement therapy in those with neural tube defects.	CPRD	Prior to 1997	Patients aged 10-69	<b>Diagnostic codes</b> for neural tube defects were identified in the identification period (methods were not described further).	None described	N/S	No
Lawrenson 2000 <sup>212</sup>	Estimate mortality and prevalence rates of neural tube defects.	CPRD	Prior to 1997	Patients aged 10-69	<b>Diagnostic codes</b> for meningocele, meningomyelocele, spina bifida and hydrocephalus were identified in the identification period (methods were not described further).	None described	N/S	No

Author	Study Aim	Data Source	Identification Period <sup>a</sup>	Population	Methods used to identify evidence of malformations	Classifications used for malformations and exclusions	Guidelines used to define, classify or exclude malformations	Code list development described?
<b>Orofacial defects</b>								
Chi 2011 <sup>213</sup>	Assess the safety of topical corticosteroids in pregnancy.	CPRD	2000-2006	Live-born singletons	<u>Read and OXMIS codes</u> were identified in clinical files of infants.	<b>Classified</b> by cleft type. <b>Excluded</b> syndromic cleft.	N/S	No
<b>Heart defects</b>								
Petersen 2016 <sup>214</sup>	Assess antidepressant safety in pregnancy.	THIN	1990-2011	Live-born singletons	<u>Read codes</u> were identified from infant records during the first five years of life.	<b>Excluded</b> Down syndrome.	N/S	No
Margulis 2013 <sup>215</sup> Hammad 2013 <sup>216</sup>	Assess the safety of anti-depressants in pregnancy; Validate specific heart defects.	CPRD	1996-2010	Live-born singletons	<u>Read codes</u> indicating a heart defect or related procedure were identified from infant records in the first year and first six years of life.	<b>Classified</b> by heart defect. <b>Excluded</b> genetic conditions and sequences. <sup>g</sup>	Published development-based classification system. <sup>241</sup>	No
Billett 2008 <sup>217</sup>	Estimate the prevalence of comorbidities, health service use & recording of clinical indicators in those with heart defects.	Q Research	N/S-2005	All patients	<u>Read codes</u> indicating a heart defect or related procedure were identified during the identification period.	<b>Classified</b> by complexity. <b>Excluded</b> cardiomyopathies, isolated arrhythmias, isolated dextrocardia, bicuspid aortic valve, mitral valve prolapse, cardiac tumours, Marfan's syndrome	Modified version of a published classification system based on anatomical hierarchy. <sup>242</sup>	No
Wurst 2007a <sup>218</sup>	Compare the prevalence of heart defects between CPRD, NCAS and EUROCAT.	CPRD	2001-2003	Live-born infants	<u>Read and OXMIS</u> codes were identified in the infant's first year and first six years of life.	<b>Classified</b> by heart defect. <b>Excluded</b> minor conditions and vascular defects.	EUROCAT & National Congenital Anomaly System guidelines, with input from a paediatric cardiologist.	Identified potential Read/OXMIS codes and then selected those equivalent to ICD-9 codes 7450-59, 7460-69, 7470-74.
Wurst 2007b <sup>219</sup>	Examine the validity of specific heart defects recorded in CPRD.	CPRD	1992-2005	Live-born infants	<u>Read and OXMIS codes</u> for diagnoses and procedures were identified from infant records during the identification period.	<b>Classified</b> by heart defect. <b>Excluded</b> codes synonymous to the conditions of interest but which did not contain the specified terms.	N/S	Identified only those codes that included the terms: 'ventricular septal defect', 'tetralogy of Fallot', 'coarctation of the aorta', 'COA', 'VSD', or 'TOF'



Author	Study Aim	Data Source	Identification Period <sup>a</sup>	Population	Methods used to identify evidence of malformations	Classifications used for malformations and exclusions	Guidelines used to define, classify or exclude malformations	Code list development described?
<b>Gastroschisis</b>								
Bannister 2018 <sup>220</sup>	Assess the incidence of infections in children with gastroschisis	THIN	1990-2013	Live-born infants	<u>Read codes</u> were identified from infant records during the first five years of life.	<b>Excluded</b> other major malformations.	EUROCAT	No
<b>Genitourinary tract or inguinal region malformations and developmental hip dysplasia</b>								
Perry 2012 <sup>221</sup>	Assess the presence of malformations in those with Perthes disease.	CPRD	1990-2008	All patients in the study	<u>Read codes</u> were identified from records anytime in the identification period.	<b>Classified</b> into subgroups for analyses.	N/S	No
<b>Developmental hip dysplasia</b>								
Broadhurst 2019 <sup>222</sup>	Estimate incidence of developmental hip dysplasia	Linked CPRD & HES	1990-2016	All patients aged 1-8 years	<u>Read codes</u> were identified from records anytime in the identification period and the first code was considered the first diagnostic evidence.	<b>Excluded</b> those with neuromuscular conditions, syndromes or traumatic hip dislocation that could result in developmental hip dysplasia.	N/S	No

<sup>a</sup>The period in which congenital malformations were identified was not always explicitly defined by authors and did not always correspond to the study period. When possible, it was estimated from available information; <sup>b</sup>CPRD medcodes, corresponding to Read codes; <sup>c</sup>If the classification of identified conditions was uncertain, complete paper records were reviewed for further information; <sup>d</sup>If the classification of identified conditions was uncertain, free-text from THIN or complete paper records from CPRD were reviewed for further information; <sup>e</sup>This appeared to involve examination of maternal records but methods were not described further; <sup>f</sup>The authors communicated that they conducted a manual review but also provided information for a code list; <sup>g</sup>These are groups of related malformations typically occurring as a result of an MCM disrupting the development of surrounding tissues. Abbreviations: MCM, Major congenital malformation; CPRD, Clinical Practice Research Datalink (formerly the General Practice Research Database); THIN, The Health Improvement Network; OXMIS, Oxford Medical Information System; ICD, International Classification of Diseases; GP, General Practitioner; N/A, Not applicable; N/S, Not specified.

**Table 2 - Read and Oxford Medical Information System (OXMIS) codes used to identify congenital malformations in primary care data.**

Study	Used a code list?	Level of detail in code list published or provided upon request	Source of code list or reason list not available	Codes included?	Types of Read and/or OXMIS codes included in code lists to identify malformations							
					Diagnosis	Diagnosis from 'P' chapter in Read	Diagnosis from other Read chapters	Procedure	Testing/ Screening	History <sup>a</sup>	Observation <sup>b</sup>	Administrative <sup>c</sup>
<b>Any malformations</b>												
Cea-Soriano, 2018 <sup>187</sup>	N/S	None	No response to request for further information	Read <sup>d</sup>	✓	N/S	N/S	N/S	N/S	N/S	N/S	N/S
Baril, 2015 <sup>188</sup>	N/S	None	No response to request for further information	N/S	N/S	N/S	N/S	N/S	N/S	N/S	N/S	N/S
Ruigomez, 1999 <sup>189</sup>	No	None	No code list used	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
<b>Major malformations</b>												
Petersen, 2016 Petersen, 2017	N/S	Subset (most common codes identified in the study population)	No response to request for further information	Read	✓	✓	No	No	No	No	No	No
Charlton, 2015 <sup>192</sup>	No	None	No code list used	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Charlton, 2010 <sup>194</sup> Charlton, 2011 <sup>193</sup>	Yes	Broad	Author	Read & OXMIS	✓	✓	✓	✓	✓	✓	✓	✓
Tata, 2008 <sup>206</sup> Sokal, 2013 <sup>201</sup> Sokal, 2014 <sup>202</sup> Ban, 2014a-c <sup>196-198</sup> Ban 2015a-b <sup>199, 200</sup> Dhalwani, 2015 <sup>195</sup>	Yes	Broad	Published <sup>e</sup>	Read	✓	✓	✓	✓	No	✓	No	✓
Vasilakis-Scaramozza, 2013a-c <sup>203-205</sup>	Yes	Broad	Author	Read	✓	✓	✓	No	No	No	No	No
Jick, 1999 <sup>207</sup> Jick, 1997 <sup>208</sup>	Yes	Broad <sup>f</sup>	Author	OXMIS	✓	No	No	N/S	N/S	N/S	N/S	N/S
<b>Neural Tube Defects</b>												
Devine, 2008 <sup>209</sup>	Likely	Subset (only codes in the study population that were validated)	Published	Read & OXMIS	✓	✓	✓ <sup>g</sup>	✓	N/S	N/S	N/S	N/S
Tata, 2005 <sup>210</sup>	Yes	Broad	Author	Read & OXMIS	✓	✓	✓	✓	N/S	N/S	No	✓
Lawrenson, 2000 <sup>212</sup> Lawrenson, 2001 <sup>211</sup>	N/S	None	No access to study material	N/S	✓	N/S	N/S	N/S	N/S	N/S	N/S	N/S

Study	Used a code list?	Level of detail in code list published or provided upon request	Source of code list or reason list not available	Codes included?	Types of Read and/or OXMIS codes included in code lists to identify malformations							
					Diagnosis	Diagnosis from 'P' chapter in Read	Diagnosis from other Read chapters	Procedure	Testing/ Screening	History <sup>a</sup>	Observation <sup>b</sup>	Administrative <sup>c</sup>
<b>Orofacial malformations</b>												
Chi, 2011 <sup>213</sup>	Yes	Specific	Author	Read & OXMIS	✓	✓	No	✓	No	✓	No	No
<b>Heart Defects</b>												
Petersen, 2014 <sup>214</sup>	N/S	Subset (most common codes identified in the study population) <sup>h</sup>	No response to request for further information	Read	✓	✓	N/S	N/S	N/S	N/S	N/S	N/S
Margulis, 2013 <sup>215</sup> Hammad, 2013 <sup>216</sup>	Likely	Subset (only codes in the study population that were validated)	Published	Read	✓	✓	N/S	✓ <sup>d</sup>	N/S	N/S	N/S	N/S
Billet, 2008 <sup>217</sup>	N/S	None	No access to study material	Read	✓ <sup>d</sup>	N/S	N/S	✓ <sup>d</sup>	N/S	N/S	N/S	N/S
Wurst, 2007a <sup>218</sup>	Yes	Broad	Author	Read & OXMIS	✓	✓	✓	No	No	No	No	No
Wurst, 2007b <sup>219</sup>	Yes	Specific	Published	Read & OXMIS	✓	✓	No	✓	No	No	No	No
<b>Gastroschisis</b>												
Bannister, 2018 <sup>220</sup>	Yes	Specific	Author	Read	✓	✓	No	✓	No	No	No	No
<b>Genitourinary tract or inguinal region malformations and developmental hip dysplasia</b>												
Perry, 2012 <sup>221</sup>	Yes	Specific	Author	Read	✓	✓	✓	✓	No	✓	No	No
<b>Developmental hip dysplasia</b>												
Broadhurst, 2019 <sup>222</sup>	Yes	Specific	Published	Read	✓	✓	✓	✓	No	✓	✓ <sup>i</sup>	✓ <sup>i</sup>

Studies using the same code list were grouped. <sup>a</sup>Codes for history of congenital malformations ('*history of cleft palate*'); <sup>b</sup>Codes for congenital malformations observed during examination ('*observed on examination – pigeon chest*'); <sup>c</sup>Codes for monitoring, counselling or transfers of care related to congenital malformations ('*transfer of care from paediatric congenital heart service*'); <sup>d</sup>Described in methods; <sup>e</sup>Published as part of a thesis; <sup>f</sup>Author noted a manual review was likely used in one study; <sup>g</sup>Codes for suspected foetal malformations; <sup>h</sup>Published Read terms only; <sup>i</sup>Codes used as supportive evidence of condition. Abbreviations: N/A, Not applicable; N/S, Not specified.

### **Defining and identifying congenital malformations in secondary care data**

All 18 studies using secondary care data and/or birth and death certificate data used code lists to search the data (**Table 3**). Studies did not specify whether computerized or manual searches were used. However, the ICD-10 code lists used to identify conditions were publicly available for all studies (**Table 3**). All ICD-10 codes were from the 'Q' chapter for congenital malformations. Half of the studies also used OPCS-4 codes, often because procedures were relevant to the study question.

Details of the methods used to develop ICD-10 code lists were publicly available for six studies. These studies examined chronic or life-limiting conditions, of which congenital malformations were a subset.<sup>223, 224, 237-240</sup> The methods described were therefore not specific to congenital malformations although two studies did use EUROCAT guidelines to define and identify them.<sup>223, 224</sup> Only two studies stratified congenital malformations by their severity or complexity.<sup>224, 225</sup> This stratification was based on previously published guidelines, with one study providing the code list for severe conditions.<sup>224</sup> Of the four studies examining orofacial clefts, three stratified clefts by type and described the codes used.<sup>229-231</sup>

**Table 3 - Studies identifying congenital malformations using secondary care data.**

Author	Congenital malformations identified	Study Aim	Data-source	Identification Period	Study population	Algorithm to identify congenital malformations of interest	Algorithm to identify subgroups, excluded conditions or those used in sensitivity analyses
Zylbersztejn, 2019 <sup>223</sup>	Chronic congenital malformations	Compare preventable deaths in Sweden and England and assessed the contribution of risk factors.	(UK) HES admissions linked to death certificates	2003-2013	Singleton live-births delivered between 2003-2012	Presence of one of the codes below in hospital admission records from the 31 <sup>st</sup> day of life until the second birthday or on the death certificate as any cause of death until the fifth birthday.	Malformation subgroups not explored.
Zylbersztejn, 2018 <sup>224</sup>		Assess the reasons for higher infant mortality in England compared to Sweden				Presence of one of the codes below in the birth admission record, hospital admission records until the second birthday or on the death certificate as any cause of death up until the fifth birthday.  <u>Codes<sup>a</sup></u> : Q00-07, Q104, Q107, Q11-12, Q130-134, Q138-139, Q14-16, Q188; Q20-26; Q30-34; Q35-37; Q380, Q383-384, Q386-388, Q39, Q402-403, Q408-409, Q41-42, Q431, Q433-437, Q439, Q44-45; Q500, Q51, Q520-522, Q524, Q540-543, Q548-550, Q555, Q56; Q601-602, Q604-606, Q61, Q620-626, Q628, Q630-632, Q638-639, Q64; Q650-652, Q658-659, Q675, Q682, Q71-74, Q750-751, Q753-759, Q761-764, Q77-78, Q790, Q792-796, Q798; Q820-824, Q829, Q85, Q860-862, Q868, Q878, Q891-893, Q897-899; Q90-93, Q952-953, Q97, Q99	Sensitivity analysis of severe malformations as defined by the codes below.  <u>Codes<sup>b</sup></u> : Q00-07; Q20, Q212-214, Q218-219, Q22-24, Q251-259, Q26, Q282-283, Q289; Q30-34; Q390-394, Q41-45; Q60-64; Q722, Q750, Q752, Q759-762, Q764-767, Q77, Q780-784, Q788-795, Q799; Q81, Q871, Q873-874, Q877-879; Q909, Q913-914, Q917, Q928, Q93, Q950, Q969, Q97-98, Q992, Q998-999
Dimopoulos, 2019 <sup>225</sup>	Heart defects	Assess transplant survival rates and the capacity for such procedures.	HES admissions linked to death certificates	1997-2015	All	Presence of any 'Q2xx.x' code with a further procedure code indicating a heart or heart-lung transplant (OPCS-4 codes K01-02).	Stratified heart defects by complexity, using guidelines from 32 <sup>nd</sup> Bethesda conference
Kempny, 2017 <sup>226</sup>	Heart defects	Examine surgical volume and mortality in patients.	HES admissions linked to death certificates	1997-2015	All	Presence of any 'Q2x.x' code and evidence of a cardiac surgery (except heart or heart-lung transplants).	Excluded CABG and mitral valve surgery in sensitivity analyses
Singhal, 2014 <sup>227</sup>	Heart defects; Spina Bifida	Assess the relationship between self-harm/suicide and chronic illnesses.	HES admissions linked to death certificates	1999-2011	All	Presence of any Q20-24 code (heart defects) or a Q05 code (spina bifida).	-
Billett, 2007 <sup>228</sup>	Heart defects	Explore trends in admissions, procedures and patient mortality.	HES admissions, Death certificates (unlinked) from England and Wales	1995-2004 1994-2003	All	Any Q20-28 code in the primary diagnosis field. Any ICD-9 code for 745-747 for underlying cause of death until 2001 and any ICD-10 Q20-28 code thereafter.	-

Author	Congenital malformations identified	Study Aim	Data-source	Identification Period	Study population	Algorithm to identify congenital malformations of interest	Algorithm to identify subgroups, excluded conditions or those used in sensitivity analyses
Fitzsimons, 2017 <sup>229</sup>	Orofacial clefts	Examine grommet insertion practices in cleft patients.	HES admissions	1997-2011	Live-births from 1997 to 2005	Presence of any diagnostic Q35, Q36, or Q37 code as well as a procedure code for primary cleft repair (OPCS-4 codes F031 or F291).	Clefts were grouped by type using repair codes (F03, F29, F30, F32) and the available diagnosis code.
Fitzsimons, 2014 <sup>230</sup>		Examine hospital admissions for dental treatment in cleft.		1997-2011	Live-births from 1997 to 2003		Clefts were grouped by type using repair codes (F03, F29, F30, F32) and the available diagnosis code.
Fitzsimons, 2013 <sup>231</sup>		Explore hospital admissions and length of stay for cleft patients.		1997-2011	Live-births from 1997 to 2008		Clefts were grouped by type using repair codes (F03, F29, F32) and the available diagnosis code.
Fitzsimons, 2012 <sup>232</sup>		Assess changes in cleft patient care following service changes.		1997-2009	Live-births from 1997 to 2008		Clefts were not grouped by type.  All 4 studies identified those with additional malformations for separate analyses or exclusion using any of the following codes in any field: D821; Q00-07; Q16; Q18; Q20-28; Q380; Q75; Q86-87; Q90-93; Q95-99
Broadhurst, 2019 <sup>222</sup>	Developmental hip dysplasia	Estimate incidence of developmental hip dysplasia	Identified cases in CPRD and then used linked HES admissions data for validation	1990-2016	All patients aged 1-8 years	Linked HES admissions data in the 2 years either side of the initial diagnosis in CPRD were searched for supportive evidence in the following order (strongest to weakest evidence): A) A <u>specific</u> diagnosis based on the presence of a Q650-656 code or evidence of a specific procedure (OPCS-4 codes X221-225, X228-229). B) The presence of a <u>related</u> diagnostic code: M244 or R294. C) Evidence of a hospital admission within 6 months. If none of the above were found, CPRD was searched for supportive evidence ( $\geq 3$ orthopaedic hospital attendances, $\geq 2$ diagnostic codes or related codes such as those for a clicking hip) in the 2 years after the initial diagnosis.	Diagnoses excluded: G80, G800-804, G808-809, Q743, Q796, Q90, Q900-902, Q909, Q980-985, Q824, Q718, Q728, Q999, Q916, G711, G819, Q929, Q824, Q931, Q773 Procedures excluded: W651-655, W658-659, W661-664, W668-669, W671-679

Author	Congenital malformations identified	Study Aim	Data-source	Identification Period	Study population	Algorithm to identify congenital malformations of interest	Algorithm to identify subgroups, excluded conditions or those used in sensitivity analyses
McAllister, 2018 <sup>233</sup>	Developmental hip dysplasia	Assess the risk of surgery for this condition following an intervention.	Scottish Morbidity Record	1997-2014	Live-births from 1997-2013	Presence of any Q650-659 code with a further procedure code (OPCS-4 codes T202, T205, W134, W144, W164, W169, W281, X221-229, W65-66).	-
Dharmasena, 2017 <sup>234</sup>	Anophthalmia; Microphthalmia; Malformations of orbit; Agnesis of lacrimal apparatus	Estimate hospital admission trends and incidence of eye malformations.	HES admissions	1999-2011 1990-1998	All <1 years old	Presence of any of the following codes in the birth record or subsequent hospital admission record: Q110-Q111 (anophthalmia), Q112 (microphthalmia), Q107 (congenital malformations of orbit), Q104 (agenesis of lacrimal apparatus).  The ICD-9 code 7431 for microphthalmia was used in further analyses that examined years prior to 1995.	-
Lansdale, 2017 <sup>235</sup>	Pyloric stenosis	Examine surgical outcomes for infantile hypertrophic pyloric stenosis.	HES admissions & Patient Episode Data for Wales	2002-2011	All	Presence of a procedure code for pyloric stenosis (OPCS-4 code G401) that occurred between the 1 <sup>st</sup> day of life and the 1 <sup>st</sup> birthday, as well as a Q400 diagnostic code.	-
Wilkinson, 2017 <sup>236</sup>	Hypospadias	Estimate the frequency of re-operations and complications following repair of hypospadias.	HES admissions	1999-2009	Boys <16 years old	Presence of a procedure code for primary repair of hypospadias (OPCS-4 code M731), with or without a diagnostic Q54 code. Post-surgery admissions for were identified from Q540-543 or Q548-549 codes or codes relating to surgical complications or revisions.	Excluded those with disorders of sexual differentiation recorded with the following codes: Q560-564; Q640-641; E250, E258-259, E345

Author	Congenital malformations identified	Study Aim	Data-source	Identification Period	Study population	Algorithm to identify congenital malformations of interest	Algorithm to identify subgroups, excluded conditions or those used in sensitivity analyses
Jarvis and Fraser, 2018 <sup>237</sup>	Life-limiting or life-threatening malformations <sup>c</sup>	Compare the identification of these conditions in inpatient data and death records.	HES admissions linked to death certificates & Scottish Birth, Morbidity and Death Records.	2001-2015 2003-2014	Patients aged 0-25 years with a death record	Searched English and Scottish hospital admission data and Scottish birth records for the codes below, except for Q445 and Q748. Death records were searched for codes among the underlying causes of death. If this was not related to a life-limiting condition, then contributing causes of death were checked.	-
Jarvis, 2017 <sup>238</sup>		Assess clinical stability in those with life-limiting conditions.	Scottish Birth & Morbidity Records	2003-2014	Patients aged 0-25 years	Searched Scottish birth records and hospital admissions data for the codes below except for Q445 and Q748.	
Fraser, 2014 <sup>239</sup>		Estimate the prevalence of life-limiting conditions.	HES admissions	2009-2010	Patients aged 0-40 years	Searched hospital admissions data for the codes below.	
Fraser, 2012 <sup>240</sup>		Estimate the prevalence of life-limiting conditions.	HES admissions	2000-2010	Patients aged 0-19 years	<u>Codes:</u> Q000, Q01, Q031, Q039-040, Q042-044, Q046, Q049, Q070, Q200, Q203-204, Q206, Q208, Q213, Q218, Q220-221, Q224-226, Q230, Q232, Q234, Q239, Q254, Q256, Q262, Q264, Q268, Q282, Q321, Q336, Q396, Q410, Q419, Q437, Q442, Q445, Q447, Q601, Q606, Q614, Q619, Q642, Q743, Q748, Q750, Q772-774, Q780, Q785, Q792-793, Q804, Q81, Q821, Q824, Q858, Q860, Q870-872, Q878, Q91, Q920-921, Q924, Q927-928, Q932-935, Q938, Q952.	

<sup>a</sup>Codes were a subset of those developed by Hardelid *et al.* to identify chronic conditions requiring medical follow-up for more than a year in half or more of cases. <sup>b</sup>Codes were a subset of those developed by Feudtner *et al.* to identify conditions likely to last at least a year and involve multiple organ systems or require tertiary care. <sup>c</sup>Codes for malformations were a subset of those used to identify all life-limiting or threatening conditions. Abbreviations: HES, Hospital Episode Statistics; ICD, International Classification of Diseases; OPCS-4, 4<sup>th</sup> Revision of the Classification of Interventions and Procedures.



## Validation of codes used to record congenital malformations in primary care.

Eight studies attempted to validate congenital malformations identified in primary care data, all of which restricted to examining the positive predictive value (PPV) of a coded diagnosis (**Table 4**).<sup>187, 192, 194, 208, 209, 216, 219, 222</sup> Most relied exclusively on GP questionnaires (n=4) as the reference standard, or a mixture of further primary care data such as anonymised free-text or complete paper records (n=3). Just one study used linked HES data to validate diagnoses of congenital malformations identified in CPRD.<sup>222</sup>

Overall, the quality of most studies was assessed as good (**Table 5**). However, the validity of the reference standard was uncertain for studies that used GP questionnaires or requested complete paper records as they often did not provide details of the information used to confirm diagnoses (e.g. whether the GP simply looked at the electronic record or whether they referred to a hospital letter to confirm the diagnosis) (**Table 5**) (**Supplementary Table 2**).

Authors also differed in the methods used to calculate PPV, with some authors including in the denominator only those individuals for whom requested information was returned and others calculating a more conservative PPV based on the total number of individuals for whom information was requested.

The one study of any congenital malformations (major or minor) reported a high PPV of 81% (95% CI, 78-84) (**Figure 2**).<sup>187</sup> This was also the case for major malformations across the three studies that examined them, with overall PPV estimates ranging from 85-100% and no evidence of between-study heterogeneity (n=3;  $\chi^2$  test=2.7 ; p=0.3).<sup>192, 194, 208</sup> However, the study by Charlton *et al.* demonstrated that the PPV varied according to the reference standard used; the PPV for cases validated by reviewing free-text was lower than that seen when complete paper records were used (**Figure 2**, 78% vs 92%,  $\chi^2$  test=7.2; p=0.007).<sup>194</sup>

The two studies of heart defects were found to consistently have PPVs  $\geq 90\%$  (with the lowest lower confidence limit being 81%) (**Figure 2**).<sup>216, 219</sup> The validity of neural tube defects was 71%

(95% CI, 63-78) overall.<sup>209</sup> Among the neural tube defects, spina bifida had the lowest PPV (47%; 95% CI, 36-58) whilst encephalocele had the highest (83%; 95% CI, 36-99).

Developmental hip dysplasia had the lowest PPV of any condition examined.<sup>222</sup> Only 34% (95% CI, 30-37) of patients with evidence of the condition in CPRD also had specific evidence of a diagnosis or procedure in HES inpatient data in the two years before or after the CPRD diagnosis. The PPV increased to 56% (95% CI, 53-60) when less specific supportive evidence from CPRD or HES was considered (**Figure 2**). The reference standard in this study was, however, considered suboptimal (**Supplementary Table 2**).

Overall, congenital malformation prevalence in stand-alone primary care data was comparable to or higher than the prevalence in national or regional population-based registries (**Supplementary Table 3**). Between 1990 and 2009, the prevalence ratio for major congenital malformations among live-births between THIN and UK EUROCAT data was 1.18 (95% CI, 1.16-1.20).<sup>201</sup> The prevalence of heart defects was higher in THIN than in EUROCAT (PR, 1.31; 95% CI, 1.26-1.35) but similar for nervous system malformations (PR, 1.06; 95% CI, 0.98-1.14). This was consistent with results from studies comparing the prevalence of heart and neural tube defects between CPRD and population-based registries.<sup>209, 218</sup> Primary care data from THIN did appear to under-ascertain urinary, orofacial, digestive and abdominal malformations as well as rare conditions such as Ebstein's anomaly.<sup>201</sup> However, the prevalence of conditions (including those considered rare) increased in both CPRD and THIN with longer follow-up time.<sup>201, 218</sup>

**Table 4 – Summary of studies performing validations of congenital malformation diagnoses identified in primary care data**

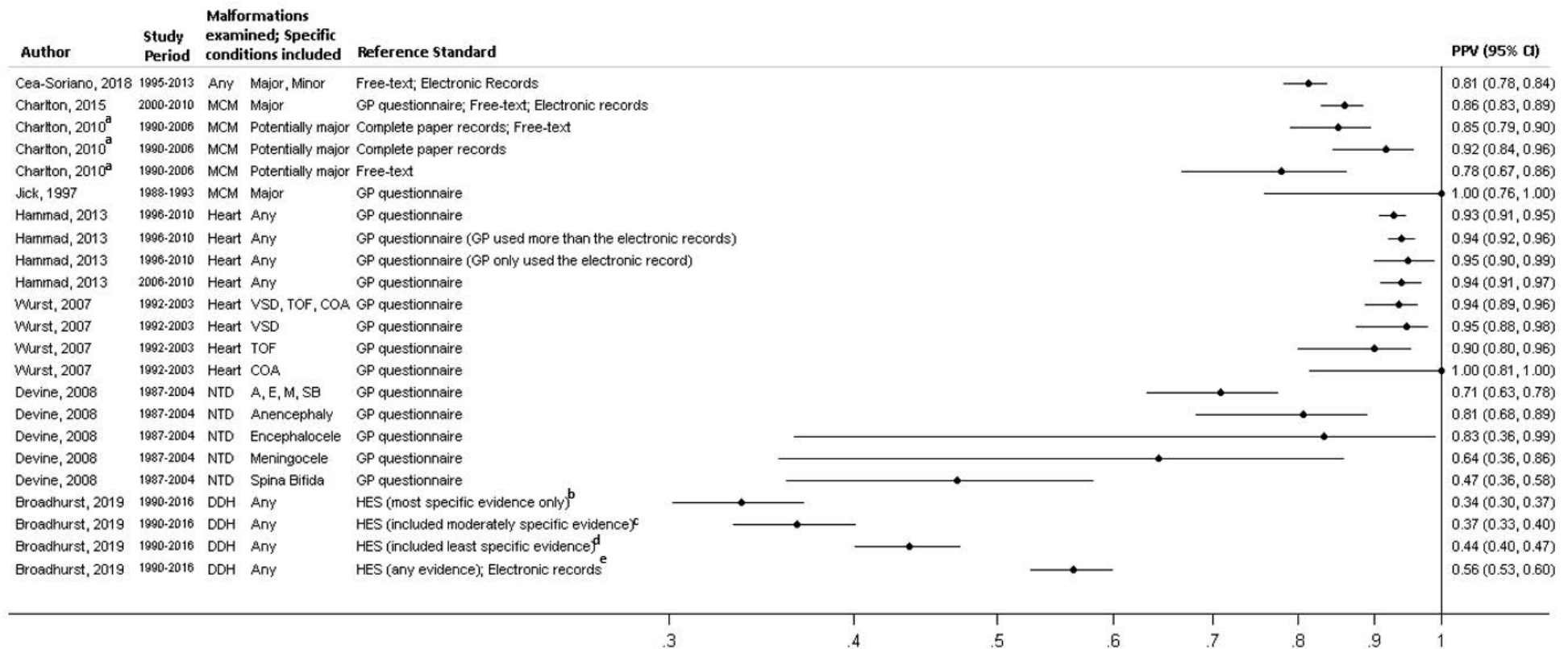
Author	Malformations validated	Study Population	Validation Method	Method summary	No. cases identified for validation	Response rate (Received/ Requested)	Reasons for non-receipt of requested information from GPs	Positive Predictive Value (95% CI)
Cea-Soriano, Any 2018 <sup>187</sup>		Live-births	Manual review of free-text and electronic records	<b>Authors:</b> Identified supporting evidence from free-text, comments associated with specialist referrals in the year before or after the first diagnosis, tests or procedures, and repeated records of malformations or symptoms.	788 <sup>a</sup>	N/A	N/A	<b>81% (78-84)</b>
Charlton, 2015 <sup>192</sup>	Major	Live-births Stillbirths Terminations	GP questionnaire; Manual review of free-text and electronic records	<b>GP confirmed:</b> Diagnosis. <b>Authors:</b> Identified supporting evidence (e.g. surgery codes).	622 <sup>b</sup>	88% (127/145) <sup>c</sup>	N/S	<b>86% (83-89)</b>
Charlton, 2010 <sup>194</sup>	Major or could potentially be classed as major under certain criteria	Live-births	Request for and review of complete paper records and free-text	<b>Authors:</b> Requested complete paper records for those registered with a practice and free-text if they could not be provided. Diagnoses were confirmed and those with sufficient information to be classified as major or minor were identified.	188 <sup>b</sup>	78% (96/123) <sup>d</sup>	15x No response 4x Refused participation 1x No records available 2x Practice left CPRD 1x Transferred out 2x No parental permission 2x No malformation <sup>e</sup>	<b>Combined: 85% (79-90)</b> Records only: 92% (84-96) Free-text only: 78% (67-86)
Jick, 1997 <sup>208</sup>	Major	Live-births	GP questionnaire	<b>GP confirmed:</b> Diagnosis and diagnosis date.	16 <sup>b</sup>	N/S	N/S	<b>100% (76-100)<sup>f</sup></b>
Hammad, 2013 <sup>216</sup>	Heart	Live-births	GP questionnaire	<b>GP confirmed:</b> Diagnosis and diagnosis date, type of exam used to determine diagnosis, information used to confirm the diagnosis.	888 <sup>a</sup>	81% (719/888)	N/S	<b>1996-2010:<sup>g</sup> 93% (91-95)</b> <b>2006-2010: 94% (91-97)</b>
Wurst, 2007 <sup>219</sup>	Heart VSD TOF COA	Live-births	GP questionnaire	<b>GP confirmed:</b> Diagnosis and diagnosis date, age at diagnosis, reason diagnosis suspected, type of doctor that made diagnosis, diagnostic tests and results, referrals to cardiology, surgery, other heart defects and VSD type.	200 <sup>b</sup> 104 VSD 72 TOF 24 COA	94% (187/200)	N/S	<b>94% (89-96)</b> 95% (88-98) 90% (80-96) 100% (81-100)

Author	Malformations validated	Study Population	Validation Method	Method summary	No. cases identified for validation	Response rate (Received/ Requested)	Reasons for non-receipt of requested information from GPs	Positive Predictive Value (95% CI)
Devine, 2008 <sup>209</sup>	Neural Tube Anencephaly Encephalocele Meningocele Spina bifida	Live-births Stillbirths Terminations Miscarriages	GP questionnaire	<b>GP confirmed:</b> Diagnosis and diagnosis date, the type of exam used to determine the diagnosis and the information used to confirm it. As this study also identified neural tube defects encoded in the maternal record around the time of pregnancy, GPs were asked to confirm if the diagnosis related to a condition in the mother or her offspring for such cases.	217 <sup>b</sup>	76% (165/217)	31x No response 18x Transferred out 3x Data entry errors <sup>h</sup>	<b>71% (63-78)<sup>g</sup></b> 81% (68-89) 83% (36-99) 64% (36-86) 47% (36-58)
Broadhurst, 2019 <sup>222</sup>	Developmental hip dysplasia	Children with a first diagnosis between 1-8 years	Review of linked HES records and CPRD records	<b>Authors:</b> Identified the initial diagnosis in CPRD and searched for supportive evidence in linked HES data in the 2 years either side of this or in CPRD in the 2 years after. Results were stratified by the strength of the supportive evidence (from strongest to weakest): A) Specific diagnostic or procedural code in HES B) Non-specific code in HES (e.g. 'clicking hip') C) Hospital admission within 6 months D) No related codes in HES but other coded supportive evidence available in CPRD ( $\geq 2$ diagnostic codes, $\geq 3$ orthopaedic follow-up visits, other supportive evidence such as Read codes for a clicking hip).	754 <sup>a</sup>	N/A	N/A	<b>Using most specific supportive evidence</b> 34% (30-37) <b>Using any available supportive evidence</b> 56% (53-60)

<sup>a</sup>Number of individuals with malformation(s) identified for validation; <sup>b</sup>Number of malformations identified for validation; <sup>c</sup>Did not specify if questionnaires were requested by individual or by malformation; <sup>d</sup>Received records for 96 patients corresponding to 109 malformations; <sup>e</sup>These were included in the PPV calculation as individuals whose record of a major malformation diagnosis was not validated; <sup>f</sup>95% CI calculated on the assumption that 16 questionnaires were sent to GPs and responses received; <sup>g</sup>Calculated additional PPVs, including PPVs for each code (not shown); <sup>h</sup>Did not include these when calculating PPV. Abbreviations: PPV, Positive Predictive Value; CI, Confidence Interval; GP, General Practitioner; VSD, Ventricular Septal Defect; TOF, Tetralogy of Fallot; COA, Coarctation of Aorta; N/A, Not Applicable; N/S, Not specified.

**Table 5 – Summary of quality assessment of validation studies.**

Criterion	Risk of bias, by study							
	Any malformation	Major malformations	Major malformations	Major malformations	Neural tube defects	Heart defects	Heart defects	Developmental Hip Dysplasia
	Cea-Soriano 2018 <sup>187</sup>	Charlton 2010 <sup>194</sup>	Charlton 2015 <sup>192</sup>	Jick 1997 <sup>208</sup>	Devine 2008 <sup>209</sup>	Wurst 2007 <sup>219</sup>	Hammad 2013 <sup>216</sup>	Broadhurst 2019 <sup>222</sup>
Was a consecutive or random sample of patients enrolled?	Low	Low	Low	Low	Low	Low	Low	Low
Did the study avoid inappropriate exclusions?	Low	Low	Low	Low	Low	Low	Low	Low
Were the index test results interpreted without knowledge of the results of the reference standard?	Low	Low	Low	Low	Low	Low	Low	Low
Is the reference standard likely to correctly classify the target condition?	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain	Low	High
Did all patients receive the same reference standard?	Uncertain	Low	High	Low	Low	Low	Low	Low
Were all patients included in the analysis?	Low	Low	Low	Low	Low	Low	Low	Low



**Figure 2 - Individual-study PPV estimates for congenital malformation diagnoses in primary care data.** <sup>a</sup>Included conditions that could potentially be classified as major under certain criteria; <sup>b</sup>Specific diagnostic or procedural codes in HES; <sup>c</sup>Searched for specific diagnostic/procedural codes or codes that were likely to relate to developmental hip dysplasia (e.g. 'clicking hip'); <sup>d</sup>Searched for specific or related codes or evidence of a hospital admission within six months of the diagnosis in the primary care record; <sup>e</sup>Searched for any evidence in HES (as defined previously) or supportive evidence anywhere in the electronic primary care record such as multiple records of the diagnosis, regular orthopaedic hospital attendances etc. Abbreviations: PPV, Positive Predictive Value; CI, Confidence Interval; MCM, Major Congenital Malformation, GP, General Practitioner; VSD, Ventricular Septal Defect; TOF, Tetralogy of Fallot; COA, Coarctation of Aorta; NTD, Neural Tube Defects; A, Anencephaly; E, Encephalocele; M, Meningocele; SB, Spina Bifida; DDH, Developmental hip dysplasia, HES, Hospital Episode Statistics

## **Validation of codes used to record congenital malformations in secondary care and other UK EHR.**

No formal validation studies of code lists for congenital malformations in secondary care data were identified, although some authors did describe evidence to suggest that the validity of these data were good. Studies identifying orofacial clefts noted that between 2000 and 2009, 85% of almost 9,000 individuals in a UK cleft registry could be linked to HES and that the concordance of diagnoses among linked individuals was >92%.<sup>229-232</sup> A study on developmental hip dysplasia reported 98% concordance between surgical interventions for this condition in Scottish admissions data (identified using ICD-10 and OPCS-4 codes) and a surgical database over the same period.<sup>233</sup>

One study identified children with life-limiting congenital malformations using inpatient HES data or linked Scottish birth and inpatient data.<sup>237</sup> The completeness of recording of life-limiting congenital malformations in linked death certificates (as underlying or contributory causes of death) was examined. Among deceased infants with a life-limiting congenital malformation recorded in inpatient HES (n=6,823) or Scottish data (n=555), 80% and 89% had a concordant or related diagnostic code on their death certificate, respectively.

## Discussion

This systematic review examined 36 studies that identified congenital malformations in UK primary care data and 18 studies that identified these conditions in secondary care data. No primary care study used linked secondary care data to increase identification of congenital malformations. Among the secondary care studies, a few also examined linked death certificate data (typically with death as an outcome of interest) or used birth data as an additional data source.

Primary care studies frequently used published guidelines to develop case definitions for the congenital malformations of interest and to develop Read code lists, with EUROCAT guidelines most commonly used. Although the Read system 'P' chapter is dedicated to congenital malformation diagnoses, studies using primary care data often considered codes from other diagnostic chapters and codes for procedures, medical histories or administrative tasks. The extent to which non-'P' chapter codes were used varied across studies. The inclusion of these additional codes was often only apparent after examining available code lists; typically, researchers did not describe the criteria used to include additional codes, or whether individuals in the study population with such codes were required to fulfil any additional criteria in order to be considered cases. For some studies, there was insufficient detail available to assess the full range of Read codes used.

In contrast, studies using secondary care data all reported the codes used to identify malformations. These studies did not include diagnostic codes outside the 'Q' chapter of ICD-10 that is dedicated to congenital malformations, although half also used OPCS-4 procedure codes. Clinical coders of diagnoses in primary and secondary care records do not follow the coding guidelines used in other contexts for malformations, and so researchers needed to consider what codes might be used. Clinical coders in hospital settings are required to record definitive diagnoses and this coding is central to financial reimbursement for hospital admissions.<sup>177</sup> This may explain why researchers chose to rely on 'Q' chapter codes to define



and capture conditions. However, ICD-10 does not categorize congenital conditions as major or minor and the secondary care studies we identified did not attempt to distinguish between these categories.

Validation studies of recorded congenital malformations were almost entirely limited to primary care data, and only eight primary care studies were identified. The PPV (the sole measure of validity assessed) was high for malformations overall, for major malformations, and for heart defects, ranging from 80-100%.<sup>187, 193, 194, 208, 216, 219</sup> These estimates are in line with findings from a previous systematic review which reported high PPV for 183 different diagnoses in CPRD (median PPV, 89%; range, 24-100%).<sup>180</sup> The PPVs of neural tube defects were slightly lower, at 71% overall, and the PPV for developmental hip dysplasia was markedly lower, at 56%.<sup>209, 222</sup> However, the reference standard for this latter study was a combination of HES hospitalisation data and additional coded CPRD data, which was considered suboptimal. First, cases diagnosed before 1997 (when inpatient HES data were unavailable) and cases treated with non-surgical interventions would not be recorded in HES inpatient data. Second, it was unclear whether the study included children whose first recording of developmental hip dysplasia occurred soon after they registered with the general practice; these could be a historical diagnosis retrospectively recorded in the first few months after registration, and thus unlikely to have further supportive evidence in CPRD.<sup>243</sup> Furthermore, GPs may not consistently encode feedback from secondary care but simply scan in hospital letters, and these are not available to researchers as part of the CPRD electronic data.

No studies examined the validity of congenital malformations recorded in secondary care. The one study that investigated the completeness of life-limiting congenital malformation recordings in death certification data used hospitalisation data as the reference standard, and found 11-20% under-reporting in death certificates.<sup>237</sup> However, as the PPV of congenital malformation diagnoses in hospitalisation data has not yet been established, these results need to be interpreted with caution.

Comparisons of prevalence between primary care data and registry data suggested that the prevalence of congenital malformations overall, and for some anatomical subgroups, were comparable or higher in primary care databases and had the potential to increase with longer follow-up.<sup>201, 209, 218</sup> This may be due in part to some registries ascertaining cases up to a younger age than that examined in primary care records, which can better capture late diagnoses in children.<sup>86, 244</sup> However, the higher prevalence recorded in primary care data may also reflect an imperfect PPV for congenital malformation codes. For example, whilst the use of Read codes from outside the 'P' chapter can increase case ascertainment of malformations, it will decrease the PPV if these codes are also used to record diseases that are non-congenital in nature. The influence of the codes used is also pertinent to studies of secondary care data. A very recent study, published after we completed the search for this review, used three different ICD-10 code lists to identify congenital malformations in UK hospitalisation data.<sup>245</sup> The study showed that the prevalence of malformations markedly depended on the code list applied, ranging from 1.8-4.1% and highlighting the impact that the choice of codes can have on study findings.<sup>245</sup>

### **Strengths and Limitations**

To our knowledge, our study is the first to examine systematically the wide array of methods and codes used by researchers to identify individuals with congenital malformations recorded in UK electronic health data, and the results of validation studies of these diagnoses. Our extensive literature search carried out as part of this systematic review, including a comprehensive search strategy and hand-searching of reference lists and bibliographies, is likely to have captured the majority of relevant studies. Our review brings together the ICD-10 code lists used to identify congenital malformations in secondary care data, which were all made publicly available by researchers. This was not always the case for the Read code lists used in primary care studies, but our efforts to contact authors enabled us to obtain additional code lists.

Our findings also have some limitations. First, despite our efforts, it was not possible to obtain detailed Read code lists from all the authors who used primary care data. Available code lists were often broad in nature and included codes that were not part of the final case definition. Therefore, our summary of the codes used to identify congenital malformations in primary care data was incomplete and it was not clear which codes were ultimately used in some studies.

Second, few validation studies have been carried out, with almost all such studies examining the validity of congenital malformations in primary care data and restricted to estimating PPV. Only three different malformation subgroups have been validated in these data, and there were insufficient studies within subgroups to obtain robust summary estimates. Furthermore, the Read code lists used to identify malformations varied across studies; few studies examined the validity of individual Read codes and none compared the validity of Read codes from the 'P' chapter for congenital malformations with codes from other chapters. Furthermore, there was heterogeneity across studies in the reference standard used. We also identified differences in how PPV was calculated for the studies that provided sufficient methodological detail. The authors who included all cases in the denominator, including those for whom the validity of the diagnosis was unclear (for example, due to GP non-response), provided a conservative estimate of PPV. Others restricted the denominator to cases for whom the true diagnosis was ascertained. This adds to the difficulty in comparing results across studies.

In addition, there was a lack of clarity about the robustness of the reference standards used to estimate validity. The underlying assumption in diagnostic validation studies is that the reference standard has perfect sensitivity and specificity for the diagnosis of interest. Our risk of bias assessment for the eight validation studies in primary care data found that the robustness of the reference standard was uncertain in six studies.<sup>187, 192, 194, 208, 209, 219</sup> Most validations relied on GP questionnaires, but studies rarely described the information the GP used to confirm diagnoses. Similarly, for studies that used anonymised free-text (data entered

by the GP alongside electronic coding) or that relied on a manual review of the patient's electronic record, it was not possible to know whether the available information in these data would provide reliable evidence of the presence of a congenital malformation. Our finding that the PPV varied according to the reference standard used, with lower PPV when using free-text compared to when paper records were examined, is consistent with the possibility that electronic free-text less completely captures the evidence for a malformation diagnosis than paper hospital correspondence. This imperfect sensitivity would lead to an underestimation of the PPV. Alternatively, there may be genuine differences in the PPV of the diagnosis among sub-populations assessed using different reference standards. For example, one study requested complete paper records for all cases, and used electronic free-text for the patients for whom records were not provided.<sup>194</sup> Lack of provision could be due to the child de-registering from the practice or dying, or having extensive case notes which take more time for the practice to process. It is feasible that these children could have a higher or lower probability of a genuine congenital malformation compared to children whose paper records were provided.

Use of a different electronic health record dataset as the reference standard may also have imperfect sensitivity. As discussed above, the results from the two studies that used HES hospitalisation data as the reference need to be interpreted with caution, as the sensitivity and PPV of congenital malformation diagnoses in HES are not currently known. Despite an improvement in the accuracy of coding in HES data after the introduction of financial incentives, clinical coders depend on the quality of hospital discharge summaries for accurate coding of diagnoses.<sup>177, 181</sup> Our review highlights the need for validation studies for congenital malformation diagnoses in secondary care data.

It is also important to remember that measures such as PPV are affected by the prevalence of the condition in the population. Some of the studies identified in this review used data that were more than 25 years old. Prevalence of some of the malformations of interest may have

changed over time due, for example, to improved screening methods resulting in increased ascertainment. Thus, the PPV estimates obtained in older studies may be less generalisable to the current data.

Finally, the small number of validation studies identified were insufficient to allow us to assess formally the risk of publication bias in this review. Validations of diagnoses in EHR are often a minor component of the main study. It is possible that validations that resulted in lower PPV estimates were less likely to be included in publications than those that found higher PPV. If this is so, the PPVs reported in this review may be a biased subset of the PPVs that have been carried out.

### **Conclusions and recommendations**

This review provides a detailed summary of the range of methods and the code lists used in studies of congenital malformations that use UK EHR. It has highlighted the lack of methodological detail provided in some published studies, and the scarcity of validation studies of malformation diagnoses recorded in these data.

With the 2015 development of reporting guidelines for studies using observational routinely-collected health data, and the opportunity to provide supplementary online material to accompany publications, it is now easier to include a fuller description of study methods and to allow sharing of code lists.<sup>246</sup> Use of linked primary and secondary care datasets in future studies would allow fuller ascertainment of malformations, including those that are diagnosed in later childhood and those that do not need inpatient care. Similarly, the gradual increase in the electronic recording of coded diagnoses in linked UK out-patient hospital data will allow their future use in malformation research studies.

Further validation studies are needed of a range of malformation subgroups, using large representative samples of cases and assessing all measures of validity (PPV, NPV, sensitivity and specificity). In particular, validation studies of diagnoses in hospital data would address

the existing information gap and facilitate interpretation of study findings that use these data. Finally, UK general practices are currently switching from use of Read codes to the SNOMED coding system.<sup>247</sup> Work will therefore be needed to assess the equivalent SNOMED codes to those currently used for congenital malformations, and their validity.

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See research paper cover sheet.

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## **References**

References are included as part of the main reference list at the end of the thesis.

## Paper 1: Supplementary material

Supplementary Table 1 – Details of the criteria used to conduct quality assessment.

Criterion	Risk of Bias
Was a consecutive or random sample of patients enrolled?	<p><b>Low risk:</b> Study attempted to validate all patients or a random/consecutive sample.</p> <p><b>High risk:</b> Study only validated a specific subset of patients.</p> <p><b>Uncertain:</b> Not enough information.</p>
Did the study avoid inappropriate exclusions?	<p><b>Low risk:</b> Study only applied exclusion criteria that were related to the study question which were not thought to be associated with validity.</p> <p><b>High risk:</b> Study applied exclusions that could not be justified by the study question and which could be associated with validity.</p> <p><b>Uncertain:</b> Not enough information.</p>
Were the index test results interpreted without knowledge of the results of the reference standard?	<p><b>Low risk:</b> The condition was identified in the data before information was received to confirm or refute the diagnosis.</p> <p><b>High risk:</b> The condition was identified in the data after information was received to confirm or refute the diagnosis.</p> <p><b>Uncertain:</b> Not enough information.</p>
Is the reference standard likely to correctly classify the target condition?	<p><b>Low risk:</b> Studies that used information from external sources to validate diagnoses (e.g. authors requested the complete paper record which included external information such as hospital letters, or authors requested confirmation of the diagnosis from a GP who relied on an external source of information such as a hospital letter).</p> <p><b>High risk:</b> Use of a reference standard that is unlikely to have high validity for the condition.</p> <p><b>Uncertain:</b> Not enough information (e.g. studies that did not specify what information was examined and how it was used to determine whether the patient did or did not have the condition).</p>
Did all patients receive the same reference standard?	<p><b>Low risk:</b> The same type of information was used to validate a diagnosis for all patients (e.g. a GP questionnaire was used for all).</p> <p><b>High risk:</b> Different information was used to validate a diagnosis between patients (e.g. some had their free-text examined whilst others had a questionnaire sent to their GP).</p> <p><b>Uncertain:</b> Not enough information.</p>
Were all patients included in the analysis?	<p><b>Low risk:</b> &gt;70% of patients undergoing validation had the information needed to be included in the analysis and were included.</p> <p><b>High risk:</b> ≤70% of patients undergoing validation did not have the information necessary to perform a validation.</p> <p><b>Uncertain:</b> Not enough information.</p>

**Supplementary Table 2 – Details of the quality assessment carried out.**

Study	Criterion	Reason for decision	Bias
Cea-Soriano, 2018 <sup>187</sup>	Was a consecutive or random sample of patients enrolled?	Yes, authors attempted validation for all 788 infants with a recorded congenital malformation.	Low
	Did the study avoid inappropriate exclusions?	Exclusions were made to obtain the study population but were not considered inappropriate as they related to the study aim which was to examine the safety of antidiabetic medication in pregnancy. For example, pregnant women were excluded if they were not registered at a practice a year before their pregnancy as information for them would be incomplete.	Low
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes.	Low
	Is the reference standard likely to correctly classify the target condition?	The reference standard was supportive evidence from free-text and the full electronic record (e.g. surgical codes, confirmation of diagnoses with imaging, repeated recording of the malformation or associated symptoms). It was unclear what information was in the free-text and whether this could be reliably used to confirm diagnoses.	Uncertain
	Did all patients receive the same reference standard?	It was unclear if free-text and electronic records were reviewed for all patients or whether different reference standards were used for different patients.	Uncertain
	Were all patients included in the analysis?	Paper records or GP questionnaires were not requested so there was no response rate. The calculated PPV was based on all 788 infants initially identified.	Low



Study	Criterion	Reason for decision	Bias
Devine, 2008 <sup>209</sup>	Was a consecutive or random sample of patients enrolled?	Yes, a validation questionnaire was sent to the GPs of all 217 identified cases.	Low
	Did the study avoid inappropriate exclusions?	A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate. For example, authors excluded those with a diagnosis outside the study period and restricted diagnoses to those recorded in childhood (in keeping with the aim of the review which was to identify cases among children for the purpose of conducting safety assessments of drugs given in pregnancy).	Low
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes.	Low
	Is the reference standard likely to correctly classify the target condition?	The reference standard was GP questionnaires. Confirmation of diagnoses and information on the evidence reviewed to confirm these was requested. The authors indicated that in 81% of cases, an examination, diagnostic or screening technique was used to confirm or refute diagnoses, but it was not clear what methods were used in remaining cases.	Uncertain
	Did all patients receive the same reference standard?	Yes, for all patients for which a response was received, the reference standard was the GP questionnaire.	Low
	Were all patients included in the analysis?	The response rate was 76% (165/217).	Low

Study	Criterion	Reason for decision	Bias
Wurst, 2007 <sup>219</sup>	Was a consecutive or random sample of patients enrolled?	Yes, a validation questionnaire was sent to the GPs of all 200 identified cases.	Low
	Did the study avoid inappropriate exclusions?	A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate. For example, authors excluded infants born before the study period or those without acceptable clinical or patient details as determined by CPRD. Due to a high number of individuals with ventricular septal defect, authors chose to retain only those patients “who had data entered for staff role of the reporter”. The remaining ventricular septal defect cases were randomized and the first 104 selected. It was unclear why the staff role of the reporter was used in this instance. However, because the staff role could include individuals with varying levels of expertise (GPs, nurses, receptionists) and because it did not appear staff role was used subsequently to exclude patients, it was decided that this would not bias the sample.	Low
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes.	Low
	Is the reference standard likely to correctly classify the target condition?	The reference standard was GP questionnaires. Confirmation and date of diagnosis was requested as well as information on the type of practitioner that made the final diagnosis, the diagnostic tests performed and the findings, whether any referrals or surgeries were performed and whether the patient had any additional defects. It was not clear what information GPs referred to in order to confirm or refute diagnoses (e.g. whether external data such as hospital letters were used), although authors noted that with the exception of the date of diagnosis, only 3% of the data for requested information was missing.	Uncertain
	Did all patients receive the same reference standard?	Yes, for all patients for which a response was received, the reference standard was the GP questionnaire.	Low
	Were all patients included in the analysis?	The response rate was 94% (187/200).	Low

Study	Criterion	Reason for decision	Bias
Hammad, 2013 <sup>216</sup>	Was a consecutive or random sample of patients enrolled?	Yes, a questionnaire was sent to the GPs of all 888 cases.	Low
	Did the study avoid inappropriate exclusions?	A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate. The study identified cases among singletons born in the study period. They excluded those with chromosomal malformations which was in line with their aim to examine the association between selective serotonin reuptake inhibitors and congenital cardiac malformations.	Low
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes.	Low
	Is the reference standard likely to correctly classify the target condition?	The reference standard was GP questionnaires. Confirmation and date of diagnosis was requested as well as the exam used to determine the diagnosis and the information used by the GP for confirmation. The authors made a distinction between GPs who only reviewed electronic medical records to confirm/refute diagnoses and those who used additional sources of information (e.g. hospital letters, consultation letters, paper chart). They calculated a PPV for those whose reference standard was based solely on electronic medical records and those based on electronic medical records as well as other information. Results were similar when compared.	Low
	Did all patients receive the same reference standard?	Yes, for all patients for which a response was received, the reference standard was the GP questionnaire.	Low
	Were all patients included in the analysis?	The response rate was 81% (719/888).	Low

Study	Criterion	Reason for decision	Bias
Charlton, 2010 <sup>194</sup>	Was a consecutive or random sample of patients enrolled?	The authors attempted to validate all cases identified. The full medical records were requested for patients that were registered with a practice at the time of the study. Free-text was requested for all those patients no longer registered with a practice as well as those patients for whom the GP did not respond to the request and those for whom the GP responded but could not provide the information. For 2 individuals, the GP informed the author that neither had a congenital malformation; The full medical record for these individuals was not provided and the free-text not requested.	Low
	Did the study avoid inappropriate exclusions?	A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate as they related to the aims of the study, which was to examine the safety of anticonvulsants used in pregnancy. The study population included all babies born to mothers with a diagnosis of epilepsy, seizures or convulsions during the study period. Babies had to be registered and present within a practice 3 months after the end of the pregnancy. Babies that were registered but died earlier than this were included.	Low
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes.	Low
	Is the reference standard likely to correctly classify the target condition?	The reference standard was the full medical record for those patients for whom it was available and free-text for the rest. The full medical record was considered to be more reliable than free-text. However, of the 123 patients for whom medical records were requested, >10% (n=19) resulted in no response or refusal to participate. It was considered possible that lack of response or refusal of GPs could be associated with the amount of time needed to send records and could therefore be more likely among unwell patients with large medical files but further information was needed.	Uncertain
	Did all patients receive the same reference standard?	The full medical record was received for some patients whilst others received full-text. This was judged to be acceptable as the authors calculated PPVs for each reference standard separately in addition to an overall PPV.	Low
	Were all patients included in the analysis?	The response rate for medical records was 78% (96/123). Free-text was received for all individuals it was requested for.	Low

Study	Criterion	Reason for decision	Bias
Charlton, 2015 <sup>192</sup>	Was a consecutive or random sample of patients enrolled?	Yes, the authors attempted to validate all 622 identified malformations.	Low
	Did the study avoid inappropriate exclusions?	A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate as they related to the aims of the study which was examine the safety of asthma medication used in pregnancy. The study population included singleton live-births, terminations and stillbirths that belonged to women with an asthma diagnosis during the study period. Syndrome-related major congenital malformations were excluded as they were unlikely to be drug induced.	Low
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes.	Low
	Is the reference standard likely to correctly classify the target condition?	The reference standard was GP questionnaires, supportive codes in the electronic record (e.g. codes for related surgeries) and supportive free-text. Further information was unavailable. It was therefore not known what information the GP used to confirm or refute diagnoses, or what information was in the free-text, and overall it was unclear whether these sources of information would be likely to correctly classify the target condition.	Uncertain
	Did all patients receive the same reference standard?	No, authors used a mixture of GP questionnaires, free-text and supportive medical codes. However, only an overall PPV was published (not separate PPVs stratified by the reference standard used).	High
	Were all patients included in the analysis?	The response rate for questionnaires was 87.6% (127/145) based on personal communication with the author. It was assumed free-text and supporting medical codes were used for remaining cases.	Low

Study	Criterion	Reason for decision	Bias
Jick, 1997 <sup>208</sup>	Was a consecutive or random sample of patients enrolled?	The authors commented that there was complete concordance between GP questionnaires and congenital malformations identified in the study population. The authors did not state how many questionnaires were sent out for the 16 cases identified but it was assumed that this information was requested for all.	Low
	Did the study avoid inappropriate exclusions?	A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate as they related to the aims of the study which was examine the safety of anticonvulsants used in pregnancy. Conditions were limited to those that could be drug-induced and identified around the time of birth.	Low
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes.	Low
	Is the reference standard likely to correctly classify the target condition?	The reference standard was GP questionnaires. Confirmation and date of diagnosis was requested. It was unclear, however, what information was used to confirm or refute diagnoses.	Uncertain
	Did all patients receive the same reference standard?	Yes, all patients received a GP questionnaire.	Low
	Were all patients included in the analysis?	The authors commented that there was complete concordance between GP questionnaires and congenital malformations identified in the study population. Based on this, we assumed they received information on all cases.	Low

Study	Criterion	Reason for decision	Bias
Broadhurst 2019 <sup>222</sup>	Was a consecutive or random sample of patients enrolled?	Yes, the authors attempted to validate all 754 patients with a diagnosis of developmental hip dysplasia in CPRD.	Low
	Did the study avoid inappropriate exclusions?	Exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate. For example, patients had to be eligible for linkage to HES as this was the main data source used for validation. Patients were excluded if they had specific neuromuscular diseases or a traumatic hip dislocation as the study question did not include secondary hip dislocations or syndromes.	Low
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes.	Low
	Is the reference standard likely to correctly classify the target condition?	<p>The authors developed a validation algorithm that first searched for specific supportive diagnostic or procedural codes in inpatient HES data in the two years before or after the diagnosis in CPRD. If this information was unavailable, the algorithm searched for less specific codes in HES that were considered likely to relate to developmental hip dysplasia (e.g. 'clicking hip'). If no such evidence was available, evidence of a hospital admission within six months of the CPRD diagnosis was searched for. If no evidence in HES was identified, the authors searched for supportive evidence in CPRD in the following order: 1) <math>\geq 3</math> orthopaedic follow-up hospital attendances, 2) <math>\geq 2</math> diagnostic codes in CPRD, 3) other supportive evidence such as codes for a clicking hip or for splinting of a dislocated hip.</p> <p>Inpatient HES and CPRD electronic data were considered sub-optimal reference standards in this study for the following reasons:</p> <p>1) The study included children with a diagnosis of developmental hip dysplasia in CPRD prior to 1997. As HES data are only available from 1997 onwards, diagnoses and procedures recorded during hospital admissions prior to this would not be captured.</p> <p>2) Children not receiving surgical treatment and managed in outpatient hospital departments would not be captured in inpatient HES data.</p> <p>3) GPs may not encode the diagnosis repeatedly or encode all orthopaedic follow-up attendances for children managed in secondary care but may instead simply scan in hospital letters (which are not available to researchers as part of the CPRD electronic data). Supportive evidence would therefore be captured sub-optimally in CPRD.</p> <p>4) It was unclear if the study population included children whose first record of developmental hip dysplasia occurred less than a year after registering with the practice. Such records could be retrospective recordings of an historical diagnosis<sup>243</sup> and the presence of further supportive evidence in CPRD would not be expected. If no surgical treatment was required, supportive evidence in inpatient HES data would also not be expected.</p>	High
	Did all patients receive the same reference standard?	No but results were appropriately stratified by reference standard.	Low
	Were all patients included in the analysis?	Yes.	Low

**Supplementary Table 3 - Comparisons of congenital malformations prevalence in electronic health records with prevalence derived from external data sources.**

Author	Malformations examined	Data sources compared	Comparison measures	Period of Comparison	Prevalence Ratio (95% CI)	Summary
<b>Sokal, 2014</b> <sup>202</sup>	Major	THIN vs published literature using data from the North of England Congenital Anomaly Register.	Male: Female prevalence ratios	THIN: 1990-2009  Register data: 1998-2003	THIN sex prevalence ratio: 1.26 (1.23-1.30)  Register sex prevalence ratio: 1.15 (1.11-1.19)	<ul style="list-style-type: none"> <li>• The overall sex prevalence ratio was slightly higher in THIN compared to published data from the Register, although the latter didn't include chromosomal anomalies, sex-linked urinary malformations and sex-linked genital malformations.</li> <li>• Sex prevalence ratios for system-specific subgroups in THIN were similar to those from the Register except for bladder extrophy/epispadias for which the ratio was greater in THIN.</li> </ul>
<b>Sokal, 2013</b> <sup>201</sup>	Major	THIN vs EUROCAT	Prevalence per 10,000 live-births	1990-2009	1.18 (1.16-1.20)	<ul style="list-style-type: none"> <li>• Overall THIN prevalence &gt; EUROCAT.</li> <li>• Prevalence ratios for system-specific subgroups varied, with the following having a lower prevalence in THIN: urinary defects, orofacial clefts, digestive defects, abdominal wall defects, chromosomal and genetic malformations, malformations due to known teratogens and other malformations.</li> <li>• Heart, limb, genital, musculoskeletal and eye malformations had higher prevalence in THIN; Nervous system, respiratory and ear, face and neck malformations had similar prevalence in THIN and EUROCAT.</li> <li>• Prevalence in THIN increased with follow-up time.</li> </ul>
<b>Tata, 2008</b> <sup>206</sup>	Major	THIN vs EUROCAT	Prevalence per 10,000 live-births vs prevalence per 10,000 births <sup>b</sup>	1988-2004	N/S	<ul style="list-style-type: none"> <li>• Overall THIN prevalence similar to EUROCAT prevalence: 289 per 10,000 live-births vs 238 per 10,000 births<sup>b</sup>.</li> </ul>
<b>Devine, 2008</b> <sup>209</sup>	Neural tube	CPRD vs National Congenital Anomaly System	Annual prevalence per 10,000 pregnancies <sup>a</sup> .	1991-2003	N/S	<ul style="list-style-type: none"> <li>• Overall CPRD prevalence &gt; National Congenital Anomaly System: 1.7 - 6.5 per 10,000 pregnancies vs 1 - 2 per 10,000 pregnancies</li> <li>• Prevalence estimates closer after 1997.</li> <li>• Confidence intervals for prevalence in CPRD included estimates from the National Congenital Anomaly System across all years.</li> </ul>
<b>Wurst, 2007</b> <sup>218</sup>	Heart	CPRD vs National Congenital Anomaly System  CPRD vs EUROCAT	Annual prevalence per 10,000 live-births	2001 2002 2003  2001 2002 2003	2.79 (2.37–3.30) 2.78 (2.34–3.31) 2.20 (1.83–2.64)  1.48 (1.21–1.83) 1.29 (1.05–1.59) 1.42 (1.15–1.77)	<ul style="list-style-type: none"> <li>• Overall CPRD prevalence &gt; National Congenital Anomaly System.</li> <li>• Overall CPRD prevalence &gt; EUROCAT.</li> <li>• For some specific heart defects, particularly those that were rare, prevalence was lower in CPRD.</li> <li>• Prevalence in CPRD increased with follow-up time.</li> </ul>

<sup>a</sup>Included live-births, stillbirths and terminations; <sup>b</sup>EUROCAT data included live-births, stillbirths, foetal deaths and terminations. Abbreviations: CPRD, Clinical Practice Research Datalink (formerly the General Practice Research Database); THIN, The Health Improvement Network; N/S, Not Specified; CI, Confidence Interval



## 2.3 Summary and conclusions

This chapter described a systematic review of 54 studies that identified congenital malformations in UK electronic health records. Congenital malformations were identified from primary care data in 36 studies and secondary care data (with some also using birth and death records) in 18. No study used linked primary care, secondary care and mortality data to increase the ascertainment of these conditions. Studies using primary care data frequently referred to published guidelines to aid the development of case definitions and code lists, and often used Read codes beyond those in the dedicated 'P' chapter for congenital malformations. Conversely, studies using secondary care data did not rely on published guidelines but did rely on ICD-10 codes in the dedicated 'Q' chapter for congenital malformations. The positive predictive value of congenital malformation diagnoses in primary care data was high for any congenital malformations, major malformations and heart defects (80-100%).<sup>187, 193, 194, 208, 216, 219</sup> No study attempted to validate congenital malformation diagnoses in secondary care data. Further validation studies are needed for additional malformation subgroups and in secondary care data.

## Methods Section

The next four chapters comprise the methods section of this thesis.

**Chapter 3** describes the electronic health records used for this work and includes information about the way the data are collected, their structure and their quality.

**Chapter 4** describes the criteria used to define pregnancies eligible for inclusion in the studies carried out to address **Objectives 3-6**. In addition, the chapter outlines the potential confounding factors for the vaccine safety analyses (**Objectives 5-6**).

**Chapter 5** describes the steps involved in developing a comprehensive algorithm to identify MCMs in multiply-linked data (**Objective 2**). This algorithm was then used to identify MCMs in all the studies that were part of this thesis.

**Chapter 6** describes the methods used to ascertain the vaccination status (including the trimester of vaccination) of pregnant women for the vaccine safety analyses (**Objectives 5-6**).

### 3. Data Sources

Studies were conducted using CPRD GOLD primary care data (referred to as 'CPRD') linked to Hospital Episode Statistics Admitted Patient Care data (referred to as 'HES'), Office for National Statistics (ONS) mortality data and deprivation data. **Section 3.1** describes CPRD data. **Section 3.2** describes the CPRD Mother-Baby Link (MBL) which links maternal and infant records but which does not identify pregnancy episodes. **Section 3.3** describes the CPRD/LSHTM Pregnancy Register (referred to as the 'Pregnancy Register'), which was used to identify pregnancies in this work. HES, ONS mortality and deprivation data are then discussed in **Sections 3.4-3.6**. A summary of the data management involved in this thesis and an overview of the ethical approvals obtained are described in **Sections 3.7-3.8**.

#### 3.1 CPRD

The CPRD was established in the UK in 1987, primarily for the purposes of pharmaco-epidemiological research.<sup>126</sup> At the time of this work, CPRD was among the largest collections of anonymised, longitudinal electronic health records from primary care.<sup>126, 248</sup> Consenting general practices across the UK collect data from patients; these data are then de-identified and transmitted to CPRD by the clinical management software system (Vision®) each month.<sup>249</sup> Data are provided for all patients within contributing practices with the exception of those who have opted out.<sup>126</sup>

At the time of this work, CPRD covered approximately 7% of the UK population and patients were thought to be broadly representative in terms of age, sex and ethnicity.<sup>126, 250</sup> The average follow-up time for patients was just over 5 years.<sup>126</sup> Patients may enter and leave contributing practices at any time and so the database itself is considered an open cohort. CPRD data can also be linked to other datasets, a process described below. CPRD data for the studies described here were extracted in September 2017 and included data up until January 2017.

### 3.1.1 Data collection and structure

General practice staff record consultations with patients on practice computers. Once a patient registers at a practice contributing to CPRD, data will be recorded until the practice stops contributing (the last collection date), or the patient dies or leaves the practice (the death or transfer out date).<sup>126</sup> Patient and practice files received by researchers contain pseudo-anonymised identifiers for the patient and practice and include registration, death, transfer out and last collection dates (**Table 3.1**).

Information recorded includes demographic data, diagnoses, symptoms, vaccinations, procedures, diagnostic tests and results, prescriptions, lifestyle/behavioural factors, referrals, and feedback from secondary or tertiary care providers.<sup>126</sup> These data are stored in the clinical, immunisation, therapy, referral and test files, with further clinical details recorded in the 'additional clinical details' file (**Table 3.1**).<sup>126</sup> For each recorded event in these files, an 'event date' is available which refers to the date the event occurred as entered by the GP. An additional date, the 'system date', indicates the date the recording itself was made.

Information across files is recorded in two ways: through coding systems or free-text. Different coding systems are used across different files and for different purposes. Diagnoses and other clinical data are primarily recorded using Version 2.0 Read codes.<sup>126</sup> Entity type codes are used to record structured data (e.g. weight, blood pressure, alcohol use, test results). Immunisation type codes in the immunisation file are used to record vaccine type. Finally, Product codes are used to record prescriptions in the therapy file.<sup>126</sup> The CPRD provides Read and Product code dictionaries which can be used to identify codes relating to clinical data, drugs, or vaccines of interest.<sup>126</sup>

Clinicians can also record patient data using free-text which includes comments made by the GP and communications received about the patient from other care providers.<sup>126</sup> In the past, it was possible to request anonymised free-text data for research but these data are no longer available for routine use.

**Table 3.1 - Overview of the data included in CPRD files.**

<b>CPRD File</b>	<b>Key information recorded in the file</b>	<b>Types of code that can be used to identify records of interest in the file</b>
Practice	The practice identifier <sup>a</sup> , the practice region (defined according to Strategic Health Authority boundaries for practices in England), the last collection date, the up-to-standard date.	-
Staff	The staff member identifier <sup>a</sup> , staff member role, staff member gender.	-
Patient	The patient identifier <sup>a</sup> , year of birth, month of birth (for those aged <16 years), gender, date of death, current registration date, transfer out date.	-
Consultation	The patient identifier <sup>a</sup> , the staff identifier <sup>a</sup> , the type of consultation (e.g. emergency consultation), the consultation identifier (can be used to identify different events recorded in the same consultation), the length of the consultation.	Consultation type codes
Clinical	The patient identifier <sup>a</sup> , medical history, diagnoses, signs and symptoms, procedures, diagnostic tests and results, lifestyle/behavioural factors (e.g. alcohol use and smoking), demographic factors (e.g. ethnicity), the event date <sup>b</sup> .	Read codes, Entity codes
Additional Clinical Details	The patient identifier <sup>a</sup> , further specific data relating to a record in the clinical file.	Entity codes
Immunisation	The patient identifier <sup>a</sup> , type of vaccine, status of vaccination (given, refused or advised), vaccination stage, compound administered, the event date <sup>b</sup> .	Read codes, Immunisation type codes
Therapy	The patient identifier <sup>a</sup> , the prescribed product, the quantity of the product, the daily dose, the number of days prescribed for, the event date <sup>b</sup> .	British National Formulary codes, Product codes
Referral	The patient identifier <sup>a</sup> , the requested referral, the referral speciality, the type of referral (e.g. inpatient), the urgency of the referral, the event date <sup>b</sup> .	Read codes
Test	The patient identifier <sup>a</sup> , the requested test, the result, the normal range of results, the event date <sup>b</sup> .	Read codes, Entity codes

<sup>a</sup>All identifiers are anonymised; <sup>b</sup>The event date is the date the associated event occurred as recorded by the general practitioner.

### 3.1.2 Data quality and completeness

Although electronic health records have a number of strengths, data are collected for clinical purposes and not research. Data collection and completeness can vary for different variables and may be affected by changes in clinical practice or guidelines over time.

Basic completeness and quality checks are carried out before data are released to researchers by CPRD.<sup>126</sup> An up-to-standard date denotes the time-point after which practice data are considered acceptable for research use.<sup>126, 249</sup> This date is based on the continuity of the recording of clinical and mortality data in the practice. If there are significant gaps in the recording of such data, the up-to-standard date is assigned to the earliest date after this gap. Patients are denoted as being acceptable for research purposes or not based on the continuity of their follow-up, and incomplete or implausible records.<sup>126, 249</sup> For example, patients lacking a recorded birth year or patients aged over 115 years are not deemed 'acceptable' for research purposes and it is advised that such patients are excluded from studies.

In 2004, the Quality and Outcomes Framework (QOF) was introduced which financially incentivized GPs to record a number of key data.<sup>126</sup> These data include chronic diseases such as diabetes and asthma, as well as other data of public health importance such as obesity and smoking status. The completeness of these data in CPRD has improved since the introduction of the QOF.<sup>126</sup> The QOF is reviewed annually and indicators may be added or removed. Patient ethnicity, for example, was added to the QOF in 2006/07 and removed in 2011/12.<sup>251</sup> This change resulted in new patients having their ethnicity recorded in more than 90% of practices and highlights the potential for completeness of data to be affected by changes in the QOF.<sup>251</sup>

The validity of diagnoses recorded in the CPRD have been examined in a number of studies. A systematic review in 2010 examined the validity of 183 unique diagnoses.<sup>180</sup> Across all diseases, a median of 89% of cases were confirmed (with a range of 24-100%).<sup>180</sup> However, the authors of the systematic review noted that the methods used in validation studies were often insufficiently described.<sup>180</sup> For example, few of the validation studies reported the types of

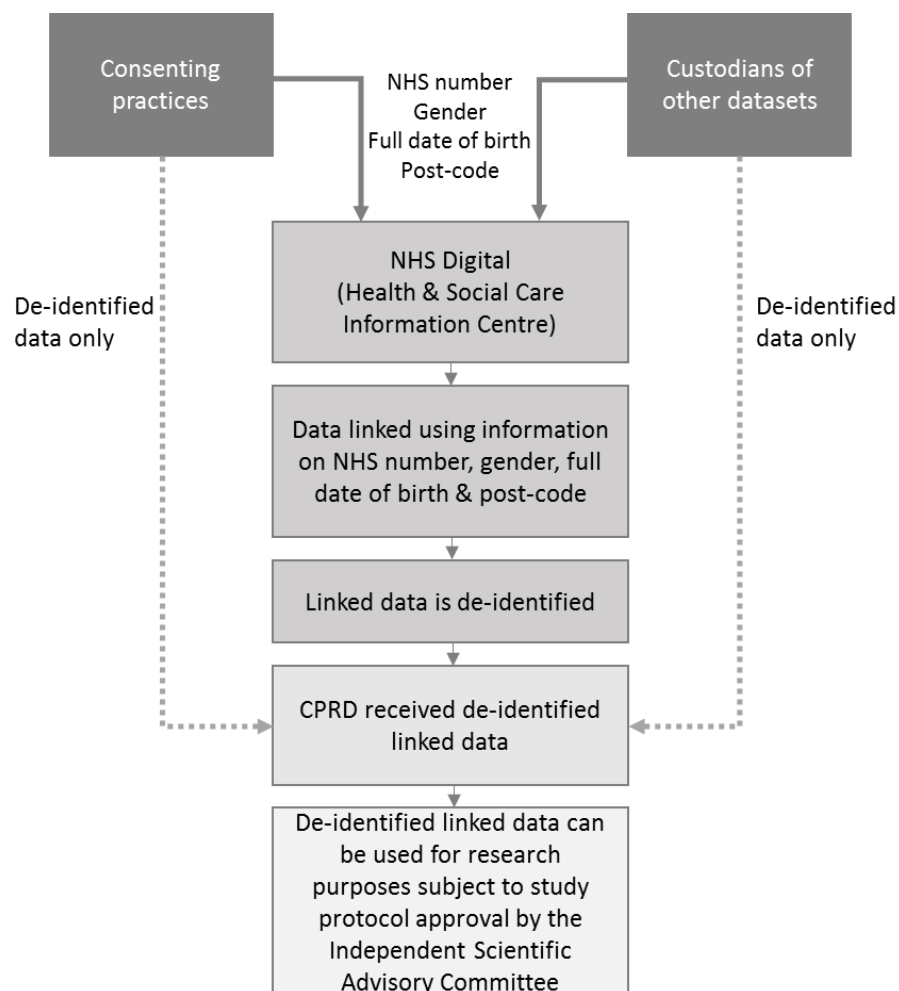
codes used to identify diagnoses so it was not possible to validate specific code lists or algorithms. Furthermore, validation studies generally examined diagnoses among populations that were highly specific (e.g. populations receiving particular treatments) or that had other supportive evidence of the diagnosis in question in their records to begin with.<sup>180</sup> Finally, the authors comment that although the positive predictive value (PPV) of validation studies may be high, this may not be the case for other validity measures such as sensitivity, specificity and negative predictive value.<sup>180</sup> The PPV for congenital malformation diagnoses is high overall and such validation studies are described in **Chapter 2**.<sup>187, 193, 194, 208, 216, 219</sup>

The validity of recorded diagnoses may also be affected by the time at which they are recorded. As described earlier, the 'event date' for a diagnosis (or other clinical event) is entered by the GP. Whilst this date should reflect the date the event occurred, GPs may instead use the date of data entry which can have implications. The incidence of diagnoses may be overestimated, for example, in the first few months after a patient registers with a practice.<sup>243</sup> In such cases, existing conditions may be recorded as new events when the patient registers with a new practice. Alternatively, past or chronic events may only be recorded for the first time some months after a patient registers. For MCMs in the work described here, the above issues were not considered to be a cause for concern because infants were followed-up from delivery in all studies. However, potential confounders relating to the mother could be under-recorded in the first few months after her registration with a practice. In addition, pregnancy data recorded shortly after registration could relate to the woman's obstetric history. Finally, it was important to consider that the 'event date' associated with a congenital malformation or vaccination record might not necessarily be the true date the diagnosis or vaccination occurred.

### 3.1.3 Linkage to other patient data

Patient-level CPRD data can be routinely linked to other datasets (**Figure 3.1**).<sup>126</sup> Linkage can be provided to hospitalisation data, mortality data, deprivation data and disease registries.<sup>126</sup> For linkage to be carried out, practices that contribute data to the CPRD have to consent.

Currently, 58% of practices contributing data to the CPRD have consented, all of which are based in England.<sup>126</sup> Patients within consenting practices are eligible for linkage provided they do not opt-out and have the required information for the linkage process. Patient eligibility for linkage is not necessarily the same for all linkages.<sup>252</sup> Despite the above restrictions, patients with linked data have been shown to be broadly representative of those in CPRD<sup>253, 254</sup>.



**Figure 3.1 - Linkage of CPRD data to other datasets.** Primary care records are linked to other datasets (e.g. hospital admission data) by NHS digital through the use of the patient NHS number, gender, date of birth and post-code. Following linkage, de-identified data are received by CPRD. Unlinked de-identified data can also be received by CPRD directly from consenting practices or from the custodians of other databases.



Linkage between primary care records and other datasets depends on the matching of patient identifiers (**Figure 3.1**).<sup>252</sup> As CPRD does not receive or hold any patient identifiable data, deterministic linkage is carried out by NHS Digital (also known as the Health and Social Care Information Centre) - a trusted third party and statutory body permitted to receive and oversee such data.<sup>252</sup> Once linkage has been carried out, NHS Digital provides CPRD with de-identified linked data.<sup>252</sup> Linked data requested for the work described here are described in **Sections 3.4-3.6**.

### 3.2 The Mother-Baby link

CPRD provide a Mother-Baby Link (MBL) which contains a list of mothers and their linked live-born infants. The linkage involves the identification of deliveries amongst women aged 12-49 years, the identification of patients born after 1986, and the joining together of the two datasets by practice and family number (a practice-specific number based on residence and used to identify individuals that live in the same household). Links are kept if the delivery date and estimated infant birth date are  $\leq 60$  days apart. Because full birth dates are not available in CPRD, the birth date of each potential infant is estimated to be the 15<sup>th</sup> of the month of birth. If no month of birth is available, the mid-point of the year of birth (June 30<sup>th</sup>) is used. Multiple infants with the same birth date and linked to the same mother are included in the MBL, these are considered to be siblings that were part of the same live-birth delivery.

Some deliveries and infants are excluded from the linkage process. Deliveries are excluded if they were recorded: more than a year before the woman registered at a practice, after they left the practice or after the practice ended data collection for CPRD. Infants are excluded if they were born before 1987, if their registration at a practice occurred before their birth year or if their birth year occurred after the practice ended data collection for CPRD.

### 3.3 The CPRD/LSHTM Pregnancy Register

Whilst the MBL enables linkage of maternal and live-born infant records, it does not enable the identification of complete pregnancy episodes. Pregnancy timings are not recorded systematically in CPRD.<sup>255</sup> A number of algorithms have therefore been developed to identify and characterize pregnancies in CPRD but are limited because they either do not attempt to estimate the start of pregnancy, do not utilize all available pregnancy data to determine timings or do not capture those pregnancies without a recorded outcome.<sup>256-260</sup>

The CPRD/LSHTM Pregnancy Register was developed to systematically identify all pregnancy episodes in CPRD and address the limitations of previous approaches.<sup>255</sup> The initial step in the algorithm was to identify the first and subsequent live-birth or stillbirth delivery records for each woman. Following this, the start of pregnancy was estimated from data in the following order, depending on availability: the projected date for delivery as recorded by the GP, the estimated conception date, the last menstrual period, the gestational age as indicated in antenatal records or the gestational age at delivery.<sup>255</sup> If no such data were available, the pregnancy start was imputed from the delivery record using a fixed duration assigned according to the pregnancy outcome. Antenatal records were then assigned to each delivery. This process was repeated for other pregnancy outcomes (such as early losses) and those pregnancies with no recorded outcome.

The Pregnancy Register identifies all pregnancies occurring since 1987 among women aged 11-49 years in CPRD.<sup>255</sup> Estimates of the pregnancy start date, end date and trimester timings are provided. The start of the first trimester is defined as the date of the last menstrual period and runs through to the end of week 13 of the pregnancy. The second trimester is defined as week 14 through to the end of week 26, whilst the third trimester is defined as week 27 through to the delivery date. The type of information used to estimate the delivery date and pregnancy start date are also provided.

The Pregnancy Register includes information on the pregnancy outcome (**Table 3.2**) and additional information on whether there was any evidence the pregnancy resulted in a pre-term, post-term or multiple delivery. Live-birth pregnancies are linked to single infant identifiers (and, therefore, the infant's records) if linkage is available from the MBL (**Section 3.2**). For multiple pregnancies resulting in more than one live-born infant, additional infants may be identified from the MBL. As the Pregnancy Register also links pregnancy episodes to maternal records, the effect of exposures in the mother during pregnancy can be followed-up in the infant. In some cases, live-births are not linked to infant records. This is discussed further in **Section 4.3.8**.

Internal validation of the Pregnancy Register is ongoing. However, thus far, validation against linked electronic maternity records in hospitalisation data has shown that most pregnancies are well-captured in the Pregnancy Register.<sup>255</sup>

**Table 3.2 – Pregnancy outcomes recorded in the CPRD/LSHTM Pregnancy Register.**

<b>Pregnancy outcome</b>	<b>Description</b>
Live-births <u>with</u> linked infant records	Pregnancies ending in delivery and with a linked infant identified in the Mother-Baby Link ( <b>Section 3.2</b> ).
Live-births <u>without</u> linked infant records	Pregnancies ending in delivery and with no linked infant identified in the Mother-Baby link. (reasons for lack of linkage are described in <b>Section 4.3.8</b> ).
Stillbirths	Pregnancies resulting in foetal death after 24 completed weeks of pregnancy.
Miscarriages	Pregnancies resulting in foetal death before 24 completed weeks of pregnancy.
Terminations/Probable terminations	Pregnancies resulting in or likely to have resulted in a termination based on available evidence in the maternal records.
Unspecified losses	Pregnancies resulting in miscarriages or terminations. Evidence in the maternal record was not specific enough to distinguish between the two.
Deliveries based on late pregnancy records	Pregnancies for which there were maternal antenatal records indicating an imminent delivery (e.g. ' <i>premature rupture of membranes</i> ') but for which no delivery record was available.
Ectopic pregnancies	Pregnancies in which implantation of the fertilized egg did not occur in the uterus.
Molar pregnancies	Pregnancies in which a foetus does not develop.
Blighted ovum pregnancies	Pregnancies in which the embryo fails to develop.
Outcome unknown pregnancies	Pregnancies for which the outcome was not known (reasons for this are described in <b>Section 4.3.6</b> ).

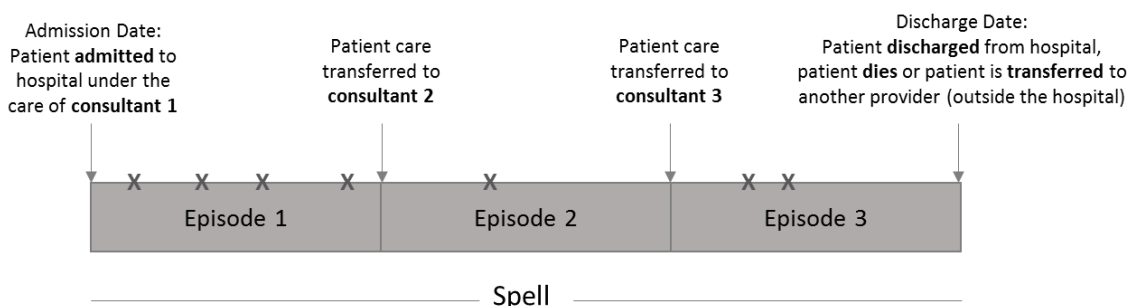
### 3.4 HES

The HES database was established in 1989 and contains information on secondary care provided at NHS-funded hospitals in England.<sup>261</sup> Since 1997, it has been possible to link CPRD to HES Admitted Patient Care data for the purposes of research.<sup>262</sup> CPRD records are linked to the full HES record, and so linked data include all past hospital admissions ever recorded for the patient, and any admissions occurring after a patient has transferred out of CPRD.

HES data are updated and published according to the financial year.<sup>177</sup> Studies described in this thesis used the 14<sup>th</sup> version of HES linked to CPRD which covered the period between 1<sup>st</sup> April 1997 and 31<sup>st</sup> March 2016. Only admitted patient care data were requested. Outpatient records were not requested as data completeness is currently poor for diagnoses and procedures.<sup>261</sup>

#### 3.4.1 Data collection and structure

In HES data, the period during which a patient is at a particular hospital is known as a ‘spell’ (**Figure 3.2**).<sup>261</sup> The admission date marks the beginning of the spell whilst the hospital discharge date marks the end. The discharge date can be a result of the patient being discharged from care entirely, or may be due to the death of the patient or their transfer to a different provider (e.g. another hospital) for further care.<sup>261</sup> A spell can be further divided into periods known as ‘episodes’. Each time the consultant or clinical team responsible for the patient changes, a new episode is generated (**Figure 3.2**).<sup>261</sup>



**Figure 3.2 - Spells and episodes of care in HES data.**

Following inpatient stays or day case admissions, diagnoses and procedures from case notes and discharge summaries are encoded by trained clinical coders for hospital reimbursement purposes.<sup>263</sup> Episode data available for researchers hold up to 20 diagnoses, recorded using the 10<sup>th</sup> version of the International Classification of Diseases (ICD-10), and up to 24 procedures recorded using version 4.6 of the UK Office of Population, Census and Surveys classification (OPCS-4).<sup>261</sup> Specific diagnosis dates are not provided in HES, although dates of procedures are recorded.

A number of data files are available for admitted patient care from HES. For this work, three files were used: the patient file, the file containing all diagnoses by episode and the file containing all procedures by episode (**Table 3.3**). Diagnoses and procedures were extracted from the latter two files, respectively.

**Table 3.3 - Overview of the data included in HES files.**

<b>HES Admitted Patient Care Files</b>	<b>Information recorded in the file</b>	<b>Types of code that can be used to identify records of interest</b>
Patient	The patient and practice identifiers <sup>a</sup> , ethnicity, an indicator for the quality of the match between HES and CPRD in the linkage process.	-
Diagnoses, by episode	The patient identifier <sup>a</sup> , the spell number, the episode identifier, dates relating to the start and end of each episode, diagnoses, the order of each diagnosis within an episode (up to 20 can be recorded per episode).	ICD-10
Procedures, by episode	The patient identifier <sup>a</sup> , the spell number, the episode identifier, the admission and discharge dates, dates relating to the start and end of each episode, the procedure (up to 24 can be recorded per episode), the order of each procedure within an episode, the date of the procedure.	OPCS-4

<sup>a</sup>All identifiers are anonymised

### 3.4.2 Data quality and completeness

HES data were initially established for the purpose of informing decisions around the delivery and management of services.<sup>261</sup> Today, the primary purpose of HES is to provide a structure for reimbursement and this has resulted in an incentive for improved data quality and completeness.<sup>261</sup> Data quality is generally thought to have improved with time; between 2001

and 2011, the accuracy of primary diagnoses is thought to have increased from 74% (IQR, 59-92) to 96% (IQR, 89-96),  $p=0.02$ .<sup>261</sup>

### 3.5 ONS Mortality Data

In England and Wales, all deaths and their causes must be registered.<sup>178</sup> For the purposes described in this thesis, linkage to ONS mortality data was requested. The 14<sup>th</sup> version of ONS mortality data was used, covering the period between the 2<sup>nd</sup> January 1998 and 17<sup>th</sup> April 2017. Similarly to linked CPRD and HES data, linked CPRD and ONS data include details of deaths occurring even after a patient has transferred out of the practice and follow-up in CPRD has ended. Linked ONS data will not, however, include details about the deaths of patients that have occurred before registration with a contributing practice.

#### 3.5.1 Data collection and structure

After a death has occurred, it is usually certified by the attending doctor through a 'Medical Certificate Of Cause Of Death' which includes the direct and underlying causes of death, and contributory factors.<sup>178</sup> In almost 80% of cases, the causes of death are encoded by specialist software.<sup>178</sup> If the cause of death is unclear, the case is referred to a coroner for further investigation and causes are encoded manually.<sup>178</sup>

Neonatal deaths (i.e. deaths occurring <28 days after delivery) and stillbirths are recorded using a separate certificate in England and Wales.<sup>264</sup> These certificates allow doctors to record conditions in the foetus/infant or mother that contributed to the death as well as other non-clinical factors.<sup>265</sup> As these deaths are recorded differently, they may be more or less likely to record congenital malformations as a cause of death compared to death certificates in later infancy or childhood.

With the exception of cases that are referred to the coroner, it is a legal requirement in England for death certificates to be received by the local death and birth registrar within 5 days of the date of death.<sup>266</sup> Although the timeliness of death registrations has decreased since

2011, 92% of deaths are registered within a month of death.<sup>267</sup> Timeliness of registrations can be affected by the age, circumstances and cause of death. In 2018, for example, 14% of neonatal deaths were certified by a coroner and 7% were subject to a coroner's inquest, compared to 21% and 11% respectively for infant deaths.<sup>265</sup> This reflects the fact that nearly all neonatal deaths occur in hospitals.<sup>265</sup>

Linked ONS mortality data are provided to researchers in a single file. This file contains patient and practice identifiers used in CPRD. It contains the underlying cause of death, coded using ICD-10, as well as the date of death. For each death, up to 15 other causes of non-neonatal death and up to 8 causes of neonatal death are provided.

### 3.5.2 Data quality and completeness

Mortality data in the UK are considered to be of high quality, completeness and coding accuracy.<sup>268</sup> Quality checks are built in at various stages of the data collection process.<sup>178</sup>

Registrars, for example, check that the death occurred in the last year and that the death certificate is correctly filled in. They may also cross-check information such as age against birth records. The use of an automated cause coding system ensures the process of determining the underlying cause is standardized across the population.<sup>178</sup> When data are received by ONS, further checks are carried out such as checking that the birth and death dates are consistent with each other.

## 3.6 ONS Deprivation data

For the purpose of the studies described in this thesis, CPRD data were linked to the 2015 ONS Index of Multiple Deprivation (IMD) at the patient and practice levels. The IMD is a measure of relative deprivation between regions in England.<sup>269</sup>

### 3.6.1 Data collection and structure

To calculate IMD, England is first divided into lower-layer super output areas (LSOAs) which have an average of 1,500 residents each. The IMD is then calculated for each of these LSOAs

based on a number of indicators which fall into seven deprivation domains: income, employment, health and disability, education, skills and training, crime, living environment, and housing and services.<sup>269</sup> The LSOAs are then ranked and divided into quintiles, with the first quintile containing the least deprived LSOAs and the last quintile containing the most deprived. Following requests for linkage to deprivation scores, researchers are provided with files that indicate which quintile a patient or practice belongs to based on their post-code. To ensure anonymity, investigators do not have access to the post-codes or IMD scores. In some cases, a patient's post-code cannot be mapped to a LSOA, in which case they will not be assigned to a quintile. In such cases, the quintile of the practice can be used instead.

### 3.6.2 Data quality and completeness

It should be noted that the IMD score is calculated at the level of the LSOA and so may not necessarily correspond to the deprivation status of an individual. Whilst most patients eligible for linkage to ONS deprivation data have post-codes that can be mapped to an LSOA, in some cases this mapping is not possible. This might occur, for example, because the patient has a non-geographic post-code, or a post-code that is not in England. In such cases, the practice post-code can be used.

## 3.7 Data management

The Pregnancy Register was first used to identify eligible pregnancies for the different studies, a process described in **Chapter 4**. To identify MCMs, Read, ICD-10 and OPSC-4 code lists were first developed using EUROCAT guidelines. To identify relevant Read codes, the CPRD Medical Browser was searched by using free-text terms and by searching hierarchically. The ICD-10 and OPCS-4 dictionaries were also searched for relevant codes. Final code lists were agreed with a consultant neonatologist and used to search the records of all eligible infants (**Appendix 2**). MCM evidence was searched for in CPRD (among clinical, referral and test files), HES admissions data (among files for diagnoses and procedures) and ONS mortality data (including all causes of death). The process of identifying MCMs is further described in **Chapter 5**.



Initial Read codes, immunisation type codes and Product codes for influenza vaccination were provided by Sara Thomas (**Appendix 6**). These were used to identify evidence of influenza vaccination in the mother by searching the CPRD clinical, immunisation and therapy files, respectively. In the clinical file, evidence of a vaccine being received, refused or advised was based on the Read code. In the immunisation file, codes were assessed in conjunction with an 'immunisation status' variable to determine whether the vaccine was received, refused or advised. In the therapy file, where records are generated automatically following a prescription, all codes were assumed to relate to the vaccine being received. Further information on determining vaccination status is described in **Chapter 6**.

All data management and analyses were carried out using Stata® version 14.2.

### 3.8 Ethics

The studies in this thesis received ethics approval from the LSHTM ethics committee (reference 13720) and from the Independent Scientific Advisory Committee of the Medicines & Healthcare Products Regulatory Agency (reference 17\_040R).

### 3.9 Chapter Summary

This chapter described the data sources used in this thesis. In the following chapters, the criteria used to identify study populations, major congenital malformations and vaccinations are described.

## 4. Identifying eligible pregnancies and defining study populations

### 4.1 Introduction

This chapter describes the inclusion and exclusion criteria for the study populations in

**Objectives 3-6.** These objectives are first summarized below.

**Objective 3: To establish the value of stand-alone and linked CPRD, HES and ONS data in identifying infants with MCMs, the unique contribution of each data source and the agreement between them.**

The prevalence of MCMs among live-born infants in the first year of life was compared in stand-alone CPRD, stand-alone HES, linked CPRD and HES (CPRD-HES) and linked CPRD, HES and ONS (CPRD-HES-ONS). The proportion of infants with an MCM that had evidence of their condition in single and multiple data sources was then quantified.

**Objective 4: To compare the prevalence of MCMs in stand-alone and linked CPRD, HES and ONS, using the methods developed for this thesis, with prevalence in external data sources.**

The prevalence of MCMs among live-born infants in the first year of life in stand-alone CPRD data was compared with published prevalence data from 'The Health Improvement Network' (THIN), another UK database of primary care records. Prevalence in stand-alone and linked data was then compared with publicly available prevalence rates from EUROCAT registries.

**Objective 5: Assessing the safety of SIIV with respect to MCMs in live-born infants, by trimester of vaccination.**

The assessment of the safety of SIIV was initially planned to include MCMs identified among live-births, miscarriages, stillbirths and terminations. MCMs would be identified by searching for evidence in maternal records during the antenatal period and, for live-births, by also searching for evidence in the infant's records postnatally. However, an examination of pregnancy losses and terminations suggested that the extent of under-recording of antenatal

diagnoses, their poor validity and the low uptake of vaccination would likely bias the measure of effect (**Section 8.6**). Objectives were revised so that analyses were restricted to live-births and MCMs were identified postnatally from infant records. Live-births without linked infant records were not included as the outcome could not be ascertained (**Section 8.8**).

A historical cohort study was carried out to examine the association between SIV receipt during pregnancy, by trimester and overall, and MCMs among live-born singletons. The primary analysis examined any MCMs identified in the first year of life using linked CPRD, HES and ONS. Secondary analyses examined any MCMs, major limb defects and major congenital heart defects in early childhood.

**Objective 6: Assessing the safety of PIV with respect to MCMs in live-born infants, by trimester of vaccination.**

A historical cohort study was used to examine the association between PIV receipt during pregnancy, by trimester and overall, and any MCMs among live-born singleton infants.

Analyses were carried out for MCMs identified in the first year of life in linked CPRD, HES and ONS data. A secondary analysis considered MCMs recorded in early childhood.

The criteria used to define potentially eligible pregnancies were the same for all objectives and are outlined in **Section 4.2**, with **Section 4.3** describing further pregnancy-related exclusion criteria. Pregnancies resulting in miscarriages, stillbirths, terminations and live-births without linked infants were not excluded at this point. **Section 4.4** summarizes the exclusion of pregnancies with evidence of an MCM with a known cause (e.g. a chromosomal abnormality) or evidence of a congenital infection known to increase the risk of MCMs. These exclusions were also applied to all study populations. **Section 4.5** outlines additional, study-specific exclusion criteria for each objective.

The methods used to identify MCMs in the data sources used in this thesis and the methods used to identify the vaccination status of pregnant women are detailed in the next two

chapters of the methods section. Further details on study design, methods and statistical analyses for **Objectives 3-4** are provided in **Chapter 7** whilst details for **Objectives 5-6** are provided in **Chapters 8-9**.

## 4.2 Identifying potentially eligible pregnancies

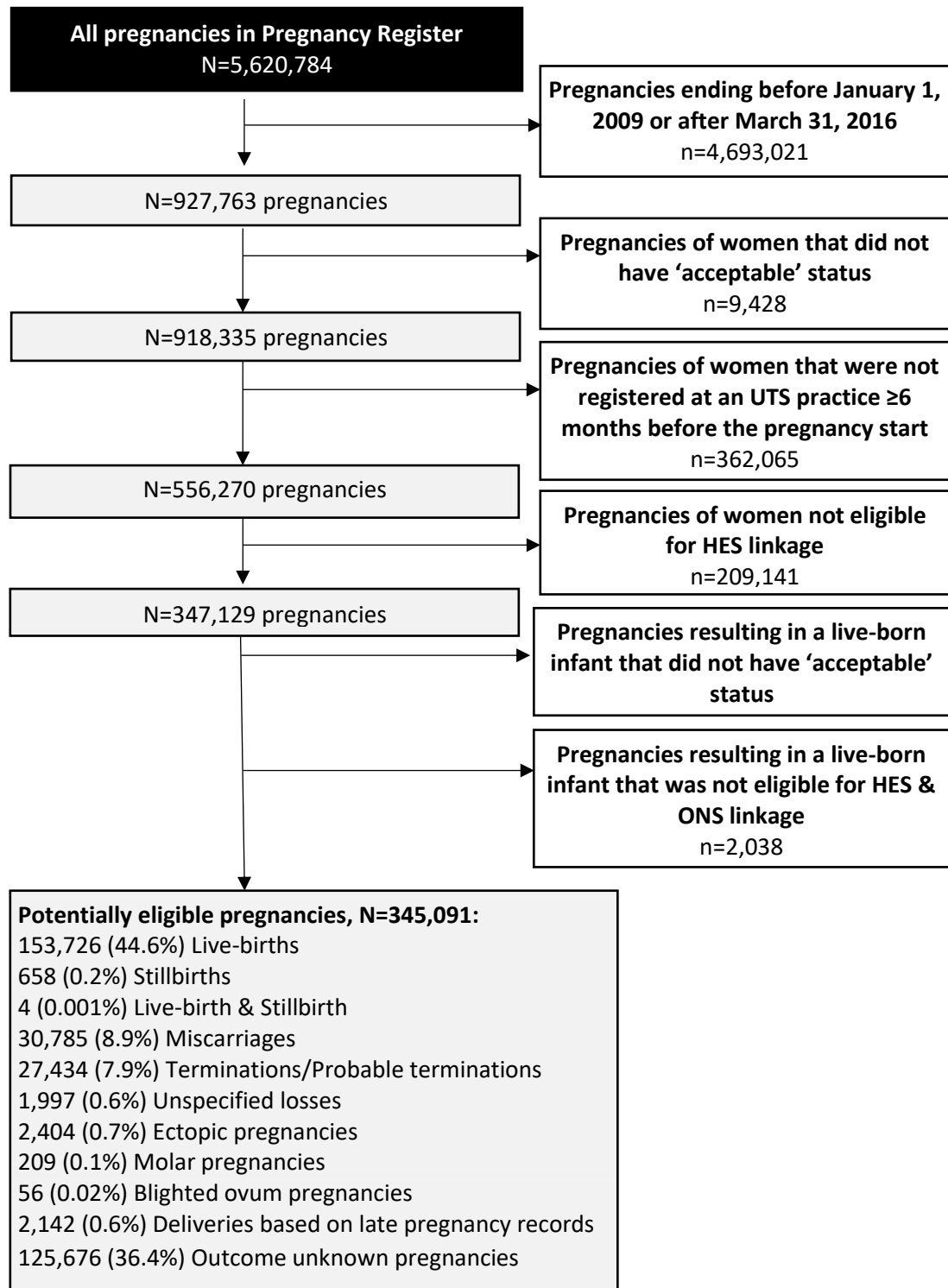
Pregnancies that were potentially eligible for inclusion in analyses were identified from the Pregnancy Register.

### 4.2.1 Criteria for potentially eligible pregnancies

The estimated delivery date of each pregnancy had to occur between January 1, 2009 and March 31, 2016 (the last date that linked data were available) (**Figure 4.1**). Pregnant women had to conform to CPRD data quality standards; they had to be considered 'acceptable' for research purposes and had to be registered at an up-to-standard practice (**Section 3.1.2**). They were also required to be registered with a practice at least six months before the start of their pregnancy. This criterion was chosen to improve the ascertainment of potential confounders, as information on maternal characteristics, behaviours and medical history could be under-recorded in the immediate period after registration. Pregnant women had to be eligible for linkage to HES to maximize the ascertainment of confounders (such as ethnicity that may be incompletely recorded in CPRD) and MCMs recorded in the antenatal period (**Section 5.6**). For the subset of pregnancies that resulted in a live-birth delivery with a linked infant, the infant also had to conform to CPRD data quality standards (**Figure 4.1**). Live-born infants had to be eligible for linkage to HES and ONS mortality data as MCMs were identified in these data sources as well as in CPRD.

### 4.2.2 Data extraction for potentially eligible pregnancies

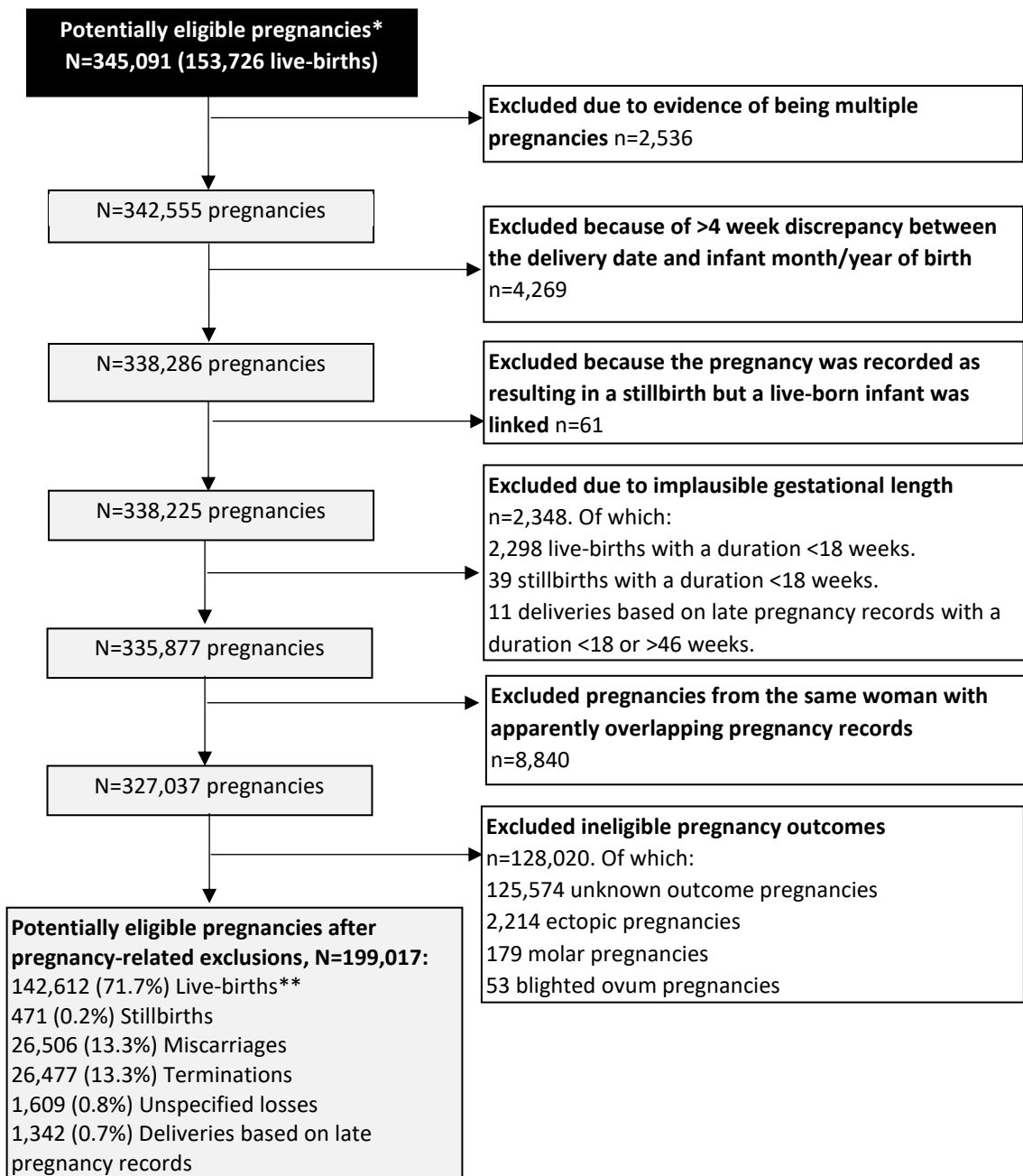
CPRD data for potentially eligible mothers and infants were extracted from the January 2017 data build and linked to the 14<sup>th</sup> version of HES and, for infants, ONS mortality data. Patient level deprivation data were also obtained for those mothers eligible for linkage.



**Figure 4.1 - Identification of potentially eligible pregnancies.** Abbreviations: UTS, up-to-standard date; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data.

### 4.3 Pregnancy-related exclusion criteria

Following the identification of potentially eligible pregnancies, the Pregnancy Register was explored and further pregnancy-related exclusion criteria were applied (**Figure 4.2**).



**Figure 4.2 - Potentially eligible pregnancies after the application of pregnancy-related exclusion criteria.** \*Pregnancies ended between January 1, 2009 and March 31, 2016 and belonged to women who had 'acceptable' status (as defined by CPRD) and were registered at an up-to-standard practice at least 6 months before the pregnancy start. All women were eligible for HES linkage. Live-born infants also had to have 'acceptable' status and had to be eligible for HES and ONS linkage; \*\*8.5% of live-births were not linked to infant records (n=16,949).

### 4.3.1 Multiple pregnancies

Multiple pregnancies are those with more than one foetus or infant. As described in **Section 3.3**, such pregnancies are included in the Pregnancy Register but are only ever linked to records from a single live-born infant. Analyses were therefore restricted to singleton pregnancies and multiple pregnancies were excluded.

The Pregnancy Register algorithm flags multiple pregnancies based on evidence from antenatal, delivery and infant records. At the time of this study, however, the algorithm did not use evidence from the MBL (which identifies multiple infants with the same month and year of birth born to the same mother, **Section 3.2**) and may have incompletely captured multiple pregnancies.

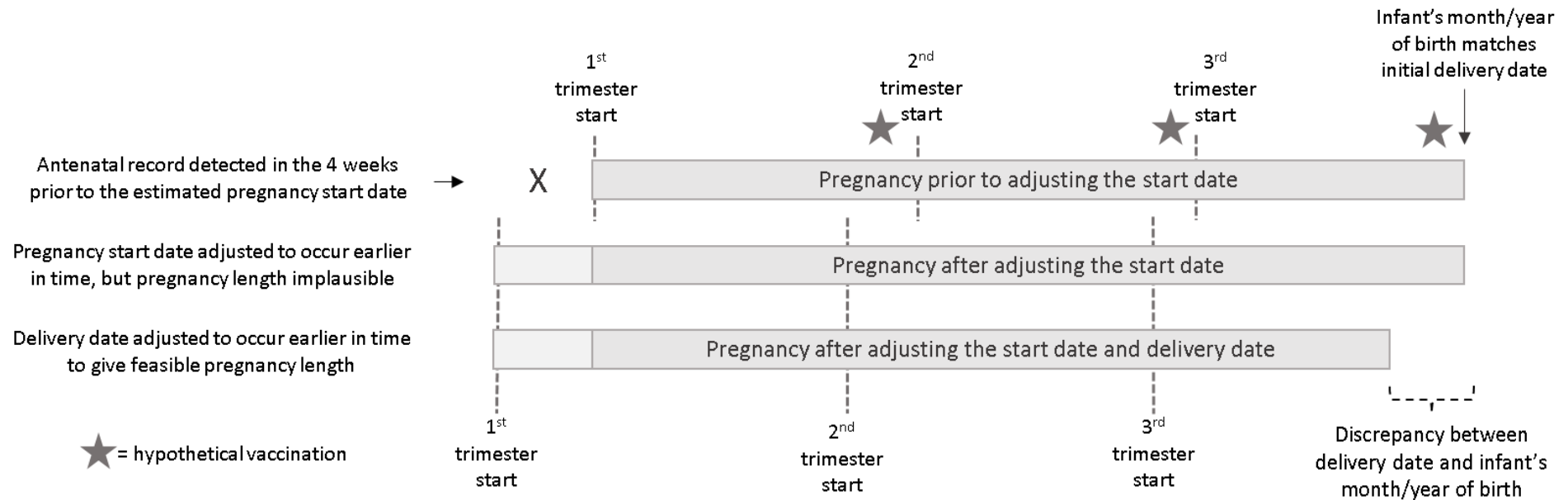
Relying solely on information in the Pregnancy Register to exclude multiple pregnancies was likely to be inadequate. Therefore, multiple pregnancies were first identified using information in the Pregnancy Register and this was supplemented with evidence from the MBL. In total, 2,536 multiple pregnancies were identified using information in the Pregnancy Register (n=1,460; 57.6%) and MBL (n=1,076; 42.4%), all of which were excluded (**Figure 4.2**).

### 4.3.2 Live-birth pregnancies with a discrepancy between the delivery date and infant month/year of birth

For some live-birth pregnancies with linked infant records, the estimated delivery date in the Pregnancy Register was found to be earlier than the infant's recorded month/year of birth. Uncertainty about the delivery date could result in the misclassification of overall vaccination status, trimester of vaccination and MCMs (**Figure 4.3**).

There were a number of potential scenarios for such a discrepancy:

1. The infant's month/year of birth was incorrectly recorded as occurring later than it did.
2. The GP recorded information about a historical delivery with a current date during an ongoing pregnancy, but the true delivery occurred later on.



**Figure 4.3 – An example of the potential misclassification of vaccination and MCMs among pregnancies with a delivery date preceding the infant's month of birth.** The Pregnancy Register algorithm adjusts the start of the pregnancy to an earlier point in time if an antenatal record is detected in the 4 weeks prior. The delivery date may also be adjusted to preserve the estimated gestational age. This can result in the delivery date occurring earlier than the infant's month/year of birth. If this adjustment is inaccurate then the pregnancy may be misclassified as unvaccinated if a vaccine was given between the delivery date and the infant's month/year of birth. Furthermore, the trimester of vaccination may be misclassified as occurring later than it truly did. For example, a vaccination that truly occurred in the first trimester could appear to occur in the second trimester. Misclassification of MCMs could also occur; for example, if the delivery date was 8 weeks early, then the end of follow-up would occur 8 weeks before the infant's first birthday and any MCM records in the 8 weeks prior to the first year of life would be missed.



3. An antenatal record was identified by the Pregnancy Register algorithm in the 4 weeks before the start of the pregnancy. As this was unlikely to relate to a woman's previous pregnancy, the estimated pregnancy start date was adjusted by the algorithm to an earlier time-point to incorporate the antenatal record. A similar adjustment was then made to the estimated delivery date to preserve the estimated gestational age of the pregnancy (this example is used in **Figure 4.3**).

It was not possible to know whether the estimated delivery date was reliable among such pregnancies. Those with a discrepancy of >4 weeks between the estimated delivery date and the infant's month/year of birth were therefore excluded from analyses (**Figure 4.2**). As the exact date of birth of the infant is not provided by CPRD in order to preserve anonymity, the mid-point of the infant's month of birth was used to calculate the discrepancy in weeks.

#### 4.3.3 Stillbirth pregnancies linked to live-born infant records

A small number of stillbirth pregnancies in the Pregnancy Register were found to be linked to live-born infant records. The Pregnancy Register relies on the MBL for linkage between mothers and infants (**Section 3.2**). As the MBL only links mothers to live-born infants (stillborn infants are never registered at a general practice and so are not included), only live-birth pregnancies in the Pregnancy Register should be linked to an infant. There were 3 potential explanations for these stillbirth pregnancies linked to live-born infant records:

1. It was truly a stillbirth pregnancy incorrectly linked to live-born infant records. Incorrect linkage could occur if the pregnant woman in the Pregnancy Register delivered a stillborn infant around the same time that another woman in the same household delivered a live-born infant. In such a scenario, the MBL could incorrectly link the woman who had a stillbirth pregnancy to the live-born infant.
2. It was actually a live-birth pregnancy, incorrectly recorded as a stillbirth pregnancy. This could occur if a woman with an ongoing pregnancy told her GP about a historical stillbirth pregnancy and the GP recorded this with a current event date. It could then appear that

the woman's current pregnancy resulted in a stillbirth when, in fact, the woman went on to deliver a live-born infant that was correctly linked to her.

3. It was actually a pregnancy resulting in both a live-birth and a stillbirth. This could occur if the pregnant woman delivered both a live-birth and stillbirth, with the latter outcome captured in the Pregnancy Register and the former linked via the MBL.

It was not possible to know whether such pregnancies were truly stillbirths (in which case the linked infant should not be included in analyses examining MCMs among live-born infants), live-births (in which case they should be included in analyses examining MCMs among live-born infants) or multiple pregnancies (in which case they should be excluded from all analyses). All 61 such pregnancies were therefore excluded (**Figure 4.2**).

#### 4.3.4 Pregnancies with implausible duration

The length of some pregnancies was implausible in the context of their outcome. In such cases it was likely that the estimated pregnancy start and/or delivery date were inaccurate, which could result in the misclassification of vaccination or MCMs. Exclusion criteria based on pregnancy outcomes and gestational age are described below.

Live-births: A plausible duration was considered to be 22-42 weeks. To ensure consistency with previous decisions, in which up to 4 weeks of imprecision in the estimated delivery date was allowed, live-birth pregnancies were excluded if they had a recorded duration of <18 or >46 weeks in the Pregnancy Register. Of the potentially eligible live-birth pregnancies at this stage, 1.5% (n=2,298) had a duration of <18 weeks and were excluded (**Figure 4.2**). No live-birth pregnancy had a duration of >46 weeks. Just 0.2% (n=378) had a duration of 18-22 weeks and 2.7% (n=4,194) had a duration of 42-46 weeks.

Stillbirths: These were defined as foetal losses occurring after 24 weeks of gestation.<sup>270</sup> The same rules were followed as for live-births. Of the potentially eligible stillbirths, 6.7% (n=39) had a duration of <18 weeks and were excluded (**Figure 4.2**). None of these pregnancies were

>46 weeks long. Stillbirth pregnancies that were 18-22 weeks long (4.7%; n=27) and those with a duration of 42-46 weeks (1.4%, n=8) were retained.

Miscarriages: These were defined as foetal losses occurring before 24 completed weeks of gestation.<sup>271</sup> It was decided that miscarriages with a gestational length of >28 weeks would be excluded but no such pregnancies were identified.

Terminations: In England, these can be conducted at any time in pregnancy but most are carried out before the 24<sup>th</sup> week.<sup>272</sup> Whilst the distribution of pregnancy duration was examined among terminations, no thresholds were set for exclusion. All pregnancies resulting in termination were <26 weeks long.

#### 4.3.5 Overlapping pregnancies

Some pregnancy episodes belonging to the same woman overlap in the Pregnancy Register and are flagged. Pregnancy episodes may overlap because the estimated pregnancy start and/or delivery dates are inaccurate. However, overlap may also occur as a result of GP recording practices. For example, a pregnancy episode resulting in a miscarriage may be found within a live-birth pregnancy episode if the pregnant woman experienced a threatened miscarriage which was recorded by the GP but then resolved, with the woman later delivering a live-born infant.

All overlapping pregnancy episodes were identified. Overlapping pregnancy episodes were excluded with the exception of those that resulted in a live-birth with linked infant records. Because of the presence of linked infant records, it was thought that if such pregnancies overlapped with pregnancies of other outcomes (e.g. miscarriages) then the latter were unlikely to be real pregnancies.

#### 4.3.6 Pregnancies with unknown outcomes

The Pregnancy Register algorithm was designed to utilize all the available pregnancy information recorded in the CPRD in order to maximize the ascertainment of pregnancy

episodes.<sup>255</sup> This approach, however, also led to the identification of some pregnancies with an unknown outcome. Such pregnancies could occur if:

1. The woman transferred out of the practice before the pregnancy ended.
2. The woman died before the pregnancy ended.
3. The practice stopped collecting data for CPRD before the pregnancy ended.
4. The woman was not pregnant but the GP recorded historical pregnancy information using a current date.
5. The GP did not record the delivery using Read or entity codes (which were used by the Pregnancy Register algorithm to identify pregnancy-related data) but instead scanned a delivery letter from the hospital or entered information using free-text.
6. The pregnancy was initially reported to the GP but then ended in an unreported miscarriage or termination.

Outcome unknown pregnancies made up 38% of all pregnancies (**Figure 4.2**) and a third of these were found to be a result of truncated follow-up due to reasons 1-3 described above. All outcome unknown pregnancies were excluded from analyses due to the uncertainty in their duration and timing, which could result in the misclassification of vaccination status.

Furthermore, ascertaining MCMs among such pregnancies was not possible; none of these pregnancies were linked to infants and an examination of antenatal diagnoses was considered inadequate due to the uncertainty in pregnancy timings.

#### 4.3.7 Ectopic, molar and blighted ovum pregnancies

Ectopic, molar and blighted ovum pregnancies are non-viable pregnancies that do not usually extend beyond the first trimester. MCMs are unlikely to be detected antenatally in these pregnancies, or at all for those where the embryo or foetus does not develop. These pregnancies were excluded from analyses.

#### 4.3.8 Pregnancy losses, terminations, live-birth deliveries without linked infant records and other pregnancy outcomes

After the above exclusion criteria had been applied, remaining pregnancy outcomes included:

- Miscarriages,
- Stillbirths,
- Unspecified pregnancy losses,
- Deliveries based on late pregnancy records,
- Live-births without linked infant records, and
- Live-births with linked infant records

All outcomes were first explored to assess the potential for bias if they were to be included in vaccine safety analyses (**Section 8.6**). The final study populations for **Objectives 3-6** only included live-birth pregnancies with linked infant records.

Of the 142,612 potentially eligible live-birth pregnancies (**Figure 4.2**), approximately 8.5% (n=16,949) were not linked to infant records and so it would not be possible to search for evidence of MCMs among these postnatally. These pregnancies were excluded from all analyses but were described to demonstrate that their exclusion was unlikely to bias results (**Section 8.8**). There are a number of reasons for incomplete linkage between mothers and infants in the MBL, which would result in the linkage also not being available in the Pregnancy Register (**Table 4.1**). Two reasons for lack of linkage that could be associated with MCMs were:

1. The woman transferring out of the practice to move to another region (either to access specialist care for an infant with an MCM or due to unstable accommodation),
2. The infant having a severe condition resulting in prolonged hospitalisation or death.

Both scenarios would prevent/delay the registration of the infant at the practice and subsequent linkage to the mother. These two scenarios are considered in **Section 8.8**.

**Table 4.1 – Potential reasons for incomplete linkage between mothers and infants in the Mother-Baby Link.**

No infant to link to	Linkage not attempted	Linkage unsuccessful
The delivery record was actually a retrospective recording of a past live-birth delivery and so there was no contemporaneous infant to link to.	The infant’s year of registration at the practice was recorded as being prior to their birth year and so the infant was excluded from linkage.	The recorded delivery date and estimated date of birth of the infant are more than 60 days apart.
The delivery was not a live-birth (the pregnancy outcome is misclassified in the Pregnancy Register) and so there is no infant to link to.	The infant’s year of registration at the practice was recorded as being after the last collection year of the practice and so the infant was excluded from linkage.	The delivery matched to more than one infant with different dates of birth.
	The mother delivered before 12 years of age and so the delivery was excluded from linkage.	More than one woman matched to the same baby.
	The delivery was recorded as occurring more than a year before the current registration date of the mother and so the delivery was excluded from linkage.	
	The delivery was recorded as occurring after the last collection date of the practice or the transfer out date of the mother and so the delivery was excluded from linkage.	
	The infant was not registered at the mother’s practice during the data collection period and so linkage was not possible.	
	The mother and infant have a different family number and so linkage was not possible.	

## 4.4 Congenital malformation exclusion criteria

### 4.4.1 Malformations with known causes

The overarching aim of this work was to assess the safety of influenza vaccination with respect to MCMs. MCMs cover a broad range of conditions, some of which have a known aetiology.

These include:

- Chromosomal aberrations (e.g. '*Down syndrome*'),
- Inherited genetic mutations (e.g. '*autosomal recessive polycystic kidney disease*'), and
- Exogenous causes such as exposures to known teratogens (e.g. '*foetal alcohol syndrome*', '*Dysmorphism due to warfarin*').

These MCMs with known aetiology would not plausibly have been caused by maternal vaccination. In addition, including such conditions in analyses could bias the association between vaccination and MCMs. Chromosomal aberrations, single-gene mutations and exposures to exogenous causes may be associated with characteristics that are also associated with vaccine uptake. For example, the risk of having a child with Down syndrome and the likelihood of receiving the influenza vaccine during pregnancy both increase with maternal age.<sup>17, 66</sup> Including these infants, and any of their MCMs, in analyses could bias the association between vaccination and MCMs upwards.

Pregnancies were excluded if an MCM with a known cause was identified in the infant or recorded antenatally in the pregnant woman. The methods used to exclude such conditions are described in **Chapter 5** and the code lists used are described in **Appendix 4**.

In the absence of a diagnosis of an MCM of known cause, it was unclear whether exposure *in utero* to potentially teratogenic drugs or vaccines or hazardous levels of alcohol were responsible for any resulting MCMs. These exposures were therefore considered confounders of the relationship between maternal vaccination and risk of MCMs, and are further outlined in **Section 4.6** and in **Chapter 8**.

#### 4.4.2 Congenital infections

Some maternal infections can be transmitted to the foetus *in utero* and cause congenital malformations (**Section 1.7.2**).<sup>273, 274</sup> These are known as congenital infections and include: Syphilis, HIV, varicella zoster virus, parvovirus, rubella, herpes simplex virus, cytomegalovirus and toxoplasmosis.<sup>273, 274</sup> With the exception of syphilis and HIV, infections typically only pose a risk if they are acquired during or around the time of pregnancy.<sup>273, 274</sup> To ensure that MCMs identified in the study population were not caused by congenital infections, pregnancies were excluded from analyses if there was evidence of:

- Varicella, parvovirus, rubella, herpes simplex virus, cytomegalovirus or toxoplasmosis in maternal records during pregnancy, four weeks before or four weeks after (to account for delays in recording infections or imprecision in recorded pregnancy timings, and to identify infections that were likely to be ongoing in the first trimester).
- Syphilis or HIV anytime in the maternal records (to account for the fact that these infections can be acquired years before diagnosis as well as the life-long nature of HIV and the fact that although syphilis can be treated there was no way to know that treatment was completed successfully before conception).
- HIV, syphilis, varicella, parvovirus, rubella, herpes simplex virus, cytomegalovirus or toxoplasmosis anytime in the infant records. Codes had to specify that the infection was congenital in origin to prevent the ascertainment of common infections acquired postnatally (i.e. congenital varicella vs. common childhood varicella).

Read code lists for these congenital infections were used to search infant and maternal clinical, referral and test files in CPRD (**Appendix 5**). Because congenital infections were likely to be ascertained in hospital around the time of delivery, ICD-10 code lists were also used to search for any evidence in HES among infants.



## 4.5 Additional study-specific exclusion criteria

For all studies, eligible pregnancies were first identified as described in **Sections 4.2-4.4**. All other pregnancy outcomes (e.g. miscarriages, stillbirths, terminations, live-births without linked infant records) were excluded at this stage and additional, study-specific exclusion criteria were then applied (**Figure 4.4**).

For **Objective 3**, pregnancies ending after March 31, 2015 (a year before linked data ended) were excluded to allow all infants the potential for a year of follow-up. For **Objective 4**, additional exclusion criteria were applied when carrying out prevalence comparisons with EUROCAT data to increase the comparability of the study populations. Pregnancies ending after December 31, 2013 were excluded, as were pregnancies of women whose practice region did not correspond to a region covered by an English EUROCAT registry.

For **Objectives 5 & 6**, vaccination-specific exclusion criteria were also applied to ensure that all pregnancies had the opportunity to be vaccinated and to reduce any uncertainty in the timing of vaccination and in the type of influenza vaccine received. These are described in greater detail in **Chapter 6**. Analyses were also restricted to those pregnancies that had complete information on potential confounding factors (**Section 4.6**).

#### **Potentially eligible pregnancies**

- Pregnancies ending between January 1, 2009 and March 31, 2016
- Pregnant women had to fulfil the following criteria: 'acceptable' status (as defined by CPRD), registered at an up-to-standard practice at least 6 months before the start of pregnancy, eligible for HES linkage.
- Any infants linked to live-birth pregnancies had to fulfil the following criteria: 'acceptable' status (as defined by CPRD), eligible for linkage to HES and ONS.

#### **Pregnancy-related exclusions**

- Multiple pregnancies
- Live-birth pregnancies with a discrepancy of >4 weeks between the delivery date & the infant's month/year of birth
- Stillbirth pregnancies with a linked infant
- Pregnancies with an implausible duration (live-births and stillbirths with a duration <18 or >46 weeks; miscarriages with a duration >28 weeks; late and third trimester deliveries with a duration <18 or >46 weeks)
- Outcome unknown pregnancies
- Overlapping pregnancies

#### **Congenital malformation exclusions**

- Pregnancies resulting in MCMs with known causes (e.g. chromosomal abnormalities).
- Pregnancies for which there was evidence of a congenital infection known to cause MCMs (Syphilis, HIV, varicella zoster, parvovirus, rubella, herpes simplex virus, cytomegalovirus, toxoplasmosis).

#### **Study-specific exclusions**

All studies were restricted to live-birth pregnancies with linked infant records (all other pregnancy outcomes were excluded).

#### **Objectives 3 & 4**

- Pregnancies ending after March 31, 2015.
- For prevalence comparisons with English EUROCAT registries, pregnancies were excluded if they ended after December 31, 2013 and if they occurred in regions that did not correspond to regions covered by the EUROCAT registries (**Objective 4 only**).

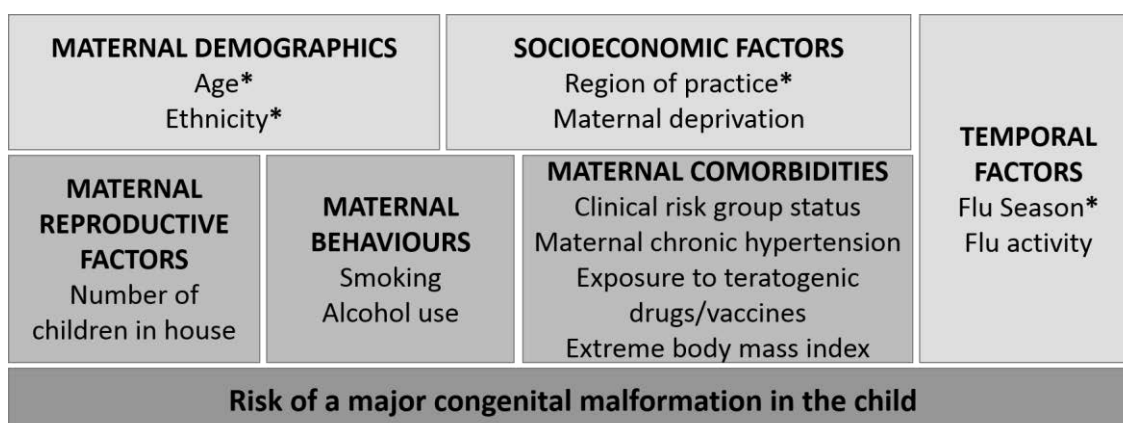
#### **Objectives 5 & 6**

- Did not overlap with period of SIV availability (defined as September 1<sup>st</sup> – March 31<sup>st</sup> from 2010-2016) (**Objective 5 only**).
- Did not overlap with a period of PIV availability (October 21, 2009-March 31, 2010). (**Objective 6 only**).
- Pregnancies for which there was uncertainty in the timing or type of vaccine received.
- Pregnancies with missing data in confounder variables.

**Figure 4.4 – Summary of the criteria used to define study populations for the objectives of the thesis.** Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, Major congenital malformation.

## 4.6 Defining potential confounders in the study population

Factors associated with vaccine uptake and factors associated with MCMs were described in **Sections 1.4** and **1.7.2**, respectively. Factors for which there was evidence to suggest an association with both vaccine uptake and MCMs were considered and a conceptual framework was developed to identify confounders for vaccine safety analyses (**Figure 4.5**).



**Figure 4.5 – Conceptual framework used to identify potential confounders for vaccine safety analyses.** Distal factors included maternal demographics and socioeconomic factors. The effect of these factors was likely mediated, in part, through more proximal risk factors such as maternal reproductive factors, lifestyle behaviours and comorbidities. Separate to these were temporal risk factors related to the flu season and flu activity (i.e. the levels of influenza circulating in the community). \*A priori confounders.

Potential confounders of interest were derived as follows:

**Maternal age (*a priori* confounder):** Maternal age at the end of each pregnancy was defined using information in the Pregnancy Register.

**Maternal ethnicity (*a priori* confounder):** Maternal ethnicity was derived using a previously published algorithm which incorporates information from both CPRD and HES.<sup>251</sup>

**Geographical region (*a priori* confounder):** The geographical region of the mother's general practice was identified from the CPRD practice file.

**The earliest influenza season a pregnancy overlapped with (*a priori* confounder):** Influenza seasons were defined as September, 1 - March, 31 each year. If a pregnancy overlapped with more than one season, the earliest was chosen.

**Household deprivation quintile (Index of Multiple Deprivation (IMD)):** Patient-level IMD quintiles were obtained through linkage with deprivation data where possible. Practice-level IMD data were used for the small proportion of pregnancies (<0.5%) where patient-level data were unavailable.

**Number of children in the maternal household:** The number of children aged  $\leq 16$  years and present in the maternal household at the start of each pregnancy was determined by identifying children registered at the mother's practice who had the same family number (a variable indicating individuals living in the same household) as the mother from CPRD patient files and practice files.

**Smoking status:** Maternal smoking records during pregnancy were identified from the clinical file and additional clinical details file in CPRD. Pregnancies were classified as belonging to a non-, ex- or current smoker. If there were multiple records during pregnancy then a current smoker record superseded all others whilst an ex-smoker record superseded a non-smoker record. If there were no records during pregnancy, the most recent record in the 10 years prior was identified and used. If there were multiple records on the same date the same rules were followed as above. If the most recent evidence indicated the woman was a non-smoker but she had evidence of smoking any time before this then she was reclassified as an ex-smoker. Pregnancies of women with unknown smoking status were excluded from analyses.

**Evidence of extreme BMI:** All available height and weight data for women in the study population were extracted from the additional clinical details file in CPRD and used to calculate BMI. BMI records that occurred from the start of the second trimester through to the end of the second month after pregnancy were excluded. The earliest BMI record in the first trimester was sought. If there was no record in the first trimester, the five years prior to the start of pregnancy were examined and the record closest to the pregnancy was used. If no records were available in the five years before the pregnancy, the year after the pregnancy was examined (excluding the first two months) and the record furthest from the end of pregnancy

was selected. If a BMI record had still not been identified, the most proximate BMI record before or after the pregnancy was used, within 10 years. Evidence of extreme BMI (<18 and ≥35) was of particular interest as a potential confounder in this study. Pregnancies of women with unknown BMI or a BMI between 18 and 34 were categorized as not having evidence of extreme BMI.

**Evidence woman belonged to at least one other clinical risk group for which influenza**

**vaccination was recommended:** Identification of clinical risk group status in pregnant women was carried out by Dr Jemma Walker using CPRD clinical and therapy files. Women were considered to be part of a clinical risk group if they had evidence of a relevant condition at the start of the influenza season the pregnancy overlapped with. The following conditions were included: Chronic respiratory disease (including asthma), chronic heart disease, chronic kidney disease, diabetes mellitus, immunosuppression due to disease or treatment, chronic liver disease, chronic neurological disease, asplenia or dysfunction of the spleen. If a woman had evidence of the above but it was not clear at what point this had occurred then her pregnancy was considered to have unknown clinical risk group status and was excluded from analyses.

**Evidence of chronic hypertension:** Maternal clinical, referral and test files in CPRD were searched for evidence of a hypertension diagnosis. If this evidence occurred before a pregnancy, any subsequent pregnancy was classified as belonging to a woman with pre-existing hypertension. If this evidence first occurred during a pregnancy then further supportive evidence was required to rule out pregnancy-related hypertension; maternal records were searched for a further diagnosis record in the 6-12 months after the end of pregnancy or a prescription of an anti-hypertensive in the therapy file. If supportive evidence was available, the woman was considered to have hypertension (not pregnancy-related hypertension) at the time of her pregnancy.

**Evidence of hazardous drinking:** Maternal records relating to alcohol consumption were identified from the maternal clinical file and additional clinical details file in CPRD. Evidence of

hazardous drinking was defined as the consumption of  $\geq 43$  units/week or by the presence of a Read code indicating heavy drinking. Evidence of hazardous alcohol consumption was first searched for during each pregnancy. If there were no records during pregnancy, the most recent record in the 10 years prior was identified and used. If there were multiple records on the same day then the highest recorded level of alcohol consumption was used.

**Exposure to teratogenic drugs/live vaccines in the period before pregnancy and up to the end of the first trimester:** Identifying live vaccines given to women in the pregnancy period required the development of Read code lists (to search the maternal clinical file), product code lists (to search the maternal therapy file) and immunisation type code lists (to search the maternal immunisation file). To manage time constraints, the immunisation file for all women in the study population was examined to identify all live vaccines given in the pregnancy period. The MMR, yellow fever and BCG vaccines were the most commonly received whereas live typhoid, shingles and varicella vaccines were used in just  $< 0.02\%$  of women. Code lists were developed for MMR, yellow fever and BCG vaccines and evidence of vaccine receipt was identified from the 3 months before pregnancy until the end of the first trimester.

There is no definitive/comprehensive list of teratogenic drugs. A list of teratogenic drugs was decided based on an exploration of the related literature and cytotoxic drugs listed by the British National Formulary.<sup>275, 276</sup> Code lists for the following teratogenic medications were obtained from Sara Thomas: ACE inhibitors, Acitretin, Amiodarone, Azathioprine, Bexarotene, Carbamezepine, Cyclophosphamide, Dronedarone, Isotretinoin, Lithium, Methotrexate, Misoprostol, Mycophenolate, Phenobarbital, Phenyoin, Primidone, Propylthiouracil, Topiramate, Valproate, and Warfarin. A code list was not created for thalidomide as any prescription of thalidomide in the UK involves a negative pregnancy test before prescription and continuous negative tests throughout treatment.<sup>277</sup> Methimazole (or thiamazole, its alternative name) was also not included as this was not listed in the current or old version of

the British National Formulary, it was not in the CPRD data dictionary under any known trade name and it was suspected that it was not available in the UK during recent times.

The maternal therapy file in CPRD was examined from 6 months before the start of pregnancy through to the end of the first trimester for evidence of prescriptions. This larger window of time was chosen to account for prescriptions issued but not collected/utilized until a later date and the long length of some prescriptions for such drugs.

#### **Number of weeks that the first trimester overlapped with influenza activity above baseline**

**levels:** This was calculated using weekly national influenza-like illness surveillance data from the Royal College of General Practitioners.<sup>278</sup> Data on the weeks in each year that had an influenza-like illness rate above the baseline threshold were provided by Public Health England. The total number of weeks in the first trimester that overlapped with a period in which the rate of influenza-like illness was above the baseline threshold was calculated for each pregnancy.

## **4.7 Chapter Summary**

This chapter summarizes the criteria used to define study populations for the objectives in this thesis. The next methods chapter discusses the development of the algorithm used to identify MCMs. In the final methods chapter, the approach taken to identify vaccination during pregnancy is described in full and includes further detail on study-specific exclusion criteria related to vaccination.

## 5. Developing an algorithm to identify major congenital malformations

### 5.1 Introduction

Identifying congenital malformations in electronic health records poses a challenge due to the large and diverse number of these conditions. Distinguishing major from minor malformations and categorizing major malformations into anatomical subgroups can further complicate the process. A systematic review of the methods used to identify congenital malformations in UK electronic health records was carried out to inform the identification of MCMs in this thesis (**Chapter 2**). Of the 54 studies examined, 36 identified congenital malformations in stand-alone primary care data and 18 used secondary care data (with some using additional data such as death records). No study used linked primary care, hospital admissions and mortality data.

An objective of this thesis was to ascertain MCMs among live-born infants using linked CPRD primary care records, HES inpatient admissions and ONS mortality data and to establish the value of each data source in ascertaining these conditions, and their agreement (**Objective 3**). The prevalence of MCMs identified in stand-alone and linked data sources was then compared to prevalence estimates from external data sources (**Objective 4**) prior to analyses examining the safety of SIIV and PIIV (**Objectives 5-6**).

This chapter describes the algorithm developed to identify evidence of MCMs in these multiply-linked electronic health records. The key lessons from the systematic review that informed the approach used here are first summarized (**Section 5.2**). The use of EUROCAT guidelines and the development of initial code lists are then described (**Section 5.3**). After developing initial code lists, the methods to refine them are discussed (**Section 5.4**). The use of code lists to identify MCMs in infant records is then outlined (**Sections 5.5**). Finally, the identification of antenatal evidence for MCMs is detailed (**Section 5.6**).



## 5.2 Recapitulation of the methods used in other studies to identify congenital malformations in UK electronic health records

This section describes the three key lessons from the systematic review of the methods used to identify congenital malformations in UK electronic health records. These were used to inform the development of a comprehensive algorithm to identify MCMs in this thesis.

### **1. Use of published guidelines to define congenital malformations.**

Studies identifying congenital malformations in primary care data frequently used published guidelines to: develop case definitions and code lists, distinguish between major and minor malformations, and classify MCMs into anatomical subgroups.<sup>279, 280</sup> EUROCAT guidelines were the most frequently used and were used for the same purposes here.

### **2. Use of Read codes outside of the 'P' chapter on congenital malformations**

Both the Read and ICD-10 coding systems contain chapters of codes dedicated to congenital malformation diagnoses - the 'P' and 'Q' chapters, respectively. A key finding of the systematic review was that studies that identified congenital malformations in HES data using ICD-10 codes relied on the 'Q' chapter whilst studies using primary care data frequently used Read codes from both the 'P' chapter and other Read chapters.

Read codes from outside the 'P' chapter could be diagnostic in nature. For example, some studies used the Read code '*congenital mitral stenosis*' from the 'P' chapter as well as the code '*mitral stenosis*' from the 'G' chapter on circulatory system diseases which could also be non-congenital in origin.<sup>281</sup> Other codes from outside the 'P' chapter could relate to relevant procedures, observations, tests, medical history or administrative tasks. Examples of such codes used by studies in the systematic review included: '*personal history of congenital malformations*', '*repair of deformity of palate*', '*congenital heart condition monitoring*' and '*transfer of care from paediatric congenital heart services*'. Relying exclusively on Read codes from the 'P' chapter would likely under-ascertain MCMs and so relevant Read codes from other chapters were included in the code lists developed here.

### 3. Use of criteria to decide on the inclusion of non-specific codes

An examination of available code lists from studies included in the systematic review demonstrated that some codes used to identify congenital malformations were non-specific. Codes were considered non-specific (and are referred to as such throughout this thesis) if they could be used to encode:

1. **Congenital malformations or non-congenital conditions.**

Example code: *'mitral stenosis'*.

2. **Major malformations or minor malformations.**

Example code: *'other congenital heart anomalies'*.

3. **Malformations from different anatomical subgroups.**

Example code: *'congenital anomaly not otherwise specified'*.

Studies identified in the systematic review did not provide details of the criteria used to decide on the inclusion of non-specific codes in code lists and/or their classification. In this work, the framework for deciding on the use of codes that could potentially relate to non-congenital conditions is described in **Section 5.4.1**. Codes that could relate to major or minor malformations are discussed in **Section 5.4.2** and codes that could refer to malformations of different anatomical subgroups are described in **Section 5.3.1**.

### 5.3 Use of EUROCAT guidelines to develop initial code lists

EUROCAT defines congenital malformations (major and minor) using ICD-10 codes that are modified by the British Paediatric Association (BPA) to include a fourth digit.<sup>86</sup> EUROCAT uses all the codes in the ICD-10 'Q' chapter to define congenital malformations as well as a small number of codes beyond this, including: D1810 (*'lymphangioma/cystic hygroma'*), D215 (*'benign neoplasm of the pelvis'*), D821 (*'DiGeorge syndrome'*), P350 (*'congenital rubella syndrome'*), P351 (*'congenital cytomegalovirus infection'*) and P371 (*'congenital toxoplasmosis'*). Codes P350, P351 and P371 related to congenital infections and so were not included in code lists developed to identify congenital malformations.

EUROCAT Guide 1.4 (published in 2016) was used to define congenital malformations for initial code lists and classify them into anatomical subgroups.<sup>282</sup> Guidelines were later used to refine these by defining codes related to:

1. **Conditions that could sometimes be a result of other non-congenital causes.**

If such a code was present in the infant record then a decision was made as to whether the code represented an MCM or a condition with another cause.

2. **Minor malformations.**

Codes that clearly related to minor malformations were removed from code lists.

Codes that were ambiguous or needed to meet certain criteria to be classified as minor were considered separately.

3. **MCMs that were a result of known causes such as chromosomal anomalies**

If such a code was present in the infant record or antenatally in the maternal record then the pregnancy was excluded.

### 5.3.1 Defining congenital malformations and anatomical subgroups using EUROCAT

Congenital malformation and their subgroups were defined according to EUROCAT guidelines (**Table 5.1**). At the time this work was carried out, EUROCAT guidelines categorized BPA-modified ICD-10 codes into the following 12 non-overlapping subgroups: 'nervous system malformations', 'eye malformations', 'ear, face and neck malformations', 'congenital heart defects', 'respiratory system malformations', 'orofacial clefts', 'abdominal wall defects', 'other malformations of the digestive system' (henceforth referred to as 'digestive system malformations'), 'genital system malformations', 'urinary system malformations', 'limb defects' and 'chromosomal anomalies'.<sup>282</sup> Codes in these subgroups could be categorized into even smaller and more specific subsets. Codes in the 'orofacial clefts' subgroup, for example, could be further categorized into subsets for 'cleft palate' and 'cleft lip with or without cleft palate'. However, in the work described here, subsets of malformations were not examined

due to the potential for data sparsity. Anatomical subgroups in this thesis were defined according to EUROCAT guidelines, with two deviations:

1. **Codes for conditions related to balanced rearrangements of chromosomes were grouped with chromosomal anomalies.** EUROCAT guidelines did not include ICD-10 codes for balanced chromosomal rearrangements (Q950-959) in the chromosomal anomalies subgroup. Because these codes related to chromosomal conditions that were later used to exclude pregnancies from analyses, they were included in the chromosomal anomalies subgroup in this thesis (**Table 5.1**).

**Table 5.1 – Congenital malformation case definitions in EUROCAT and in the initial code lists developed for this thesis.**

Congenital malformation	BPA-modified ICD-10 codes used to define congenital malformations	
	EUROCAT	Thesis <sup>a</sup>
Any	Q chapter, D215, D821, D1810, P350, P351, P371	Q chapter, D215, D821, D1810
Nervous system	Q00-07	Followed EUROCAT guidelines
Eye	Q10-15	Followed EUROCAT guidelines
Ear, Face & Neck	Q16-18	Followed EUROCAT guidelines
Congenital Heart Defects	Q20-26	Followed EUROCAT guidelines
Respiratory	Q300, Q32-34	Followed EUROCAT guidelines
Oro-facial clefts	Q35-37	Followed EUROCAT guidelines
Digestive	Q38-45, Q790	Followed EUROCAT guidelines
Abdominal Wall Defects	Q792, Q793, Q795	Followed EUROCAT guidelines
Genital	Q50-52, Q54-56	Followed EUROCAT guidelines
Urinary	Q60-64, Q794	Followed EUROCAT guidelines
Limb	Q65-74	Followed EUROCAT guidelines
Chromosomal	Q90-93, Q96-99	Q90-93, Q95, Q96-99
Other	D821, P350, P351, P371, Q0435, Q206, Q240, Q3381, Q411, Q412, Q418, Q4471, Q6190, Q710, Q712, Q713, Q720, Q722, Q723, Q730, Q7402, Q7484, Q750, Q751, Q754, Q7581, Q77, Q7800, Q782-Q788, Q793, Q795, Q7980, Q7982, Q80-Q82, Q86, Q87, Q890, Q893, Q894, Q936	Q27, Q28, Q301-309, Q31, Q53, Q75-79 (except for Q790 and Q792-795 which were defined as digestive, abdominal wall and urinary malformations), Q80-89

<sup>a</sup>Minor malformations, malformations relating to prematurity, poorly-specified malformations and malformations with known causes were included in initial code lists. Code lists were later refined.

2. **Only codes that did not fall into one of the 12 main EUROCAT subgroups or that were non-specific were grouped into an ‘other’ subgroup.** EUROCAT guidelines defined an additional subgroup for ‘other anomalies/syndromes’ which covered a broad range of conditions.<sup>282</sup> Codes in this subgroup sometimes overlapped with codes in the 12 main subgroups described earlier. For example, the code Q793 for ‘*gastroschisis*’ was part of both the ‘abdominal wall defects’ subgroup and ‘other anomalies/syndromes’ subgroup. Because of this overlap, guidelines for this subgroup were not followed and defining a directly equivalent subgroup for this thesis was not attempted. Instead, only those codes that did not come under any of the 12 main anatomical subgroups were classified as ‘other’ malformations. For example, codes Q270-279 and codes Q280-289, which refer to malformations of the peripheral vasculature, were not part of any subgroup and were therefore defined as ‘other’ malformations. In addition to the above, non-specific codes that could not be classified into a subgroup were defined as ‘other malformations’ (e.g. ‘*congenital anomaly not otherwise specified*’) (**Table 5.1**).

### 5.3.2 Developing Read code lists

To develop Read code lists, EUROCAT BPA-modified ICD-10 codes in each subgroup were first used to create search terms of interest. For example, to identify Read codes for abdominal wall defects, the relevant BPA-modified ICD-10 codes used by EUROCAT were identified as being Q792, Q793 and Q795. The ICD-10 descriptions attached to these codes were then used to establish a list of search terms in free-text form, with wildcards used to account for any variation in the spelling or ordering of words (**Table 5.2**). The list of search terms was then used to search the Read code dictionary and relevant Read codes were retrieved. At this stage, all potentially relevant codes were retained regardless of what Read chapter they were from.

The hierarchical structure of the Read code system was utilized to increase the likelihood of capturing potentially relevant codes. When Read codes were identified through the use of search terms, they were examined and their common stems were noted. These stems were

then used to search for other codes in their vicinity. For example, a number of Read codes for omphalocele were identified which all began with 'J32'. The Read code dictionary was therefore searched for all codes with this stem to identify any others that might be relevant. Searches for 'J31', 'J33', 'J3' and 'J' were also carried out to assess whether any relevant codes might be found in other areas of the same chapter.

After identifying Read codes using the above methods, they were checked against the full 'P' chapter in the Read dictionary. The vast majority of codes in the 'P' chapter had been captured through the above methods. The few that weren't were added to the code list. Finally, Read codes identified in this work were cross-checked with those used by the authors of studies included in the systematic review (described in **Chapter 2**). Potentially relevant Read codes that had been included by other authors but had not been identified in the search here were added to the code list.

**Table 5.2 - Defining search terms for Read codes based on EUROCAT BPA ICD-10 codes**

<b>BPA-modified ICD-10 code</b>	<b>ICD-10 description</b>	<b>Search terms created</b>
Q792	Exomphalos; Omphalocele	*exomphal*; *omphalo*
Q793	Gastroschisis	*gastroschis*
Q795	Other congenital malformations of abdominal wall	*congen*abdom*; *mal*abdom*; *anomal*abdom*; *abdom*defect*; *abdom*wall*

### 5.3.2 Developing ICD-10 code lists

As EUROCAT defined malformations using ICD-10 (albeit a BPA-modified version), developing ICD-10 code lists was considerably more straightforward than developing Read code lists as the creation of search terms was not necessary to identify relevant codes. ICD-10 codes were selected from the ICD-10 dictionary and categorized into groups based on EUROCAT guidelines. However, because EUROCAT ICD-10 codes were modified to include an extra digit, it was sometimes not possible to identify an exact equivalent in the ICD-10 dictionary (**Table 5.3**).

**Table 5.3 - Identifying ICD-10 codes based on EUROCAT BPA-modified ICD-10 codes.**

<b>BPA-modified ICD-10 code</b>	<b>Description provided by EUROCAT</b>	<b>ICD-10 code</b>	<b>Description in the ICD-10 dictionary</b>
Q254	Other congenital malformations of aorta	Q254	Other congenital malformations of aorta
Q2540	Hypoplasia of aorta	No equivalent code	-
Q2541	Persistent right aortic arch	No equivalent code	-
Q2542	Overriding aorta	No equivalent code	-
Q2543	Aneurysm of sinus of Valsalva	No equivalent code	-
Q2544	Double aortic arch	No equivalent code	-
Q2545	Congenital aneurysm of aorta	No equivalent code	-
Q255	Atresia of pulmonary artery	Q255	Atresia of pulmonary artery

#### 5.3.4 Developing OPCS-4 code lists

The OPCS-4 code system is divided into chapters based predominantly on organ systems. For each EUROCAT subgroup, the OPCS-4 chapter for the equivalent organ system was searched for potentially relevant codes by myself and Sara Thomas. For example, for congenital heart defects, relevant procedures were searched for in the 'K' chapter of the OPCS-4 code system which related specifically to heart procedures. Procedures known to be associated with congenital malformations were included in the code list.

#### 5.4 Refining code lists

The first stages in the development of code lists for MCMs aimed to prioritize sensitivity in order to ensure that all potentially relevant codes were captured. Code lists were then reviewed by myself, Sara Thomas and Punam Mangtani (both of whom are clinical epidemiologists), and a consultant neonatologist (Steve Kempsey). The following types of code were reviewed and discussed:

1. Codes that could relate to non-congenital conditions (**Section 5.4.1**)
2. Codes that could relate to minor or potentially minor malformations (**Section 5.4.2**)
3. Codes for which the classification of the subgroup was unclear (**Section 5.4.3**)
4. Codes relating to MCMs with known causes (**Section 5.4.4**)

#### 5.4.1 Codes that could relate to non-congenital conditions.

Some of the codes in the initial code lists were from chapters outside of those dedicated to congenital malformations and could have been used by clinicians to encode non-congenital conditions. Other codes were from dedicated chapters for congenital malformations but were not always considered by EUROCAT to be 'true' malformations if they were associated with preterm birth or other circumstances.<sup>282</sup> The way such codes were treated is defined below.

##### **Codes from outside the dedicated chapters for congenital malformations**

All codes in the 'P' chapter of the Read code system and 'Q' chapter of ICD-10 relate to congenital malformation diagnoses. Therefore, only codes outside of these chapters were examined to determine whether they were likely to refer to non-congenital conditions. The following types of code were considered:

1. **Non-specific diagnostic Read codes from outside the 'P' chapter that referred to conditions that could result from multiple causes, including congenital causes:** These codes were retained in code lists if the most prevalent cause of the condition in the UK among this study population was likely to be congenital. If the condition was thought to have non-congenital causes more than 50% of the time then the code was removed from the code list. An example of such a condition was '*mitral stenosis*' from the 'G' chapter. Whilst mitral stenosis can occur following rheumatic fever, the consultant neonatologist advised that the prevalence of this was rare in the UK. The cause of mitral stenosis in the first few years of life was most likely to be congenital and so the code was retained.
2. **OPCS-4 codes and Read codes outside the 'P' chapter that referred to procedures, tests, monitoring of conditions, transfers of care and other administrative tasks:** These codes were included in the final code list if the procedure was known to be specific to a congenital malformation or if the procedure was likely to be carried out to correct a congenital malformation in the study population. For example '*correction of pectus excavatum*' was included as pectus excavatum is a known congenital malformation.



Conversely, '*insertion of prosthesis into chest wall*' was not included because this did not specifically refer to a congenital malformation and could be performed for other reasons in the study population (e.g. to correct disfigurement following an injury).

#### **Codes defined by EUROCAT as having other potential causes**

EUROCAT guidelines also defined conditions that could be considered MCMs but could, in some cases, be a result of preterm birth or some other cause (e.g. traumatic injury, intrauterine posture).<sup>282</sup> For some of these conditions, there were specific criteria that could be used to determine whether a condition in a particular individual was a "true" MCM or a result of another cause. For other conditions, no specific criteria were available. These were handled as follows:

1. **Conditions with specific criteria:** Patent ductus arteriosus and peripheral pulmonary artery stenosis were not considered MCMs when occurring in infants born before the 37<sup>th</sup> week of gestation (instead, their conditions were considered to be a result of prematurity).<sup>282</sup> Codes relating to such conditions were flagged and infants with such codes were then classified as having an MCM if they had a gestational age of  $\geq 37$  weeks.
2. **Conditions without specific criteria:** An example of such a condition was hydrocephaly. EUROCAT specifies that all cases should be investigated to determine if the condition could be a result of prematurity, but does not define specific criteria.<sup>282</sup> Furthermore, hydrocephalus may also be a result of traumatic injury or infection. Examining the entire medical record of all infants with such a code was not feasible and would not necessarily provide information about the cause of the condition. It was decided that codes from the 'P' chapter that described '*congenital hydrocephalus*' would be retained, conservatively. However, codes outside the P chapter that simply said '*hydrocephalus*' were excluded as they could be used to record hydrocephaly that was not congenital in origin.

#### 5.4.2 Codes that could relate to minor or potentially minor malformations

Some of the codes in the initial code list related to minor malformations and could be removed from code lists. Others were only considered minor if certain criteria defined by EUROCAT were met and had to be considered on a case-by-case basis. Finally, there were also codes that were non-specific and could have been used to encode major or minor conditions. Criteria for the inclusion or exclusion of such codes were discussed and defined as follows:

1. **Clearly related to minor malformations.** Some codes were clearly defined as being minor in EUROCAT guidelines and therefore were flagged for exclusion from code lists. An example of such a code was *'tongue tie'*.
2. **Minor only if specific criteria were met.** *'Hydronephrosis'*, for example, was only considered minor by EUROCAT when there was a pelvic dilatation of <10 millimetres but available codes did not provide this level of detail. Such codes were therefore considered based on the neonatologist's experience. If the majority of such conditions recorded in electronic health records in early childhood were likely to be major then the code was retained in the code list.
3. **Non-specific and could potentially be used to record MCMs.** The purpose of EUROCAT guidelines is to provide registries with a standardized framework to code and transmit data on MCMs to the central registry.<sup>282</sup> These guidelines have not been adopted in clinical practice, however, and so some of the ICD-10 codes defined by EUROCAT as relating to minor malformations may have been used to encode major or minor malformations in electronic health records. For example, EUROCAT specifies that the ICD-10 code *'other congenital deformities of skull, face and jaw'* should be used to encode minor malformations but this code may be used variably by clinicians to record major or minor malformations in hospital records. Such codes were discussed with the consultant neonatologist. It was agreed that clinicians were unlikely to be using these codes to refer

exclusively to minor conditions and that, to ensure that all MCMs were captured, such codes would be retained in code lists.

#### 5.4.4 Codes relating to major malformations with known causes

As described in **Section 4.4.1**, pregnancies were excluded if they resulted in an MCM that had a known cause (i.e. a chromosomal abnormality, inherited genetic mutation or a specified exogenous cause such as exposure to a known teratogen like warfarin). As there was no complete guide to define codes for such MCMs, they were defined using a combination of EUROCAT guidelines and discussion with the consultant neonatologist.<sup>283</sup> Their presence in infant records or maternal records during the antenatal period was used to exclude pregnancies from analyses (**Appendix 4**).

All BPA-modified ICD-10 codes in the Q900-999 (*chromosomal anomalies*) subgroup were used to define major malformations with known causes as well as: Q800-809 (*congenital ichthyosis*), Q810-819 (*epidermolysis bullosa*), D1810 (*lymphangioma*), D215 (*benign neoplasm of the pelvis*), D821 (*DiGeorge Syndrome*), Q860-868 (*congenital malformation syndromes due to exogenous causes, not elsewhere classified*), and the equivalent Read codes. Next, codes for syndromes with a known cause were considered. Syndromes are recognizable patterns of malformations that can be related to the same known cause such as a chromosomal abnormality, although not all syndromes fit this definition (e.g. Arnold-Chiari syndrome).<sup>282</sup> Remaining codes were identified if the consultant neonatologist advised that the majority of individuals with such a condition had a chromosomal aberration, inherited mutation or that the condition was known to be caused by a specified exogenous cause such as a particular teratogenic drug.

#### 5.5 Use of code lists to identify congenital malformations in live-born infants

Following their development and refinement, code lists were used to search the records of eligible live-born infants for evidence of MCMs. The Read code list was used to search the clinical, referral and test files in CPRD. The ICD-10 code list was then used to search all

diagnoses in the HES episode file whilst the OPSC-4 code list was used to search all procedures in the HES procedures file. Finally, ICD-10 codes were also used to identify evidence from ONS mortality data; all causes of death were examined.

Each live-born infant could have multiple records from various data sources indicating evidence of an MCM. Each infant could be classified as having an MCM in more than one anatomical subgroup but was only counted once as having evidence of any MCM. Infants with an MCM with a known cause (or a congenital infection known to cause MCMs) were identified and the related pregnancies was excluded from analyses.

As congenital malformations arise *in utero*, it is not possible to know the date on which they occurred. The date on which they were recorded was used instead. For MCMs recorded in the CPRD, this was the 'event date' recorded by the GP. In HES data, the date on which a diagnosis is made is not provided. The 'episode start date' was therefore used as the earliest alternative when using HES data. For ONS mortality data, the ONS 'death date' was used.

Of the 53,582 records of MCMs among eligible infants, 2% (n=1,057) appeared to have a recording earlier than the pregnancy's estimated delivery date in the Pregnancy Register. In such cases, either the delivery date for the pregnancy was inaccurate (and actually occurred earlier) or the recording of the MCM was inaccurate (and actually occurred later). It was not possible to know with any certainty which of these was the case. Adjusting the pregnancy delivery date would have implications on how the start of pregnancy and trimester dates were defined. Furthermore, it would involve adjusting only those pregnancies that resulted in an MCM and could result in bias. Therefore, it was decided that the delivery date would remain the same. Instead, for these records, the date that the MCM was ascertained would be adjusted to be the same as the delivery date as this is the earliest that an MCM could be recorded in the live-born infant's records.

## 5.6 Identifying antenatal diagnoses of MCMs

Vaccine safety analyses were originally planned to include MCMs identified antenatally and postnatally. Antenatal evidence of MCMs would be identified by searching for evidence in maternal records during pregnancy. The limitations of this approach, and the potential to introduce bias, were assessed by examining antenatal diagnoses and vaccine uptake for those pregnancies that did not result in a live-birth with a linked infant (**Section 8.6**). Based on results from this assessment, safety analyses were restricted to MCMs diagnosed postnatally among live-births with linked infant records.

An initial set of Read and ICD-10 codes relating to MCMs detected antenatally was provided by Sara Thomas. This was then supplemented by examining codes from the 'L' chapter that covers obstetric care; relevant conditions were added to the code list. All codes were required to specify that they related to the foetus or the pregnancy in some way so as not to be confused with evidence of the mother having an MCM herself.

Codes relating to antenatal evidence of MCMs often lacked specificity. To aid in the interpretation of evidence, codes were classified as follows:

1. **Level 1 codes were the most specific.** They included terms which described the presence of a foetal malformation (e.g. '*Fetus with central nervous system malformation*').
2. **Level 2 codes were moderately specific.** They included terms which indicated that there was a suspected foetal malformation (e.g. '*Suspect fetal spina bifida*').
3. **Level 3 codes were the least specific.** They described an abnormality that could relate to a malformation or could relate to some other abnormality of the pregnancy (e.g. '*Antenatal ultrasound scan abnormal*').

Evidence of an antenatal malformation was searched for anytime during the pregnancy and up to 8 weeks after estimated delivery date to account for any delayed recording (e.g. a GP noting

that there was antenatal evidence of a diagnosis that was then confirmed after delivery). Code lists to identify antenatal evidence of eligible MCMs in maternal records are provided in **Appendix 3**.

## 5.7 Chapter Summary

This chapter considered the key lessons from the systematic review of the methods used to identify congenital malformations in UK electronic health records. These were applied here to develop a comprehensive algorithm to identify MCMs from linked CPRD, HES and ONS mortality data. Unlike previous approaches, the methods described here include an overview of the rationale used when considering codes that are non-specific. Among Read codes, the greatest challenge was considering the inclusion/exclusion of codes that were from chapters not dedicated to congenital malformations, and which could therefore refer to non-congenital conditions. For ICD-10 codes, this was less of a challenge due to the fact that only codes from the dedicated 'Q' chapter were considered. Instead, for ICD-10 codes, the greatest challenge was the lack of granularity between codes. Unlike the EUROCAT BPA-modified ICD-10 codes, the ICD-10 codes used in HES have three digits. Furthermore, clinical coders do not follow these guidelines when coding congenital malformations. This meant that some codes could be used to record major or minor malformations. Decisions on how to handle these challenges and codes were made with the input of an experienced consultant neonatologist.

## 6. Identifying the influenza vaccination status of pregnant women

### 6.1 Introduction

This chapter describes how the influenza vaccination status was determined for each pregnancy using CPRD primary care data. The background to maternal influenza vaccination in the UK is described in **Section 1.5**. The CPRD database is described in **Section 3.1** and the general approach to data management in CPRD is described in **Section 3.7**. This chapter covers the availability of the influenza vaccine (**Section 6.2**) and the data used to identify evidence of vaccination (**Section 6.3**). Vaccination-related criteria used to exclude pregnancies from analyses on the safety of SIIV and PIIV are also described. Exclusions were grouped into those due to uncertainty in vaccination timing (**Section 6.4**) and those due to uncertainty in the type of influenza vaccine received (**Section 6.5**).

### 6.2 Annual availability of the influenza vaccine

UK guidelines for maternal influenza vaccination have varied over the last decade (**Figure 1.1**). Prior to the 2009/10 pandemic, only pregnant women in clinical risk groups were vaccinated against influenza. During the 2009/10 pandemic, all pregnant women were offered PIIV and those in clinical risk groups could also have been offered SIIV until PIIV became available.<sup>12</sup> In 2010/11, guidelines stated that all pregnant women should be offered SIIV, unless they had already received PIIV (which was available for use in the event of a shortage of SIIV).<sup>13</sup> From 2011/12 onwards, all pregnant women have been offered SIIV and PIIV has not been used.<sup>4, 13</sup>

To be eligible for inclusion in either the SIIV or PIIV safety analysis, pregnancies had to overlap with a period of influenza vaccine availability by at least one week. In the UK, SIIV becomes available as early as September each year in preparation for the seasonal influenza epidemic. Circulation of influenza can continue into March and SIIV may be offered as late as this.<sup>284, 285</sup> The period during which influenza vaccine was likely to be available (and eligible pregnancies

had to overlap with), referred to as the 'vaccination period,' was defined as follows for analyses on SIIV and PIIV:

1. **SIIV:** 1<sup>st</sup> September - 31<sup>st</sup> March for influenza seasons between 2010/2011 - 2015/16.
2. **PIIV:** 21<sup>st</sup> October 2009 (the date PIIV became available in the UK) - 31<sup>st</sup> March 2010.<sup>12</sup>

### 6.3 Evidence of vaccination in primary care records

#### **CPRD files containing vaccination evidence**

In CPRD, information on vaccinations can be found in the 'immunisation' file, 'therapy' file or 'clinical' file. In the immunisation file, immunisation type codes are used to record the vaccine type and can be used in conjunction with an immunisation status variable to determine whether the vaccine in question was given, refused or advised. In the therapy file, records are automatically created when prescriptions are generated and therefore vaccines can be assumed to have been administered when patients have a relevant product code in this file. In the clinical file, Read codes can also be used to record information about vaccination.

#### **Code lists used to identify vaccinations**

Initial immunisation type, product and Read code lists to identify records relating to influenza vaccination in maternal immunisation, therapy and clinical files were provided by Sara Thomas (a clinical epidemiologist) (**Appendix 6**). Codes were then classified by:

1. **Vaccine type:** SIIV, PIIV or unknown/unspecified type.
2. **Status:** received, refused, advised, contraindicated/not indicated, given elsewhere, adverse effects following administration.

Codes relating to the vaccine being advised or adverse effects of vaccination were not utilized because they were not necessarily indicative of the timing of vaccination. Using the above files and code lists, all vaccination records were identified for all eligible pregnant women at any time. For each woman, vaccination records were then divided into those that occurred within a vaccination period and those that occurred outside (April 1<sup>st</sup> – August 31<sup>st</sup>).



## Using evidence from the clinical file

The clinical file is considered to be the least reliable file for identifying vaccinations. This is because, unlike the immunisation and therapy files, Read codes in the clinical file tend to be less specific about whether a vaccine was given. For example, in the clinical file, Read codes such as '*consent given for seasonal influenza vaccination*' could mean a patient consented to receiving the vaccine but does not necessarily mean the vaccine was administered.

The proportion of pregnant women for whom the clinical file was the sole source of evidence of vaccine receipt evidence across a particular vaccination period was very low (0.5%, n=550) (**Table 6.1**). An examination of the Read codes used among these women indicated that just 21.2% specified a vaccine had been given whilst the rest were non-specific (**Table 6.2**).

However, because only a small proportion of women had evidence of vaccine receipt from just the clinical file, it was judged that the overall potential for misclassification of vaccination status by including these women was low.

**Table 6.1 - Source of vaccination receipt evidence for each woman and vaccination period.**

<b>File(s) from which vaccination receipt evidence was identified</b>	<b>Number of women (%)</b>
Therapy file only	727 (0.6)
Immunisation file only	81,095 (67.4)
Clinical file only	550 (0.5)
Therapy and immunisation files	17,828 (14.8)
Therapy and clinical files	234 (0.2)
Immunisation and clinical files	15,278 (12.7)
Therapy, immunisation and clinical files	4,559 (3.8)

**Table 6.2 - Read terms used among women whose only evidence of vaccination receipt across a vaccination period came from the clinical file.**

<b>Read term</b>	<b>Number of women with Read code (%)</b>
Consent given for pandemic influenza vaccination	25 (4.2)
Consent given for seasonal influenza vaccination	24 (4.1)
First pandemic influenza vaccination	11 (1.9)
Influenza vacc consent given	80 (13.6)
Influenza vaccination	294 (49.8)
PANDEMRIX - first influenza A (H1N1v)2009 vaccination given*	125 (21.2)
Seasonal influenza vaccination	23 (3.9)
[V]Flu - influenza vaccination	7 (1.2)
[V]Influenza vaccination	1 (0.2)

\*The most specific vaccination receipt code. Remaining codes were non-specific in terms of whether or not the vaccine was received.

## Deciding on the use of evidence from multiple files

Within a vaccination season, it was possible for a woman to have multiple records indicating a vaccine had been received and for these to occur on different days, in different files and relate to different types of influenza vaccine (**Table 6.3**). The earliest record of vaccination receipt within a vaccination period was considered the most accurate vaccination date for the woman, as subsequent records in the season could indicate re-recording of a previously received vaccine. However, if a woman's earliest evidence was recorded in the clinical file and was followed by a later record in the more reliable immunisation or therapy file, it was not clear which information should be used. As the gestational age at the time of vaccination was critical in the planned safety analyses, this was explored.

**Table 6.3 – Scenarios of conflicting influenza vaccination receipt records in pregnant women, within a single vaccination period.**

Woman	Vaccination Period	Vaccination Date	Flu Vaccine Type	File	Summary of evidence for each woman, by vaccination season
1	2010/11	01 Nov 2010	Seasonal	Therapy	<b>Woman 1</b> has two vaccine receipt records in the <b>2010/11</b> period. They are both from the therapy file. The earliest record occurs in November 2010. Both records relate to SIIV.
1	2010/11	01 Jan 2011	Seasonal	Therapy	
1	2011/12	01 Feb 2012	Seasonal	Therapy	<b>Woman 1</b> has two vaccine receipt records in the <b>2011/12</b> period. They are from the therapy and immunisation files but occur on the same date. One record indicates an SIIV, the other record does not specify the vaccine type.
1	2011/12	01 Feb 2012	Unspecified	Immunisation	
2	2013/14	15 Sept 2013	Unspecified	Clinical	<b>Woman 2</b> has three vaccine receipt records in the <b>2013/14</b> period. The earliest comes from the clinical file but a month later she has two further records in the immunisation file. There is one record relating to an SIIV, the other two records do not specify the vaccine type.
2	2013/14	15 Oct 2013	Seasonal	Immunisation	
2	2013/14	15 Oct 2013	Unspecified	Immunisation	
3	2010/11	01 Dec 2010	Pandemic	Clinical	<b>Woman 3</b> had two vaccine receipt records in the <b>2010/11</b> period. They are both from the clinical file on the same day. One record specifies a PIIV, the other an SIIV.
3	2010/11	01 Dec 2010	Seasonal	Clinical	
4	2010/11	01 Dec 2010	Unspecified	Clinical	<b>Woman 4</b> has two vaccine receipt records in the <b>2010/11</b> period. They are both from the clinical file, with the earliest in December. Neither record specifies the type of vaccine used.
4	2010/11	01 Jan 2011	Unspecified	Clinical	

**Records relating to vaccination were identified from maternal therapy, immunisation and clinical files. A woman could have multiple records indicating a vaccine was received on different dates and from different files. The influenza vaccine type could also be inconsistent across the vaccination period.**

Across a vaccination period, almost 13% of women had evidence of vaccine receipt in both the immunisation and clinical files (n=15,278) whilst fewer women had evidence in both the therapy and clinical file (0.2%; n=234) or all three files (3.8%; n=4,559) (Table 6.1). However, very few of the women with vaccination evidence from multiple files had their earliest vaccination evidence from the clinical file. Among those with evidence in the immunisation and clinical files, 2.8% had their earliest evidence in the clinical file (n=432) and over 75% of these had specific Read codes that indicated a vaccine had been given (Table 6.4 & 6.5). Just 3.4% (n=8) of those with evidence in the therapy and clinical files had their earliest evidence in the clinical file and this was even lower for those with evidence from all three files (0.5%; n=23)(Table 6.4). These data demonstrated that the earliest evidence of vaccination was most likely to be recorded in the therapy or immunisation file and that few women had their earliest evidence in the clinical file. Treating all files equally and choosing the earliest evidence of vaccination was, therefore, unlikely to introduce considerable misclassification in vaccination timing.

**Table 6.4 - Source of the earliest evidence of vaccine receipt among women with evidence of receipt from multiple files.**

All files in which a woman had evidence of vaccine receipt	File(s) earliest evidence of vaccination receipt came from						
	No. of women (%)						
	Therapy	Immunisation	Clinical	Therapy & Clinical	Therapy & Immunisation	Immunisation & Clinical	Therapy, Immunisation & Clinical
Therapy & immunisation (n=17,828)	583 (3.3)	177 (1.0)	-	-	17,068 (95.7)	-	-
Therapy & clinical (n=234)	63 (26.9)	-	8 (3.4)	163 (69.7)	-	-	-
Immunisation & clinical (n=15,278)	-	956 (6.3)	432 (2.8)	-	-	13,890 (90.9)	-
Therapy, immunisation & clinical (n=4,559)	72 (1.6)	7 (0.2)	23 (0.5)	9 (0.2)	115 (2.5)	23 (0.5)	4,310 (94.5)

**Table 6.5: Read terms used among women with evidence of vaccination in the immunisation and clinical file but whose earliest evidence of vaccination receipt came from the clinical file.**

<b>Read term</b>	<b>Number of women with Read code (%)</b>
Consent given for pandemic influenza vaccination	3 (0.7)
Consent given for seasonal influenza vaccination	6 (1.4)
First pandemic influenza vaccination	19 (4.4)
Influenza vacc consent given	11 (2.5)
Influenza vaccination	56 (12.9)
PANDEMRIX - first influenza A (H1N1v)2009 vaccination given*	334 (76.8)
PANDEMRIX - second influenza A (H1N1v) 2009 vaccination given*	1 (0.2)
Seasonal influenza vaccination	4 (0.9)
[V]Influenza vaccination	1 (0.2)

\*Most specific evidence of vaccination

#### 6.4 Exclusion criteria for pregnancies with uncertainty in vaccination timing.

Determining the trimester of vaccination was crucial for the work described in this thesis as most MCMs are likely to occur in the first trimester, when the majority of organogenesis occurs. In **Section 4.3**, a number of pregnancy-related exclusion criteria were described. The purpose of some of these was to minimize the potential for misclassification of the trimester of vaccination when pregnancy timings were uncertain. Here, exclusions to minimize the potential for misclassification when the timing of vaccination was uncertain are described.

##### **1. Vaccine refusal, contraindication or non-indication on the same date as the earliest evidence of vaccine receipt within a vaccination period.**

Within a vaccination period, all records relating to vaccination refusal, contraindication or non-indication were identified. If a woman's earliest record of vaccination receipt coincided with such a record it was impossible to know whether or not she had received the vaccine. Evidence of such a record before or after the earliest evidence of receipt did not constitute a conflict because a woman could accept or be given a vaccine at a later date or could decline vaccination if she had been vaccinated earlier in the season. Pregnancies belonging to women that had concurrent records of vaccination receipt and refusal, contraindication or non-indication were excluded.

## **2. Vaccination evidence outside of the vaccination period.**

Records relating to vaccination between the 1<sup>st</sup> April and 31<sup>st</sup> August each year were identified. Evidence of vaccination between April and August was considered to be a retrospective recording of a vaccine that had been received in the prior vaccination season. Pregnancies were excluded if the only evidence of a vaccination occurred between vaccination periods because it was not possible to determine when the vaccination had occurred. If there was evidence of vaccination within the vaccination period and then further vaccination evidence between April and August, the pregnancy was not excluded and the earliest evidence of vaccination within the vaccination period was used.

## **3. Evidence of vaccination given outside the practice.**

Evidence of the vaccine being given outside the practice was established using information in the immunisation and/or clinical files. Although GPs are required to record vaccinations occurring outside of the practice, it was not possible to know when these occurred.<sup>73</sup> For this reason, it was decided that if any such evidence occurred within the period of the pregnancy, the pregnancy would be excluded. It was considered possible that women with such evidence before their pregnancy could continue to receive their vaccinations elsewhere. Preliminary checks of the data indicated that among 1,222 pregnancies with such evidence anytime before their estimated start date, over 60% had this evidence in the 2 years prior. Excluding pregnancies with evidence anytime before the estimated start date would not significantly reduce the number of available pregnancies and so it was decided that a conservative approach would be taken and all such pregnancies excluded. Pregnancies with a record of vaccination given elsewhere in the year after the pregnancy had ended were also excluded to account for any retrospective recording by GPs.

## **4. Vaccination receipt records before or after the pregnancy.**

It was possible for a woman's earliest evidence of vaccination within a vaccination period to occur before or after her pregnancy. Vaccination could occur before the pregnancy if the woman was in a clinical risk group or was a healthcare worker and was offered the vaccine

regardless of her pregnancy status. Alternatively, it was possible that the pregnancy start date was inaccurate and the pregnancy occurred earlier. Therefore, it was not possible to be certain that the vaccine hadn't been received during pregnancy and such pregnancies were excluded from analyses. To account for imprecision in the timing of the start of pregnancy and the fact that vaccination occurring shortly before pregnancy could have residual effects that lasted into the first trimester, pregnancies were included in a sensitivity analysis if a vaccine had been received in the 4 weeks prior to the pregnancy start date.

Vaccination could occur after a pregnancy if the woman had some other reason to be offered the vaccine such as being in a clinical risk group or being a healthcare worker. It was unclear why such women would not be offered the vaccine during their pregnancy, instead. Although the earliest vaccination receipt record in each season was used, it was also possible that a vaccination record occurring after pregnancy could be a retrospective recording of a vaccination that occurred during pregnancy. Again, because it was not possible to know whether and when such pregnancies were truly unvaccinated, they were excluded from analyses.

#### **5. Pregnancies that overlapped with two vaccination periods and received a vaccine in both.**

Pregnancies could overlap with two vaccination periods and have evidence of vaccination in both. Four scenarios were considered:

The first involved two vaccination records during pregnancy, one in each season (**Figure 6.1A**). Whilst it was possible that a vaccine was given in both seasons, it was also possible that the second vaccination was a retrospective recording by the GP. To account for the possibility that the pregnancy had been vaccinated twice, one strategy would be to examine effect modification between vaccinations in different trimesters. However, the number of such pregnancies was too low for this and so these pregnancies were excluded.

The second scenario involved a vaccination record before pregnancy in the first season and a further vaccination record during pregnancy in the second season (**Figure 6.1B**). The third

scenario related to those pregnancies that had a vaccine record during their pregnancy in the first season and another after the pregnancy in the second season (**Figure 6.1C**). The reasons for a vaccination record occurring before the start of a pregnancy or after the end of a pregnancy are described in the previous section. It was not possible to know whether such pregnancies had received two vaccines or not and so they were excluded.

The final scenario involved one vaccine being given in the first season before the pregnancy and one vaccine being given in the second season after the pregnancy (**Figure 6.1D**). The reasons for this occurrence were a combination of those described in the previous section. As it was not possible to be certain that such pregnancies were unvaccinated, they too were excluded.



Figure 6.1 – Scenarios for pregnancies overlapping with two vaccination periods, with vaccination receipt records in both.

## 6.5 Exclusion criteria for pregnancies with uncertain vaccine type

As described in **Section 1.6.2**, one of the key limitations of the available safety evidence for maternal influenza vaccination with respect to MCMs was the small number of studies examining SIIV alone. To minimize the possibility that analyses examining SIIV included pregnant women who had received PIIV (and vice versa for the analysis on PIIV safety), pregnancies were excluded if there was any uncertainty in the type of influenza vaccine received.

Uncertainty in the type of influenza vaccine received could occur because of vaccination codes that did not specify whether the vaccine given was SIIV or PIIV. Furthermore, women could have multiple records within a vaccination period indicating a vaccine was received and the type of vaccine given was not always consistent (**Table 6.3**). Uncertainty about the vaccine type had to be considered in the context of the vaccines available and recommended for pregnancies in a particular vaccination period. The scenarios considered, and the exclusion criteria developed, are described below.

### **1. Uncertainty around the type of influenza vaccine received for those pregnancies potentially eligible for the safety analysis of SIIV**

To be potentially eligible for the seasonal vaccine safety analyses, women had to be pregnant for at least one week in the 2010/11 vaccination period or a subsequent vaccination period.

In 2010/11, SIIV was offered to all pregnant women in any trimester but PIIV was still available and some may have received PIIV if stocks of SIIV were low (**Figure 1.1**).<sup>12</sup> Pregnancies were therefore excluded from this analysis if there was any evidence PIIV had been received or if there was only evidence of an unspecified vaccine type across the season (as it was not possible to know if the woman received PIIV).

In seasons after 2010/11, only SIIV was offered to pregnant women. A small number of pregnancies that had evidence of PIIV were excluded. It was thought these records could



relate to the GP re-recording that the woman had received PIIV during the pandemic or that these were data entry errors. Unspecified vaccine type in the years after 2010/11 was thought to relate to SIIV (as PIIV was no longer available) and was not used as an exclusion criterion.

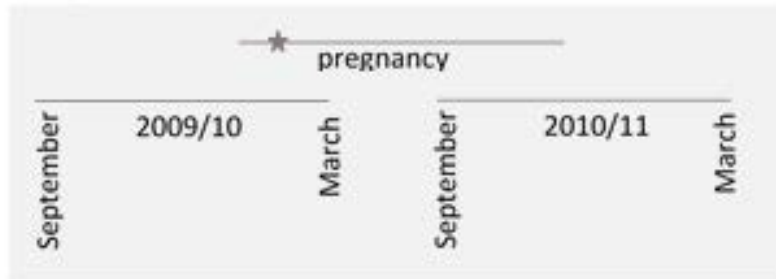
## **2. Uncertainty around the type of influenza vaccine received for those pregnancies potentially eligible for the safety analysis of PIIV**

To be potentially eligible for pandemic vaccine safety analyses, women had to be pregnant for at least one week in the 2009/10 vaccination period. During the 2009/10 pandemic, PIIV was available for all pregnant women but some women, such as those who were in clinical risk groups and healthcare workers, may also have been offered SIIV until PIIV became available (**Figure 1.1**).<sup>12</sup> Pregnancies were excluded from analyses of the safety of PIIV if there was any evidence SIIV had been received within the season or if there was only evidence of an unspecified vaccine type across the season (as it was not possible to know if this was SIIV).

## **3. Uncertainty around the type of influenza vaccine received for those pregnancies potentially eligible for either SIIV or PIIV safety analyses**

Pregnancies that overlapped with both 2009/10 and 2010/11 vaccination periods by a week were potentially eligible for both the SIIV and PIIV safety analysis. In addition to following the exclusion criteria set out for pregnancies overlapping two vaccination periods (**Figure 6.1**), uncertainty in the type of vaccine received was also considered. Pregnancies that overlapped with both 2009/10 and 2010/11 were excluded from SIIV analyses if there was any evidence of a vaccine being received in the 2009/10 season (**Figure 6.2A**). Pregnancies overlapping both seasons were excluded from the PIIV analyses if there was any evidence of a vaccine being received in the subsequent 2010/11 season (**Figure 6.2B**). Pregnancies could be included in both analyses if there was no evidence of a vaccine being received in either (**Figure 6.2C**).

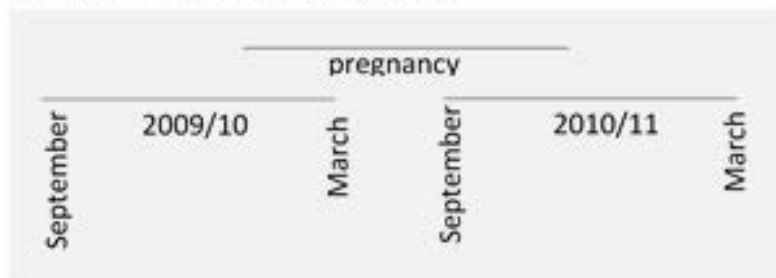
**A. Pregnancies included in the pandemic vaccine safety analysis but excluded from the seasonal vaccine safety analysis**



**B. Pregnancies included in the seasonal vaccine safety analysis but excluded from the pandemic vaccine safety analysis**



**C. Pregnancies included in both seasonal vaccine safety and pandemic vaccine safety analyses.**



★ = vaccination

**Figure 6.2 – Additional exclusion criteria for pregnancies that overlapped with both the 2009/10 and 2010/11 seasons.** Pregnancies that overlapped with the 2009/10 and 2010/11 seasons were considered for pandemic vaccine safety analyses and seasonal vaccine safety analyses as described above. It should be noted that pregnancies where a vaccine was received before or after the start or end of pregnancy were excluded based on criteria described in **Section 6.4.5**.

## 6.6 Summary of vaccination exclusion criteria

In summary, pregnancies were excluded from vaccine safety analyses if:

1. They did not have at least one week of overlap with a period in which SIV or PIV was available.
2. The earliest evidence of vaccination receipt coincided with a record indicating non-receipt.
3. The only evidence of a vaccine being received occurred between April and August, after the vaccination period had ended.
4. There was evidence of the vaccine being given elsewhere anytime before the pregnancy, during the pregnancy, or in the year after the pregnancy.
5. There was evidence of a vaccination occurring within a vaccination period but before or after pregnancy.
6. The pregnancy overlapped with two vaccination periods and there was evidence that a vaccine had been received in both.
7. The pregnancy was potentially eligible for the pandemic analysis but had evidence of receiving SIV or no information about the vaccine type received.
8. The pregnancy was potentially eligible for the seasonal analysis but had evidence of receiving PIV or no information about the vaccine type received.

## Results Section

The findings of the work conducted in this thesis are presented in this section.

**Chapter 7** addresses **Objective 3** and examines the value of CPRD, HES and ONS data in identifying MCMs among live-born infants. It also addresses **Objective 4** and compares the prevalence of MCMs in these data with external data sources.

**Chapter 8** presents the results from a large, historical cohort study that examined the association between SIV given during pregnancy and MCMs in the first year of life. Analyses are stratified by trimester. This chapter addresses **Objective 5**.

**Chapter 9** presents the results from a historical cohort study that examined the association between PIV given during pregnancy and MCMs in the first year of life. Analyses are stratified by trimester. The chapter also describes the relationships observed between confounding factors, maternal influenza vaccination and MCMs in the context of what is known from the literature. This chapter addresses **Objective 6**.

## 7. The ascertainment of major congenital malformations in linked UK electronic health records

### 7.1 Introduction

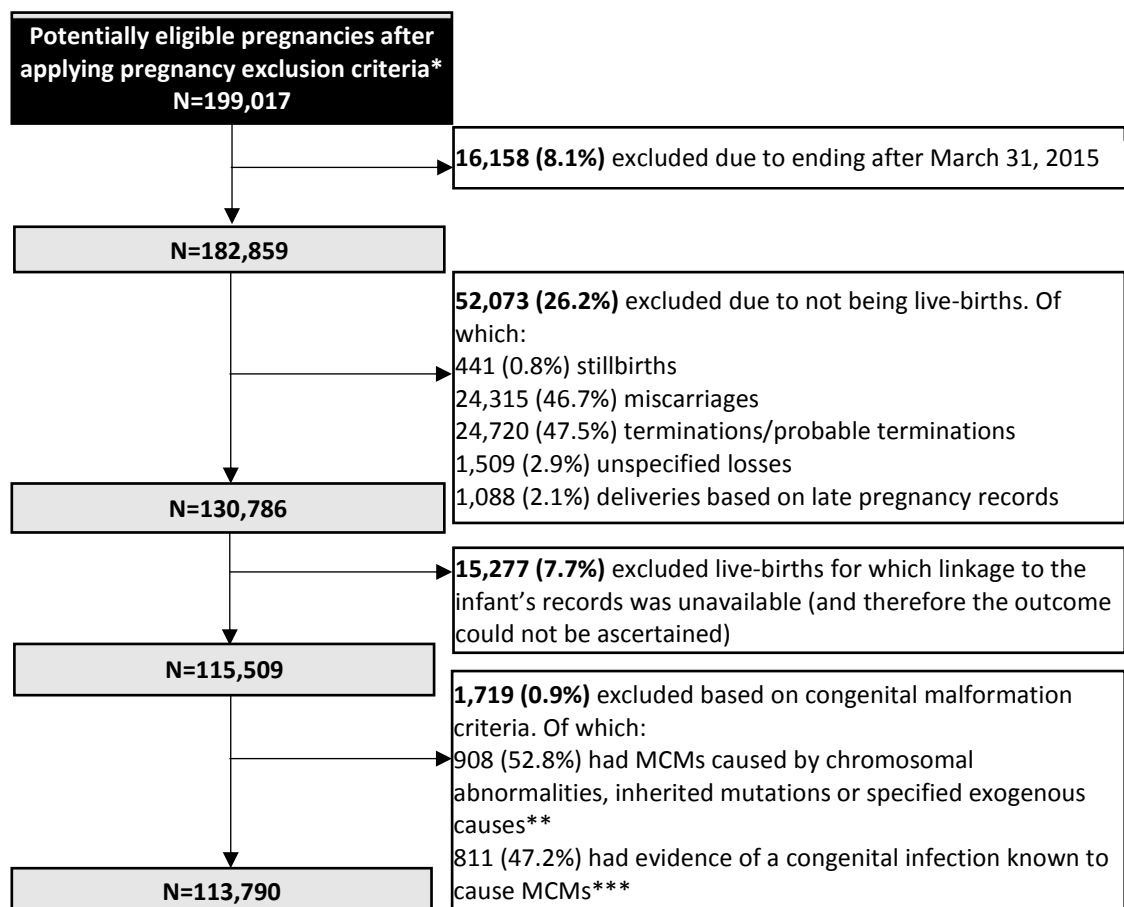
A systematic review of the methods used to identify congenital malformations in UK electronic health records (**Chapter 2**) informed the development of an algorithm to identify MCMs in linked primary care records, hospital admissions and death certificates (**Chapter 5**). In this chapter, the algorithm was used to identify MCMs among live-born infants and **Objectives 3 & 4** were addressed.

The value of linked data in ascertaining individuals with MCMs was first assessed. The prevalence of MCMs in stand-alone and linked data sources was compared and the agreement between data sources, as well as their unique contribution, was examined (**Objective 3**). The prevalence of MCMs identified from the data sources used in this thesis was then compared with the prevalence from a published study using THIN (another population-based database of electronic primary care records in the UK) and English EUROCAT registries (**Objective 4**).

The chapter begins with an overview of the way in which the study population was derived in **Section 7.2**. In **Section 7.3**, which is presented in the form of a manuscript prepared for submission, the value of linked data in ascertaining individuals with MCMs is explored (**Objective 3**). In **Sections 7.4-7.5**, prevalence comparisons with external data sources are presented (**Objective 4**). Results from the chapter are summarized in **Section 7.6**.

## 7.2 Deriving the eligible study population

After applying the pregnancy exclusion criteria described in **Chapter 4**, there were 199,017 potentially eligible pregnancies that ended between January 1, 2009 and March 31, 2016. All infants delivered were eligible for HES and ONS linkage. For the studies described in this chapter, all infants were required to have the potential for a year of follow-up. Linked data were available until March 31, 2016 and so this was achieved by excluding pregnancies delivering after March 31, 2015. The study population was then restricted to live-birth pregnancies with a linked infant. Finally, to align with future exclusion criteria for vaccine safety studies, pregnancies were excluded if there was evidence of a congenital infection known to be associated with MCMs or evidence of an MCM with a known cause such as a chromosomal abnormality. The derivation of the study population is summarized in **Figure 7.1**.



**Figure 7.1 - Deriving the study population to assess the ascertainment of MCMs in different data sources.** \*The initial population of 199,017 pregnancies included those ending between January 1, 2009 and March 31, 2016. All live-born infants were eligible for linkage to HES and ONS. This flow diagram includes all potentially eligible pregnancies, in comparison to Figure 1 of the paper which presents only those pregnancies ending in live-births; \*\*See Section 4.4.1; \*\*\*See Section 4.4.2. Abbreviations: MCM, Major Congenital Malformation; HES, Hospital Episode Statistics; ONS, Office for National Statistics.

## RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

### SECTION A – Student Details

Student ID Number	1300677	Title	Miss
First Name(s)	Maria		
Surname/Family Name	Peppa		
Thesis Title	The safety of influenza vaccination in pregnancy: Examining major congenital malformations as potential adverse outcomes using UK electronic health records		
Primary Supervisor	Professor Punam Mangtani		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

### SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

\*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

### SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Pharmacoepidemiology & Drug Safety
Please list the paper's authors in the intended authorship order:	Maria Peppa, Caroline Minassian, Punam Mangtani, Jemma L Walker, Stephen T Kempley, Nick J Andrews, Sara L Thomas

Stage of publication	<b>Not yet submitted</b>
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#### **SECTION D – Multi-authored work**

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This study was conceptualized and designed by P Mangtani, S Thomas, C Minassian and myself. I developed initial code-lists for MCMs and these were discussed and agreed with S Kempley, P Mangtani and S Thomas. I carried out the data management and analyses involved, with frequent discussion with co-authors to ensure agreement. I drafted the manuscript and revised it following comments from co-authors.
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#### **SECTION E**

<b>Student Signature</b>	Maria Peppa
<b>Date</b>	19.03.2020

<b>Supervisor Signature</b>	Punam Mangtani
<b>Date</b>	20.03.2020



### 7.3 Paper 2: Identifying major congenital malformations in anonymised UK electronic health records: the value of primary care, hospital admissions and mortality data.

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## **Abstract**

### **Purpose**

Anonymised UK electronic primary care data are increasingly used to identify major congenital malformations in post-licensure safety studies of drugs and vaccines given in pregnancy.

However, these data may under-record major malformations identified during hospital admissions or after infant death. This study explored the value of different UK data sources in identifying congenital malformations.

### **Methods**

Live-born singleton infants delivered between 2009 and 2015 and recorded in the UK Clinical Practice Research Datalink were selected. The prevalence of major malformations in the year after delivery was calculated using stand-alone and linked records from primary care, hospitalisations and death certificates. The proportion of infants with a recorded major malformation in multiple and single data sources was calculated to assess the agreement and contribution of each source.

### **Results**

The study population included 113,790 infants of whom 7,931 (7%) had a major malformation recorded in at least one data source in the year after delivery. The prevalence of major malformations in the year after delivery was 265.7/10,000 person-years (95% CI, 256.0-275.8) in the primary care data and 745.8/10,000 person-years (95% CI, 729.6-762.4) in linked data. Among infants with a major malformation recorded in the year after delivery, 20% had evidence of their condition in both their primary care and hospitalisation records, 65% had evidence exclusively in hospitalisation data and 15% had evidence solely in their primary care records. Just 0.2% had evidence recorded on a death certificate.

### **Conclusions**

Stand-alone Clinical Practice Research Datalink primary care data under-ascertain major congenital malformations. Linkage to hospitalisation data should be considered to maximize their ascertainment.

## Introduction

Anonymised electronic health records are frequently used to conduct post-marketing safety assessments of drugs and vaccines used during pregnancy.<sup>175, 286</sup> As they often cover large populations, they are well-suited to the examination of rare outcomes such as major congenital malformations (MCMs).<sup>192, 215</sup> The ability to link electronic health records from different health service settings further increases their potential to ascertain such conditions.<sup>126, 177</sup>

In the UK, safety studies examining MCMs as an outcome have relied on stand-alone primary care databases and linkage to hospitalisation or mortality data has not been explored. Whilst it is a requirement for information about hospitalisations and deaths to be transmitted to general practices, this can be delayed or incompletely recorded in the electronic primary care record which could result in the under-ascertainment of MCMs.<sup>287</sup> Indeed, several studies have demonstrated this to be the case for other clinical outcomes in stand-alone primary care data compared to hospitalisation data.<sup>288-291</sup> Under-ascertainment, if differential by exposure status, can bias effect measures and lead to incorrect conclusions about the safety of the drugs or vaccines examined. More broadly, under-ascertainment can result in underestimates of the burden of disease which can lead to insufficient commissioning of necessary health services.

This open cohort study used UK Clinical Practice Research Datalink (CPRD) primary care data linked to hospitalisation and mortality data to compare the prevalence of MCMs in stand-alone and linked data sources in the year after delivery. The agreement between data sources and the unique contribution of each was quantified. Finally, to establish the value of different follow-up periods in ascertainment, we examined the cumulative ascertainment of MCM records after delivery and until the end of the study period (which ran from January 1, 2009 – March 31, 2016) in stand-alone CPRD and stand-alone HES.

## Methods

### Data Sources

This study was conducted using anonymised, longitudinal primary care data from CPRD GOLD (referred to as CPRD) linked to hospitalisation data from the Hospital Episode Statistics (HES) database and Office for National Statistics (ONS) mortality data. The CPRD/London School of Hygiene and Tropical Medicine Pregnancy Register was used to identify the study population.<sup>255</sup>

At the time of the study, CPRD contained the medical records for 7% of the UK population registered with a general practice and was considered representative in terms of age, sex and ethnicity.<sup>126</sup> Upon joining a practice, data are captured until the patient dies, leaves the practice or the practice ends data collection for CPRD. Clinical data, including diagnoses and procedures, are recorded using Read codes based on consultations at the practice or information relayed from hospitals and specialist units.<sup>126</sup> Diagnostic validity has been shown to be good, including for MCMs.<sup>180, 192, 194, 292, 293</sup>

Of the English practices contributing primary care data to CPRD, 75% are linked to HES and ONS data.<sup>126</sup> Patients with linked data are considered to be broadly similar to those in the whole of CPRD.<sup>253, 254</sup> HES data include diagnoses and procedures, recorded using the International Classification of Diseases (ICD-10) and the Classification of Surgical Operations and Procedures (OPCS-4) coding, respectively.<sup>177</sup> ONS data contain the underlying and contributory causes of death, recorded using ICD-10. Follow-up in HES and ONS ends when the patient dies and is unaffected by the patient leaving the CPRD practice or the practice ending data collection.

The Pregnancy Register contains all pregnancy episodes identified in CPRD, and their outcomes, for women aged 11-49 years.<sup>255</sup> Pregnancies resulting in a live-birth delivery are linked to infant records for those infants registered at the same practice as their mother. Validation against

electronic maternity records in HES has shown most pregnancies to be well-captured in the Pregnancy Register.<sup>255</sup>

### **Study Population**

We selected live-born singletons delivered between January 1, 2009 and March 31, 2015 and eligible for HES and ONS linkage. Infants had to be born to mothers registered at an up-to-standard practice (a research quality criterion defined by CPRD)<sup>126</sup> at least six months before the start of pregnancy. As the MCMs of interest in this study were those likely to be assessed in safety studies, infants were excluded if they had a malformation due to known causes (e.g. a chromosomal abnormality).

### **Identifying MCMs**

The EUROCAT classification system was used to develop Read, ICD-10 and OPCS-4 code lists for MCMs which were subsequently reviewed by a consultant neonatologist (SK) (these are available at <https://datacompass.lshtm.ac.uk/1630/>).<sup>86, 282</sup> Codes which could be used to encode major or minor malformations (e.g. '*unspecified congenital malformation of limbs*') were retained to ensure all MCMs were captured. Codes that could potentially relate to non-congenital conditions (e.g. '*pulmonary valve disorders*') were retained if it was likely that they referred to an MCM in the majority of infants.

EUROCAT further classifies MCMs by the anatomical system affected.<sup>86, 282</sup> Subgroups were defined for heart, limb, genital, urinary, nervous system, respiratory, digestive, abdominal, orofacial, eye, and ear, face and neck malformations.<sup>86, 282</sup> MCMs that were not classified by EUROCAT as belonging to one of these subgroups, as well as undefined malformations (e.g. '*congenital anomaly not otherwise specified*'), were categorized as 'other' MCMs. Code lists were then used to search clinical, referral and test files in the CPRD data, episode and procedure files in HES, and all causes of death in ONS.

## **Statistical analysis**

### *Comparing MCM prevalence in stand-alone and linked data*

The number of infants with evidence of an MCM in the year after delivery was first ascertained in stand-alone CPRD, stand-alone HES and stand-alone ONS data. Prevalence calculations for stand-alone data sources were independent and follow-up was defined separately for each of these to reflect their maximum potential for ascertainment. Follow-up started at delivery and, for CPRD, ended at the earliest of: the date the infant left the practice or died, the date the practice last provided data to CPRD or one year after delivery. For stand-alone HES and stand-alone ONS, follow-up ended at the earliest of: the date the infant died or one year after delivery. Prevalence per 10,000 person-years was calculated alongside 95% confidence intervals. This was repeated for linked CPRD and HES (CPRD-HES) data as well as for linked CPRD, HES and ONS (CPRD-HES-ONS). Follow-up in linked data ended when the infant died or a year after delivery. Prevalence ratios (PRs) were then calculated to compare the prevalence in stand-alone HES with that in stand-alone CPRD and the prevalence in CPRD-HES-ONS with that in stand-alone CPRD and stand-alone HES.

### *Assessing agreement and unique contributions of data sources in MCM ascertainment*

To assess agreement in the year after delivery, the proportion of infants with an MCM that had evidence in two or more data sources was calculated. The proportion of infants with evidence exclusively in CPRD, HES or ONS was then calculated to assess the unique contributions of individual data sources. For this analysis, to ensure the opportunity to ascertain MCMs was the same across all three data sources, the same follow-up criteria were used in each of them.

The start of follow-up was delivery and follow-up ended a year after or earlier if the patient died, left the practice or the practice ended data collection. To assess any changes in agreement over time, the analysis was repeated with follow-up extended up to the end of the study period (March 31, 2016).

*Assessing the proportion of infants with non-specific evidence of MCMs in different data sources: Non-specific limb malformation codes as an example.*

We noted that several Read and ICD-10 codes for limb malformations were non-specific and could potentially be used to record major limb malformations, minor limb malformations or even limb conditions that were not congenital in origin (Read and ICD-10 codes considered to be non-specific are detailed in **Supplementary Tables 1-2**). We used the major limb malformation subgroup as an example to assess the extent to which infants only had non-specific evidence of their condition in the different data sources.

All Read and ICD-10 codes for limb malformations, recorded in the year after delivery, were identified in the study population. Follow-up was standardized across data sources as described earlier. The proportion of infants that only had non-specific limb malformation codes and no additional specific codes for major limb malformations was calculated for those that had evidence of their condition exclusively in HES, exclusively in CPRD, or in both.

*Assessing the cumulative ascertainment of MCM from delivery*

For each infant with an MCM, we identified the earliest recording of an MCM in stand-alone CPRD and stand-alone HES during the study period (January 1, 2009 – March 31, 2016). For each data source, we established the cumulative ascertainment of MCMs over the course of the study period as well as the proportion of diagnoses that were identified at delivery and by one year of age.

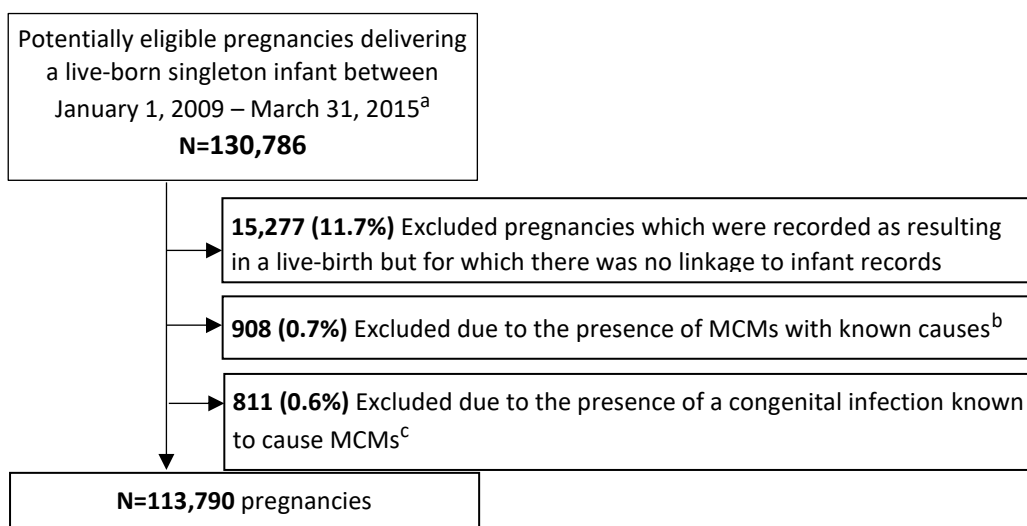
**Ethics**

Approval for the study protocol was received from the Independent Scientific Advisory Committee of the Medicines & Healthcare Products Regulatory Agency (reference 17\_040RA) and made available to the reviewers. Institutional ethical approval was also received (reference 13720). In accordance with CPRD guidelines, results were suppressed when fewer than five patients were described in order to prevent deductive disclosure of patient identities.

## Results

### Study Population

We identified 113,790 eligible live-born singleton infants for inclusion in the study (**Figure 1**). The majority of infants were male (51.4%) and of white ethnicity (82.9%) (**Table 1**). Available follow-up time varied by data source. In stand-alone CPRD, 86% of infants had a full year of follow-up compared to 99.9% in stand-alone HES and linked data. In total, 7% (n=7,931) of infants had an MCM recorded in at least one data source in the year after delivery.



**Figure 1 - Identifying the eligible study population.** <sup>a</sup>Live-born infants were born to mothers registered at up-to-standard practices at least six months before the start of pregnancy. Infants were eligible for HES and ONS linkage. <sup>b</sup>Chromosomal anomalies (e.g. Down syndrome), heritable conditions (e.g. polycystic kidney disease), or specified exogenous causes (e.g. foetal alcohol syndrome). <sup>c</sup>Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Parvovirus, Varicella-zoster, Syphilis, HIV.



**Table 1 - Characteristics of infants in the study population.**

	All infants N=113,790 (column %)	Infants with evidence of an MCM in at least one data source in the year after delivery N=7,931 (row %)
<b>Sex of infant</b>		
Male	58,447 (51.4)	4,144 (7.1)
Female	55,343 (48.6)	3,787 (6.8)
<b>Ethnicity of infant</b>		
White	94,364 (82.9)	6,446 (6.8)
South Asian	6,880 (6.1)	617 (9.0)
Black	3,372 (3.0)	259 (7.7)
Other	1,994 (1.8)	146 (7.3)
Mixed	4,192 (3.7)	336 (8.0)
Unknown	2,988 (2.6)	127 (4.3)
<b>Index of Multiple Deprivation quintile<sup>a</sup></b>		
1 (Least deprived)	24,053 (21.1)	1,746 (7.3)
2	22,227 (19.5)	1,614 (7.3)
3	22,035 (19.4)	1,503 (6.8)
4	23,088 (20.3)	1,500 (6.5)
5 (Most deprived)	22,387 (19.7)	1,568 (7.0)
<b>Geographic region</b>		
North East	2,801 (2.5)	197 (7.0)
North West	17,112 (15.0)	1,330 (7.8)
Yorkshire & The Humber	2,601 (2.3)	165 (6.3)
East Midlands	1,999 (1.8)	84 (4.2)
West Midlands	12,646 (11.1)	1,258 (10.0)
East of England	12,156 (10.7)	877 (7.2)
South West	14,358 (12.6)	857 (6.0)
South Central	17,083 (15.0)	1,153 (6.8)
London	17,572 (15.4)	992 (5.7)
South East Coast	15,462 (13.6)	1,018 (6.6)
<b>Year of birth</b>		
2009	19,946 (17.5)	1,180 (5.9)
2010	20,281 (17.8)	1,384 (6.8)
2011	19,739 (17.4)	1,353 (6.9)
2012	19,592 (17.2)	1,361 (7.0)
2013	16,892 (14.8)	1,291 (7.6)
2014	14,320 (12.6)	1,128 (7.9)
2015	3,020 (2.7)	234 (7.8)

<sup>a</sup>Deprivation at the maternal household level was used except for 0.07% (n=76) of infants where this was unavailable and practice-level deprivation was used. Abbreviations: MCM, major congenital malformation.

## Prevalence comparisons between stand-alone and linked data

### HES and CPRD

The prevalence of MCMs in HES data in the year after delivery was 630 per 10,000 person-years (95% CI, 615.2-645.2) whereas in stand-alone CPRD it was 265.7 (95% CI, 256.0-275.8), a prevalence ratio (PR) of 2.4 (95% CI, 2.3-2.5) (**Table 2**). Almost all MCM subgroups had a higher prevalence in HES compared to CPRD (**Table 2**). The most notable increases were seen for limb (PR, 2.9; 95% CI 2.7-3.1), nervous system (PR, 2.0; 95% CI, 1.5-2.6), ear, face and neck (PR, 2.5; 95% CI, 1.4-4.7) and other malformations (PR, 10.7; 95% CI: 9.2-12.5). The only exceptions were for eye malformations, which were twice as prevalent in CPRD, and abdominal, heart and orofacial malformations which displayed similar prevalence in both data sources (**Table 2**).

### CPRD-HES-ONS and CPRD

In linked CPRD-HES-ONS data, the prevalence of MCMs was almost three-fold that in stand-alone CPRD (PR, 2.8; 95% CI, 2.7-2.9) (**Table 2**). This increase was mainly due to additional cases identified in HES; few additional cases were identified from ONS. The prevalence of all subgroups was higher in CPRD-HES-ONS compared to stand-alone CPRD with the exception of abdominal, orofacial and eye malformations which were similar. Two-fold or greater increases in prevalence were observed for limb, genital, nervous system, respiratory, digestive, ear, face and neck, and other malformations (**Table 2**).

### CPRD-HES-ONS and HES

Linked CPRD-HES-ONS data showed an increased prevalence of MCMs compared to stand-alone HES (PR, 1.2; 95% CI, 1.1-1.2), though this was less than the increase seen in comparison to CPRD (**Table 2**). Among the subgroups, an increase compared to stand-alone HES was seen for limb, heart, genital, urinary and eye malformations. Remaining subgroups showed similar prevalence.

**Table 2 - Prevalence of MCMs in the year after delivery, by data source.**

Type of MCM	Stand-alone CPRD		Stand-alone HES		CPRD-HES <sup>a</sup>	CPRD-HES-ONS <sup>a,b</sup>	Prevalence Ratios (95% CI)		
	n	Prevalence per 10,000 person-years (95% CI)	n	Prevalence per 10,000 person-years (95% CI)	Prevalence per 10,000 person-years (95% CI)	Prevalence per 10,000 person-years (95% CI)	HES vs CPRD	CPRD-HES-ONS vs CPRD	CPRD-HES-ONS vs HES
Any	2780	265.7 (256.0-275.8)	6757	630.0 (615.2-645.2)	745.3 (729.1-761.9)	745.8 (729.6-762.4)	2.4 (2.3-2.5)	2.8 (2.7-2.9)	1.2 (1.1-1.2)
Limb	904	85.3 (79.9-91.0)	2721	245.1 (236.1-254.5)	290.5 (280.7-300.7)	290.5 (280.7-300.7)	2.9 (2.7-3.1)	3.4 (3.2-3.7)	1.2 (1.1-1.2)
Heart	685	64.5 (59.8-69.5)	803	71.1 (66.3-76.2)	94.2 (88.7-100.0)	94.3 (88.8-100.1)	1.1 (1.0-1.2)	1.5 (1.3-1.6)	1.3 (1.2-1.5)
Genital	300	28.2 (25.2-31.6)	489	43.2 (39.5-47.2)	53.9 (49.8-58.4)	53.9 (49.8-58.4)	1.5 (1.3-1.8)	1.9 (1.7-2.2)	1.2 (1.1-1.4)
Urinary	318	29.9 (26.8-33.3)	445	39.3 (35.8-43.1)	49.7 (45.7-54.0)	49.8 (45.8-54.0)	1.3 (1.1-1.5)	1.7 (1.4-1.9)	1.3 (1.1-1.4)
Nervous system	80	7.5 (6.0-9.3)	168	14.8 (12.7-17.2)	18.2 (15.8-20.8)	18.2 (15.9-20.9)	2.0 (1.5-2.6)	2.4 (1.9-3.2)	1.2 (1.0-1.5)
Respiratory	48	4.5 (3.4-6.0)	80	7.0 (5.7-8.8)	8.9 (7.3-10.8)	9.0 (7.4-10.9)	1.6 (1.1-2.3)	2.0 (1.4-2.9)	1.3 (0.9-1.7)
Digestive	121	11.3 (9.5-13.6)	225	19.8 (17.4-22.6)	21.5 (19.0-24.4)	21.7 (19.1-24.6)	1.7 (1.4-2.2)	1.9 (1.5-2.4)	1.1 (0.9-1.3)
Abdominal	34	3.2 (2.3-4.5)	55	4.8 (3.7-6.3)	4.8 (3.7-6.3)	4.8 (3.7-6.3)	1.5 (1.0-2.4)	1.5 (1.0-2.4)	1.0 (0.7-1.5)
Orofacial	129	12.1 (10.2-14.4)	141	12.4 (10.5-14.6)	12.8 (10.9-15.0)	12.8 (10.9-15.0)	1.0 (0.8-1.3)	1.1 (0.8-1.3)	1.0 (0.8-1.3)
Eye	105	9.8 (8.1-11.9)	52	4.6 (3.5-6.0)	12.0 (10.1-14.2)	12.0 (10.1-14.2)	0.5 (0.3-0.7)	1.2 (0.9-1.6)	2.6 (1.9-3.7)
Ear, Face & Neck	17	1.6 (1.0-2.6)	46	4.0 (3.0-5.4)	5.2 (4.0-6.7)	5.2 (4.0-6.7)	2.5 (1.4-4.7)	3.3 (1.9-6.0)	1.3 (0.9-1.9)
Other	187	17.5 (15.2-20.2)	2092	187.4 (179.5-195.6)	201.1 (192.9-209.6)	201.1 (192.9-209.6)	10.7 (9.2-12.5)	11.5 (9.9-13.4)	1.1 (1.0-1.1)

<sup>a</sup>The number of infants with MCMs in CPRD-HES and CPRD-HES-ONS are suppressed to prevent deductive disclosure of identities in accordance with CPRD guidelines; <sup>b</sup>Prevalence estimates in CPRD-HES-ONS were sometimes the same as those in CPRD-HES as very few or no additional cases were identified in ONS data. Abbreviations: 95% CI, 95% confidence interval; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data; MCM, major congenital malformation.

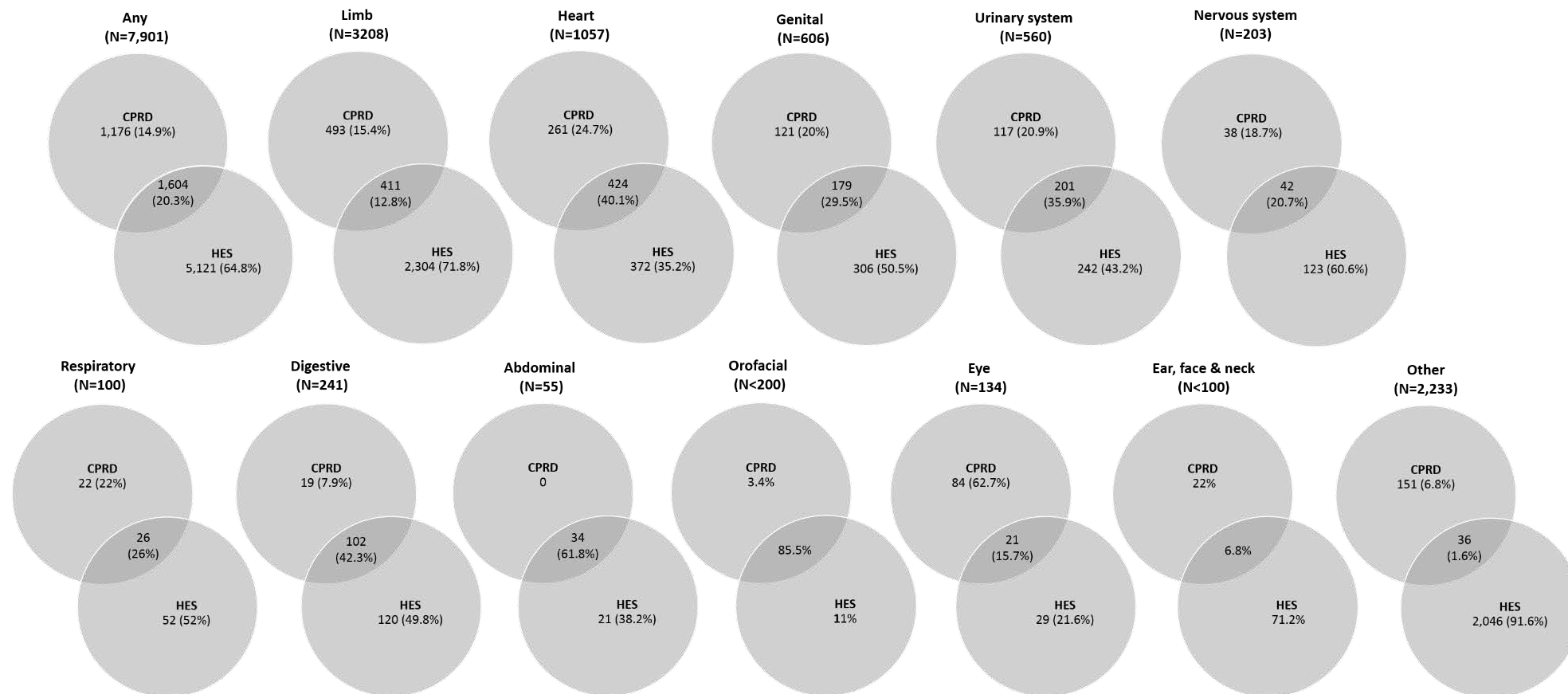
## **Agreement and contribution of data sources**

After standardizing follow-up across data sources, the proportion of infants with a recorded MCM in the year after delivery remained similar to that described earlier (6.9%; n=7,901) (**Figure 2**). After extending standardized follow-up to the end of the study period, 64% of infants had >2 years of follow-up and a further 679 infants with an MCM were identified (**Supplementary Tables 3-4**).

### *Agreement between data sources*

Of the infants with a recorded MCM in the year after delivery, 20.3% had evidence of their condition in both CPRD and HES (**Figure 2**). Orofacial and abdominal malformations were the only subgroups for which the majority of infants, 85.5% and 61.8% respectively, had agreement in CPRD and in HES. For remaining subgroups, the proportion of infants with evidence of their condition in both data sources varied. Infants with digestive or heart malformations had approximately 40% agreement, followed by infants with urinary (35.9%), genital (29.5%), respiratory (26%) and nervous system malformations (20.7%). Agreement between CPRD and HES was lower for infants with eye (15.7%), limb (12.8%), ear, face and neck malformations (6.8%) and those with other malformations (1.6%).

In general, the proportion of infants that had agreement between both data sources did not increase considerably when followed up to the end of the study period. The greatest increase in agreement were seen for genital malformations (29.5% to 37.3%) (**Supplementary Table 4**).



**Figure 2 – Number and proportion of infants with evidence of an MCM in the year after delivery, by data source.** The number and proportion of infants with an MCM identified from death certificates is not shown to prevent deductive disclosure of patient identities. Similarly, for some subgroups with small numbers of infants only the proportions are shown and denominators are suppressed. Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, major congenital malformation.

### Ascertainment of MCMs in individual data sources

The majority of the 7,901 infants with an MCM were identified exclusively from evidence in HES (64.8%) (**Figure 2**). This was also the case for infants that had limb (71.8%), ear, face and neck (71.2%), nervous system (60.6%), genital (50.5%) or respiratory malformations (52%), as well as those that had 'other' malformations (91.6%). Although the majority of infants with an MCM only had evidence of their condition in HES, the proportion of infants with evidence solely in CPRD remained substantial (14.9%) (**Figure 2**). This was also observed for all subgroups except for infants with orofacial and abdominal malformations, for which few or none had evidence of their condition exclusively in CPRD. Eye malformations were the only conditions for which the majority of infants were identified from evidence in CPRD alone (62.7%).

Of the 7,901 infants with any type of MCM, 28.3% (n=2,233) had evidence of an 'other' MCM. Due to the unexpectedly high proportion of infants in this category that were identified exclusively in HES (91.6%), we carried out a further exploratory analysis. Of the 2,233 infants with an 'other' MCM code in their records, 349 (15.6%) had at least one additional MCM code elsewhere in their records that could be classified into one of the 11 MCM subgroups. Among the remaining 1,884 infants who had no evidence to suggest they belonged to another MCM subgroup, 57% (n=1,064) had an ICD-10 code Q825 for '*congenital non-neoplastic naevus*', and 30% (n=566) had an ICD-10 code Q828 for '*other specified congenital malformations of skin*'. We excluded all 1,884 infants with solely an 'other' MCM code and re-ran the analysis for any MCM. The preponderance of any MCM recorded only in HES remained, with 56% of infants having an MCM code in HES alone (**Supplementary Figure 1**).

Neither ONS mortality data nor HES procedures were useful in ascertaining MCMs. Just 0.2% (n=14) of infants with an MCM had evidence of their condition in ONS. Subgroups with such evidence included heart, urinary, nervous system, respiratory, digestive and other MCMs. Similarly, few infants with an MCM were identified through HES procedure codes alone; the

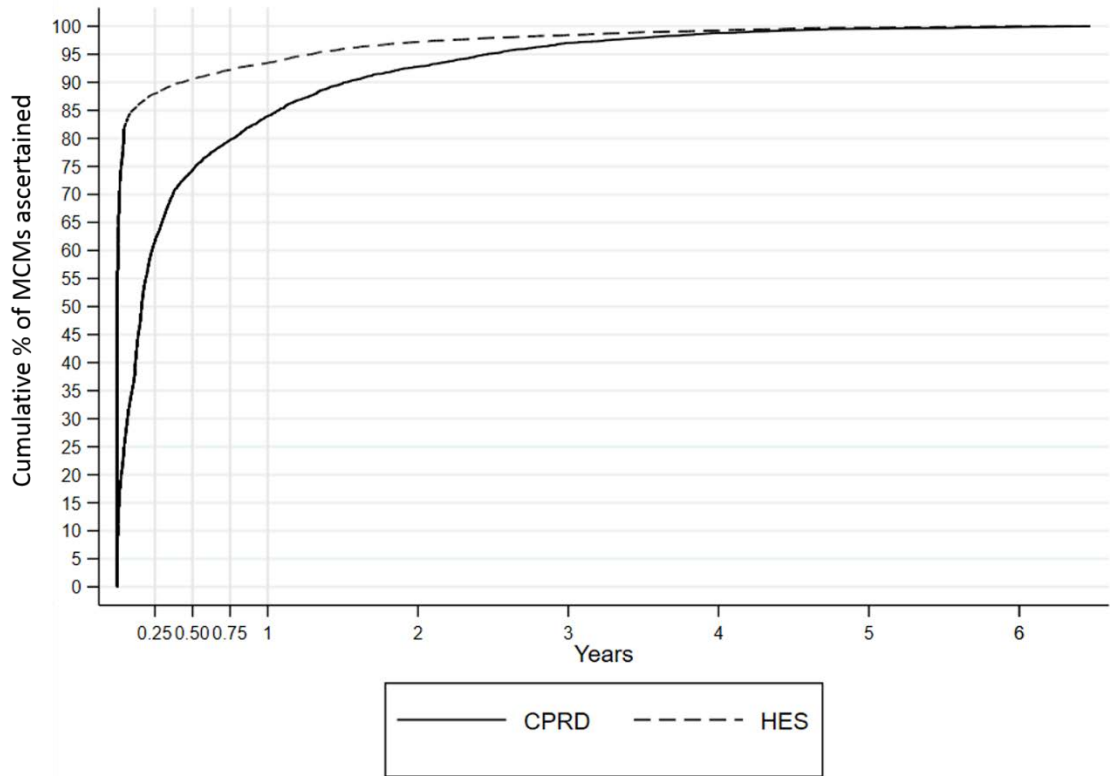
majority of infants with an OPCS-4 procedure code had an additional ICD-10 code in HES or Read code in CPRD. Extending follow-up time to the end of the study period did not alter the contribution of ONS or HES procedure data. To prevent deductive disclosure of patient identities due to small numbers, further details are not presented.

#### **Non-specific limb malformation codes**

Among the 2,304 infants that had a limb malformation identified exclusively in HES, 91.9% only had a non-specific ICD-10 code without additional specific evidence. This was considerably higher than for the 493 infants with a limb malformation identified exclusively in CPRD, for which 52.7% only had a non-specific Read code. For those 411 infants that had evidence of their condition in both data sources, 51.3% had a non-specific code without a more specific Read or ICD-10 code.

#### **Cumulative ascertainment of MCM recordings over time in stand-alone and linked data**

Extending follow-up time to the end of the study period and comparing the cumulative ascertainment of the earliest MCM recordings in stand-alone CPRD and HES indicated that longer follow-up was required for the ascertainment of MCMs in CPRD. At delivery, just 9% of MCM cases recorded in CPRD had been identified, compared to 56% in HES. By one year, 84% of cases in CPRD had been identified compared to 93% of those in HES (**Figure 3**).



**Figure 3 – Distribution of MCM records from delivery until the end of the study period in stand-alone CPRD and stand-alone HES.** Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, major congenital malformation.



## Discussion

This study compared the ascertainment of MCMs among live-born infants in CPRD, HES and ONS data between January 1, 2009 and March 31, 2016. Both CPRD and HES were important sources of information for the identification of such conditions and linked CPRD-HES data maximized ascertainment, whilst further linkage to ONS data made little difference. Almost two thirds of infants had evidence of an MCM exclusively in HES and would not have had their condition identified in another data source, with similar results seen for most MCM subgroups. Furthermore, infants with a diagnosis in HES were identified earlier than those with a diagnosis in CPRD, with more than half identified at delivery. Nevertheless, 15% of MCM cases were only identified in CPRD; this proportion was higher for some subgroups, most notably for eye malformations for which more than half of cases were identified through CPRD. We found that despite the severity and often life-long implications of MCMs, just 20% of infants with any such condition had evidence in both CPRD and HES. Agreement varied for MCM subgroups but was generally low and did not improve appreciably with increased follow-up time.

There are a number of potential reasons for the higher ascertainment of MCMs in HES compared to CPRD. First, whilst hospitalisations and deaths are required to be communicated to general practice, communications may be delayed or may not be encoded in the patient's electronic primary care record.<sup>287</sup> Instead, the general practitioner may scan the hospital letter or enter information from the letter as free-text, both of which are unavailable to investigators as part of CPRD.<sup>291</sup>

Second, it is possible that some of the diagnoses recorded in HES did not actually relate to MCMs. Whilst EUROCAT offers a framework for defining MCMs, health professionals do not use the guidelines to encode diagnoses, and so some identified codes could have been used by clinicians to record minor malformations or even other conditions. This might apply in particular to the non-specific MCM codes; our examination of non-specific limb malformation

codes revealed a particularly high proportion of infants with exclusively non-specific codes among those with evidence solely in HES.

It is also notable that 'other' MCM codes were recorded far more frequently in HES compared to CPRD, and that the majority of these were due to two ICD-10 codes for congenital malformations of the skin, namely Q825 and Q828. In EUROCAT, ICD-10 codes are modified to include a fourth digit.<sup>86</sup> At the time of the study period, EUROCAT considered all 4-digit versions of Q828 (*'other specified congenital malformations of the skin'*) to be major malformations except for Q82.80 (*'simple/abnormal palmar crease'*).<sup>86</sup> Q825 codes (*'congenital non-neoplastic naevus'*) are further classified by EUROCAT into Q8250 – Q8252 (considered minor malformations) and Q82.58 (considered a major malformation).<sup>86</sup> In HES, this level of granularity is not available and so all Q825 and Q828 ICD-10 codes were considered conservatively to relate to MCMs in this study. Conversely, in Read, codes equivalent to Q8250-8252 and Q8280 are available and could therefore (if used by primary care physicians) be classified as minor and excluded from our analyses. This could partially explain the high proportion of infants with evidence of an 'other' MCM exclusively in HES and could contribute to the similar results seen for any MCM. However, even after excluding the infants with only an 'other' MCM, some of whom may have had a minor skin malformation, 56% of infants still had evidence of 'any' MCM exclusively in HES. In addition, it is important to note that clinical coders considered these malformations of sufficient importance to document in the infants' inpatient records. Studies examining the validity of MCM codes in HES have not been undertaken to date, although a government audit estimated the positive predictive value (PPV) of primary diagnoses in HES was 96% (IQR 89-96%) in 2011.<sup>181</sup> Validation studies of MCM diagnoses in HES would help to clarify the PPV of both specific and non-specific MCM codes.

Similarly, recording of MCMs in CPRD but not in HES might be due in part to general practitioners choosing MCM codes to record non-MCM conditions, or reflecting tentative diagnoses made before referring infants to specialists. A few validation studies of MCM

diagnoses in CPRD have been performed, showing generally good PPV for major cardiac (94%; 95% CI, 91-97) and neural tube (71%; 95% CI, 64-77) malformations as well as for MCMs overall (85%; 95% CI, 79-89).<sup>192, 194, 209, 292</sup> Alternatively, as the HES data comprised only hospitalisations (not hospital outpatient visits), the CPRD data may have captured true MCMs that were not diagnosed in hospital at delivery, and for which the young child did not receive inpatient care during the follow-up period.

Our prevalence rates in stand-alone CPRD were found to be higher or consistent with those found in a previous study using The Health Improvement Network, a different UK electronic primary care dataset, with the exception of nervous system malformations which had a slightly lower prevalence in our study.<sup>201</sup> Our prevalence of congenital heart defects in stand-alone CPRD was also consistent with that estimated by another study using CPRD data between 2001-2003.<sup>218</sup> Studies of other conditions have also shown, as we have for MCMs, the agreement between CPRD and HES to be low. Agreement for poisonings, upper gastrointestinal bleeds and bleeds occurring in hospitalised patients using anticoagulants was similar to the low agreement we found for MCMs, at approximately 20%.<sup>288-290</sup> Some conditions such as burns and fractures had even lower agreement, whilst myocardial infarctions had higher levels (51%).<sup>288, 291</sup>

### **Strengths & Limitations**

This study has a number of strengths. First, we included a large number of live-born infants which allowed for a thorough exploration of MCMs and rarer subgroups. Second, we went beyond linkage of CPRD and HES diagnoses, including ONS data to identify any diagnoses recorded following the infant's death and searching HES procedures using OPCS-4 codes. With this new approach we demonstrated that neither of these contributed many additional cases. Third, we maximised ascertainment of MCMs by drawing up a rigorous MCM diagnostic code list based on the EUROCAT framework, with the input of a consultant neonatologist. Fourth, whilst we examined MCMs recorded in the year after delivery, we also followed infants up

beyond a year when possible; almost two thirds of infants had two or more years of available follow-up. The value of this is demonstrated by the fact that 8% of all MCMs identified over the course of the study period were recorded more than a year after delivery.

Despite the above, inherent limitations of the data meant that complete ascertainment of cases was not possible. As described earlier, free-text in CPRD (a potential source of feedback from inpatient and outpatient secondary care) is no longer available to investigators.

Furthermore, we did not use outpatient HES data due to the very low proportion of records with diagnostic codes.<sup>261</sup> Our use of the Pregnancy Register enabled identification of 11.7% of potentially eligible pregnancies during the study period recorded as resulting in a live-birth but with no linked infant. Lack of linkage could arise if the mother left the practice or the practice stopped collecting data shortly after the infant's birth. However, it could also occur if infants died shortly after birth or had a prolonged hospitalisation that prevented or delayed registration with a practice, which could include some infants with severe MCMs. Thus, the generalisability of our findings is restricted to infants who were registered with their mother's general practice at some point during the study period.

## **Conclusion**

This first study of the completeness of recording of MCMs in UK electronic health data adds to the growing body of evidence that the use of stand-alone primary care data can under-ascertain outcomes of interest. Linkage of CPRD to diagnostic data from hospitalisations markedly increases MCM ascertainment whilst linkage to hospitalisation procedure and mortality data identifies few additional cases. Use of linked data has the potential to maximize the ascertainment of MCMs and may allow for earlier ascertainment of diagnoses, although there is still value in long-term follow-up of infants beyond the first year of life. Our findings highlight the need for further research on the validity of MCM codes in HES and in CPRD data, notably the PPV of non-specific MCM codes. The recent availability of additional linked primary care data (CPRD Aurum) will increase sample sizes further but the different coding structure of

these data will necessitate separate assessment of data completeness. Likely improvements to diagnostic coding in outpatient HES data over time should also allow further ascertainment of MCMs in future studies using linked UK electronic health data.

## **Acknowledgements**

See research paper cover sheet.

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## **References**

References are included as part of the main reference list at the end of the thesis.

## Paper 2: Supplementary material

Supplementary Table 1 – Non-specific Read codes for limb malformations.

Read Term	Read Code
correction of congenital deformity of hand	710f.00
correction of congenital deformity of hand nos	710fz00
correction of congenital deformity of hip	710g.00
primary correction of congenital deformity of foot	710j.00
primary correction of club foot	710j.11
primary correction of talipes	710j.12
other correction of congenital deformity of foot	710k.00
other operations for club foot	710k.11
other correction of talipes	710k.12
skull, face and jaw congenital deformities	PE0..00
skull congenital deformities	pe0..13
congenital spine deformity	pe2..00
congenital postural scoliosis	PE22.00
congenital talipes varus	pe50.00
congenital clubfoot - varus	pe50.12
congenital talipes equinovarus	pe51.00
other deformities of feet	pe7..00
talipes, unspecified	pe70.00
clubfoot nos	pe70.11
congenital talipes equinus	pe7y200
feet deformities nos	pe7z.00
other congenital limb anomalies	pf...00
syndactyly - webbing of digits	pf1..00
syndactyly of toes without bone fusion	pf13.00
webbed toes	pf13.11
fused toes	pf14.11
conjoined toes	pf14.12
syndactyly nos	pf1z.00
upper limb anomaly, unspecified	pf50.00
other congenital anomalies of fingers	pf5r.00
other anomaly of fingers nos	pf5rz00
lower limb anomaly, unspecified	pf60.00
other congenital hip joint deformity	pf63.00
congenital deformity of hip, unspecified	pf63x00
other congenital hip joint deformity nos	pf63z00
other congenital anomalies of toe	pf66.00
skull and face bone anomalies	pg0..00
anomalies of spine	pg1..00
other anomaly of spine	pg1y.00
anomalies of spine nos	pg1z.00

These were codes that could potentially be used to record major limb malformations, minor limb malformations or limb conditions that were not congenital in origin. For example, EUROCAT considered syndactyly of the 2<sup>nd</sup> and 3<sup>rd</sup> toes to be a minor malformation but Read codes for syndactyly did not specify the affected toes and could also have been used for major malformations. These non-specific codes were retained but some infants with these codes may not have had a major limb malformation.

**Supplementary Table 2 – Non-specific ICD-10 codes for limb malformations.**

<b>ICD-10 Description</b>	<b>ICD-10 Code</b>
<b>other congenital deformities of hip</b>	Q658
<b>congenital deformity of hip, unspecified</b>	Q659
<b>talipes equinovarus</b>	Q660
<b>other congenital varus deformities of feet</b>	Q663
<b>other congenital deformities of feet</b>	Q668
<b>congenital deformity of feet, unspecified</b>	Q669
<b>other congenital deformities of skull, face and jaw</b>	Q674
<b>congenital deformity of spine</b>	Q675
<b>congenital deformity of hand</b>	Q681
<b>congenital deformity of knee</b>	Q682
<b>other specified congenital musculoskeletal deformities</b>	Q688
<b>fused toes</b>	Q702
<b>webbed toes</b>	Q703
<b>syndactyly, unspecified</b>	Q709
<b>oth cong malformation of upper limb(s) inc shoulder girdle</b>	Q740
<b>congenital malformation of knee</b>	Q741
<b>other cong malformation of lower limb(s) incl pelvic girdle</b>	Q742
<b>other specified congenital malformations of limb(s)</b>	Q748
<b>unspecified congenital malformation of limb(s)</b>	Q749
<b>other congenital deformities of hip</b>	Q658

These were ICD-10 codes that could potentially be used to record major limb malformations, minor limb malformations or limb conditions that were not congenital in origin. For example, EUROCAT considered syndactyly of the 2<sup>nd</sup> and 3<sup>rd</sup> toes to be a minor malformation but ICD-10 codes for syndactyly did not specify the affected toes and could also have been used for major malformations. These non-specific codes were retained but some infants with these codes may not have had a major limb malformation. Abbreviations: ICD-10, International Classification of Diseases version 10.

**Supplementary Table 3 – Total follow-up time for infants in linked CPRD-HES-ONS after standardizing follow-up across all data sources.**

<b>Follow-up time (years)</b>	<b>Number of infants (%)</b>
	<b>N=113,790</b>
≤1	16017 (14.1)
1-2	24711 (21.7)
2-3	20565 (18.1)
3-4	17601 (15.5)
4-5	14246 (12.5)
5-6	11268 (9.9)
6-7	8008 (7.0)
>7	1374 (1.2)

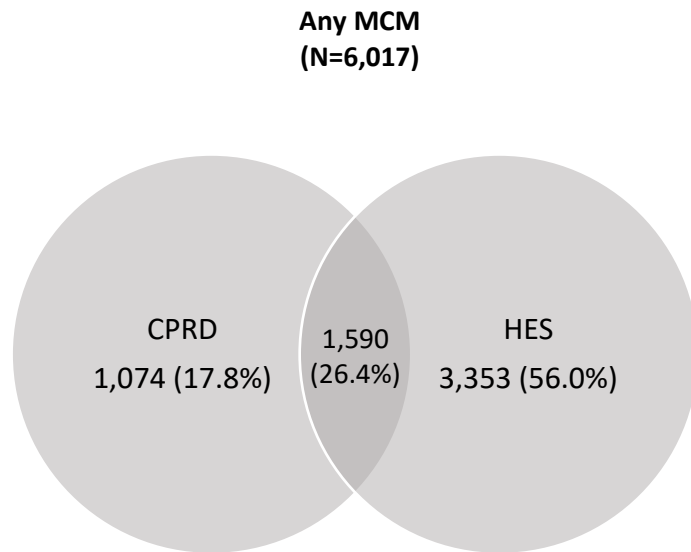
Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data.

**Supplementary Table 4 - Number and proportion of infants with evidence of an MCM in CPRD, HES or both in the year after delivery or anytime in the study period.**

Type of MCM	Total number of infants with evidence in CPRD or HES		Number and proportion of infants with evidence only in CPRD				Number and proportion of infants with evidence only in HES				Number and proportion of infants with agreement in CPRD & HES			
	Year after delivery	Anytime in the study period	Year after delivery		Anytime in study period		Year after delivery		Anytime in study period		Year after delivery		Anytime in study period	
			n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Any	7901	8580	1176	14.9 (14.1-15.7)	1383	16.1 (15.3-16.9)	5121	64.8 (63.7-65.9)	5269	61.4 (60.4-62.4)	1604	20.3 (19.4-21.2)	1928	22.5 (21.6-23.4)
Limb	3208	3403	493	15.4 (14.1-16.7)	586	17.2 (16.0-18.5)	2304	71.8 (70.2-73.4)	2333	68.6 (67.0-70.1)	411	12.8 (11.7-14.0)	484	14.2 (13.1-15.4)
Heart	1057	1165	261	24.7 (22.1-27.4)	293	25.2 (22.7-27.7)	372	35.2 (32.3-38.2)	396	34.0 (31.3-36.8)	424	40.1 (37.1-43.1)	476	40.9 (38.0-43.7)
Genital	606	732	121	20.0 (16.9-23.4)	102	13.9 (11.5-16.7)	306	50.5 (46.4-54.5)	357	48.8 (45.1-52.5)	179	29.5 (25.9-33.3)	273	37.3 (33.8-40.9)
Urinary	560	605	117	20.9 (17.6-24.5)	132	21.8 (18.6-25.3)	242	43.2 (39.1-47.4)	251	41.5 (37.5-45.5)	201	35.9 (31.9-40.0)	222	36.7 (32.8-40.7)
Nervous system	203	280	38	18.7 (13.6-24.8)	74	26.4 (21.4-32.0)	123	60.6 (53.5-67.4)	142	50.7 (44.7-56.7)	42	20.7 (15.3-26.9)	64	22.9 (18.1-28.2)
Respiratory	100	109	22	22.0 (14.3-31.4)	22	20.2 (13.1-28.9)	52	52.0 (41.8-62.1)	58	53.2 (43.4-62.8)	26	26.0 (17.7-35.7)	29	26.6 (18.6-35.9)
Digestive	241	275	19	7.9 (4.8-12.0)	28	10.2 (6.9-14.4)	120	49.8 (43.3-56.3)	139	50.5 (44.5-56.6)	102	42.3 (36.0-48.8)	108	39.3 (33.5-45.3)
Abdominal	55	56	0	-	0	-	21	38.2 (25.4-52.3)	22	39.3 (26.5-53.2)	34	61.8 (47.7-74.6)	34	60.7 (46.8-73.5)
Orofacial <sup>a</sup>	<200	<200	-	3.4	-	5.0	-	11.0	-	11.3	-	85.5	-	83.6
Eye	134	172	84	62.7 (53.9-70.9)	97	56.4 (48.6-63.9)	29	21.6 (15.0-29.6)	39	22.7 (16.6-29.7)	21	15.7 (10.0-23.0)	36	20.9 (15.1-27.8)
Ear, Face & Neck <sup>a</sup>	<100	<100	-	22.0	-	23.9	-	71.2	-	68.7	-	6.8	-	7.5
Other	2233	2394	151	6.8 (5.8-7.9)	207	8.6 (7.6-9.8)	2046	91.6 (90.4-92.7)	2124	88.7 (87.4-90.0)	36	1.6 (1.1-2.2)	63	2.6 (2.0-3.4)

<sup>a</sup>Number of infants and confidence intervals suppressed to prevent deductive disclosure in accordance with CPRD guidelines. Abbreviations: 95% CI, 95% confidence interval; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, major congenital malformation.





**Supplementary Figure 1 – Number and proportion of infants with evidence of an MCM in the year after delivery, by data source.** These data exclude 1,884 infants with an ‘other’ MCM but no evidence of an MCM in another subgroup. Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, major congenital malformation.

## 7.4 External validation of MCMs identified in CPRD with published THIN data

The discussion section of Paper 2 (**Section 7.3**) noted that the prevalence of any MCMs and MCM subgroups in stand-alone CPRD were found to be higher or consistent with those from a previous study using THIN, a different UK electronic primary care dataset (**Table 1.7**).<sup>201</sup> This section provides the details of this comparison. The study population in CPRD included 113,790 infants delivered in England between 2009 and 2015, as described earlier (**Figure 7.1**). The THIN study included 794,209 live-births delivered in the UK between 1990 and 2009.<sup>201</sup> In both data sources, follow-up started at delivery and ended a year later or earlier if the practice stopped collecting data or the infant left the practice or died.

### 7.4.1 Results of prevalence comparisons between CPRD & THIN

In stand-alone CPRD, the prevalence of MCMs was 1.2 times (95% CI, 1.2-1.3) that in THIN in the year after delivery (**Table 7.1**).<sup>201</sup> Most MCM subgroups had similar prevalence rates in both data sources. However, prevalence rates in CPRD were higher for limb (Prevalence Ratio (PR), 2.1; 95% CI, 2.0-2.3), digestive (PR, 1.3; 95% CI, 1.1-1.6), urinary (PR, 1.6; 95% CI, 1.4-1.8), and eye malformations (PR, 1.6; 95% CI, 1.3-1.9) (**Table 7.1**). Only nervous system malformations had a lower prevalence in CPRD (PR, 0.7; 95% CI, 0.6-0.9).

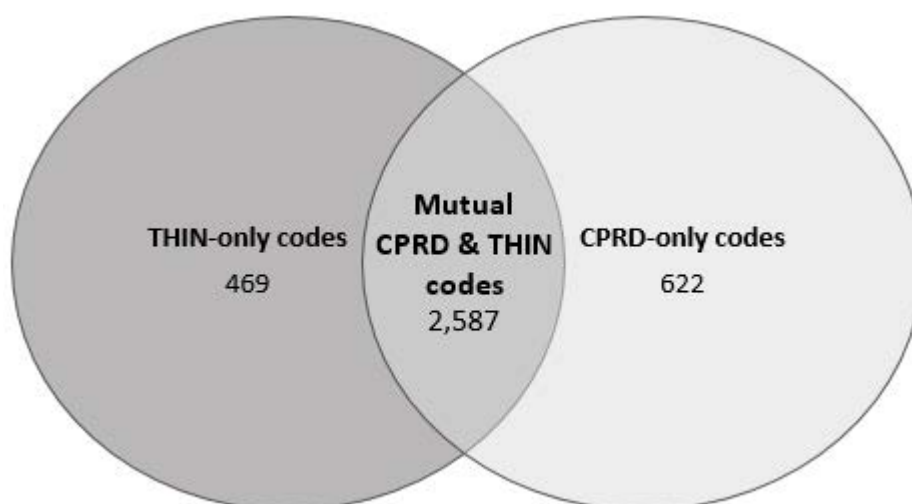
**Table 7.3 - Prevalence of MCMs in stand-alone CPRD and published THIN data in the year after delivery.**

	Stand-alone CPRD (N=113,790)		Published THIN Data (N=794,209)		Prevalence Ratios (95% CI)
	n	Prevalence per 10,000 live-births (95% CI)	n	Prevalence per 10,000 live-births (95% CI)	CPRD vs. THIN
Any MCM	2780	244.3 (235.5-253.4)	15,741	198.0 (195.0-201.0)	1.2 (1.2-1.3)*
Limb	904	79.4 (74.5-84.8)	2,970	37.4 (36.1-38.8)	2.1 (2.0-2.3)*
Heart	685	60.2 (55.9-64.9)	4,778	60.2 (58.5-61.9)	1.0 (0.9-1.1)
Genital	300	26.4 (23.5-29.5)	1,970	24.8 (23.7-25.9)	1.1 (0.9-1.2)
Urinary	318	27.9 (25.0-31.2)	1,362	17.1 (16.3-18.1)	1.6 (1.4-1.8)*
Nervous	80	7.0 (5.7-8.7)	759	9.6 (8.9-10.3)	0.7 (0.6-0.9)**
Respiratory	48	4.2 (3.2-5.6)	419	5.3 (4.8-5.8)	0.8 (0.6-1.1)
Digestive	121	10.6 (8.9-12.7)	637	8.0 (7.4-8.7)	1.3 (1.1-1.6)*
Abdominal	34	3.0 (2.1-4.2)	208	2.6 (2.3-3.0)	1.1 (0.8-1.6)
Orofacial	129	11.3 (9.5-13.5)	978	12.3 (11.6-13.1)	0.9 (0.8-1.1)
Eye	105	9.2 (7.6-11.2)	469	5.9 (5.4-6.5)	1.6 (1.3-1.9)*
Ear, Face & Neck	17	1.5 (0.9-2.4)	84	1.1 (0.8-1.3)	1.4 (0.8-2.4)

\*Prevalence higher in CPRD than THIN; \*\*Prevalence higher in THIN than in CPRD. Abbreviations: CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; 95% CI, 95% confidence interval; MCM, major congenital malformation.

#### 7.4.2 Could differences in Read code lists used to identify MCMs explain the higher prevalence of limb, digestive, urinary and eye malformations in CPRD compared to THIN?

The Read code list developed in **Chapter 5** of this thesis to identify MCMs in CPRD included 3,209 codes. Of these codes, 2,587 (80.6%) were also part of the Read code list used in the published THIN study to identify MCMs (**Figure 7.2**). These are referred to as “mutual codes”. The remaining 622 codes that were part of the Read code list developed to identify MCMs in CPRD but were not part of the Read code list used in the THIN study are referred to as “CPRD-only codes” (**Figure 7.2**). The majority of infants in CPRD with limb, digestive, urinary and eye malformations were identified from mutual codes but some were identified from CPRD-only codes. The use of these codes could result in the increased prevalence in CPRD compared to THIN if they usefully captured MCMs that were not captured in the THIN study. Increased prevalence in CPRD could also occur if CPRD-only codes were non-specific and resulted in the identification of individuals who did not have an MCM.



**Figure 7.4 - Distribution of codes used to identify MCMs in the CPRD study and published THIN study.** Abbreviations: CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; MCM, major congenital malformation.

### Limb malformations

Only 0.6% of those with limb malformations in CPRD were identified from CPRD-only codes (the rest were identified from mutual codes); the higher prevalence of these conditions in the CPRD study compared to the THIN study could therefore not be explained by the use of CPRD-only codes.

### Digestive malformations

In total, 16.5% of those in CPRD with a digestive malformation were identified from CPRD-only codes. An examination of the CPRD-only codes in the records of these infants showed that these codes usefully ascertained additional infants with diaphragmatic hernias and tracheo-oesophageal fistulas that were not captured through the use of mutual codes (**Table 7.2**). If CPRD-only codes had not been used, and these infants were not identified as having a digestive malformation, the prevalence rate in CPRD would be slightly lower (9.3 per 10,000 live-births; 95% CI, 7.6-11.3) and similar to that in THIN (8.0 per 10,000 live-births; 95% CI, 7.4-8.7).<sup>201</sup>

### Urinary malformations

In total, 40.3% of those in CPRD with a urinary malformation were identified from CPRD-only codes. Most of these infants were identified from a CPRD-only code for hydronephrosis – a malformation defined by EUROCAT as being minor when associated with a pelvis dilatation of <10 mm (**Table 7.2**).<sup>86</sup> As it was not possible to know whether an infant had major or minor hydronephrosis, such codes were conservatively treated as being major across all studies described in this thesis. However, if all hydronephrosis codes were treated as minor malformations and excluded, the prevalence rate of urinary malformations in CPRD decreased to 18.1 per 10,000 live-births (95% CI, 15.7-20.7), similar to the prevalence rate observed in THIN (17.1 per 10,000 live-births; 95% CI, 16.3-18.1).<sup>201</sup>

## Eye malformations

In total, 31.4% of those with eye malformations in CPRD were identified from CPRD-only codes. Most of these infants had a CPRD-only code for anisocoria (**Table 7.2**). During the period in which the studies described in this thesis were conducted, anisocoria was not classified by EUROCAT as a minor malformation and so such records were treated as evidence of an MCM.<sup>86</sup> However, treating anisocoria as a minor malformation (in line with the most recent EUROCAT guidelines) reduced the prevalence of eye malformations to 6.9 per 10,000 live-births (95% CI, 5.5-8.7), similar to that in THIN (5.9 per 10,000 live-births; 95% CI, 5.4-6.5).<sup>201</sup>

**Table 7.2 - Number of infants whose only evidence of an MCM was from a CPRD-only code, by subgroup.**

MCM subgroup	% infants identified exclusively from a CPRD-only Read code (%)	Read code description (Read code)	No. of infants with Read code
Limb	0.6 (≤5)	Arthrogryposis (N233000)	≤5
Urinary	40.3 (128)	Bifid kidney (PD3F.00)	≤5
Urinary		Closure of exstrophy of bladder (7B23400)	≤5
Urinary		Congenital abnormality of the kidney (PD8..00)	≤5
Urinary		Duplex kidney (PD80.00)	≤5
Urinary		Endoscopic dilatation of ureteric orifice (7B1D400)	≤5
Urinary		Endoscopic incision of ureterocele (7B1D300)	≤5
Urinary		Endoscopic incision of ureterocele (7B1D600)	≤5
Urinary		Heminephrectomy for duplex kidney (7B02000)	≤5
Urinary		Hydronephrosis (K11..00)	113
Urinary		Hydronephrosis nos (K11Z.00)	≤5
Urinary		Hydronephrosis with pelviureteric junction obstruction (K113.11)	≤5
Urinary		Hydronephrosis with ureteropelvic junction obstruction (K113.00)	≤5
Urinary		Hydroureteronephrosis (K111.00)	≤5
Urinary		Open excision of ureterocele (7B16000)	≤5
Urinary		Small kidney of unknown cause (K09..00)	≤5
Urinary	Stricture of pelviureteric junction (K133100)	≤5	
Digestive	16.5 (20)	Diaphragmatic hernia (J34..00)	≤5
Digestive		Duhamel hirschsprung abdoperin (7726Y11)	≤5
Digestive		Freeing of adhesions of tongue (7523200)	≤5
Digestive		Repair of diaphragmatic hernia (760K.00)	14
Digestive		Stenosis of intestine nos (J50Z200)	≤5
Digestive		Tracheo-oesophageal fistula (J10Y200)	≤5
Eye	31.4 (33)	Anisocoria - unequal pupil diameter (F4K4100)	26
Eye		Aphakia (F4K3000)	≤5
Eye		Coloboma of optic disc (F4H2200)	≤5
Eye		Corneal scar or opacity nos (F4B0Z00)	≤5
Eye		Glaucoma (F45..00)	≤5
Eye		H/O: glaucoma (1482)	≤5

Numbers suppressed to prevent deductive disclosure. Abbreviations: MCM, major congenital malformation; CPRD, Clinical Practice Research Datalink.

### 7.4.3 Could Read codes used to identify MCMs in the THIN study but not in CPRD

explain the lower prevalence of nervous system malformations in CPRD?

In total, 469 codes were used in the THIN study that were not included in the code list developed for CPRD (referred to as “THIN-only codes”) (**Figure 7.2**). It was possible that by not including these codes, the prevalence of nervous system malformations in CPRD could be under-ascertained.

The majority of the 469 THIN-only Read codes were not included because they had been retired from the Read dictionary when the code list for the work described in this thesis was developed (86.8%; n=407). Once retired, Read codes are no longer used to encode clinical data and retired codes present in patient records are replaced with newer versions. It is therefore unlikely that the use of these codes by the THIN study could explain the difference in prevalence. As these codes were no longer part of the Read dictionary, it was not possible to examine their descriptions and explore differences further.

The remaining 62 THIN-only Read codes were not included in the CPRD study either because the conditions they referred to did not fit inclusion criteria (7.7%; n=36) or because they were not identified during the development of the code lists (5.5%; n=26) (**Appendix 7**). Among the 113,790 infants in the study population, just a single infant had one of these latter codes in their infant record. The code related to the procedure ‘*freeing of spinal tether*’ which could indicate the infant had spina bifida, a nervous system malformation. This was not enough, however, to explain the lower prevalence of these malformations in CPRD.

### 7.4.4 Could differences in the study periods explain differences in the prevalence rates between CPRD & THIN?

Another potential reason for differences in prevalence was that rates were calculated for different study periods. Infants in the THIN study were born between 1990-2009 whereas infants included in this CPRD study were born between 2009-2015.<sup>201</sup> English registry data from EUROCAT showed that annual prevalence rates among live-births fluctuated between

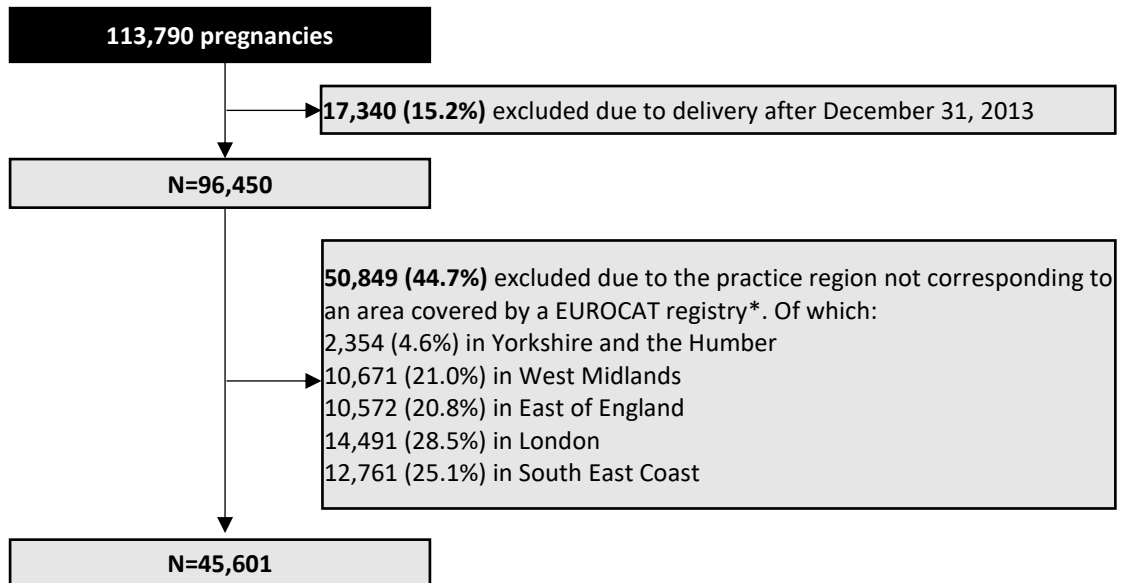
1990 and 2016 but average prevalence rates before and after 2009 were similar for the MCM subgroups for which differences were seen.<sup>294</sup> Therefore, it is unlikely that the reason for the differences observed between the two data sources is a result of MCM prevalence increasing or decreasing although it is possible that recording of conditions changed over time.

#### 7.4.5 Could differences in the criteria used to define study populations explain differences in the prevalence rates between CPRD & THIN?

Different criteria to define study populations were also considered as a possible reason for differences. In the THIN study, infants were required to be registered with a general practice in the first year of life.<sup>201</sup> In the work described in this thesis, no such requirement was placed on the study population as it was thought that this could potentially exclude infants with severe MCMs that were delayed in registering at the practice. However, this seemed unlikely to explain the differences in prevalence as just 0.6% of infants in the CPRD study registered with a practice more than 12 months after delivery and excluding them made no difference to the overall prevalence of MCMs.

#### 7.5 External validation of MCMs identified in CPRD, HES and linked data with data from English EUROCAT registries

This section describes a comparison of the prevalence of MCMs among live-born infants in the year after delivery between stand-alone and linked CPRD, HES and ONS data with English EUROCAT data. To make the study populations as comparable as possible, the 113,790 infants identified in **Figure 7.1** were further restricted to those delivered between 2009-2013 (prior to the transfer of UK EUROCAT registries to the National Congenital Anomaly and Rare Disease Registration Service which could have disrupted data collection) and registered at a practice in a similar geographic region to the included registries. After restrictions, there were 45,601 infants in the study population (**Figure 7.3**). In comparison, English EUROCAT registries had a study population of over 1 million infants.<sup>294</sup>



**Figure 7.3 - Derivation of pregnancies included in the comparison of MCM prevalence rates with English EUROCAT data.** \*Between 2009 and 2013, EUROCAT received data from the following registries in England: NorCAS, EMSYCAR, CAROBB, WANDA and SWCAR. The most closely corresponding CPRD practice regions were: North East and North West (corresponding to NorCAS), East Midlands (corresponding to EMSYCAR), South Central (corresponding to CAROBB and WANDA) and South West (corresponding to SWCAR). Pregnancies in any other CPRD region were excluded.



## 7.5.1 Results of prevalence comparisons with English EUROCAT registries

### CPRD and EUROCAT

Overall, the prevalence of MCMs in CPRD was 1.7 times higher (95% CI, 1.6-1.8) than that in EUROCAT (**Table 7.3**).<sup>294</sup> Prevalence was higher in CPRD than in EUROCAT for limb (PR, 3.2; 95% CI, 2.9-3.6), heart (PR, 1.4; 95% CI, 1.2-1.6), genital (PR, 1.4; 95% CI, 1.2-1.7) and eye malformations (PR, 5.3; 95% CI, 3.8-7.3) but was similar for other subgroups. This was in line with results from a study by Sokal *et al.*, which demonstrated a higher prevalence in THIN compared to UK EUROCAT registries for the same subgroups.<sup>201</sup> Results were also consistent with a study by Wurst *et al.* which examined heart defects and found them to be more prevalent in CPRD compared to UK registries.<sup>218</sup>

### HES and EUROCAT

The prevalence of MCMs in HES was over three times that in EUROCAT (PR, 3.6; 95% CI, 3.5-3.8) (**Table 7.3**).<sup>294</sup> All MCM subgroups had higher prevalence rates in HES with the exception of abdominal and orofacial malformations which had similar prevalence rates to those seen in EUROCAT. Of all subgroups, limb defects had the greatest difference in prevalence with EUROCAT data (PR, 8.3; 95% CI, 7.7-8.9).

### CPRD-HES-ONS and EUROCAT

The prevalence of MCMs in linked CPRD-HES-ONS data was more than four times that in EUROCAT (PR, 4.3; 95% CI, 4.1-4.5).<sup>294</sup> As with HES, similar prevalence rates for orofacial and abdominal malformations were seen between CPRD-HES-ONS and EUROCAT whilst all other subgroups had a higher prevalence in CPRD-HES-ONS. Limb defects, eye malformations and malformations of the ear, neck and face had the highest increases in prevalence compared to EUROCAT.

**Table 7.3 - The prevalence of MCMs in stand-alone CPRD, stand-alone HES, linked CPRD-HES-ONS and English EUROCAT registries.** Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data; 95% CI, 95% confidence interval; MCM, major congenital malformation.

	Stand-alone CPRD (N=45,601)		Stand-alone HES (N=45,601)		CPRD-HES-ONS (N=45,601)		EUROCAT (N=1,034,278)		Prevalence Ratios (95% CI)		
	n	Prevalence per 10,000 live-births (95% CI)	N	Prevalence per 10,000 live-births (95% CI)	n	Prevalence per 10,000 live-births (95% CI)	n	Prevalence per 10,000 live-births (95% CI)	CPRD vs. EUROCAT	HES vs. EUROCAT	CPRD-HES-ONS vs. EUROCAT
Any MCM	1,176	257.9 (243.7-272.8)	2,535	555.9 (535.3-577.3)	3,033	665.1 (642.6-688.4)	15,967	154.4 (152.0-156.8)	1.7 (1.6-1.8)	3.6 (3.5-3.8)	4.3 (4.1-4.5)
Limb	400	87.7 (79.6-96.7)	1,034	226.7 (213.5-240.8)	1,255	275.2 (260.6-290.6)	2,831	27.4 (26.4-28.4)	3.2 (2.9-3.6)	8.3 (7.7-8.9)	10.1 (9.4-10.7)
Heart	288	63.2 (56.3-70.9)	327	71.7 (64.4-79.9)	437	95.8 (87.3-105.2)	4,691	45.4 (44.1-46.7)	1.4 (1.2-1.6)	1.6 (1.4-1.8)	2.1 (1.9-2.3)
Genital	121	26.5 (22.2-31.7)	172	37.7 (32.5-43.8)	220	48.2 (42.3-55.0)	1,910	18.5 (17.7-19.3)	1.4 (1.2-1.7)	2.0 (1.7-2.4)	2.6 (2.3-3.0)
Urinary	122	26.8 (22.4-31.9)	166	36.4 (31.3-42.4)	209	45.8 (40.0-52.5)	2,216	21.4 (20.5-22.3)	1.2 (1.0-1.5)	1.7 (1.4-2.0)	2.1 (1.8-2.5)
Nervous	28	6.1 (4.2-8.9)	68	14.9 (11.8-18.9)	81	17.8 (14.3-22.1)	943	9.1 (8.6-9.7)	0.7 (0.4-1.0)	1.6 (1.3-2.1)	1.9 (1.5-2.4)
Respiratory	19	4.2 (2.7-6.5)	30	6.6 (4.6-9.4)	39	8.6 (6.3-11.7)	388	3.8 (3.4-4.1)	1.1 (0.7-1.8)	1.8 (1.2-2.5)	2.3 (1.6-3.2)
Digestive	57	12.5 (9.7-16.2)	94	20.6 (16.8-25.2)	107	23.5 (19.4-28.3)	1,447	14.0 (13.3-14.7)	0.9 (0.7-1.2)	1.5 (1.2-1.8)	1.7 (1.4-2.0)
Abdominal	20	4.4 (2.8-6.8)	28	6.1 (4.2-8.9)	28	6.1 (4.2-8.9)	551	5.3 (4.9-5.8)	0.8 (0.5-1.3)	1.2 (0.8-1.7)	1.2 (0.8-1.7)
Orofacial	56	12.3 (9.5-15.9)	65	14.3 (11.2-18.2)	66	14.5 (11.4-18.4)	1,281	12.4 (11.7-13.1)	1.0 (0.7-1.3)	1.2 (0.9-1.5)	1.2 (0.9-1.5)
Eye	46	10.1 (7.6-13.5)	22	4.8 (3.2-7.3)	57	12.5 (9.7-16.2)	197	1.9 (1.7-2.2)	5.3 (3.8-7.3)	2.5 (1.6-3.9)	6.6 (4.8-8.9)
Ear, Face & Neck	6	1.3 (0.6-2.9)	20	4.4 (2.8-6.8)	25	5.5 (3.7-8.1)	92	0.9 (0.7-1.1)	1.5 (0.5-3.3)	4.9 (2.9-8.1)	6.2 (3.8-9.7)

## 7.5.2 Could limited follow-up in some English registries explain differences in prevalence rates?

As described in **Section 1.7.1**, English registries receive notifications from multiple sources to ascertain MCMs and also conduct active case ascertainment.<sup>118, 119</sup> This approach enhances the completeness of data and also provides opportunities for quality control. Together with the standardized manner by which data on MCMs are collected (i.e. the use of common coding guidelines), these strengths have established EUROCAT as a reliable source on the prevalence of these conditions and have resulted in registry data being used extensively for research.

Individual registries may, however, differ in their ascertainment of MCMs. Notification of cases is not compulsory by law and active case ascertainment may be limited by available resources and access to data sources.<sup>118</sup> For example, although registries strive to ascertain MCMs throughout the first year of life, this is not always possible in practice (Judith Rankin, personal communication). Indeed, some registries caution that although ascertainment is high for MCMs identified in the antenatal period, data can be more limited for diagnoses made postnatally.<sup>120, 121, 124</sup>

Variation in full reporting of MCMs throughout the first year of life could partly explain the higher prevalence of MCMs in electronic health records compared to UK EUROCAT registries. A EUROCAT report on the data quality of all contributing European registries between 2011 and 2015, which roughly corresponded to the study period, examined the prevalence rate of six MCMs likely to be diagnosed after the neonatal period.<sup>295</sup> The report showed that the total congenital anomaly prevalence for these conditions was lower in four of the five English registries compared to the average rate from all registries contributing to EUROCAT.<sup>295</sup> These results suggested potentially lower levels of notifications from paediatric, surgical and other units during this period.

This explanation is supported by findings that abdominal and orofacial malformations, both of which represent a small number of conditions that are apparent at birth and require corrective

procedures immediately or shortly thereafter, had similar prevalence rates in electronic health records used in this thesis and in registry data. Other MCM subgroups generally captured broader spectra of conditions, some of which might only be detected after prolonged investigation or may not require immediate treatment. These conditions had lower prevalence rates in registry data than in HES or linked data, suggesting that differences in prevalence may sometimes occur when longer follow-up is needed to ascertain conditions.

### 7.5.3 Could limitations of clinical coding systems and practices in UK electronic health records explain differences in prevalence rates?

The higher prevalence of MCMs in electronic health records could be explained by the inherent limitations of clinical coding systems and practices. Whilst EUROCAT publishes detailed guidelines on how MCMs should be coded by registries, these guidelines have not been adopted as part of clinical coding practice in the UK.<sup>283</sup> Clinicians have flexibility in the codes they use to record MCMs. As discussed in **Section 5.4**, this flexibility in coding choice was accounted for when developing code-lists for the work described in this thesis, but may have led to the inflation of prevalence rates in electronic health records. Clinicians may:

**1. Use non-specific codes from chapters outside of the dedicated Read 'P' or ICD-10 'Q' chapters for congenital malformation diagnoses.** These non-specific codes could refer to congenital or non-congenital conditions (e.g. mitral stenosis which could be congenital or could have other causes). Such codes were included in code-lists used to search patient records if they were thought to relate to MCMs in the majority of the study population during the study period. However, because such codes may also be used by clinicians to encode non-congenital conditions, the possibility that some individuals were classified as having an MCM when they had a non-congenital condition could not be discounted.

**2. Use non-specific Read or ICD-10 codes from the dedicated chapters for congenital malformation diagnoses.** These non-specific codes could refer to major or minor malformations (e.g. '*unspecified congenital malformation of limbs*') or conditions that require

additional information to be classified as true MCMs (e.g. congenital hydronephrosis is only considered a true MCM if there is a pelvis dilatation of >10mm).<sup>283</sup> Although the inclusion of such non-specific codes in code-lists used to search patient records were carefully considered together with a consultant neonatologist, there was a possibility that some individuals were classified as having an MCM when they had a minor malformation or did not meet the necessary criteria to be defined as a true MCM.

These limitations may have been further exacerbated by the difference in the BPA-modified ICD-10 coding system used by EUROCAT and the ICD-10 coding system used in HES. The BPA-modified coding system adds an extra digit to the ICD-10 codes which allows for additional granularity and allows generic diagnostic codes to be split into more specific diagnostic codes that can then be defined as major or minor. For example, in EUROCAT, code Q825 for '*congenital non-neoplastic naevus*' is further split into codes Q8251, Q8252 and Q8258 which are then separately defined as major (Q8258) and minor (Q8250-8252).<sup>283</sup>

The prevalence rate of limb malformations appeared to be particularly elevated in routine data compared to EUROCAT registries, particularly among data from HES. It was thought that this was likely a result of non-specific ICD-10 codes that could be used to encode both major and minor malformations or other conditions, thereby inflating prevalence estimates. For example, the ICD-10 code '*other congenital deformities of feet*' could be used to refer to a number of conditions, such as: syndactyly of the 2nd and 3rd toes (defined as a minor malformation by EUROCAT), talipes equinovarus of postural origin (described by EUROCAT as not being a true MCM), talipes equinovarus of congenital origin (defined as an MCM by EUROCAT) or talipes calcaneovarus (defined as an MCM by EUROCAT).<sup>283</sup> Indeed, among infants whose only evidence of a limb malformation was in HES, the proportion that had an ICD-10 code that could be considered non-specific was >90% (described in **Section 7.3**). This could explain why the prevalence of these conditions was so high when HES data were used. To a lesser extent but likely for the same reasons, the prevalence of limb malformations was also elevated in

CPRD.

**3. Have a lower threshold for coding diagnoses than registries.** For example, clinicians may routinely use the code '*patent ductus arteriosus*' regardless of whether the opening in the heart was a result of preterm birth and resolved in its own time or whether the infant had a severe patent ductus arteriosus. Conversely, EUROCAT has robust and standardized coding guidelines that emphasize the need to only encode patent ductus arteriosus that is not associated with prematurity.<sup>283</sup>

**4. Encode tentative diagnoses.** Clinicians, particularly in primary care, may encode suspected diagnoses which require further investigation. It is possible that a proportion of MCMs recorded in primary care relate to other conditions. Tentative coding is less likely to occur in secondary care where clinical coding is related to reimbursement.<sup>261</sup>

The above examples are likely to explain the higher prevalence of MCMs in electronic health records compared to registry data. These are expanded upon further in **Chapter 11**.

## 7.6 Chapter summary and conclusions

Using the algorithm developed to identify MCMs in **Chapter 5**, this chapter demonstrated that the proportion of infants with an MCM that had coded evidence of their condition in both CPRD and HES was just 20%. Previous studies examining vaccine and drug safety in pregnancy have relied on stand-alone primary care data (**Chapter 2**). However, the study in this chapter found that 65% of infants with an MCM had evidence of their condition exclusively in HES and that reliance on primary care data would tend to under-ascertain these conditions. Prevalence rates in CPRD were generally similar to or higher than those in equivalent primary care records from THIN. Prevalence rates in CPRD, HES and CPRD-HES-ONS were also similar to or higher than those in EUROCAT. Elevated prevalence rates of some MCM subgroups could potentially be explained by the use of non-specific Read and ICD-10 codes which could be used to record minor malformations or non-congenital conditions as well as MCMs.

## 8. Examining seasonal influenza vaccination during pregnancy and major congenital malformations

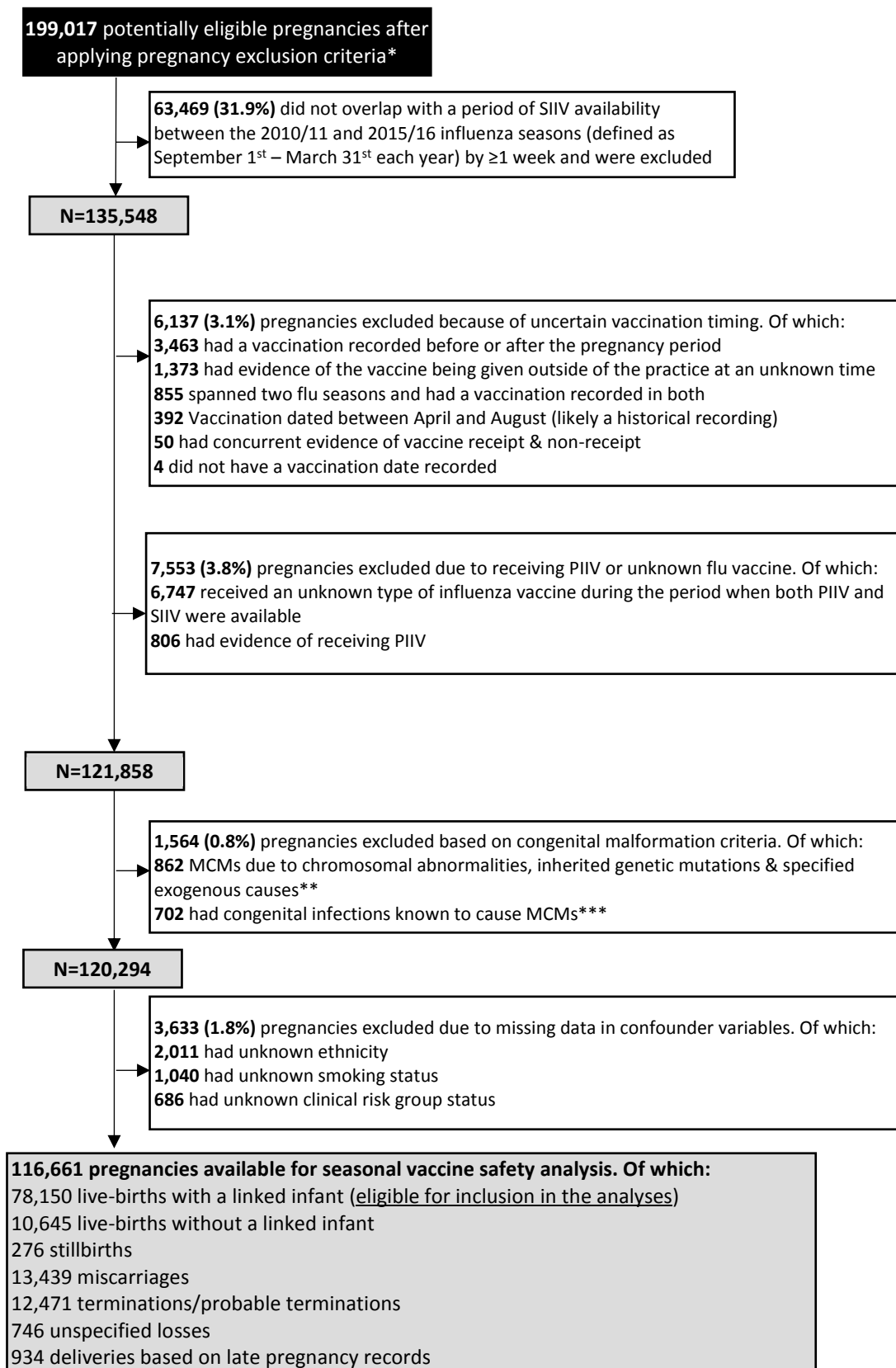
### 8.1 Introduction

This results chapter addresses **Objective 5**. It contains the results of a large, population-based cohort study used to assess the safety of SIV receipt during pregnancy, with MCMs as the outcome of interest. The chapter builds on previous work, including the systematic review of the identification of MCMs in UK electronic health records (**Chapter 2**), the development of an algorithm to identify such conditions (**Chapter 5**) and the exploration of the value of different data sources in their ascertainment (**Chapter 7**). It is followed by **Chapter 9** which examines the safety of PIV during pregnancy, with MCMs as the outcome of interest (**Objective 6**).

In this chapter, **Section 8.2** summarizes the derivation of the final study population for SIV safety analyses. **Section 8.3** presents results from the analysis in the form of a submitted manuscript along with supplementary material. **Section 8.4** describes the prevalence of ICD-10 coded MCM subgroups and conditions by vaccination status. **Section 8.5** explains why analyses examined vaccination in each trimester and **Section 8.6** provides the rationale for restricting analyses to live-births. **Section 8.7** and **Section 8.8** consider whether the exclusion of terminations due to foetal anomaly and other pregnancy outcomes could have biased results.

### 8.2 Deriving the final study population for analyses on SIV safety

The methods used to identify potentially eligible pregnancies are described in **Chapter 4**. After applying these criteria, 199,017 potentially eligible pregnancies were identified. **Figure 8.1** shows how the final study population for the examination of the safety of SIV was derived after applying study-specific exclusion criteria (**Section 4.5**). A total of 116,661 pregnancies were identified, of which 78,150 were live-births with linked infant records and went on to be used in the main analysis described in **Section 8.3**. Reasons for excluding other pregnancy types are described in **Section 8.6**.



**Figure 8.1 – Deriving the study population for seasonal influenza vaccine safety analyses.** \*The initial population of 199,017 pregnancies included those ending between January 1, 2009 and March 31, 2016. All live-born infants were eligible for linkage to HES and ONS. The identification of the 199,017 potentially eligible pregnancies is described in Sections 4.2-4.3. This flow diagram includes all potentially eligible pregnancies, in comparison to Figure 1 of the submitted paper which presents only those pregnancies ending in live-births. \*\*See Section 4.4.1; \*\*\*See Section 4.4.2.



## RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

### SECTION A – Student Details

Student ID Number	1300677	Title	Miss
First Name(s)	Maria		
Surname/Family Name	Peppa		
Thesis Title	The safety of influenza vaccination in pregnancy: Examining major congenital malformations as potential adverse outcomes using UK electronic health records		
Primary Supervisor	Professor Punam Mangtani		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

### SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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### SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Clinical Infectious Diseases
Please list the paper's authors in the intended authorship order:	Maria Peppa, Sara L Thomas, Caroline Minassian, Jemma L Walker, Helen I McDonald, Nick J Andrews, Stephen T Kempley, Punam Mangtani

Stage of publication	<b>Undergoing revision</b>
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**SECTION D – Multi-authored work**

<p>For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)</p>	<p>This study was conceptualized by P Mangtani and designed by P Mangtani, S Thomas, C Minassian, J Walker, N Andrews and myself. I developed initial code-lists for MCMs and these were discussed and agreed with S Kempley, P Mangtani and S Thomas. Code-lists for vaccines had been previously developed by S Thomas. J Walker contributed code-lists for clinical risk groups. I developed code-lists and algorithms for remaining covariates and carried out data management and analyses. These were discussed with co-authors to ensure agreement. I drafted the manuscript and revised it following comments from co-authors.</p>
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**SECTION E**

<b>Student Signature</b>	Maria Peppia
<b>Date</b>	19.03.2020

<b>Supervisor Signature</b>	Punam Mangtani
<b>Date</b>	20.03.2020

### 8.3 Submitted Paper: Seasonal influenza vaccination during pregnancy and the risk of major congenital malformations in live-born infants

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## Abstract

**Background:** Available evidence indicates that seasonal inactivated influenza vaccination during pregnancy protects both the mother and her newborn, and is safe. Nevertheless, ongoing safety assessments are important in sustaining vaccine uptake. Few studies have explored safety in relation to major congenital malformations, particularly in the first trimester when most organogenesis occurs.

**Methods:** Anonymised UK primary care data (the Clinical Practice Research Datalink), including a recently developed Pregnancy Register, were used to identify live-born singletons delivered between 2010 and 2016. Maternal influenza vaccination was determined using primary care records and stratified by trimester. Ascertainment of major malformations from infant primary care records was maximized by linkage to hospitalisation data and death certificates. The relationship between vaccination and major malformations recorded in the year after delivery and in early childhood was then assessed using multivariable Cox regression.

**Results:** A total of 78,150 live-birth pregnancies were identified: 6,872 (8.8%) were vaccinated in the first trimester, 11,678 (14.9%) in the second and 12,931 (16.5%) in the third. Overall, 5,707 live-births resulted in an infant with a major malformation recorded in the year after delivery and the adjusted hazard ratio when comparing first-trimester vaccination to no vaccination was 1.06 (99%CI, 0.94-1.19; p=0.2). Results were similar for second and third-trimester vaccination and for analyses considering major malformations recorded beyond the first birthday.

**Conclusions:** In this large, population-based historical cohort study there was no evidence to suggest that seasonal influenza vaccine was associated with major malformations when given in the first trimester or subsequently in pregnancy.

## Introduction

Pregnant women and newborn infants are at increased risk of complications following influenza infection.<sup>37, 296</sup> Seasonal influenza vaccination (SIV) during pregnancy has been shown to provide good protection to both groups.<sup>63, 297, 298</sup> The World Health Organization recommended SIV for all pregnant women, regardless of trimester, in 2012.<sup>299</sup> Women, however, are concerned about the safety of vaccination during pregnancy for their child.<sup>16, 300</sup>

Several studies have demonstrated the safety of the 2009/10 monovalent pandemic vaccine with respect to major congenital malformations (MCMs), but few have assessed SIV.<sup>20-23</sup> Those that have examined SIV, and have stratified by trimester of vaccination, have generally been limited by low numbers of first-trimester vaccinations and inadequate infant follow-up which could result in under-ascertainment of MCMs.<sup>20-23</sup> To date, there has only been one large US study of first-trimester vaccination with adequate infant follow-up.<sup>103</sup>

We examined the association between SIV administered in the first and subsequent trimesters, and the risk of MCMs in a different setting by using a large UK cohort, with ascertainment of malformations using long-term follow-up in linked primary care, hospitalisation and mortality datasets.

## Methods

### Data Sources

This study utilized the Clinical Practice Research Datalink (CPRD), the CPRD/London School of Hygiene and Tropical Medicine (LSHTM) Pregnancy Register, hospital admissions data from the Hospital Episode Statistics database (HES), Office for National Statistics (ONS) death certificate data, deprivation quintiles linked to household post-codes, and data on influenza activity from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre.

The CPRD contains anonymised, electronic primary care records for 7% of the UK population registered at a general practice. It includes diagnoses and procedures recorded using Read codes, vaccination records and prescriptions.<sup>126</sup> The CPRD has been shown to be broadly representative of the UK population and diagnostic validity is high.<sup>126, 180</sup>

The Pregnancy Register lists all pregnancies identified in CPRD, for women aged 11-49 years.<sup>255</sup> It includes pregnancy outcomes and estimates of pregnancy timings derived from all available pregnancy data in CPRD including estimated delivery dates, last menstrual period dates, ultrasound dating scans and prematurity records. The first, second and third trimesters are defined as the pregnancy start through week 13, week 14 through 26 and week 27 through the pregnancy end, respectively. Live-birth deliveries are linked to records of infants registered at the same practice as their mother. Validation of the Pregnancy Register against linked electronic maternity records in HES has indicated overall good agreement, suggesting most pregnancies are well-captured in the Register.<sup>255</sup>

Patient data in CPRD can be linked to the HES and ONS data for 75% of English practices.<sup>126</sup>

Linked HES data include information on diagnoses and procedures, recorded using the International Classification of Diseases (ICD-10) and the Classification of Surgical Operations and Procedures (OPCS-4), respectively. ONS death certificate data include primary and

contributory causes of death recorded using ICD-10. Deprivation quintiles are derived from the 2015 Index of Multiple Deprivation (IMD) for Lower Super Output Areas.<sup>269</sup>

Weekly general practice consultation rates for influenza-like illness from the RCGP were used to identify periods of influenza circulation above baseline levels for each season. The validity of these data has been confirmed through microbiological surveillance.<sup>278</sup>

This study received approval from the Independent Scientific Advisory Committee of the Medicines & Healthcare Products Regulatory Agency (reference 17\_040RA); the approved protocol was made available to the reviewers. Approval was also received from LSHTM's ethics committee (reference 13720).

### **Study design**

This historical cohort study compared live-birth pregnancies that received SIV, stratified by trimester of vaccination, to those unvaccinated. The primary outcome was the presence of any MCMs among infants in the year after delivery. Secondary outcomes examined any MCMs, major limb malformations and congenital heart defects recorded after delivery and anytime in the study period between September 1, 2010 and March 31, 2016 (the latest date for which all linked data were available).

### **Study population**

Pregnancies resulting in a live-born singleton during the study period were identified from the Pregnancy Register. Pregnant women had to be registered at an up-to-standard practice (a quality standard set by CPRD to indicate continuous recording of data within the practice)<sup>126</sup> for at least 6 months before the start of pregnancy to enable the ascertainment of pre-conception exposures. Live-born infants had to be eligible for HES and ONS linkage. Finally, pregnancies were required to overlap with a period of influenza vaccine availability (1<sup>st</sup> September to 31<sup>st</sup> March, annually) by at least one week.

### **Identifying vaccinations**

In the UK, pregnant women are offered SIV in any trimester.<sup>5</sup> The earliest vaccination record in each influenza season was identified in CPRD from immunisation records, prescriptions or Read codes, and used to determine the trimester of vaccination. Pregnancies were excluded if the timing or nature of vaccination was uncertain (e.g. if there was a possibility that SIV was received outside of the practice at an unknown time or a possibility that pandemic vaccine was received) (**Figure 1**).

### **Identifying MCMs**

Code lists for MCMs were developed with a consultant neonatologist (SK), following EUROCAT guidelines.<sup>283</sup> MCMs were then ascertained from infant records in CPRD, HES data for diagnoses and procedures, and ONS. Pregnancies were excluded if there was an antenatal or infant record indicating a chromosomal or heritable anomaly, a malformation due to a known teratogen (e.g. foetal alcohol syndrome), or a congenital infection associated with malformations. Infants were followed-up from delivery for a year or until the end of the study period. Follow-up ended earlier if they died, left the practice or the practice stopped collecting data for CPRD.

### **Potential confounders**

We considered *a priori* confounders to be maternal age and ethnicity, geographical region (due to variation in vaccine uptake and MCM ascertainment) and the earliest influenza season a pregnancy overlapped with. Other potential confounders included: household deprivation quintile (IMD), number of children in the household, maternal smoking, hazardous drinking, extreme body mass index (BMI) of <18 or ≥35, belonging to another clinical risk group for which vaccination was recommended during the study period,<sup>5</sup> non-pregnancy related chronic hypertension, exposure to teratogenic drugs or live vaccines, and number of weeks the first



trimester overlapped with influenza activity above baseline levels (see **Supplementary Table 1** for details of how these were derived).

### **Statistical analyses**

Baseline pregnancy characteristics were described by vaccination status. Logistic regression was used initially to model the univariable relationship between vaccination and MCMs recorded in the year after delivery and assess confounding. After *a priori* confounders, remaining potential confounders were added individually to the logistic regression model and assessed for a  $\geq 5\%$  change in the odds ratios between first-trimester vaccination or vaccination anytime and MCMs. Multicollinearity was monitored between IMD, ethnicity and region and between the number of children in the household and maternal age. Finally, random effects models were used to assess clustering by mother and practice. Once confounders had been identified using logistic regression models, all final analyses were conducted using Cox proportional hazards models to account for improved ascertainment of the outcome among infants with longer follow-up time. Results were compared to those from logistic regression. To account for multiple analyses, 99% confidence intervals (CIs) were calculated. All models were complete case analyses.

Three sensitivity analyses were conducted. First, we included pregnancies that received SIV in the 4 weeks prior to their start to account for any imprecision in the estimated pregnancy start dates. Second, we included MCMs recorded in HES or ONS after follow-up in CPRD had ended because the infant left the practice or the practice ended data collection. In the main analyses, pregnancies of women with unknown BMI or a BMI between 18 and 34 were combined in a single category as they had comparable associations with MCMs. The third sensitivity analysis excluded pregnancies of women with unknown BMI.

STATA version 14.2 was used for all analyses.

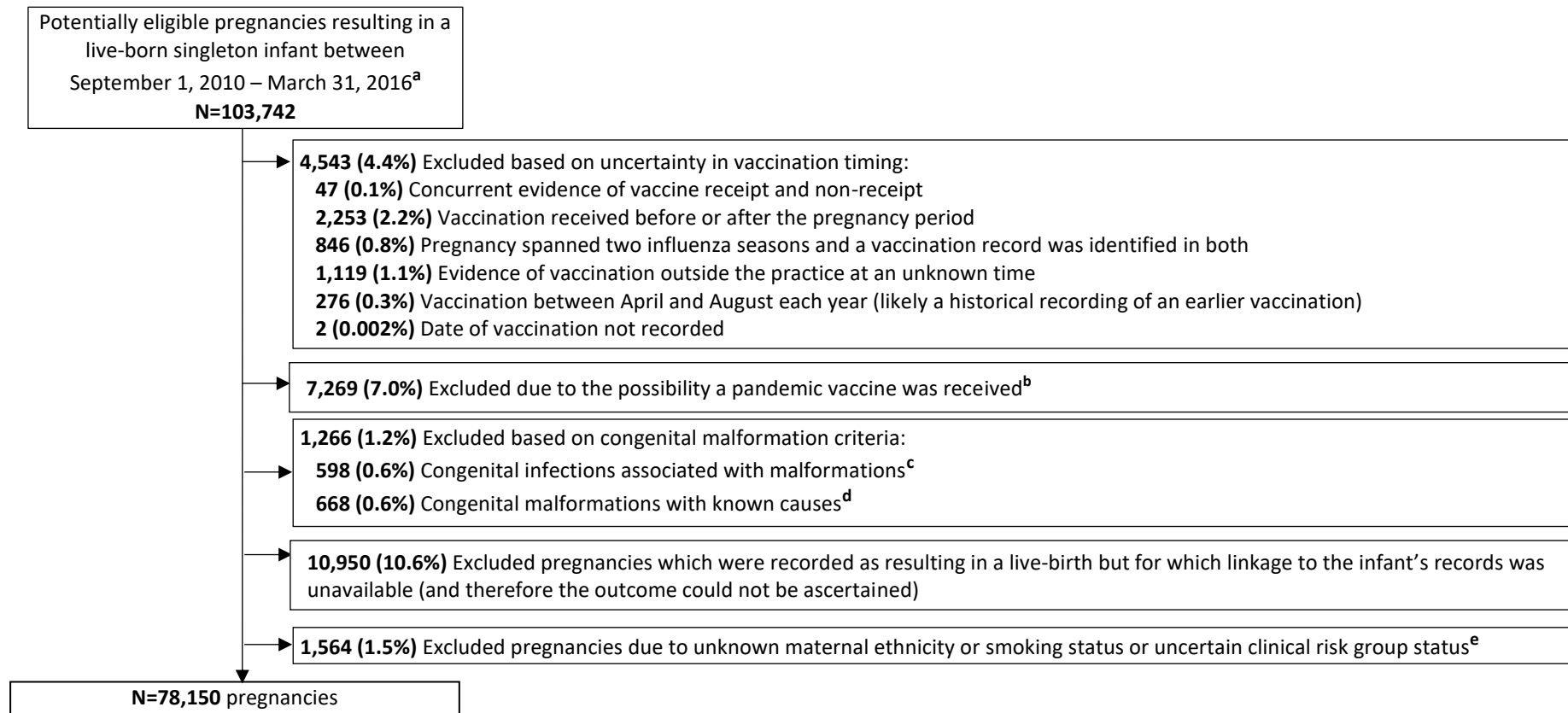
## Results

### Characteristics of the eligible study cohort

We identified 103,742 potentially eligible pregnancies resulting in live-born singletons during the study period. After exclusions were applied, the final cohort included 78,150 pregnancies among 71,124 women (**Figure 1**). Most pregnancies were of white women (85.5%), aged 25-34 (58.9%) years (**Table 1**).

Vaccine uptake was 40.3% (n=31,481): 8.8% (n=6,872) in the first trimester, 14.9% (n=11,678) in the second and 16.5% (n=12,931) in the third. Vaccination in the first trimester or anytime in pregnancy was less likely if the woman was: young, of Black ethnicity, living in a more deprived area, not part of a clinical risk group for which vaccination was recommended,<sup>5</sup> unexposed to teratogenic medications and/or live vaccines, a current smoker or part of a household with children (**Table 1; Supplementary Table 2**). Vaccination also varied by region and the earliest influenza season the pregnancy overlapped with.

Of the 78,150 pregnancies, 7.3% (n=5,707) resulted in an infant with an MCM recorded in the year after delivery, whilst 7.7% (n=6,029) had an MCM recorded after delivery and anytime in the study period. Most MCMs were recorded early in life, with 51% recorded at delivery and 87.2% in the following three months (**Supplementary Figure 1**). Most infants had at least one year of follow-up (73.5%) and almost half had at least two (48.9%) (**Supplementary Table 3**).



**Figure 5 - Derivation of pregnancies used in analyses.** <sup>a</sup>At least one week of the pregnancy had to occur when influenza vaccine was available. All infants had to be eligible for linkage to HES and ONS data. <sup>b</sup>Pandemic vaccine was available alongside SIV in 2009/10 and 2010/11. Pregnant women could be offered the pandemic vaccine in 2010/11, or in 2009/10 if their pregnancy ended after September 1, 2010 but started in the prior influenza season. Pregnancies that received pandemic vaccine or an unspecified influenza vaccine in 2009/10 or 2010/11 were excluded. <sup>c</sup>Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Parvovirus, Varicella-zoster, Syphilis, HIV. <sup>d</sup>Chromosomal anomalies, heritable conditions, or malformations due to a known teratogen. <sup>e</sup>Among pregnancies for which linkage to the infant record was available, 720 had unknown maternal ethnicity, 403 had unknown maternal smoking status and 449 had an uncertain maternal clinical risk group status.

**Table 5 - Characteristics of eligible pregnancies included in analyses, by vaccination status.**

	No. pregnancies (%) N=78,150	No. pregnancies unvaccinated (%) n=46,669	No. pregnancies vaccinated in trimester 1 (%) n=6,872	No. pregnancies vaccinated anytime (%) n=31,481
<b>Maternal age (years)</b>				
<18	719 (0.9)	458 (63.7)	33 (4.6)	261 (36.3)
18-24	13,243 (17.0)	8,451 (63.8)	982 (7.4)	4,792 (36.2)
25-34	46,030 (58.9)	27,138 (59.0)	4,150 (9.0)	18,892 (41.0)
≥35	18,158 (23.2)	10,622 (58.5)	1,707 (9.4)	7,536 (41.5)
<b>Maternal ethnicity</b>				
White	66,849 (85.5)	39,618 (59.3)	5,939 (8.9)	27,231 (40.7)
South Asian	5,501 (7.0)	3,272 (59.5)	507 (9.2)	2,229 (40.5)
Black	2,881 (3.7)	1,953 (67.8)	196 (6.8)	928 (32.2)
Other	1,850 (2.4)	1,171 (63.3)	146 (7.9)	679 (36.7)
Mixed	1,069 (1.4)	655 (61.3)	84 (7.9)	414 (38.7)
<b>Maternal IMD status<sup>a</sup></b>				
1=least deprived	15,847 (20.3)	8,730 (55.1)	1,579 (10.0)	7,117 (44.9)
2	14,905 (19.1)	8,569 (57.5)	1,345 (9.0)	6,336 (42.5)
3	15,144 (19.4)	8,880 (58.6)	1,406 (9.3)	6,264 (41.4)
4	16,064 (20.6)	10,015 (62.3)	1,304 (8.1)	6,049 (37.7)
5=most deprived	16,190 (20.7)	10,475 (64.7)	1,238 (7.7)	5,715 (35.3)
<b>Region</b>				
London	12,922 (16.5)	8,295 (64.2)	991 (7.7)	4,627 (35.8)
North East	1,811 (2.3)	1,203 (66.4)	113 (6.2)	608 (33.6)
North West	11,636 (14.9)	6,771 (58.2)	1,133 (9.7)	4,865 (41.8)
Yorkshire & The Humber	1,453 (1.9)	922 (63.5)	123 (8.5)	531 (36.6)
East Midlands	780 (1.0)	549 (70.4)	45 (5.8)	231 (29.6)
West Midlands	8,545 (10.9)	4,561 (53.4)	997 (11.7)	3,984 (46.6)
East of England	7,862 (10.1)	4,463 (56.8)	741 (9.4)	3,399 (43.2)
South West	9,974 (12.8)	5,936 (59.5)	777 (7.8)	4,038 (40.5)
South Central	11,670 (14.9)	6,710 (57.5)	1,157 (9.9)	4,960 (42.5)
South East Coast	11,497 (14.7)	7,259 (63.1)	795 (6.9)	4,238 (36.9)
<b>Mother was part of a clinical risk group<sup>b</sup></b>				
No	73,804 (94.4)	44,513 (60.3)	6,230 (8.4)	29,291 (39.7)
Yes	4,346 (5.6)	2,156 (49.6)	642 (14.8)	2,190 (50.4)
<b>Maternal smoking status</b>				
Non	41,081 (52.6)	23,922 (58.2)	3,729 (9.1)	17,159 (41.8)
Current	17,687 (22.6)	11,630 (65.8)	1,278 (7.2)	6,057 (34.3)
Ex	19,382 (24.8)	11,117 (57.4)	1,865 (9.6)	8,265 (42.6)
<b>Maternal hazardous drinking</b>				
No	77,502 (99.2)	46,308 (59.8)	6,811 (8.8)	31,194 (40.3)
Yes	648 (0.8)	361 (55.7)	61 (9.4)	287 (44.3)
<b>Extreme maternal BMI</b>				
No	71,335 (91.3)	42,560 (59.7)	6,235 (8.7)	28,775 (40.3)
Underweight (<18)	1,656 (2.1)	1,042 (62.9)	147 (8.9)	614 (37.1)
Obese (≥35)	5,159 (6.6)	3,067 (59.5)	490 (9.5)	2,092 (40.6)
<b>Maternal chronic hypertension (non-pregnancy related)</b>				
No	77,097 (98.7)	46,074 (59.8)	6,760 (8.8)	31,023 (40.2)
Yes	1,053 (1.4)	595 (56.5)	112 (10.6)	458 (43.5)
<b>Maternal exposure to teratogenic medication(s)<sup>c</sup> or live vaccines<sup>d</sup></b>				
No	73,370 (93.9)	43,928 (59.9)	6,386 (8.7)	29,442 (40.1)
Yes	4,780 (6.1)	2,741 (57.3)	486 (10.2)	2,039 (42.7)
<b>Earliest influenza season a pregnancy overlapped with</b>				

	No. pregnancies (%) N=78,150	No. pregnancies unvaccinated (%) n=46,669	No. pregnancies vaccinated in trimester 1 (%) n=6,872	No. pregnancies vaccinated anytime (%) n=31,481
2009/10	5,234 (6.7)	5,171 (98.8)	0 (0.0)	63 (1.2)
2010/11	13,040 (16.7)	10,135 (77.7)	425 (3.3)	2,905 (22.3)
2011/12	18,468 (23.6)	11,254 (60.9)	1,607 (8.7)	7,214 (39.1)
2012/13	15,910 (20.4)	7,833 (49.2)	2,067 (13.0)	8,077 (50.8)
2013/14	13,383 (17.1)	6,906 (51.6)	1,503 (11.2)	6,477 (48.4)
2014/15	9,987 (12.8)	4,715 (47.2)	1,251 (12.5)	5,272 (52.8)
2015/16	2,128 (2.7)	655 (30.8)	19 (0.9)	1,473 (69.2)
<b>No. of weeks the first trimester overlapped with influenza activity above baseline levels</b>				
None	63,145 (80.8)	35,467 (56.2)	4,813 (7.6)	27,678 (43.8)
0-2	6,556 (8.4)	4,649 (70.9)	1,091 (16.6)	1,907 (29.1)
2-4	1,668 (2.1)	1,200 (71.9)	154 (9.2)	468 (28.1)
4-6	2,059 (2.6)	1,525 (74.1)	260 (12.6)	534 (25.9)
6-8	2,954 (3.8)	2,377 (80.5)	346 (11.7)	577 (19.5)
8-10	703 (0.9)	541 (77.0)	88 (12.5)	162 (23.0)
10-12	1,065 (1.4)	910 (85.5)	120 (11.3)	155 (14.6)
<b>No. of children in the maternal household</b>				
None	27,868 (35.7)	15,211 (54.6)	2,833 (10.2)	12,657 (45.4)
1-2	42,911 (54.9)	26,419 (61.6)	3,565 (8.3)	16,492 (38.4)
≥3	7,371 (9.4)	5,039 (68.4)	474 (6.4)	2,332 (31.6)

<sup>a</sup>For 46 (0.06%) pregnancies, maternal household IMD was unavailable and practice-level IMD was used.

<sup>b</sup>Chronic respiratory, heart, kidney, liver or neurological disease, diabetes, immunosuppression due to disease or treatment, asplenia or dysfunction of the spleen. <sup>c</sup>Exposure from six months before pregnancy start until the end of the first trimester. <sup>d</sup>Exposure from three months before pregnancy start until the end of the first trimester. Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index.

### Primary analyses

The univariable Cox regression analysis showed evidence for a crude association between vaccination anytime in pregnancy and MCMs recorded in the year after delivery; results were similar for first and second-trimester vaccination (**Table 2**). However, all associations were eliminated following adjustment for *a priori* confounders: maternal age and ethnicity, region and the earliest influenza season a pregnancy overlapped with (**Table 2**). The most important of these appeared to be region and season; hazard ratios (HRs) remained similar upon the addition of age and ethnicity (**Supplementary Tables 4-5**). Both region and season were associated with age and ethnicity ( $\chi^2$   $p < 0.001$ ), suggesting that adjustment for the former likely resulted in partial adjustment for the latter.

Of the remaining potential confounders, only maternal IMD and number of children in the household were associated with both vaccination and MCMs in univariable analyses

(**Supplementary Tables 2 and 6**). However, upon addition to the model, neither these nor any others altered HRs by  $\geq 5\%$  (**Supplementary Tables 4 and 5**). Fully-adjusted models showed no evidence of an association between vaccination anytime (HR, 1.02; 99% CI, 0.94-1.10;  $p=0.54$ ), vaccination in the first trimester (HR, 1.06; 99% CI, 0.94-1.19;  $p=0.23$ ) or the second (HR, 1.02; 99% CI, 0.92-1.13;  $p=0.63$ ) and MCMs recorded in the year after delivery (**Table 2**). The logistic regression models used to investigate confounding gave very similar results to our final Cox regression models (**Supplementary Tables 4 and 5**).

### **Secondary analyses**

Results from analyses in which follow-up was extended to include any MCMs ascertained from delivery until the end of the study period were almost identical (**Table 2**). Unadjusted models examining major limb malformations showed a crude association with vaccination in all trimesters (**Table 3**). However, adjusting for *a priori* or all potential confounders removed any associations. For congenital heart defects, no association was seen with vaccination in any model.

### **Sensitivity analyses**

Sensitivity analyses that included 216 additional pregnancies for which vaccination occurred four weeks prior to their estimated start, or allowed for follow-up in HES and ONS data to continue after follow-up in CPRD had ended, or excluded 8,093 pregnancies of women with unknown BMI did not differ substantially from main analyses (**Table 4**).

**Table 2 – Examining the association between vaccination and MCMs.**

Vaccination (No. pregnancies)	No. MCMs/person- years (rate per 100 person-years)	HR, unadjusted (99% CI)	<i>P</i> value	HR, adjusted for <i>a</i> <i>priori</i> confounders (99% CI)	<i>P</i> value	HR, adjusted for all potential confounders (99% CI)	<i>P</i> value
<b>Models including MCMs ascertained in the year after delivery (N=5,707 MCMs)</b>							
Never (46,669)	3,289/38,898 (8.5)	1.00		1.00		1.00	
Any trimester (31,481)	2,418/24,827 (9.7)	1.10 (1.03-1.18)	<0.001	1.03 (0.96-1.11)	0.33	1.02 (0.94-1.10)	0.54
Trimester 1 (6,872)	565/5,560 (10.2)	1.17 (1.04-1.32)	<0.001	1.08 (0.96-1.22)	0.11	1.06 (0.94-1.19)	0.23
Trimester 2 (11,678)	902/9,153 (9.9)	1.11 (1.01-1.22)	0.006	1.03 (0.93-1.14)	0.45	1.02 (0.92-1.13)	0.63
Trimester 3 (12,931)	951/10,115 (9.4)	1.05 (0.96-1.16)	0.17	1.00 (0.91-1.10)	>0.99	0.99 (0.90-1.10)	0.86
<b>Models including MCMs ascertained after delivery and anytime in the study period (N=6,029 MCMs)</b>							
Never (46,669)	3,505/102,311 (3.4)	1.00		1.00		1.00	
Any trimester (31,481)	2,524/54,389 (4.6)	1.09 (1.02-1.17)	0.001	1.03 (0.96-1.10)	0.36	1.02 (0.94-1.09)	0.56
Trimester 1 (6,872)	594/11,648 (5.1)	1.18 (1.05-1.32)	<0.001	1.09 (0.97-1.22)	0.07	1.07 (0.95-1.20)	0.16
Trimester 2 (11,678)	941/20,203 (4.7)	1.10 (1.00-1.21)	0.008	1.03 (0.93-1.13)	0.48	1.02 (0.92-1.13)	0.65
Trimester 3 (12,931)	989/22,539 (4.4)	1.04 (0.95-1.14)	0.27	0.99 (0.90-1.09)	0.85	0.99 (0.90-1.09)	0.73

A priori confounders were maternal age, maternal ethnicity, region and the earliest influenza season a pregnancy overlapped with. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. Abbreviations: MCM, major congenital malformations; IMD, Index of Multiple Deprivation; BMI, body mass index; HR, Hazard Ratio; CI, Confidence Interval.

**Table 3 - Examining the association between vaccination, major limb malformations and congenital heart defects.**

Vaccination (No. pregnancies)	No. MCMs/person-years (rate per 100 person- years)	HR, unadjusted (99% CI)	<i>P</i> value	HR, adjusted for <i>a priori</i> confounders (99% CI)	<i>P</i> value	HR, adjusted for all potential confounders (99% CI)	<i>P</i> value
<b>Models including limb malformations ascertained after delivery and anytime in the study period (N=2,425 limb malformations)</b>							
Never (46,669)	1,350/107,080 (1.3)	1.00		1.00		1.00	
Any trimester (31,481)	1,075/56,940 (1.9)	1.20 (1.08-1.33)	<0.001	1.10 (0.99-1.23)	0.03	1.07 (0.96-1.21)	0.11
Trimester 1 (6,872)	235/12,259 (1.9)	1.20 (1.00-1.44)	0.01	1.07 (0.89-1.29)	0.34	1.03 (0.86-1.25)	0.66
Trimester 2 (11,678)	405/21,145 (1.9)	1.22 (1.06-1.41)	<0.001	1.11 (0.96-1.29)	0.07	1.09 (0.93-1.27)	0.17
Trimester 3 (12,931)	435/23,536 (1.9)	1.18 (1.02-1.36)	0.003	1.11 (0.96-1.28)	0.07	1.09 (0.94-1.26)	0.14
<b>Models including congenital heart defects ascertained after delivery and anytime in the study period (N=789 heart defects)</b>							
Never (46,669)	479/109,133 (0.4)	1.00		1.00		1.00	
Any trimester (31,481)	310/58,303 (0.5)	0.99 (0.82-1.20)	0.90	0.96 (0.79-1.17)	0.58	0.93 (0.76-1.15)	0.39
Trimester 1 (6,872)	67/12,568 (0.5)	0.97 (0.69-1.36)	0.82	0.93 (0.66-1.31)	0.58	0.91 (0.64-1.29)	0.49
Trimester 2 (11,678)	129/21,621 (0.6)	1.12 (0.87-1.44)	0.26	1.08 (0.83-1.41)	0.45	1.04 (0.79-1.37)	0.68
Trimester 3 (12,931)	114/24,114 (0.5)	0.89 (0.68-1.16)	0.25	0.87 (0.66-1.14)	0.18	0.85 (0.65-1.13)	0.14

A priori confounders were maternal age, maternal ethnicity, region and the earliest influenza season a pregnancy overlapped with. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. Abbreviations: MCM, major congenital malformations; IMD, Index of Multiple Deprivation; BMI, body mass index; HR, Hazard Ratio; CI, Confidence Interval.



**Table 4 - Examining the association between first-trimester vaccination and MCMs in sensitivity analyses.**

<b>Models</b>	<b>HR, unadjusted (99% CI)</b>	<b>P value</b>	<b>HR, adjusted for <i>a priori</i> confounders (99% CI)</b>	<b>P value</b>	<b>HR, adjusted for all potential confounders (99% CI)</b>	<b>P value</b>
<b>Models including MCMs diagnosed in the year after delivery</b>						
<b>Main model</b>	<b>1.17 (1.04-1.32)</b>	<b>&lt;0.001</b>	<b>1.08 (0.96-1.22)</b>	<b>0.11</b>	<b>1.06 (0.94-1.19)</b>	<b>0.23</b>
Including pregnancies vaccinated in the 4 weeks prior to the start <sup>a</sup>	1.19 (1.06-1.33)	<0.001	1.09 (0.97-1.23)	0.06	1.07 (0.95-1.21)	0.14
Including diagnoses made beyond truncation of follow-up in CPRD <sup>b</sup>	1.17 (1.04-1.32)	<0.001	1.08 (0.96-1.22)	0.11	1.06 (0.94-1.19)	0.23
Excluding pregnancies with unknown BMI <sup>c</sup>	1.18 (1.05-1.33)	<0.001	1.09 (0.96-1.23)	0.09	1.07 (0.94-1.21)	0.19
<b>Models including MCMs diagnosed after delivery and anytime in the study period</b>						
<b>Main model</b>	<b>1.18 (1.05-1.32)</b>	<b>&lt;0.001</b>	<b>1.09 (0.97-1.22)</b>	<b>0.07</b>	<b>1.07 (0.95-1.20)</b>	<b>0.16</b>
Including pregnancies vaccinated in the 4 weeks prior to the start <sup>a</sup>	1.19 (1.07-1.33)	<0.001	1.10 (0.98-1.24)	0.03	1.08 (0.96-1.21)	0.09
Including diagnoses made beyond truncation of follow-up in CPRD <sup>d</sup>	1.17 (1.05-1.31)	<0.001	1.09 (0.97-1.22)	0.06	1.07 (0.95-1.20)	0.14
Excluding pregnancies with unknown BMI <sup>c</sup>	1.18 (1.05-1.33)	<0.001	1.09 (0.96-1.23)	0.08	1.07 (0.95-1.21)	0.16

A priori confounders were maternal age, maternal ethnicity, region and the earliest influenza season a pregnancy overlapped with. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. <sup>a</sup>This model included an additional 216 pregnancies with a vaccination in the 4 weeks before the pregnancy start. <sup>b</sup>There were 22 infants with an MCM recorded in HES or ONS after follow-up in CPRD had ended. <sup>c</sup>This model excluded 8,093 pregnancies that belonged to women with unknown BMI. <sup>d</sup>There were 110 infants with an MCM recorded in HES or ONS after follow-up in CPRD had ended. Abbreviations: MCM, major congenital malformations; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics death certificate data; BMI, body mass index; IMD, Index of Multiple Deprivation; HR, Hazard Ratio; CI, Confidence Interval.

## Discussion

This UK-based historical cohort study examined the association between SIV during pregnancy and MCMs in live-born infants, between the 2010/11 and 2015/16 influenza seasons. Based on 6,872 pregnancies vaccinated in the first trimester, there was no evidence for an association with MCMs recorded in the year after delivery (adjusted HR, 1.06; 99% CI, 0.94-1.19; p=0.2). No evidence of an association was seen in analyses assessing subsequent trimesters or pregnancy overall, or analyses including MCMs recorded after delivery and anytime in the study period. Analyses of major limb and congenital heart defects adjusted for confounding also showed no evidence for an association with first-trimester or later vaccination.

### Strengths

Reviews examining the safety of influenza vaccination with respect to MCMs have highlighted the limited number of studies examining first-trimester vaccination with SIV. Among the few such studies, further limitations such as the low number of pregnancies vaccinated in the first trimester and short follow-up time of infants have prompted calls for further safety evidence.<sup>20-23</sup>

The utilization of the Pregnancy Register, which includes information on trimester dates, allowed for the identification of a large number of pregnancies vaccinated in the first trimester. Follow-up in most studies has been limited to the immediate period around delivery.<sup>50, 90, 104</sup> Whilst a few studies have attempted follow-up for the year after delivery,<sup>101, 103</sup> extending follow-up beyond a year has been shown to still increase the prevalence of recorded MCMs in CPRD.<sup>201, 218, 301</sup> The majority of infants in our cohort had at least one year of follow-up and almost half had at least two. The value of longer follow-up is demonstrated by the fact that 12.8% of MCMs in our cohort were identified after 3 months and 5.3% after a year.

A further strength of this study was the linkage of CPRD data to HES and ONS to maximize MCM ascertainment. Previous research suggests that reliance on sole data sources can lead to significant under-ascertainment of conditions.<sup>302</sup> This may be particularly true for MCMs, many of which are likely to be identified in hospital and communicated in letters not available to researchers in the electronic primary care record unless encoded, which may be incomplete or delayed. Linkage to ONS further serves to ascertain those cases that may have been detected following the infant's death. For completeness, we also examined MCM recordings made in HES or ONS after follow-up in CPRD had ended, but this made minimal difference.

### **Limitations**

Whilst our study had a number of strengths, there were also limitations. Coding algorithms to identify MCMs were developed in accordance with EUROCAT guidelines and with a consultant neonatologist. The few studies that have assessed the positive predictive value of MCMs recorded in CPRD have found this to be good overall (78-86%), with results for congenital heart defects being above 90%.<sup>192, 194, 292, 293</sup> However, validation of diagnoses in HES have not been undertaken.

The estimate of gestation at the time of vaccination is based on the Pregnancy Register's use of a wide range of information recorded in primary care which is thought to give rise to increased accuracy. However, any imprecision in the estimated pregnancy start date could result in misclassification of the timing of vaccination during pregnancy. Sensitivity analyses including pregnancies that received SIV in the 4 weeks prior to their start went some way in addressing this and did not reveal evidence for an association with MCMs. In addition to the above, whilst general practitioners are required to document vaccinations received outside of the surgery and the maternal influenza vaccination programme was delivered almost entirely through general practices over the study period, misclassification of vaccination could potentially occur if women were vaccinated elsewhere and practitioners were not notified.<sup>73</sup>

We adjusted for a number of potential confounders but were not always able to determine maternal smoking, hazardous drinking or BMI at the start of pregnancy and sometimes had to rely on the most proximate record. Although in our main analyses women with unknown BMI were categorized as not having any evidence of extreme BMI, our sensitivity analyses excluding these pregnancies yielded similar results. We cannot discount the possibility of residual confounding from other risk factors for MCMs that may also be associated with vaccine uptake in pregnancy and that are likely to be poorly recorded in CPRD, such as religion.<sup>303</sup>

This study only examined live-birth pregnancies with linked infant records, excluding 10.6% of pregnancies because they lacked linkage. There are many reasons for non-linkage, including the practice stopping contributing to CPRD or mothers moving away. It is possible that severe malformations resulting in the death or prolonged hospitalisation of neonates could also prevent linkage, but it seems unlikely that this incomplete ascertainment would depend on maternal vaccination status. This study also did not explore any potential role of malformations on the causal pathway between vaccination and pregnancy losses. However, studies thus far have found no evidence for an association between vaccination and such outcomes.<sup>18-20</sup>

### **Comparison with other studies**

Our results are consistent with those from other studies that have examined SIV receipt during pregnancy and have shown no association with MCMs; this includes analyses of first-trimester vaccination for which point estimates from other studies ranged between 0.67 and 1.91, with confidence intervals including the null.<sup>90, 101, 103, 104</sup> Reassuringly, our point estimates for MCMs following first-trimester vaccination are in line with those from the largest study to date, which examined SIV receipt between 2004-2013 in the US (adjusted prevalence ratio, 1.02; 95% CI, 0.94-1.10; p=0.55).<sup>103</sup> Ours is the next largest study and provides further evidence on the safety of SIV during pregnancy in another setting and for subsequent years, using a recently-

developed Pregnancy Register that considers all available data in CPRD to estimate gestation at the time of vaccination as well as maximizing ascertainment of MCMs through long-term follow-up in linked data.

The lack of an association between first-trimester vaccination and congenital heart defects in our study was consistent with results from two other studies, including the large US study.<sup>103, 104</sup> Whilst other studies have examined limb malformations and not found any association with vaccination, they have grouped these with defects in other organ systems or examined a limited selection of particular diagnoses such as talipes equinovarus (clubfoot).<sup>103, 104</sup> This study assessed all major limb malformations as a stand-alone subgroup and confirmed the lack of association with SIV.

## **Conclusions**

The findings from this large cohort study, in which the majority of infants were followed-up for at least one year, provide further evidence on the safety profile of influenza vaccination in pregnancy. There was no evidence for an association between first-trimester vaccination and MCMs, limb malformations or congenital heart defects after controlling for confounding. This study shows ongoing monitoring of the safety of first-trimester vaccination is possible using CPRD and could usefully include additional MCM subgroups when sufficient numbers become available.

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See research paper cover sheet.

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## References

References are included as part of the main reference list at the end of the thesis.

## Submitted Paper: Supplementary Material

**Supplementary Table 1** - See Section 4.6 for details of how potential confounders were defined.

**Supplementary Table 2** - Examination of the association between all potential confounders and vaccination.

**Supplementary Table 3** - Follow-up time among eligible infants.

**Supplementary Table 4** - Logistic and Cox regression models examining the relative odds and hazards of major malformations diagnosed in the year after delivery for those pregnancies vaccinated in the first trimester.

**Supplementary Table 5** - Logistic and Cox regression models examining the relative odds and hazards of major malformations diagnosed in the year after delivery for those pregnancies vaccinated anytime.

**Supplementary Table 6** - Examination of the association between all potential confounders and major malformations recorded in the first year of life.

**Supplementary Figure 1** - Distribution of the timing of major malformation recordings in the study period.

**Supplementary Table 6 - Examination of the association between all potential confounders and vaccination.**

	No. pregnancies unvaccinated (%) n=47,661	No. pregnancies vaccinated anytime in pregnancy (%) n=32,053	No. pregnancies vaccinated in 1 <sup>st</sup> trimester (%) n=7,009	Odds ratio for vaccination anytime (99% CI)	P value	Odds ratio for vaccination in the 1 <sup>st</sup> trimester (99% CI)	P value
<b>Maternal age (years)</b>							
<18	531 (65.7)	277 (34.3)	35 (4.3)	0.75 (0.62-0.91)	<0.0001	0.43 (0.27-0.67)	<0.0001
18-24	8,661 (63.8)	4,910 (36.2)	1,009 (7.4)	0.81 (0.77-0.86)		0.76 (0.69-0.84)	
25-34	27,598 (59.0)	19,217 (41.1)	4,235 (9.1)	1.00		1.00	
≥35	10,871 (58.7)	7,649 (41.3)	1,730 (9.3)	1.01 (0.97-1.06)		1.04 (0.96-1.12)	
<b>Maternal ethnicity</b>							
White	40,106 (59.3)	27,493 (40.7)	6,001 (8.9)	1.00	<0.0001	1.00	<0.0001
South Asian	3,303 (59.5)	2,246 (40.5)	511 (9.2)	0.99 (0.92-1.07)		1.03 (0.91-1.17)	
Black	1,965 (67.7)	936 (32.3)	198 (6.8)	0.69 (0.63-0.77)		0.67 (0.55-0.82)	
Other	1,182 (63.3)	684 (36.7)	148 (7.9)	0.84 (0.74-0.96)		0.84 (0.67-1.05)	
Mixed	664 (61.5)	415 (38.5)	84 (7.8)	0.91 (0.78-1.07)		0.85 (0.63-1.14)	
Unknown	441 (61.3)	279 (38.8)	67 (9.3)	-		-	
<b>Maternal IMD status</b>							
1=least deprived	8,958 (55.2)	7,258 (44.8)	1,620 (10.0)	1.00	<0.0001	1.00	<0.0001
2	8,746 (57.5)	6,456 (42.5)	1,371 (9.0)	0.91 (0.86-0.97)		0.87 (0.78-0.96)	
3	9,079 (58.6)	6,403 (41.4)	1,443 (9.3)	0.87 (0.82-0.92)		0.88 (0.79-0.97)	
4	10,198 (62.4)	6,143 (37.6)	1,319 (8.1)	0.74 (0.70-0.79)		0.72 (0.65-0.79)	
5=most deprived	10,680 (64.8)	5,793 (35.2)	1,256 (7.6)	0.67 (0.63-0.71)		0.65 (0.59-0.72)	
<b>Region</b>							
London	8,415 (64.2)	4,697 (35.8)	1,008 (7.7)	1.00	<0.0001	1.00	<0.0001
North East	1,232 (66.8)	612 (33.2)	113 (6.1)	0.89 (0.78-1.02)		0.77 (0.59-1.00)	
North West	6,879 (58.2)	4,932 (41.8)	1,147 (9.7)	1.28(1.20-1.37)		1.39 (1.24-1.57)	
Yorkshire & The Humber	934 (63.6)	535 (36.4)	125 (8.5)	1.03 (0.89-1.19)		1.12 (0.86-1.45)	
East Midlands	570 (71.0)	233 (29.0)	46 (5.7)	0.73 (0.60-0.90)		0.67 (0.45-1.01)	
West Midlands	4,663 (53.4)	4,065 (46.6)	1,025 (11.7)	1.56 (1.45-1.68)		1.84 (1.62-2.08)	
East of England	4,588 (57.0)	3,459 (43.0)	759 (9.4)	1.35 (1.25-1.46)		1.38 (1.21-1.58)	
South West	6,026 (59.5)	4,099 (40.5)	788 (7.8)	1.22 (1.14-1.31)		1.09 (0.96-1.24)	
South Central	6,850 (57.5)	5,074 (42.6)	1,188 (10.0)	1.33 (1.24-1.42)		1.45 (1.29-1.63)	
South East Coast	7,504 (63.3)	4,347 (36.7)	810 (6.8)	1.04 (0.97-1.11)		0.90 (0.79-1.02)	

	No. pregnancies unvaccinated (%) n=47,661	No. pregnancies vaccinated anytime in pregnancy (%) n=32,053	No. pregnancies vaccinated in 1 <sup>st</sup> trimester (%) n=7,009	Odds ratio for vaccination anytime (99% CI)	P value	Odds ratio for vaccination in the 1 <sup>st</sup> trimester (99% CI)	P value
<b>Mother was part of a clinical risk group</b>							
No	45,240 (60.4)	29,659 (39.6)	6,312 (8.4)	1.00	<0.0001	1.00	<0.0001
Yes	2,172 (49.8)	2,194 (50.3)	643 (14.7)	1.54 (1.42-1.67)		2.12 (1.88-2.39)	
Unknown	249 (55.5)	200 (44.5)	54 (12.0)	-		-	
<b>Maternal smoking status</b>							
Non	24,280 (58.2)	17,433 (41.8)	3,801 (9.1)	1.00	<0.0001	1.00	<0.0001
Current	11,784 (65.8)	6,136 (34.2)	1,296 (7.2)	0.73 (0.69-0.76)		0.70 (0.64-0.77)	
Ex	11,289 (57.4)	8,389 (42.6)	1,896 (9.6)	1.03 (0.99-1.08)		1.07 (0.99-1.16)	
Unknown	308 (76.4)	95 (23.6)	16 (4.0)	-		-	
<b>Maternal hazardous drinking</b>							
No	47,289 (59.8)	31,764 (40.2)	6,947 (8.8)	1.00	0.07	1.00	0.37
Yes	372 (56.3)	289 (43.7)	62 (9.4)	1.16 (0.94-1.42)		1.13 (0.80-1.62)	
<b>Extreme maternal BMI</b>							
No	43,469 (59.7)	29,302 (40.3)	6,361 (8.7)	1.00	0.03	1.00	0.25
Underweight	1,063 (62.9)	627 (37.1)	151 (8.9)	0.88 (0.77-1.00)		0.97 (0.77-1.22)	
Obese	3,129 (59.6)	2,124 (40.4)	497 (9.5)	1.01 (0.93-1.09)		1.09 (0.95-1.24)	
<b>Maternal chronic hypertension (non-pregnancy related)</b>							
No	47,058 (59.8)	31,586 (40.2)	6,896 (8.8)	1.00	0.02	1.00	0.02
Yes	603 (56.4)	467 (43.6)	113 (10.6)	1.15 (0.98-1.35)		1.28 (0.98-1.67)	
<b>Maternal exposure to teratogenic medication(s) or live vaccines</b>							
No	44,876 (60.0)	29,980 (40.1)	6,514 (8.7)	1.00	0.0003	1.00	0.0001
Yes	2,785 (57.3)	2,073 (42.7)	495 (10.2)	1.11 (1.03-1.20)		1.22 (1.07-1.39)	
<b>Earliest influenza season a pregnancy overlapped with</b>							
2009/10	5,292 (98.8)	63 (1.2)	0 (0.0)	0.02 (0.01-0.03)	<0.0001	1.00 (empty)	<0.0001
2010/11	10,358 (77.8)	2,954 (22.2)	439 (3.3)	0.45 (0.42-0.48)		0.30 (0.26-0.34)	
2011/12	11,473 (61.0)	7,332 (39.0)	1,639 (8.7)	1.00		1.00	
2012/13	7,977 (49.4)	8,185 (50.6)	2,100 (13.0)	1.61 (1.52-1.70)		1.84 (1.68-2.02)	
2013/14	7,030 (51.6)	6,596 (48.4)	1,527 (11.2)	1.47 (1.38-1.56)		1.52 (1.38-1.68)	
2014/15	4,846 (47.3)	5,409 (52.8)	1,283 (12.5)	1.75 (1.64-1.86)		1.85 (1.67-2.06)	
2015/16	685 (31.2)	1,514 (68.9)	21 (1.0)	3.46 (3.05-3.92)		0.21 (0.12-0.38)	



	No. pregnancies unvaccinated (%) n=47,661	No. pregnancies vaccinated anytime in pregnancy (%) n=32,053	No. pregnancies vaccinated in 1 <sup>st</sup> trimester (%) n=7,009	Odds ratio for vaccination anytime (99% CI)	P value	Odds ratio for vaccination in the 1 <sup>st</sup> trimester (99% CI)	P value
<b>No. of weeks the first trimester overlapped with influenza activity above baseline levels</b>							
None	36,207 (56.3)	28,161 (43.8)	4,901 (7.6)	1.00	<0.0001	1.00	<0.0001
0-2	4,737 (70.9)	1,943 (29.1)	1,113 (16.7)	0.53 (0.49-0.57)		1.74 (1.58-1.91)	
2-4	1,236 (72.1)	479 (27.9)	157 (9.2)	0.50 (0.43-0.57)		0.94 (0.75-1.17)	
4-6	1,554 (73.7)	554 (26.3)	269 (12.8)	0.46 (0.40-0.52)		1.28 (1.07-1.52)	
6-8	2,433 (80.5)	588 (19.5)	354 (11.7)	0.31 (0.28-0.35)		1.07 (0.92-1.25)	
8-10	561 (76.9)	169 (23.2)	91 (12.5)	0.39 (0.31-0.49)		1.20 (0.89-1.61)	
10-12	933 (85.4)	159 (14.6)	124 (11.4)	0.22 (0.18-0.27)		0.98 (0.77-1.26)	
<b>No. of children in maternal household</b>							
None	15,629 (54.7)	12,934 (45.3)	2,900 (10.3)	1.00	<0.0001	1.00	<0.0001
1-2	26,891 (61.6)	16,751 (38.4)	3,629 (8.3)	0.75 (0.72-0.78)		0.73 (0.68-0.78)	
≥3	5,141 (68.5)	2,368 (31.5)	480 (6.4)	0.56 (0.52-0.60)		0.50 (0.44-0.58)	

Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index; CI, confidence interval.

**Supplementary Table 3 - Follow-up time among eligible infants.**

<b>Follow-up time</b>	<b>Proportion of infants (No.)</b> <b>N=78,150</b>
≥3 months	94.7 (74,031)
≥6 months	87.8 (68,589)
≥1 year	73.5 (57,442)
≥2 years	48.9 (38,184)
≥3 years	28.7 (22,446)
≥4 years	13.3 (10,369)
≥5 years	3.8 (2,995)

Follow-up time was calculated as the length of time between delivery and the earliest of the following dates: the date the infant left the practice, the date the practice stopped collecting data, the date of death of the infant or the end of the study period (March 31, 2016).

**Supplementary Table 4 - Logistic and Cox regression models examining the relative odds and hazards of major malformations diagnosed in the year after delivery for those pregnancies vaccinated in the first trimester.**

Model	First trimester vaccination + <i>a priori</i> confounders added	Other potential confounders added	ORs for major malformations using logistic regression (99% CI)	<i>P</i> values	HRs for major malformations using Cox regression (99% CI)	<i>P</i> values	Rho and <i>P</i> values for clustering
1	Vaccination	-	1.18 (1.05-1.34)	<0.001	1.17 (1.04-1.32)	<0.001	
2a	Vaccination + Age	-	1.18 (1.04-1.33)		1.17 (1.04-1.32)		
2b	Vaccination + Ethnicity	-	1.18 (1.05-1.34)		1.18 (1.04-1.32)		
2c	Vaccination + Region	-	1.13 (1.00-1.28)		1.13 (1.00-1.27)		
2d	Vaccination + Year	-	1.14 (1.01-1.29)		1.13 (1.00-1.28)		
2e	Vaccination + Region + Year	-	1.08 (0.95-1.23)		1.08 (0.96-1.22)		
2f	Vaccination + Region + Year + Age	-	1.08 (0.95-1.22)		1.08 (0.95-1.21)		
2g	Vaccination + Region + Year + Ethnicity	-	1.09 (0.96-1.23)		1.08 (0.96-1.22)		
2h	Vaccination + Age, Ethnicity, Region, Year	-	1.08 (0.95-1.23)	0.10	1.08 (0.96-1.22)	0.11	
3	Vaccination + Age, Ethnicity, Region, Year	IMD	1.08 (0.95-1.22)		1.07 (0.95-1.21)		
4	Vaccination + Age, Ethnicity, Region, Year	No. children in home	1.07 (0.94-1.21)		1.06 (0.94-1.20)		
5	Vaccination + Age, Ethnicity, Region, Year	IMD, No. children in home	1.06 (0.94-1.21)		1.06 (0.94-1.19)		
6a	Vaccination + Age, Ethnicity, Region, Year	Smoking	1.08 (0.95-1.22)		1.08 (0.95-1.21)		
6b	Vaccination + Age, Ethnicity, Region, Year	Drinking	1.08 (0.95-1.23)		1.08 (0.96-1.22)		
6c	Vaccination + Age, Ethnicity, Region, Year	Smoking, Drinking	1.08 (0.95-1.23)		1.08 (0.95-1.21)		
7a	Vaccination + Age, Ethnicity, Region, Year	BMI	1.08 (0.95-1.23)		1.08 (0.96-1.22)		
7b	Vaccination + Age, Ethnicity, Region, Year	Clinical risk group	1.08 (0.95-1.22)		1.08 (0.95-1.21)		
7c	Vaccination + Age, Ethnicity, Region, Year	Hypertension	1.08 (0.95-1.23)		1.08 (0.96-1.22)		
7d	Vaccination + Age, Ethnicity, Region, Year	Exposure to teratogenic medication/live vaccines	1.08 (0.96-1.23)		1.08 (0.96-1.22)		
7e	Vaccination + Age, Ethnicity, Region, Year	BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines	1.08 (0.95-1.23)		1.08 (0.95-1.21)		
8	Vaccination + Age, Ethnicity, Region, Year	Influenza activity above baseline levels	1.09 (0.96-1.23)		1.08 (0.96-1.22)		

Model	First trimester vaccination + <i>a priori</i> confounders added	Other potential confounders added	ORs for major malformations using logistic regression (99% CI)	<i>P</i> values	HRs for major malformations using Cox regression (99% CI)	<i>P</i> values	Rho and <i>P</i> values for clustering
9	Vaccination + Age, Ethnicity, Region, Year	Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza activity above baseline levels	1.06 (0.94-1.21)	0.22	1.06 (0.94-1.19)	0.23	
10	Vaccination + Age, Ethnicity, Region, Year	cluster(mother)	1.09 (0.95-1.24)	-			rho=0.18, p<0.001
11	Vaccination + Age, Ethnicity, Region, Year	cluster(practice)	1.09 (0.96-1.24)	-			rho=0.04, p<0.001
12	Vaccination + Age, Ethnicity, Region, Year	Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza Activity + cluster(mother)	1.07 (0.93-1.22)	-			rho=0.18, p<0.001
13	Vaccination + Age, Ethnicity, Region, Year	Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza Activity + cluster(practice)	1.07 (0.94-1.22)	-			rho=0.04, p<0.001

These models were complete case analyses and included all 78,150 eligible pregnancies. The univariable model (1), model adjusted for all *a priori* confounders (2h) and fully-adjusted model (9) are highlighted. Results were strikingly similar regardless of whether logistic or Cox regression were used. Abbreviations: Year, earliest influenza season the pregnancy overlapped with; IMD, Index of Multiple Deprivation; BMI, body mass index; OR, odds ratios; HR, hazard ratios; CI, confidence interval.

**Supplementary Table 5 - Logistic and Cox regression models examining the relative odds and hazards of major malformations diagnosed in the year after delivery for those pregnancies vaccinated anytime.**

Model	Vaccination <u>anytime</u> in pregnancy + <i>a priori</i> confounders added	Other potential confounders added	ORs for major malformations using logistic regression (99% CI)	<i>P</i> values	HRs for major malformations using Cox regression (99% CI)	<i>P</i> values	Rho and <i>P</i> values for clustering
1	Vaccination	-	1.10 (1.02-1.18)	0.001	1.10 (1.03-1.18)	<0.001	
2a	Vaccination + Age	-	1.10 (1.02-1.18)		1.10 (1.02-1.18)		
2b	Vaccination + Ethnicity	-	1.10 (1.02-1.18)		1.10 (1.03-1.18)		
2c	Vaccination + Region	-	1.07 (0.99-1.15)		1.07 (1.00-1.15)		
2d	Vaccination + Year	-	1.07 (0.99-1.15)		1.06 (0.99-1.14)		
2e	Vaccination + Region + Year	-	1.03 (0.96-1.11)		1.03 (0.95-1.10)		
2f	Vaccination + Region + Year + Age	-	1.03 (0.95-1.11)		1.02 (0.95-1.10)		
2g	Vaccination + Region + Year + Ethnicity	-	1.03 (0.96-1.12)		1.03 (0.96-1.11)		
2h	Vaccination + Age, Ethnicity, Region, Year	-	1.03 (0.96-1.11)	0.29	1.03 (0.96-1.11)	0.33	
3	Vaccination + Age, Ethnicity, Region, Year	IMD	1.02 (0.95-1.11)		1.02 (0.95-1.10)		
4	Vaccination + Age, Ethnicity, Region, Year	No. children in home	1.02 (0.94-1.10)		1.02 (0.94-1.09)		
5	Vaccination + Age, Ethnicity, Region, Year	IMD, No. children in home	1.01 (0.94-1.09)		1.01 (0.94-1.09)		
6a	Vaccination + Age, Ethnicity, Region, Year	Smoking	1.03 (0.95-1.11)		1.03 (0.95-1.10)		
6b	Vaccination + Age, Ethnicity, Region, Year	Drinking	1.03 (0.96-1.11)		1.03 (0.96-1.11)		
6c	Vaccination + Age, Ethnicity, Region, Year	Smoking, Drinking	1.03 (0.95-1.11)		1.03 (0.95-1.10)		
7a	Vaccination + Age, Ethnicity, Region, Year	BMI	1.03 (0.96-1.11)		1.03 (0.96-1.11)		
7b	Vaccination + Age, Ethnicity, Region, Year	Clinical risk group	1.03 (0.95-1.11)		1.03 (0.95-1.10)		
7c	Vaccination + Age, Ethnicity, Region, Year	Hypertension	1.03 (0.96-1.11)		1.03 (0.96-1.11)		
7d	Vaccination + Age, Ethnicity, Region, Year	Exposure to teratogenic medication/live vaccines	1.03 (0.96-1.11)		1.03 (0.96-1.11)		
7e	Vaccination + Age, Ethnicity, Region, Year	BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines	1.03 (0.96-1.11)		1.03 (0.96-1.11)		
8	Vaccination + Age, Ethnicity, Region, Year	Influenza activity above baseline levels	1.04 (0.96-1.12)		1.04 (0.96-1.12)		
9	Vaccination + Age, Ethnicity, Region, Year	Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic	1.02 (0.94-1.10)	0.51	1.02 (0.94-1.10)	0.54	

Model	Vaccination anytime in pregnancy + a priori confounders added	Other potential confounders added	ORs for major malformations using logistic regression (99% CI)	P values	HRs for major malformations using Cox regression (99% CI)	P values	Rho and P values for clustering
		medications/live vaccines, Influenza Activity above baseline levels					
10	Vaccination + Age, Ethnicity, Region, Year	cluster(mother)	1.03 (0.95-1.12)	-			rho=0.18, p<0.001
11	Vaccination + Age, Ethnicity, Region, Year	cluster(practice)	1.03 (0.96-1.12)	-			rho=0.04, p<0.001
12	Vaccination + Age, Ethnicity, Region, Year	Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza Activity + cluster(mother)	1.02 (0.94-1.11)	-			rho=0.18, p<0.001
13	Vaccination + Age, Ethnicity, Region, Year	Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza Activity + cluster(practice)	1.02 (0.95-1.11)	-			rho=0.04, p<0.001

These models were complete case analyses and included all 78,150 eligible pregnancies. The univariable model (1), model adjusted for all a priori confounders (2h) and fully-adjusted model (9) are highlighted. Results were strikingly similar regardless of whether logistic or Cox regression were used. Abbreviations: Year, earliest influenza season the pregnancy overlapped with; IMD, Index of Multiple Deprivation; BMI, body mass index; OR, odds ratios; HR, hazard ratios; CI, confidence interval.

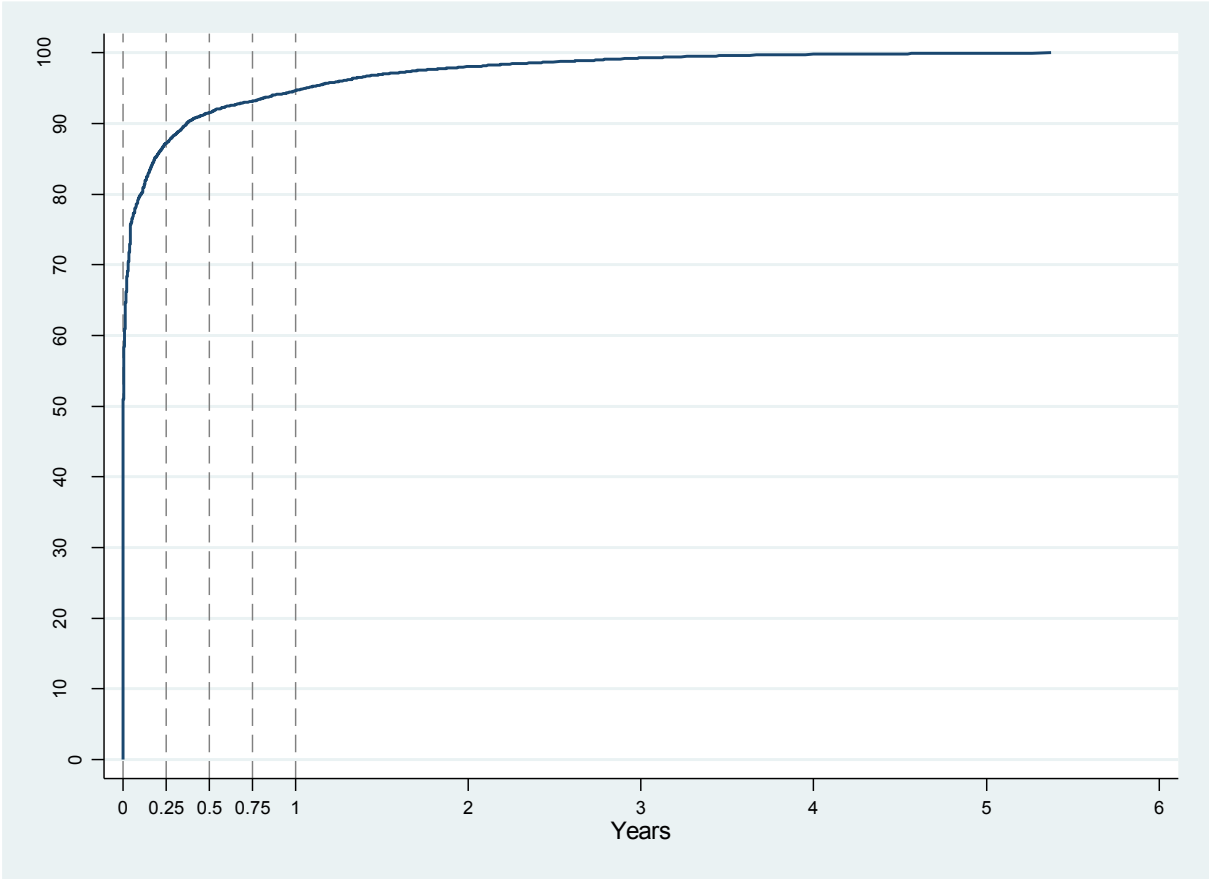
**Supplementary Table 6 - Examination of the association between all potential confounders and major malformations recorded in the first year of life.**

	No. pregnancies resulting in no major malformation (%) n=73,898	No. pregnancies resulting in a major malformation (%) n=5,816	Odds ratios for major malformation (99% CI)	P value
<b>Maternal age (years)</b>				
<18	753 (93.2)	55 (6.8)	0.93 (0.65-1.34)	0.09
18-24	12,628 (93.1)	943 (7.0)	0.95 (0.86-1.05)	
25-34	43,417 (92.7)	3,398 (7.3)	1.00	
≥35	17,100 (92.3)	1,420 (7.7)	1.06 (0.97-1.15)	
<b>Maternal ethnicity</b>				
White	62,755 (92.8)	4,844 (7.2)	1.00	0.001
South Asian	5,075 (91.5)	474 (8.5)	1.21 (1.06-1.38)	
Black	2,665 (91.9)	236 (8.1)	1.15 (0.96-1.37)	
Other	1,721 (92.2)	145 (7.8)	1.09 (0.87-1.37)	
Mixed	1,007 (93.3)	72 (6.7)	0.93 (0.67-1.27)	
Unknown	675 (93.8)	45 (6.3)	-	
<b>Maternal IMD status</b>				
1=least deprived	14,954 (92.2)	1,262 (7.8)	1.00	0.0009
2	14,048 (92.4)	1,154 (7.6)	0.97 (0.87-1.09)	
3	14,388 (92.9)	1,094 (7.1)	0.90 (0.81-1.01)	
4	15,251 (93.3)	1,090 (6.7)	0.85 (0.76-0.95)	
5=most deprived	15,257 (92.6)	1,216 (7.4)	0.94 (0.85-1.05)	
<b>Region</b>				
London	12,343 (94.1)	769 (5.9)	1.00	<0.0001
North East	1,694 (91.9)	150 (8.1)	1.42 (1.12-1.81)	
North West	10,852 (91.9)	959 (8.1)	1.42 (1.25-1.61)	
Yorkshire & The Humber	1,364 (92.9)	105 (7.2)	1.24 (0.94-1.63)	
East Midlands	776 (96.6)	27 (3.4)	0.56 (0.33-0.93)	
West Midlands	7,799 (89.4)	929 (10.6)	1.91 (1.68-2.18)	
East of England	7,397 (91.9)	650 (8.1)	1.41 (1.22-1.63)	
South West	9,509 (93.9)	616 (6.1)	1.04 (0.90-1.20)	
South Central	11,061 (92.8)	863 (7.2)	1.25 (1.10-1.43)	
South East Coast	11,103 (93.7)	748 (6.3)	1.08 (0.94-1.24)	
<b>Mother was part of a clinical risk group</b>				
No	69,458 (92.7)	5,441 (7.3)	1.00	0.16
Yes	4,024 (92.2)	342 (7.8)	1.08 (0.93-1.26)	
Unknown	416 (92.7)	33 (7.4)	-	
<b>Maternal smoking status</b>				
Non	38,574 (92.5)	3,139 (7.5)	1.00	0.02
Current	16,680 (93.1)	1,240 (6.9)	0.91 (0.84-1.00)	
Ex	18,273 (92.9)	1,405 (7.1)	0.94 (0.87-1.03)	
Unknown	371 (92.1)	32 (7.9)	-	
<b>Maternal hazardous drinking</b>				
No	73,274 (92.7)	5,779 (7.3)	1.00	0.08
Yes	624 (94.4)	37 (5.6)	0.75 (0.49-1.16)	
<b>Extreme maternal BMI</b>				
No	67,514 (92.8)	5,257 (7.2)	1.00	0.04
Underweight	1,552 (91.8)	138 (8.2)	1.14 (0.91-1.44)	
Obese	4,832 (92.0)	421 (8.0)	1.12 (0.98-1.28)	
<b>Maternal chronic hypertension (non-pregnancy related)</b>				
No	72,907 (92.7)	5,737 (7.3)	1.00	0.91
Yes	991 (92.6)	79 (7.4)	1.01 (0.75-1.37)	
<b>Maternal exposure to teratogenic medication(s) or live vaccines</b>				
No	69,382 (92.7)	5,474 (7.3)	1.00	0.48
Yes	4,516 (93.0)	342 (7.0)	0.96 (0.83-1.11)	

	No. pregnancies resulting in no major malformation (%) n=73,898	No. pregnancies resulting in a major malformation (%) n=5,816	Odds ratios for major malformation (99% CI)	P value
<b>Earliest influenza season a pregnancy overlapped with</b>				
2009/10	4,997 (93.3)	358 (6.7)	0.96 (0.82-1.13)	<0.0001
2010/11	12,422 (93.3)	890 (6.7)	0.96 (0.86-1.08)	
2011/12	17,503 (93.1)	1,302 (6.9)	1.00	
2012/13	14,926 (92.4)	1,236 (7.7)	1.11 (1.00-1.24)	
2013/14	12,549 (92.1)	1,077 (7.9)	1.15 (1.03-1.29)	
2014/15	9,452 (92.2)	803 (7.8)	1.14 (1.01-1.29)	
2015/16	2,049 (93.2)	150 (6.8)	0.98 (0.78-1.24)	
<b>No. of weeks the first trimester overlapped with influenza activity above baseline levels</b>				
None	59,688 (92.7)	4,680 (7.3)	1.00	0.13
0-2	6,182 (92.5)	498 (7.5)	1.03 (0.91-1.17)	
2-4	1,588 (92.6)	127 (7.4)	1.02 (0.80-1.30)	
4-6	1,976 (93.7)	132 (6.3)	0.85 (0.67-1.08)	
6-8	2,800 (92.7)	221 (7.3)	1.01 (0.84-1.21)	
8-10	673 (92.2)	57 (7.8)	1.08 (0.76-1.54)	
10-12	991 (90.8)	101 (9.3)	1.30 (0.99-1.71)	
<b>No. of children in maternal household</b>				
0	26,356 (92.3)	2,207 (7.7)	1.00	0.002
1-2	40,561 (92.9)	3,081 (7.1)	0.91 (0.84-0.98)	
≥3	6,981 (93.0)	528 (7.0)	0.90 (0.79-1.03)	

Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index; CI, confidence interval.





Supplementary Figure 1 - Distribution of the timing of major malformation recordings in the study period.

## 8.4 The prevalence of system-specific major congenital malformations by vaccination status

Ideally, safety studies examining MCMs as an outcome should examine the risk of individual conditions. This is because the types of malformation that occur following exposure to a teratogen depend on the timing and duration of the exposure in relation to the developmental stage of the foetus, as well as the molecular mechanism by which the teratogen disrupts development.<sup>81</sup> For example, thalidomide is known to cause severe limb reduction defects whereas anticonvulsants have been associated with neural tube defects (among other malformations).<sup>81</sup>

However, studies seldom examine specific MCMs due to their individual rarity which reduces statistical power and increases the risk of a type II error, particularly if analyses are also stratified by trimester of vaccination (or other exposure). Despite the large cohort identified for the analyses presented in this chapter, and follow-up beyond the first year of life, there were still low numbers of MCMs when these were divided into system-specific EUROCAT subgroups. The largest subgroups were limb (n=2,425) and congenital heart defects (n=789). The number of infants whose mother had received a seasonal influenza vaccine in the first trimester of pregnancy was low for most system-specific MCMs – with the highest numbers again seen among limb malformations (n=235), and congenital heart defects (n=67).

Numbers were even lower for particular subsets of conditions within the system-specific subgroups defined by EUROCAT. For example, an examination of ICD-10 coded diagnoses in HES (which could be mapped directly onto diagnoses defined by EUROCAT, unlike Read-coded diagnoses in CPRD) indicated that just 28 infants in the study population had evidence of a limb reduction defect (**Table 8.1**) and  $\leq 5$  of these infants were born to mothers who were vaccinated in the first trimester (**Table 8.1**; exact number not given to prevent deductive disclosure). The power to detect a doubling of the rate of limb reduction defects in the 6,872 infants whose mothers were vaccinated in the first trimester compared to the 46,669 infants

of mothers unvaccinated during pregnancy was approximately 30%. To achieve 80% power, both the number of women vaccinated in the first trimester and the number never vaccinated would need to be quadrupled.

Low statistical power and data sparsity leads many safety studies, including this one, to examine MCMs as an aggregate outcome. The caveat of this approach is that positive associations between vaccination and specific MCMs may be diluted. As an example, the prevalence rates of specific MCMs reported in **Table 8.1** suggest that limb defects occurred more frequently in infants of first-trimester vaccinated mothers than in infants whose mothers were never vaccinated (297 vs 244 per 10,000 live-births) (though it should be noted that this crude comparison of prevalence does not account for confounding). In an analysis examining MCMs as an aggregate outcome, a positive association between first-trimester vaccination and limb defects could be diluted by a lack of association (or associations in the opposite direction) for other MCMs.

One approach is to examine MCMs as an aggregate outcome and then examine those anatomical subgroups that are relatively homogeneous where there is sufficient power. In this work, limb and heart defects were separately examined as secondary outcomes (in addition to including them aggregated together with other MCMs in the main analysis) and no association with vaccination was found. However, even among these subgroups, the possibility of an association between first-trimester vaccination and particular limb or heart conditions cannot be discounted. For example, a positive association between first-trimester vaccination and limb reduction defects could be diluted by a null association between first-trimester vaccination and polydactyly, or by a negative association (if, for example, influenza itself increases the risk of this MCM, and influenza vaccination prevents infection) (**Table 8.1**).

The prevalence of system-specific MCMs among infants born to mothers vaccinated in the first trimester can be compared to the prevalence among infants whose mothers were unvaccinated throughout pregnancy to identify conditions for future exploration as numbers

become available. **Table 8.1** demonstrates that compared to infants born to unvaccinated mothers, infants whose mothers were vaccinated in the first trimester had an increased prevalence of:

- Atrial septal defects,
- Digestive malformations (driven by a small increase in the prevalence of congenital diaphragmatic hernias),
- Malformations of the ear, face and neck,
- Genital malformations (driven by an increase in the prevalence of hypospadias),
- Limb malformations (driven by an increase in the prevalence of talipes equinovarus and use of non-specific codes such as '*other congenital deformities of feet*'),
- Cleft lip with or without cleft palate, and
- Urinary malformations

These results should, however, be interpreted with caution due to very small numbers of infants born to mothers vaccinated in the first trimester (some numbers are suppressed in **Table 8.1** to prevent deductive disclosure of patient identities). Where entire subgroups (e.g. urinary malformations) demonstrated increased prevalence in infants born to mothers vaccinated in the first trimester, it was not always possible to pin-point what specific diagnoses were driving these increases (for example, examination of individual diagnoses such as congenital hydronephrosis did not explain the increase in prevalence of urinary malformations among infants born to mothers vaccinated in the first trimester). These MCMs could be usefully explored in future studies as numbers accumulate.

**Table 8.1 – Prevalence of system-specific major congenital malformations in the first year of life per 10,000 live-births, by vaccination status.**

System-specific major congenital malformations	Total prevalence in EUROCAT (95% CI) (N=816,423)	Total prevalence in the study population (no.) (N=78,150)	Prevalence (no.), by vaccination status	
			Trimester 1 <sup>a</sup> (N=6,872)	Never <sup>a</sup> (N=46,669)
<b>Abdominal</b>	5.2 (4.8 - 5.8)	4.4 (34)	-	4.9 (23)
Gastroschisis	4.0 (3.6 - 4.5)	3.1 (24)	-	4.1 (19)
Omphalocele	1.0 (0.9 - 1.3)	0.9 (7)	-	-
<b>Congenital heart defects</b>	44.9 (43.5 - 46.4)	72.0 (566)	73.0 (50)	72.0 (337)
Severe congenital heart disease	17.2 (16.3 - 18.1)	15.0 (118)	12.0 (8)	15.0 (69)
<i>Common arterial truncus</i>	0.4 (0.3 - 0.6)	-	-	-
<i>Double outlet right ventricle</i>	1.3 (1.1 - 1.6)	1.7 (13)	-	1.7 (8)
<i>Transposition of great vessels</i>	3.6 (3.2 - 4.1)	2.3 (18)	-	2.1 (10)
<i>Single ventricle</i>	0.4 (0.3 - 0.5)	-	-	-
<i>Atrioventricular septal defect</i>	1.9 (1.6 - 2.2)	2.0 (16)	-	2.8 (13)
<i>Tetralogy of Fallot</i>	3.1 (2.8 - 3.5)	3.2 (25)	-	3.0 (14)
<i>Tricuspid atresia and stenosis</i>	0.6 (0.5 - 0.8)	-	-	-
<i>Ebstein's anomaly</i>	0.3 (0.2 - 0.5)	-	-	-
<i>Pulmonary valve atresia</i>	0.9 (0.7 - 1.1)	-	-	-
<i>Aortic valve atresia/stenosis</i>	1.1 (0.9 - 1.3)	1.2 (9)	-	1.3 (6)
<i>Mitral valve anomalies</i>	1.0 (0.8 - 1.3)	2.2 (17)	-	1.9 (9)
<i>Hypoplastic left heart</i>	1.7 (1.5 - 2.1)	-	-	-
<i>Hypoplastic right heart</i>	0.4 (0.2 - 0.5)	-	-	-
<i>Coarctation of aorta</i>	3.6 (3.2 - 4.0)	3.7 (29)	-	3.4 (16)
<i>Aortic atresia/interrupted aortic arch</i>	0.5 (0.4 - 0.7)	-	-	-
<i>Total anomalous pulmonary venous return</i>	0.7 (0.5 - 0.9)	0.9 (7)	-	-
Ventricular septal defect	21.7 (20.7 - 22.7)	22.1 (173)	20.4 (14)	23.8 (111)
Atrial septal defect	7.5 (6.9 - 8.1)	33.7 (263)	39.3 (27)	32.6 (152)
Pulmonary valve stenosis	3.3 (3.0 - 3.8)	2.7 (21)	-	2.4 (11)
Patent ductus arteriosus <sup>p</sup>	1.1 (0.9 - 1.4)	25.0 (195)	23.3 (16)	24.9 (116)
<b>Digestive</b>	14.0 (13.2 - 14.8)	19.0 (151)	28.0 (19)	18.0 (82)
Oesophageal atresia ± trachea-oesophageal fistula	2.1 (1.8 - 2.5)	2.2 (17)	-	2.4 (11)
Duodenal atresia or stenosis	1.2 (0.9 - 1.4)	0.8 (6)	-	-
Atresia or stenosis of other parts of the small intestine	0.9 (0.7 - 1.1)	1.0 (8)	-	-
Anorectal atresia and stenosis	2.1 (1.8 - 2.5)	1.8 (14)	-	1.9 (9)
Hirschprung's disease	1.3 (1.1 - 1.6)	1.3 (10)	-	1.5 (7)
Atresia of bile ducts	0.2 (0.1 - 0.4)	-	-	-
Annular pancreas	0.02 (0.0 - 0.2)	-	-	-
Diaphragmatic hernia	2.1 (1.8 - 2.4)	1.9 (15)	-	1.9 (9)
<b>Ear, Face &amp; Neck</b>	0.9 (0.7 - 1.2)	5.0 (39)	8.7 (6)	4.7 (22)
Anotia	0.1 (0.03 - 0.2)	-	-	-

<b>Eye</b>	1.8 (1.5 - 2.1)	3.7 (29)	-	2.8 (13)
Anophthalmos/microphthalmos	0.4 (0.3 - 0.5)	-	-	-
Congenital cataract	0.5 (0.4 - 0.7)	1.7 (13)	-	1.5 (7)
Congenital glaucoma	0.1 (0.04 - 0.2)	-	-	-
<b>Genital</b>	18.4 (17.4 - 19.3)	43.0 (335)	52.0 (36)	42.0 (197)
Hypospadias	14.6 (13.8 - 15.4)	31.0 (240)	39.0 (27)	31.0 (146)
Indeterminate sex	0.5 (0.4 - 0.7)	-	-	-
<b>Limb</b>	26.6 (25.5 - 27.7)	260.0 (2029)	297.0 (204)	244.0 (1137)
Hip dislocation or dysplasia <sup>c</sup>	4.9 (4.4 - 5.4)	8.6 (67)	8.7 (6)	9.2 (43)
Club foot/Talipes equinovarus	7.1 (6.6 - 7.7)	11.8 (92)	18.9 (13)	11.1 (52)
Polydactyly	6.3 (5.8 - 6.9)	17.0 (133)	12.0 (8)	17.0 (78)
Syndactyly	3.7 (3.3 - 4.1)	9.3 (73)	-	10.0 (48)
Limb reduction defects	2.8 (2.4 - 3.2)	3.6 (28)	-	4.1 (19)
<b>Nervous system</b>	9.0 (8.4 - 9.7)	15.0 (117)	17.0 (12)	16.0 (75)
Neural tube defects	2.1 (1.8 - 2.4)	2.4 (19)	-	3.0 (14)
<i>Anencephalus</i>	0.2 (0.1 - 0.3)	-	-	-
<i>Encephalocele</i>	0.3 (0.3 - 0.4)	-	-	-
<i>Spina bifida</i>	1.6 (1.3 - 1.9)	2.0 (16)	-	2.4 (11)
Microcephaly	0.8 (0.6 - 1.0)	1.5 (12)	-	1.3 (6)
Hydrocephalus	3.1 (2.8 - 3.5)	3.6 (28)	-	3.9 (18)
Arhinencephaly/Holoprosencephaly	0.1 (0.1 - 0.2)	-	-	-
<b>Orofacial</b>	12.7 (12.0 - 13.5)	12.0 (94)	15.0 (10)	12.0 (57)
Cleft palate	4.9 (4.4 - 5.4)	5.2 (41)	-	5.4 (25)
Cleft lip ± Cleft palate	7.8 (7.2 - 8.5)	7.8 (61)	12.0 (8)	7.7 (36)
<b>Respiratory</b>	3.7 (3.3 - 4.2)	7.3 (57)	-	7.9 (37)
Choanal atresia	0.7 (0.5 - 0.9)	0.8 (6)	-	-
Cystic adenomatous malformation of lung <sup>d</sup>	1.9 (1.6 - 2.2)	1.4 (11)	-	-
<b>Urinary</b>	20.8 (19.8 - 21.8)	36.0 (283)	41.0 (28)	34.0 (158)
Bilateral renal agenesis including Potter syndrome	0.2 (0.1 - 0.3)	-	-	-
Multicystic renal dysplasia <sup>e</sup>	3.2 (2.8 - 3.6)	2.3 (18)	-	1.7 (8)
Congenital hydronephrosis	8.3 (7.7 - 9.0)	16.0 (125)	13.1 (9)	14.6 (68)
Bladder exstrophy ± epispadia	0.5 (0.4 - 0.7)	1.4 (11)	-	1.7 (8)
Posterior urethral valve and/or prune belly <sup>f</sup>	0.4 (0.3 - 0.5)	1.2 (9)	-	1.3 (6)

Major malformations were defined according to EUROCAT guidelines and identified in the first year of life from hospital admissions data. Prevalence rates in UK EUROCAT registries between 2010 and 2013 (prior to changes in the management of registries) are also included for reference. Some cells suppressed to prevent deductive disclosure. <sup>a</sup>Numbers in these columns do not sum to total number of infants; <sup>b</sup>Infants born ≥37 weeks; <sup>c</sup>EUROCAT included Q6580-6581 but only Q658 was available in HES; <sup>d</sup>EUROCAT included Q3380 but only Q338 was available in HES; <sup>e</sup>EUROCAT included Q6140-6141 but only Q614 was available in HES; <sup>f</sup>EUROCAT included Q6420 but only Q642 was available in HES.

## 8.5 Why did the analysis examine the safety of vaccination in the second and third trimesters as well as the first trimester?

The majority of organogenesis occurs in the first trimester of pregnancy and this is therefore the trimester of greatest interest when carrying out safety studies for which the outcome of interest is MCMs. Vaccination in the second trimester was examined for two reasons. First, although the risk of MCMs is highest for all organ systems in the first trimester, development continues beyond this period and some organ systems (e.g. the central nervous system) continue to be susceptible to teratogens.<sup>304</sup> Analyses of vaccinations occurring in the second trimester were therefore intended to account for this. Second, although gestational age at the time of vaccination was thought to have high accuracy (the Pregnancy Register uses all available information from primary care records and has demonstrated close agreement with gestational age data from HES), the possibility of misclassifying the trimester of exposure could not be discounted.<sup>255</sup> Analyses of the second trimester would capture any vaccinations that occurred in the first trimester but which were misclassified as occurring later (e.g. if the vaccination was recorded late). The sensitivity of the foetus to teratogens in the third trimester is very low and vaccination in this trimester should not demonstrate an association with MCMs. Including this trimester in analyses was therefore a pragmatic and feasible way of including a negative control. It was reassuring that there was no evidence of an association between vaccination in any trimester and MCMs.

## 8.6 Why were analyses restricted to live-births?

Vaccine safety analyses were originally planned to identify MCMs among live-births, miscarriages, terminations and stillbirths. For live-birth pregnancies with linked infant records, evidence of an MCM would be identified postnatally (in the infant record) or antenatally (in the maternal record). For remaining pregnancies, evidence of MCMs would be searched for antenatally in maternal records due to the absence of linked infant records.

MCMs in the antenatal period were likely to be under-ascertained, though the extent of this under-ascertainment was not initially known. Potential reasons for under-ascertainment included the moderate sensitivity of the 20-week ultrasound scan to detect MCMs and that many miscarriages and terminations would end before the scan took place.<sup>305</sup> However, under-ascertainment of MCMs would only bias effect measures if it occurred differentially among vaccinated or unvaccinated pregnancies. The shorter duration of miscarriages and terminations, as well as other factors such as maternal/foetal health concerns, meant that vaccination was thought to be less likely among such pregnancies. If most of these types of pregnancies were unvaccinated and MCMs were also under-ascertained, this could bias the effect measure upwards if these types of pregnancies were included in analyses. The potential for bias was therefore considered in detail for different pregnancy outcomes (**Table 8.2**).

Following this, the antenatal ascertainment of MCMs and the vaccine uptake among different pregnancy outcomes were examined using the wider study population of 116,661 pregnancies (**Figure 8.2**). Results are described in **Sections 8.6.1-8.6.3**



**Table 8.2 - Potential bias in the hazard ratios for MCMs, by pregnancy outcome**

Pregnancy outcome	Is vaccination* more or less likely among these pregnancies?	Are malformations likely to be under-ascertained among these pregnancies?	Effect on the hazard ratio for MCMs
<b>Termination; pregnancy unwanted from the outset.</b>	Less likely because the woman does not intend to continue with the pregnancy.	Yes because these women may be less likely to attend scans and terminations are also likely to occur before the 20-week anomaly scan.	If the majority of these pregnancies are unvaccinated and there is also under-ascertainment of MCMs, the hazard ratio for MCMs may be <b>inflated</b> .
<b>Termination; pregnancy wanted but complicated by maternal or foetal health.</b>	Less likely because the pregnancy is shorter in duration (therefore less opportunity). Maternal/foetal health concerns could also result in lower vaccine uptake.	Yes because most terminations are likely to occur before the 20-week anomaly scan.	If the majority of these pregnancies are unvaccinated and there is also under-ascertainment of MCMs, the hazard ratio for MCMs may be <b>inflated</b> .
<b>Termination; pregnancy wanted but complicated by foetal MCM.</b>	Less likely because the pregnancy is shorter in duration (therefore less opportunity). Maternal/foetal health concerns could also result in lower vaccine uptake.	No.	If the majority of these pregnancies are unvaccinated and there is no under-ascertainment of malformations then the hazard ratio may be biased to the <b>null</b> .
<b>Miscarriage</b>	Less likely because the pregnancy is shorter in duration (therefore less opportunity).	Yes because most miscarriages are likely to occur before the 20-week anomaly scan.	If the majority of these pregnancies are unvaccinated and there is also under-ascertainment of MCMs, the hazard ratio for MCMs may be <b>inflated</b> .
<b>Early stillbirth</b>	Less likely because the pregnancy is shorter in duration (therefore less opportunity).	Yes because although the 20-week anomaly scan is likely to have taken place, its sensitivity is known to be low.	If the majority of these pregnancies are unvaccinated and there is also under-ascertainment of MCMs, the hazard ratio for MCMs may be <b>inflated</b> .
<b>Late stillbirth</b>	Not necessarily more or less likely to be vaccinated as the pregnancy length is normal.	Yes because although the 20-week anomaly scan is likely to have taken place, its sensitivity is known to be low.	Assuming the likelihood of vaccination is not biased and that the outcome is under-ascertained, the hazard ratio may be <b>unaffected</b> .
<b>Deliveries based on late pregnancy records</b>	Not necessarily more or less likely to be vaccinated as the pregnancy length is normal.	Yes because although the 20-week anomaly scan is likely to have taken place, its sensitivity is known to be low.	Assuming the likelihood of vaccination is not biased and that the outcome is under-ascertained, the hazard ratio may be <b>unaffected</b> .
<b>Live-births without a linked baby</b>	Not necessarily more or less likely to be vaccinated as the pregnancy length is normal.	Yes because although the 20-week anomaly scan is likely to have taken place, its sensitivity is known to be low.	Assuming the likelihood of vaccination is not biased and that the outcome is under-ascertained, the hazard ratio may be <b>unaffected</b> .

\*Vaccination anytime in pregnancy.

### 8.6.1 MCMs are under-recorded in the antenatal period

The proportion of pregnancies with an antenatal record of an MCM was much lower than the proportion of live-birth pregnancies linked to infant records that had postnatal evidence of an MCM. This suggested that MCMs were likely to be considerably under-ascertained in the antenatal period. Among the 78,150 pregnancies that resulted in a live-birth with linked infant records, the proportion with evidence of an MCM after delivery and anytime during the study period was 7.7% (n=6,029). Conversely, among the 116,661 pregnancies in the wider study population, just 0.3% (n=298) had antenatal evidence in the maternal record that could potentially relate to an MCM (**Table 8.3**). The proportion of pregnancies with antenatal evidence of an MCM varied by pregnancy outcome but was generally very low. The only exception was for stillbirths, of which 3.3% had evidence of an MCM recorded antenatally, although the absolute number of such cases was small (n=9) (**Table 8.3**).

**Table 8.3 - Number and proportion of pregnancies with an antenatal MCM record, by pregnancy outcome.**

<b>Pregnancy outcome (number of pregnancies)</b>	<b>No. of pregnancies with an antenatal MCM record in the maternal file (% of total pregnancies of the same outcome).</b>
All pregnancy outcomes (n=116,661)	298 (0.3)
Live-birth with linked infant records (n=78,150)	149* (0.2)
Live-birth with no linked infant records (n=10,645)	32 (0.3)
Stillbirth (n=276)	9 (3.3)
Miscarriage (n=13,439)	15 (0.1)
Termination/Probable termination (n=12,471)	91 (0.7)
Unspecified loss (n=746)	2 (0.3)
Deliveries based on late pregnancy records (n=934)	0 (0.0)

\*Of the live-births with a linked infant, only 38 of the 149 (25.5%) with an antenatal malformation record went on to have a postnatal MCM record.

## 8.6.2 MCMs recorded antenatally have poor validity

Evidence of antenatal MCMs are based on the limited records available during pregnancy and may be less accurate and less reliable than postnatal diagnoses. As described in **Section 5.6**, antenatal codes used to identify MCMs were often non-specific and could represent eligible MCMs but also: ineligible anomalies (such as Down syndrome), suspected but unconfirmed anomalies, or problems noted on the ultrasound scan relating to the mother or the placenta rather than the foetus. Antenatal codes were therefore categorized from most (level 1 codes) to least (level 3 codes) specific.

Of the 298 pregnancies with antenatal evidence of an MCM, the majority (77.5%) had level 2 codes that related to suspected but unconfirmed anomalies as their most specific evidence (**Table 8.4**). The most frequently used codes among all 298 pregnancies were '*maternal care for suspected central nervous system malformation in fetus*' and '*maternal care for suspected fetal abnormality and damage, unspecified*' (**Table 8.5**). Only 19.1% (n=57) of pregnancies with antenatal evidence had level 1 codes (**Table 8.4**). The only types of pregnancy with level 1 codes were live-births (n=54) and terminations (n=3). Level 1 codes were not observed among stillbirths, miscarriages or unspecified losses.

**Table 8.4 - Most specific available antenatal evidence of MCM, by pregnancy outcome.**

Pregnancy outcome	No. of pregnancies with antenatal evidence	No. of pregnancies with level 1 code as most specific evidence (%)	No. of pregnancies with level 2 code as most specific evidence (%)	No. of pregnancies with level 3 code as most specific evidence (%)
All pregnancy outcomes	298	57 (19.1)	231 (77.5)	10 (3.4)
Live-birth with linked infant	149	47 (31.5)*	95 (63.8)**	7 (4.7)***
Live-birth with no linked infant	32	7 (21.9)	25 (78.1)	0
Stillbirth	9	0	9 (100.0)	0
Miscarriage	15	0	14 (93.3)	1 (6.7)
Termination/Probable termination	91	3 (3.3)	86 (94.5)	2 (2.2)
Unspecified loss	2	0	2 (100.0)	0
Deliveries based on late pregnancy records	0	0	0	0

\*14.9% of these (n=7) went on to have a postnatal malformation recording; \*\*31.6% of these (n=30) went on to have a postnatal malformation recording; \*\*\*14.3% of these (n=1) went on to have a postnatal malformation recording.

**Table 8.5 - Antenatal codes used among all pregnancy outcomes.**

Antenatal Code Description	Specificity Level	No. of pregnancies code used in (%)
Maternal care for (suspected) central nervous system malformation in fetus	2	111 (37.2)
Maternal care for (suspected) fetal abnormality and damage, unspecified	2	108 (36.2)
U-S scan - fetal abnormality	1	50 (16.8)
Known or suspected fetal abnormality	2	14 (4.7)
A/N U/S scan for ? abnormality	3	4 (1.3)
Suspect fetal anencephaly	2	4 (1.3)
Abnormal findings on antenatal screening of mother	3	3 (1.0)
Obstructed labour due to other abnormalities of fetus	1	3 (1.0)
Maternal care for disproportion due to hydrocephalic fetus	1	2 (0.7)
Suspect fetal spina bifida	2	1 (0.3)
Abnormal ultrasonic finding on antenatal screening of mother	3	1 (0.3)
Other fetal abnormality causing disproportion	1	1 (0.3)
Fetus with cardiovascular abnormality	1	1 (0.3)
A/N U/S scan abnormal	3	1 (0.3)
[X]Maternal care/oth spcf known or suspected fetal problems	2	1 (0.3)
U-S obstetric scan abnormal	3	1 (0.3)

Percentages do not add to 100 as some pregnancies could have more than one code.

Antenatal codes were also found to be poorly predictive of a postnatal diagnosis, which further suggested that their validity was likely to be low. Among the live-births with a linked infant, 149 had a code for an MCM detected antenatally but just 38 (25.5%) of these also had postnatal evidence in the infant record. This was not higher among those that had a level 1 code; of the 47 such live-birth pregnancies with a linked infant just 14.9% (n=7) had a postnatal malformation record.

The positive predictive value of antenatal codes could be estimated by calculating the proportion of live-births with a linked infant that had a particular antenatal code and went on to have postnatal evidence (assuming the latter was the 'gold standard') (**Table 8.6**). The positive predictive value of codes was highly variable but appeared to be lowest for most level 3 codes, as expected. Neither level 1 or 2 codes had consistently high positive predictive values. Based on all the above, the value of antenatal MCM codes appeared limited.

**Table 8.6 - Positive predictive values of antenatal codes used among live-birth pregnancies with a linked infant.**

Antenatal Code Description	Specificity Level	No. of live-birth pregnancies code used in	No. of live-birth pregnancies with postnatal MCM evidence	Positive Predictive Value of code (95% CI)
Fetus with cardiovascular abnormality	1	1	0	0 (0-97.5)
Obstructed labour due to other abnormalities of fetus	1	1	0	0 (0-97.5)
U-S scan - fetal abnormality	1	44	6	13.6 (5.2-27.4)
Maternal care for disproportion due to hydrocephalic fetus	1	1	1	100.0 (2.5-100.0)
Known or suspected fetal abnormality	2	6	4	66.7 (22.3-95.7)
Maternal care for (suspected) fetal abnormality and damage, unspecified	2	68	10	14.7 (7.3-25.4)
[X]Maternal care/oth spcf known or suspected fetal problems	2	1	0	0 (0-97.5)
Maternal care for (suspected) central nervous system malformation in fetus	2	22	17	77.3 (54.6-92.2)
A/N U/S scan for ? abnormality	3	2	0	0 (0-84.2)
Abnormal ultrasonic finding on antenatal screening of mother	3	1	1	100.0 (2.5-100.0)
A/N U/S scan abnormal	3	1	0	0 (0-97.5)
Abnormal findings on antenatal screening of mother	3	2	0	0 (0-84.2)
U-S obstetric scan abnormal	3	1	0	0 (0-97.5)

Postnatal diagnoses were used as a gold standard.

### 8.6.3 Vaccine uptake is low among miscarriages and terminations

As expected, vaccine uptake was higher among live-births, stillbirths and deliveries based on late pregnancy records. The average uptake for these pregnancy outcomes was 39.5% which was similar to the average of published estimates of vaccine uptake for England over the same years.<sup>76, 284, 306-309</sup> Vaccine uptake was, however, very low among miscarriages (5.6%), terminations (1.2%) and unspecified losses (4.8%) – as expected due to their shorter duration and the likelihood of lower uptake of antenatal screening among pregnancies which were terminated (**Table 8.7**).

**Table 8.7 - Vaccine uptake by pregnancy outcome**

Pregnancy outcome (number of pregnancies)	No. of pregnancies vaccinated (%)
All pregnancy outcomes (n=116,661)	36,461 (31.3)
Live-birth with linked infant (n=78,150)	31,481 (40.3)
Live-birth with no linked infant (n=10,645)	3,650 (34.3)
Stillbirth (n=276)	85 (30.8)
Miscarriage (n=13,439)	756 (5.6)
Termination/Probable termination (n=12,471)	149 (1.2)
Unspecified loss (n=746)	36 (4.8)
Deliveries based on late pregnancy records (n=934)	304 (32.5)

#### 8.6.4 Summary of exploration of antenatally-recorded MCMs

In summary, results indicated that under-ascertainment of MCMs was considerable during the antenatal period and there was also evidence to suggest that antenatal codes had low validity. Furthermore, vaccine uptake among miscarriages and terminations was particularly low. Therefore, including all pregnancy outcomes would result in under-ascertainment of the outcome and would occur differentially among the unvaccinated which would bias effect measures away from the null. Based on these results, it was decided that all vaccine safety analyses would be restricted to live-birth pregnancies with linked infants and all MCMs would be ascertained using only postnatal evidence from infant records (for which validity was thought to be good).<sup>187, 192, 194, 216, 219</sup>

#### 8.7 Could the exclusion of terminations due to foetal anomalies have biased results?

Pregnant women are offered an ultrasound scan between 18 and 21 gestational weeks (referred to as the 20-week anomaly scan).<sup>310</sup> The main purpose of the scan is to screen for the presence of 11 different conditions, which include: anencephaly, spina bifida, cleft lip, congenital diaphragmatic hernia, gastroschisis, exomphalos, severe congenital heart defects, bilateral renal agenesis, lethal skeletal dysplasia and Edwards' or Patau's syndrome.<sup>310</sup> Over time, as technology has improved, scans have also been able to detect other conditions, including some that are minor and whose clinical significance is uncertain.<sup>305</sup> The 20-week scan provides prospective parents the opportunity to consider termination in the presence of a serious condition.

Between 2010 and 2013 (which coincided with the study period), 14.3% of MCMs identified by UK EUROCAT registries were identified among terminations due to foetal anomalies (TOPFAs).<sup>294</sup> The organ system with the highest proportion of malformations identified from TOPFAs was the nervous system (56.7% of nervous system malformations were identified among TOPFAs).<sup>294</sup> The conditions most commonly identified from TOPFAs in UK registry data

are presented in **Table 8.8** and include neural tube defects and other specific nervous system malformations, severe congenital heart defects, urinary and abdominal malformations. These conditions are therefore likely to have been considerably underrepresented in the study population used in this work, which relied exclusively on live-births.

**Table 8.8 – Most common non-chromosomal major congenital malformations among terminations due to foetal anomalies in UK EUROCAT registries between 2010 and 2013.**<sup>294</sup>

Major congenital malformation	Total no. of cases	Percentage of cases by pregnancy outcome (95% CI)		
		Live-births	Stillbirths	Termination due to foetal anomaly
Anencephalus and similar	426	3.8 (2.3-6.0)	4.7 (3.2-7.1)	91.6 (88.5-93.8)
Arhinencephaly/holoprosencephaly	68	13.2 (7.1-23.3)	5.9 (2.3-14.2)	80.9 (70.0-88.5)
Bilateral renal agenesis*	109	12.8 (7.8-20.4)	7.3 (3.8-13.8)	79.8 (71.3-86.3)
Spina Bifida	466	28.1 (24.2-32.4)	2.4 (1.3-4.2)	69.5 (65.2-73.5)
Encephalocele	83	27.7 (19.2-38.2)	3.6 (1.2-10.1)	68.7 (58.1-77.6)
Omphalocele	205	42.4 (35.9-49.3)	4.9 (2.7-8.8)	52.7 (45.9-59.4)
Hypoplastic left heart	244	58.2 (51.9-64.2)	3.3 (1.7-6.3)	38.5 (32.6-44.8)
Single ventricle	50	62.0 (48.2-74.1)	0.0 (0.0-7.1)	38.0 (25.9-51.9)
Hydrocephalus	415	61.5 (56.7-66.0)	3.6 (2.2-5.9)	34.9 (30.5-39.7)
Hypoplastic right heart	46	63.0 (48.6-75.5)	2.2 (0.4-11.3)	34.8 (22.7-49.2)
Congenital diaphragmatic hernia	222	76.6 (70.6-81.7)	2.3 (1.0-5.2)	21.2 (16.3-27.0)

\*Including Potter syndrome.

Not including pregnancies resulting in terminations due to foetal anomaly in vaccine safety analyses could bias results under certain circumstances. For example, women who register late for antenatal care are less likely to receive vaccination in the first trimester and may also be less likely to have the 20-week anomaly scan and an antenatal diagnosis of an MCM. These women would not have the opportunity to undergo a TOPFA and, if they went on to deliver a live-born infant, would be included in the study population. In contrast, women carrying a foetus with the same MCM who registered earlier for antenatal care would have a greater opportunity for both first trimester vaccination and antenatal diagnosis of the MCM; if these women chose to terminate after their 20-week scan, they would not be included in the study population. The differential inclusion of infants with MCMs born to unvaccinated vs vaccinated mothers would lead to an underestimate of the association between vaccination and these MCMs.

In England, data from Public Health England show high uptake of the antenatal 20-week scan; the national average was 96.6% in 2016/17, rising to 99.1% in 2018/19.<sup>311</sup> However, these

figures refer to women who had booked into antenatal care by 24 weeks gestation. A 2015/16 audit of the timeliness of antenatal bookings in London found that among 122,275 pregnant women, 9.9% had their booking after 21 weeks of gestation and would therefore not have been offered first-trimester vaccination and may not have received a scan.<sup>70</sup>

In the data used for the studies described in this thesis, 13,217 terminations and unspecified losses were identified and excluded. Of these, more than 98% occurred before the 16<sup>th</sup> week, before the 20-week anomaly scan, and therefore could not reasonably be TOPFAs. This is consistent with reports suggesting that TOPFAs account for approximately 1% of all terminations.<sup>321</sup> Although the Pregnancy Register may not capture all terminations (e.g. those performed by independent providers) there is no obvious reason to suggest that late terminations are less likely to be ascertained.

Further investigation of the conditions most likely to result in TOPFAs (**Table 8.8**), showed no evidence of higher prevalence of these MCMs among infants born to unvaccinated mothers included in this study compared to infants born to mothers who were vaccinated in the first trimester (**Table 8.1**). For eight of the 11 conditions, there were less than five infants in each group. Even after combining all 11 conditions, prevalence was not higher in infants born to unvaccinated women (10.1 per 10,000 live-births, n=47) compared to infants born to women vaccinated in the first trimester (14.6 per 10,000 live-births, n=10).

## 8.8 Could the exclusion of live-births without linked infant records have biased results?

A limitation of the SIIV safety analysis was the exclusion of approximately 11% of live-birth pregnancies, due to the lack of linked infant records. In the context of this study, selection bias could occur if live-birth pregnancies with linked infant records were more or less likely to have received the vaccine and more or less likely to result in an MCM than live-birth pregnancies without linked infant records.



Reasons for absence of a linked infant record were outlined in **Section 4.3.8 (Table 4.1)**, most of which were unlikely to be associated with vaccination or MCMs. Of the live-birth pregnancies without a linked infant, 7% could potentially have their lack of linkage explained by follow-up ending at the latest collection of practice data and 25% could have their lack of linkage explained by the mother leaving the practice before the infant had an opportunity to register. The end of data collection at practices was not associated with vaccination or MCMs and would therefore not result in selection bias. Mothers might leave the practice for a number of reasons after giving birth, many of which would be independent of vaccine uptake and MCMs (such as moving home to adjust to the new family size). However, two scenarios which could potentially be associated with vaccine uptake and MCMs were considered:

1. Mothers whose infants have an MCM leave the practice in order to move closer to a specialist hospital. If these women also tend to be more engaged with healthcare and are more likely to accept a vaccine then their exclusion may result in an underestimation of the hazard ratio.
2. Mothers may leave the practice as a result of unstable accommodation. These women may have fragmented healthcare and so may be more likely to be unvaccinated. They might be less likely to benefit from preventive healthcare and screening (so may have higher incidence of MCMs), but may also be less likely to have an MCM in their infant ascertained. Their exclusion could therefore result in under- or overestimation of the hazard ratio.

Both these scenarios are likely to be rare and only apply to a small percentage of mothers leaving the practice before the infant is registered. It was considered unlikely that either of these scenarios would result in considerable selection bias.

Linkage to infant records might not occur or may be delayed if delivery is followed by neonatal death or prolonged hospitalisation which would prevent registration at the mother's practice. Such a scenario could occur among infants with a severe MCM and was also considered. Less than 1% of live-births without linked infant records were found to have evidence of a

bereavement or neonatal hospitalisation in the maternal record around the time of delivery. Whilst it was somewhat reassuring that this proportion was not high (as it could suggest the death or hospitalisation of infants due to MCMs), it was difficult to draw any concrete conclusions given that these events are unlikely to be fully recorded in the maternal record.

## 8.9 Chapter summary and conclusions

The large, historical cohort study described in this chapter found no evidence to suggest an association between SIV receipt in any trimester and major congenital malformations overall, congenital heart defects or limb defects. This was the largest such safety study examining first-trimester vaccination in Europe and provides further evidence to support the safety profile of SIV among pregnancies that result in a live-birth.

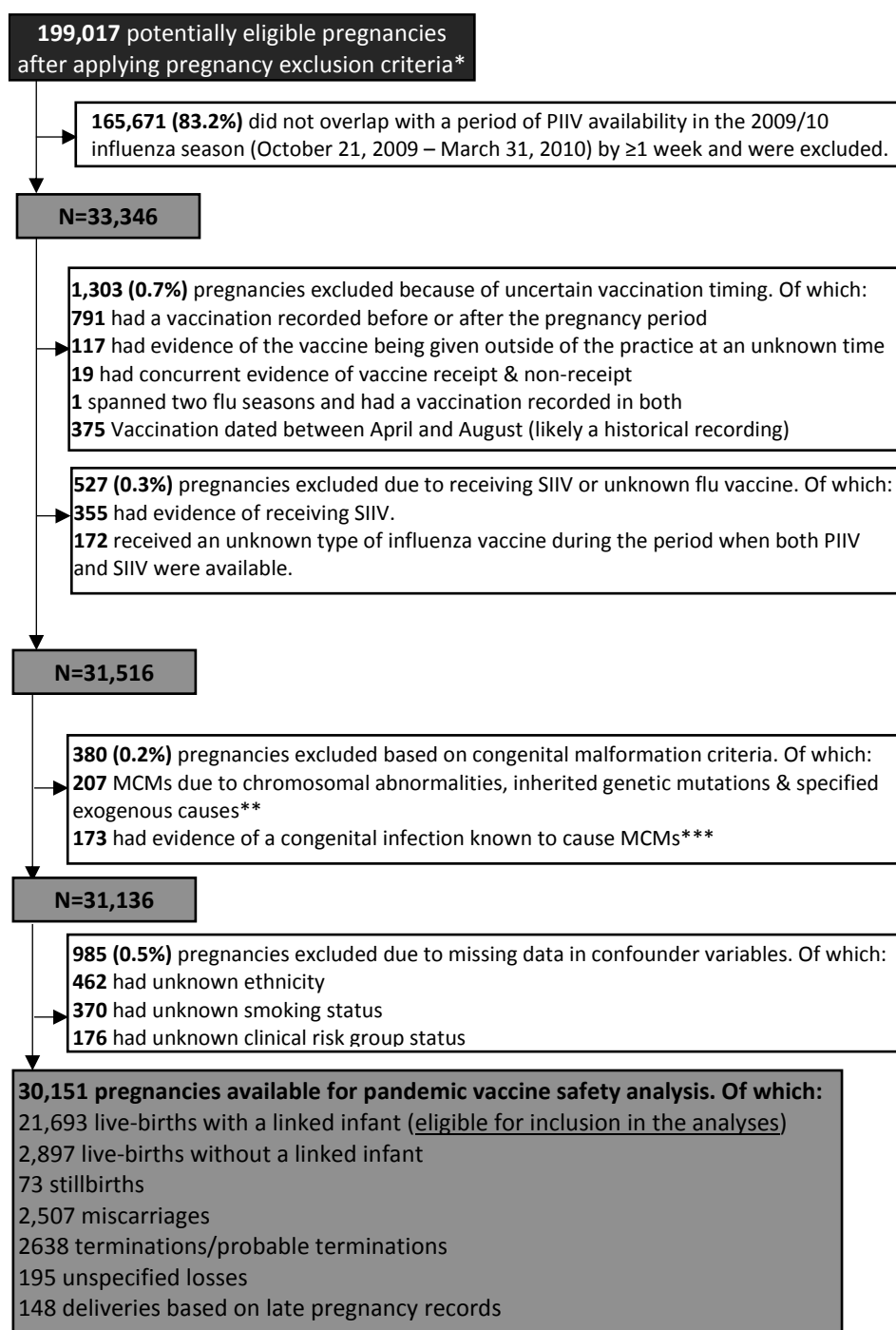
## 9. Examining the association between pandemic influenza vaccination during pregnancy and major congenital malformations.

### 9.1 Introduction

This is the final results chapter of the thesis and addresses **Objective 6** which was to examine the association between maternal vaccination with PIVV and major congenital malformations in live-born infants. The steps involved in deriving the final study population for the analyses described here are provided in **Section 9.2**. In **Section 9.3**, the characteristics of the study population are described. In **Section 9.4**, results from the primary and secondary analyses on PIVV safety during pregnancy are outlined; these analyses examined major malformations in the year after delivery and from delivery until the end of the study period (March 31, 2016), respectively. The methods used were the same as those described in **Chapter 8. Section 9.5** describes the sensitivity analyses carried out; the first of these included vaccinations in the four weeks before pregnancy start, the second included major malformation diagnoses made after follow-up in CPRD had ended and the third excluded pregnant women with unknown BMI (the rationale for these is described in **Chapter 8**). Finally, **Section 9.6** provides a brief summary of the conclusions.

### 9.2 Deriving the final study population for analyses on PIVV safety

In **Chapter 4**, the criteria used to identify potentially eligible pregnancies for analyses in this thesis were outlined. These criteria identified 199,017 potentially eligible pregnancies. Further study-specific exclusion were then applied (**Figure 9.1**). A total of 21,693 live-births linked to an infant were identified for the analysis.



**Figure 9.1 – Deriving the study population for pandemic vaccine safety analyses.** \*The initial population of 199,017 pregnancies included those ending between January 1, 2009 and March 31, 2016. All live-born infants were eligible for linkage to HES and ONS. The identification of the 199,017 potentially eligible pregnancies is described in Sections 4.2-4.3. \*\*See Section 4.4.1; \*\*\*See Section 4.4.2.

### 9.3 Characteristics of the eligible study cohort

The PIIV safety analysis included 21,693 live-birth pregnancies (**Figure 9.1**). Vaccine uptake in this population was lower than that observed in the population eligible for the SIV safety analysis. Just 19.4% (n=4,204) of pregnancies eligible to be included in this analysis received a vaccine; 3.8% (n=825) in the first trimester, 8.7% (n=1,893) in the second and 6.9% (n=1,486) in the third. Overall vaccine uptake in this population was consistent with an estimated uptake of 19.3% by another study using CPRD for the same period.<sup>312</sup>

Of the 21,693 infants born to eligible pregnancies, 90.2% (n=19,573) had at least one full year of follow-up and 44.1% (n=9,556) had at least five years (**Table 9.1**). In the year after delivery, 6.7% (n=1,444) of infants had evidence of an MCM. This increased to 7.6% (n=1,644) when follow-up was extended to the end of the study period (March 31, 2016).

**Table 9.1 - Follow-up time among infants included in the PIIV safety analysis**

Follow-up time	Number of infants (%) N=21,693
≥3 months	21,345 (98.4)
≥6 months	20,810 (95.9)
≥1 year	19,573 (90.2)
≥2 years	17,487 (80.6)
≥3 years	15,166 (69.9)
≥4 years	12,303 (56.7)
≥5 years	9,556 (44.1)
≥6 years	2,654 (12.2)

Similarly to the uptake of SIV during pregnancy, the likelihood of vaccination anytime in pregnancy with PIIV varied by region and was lower among women that were young, of black ethnicity, living in more deprived areas, current smokers or not part of a clinical risk group for which vaccination was recommended (**Table 9.2**). This was consistent with the sociodemographic, health and lifestyle factors known to be associated lower vaccine uptake and described in **Section 1.4**.

There were, however, some differences in the uptake of PIIV during pregnancy compared to SIV. Receipt of SIV during pregnancy was more likely among women exposed to other

potentially teratogenic drugs and/or live vaccines whereas this was not associated with PIIV receipt in pregnancy (**Supplementary Table 2** of Paper 2; **Table 9.2**). SIV receipt was more likely among women whose first trimester did not overlap with a period of influenza activity above baseline levels whereas the converse was true for PIIV (**Supplementary Table 2** of Paper 2; **Table 9.2**). Differences in the timing of vaccine availability and motivation to offer and accept the vaccine in the pandemic and normal influenza seasons could explain these findings. Receipt of SIV during pregnancy was less likely in multiparous women, which was consistent with observations about parity and vaccine uptake in the literature.<sup>17</sup> Conversely, PIIV receipt was more likely in households with 1-2 children.

In the study population used for the SIV safety analysis, there was strong evidence to suggest that MCMs were associated with ethnicity, with increased odds among those born to South Asian mothers which was consistent with the previous literature (**Section 1.7.2**).<sup>139</sup> There was strong evidence for an association with region, with those in the West Midlands having the highest odds. There was also an association with maternal deprivation, flu season and the number of children in the household.

In this population, which was used for the PIIV safety analysis, the only baseline characteristic that exhibited strong evidence for an association with MCMs recorded in the first year of life was region (**Table 9.3**). Infants in the West Midlands and South East Coast had higher odds of an MCM than for any other region. Infants born to South Asian mothers also displayed increased odds of having an MCM recorded in the first year of life. However, ethnicity overall did not display strong evidence of an association with MCMs. It is possible that some of the associations seen in the study population for SIV safety analyses were not observed in the population for this analysis on PIIV due to lower numbers in individual categories.

**Table 9.2- Receipt of PIIV in pregnancy, by characteristics.**

	No. pregnancies unvaccinated (row %) n=17,894	No. pregnancies vaccinated at anytime (row %) n=4,285	No. pregnancies vaccinated in trimester 1 (row %) n=837	Odds ratio for vaccination anytime (99% CI)	P value	Odds ratio for vaccination in the first trimester (99% CI)	P value
<b>Maternal age (years)</b>							
<18	240 (87.9)	33 (12.1)	10 (3.7)	0.57 (0.35-0.93)	<0.0001	0.87 (0.38-2.02)	0.0008
18-24	3,453 (83.6)	678 (16.4)	120 (2.9)	0.82 (0.72-0.92)		0.73 (0.56-0.95)	
25-34	10,173 (80.6)	2,444 (19.4)	486 (3.9)	1.00		1.00	
≥35	4,028 (78.1)	1,130 (21.9)	221 (4.3)	1.17 (1.05-1.30)		1.15 (0.93-1.42)	
<b>Maternal ethnicity</b>							
White	15,595 (80.8)	3,708 (19.2)	711 (3.7)	1.00	<0.0001	1.00	0.0006
S. Asian	1,032 (75.6)	334 (24.5)	73 (5.3)	1.36 (1.15-1.61)		1.55 (1.12-2.15)	
Black	568 (86.5)	89 (13.6)	23 (3.5)	0.66 (0.49-0.89)		0.89 (0.51-1.55)	
Other	331 (79.6)	85 (20.4)	22 (5.3)	1.08 (0.79-1.48)		1.46 (0.82-2.59)	
Mixed	207 (86.3)	33 (13.8)	<5	0.67 (0.41-1.09)		0.32 (0.07-1.43)	
Unknown	161 (81.7)	36 (18.3)	<5	-		-	
<b>Maternal IMD status</b>							
1=Least Deprived	3,790 (77.5)	1,102 (22.5)	196 (4.0)	1.00	<0.0001	1.00	0.1497
2	3,475 (78.8)	933 (21.2)	175 (4.0)	0.92 (0.81-1.05)		0.97 (0.74-1.28)	
3	3,448 (82.2)	754 (17.9)	166 (4.0)	0.75 (0.66-0.86)		0.93 (0.70-1.23)	
4	3,715 (82.2)	807 (17.9)	158 (3.5)	0.75 (0.65-0.85)		0.82 (0.62-1.09)	
5 = Most Deprived	3,466 (83.4)	689 (16.6)	142 (3.4)	0.68 (0.59-0.79)		0.79 (0.59-1.06)	
<b>Region</b>							
London	2,686 (83.3)	540 (16.7)	130 (4.0)	1.00	<0.0001	1.00	0.0056
North East	473 (79.0)	126 (21.0)	28 (4.7)	1.33 (1.00-1.76)		1.22 (0.70-2.12)	
North West	2,704 (82.0)	592 (18.0)	115 (3.5)	1.09 (0.92-1.29)		0.88 (0.63-1.23)	
Yorkshire & Humber	536 (81.2)	125 (18.9)	38 (5.8)	1.16 (0.87-1.54)		1.46 (0.90-2.39)	
East Midlands	471 (81.9)	104 (18.1)	16 (2.8)	1.10 (0.81-1.49)		0.70 (0.35-1.41)	
West Midlands	1,918 (80.4)	469 (19.7)	93 (3.9)	1.22 (1.02-1.46)		1.00 (0.70-1.43)	
East of England	2,010 (77.8)	573 (22.2)	114 (4.4)	1.42 (1.19-1.68)		1.17 (0.83-1.64)	
South West	2,122 (78.0)	598 (22.0)	105 (3.9)	1.40 (1.18-1.66)		1.02 (0.72-1.45)	
South Central	2,626 (80.5)	636 (19.5)	90 (2.8)	1.20 (1.02-1.42)		0.71 (0.49-1.02)	
South East Coast	2,348 (81.8)	522 (18.2)	108 (3.8)	1.11 (0.93-1.32)		0.95 (0.67-1.34)	
<b>Mother was part of clinical risk group</b>							
None	16,974 (81.3)	3,909 (18.7)	740 (3.5)	1.00	<0.0001	1.00	<0.0001
Yes	810 (69.3)	359 (30.7)	92 (7.9)	1.92 (1.62-2.28)		2.61 (1.93-3.51)	
Unknown	110 (86.6)	17 (13.4)	<5	-		-	
<b>Maternal smoking status</b>							
Non	9,140 (80.0)	2,287 (20.0)	421 (3.7)	1.00	<0.0001	1.00	0.0009
Current	4,488 (83.5)	885 (16.5)	177 (3.3)	0.79 (0.70-0.88)		0.86 (0.68-1.08)	
Ex	4,129 (79.2)	1,085 (20.8)	237 (4.6)	1.05 (0.94-1.17)		1.25 (1.01-1.54)	
Unknown	137 (83.0)	28 (17.0)	<5	-		-	
<b>Maternal hazardous drinking</b>							
No	17,809 (80.7)	4,268 (19.3)	832 (3.8)	1.00	0.4883	1.00	0.6292
Yes	85 (83.3)	17 (16.7)	<5	0.83 (0.42-1.66)		1.26 (0.38-4.13)	
<b>Extreme maternal BMI</b>							
No	16,439 (80.7)	3,939 (19.3)	768 (3.8)	1.00	0.6850	1.00	0.8579
Underweight	338 (79.3)	88 (20.7)	18 (4.2)	1.09 (0.80-1.48)		1.14 (0.61-2.14)	
Obese	1,117 (81.2)	258 (18.8)	51 (3.7)	0.96 (0.80-1.16)		0.98 (0.67-1.43)	
<b>Maternal chronic hypertension (non-pregnancy related)</b>							
None	17,646 (80.7)	4,222 (19.3)	828 (3.8)	1.00	0.6752	1.00	0.4334
Yes	248 (79.7)	63 (20.3)	9 (2.9)	1.06 (0.74-1.53)		0.77 (0.32-1.86)	
<b>Maternal exposure to teratogenic medication(s) or live vaccines</b>							
No	16,805 (80.8)	4,001 (19.2)	774 (3.7)	1.00	0.1897	1.00	0.1001
Yes	1,089 (79.3)	284 (20.7)	63 (4.6)	1.10 (0.92-1.31)		1.26 (0.89-1.78)	
<b>No. of weeks the first trimester overlapped with influenza activity above baseline levels</b>							
None	11,685 (83.1)	2,373 (16.9)	82 (0.6)	1.00	<0.0001	1.00	<0.0001
0-2	1,115 (79.0)	296 (21.0)	36 (2.6)	1.31 (1.09-1.56)		4.60 (2.73-7.75)	
2-4	1,159 (76.6)	354 (23.4)	68 (4.5)	1.50 (1.27-1.78)		8.36 (5.44-12.85)	
4-6	1,206 (77.5)	351 (22.5)	108 (6.9)	1.43 (1.21-1.69)		12.76 (8.68-18.76)	
6-8	2,729 (75.0)	911 (25.0)	543 (14.9)	1.64 (1.47-1.84)		28.35 (20.79-38.66)	
<b>No. of children in maternal household</b>							
0	7,095 (82.6)	1,495 (17.4)	311 (3.6)	1.00	<0.0001	1.00	0.0091
1-2	9,349 (79.0)	2,480 (21.0)	476 (4.0)	1.26 (1.15-1.38)		1.16 (0.96-1.41)	
≥3	1,450 (82.4)	310 (17.6)	50 (2.8)	1.01 (0.85-1.21)		0.79 (0.53-1.17)	

Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index; CI, confidence interval.

**Table 9.3 - Major malformations among those eligible for the PIVV safety analysis, by characteristics.**

	No major malformation (row %) N=20,699	Major malformation (row %) N=1,480	Odds ratios for major malformations in the year after delivery (99% CI)	P value
<b>Maternal age (years)</b>				
<18	258 (94.5)	15 (5.5)	0.80 (0.40-1.61)	0.7039
18-24	3,867 (93.6)	264 (6.4)	0.95 (0.78-1.14)	
25-34	11,767 (93.3)	850 (6.7)	1.00	
≥35	4,807 (93.2)	351 (6.8)	1.01 (0.85-1.20)	
<b>Maternal ethnicity</b>				
White	18,047 (93.5)	1,256 (6.5)	1.00	0.0807
S. Asian	1,252 (91.7)	114 (8.4)	1.31 (1.01-1.70)	
Black	615 (93.6)	42 (6.4)	0.98 (0.65-1.49)	
Other	382 (91.8)	34 (8.2)	1.28 (0.80-2.04)	
Mixed	222 (92.5)	18 (7.5)	1.17 (0.62-2.20)	
Unknown	181 (91.9)	16 (8.1)	-	
<b>Region</b>				
North East	560 (93.5)	39 (6.5)	1.21 (0.76-1.95)	<0.0001
North West	3,072 (93.2)	224 (6.8)	1.27 (0.97-1.66)	
Yorkshire & Humber	619 (93.7)	42 (6.4)	1.18 (0.75-1.87)	
East Midlands	547 (95.1)	28 (4.9)	0.89 (0.52-1.53)	
West Midlands	2,151 (90.1)	236 (9.9)	1.91 (1.46-2.50)	
East of England	2,424 (93.8)	159 (6.3)	1.14 (0.86-1.53)	
South West	2,553 (93.9)	167 (6.1)	1.14 (0.86-1.52)	
South Central	3,069 (94.1)	193 (5.9)	1.10 (0.83-1.45)	
London	3,051 (94.6)	175 (5.4)	1.00	
South East Coast	2,653 (92.4)	217 (7.6)	1.43 (1.09-1.87)	
<b>Maternal IMD status</b>				
1=Least Deprived	4,556 (93.1)	336 (6.9)	1.00	0.0664
2	4,079 (92.5)	329 (7.5)	1.09 (0.89-1.35)	
3	3,944 (93.9)	258 (6.1)	0.89 (0.71-1.11)	
4	4,245 (93.9)	277 (6.1)	0.88 (0.71-1.10)	
5 = Most Deprived	3,875 (93.3)	280 (6.8)	0.98 (0.79-1.22)	
<b>No. of children in maternal household</b>				
0	7,999 (93.1)	591 (6.9)	1.00	0.5635
1-2	11,051 (93.4)	778 (6.6)	0.95 (0.82-1.10)	
≥3	1,649 (93.7)	111 (6.3)	0.91 (0.69-1.20)	
<b>Maternal smoking status</b>				
Non	10,637 (93.1)	790 (6.9)	1.00	0.3445
Current	5,029 (93.6)	344 (6.4)	0.92 (0.78-1.09)	
Ex	4,878 (93.6)	336 (6.4)	0.93 (0.78-1.10)	
Unknown	155 (93.9)	10 (6.1)	-	
<b>Maternal hazardous drinking</b>				
No	20,601 (93.3)	1,476 (6.7)	1.00	0.2289
Yes	98 (96.1)	<5	0.57 (0.15-2.12)	
<b>Extreme maternal BMI</b>				
No	19,006 (93.3)	1,372 (6.7)	1.00	0.4500
Underweight	399 (93.7)	27 (6.3)	0.94 (0.56-1.57)	
Obese	1,294 (94.1)	81 (5.9)	0.87 (0.64-1.17)	
<b>Mother was part of clinical risk group</b>				
No	19,475 (93.3)	1,408 (6.7)	1.00	0.0353
Yes	1,108 (94.8)	61 (5.2)	0.76 (0.54-1.08)	
Unknown	116 (91.3)	11 (8.7)	-	
<b>Maternal chronic hypertension (non-pregnancy related)</b>				
No	20,410 (93.3)	1,458 (6.7)	1.00	0.7773
Yes	289 (92.9)	22 (7.1)	1.07 (0.60-1.89)	
<b>Maternal exposure to teratogenic medication(s) or live vaccines</b>				
No	19,406 (93.3)	1,400 (6.7)	1.00	0.1860
Yes	1,293 (94.2)	80 (5.8)	0.86 (0.63-1.16)	
<b>No. of weeks the first trimester overlapped with influenza activity above baseline levels</b>				
None	13,141 (93.5)	917 (6.5)	1.00	0.0371
0-2	1,338 (94.8)	73 (5.2)	0.78 (0.57-1.08)	
2-4	1,401 (92.6)	112 (7.4)	1.15 (0.88-1.50)	
4-6	1,445 (92.8)	112 (7.2)	1.11 (0.85-1.45)	
6-8	3,374 (92.7)	266 (7.3)	1.13 (0.94-1.36)	

Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index; CI, confidence interval.



## 9.4 Primary and secondary analyses

There was no evidence to suggest an association between receipt of PIIV anytime in pregnancy and MCMs recorded in the year after delivery in univariable or fully-adjusted Cox regression models ( $HR_{adjusted}$ , 0.97; 99% CI, 0.81-1.15;  $p=0.62$ ), with point estimates being highly similar in both (**Table 9.4**). The lack of association persisted when stratifying by trimester of vaccination, with the first trimester having a HR of 1.02 (99% CI, 0.72-1.46;  $p=0.86$ ) in the fully-adjusted model (**Table 9.4**). Results were similar in models that included MCMs ascertained anytime from delivery until the end of the study period (**Table 9.4**).

## 9.5 Sensitivity analyses

Results were robust in sensitivity analyses examining first-trimester vaccination and MCMs ascertained in the year after delivery or anytime in the study period. Whilst point estimates increased slightly in sensitivity analyses that excluded 2,030 pregnancies with unknown BMI and those that included 39 additional pregnancies that received PIIV in the 4 weeks prior to the pregnancy start, there was no evidence of an association (**Table 9.5**). Allowing follow-up time in HES and ONS to continue after follow-up in CPRD had ended resulted in the identification of just 4 additional infants with MCMs in the year after delivery and just 52 by the end of the study period. Neither of these analyses revealed an association between first-trimester vaccination and MCMs (**Table 9.5**).

**Table 9.4 - Examining the association between pandemic influenza vaccination in pregnancy and MCMs.**

Timing of vaccination (No. pregnancies)	No. MCMs/person-years (rate per 100 person-years)	HR, unadjusted (99% CI)	<i>P</i> value	HR, adjusted for <i>a priori</i> confounders (99% CI)	<i>P</i> value	HR, adjusted for all potential confounders (99% CI)	<i>P</i> value
<b>Models including MCMs ascertained in the year after delivery (N=1,444 MCMs)</b>							
Never (N=17,489)	1,168/15,699 (7.4)	1.00		1.00		1.00	
Any trimester (N=4,204)	276/3,784 (7.3)	0.98 (0.83-1.17)	0.79	0.97 (0.82-1.15)	0.65	0.97 (0.81-1.15)	0.62
Trimester 1 (N=825)	60/731 (8.2)	1.09 (0.78-1.53)	0.52	1.07 (0.76-1.51)	0.60	1.02 (0.72-1.46)	0.86
Trimester 2 (N=1,893)	124/1,697 (7.3)	0.98 (0.77-1.25)	0.84	0.98 (0.77-1.25)	0.81	0.98 (0.76-1.25)	0.82
Trimester 3 (N=1,486)	92/1,356 (6.8)	0.92 (0.70-1.22)	0.46	0.91 (0.69-1.20)	0.36	0.92 (0.69-1.23)	0.47
<b>Models including MCMs ascertained after delivery and anytime in the study period (N=1,644 MCMs)</b>							
Never (N=17,489)	1,335/65,144 (2.0)	1.00		1.00		1.00	
Any trimester (N=4,204)	309/15,989 (1.9)	0.96 (0.81-1.13)	0.50	0.95 (0.81-1.12)	0.41	0.95 (0.81-1.12)	0.45
Trimester 1 (N=825)	68/2,922 (2.3)	1.09 (0.79-1.50)	0.49	1.07 (0.78-1.48)	0.56	1.06 (0.76-1.48)	0.66
Trimester 2 (N=1,893)	135/7,121 (1.9)	0.93 (0.74-1.18)	0.43	0.93 (0.74-1.17)	0.41	0.94 (0.75-1.20)	0.53
Trimester 3 (N=1,486)	106/5,946 (1.8)	0.92 (0.71-1.19)	0.42	0.91 (0.70-1.18)	0.33	0.91 (0.70-1.18)	0.35

*A priori* confounders were maternal age, maternal ethnicity and region. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. Abbreviations: MCM, major congenital malformations; IMD, Index of Multiple Deprivation; BMI, body mass index; HR, Hazard Ratio; CI, Confidence Interval.

**Table 9.5 - Examining the association between first trimester vaccination with pandemic influenza vaccine and MCMs in sensitivity analyses.**

<b>Models</b>	<b>HR, unadjusted (99% CI)</b>	<b>P value</b>	<b>HR, adjusted for <i>a priori</i> confounders (99% CI)</b>	<b>P value</b>	<b>HR, adjusted for all potential confounders (99% CI)</b>	<b>P value</b>
<b>Models including MCMs diagnosed in the year after delivery</b>						
<b>Main model</b>	1.09 (0.78-1.53)	0.52	1.07 (0.76-1.51)	0.60	1.02 (0.72-1.46)	0.86
Including pregnancies vaccinated in the 4 weeks prior to the start <sup>a</sup>	1.13 (0.81-1.57)	0.34	1.11 (0.80-1.54)	0.41	1.07 (0.76-1.51)	0.60
Including diagnoses made beyond truncation of follow-up in CPRD <sup>b</sup>	1.09 (0.77-1.53)	0.53	1.07 (0.76-1.50)	0.62	1.02 (0.71-1.46)	0.89
Excluding pregnancies with unknown BMI <sup>c</sup>	1.12 (0.78-1.59)	0.43	1.10 (0.77-1.57)	0.48	1.07 (0.74-1.55)	0.65
<b>Models including MCMs diagnosed after delivery and anytime in the study period</b>						
<b>Main model</b>	1.09 (0.79-1.50)	0.49	1.07 (0.78-1.48)	0.56	1.06 (0.76-1.48)	0.66
Including pregnancies vaccinated in the 4 weeks prior to the start <sup>a</sup>	1.13 (0.83-1.54)	0.29	1.12 (0.82-1.53)	0.34	1.12 (0.81-1.54)	0.38
Including diagnoses made beyond truncation of follow-up in CPRD <sup>d</sup>	1.05 (0.76-1.45)	0.70	1.04 (0.75-1.43)	0.76	1.03 (0.74-1.44)	0.83
Excluding pregnancies with unknown BMI <sup>c</sup>	1.12 (0.80-1.55)	0.39	1.10 (0.79-1.54)	0.44	1.10 (0.78-1.56)	0.47

*A priori* confounders were maternal age, maternal ethnicity and region. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. Abbreviations: MCM, major congenital malformations; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics death certificate data; BMI, body mass index; IMD, Index of Multiple Deprivation; HR, Hazard Ratio; CI, Confidence Interval

## 9.6 Chapter summary and conclusions

This historical cohort study examined PIIV receipt during pregnancy, stratified by trimester, and MCMs in live-born infants. No evidence was found to suggest an association between vaccination anytime in pregnancy (HR, 0.97; 95% CI, 0.81-1.15;  $p=0.62$ ) or first-trimester vaccination (HR, 1.02; 99% CI, 0.72-1.46;  $p=0.86$ ) and MCMs in the year after delivery. Results were almost identical to those of a pooled analysis of six studies examining first-trimester PIIV and MCMs (Odds Ratio, 1.02; 95% CI, 0.89-1.17).<sup>23</sup> The lack of evidence for an association with MCMs persisted with longer follow-up and across all sensitivity analyses.

The strengths and limitations of these analyses have already been described in the previous chapter, which explored the safety of SIIV. Whilst the safety of PIIV with respect to MCMs has been explored by a number of studies, replicating these analyses here provided confidence in the methods used in this thesis (and consequently, the methods used to assess SIIV safety).

The results of the analysis carried out here were not only almost identical to pooled estimates from other studies, but the characteristics of the vaccinated and unvaccinated populations as well as the characteristics of those with and without major malformations were in line with what was expected based on published literature.

## Discussion

This section brings together the findings from **Chapter 2** and **Chapters 7-9**, and their interpretation. In **Chapter 10**, the aims and objectives of the thesis are summarized, the key results are described, and an overview of the main strengths of the work is provided. In **Chapter 11**, the challenges of using electronic health records to examine the safety of drugs and vaccines given in pregnancy with respect to MCMs are discussed. Interpretation of the findings, recommendations for further research and conclusions are provided in **Chapter 12**.

## 10. Discussion I: Key results and strengths of the research

### 10.1 Recapitulation of the aims and objectives of the thesis

The aim of this thesis was to use routinely-collected, multiply-linked UK electronic health records to assess the safety of SIIV and PIIV administration during pregnancy with respect to major congenital malformations. A systematic review of the methods used to identify recorded diagnoses of congenital malformations and the validity of these diagnoses in UK electronic health records was first carried out (**Objective 1**). This informed the development of an algorithm to identify major malformations in linked CPRD, HES and ONS data (**Objective 2**). Using this novel algorithm, major malformations were identified in linked data. The agreement between data sources in ascertaining major malformations and the unique contribution of each was quantified (**Objective 3**). The rates of major malformations in stand-alone CPRD were compared with rates in previously published stand-alone THIN data whilst rates in stand-alone CPRD, stand-alone HES and linked CPRD-HES-ONS were compared with those from EUROCAT (**Objective 4**). The association between maternal SIIV and major malformations, stratified by the trimester of pregnancy, was then examined (**Objective 5**). Finally, the association between maternal PIIV and major malformations was explored (**Objective 6**).

## 10.2 Summary of main results

### 10.2.1 The identification and validity of congenital malformation diagnoses in UK EHR

#### **What was known?**

Data available in UK electronic health records are collected for clinical purposes, not for research. Therefore, although there are chapters dedicated to congenital malformations in both the Read code system ('P' chapter) and ICD-10 ('Q' chapter), diagnoses may be recorded using different codes within each chapter as well as codes outside of these chapters.

Standardized code lists to define and identify diagnoses of interest in UK EHR are not typically available and researchers develop their own code lists for their own studies.<sup>126</sup> This can lead to differences between code lists for the same condition(s) depending on the inclusion criteria used. The implications of this were demonstrated in a recent study in which the prevalence of congenital malformations among live born infants ranged from 1.8% to 4.1% depending on the ICD-10 code list used to interrogate hospital data linked to birth and death records.<sup>245</sup>

The validity of diagnoses recorded in UK electronic health records is generally considered to be good. In 2010, a systematic review of validation studies of 183 different clinical diagnoses in the CPRD reported a high median PPV of 89% (range, 24-100), with most validations carried out by requesting additional information from GPs (e.g. questionnaires or complete paper records).<sup>180</sup> In 2011, another systematic review examined diagnostic and procedure coding accuracy in hospital data for a range of diagnoses, with most validations relying on case notes as the reference standard.<sup>181</sup> The median diagnostic PPV was also high (80%; IQR, 63-94) although most studies examined ICD-9 codes rather than the currently used ICD-10 codes. The PPV of primary diagnoses was particularly high (96%; IQR 89-96) and was thought to have improved as a result of annual audits of data quality and the requirement to record definitive diagnoses for reimbursement purposes.<sup>181</sup>

To date, no study has examined the methods used to identify congenital malformations in UK electronic health records despite their importance in post-marketing safety studies and the

challenges involved in capturing this wide array of conditions. Previous systematic reviews of validation studies in CPRD and HES are almost a decade old and have not specifically examined congenital malformations.<sup>180,181</sup>

### **What does this thesis add?**

As part of this thesis, 54 studies were reviewed systematically to summarize the methods used to identify congenital malformations in UK EHR. The validity of malformation diagnoses recorded in these data sources was also explored.

The 36 studies using primary care data to identify congenital malformations used diagnostic codes from several areas of the Read coding system, including the 'P' chapter dedicated to such diagnoses, and frequently used EUROCAT guidelines to develop case definitions. The types of codes used varied across studies. Most striking was the use of diagnostic codes from non-'P' chapters in 53% of primary care studies as these could potentially be used to record either congenital or non-congenital conditions. Codes relating to procedures were used in 56% of studies, codes for a history of congenital malformations in 39% and codes for relevant administrative tasks in 33%. Conversely, the 18 studies using secondary care data (of which almost half also used birth and death records) relied on codes from the ICD-10 'Q' chapter – half also used OPCS-4 procedure codes.

Eight studies validated congenital malformations identified in primary care data,<sup>187, 192, 194, 208, 209, 216, 219, 222</sup> of which only one was included in the previous systematic review of validations in CPRD.<sup>219</sup> The PPV (the only measure of validity assessed) was high for congenital malformations overall, major malformations and heart defects (80-100%), moderate for neural tube defects (71%) and lowest for developmental hip dysplasia (56%).<sup>187, 192, 194, 208, 209, 216, 219, 222</sup>

There was heterogeneity across studies in the reference standard used, and the PPV was shown to vary according to the reference standard that was chosen.<sup>194</sup> None of the studies identifying congenital malformations in secondary care data performed validations. Just one study examined the validity of diagnoses recorded in death records and, using hospital



admissions as a reference standard, demonstrated that death records under-ascertained life-limiting congenital malformations by 11-20%.<sup>237</sup>

The review here has not only highlighted the need for fuller reporting of the methods and code lists used in EHR studies of congenital malformations, but also the need for further validation studies. Ideally, these should assess a wide range of malformation subgroups and other measures of validity in addition to PPV.

## 10.2.2 The value of primary care, hospital admissions and mortality data in identifying major congenital malformations in anonymised UK EHR

### **What was known?**

Studies using UK EHR to identify congenital malformations have not used linked primary and secondary care data to increase ascertainment. Instead, as described in the systematic review presented in this thesis, they typically used stand-alone primary care data or stand-alone secondary care data (with some also using linked or unlinked birth or death records). Studies carrying out post-marketing safety assessments of drugs and vaccines given in pregnancy relied chiefly on primary care data. However, there is a growing body of evidence to suggest that agreement between electronic health record databases can be low and that using stand-alone data sources risks under-ascertaining conditions.<sup>288-291</sup> At the time of this work, this had not yet been explored for congenital malformations.

### **What does this thesis add?**

Work presented in this thesis demonstrated the value of linked CPRD and HES in increasing ascertainment of congenital malformations. Code lists to identify major malformations in linked primary care, hospital admission and mortality data were developed in accordance with EUROCAT guidelines and with the input of a consultant neonatologist.<sup>86, 283</sup> Among 7,901 infants with a major malformation diagnosed in the year after delivery, agreement between CPRD and HES was low - just 20%. Almost 65% of infants had a diagnosis exclusively in HES and 15% exclusively in CPRD. Results were robust to increased follow-up beyond one year. Even

after excluding non-specific skin malformation diagnoses in ICD-10, some of which may have referred to minor conditions, the proportion with evidence exclusively in HES remained high (56%). Death certificates or procedures carried out during hospital admissions identified very few additional individuals that did not already have evidence of their diagnosis in CPRD or HES. For most malformation subgroups, agreement between CPRD and HES was also low and did not improve markedly with longer follow-up.

### 10.2.3 Prevalence comparisons of major malformations identified in UK EHR data sources and in registries

#### **What was known?**

In previous studies, the prevalence of major malformations was generally higher in primary care data than in registries, or was comparable.<sup>201, 209, 218</sup> However, prevalence comparisons were mainly limited to THIN data.<sup>201</sup> Between 1990 and 2009, the prevalence ratio for major malformations among live-births between THIN and UK EUROCAT data was 1.18 (95% CI, 1.16-1.20).<sup>201</sup> Heart, limb, genital, musculoskeletal and eye malformations all had higher prevalence in THIN. In CPRD, just two subgroups were examined; congenital heart malformations had a higher prevalence than in EUROCAT whilst the prevalence of nervous system malformations was comparable.<sup>209, 218</sup> For some subgroups or rare malformations the prevalence was lower in primary care data although prevalence increased with longer follow-up.<sup>201, 218</sup>

#### **What does this thesis add?**

Use of the code list developed for this thesis enabled good ascertainment of major malformations in the electronic health record datasets examined. The prevalence of major malformations in stand-alone CPRD data was 244 per 10,000 live-births (95% CI, 236-253), compared to 198 per 10,000 live-births (95% CI, 195-201) in published data from THIN.<sup>201</sup> Malformation subgroups had similar prevalence in CPRD and THIN with the exception of limb, urinary, digestive and eye malformations which had higher prevalence in CPRD, and nervous system malformations which had higher prevalence in THIN.<sup>201</sup>

After comparing the code list developed here to identify major malformations in CPRD with that used for the THIN study, the higher prevalence of digestive, eye and urinary malformations in CPRD could be explained by the greater sensitivity of the Read code list developed for the studies described in this thesis. Differences in code lists did not appear to explain the higher prevalence of limb malformations or lower prevalence of nervous system malformations in CPRD.

The prevalence of major malformations overall was higher in stand-alone CPRD, stand-alone HES and linked CPRD-HES-ONS than in EUROCAT between 2009 and 2013 (the period before changes in the organization of contributing EUROCAT registries). Prevalence was higher in stand-alone CPRD than in EUROCAT for limb, heart, genital and eye malformations, consistent with published comparisons between THIN and EUROCAT.<sup>201</sup> In stand-alone HES and in linked CPRD-HES-ONS data, all subgroups had a higher prevalence than in EUROCAT except for abdominal and orofacial malformations, which had comparable prevalence. Finally, major limb malformations had a considerably higher prevalence in stand-alone HES compared to EUROCAT (Prevalence Ratio, 8.3; 95% CI, 7.7-8.9) and this was similar in linked CPRD-HES-ONS data. This was likely a result of the large number of non-specific limb codes in ICD-10; >90% of infants with a limb malformation in HES had such a code.

#### 10.2.4 The safety of influenza vaccination during pregnancy and major congenital malformations

##### **What was known?**

A small number of observational studies, all based in North America, have examined the safety of maternal receipt of SIIV with respect to major malformations in live-born infants.<sup>50, 90, 101, 103, 104</sup> None of these have identified evidence of an association. However, with the exception of a study by Kharbanda *et al.*<sup>103</sup> which was published after the work in this thesis had started, available evidence was limited by short follow-up (restricted to the period around delivery) and low numbers of first-trimester vaccinations.<sup>50, 90, 101, 104</sup>

The study by Kharbanda *et al.* is the only study to have examined a large number of first-trimester vaccinated pregnancies (n>52,000) and followed infants up for a year after delivery.<sup>103</sup> The adjusted prevalence ratio for major malformations comparing pregnancies vaccinated in the first trimester to unvaccinated pregnancies was 1.02 (95% CI, 0.94-1.10; p=0.6). This was similar for subgroups such as cardiac defects (Prevalence Ratio, 0.98; 95% CI, 0.87-1.10; p=0.8) and muscular or limb defects (Prevalence Ratio, 0.93; 95% CI, 0.67-1.30; p=0.7). To date, no study in Europe or the UK has assessed the safety of maternal SIV with respect to major malformations.

The majority of studies that have examined the safety of maternal influenza vaccination and major malformations have examined PIV. Individually, none of the studies have identified evidence of an association with major malformations overall. One systematic review pooled ten analyses examining major malformations following PIV receipt anytime in pregnancy and reported an odds ratio of 1.02 (95% CI, 0.91-1.14).<sup>23</sup> Restricting to six analyses in which PIV was received in the first trimester gave an identical odds ratio of 1.02 (95% CI, 0.89-1.17).<sup>23</sup> A more recent systematic review pooled seven analyses and calculated an adjusted odds ratio of 1.03 (95% CI, 0.99-1.07) for major malformations following PIV receipt in pregnancy.<sup>22</sup> The limitations of these studies are similar to those for SIV. Most studies had low numbers of first-trimester vaccinations and short follow-up. However, unlike safety studies on SIV, studies examining PIV have assessed safety in relation to MCMs in a wider range of settings.

### **What does this thesis add?**

This thesis presents the largest European safety study on maternal SIV and major malformations using a large UK-based historical cohort to date. In addition to providing further evidence of safety in a different setting, it addresses several limitations highlighted by previous systematic reviews of the related literature, with an appreciably longer follow-up of infants (including beyond the first year of life) and a large numbers of pregnancies vaccinated in the first trimester.

Use of the CPRD/LSHTM Pregnancy Register enabled examination of vaccine uptake by UK pregnant women by trimester.<sup>255</sup> Among 78,150 pregnancies delivering a live-born singleton infant between September 2010 and March 2016, 8.8% had received a vaccine in the first trimester, 14.9% in the second and 16.5% in the third. In fully-adjusted models, the hazard ratio for major malformations recorded in the year after delivery among those vaccinated in the first trimester compared to those never vaccinated was 1.06 (99% CI, 0.94-1.19; p=0.23). There was no evidence for an association between first-trimester SIV and major malformations. Results were very similar for those vaccinated anytime in pregnancy (HR, 1.02; 99% CI, 0.94-1.10; p=0.54) or in subsequent trimesters. Similar estimates were obtained after including diagnoses made after the first year of life. There was also no evidence of an association between first-trimester vaccination and limb malformations (HR<sub>adj</sub>, 1.03; 99% CI, 0.86-1.25; p=0.66) or congenital heart defects (HR<sub>adj</sub>, 0.91; 99% CI, 0.64-1.29; p=0.49). These results were consistent with those presented by Kharbanda *et al.*

This thesis also presents the largest examination of PIIV and major malformations in UK data. The analysis included 21,693 pregnancies delivering a live-born singleton between 2009 and 2010. Of these, 3.8% received a vaccine in the first trimester, 8.7% in the second and 6.9% in the third. The fully-adjusted model did not reveal any evidence for an association between first-trimester vaccination and major malformations in the first year of life, with a hazard ratio of 1.02 (99% CI, 0.72-1.46; p=0.86). Results were similar for vaccination anytime in pregnancy (HR<sub>adj</sub>, 0.97; 99% CI, 0.81-1.15; p=0.62). These results were in line with pooled analyses of the safety of PIIV in systematic reviews.<sup>22, 23</sup>

## 10.3 Strengths

### 10.3.1 The use of large, multiply-linked EHR databases

This research was conducted using large, representative, routinely-collected primary care data linked to hospital admissions and mortality data. At the time this work began, CPRD comprised data on over 11 million patients and included almost 700 practices across the UK, making it

one of the largest electronic health record databases worldwide.<sup>126</sup> The large size of this database was key in allowing the examination of major congenital malformations, a rare outcome, and (as discussed further below) increasing study power to examine vaccination by the trimester of pregnancy.

The ascertainment of MCMs was maximised by the existing linkage of primary care records to hospitalisation and mortality data for 75% of English practices.<sup>126</sup> Many congenital malformations are likely to be diagnosed in hospital, at the time of delivery or in early childhood, and some may only be identified following death. Hospitalisations and deaths are required to be communicated to general practice but these may be delayed or incompletely encoded in the electronic primary care record (researchers, for example, do not have access to information entered by the general practitioner as free-text or scanning hospital letters).<sup>287</sup> Linkage of these databases enabled more complete capture of these rare conditions, as demonstrated by the finding that the majority of infants with a major congenital malformation had evidence of their condition exclusively in HES.

A further key strength of these data is their potential for long-term follow-up. A frequently cited limitation of previous safety studies examining maternal influenza vaccination was that these studies ascertained congenital malformations around the time of delivery and did not capture later diagnoses.<sup>20-24</sup> In an attempt to address this, more recent studies have attempted follow-up of one year. However, there is evidence that some congenital malformations may be diagnosed or recorded after the first year of life.<sup>218, 244, 313</sup> Others have also emphasized the need for further evidence on long-term paediatric outcomes following maternal influenza vaccination.<sup>314</sup> In the maternal vaccine safety assessments described in this thesis, in addition to examining congenital malformations in the first year of life, a further analysis was carried out in which all available follow-up time in the study period was used. Almost 50% of infants had more than two years of follow-up and over 5% of all major malformations in the cohort were identified after the first year of life.

### 10.3.2 The use of the newly-developed CPRD/LSHTM Pregnancy Register

The use of the newly-developed and recently validated CPRD/LSHTM Pregnancy Register, which aims to identify all pregnancy episodes among women aged 11-49 years, was a key strength of the work described in this thesis.<sup>255</sup> Whilst the potential of EHR for post-marketing safety studies in pregnancy is widely recognized, identifying pregnancy episodes and their timing in these data is challenging as this information is not systematically recorded.<sup>255</sup> This complicates the ascertainment of gestational age at the time of exposure and the examination of exposures in different trimesters.

The Pregnancy Register algorithm is unique in that it uses all the available pregnancy data to identify pregnancy episodes and their onset, end and trimester dates.<sup>255</sup> The work conducted in this thesis benefitted from this comprehensive approach in three ways:

1. A large number of first-trimester vaccinated pregnancies were easily identified. This was crucial in the safety studies described here because congenital malformations were the outcome of interest and most organogenesis occurs in the first trimester. In the wider literature, available evidence on the safety of first-trimester vaccination with respect to congenital malformations has been limited by low numbers of pregnant women vaccinated in the first trimester.<sup>20-24</sup> The use of the Pregnancy Register meant that the safety assessment of SIV in the first trimester presented here is the largest such assessment outside of the US.
2. The potential misclassification of vaccination timing was minimized. The accuracy of estimated gestational age at the time of vaccination is important when examining trimester-sensitive outcomes such as congenital malformations. In this work, gestational age at the time of vaccination was thought to have high accuracy due to the use of all available information on gestational age in primary care records by the Pregnancy Register algorithm. Gestational age in the Pregnancy Register has been

validated using linked HES data and close agreement was observed (median difference of 0 weeks' gestation, IQR 0-0 weeks).<sup>255</sup>

3. Transparency with regards to live-birth pregnancies that could not be linked to the records of a live-born infant. In **Section 4.3.8**, the possible reasons for incomplete linkage between the mother and infant in the Mother-Baby Link were outlined. Incomplete linkage is a complicating factor for safety studies of drugs and vaccines given in pregnancy. In the Pregnancy Register, live-birth pregnancies that are not linked to infant records are captured and can be easily identified.<sup>255</sup> This allowed the extent of incomplete linkage to be explored and reported, in contrast to other drug safety studies in pregnancy that have typically not provided this information.

### 10.3.3 Development and use of a novel algorithm for identifying congenital malformations

At the time this work was conducted there was no established algorithm for the identification of congenital malformations in UK electronic health records. Developing Read, ICD-10 and OPCS-4 code lists to identify the wide array of conditions in these data posed a challenge. A systematic review of the methods used to identify these conditions in UK electronic health records, and any validations, was first carried out and was invaluable in informing the development of a novel algorithm to identify congenital malformations in this thesis.

Guidelines published by EUROCAT, a well-established network of population-based registries for congenital malformations with over 40 years of surveillance experience across Europe, were used to define major malformations and subgroups.<sup>86</sup> Code lists developed using these guidelines were reviewed with a consultant neonatologist. Read codes outside of the 'P' chapter, which might not always be congenital in nature, were considered for inclusion in code lists to increase the ascertainment of major malformations in primary care data (an approach observed in several other studies included in the systematic review) but were only included if they were likely to relate to conditions with congenital causes in the majority of the study



population. The ascertainment of major malformations overall in stand-alone and linked data using these code lists was found to be higher than that in THIN or EUROCAT registries and similar results were seen for many subgroups.<sup>201</sup>

#### 10.3.4 Careful approach in determining exposed and unexposed cohorts

Establishing the vaccination status and trimester of vaccination receipt was critical in the maternal vaccination safety studies carried out here. Each pregnant woman could have multiple records relating to influenza vaccination across a particular vaccination season, some of which could be conflicting. To establish the best possible consensus, all the available evidence for each woman across each pregnancy and season was considered.

The earliest record of vaccine receipt during a vaccination season was considered to be the most accurate information on vaccination timing. This assumed that vaccination evidence from different files in CPRD could be treated equally when, conventionally, evidence from the clinical file is thought to be the least reliable. To explore this assumption, the proportion of pregnant women whose earliest evidence of vaccination came from the clinical file was quantified and found to be <1% (outlined in **Section 6.3**), which indicated that the potential misclassification introduced by using the earliest record of vaccination was minimal. Pregnant women for whom there was uncertainty in vaccination timing or the type of influenza vaccine received were excluded from analyses using detailed criteria (outlined in **Sections 6.4-6.5**).

Seasonal influenza vaccine uptake in the study population, established using this approach, was found to be similar to national '*Immform*' data.<sup>284, 307-309</sup> Pandemic influenza vaccination uptake established here was also similar to the uptake observed by another study using CPRD over the same period.<sup>312</sup> This detailed and comprehensive approach is likely to have minimized the misclassification of the trimester of vaccination.

Despite the various strengths outlined in this chapter, there are also several challenges in using UK electronic health records to examine the safety of drugs and vaccines administered during pregnancy and the risk of MCMs. These challenges are highlighted in the subsequent chapter.

## 11. Discussion II : Challenges in using UK electronic health records for safety studies concerning major congenital malformations.

The large size, longitudinal nature, generalizability and richness of electronic health record databases makes them a useful resource for pharmacoepidemiological research. Nevertheless, there are a number of potential limitations that need to be considered.

This discussion chapter describes the challenges of using these data to ascertain MCMs and conduct safety studies. These are of course not the only challenges encountered when conducting safety studies with MCMs as the outcome of interest but, rather, the key issues which require particular attention when using electronic health records. **Section 11.1** summarizes the limitations of clinical coding systems and practices, how these affect validity and ascertainment of MCMs, and alternative approaches. **Section 11.2** describes other potential sources of misclassification. **Section 11.3** summarizes the limited ability of these data to examine terminations due to foetal anomaly and the implications of this. **Section 11.4** summarizes the implications of having limited ability to examine major malformation subgroups and individual conditions. In **Sections 11.5 to 11.7**, other potential limitations are considered, including other possible selection bias, residual confounding, and limitations to generalisability.

## 11.1 Validity of MCMs recorded in UK electronic health records: limitations of clinical coding systems and practices.

Misclassification occurs when the information on the outcome, exposure or covariates is incorrect. The systematic review carried out in **Chapter 2** found that validation studies in CPRD have demonstrated high PPVs for congenital malformations overall, major malformations and heart defects (80-100%) and moderate or low PPVs for neural tube defects (71%) and developmental hip dysplasia (56%), respectively.<sup>187, 192, 194, 208, 209, 216, 219, 222</sup>

No estimates of PPV for congenital malformations in HES data were identified but, internationally, studies have examined the validity of ICD codes for MCMs and demonstrated variation in PPV. For example, validation studies of congenital heart defects recorded using ICD-8 and ICD-10 codes in the Danish National Patient Registry have shown high PPV (86-100%) using medical records, echocardiography and/or autopsy reports as reference standards.<sup>315</sup> In the US, validation studies of congenital heart defects recorded using ICD-9 codes in Medicaid claims data, with medical records as the reference standard, have estimated lower PPVs than Danish studies (68-78%).<sup>316, 317</sup> Another US study that examined the validity of congenital heart defects from ICD-9 codes in the US Vaccine Safety Datalink by reviewing medical records found a high PPV (88%).<sup>318</sup> Coding practices across countries vary and so these PPVs are not reliable indicators of the PPV in HES data. However, these studies demonstrate a wide range of PPVs for a single MCM subgroup in secondary care data and therefore highlight the importance of considering the validity of code-lists used to identify MCMs and any resulting misclassification of the outcome of interest in the studies comprising this thesis.

The prevalence of all congenital malformations among live-births is estimated to be 2-3%.<sup>80-82</sup> However, in the work described here, the prevalence of just MCMs was considerably higher. Among the 78,150 infants in the seasonal influenza vaccine safety study, more than 7% had evidence of an MCM recorded in the first year of life. Compared to UK EUROCAT registries, CPRD-HES-ONS data displayed higher prevalence for almost all MCM subgroups, with HES data

accounting for the majority of the difference. Interestingly, MCM prevalence in the US Vaccine Safety Datalink (which includes diagnoses made in hospital) was similar to EUROCAT (1.7% VS 2%) although for some subgroups the prevalence of MCM subgroups was considerably higher than that seen in EUROCAT.<sup>318</sup> The high prevalence of MCMs in the data used in this thesis suggested that although the algorithm developed to identify MCMs for this work had high sensitivity, this may have been at the expense of PPV. Inherent limitations of clinical coding systems and practices could contribute to this elevated prevalence. These limitations and their potential to inflate prevalence estimates are summarized below.

### 11.1.1 Non-specific codes outside of the dedicated congenital malformation chapters

#### **Diagnostic Read codes from outside the Read 'P' chapter for congenital malformations**

In primary and secondary care records, MCM diagnoses can be encoded using codes from the Read 'P' and ICD-10 'Q' chapters for congenital malformation diagnoses, respectively. MCMs may, however, also be recorded using codes from other chapters that can be used to encode non-congenital conditions. When developing code-lists to identify MCMs from electronic health records, researchers may include codes from dedicated chapters as well as codes from other chapters that could relate to congenital or non-congenital conditions.

Including codes from other chapters may result in more complete ascertainment of individuals with MCMs but may also capture some individuals with non-congenital conditions, thus lowering PPV. The systematic review in **Chapter 2** demonstrated that researchers often considered including relevant diagnostic codes from outside the Read 'P' chapter in their code-lists but did not specify the criteria used to decide their inclusion. Codes beyond the 'Q' ICD-10 chapter were not considered, possibly because clinical coding in hospital data is directly tied to reimbursement and therefore it is less likely that MCMs will be recorded using codes outside of the dedicated chapter for congenital malformation diagnoses.<sup>261</sup>

In line with the above, the ICD-10 code-list developed here to identify individuals with MCMs only included diagnosis codes from the 'Q' ICD-10 chapter whereas the Read code-list included

relevant diagnosis codes regardless of whether they were part of the 'P' chapter for congenital malformations or not (**Chapter 5**). For example, the 'P' chapter code '*congenital mitral stenosis*' was considered alongside the 'G' chapter code '*mitral stenosis*'. Whilst the former code could only relate to a congenital condition, the latter could also be used to encode non-congenital conditions such as mitral stenosis following rheumatic fever.

Read codes outside the 'P' chapter dedicated to congenital malformations were only included if the consultant neonatologist agreed that they were most likely to indicate an MCM in the study population and in the study period. In this example, the 'G' chapter code '*mitral stenosis*' was included because rheumatic fever was not prevalent among children in the UK during the study period. If such a code was present in an individual under 5 years of age, the cause was overwhelmingly likely to be congenital.

The possibility that a small number of infants with diagnosis codes from outside the Read 'P' chapter did not have an MCM cannot be discounted but it is unlikely that the inclusion of such codes drove the large difference in prevalence between CPRD-HES-ONS data and EUROCAT. The requirement for non-'P' chapter Read diagnosis codes to have a congenital aetiology in the majority of the study population during the study period, and the clinical input of a consultant neonatologist, meant their inclusion was unlikely to have lowered the PPV of the algorithm. Furthermore, the difference in prevalence between CPRD-HES-ONS data and EUROCAT appeared to be driven primarily through increased ascertainment in HES data and diagnostic codes from outside the 'Q' chapter for congenital malformations were not used.

#### **Non-diagnostic codes outside of the 'P' and 'Q' chapters for congenital malformations**

Procedures to repair MCMs are recorded using Read codes in CPRD and OPCS-4 codes in HES but there are no chapters dedicated to procedures for congenital malformations in either coding system. The Read system also allows clinicians to encode other information such as administrative tasks relating to the management of chronic conditions, observations following

examination, and clinical history but again there is no dedicated chapter for those relating specifically to congenital malformations.

Relevant non-diagnostic Read codes from outside the congenital malformation 'P' chapter, and OPCS-4 procedure codes, were only included in code-lists if they were known to relate to a particular MCM. For example, the Read code for '*correction of pectus excavatum*' was included because pectus excavatum is an MCM. Conversely, the Read code for '*insertion of prosthesis into chest wall*' was not included because even though it could relate to a corrective procedure for an MCM, it could also relate to procedures for traumatic injury. Based on these criteria, the use of these codes was also unlikely to explain the elevated prevalence of MCMs observed in these studies.

### 11.1.2 Non-specific codes within chapters dedicated to congenital malformations

#### **Codes from the 'P' and 'Q' chapters that could relate to major or minor malformations**

Although both the 'P' chapter in the Read system and 'Q' chapter in ICD-10 are dedicated to diagnostic codes for congenital malformations, both contain non-specific codes that could relate to an array of congenital malformations, major and minor. Examples of such codes include '*other congenital deformities of feet*' and '*other congenital deformities of skull, face and jaw*'.

EUROCAT guidelines specify that some non-specific codes should not be used to record MCMs, including '*other congenital deformities of skull, face and jaw*' and '*other congenital deformities of feet*'.<sup>282</sup> However, clinical coders in primary and secondary care do not follow EUROCAT guidelines and may use these codes to record MCM diagnoses. Such codes were retained in code-lists to ensure the ascertainment of those infants who did have an MCM. However, some infants identified using these codes will have had minor malformations which would inflate the prevalence estimates.

The prevalence of limb malformations was 10 times higher in CPRD-HES-ONS compared to EUROCAT, with the majority of this increase attributed to high prevalence in HES (**Section 7.5.1**). This increased prevalence could be explained by the large number of potentially non-specific codes for these conditions in the ICD-10 'Q' chapter and, to a lesser extent, in the Read 'P' chapter. In the work described in this thesis, the proportion of infants with a limb malformation that had a non-specific code as the only recorded evidence of their condition was 52.7% in CPRD and 91.9% in HES (**Section 7.3**). The most common non-specific code among infants with a limb malformation was '*other congenital deformities of feet*' which could refer to any major or minor malformation. Other relatively common, non-specific codes included:

- '*Syndactyly*' and '*fused toes*' - EUROCAT specifies that syndactyly of the 2<sup>nd</sup> and 3<sup>rd</sup> toes is a minor malformation but Read and ICD-10 codes do not specify the affected toes.<sup>283</sup>
- Codes relating to hip anomalies such as '*other congenital deformities of hip*' - which could refer to hip dislocations defined as major by EUROCAT, or hip subluxations defined as minor by EUROCAT.<sup>283</sup>
- '*Talipes equinovarus*' - EUROCAT distinguishes between those that are malformations and those that are postural in origin but Read and ICD-10 codes do not.<sup>283</sup>

The ICD-10 coding system used in HES lacks the granularity of the BPA-modified ICD-10 system used by EUROCAT. The BPA-modification adds an extra digit to certain ICD-10 codes which can be used to define malformations not specified explicitly in ICD-10, demonstrate uncertainty in the diagnosis, specify laterality and/or help distinguish between major and minor conditions. For example, in EUROCAT, code Q825 '*congenital non-neoplastic naevus*' can be further specified as Q8250 '*naevus flammeus*', Q8251 '*strawberry naevus*', Q8252 '*mongolian blue spot*' and, Q8258 '*other specified congenital non-neoplastic naevus*'.<sup>283</sup> EUROCAT guidelines define Q8250-8252 as minor, but these more detailed codes are unavailable in ICD-10 and so

code Q825 was included.<sup>283</sup> Read codes tend to be more granular than ICD-10 codes as there are often multiple Read codes that relate to a single ICD-10 code. A lack of granularity, among ICD-10 codes in particular, means that minor conditions are likely to be captured and inflate prevalence estimates for MCMs.

Based on the above, non-specific ICD-10 codes from the 'Q' chapter dedicated to congenital malformation diagnoses appeared to be a main driver of the increased prevalence of MCMs seen in the studies described here. Including these non-specific codes in code-lists developed for this work is likely to have identified a number of children with minor malformations and explains the high prevalence of MCMs compared to EUROCAT. Indeed, among the study population for the seasonal vaccine safety analyses, hip conditions, talipes equinovarus and syndactyly were approximately two or more times as prevalent in HES than in EUROCAT, suggesting they played a large part in increasing the prevalence of limb malformations overall. **(Table 8.1).**<sup>294</sup>

The above demonstrates that some individuals who had only a minor malformation are likely to have been included in the study. It is possible that this could occur more frequently among vaccinated women. Women with higher levels of healthcare engagement might be more likely to accept the vaccine and more likely to present infants with minor conditions to healthcare professionals. If these are coded with non-specific codes, infants would be misclassified as having a major malformation and the measure of effect would be inflated. However, there was no evidence for an association between vaccination in pregnancy and any of the major malformations examined in adjusted models.

#### **Codes for which additional criteria were required to identify MCMs**

Some conditions are only considered by EUROCAT to be true MCMs if they meet additional criteria which may or may not be available to researchers using electronic health records. For example, '*congenital hydronephrosis*' is defined by EUROCAT as an MCM only if there is a pelvis dilatation of >10 mm.<sup>283</sup> Such details are not captured by Read or ICD-10 codes.



Additional details recorded in the free-text of primary care records are not available to researchers. It was therefore not possible to discern whether infants with these codes had an MCM or not. All infants with such codes were conservatively treated as having MCMs. The inclusion of congenital hydronephrosis Read codes were shown to account for an increased prevalence of urinary system malformations in CPRD (**Section 7.4.2**). This was also demonstrated in **Chapter 8**, where the prevalence of congenital hydronephrosis in the HES records of infants in the seasonal influenza vaccines safety study was 16 per 10,000 live-births (**Table 8.1**), twice as high as that reported by EUROCAT.<sup>294</sup>

Some codes are defined as MCMs by EUROCAT provided they are not related to a premature birth. An example of this is '*patent ductus arteriosus*' which is defined as an MCM if the gestational age at birth is at least 37 weeks.<sup>283</sup> In the vaccine safety analyses carried out for this thesis, gestational age at birth was obtained from the Pregnancy Register and was used to determine whether infants with patent ductus arteriosus had an MCM that was unrelated to prematurity. The prevalence of this condition among the study population for the seasonal vaccine safety analysis was considerably higher than the prevalence in UK EUROCAT registries (25 vs 1 per 10,000 births).<sup>294</sup> This could be due to inaccuracies in the recorded gestational age at birth although validation of the Pregnancy Register against matched delivery records in HES found the median weeks difference in gestational age to be 0 (IQR 0-0).<sup>255</sup> The difference in prevalence is more likely to be a result of differences in the thresholds for recording such conditions in electronic health records and EUROCAT (see **Section 11.1.3**).

These two examples demonstrate that non-specific codes for which additional details are required to determine whether they relate to MCMs are likely to have contributed considerably to the elevated prevalence of MCMs seen in this work. These codes were included to ensure that children with severe congenital hydronephrosis or patent ductus arteriosus were not missed.

### 11.1.3 Coding thresholds

The threshold for coding diagnoses in electronic health records is likely lower than that in EUROCAT due to the need for the former to capture the entirety of the patient's medical history. Some MCMs, such as atrial septal defects and patent ductus arteriosus, vary in their severity and may sometimes resolve on their own with time. Less severe MCMs which resolve on their own or do not cause symptoms are less likely to be captured by EUROCAT but may still be encoded in the patient's routine clinical records. As Read and ICD-10 codes do not contain information about the severity of the condition, it is not possible for researchers to distinguish between those conditions which are MCMs and those which resolve on their own or those with no clinical significance. There was evidence to suggest different coding thresholds were another key driver of the increased prevalence seen in CPRD-HES-ONS, with both atrial septal defects and patent ductus arteriosus displaying considerably higher prevalence compared to EUROCAT (**Table 8.1**).<sup>294</sup>

### 11.1.4 Tentative diagnoses

Codes in the patient's record may sometimes reflect tentative diagnoses made by clinicians that require further investigation and have not yet been confirmed. Some may later be found to be unrelated conditions but this will not be known to researchers. Tentative coding is more likely to occur in primary care records due to the role of GPs in referring patients to other areas of the health service for further care and investigation. It may also be less likely in secondary care records due to the close ties between clinical coding and reimbursement.<sup>261</sup> Nevertheless, this could have contributed to an increased prevalence in electronic health records compared to EUROCAT.

### 11.1.5 Temporal changes in coding practices

The quality of coding in electronic health records can vary over time due to changes in coding practices. In primary care, financial incentives are used to drive improvements in the recording of specific data items as part of the Quality and Outcomes Framework.<sup>126</sup> This is unlikely to

have affected the prevalence of MCMs in CPRD as the recording of these conditions is not incentivised. In HES, a 2010 audit report highlighted the need to improve recording of diagnoses and procedures across specialist NHS Trusts as well as the recording of co-morbidities nationally.<sup>319</sup> While this could have resulted in an increase of non-specific coding of co-morbidities, a 2014 audit showed that co-morbidities continued to be under-recorded.<sup>320</sup> The impact of these changes on MCMs recorded in HES is therefore uncertain.

#### **11.1.6 Summary of the key factors that may have increased the prevalence of MCMs**

The key limitation when identifying MCMs from electronic health records is the uncertainty in the PPV of non-specific codes that are part of the dedicated 'P' and 'Q' chapters for congenital malformations in Read and ICD-10. These non-specific codes can refer to major or minor malformations. Alternatively, they may relate to conditions for which additional details are required to make a judgement on the clinical significance of the condition. Lower coding thresholds in routinely collected electronic health records (compared to EUROCAT) and the potential for tentative diagnoses to be recorded in primary care also have the potential to lower the PPV of code-lists. Finally, whilst diagnostic, procedure and other codes outside of the dedicated congenital malformation chapters were unlikely to have had a considerable effect on the PPV of the code-lists used in this work due to the stringent inclusion criteria employed, they should be recognized as a potential source of non-specificity when planning new studies.

#### **11.1.7 Alternative approaches**

To increase the PPV of algorithms for the identification of MCMs, some researchers using other electronic data sources incorporated additional rules requiring multiple records of the same diagnosis on different dates or the presence of diagnostic codes in multiple data sources. Studies which have required congenital heart defect codes to be present on at least two dates or present in both in-patient and out-patient records have demonstrated increased PPV compared to algorithms that do not include such rules.<sup>316-318</sup>

Studies using electronic health records should consider developing bespoke algorithms reflecting the expected clinical trajectory of particular MCMs. For example, most congenital diaphragmatic hernias are diagnosed shortly after delivery and undergo a procedure for repair by their first birthday. The identification rule for this condition could be the presence of a diagnosis and procedure in the first year of life. The caveat is that, in this case, the identification rule would not pick up those infants who are diagnosed but not clinically stable enough to undergo a procedure in their first year of life. Further refinement to the algorithm would be needed; for example to consider evidence from death certificates in the absence of other evidence or to consider evidence reflecting sequelae that occur commonly in infants with severe congenital diaphragmatic hernia that are clinically unstable.

This approach would necessitate considerable expert input from a range of clinicians including neonatologists and paediatric surgeons. Furthermore, the usefulness of this approach when using UK hospitalisation data may be limited for those conditions which may be diagnosed around the time of delivery but which are managed in out-patient facilities, as the completeness of recording of diagnoses and procedures in HES out-patient data is currently very low.<sup>261</sup> The low agreement seen between HES admissions data and CPRD in this work (**Chapter 7**) also raises questions about potentially defining MCMs based on the presence of codes in both these data sources. Validation studies examining the PPV of different algorithms for the same condition would be useful when considering combinations of codes and data sources used to identify MCMs.

## 11.2 Other misclassification

### 11.2.1 Misclassification of influenza vaccination status and its timing within pregnancy

As discussed previously, the overall estimates of vaccine uptake were highly comparable to those from the national '*Immform*' data.<sup>284, 307-309</sup> The immunisation and therapy files in CPRD, from which the vast majority of evidence of influenza vaccination receipt was identified, are also considered highly reliable. GPs are also required to document vaccinations that are given

by other healthcare providers, although at the time of the safety study that was carried out for this thesis, vaccination was almost entirely carried out in primary care.<sup>73</sup> Any under-ascertainment of vaccination is likely to be non-differential with respect to major malformations in the infant and would therefore bias the hazard ratio to the null.

A key strength of the work described in this thesis was the use of the Pregnancy Register algorithm, which considers all the available pregnancy data recorded in CPRD to estimate the timing and duration of pregnancy, an approach thought to increase accuracy.<sup>255</sup> However, imprecision in timings could still occur and result in misclassification of the timing of vaccination if, for example, pregnancies were assigned a fixed pregnancy duration due to the absence of records used to estimate the onset of pregnancy.

Pregnancies in the Pregnancy Register were examined carefully to identify any potential for misclassification of the trimester of vaccination. Pregnancies were excluded if the estimated delivery date preceded the infant's month/year of birth or if the duration of the pregnancy was incompatible with a live-birth (**Sections 4.3.2 & 4.3.4**). When determining the trimester in which a woman was vaccinated, all vaccination records across a season were considered and the earliest record was used only after the potential for misclassification introduced by the clinical file was assessed and judged to be very low (**Section 6.3**). Pregnancies were also excluded from analyses if the timing of vaccination was uncertain such as if the woman had evidence of receiving the vaccine somewhere other than her practice. Finally, it was reassuring that a sensitivity analysis exploring first-trimester vaccination and including those vaccinations occurring in the 4 weeks prior to pregnancy also did not find evidence of an association with MCMs.

### 11.2.2 Misclassification of potential confounders

The severe nature of major malformations and the contractual requirement of GPs to document vaccinations means that these are likely to be well-recorded overall. This was not the case for all potential confounders, although the use of multiply-linked data was used to

increase their ascertainment where possible (e.g. for ethnicity) and women had to be registered at a practice for at least six months before the start of pregnancy for the same reason. For smoking, hazardous drinking, and BMI, there was often no record to indicate maternal status at the start of pregnancy and the best possible estimate was obtained by examining all the woman's available records using a series of hierarchical decisions (**Section 4.6**). For smoking and drinking, which are widely discouraged during pregnancy, it was possible that some pregnant women who did participate in these activities did not report doing so and consequently their status was misclassified. Accurate and timely recording of these data is more likely to occur among women who accept vaccination. Misclassification of confounders could have resulted in residual confounding, discussed in **Section 11.6**, below.

### 11.2.3 Further approaches to explore the impact of misclassification.

As discussed above, misclassification of MCMs, maternal influenza vaccination and its timing, and confounders could result, under certain scenarios, in biasing the hazard ratio towards the null. One approach to examine this and to test the dataset's capability to detect associations with MCMs is to use known teratogens as positive controls.

In their 2011 publication, Charlton *et al.* demonstrated that CPRD data could be used to identify the known associations between first trimester sodium valproate monotherapy and risk of spina bifida, and first trimester anti-epileptic drug polytherapy and risk of any MCM, when compared to women with no anti-epileptic drug exposure.<sup>193</sup> However, the effect estimate for spina bifida had very wide 95% confidence intervals due to the small numbers, and evidence for an association between first trimester sodium valproate monotherapy and risk of any MCM was weak (RR, 2.00; 95% CI, 0.99-4.07). When compared to data from the UK Epilepsy and Pregnancy Register, CPRD identified fewer first-trimester exposures to valproate and a lower prevalence of MCMs among such pregnancies; the latter is likely to be due to the use of stand-alone primary care CPRD data, with no linked HES data to maximise ascertainment of MCMs.<sup>193</sup>

In the studies carried out for this thesis, pregnant women in the study population with evidence of exposure to several known teratogenic medications were identified. However, the medications were not used as positive controls. Of the 78,150 pregnancies in the seasonal vaccine safety analysis, 6.1% were found to have an exposure to a teratogenic medication in the period spanning six months before the start of pregnancy and the end of the first trimester. However, only 0.6% of these had a prescription which occurred in the first trimester and the number of MCMs among these was low (n=39). Given these small numbers, it was considered unlikely that these medications would be able to usefully act as positive controls. However, the possibility that an association between influenza vaccination and MCMs was not detected cannot be discounted and future studies should consider the potential use of positive controls to test the ability of such databases to identify the effects of drugs and vaccinations.

### 11.3 Limited ability to examine terminations due to foetal anomaly

UK electronic health records have limited ability to examine MCMs among pregnancies that do not end in a live-birth. MCMs are poorly recorded in the mother's record during the antenatal period and those that are recorded were found to have poor validity (**Section 8.6.1-8.6.2**).

Terminations due to foetal anomaly are of particular interest because over 14% of MCMs reported in UK EUROCAT data between 2010 and 2013 occurred among this particular pregnancy outcome.<sup>294</sup> Terminations due to foetal anomaly can occur if an MCM is detected during the 20-week anomaly scan. TOPFAs account for 1-2% of all terminations and approximately half of these are a result of an MCM, with the most common conditions being malformations of the nervous system and congenital heart defects (the other 50% of TOPFAs are a result of chromosomal anomalies or conditions in which the foetus is affected by maternal factors such as inherited disorders) (**Section 8.7**).<sup>321</sup> UK electronic health records are currently not well placed to examine these outcomes, not only because MCMs detected antenatally are poorly recorded but also because terminations may be carried out by

independent providers and may never be recorded in the pregnant woman's primary care record.

A concern in relation to the safety analyses carried out for this thesis was that restricting the study population to live-born infants could have biased the study findings. This could have occurred if there was differential inclusion of infants with MCMs born to unvaccinated mothers, if these mothers were less likely to attend the 20-week anomaly scan and have the opportunity for a TOPFA. However, almost all the recorded terminations occurred before the 16<sup>th</sup> week of pregnancy, before the 20-week anomaly scan could take place. In addition, among infants born to unvaccinated women there was no evidence of higher prevalence of the 11 MCMs most likely to result in a TOPFA (**Section 8.7**).

Nevertheless, MCMs that occur frequently among terminated pregnancies are underrepresented in analyses examining live-births and this means that associations between vaccination and these conditions could not be determined. UK EUROCAT registries that collect information on terminations due to foetal anomaly could usefully complement safety studies carried out using electronic health records.

#### 11.4 Limited ability to examine major malformation subgroups

Electronic health record databases offer a number of advantages for post-marketing safety studies of drugs and vaccines given in pregnancy including large cohorts, the potential for long-term follow-up and routine data collection. However, even these data may be limited in their ability to detect associations between particular drugs or vaccines and adverse outcomes – particularly if both the exposure to the drug/vaccine and the adverse outcome occur with low frequency in the population.

In the safety analyses, it was not possible to examine the risk of individual MCMs or most MCM subgroups due to their rarity, especially after stratifying by trimester of vaccination. For some MCMs, it was estimated that both the number of women receiving first trimester



vaccination and the number of women never vaccinated would need to be quadrupled to achieve sufficient study power (**Section 8.4**). The decision was therefore taken to examine MCMs as an aggregate outcome, which allowed sufficient power. However, using this aggregate outcome raises the issue that a positive association between first-trimester vaccination and specific MCMs could be masked by a lack of association for other MCMs. As UK electronic health data continue to accumulate, there may be sufficient numbers for future studies to explore the safety of maternal vaccination with respect to specific malformation subgroups or conditions.

### 11.5 Other selection bias

In cohort studies, selection bias can occur when exposed and unexposed groups differ in their follow-up or outcome ascertainment. In **Section 8.7 and 11.3**, the potential for bias due to vaccinated women being more likely to undergo anomaly screening and subsequent termination is discussed. Other possible selection bias also needs consideration.

Over 10% of eligible live-birth pregnancies were excluded from analyses because linkage to infant records was unavailable and the outcome could not be ascertained. The many possible reasons for lack of linkage were discussed in **Section 4.3.8**, the vast majority of which are unlikely to be associated with vaccination. There was a possibility that a small number of infants were not linked because they never registered at the same practice as the mother and these infants may have been more likely to have MCMs (e.g. they never registered because they were hospitalized for prolonged periods, because they died or because the mother moved away). As these scenarios were considered rare and were not necessarily associated with vaccine uptake, the likelihood of selection bias was judged to be low (**Section 8.8**).

### 11.6 Residual confounding

Residual confounding occurs when there are unmeasured differences between exposed and unexposed cohorts that are not adjusted for. Systematic reviews of studies examining

congenital malformations following maternal influenza vaccination highlighted the lack of adjustment for confounders as a key limitation of the available evidence.<sup>20-24</sup> In this work, a large number of potential confounders were identified with the use of a conceptual framework and adjusted for individually and in groups.

The potential for the misclassification of confounders is described in **Section 11.2.2**. There were also some potential confounders that could not be directly measured. One such example was healthcare engagement. Women with higher levels of healthcare engagement are likely to have higher vaccine uptake and may also be more likely to seek care earlier when they become aware that their infant may have a medical condition. This can bias the association of the hazard ratio upwards if infants of women with lower levels of healthcare engagement were less likely to have a major malformation ascertained during follow-up. To some extent, this may have been addressed through analyses that allowed for longer follow-up and by adjusting for factors such as deprivation, ethnicity and geographic region, which could influence healthcare engagement by affecting health beliefs and/or healthcare access. Assessing health beliefs, access and engagement and their contributions as risk factors for congenital malformations has been an area of difficulty in the wider literature and studies have similarly relied on characteristics that are more straightforward to measure. The possibility of residual confounding cannot be discounted, although it was reassuring that fully-adjusted models did not suggest any evidence for an association between maternal influenza vaccination and all major malformations, or limb or heart defects.

## 11.7 Generalisability

The studies described here are only generalizable to pregnancies resulting in a live-born singleton with linked infant records. Results cannot be extrapolated to multiple births or foetal malformations among other pregnancy outcomes such as terminations and pregnancy losses. Although the devolved administrations in the UK are very similar, it is important to note that linked data only include patients from English practices and so may not be generalizable to the

whole of the UK. However, given the biological nature of any associations and the fact that the population of patients with linked data is not considered to be appreciably different to those in the whole of CPRD (which includes patients across the UK), this is unlikely to be the case.<sup>254</sup>

### **11.8 Chapter summary**

This chapter highlights the challenges involved when using UK electronic health records to examine MCMs as an outcome of interest in post-marketing safety studies. Previous studies have relied exclusively on primary care data to carry out such analyses. As many MCMs will be diagnosed in a hospital setting, relying on primary care data may result in incomplete capture of MCMs (for example, because encoding these diagnoses may be delayed or because the GP may record diagnoses using free-text or by scanning hospital letters which are unavailable to researchers). Linked primary care, secondary care and mortality data were used to maximize ascertainment of MCMs in this work but limitations of the coding systems, particularly in ICD-10 which contains a large number of non-specific codes, meant that conditions which were minor or non-congenital may have been captured. It was also not possible to examine terminations due to foetal anomalies or specific MCM subgroups and individual conditions in these data. The conclusions that could be drawn from the analyses conducted were therefore limited to live-birth pregnancies and all MCMs, congenital heart defects and limb defects. The final chapter provides a full interpretation of the work as well as recommendations for future research.

## 12. Interpretation, recommendations for future work and conclusions

This chapter begins with a summary of the findings from the studies in this thesis.

Recommendations for future research are provided and the chapter ends with the overall conclusions from this work.

### 12.1 Interpretation

Routinely-collected, linked UK electronic health records have a number of strengths that make them well-suited for studies examining the post-marketing safety of drugs and vaccines in pregnancy. However, identifying congenital malformations in these data is not without its challenges and limitations and researchers must consider these for each individual data source.

In primary care data, researchers have to contend with: the use of codes from many different chapters to encode diagnoses; potential delays in recording diagnoses; the possibility that diagnoses have been recorded tentatively and the possibility that diagnoses have been recorded using free-text or by scanning hospital letters which are not available to researchers. However, there is evidence to suggest that congenital malformation diagnoses identified in primary care records are true diagnoses which might explain why post-marketing safety studies have relied on stand-alone primary care records.<sup>187, 192, 194, 208, 209, 216, 219</sup>

In hospital admissions data, there is a paucity of evidence with regards to the validity of congenital malformation diagnoses although the need to record definitive diagnoses for reimbursements suggests the majority of diagnoses are likely to be accurate.<sup>181</sup> This need to record definitive diagnoses is also likely to explain why studies utilizing these data have been able to rely exclusively on the comparatively small number of ICD-10 codes from the dedicated chapter on congenital malformations. A caveat, however, seems to be that ICD-10 codes are sometimes non-specific – making it difficult to distinguish in some instances whether individuals with such codes have major or minor conditions, and increasing prevalence

estimates of MCMs. This perhaps explains why no previous study using secondary care data has attempted to distinguish between major and minor malformations.

Linkage of primary care records and hospital admissions data has the potential to increase the ascertainment of congenital malformations and mitigate the issues around delayed recording and use of free-text or scanned hospital letters in primary care. Indeed, linkage in the work described here demonstrated that a sizeable proportion of these diagnoses are recorded exclusively in hospital admissions data. However, this needs to be carefully balanced against the potential loss of power that can come with linkage as well as the potential of decreased PPV if non-specific ICD-10 codes are included. Validation studies using hospitalization data are needed to inform the inclusion of these non-specific codes. Linked death records and procedure data from hospital admissions only identified a small number of additional individuals but may prove useful for future studies requiring evidence of MCMs from multiple codes or data sources.

Linked primary care, secondary care and mortality data were used to conduct the vaccine safety studies in this thesis. There is a fairly large body of evidence on the safety of PIIV and the results in this study were highly consistent with that.<sup>20-24</sup> No association with major malformations was found in any trimester, regardless of follow-up time, and measures of effect were similar to those pooled from several previous studies. This supports the methods used in this thesis and the analysis of the safety of SIIV which also found no evidence for an association with major malformations, limb malformations or heart defects among live-births. This was the first such study in the UK and in Europe. Overall, it adds further weight to the good safety profile of this vaccine in pregnant women. Based on this evidence and the evidence that the vaccine is known to provide moderate/good protection against lab-confirmed influenza in pregnant women and their newborn infants, healthcare providers should continue to feel confident in offering the vaccine to pregnant women. This work did not, however, examine terminations due to foetal anomaly and therefore the interpretation of

results cannot be extrapolated to the MCMs that are typically detected antenatally and associated with induced terminations.

## 12.2 Recommendations for further research

The work in this thesis has consistently highlighted that further validation studies of congenital malformation diagnoses in UK electronic health records would be useful. Validation studies of MCM diagnoses recorded in HES have not been carried out and are needed to establish the PPV of codes from the 'Q' ICD-10 chapter, with a particular emphasis on the PPV of non-specific 'Q' chapter codes that could refer to major or minor conditions.

Although validation studies in primary care data are available and have indicated generally good PPV for congenital malformations overall, for MCMs and for congenital heart defects, validation studies of additional MCM subgroups are needed. Furthermore, validation studies have mainly examined the PPV of recorded diagnoses and little is known about other measures of validity (e.g. sensitivity, specificity and negative predictive value). Future studies should consider examining these other measures of validity. Further validation studies could also provide an opportunity to assess the validity of non-specific Read codes in the 'P' chapter that could encode major or minor malformations, and codes outside the 'P' chapter that could be used by clinicians to code both congenital and non-congenital conditions. Work will also be needed to assess the validity of the equivalent SNOMED codes to the Read codes currently used for MCMs as UK general practices switch from the Read coding system to use of SNOMED.<sup>247</sup>

One future potential and feasible approach to increase the PPV of algorithms used to identify MCMs, is to consider defining cases as those with multiple records of the same diagnosis (or a diagnosis and procedure) on different dates or as those with codes in multiple data sources. The validity of these algorithms could be tested and compared with those that require only a single code to be present. A current constraint to such an approach is that primary care physicians are not obliged to record diagnoses repeatedly, and in-patient HES data are

restricted to diagnoses made during a hospital admission. Children with MCMs may have multiple encounters with healthcare but many such encounters will be in hospital outpatient settings and, currently, diagnostic information in outpatient HES has very low levels of completeness. As diagnostic coding in these outpatient data improves with time, safety studies may be able to better identify children with MCMs who have multiple diagnostic codes recorded, as well as including individuals with MCMs who are managed predominantly in these settings. The work in this thesis also identified variation in the recording of congenital malformation diagnoses across data sources. Therefore, in parallel, future researchers should also attempt to examine whether there are any factors that increase the propensity of a diagnosis to be encoded in one data source but not another.

Although further validation studies are needed, this will not be feasible for many researchers due to constraints around time and funding. The validity of the dataset can, in these cases, be examined in part by testing its ability to detect a known teratogenic association such as the one between valproate and spina bifida – although this does depend on having sufficient numbers and statistical power to detect such an association.

Indeed, as data accrue, future research on maternal influenza vaccination safety should attempt to assess additional malformation subgroups and individual conditions. With the exception of limb and heart defects, there were not enough cases in the data used for this thesis to examine particular subgroups or conditions. As data continue to accumulate over time, and with the new availability of linked hospital and primary care data from CPRD Aurum practices and the planned extension of the Pregnancy Register to CPRD Aurum data, it may be possible to explore these when sufficient numbers become available.<sup>322</sup>

If possible, future work should also aim to complement available evidence which has focused primarily on MCMs among live-births with assessments of terminations due to foetal anomalies. In the short term, possible complementary studies could be explored using data from UK EUROCAT registries that collect information on terminations due to foetal anomaly,

with additional data collection on vaccination status. In the longer term, any future move to link CPRD data to the UK National Congenital Anomaly and Rare Disease Registration Service data would enable examination of associations between maternal influenza vaccination and malformations that are diagnosed antenatally and result in a termination.

Examining longer-term paediatric outcomes such as pervasive developmental disorders would also be useful as numbers become available. Ongoing efforts to link hospital data to educational databases is also likely to provide an opportunity to examine long-term educational outcomes. Although this thesis has focused on outcomes among infants, future research should also consider other pregnancy and maternal outcomes which continue to concern pregnant women.

### 12.3 Conclusions

Routinely-collected, multiply-linked UK electronic health records can be used to investigate congenital malformations in post-marketing safety studies of drugs and vaccines given in pregnancy. Linkage of these data maximizes ascertainment of these rare conditions but raises important questions about how to interpret and handle differential recording of diagnoses across data sources. Population-based historical cohort studies using linked primary care records, hospital admissions and mortality data were carried out to assess the safety of SIIV and PIIV in pregnancy, stratified by trimester. There was no evidence to suggest that receipt of either of these vaccines, in any individual trimester or at any time in pregnancy, was associated with major malformations recorded in the year after delivery. Results were similar when examining major malformations in early childhood. Future studies should consider examining terminations due to foetal anomalies, additional malformation subgroups and long-term paediatric outcomes such as pervasive developmental disorder.



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## Appendices

### Appendix 1 – Systematic review search strategy

The search strategy used in Medline is provided as an example, below. The systematic review was a component of a wider search strategy that included publications in the US and Europe and also examined additional diagnoses such as pervasive developmental disorders.

Search #	Search term (keyword/free text or MeSH)
1	Malformatio*
2	Congenital
3	Birth defect*
4	Developmental adj5 defect*
5	Developmental adj5 anomal*
6	Developmental adj5 abnormalit*
7	Developmental adj5 disabilit*
8	Developmental adj5 disorder*
9	Developmental adj5 deform*
10	Minor anomal*
11	Minor abnormalit*
12	Minor disorde*
13	Minor defect*
14	Minor deform*
15	Major anomal*
16	Major abnormalit*
17	Major disorde*
18	Major defect*
19	Major deform*
20	Teratogen*
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	Septal defect*
23	Transposition* of great vessel*
24	Tetralog* of fallot
25	Pulmonary valve stenosis*
26	Coarctation of aorta
27	Hypoplastic left heart
28	Patent ductus arteriosus
29	Limb adj3 defect*
30	Clubfoot
31	Club-foot
32	Talipes
33	Polydactyl*
34	Syndactyl*
35	Neural tube defect*
36	Hydrocephal*
37	Anencephal*
38	Microcephal*
39	Spina bifida
40	Hypospadias*
41	Oesophageal atresia*
42	Anorectal atresia*
43	Anorectal stenosis*

Search #	Search term (keyword/free text or MeSH)
44	Diaphragmatic hernia*
45	Abdominal wall defect*
46	Gastroschisis
47	Omphalocele
48	Oro-facial cleft*
49	Orofacial cleft*
50	Skeletal dysplasia*
51	Cleft lip
52	Cleft palate
53	Craniosynostosis*
54	Vascular disruption anomaly*
55	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56	Asymmetric skull*
57	Plagiocephaly*
58	Microtia*
59	Anotia*
60	Microtia-antia*
61	Patent foramen ovale*
62	Hemangioma*
63	56 or 57 or 58 or 59 or 60 or 61 or 62
64	Exp Teratogens/
65	Prenatal Exposure Delayed Effects/
66	Teratogenesis/
67	Exp Congenital Abnormalities/
68	64 or 65 or 66 or 67
69	21 or 55 or 63
70	68 OR 69
71	Electronic health* record*
72	Electronic medical record*
73	Electronic clinical record*
74	Electronic patient record*
75	Digital health* record*
76	Digital medical record*
77	Digital clinical record*
78	Digital patient record*
79	Computerized health* record*
80	Computerized medical record*
81	Computerized clinical record*
82	Computerized patient record*
83	EHR
84	EHRs
85	EMR
86	EMRs
87	HMO
88	HMOs
89	Longitudinal medical record*
90	Longitudinal health* record*
91	Longitudinal clinical record*
92	Health-care data*
93	Healthcare data*

Search #	Search term (keyword/free text or MeSH)
94	Medical record* data*
95	Health record* data*
96	Clinical record* data*
97	Longitudinal healt* data*
98	Longitudinal clinical data*
99	Longitudinal medical data*
100	Administrative adj3 data*
101	Automated adj3 data*
102	Administrative claim*
103	Claim* data*
104	CPRD
105	GPRD
106	Clinical Practice Research Datalink
107	General Practice Research Database
108	The Health Improvement Network
109	QResearch
110	ResearchOne
111	IMS Health
112	Medicaid
113	Kaiser Permanente
114	Hospital Episode Statistics
115	Primary care data*
116	Primary care record*
117	Routinely collected data
118	Read cod*
119	Clinical cod*
120	Medical cod*
121	ICD-9*
122	ICD9*
123	ICD-10*
124	ICD10*
125	71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 r 121 or 122 or 123 or 124
126	Electronic Health Records/
127	Medical Records System, Computerized/
128	Medicaid/
129	Administrative Claims, Healthcare/
130	Health Maintenance Organizations/
131	Databases, Factual/
132	International Classification of Diseases
133	Clinical Coding
134	126 or 127 or 128 or 129 or 130 or 131 or 132 or 133
135	125 or 134
136	135 AND 70
137	Limits: English and Human
138	Autism (free text)
139	Autistic* (free text)
140	Autistic Disorder/ (Mesh)
141	Autism Spectrum Disorder/ (MeSH)
142	138 or 139 or 140 or 141
143	142 or 70

Search #	Search term (keyword/free text or MeSH)
144	143 AND 135
145	144 NOT 136
146	English Language and Humans

## Appendix 2 – Code lists for identifying major congenital malformations

### Read codes

Read Code	Read term	Minor malformation?	Subgroup
7H19511	Closure of exomphalos		Abdominal Wall
J32..11	Omphalocele		Abdominal Wall
J321000	Omphalocele with obstruction		Abdominal Wall
J323000	Simple omphalocele		Abdominal Wall
J32y000	Unspecified omphalocele		Abdominal Wall
PG7..00	Abdominal wall anomalies		Abdominal Wall
PG70.00	Exomphalos		Abdominal Wall
PG71.00	Gastroschisis		Abdominal Wall
PG7y.00	Other specified anomaly of abdominal wall		Abdominal Wall
PG7z.00	Abdominal wall anomaly nos		Abdominal Wall
P70..00	Patent ductus arteriosus	If gest. age <37 weeks	Heart
P70..11	Botalli's patent ductus	If gest. age <37 weeks	Heart
P551.00	Patent foramen ovale	Yes	Heart
P721500	Persistent right aortic arch	Yes	Heart
P74z500	Persistent left superior vena cava	Yes	Heart
7A01.00	Open correction of patent ductus arteriosus		Heart
7A01.11	Open correction of patent ductus arteriosus (PDA)		Heart
7A01000	Division of patent ductus arteriosus		Heart
7A01100	Ligation of patent ductus arteriosus		Heart
7A01200	Closure of patent ductus arteriosus NEC		Heart
7A01300	Revision of correction of patent ductus arteriosus		Heart
7A01y00	Other specified open correction of patent ductus arteriosus		Heart
7A01z00	Open correction of patent ductus arteriosus NOS		Heart
7A02000	Percut transluminal prosth occlusion patent ductus arterios		Heart
7A02011	Percut translum prosth occlus patent ductus arteriosus (PDA)		Heart
G543100	Pulmonary stenosis, non-rheumatic		Heart
G543300	Pulmonary stenosis, cause unspecified		Heart
G543311	Pulmonary stenosis, cause unspecified		Heart
P602.00	Congenital pulmonary stenosis		Heart
P602z00	Congenital pulmonary stenosis NOS		Heart
14AV.00	History of ventricular septal defect		Heart
14H1.00	H/O: cardiac anomaly		Heart
14H1.11	H/O: heart anomaly		Heart
2126800	Ostium secundum atrial septal defect resolved		Heart
24M..00	Spontaneous closure of ventricular septal defect		Heart
33B8.00	Detection of cardiac shunt		Heart
66g..00	Congenital heart condition monitoring		Heart
7902.00	Correction of tetralogy of Fallot		Heart
7902.11	Repair of tetralogy of Fallot		Heart
7902000	Correct Fallot tetralogy- valved right ventr outflow conduit		Heart
7902100	Correct Fallot tetralogy- right ventric outflow conduit NEC		Heart
7902200	Correct Fallot tetralogy- right ventricular outflow patch		Heart
7902300	Revision of correction of tetralogy of Fallot		Heart
7902400	Repair of tetralogy of Fallot using transannular patch		Heart
7902500	Repair of tetralogy of Fallot with absent pulmonary valve		Heart
7902600	Repair Fallot-type pulmonary atresia aortopulmonary collater		Heart
7902y00	Other specified correction of tetralogy of Fallot		Heart

Read Code	Read term	Minor malformation?	Subgroup
7902z00	Correction of tetralogy of Fallot NOS		Heart
7902z11	Repair of tetralogy of Fallot NOS		Heart
7903.00	Atrial inversion ops for transposition of great vessels		Heart
7903.11	Mustard interatrial tr venous return		Heart
7903.12	Senning correction for transposition of great vessels		Heart
7903.13	Atrial inversion operations for transposition of great art		Heart
7903000	Atrium reconstruction atrial patch for transpos great vessel		Heart
7903100	Atrium reconstruction atrial wall for transpos great vessels		Heart
7903y00	Atrial inversion op for transposition of great vessels OS		Heart
7903z00	Atrial inversion op for transposition of great vessels NOS		Heart
7904.00	Other correction of transposition of great vessels		Heart
7904000	Repositioning of transposed great vessels		Heart
7904200	Left ventricle aorta tunnel right ventricle pul art val con		Heart
7904300	Atrial switch and arterial switch		Heart
7904y00	Other correction of transposition of great vessels OS		Heart
7904z00	Other correction of transposition of great vessels NOS		Heart
7905.00	Correction of total anomalous pulmonary venous connection		Heart
7905000	Correct total anomal pulm venous connect to supracard vessel		Heart
7905100	Correct total anomal pulm venous connect to coronary sinus		Heart
7905y00	Correction of total anomalous pulmonary venous connection OS		Heart
7905z00	Correction total anomalous pulmonary venous connection NOS		Heart
7906.00	Closure of defect of atrioventricular septum		Heart
7906.11	Repair of defect of the atrioventricular septum		Heart
7906000	Close defect atrioventric septum using dual prosthetic patch		Heart
7906011	Rep defect atrioventricular septum dual prosthetic patches		Heart
7906100	Close defect atrioventric septum using prosthetic patch NEC		Heart
7906111	Repair defect atrioventricular septum prosthetic patch NEC		Heart
7906200	Closure defect atrioventricular septum using tissue graft		Heart
7906211	Repair defect of atrioventricular septum using tissue graft		Heart
7906300	Closure of persistent ostium primum		Heart
7906311	Repair of persistent ostium primum		Heart
7906400	Primary closure of defect of atrioventricular septum NEC		Heart
7906500	Revision of closure of defect of atrioventricular septum		Heart
7906y00	Other specified closure of defect of atrioventricular septum		Heart
7906z00	Closure of defect of atrioventricular septum NOS		Heart
7907.00	Closure of defect of interatrial septum		Heart
7907.11	Repair of defect of interatrial septum		Heart
7907000	Closure defect of interatrial septum using prosthetic patch		Heart
7907011	Repair defect of interatrial septum using prosthetic patch		Heart
7907100	Closure defect of interatrial septum using pericardial patch		Heart
7907111	Repair defect of interatrial septum using pericardial patch		Heart
7907200	Closure defect of interatrial septum using tissue graft NEC		Heart
7907300	Primary closure of defect of interatrial septum NEC		Heart
7907311	Primary repair of defect of interatrial septum NEC		Heart
7907400	Revision of closure of defect of interatrial septum		Heart
7907y00	Other specified closure of defect of interatrial septum		Heart
7907z00	Closure of defect of interatrial septum NOS		Heart
7908.00	Closure of defect of interventricular septum		Heart
7908.11	Repair of defect of interventricular septum		Heart
7908000	Close defect interventricular septum using prosthetic patch		Heart
7908011	Repair defect interventricular septum us prosthetic patch		Heart
7908100	Close defect interventricular septum using pericardial patch		Heart



Read Code	Read term	Minor malformation?	Subgroup
7908111	Repair defect interventricular septum us pericardial patch		Heart
7908200	Close defect interventricular septum using tissue graft NEC		Heart
7908300	Primary closure of defect of interventricular septum NEC		Heart
7908311	Primary repair of defect of interventricular septum NEC		Heart
7908400	Revision of closure of defect of interventricular septum		Heart
7908500	Closure of multiple interventricular septal defects		Heart
7908511	Repair of multiple interventricular septal defects		Heart
7908600	Closure interventricular septal defect us intraop trans pros		Heart
7908611	Repair interventricular septal defect us intraop trans pros		Heart
7908y00	Other specified closure of defect of interventricular septum		Heart
7908z00	Closure of defect of interventricular septum NOS		Heart
7909.00	Closure of defect of unspecified septum of heart		Heart
7909.11	Repair of defect of unspecified septum of heart		Heart
7909000	Closure of defect of heart septum using prosthetic patch NEC		Heart
7909100	Closure defect of heart septum using pericardial patch NEC		Heart
7909300	Primary closure of defect of septum of heart NEC		Heart
7909y00	Other specified closure of defect unspecified heart septum		Heart
7909z00	Closure of defect of unspecified septum of heart NOS		Heart
7909z11	Repair of defect of unspecified septum of heart NOS		Heart
790A.00	Other open operations on septum of heart		Heart
790A000	Open enlargement of defect of atrial septum		Heart
790A100	Open atrial septostomy		Heart
790A111	Atrial septostomy NEC		Heart
790A200	Open atrial septum fenestration		Heart
790A300	Atrial septectomy		Heart
790A400	Atrial septation procedure		Heart
790A600	Surgical atrial septation		Heart
790Ay00	Other specified other open operation on septum of heart		Heart
790Az00	Other open operation on septum of heart NOS		Heart
790B.00	Closed operations on septum of heart		Heart
790B000	Closed enlargement of defect of atrial septum		Heart
790B011	Blalock creation of defect in atrial septum		Heart
790B012	Hanlon creation of defect in atrial septum		Heart
790B100	Closed atrial septostomy		Heart
790By00	Other specified closed operation on septum of heart		Heart
790Bz00	Closed operation on septum of heart NOS		Heart
790F.00	Refashioning of atrium		Heart
790F000	Correction of persistent sinus venosus		Heart
790F100	Correction of partial anomalous pulmonary venous drainage		Heart
790F200	Repair of cor triatriatum		Heart
790F300	Repair of coronary sinus abnormality		Heart
790Fy00	Other specified refashioning of atrium		Heart
790J.00	Other repair of transposition of great arteries		Heart
790J000	Repositioning of transposed great arteries		Heart
790Jz00	Other repair of transposition of great arteries NOS		Heart
790K.00	Repair of double outlet ventricle		Heart
790K100	Repair of Fallot-type double outlet right ventricle		Heart
790K200	Repair of double outlet right ventricle		Heart
790L.00	Transluminal closure of defect of septum		Heart
790L000	Percutan transluminal closure defect intervent sept us pros		Heart
790L111	Percutaneous translum repair defect intervent septum NEC		Heart
790L200	Percutan translum closure defect interatr septum us prosth		Heart

Read Code	Read term	Minor malformation?	Subgroup
790L300	Percutan transluminal closure defect interatrial septum NEC		Heart
790L311	Percutan transluminal repair defect interatrial septum NEC		Heart
790L400	Percut translum closure defect unspecified septum us prosth		Heart
790Ly00	Other specified transluminal closure of defect of septum		Heart
790Lz00	Transluminal closure of defect of septum NOS		Heart
790M.00	Repair of univentricular heart		Heart
790M000	Total cavopulmonary con extrac inf cav vein pulmon art con		Heart
790M100	Total cavopulmonary connection with lateral atrial tunnel		Heart
790M200	Radical aortopulmonary reconstr systemic-to-pulmon art shunt		Heart
790M400	Biventricular repair of hypoplastic left heart syndrome		Heart
790M500	Takedown of total cavopulmonary connection		Heart
790M600	Conversion atrial pulmonary anastomosis total pulmon connect		Heart
790M700	Aortopulm reconstruct with systemic to pulmon arterial shunt		Heart
790My00	Other specified repair of univentricular heart		Heart
790Mz00	Repair of univentricular heart NOS		Heart
790N000	Relief of right ventricular outflow tract obstruction		Heart
790N100	Repair of double chambered right ventricle		Heart
790N400	Relief of left ventricular outflow tract obstruction		Heart
790N500	Myectomy of left ventricular outflow tract		Heart
791A000	Infundibulectomy of heart using patch		Heart
791A100	Infundibulectomy of heart NEC		Heart
791A200	Repair of subaortic stenosis		Heart
791A300	Repair of supraaortic stenosis		Heart
791B400	Closure of aortic sinus of Valsalva fistula		Heart
791B500	Repair of aortic sinus of Valsalva aneurysm		Heart
7927000	Repair of arteriovenous fistula of coronary artery		Heart
7927300	Transposition of coronary artery NEC		Heart
792B200	Repair of arteriovenous malformation of coronary artery		Heart
7934700	Percutaneous transluminal ablation congenit heart malformat		Heart
7A0..00	Great vessels and pulmonary artery operations		Heart
7A0..11	Great vessel operations		Heart
7A00.00	Open operations for combined abnormality of great vessels		Heart
7A00000	Correction of persistent truncus arteriosus		Heart
7A00200	Repair of hemitruncus arteriosus		Heart
7A00300	Closure of aortopulmonary window		Heart
7A00400	Repair anomalous pulmonary artery origin ascending aorta		Heart
7A00y00	Open operation for combined abnormality of great vessels OS		Heart
7A00z00	Open operation for combined abnormality of great vessels NOS		Heart
7A02.00	Transluminal operations on abnormality of great vessel		Heart
7A02100	Percutaneous transluminal stent implantation arterial duct		Heart
7A02y00	Transluminal operation on abnormality of great vessel OS		Heart
7A02z00	Transluminal operation on abnormality of great vessel NOS		Heart
7A03.00	Creation interposition tube prosth shunt aorta to pulm art		Heart
7A03000	Creation interpos tube prosth shunt asc aorta to main pulm a		Heart
7A03100	Create interpos tube prosth shunt asc aorta to right pulm a		Heart
7A03200	Creation interpos tube prosth shunt asc aorta to left pulm a		Heart
7A03y00	Create interpos tube prosth shunt fr aorta to pulm artery OS		Heart
7A03z00	Create interpos tube prosth shunt aorta to pulm artery NOS		Heart
7A04.00	Other connection from aorta to pulmonary artery		Heart
7A04000	Creation of aortopulmonary window		Heart
7A04100	Creation of anastomosis ascending aorta to main pulm art NEC		Heart
7A04200	Creation anastomosis ascending aorta to right pulm art NEC		Heart

Read Code	Read term	Minor malformation?	Subgroup
7A04211	Waterson anastomosis ascending aorta to right pulmonary art		Heart
7A05.00	Create interpos tube prosth shunt subclavian art to pulm art		Heart
7A05000	Create interpos tube prosth shunt R subclavian a to R pulm a		Heart
7A05100	Create interpos tube prosth shunt L subclavian a to L pulm a		Heart
7A05200	Closure prosthetic shunt pulmonary artery subclavian artery		Heart
7A06.00	Other connection from subclavian artery to pulmonary artery		Heart
7A06000	Creation anastomosis right subclav art to right pulm art NEC		Heart
7A06100	Creation anastomosis left subclav art to left pulm art NEC		Heart
7A06200	Creation anastomosis subclavian artery to pulmonary art NEC		Heart
7A06211	Blalock anastomosis of subclavian artery to pulmonary artery		Heart
7A06212	Taussig anastomosis of subclavian artery to pulmonary artery		Heart
7A06300	Revision anastomosis subclavian artery to pulmonary artery		Heart
7A06500	Perc trans ball dilat anas bet pulmon artery subclav artery		Heart
7A06600	Perc transluc occlusion anast pulmonary artery subclavian art		Heart
7A07.00	Other connection to pulmonary artery		Heart
7A07000	Creation of anastomosis from vena cava to pulmonary artery		Heart
7A07011	Creation Glenn anastomosis from vena cava to pulmonary art		Heart
7A07y00	Other specified other connection to pulmonary artery		Heart
7A07z00	Other connection to pulmonary artery NOS		Heart
7A08200	Repair of anomalous pulmonary artery NEC		Heart
7A08300	Repair of pulmonary arterial sling		Heart
7A09000	Application of band to pulmonary artery		Heart
7A09100	Adjustment of band to pulmonary artery		Heart
7A09200	Removal of band from pulmonary artery		Heart
7A09500	Pulmonary artery ligation		Heart
7A0A.00	Transluminal operations on pulmonary artery		Heart
7A0A700	Percut transluminal insertion of stent into pulmonary artery		Heart
7A0Ay00	Other specified transluminal operation on pulmonary artery		Heart
7A0Az00	Transluminal operation on pulmonary artery NOS		Heart
7A0B.00	Open operations on both pulmonary arteries		Heart
7A0C.00	Operation on major systemic to pulmonary collateral arteries		Heart
7A0C000	Major systemic to pulmonary collateral artery occlusion		Heart
7A0C100	Pulmonary unifocalisation		Heart
7A0C400	Percut translumin stent major systemic pulmon collateral art		Heart
7A0y.00	Great vessel or pulmonary artery operations OS		Heart
7A0z.00	Great vessel and pulmonary artery operations NOS		Heart
7A18111	Hamilton repair coarctation of aorta using subclavian flap		Heart
7A18600	Repair of interrupted aortic arch		Heart
7A63500	Repair of anomalous caval vein connection		Heart
7A6K000	Repair of pulmonary vein stenosis		Heart
9RD0.00	Transfer of care from paediatric congenital heart service		Heart
D410200	Polycythaemia due to cyanotic heart disease		Heart
G11..00	Mitral valve diseases		Heart
G110.00	Mitral stenosis		Heart
G112.00	Mitral stenosis with insufficiency		Heart
G112.12	Mitral stenosis with incompetence		Heart
G112.13	Mitral stenosis with regurgitation		Heart
G113.00	Nonrheumatic mitral valve stenosis		Heart
G114.00	Ruptured mitral valve cusp		Heart
G11z.00	Mitral valve disease NOS		Heart
G13..00	Diseases of mitral and aortic valves		Heart
G130.00	Mitral and aortic stenosis		Heart

Read Code	Read term	Minor malformation?	Subgroup
G131.00	Mitral stenosis and aortic insufficiency		Heart
G131.13	Mitral stenosis and aortic incompetence		Heart
G131.14	Mitral stenosis and aortic regurgitation		Heart
G132.00	Mitral insufficiency and aortic stenosis		Heart
G132.12	Mitral incompetence and aortic stenosis		Heart
G132.13	Mitral regurgitation and aortic stenosis		Heart
G133.00	Mitral and aortic incompetence		Heart
G133.11	Mitral and aortic insufficiency		Heart
G133.12	Mitral and aortic regurgitation		Heart
G13y.00	Multiple mitral and aortic valve involvement		Heart
G13z.00	Mitral and aortic valve disease NOS		Heart
G140.00	Tricuspid valve disease NEC		Heart
G140300	Tricuspid stenosis, cause unspecified		Heart
G140400	Tricuspid insufficiency, cause unspecified		Heart
G140412	Tricuspid incompetence, cause unspecified		Heart
G140413	Tricuspid regurgitation, cause unspecified		Heart
G140500	Tricuspid stenosis and insufficiency, cause unspecified		Heart
G140514	Tricuspid stenosis and regurgitation, cause unspecified		Heart
G420.00	Arteriovenous fistula of pulmonary vessels		Heart
G54..11	Heart valve disorders - non rheumatic		Heart
G540.00	Mitral valve incompetence		Heart
G540.12	Mitral valve insufficiency		Heart
G540000	Mitral incompetence, non-rheumatic		Heart
G540100	Mitral incompetence, cause unspecified		Heart
G541011	Aortic insufficiency, non-rheumatic		Heart
G541012	Aortic regurgitation, non-rheumatic		Heart
G541211	Aortic insufficiency alone, cause unspecified		Heart
G541212	Aortic regurgitation alone, cause unspecified		Heart
G541400	Aortic valve stenosis with insufficiency		Heart
G542000	Tricuspid incompetence, non-rheumatic		Heart
G542011	Tricuspid insufficiency, non-rheumatic		Heart
G542100	Tricuspid stenosis, non-rheumatic		Heart
G542200	Nonrheumatic tricuspid valve stenosis with insufficiency		Heart
G542X00	Nonrheumatic tricuspid valve disorder, unspecified		Heart
G543.00	Pulmonary valve disorders		Heart
G543400	Pulmonary valve stenosis with insufficiency		Heart
G543z00	Pulmonary valve disorders NOS		Heart
G54z000	Incompetence of unspecified heart valve		Heart
G54z014	Insufficiency of unspecified heart valve		Heart
G553.00	Endocardial fibroelastosis		Heart
Gyu1000	[X]Other mitral valve diseases		Heart
Gyu1200	[X]Other tricuspid valve diseases		Heart
Gyu5500	[X]Other nonrheumatic mitral valve disorders		Heart
Gyu5600	[X]Other aortic valve disorders		Heart
Gyu5800	[X]Other pulmonary valve disorders		Heart
L258.00	Fetus with cardiovascular abnormality		Heart
P5...00	Bulbus cordis and cardiac septal closure anomalies		Heart
P5...11	Cardiac septal defects		Heart
P5...12	Congenital heart disease, septal and bulbar anomalies		Heart
P5...13	Heart septal defects		Heart
P50..00	Common aorto-pulmonary trunk		Heart
P50..11	Aortic septal defect		Heart

Read Code	Read term	Minor malformation?	Subgroup
P50..12	Common truncus		Heart
P500.00	Absent septum between aorta and pulmonary artery		Heart
P500.11	Persistent truncus arteriosus		Heart
P500.12	Truncus arteriosus		Heart
P501.00	Aortic septal defect		Heart
P501.11	Aortopulmonary window		Heart
P501.12	Aorticopulmonary septal defect		Heart
P502.00	Persistent truncus arteriosus		Heart
P502.11	Truncus arteriosus		Heart
P50z.00	Common aorto-pulmonary trunk NOS		Heart
P51..00	Transposition of great vessels		Heart
P510.00	Total great vessel transposition		Heart
P511.00	Double outlet right ventricle		Heart
P511100	Dextratransposition of aorta		Heart
P511200	Incomplete great vessel transposition		Heart
P511300	Taussig-Bing syndrome		Heart
P511z00	Double outlet right ventricle NOS		Heart
P512.00	Corrected great vessel transposition		Heart
P51y.00	Other specified transposition of great vessels		Heart
P51y.11	Transposition of aorta		Heart
P51z.00	Great vessel transposition NOS		Heart
P51z.11	Transposition of arterial trunk NEC		Heart
P52..00	Tetralogy of Fallot		Heart
P520.00	Tetralogy of Fallot, unspecified		Heart
P520.11	Ventricular septal defect in Fallot's tetralogy		Heart
P520.12	Dextraposition of aorta in Fallot's tetralogy		Heart
P521.00	Pentalogy of Fallot		Heart
P52z.00	Tetralogy of Fallot NOS		Heart
P53..00	Common ventricle		Heart
P54..00	Ventricular septal defect		Heart
P540.00	Ventricular septal defect, unspecified		Heart
P541.00	Interventricular septal defect		Heart
P542.00	Left ventricle to right atrial communication		Heart
P543.00	Eisenmenger's complex		Heart
P544.00	Gerbode's defect		Heart
P545.00	Roger's disease		Heart
P54y.00	Other specified ventricular septal defect		Heart
P54z.00	Ventricular septal defect NOS		Heart
P55..00	Ostium secundum atrial septal defect		Heart
P550.00	Atrial septal defect NOS		Heart
P550.11	Auricular septal defect NOS		Heart
P550.12	Interatrial septal defect NEC		Heart
P550.13	Interauricular septal defect		Heart
P552.00	Persistent ostium secundum		Heart
P552.11	Patent ostium secundum		Heart
P553.00	Lutembacher's syndrome		Heart
P55y.00	Other specified ostium secundum atrial septal defect		Heart
P55y.11	Other specified atrial septal defect		Heart
P55z.00	Ostium secundum atrial septal defect NOS		Heart
P56..00	Endocardial cushion defects		Heart
P561.00	Ostium primum defect		Heart
P561.11	Persistent ostium primum		Heart

Read Code	Read term	Minor malformation?	Subgroup
P56y.00	Other specified endocardial cushion defects		Heart
P56z.00	Endocardial cushion defects NOS		Heart
P56z000	Common atrium		Heart
P56z011	Cor triloculare biventriculare		Heart
P56z100	Common atrioventricular canal		Heart
P56z200	Common atrioventricular-type ventricular septal defect		Heart
P56zz00	Endocardial cushion defects NOS		Heart
P58..00	Double outlet left ventricle		Heart
P59..00	Isomerism of atrial appendages		Heart
P5X..00	Congenital malforms of cardiac chambers+connections unsp		Heart
P5y..00	Other heart bulb and septal closure defect		Heart
P5z..00	Heart bulb or septal closure defects NOS		Heart
P6...00	Other congenital heart anomalies		Heart
P60..00	Pulmonary valve anomalies		Heart
P600.00	Pulmonary valve anomaly, unspecified		Heart
P601.00	Congenital atresia of the pulmonary valve		Heart
P601000	Hypoplasia of pulmonary valve		Heart
P601z00	Congenital atresia of pulmonary valve NOS		Heart
P602100	Congenital fusion of pulmonary valve segment		Heart
P603.00	Right hypoplastic heart syndrome		Heart
P603.11	Pseudotruncus arteriosus		Heart
P60z.00	Other pulmonary valve anomalies		Heart
P60z000	Congenital insufficiency of the pulmonary valve		Heart
P60z100	Fallot's trilogy		Heart
P60zz00	Other pulmonary valve anomaly NOS		Heart
P61..00	Congenital tricuspid atresia and stenosis		Heart
P610.00	Congenital tricuspid atresia		Heart
P611.00	Congenital tricuspid stenosis		Heart
P61z.00	Congenital tricuspid atresia or stenosis NOS		Heart
P62..00	Ebstein's anomaly		Heart
P63..00	Congenital aortic valve stenosis		Heart
P64..00	Congenital aortic valve insufficiency		Heart
P640.00	Congenital aortic valve insufficiency, unspecified		Heart
P641.00	Bicuspid aortic valve		Heart
P64z.00	Congenital aortic valve insufficiency NOS		Heart
P65..00	Congenital mitral stenosis		Heart
P65..11	Duroziez's disease		Heart
P650.00	Congenital mitral stenosis, unspecified		Heart
P651.00	Fused commissure of the mitral valve		Heart
P652.00	Parachute deformity of the mitral valve		Heart
P65z.00	Congenital mitral stenosis NOS		Heart
P66..00	Congenital mitral insufficiency		Heart
P67..00	Hypoplastic left heart syndrome		Heart
P68..00	Congenital heart disease		Heart
P69..00	Left ventricular outflow tract obstruction		Heart
P6W..00	Congenital malformation of aortic and mitral valves unsp		Heart
P6X..00	Congenital malformation of tricuspid valve, unspecified		Heart
P6y..00	Other specified heart anomalies		Heart
P6y0.00	Subaortic stenosis		Heart
P6y1.00	Cor triatriatum		Heart
P6y2.00	Pulmonary infundibular stenosis		Heart
P6y3.00	Obstructive heart anomaly NEC		Heart

Read Code	Read term	Minor malformation?	Subgroup
P6y3000	Uhl's disease		Heart
P6y3100	Right ventricular outflow tract obstruction		Heart
P6y3z00	Obstructive heart anomaly NEC NOS		Heart
P6y4.00	Coronary artery anomaly		Heart
P6y4000	Congenital absence of coronary artery		Heart
P6y4100	Single coronary artery		Heart
P6y4300	Coronary artery from pulmonary trunk		Heart
P6y4400	Anomalous coronary artery communication		Heart
P6y4411	Congenital coronary arterio-venous fistula		Heart
P6y4500	Congenital coronary aneurysm		Heart
P6y4600	Congenital stricture of coronary artery		Heart
P6y4z00	Coronary artery anomaly NOS		Heart
P6y5.00	Congenital heart block		Heart
P6y5000	Congenital heart block, unspecified		Heart
P6y5100	Congenital complete atrio-ventricular heart block		Heart
P6y5200	Congenital incomplete atrio-ventricular heart block		Heart
P6y5z00	Congenital heart block NOS		Heart
P6y6.00	Heart and cardiac apex malposition		Heart
P6y6.11	Ectopic heart		Heart
P6y6000	Dextrocardia		Heart
P6y6100	Levocardia		Heart
P6y6111	Laevocardia		Heart
P6y6200	Mesocardia		Heart
P6y6300	Ectopia cordis		Heart
P6y6400	Abdominal heart		Heart
P6y6z00	Heart or cardiac apex malposition NOS		Heart
P6y7.00	Myocardial bridge of coronary artery		Heart
P6y8.00	Congenital dextroposition of heart		Heart
P6yy.00	Other specified heart anomalies		Heart
P6yy.11	Hypoplastic aortic orifice or valve		Heart
P6yy.12	Hypoplasia of heart NOS		Heart
P6yy000	Atresia of cardiac vein		Heart
P6yy100	Hypoplasia of cardiac vein		Heart
P6yy200	Congenital cardiomegaly		Heart
P6yy300	Congenital left ventricular diverticulum		Heart
P6yy400	Congenital pericardial defect		Heart
P6yy411	Congenital absence of pericardium		Heart
P6yy500	Congenital anomaly of myocardium		Heart
P6yy600	Congenital aneurysm of heart		Heart
P6yy700	Atresia of heart valve NEC		Heart
P6yy900	Congenital epicardial cyst		Heart
P6yyA00	Hemicardia		Heart
P6yyB00	Supernumerary heart valve cusps NEC		Heart
P6yyz00	Other specified heart anomalies NOS		Heart
P6z..00	Congenital heart anomaly NOS		Heart
P6z0.00	Unspecified anomaly of heart valve		Heart
P6z1.00	Anomalous bands of heart		Heart
P6z1000	Anomalous atrial bands		Heart
P6z1100	Anomalous ventricular bands		Heart
P6z2.00	Acyanotic congenital heart disease NOS		Heart
P6z3.00	Cyanotic congenital heart disease NOS		Heart
P6z3.11	Blue baby		Heart

Read Code	Read term	Minor malformation?	Subgroup
P6zz.00	Congenital heart anomaly NOS		Heart
P71..00	Coarctation of aorta		Heart
P710.00	Hypoplasia of aortic arch, unspecified		Heart
P711.00	Preductal coarctation of aorta		Heart
P711.13	Preductal aortic stenosis		Heart
P712.00	Postductal coarctation of aorta		Heart
P712.12	Postductal interruption of aorta		Heart
P712.13	Postductal aortic stenosis		Heart
P713.00	Interruption of aortic arch		Heart
P713.11	Stenosis of aortic arch		Heart
P71z.00	Coarctation of aorta NOS		Heart
P72..00	Other anomalies of aorta		Heart
P72..11	Anomalies of the aorta excluding coarction		Heart
P720.00	Anomaly of aorta, unspecified		Heart
P721.00	Aortic arch anomalies		Heart
P721000	Anomalous origin of the aortic arch		Heart
P721100	Dextraposition of aorta		Heart
P721111	Overriding aorta		Heart
P721200	Double aortic arch		Heart
P721211	Vascular ring		Heart
P721300	Kommerell's diverticulum		Heart
P721600	Vascular ring, aorta		Heart
P721700	Overriding aorta		Heart
P721z00	Aortic arch anomalies NOS		Heart
P722.00	Atresia and stenosis of aorta		Heart
P722100	Aplasia of aorta		Heart
P722200	Hypoplasia of aorta		Heart
P722300	Stricture of aorta		Heart
P722400	Supra-valvular aortic stenosis		Heart
P722411	Congenital stenosis of ascending aorta		Heart
P722500	Atresia of aorta		Heart
P722z00	Atresia or stenosis of aorta NOS		Heart
P72z.00	Other anomalies of aorta NOS		Heart
P72z000	Aneurysm of sinus of Valsalva		Heart
P72z100	Congenital aneurysm of aorta		Heart
P72z111	Congenital dilatation of aorta		Heart
P72zz00	Other anomaly of aorta NOS		Heart
P73..00	Pulmonary artery anomalies		Heart
P730.00	Pulmonary artery anomaly, unspecified		Heart
P731.00	Pulmonary artery agenesis		Heart
P731.11	Congenital absence of pulmonary artery		Heart
P732.00	Pulmonary artery atresia		Heart
P733.00	Coarctation of the pulmonary artery		Heart
P734.00	Hypoplasia of the pulmonary artery		Heart
P735.00	Stenosis of pulmonary artery	If gest. age <37 weeks	Heart
P735.11	Congenital stricture of pulmonary artery		Heart
P736.00	Pulmonary arterio-venous aneurysm		Heart
P736.11	Pulmonary arterio-venous fistula		Heart
P736.12	Pulmonary arterio-venous malformation		Heart
P737.00	Pulmonary artery aneurysm		Heart
P737.11	Dilatation of pulmonary artery		Heart
P738.00	Atresia of pulmonary artery with septal defect		Heart



Read Code	Read term	Minor malformation?	Subgroup
P73y.00	Other specified anomaly of pulmonary artery		Heart
P73z.00	Pulmonary artery anomaly NOS		Heart
P74..00	Anomalies of great veins		Heart
P740.00	Anomaly of great veins, unspecified		Heart
P740000	Anomaly of the pulmonary veins, unspecified		Heart
P740100	Anomaly of the vena cava, unspecified		Heart
P741.00	Total anomalous pulmonary venous return - TAPVR		Heart
P741000	Subdiaphragmatic total anomalous pulmonary venous return		Heart
P741100	Supradiaphragmatic total anomalous pulmonary venous return		Heart
P741z00	Total anomalous pulmonary venous return NOS		Heart
P742.00	Partial anomalous pulmonary venous return		Heart
P742.11	Anomalous termination of right pulmonary vein		Heart
P743.00	Anomalous portal vein termination		Heart
P744.00	Portal vein - hepatic artery fistula		Heart
P74z.00	Other great vein anomalies		Heart
P74z.11	Persistent left posterior cardinal vein		Heart
P74z000	Absence of inferior vena cava		Heart
P74z100	Absence of superior vena cava		Heart
P74z200	Stenosis of inferior vena cava		Heart
P74z300	Stenosis of superior vena cava		Heart
P74z600	Scimitar syndrome		Heart
P74z700	Transposition of pulmonary veins		Heart
P74z800	Atresia of pulmonary vein		Heart
P74z00	Other great vein anomaly NOS		Heart
P8y0.00	Abnormal pericardio-pleural communication		Heart
Pyu2100	[X]Other congenital malformations of cardiac septa		Heart
Pyu2200	[X]Other congenital malformations of pulmonary valve		Heart
Pyu2500	[X]Other specified congenital malformations of the heart		Heart
Pyu2600	[X]Other congenital malformations of aorta		Heart
Pyu2700	[X]Other congenital malformations of pulmonary artery		Heart
Pyu2F00	[X]Congenital malforms of cardiac chambers+connections unsp		Heart
Pyu2G00	[X]Congenital malformation of tricuspid valve, unspecified		Heart
Pyu2H00	[X]Congenital malformation of aortic and mitral valves unsp		Heart
Q48y100	Congenital cardiac failure		Heart
ZV15100	[V]Personal history of heart or great vessel operation		Heart
2565.00	O/e - macroglossia	Yes	Digestive
7523100	Incision of frenulum of tongue	Yes	Digestive
7523111	Frenotomy of tongue	Yes	Digestive
7523112	Release of tongue tie	Yes	Digestive
7523400	Excision of frenulum of tongue	Yes	Digestive
760K.11	Repair of oesophageal hiatus hernia	Yes	Digestive
760K.12	Repair of hiatus hernia	Yes	Digestive
760K000	Repair of oesophageal hiatus using thoracic approach	Yes	Digestive
760K011	Allison repair of oesophageal hiatus hernia	Yes	Digestive
760K012	Mason repair of oesophageal hiatus hernia	Yes	Digestive
760K200	Repair of oesophageal hiatus using abdominal approach	Yes	Digestive
760K400	Boerema repair of hiatus hernia	Yes	Digestive
760K500	Laparoscopic repair of hiatus hernia	Yes	Digestive
760L312	Hill repair of hiatus hernia and gastropexy	Yes	Digestive
7641000	Excision of meckel diverticulum	Yes	Digestive
7H11.11	Primary inguinal herniorrhaphy	Yes	Digestive
J34..11	Hiatus hernia	Yes	Digestive

Read Code	Read term	Minor malformation?	Subgroup
J344.00	Hiatus hernia with gangrene	Yes	Digestive
J345.00	Hiatus hernia with obstruction	Yes	Digestive
J346.00	Hiatus hernia - irreducible	Yes	Digestive
J347.00	Simple hiatus hernia	Yes	Digestive
J348.00	Sliding hiatus hernia	Yes	Digestive
J34z000	Hiatus hernia nos	Yes	Digestive
PA0..00	Tongue tie - ankyloglossia	Yes	Digestive
PA0..11	Ankyloglossia	Yes	Digestive
PA0..12	Tongue tie	Yes	Digestive
PA13.00	Fissure of tongue	Yes	Digestive
PA14.00	Macroglossia	Yes	Digestive
PA14.11	Congenital tongue hypertrophy	Yes	Digestive
PA24.00	Congenital fistula of lip	Yes	Digestive
PA25100	High arched palate	Yes	Digestive
PA28.00	Ranula, congenital	Yes	Digestive
PA5..00	Congenital hypertrophic pyloric stenosis	Yes	Digestive
PA50.00	Congenital pyloric hypertrophy	Yes	Digestive
PA51.00	Congenital pyloric spasm	Yes	Digestive
PA51.11	Congenital pylorospasm	Yes	Digestive
PA52.00	Congenital pyloric stenosis	Yes	Digestive
PA52.11	Congenital pyloric stricture	Yes	Digestive
PA6..00	Congenital hiatus hernia	Yes	Digestive
PB0..00	Meckel's diverticulum	Yes	Digestive
PB00.00	Meckel's diverticulum, unspecified	Yes	Digestive
PB01.00	Displaced meckel's diverticulum	Yes	Digestive
PB0z.00	Meckel's diverticulum nos	Yes	Digestive
7523200	Freeing of adhesions of tongue		Digestive
7523500	Glossopexy		Digestive
7606000	Closure of tracheoesophageal fistula		Digestive
7606011	Excision of tracheoesophageal fistula		Digestive
7606100	Closure of fistula of oesophagus nec		Digestive
7606200	Correction of congenital atresia of oesophagus		Digestive
7607000	Exteriorisation of pouch of oesophagus		Digestive
7608200	Division of web of oesophagus		Digestive
760D400	Fibreoptic endoscopic dilation of web of oesophagus		Digestive
760G400	Dilation of web of oesophagus using rigid oesophagoscope		Digestive
760K.00	Repair of diaphragmatic hernia		Digestive
760K100	Repair of diaphragmatic hernia using thoracic approach nec		Digestive
760K300	Repair of diaphragmatic hernia using abdominal approach nec		Digestive
760Ky00	Other specified repair of diaphragmatic hernia		Digestive
760Kz00	Repair of diaphragmatic hernia nos		Digestive
761B100	Repair of congenital atresia of pylorus		Digestive
7726y11	Duhamel hirschsprung abdoperin		Digestive
7726y12	Soave endorectal pull through op for hirschsprung's disease		Digestive
7726y13	Swenson hirschsprung proctect		Digestive
7733300	Reanastomosis rectum-anal canal correct cong rectal atresia		Digestive
7838000	Division of annular pancreas		Digestive
7H0D300	Repair of congenital diaphragmatic hernia		Digestive
J074.00	Fistula of salivary gland		Digestive
J074000	Fistula of parotid gland		Digestive
J074100	Fistula of submandibular gland		Digestive
J074200	Fistula of sublingual gland		Digestive

Read Code	Read term	Minor malformation?	Subgroup
J074z00	Fistula of salivary gland nos		Digestive
J085200	Fistula of lip		Digestive
J10y200	Tracheo-oesophageal fistula		Digestive
J34..00	Diaphragmatic hernia		Digestive
J340.00	Diaphragmatic hernia with gangrene		Digestive
J341.00	Diaphragmatic hernia with obstruction		Digestive
J342.00	Diaphragmatic hernia - irreducible		Digestive
J343.00	Simple diaphragmatic hernia		Digestive
J34y.00	Unspecified diaphragmatic hernia		Digestive
J34z.00	Diaphragmatic hernia nos		Digestive
J50z200	Stenosis of intestine nos		Digestive
J50z300	Stricture of intestine nos		Digestive
J527100	Secondary megacolon - congenital		Digestive
J572.00	Stenosis of rectum and anus		Digestive
J572000	Stenosis of rectum		Digestive
J572111	Anal stenosis		Digestive
J572z00	Stenosis of rectum and anus nos		Digestive
PA...00	Other congenital upper alimentary tract anomalies		Digestive
PA1..00	Other tongue anomalies		Digestive
PA10.00	Anomaly of tongue, unspecified		Digestive
PA11.00	Aglossia		Digestive
PA12.00	Congenital adhesions of tongue		Digestive
PA13.11	Bifid tongue		Digestive
PA13.12	Double tongue		Digestive
PA15.00	Microglossia		Digestive
PA15.11	Hypoplasia of tongue		Digestive
PA15.12	Short tongue		Digestive
PA16.00	Dislocation of tongue		Digestive
PA17.00	Cleft tongue		Digestive
PA18.00	Congenital plicated tongue		Digestive
PA1z.00	Other tongue anomalies nos		Digestive
PA2..00	Other specified mouth and pharynx anomalies		Digestive
PA20.00	Congenital absence of salivary gland		Digestive
PA21.00	Accessory salivary gland		Digestive
PA22.00	Atresia, salivary duct		Digestive
PA23.00	Congenital salivary gland fistula		Digestive
PA25.00	Other mouth anomalies		Digestive
PA25.11	Fordyce's disease of mouth		Digestive
PA25000	Congenital absence of uvula		Digestive
PA25y00	Other congenital anomaly of palate		Digestive
PA25z00	Other mouth anomalies nos		Digestive
PA26.00	Diverticulum of pharynx		Digestive
PA26.11	Pharyngeal pouch		Digestive
PA27.00	Other pharynx anomalies		Digestive
PA27000	Imperforate pharynx		Digestive
PA27z00	Other pharynx anomalies nos		Digestive
PA29.00	Other anomalies of salivary glands or ducts		Digestive
PA29.11	Displacement of wharton's duct		Digestive
PA2A.00	Other anomalies of lip		Digestive
PA2Az00	Other anomaly of lip nos		Digestive
PA2z.00	Other mouth and pharynx anomalies nos		Digestive
PA3..00	Oesophageal atresia, stenosis and fistula		Digestive

Read Code	Read term	Minor malformation?	Subgroup
PA3..11	Congenital oesophageal ring		Digestive
PA30.00	Atresia of oesophagus		Digestive
PA31.00	Congenital oesophageal stricture		Digestive
PA31.11	Congenital oesophageal stenosis		Digestive
PA32.00	Congenital oesophageal fistula		Digestive
PA32000	Oesophagobronchial fistula		Digestive
PA32100	Oesophagotracheal fistula		Digestive
PA32111	Congenital tracheo-oesophageal fistula		Digestive
PA32z00	Congenital oesophageal fistula nos		Digestive
PA33.00	Imperforate oesophagus		Digestive
PA34.00	Webbed oesophagus		Digestive
PA35.00	Congenital absence of oesophagus		Digestive
PA36.00	Cong.absence of oesophagus with tracheo-oesophageal fistula		Digestive
PA37.00	Atresia of oesophagus with tracheo-oesophageal fistula		Digestive
PA3y.00	Other specified oesophageal atresia, stenosis or fistula		Digestive
PA3z.00	Oesophageal atresia, stenosis or fistula nos		Digestive
PA4..00	Other specified oesophageal anomalies		Digestive
PA40.00	Congenital dilatation of oesophagus		Digestive
PA42.00	Congenital diverticulum of oesophagus		Digestive
PA43.00	Congenital duplication of oesophagus		Digestive
PA44.00	Giant oesophagus		Digestive
PA45.00	Congenital oesophageal pouch		Digestive
PA4z.00	Other specified oesophageal anomaly nos		Digestive
PA5y.00	Other specified congenital pyloric obstruction		Digestive
PA5z.00	Congenital pyloric obstruction nos		Digestive
PA7..00	Other specified stomach anomalies		Digestive
PA70.00	Congenital cardiospasm		Digestive
PA70.11	Congenital achalasia of cardia		Digestive
PA71.00	Congenital hourglass stomach		Digestive
PA73.00	Congenital stomach diverticulum		Digestive
PA74.00	Duplication of stomach		Digestive
PA75.00	Megalogastria		Digestive
PA76.00	Microgastria		Digestive
PA77.00	Transposition of stomach		Digestive
PA78.00	Ectopic gastric mucosa		Digestive
PA7z.00	Other specified stomach anomaly nos		Digestive
PAy..00	Other specified upper alimentary tract anomaly		Digestive
PAz..00	Upper alimentary tract anomalies nos		Digestive
PAz0.00	Unspecified anomalies of mouth and pharynx		Digestive
PAz1.00	Unspecified anomalies of oesophagus		Digestive
PAz2.00	Unspecified anomalies of stomach		Digestive
PAzz.00	Anomalies of upper alimentary tract nos		Digestive
PAzz.11	Malformation of throat		Digestive
PB...00	Other congenital digestive system anomaly		Digestive
PB0..12	Persistent vitelline duct		Digestive
PB03.00	Persistent omphalomesenteric duct		Digestive
PB03.11	Persistent vitelline duct		Digestive
PB1..00	Small intestine atresia and stenosis		Digestive
PB10.00	Atresia of small intestine		Digestive
PB10000	Atresia of small intestine, unspecified		Digestive
PB10100	Atresia of duodenum		Digestive
PB10200	Atresia of ileum		Digestive

Read Code	Read term	Minor malformation?	Subgroup
PB10300	Atresia of jejunum		Digestive
PB10z00	Small intestine atresia nos		Digestive
PB11200	Congenital absence of ileum		Digestive
PB12.00	Congenital obstruction of small intestine		Digestive
PB13.00	Congenital stenosis of small intestine		Digestive
PB13000	Congenital stenosis of duodenum		Digestive
PB13100	Congenital stenosis of jejunum		Digestive
PB13200	Congenital stenosis of ileum		Digestive
PB13z00	Congenital stenosis of small intestine nos		Digestive
PB13z11	Congenital stricture of small intestine		Digestive
PB14.00	Imperforate jejunum		Digestive
PB1z.00	Small intestine atresia or stenosis nos		Digestive
PB2..00	Atresia and stenosis of large intestine/rectum/anal canal		Digestive
PB2..11	Atresia large intestine		Digestive
PB2..12	Stenosis large intestine		Digestive
PB20.00	Congenital absence of large intestine		Digestive
PB20000	Congenital absence of anus		Digestive
PB20100	Congenital absence of appendix		Digestive
PB20200	Congenital absence of rectum		Digestive
PB20211	Agenesis of rectum		Digestive
PB20300	Congenital absence of anus with fistula		Digestive
PB20400	Congenital absence of rectum with fistula		Digestive
PB20411	Agenesis of rectum with fistula		Digestive
PB21.00	Atresia of large intestine		Digestive
PB21000	Atresia of anus		Digestive
PB21100	Atresia of colon		Digestive
PB21200	Atresia of rectum		Digestive
PB21300	Atresia of appendix		Digestive
PB21400	Atresia of anus with fistula		Digestive
PB21500	Atresia of rectum with fistula		Digestive
PB22.00	Congenital obstruction of large intestine		Digestive
PB22.11	Congenital stenosis of large intestine		Digestive
PB23.00	Congenital occlusion of anus		Digestive
PB23.11	Anal septum		Digestive
PB23000	Congenital occlusion of anus with fistula		Digestive
PB23z00	Congenital occlusion of anus nos		Digestive
PB24.00	Congenital stricture of anus		Digestive
PB24.11	Congenital anal stricture		Digestive
PB24000	Congenital stricture of anus with fistula		Digestive
PB24011	Congenital stenosis of anus with fistula		Digestive
PB24100	Congenital stricture of anus without mention of fistula		Digestive
PB24111	Congenital stenosis of anus without mention of fistula		Digestive
PB24z00	Congenital stricture of anus nos		Digestive
PB25.00	Congenital stricture of rectum		Digestive
PB25.11	Congenital rectal stricture		Digestive
PB25000	Congenital stricture of rectum with fistula		Digestive
PB25011	Congenital stenosis of rectum with fistula		Digestive
PB25111	Congenital stenosis of rectum without mention of fistula		Digestive
PB25z00	Congenital stricture of rectum nos		Digestive
PB26.00	Imperforate anus		Digestive
PB26000	Imperforate anus with fistula		Digestive
PB26z00	Imperforate anus nos		Digestive

Read Code	Read term	Minor malformation?	Subgroup
PB27.00	Imperforate rectum		Digestive
PB27000	Imperforate rectum with fistula		Digestive
PB2z.00	Atresia and stenosis of large intestine/rectum/anus nos		Digestive
PB3..00	Hirschsprung's disease and allied congenital conditions		Digestive
PB3..11	Aganglioneosis		Digestive
PB30.00	Hirschsprung's disease		Digestive
PB30000	Long segment hirschsprung's disease		Digestive
PB30100	Short segment hirschsprung's disease		Digestive
PB30z00	Hirschsprung's disease nos		Digestive
PB31.00	Idiopathic congenital megacolon		Digestive
PB33.00	Total intestinal aganglioneosis		Digestive
PB33.11	Aganglionic macrocolon		Digestive
PB33.12	Congenital aganglionic megacolon		Digestive
PB3z.00	Hirschsprung's disease and allied congenital conditions nos		Digestive
PB4..00	Intestinal fixation anomalies		Digestive
PB40.00	Congenital intestinal adhesions		Digestive
PB40000	Congenital omental adhesions		Digestive
PB40100	Jackson's membrane		Digestive
PB40200	Congenital peritoneal adhesions		Digestive
PB40211	Congenital peritoneal bands		Digestive
PB40z00	Congenital intestinal adhesions nos		Digestive
PB41.00	Malrotation of colon and caecum		Digestive
PB41000	Malrotation of colon		Digestive
PB41100	Malrotation of caecum		Digestive
PB41z00	Malrotation of colon or caecum nos		Digestive
PB42.00	Universal mesentery		Digestive
PB43.00	Other anomalies of mesentery		Digestive
PB4y.00	Other specified intestinal fixation anomaly		Digestive
PB4z.00	Intestinal fixation anomaly nos		Digestive
PB4z.11	Malfixation of gut nec		Digestive
PB4z.12	Malrotation of gut		Digestive
PB4z.13	Malrotation of intestine		Digestive
PB5..00	Other anomalies of intestine		Digestive
PB50.00	Congenital diverticulum of colon		Digestive
PB51.00	Dolichocolon		Digestive
PB52.00	Duplication of intestine		Digestive
PB52000	Duplication of intestine, unspecified		Digestive
PB52100	Duplication of anus		Digestive
PB52300	Duplication of caecum		Digestive
PB52z00	Duplication of intestine nos		Digestive
PB52z11	Congenital redundant rectal mucosa		Digestive
PB52z12	Congenital redundant colon		Digestive
PB53.00	Transposition of intestine		Digestive
PB53000	Transposition of intestine, unspecified		Digestive
PB53100	Transposition of appendix		Digestive
PB53200	Transposition of caecum		Digestive
PB53300	Transposition of colon		Digestive
PB53z00	Transposition of intestine nos		Digestive
PB54.00	Ectopic anus		Digestive
PB56.00	Megaloduodenum		Digestive
PB57.00	Microcolon		Digestive
PB58.00	Persistent cloaca		Digestive

Read Code	Read term	Minor malformation?	Subgroup
PB58.11	Anal fusion		Digestive
PB59.00	Congenital anal fistula		Digestive
PB5A.00	Enterogenous cyst		Digestive
PB5X.00	Congenital malformation of intestine, unspecified		Digestive
PB5z.00	Other intestine anomalies nos		Digestive
PB5z.11	Congenital volvulus		Digestive
PB5z000	Congenital faecal fistula		Digestive
PB6..00	Liver and biliary system anomalies		Digestive
PB6..11	Bile duct anomalies		Digestive
PB6..12	Biliary anomalies		Digestive
PB6..13	Gallbladder anomalies		Digestive
PB6..14	Liver anomalies		Digestive
PB60.00	Liver and biliary system anomalies, unspecified		Digestive
PB60000	Liver anomaly, unspecified		Digestive
PB60100	Gallbladder anomaly, unspecified		Digestive
PB60200	Bile duct anomaly, unspecified		Digestive
PB60z00	Unspecified liver and biliary system anomaly nos		Digestive
PB61.00	Biliary atresia		Digestive
PB61000	Congenital absence of bile duct		Digestive
PB61200	Congenital obstruction of bile duct		Digestive
PB61300	Congenital stricture of bile duct		Digestive
PB61311	Congenital stricture of common bile duct		Digestive
PB61400	Atresia of bile duct		Digestive
PB61411	Intrahepatic atresia of bile duct		Digestive
PB61412	Extrahepatic atresia of bile duct		Digestive
PB61500	Congenital absence of hepatic ducts		Digestive
PB61600	Atresia of hepatic ducts		Digestive
PB61z00	Biliary atresia nos		Digestive
PB62.00	Congenital cystic liver disease		Digestive
PB62.11	Congenital hepatic cyst		Digestive
PB62000	Congenital polycystic liver disease		Digestive
PB62100	Fibrocystic liver disease		Digestive
PB62z00	Congenital cystic liver disease nos		Digestive
PB63000	Congenital absence of gallbladder		Digestive
PB63011	Agenesis of gallbladder		Digestive
PB63100	Congenital absence of liver lobe		Digestive
PB63300	Riedel's lobe liver		Digestive
PB64000	Duplication of biliary duct		Digestive
PB64100	Duplication of cystic duct		Digestive
PB64200	Duplication of gallbladder		Digestive
PB64311	Accessory liver		Digestive
PB6y.00	Other liver and biliary anomalies		Digestive
PB6y000	Congenital choledochal cyst		Digestive
PB6y100	Congenital hepatomegaly		Digestive
PB6y200	Congenital floating gallbladder		Digestive
PB6y400	Intrahepatic gallbladder		Digestive
PB6y500	Hypoplasia of gallbladder		Digestive
PB6y600	Atrophy of left lobe of liver		Digestive
PB6y700	Congenital dilation of bile duct		Digestive
PB6y800	Congenital diverticulum of bile duct		Digestive
PB6y900	Liver hyperplasia		Digestive
PB6yw00	Other congenital anomaly of liver		Digestive

Read Code	Read term	Minor malformation?	Subgroup
PB6yw12	Abnormal liver lobulation		Digestive
PB6yw13	Trilobular liver		Digestive
PB6yx00	Other congenital anomaly of gallbladder		Digestive
PB6yy00	Other congenital anomaly of hepatic or bile ducts		Digestive
PB6yz00	Other liver or biliary system anomalies nos		Digestive
PB6z.00	Liver or biliary system anomalies nos		Digestive
PB7..00	Anomalies of pancreas		Digestive
PB72.00	Hypoplasia of pancreas		Digestive
PB73.00	Accessory pancreas		Digestive
PB74.00	Annular pancreas		Digestive
PB75.00	Ectopic pancreas		Digestive
PB76.00	Pancreatic heterotopia		Digestive
PB77.00	Pancreatic cyst, congenital		Digestive
PB7y.00	Other specified anomalies of pancreas		Digestive
PB7z.00	Anomalies of pancreas nos		Digestive
PBy..00	Other specified digestive system anomalies		Digestive
PBy0.00	Congenital absence of digestive system nos		Digestive
PBy1.00	Duplication of digestive system nos		Digestive
PBy2.00	Congenital malposition of digestive system nos		Digestive
PBy2.11	Ectopic digestive organs nos		Digestive
PByz.00	Other specified digestive system anomalies nos		Digestive
PBz..00	Digestive system anomalies nos		Digestive
PG61.00	Congenital diaphragmatic hernia		Digestive
Pyu5000	[X]other congenital malformations of tongue		Digestive
Pyu5100	[X]Congenital malformations of palate, NEC		Digestive
Pyu5200	[X]Other congenital malformations of mouth		Digestive
Pyu5700	[X]Cong absence/atresia/stenos oth spec parts small intest		Digestive
Pyu5D00	[X]Other congenital malformations of bile ducts		Digestive
Pyu5E00	[X]Other congenital malformations of liver		Digestive
Pyu5F00	[X]Other congen malformation of pancreas & pancreatic duct		Digestive
Q435000	Perinatal jaundice due to congenital obstruction bile duct		Digestive
7300200	Excision of preauricular abnormality	Yes	Ear, Face & Neck
7302200	Pinnaplasty	Yes	Ear, Face & Neck
7302211	Bat ear pinnaplasty	Yes	Ear, Face & Neck
7302212	Correction of prominent ear	Yes	Ear, Face & Neck
7302213	Mustarde pinnaplasty	Yes	Ear, Face & Neck
7302214	Revision pinnaplasty	Yes	Ear, Face & Neck
7H67100	Operation on branchial cleft nec	Yes	Ear, Face & Neck
7H67200	Excision of branchial cyst	Yes	Ear, Face & Neck
7H67300	Closure of branchial fistula	Yes	Ear, Face & Neck
7H67w00	Other specified operation on branchial cleft	Yes	Ear, Face & Neck
7H67x00	Operation on branchial cleft nos	Yes	Ear, Face & Neck
J085300	Hypertrophy of lip	Yes	Ear, Face & Neck
P402100	Stenosis of external auditory canal	Yes	Ear, Face & Neck
P402111	Congenital stricture of external auditory canal	Yes	Ear, Face & Neck
P402112	Congenital stricture of osseous meatus	Yes	Ear, Face & Neck
P41..00	Accessory ear auricle	Yes	Ear, Face & Neck
P41..11	Polyotia	Yes	Ear, Face & Neck
P410.00	Supernumerary ear	Yes	Ear, Face & Neck
P411.00	Accessory tragus	Yes	Ear, Face & Neck
P412.00	Supernumerary ear lobule	Yes	Ear, Face & Neck
P413.00	Preauricular appendage, tag or lobule	Yes	Ear, Face & Neck



Read Code	Read term	Minor malformation?	Subgroup
P413.11	Preauricular appendage	Yes	Ear, Face & Neck
P413.12	Preauricular tag	Yes	Ear, Face & Neck
P413.13	Preauricular lobule	Yes	Ear, Face & Neck
P414.00	Other ear appendage or tag	Yes	Ear, Face & Neck
P414.11	Other ear appendage	Yes	Ear, Face & Neck
P414.12	Other ear tag	Yes	Ear, Face & Neck
P41z.00	Accessory ear auricle nos	Yes	Ear, Face & Neck
P421.00	Macrotia - abnormally big ears	Yes	Ear, Face & Neck
P421.11	Congenital big ears	Yes	Ear, Face & Neck
P422.00	Microtia - abnormally small ears	Yes	Ear, Face & Neck
P422.11	Congenital small ears	Yes	Ear, Face & Neck
P42z000	Congenital bat ear	Yes	Ear, Face & Neck
P42z100	Darwin's tubercle	Yes	Ear, Face & Neck
P42z200	Congenital pointed ear	Yes	Ear, Face & Neck
P42z300	Congenital prominent auricle	Yes	Ear, Face & Neck
P42z400	Congenital ridge ear	Yes	Ear, Face & Neck
P42z500	Other mis-shapen ear	Yes	Ear, Face & Neck
P42z511	Aztec ear	Yes	Ear, Face & Neck
P42z512	Cat ear	Yes	Ear, Face & Neck
P42z513	Vulcan ear	Yes	Ear, Face & Neck
P42z600	Misplaced ears	Yes	Ear, Face & Neck
P42z611	Low-set ears	Yes	Ear, Face & Neck
P44..00	Branchial cleft, cyst or fistula; preauricular sinus	Yes	Ear, Face & Neck
P440.00	Branchial cleft sinus and fistula	Yes	Ear, Face & Neck
P440.11	Branchial cleft	Yes	Ear, Face & Neck
P440.12	Branchial cleft sinus	Yes	Ear, Face & Neck
P440000	Branchial cleft vestige, unspecified	Yes	Ear, Face & Neck
P440100	Branchial cleft external sinus	Yes	Ear, Face & Neck
P440200	Branchial cleft internal sinus	Yes	Ear, Face & Neck
P440300	Branchial cleft fistula	Yes	Ear, Face & Neck
P440z00	Branchial cleft vestige nos	Yes	Ear, Face & Neck
P441.00	Branchial cleft cyst	Yes	Ear, Face & Neck
P442.00	Cervical auricle	Yes	Ear, Face & Neck
P443.00	Preauricular sinus and fistula	Yes	Ear, Face & Neck
P443000	Preauricular sinus	Yes	Ear, Face & Neck
P443100	Preauricular fistula	Yes	Ear, Face & Neck
P443z00	Preauricular sinus or fistula nos	Yes	Ear, Face & Neck
P444.00	Preauricular cyst	Yes	Ear, Face & Neck
P44y.00	Other branchial cleft anomalies	Yes	Ear, Face & Neck
P44z.00	Branchial cleft,cyst,or fistula preauricular anomaly os/nos	Yes	Ear, Face & Neck
P44z000	Fistula of congenital auricle	Yes	Ear, Face & Neck
P44z100	Cervicoaural fistula	Yes	Ear, Face & Neck
P44z200	Branchial cleft, cyst or fistula preauricular anomaly nos	Yes	Ear, Face & Neck
P4y0.00	Macrocheilia	Yes	Ear, Face & Neck
P4y0.11	Lip hypertrophy	Yes	Ear, Face & Neck
P4y1.00	Microcheilia	Yes	Ear, Face & Neck
P4y2.00	Macrostomia	Yes	Ear, Face & Neck
P4y3.00	Microstomia	Yes	Ear, Face & Neck
Pyu1E00	[X]other branchial cleft malformations	Yes	Ear, Face & Neck
7306100	Reconstruction of external auditory canal		Ear, Face & Neck
7306111	Pattee reconstruction of external auditory canal		Ear, Face & Neck
7308.00	Attachment of auricular prosthesis		Ear, Face & Neck

Read Code	Read term	Minor malformation?	Subgroup
7308000	Insertion of fixtures for auricular prosthesis stage 1		Ear, Face & Neck
7308100	Insertion of fixtures for auricular prosthesis stage 2		Ear, Face & Neck
7308300	Attention to fixtures for auricular prosthesis		Ear, Face & Neck
7K6T000	Release of webbing of neck		Ear, Face & Neck
J040.15	Micrognathism		Ear, Face & Neck
J040300	Mandibular micrognathism		Ear, Face & Neck
J040800	Maxillary micrognathism		Ear, Face & Neck
J040B00	Micrognathism unspecified		Ear, Face & Neck
P4...00	Ear, face and neck congenital anomalies		Ear, Face & Neck
P40..00	Ear anomalies with hearing impairment		Ear, Face & Neck
P400.00	Ear anomalies with hearing impaired, unspecified		Ear, Face & Neck
P401.00	Congenital absence of external ear		Ear, Face & Neck
P401000	Congenital absence of external ear, unspecified		Ear, Face & Neck
P401011	Absence of ear nos		Ear, Face & Neck
P401100	Absence of external auditory canal		Ear, Face & Neck
P401200	Ear auricle and external auditory canal absent		Ear, Face & Neck
P401211	Congenital absence ear auricle		Ear, Face & Neck
P401300	Congenital absence of auricle		Ear, Face & Neck
P401z00	Absence of external ear nos		Ear, Face & Neck
P402.00	Other external ear anomaly with hearing impairment		Ear, Face & Neck
P402000	Atresia of external auditory canal		Ear, Face & Neck
P402z00	Other external ear anomaly with hearing impairment nos		Ear, Face & Neck
P403.00	Middle ear anomaly, excluding ossicles		Ear, Face & Neck
P403000	Ear osseous meatus atresia		Ear, Face & Neck
P403z00	Middle ear anomaly nec nos		Ear, Face & Neck
P404.00	Anomaly of ossicles		Ear, Face & Neck
P404000	Congenital fusion of ear ossicles		Ear, Face & Neck
P404z00	Anomaly of ossicles nos		Ear, Face & Neck
P405.00	Inner ear anomalies		Ear, Face & Neck
P405z00	Inner ear anomalies nos		Ear, Face & Neck
P40z.00	Other and unspecified ear anomaly with hearing impaired		Ear, Face & Neck
P40z.11	Deafness due to congenital anomaly nec		Ear, Face & Neck
P40z000	Congenital absence of ear nos		Ear, Face & Neck
P40zz00	Ear anomaly with hearing impaired nos		Ear, Face & Neck
P42..00	Other specified ear anomalies		Ear, Face & Neck
P420.00	Congenital ear lobe absence		Ear, Face & Neck
P423.00	Eustachian tube anomalies		Ear, Face & Neck
P423100	Congenital stenosis of eustachian tube		Ear, Face & Neck
P423z00	Eustachian tube anomalies nos		Ear, Face & Neck
P42z.00	Other specified ear anomalies nos		Ear, Face & Neck
P42zz00	Other ear anomalies nos		Ear, Face & Neck
P43..00	Congenital ear anomaly nos		Ear, Face & Neck
P45..00	Congenital webbing of neck		Ear, Face & Neck
P451.00	Pterygium colli		Ear, Face & Neck
P45z.00	Congenital webbing of neck nos		Ear, Face & Neck
P4y..00	Other specified face and neck anomalies		Ear, Face & Neck
P4y4.00	Congenital absence of chin		Ear, Face & Neck
P4y5.00	Mid-facial hypoplasia		Ear, Face & Neck
P4yz.00	Other specified face and neck anomalies nos		Ear, Face & Neck
P4z..00	Congenital face or neck anomaly nos		Ear, Face & Neck
P4z0.00	Congenital anomaly of neck nos		Ear, Face & Neck
P4z1.00	Congenital anomaly of face nos		Ear, Face & Neck

Read Code	Read term	Minor malformation?	Subgroup
PE0..11	Face congenital deformities		Ear, Face & Neck
Pyu1.00	[X]congenital malformations of eye, ear, face and neck		Ear, Face & Neck
Pyu1900	[X]other congenital malformations of middle ear		Ear, Face & Neck
Pyu1A00	[X]congenital malformation of inner ear		Ear, Face & Neck
Pyu1B00	[X]malformation of ear with impairment of hearing, unspec		Ear, Face & Neck
Pyu1D00	[X]other specified congenital malformations of ear		Ear, Face & Neck
Pyu1F00	[X]other specified congenital malformations of face & neck		Ear, Face & Neck
F4E4600	Other blepharophimosis	Yes	Eye
P361.00	Congenital eyelid deformity	Yes	Eye
P361000	Ablepharon -absent eyelids	Yes	Eye
P361100	Accessory eyelid	Yes	Eye
P361200	Congenital entropion	Yes	Eye
P361300	Congenital ectropion	Yes	Eye
P361400	Congenital blepharophimosis	Yes	Eye
P361500	Coloboma of eyelids	Yes	Eye
P361z00	Congenital eyelid deformity nos	Yes	Eye
P362.00	Other specified congenital eyelid anomalies	Yes	Eye
P362000	Agenesis of cilia	Yes	Eye
P362100	Agenesis of eyelid	Yes	Eye
P362200	Fused eyelids	Yes	Eye
P362z00	Other specified congenital eyelid anomalies nos	Yes	Eye
P364300	Stenosis or stricture of lacrimal duct	Yes	Eye
P364y00	Other specified congenital anomaly of lacrimal passages	Yes	Eye
P364z00	Congenital anomaly of lacrimal passages nos	Yes	Eye
P36z000	Accessory eye muscles	Yes	Eye
P36z100	Hypoplasia of eye muscle	Yes	Eye
p341.11	Arcus juvenilis	Yes	Eye
p364200	Accessory lacrimal canal	Yes	Eye
1482.00	H/o: glaucoma		Eye
2BB4.00	O/e - retinal microaneurysms		Eye
7255411	Insertion molteno implantation tube in anterior chamber eye		Eye
7258600	Excision of pupillary membrane		Eye
7259.00	Operations following glaucoma surgery		Eye
7259000	Needling of bleb following glaucoma surgery		Eye
7259100	Injection of bleb following glaucoma surgery		Eye
7259200	Revision of bleb nec following glaucoma surgery		Eye
7259300	Removal of releasable suture following glaucoma surgery		Eye
7259400	Laser suture lysis following glaucoma surgery		Eye
7259y00	Other specified operations following glaucoma surgery		Eye
7259z00	Operations following glaucoma surgery nos		Eye
7275.00	Pan retinal photocoagulation for glaucoma		Eye
8D35.00	Spectacles for aphakia		Eye
F404211	Glaucoma - absolute		Eye
F421800	Retinal microaneurysms nos		Eye
F442100	Glaucomatocyclitic crises		Eye
F447700	Pupillary membranes nos		Eye
F45..00	Glaucoma		Eye
F450.00	Borderline glaucoma		Eye
F450000	Unspecified preglaucoma		Eye
F450100	Open angle glaucoma with borderline intraocular pressure		Eye
F450200	Borderline glaucoma with anatomical narrow angle		Eye
F450300	Borderline glaucoma steroid responder		Eye

Read Code	Read term	Minor malformation?	Subgroup
F450z00	Borderline glaucoma nos		Eye
F451.00	Open-angle glaucoma		Eye
F451000	Unspecified open-angle glaucoma		Eye
F451100	Primary open-angle glaucoma		Eye
F451111	Simple chronic glaucoma		Eye
F451200	Low tension glaucoma		Eye
F451211	Normal pressure glaucoma		Eye
F451300	Pigmentary glaucoma		Eye
F451400	Glaucoma of childhood		Eye
F451500	Open-angle glaucoma residual stage		Eye
F451z00	Open-angle glaucoma nos		Eye
F452.00	Primary angle-closure glaucoma		Eye
F452.11	Closed angle glaucoma		Eye
F452000	Unspecified primary angle-closure glaucoma		Eye
F452100	Intermittent primary angle-closure glaucoma		Eye
F452200	Acute primary angle-closure glaucoma		Eye
F452300	Chronic primary angle-closure glaucoma		Eye
F452400	Primary angle-closure glaucoma residual stage		Eye
F452z00	Primary angle-closure glaucoma nos		Eye
F454000	Glaucoma due to chamber angle anomaly		Eye
F454100	Glaucoma due to iris anomaly		Eye
F454200	Glaucoma due to other anterior segment anomaly		Eye
F455.00	Glaucoma associated with disorders of the lens		Eye
F455000	Phacolytic glaucoma		Eye
F455100	Pseudoexfoliation glaucoma		Eye
F455z00	Glaucoma associated with disorders of the lens nos		Eye
F456100	Glaucoma due to pupillary block		Eye
F45y.00	Other specified forms of glaucoma		Eye
F45yz00	Other specified glaucoma nos		Eye
F45z.00	Glaucoma nos		Eye
F463100	Glaucomatous subcapsular flecks		Eye
F4B..00	Corneal opacity and other disorders of cornea		Eye
F4B0.00	Corneal scars and opacities		Eye
F4B0000	Unspecified corneal opacity		Eye
F4B0100	Minor opacity of cornea		Eye
F4B0200	Peripheral opacity of cornea		Eye
F4B0300	Central opacity of cornea		Eye
F4B0z00	Corneal scar or opacity nos		Eye
F4E6.00	Blepharochalasis		Eye
F4H1400	Optic disc glaucomatous atrophy		Eye
F4H2200	Coloboma of optic disc		Eye
F4K3.00	Aphakia and other disorders of lens		Eye
F4K3000	Aphakia		Eye
F4K3z00	Aphakia and other disorders of lens nos		Eye
F4K4100	Anisocoria - unequal pupil diameter		Eye
FyuG.00	[X]glaucoma		Eye
FyuG000	[X]other glaucoma		Eye
P3...00	Congenital eye anomalies		Eye
P30..00	Anophthalmos		Eye
P300.00	Clinical anophthalmos, unspecified		Eye
P300100	Agnesis of eye		Eye
P300200	Congenital absence of eye		Eye

Read Code	Read term	Minor malformation?	Subgroup
P300z00	Anophthalmos nos		Eye
P301.00	Congenital cystic eyeball		Eye
P303.00	Congenital absence of eyes		Eye
P30z.00	Anophthalmos nos		Eye
P31..00	Microphthalmos		Eye
P310.00	Microphthalmos, unspecified		Eye
P310000	Dysplasia of eye		Eye
P310100	Hypoplasia of eye		Eye
P310200	Rudimentary eye		Eye
P310z00	Unspecified microphthalmos nos		Eye
P311.00	Simple microphthalmos		Eye
P312.00	Microphthalmos with other eye anomaly		Eye
P31z.00	Microphthalmos nos		Eye
P32..00	Buphthalmos		Eye
P320000	Congenital glaucoma		Eye
P320011	Newborn glaucoma		Eye
P320z00	Unspecified buphthalmos nos		Eye
P321.00	Simple buphthalmos		Eye
P32z.00	Buphthalmos nos		Eye
P33..00	Congenital cataract and lens anomalies		Eye
P33..11	Congenital lens anomaly		Eye
P330.00	Congenital cataract, unspecified		Eye
P332000	Cortical cataract - congenital		Eye
P333.00	Nuclear cataract - congenital		Eye
P334000	Total congenital cataract		Eye
P334z00	Total or subtotal congenital cataract nos		Eye
P335.00	Congenital aphakia		Eye
P335.11	Congenital absence of lens		Eye
P336.00	Anomalies of lens shape		Eye
P336200	Coloboma of lens		Eye
P336z00	Anomalies of lens shape nos		Eye
P337.00	Congenital ectopic lens		Eye
P337.11	Congenital displaced lens		Eye
P337.12	Congenital dislocation of lens		Eye
P33y.00	Other specified congenital cataract or lens anomaly		Eye
P33y100	Congenital membranous cataract		Eye
P33yz00	Other congenital cataract or lens anomaly nos		Eye
P33z.00	Congenital cataract or lens anomaly nos		Eye
P340.00	Corneal size and shape anomalies		Eye
P340000	Microcornea		Eye
P340z00	Corneal size or shape anomalies nos		Eye
P341.00	Congenital corneal opacities		Eye
P341000	Congenital corneal opacity with visual deficit		Eye
P341100	Congenital corneal opacity without visual deficit		Eye
P341z00	Congenital corneal opacities nos		Eye
P344.11	Goniodysgenesis		Eye
P344000	Congenital anisocoria		Eye
P344100	Atresia of pupil		Eye
P344200	Coloboma of iris		Eye
P344300	Corectopia		Eye
P344400	Polycoria		Eye
P344z00	Other iris or ciliary body anomalies nos		Eye

Read Code	Read term	Minor malformation?	Subgroup
P35..00	Posterior chamber congenital anomalies		Eye
P350.00	Vitreous anomalies		Eye
P350000	Congenital vitreous opacity		Eye
P350z00	Vitreous anomalies nos		Eye
P351.00	Fundus coloboma		Eye
P352.00	Congenital chorioretinal degeneration		Eye
P353000	Congenital folds of the posterior segment		Eye
P353100	Congenital cysts of the posterior segment		Eye
P355.00	Other congenital retinal changes		Eye
P355000	Coloboma of retina		Eye
P355100	Congenital retinal fold		Eye
P355200	Congenital hypertrophy of retinal pigment epithelium		Eye
P355z00	Other congenital retinal changes nos		Eye
P356.00	Specified optic disc anomalies		Eye
P356.11	Optic disc congenital anomalies		Eye
P356000	Congenital optic disc coloboma		Eye
P356z00	Specified optic disc anomaly nos		Eye
P357000	Congenital retinal aneurysm		Eye
P358.00	Specified anomalies of choroid		Eye
P358000	Coloboma of choroid		Eye
P358z00	Specified anomaly of choroid nos		Eye
P35y.00	Other specified congenital anomalies of posterior chamber		Eye
P35z.00	Congenital anomalies of posterior chamber nos		Eye
P36..00	Congenital anomalies of eyelid, lacrimal system and orbit		Eye
P360.00	Congenital ptosis		Eye
P360.11	Blepharoptosis		Eye
P362300	Hypoplasia of eyelid		Eye
P363.00	Congenital lacrimal gland anomalies		Eye
P364.00	Congenital lacrimal passage anomalies		Eye
P364.11	Congenital blocked tear duct		Eye
P364000	Agenesis of lacrimal apparatus		Eye
P364011	Congenital absence of lacrimal apparatus		Eye
P364100	Agenesis of punctum lacrimale		Eye
P364111	Congenital absence of punctum lacrimale		Eye
P364400	Congenital blocked tear duct		Eye
P365.00	Congenital orbit anomalies		Eye
P36z.00	Other/unspecified anomalies of eyelid/lacrimal system/orbit		Eye
P36zz00	Eyelid, lacrimal system and orbit congenital anomalies nos		Eye
P37..00	Macrophthalmos		Eye
P3y..00	Other specified eye anomalies		Eye
P3yz.00	Other eye anomalies nos		Eye
P3z..00	Congenital eye anomalies nos		Eye
Pyu1100	[X]other congenital malformations of lacrimal apparatus		Eye
Pyu1200	[X]other anophthalmos		Eye
Pyu1300	[X]other congenital lens malformations		Eye
Pyu1400	[X]other congenital malformations of iris		Eye
Pyu1600	[X]other congenital malforms of anterior segment of eye		Eye
Pyu1800	[X]other specified congenital malformations of eye		Eye
p321.11	Enlarged eye nos		Eye
p331.00	Capsular and subcapsular cataract		Eye
p331000	Capsular cataract		Eye
p331100	Subcapsular cataract		Eye

Read Code	Read term	Minor malformation?	Subgroup
p331z00	Capsular or subcapsular cataract nos		Eye
p332.00	Cortical and zonular cataract		Eye
p332100	Zonular cataract		Eye
p332z00	Cortical or zonular cataract nos		Eye
p335.12	Agenesis of lens		Eye
p33y000	Blue dot cataract		Eye
p34..00	Anterior chamber anomalies		Eye
p340100	Congenital keratoconus		Eye
p340200	Cornea plana		Eye
p342.00	Specified anterior chamber anomalies		Eye
p342z00	Specified anterior chamber anomalies nos		Eye
p344500	Hypoplasia of iris		Eye
p344600	Aplasia of iris		Eye
p345.00	Specified anomalies of sclera		Eye
p345z00	Specified anomaly of sclera nos		Eye
p34z.00	Anterior segment anomalies nos		Eye
PC6..00	Hypospadias and epispadias		Genital/Urinary
PC6z.00	Hypospadias or epispadias nos		Genital/Urinary
7C08600	Correction of hydrocele of infancy	Yes	Genital
7D14.00	Excision of band of vagina	Yes	Genital
7D14000	Laser excision of septum of vagina	Yes	Genital
7D14100	Excision of septum of vagina nec	Yes	Genital
7D14200	Excision of transverse vaginal septum high	Yes	Genital
7D14300	Excision of transverse vaginal septum low	Yes	Genital
7D14400	Excision of transverse vaginal septum vertical	Yes	Genital
7D14y00	Other specified excision of band of vagina	Yes	Genital
7D14z00	Excision of band of vagina nos	Yes	Genital
7H10200	Ligation of patent processus vaginalis	Yes	Genital
K562z11	Vaginal band	Yes	Genital
PC04.00	Developmental ovarian cyst	Yes	Genital
PC41200	Congenital cyst of vulva	Yes	Genital
PC42.00	Imperforate hymen	Yes	Genital
PC4y600	Congenital absence of vulva	Yes	Genital
PC4y700	Agenesis of vulva	Yes	Genital
PC4yB11	Imperforate vagina	Yes	Genital
PC4yD11	Fusion of labia	Yes	Genital
PC4yE00	Congenital labial adhesions	Yes	Genital
PC4yy12	Hypertrophy of clitoris	Yes	Genital
PCy2000	Hypoplasia of penis	Yes	Genital
PCy7.00	Congenital lateral curvature of penis	Yes	Genital
PCyw.00	Other congenital anomaly of testis or scrotum	Yes	Genital
PCyy000	Hooded penis	Yes	Genital
PCyy100	Webbed penis	Yes	Genital
Q476.00	Congenital hydrocele	Yes	Genital
Q476.11	Patent processus vaginalis	Yes	Genital
7B41000	Other hypospadias repair		Genital
7B41011	Byars hypospadias repair		Genital
7B41012	Cecil reconstruction of urethra		Genital
7B41013	Denis - browne hypospadias repair		Genital
7B41014	Ombredanne hypospadias repair		Genital
7B41015	Van der meulen hypospadias repair		Genital
7B41016	Young hypospadias repair		Genital

Read Code	Read term	Minor malformation?	Subgroup
7B41017	First stage hypospadias repair		Genital
7B41018	Second stage hypospadias repair		Genital
7B41700	Magpi hypospadias repair		Genital
7B41800	Duckett hypospadias repair		Genital
7C04200	Excision of cyst of male hydatid of morgagni		Genital
7C09700	Excision of appendix of testis		Genital
7C09711	Excision of male hydatid of morgagni		Genital
7C25400	Correction of chordee		Genital
7C25411	Release of chordee		Genital
7D1A200	Repair of rectovaginal fistula		Genital
7E0D014	Endoscopic resection of uterine septum		Genital
7E1A200	Excision of hydatid of morgagni		Genital
7LOB200	Excision of ovotestis		Genital
K521200	Rectovaginal fistula		Genital
K562.00	Stricture or atresia of the vagina		Genital
K562.12	Atresia of vagina		Genital
K562300	Atresia of vagina		Genital
K562z00	Stricture or atresia of the vagina nos		Genital
PC...00	Congenital genital organ anomalies		Genital
PC0..00	Anomalies of ovaries		Genital
PC00.00	Congenital absence of ovary		Genital
PC00.11	Agenesis of ovary		Genital
PC02.00	Ectopic ovary		Genital
PC05.00	Congenital torsion of ovary		Genital
PC0y.00	Other specified congenital anomalies of ovaries		Genital
PC0y.11	Congenital ovarian dysplasia		Genital
PC0z.00	Congenital anomalies of ovaries nos		Genital
PC1..00	Fallopian tube and broad ligament anomalies		Genital
PC10.00	Fallopian tube and broad ligament anomalies, unspecified		Genital
PC11.00	Embryonic cyst of fallopian tube and broad ligament		Genital
PC11.11	Cyst of mesenteric remnant		Genital
PC11000	Epoophoron cyst		Genital
PC11100	Fimbrial cyst		Genital
PC11200	Gartner's duct cyst		Genital
PC11211	Persistent gartner's duct		Genital
PC11300	Parovarian cyst		Genital
PC11z00	Embryonic cyst of fallopian tube or broad ligament nos		Genital
PC1y.00	Other fallopian tube and broad ligament anomalies		Genital
PC1y000	Congenital absence of fallopian tube		Genital
PC1y100	Accessory fallopian tube		Genital
PC1y200	Atresia of fallopian tube		Genital
PC1y300	Absent broad ligament		Genital
PC1y400	Accessory broad ligament		Genital
PC1yz00	Other fallopian tube or broad ligament anomalies nos		Genital
PC1z.00	Fallopian tube or broad ligament anomalies nos		Genital
PC2..00	Doubling of uterus		Genital
PC20.00	Doubling of uterus, unspecified		Genital
PC21.00	Didelphic uterus		Genital
PC22.00	Doubling of uterus, including cervix and vagina		Genital
PC2z.00	Doubling of uterus nos		Genital
PC3..00	Other anomalies of uterus		Genital
PC30.00	Congenital absence of uterus		Genital



Read Code	Read term	Minor malformation?	Subgroup
PC31.00	Agenesis of uterus		Genital
PC32.00	Aplasia of uterus		Genital
PC33.00	Bicornuate uterus		Genital
PC34.00	Uterus unicornis		Genital
PC35.00	Displaced uterus		Genital
PC35.11	Congenital prolapse of uterus		Genital
PC36.00	Fistulae involving uterus with digestive or urinary tract		Genital
PC36100	Uterovesical fistula, congenital		Genital
PC36z00	Fistula involving uterus with digestive or urinary tract nos		Genital
PC3y.00	Other specified anomalies of uterus		Genital
PC3z.00	Anomalies of uterus nos		Genital
PC4.00	Cervical, vaginal and external female genital anomalies		Genital
PC40.00	Cervical/vaginal/external female genital anomalies, unspec		Genital
PC41.00	Embryonic cyst of cervix/vagina/external female genitalia		Genital
PC41000	Congenital cyst of canal of nuck		Genital
PC41011	Patent canal of nuck		Genital
PC41100	Embryonal cyst of vagina		Genital
PC41300	Embryonic cyst of cervix		Genital
PC41z00	Embryonic cyst cervix/vagina/external female genitalia nos		Genital
PC43.00	Rectovaginal fistula, congenital		Genital
PC4y.00	Other cervical, vaginal and external female genital anomaly		Genital
PC4y000	Congenital absence of cervix		Genital
PC4y100	Agenesis of cervix		Genital
PC4y200	Congenital absence of clitoris		Genital
PC4y400	Congenital absence of vagina		Genital
PC4y411	Rudimentary vagina		Genital
PC4y500	Agenesis of vagina		Genital
PC4y611	Congenital absence of labium major		Genital
PC4y612	Congenital absence of labium minor		Genital
PC4y800	Congenital stenosis of cervical canal		Genital
PC4y900	Congenital stenosis of vagina		Genital
PC4y911	Congenital stricture of vagina		Genital
PC4yA00	Atresia of cervix		Genital
PC4yB00	Atresia of vagina		Genital
PC4yC00	Congenital vaginal cyst nec		Genital
PC4yD00	Fusion of vulva		Genital
PC4yv00	Other congenital anomaly of cervix		Genital
PC4yw00	Other congenital anomaly of vagina		Genital
PC4yw11	Vaginal septum		Genital
PC4yx00	Other congenital anomaly of vulva		Genital
PC4yy00	Other congenital anomaly of clitoris		Genital
PC4yy11	Hooded clitoris		Genital
PC4yz00	Other cervical/vaginal/external female genital anomaly nos		Genital
PC4z.00	Cervical, vaginal and external female genital anomaly nos		Genital
PC60.00	Hypospadias		Genital
PC60000	Hypospadias, penile		Genital
PC60100	Hypospadias, penoscrotal		Genital
PC60200	Hypospadias, perineal		Genital
PC60300	Hypospadias, balanic		Genital
PC60311	Hypospadias, glanular		Genital
PC60312	Hypospadias, glandular		Genital
PC62.00	Congenital chordee		Genital

Read Code	Read term	Minor malformation?	Subgroup
PC7..00	Indeterminate sex and pseudohermaphroditism		Genital
PC70.00	True hermaphroditism		Genital
PC70.11	Ovotestis		Genital
PC71.00	Male pseudohermaphroditism		Genital
PC72.00	Female pseudohermaphroditism		Genital
PC7z.00	Indeterminate sex or pseudohermaphroditism nos		Genital
PC7z000	Indeterminate sex nos		Genital
PC7z011	Intersex nec		Genital
PC7z100	Pseudohermaphrodite nos		Genital
PC7z111	False hermaphrodite		Genital
PC8..00	Congenital anomaly of male genital system		Genital
PC80.00	Other specified congenital anomaly of male genital system		Genital
PCy..00	Other specified genital organ anomaly		Genital
PCy0.00	Absence of genital organ nec		Genital
PCy0000	Congenital absence of penis		Genital
PCy0200	Congenital absence of spermatic cord		Genital
PCy0300	Congenital absence of vas deferens		Genital
PCy0z00	Genital organ absence nec nos		Genital
PCy1.00	Congenital aplasia of genital organ nec		Genital
PCy1000	Congenital aplasia of prostate		Genital
PCy1200	Congenital aplasia of testicle		Genital
PCy1300	Congenital aplasia of scrotum		Genital
PCy1400	Aplasia of penis		Genital
PCy2.00	Hypoplasia of genital organ nec		Genital
PCy2100	Hypoplasia of testis		Genital
PCy2200	Hypoplasia of scrotum		Genital
PCy2z00	Hypoplasia of genital organ nec nos		Genital
PCy3.00	Atresia of genital organ nec		Genital
PCy3000	Atresia of ejaculatory duct		Genital
PCy3z00	Atresia of genital organ nec nos		Genital
PCy4.00	Anorchism		Genital
PCy4.11	Congenital absence of both testes		Genital
PCy4.12	Testicular agenesis, bilateral		Genital
PCy5.00	Monorchism		Genital
PCy5.11	Congenital absence of testis, unilateral		Genital
PCy5.12	Testicular agenesis, unilateral		Genital
PCy6.00	Polyorchism		Genital
PCy8.00	Fusion of testes		Genital
PCyA.00	Cysts of embryonic remnants nec		Genital
PCyA000	Hydatid cyst of Morgagni		Genital
PCyA100	Wolffian duct cyst		Genital
PCyA200	Hydatid cyst of morgagni - male		Genital
PCyA300	Hydatid cyst of morgagni - female		Genital
PCyA400	Wolffian duct cyst – male		Genital
PCyA500	Wolffian duct cyst – female		Genital
PCyA600	Cyst of embryonic remnant - male		Genital
PCyA700	Cyst of embryonic remnant - female		Genital
PCyB.00	Doubling of vagina		Genital
PCyx.00	Other congenital anomaly of vas deferens or prostate		Genital
PCyy.00	Other congenital anomaly of penis		Genital
PCyyz00	Other congenital anomaly of penis nos		Genital
PCyz.00	Other specified genital organ anomaly nos		Genital

Read Code	Read term	Minor malformation?	Subgroup
PCz..00	Genital organ anomaly nos		Genital
PDyz100	Hypospadias, female		Genital
Pyu6.00	[X]congenital malformations of genital organs		Genital
Pyu6300	[X]other congenital malformations of uterus and cervix		Genital
Pyu6400	[X]other congenital malformations of vagina		Genital
Pyu6600	[X]other specified congenital malform of female genitalia		Genital
Pyu6700	[X]other specified hypospadias		Genital
Pyu6800	[X]other congenital malformations of testis and scrotum		Genital
Pyu6A00	[X]other congenital malformations of penis		Genital
Pyu6B00	[X]other specified congenit malform of male genital organs		Genital
pe8yz11	Specified intrauterine postural deformity nec		Genital
2371	O/e - pigeon chest	Yes	Limb
2373	O/e - funnel chest	Yes	Limb
7L0L300	Correction of curly fifth toe	Yes	Limb
7L0L400	Correction of congenital crossed toes	Yes	Limb
7L0N000	Cranio-orbital remodelling for plagiocephaly	Yes	Limb
7h01000	Correction of pectus deformity of chest wall	Yes	Limb
7h01011	Correction of pectus carinatum	Yes	Limb
7h01012	Correction of pectus excavatum	Yes	Limb
7h01100	Insertion of silicone implant correction of pectus excavatum	Yes	Limb
7k02500	Correction of metatarsus varus	Yes	Limb
7k02511	Herndon correction of metatarsus varus	Yes	Limb
7k02512	Heymann correction of metatarsus varus	Yes	Limb
7k51200	Syndactylisation of lesser toes	Yes	Limb
7l0j700	Correction of congenital vertical talus	Yes	Limb
7l0k300	Separation of tarsal coalition	Yes	Limb
7l0l500	Reduction of macrodactyly of toe	Yes	Limb
7l0ly00	Correction of minor congenital deformity of foot os	Yes	Limb
7l0lz00	Correction of minor congenital deformity of foot nos	Yes	Limb
PE06.00	Congenital nasal septum deviation	Yes	Limb
PE07.00	Congenital bent or squashed nose	Yes	Limb
n34..00	Flat foot	Yes	Limb
n340000	Hypermobility flat foot	Yes	Limb
n340100	Rigid flat foot	Yes	Limb
n340200	Peroneal spastic flat foot	Yes	Limb
n34z.00	Flat foot nos	Yes	Limb
n357.00	Crossover toe	Yes	Limb
n358.00	Mallet toe	Yes	Limb
n35a.00	Over-riding 5th toe	Yes	Limb
n361.00	Mallet finger	Yes	Limb
n364011	Knock knee	Yes	Limb
n364111	Bow legged	Yes	Limb
n36yh00	Deformity of talus	Yes	Limb
n36yj00	Deformity of other tarsal bone	Yes	Limb
n36yk00	Deformity of metatarsal	Yes	Limb
n36yl00	Deformity of phalanx of toe	Yes	Limb
pe00.00	Asymmetry of face	Yes	Limb
pe01.00	Compression facies	Yes	Limb
pe03.00	Depressions in skull	Yes	Limb
pe04.00	Dolichocephaly	Yes	Limb
pe05.00	Plagiocephaly	Yes	Limb
pe05.11	Asymmetric head	Yes	Limb

Read Code	Read term	Minor malformation?	Subgroup
pe1..00	Congenital sternomastoid torticollis	Yes	Limb
pe1..11	Congenital wry neck	Yes	Limb
pe3..00	Congenital dislocation and subluxation of the hip	Yes	Limb
pe31.00	Congenital subluxation of hip	Yes	Limb
pe31000	Unilateral congenital subluxation of hip	Yes	Limb
pe31011	Unstable hip	Yes	Limb
pe31012	Preluxation of hip	Yes	Limb
pe31013	Predislocation status of hip at birth	Yes	Limb
pe31014	Congenital instability of hip joint	Yes	Limb
pe31100	Bilateral congenital subluxation of hip	Yes	Limb
pe31z00	Congenital subluxation of hip nos	Yes	Limb
pe32.00	Congenital dislocation one hip with subluxation other hip	Yes	Limb
pe35.00	Unstable hip	Yes	Limb
pe35000	Unilateral unstable hip	Yes	Limb
pe35100	Bilateral unstable hip	Yes	Limb
pe4..00	Genu recurvatum and long leg bone bowing	Yes	Limb
pe4..11	Congenital leg bone bowing	Yes	Limb
pe40.00	Congenital genu recurvatum	Yes	Limb
pe42.00	Congenital bowing of femur	Yes	Limb
pe43.00	Congenital bowing of tibia and fibula	Yes	Limb
pe43000	Congenital bowing of tibia	Yes	Limb
pe43100	Congenital bowing of fibula	Yes	Limb
pe44.00	Congenital bowing of long leg bone, unspecified	Yes	Limb
pe44.11	Bow legs nos	Yes	Limb
pe4z.00	Genu recurvatum and long leg bone bowing nos	Yes	Limb
pe5..00	Varus deformities of feet	Yes	Limb
pe52.00	Metatarsus primus varus	Yes	Limb
pe53.00	Congenital metatarsus varus	Yes	Limb
pe54.00	Congenital metatarsus adductus	Yes	Limb
pe5z.00	Varus foot deformity nos	Yes	Limb
pe6..00	Valgus deformities of feet	Yes	Limb
pe60.00	Congenital talipes valgus	Yes	Limb
pe60.11	Congenital clubfoot – valgus	Yes	Limb
pe61.00	Congenital pes planus	Yes	Limb
pe61.11	Congenital flat foot	Yes	Limb
pe61.13	Rigid flat foot	Yes	Limb
pe61.14	Spastic flat foot	Yes	Limb
pe61000	Congenital vertical talus	Yes	Limb
pe62.00	Congenital talipes calcaneovalgus	Yes	Limb
pe6y.00	Other valgus foot deformities	Yes	Limb
pe6y000	Congenital talipes equinovalgus	Yes	Limb
pe6y100	Congenital planovalgus	Yes	Limb
pe6yz00	Other valgus foot deformity nos	Yes	Limb
pe6z.00	Valgus foot deformity nos	Yes	Limb
pe6z.11	Congenital metatarsus valgus	Yes	Limb
pe71.00	Talipes cavus	Yes	Limb
pe71.12	Pes cavus	Yes	Limb
pe72.00	Congenital pes cavus	Yes	Limb
pe74.00	Short achilles tendon, congenital	Yes	Limb
pe7y000	Asymmetric talipes	Yes	Limb
pe7y300	Congenital positional talipes	Yes	Limb
pe80.00	Pectus excavatum, congenital	Yes	Limb

Read Code	Read term	Minor malformation?	Subgroup
pe80.11	Congenital funnel chest	Yes	Limb
pe81.00	Pectus carinatum, congenital	Yes	Limb
pe81.11	Congenital pigeon chest	Yes	Limb
pe8y100	Congenital chest wall deformity nec	Yes	Limb
pf13100	Simple syndactyly lesser toes	Yes	Limb
pf56.00	Accessory carpal bones	Yes	Limb
pf5y100	Congenital cubitus valgus	Yes	Limb
pf64100	Congenital genu valgum - knock-knee	Yes	Limb
pf64200	Congenital genu varum - bowleg	Yes	Limb
pf65.00	Macroductyilia of toes	Yes	Limb
pf65000	Macroductyly of toes - simple	Yes	Limb
pf66100	Congenital hallux varus	Yes	Limb
pf66200	Congenital hammer toe	Yes	Limb
pf66400	Congenital crossed toes	Yes	Limb
pf66411	Congenital overlapping toes	Yes	Limb
pf66500	Congenital curly toes	Yes	Limb
pf66600	Brachyphalangia of little toe	Yes	Limb
pf67400	Tarsal coalitions	Yes	Limb
pf67a00	Complex tarsal coalition	Yes	Limb
pf6y500	Congenital valgus ankle	Yes	Limb
pyu8200	[X]other congenital valgus deformities of feet	Yes	Limb
z1ni.00	Talipes strapping	Yes	Limb
14h5.00	H/o: cong. Dislocation – hip		Limb
7L0D.00	Correction of congenital deformity of shoulder or upper arm		Limb
7L0Dy00	Correction of congenital deformity shoulder or upper arm OS		Limb
7L0Dz00	Correction of congenital deformity shoulder or upper arm NOS		Limb
7LOF400	Amputation of duplicate thumb		Limb
7LOF500	Amputation of supernumerary finger NEC		Limb
7LOH.00	Correction of congenital deformity of leg		Limb
7LOH900	Tibiofibular synostosis for congenital deformity		Limb
7LOHy00	Other specified correction of congenital deformity of leg		Limb
7LOHz00	Correction of congenital deformity of leg NOS		Limb
7LOK400	Triple arthrodesis for correction of congenital deformity		Limb
7LOK500	Dilwyn Evans proc for correction of congenital deformity		Limb
7L0L200	Amputation of supernumerary toe		Limb
7L0N.00	Correction of complex craniofacial deformity		Limb
7L0N200	Cranio-orbital remodelling, unspecified		Limb
7L0N500	Correction of oblique facial cleft		Limb
7L0Nz00	Correction of complex craniofacial deformity NOS		Limb
7j44y00	Instrumental correction of deformity of spine os		Limb
7j44z00	Instrumental correction deformity of spine nos		Limb
7j45.00	Other correction of deformity of spine		Limb
7j45y00	Other specified correction of deformity of spine		Limb
7j45z00	Correction of deformity of spine nos		Limb
7I0d000	Reduction of sprenge deformity		Limb
7I0e.00	Correction of congenital deformity of forearm		Limb
7I0e200	Centralisation carpus- correctn congenital deformity forearm		Limb
7I0e300	Revisn release radius- correctn congenital deformity forearm		Limb
7I0e400	Revisn release ulna- correction congenital deformity forearm		Limb
7I0e500	Correction of congenital absence of radius		Limb
7I0e600	Radialialization correction for radial club hand		Limb
7I0ey00	Correction of congenital deformity of forearm os		Limb

Read Code	Read term	Minor malformation?	Subgroup
710ez00	Correction of congenital deformity of forearm nos		Limb
710f.00	Correction of congenital deformity of hand		Limb
710f200	Correction of syndactyly of fingers using skin graft		Limb
710f300	Correction of syndactyly of fingers using skin expander		Limb
710fa00	Realignment of congenital ulnar drift		Limb
710ff00	Correction of radial polydactyly		Limb
710fg00	Excision of radial digit & skeletal repair for polydactyly		Limb
710fh00	Excision of ulnar digit and skeletal repair for polydactyly		Limb
710fj00	Correction of macrodactyly		Limb
710fk00	Reconstruction of radial club hand		Limb
710fy00	Other specified correction of congenital deformity of hand		Limb
710fz00	Correction of congenital deformity of hand nos		Limb
710g.00	Correction of congenital deformity of hip		Limb
710g000	Open reduction of congenital dislocation of hip		Limb
710g011	Ferguson open reduction of congenital deformity of hip		Limb
710g012	Ludloff open reduction of congenital deformity of hip		Limb
710g100	Primary osteotomy pelvis correction congenital deformity hip		Limb
710g200	Secndry arthroplasty hip for correctn congenital deformity		Limb
710g300	Intraartic soft tiss proced correct congenital deformity hip		Limb
710g500	Osteotomy of ilium correction of congenital deformity of hip		Limb
710g600	Femoral osteotomy for correction congenital deformity of hip		Limb
710g700	Pelvic osteotomy for congenital deformity of hip		Limb
710g800	Salter osteotomy for congenital deformity of hip		Limb
710g900	Pemberton osteotomy for congenital deformity of hip		Limb
710ga00	Chiari osteotomy for congenital deformity of hip		Limb
710gb00	Colonna osteotomy for congenital deformity of hip		Limb
710gc00	Shelf procedure for correction congenital deformity of hip		Limb
710gy00	Other specified correction of congenital deformity of hip		Limb
710gz00	Correction of congenital deformity of hip nos		Limb
710gz11	Adams correction of congenital dislocation of hip		Limb
710h000	Open reduction of congenital dislocation of knee		Limb
710h800	Open reduction congenital dislocation of patella		Limb
710j.00	Primary correction of congenital deformity of foot		Limb
710j.11	Primary correction of club foot		Limb
710j.12	Primary correction of talipes		Limb
710j000	Release pantalar joints correction congenital deformity foot		Limb
710j011	Turco soft tissue release for club foot		Limb
710j100	Post release foot joints for correction congenital deformity		Limb
710j200	Medial release foot joints- correction congenital deformity		Limb
710j211	Dillwyn operation for club foot		Limb
710j212	Evans operation for club foot		Limb
710j213	Medial release of joints of foot for correction of club foot		Limb
710j214	Perkins operation for club foot		Limb
710j300	Anterior release foot joints correction congenital deformity		Limb
710j400	Posteromedial release of clubfoot		Limb
710j500	Combined posteromedial + posterolateral release of clubfoot		Limb
710j600	Lateral release for congenital deformity of foot		Limb
710j800	Complete subtalar release of clubfoot		Limb
710jy00	Primary correction of congenital deformity of foot os		Limb
710jz00	Primary correction of congenital deformity of foot nos		Limb
710k.00	Other correction of congenital deformity of foot		Limb
710k.11	Other operations for club foot		Limb

Read Code	Read term	Minor malformation?	Subgroup
710k.12	Other correction of talipes		Limb
710k100	Wedge tarsectomy for correction congenital deformity of foot		Limb
710ky00	Other correction of congenital deformity of foot os		Limb
710kz00	Other correction of congenital deformity of foot nos		Limb
710l.00	Correction of minor congenital deformity of foot		Limb
710l100	Release of syndactyly of toes		Limb
PE0..00	Skull, face and jaw congenital deformities		Limb
PE0..12	Jaw congenital deformities		Limb
PE0z.00	Skull, face or jaw congenital deformities NOS		Limb
PE22.00	Congenital postural scoliosis		Limb
PE2z.11	Congenital postural curvature of spine nos		Limb
PF01200	Radial polydactyly Wassel 3		Limb
PF4y.00	Symphus		Limb
PF5y011	Cleidocranial dysplasia		Limb
PF6C300	Other specified reduction deformities of unspecified limb		Limb
PG0y.12	Cranial dysostosis nec		Limb
Pyu8000	[X]Other congenital deformities of hip		Limb
Pyu8400	[X]other congenital deformities of skull, face and jaw		Limb
f233.11	Congenital spastic foot		Limb
n233000	Arthrogryposis		Limb
n233011	Arthrogryposis multiplex congenita.		Limb
n363400	Persistent femoral anteversion		Limb
n36y300	Deformity of clavicle		Limb
n36y400	Deformity of scapula		Limb
n36y500	Deformity of humerus		Limb
n36y600	Deformity of radius		Limb
n36y700	Deformity of ulna		Limb
n36y800	Deformity of carpal bone		Limb
n36y900	Deformity of metacarpal		Limb
n36ya00	Deformity of phalanx of finger/thumb		Limb
n36yb00	Deformity of pelvis		Limb
n36yc00	Deformity of femur		Limb
n36yd00	Deformity of patella		Limb
n36ye00	Deformity of tibia		Limb
n36yf00	Deformity of fibula		Limb
n36yg00	Deformity of calcaneum		Limb
pe...00	Certain congenital musculoskeletal deformities		Limb
pe...11	Congenital musculoskeletal deformities		Limb
pe0..13	Skull congenital deformities		Limb
pe2..00	Congenital spine deformity		Limb
pe20.00	Congenital spine deformity, unspecified		Limb
pe2z.00	Congenital spine deformity nos		Limb
pe30.00	Congenital dislocation of hip		Limb
pe30000	Unilateral congenital dislocation of hip		Limb
pe30100	Bilateral congenital dislocation of hip		Limb
pe30z00	Congenital dislocation of hip nos		Limb
pe34.00	Dysplastic hip		Limb
pe34000	Unilateral dysplastic hip		Limb
pe34100	Bilateral dysplastic hip		Limb
pe3z.00	Congenital dislocation of hip nos		Limb
pe41.00	Congenital dislocation of knee		Limb
pe41100	Congenital dislocation of knee grade ii		Limb

Read Code	Read term	Minor malformation?	Subgroup
pe41300	Congenital dislocation of patella		Limb
pe50.00	Congenital talipes varus		Limb
pe50.11	Pes varus		Limb
pe50.12	Congenital clubfoot – varus		Limb
pe51.00	Congenital talipes equinovarus		Limb
pe5x.00	Complex varus foot deformities		Limb
pe5y.00	Other specified varus feet deformity		Limb
pe5y000	Congenital talipes calcaneovarus		Limb
pe5yz00	Other specified varus foot deformity nos		Limb
pe7..00	Other deformities of feet		Limb
pe70.00	Talipes, unspecified		Limb
pe70.11	Clubfoot nos		Limb
pe71.11	Congenital claw toe		Limb
pe73.00	Congenital claw foot		Limb
pe7y.00	Other specified foot deformity		Limb
pe7y100	Congenital talipes calcaneus		Limb
pe7y200	Congenital talipes equinus		Limb
pe7yz00	Other specified foot deformity nos		Limb
pe7z.00	Feet deformities nos		Limb
pe8y000	Congenital club hand		Limb
pe8y011	Congenital club fingers		Limb
pe8y111	Congenital thoracic wall deformity nec		Limb
pe8y200	Congenital dislocation of elbow		Limb
pe8y300	Congenital flexion contractures of leg		Limb
pe8y400	Congenital spade-like hand		Limb
pe8y500	Guerin - stern syndrome		Limb
pe8y600	Congenital flexion contracture of hip		Limb
pe8y700	Congenital abduction contracture of hip		Limb
pe8y800	Congenital flexion contracture of knee		Limb
pe8y900	Congenital short quadriceps		Limb
pe8ya00	Congenital dislocation of radial head		Limb
pe9..00	Other musc skeletal deformity		Limb
pe9..11	Other congenital musculoskeletal deformity		Limb
pf...00	Other congenital limb anomalies		Limb
pf0..00	Polydactyly - supernumerary digits		Limb
pf00.00	Supernumerary digits, unspecified		Limb
pf01.00	Accessory fingers		Limb
pf01000	Radial polydactyly wassel 1		Limb
pf01100	Radial polydactyly wassel 2		Limb
pf01300	Radial polydactyly wassel 4		Limb
pf01700	Central polydactyly		Limb
pf01800	Ulnar polydactyly		Limb
pf02.00	Accessory toes		Limb
pf02000	Accessory hallux		Limb
pf02100	Accessory little toe		Limb
pf02200	Other accessory toe		Limb
pf03.00	Accessory thumbs		Limb
pf0z.00	Polydactyly nos		Limb
pf1..00	Syndactyly - webbing of digits		Limb
pf10.00	Syndactyly of multiple digits, unspecified		Limb
pf11.00	Syndactyly of fingers without bone fusion		Limb
pf11.11	Webbed fingers		Limb



Read Code	Read term	Minor malformation?	Subgroup
pf11000	Simple syndactyly - 1st web		Limb
pf11100	Simple syndactyly - 2nd to 4th web		Limb
pf12.00	Syndactyly of fingers with bone fusion		Limb
pf12.11	Fused fingers		Limb
pf12.12	Osseous syndactyly of fingers		Limb
pf13.00	Syndactyly of toes without bone fusion		Limb
pf13.11	Webbed toes		Limb
pf13000	Simple syndactyly of toes 1st web space		Limb
pf14.00	Syndactyly of toes with bone fusion		Limb
pf14.11	Fused toes		Limb
pf14.12	Conjoined toes		Limb
pf14.13	Syndactyly of toes with bone fusion		Limb
pf14100	Osseous syndactyly lesser toes		Limb
pf15.00	Polysyndactyly		Limb
pf1z.00	Syndactyly nos		Limb
pf1z.11	Polysyndactyly		Limb
pf1z.12	Symphalangism		Limb
pf2..00	Reduction deformity of upper limb		Limb
pf2..11	Arm reduction deformity		Limb
pf20.00	Congenital shortening of arm, unspecified		Limb
pf20.11	Brachymelia of arm		Limb
pf20100	Ectromelia of upper limb nos		Limb
pf20200	Hemimelia of upper limb nos		Limb
pf20z00	Unspecified congenital shortening of arm nos		Limb
pf21.00	Transverse deficiency of arm		Limb
pf21.11	Congenital absence part of arm		Limb
pf21000	Transverse deficiency of arm,unspecified		Limb
pf21100	Transverse deficiency of arm, phalangeal level, all fingers		Limb
pf21200	Transverse deficiency of arm, forearm level		Limb
pf21300	Transverse deficiency of arm, shoulder level(amelia)		Limb
pf21400	Congenital amputation of upper limb		Limb
pf21500	Transverse deficiency of arm, elbow level(hemimelia)		Limb
pf21600	Transverse deficiency of arm, wrist level(hemimelia)		Limb
pf21611	Acheiria		Limb
pf21612	Rudimentary hand		Limb
pf21613	Congenital absence of hand		Limb
pf21z00	Transverse deficiency of arm nos		Limb
pf21z11	Agenesis of hand		Limb
pf22.00	Longitudinal deficiency of arm nec		Limb
pf22000	Phocomelia of upper limb nos		Limb
pf22100	Rudimentary arm		Limb
pf22z00	Longitudinal deficiency of arm nec nos		Limb
pf23.00	Congenital absence upper arm and forearm with hand present		Limb
pf23.11	Complete phocomelia of upper limb		Limb
pf24.00	Congenital absence of upper arm only		Limb
pf24.11	Proximal phocomelia of upper limb		Limb
pf25.00	Congenital absence of forearm only		Limb
pf25.11	Distal phocomelia of upper limb		Limb
pf26.00	Agenesis of radial ray		Limb
pf26.11	Congenital absence of radius		Limb
pf26000	Hypoplasia of radius		Limb
pf26100	Partial radial absence		Limb

Read Code	Read term	Minor malformation?	Subgroup
pf26200	Total radial absence		Limb
pf26300	Absent thumb		Limb
pf26400	Hypoplastic thumb-blauth 1		Limb
pf26500	Hypoplastic thumb-blauth 2		Limb
pf26600	Hypoplastic thumb-blauth 3		Limb
pf26700	Hypoplastic thumb-blauth 4		Limb
pf26800	Hypoplastic thumb-blauth 5		Limb
pf27.00	Agenesis of ulna		Limb
pf27000	Partial defect of ulna		Limb
pf27100	Total absence of ulna		Limb
pf27200	Ulnar and humeroulnar synostosis		Limb
pf28.00	Agenesis of carpals and metacarpals		Limb
pf28.11	Transverse arrest of carpals and metacarpals		Limb
pf28000	Transverse arrest carpal level		Limb
pf28100	Transverse arrest metacarpal 1st ray		Limb
pf28200	Transverse arrest metacarpal other		Limb
pf29.00	Congenital absence of finger		Limb
pf29.12	Transverse arrest of phalanges		Limb
pf29000	Transverse arrest phalangeal level 1st ray		Limb
pf29100	Transverse arrest phalangeal level 2nd ray		Limb
pf29300	Transverse arrest phalangeal level 4th ray		Limb
pf29400	Transverse arrest phalangeal level 5th ray		Limb
pf29z00	Congenital absence finger nos		Limb
pf2y.00	Other specified reduction deformities of upper limb		Limb
pf2z.00	Reduction deformity of upper limb nos		Limb
pf2z.11	Hypoplasia of upper limb		Limb
pf3..00	Reduction deformity of lower limb		Limb
pf3..11	Leg reduction deformity		Limb
pf30.00	Congenital shortening of leg, unspecified		Limb
pf30.11	Brachymelia of leg		Limb
pf30000	Ectromelia of lower limb nos		Limb
pf30100	Hemimelia of lower limb nos		Limb
pf30z00	Unspecified congenital leg shortening nos		Limb
pf31.00	Transverse deficiency of leg		Limb
pf31100	Transverse deficiency lower limb - ankle level		Limb
pf31112	Hemimelia - ankle level		Limb
pf31200	Congenital absence of leg and foot		Limb
pf31311	Amelia - lower limb		Limb
pf31500	Transverse deficiency lower limb - knee level		Limb
pf31511	Hemimelia - knee level		Limb
pf32.00	Longitudinal reduction deformity of lower limb nec		Limb
pf32.11	Phocomelia of lower limb nos		Limb
pf33.00	Congenital absence of thigh and lower leg with foot present		Limb
pf33.11	Complete phocomelia of lower limb		Limb
pf34.00	Congenital absence of thigh only		Limb
pf34.11	Proximal phocomelia of lower limb		Limb
pf34000	Proximal femoral focal deficiency		Limb
pf34100	Congenital short femur		Limb
pf35.00	Congenital absence of lower leg only		Limb
pf35.11	Distal phocomelia of lower limb		Limb
pf36.00	Agenesis of tibia		Limb
pf36200	Congenital tibial deficiency type iii		Limb

Read Code	Read term	Minor malformation?	Subgroup
pf37.00	Agenesis of fibula		Limb
pf37100	Congenital fibular deficiency type ii		Limb
pf38.00	Agenesis of tarsals and metatarsals		Limb
pf38000	Agenesis of talus		Limb
pf38200	Agenesis of other tarsal bone		Limb
pf38500	Agenesis of 5th metatarsal		Limb
pf38600	Agenesis of other metatarsal		Limb
pf38700	Agenesis of 4th and 5th metatarsals		Limb
pf39.00	Congenital absence of toe		Limb
pf39000	Congenital absence of great toe		Limb
pf39100	Congenital absence of 5th toe		Limb
pf39200	Congenital absence of other lesser toe		Limb
pf39400	Congenital absence of other multiple toes		Limb
pf3y.00	Other specified reduction deformities of lower limb		Limb
pf3z.00	Reduction deformity of lower limb nos		Limb
pf3z.11	Hypoplasia of lower limb		Limb
pf4..00	Reduction deformity of unspecified limb		Limb
pf40.00	Congenital absence of limb nos		Limb
pf41.00	Amelia of unspecified limb		Limb
pf43.00	Hemimelia of unspecified limb		Limb
pf44.00	Phocomelia of unspecified limb		Limb
pf45.00	Congenital amputation of unspecified limb		Limb
pf46.00	Longitudinal reduction deformity of unspecified limb		Limb
pf47.00	Congenital absence of digits nos		Limb
pf47.11	Adactyly		Limb
pf4y000	Brachymelia nos		Limb
pf4z.00	Reduction deformity of unspecified limb nos		Limb
pf4z.11	Brachydactyly nos		Limb
pf4z.12	Withered limb		Limb
pf4z.13	Hypoplasia of limb nos		Limb
pf5..00	Other upper limb and shoulder anomaly		Limb
pf50.00	Upper limb anomaly, unspecified		Limb
pf51.00	Congenital deformity of clavicle		Limb
pf51.11	Clavicle agenesis		Limb
pf52.00	Congenital elevation of scapula		Limb
pf52.11	Sprengel's deformity		Limb
pf53.00	Radio-ulnar synostosis		Limb
pf53000	Proximal radioulnar synostosis		Limb
pf53100	Radioulnar synostosis and dislocation of radial head		Limb
pf53200	Distal radioulnar synostosis		Limb
pf54.00	Madelung's deformity		Limb
pf57.00	Macroductyia (fingers)		Limb
pf57000	Macroductyly – simple		Limb
pf57100	Macroductyly - fatty nerve tumor		Limb
pf59000	Windblown hand		Limb
pf59300	Aberrant intrinsic muscles		Limb
pf59500	Thumb in palm deformity		Limb
pf59600	Congenital trigger thumb		Limb
pf5a.00	Other failure of differentiation, skeletal tissues of arm		Limb
pf5a100	Capitate-hamate synostosis		Limb
pf5a200	Scaphoid-lunate synostosis		Limb
pf5a300	Other carpal synostosis		Limb

Read Code	Read term	Minor malformation?	Subgroup
pf5a400	Pip joint symphalangism		Limb
pf5a500	Dip joint symphalangism		Limb
pf5b.00	Other duplication of limb		Limb
pf5bz00	Duplication of limb nos		Limb
pf5c.00	Other overgrowth of upper limb		Limb
pf5c100	Overgrowth of partial upper limb		Limb
pf5cz00	Other overgrowth of limb nos		Limb
pf5d100	Undergrowth of whole hand		Limb
pf5d200	Brachymetacarpia		Limb
pf5dz00	Other undergrowth of limb nos		Limb
pf5e.00	Constriction ring syndrome of upper limb		Limb
pf5e000	Constriction ring		Limb
pf5e100	Constriction ring with lymphoedema		Limb
pf5e200	Acrosyndactyly		Limb
pf5e300	Intra-uterine amputation		Limb
pf5e400	Constriction ring with acrosyndactyly and amputation		Limb
pf5f.00	Congenital absence of both forearm and hand		Limb
pf5g.00	Congenital complete absence of upper limb(s)		Limb
pf5r.00	Other congenital anomalies of fingers		Limb
pf5r000	Triphalangeal thumb		Limb
pf5r100	Brachydactyly of fingers, unspecified		Limb
pf5r400	Flexion deformity of fingers		Limb
pf5r500	Brachydactyly-all 3 phalanges		Limb
pf5r600	Brachydactyly-missing phalanx		Limb
pf5r700	Symbrachydactyly		Limb
pf5rc00	Brachymesophalangia		Limb
pf5rd00	Congenital malformation of thumb		Limb
pf5rz00	Other anomaly of fingers nos		Limb
pf5s.00	Other congenital anomalies of hand		Limb
pf5t.00	Other congenital anomalies of wrist		Limb
pf5u.00	Other congenital anomalies of forearm		Limb
pf5u000	Radio-ulnar dysostosis		Limb
pf5uz00	Other congenital anomaly forearm nos		Limb
pf5v.00	Congenital anomalies of elbow and upper arm		Limb
pf5v.11	Cubitus nos		Limb
pf5w.00	Other congenital anomalies of shoulder		Limb
pf5w.11	Congenital deformity of scapula nec		Limb
pf5x.00	Other congenital anomalies of whole arm		Limb
pf5y.00	Other upper limb and shoulder anomaly os		Limb
pf5y000	Cleidocranial dysostosis		Limb
pf5y200	Congenital cubitus varus		Limb
pf5y300	Congenital humeral varus		Limb
pf5y400	Humeroradial synostosis		Limb
pf5y500	Humeroulnar synostosis		Limb
pf5y600	Total elbow synostosis		Limb
pf5yz00	Other upper limb and shoulder anomaly nos		Limb
pf5z.00	Upper limb or shoulder anomaly nos		Limb
pf6..00	Other lower limb and pelvic girdle anomalies		Limb
pf60.00	Lower limb anomaly, unspecified		Limb
pf61.00	Congenital coxa valga		Limb
pf62.00	Congenital coxa vara		Limb
pf63.00	Other congenital hip joint deformity		Limb

Read Code	Read term	Minor malformation?	Subgroup
pf63000	Congenital anteversion of femoral neck		Limb
pf63100	Congenital hip dysplasia		Limb
pf63111	Developmental dysplasia of the hip		Limb
pf63200	Congenital acetabular dysplasia		Limb
pf63x00	Congenital deformity of hip, unspecified		Limb
pf63z00	Other congenital hip joint deformity nos		Limb
pf64.00	Congenital knee joint deformity		Limb
pf64000	Congenital absence of patella		Limb
pf64300	Rudimentary patella		Limb
pf64400	Congenital dislocation of patella		Limb
pf64500	Bipartite patella		Limb
pf64z00	Congenital knee joint deformity nos		Limb
pf66.00	Other congenital anomalies of toe		Limb
pf66000	Congenital hallux valgus		Limb
pf66300	Brachydactyly of toes		Limb
pf66800	Perodactylia of great toe		Limb
pf66900	Perodactylia of lesser toe		Limb
pf66b00	Triphalangeal great toe		Limb
pf66z00	Other toe anomalies nos		Limb
pf67.00	Congenital anomalies of foot nec		Limb
pf67000	Astragaloscaphoid synostosis		Limb
pf67100	Calcaneonavicular bar		Limb
pf67200	Coalition of calcaneous		Limb
pf67300	Talonavicular synostosis		Limb
pf67700	Accessory tarsal bones		Limb
pf67800	Talocalcaneal bar		Limb
pf67900	Naviculocuneiform bar		Limb
pf67z00	Anomalies of foot nec nos		Limb
pf69.00	Failure of differentiation of skeletal tissues of lower limb		Limb
pf69000	Congenital synostosis of lower limb bones		Limb
pf6a.00	Duplication of lower limb bone		Limb
pf6b.00	Congenital overgrowth of lower limb		Limb
pf6b200	Congenital overgrowth of foot		Limb
pf6b300	Congen overgrowth of whole lower limb		Limb
pf6c.00	Congenital undergrowth of lower limb		Limb
pf6c000	Congenital undergrowth of proximal part of limb		Limb
pf6c100	Congenital undergrowth of distal part of limb		Limb
pf6d.00	Constriction ring syndrome of lower limb		Limb
pf6d000	Constriction ring of lower limb		Limb
pf6d200	Intrauterine amputation of lower limb		Limb
pf6d300	Constriction ring syndrome of lower limb with amputation		Limb
pf6e.00	Congenital absence of thigh and lower leg with foot present		Limb
pf6v.00	Other congenital anomalies of lower leg		Limb
pf6w.00	Other congenital anomalies of upper leg		Limb
pf6x.00	Other congenital anomalies of pelvis		Limb
pf6xz00	Other congenital anomalies of pelvis nos		Limb
pf6y.00	Other lower limb anomalies		Limb
pf6y000	Congenital angulation of tibia		Limb
pf6y100	Congenital deformity of ankle joint		Limb
pf6y200	Congenital deformity of sacroiliac joint		Limb
pf6y300	Congenital fusion of sacroiliac joint		Limb
pf6y400	Congenital varus ankle		Limb

Read Code	Read term	Minor malformation?	Subgroup
pf6y600	Congenital pseudarthrosis of tibia		Limb
pf6yz00	Other lower limb and pelvic girdle anomaly nos		Limb
pfy..00	Other specified anomalies of unspecified limb		Limb
pfy0.00	Arthrogryposis multiplex congenita		Limb
pfy4.00	Other arthrogryposis syndromes		Limb
pfyz.00	Other anomaly of unspecified limb nos		Limb
pfz..00	Congenital anomaly of unspecified limb nos		Limb
pg...00	Other congenital musculoskeletal anomalies		Limb
pg0..00	Skull and face bone anomalies		Limb
pg0..11	Face bone anomalies		Limb
pg1..00	Anomalies of spine		Limb
pg10.00	Anomaly of spine, unspecified		Limb
pg1y.00	Other anomaly of spine		Limb
pg1yz00	Other anomaly of spine nos		Limb
pg1z.00	Anomalies of spine nos		Limb
pyu8100	[X]other congenital varus deformities of feet		Limb
pyu8300	[X]other congenital deformities of feet		Limb
pyu8500	[X]other congenital deformities of chest		Limb
pyu8700	[X]other reduction defects of upper limb(s)		Limb
pyu8a00	[X]other congenital malform upper limb(s), incl shoulder girdle		Limb
pyu8c00	[X]other specified congenital malformations of limb(s)		Limb
pyu8m00	[X]other congenital malforms of the musculoskeletal system		Limb
pyu8n00	[X]congenital deformity of hip, unspecified		Limb
zv49000	[V]deficiencies of limbs problems		Limb
p240.00	Congenital cerebral cyst	Yes	Nervous System
p240000	Single congenital cerebral cyst	Yes	Nervous System
p240z00	Congenital cerebral cyst nos	Yes	Nervous System
p240.11	Congenital intracerebral cyst		Nervous System
7010111	Insertion of halber valve for spina bifida		Nervous System
7031000	Repair of meningoencephalocele		Nervous System
7043.00	Repair of spina bifida		Nervous System
7043100	Closure of spinal myelomeningocele		Nervous System
7043200	Closure of spinal meningocele		Nervous System
7043y00	Other specified repair of spina bifida		Nervous System
7043z00	Repair of spina bifida nos		Nervous System
7f1a300	Drainage of hydrocephalus of fetus to facilitate delivery		Nervous System
P227z00	Anomaly of cerebrum NOS		Nervous System
P23y.00	Other specified congenital hydrocephalus		Nervous System
P244.00	Ulegyria		Nervous System
P26..00	Disorder of neuronal migration and differentiation		Nervous System
P6z..11	Chiari's malformation		Nervous System
f23..00	Congenital cerebral palsy		Nervous System
f23..11	Congenital spastic cerebral palsy		Nervous System
f230.11	Paraplegia – congenital		Nervous System
f230000	Congenital paraplegia		Nervous System
f230z00	Congenital diplegia nos		Nervous System
f231.00	Congenital hemiplegia		Nervous System
f232.00	Congenital quadriplegia		Nervous System
f232.11	Tetraplegia – congenital		Nervous System
f233.00	Congenital monoplegia		Nervous System
f23y.00	Other congenital cerebral palsy		Nervous System
f23y511	Congenital suprabulbar paresis		Nervous System

Read Code	Read term	Minor malformation?	Subgroup
f23z.00	Congenital cerebral palsy nos		Nervous System
l236.00	Hydrocephalic disproportion		Nervous System
l236000	Hydrocephalic disproportion unspecified		Nervous System
l236100	Hydrocephalic disproportion - delivered		Nervous System
l236200	Hydrocephalic disproportion with antenatal problem		Nervous System
l236z00	Hydrocephalic disproportion nos		Nervous System
l250.00	Fetus with central nervous system malformation		Nervous System
l250.11	Suspect fetal anencephaly		Nervous System
l250.12	Suspect fetal hydrocephaly		Nervous System
l250.13	Suspect fetal spina bifida		Nervous System
l250000	Fetus with central nervous system malformation unspecified		Nervous System
l250100	Fetus with central nervous system malformation – delivered		Nervous System
l250200	Fetus with central nervous system malformation + a/n problem		Nervous System
l250300	Maternal care for suspected cns malformation in fetus		Nervous System
l250400	Maternal care for cns malformation in fetus		Nervous System
l250z00	Fetus with central nervous system malformation nos		Nervous System
p0...00	Anencephalus and similar anomalies		Nervous System
p00..00	Anencephalus		Nervous System
p00..11	Congenital absence of brain		Nervous System
p000.00	Acrania		Nervous System
p001.00	Amyelencephalus		Nervous System
p002.00	Hemicephaly		Nervous System
p002.11	Hemianencephaly		Nervous System
p00y.00	Other specified anencephalus		Nervous System
p00z.00	Anencephalus nos		Nervous System
p01..00	Craniorachischisis		Nervous System
p02..00	Iniencephaly		Nervous System
p0z..00	Anencephalus and similar anomalies nos		Nervous System
p1...00	Spina bifida		Nervous System
p10..00	Spina bifida with hydrocephalus		Nervous System
p10..11	Arnold - chiari syndrome		Nervous System
p100.00	Unspecified spina bifida with hydrocephalus		Nervous System
p100000	Spina bifida with hydrocephalus, unspecified		Nervous System
p100100	Cervical spina bifida with hydrocephalus		Nervous System
p100200	Thoracic spina bifida with hydrocephalus		Nervous System
p100300	Lumbar spina bifida with hydrocephalus		Nervous System
p100z00	Spina bifida with hydrocephalus nos		Nervous System
p101.00	Arnold - chiari syndrome		Nervous System
p101.11	Closed spina bifida with arnold-chiari malformation		Nervous System
p101000	Chiari malformation type i		Nervous System
p101100	Chiari malformation type ii		Nervous System
p102.00	Spina bifida with hydrocephalus - open		Nervous System
p102.11	Fissured spine with hydrocephalus		Nervous System
p102.13	Myelocele with hydrocephalus		Nervous System
p102.14	Rachischisis with hydrocephalus		Nervous System
p102200	Thoracic spina bifida with hydrocephalus - open		Nervous System
p102300	Lumbar spina bifida with hydrocephalus - open		Nervous System
p102400	Sacral spina bifida with hydrocephalus - open		Nervous System
p102z00	Spina bifida with hydrocephalus - open nos		Nervous System
p103.00	Spina bifida with hydrocephalus - closed		Nervous System
p103300	Lumbar spina bifida with hydrocephalus - closed		Nervous System
p103400	Sacral spina bifida with hydrocephalus - closed		Nervous System

Read Code	Read term	Minor malformation?	Subgroup
p103z11	Thoracolumbar spina bifida with hydrocephalus – closed		Nervous System
p104.00	Spina bifida with hydrocephalus of late onset		Nervous System
p105.00	Spina bifida with stenosis of aqueduct of sylvius		Nervous System
p10y.00	Other specified spina bifida with hydrocephalus		Nervous System
p10y000	Dandy - walker syndrome with spina bifida		Nervous System
p10z.00	Spina bifida with hydrocephalus nos		Nervous System
p11..00	Spina bifida without mention of hydrocephalus		Nervous System
p110000	Spina bifida without hydrocephalus, site unspecified		Nervous System
p110100	Cervical spina bifida without mention of hydrocephalus		Nervous System
p110200	Thoracic spina bifida without mention of hydrocephalus		Nervous System
p110300	Lumbar spina bifida without mention of hydrocephalus		Nervous System
p110z00	Unspecified spina bifida without hydrocephalus nos		Nervous System
p111.00	Spinal hydromeningocele		Nervous System
p112.00	Hydromyelocele		Nervous System
p113.00	Spinal meningocele		Nervous System
p113000	Spinal meningocele of unspecified site		Nervous System
p113100	Cervical spinal meningocele		Nervous System
p113200	Thoracic spinal meningocele		Nervous System
p113300	Lumbar spinal meningocele		Nervous System
p113z00	Spinal meningocele nos		Nervous System
p114.00	Meningomyelocele		Nervous System
p114000	Meningomyelocele of unspecified site		Nervous System
p114100	Cervical meningomyelocele		Nervous System
p114200	Thoracic meningomyelocele		Nervous System
p114300	Lumbar meningomyelocele		Nervous System
p114z00	Meningomyelocele nos		Nervous System
p115.00	Myelocele		Nervous System
p115100	Cervical myelocele		Nervous System
p115300	Lumbar myelocele		Nervous System
p115z00	Myelocele nos		Nervous System
p116.00	Myelocystocele		Nervous System
p116100	Cervical myelocystocele		Nervous System
p116300	Lumbar myelocystocele		Nervous System
p116z00	Myelocystocele nos		Nervous System
p117.00	Spina bifida without hydrocephalus - open		Nervous System
p117.11	Fissured spine		Nervous System
p117.12	Rachischisis		Nervous System
p117200	Thoracic spina bifida without hydrocephalus - open		Nervous System
p117300	Lumbar spina bifida without hydrocephalus - open		Nervous System
p117400	Sacral spina bifida without hydrocephalus - open		Nervous System
p117z00	Spina bifida without hydrocephalus - open nos		Nervous System
p118.00	Spina bifida without hydrocephalus - closed		Nervous System
p118000	Unspecified spina bifida without hydrocephalus – closed		Nervous System
p118100	Cervical spina bifida without hydrocephalus - closed		Nervous System
p118300	Lumbar spina bifida without hydrocephalus - closed		Nervous System
p118400	Sacral spina bifida without hydrocephalus - closed		Nervous System
p118z00	Spina bifida without hydrocephalus - closed nos		Nervous System
p11y.00	Other specified spina bifida without hydrocephalus		Nervous System
p11y.11	Syringomyelocele		Nervous System
p11z.00	Spina bifida without mention of hydrocephalus nos		Nervous System
p11z.14	Congenital hernia of dura mater		Nervous System
p1z..00	Spina bifida nos		Nervous System



Read Code	Read term	Minor malformation?	Subgroup
p2...00	Other nervous system congenital anomalies		Nervous System
p20..00	Encephalocele		Nervous System
p20..11	Hydroencephalocele		Nervous System
p20..12	Cephalocele		Nervous System
p20..13	Congenital cerebral hernia		Nervous System
p20..14	Congenital endaural hernia		Nervous System
p20..15	Sinus pericranii		Nervous System
p200.00	Encephalocystocele		Nervous System
p201.00	Encephalomyelocele		Nervous System
p202.00	Hydromeningocele – cranial		Nervous System
p203.00	Meningocele – cerebral		Nervous System
p203.11	Meningocele – cranial		Nervous System
p204.00	Meningoencephalocele		Nervous System
p205.00	Frontal encephalocele		Nervous System
p206.00	Nasofrontal encephalocele		Nervous System
p20z.00	Encephalocele nos		Nervous System
p20z000	Occipital encephalocele		Nervous System
p20z100	Encephalocele of other specified site		Nervous System
p21..00	Microcephalus		Nervous System
p210.00	Hydromicrocephaly		Nervous System
p211.00	Micrencephaly		Nervous System
p21z.00	Microcephalus nos		Nervous System
p22..00	Reduction deformities of brain		Nervous System
p220.00	Agenesis of brain, part unspecified		Nervous System
p221.00	Aplasia of brain, part unspecified		Nervous System
p222.00	Hypoplasia of brain, part unspecified		Nervous System
p223.00	Agyria		Nervous System
p223.11	Lissencephaly		Nervous System
p224.00	Arhinencephaly		Nervous System
p225.00	Holoprosencephaly		Nervous System
p226.00	Microgyria		Nervous System
p227.00	Anomalies of cerebrum		Nervous System
p227000	Agenesis of cerebrum		Nervous System
p227100	Congenital hypoplasia of cerebrum		Nervous System
p228.00	Anomalies of corpus callosum		Nervous System
p228000	Congenital absence of corpus callosum		Nervous System
p228011	Agenesis of corpus callosum		Nervous System
p228100	Hypoplasia of corpus callosum		Nervous System
p228200	Aplasia of corpus callosum		Nervous System
p228z00	Anomaly of corpus callosum nos		Nervous System
p229.00	Anomalies of hypothalamus		Nervous System
p22a.00	Anomalies of cerebellum		Nervous System
p22a000	Congenital absence of cerebellum		Nervous System
p22a011	Agenesis of cerebellum		Nervous System
p22a100	Hypoplasia of cerebellum		Nervous System
p22a200	Aplasia of cerebellum		Nervous System
p22az00	Anomaly of cerebellum nos		Nervous System
p22y.00	Other specified reduction deformities of brain		Nervous System
p22y300	Partial absence of septum pellucidum		Nervous System
p22yz00	Other reduction deformity of brain nos		Nervous System
p22z.00	Reduction deformities of brain nos		Nervous System
p22z.11	Cerebellar hypoplasia		Nervous System

Read Code	Read term	Minor malformation?	Subgroup
p22z.12	Agenesis of part of brain nec		Nervous System
p22z.13	Hypoplasia of part of brain nec		Nervous System
p23..00	Congenital hydrocephalus		Nervous System
p230.00	Aqueduct of sylvius anomaly		Nervous System
p230.11	Hydrocephalus with anomaly of aqueduct of sylvius		Nervous System
p230.12	Stenosis of aqueduct of sylvius		Nervous System
p230100	Aqueduct of sylvius stenosis		Nervous System
p231.00	Foramen of magendie atresia		Nervous System
p232.00	Foramen of luschka atresia		Nervous System
p233.00	Atresia of foramina of magendie and luschka		Nervous System
p233.11	Dandy - walker syndrome		Nervous System
p233.12	Hydrocephalus with atresia of foramina of magendie+luschka		Nervous System
p234.00	Hydranencephaly		Nervous System
p23z.00	Congenital hydrocephalus nos		Nervous System
p24..00	Other specified brain anomalies		Nervous System
p240100	Multiple congenital cerebral cysts		Nervous System
p240200	Schizencephaly		Nervous System
p241.00	Macrocephaly		Nervous System
p241.11	Megalencephaly		Nervous System
p241.12	Enlarged brain		Nervous System
p242.00	Macrogyria		Nervous System
p243.00	Porencephaly		Nervous System
p245.00	Congenital adhesions of cerebral meninges		Nervous System
p246.00	Septo-optic dysplasia		Nervous System
p247.00	Dysplasia of cerebral cortex		Nervous System
p248.00	Congenital dilated lateral ventricles of brain		Nervous System
p249.00	Megalencephaly		Nervous System
p24a.00	Hemimegalencephaly		Nervous System
p24z.00	Other specified brain anomalies nos		Nervous System
p25..00	Other specified spinal cord anomalies		Nervous System
p250.00	Diastematomyelia		Nervous System
p251.00	Hydromyelia		Nervous System
p252.00	Congenital tethering of spinal cord		Nervous System
p25y.00	Other specified anomalies of spinal cord		Nervous System
p25y.11	Neuroenteric cyst		Nervous System
p25y000	Amyelia		Nervous System
p25y100	Atelomyelia		Nervous System
p25y111	Myelataelia		Nervous System
p25y112	Myelodysplasia of spinal cord		Nervous System
p25y200	Congenital anomaly of spinal meninges		Nervous System
p25y300	Defective development of the cauda equina		Nervous System
p25y400	Spinal cord hypoplasia		Nervous System
p25yz00	Other specified spinal cord anomalies nos		Nervous System
p25z.00	Spinal cord anomalies nos		Nervous System
p2x..00	Other specified nervous system anomalies		Nervous System
p2x0.00	Agenesis of nerve, unspecified		Nervous System
p2x1.00	Brachial plexus displacement		Nervous System
p2x6.00	Chiari malformation type i		Nervous System
p2x7.00	Congenital facial nerve palsy		Nervous System
p2xz.00	Other specified nervous system anomalies nos		Nervous System
p2xz000	Agenesis of nerve nec		Nervous System
p2xz100	Congenital optic atrophy		Nervous System

Read Code	Read term	Minor malformation?	Subgroup
p2y..00	Unspec nervous system anomaly of brain/cord/nervous system		Nervous System
p2y0.00	Congenital brain anomaly		Nervous System
p2y1.00	Congenital spinal cord anomaly		Nervous System
p2yz.00	Unspecified nervous system anomaly nos		Nervous System
p2z..00	Nervous system anomalies nos		Nervous System
pyu0100	[X]other congenital hydrocephalus		Nervous System
pyu0300	[X]other specified congenital malformations of brain		Nervous System
pyu0400	[X]unspecified spina bifida with hydrocephalus		Nervous System
pyu0600	[X]other specified congenital malformations of spinal cord		Nervous System
q48y500	Megalencephaly		Nervous System
14H2.00	H/O: cleft palate		Orofacial Clefts
14H3.00	H/O: cleft lip		Orofacial Clefts
7409.00	Correction of cleft lip nasal deformity		Orofacial Clefts
7409000	Primary correction of cleft lip nasal deformity		Orofacial Clefts
7409011	Primary correction of alar cartilage		Orofacial Clefts
7409013	Pigott alar leap-frog correction		Orofacial Clefts
7409100	Secondary correction of cleft lip nasal deformity		Orofacial Clefts
7409111	Secondary correction of alar slump		Orofacial Clefts
7409113	Skoog correction of alar slump		Orofacial Clefts
7409114	Dibbell correction of alar slump		Orofacial Clefts
7409200	Correction of cleft lip nasal tip deformity		Orofacial Clefts
7409211	Alar base advancement		Orofacial Clefts
7409300	Columella lengthening procedure unspecified		Orofacial Clefts
7409400	Unilateral columella lengthening operation		Orofacial Clefts
7409411	Tajima unilateral columella lengthening operation		Orofacial Clefts
7409500	Rhinoplasty for cleft lip nasal deformity		Orofacial Clefts
7409600	Septorhinoplasty for cleft lip nasal deformity		Orofacial Clefts
7409700	Septoplasty for cleft lip nasal deformity		Orofacial Clefts
7502.11	Repair of cleft lip operations		Orofacial Clefts
7502000	Primary closure of cleft lip, unspecified		Orofacial Clefts
7502011	Lemesurier cleft lip repair		Orofacial Clefts
7502012	Millard cleft lip correction		Orofacial Clefts
7502014	Tenison cleft lip repair		Orofacial Clefts
7502100	Revision of primary closure of cleft lip		Orofacial Clefts
7502300	Unilateral lip adhesion		Orofacial Clefts
7502400	Bilateral lip adhesion		Orofacial Clefts
7502500	Repair of unilateral cleft lip using straight line technique		Orofacial Clefts
7502600	Repair unilat cleft lip - rotation advancement flap technique		Orofacial Clefts
7502611	Millard repair unilateral cleft lip		Orofacial Clefts
7502700	Repair of unilateral cleft lip with triangular flap		Orofacial Clefts
7502712	Skoog repair unilateral cleft lip		Orofacial Clefts
7502713	Tennyson repair unilateral cleft lip		Orofacial Clefts
7502800	Repair unilateral cleft lip with quadrilateral flap		Orofacial Clefts
7502811	Repair unilateral cleft lip with quadrilateral flap		Orofacial Clefts
7502900	Repair of unilateral cleft lip unspecified		Orofacial Clefts
7502A00	Repair bilateral cleft lip - rotation advancement flap tech		Orofacial Clefts
7502A11	Rep bilat cleft lip Millard		Orofacial Clefts
7502B00	Repair of bilateral cleft lip with quadrilateral flap		Orofacial Clefts
7502C11	Manchester bilateral cleft lip repair		Orofacial Clefts
7502C12	Veau type III bilateral cleft lip repair		Orofacial Clefts
7502D00	Repair of bilateral cleft lip unspecified		Orofacial Clefts
7502E00	Synchronous bilateral cleft lip repair		Orofacial Clefts

Read Code	Read term	Minor malformation?	Subgroup
7502F00	Asynchronous bilateral cleft lip repair		Orofacial Clefts
7525.12	Repair of cleft palate		Orofacial Clefts
7525000	Primary repair of cleft palate, unspecified		Orofacial Clefts
7525011	Kilner repair of cleft palate		Orofacial Clefts
7525012	Langenbeck repair of cleft palate		Orofacial Clefts
7525013	Wardill repair of cleft palate		Orofacial Clefts
7525100	Revision of repair of cleft palate		Orofacial Clefts
7525200	Repair cleft hard palate post based axial transposition flap		Orofacial Clefts
7525212	Wardill repair cleft palate		Orofacial Clefts
7525213	Veau flap repair cleft palate		Orofacial Clefts
7525300	Repair of cleft hard palate with bipediced flaps		Orofacial Clefts
7525311	Langenbeck repair cleft palate		Orofacial Clefts
7525400	Repair of cleft soft palate with Z-plasty		Orofacial Clefts
7525411	Furlow repair cleft palate		Orofacial Clefts
7525500	Repair of anterior cleft palate with local flap		Orofacial Clefts
7525600	Repair of anterior cleft palate with vomerine flap		Orofacial Clefts
7525700	Repair of cleft soft palate with intra-velar veloplasty		Orofacial Clefts
7525711	Rep anterior cleft palate local flap		Orofacial Clefts
7525800	Repair cleft soft palate with other musculature correction		Orofacial Clefts
P9...00	Cleft palate and lip		Orofacial Clefts
P90..00	Cleft palate		Orofacial Clefts
P900.00	Cleft palate, unspecified		Orofacial Clefts
P900.11	Palatoschisis		Orofacial Clefts
P901.00	Unilateral complete cleft palate		Orofacial Clefts
P901.11	Cleft hard palate, unilateral		Orofacial Clefts
P902.00	Unilateral incomplete cleft palate		Orofacial Clefts
P902.11	Cleft uvula		Orofacial Clefts
P902.12	Cleft soft palate, unilateral		Orofacial Clefts
P903.00	Bilateral complete cleft palate		Orofacial Clefts
P904.00	Bilateral incomplete cleft palate		Orofacial Clefts
P904.11	Cleft soft palate, bilateral		Orofacial Clefts
P905.00	Central complete cleft palate		Orofacial Clefts
P906.00	Central incomplete cleft palate		Orofacial Clefts
P906.11	Cleft soft palate, central		Orofacial Clefts
P907.00	Complete cleft palate NOS		Orofacial Clefts
P907.11	Cleft hard palate NOS		Orofacial Clefts
P908.00	Incomplete cleft palate NOS		Orofacial Clefts
P908.11	Cleft soft palate NOS		Orofacial Clefts
P909.00	Cleft uvula		Orofacial Clefts
P90A.00	Cleft soft palate, bilateral		Orofacial Clefts
P90B.00	Cleft hard palate, bilateral		Orofacial Clefts
P90C.00	Cleft hard palate, unilateral		Orofacial Clefts
P90z.00	Cleft palate NOS		Orofacial Clefts
P91..00	Cleft lip (harelip)		Orofacial Clefts
P91..11	Cheiloschisis		Orofacial Clefts
P91..12	Congenital fissure of lip		Orofacial Clefts
P910.00	Cleft lip, unspecified		Orofacial Clefts
P911.00	Unilateral complete cleft lip		Orofacial Clefts
P912.00	Unilateral incomplete cleft lip		Orofacial Clefts
P913.00	Bilateral complete cleft lip		Orofacial Clefts
P914.00	Bilateral incomplete cleft lip		Orofacial Clefts
P915.00	Central cleft lip		Orofacial Clefts

Read Code	Read term	Minor malformation?	Subgroup
P91z.00	Cleft lip NOS		Orofacial Clefts
P92..00	Cleft palate with cleft lip		Orofacial Clefts
P92..11	Cheilopalatoschisis		Orofacial Clefts
P920.00	Cleft palate with cleft lip, unspecified		Orofacial Clefts
P921.00	Unilateral complete cleft palate with cleft lip		Orofacial Clefts
P922.00	Unilateral incomplete cleft palate with cleft lip		Orofacial Clefts
P923.00	Bilateral complete cleft palate with cleft lip		Orofacial Clefts
P924.00	Bilateral incomplete cleft palate with cleft lip		Orofacial Clefts
P928.00	Cleft hard palate with cleft soft palate, unilateral		Orofacial Clefts
P92A.00	Cleft hard palate with cleft lip, bilateral		Orofacial Clefts
P92B.00	Cleft hard palate with cleft lip, unilateral		Orofacial Clefts
P92z.00	Cleft palate with cleft lip NOS		Orofacial Clefts
P9z..00	Cleft palate or cleft lip NOS		Orofacial Clefts
Pyu4.00	[X]Cleft lip and cleft palate		Orofacial Clefts
Pyu4000	[X]Cleft palate, unspecified, bilateral		Orofacial Clefts
Pyu4100	[X]Unspecified cleft palate with cleft lip, bilateral		Orofacial Clefts
7H10.00	Simple excision of inguinal hernial sac	Yes	Other
7H10y00	Other specified simple excision of inguinal hernial sac	Yes	Other
7H10z00	Simple excision of inguinal hernial sac nos	Yes	Other
7H11.00	Primary repair of inguinal hernia	Yes	Other
7H11000	Primary repair inguinal hernia using insert natural material	Yes	Other
7H11100	Prim repair inguinal hernia using insert prosthet material	Yes	Other
7H11111	Primary mesh repair of inguinal hernia	Yes	Other
7H11200	Primary repair of inguinal hernia using sutures	Yes	Other
7H11211	Bassini repair of inguinal hernia	Yes	Other
7H11212	Ferguson repair of inguinal hernia	Yes	Other
7H11213	Mcvay repair of inguinal hernia	Yes	Other
7H11214	Shouldice repair of inguinal hernia	Yes	Other
7H11300	Primary repair inguinal hernia & reduction of sliding hernia	Yes	Other
7H11400	Endoscopic primary repair of inguinal hernia	Yes	Other
7H11500	Bilateral inguinal hernia repair	Yes	Other
7H11600	Primary laparoscopic repair of inguinal hernia	Yes	Other
7H11y00	Other specified primary repair of inguinal hernia	Yes	Other
7H11y11	Halsted repair of inguinal hernia	Yes	Other
7H11z00	Primary repair of inguinal hernia nos	Yes	Other
7H12.00	Repair of recurrent inguinal hernia	Yes	Other
7H12.11	Herniorrhaphy for recurrent inguinal hernia	Yes	Other
7H12000	Repair recurr inguinal hernia using insert natural material	Yes	Other
7H12100	Repair recurr inguinal hernia using insert prosthet material	Yes	Other
7H12200	Repair of recurrent inguinal hernia using sutures	Yes	Other
7H12300	Removal prosthet material fr previous repair inguinal hernia	Yes	Other
7H12y00	Other specified repair of recurrent inguinal hernia	Yes	Other
7H12z00	Repair of recurrent inguinal hernia nos	Yes	Other
J30..00	Inguinal hernia	Yes	Other
J30..12	Direct inguinal hernia	Yes	Other
J30..13	Indirect inguinal hernia	Yes	Other
J300.00	Inguinal hernia with gangrene	Yes	Other
J300000	Unilateral inguinal hernia with gangrene	Yes	Other
J300300	Bilateral recurrent inguinal hernia with gangrene	Yes	Other
J300z00	Inguinal hernia with gangrene nos	Yes	Other
J301.00	Inguinal hernia with obstruction	Yes	Other
J301000	Unilateral inguinal hernia with obstruction	Yes	Other

Read Code	Read term	Minor malformation?	Subgroup
J301100	Unilateral recurrent inguinal hernia with obstruction	Yes	Other
J301200	Bilateral inguinal hernia with obstruction	Yes	Other
J301z00	Inguinal hernia with obstruction nos	Yes	Other
J302.00	Inguinal hernia – irreducible	Yes	Other
J302000	Unilateral inguinal hernia - irreducible	Yes	Other
J302100	Unilateral recurrent inguinal hernia - irreducible	Yes	Other
J302200	Bilateral inguinal hernia - irreducible	Yes	Other
J302300	Bilateral recurrent inguinal hernia - irreducible	Yes	Other
J302z00	Inguinal hernia - irreducible and nos	Yes	Other
J303.00	Simple inguinal hernia	Yes	Other
J303000	Unilateral inguinal hernia – simple	Yes	Other
J303011	Left inguinal hernia	Yes	Other
J303012	Right inguinal hernia	Yes	Other
J303100	Unilateral recurrent inguinal hernia - simple	Yes	Other
J303200	Bilateral inguinal hernia – simple	Yes	Other
J303300	Bilateral recurrent inguinal hernia - simple	Yes	Other
J303z00	Simple inguinal hernia nos	Yes	Other
J304.00	Direct inguinal hernia	Yes	Other
J305.00	Indirect inguinal hernia	Yes	Other
J30y.00	Inguinal hernia unspecified	Yes	Other
J30y000	Unilateral inguinal hernia unspecified	Yes	Other
J30y100	Unilateral recurrent inguinal hernia unspecified	Yes	Other
J30y200	Bilateral inguinal hernia unspecified	Yes	Other
J30y300	Bilateral recurrent inguinal hernia unspecified	Yes	Other
J30yz00	Unspecified inguinal hernia nos	Yes	Other
J30z.00	Inguinal hernia nos	Yes	Other
PG8..00	Congenital inguinal hernia	Yes	Other
P75..00	Absence or hypoplasia of the umbilical artery	Yes	Other
P750.00	Congenital absence of umbilical artery, unspecified	Yes	Other
P752.00	Single umbilical artery	Yes	Other
P75z.00	Absence or hypoplasia of the umbilical artery NOS	Yes	Other
P831600	Laryngomalacia	Yes	Other
P831700	Congenital laryngomalacia	Yes	Other
P83y900	Congenital laryngeal stridor	Yes	Other
7204A00	Correction of hypertelorism with orbital osteotomies	Yes	Other
7204B00	Corr hypertelorism c orbital osteotomies+facial bipartition	Yes	Other
7204C00	Corr hypertelorism c orbital osteotomies+nasal reconstruct	Yes	Other
7204D00	Correction of hypotelorism with orbital osteotomies	Yes	Other
F4G4100	Hypertelorism of orbit	Yes	Other
P241.13	Macrocephaly	Yes	Other
PG05.00	Hypertelorism	Yes	Other
PG0H.00	Macrocephaly	Yes	Other
PG0y000	Brachycephaly	Yes	Other
PG2..00	Cervical rib	Yes	Other
PG30.00	Congenital absence of rib	Yes	Other
PG33.00	Congenital fusion of ribs	Yes	Other
PG34.00	Sternum bifidum	Yes	Other
PG36.00	Extra ribs	Yes	Other
PG36.11	Supernumerary ribs	Yes	Other
PG37.00	Mis-shapen sternum	Yes	Other
pe21.00	Congenital postural lordosis	Yes	Other
pg17.00	Spina bifida occulta	Yes	Other

Read Code	Read term	Minor malformation?	Subgroup
p814.00	Deformity of nasal sinus wall	Yes	Other
p815.00	Congenital notching of tip of nose	Yes	Other
7136800	Excision of accessory nipple	Yes	Other
PH31.11	Vascular naevus	Yes	Other
PH31.12	Naevus flammeus	Yes	Other
PH31000	Birth mark, unspecified	Yes	Other
PH31100	Port wine stain	Yes	Other
PH31200	Strawberry naevus	Yes	Other
PH32.00	Congenital pigmentary skin anomalies	Yes	Other
PH34.00	Other specified birthmark	Yes	Other
PH34.11	Naevus nec	Yes	Other
PH34000	Naevus sebaceous	Yes	Other
PH35.00	Mongolian blue spot	Yes	Other
PH3y.00	Other congenital skin anomalies	Yes	Other
PH3y.11	Keratosis palmaris	Yes	Other
PH3y000	Congenital accessory skin tags	Yes	Other
PH3y600	Keratosis palmaris et plantaris	Yes	Other
PH3yz00	Other congenital skin anomaly nos	Yes	Other
PH3z.00	Integument anomalies nos	Yes	Other
PH41.11	Beaded hair	Yes	Other
PH43.00	Persistent lanugo	Yes	Other
PH4z.00	Specified hair anomalies nos	Yes	Other
PH53.00	Congenital leukonychia	Yes	Other
PH54.11	Enlarged nails	Yes	Other
PH63.00	Accessory nipple	Yes	Other
PH65.00	Supernumerary nipple	Yes	Other
PHz..11	Congenital ectodermal defect	Yes	Other
PHz0.00	Unspecified congenital anomalies of skin	Yes	Other
PHz0.11	Congenital dermal defect	Yes	Other
7C03111	Excision of aberrant testis	Yes	Other
PC5..00	Undescended testicle	Yes	Other
PC50.00	Cryptorchidism	Yes	Other
PC50000	Cryptorchidism, unilateral	Yes	Other
PC50100	Cryptorchidism, bilateral	Yes	Other
PC50z00	Cryptorchidism NOS	Yes	Other
PC51.00	Ectopic testis	Yes	Other
PC5z.00	Undescended testicle NOS	Yes	Other
PC5z.12	Maldescent of testicle	Yes	Other
PC5z000	Undescended testis, unilateral	Yes	Other
PC5z011	Maldescent of testis, unilateral	Yes	Other
PC5z100	Undescended testis, bilateral	Yes	Other
PC5z111	Maldescent of testis, bilateral	Yes	Other
7A61000	Excision of congenital arteriovenous malformation		Other
7A61200	Embolisation of arteriovenous abnormality		Other
7A61300	Ligation of congenital arteriovenous malformation		Other
7A61500	Percutan transluminal embolis arteriovenous malformation NEC		Other
7A61600	Percut translumin venous embolisat arteriovenous malform		Other
7A61700	Perc translum arterial venous embolis arteriovenous malform		Other
7A61800	Embolisation of arteriovenous abnormality NEC		Other
P357.00	Posterior chamber vascular anomalies		Other
P357100	Congenital arteriovenous malformation of retina		Other
P357z00	Posterior chamber vascular anomalies NOS		Other

Read Code	Read term	Minor malformation?	Subgroup
P7...00	Other congenital circulatory system anomalies		Other
P753.00	Two umbilical vessels		Other
P76..00	Other peripheral vascular system anomalies		Other
P76..11	Other congenital anomalies of peripheral arteries		Other
P76..12	Other congenital anomalies of peripheral veins		Other
P760.00	Absence of artery NEC		Other
P761.00	Anomaly of artery NEC		Other
P762.00	Atresia of artery NEC		Other
P763.00	Absence of vein NEC		Other
P764.00	Anomaly of vein NEC		Other
P766.00	Peripheral arterio-venous aneurysm		Other
P766.11	Peripheral arterio-venous malformation		Other
P767.00	Congenital peripheral aneurysm		Other
P767.11	Cirsoid aneurysm		Other
P768.00	Congenital phlebectasia		Other
P769.00	Congenital arterial stricture		Other
P769000	Renal artery stenosis		Other
P76A.00	Congenital varix		Other
P76B.00	Multiple renal arteries		Other
P76B.11	Accessory renal artery		Other
P76C.00	Anomalies of renal artery NEC		Other
P76C000	Aberrant main renal artery		Other
P76Cz00	Anomaly of renal artery NEC NOS		Other
P76D.00	Arteriovenous malformation		Other
P76E.00	Aber retro-oesophag subclavian artery causing dysphag lusori		Other
P76y.00	Congenital anomaly of peripheral vascular system OS		Other
P76y100	Four vessels in umbilical cord		Other
P76yz00	Other congenital anomaly of peripheral vascular system NOS		Other
P76z.00	Peripheral vascular system anomaly NOS		Other
P77..00	Arteriovenous malformation of precerebral vessels		Other
P7W..00	Congenital malformation of circulatory system, unspecif		Other
P7X..00	Congenital malformation of great arteries, unspecified		Other
P7y..00	Other specified circulatory system anomalies		Other
P7y0.00	Cerebrovascular system anomalies		Other
P7y0000	Congenital anomaly of cerebral vessel, unspecified		Other
P7y0100	Congenital cerebral arteriovenous aneurysm		Other
P7y0111	Congenital arteriovenous fistula of brain		Other
P7y0112	Congenital cerebral arteriovenous malformation		Other
P7y0200	Congenital brain aneurysm NEC		Other
P7y0400	Vein of Galen malformation		Other
P7y0y00	Other specified cerebrovascular anomaly		Other
P7y0z00	Cerebrovascular system anomaly NOS		Other
P7yz.00	Other cardiovascular system anomaly NOS		Other
P7yz000	Congenital aneurysm NEC		Other
P7yzz00	Other cardiovascular system anomaly NOS		Other
P7z..00	Circulatory system anomaly NOS		Other
PKyG.00	Men ret congen heart dis blepharophim blepharop hypopl teeth		Other
Pyu2.00	[X]Congenital malformations of the circulatory system		Other
Pyu2B00	[X]Oth specified cong malform of peripheral vascular system		Other
Pyu2D00	[X]Other malformations of cerebral vessels		Other
Pyu2E00	[X]Other specified cong malformations of circulatory system		Other
Pyu2K00	[X]Congenital malformation of circulatory system, unspecif		Other



Read Code	Read term	Minor malformation?	Subgroup
PB6yw11	Liver hamartoma		Other
PKz0.00	Anomalies of umbilicus		Other
pd73.00	Persistent umbilical sinus		Other
14H..00	H/O: congenital anomaly		Other
14HZ.00	H/O: congenital anomaly NOS		Other
P....00	Congenital anomalies		Other
PE8..00	Other specified nonteratogenic anomalies		Other
PE8y.00	Other nonteratogenic anomalies OS		Other
PE8yz00	Other nonteratogenic anomaly NOS		Other
PE8z.00	Nonteratogenic anomalies NOS		Other
PK...00	Other and unspecified congenital anomalies		Other
PK7..00	Multiple congenital anomalies NOS		Other
PK7z.00	Multiple congenital anomalies NOS		Other
PKy0.00	Multiple system congenital anomalies NEC		Other
PKyz.00	Other specified anomalies NOS		Other
PKz..00	Other anomalies NOS		Other
Py...00	Other specified congenital anomaly		Other
Pyu..00	[X]Additional congenital disease classification terms		Other
Pyu9.00	[X]Other congenital malformations		Other
ZV13600	[V]Personal history of congenital malformations		Other
P82..00	Congenital web of larynx		Other
P820.00	Congenital web of larynx, unspecified		Other
P821.00	Congenital glottic web of larynx		Other
P822.00	Congenital subglottic web of larynx		Other
P82z.00	Congenital web of larynx nos		Other
P831000	Anomaly of cricoid cartilage		Other
P831100	Anomaly of epiglottis		Other
P831200	Anomaly of thyroid cartilage		Other
P831500	Laryngeal hypoplasia		Other
P832000	Atresia of epiglottis		Other
P832100	Atresia of glottis		Other
P833000	Congenital stenosis of larynx		Other
P833300	Congenital subglottic stenosis		Other
P833400	Congenital supraglottic stenosis		Other
P83y300	Congenital laryngocele		Other
P83y600	Congenital fissure of epiglottis		Other
P83y700	Congenital cleft of posterior cricoid cartilage		Other
P83yX00	Congenital malformation of larynx, unspecified		Other
P83yw00	Other anomaly of larynx		Other
7LON100	Cranio-orbital remodelling for trigonocephaly		Other
J34..12	Parasternal hernia		Other
J34..13	Retrosternal hernia		Other
PG0..12	Skull and face bone anomalies		Other
PG00.00	Congenital absence of skull bones		Other
PG01.00	Acrocephaly		Other
PG02.00	Congenital forehead deformity		Other
PG03.00	Craniosynostosis		Other
PG03.11	Scaphocephaly		Other
PG03100	Lambdoid synostosis		Other
PG06.00	Imperfect fusion of skull		Other
PG07.00	Oxycephaly		Other
PG08.00	Platybasia		Other

Read Code	Read term	Minor malformation?	Subgroup
PG09.00	Premature cranial suture closure		Other
PG0B.00	Trigonocephaly		Other
PG0G.00	Localised skull defects		Other
PG0G.11	Craniolacunia		Other
PG0G.12	Lacunar skull		Other
PG0y.00	Other specified skull or face bone anomaly		Other
PG0y.11	Defect of skull ossification		Other
PG0yz00	Other anomaly of skull or face bone nos		Other
PG0z.00	Skull or face bone anomaly nos		Other
PG13000	Congenital absence of cervical vertebra		Other
PG1u.00	Congenital anomalies of cervical vertebrae nec		Other
PG1uz00	Congenital anomaly of cervical vertebrae nec nos		Other
PG3..00	Other rib and sternum anomalies		Other
PG31.00	Congenital absence of sternum		Other
PG32.00	Congenital fissure of sternum		Other
PG35.00	Mis-shapen ribs		Other
PG3x.00	Other congenital anomalies of ribs		Other
PG3y.00	Other congenital anomalies of sternum		Other
PG3z.00	Other rib or sternum anomaly nos		Other
PG3z.11	Anomalies of thoracic cage unspecified		Other
PG42.00	Multiple enchondromata		Other
PG42.11	Enchondromatosis		Other
PG42.12	Ollier's disease		Other
PG42.18	Dyschondroplasia		Other
PG42000	Multiple enchondromata with haemangioma		Other
PG42011	Kast's syndrome		Other
PG42012	Maffuci's syndrome		Other
PG42z00	Dyschondroplasia nos		Other
PG49.00	Dysplasia epiphysealis hemimelica		Other
PG5..00	Osteodysplasia		Other
PG5..11	Osteodystrophy		Other
PG50.00	Osteodysplasia, unspecified		Other
PG54.00	Polyostotic fibrous dysplasia		Other
PG5y.00	Other specified osteodysplasia		Other
PG5y000	Albright-sternberg syndrome		Other
PG5y011	Albright-mccune-sternberg syndrome		Other
PG5y012	Albright's polyostotic dysplasia		Other
PG5yz00	Other osteodysplasia nos		Other
PG5z.00	Osteodysplasia nos		Other
PG5z.11	Osteochondrodysplasia		Other
PG6..00	Anomalies of diaphragm		Other
PG61.11	Congenital defect of diaphragmatic nec		Other
PG62.00	Congenital foramen morgagni hernia		Other
PG63.00	Eventration of diaphragm		Other
PG6y.00	Other specified anomalies of diaphragm		Other
PG6z.00	Diaphragm anomalies nos		Other
PGX..00	Congenital malformation of bony thorax, unspecified		Other
PGy..00	Other specified muscle, tendon and fascia anomaly		Other
PGy0.00	Congenital absence of muscle and tendon		Other
PGy0000	Absent tendon		Other
PGy0200	Other absent muscle		Other
PGy0211	Muscle agenesis		Other

Read Code	Read term	Minor malformation?	Subgroup
PGy0212	Orbinsky syndrome		Other
PGy0z00	Absent muscle or tendon nos		Other
PGy1.00	Accessory muscle		Other
PGyy.00	Other specified other anomalies of muscle, tendon and fascia		Other
PGyy.11	Ayala's disease		Other
PGyy000	Amyotrophica congenital		Other
PGyy200	Hypoplasia of muscle		Other
PGyy400	Aplasia of muscle		Other
PGyyz00	Other anomaly of tendon, fascia or muscle nos		Other
PGyz.00	Other muscle, tendon or fascia anomalies nos		Other
Pyu8D00	[X]other specified congenit malformation skull & face bones		Other
n384000	Dysplastic spondylolisthesis		Other
pe23.00	Congenital scoliosis due to congenital bony malformation		Other
pe8yb00	Discoïd meniscus – congenital		Other
pez..00	Congenital musculoskeletal deformity nos		Other
pf59400	Poland's syndrome		Other
pg11.00	Congenital lumbosacral spondylolysis		Other
pg12.00	Congenital spondylolisthesis		Other
pg13.00	Congenital absence of vertebra		Other
pg13200	Congenital absence of lumbar vertebra		Other
pg13300	Congenital absence of sacrum		Other
pg13311	Sacral agenesis		Other
pg14.00	Hemivertebra		Other
pg14000	Cervical hemivertebra		Other
pg14100	Thoracic hemivertebra		Other
pg14200	Lumbar hemivertebra		Other
pg14800	Lumbar hemivertebra - unbalanced		Other
pg14z00	Hemivertebra nos		Other
pg15.00	Congenital fusion of spine		Other
pg15.11	Congenital lumbosacral fusion		Other
pg15000	Congenital complete fusion of spine		Other
pg15100	Congenital partial fusion of spine - balanced		Other
pg15200	Congenital partial fusion of spine - unbalanced		Other
pg16000	Wilderwanck's syndrome		Other
pg18.00	Congenital kyphosis		Other
pg18.11	Congenital kyphoscoliosis		Other
pg1u000	Supernumerary cervical vertebra		Other
pg1v.00	Congenital anomalies of thoracic vertebrae nec		Other
pg1vz00	Congenital anomaly of thoracic vertebrae nec nos		Other
pg1w.00	Congenital anomalies of lumbar vertebrae nec		Other
pg1w000	Supernumerary lumbar vertebra		Other
pg1wz00	Congenital anomaly of lumbar vertebra nec nos		Other
pg1x.00	Congenital sacrococcygeal anomalies nec		Other
pg1x000	Congenital absence of coccyx		Other
pg1x100	Congenital absence of sacrum		Other
pg1xz00	Congenital sacrococcygeal anomaly nos		Other
pg1y.11	Congenital deformity of lumbosacral joint		Other
pg1y.12	Congenital deformity of lumbosacral region		Other
pg1y000	Platyspondylia		Other
pg1y100	Supernumerary vertebra		Other
pg1y300	Defect of vertebral segmentation		Other
pg1y400	Hypoplasia of spine		Other

Read Code	Read term	Minor malformation?	Subgroup
pgw..00	Osteochondrodyspl with defct growth tub bone spine unspec		Other
pgy0100	Poland's syndrome		Other
pgyy100	Congenital shortening of tendon		Other
pgz..00	Congenital musculoskeletal anomalies nos		Other
pgz..11	Congenital deformity of musculoskeletal system nec		Other
pgz0.00	Unspecified anomaly of muscle		Other
pgz1.00	Unspecified anomaly of tendon		Other
pgz2.00	Unspecified anomaly of bones		Other
pgz3.00	Unspecified anomaly of cartilage		Other
pgz4.00	Unspecified anomaly of connective tissue		Other
pyu8f00	[X]other congenital malformations of ribs		Other
pyu8p00	[X]congenital malformation of bony thorax, unspecified		Other
Pyu3000	[X]Other congenital malformations of nose		Other
p81..00	Other anomalies of nose		Other
p810.00	Congenital nose deformity, unspecified		Other
p811.00	Absent nose		Other
p811000	Agenesis of nose		Other
p812.00	Accessory nose		Other
p813.00	Congenital cleft nose		Other
p816.00	Congenital perforation of the nasal sinus wall		Other
p817.00	Perforated nasal septum		Other
p818.00	Congenital fissure of nose		Other
p819.00	Congenital hypoplastic nose		Other
p81z.00	Other anomalies of nose nos		Other
p81z.11	Single nostril		Other
7525.00	Correction of deformity of palate		Other
7525.11	Repair of deformity of palate		Other
7525712	Plastic repair palate mucosal graft		Other
7525y00	Other specified correction of deformity of palate		Other
7525z00	Correction of deformity of palate NOS		Other
PA24.11	Congenital pits of lip		Other
PA27100	Congenital pharyngeal polyp		Other
PA2A000	Congenital ectropion of lip		Other
7131900	Excision of accessory breast tissue		Other
PH...00	Congenital integument anomalies		Other
PH...11	Congenital skin anomalies		Other
PH00.00	Congenital lymphoedema		Other
PH3..00	Other specified skin anomalies		Other
PH31.00	Vascular hamartomas		Other
PH31z00	Vascular hamartoma nos		Other
PH32000	Congenital poikiloderma		Other
PH32100	Urticaria pigmentosa		Other
PH32111	Mast cell disease		Other
PH32112	Mastocytosis		Other
PH32z00	Congenital pigmentary skin anomaly nos		Other
PH33.00	Specified syndromes NEC involving skin anomalies		Other
PH33200	Mibelli's disease		Other
PH33z00	Specified syndromes involving skin anomalies NEC NOS		Other
PH3y100	Congenital scar		Other
PH3y213	Bullous eruption of hand		Other
PH3yz11	Lichen spinulosus		Other
PH4..00	Specified hair anomalies		Other

Read Code	Read term	Minor malformation?	Subgroup
PH40.00	Congenital alopecia		Other
PH40.11	Congenital atrichosis		Other
PH40000	Congenital alopecia, unspecified		Other
PH40100	Congenital localised alopecia		Other
PH40200	Congenital generalised alopecia		Other
PH40211	Atrichosis		Other
PH40z00	Congenital alopecia nos		Other
PH42.00	Congenital hypertrichosis		Other
PH43.11	Hypertrichosis lanuginose		Other
PH44.00	Twisted hair		Other
PH44.11	Pili torti		Other
PH5..00	Specified anomalies of nails		Other
PH50.00	Anonychia		Other
PH50.11	Congenital absence of nails		Other
PH51.00	Congenital clubnail		Other
PH52.00	Congenital koilonychias		Other
PH54.00	Congenital onychauxis		Other
PH55.00	Congenital pachyonychia		Other
PH55.11	Hypertrophic nails		Other
PH5z.00	Specified nail anomalies nos		Other
PH6..00	Specified anomalies of breast		Other
PH60.00	Absent breast		Other
PH61.00	Absent nipple		Other
PH62.00	Accessory breast		Other
PH64.00	Supernumerary breast		Other
PH66.00	Hypoplasia of breast		Other
PH67.00	Small nipple		Other
PH67.11	Hypoplasia of nipple		Other
PH68.00	Ectopic breast tissue		Other
PH6X.00	Congenital malformation of breast, unspecified		Other
PH6z.00	Specified breast anomalies nos		Other
PH7..00	Cutis marmorata telangiectasia congenita		Other
PHy..00	Other specified integument anomaly		Other
PHz..00	Integument anomalies nos		Other
PHz1.00	Unspecified congenital anomalies of hair		Other
PHz2.00	Unspecified congenital anomalies of nail		Other
PHz2.11	Congenital deformity of nail		Other
PK0..00	Anomalies of spleen		Other
PK00.00	Aberrant spleen		Other
PK01.00	Absent spleen		Other
PK01.11	Asplenia		Other
PK02.00	Accessory spleen		Other
PK03.00	Congenital splenomegaly		Other
PK03.11	Hyperplasia of spleen		Other
PK04.00	Ectopic spleen		Other
PK06.00	Hypoplasia of spleen		Other
PK07.00	Mis-shapen spleen		Other
PK0y.00	Other specified anomalies of spleen		Other
PK0z.00	Anomalies of spleen nos		Other
PK1..00	Anomalies of adrenal gland		Other
PK10.00	Aberrant adrenal gland		Other
PK11.00	Absent adrenal gland		Other

Read Code	Read term	Minor malformation?	Subgroup
PK12.00	Accessory adrenal gland		Other
PK13.00	Hypoplasia of adrenal gland		Other
PK14.00	Ectopic adrenal gland		Other
PK15.00	Aplasia of adrenal gland		Other
PK1y.00	Other specified anomalies of adrenal gland		Other
PK1y000	Congenital cyst of adrenal gland		Other
PK1yz00	Other congenital anomaly of adrenal gland nos		Other
PK1z.00	Anomalies of adrenal gland nos		Other
PK2..00	Other endocrine gland anomalies		Other
PK20.00	Absent parathyroid gland		Other
PK21.00	Accessory thyroid gland		Other
PK22.00	Persistent thyroglossal duct		Other
PK23.00	Thyroglossal duct cyst		Other
PK24.00	Anomalies of pituitary gland		Other
PK24000	Aberrant pituitary gland		Other
PK24100	Congenital absence of pituitary gland		Other
PK24z00	Anomaly of pituitary gland nos		Other
PK25.00	Anomalies of thyroid gland nec		Other
PK25000	Aberrant thyroid gland		Other
PK25011	Retrosternal thyroid gland		Other
PK25100	Congenital absence of thyroid gland		Other
PK25z00	Anomaly of thyroid gland nec nos		Other
PK26.00	Anomalies of thyroglossal duct nec		Other
PK27.00	Anomalies of parathyroid gland nec		Other
PK27z00	Anomaly of parathyroid gland nec nos		Other
PK28.00	Anomalies of thymus		Other
PK28000	Aberrant thymus gland		Other
PK28100	Congenital absence of thymus		Other
PK28z00	Anomaly of thymus gland nos		Other
PK2y.00	Other specified endocrine gland anomaly		Other
PK2z.00	Endocrine gland anomaly nos		Other
PK3..00	Situs inversus		Other
PK30.00	Situs inversus, unspecified		Other
PK30.11	Transposition of viscera unspecified		Other
PK31.00	Situs inversus abdominalis		Other
PK31.11	Transposition of abdominal viscera		Other
PK32.00	Situs inversus thoracis		Other
PK33.00	Complete situs inversus with dextrocardia		Other
PK34.00	Situs inversus with levocardia		Other
PK3z.00	Situs inversus nos		Other
PK4..00	Conjoined twins		Other
PK40.00	Craniopagus		Other
PK40100	Craniopagus occipitalis		Other
PK40300	Craniopagus parasiticus		Other
PK42.11	Buttock-joined twins		Other
PK44.00	Xiphopagus		Other
PK44.11	Xiphoid- and pelvis-joined twins		Other
PK45.00	Di axial (double) monster		Other
PK4z.00	Conjoined twins nos		Other
PK6..00	Other hamartoses nec		Other
PK61.00	Sturge-weber syndrome		Other
PK61.11	Kalischer's disease		Other

Read Code	Read term	Minor malformation?	Subgroup
PK61.12	Encephalocutaneous angiomatosis		Other
PK64.00	Proteus syndrome		Other
PK6y.00	Other specified hamartoses nec		Other
PK6z.00	Hamartoses nos		Other
PK70.00	Monster NOS		Other
PKy..00	Other specified anomalies		Other
PKy0400	Marshall-Smith syndrome		Other
PKy3.00	Single monster, specified type		Other
PKy7700	Caudal dysplasia sequence		Other
PKyH.00	Moulded baby syndrome		Other
PKyz.12	Local gigantism NEC		Other
PKyz100	Acardia		Other
PKyz600	Congenital hemihypertrophy		Other
PKzz.00	Congenital anomaly nos		Other
Pyu9200	[X]other specified congenital malformations of skin		Other
Pyu9300	[X]other congenital malformations of breast		Other
Pyu9B00	[X]other specified congenital malformations		Other
Pyu9C00	[X]congenital malformation of breast, unspecified		Other
Pz...00	Congenital anomaly nos		Other
PB5z.12	Short bowel syndrome		Other
p110.11	Split notochord syndrome		Other
P7yz100	Congenital chylothorax		Other
PB58.12	Anal and urogenital canal fusion		Other
P831400	Tracheomalacia	Yes	Respiratory
P86y100	Azygos lobe of lung	Yes	Respiratory
P86y200	Accessory lobe of lung	Yes	Respiratory
7406200	Correction of congenital atresia of choana		Respiratory
7448100	Excision of cyst of bronchus		Respiratory
P8...00	Respiratory system congenital anomalies		Respiratory
P80..00	Choanal atresia		Respiratory
P800.00	Choanal atresia, unspecified		Respiratory
P802.00	Atresia of the posterior nares		Respiratory
P803.00	Congenital stenosis of the anterior nares		Respiratory
P804.00	Congenital stenosis of the posterior nares		Respiratory
P80z.00	Choanal atresia nos		Respiratory
P83..00	Other anomalies of larynx, trachea and bronchus		Respiratory
P830200	Agenesis of trachea		Respiratory
P831.00	Anomaly of laryngeal and tracheal cartilage		Respiratory
P831300	Anomaly of tracheal cartilage		Respiratory
P831z00	Anomaly of laryngeal or tracheal cartilage nos		Respiratory
P832.00	Atresia of larynx and trachea		Respiratory
P832300	Atresia of trachea		Respiratory
P833.00	Congenital stenosis of larynx, trachea and bronchus		Respiratory
P833100	Congenital stenosis of trachea		Respiratory
P833200	Congenital stenosis of bronchus		Respiratory
P83y.00	Other anomaly of larynx, trachea and bronchus		Respiratory
P83y100	Congenital dilatation of trachea		Respiratory
P83y500	Congenital diverticulum of trachea		Respiratory
P83y800	Rudimentary tracheal bronchus		Respiratory
P83yB00	Congenital bronchomalacia		Respiratory
P83yx00	Other anomaly of trachea		Respiratory
P83yy00	Other anomaly of bronchus		Respiratory

Read Code	Read term	Minor malformation?	Subgroup
P83yz00	Other anomaly of larynx, trachea or bronchus nos		Respiratory
P83z.00	Other anomalies of larynx, trachea or bronchus nos		Respiratory
P84..00	Congenital cystic lung		Respiratory
P840.00	Congenital cystic lung disease, unspecified		Respiratory
P841.00	Congenital polycystic lung		Respiratory
P841.11	Multiple lung cysts		Respiratory
P841.12	Multiple congenital bronchogenic cysts		Respiratory
P842.00	Congenital honeycomb lung		Respiratory
P843.00	Single lung cyst		Respiratory
P843.11	Lung cyst		Respiratory
P843.12	Congenital bronchogenic cyst		Respiratory
P844.00	Congenital cystic adenomatoid malformation of the lung		Respiratory
P84y.00	Other specified congenital cystic lung		Respiratory
P84z.00	Congenital cystic lung nos		Respiratory
P85..00	Lung agenesis, hypoplasia and dysplasia		Respiratory
P850.00	Aplasia of lung		Respiratory
P851.00	Hypoplasia of lung		Respiratory
P852.00	Sequestration of lung		Respiratory
P853.00	Agenesis of lung		Respiratory
P853.11	Congenital absence of lung		Respiratory
P853000	Congenital absence of lung fissures		Respiratory
P853100	Congenital absence of lobe of lung		Respiratory
P853z00	Agenesis of lung nos		Respiratory
P85y.00	Other specified lung agenesis, hypoplasia or dysplasia		Respiratory
P85y000	Fusion of lobes of lung		Respiratory
P85yz00	Other lung agenesis, hypoplasia or dysplasia nos		Respiratory
P85z.00	Lung agenesis, hypoplasia or dysplasia nos		Respiratory
P86..00	Other lung anomalies		Respiratory
P860.00	Anomaly of lung, unspecified		Respiratory
P861.00	Congenital bronchiectasis		Respiratory
P86y.00	Other lung anomaly		Respiratory
P86yz00	Other lung anomaly nos		Respiratory
P86z.00	Lung anomaly nos		Respiratory
P8y..00	Other specified respiratory system anomalies		Respiratory
P8y1.00	Anomaly, pleural folds		Respiratory
P8y2.00	Atresia of nasopharynx		Respiratory
P8y3.00	Congenital cyst of mediastinum		Respiratory
P8y4.00	Congenital pulmonary lymphangiectasis		Respiratory
P8yz.00	Other specified respiratory system anomaly nos		Respiratory
P8z..00	Respiratory system anomaly nos		Respiratory
Pyu3.00	[X]congenital malformations of the respiratory system		Respiratory
Pyu3300	[X]other congenital malformations of bronchus		Respiratory
Pyu3400	[X]other congenital malformations of lung		Respiratory
Pyu3500	[X]other specified congen malformation respiratory system		Respiratory
pd10.00	Congenital renal cyst, single	Yes	Urinary
pd37.00	Giant kidney	Yes	Urinary
pd47.00	Congenital vesico-uretero-renal reflux	Yes	Urinary
14h4.00	H/o: urinary anomaly		Urinary
7B41200	Closure of urethral fistula		Urinary
7B41211	Excision of urethral fistula		Urinary
7b01300	Heminephrectomy for horseshoe kidney		Urinary
7b01311	Excision of half of horseshoe kidney		Urinary



Read Code	Read term	Minor malformation?	Subgroup
7b02000	Heminephrectomy for duplex kidney		Urinary
7b02100	Division of isthmus of horseshoe kidney		Urinary
7b10400	Excision of duplex ureter		Urinary
7b12.00	Reimplantation of ureter		Urinary
7b12000	Unspecified bilateral reimplantation of ureter		Urinary
7b12100	Unspecified unilateral reimplantation of ureter		Urinary
7b12500	Extravesical bilateral reimplantation of ureters		Urinary
7b12511	Leadbetter bilateral reimplantation of ureters		Urinary
7b12512	Politano bilateral reimplantation of ureters		Urinary
7b12611	Cohen unilateral reimplantation of ureter		Urinary
7b12800	Extravesical unilateral reimplantation of ureter		Urinary
7b12811	Leadbetter unilateral reimplantation of ureter		Urinary
7b12812	Politano unilateral reimplantation of ureter		Urinary
7b12y00	Other specified reimplantation of ureter		Urinary
7b12z00	Reimplantation of ureter nos		Urinary
7b16000	Open excision of ureterocele		Urinary
7b17400	Percut nephroscopic balloon dilatation of ureter		Urinary
7b17411	Percut antegrade balloon dilatation of ureter		Urinary
7b18500	Ureteroscopic endoluminal balloon rupture of stenosis ureter		Urinary
7b1a300	Endoscopic dilatation of ureter		Urinary
7b1d300	Endoscopic incision of ureterocele		Urinary
7b1d400	Endoscopic dilatation of ureteric orifice		Urinary
7b1d600	Endoscopic incision of ureterocele		Urinary
7b23400	Closure of exstrophy of bladder		Urinary
7b41100	Epispadias repair		Urinary
7b41112	Denis-browne epispadias repair		Urinary
7b41113	Young-dees epispadias repair		Urinary
7b43500	Endoscopic destruction of posterior urethral valve		Urinary
7b43a00	Endoscopic destruction of urethral valves		Urinary
7b45600	Hook ablation of posterior urethral valve		Urinary
PD8..00	Congenital abnormality of the kidney		Urinary
PD80.00	Duplex kidney		Urinary
PE02.00	Potter's facies		Urinary
PG72.00	Prune belly syndrome		Urinary
PKyA.00	Cloacal exstrophy		Urinary
Pyu7200	[X]Other congenital malformations of ureter		Urinary
k09..00	Small kidney of unknown cause		Urinary
k090.00	Unilateral small kidney		Urinary
k090100	Unilateral small kidney with contralateral hypertrophy		Urinary
k091.00	Bilateral small kidneys		Urinary
k09z.00	Small kidneys unspecified		Urinary
k11..00	Hydronephrosis		Urinary
k111.00	Hydroureteronephrosis		Urinary
k113.00	Hydronephrosis with ureteropelvic junction obstruction		Urinary
k113.11	Hydronephrosis with pelviureteric junction obstruction		Urinary
k11x.00	Hydronephrosis with ureteral stricture nec		Urinary
k11z.00	Hydronephrosis nos		Urinary
k133.00	Stricture of ureter		Urinary
k133100	Stricture of pelviureteric junction		Urinary
k133z00	Stricture of ureter nos		Urinary
k13b.00	Calyceal diverticulum		Urinary
k140000	Calculus in diverticulum of bladder		Urinary

Read Code	Read term	Minor malformation?	Subgroup
k163.00	Diverticulum of bladder		Urinary
k191100	Urethrorectal fistula		Urinary
kyu1100	[X]other and unspecified hydronephrosis		Urinary
kyu1f00	[X]hydronephrosis with ureteral stricture nec		Urinary
pc61.00	Epispadias		Urinary
pd...00	Urinary system congenital anomalies		Urinary
pd0..00	Renal agenesis and dysgenesis		Urinary
pd00.00	Renal agenesis, unspecified		Urinary
pd00000	Bilateral renal agenesis		Urinary
pd00100	Unilateral renal agenesis		Urinary
pd00z00	Renal agenesis, unspecified nos		Urinary
pd01.00	Congenital renal atrophy		Urinary
pd02.00	Congenital absence of kidney		Urinary
pd02000	Bilateral congenital absence of kidneys		Urinary
pd02100	Unilateral congenital absence of kidney		Urinary
pd02z00	Congenital absence of kidney nos		Urinary
pd03.00	Hypoplasia of kidney		Urinary
pd03000	Bilateral renal hypoplasia		Urinary
pd03011	Potter's syndrome		Urinary
pd03100	Unilateral renal hypoplasia		Urinary
pd04.00	Dysplasia of kidney		Urinary
pd04000	Bilateral renal dysplasia		Urinary
pd04011	Bilateral renal dysgenesis		Urinary
pd04100	Unilateral renal dysplasia		Urinary
pd04111	Unilateral renal dysgenesis		Urinary
pd04200	Renal dysplasia and retinal aplasia		Urinary
pd04z00	Dysplasia of kidney nos		Urinary
pd0z.00	Renal agenesis or dysgenesis nos		Urinary
pd1..00	Congenital cystic kidney disease		Urinary
pd1..11	Congenital cystic renal disease		Urinary
pd13.00	Multicystic renal dysplasia		Urinary
pd1y.00	Other specified congenital cystic kidney disease		Urinary
pd1yz00	Other congenital cystic kidney disease nos		Urinary
pd1z.00	Congenital cystic kidney disease nos		Urinary
pd2..00	Renal pelvis and ureter obstructive defects		Urinary
pd20.00	Atresia of ureter		Urinary
pd21.00	Occlusion of ureter		Urinary
pd21.11	Congenital ureteric valves		Urinary
pd22.00	Congenital stricture of ureter		Urinary
pd22.11	Congenital stenosis of ureter		Urinary
pd22000	Congenital stricture of ureter, unspecified		Urinary
pd22100	Congenital stricture of ureteropelvic junction		Urinary
pd22200	Congenital stricture of ureterovesical orifice		Urinary
pd22z00	Congenital stricture of ureter nos		Urinary
pd23.00	Congenital hydronephrosis		Urinary
pd23.11	Congenital dilated renal pelvis		Urinary
pd24.00	Congenital dilatation of ureter		Urinary
pd25.00	Hydroureter – congenital		Urinary
pd26.00	Megaloureter – congenital		Urinary
pd27.00	Ureterocele – congenital		Urinary
pd2y.00	Other specified obstructive defect of renal pelvis or ureter		Urinary
pd2z.00	Obstructive defect of renal pelvis or ureter nos		Urinary

Read Code	Read term	Minor malformation?	Subgroup
pd3..00	Other specified renal anomaly		Urinary
pd30.00	Accessory kidney		Urinary
pd30.11	Duplication of kidney		Urinary
pd30.12	Renal duplication nec		Urinary
pd30.13	Supernumerary kidney		Urinary
pd31.00	Congenital calculus of kidney		Urinary
pd32.00	Congenital displaced kidney		Urinary
pd33.00	Discoid kidney		Urinary
pd34.00	Double kidney with double pelvis		Urinary
pd34.11	Duplex kidneys		Urinary
pd34.12	Pyelon duplex		Urinary
pd35.00	Ectopic kidney		Urinary
pd35.11	Pelvic kidney		Urinary
pd36.00	Fusion of kidneys		Urinary
pd38.00	Horseshoe kidney		Urinary
pd39.00	Hyperplasia of kidney		Urinary
pd3a.00	Lobulation of kidney		Urinary
pd3b.00	Malrotation of kidney		Urinary
pd3c.00	Triple kidney with triple pelvis		Urinary
pd3c.12	Pyelon triplex		Urinary
pd3d.00	Enlarged kidney		Urinary
pd3e.00	Cake kidney		Urinary
pd3f.00	Bifid kidney		Urinary
pd3z.00	Other specified renal anomaly nos		Urinary
pd4..00	Other specified ureter anomalies		Urinary
pd40.00	Absent ureter		Urinary
pd41.00	Accessory ureter		Urinary
pd42.00	Deviation of ureter		Urinary
pd43.00	Displaced ureteric orifice		Urinary
pd44.00	Double ureter		Urinary
pd44.11	Duplication of ureter		Urinary
pd45.00	Ectopic ureter		Urinary
pd45.12	Ectopic insertion of ureter		Urinary
pd46.00	Anomalous ureter implantation		Urinary
pd4z.00	Other specified ureter anomaly nos		Urinary
pd5..00	Exstrophy of urinary bladder		Urinary
pd5..11	Ectopia vesicae		Urinary
pd5..12	Ectopic bladder		Urinary
pd50.00	Ectopic bladder		Urinary
pd50.11	Ectopia vesicae		Urinary
pd5z.00	Exstrophy of urinary bladder nos		Urinary
pd6..00	Urethra and bladder neck atresia and stenosis		Urinary
pd60.00	Congenital bladder neck obstruction		Urinary
pd60000	Atresia of bladder neck		Urinary
pd60100	Stenosis of bladder neck		Urinary
pd60z00	Congenital bladder neck obstruction nos		Urinary
pd61.00	Congenital obstruction of urethra		Urinary
pd61000	Atresia of anterior urethra		Urinary
pd61100	Stenosis of anterior urethra		Urinary
pd61z00	Congenital obstruction of urethra nos		Urinary
pd62.00	Congenital urethral valvular stricture		Urinary
pd62.11	Congenital posterior urethral valves		Urinary

Read Code	Read term	Minor malformation?	Subgroup
pd63.00	Congenital urinary meatus stricture		Urinary
pd63.11	Congenital urinary meatus obstruction		Urinary
pd63.12	Congenital pinhole urinary meatus		Urinary
pd63100	Stenosis of urinary meatus		Urinary
pd63z00	Congenital urinary meatus stricture nos		Urinary
pd64.00	Congenital vesicourethral orifice stricture		Urinary
pd65.00	Imperforate urinary meatus		Urinary
pd66.00	Impervious urethra		Urinary
pd67.00	Congenital posterior urethral valves		Urinary
pd6y.00	Other specified urethra or bladder neck atresia or stenosis		Urinary
pd6z.00	Urethra or bladder neck atresia or stenosis nos		Urinary
pd7..00	Anomalies of urachus		Urinary
pd70.00	Cyst of urachus		Urinary
pd71.00	Fistula of urachus		Urinary
pd72.00	Patent urachus		Urinary
pd72.11	Persistent urachus		Urinary
pd7y.00	Other specified anomalies of urachus		Urinary
pd7z.00	Anomalies of urachus nos		Urinary
pdy..00	Other specified bladder and urethral anomalies		Urinary
pdy0.00	Congenital absence of bladder		Urinary
pdy2.00	Accessory bladder		Urinary
pdy3.00	Accessory urethra		Urinary
pdy4.00	Congenital bladder diverticulum		Urinary
pdy5.00	Congenital bladder hernia		Urinary
pdy6.00	Congenital urethrorectal fistula		Urinary
pdy7.00	Congenital prolapse of bladder mucosa		Urinary
pdy8.00	Congenital prolapse of urethra		Urinary
pdy9.00	Double urethra		Urinary
pdya.00	Double urinary meatus		Urinary
pdyz.00	Other bladder or urethral anomaly nos		Urinary
pdyz000	Epispadias, female		Urinary
pdz..00	Urinary system anomalies nos		Urinary
pdz0.00	Unspecified anomaly of kidney		Urinary
pdz1.00	Unspecified anomaly of ureter		Urinary
pdz2.00	Unspecified anomaly of bladder		Urinary
pdz3.00	Unspecified anomaly of urethra		Urinary
pky5e00	Branchio-otorenal dysplasia		Urinary
pyu7.00	[X]congenital malformations of the urinary system		Urinary
pyu7000	[X]other cystic kidney diseases		Urinary
pyu7100	[X]other obstructive defects of renal pelvis and ureter		Urinary
pyu7300	[X]other specified congenital malformations of kidney		Urinary
pyu7500	[X]other congenital malformations of bladder and urethra		Urinary

## ICD-10 codes

ICD-10 Code	Description	Minor malformation?	Subgroup
Q79.2	Exomphalos		Abdominal Wall
Q79.3	Gastroschisis		Abdominal Wall
Q79.5	Other congenital malformations of abdominal wall		Abdominal Wall
Q25.0	Patent ductus arteriosus	If gest. age <37 weeks	Heart
Q25.6	Stenosis of pulmonary artery	If gest. age <37 weeks	Heart
Q26.1	Persistent left superior vena cava	Yes	Heart
Q20	Congenital malformations of cardiac chambers and connections		Heart
Q20.0	Common arterial trunk		Heart
Q20.1	Double outlet right ventricle		Heart
Q20.2	Double outlet left ventricle		Heart
Q20.3	Discordant ventriculoarterial connection		Heart
Q20.4	Double inlet ventricle		Heart
Q20.5	Discordant atrioventricular connection		Heart
Q20.6	Isomerism of atrial appendages		Heart
Q20.8	Other cong malforms of cardiac chambers and connections		Heart
Q20.9	Cong malforms of cardiac chambers and connections unspec		Heart
Q21	Congenital malformations of cardiac septa		Heart
Q21.0	Ventricular septal defect		Heart
Q21.1	Atrial septal defect		Heart
Q21.2	Atrioventricular septal defect		Heart
Q21.3	Tetralogy of Fallot		Heart
Q21.4	Aortopulmonary septal defect		Heart
Q21.8	Other congenital malformations of cardiac septa		Heart
Q21.9	Congenital malformation of cardiac septum, unspecified		Heart
Q22	Congenital malformations of pulmonary and tricuspid valves		Heart
Q22.0	Pulmonary valve atresia		Heart
Q22.1	Congenital pulmonary valve stenosis		Heart
Q22.2	Congenital pulmonary valve insufficiency		Heart
Q22.3	Other congenital malformations of pulmonary valve		Heart
Q22.4	Congenital tricuspid stenosis		Heart
Q22.5	Ebstein's anomaly		Heart
Q22.6	Hypoplastic right heart syndrome		Heart
Q22.8	Other congenital malformations of tricuspid valve		Heart
Q22.9	Congenital malformation of tricuspid valve, unspecified		Heart
Q23	Congenital malformations of aortic and mitral valves		Heart
Q23.0	Congenital stenosis of aortic valve		Heart
Q23.1	Congenital insufficiency of aortic valve		Heart
Q23.2	Congenital mitral stenosis		Heart
Q23.3	Congenital mitral insufficiency		Heart
Q23.4	Hypoplastic left heart syndrome		Heart
Q23.8	Other congenital malformations of aortic and mitral valves		Heart
Q23.9	Congenital malformation of aortic and mitral valves unspec		Heart
Q24	Other congenital malformations of heart		Heart
Q24.0	Dextrocardia		Heart
Q24.1	Laevocardia		Heart
Q24.2	Cor triatriatum		Heart
Q24.3	Pulmonary infundibular stenosis		Heart
Q24.4	Congenital subaortic stenosis		Heart
Q24.5	Malformation of coronary vessels		Heart
Q24.6	Congenital heart block		Heart

ICD-10 Code	Description	Minor malformation?	Subgroup
Q24.8	Other specified congenital malformations of heart		Heart
Q24.9	Congenital malformation of heart, unspecified		Heart
Q25	Congenital malformations of great arteries		Heart
Q25.1	Coarctation of aorta		Heart
Q25.2	Atresia of aorta		Heart
Q25.3	Stenosis of aorta		Heart
Q25.4	Other congenital malformations of aorta		Heart
Q25.5	Atresia of pulmonary artery		Heart
Q25.7	Other congenital malformations of pulmonary artery		Heart
Q25.8	Other congenital malformations of great arteries		Heart
Q25.9	Congenital malformation of great arteries, unspecified		Heart
Q26	Congenital malformations of great veins		Heart
Q26.0	Congenital stenosis of vena cava		Heart
Q26.2	Total anomalous pulmonary venous connection		Heart
Q26.3	Partial anomalous pulmonary venous connection		Heart
Q26.4	Anomalous pulmonary venous connection, unspecified		Heart
Q26.5	Anomalous portal venous connection		Heart
Q26.6	Portal vein-hepatic artery fistula		Heart
Q26.8	Other congenital malformations of great veins		Heart
Q26.9	Congenital malformation of great vein, unspecified		Heart
Q38.1	Ankyloglossia	Yes	Digestive
Q38.2	Macroglossia	Yes	Digestive
Q40.0	Congenital hypertrophic pyloric stenosis	Yes	Digestive
Q40.1	Congenital hiatus hernia	Yes	Digestive
Q43.0	Meckel's diverticulum	Yes	Digestive
Q44.4	Choledochal cyst		Digestive
Q38	Other congenital malformations of tongue, mouth and pharynx		Digestive
Q38.0	Congenital malformations of lips, not elsewhere classified		Digestive
Q38.3	Other congenital malformations of tongue		Digestive
Q38.4	Congenital malformations of salivary glands and ducts		Digestive
Q38.5	Congenital malformations of palate, not elsewhere classified		Digestive
Q38.6	Other congenital malformations of mouth		Digestive
Q38.7	Pharyngeal pouch		Digestive
Q38.8	Other congenital malformations of pharynx		Digestive
Q39	Congenital malformations of oesophagus		Digestive
Q39.0	Atresia of oesophagus without fistula		Digestive
Q39.1	Atresia of oesophagus with tracheo-oesophageal fistula		Digestive
Q39.2	Congenital tracheo-oesophageal fistula without atresia		Digestive
Q39.3	Congenital stenosis and stricture of oesophagus		Digestive
Q39.4	Oesophageal web		Digestive
Q39.5	Congenital dilatation of oesophagus		Digestive
Q39.6	Diverticulum of oesophagus		Digestive
Q39.8	Other congenital malformations of oesophagus		Digestive
Q39.9	Congenital malformation of oesophagus, unspecified		Digestive
Q40	Other congenital malformations of upper alimentary tract		Digestive
Q40.2	Other specified congenital malformations of stomach		Digestive
Q40.3	Congenital malformation of stomach, unspecified		Digestive
Q40.8	Other spec congenital malforms of upper alimentary tract		Digestive
Q40.9	Congenital malformation of upper alimentary tract		Digestive
Q41	Congenital absence, atresia and stenosis of small intestine		Digestive
Q41.0	Congenital absence, atresia and stenosis of duodenum		Digestive
Q41.1	Congenital absence, atresia and stenosis of jejunum		Digestive

ICD-10 Code	Description	Minor malformation?	Subgroup
Q41.2	Congenital absence, atresia and stenosis of ileum		Digestive
Q41.8	Congen absence atresia stenosis oth spec parts small intest		Digestive
Q41.9	Cong absce atresia and stenosis small intestine part unspec		Digestive
Q42	Congenital absence, atresia and stenosis of large intestine		Digestive
Q42.0	Cong absence atresia and stenosis of rectum with fistula		Digestive
Q42.1	Cong absence atresia and stenosis rectum without fistula		Digestive
Q42.2	Cong absence atresia and stenosis anus with fistula		Digestive
Q42.3	Cong absence atresia and stenosis anus without fistula		Digestive
Q42.8	Congen absence atresia and sten oth parts of large intest		Digestive
Q42.9	Cong absce atresia and sten of large intest part unspec		Digestive
Q43	Other congenital malformations of intestine		Digestive
Q43.1	Hirschsprung's disease		Digestive
Q43.2	Other congenital functional disorders of colon		Digestive
Q43.3	Congenital malformations of intestinal fixation		Digestive
Q43.4	Duplication of intestine		Digestive
Q43.5	Ectopic anus		Digestive
Q43.6	Congenital fistula of rectum and anus		Digestive
Q43.7	Persistent cloaca		Digestive
Q43.8	Other specified congenital malformations of intestine		Digestive
Q43.9	Congenital malformation of intestine, unspecified		Digestive
Q44	Congenital malformations of gallbladder, bile ducts & liver		Digestive
Q44.0	Agnesis, aplasia and hypoplasia of gallbladder		Digestive
Q44.1	Other congenital malformations of gallbladder		Digestive
Q44.2	Atresia of bile ducts		Digestive
Q44.3	Congenital stenosis and stricture of bile ducts		Digestive
Q44.5	Other congenital malformations of bile ducts		Digestive
Q44.6	Cystic disease of liver		Digestive
Q44.7	Other congenital malformations of liver		Digestive
Q45	Other congenital malformations of digestive system		Digestive
Q45.0	Agnesis, aplasia and hypoplasia of pancreas		Digestive
Q45.1	Annular pancreas		Digestive
Q45.2	Congenital pancreatic cyst		Digestive
Q45.3	Other cong malformations of pancreas and pancreatic duct		Digestive
Q45.8	Other specified congenital malformations of digestive system		Digestive
Q45.9	Congenital malformation of digestive system, unspecified		Digestive
Q79.0	Congenital diaphragmatic hernia		Digestive
Q17.0	Accessory auricle	Yes	Ear, Face & Neck
Q17.1	Macrotia	Yes	Ear, Face & Neck
Q17.2	Microtia	Yes	Ear, Face & Neck
Q17.3	Other misshapen ear	Yes	Ear, Face & Neck
Q17.4	Misplaced ear	Yes	Ear, Face & Neck
Q17.5	Prominent ear	Yes	Ear, Face & Neck
Q18.0	Sinus, fistula and cyst of branchial cleft	Yes	Ear, Face & Neck
Q18.1	Preauricular sinus and cyst	Yes	Ear, Face & Neck
Q18.2	Other branchial cleft malformations	Yes	Ear, Face & Neck
Q18.4	Macrostomia	Yes	Ear, Face & Neck
Q18.5	Microstomia	Yes	Ear, Face & Neck
Q18.6	Macrocheilia	Yes	Ear, Face & Neck
Q18.7	Microcheilia	Yes	Ear, Face & Neck
Q16	Congenital malforms of ear causing impairment of hearing		Ear, Face & Neck
Q16.0	Congenital absence of (ear) auricle		Ear, Face & Neck
Q16.1	Cong absence atresia & stricture auditory canal (external)		Ear, Face & Neck

ICD-10 Code	Description	Minor malformation?	Subgroup
Q16.2	Absence of eustachian tube		Ear, Face & Neck
Q16.3	Congenital malformation of ear ossicles		Ear, Face & Neck
Q16.4	Other congenital malformations of middle ear		Ear, Face & Neck
Q16.5	Congenital malformation of inner ear		Ear, Face & Neck
Q16.9	Cong malform of ear causing impairment of hearing unspec		Ear, Face & Neck
Q17	Other congenital malformations of ear		Ear, Face & Neck
Q17.8	Other specified congenital malformations of ear		Ear, Face & Neck
Q17.9	Congenital malformation of ear, unspecified		Ear, Face & Neck
Q18	Other congenital malformations of face and neck		Ear, Face & Neck
Q18.3	Webbing of neck		Ear, Face & Neck
Q18.8	Other specified congenital malformations of face and neck		Ear, Face & Neck
Q18.9	Congenital malformation of face and neck, unspecified		Ear, Face & Neck
Q10.1	Congenital ectropion	Yes	Eye
Q10.2	Congenital entropion	Yes	Eye
Q10.3	Other congenital malformations of eyelid	Yes	Eye
Q10.5	Congenital stenosis and stricture of lacrimal duct	Yes	Eye
Q10	Congen malformations of eyelid lacrimal apparatus & orbit		Eye
Q10.0	Congenital ptosis		Eye
Q10.4	Absence and agenesis of lacrimal apparatus		Eye
Q10.6	Other congenital malformations of lacrimal apparatus		Eye
Q10.7	Congenital malformation of orbit		Eye
Q11	Anophthalmos, microphthalmos and macrophthalmos		Eye
Q11.0	Cystic eyeball		Eye
Q11.1	Other anophthalmos		Eye
Q11.2	Microphthalmos		Eye
Q11.3	Macrophthalmos		Eye
Q12	Congenital lens malformations		Eye
Q12.0	Congenital cataract		Eye
Q12.1	Congenital displaced lens		Eye
Q12.2	Coloboma of lens		Eye
Q12.3	Congenital aphakia		Eye
Q12.8	Other congenital lens malformations		Eye
Q12.9	Congenital lens malformation, unspecified		Eye
Q13	Congenital malformations of anterior segment of eye		Eye
Q13.0	Coloboma of iris		Eye
Q13.2	Other congenital malformations of iris		Eye
Q13.3	Congenital corneal opacity		Eye
Q13.4	Other congenital corneal malformations		Eye
Q13.8	Other congenital malformations of anterior segment of eye		Eye
Q13.9	Congenital malformation of anterior segment of eye unspec		Eye
Q14	Congenital malformations of posterior segment of eye		Eye
Q14.0	Congenital malformation of vitreous humour		Eye
Q14.1	Congenital malformation of retina		Eye
Q14.2	Congenital malformation of optic disc		Eye
Q14.3	Congenital malformation of choroid		Eye
Q14.8	Other congenital malformations of posterior segment of eye		Eye
Q14.9	Congenital malformation of posterior segment of eye unspec		Eye
Q15	Other congenital malformations of eye		Eye
Q15.0	Congenital glaucoma		Eye
Q15.8	Other specified congenital malformations of eye		Eye
Q15.9	Congenital malformation of eye, unspecified		Eye
Q50.1	Developmental ovarian cyst	Yes	Genital



ICD-10 Description Code	Minor malformation?	Subgroup
Q52.3 Imperforate hymen	Yes	Genital
Q52.5 Fusion of labia	Yes	Genital
Q50 Cong malforms ovaries fallopian tubes and broad ligaments		Genital
Q50.0 Congenital absence of ovary		Genital
Q50.2 Congenital torsion of ovary		Genital
Q50.3 Other congenital malformations of ovary		Genital
Q50.4 Embryonic cyst of fallopian tube		Genital
Q50.5 Embryonic cyst of broad ligament		Genital
Q50.6 Other cong malformations of fallop tube and broad ligament		Genital
Q51 Congenital malformations of uterus and cervix		Genital
Q51.0 Agenesis and aplasia of uterus		Genital
Q51.1 Doubling of uterus with doubling of cervix and vagina		Genital
Q51.2 Other doubling of uterus		Genital
Q51.3 Bicornate uterus		Genital
Q51.4 Unicornate uterus		Genital
Q51.5 Agenesis and aplasia of cervix		Genital
Q51.6 Embryonic cyst of cervix		Genital
Q51.7 Cong fistulae btwn uterus and digestive and urinary tracts		Genital
Q51.8 Other congenital malformations of uterus and cervix		Genital
Q51.9 Congenital malformation of uterus and cervix, unspecified		Genital
Q52 Other congenital malformations of female genitalia		Genital
Q52.0 Congenital absence of vagina		Genital
Q52.1 Doubling of vagina		Genital
Q52.2 Congenital rectovaginal fistula		Genital
Q52.4 Other congenital malformations of vagina		Genital
Q52.6 Congenital malformation of clitoris		Genital
Q52.7 Other congenital malformations of vulva		Genital
Q52.8 Other specified congenital malformations of female genitalia		Genital
Q52.9 Congenital malformation of female genitalia, unspecified		Genital
Q54 Hypospadias		Genital
Q54.0 Hypospadias, balanic		Genital
Q54.1 Hypospadias, penile		Genital
Q54.2 Hypospadias, penoscrotal		Genital
Q54.3 Hypospadias, perineal		Genital
Q54.4 Congenital chordee		Genital
Q54.8 Other hypospadias		Genital
Q54.9 Hypospadias, unspecified		Genital
Q55 Other congenital malformations of male genital organs		Genital
Q55.0 Absence and aplasia of testis		Genital
Q55.1 Hypoplasia of testis and scrotum		Genital
Q55.2 Other congenital malformations of testis and scrotum		Genital
Q55.3 Atresia of vas deferens		Genital
Q55.4 Oth cong malform vas def epidid sem vesicle and prostate		Genital
Q55.5 Congenital absence and aplasia of penis		Genital
Q55.6 Other congenital malformations of penis		Genital
Q55.8 Other specified congen malformations of male genital organs		Genital
Q55.9 Congenital malformation of male genital organ, unspecified		Genital
Q56 Indeterminate sex and pseudohermaphroditism		Genital
Q56.0 Hermaphroditism, not elsewhere classified		Genital
Q56.1 Male pseudohermaphroditism, not elsewhere classified		Genital
Q56.2 Female pseudohermaphroditism, not elsewhere classified		Genital
Q56.3 Pseudohermaphroditism, unspecified		Genital

ICD-10 Code	Description	Minor malformation?	Subgroup
Q56.4	Indeterminate sex, unspecified		Genital
Q65.3	Congenital subluxation of hip, unilateral	Yes	Limb
Q65.4	Congenital subluxation of hip, bilateral	Yes	Limb
Q65.5	Congenital subluxation of hip, unspecified	Yes	Limb
Q65.6	Unstable hip	Yes	Limb
Q66.2	Metatarsus varus	Yes	Limb
Q66.4	Talipes calcaneovalgus	Yes	Limb
Q66.5	Congenital pes planus	Yes	Limb
Q66.6	Other congenital valgus deformities of feet	Yes	Limb
Q66.7	Pes cavus	Yes	Limb
Q67.0	Facial asymmetry	Yes	Limb
Q67.1	Compression facies	Yes	Limb
Q67.2	Dolichocephaly	Yes	Limb
Q67.3	Plagiocephaly	Yes	Limb
Q67.6	Pectus excavatum	Yes	Limb
Q67.7	Pectus carinatum	Yes	Limb
Q67.8	Other congenital deformities of chest	Yes	Limb
Q68.0	Congenital deformity of sternocleidomastoid muscle	Yes	Limb
Q68.3	Congenital bowing of femur	Yes	Limb
Q68.4	Congenital bowing of tibia and fibula	Yes	Limb
Q68.5	Congenital bowing of long bones of leg, unspecified	Yes	Limb
Q65	Congenital deformities of hip		Limb
Q65.0	Congenital dislocation of hip, unilateral		Limb
Q65.1	Congenital dislocation of hip, bilateral		Limb
Q65.2	Congenital dislocation of hip, unspecified		Limb
Q65.8	Other congenital deformities of hip		Limb
Q65.9	Congenital deformity of hip, unspecified		Limb
Q66	Congenital deformities of feet		Limb
Q66.0	Talipes equinovarus		Limb
Q66.1	Talipes calcaneovarus		Limb
Q66.3	Other congenital varus deformities of feet		Limb
Q66.8	Other congenital deformities of feet		Limb
Q66.9	Congenital deformity of feet, unspecified		Limb
Q67	Cong musculoskel deformities of head face spine and chest		Limb
Q67.4	Other congenital deformities of skull, face and jaw		Limb
Q67.5	Congenital deformity of spine		Limb
Q68	Other congenital musculoskeletal deformities		Limb
Q68.1	Congenital deformity of hand		Limb
Q68.2	Congenital deformity of knee		Limb
Q68.8	Other specified congenital musculoskeletal deformities		Limb
Q69	Polydactyly		Limb
Q69.0	Accessory finger(s)		Limb
Q69.1	Accessory thumb(s)		Limb
Q69.2	Accessory toe(s)		Limb
Q69.9	Polydactyly, unspecified		Limb
Q70	Syndactyly		Limb
Q70.0	Fused fingers		Limb
Q70.1	Webbed fingers		Limb
Q70.2	Fused toes		Limb
Q70.3	Webbed toes		Limb
Q70.4	Polysyndactyly		Limb
Q70.9	Syndactyly, unspecified		Limb

ICD-10 Code	Description	Minor malformation?	Subgroup
Q71	Reduction defects of upper limb		Limb
Q71.0	Congenital complete absence of upper limb(s)		Limb
Q71.1	Cong absence of upper arm and forearm with hand present		Limb
Q71.2	Congenital absence of both forearm and hand		Limb
Q71.3	Congenital absence of hand and finger(s)		Limb
Q71.4	Longitudinal reduction defect of radius		Limb
Q71.5	Longitudinal reduction defect of ulna		Limb
Q71.8	Other reduction defects of upper limb(s)		Limb
Q71.9	Reduction defect of upper limb, unspecified		Limb
Q72	Reduction defects of lower limb		Limb
Q72.0	Congenital complete absence of lower limb(s)		Limb
Q72.1	Congenital absence of thigh and lower leg with foot present		Limb
Q72.2	Congenital absence of both lower leg and foot		Limb
Q72.3	Congenital absence of foot and toe(s)		Limb
Q72.4	Longitudinal reduction defect of femur		Limb
Q72.5	Longitudinal reduction defect of tibia		Limb
Q72.6	Longitudinal reduction defect of fibula		Limb
Q72.8	Other reduction defects of lower limb(s)		Limb
Q72.9	Reduction defect of lower limb, unspecified		Limb
Q73	Reduction defects of unspecified limb		Limb
Q73.0	Congenital absence of unspecified limb(s)		Limb
Q73.1	Phocomelia, unspecified limb(s)		Limb
Q73.8	Other reduction defects of unspecified limb(s)		Limb
Q74	Other congenital malformations of limb(s)		Limb
Q74.0	Oth cong malformation of upper limb(s) inc shoulder girdle		Limb
Q74.1	Congenital malformation of knee		Limb
Q74.2	Other cong malformation of lower limb(s) incl pelvic girdle		Limb
Q74.3	Arthrogryposis multiplex congenita		Limb
Q74.8	Other specified congenital malformations of limb(s)		Limb
Q74.9	Unspecified congenital malformation of limb(s)		Limb
Q04.6	Congenital cerebral cysts		Nervous System
Q00	Anencephaly and similar malformations		Nervous System
Q00.0	Anencephaly		Nervous System
Q00.1	Craniorachischisis		Nervous System
Q00.2	Iniencephaly		Nervous System
Q01	Encephalocele		Nervous System
Q01.0	Frontal encephalocele		Nervous System
Q01.1	Nasofrontal encephalocele		Nervous System
Q01.2	Occipital encephalocele		Nervous System
Q01.8	Encephalocele of other sites		Nervous System
Q01.9	Encephalocele, unspecified		Nervous System
Q02	Microcephaly		Nervous System
Q03	Congenital hydrocephalus		Nervous System
Q03.0	Malformations of aqueduct of Sylvius		Nervous System
Q03.1	Atresia of foramina of Magendie and Luschka		Nervous System
Q03.8	Other congenital hydrocephalus		Nervous System
Q03.9	Congenital hydrocephalus, unspecified		Nervous System
Q04	Other congenital malformations of brain		Nervous System
Q04.0	Congenital malformations of corpus callosum		Nervous System
Q04.1	Arhinencephaly		Nervous System
Q04.2	Holoprosencephaly		Nervous System
Q04.3	Other reduction deformities of brain		Nervous System

ICD-10 Code	Description	Minor malformation?	Subgroup
Q04.4	Septo-optic dysplasia		Nervous System
Q04.5	Megalencephaly		Nervous System
Q04.8	Other specified congenital malformations of brain		Nervous System
Q04.9	Congenital malformation of brain, unspecified		Nervous System
Q05	Spina bifida		Nervous System
Q05.0	Cervical spina bifida with hydrocephalus		Nervous System
Q05.1	Thoracic spina bifida with hydrocephalus		Nervous System
Q05.2	Lumbar spina bifida with hydrocephalus		Nervous System
Q05.3	Sacral spina bifida with hydrocephalus		Nervous System
Q05.4	Unspecified spina bifida with hydrocephalus		Nervous System
Q05.5	Cervical spina bifida without hydrocephalus		Nervous System
Q05.6	Thoracic spina bifida without hydrocephalus		Nervous System
Q05.7	Lumbar spina bifida without hydrocephalus		Nervous System
Q05.8	Sacral spina bifida without hydrocephalus		Nervous System
Q05.9	Spina bifida, unspecified		Nervous System
Q06	Other congenital malformations of spinal cord		Nervous System
Q06.0	Amyelia		Nervous System
Q06.1	Hypoplasia and dysplasia of spinal cord		Nervous System
Q06.2	Diastematomyelia		Nervous System
Q06.3	Other congenital cauda equina malformations		Nervous System
Q06.4	Hydromyelia		Nervous System
Q06.8	Other specified congenital malformations of spinal cord		Nervous System
Q06.9	Congenital malformation of spinal cord, unspecified		Nervous System
Q07	Other congenital malformations of nervous system		Nervous System
Q07.0	Arnold-Chiari syndrome		Nervous System
Q07.8	Other specified congenital malformations of nervous system		Nervous System
Q07.9	Congenital malformation of nervous system, unspecified		Nervous System
Q35	Cleft palate		Orofacial Clefts
Q35.1	Cleft hard palate		Orofacial Clefts
Q35.3	Cleft soft palate		Orofacial Clefts
Q35.5	Cleft hard palate with cleft soft palate		Orofacial Clefts
Q35.6	Cleft palate, medial		Orofacial Clefts
Q35.7	Cleft uvula		Orofacial Clefts
Q35.9	Cleft palate, unspecified		Orofacial Clefts
Q36	Cleft lip		Orofacial Clefts
Q36.0	Cleft lip, bilateral		Orofacial Clefts
Q36.1	Cleft lip, medial		Orofacial Clefts
Q36.9	Cleft lip, unilateral		Orofacial Clefts
Q37	Cleft palate with cleft lip		Orofacial Clefts
Q37.0	Cleft hard palate with bilateral cleft lip		Orofacial Clefts
Q37.1	Cleft hard palate with unilateral cleft lip		Orofacial Clefts
Q37.2	Cleft soft palate with bilateral cleft lip		Orofacial Clefts
Q37.3	Cleft soft palate with unilateral cleft lip		Orofacial Clefts
Q37.4	Cleft hard and soft palate with bilateral cleft lip		Orofacial Clefts
Q37.5	Cleft hard and soft palate with unilateral cleft lip		Orofacial Clefts
Q37.8	Unspecified cleft palate with bilateral cleft lip		Orofacial Clefts
Q37.9	Unspecified cleft palate with unilateral cleft lip		Orofacial Clefts
Q27.0	Congenital absence and hypoplasia of umbilical artery	Yes	Other
Q31.4	Congenital laryngeal stridor	Yes	Other
Q75.2	Hypertelorism	Yes	Other
Q75.3	Macrocephaly	Yes	Other
Q76.5	Cervical rib	Yes	Other

ICD-10 Code	Description	Minor malformation?	Subgroup
Q53	Undescended testicle	Yes	Other
Q53.0	Ectopic testis	Yes	Other
Q53.1	Undescended testicle, unilateral	Yes	Other
Q53.2	Undescended testicle, bilateral	Yes	Other
Q53.9	Undescended testicle, unspecified	Yes	Other
Q27	Other congenital malformations of peripheral vascular system		Other
Q27.1	Congenital renal artery stenosis		Other
Q27.2	Other congenital malformations of renal artery		Other
Q27.3	Peripheral arteriovenous malformation		Other
Q27.4	Congenital phlebectasia		Other
Q27.8	Other spec cong malformations of peripheral vasc system		Other
Q27.9	Cong malformation of peripheral vascular system unspecified		Other
Q28	Other congenital malformations of circulatory system		Other
Q28.0	Arteriovenous malformation of precerebral vessels		Other
Q28.1	Other malformations of precerebral vessels		Other
Q28.2	Arteriovenous malformation of cerebral vessels		Other
Q28.3	Other malformations of cerebral vessels		Other
Q28.8	Other spec congenital malformations of circulatory system		Other
Q28.9	Congenital malformation of circulatory system, unspecified		Other
Q31	Congenital malformations of larynx		Other
Q31.0	Web of larynx		Other
Q31.1	Congenital subglottic stenosis		Other
Q31.2	Laryngeal hypoplasia		Other
Q31.3	Laryngocele		Other
Q31.8	Other congenital malformations of larynx		Other
Q31.9	Congenital malformation of larynx, unspecified		Other
Q75	Other congenital malformations of skull and face bones		Other
Q75.0	Craniosynostosis		Other
Q75.8	Other spec congenital malformations of skull and face bones		Other
Q75.9	Congenital malformation of skull and face bones, unspecified		Other
Q76	Congenital malformations of spine and bony thorax		Other
Q76.0	Spina bifida occulta		Other
Q76.2	Congenital spondylolisthesis		Other
Q76.3	Congenital scoliosis due to congenital bony malformation		Other
Q76.4	Oth cong malformation of spine not associated with scoliosis		Other
Q76.6	Other congenital malformations of ribs		Other
Q76.7	Congenital malformation of sternum		Other
Q76.8	Other congenital malformations of bony thorax		Other
Q76.9	Congenital malformation of bony thorax, unspecified		Other
Q77	Osteochondrodysplasia with defect growth tub bones spine		Other
Q77.8	Oth osteochondrodysplas with defect growth tub bone spine		Other
Q77.9	Osteochondrodyspl with defct growth tub bone spine unspec		Other
Q78	Other osteochondrodysplasias		Other
Q78.1	Polyostotic fibrous dysplasia		Other
Q78.4	Enchondromatosis		Other
Q78.8	Other specified osteochondrodysplasias		Other
Q78.9	Osteochondrodysplasia, unspecified		Other
Q79	Congenital malformations of the musculoskel system NEC		Other
Q79.1	Other congenital malformations of diaphragm		Other
Q79.8	Other congenital malformations of musculoskeletal system		Other
Q79.9	Congenital malformation of musculoskeletal system unspecf		Other
Q30	Congenital malformations of nose		Other

ICD-10 Code	Description	Minor malformation?	Subgroup
Q30.1	Agnesis and underdevelopment of nose		Other
Q30.2	Fissured, notched and cleft nose		Other
Q30.3	Congenital perforated nasal septum		Other
Q30.8	Other congenital malformations of nose		Other
Q30.9	Congenital malformation of nose, unspecified		Other
Q82	Other congenital malformations of skin		Other
Q82.2	Mastocytosis		Other
Q82.5	Congenital non-neoplastic naevus		Other
Q82.8	Other specified congenital malformations of skin		Other
Q82.9	Congenital malformation of skin, unspecified		Other
Q83	Congenital malformations of breast		Other
Q83.0	Congenital absence of breast with absent nipple		Other
Q83.1	Accessory breast		Other
Q83.2	Absent nipple		Other
Q83.3	Accessory nipple		Other
Q83.8	Other congenital malformations of breast		Other
Q83.9	Congenital malformation of breast, unspecified		Other
Q84	Other congenital malformations of integument		Other
Q84.0	Congenital alopecia		Other
Q84.1	Congenital morphological disturbances of hair NEC		Other
Q84.2	Other congenital malformations of hair		Other
Q84.3	Anonychia		Other
Q84.4	Congenital leukonychia		Other
Q84.5	Enlarged and hypertrophic nails		Other
Q84.6	Other congenital malformations of nails		Other
Q84.8	Other specified congenital malformations of integument		Other
Q84.9	Congenital malformation of integument, unspecified		Other
Q89	Other congenital malformations, not elsewhere classified		Other
Q89.0	Congenital malformations of spleen		Other
Q89.1	Congenital malformations of adrenal gland		Other
Q89.2	Congenital malformations of other endocrine glands		Other
Q89.3	Situs inversus		Other
Q89.4	Conjoined twins		Other
Q89.7	Multiple congenital malformations, not elsewhere classified		Other
Q89.8	Other specified congenital malformations		Other
Q89.9	Congenital malformation, unspecified		Other
Q32.0	Congenital tracheomalacia	Yes	Respiratory
Q33.1	Accessory lobe of lung	Yes	Respiratory
Q30.0	Choanal atresia		Respiratory
Q32	Congenital malformations of trachea and bronchus		Respiratory
Q32.1	Other congenital malformations of trachea		Respiratory
Q32.2	Congenital bronchomalacia		Respiratory
Q32.3	Congenital stenosis of bronchus		Respiratory
Q32.4	Other congenital malformations of bronchus		Respiratory
Q33	Congenital malformations of lung		Respiratory
Q33.0	Congenital cystic lung		Respiratory
Q33.2	Sequestration of lung		Respiratory
Q33.3	Agnesis of lung		Respiratory
Q33.4	Congenital bronchiectasis		Respiratory
Q33.5	Ectopic tissue in lung		Respiratory
Q33.6	Hypoplasia and dysplasia of lung		Respiratory
Q33.8	Other congenital malformations of lung		Respiratory

ICD-10 Code	Description	Minor malformation?	Subgroup
Q33.9	Congenital malformation of lung, unspecified		Respiratory
Q34	Other congenital malformations of respiratory system		Respiratory
Q34.0	Anomaly of pleura		Respiratory
Q34.1	Congenital cyst of mediastinum		Respiratory
Q34.8	Other spec congenital malformations of respiratory system		Respiratory
Q34.9	Congenital malformation of respiratory system, unspecified		Respiratory
Q61.0	Congenital single renal cyst	Yes	Urinary
Q62.7	Congenital vesico-uretero-renal reflux	Yes	Urinary
Q63.3	Hyperplastic and giant kidney	Yes	Urinary
Q60	Renal agenesis and other reduction defects of kidney		Urinary
Q60.0	Renal agenesis, unilateral		Urinary
Q60.1	Renal agenesis, bilateral		Urinary
Q60.2	Renal agenesis, unspecified		Urinary
Q60.3	Renal hypoplasia, unilateral		Urinary
Q60.4	Renal hypoplasia, bilateral		Urinary
Q60.5	Renal hypoplasia, unspecified		Urinary
Q60.6	Potter's syndrome		Urinary
Q61	Cystic kidney disease		Urinary
Q61.4	Renal dysplasia		Urinary
Q61.8	Other cystic kidney diseases		Urinary
Q61.9	Cystic kidney disease, unspecified		Urinary
Q62	Cong obstructive defect renal pelvis and cong malform ureter		Urinary
Q62.0	Congenital hydronephrosis		Urinary
Q62.1	Atresia and stenosis of ureter		Urinary
Q62.2	Congenital megaloureter		Urinary
Q62.3	Other obstructive defects of renal pelvis and ureter		Urinary
Q62.4	Agenesis of ureter		Urinary
Q62.5	Duplication of ureter		Urinary
Q62.6	Malposition of ureter		Urinary
Q62.8	Other congenital malformations of ureter		Urinary
Q63	Other congenital malformations of kidney		Urinary
Q63.0	Accessory kidney		Urinary
Q63.1	Lobulated, fused and horseshoe kidney		Urinary
Q63.2	Ectopic kidney		Urinary
Q63.8	Other specified congenital malformations of kidney		Urinary
Q63.9	Congenital malformation of kidney, unspecified		Urinary
Q64	Other congenital malformations of urinary system		Urinary
Q64.0	Epispadias		Urinary
Q64.1	Exstrophy of urinary bladder		Urinary
Q64.2	Congenital posterior urethral valves		Urinary
Q64.3	Other atresia and stenosis of urethra and bladder neck		Urinary
Q64.4	Malformation of urachus		Urinary
Q64.5	Congenital absence of bladder and urethra		Urinary
Q64.6	Congenital diverticulum of bladder		Urinary
Q64.7	Other congenital malformations of bladder and urethra		Urinary
Q64.8	Other specified congenital malformations of urinary system		Urinary
Q64.9	Congenital malformation of urinary system, unspecified		Urinary
Q79.4	Prune belly syndrome		Urinary

## OPCS-4 codes

OPCS-4 Code	General description	Minor malformation?	Subgroup
T281	Other repair of anterior abdominal wall		Abdominal Wall
K196	Creation of other cardiac conduit		Heart
L021	Open correction of patent ductus arteriosus		Heart
L022	Open correction of patent ductus arteriosus		Heart
L023	Open correction of patent ductus arteriosus		Heart
L024	Open correction of patent ductus arteriosus		Heart
L028	Open correction of patent ductus arteriosus		Heart
L029	Open correction of patent ductus arteriosus		Heart
L031	Transluminal operations on abnormality of great vessel		Heart
K041	Repair of tetralogy of fallot		Heart
K042	Repair of tetralogy of fallot		Heart
K043	Repair of tetralogy of fallot		Heart
K044	Repair of tetralogy of fallot		Heart
K045	Repair of tetralogy of fallot		Heart
K046	Repair of tetralogy of fallot		Heart
K048	Repair of tetralogy of fallot		Heart
K049	Repair of tetralogy of fallot		Heart
K051	Atrial inversion operations/transposition/great arterie		Heart
K052	Atrial inversion operations/transposition/great arterie		Heart
K058	Atrial inversion operations/transposition/great arterie		Heart
K059	Atrial inversion operations/transposition/great arterie		Heart
K061	Other repair of transposition of great arteries		Heart
K062	Other repair of transposition of great arteries		Heart
K063	Other repair of transposition of great arteries		Heart
K064	Other repair of transposition of great arteries		Heart
K068	Other repair of transposition of great arteries		Heart
K069	Other repair of transposition of great arteries		Heart
K071	Correction/total anomalous pulmonary venous connection		Heart
K072	Correction/total anomalous pulmonary venous connection		Heart
K073	Correction/total anomalous pulmonary venous connection		Heart
K078	Correction/total anomalous pulmonary venous connection		Heart
K079	Correction/total anomalous pulmonary venous connection		Heart
K081	Repair of double outlet ventricle		Heart
K082	Repair of double outlet ventricle		Heart
K083	Repair of double outlet ventricle		Heart
K084	Repair of double outlet ventricle		Heart
K088	Repair of double outlet ventricle		Heart
K089	Repair of double outlet ventricle		Heart
K091	Repair of defect of atrioventricular septum		Heart
K092	Repair of defect of atrioventricular septum		Heart
K093	Repair of defect of atrioventricular septum		Heart
K094	Repair of defect of atrioventricular septum		Heart
K095	Repair of defect of atrioventricular septum		Heart
K096	Repair of defect of atrioventricular septum		Heart
K098	Repair of defect of atrioventricular septum		Heart
K099	Repair of defect of atrioventricular septum		Heart
K101	Repair of defect of interatrial septum		Heart
K102	Repair of defect of interatrial septum		Heart
K103	Repair of defect of interatrial septum		Heart
K104	Repair of defect of interatrial septum		Heart



OPCS-4 Code	General description	Minor malformation?	Subgroup
K105	Repair of defect of interatrial septum		Heart
K108	Repair of defect of interatrial septum		Heart
K109	Repair of defect of interatrial septum		Heart
K111	Repair of defect of interventricular septum		Heart
K112	Repair of defect of interventricular septum		Heart
K113	Repair of defect of interventricular septum		Heart
K114	Repair of defect of interventricular septum		Heart
K115	Repair of defect of interventricular septum		Heart
K116	Repair of defect of interventricular septum		Heart
K117	Repair of defect of interventricular septum		Heart
K118	Repair of defect of interventricular septum		Heart
K119	Repair of defect of interventricular septum		Heart
K121	Repair of defect of unspecified septum of heart		Heart
K122	Repair of defect of unspecified septum of heart		Heart
K123	Repair of defect of unspecified septum of heart		Heart
K124	Repair of defect of unspecified septum of heart		Heart
K125	Repair of defect of unspecified septum of heart		Heart
K128	Repair of defect of unspecified septum of heart		Heart
K129	Repair of defect of unspecified septum of heart		Heart
K131	Transluminal repair of defect of septum		Heart
K132	Transluminal repair of defect of septum		Heart
K133	Transluminal repair of defect of septum		Heart
K134	Transluminal repair of defect of septum		Heart
K135	Transluminal repair of defect of septum		Heart
K138	Transluminal repair of defect of septum		Heart
K139	Transluminal repair of defect of septum		Heart
K141	Other open operations on septum of heart		Heart
K142	Other open operations on septum of heart		Heart
K143	Other open operations on septum of heart		Heart
K144	Other open operations on septum of heart		Heart
K145	Other open operations on septum of heart		Heart
K148	Other open operations on septum of heart		Heart
K149	Other open operations on septum of heart		Heart
K151	Closed operations on septum of heart		Heart
K152	Closed operations on septum of heart		Heart
K158	Closed operations on septum of heart		Heart
K159	Closed operations on septum of heart		Heart
K161	Other therapeutic transluminal operations on septum of		Heart
K162	Other therapeutic transluminal operations on septum of		Heart
K163	Other therapeutic transluminal operations on septum of		Heart
K164	Other therapeutic transluminal operations on septum of		Heart
K165	Other therapeutic transluminal operations on septum of		Heart
K166	Other therapeutic transluminal operations on septum of		Heart
K168	Other therapeutic transluminal operations on septum of		Heart
K169	Other therapeutic transluminal operations on septum of		Heart
K171	Repair of univentricular heart		Heart
K172	Repair of univentricular heart		Heart
K173	Repair of univentricular heart		Heart
K174	Repair of univentricular heart		Heart
K175	Repair of univentricular heart		Heart
K176	Repair of univentricular heart		Heart
K177	Repair of univentricular heart		Heart

OPCS-4 Code	General description	Minor malformation?	Subgroup
K178	Repair of univentricular heart		Heart
K179	Repair of univentricular heart		Heart
K181	Creation of valved cardiac conduit		Heart
K182	Creation of valved cardiac conduit		Heart
K183	Creation of valved cardiac conduit		Heart
K184	Creation of valved cardiac conduit		Heart
K185	Creation of valved cardiac conduit		Heart
K186	Creation of valved cardiac conduit		Heart
K187	Creation of valved cardiac conduit		Heart
K188	Creation of valved cardiac conduit		Heart
K189	Creation of valved cardiac conduit		Heart
K191	Creation of other cardiac conduit		Heart
K192	Creation of other cardiac conduit		Heart
K193	Creation of other cardiac conduit		Heart
K194	Creation of other cardiac conduit		Heart
K195	Creation of other cardiac conduit		Heart
K198	Creation of other cardiac conduit		Heart
K199	Creation of other cardiac conduit		Heart
K201	Refashioning of atrium		Heart
K202	Refashioning of atrium		Heart
K203	Refashioning of atrium		Heart
K204	Refashioning of atrium		Heart
K208	Refashioning of atrium		Heart
K209	Refashioning of atrium		Heart
K222	Other operations on wall of atrium		Heart
K241	Other operations on ventricles of heart		Heart
K242	Other operations on ventricles of heart		Heart
K245	Other operations on ventricles of heart		Heart
K246	Other operations on ventricles of heart		Heart
K247	Other operations on ventricles of heart		Heart
K251	Plastic repair of mitral valve		Heart
K252	Plastic repair of mitral valve		Heart
K253	Plastic repair of mitral valve		Heart
K254	Plastic repair of mitral valve		Heart
K255	Plastic repair of mitral valve		Heart
K258	Plastic repair of mitral valve		Heart
K259	Plastic repair of mitral valve		Heart
K261	Plastic repair of aortic valve		Heart
K262	Plastic repair of aortic valve		Heart
K263	Plastic repair of aortic valve		Heart
K264	Plastic repair of aortic valve		Heart
K265	Plastic repair of aortic valve		Heart
K268	Plastic repair of aortic valve		Heart
K269	Plastic repair of aortic valve		Heart
K271	Plastic repair of tricuspid valve		Heart
K272	Plastic repair of tricuspid valve		Heart
K273	Plastic repair of tricuspid valve		Heart
K274	Plastic repair of tricuspid valve		Heart
K275	Plastic repair of tricuspid valve		Heart
K276	Plastic repair of tricuspid valve		Heart
K278	Plastic repair of tricuspid valve		Heart
K279	Plastic repair of tricuspid valve		Heart

OPCS-4 Code	General description	Minor malformation?	Subgroup
K281	Plastic repair of pulmonary valve		Heart
K282	Plastic repair of pulmonary valve		Heart
K283	Plastic repair of pulmonary valve		Heart
K284	Plastic repair of pulmonary valve		Heart
K285	Plastic repair of pulmonary valve		Heart
K288	Plastic repair of pulmonary valve		Heart
K289	Plastic repair of pulmonary valve		Heart
K291	Plastic repair of unspecified valve of heart		Heart
K292	Plastic repair of unspecified valve of heart		Heart
K293	Plastic repair of unspecified valve of heart		Heart
K294	Plastic repair of unspecified valve of heart		Heart
K295	Plastic repair of unspecified valve of heart		Heart
K296	Plastic repair of unspecified valve of heart		Heart
K297	Plastic repair of unspecified valve of heart		Heart
K298	Plastic repair of unspecified valve of heart		Heart
K299	Plastic repair of unspecified valve of heart		Heart
K301	Revision of plastic repair of valve of heart		Heart
K302	Revision of plastic repair of valve of heart		Heart
K303	Revision of plastic repair of valve of heart		Heart
K304	Revision of plastic repair of valve of heart		Heart
K305	Revision of plastic repair of valve of heart		Heart
K308	Revision of plastic repair of valve of heart		Heart
K309	Revision of plastic repair of valve of heart		Heart
K311	Open incision of valve of heart		Heart
K312	Open incision of valve of heart		Heart
K313	Open incision of valve of heart		Heart
K314	Open incision of valve of heart		Heart
K315	Open incision of valve of heart		Heart
K318	Open incision of valve of heart		Heart
K319	Open incision of valve of heart		Heart
K321	Closed incision of valve of heart		Heart
K322	Closed incision of valve of heart		Heart
K323	Closed incision of valve of heart		Heart
K324	Closed incision of valve of heart		Heart
K328	Closed incision of valve of heart		Heart
K329	Closed incision of valve of heart		Heart
K331	Operations on aortic root		Heart
K332	Operations on aortic root		Heart
K333	Operations on aortic root		Heart
K334	Operations on aortic root		Heart
K335	Operations on aortic root		Heart
K336	Operations on aortic root		Heart
K338	Operations on aortic root		Heart
K339	Operations on aortic root		Heart
K341	Other open operations on valve of heart		Heart
K342	Other open operations on valve of heart		Heart
K343	Other open operations on valve of heart		Heart
K344	Other open operations on valve of heart		Heart
K345	Other open operations on valve of heart		Heart
K346	Other open operations on valve of heart		Heart
K348	Other open operations on valve of heart		Heart
K349	Other open operations on valve of heart		Heart

OPCS-4 Code	General description	Minor malformation?	Subgroup
K351	Therapeutic transluminal operations on valve of heart		Heart
K352	Therapeutic transluminal operations on valve of heart		Heart
K353	Therapeutic transluminal operations on valve of heart		Heart
K354	Therapeutic transluminal operations on valve of heart		Heart
K355	Therapeutic transluminal operations on valve of heart		Heart
K356	Therapeutic transluminal operations on valve of heart		Heart
K357	Therapeutic transluminal operations on valve of heart		Heart
K358	Therapeutic transluminal operations on valve of heart		Heart
K359	Therapeutic transluminal operations on valve of heart		Heart
K361	Excision of valve of heart		Heart
K362	Excision of valve of heart		Heart
K368	Excision of valve of heart		Heart
K369	Excision of valve of heart		Heart
K371	Removal/obstruction from structure adjacent/valve heart		Heart
K372	Removal/obstruction from structure adjacent/valve heart		Heart
K373	Removal/obstruction from structure adjacent/valve heart		Heart
K374	Removal/obstruction from structure adjacent/valve heart		Heart
K375	Removal/obstruction from structure adjacent/valve heart		Heart
K376	Removal/obstruction from structure adjacent/valve heart		Heart
K378	Removal/obstruction from structure adjacent/valve heart		Heart
K379	Removal/obstruction from structure adjacent/valve heart		Heart
K381	Other operations on structure adjacent to valve of hear		Heart
K382	Other operations on structure adjacent to valve of hear		Heart
K383	Other operations on structure adjacent to valve of hear		Heart
K384	Other operations on structure adjacent to valve of hear		Heart
K385	Other operations on structure adjacent to valve of hear		Heart
K386	Other operations on structure adjacent to valve of hear		Heart
K388	Other operations on structure adjacent to valve of hear		Heart
K389	Other operations on structure adjacent to valve of hear		Heart
L011	Open operations for combined abnormality of great vesse		Heart
L012	Open operations for combined abnormality of great vesse		Heart
L013	Open operations for combined abnormality of great vesse		Heart
L014	Open operations for combined abnormality of great vesse		Heart
L018	Open operations for combined abnormality of great vesse		Heart
L019	Open operations for combined abnormality of great vesse		Heart
L032	Transluminal operations on abnormality of great vessel		Heart
L038	Transluminal operations on abnormality of great vessel		Heart
L039	Transluminal operations on abnormality of great vessel		Heart
G401	Incision of pylorus	Yes	Digestive
G701	Open extirpation of lesion of ileum	Yes	Digestive
G073	Repair of oesophagus		Digestive
G231	Repair of diaphragmatic hernia		Digestive
G232	Repair of diaphragmatic hernia		Digestive
G233	Repair of diaphragmatic hernia		Digestive
G234	Repair of diaphragmatic hernia		Digestive
G238	Repair of diaphragmatic hernia		Digestive
G239	Repair of diaphragmatic hernia		Digestive
G402	Incision of pylorus		Digestive
T164	Other repair of diaphragm		Digestive
T803	Release of contracture of muscle		Ear, Face & Neck
M731	Repair of urethra		Genital
N285	Plastic operations on penis		Genital

OPCS-4 Code	General description	Minor malformation?	Subgroup
X272	Correction of minor congenital deformity of foot	Yes	Limb
X273	Correction of minor congenital deformity of foot	Yes	Limb
X274	Correction of minor congenital deformity of foot	Yes	Limb
X275	Correction of minor congenital deformity of foot	Yes	Limb
T021	Reconstruction of chest wall		Limb
T022	Reconstruction of chest wall		Limb
X191	Correction of congenital deformity of shoulder or upper		Limb
X198	Correction of congenital deformity of shoulder or upper		Limb
X199	Correction of congenital deformity of shoulder or upper		Limb
X201	Correction of congenital deformity of forearm		Limb
X202	Correction of congenital deformity of forearm		Limb
X203	Correction of congenital deformity of forearm		Limb
X204	Correction of congenital deformity of forearm		Limb
X205	Correction of congenital deformity of forearm		Limb
X208	Correction of congenital deformity of forearm		Limb
X209	Correction of congenital deformity of forearm		Limb
X211	Correction of congenital deformity of hand		Limb
X212	Correction of congenital deformity of hand		Limb
X213	Correction of congenital deformity of hand		Limb
X214	Correction of congenital deformity of hand		Limb
X215	Correction of congenital deformity of hand		Limb
X216	Correction of congenital deformity of hand		Limb
X217	Correction of congenital deformity of hand		Limb
X218	Correction of congenital deformity of hand		Limb
X219	Correction of congenital deformity of hand		Limb
X221	Correction of congenital deformity of hip		Limb
X222	Correction of congenital deformity of hip		Limb
X223	Correction of congenital deformity of hip		Limb
X224	Correction of congenital deformity of hip		Limb
X225	Correction of congenital deformity of hip		Limb
X228	Correction of congenital deformity of hip		Limb
X229	Correction of congenital deformity of hip		Limb
X231	Correction of congenital deformity of leg		Limb
X232	Correction of congenital deformity of leg		Limb
X233	Correction of congenital deformity of leg		Limb
X234	Correction of congenital deformity of leg		Limb
X235	Correction of congenital deformity of leg		Limb
X236	Correction of congenital deformity of leg		Limb
X238	Correction of congenital deformity of leg		Limb
X239	Correction of congenital deformity of leg		Limb
X241	Primary correction of congenital deformity of foot		Limb
X242	Primary correction of congenital deformity of foot		Limb
X243	Primary correction of congenital deformity of foot		Limb
X244	Primary correction of congenital deformity of foot		Limb
X248	Primary correction of congenital deformity of foot		Limb
X249	Primary correction of congenital deformity of foot		Limb
X251	Other correction of congenital deformity of foot		Limb
X252	Other correction of congenital deformity of foot		Limb
X253	Other correction of congenital deformity of foot		Limb
X254	Other correction of congenital deformity of foot		Limb
X258	Other correction of congenital deformity of foot		Limb
X259	Other correction of congenital deformity of foot		Limb

OPCS-4 Code	General description	Minor malformation?	Subgroup
X271	Correction of minor congenital deformity of foot		Limb
X278	Correction of minor congenital deformity of foot		Limb
X279	Correction of minor congenital deformity of foot		Limb
A391	Repair of dura		Nervous System
A491	Repair of spina bifida		Nervous System
A492	Repair of spina bifida		Nervous System
A493	Repair of spina bifida		Nervous System
A494	Repair of spina bifida		Nervous System
A498	Repair of spina bifida		Nervous System
A499	Repair of spina bifida		Nervous System
F031	Correction of deformity of lip		Orofacial Clefts
F032	Correction of deformity of lip		Orofacial Clefts
F291	Correction of deformity of palate		Orofacial Clefts
F292	Correction of deformity of palate		Orofacial Clefts
F298	Correction of deformity of palate		Orofacial Clefts
F299	Correction of deformity of palate		Orofacial Clefts
T191	Simple excision of inguinal hernial sac	Yes	Other
T192	Simple excision of inguinal hernial sac	Yes	Other
T193	Simple excision of inguinal hernial sac	Yes	Other
T198	Simple excision of inguinal hernial sac	Yes	Other
T199	Simple excision of inguinal hernial sac	Yes	Other
T201	Primary repair of inguinal hernia	Yes	Other
T202	Primary repair of inguinal hernia	Yes	Other
T203	Primary repair of inguinal hernia	Yes	Other
T204	Primary repair of inguinal hernia	Yes	Other
T208	Primary repair of inguinal hernia	Yes	Other
T209	Primary repair of inguinal hernia	Yes	Other
T211	Repair of recurrent inguinal hernia	Yes	Other
T212	Repair of recurrent inguinal hernia	Yes	Other
T213	Repair of recurrent inguinal hernia	Yes	Other
T214	Repair of recurrent inguinal hernia	Yes	Other
T218	Repair of recurrent inguinal hernia	Yes	Other
T219	Repair of recurrent inguinal hernia	Yes	Other
L751	Other arteriovenous operations		Other
E083	Other operations on internal nose		Respiratory
M024	Total excision of kidney		Urinary
M031	Partial excision of kidney		Urinary
M032	Partial excision of kidney		Urinary
M184	Excision of ureter		Urinary
M201	Replantation of ureter		Urinary
M202	Replantation of ureter		Urinary
M203	Replantation of ureter		Urinary
M208	Replantation of ureter		Urinary
M209	Replantation of ureter		Urinary
M211	Other connection of ureter		Urinary
M212	Other connection of ureter		Urinary
M213	Other connection of ureter		Urinary
M214	Other connection of ureter		Urinary
M215	Other connection of ureter		Urinary
M216	Other connection of ureter		Urinary
M218	Other connection of ureter		Urinary
M219	Other connection of ureter		Urinary

OPCS-4 Code	General description	Minor malformation?	Subgroup
M221	Repair of ureter		Urinary
M222	Repair of ureter		Urinary
M223	Repair of ureter		Urinary
M228	Repair of ureter		Urinary
M229	Repair of ureter		Urinary
M231	Incision of ureter		Urinary
M238	Incision of ureter		Urinary
M239	Incision of ureter		Urinary
M251	Other open operations on ureter		Urinary
M732	Repair of urethra		Urinary

## Appendix 3 – Code lists for antenatal diagnoses of major congenital malformations

Read codes for use in pregnant women

Specificity Level: 1 = Most specific; 2 = Moderately Specific; 3 = Least specific

Read Code	Read Term	Specificity Level
L250100	Fetus with central nervous system malformation - delivered	1
7F1A300	Drainage of hydrocephalus of fetus to facilitate delivery	1
L236.00	Hydrocephalic disproportion	1
L250.00	Fetus with central nervous system malformation	1
7F03000	Percutaneous insertion of fetal vesicoamniotic shunt	1
L250400	Maternal care for CNS malformation in fetus	1
L250200	Fetus with central nervous system malformation + a/n problem	1
L250000	Fetus with central nervous system malformation unspecified	1
L250z00	Fetus with central nervous system malformation NOS	1
L236100	Hydrocephalic disproportion - delivered	1
L258.00	Fetus with cardiovascular abnormality	1
L236z00	Hydrocephalic disproportion NOS	1
7F03400	Percutaneous insertion of bladder drain to fetus	1
L236000	Hydrocephalic disproportion unspecified	1
L236200	Hydrocephalic disproportion with antenatal problem	1
L237.00	Other fetal abnormality causing disproportion	1
L237100	Other fetal abnormality causing disproportion - delivered	1
L237200	Other fetal abnormality causing disproportion with a/n prob	1
5847	U-S scan - fetal abnormality	1
Lyu4500	[X]Obstructed labour due to other abnormalities of fetus	1
L25z400	Maternal care for fetal abnormality and damage	1
L250.13	Suspect fetal spina bifida	2
L250.11	Suspect fetal anencephaly	2
L250.12	Suspect fetal hydrocephaly	2
L250300	Maternal care for suspected CNS malformation in fetus	2
L25..00	Known or suspected fetal abnormality	2
62F9.00	A/N amnio. for ? neural tube	2
Lyu3900	[X]Maternal care/oth spcf known or suspected fetal problems	2
L51X.00	Maternal care/known or suspected fetal problem	2
L51..00	Maternal care for other known or suspected fetal problems	2
Lyu3A00	[X]Maternal care/known or suspected fetal problem	2
L25z300	Maternal care for suspect fetal abnormal and damage	2
62G8.00	A/N U/S scan abnormal	3
L2A..00	Abnormal findings on antenatal screening of mother	3
64B3.00	Birth exam. abnormal -for obs.	3
64D6.00	6 week exam.abnormal -referred	3
64a6.00	8 week exam.abnormal -referred	3



Read Code	Read Term	Specificity Level
64D5.00	6 week exam.abnormal -for obs.	3
62G9.00	A/N U/S scan for ? abnormality	3
L2A3.00	Abnormal ultrasonic finding on antenatal screening of mother	3
5843	U-S obstetric scan abnormal	3
68b3.00	Antenatal screening shows significant disorder	3
64B4.00	Birth exam. abnormal -referred	3
64B5.00	Birth exam abn. - on treatment	3
64a5.00	8 week exam.abnormal -for obs.	3

### ICD-10 codes for use in pregnant women

Specificity Level: 1 = Most specific; 2 = Moderately Specific

ICD-10 code	Description	Specificity Level
O33.6	Maternal care for disproportion due to hydrocephalic fetus	1
O66.3	Obstructed labour due to other abnormalities of fetus	1
O35.0	Maternal care for (suspected) central nervous system malformation in fetus	2
O35.9	Maternal care for (suspected) fetal abnormality and damage, unspecified	2

## Appendix 4 – Code lists for malformations with known causes

### Read codes for antenatal diagnoses

Read Code	Read Term
62F7.00	A/N amniocentesis - abnormal
L251.00	Fetus with chromosomal abnormality
L251100	Fetus with chromosomal abnormality - delivered
L251z00	Fetus with chromosomal abnormality NOS
L251400	Maternal care for chromosomal abnormality in fetus
L251000	Fetus with chromosomal abnormality unspecified
L252000	Fetus with hereditary disease unspecified
L251.11	Suspect cystic fibrosis fetus
L252.00	Fetus with hereditary disease
L252100	Fetus with hereditary disease - delivered
L251.12	Suspect mongol fetus
L252z00	Fetus with hereditary disease NOS
L251300	Maternal care for suspected chromosomal abnormality in fetus

### Read codes for postnatal diagnoses

Read Code	Read Term
PH3yA00	Bloom syndrome
PH33600	Siemen's syndrome
PH02.00	Milroy's disease
PH33011	Acropachyderma
PD12100	Medullary cystic disease, adult type
PG4B200	Fibrochondrogenesis
PG55.00	Chondroectodermal dysplasia
PK82.00	Dysmorphism due to warfarin
PJ50600	Trisomy 12
PG51400	Osteogenesis imperfecta type II
PJ72.00	Klinefelter's syndrome, male with 46XX karyotype
PG58.12	Camurati-Engelmann disease
PJ22.00	Trisomy 18, translocation
PG46100	Spondyloepiphyseal dysplasia tarda
PE00100	Asymmetrical crying face syndrome
PG51600	Osteogenesis imperfecta type IV
PJ63300	Turner's,karyotype 46X + abnorm. sex chromosome,not iso(Xq)
PH1z.12	Alligator skin
PJ53300	Individual with marker heterochromatin
PG51500	Osteogenesis imperfecta type III
PJ53500	Shwachman-Diamond syndrome
P22y200	Gillespie syndrome
PG56.00	Multiple epiphyseal dysplasia

Read Code	Read Term
PJ4..00	Balanced autosomal translocation
PH02.11	Meige's disease
PKyP.11	Wolfram syndrome
PG5D.00	Craniodiaphyseal dysplasia
PH33111	Benign familial chronic pemphigus
PKyB.00	CHARGE association
PD12y00	Medullary cystic disease OS
PH3y411	Darier's disease - keratosis follicularis
PJ01.00	Trisomy 21, mosaicism
PJyz.00	Sex chromosome anomaly NOS
PJ1z.00	Patau's syndrome NOS
PF58.00	Congenital cleft hand
PKy5400	Waardenburg's syndrome
PF55.00	Acrocephalosyndactyly
P336111	Spherical lens
PF55000	Acrocephalosyndactyly (Apert)
PJ36.00	Whole chromosome monosomy, meiotic nondisjunction
PJ50w00	Whole chromosome trisomy, meiotic nondisjunction
PKy9111	Wiedemann - Beckwith syndrome
PKyP.00	Diab insipidus, diab mell, optic atrophy and deafness
PD12011	Nephronophthisis
PJ52400	Polyploidy
PJ...00	Chromosomal anomalies
PJ21.00	Trisomy 18, mosaicism
PKy6600	Dubowitz syndrome
PG4B100	Hypochondrogenesis
62Uz.00	Downs screening blood test NOS
PG51300	Osteogenesis imperfecta type I
PJ38.11	Chromosome replaced with dicentric
PGy4.00	Fibrodysplasia ossificans congenita
PJ63z11	Bonnevie-Ullrich syndrome NOS
PKy6.00	Congenital malformation syndromes with short stature
PD1y000	Fibrocystic kidney disease
PJ50z00	Whole chromosome trisomy syndrome NOS
PH03.00	Congenital elephantiasis
PG4z.00	Chondrodysplasia NOS
PG04.12	Triglorhinophalangeal dysplasia
PKy7311	Rubinstein-Taybi syndrome
PJzz.00	Conditions due to anomaly of unspecified chromosome NOS
PJ74.00	Klinefelter's syndrome, XY/XXY mosaic
PG4C.00	Chondrodysplasia punctata
PJ0..11	Mongolism
PK62.11	Lindau's disease
PH3y611	Tylosis palmaris et plantaris
PJ33212	18p- syndrome

Read Code	Read Term
p226000	congenital bilateral perisylvian syndrome
PH33400	Focal dermal hypoplasia
PA17.11	Whiteman's syndrome
PJ3y011	Velocardiofacial syndrome
PJz3.00	Duplication of chromosome
PG4B.00	lethal retarded ossification syndromes
PJ12.11	Partial trisomy 13 in Patau's syndrome
PJ33000	Deletion of long arm of chromosome 13
PJ33400	Jacobsen syndrome
PG52100	Osteopetrosis - congenita type
PH10.00	Congenital ichthyosis, unspecified
PG5y.11	Dyschondrosteosis
PFy1.00	Larsen's syndrome
PD11011	Autosomal recessive polycystic kidney disease
PJ3y000	Shprintzen syndrome
PF5r300	Clinodactyly
PG5C.00	Craniometaphyseal dysplasia
PF58.11	Lobster-claw hand
PJ33500	Greig cephalopolysyndactyly syndrome
PJ63600	Turner's phenotype, other variant karyotypes
PJ31.11	Deletion of short arm of chromosome 5
PG5A.00	Diaphyseal dysplasia
PyuAC00	[X]Townes-Brocks syndrome
PG55.11	Ellis - Van Creveld syndrome
PKy5200	Cyclops
PG56000	Chondrodysplasia calcificans congenita
PJy1100	Mosaic XO/XX
PD11100	Polycystic kidneys, adult type
PKyE.00	Barber-Say syndrome
P345000	Blue sclera
PG0z.11	Dysmorphic features
PJ62.00	Ovarian dysgenesis
PyuAB00	[X]Pallister-Killian syndrome
PJy2.11	Triple X female
P343.11	Congenital absence of iris
PJ7..00	Klinefelter's syndrome
PGy3.11	Osteo-onychodysostosis
PJz3100	MeCP2 duplication syndrome
PJ31.00	Cri-du-chat syndrome
PH32300	Incontinentia pigmenti
PyuA900	[X]Other specified chromosome abnormalities
PJ52.00	Trisomies of autosomes NEC
PJ51z00	Partial trisomy syndrome NOS
PH3y400	Congenital keratosis follicularis
PH1z.11	Congenital ichthyosiform erythroderma

Read Code	Read Term
PG45.00	Metaphyseal dysostosis
PG53.11	Buschke-Ollendorff syndrome
PG44211	Thanatophoric dysplasia
PKy7400	Sirenomelia
PG44500	Kniest dysplasia
P342200	Rieger's anomaly
PG4A.00	Metachondromatosis
PG5F.00	Acrodysostosis
PyuA.00	[X]Chromosomal abnormalities, not elsewhere classified
PJ33800	Chromosome 4q deletion syndrome
PKy5311	Freeman Sheldon syndrome
C391100	Di George syndrome
F4J7011	stilling-turck-duane syndrome
P11z.13	Billroth's disease
PKy6400	Seckel syndrome
PGy3.12	Onycho-osteodysplasia
PG44000	Diastrophic dwarfism
PKy7.00	Congenital malformation syndromes involving limbs
P313.00	Lenz microphthalmia syndrome
P336000	Microphakia
PG52200	Osteopetrosis - tarda type
P342100	Peter's anomaly
P342300	Peters-plus syndrome
PH41.00	Congenital monilethrix
PH3y200	Epidermolysis bullosa
PG52.00	Osteopetrosis
PH33311	Atrophic heredofamilial dermatosis
PC4yF00	Rokitansky sequence
PD1..14	Sponge kidney
PJ33300	Smith-Magenis syndrome
PD13.11	Multicystic kidney
PGy2100	Ehlers-Danlos syndrome type II
PKy8.00	Congenital malformation syndromes with other skeletal change
PD11z11	Cystic kidney disease NEC
PD12000	Medullary cystic disease, juvenile type
PJ11.00	Trisomy 13, mosaicism
PD12211	Autosomal dominant medullary cystic disease
P22y100	Familial aplasia of the vermis
PD12z00	Medullary cystic disease NOS
PKy5z00	Congenital malform syndrome affecting facial appearance NOS
PD1y100	Cortical cystic disease
PJ51400	Trisomy 9p syndrome
PGy3.00	Nail-patella syndrome
PF55.11	Apert's syndrome
P342000	Axenfield's anomaly

Read Code	Read Term
PJ71.00	Klinefelter's syndrome,male with more than two X chromosomes
PF5r800	Camptodactyly-little finger
PG0G.13	Parietal foramina
PKyC.00	Pena-Shokeir syndrome type I
PJ54.00	Ulnar mammary syndrome
PG45.13	Cranio metaphyseal dysostosis
PG0E.11	Hallerman - Streif syndrome
P344.00	Other iris and ciliary body anomalies
PG41.00	Achondroplasia
PH33100	Hailey-Hailey disease
PJ50.00	Whole chromosome trisomy syndromes
PG47.00	Congenital exostosis
PG4..00	Chondrodysplasia
PH32311	Bloch - Sulzberger syndrome
62U8.00	Downs screening - blood sent
P354.00	Congenital macular changes
PKy9.00	Congenital malformation syndromes with metabolic disturbance
PGy2300	Ehlers-Danlos syndrome type IV
PJ12.00	Trisomy 13, translocation
PKy0511	Multiple hamartoma syndrome
PG4B300	Short-rib/polydactyly syndrome
PH2..00	Dermatoglyphic anomalies
PG51.12	Eddowes's syndrome
1JB0.00	Suspected Downs syndrome
PH33711	Zinsser-Cole-Engman syndrome
PKy5L00	Cardio-facio-cutaneous syndrome
PJ33200	Deletion of short arm of chromosome 18
PG56z00	Multiple epiphyseal dysplasia NOS
PJ1z.11	Trisomy 13 NOS
PKy8000	Noonan's syndrome
PJX..00	Sex chromosome abnormality, male phenotype, unspecified
PH33312	Thomson's disease
PKy7z00	Congenital malformation syndrome involving limbs NOS
PJ52z00	Trisomy of autosomes NEC NOS
PKy7600	Aglossia - adactyly syndrome
PG41.11	Dwarfism
PKyz.11	Cockayne's syndrome
PJyyz00	Other sex chromosome abnormality NOS
PKyz711	Angelman syndrome
PG43.00	Asphyxiating thoracic dysplasia
PG51.14	Lobstein's syndrome
PJ37z00	Whole chromosome monosomy, mosaicism NOS
PH33511	Darier's disease - pseudoxanthoma elasticum
PGy2.00	Ehlers-Danlos syndrome
Pyu9D00	[X]Primary ciliary dyskinesia

Read Code	Read Term
PG41.13	Achondroplastic dwarf
PK63.00	Gardner's syndrome
PKy5600	Marchesani syndrome
PyuA100	[X]Other deletions of part of a chromosome
PKy1.11	Biedl-Bardet syndrome
pg16.00	klippel-feil syndrome
PKy5500	Gorlin-Chaudhry-Moss syndrome
PKy0.12	Prader-Willi syndrome
PKyZ000	Ullrich - Feichtiger syndrome, chimaera
PG57.00	Infantile cortical hyperostosis
PG52000	Osteopetrosis - unclassified
PK8..00	Congenital malformation syndromes due to known exogen causes
PG56011	Chondrodysplasia calcificans congenita
PJ00.00	Trisomy 21, meiotic nondisjunction
PKy9600	VATER association
PKy5B00	Costello syndrome
PKyM.00	Johanson-Blizzard syndrome
44qH.00	Downs screening test
PF67600	Rocker bottom foot
PJ2..00	Edward's syndrome - trisomy 18
PKy5F00	Coffin-Lowry syndrome
PH01.00	Hereditary trophoedema
PJ70.00	Klinefelter's phenotype, karyotype 47XXY
PKy9200	Menke's syndrome
PKyF.00	Alstrom syndrome
PG52.11	Albers - Schonberg syndrome
PJy1.00	Sex chromosome mosaicism
PKy9400	Zellweger's syndrome
PJ3z.00	Monosomies and deletions from the autosomes NOS
PKyD.00	Nicolaidis-Baraitser syndrome
PJ01.11	Trisomy 21, mitotic nondisjunction
PJ52200	Extra marker chromosomes
PJ1..00	Patau's syndrome - trisomy 13
PG04.11	Crouzon's disease
PKy0000	Bannayan-Riley-Ruvalcaba syndrome
PKy5.00	Congen malformation syndromes affecting facial appearance
PJ51500	15q partial trisomy syndrome
PKy9100	Beckwith's syndrome
PD11111	Autosomal dominant polycystic kidney disease
PG43.11	Jeune's syndrome
PJ63.00	Turner's syndrome
PJ6..00	Gonadal dysgenesis
PJ37.00	Whole chromosome monosomy, mosaicism
PJ5y.00	Other specified conditions due to autosomal anomalies
PG5y.12	furst-ostrum syndrome

Read Code	Read Term
PJ53100	Balanced autosomal rearrangement in abnormal individual
PGy2500	Ehlers-Danlos syndrome type VI
PJ51411	9p duplication syndrome
PJyy400	Fragile X syndrome
PKy5011	Papillon-Leage-Psaume syndrome
PF5r900	Camptodactyly-other or multiple
PH3y800	Epidermolysis bullosa letalis
PJ0..00	Down's syndrome - trisomy 21
PKyB.11	CHARGE syndrome
P322112	Congenital macrocornea
PJ33900	Langer-Giedion syndrome
PJ51100	Minor partial trisomy
PJ50400	Trisomy 10
PJ33A00	Kleefstra syndrome
pfy3.00	distal arthrogryposis syndrome
PJ50200	Trisomy 8
PJ10.00	Trisomy 13, meiotic nondisjunction
PJ5..00	Other condition due to autosomal anomaly
PJ50311	Trisomy 9 Mosaic Syndrome
PD12200	Nephronophthisis - medullary cystic disease
P2x3.00	Jaw-winking syndrome
PG44400	Acromesomelic dysplasia
P2x5.00	Riley - Day syndrome
PKy9211	Kinky hair syndrome
PKy5J00	Branchio-oculo-facial syndrome
PJ51.00	Partial trisomy syndromes
PJ33113	18q deletion syndrome
PF55100	Acrocephalosyndactyly (Pfeiffer)
PJ0..12	Trisomy 21
PG53.00	Osteopoikilosis
PJ3..00	Monosomies and deletions from the autosomes
F4J7000	duane's syndrome
PKy5700	Otopalatodigital syndrome
PJ63500	Turner's,mosaic, 45X/other cell line with abn.sex chromosome
PJ30.11	Deletion of long arm of chromosome 21
PK35.00	Kartagener's syndrome
PH3y212	Koebner's disease
PG4D.00	Metaphyseal chondrodysplasia
PJy..00	Other sex chromosome anomaly
PKy5M00	Oculofaciocardiodental syndrome
PH11.00	Harlequin fetus
PJ32.00	Deletion of short arm of chromosome 4
PJyy200	Fragile X chromosome
PJyy000	Chimera 46XX/46XY
PJy3.00	XXY syndrome



Read Code	Read Term
PF5rA00	Clinodactyly with delta phalanx
PKy1.00	Laurence-Moon-Biedl syndrome
PH1y000	Netherton's syndrome
PJy2.12	Karyotype 47, XXX
PG45.11	Jansen's metaphyseal dysostosis
PKy5612	Spherophakia-brachymorphia syndrome
PG46000	Spondyloepiphyseal dysplasia congenita
PJy1000	Mosaic XO/XY
PG44200	Thanatophoric dwarfism
PG4F.00	Lei-Weill dyschondrosteosis
PJ9..00	Mowat-Wilson syndrome
PJ71.12	Klinefelter's syndrome, XXXXY
PJ30.00	Antimongolism syndrome
PK5..12	Epiloia
PKyK.00	Loeys-Dietz syndrome
PK83.00	Fetus and newborn affected by maternal use of alcohol
PJ64.00	Other gonadal dysgenesis phenotype
PJ63612	Turner's phenotype, partial X deletion karyotype
PF29.11	Ectrodactyly of finger
PK81.00	Fetal hydantoin syndrome
PG0D.12	Treacher - Collins syndrome
PJ8..00	Balanced translocation and insertion in normal individual
PKy7500	Arachnodactyly
PC03.00	Streak ovary
PJ33100	Deletion of long arm of chromosome 18
PJy5.00	Mosaicism, lines with various numbers of X chromosomes
62UA.00	Downs screen blood test abnormal
PKyz500	Happy puppet syndrome
PKy5800	Usher's syndrome
PG51.15	Van der Hoeve's syndrome
PKy7300	Rubenstein - Tayi syndrome
PJyy.00	Other specified sex chromosome anomaly
PKy6z00	Congenital malformation syndrome with short stature NOS
P344311	Ectopic pupil
PJ50100	Trisomy 7
PJ51200	10q partial trisomy syndrome
PK5..00	Tuberous sclerosis
PKy5900	Oculo-palato-digital syndrome
PKy5D00	Kabuki make-up syndrome
PJ64000	XY, female phenotype
PH33300	Rothmund-Thomson syndrome
PG40.00	Chondrodysplasia, unspecified
PGy2600	Ehlers-Danlos syndrome type VII
P228300	Aicardi syndrome
PJ50x00	Whole chromosome trisomy, mosaicism

Read Code	Read Term
PG4B000	Achondrogenesis
PJ60.00	Mixed gonadal dysgenesis
PJ0z.11	Trisomy 21 NOS
PG51000	Fragilitas ossium
PH2z.00	Dermatoglyphic anomalies NOS
PJ51000	Major partial trisomy
PH32113	Nettleship's syndrome
PG0F.00	Goldenhar's syndrome
PGy2000	Ehlers-Danlos syndrome type I
PH1y.00	Other specified ichthyosis congenita
PJ50300	Trisomy 9
Pyu9100	[X]Other epidermolysis bullosa
PJ33111	18p- syndrome
PH0..00	Hereditary oedema of legs
PKy0.13	Noonan's syndrome
PH32200	Xeroderma pigmentosum
PG51.13	Adair-Dighton syndrome
PD11z00	Polycystic kidney disease NOS
PKy5000	Oral - facial - digital syndrome
PKy6100	Cockayne syndrome
PKy0200	Adams-Oliver syndrome
PG44300	Mesomelic dysplasia
PG56012	Conradi - Hunermann syndrome
PKy5K00	Cohen syndrome
PJz3000	Potocki-Lupski syndrome
PJ0z.00	Down's syndrome NOS
PKy700	Angelman's syndrome
PH3y500	Acanthosis nigricans, congenital
PH3y900	Epidermolysis bullosa dystrophica
PJ02.11	Partial trisomy 21 in Down's syndrome
pg16z00	klippel - feil syndrome nos
PGy2700	Ehlers-Danlos syndrome type VIII
PKy5300	Whistling face syndrome
PJ50y00	Other specified whole chromosome trisomy syndrome
PG58.11	Engelmann's syndrome
PKy0300	Weaver syndrome
PG52.12	Marble bones
PG47.11	Multiple congenital exostosis
PK60.00	Peutz - Jegher's syndrome
PKy7000	Carpenter's syndrome
PJy2.00	XXX syndrome
PKy9300	Prader - Willi syndrome
PJ33.00	Other deletions of part of a chromosome
PD12012	Autosomal recessive medullary cystic disease
PK80.00	Fetal alcohol syndrome

Read Code	Read Term
PyuA500	[X]Other variants of Turner's syndrome
PG44100	Metatropic dwarfism
PJ3y.00	Other deletions from the autosomes
PKy7900	Popliteal pterygium syndrome
PG42.17	Pseudochondroplasia
P322100	Congenital megalocornea
PG51.16	Brittle bone disease
PKy9000	Alport's syndrome
PJ5z.11	Aneuploidy NEC
PJy1300	Mosaic including XXXXY
PJ38.00	Chromosome replaced with ring or dicentric
PF58200	Cleft hand with syndactyly
PKy7A00	Congenital contractural arachnodactyly
PJ6z.00	Gonadal dysgenesis NOS
PJ63611	Turner's phenotype, ring chromosome karyotype
PJ7z.00	Klinefelter's syndrome NOS
PF67500	Lobster claw foot
PJ20.00	Trisomy 18, meiotic nondisjunction
PG48.00	Diaphyseal aclasis
PJ2z.11	TRISOMY 18 NOS
PH15.00	X-linked ichthyosis
PF5rB00	Clinodactyly, no delta phalanx
PKy6900	Borjeson-Forssman-Lehmann syndrome
PJy1200	Mosaic XY/XXY
P336100	Spherophakia
PJ22.11	Partial trisomy 18 in Edward's syndrome
PKy7B00	Stickler syndrome
P3y0.00	Ocular albinism
PG44.00	Other specified dwarfing syndromes
PKy5H00	Simpson-Golabi-Behmel syndrome
PJz1.00	Additional chromosome NOS
PJ53000	Chromosome inversion in normal individual
PG0J.00	Pierre Robin association
PJ37.12	Autosomal deletion - mosaicism
PJyy300	Karyotype 47,XXY
PG44011	Diastrophic dysplasia
PG42.14	Chondrodystrophy NEC
PJ38.12	Chromosome replaced with ring
PH31300	Angiomatosis
PKy7100	Holt - Oram syndrome
PKy5611	Weill-Marchesani syndrome
P322111	Enlarged cornea
PyuAD00	[X]Li-Fraumeni syndrome
PJ2z.00	Edward's syndrome NOS
PJy4.00	Female with more than three X chromosomes

Read Code	Read Term
PG03000	Muenke syndrome
P2x2.00	Familial dysautonomia
PKy7800	Multiple pterygium syndrome
PG46.00	Spondyloepiphyseal dysplasia
Pyu9000	[X]Other congenital ichthyosis
PJ73.00	Klinefelter's syndrome, XXYY
PJ53.11	Balanced translocations
P343.00	Aniridia
PH0z.00	Hereditary oedema of legs NOS
PK84.00	Fetal valproate syndrome
PD12111	Medullary sponge kidney
PJ63z12	Ovarian dwarfism NEC
P322000	Congenital keratoglobus
62U9.00	Downs screen blood test normal
PG45.12	Schmid's metaphyseal dysostosis
PH13.00	Collodion baby
PJ52100	Duplications with other complex rearrangements
PKy6000	Amsterdam dwarf
PG41000	Hypochondroplasia
PD1..13	Polycystic kidney
PG51200	Osteogenesis imperfecta - unclassifiable
PD1y011	Fibrocystic renal degeneration
PJ52300	Triploidy
PH33700	Dyskeratosis congenita
PKy6500	Aarskog syndrome
PH20.00	Abnormal palmar creases
PKyJ.00	Lujan-Fryns syndrome
PH3y700	Epidermolysis bullosa simplex
PKy0.11	Prader-Willi Syndrome
PG45.15	Metaphyseal dysplasia
PJ33211	18q- syndrome
PJy6.00	Male with structurally abnormal sex chromosome
P22y111	Joubert syndrome
P302.00	Cryptophthalmos syndrome
P2x4.00	Marcus - Gunn syndrome
PG42.15	Hypochondroplasia
PKy0100	Currarino triad
PKy5A00	Trichorhinophalangeal syndrome
13L2.11	Downs child in family
PH14.00	Ichthyosis vulgaris
PKy6700	Robinow syndrome
PJ32.11	Wolff - Hirschorn syndrome
PE00000	Hemifacial microsomia
PH30.00	Congenital ectodermal dysplasia
PJ63200	Turner's phenotype, karyotype 46X iso (Xq)

Read Code	Read Term
PJy0.00	Additional sex chromosome
PKy5100	Mohr's syndrome
PKy4.00	William syndrome
PF55300	Saethre-Chotzen syndrome
PD11000	Polycystic kidneys, infantile type
PG58.00	Progressive diaphyseal dysplasia
PK5..11	Bourneville's disease
PKy8z00	Congenital malformation syndrome+other skeletal changes NOS
PJ63000	Turner's phenotype, karyotype normal
PG0D.00	Mandibulofacial dysostosis
PJ51311	4p duplication syndrome
PJy1z00	Sex chromosome mosaicism NOS
PKy6800	Floating-Harbor syndrome
PG0C.00	Pierre - Robin syndrome
PF58300	Cleft hand with polydactyly
PG51.00	Osteogenesis imperfecta
PH1..00	Ichthyosis congenita
PJ52000	Duplications seen only at prometaphase
PJyy.11	Absence of sex chromosome
PJyy100	46XX true hermaphrodite
PKy6011	Cornelia de Lange syndrome
P235.00	X-linked hydrocephalus
PJ71.11	Klinefelter's syndrome, XXXY
PH1z.00	Ichthyosis congenita NOS
PF5r200	Camptodactyly
PG0E.00	Oculomandibular dysostosis
PJz0.00	Mosaicism NOS
PKy7412	Mermaid sirenómelia
PKyz511	Angelman syndrome
PJ33z00	Other deletion of part of a chromosome NOS
PG51100	Osteopsathyrosis
PJ50800	Trisomy 22
62U..00	Downs screen - blood test
PJ63z00	Turner's syndrome NOS
8CEM.00	Downs syndrome antenatal screening information leaflet given
PC73.00	Pure gonadal dysgenesis
PG4B400	Camptomelia dysplasia
PKy0600	Feingold syndrome
PG44600	Pseudoachondroplasia
PH33500	Pseudoxanthoma elasticum
PG42.16	Osteopathia striata
PH3y300	Congenital keratoderma
PF3A.00	Split foot
PH12.11	Sjogren - Larsson syndrome
PE1..12	Sternomastoid tumour

Read Code	Read Term
PKy7A11	Beals syndrome
PKy6200	Russell - Silver syndrome
PKy0500	Cowden syndrome
PKy7200	Klippel - Trenaunay - Weber syndrome
PD11.00	Polycystic kidney disease
PK62.00	Von Hippel-Lindau syndrome
PKy7611	Hanhart syndrome
PJ53400	Individual with autosomal fragile site
PG4E.00	Spondylometaphyseal dysplasia
PJ63400	Turner's phenotype, mosaicism 45X/46XX or 45X/46XY
PJ63100	Turner's phenotype, karyotype 45X
PG57.11	Caffey's syndrome
PJ33600	Chromosome 22q11 deletion syndrome
PG42100	Myotonic chondrodysplasia
PKy6300	Smith - Lemli - Opitz syndrome
PJz2.00	Deletion of chromosome NOS
PH12.00	Ichthyosiform erythroderma
PD12.00	Medullary cystic disease
PJ53.00	Balanced rearrangements and structural markers NEC
PGy2200	Ehlers-Danlos syndrome type III
PG5B.00	Multiple synostosis syndrome
PG51z00	Osteogenesis imperfecta NOS
PKy5C00	Treacher Collins syndrome
PJ5z.00	Unspecified conditions due to autosomal anomalies
PG51.11	Vrolik's disease
PGyy300	Popliteal web syndrome
PKyL.00	FG syndrome
PJz..00	Chromosomal anomalies NOS
PG44z00	Other dwarfing syndromes NOS
PG04.00	Craniofacial dysostosis
PB63500	Alagille syndrome
PJ02.00	Trisomy 21, translocation
PKyG.11	Ohdo blepharophimosis syndrome
PKy2.00	Marfan's syndrome
PD1..12	Fibrocystic kidney
PH33000	Brugsch's syndrome

### ICD-10 codes for antenatal diagnoses

ICD-10 Code	Description
O28.5	Abnrm chromosom and genet find antenat screen of mother
O35.1	Mat care for (suspected) chromosomal abnormality in fetus
O35.2	Maternal care for (suspected) hereditary disease in fetus

## ICD-10 codes for postnatal diagnoses

ICD-10	Description
D18.1	Lymphangioma, any site
D82.1	Di George's syndrome
Q12.4	Spherophakia
Q13.1	Absence of iris
Q13.5	Blue sclera
Q61.1	Polycystic kidney, infantile type
Q61.2	Polycystic kidney, adult type
Q61.3	Polycystic kidney, unspecified
Q61.5	Medullary cystic kidney
Q71.6	Lobster-claw hand
Q72.7	Split foot
Q75.1	Craniofacial dysostosis
Q75.4	Mandibulofacial dysostosis
Q75.5	Oculomandibular dysostosis
Q76.1	Klippel-Feil syndrome
Q77.0	Achondrogenesis
Q77.1	Thanatophoric short stature
Q77.2	Short rib syndrome
Q77.3	Chondrodysplasia punctata
Q77.4	Achondroplasia
Q77.5	Dystrophic dysplasia
Q77.6	Chondroectodermal dysplasia
Q77.7	Spondyloepiphyseal dysplasia
Q78.0	Osteogenesis imperfecta
Q78.2	Osteopetrosis
Q78.3	Progressive diaphyseal dysplasia
Q78.5	Metaphyseal dysplasia
Q78.6	Multiple congenital exostoses
Q79.6	Ehlers-Danlos syndrome
Q80	Congenital ichthyosis
Q80.0	Ichthyosis vulgaris
Q80.1	X-linked ichthyosis
Q80.2	Lamellar ichthyosis
Q80.3	Congenital bullous ichthyosiform erythroderma
Q80.4	Harlequin fetus
Q80.8	Other congenital ichthyosis
Q80.9	Congenital ichthyosis, unspecified
Q81	Epidermolysis bullosa
Q81.0	Epidermolysis bullosa simplex
Q81.1	Epidermolysis bullosa letalis
Q81.2	Epidermolysis bullosa dystrophica
Q81.8	Other epidermolysis bullosa

ICD-10	Description
Q81.9	Epidermolysis bullosa, unspecified
Q82.0	Hereditary lymphoedema
Q82.1	Xeroderma pigmentosum
Q82.3	Incontinentia pigmenti
Q82.4	Ectodermal dysplasia (anhidrotic)
Q85	Phakomatoses, not elsewhere classified
Q85.0	Neurofibromatosis (nonmalignant)
Q85.1	Tuberous sclerosis
Q85.8	Other phakomatoses, not elsewhere classified
Q85.9	Phakomatosis, unspecified
Q86	Cong malformation syndromes due to known exogen causes NEC
Q86.0	Fetal alcohol syndrome (dysmorphic)
Q86.1	Fetal hydantoin syndrome
Q86.2	Dysmorphism due to warfarin
Q86.8	Oth cong malform syndromes due to known exogen causes
Q87	Oth spec cong malform syndromes affecting multiple sys
Q87.0	Cong malform syndromes predom affect facial appearance
Q87.1	Cong malform syndromes predomin assoc with short stature
Q87.2	Cong malformation syndromes predominantly involving limbs
Q87.3	Congenital malformation syndromes involving early overgrowth
Q87.4	Marfan's syndrome
Q87.5	Other cong malform syndromes with other skeletal changes
Q87.8	Other specified congenital malformation syndromes NEC
Q90	Down's syndrome
Q90.0	Trisomy 21, meiotic nondisjunction
Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	Trisomy 21, translocation
Q90.9	Down's syndrome, unspecified
Q91	Edwards' syndrome and Patau's syndrome
Q91.0	Trisomy 18, meiotic nondisjunction
Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	Trisomy 18, translocation
Q91.3	Edwards' syndrome, unspecified
Q91.4	Trisomy 13, meiotic nondisjunction
Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
Q91.6	Trisomy 13, translocation
Q91.7	Patau's syndrome, unspecified
Q92	Other trisomies and partial trisomies of the autosomes NEC
Q92.0	Whole chromosome trisomy, meiotic nondisjunction
Q92.1	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)
Q92.2	Major partial trisomy
Q92.3	Minor partial trisomy
Q92.4	Duplications seen only at prometaphase
Q92.5	Duplications with other complex rearrangements
Q92.6	Extra marker chromosomes



ICD-10	Description
Q92.7	Triploidy and polyploidy
Q92.8	Other specified trisomies and partial trisomies of autosomes
Q92.9	Trisomy and partial trisomy of autosomes, unspecified
Q93	Monosomies and deletions from the autosomes NEC
Q93.0	Whole chromosome monosomy, meiotic nondisjunction
Q93.1	Whole chrom monosomy mosaicism (mitotic nondisjunction)
Q93.2	Chromosome replaced with ring or dicentric
Q93.3	Deletion of short arm of chromosome 4
Q93.4	Deletion of short arm of chromosome 5
Q93.5	Other deletions of part of a chromosome
Q93.6	Deletions seen only at prometaphase
Q93.7	Deletions with other complex rearrangements
Q93.8	Other deletions from the autosomes
Q93.9	Deletion from autosomes, unspecified
Q95	Balanced rearrangements and structural markers NEC
Q95.0	Balanced translocation and insertion in normal individual
Q95.1	Chromosome inversion in normal individual
Q95.2	Balanced autosomal rearrangement in abnormal individual
Q95.3	Balanced sex/autosomal rearrangement in abnormal individual
Q95.4	Individuals with marker heterochromatin
Q95.5	Individuals with autosomal fragile site
Q95.8	Other balanced rearrangements and structural markers
Q95.9	Balanced rearrangement and structural marker, unspecified
Q96	Turner's syndrome
Q96.0	Karyotype 45,X
Q96.1	Karyotype 46,X iso (Xq)
Q96.2	Karyotype 46,X with abnormal sex chromosome, except iso (Xq)
Q96.3	Mosaicism, 45,X/46,XX or XY
Q96.4	Mosaicism 45X/oth cell line(s) with abnorm sex chromosome
Q96.8	Other variants of Turner's syndrome
Q96.9	Turner's syndrome, unspecified
Q97	Other sex chromosome abnormalities, female phenotype NEC
Q97.0	Karyotype 47,XXX
Q97.1	Female with more than three X chromosomes
Q97.2	Mosaicism, lines with various numbers of X chromosomes
Q97.3	Female with 46,XY karyotype
Q97.8	Oth spec sex chromosome abnormalities female phrenotype
Q97.9	Sex chromosome abnormality, female phenotype, unspecified
Q98	Other sex chromosome abnormalities, male phenotype NEC
Q98.0	Klinefelter's syndrome karyotype 47,XXY
Q98.1	Klinefelter's syn male with more than two X chromosomes
Q98.2	Klinefelter's syndrome, male with 46,XX karyotype
Q98.3	Other male with 46,XX karyotype
Q98.4	Klinefelter's syndrome, unspecified
Q98.5	Karyotype 47,XXY

ICD-10	Description
Q98.6	Male with structurally abnormal sex chromosome
Q98.7	Male with sex chromosome mosaicism
Q98.8	Other specified sex chromosome abnormalities, male phenotype
Q98.9	Sex chromosome abnormality, male phenotype, unspecified
Q99	Other chromosome abnormalities, not elsewhere classified
Q99.0	Chimera 46,XX/46,XY
Q99.1	46,XX true hermaphrodite
Q99.2	Fragile X chromosome
Q99.8	Other specified chromosome abnormalities
Q99.9	Chromosomal abnormality, unspecified

## Appendix 5 – Code lists for congenital infections

### Read codes for use in pregnant women

Read code	Read Term
43C3.11	HIV positive
A788200	HIV infection with persistent generalised lymphadenopathy
A788U00	HIV disease result/haematological+immunologic abnorms,NEC
A788W00	HIV disease resulting in unspecified malignant neoplasm
A788X00	HIV disease resulting/unspsc infectious+parasitic disease
A789000	HIV disease resulting in mycobacterial infection
A789100	HIV disease resulting in cytomegaloviral disease
A789200	HIV disease resulting in candidiasis
A789300	HIV disease resulting in Pneumocystis carinii pneumonia
A789311	HIV disease resulting in Pneumocystis jirovecii pneumonia
A789400	HIV disease resulting in multiple infections
A789500	HIV disease resulting in Kaposi's sarcoma
A789511	HIV disease resulting in Kaposi sarcoma
A789600	HIV disease resulting in Burkitt's lymphoma
A789700	HIV dis resulting oth types of non-Hodgkin's lymphoma
A789800	HIV disease resulting in multiple malignant neoplasms
A789900	HIV disease resulting in lymphoid interstitial pneumonitis
A789A00	HIV disease resulting in wasting syndrome
A789X00	HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu
AyuC100	[X]HIV disease resulting in other viral infections
AyuC300	[X]HIV disease resulting in multiple infections
AyuC400	[X]HIV disease resulting/other infectious+parasitic diseases
AyuC600	[X]HIV disease resulting in other non-Hodgkin's lymphoma
AyuCB00	[X]HIV disease result/haematological+immunologic abnorms,NEC
AyuCC00	[X]HIV disease resulting in other specified conditions
AyuCD00	[X]Unspecified human immunodeficiency virus [HIV] disease
L179.00	HIV disease complicating pregnancy childbirth puerperium
R109.00	[D]Laboratory evidence of human immunodeficiency virus [HIV]
Eu02400	[X]Dementia in human immunodef virus [HIV] disease
A788.11	Human immunodeficiency virus infection
65QA.00	AIDS carrier
A788.00	Acquired immune deficiency syndrome
ZV01A00	[V]Asymptomatic human immunodeficiency virus infection status
4J34.00	HIV viral load
65VE.00	Notification of AIDS
A788z00	Acquired human immunodeficiency virus infection syndrome NOS
43j7.00	HIV 1 nucleic acid detection
A789.00	Human immunodef virus resulting in other disease
A788400	Human immunodeficiency virus with neurological disease
A788000	Acute human immunodeficiency virus infection
A788100	Asymptomatic human immunodeficiency virus infection

Read code	Read Term
AyuC.00	[X]Human immunodeficiency virus disease
A788y00	Human immunodeficiency virus with other clinical findings
A788500	Human immunodeficiency virus with secondary infection
A788300	Human immunodeficiency virus with constitutional disease
43w3.00	Human immunodeficiency virus RNA/DNA ratio
4J3F.00	Human immunodeficiency virus viral load by log rank
66j0.00	Human immunodeficiency virus annual review
A788600	Human immunodeficiency virus with secondary cancers
9kl..00	HIV pos gen health check serv declind - enhanc service admin
4J3N.00	Human immunodeficiency virus drug resistance test
4J3P.00	Human immunodeficiency virus type 1 subtype identification
43wC.00	Detection of Varicella zoster virus using PCR technique
A52..00	Chickenpox - varicella
A52..11	Chickenpox
A520.00	Postvaricella encephalitis
A521.00	Varicella pneumonitis
A52x.00	Varicella with other specified complications
A52y.00	Varicella with unspecified complications NOS
A52z.00	Varicella with no complication NOS
AyuA200	[X]Varicella with other complications
AyuA300	[X]Varicella without complications
F011700	Varicella meningitis
F035000	Encephalitis following chickenpox
F035011	Encephalitis due to varicella
F037000	Varicella transverse myelitis
H24y700	Pneumonia with varicella
43jF.00	Varicella zoster nucleic acid detection
A570.00	Erythema infectiosum - fifth disease
A570.11	Fifth disease
A570.12	Slapped cheek syndrome
A796.00	Parvovirus infection
A7y0400	Parvovirus as cause of diseases classified to oth chapters
AyuDD00	[X]Parvovirus infection, unspecified
43jB.00	Parvovirus B19 nucleic acid detection
L175.00	Maternal rubella in pregnancy, childbirth and the puerperium
L175.11	Rubella contact in pregnancy
L175000	Maternal rubella, unspecified whether pregnancy/puerperium
L175100	Maternal rubella during pregnancy - baby delivered
L175300	Maternal rubella during pregnancy - baby not yet delivered
L175z00	Maternal rubella in pregnancy/childbirth/puerperium NOS
L253.11	Fetus with suspected rubella damage via mother
L253300	Maternal care for damage to fetus from maternal rubella
43jm.00	Rubella virus nucleic acid detection
65VG.00	Notification of rubella
A56..00	Rubella

Read code	Read Term
A56..11	German measles
A56xz00	Rubella with other specified complication NOS
A56y.00	Rubella with unspecified complication
A56z.00	Rubella with no complication NOS
AyuA900	[X]Rubella with other complications
AyuAA00	[X]Rubella without complication
A56..12	French measles
A56..13	Liberty measles
L169.00	Herpes gestationis
L169000	Herpes gestationis unspecified
L169100	Herpes gestationis - delivered
L169200	Herpes gestationis - delivered with postnatal complication
L169300	Herpes gestationis - not delivered
L169400	Herpes gestationis with postnatal complication
L169z00	Herpes gestationis NOS
43j6.00	Herpes simplex nucleic acid detection
43jt.00	Human herpes virus 6 nucleic acid detection
43ju.00	Human herpes virus 7 nucleic acid detection
43jv.00	Human herpes virus 8 nucleic acid detection
43w5.00	Herpes simplex virus type 2 nucleic acid detection
4J3C.00	Herpes simplex virus isolation
A54..00	Herpes simplex
A54..11	Herpes simplex viral infection
A546.00	Herpes simplex whitlow
A54x.00	Herpes simplex with other specified complication
A54x000	Visceral herpes simplex
A54x300	Herpesviral vesicular dermatitis
A54xz00	Herpes simplex with other specified complication NOS
A54y.00	Herpes simplex with unspecified complication
A54z.00	Herpes simplex no complication NOS
A54z.11	Herpes labialis
AyuA000	[X]Other forms of herpesviral infections
AyuA100	[X]Herpesviral infection, unspecified
43w4.00	Herpes simplex virus type 1 nucleic acid detection
L170.00	Maternal syphilis in pregnancy/childbirth/puerperium
L170000	Maternal syphilis, unspec whether in pregnancy or puerperium
L170100	Maternal syphilis during pregnancy - baby delivered
L170200	Maternal syphilis in puerperium - baby delivered
L170z00	Maternal syphilis in pregnancy/childbirth/puerperium NOS
L254.12	Suspect fetal damage from maternal toxoplasmosis
43j0.00	Cytomegalovirus nucleic acid detection
A751.00	Cytomegaloviral mononucleosis
A785000	Cytomegaloviral pneumonitis
A785100	Cytomegaloviral pancreatitis
A785200	Cytomegaloviral hepatitis

Read code	Read Term
A785X00	Cytomegaloviral disease, unspecified
A799.00	Cytomegalovirus infection
A799.11	CMV - Cytomegalovirus infection
AyuD000	[X]Other cytomegaloviral diseases
AyuD100	[X]Cytomegaloviral disease, unspecified

### Read codes for use in infants

Read code	Read Term
Q400.00	Congenital rubella
Q401.00	Congenital cytomegalovirus infection
Q402000	Congenital herpes simplex
Q402300	Congenital toxoplasmosis
Q402311	Congenital hydrocephalus due to toxoplasmosis
Q402312	Lymphadenopathy due to congenital toxoplasmosis
A90..00	Congenital syphilis
A900.00	Early congenital syphilis with symptoms
A900.12	Congenital syphilitic choroiditis
A900.13	Congenital syphilitic chronic coryza
A900.14	Congenital syphilitic epiphysitis
A900.16	Congenital syphilitic osteochondritis
A901.00	Early latent congenital syphilis
A902.00	Early congenital syphilis NOS
A904200	Congenital syphilitic meningitis
A905.00	Other late congenital syphilis
A905000	Congenital syphilitic gumma
A905300	Late congenital syphilitic oculopathy
A906.00	Latent late congenital syphilis
A907.00	Unspecified late congenital syphilis
A90z.00	Congenital syphilis NOS
Ayu4300	[X]Congenital syphilis, unspecified
F007400	Meningitis due to congenital syphilis
F033100	Encephalitis due to congenital syphilis

### ICD-10 codes for use in infants

ICD-10 code	Description
A50	congenital syphilis
A500	early congenital syphilis, symptomatic
A501	early congenital syphilis, latent
A502	early congenital syphilis, unspecified
A503	late congenital syphilitic oculopathy
A504	late congenital neurosyphilis [juvenile neurosyphilis]
A505	other late congenital syphilis, symptomatic

ICD-10 code	Description
A506	late congenital syphilis, latent
A507	late congenital syphilis, unspecified
A509	congenital syphilis, unspecified
A51	early syphilis
A513	secondary syphilis of skin and mucous membranes
A514	other secondary syphilis
A515	early syphilis, latent
A519	early syphilis, unspecified
A52	late syphilis
A520	cardiovascular syphilis
A521	symptomatic neurosyphilis
A522	asymptomatic neurosyphilis
A523	neurosyphilis, unspecified
A527	other symptomatic late syphilis
A528	late syphilis, latent
A529	late syphilis, unspecified
A53	other and unspecified syphilis
A530	latent syphilis, unspecified as early or late
A539	syphilis, unspecified
I980	cardiovascular syphilis
K672	syphilitic peritonitis
M031	postinfective arthropathy in syphilis
M731	syphilitic bursitis
N290	late syphilis of kidney
B20	human immunodeficiency virus disease resulting in infectious and parasitic diseases
B200	human immunodeficiency virus disease resulting in mycobacterial infection
B201	human immunodeficiency virus disease resulting in other bacterial infections
B202	human immunodeficiency virus disease resulting in cytomegalovirus disease
B203	human immunodeficiency virus disease resulting in other viral infections
B204	human immunodeficiency virus disease resulting in candidiasis
B205	human immunodeficiency virus disease resulting in other mycoses
B206	human immunodeficiency virus disease resulting in pneumocystis carinii pneumonia
B207	human immunodeficiency virus disease resulting in multiple infections
B208	human immunodeficiency virus disease resulting in other infectious and parasitic diseases
B209	human immunodeficiency virus disease resulting in unspecified infectious or parasitic disease
B21	human immunodeficiency virus disease resulting in malignant neoplasms
B210	human immunodeficiency virus disease resulting in Kaposi's sarcoma
B211	human immunodeficiency virus disease resulting in Burkitt's lymphoma
B212	human immunodeficiency virus disease resulting in other types of non-Hodgkin's lymphoma
B213	human immunodeficiency virus disease resulting in other malignant neoplasms of lymphoid and hematopoietic tissues
B217	human immunodeficiency virus disease resulting in multiple malignant neoplasms
B218	human immunodeficiency virus disease resulting in other malignant neoplasms
B219	human immunodeficiency virus disease resulting in unspecified malignant neoplasm
B22	human immunodeficiency virus disease resulting in other specified diseases
B220	human immunodeficiency virus disease resulting in encephalopathy

ICD-10 code	Description
B221	hiv disease resulting in lymphoid interstitial pneumonitis
B222	hiv disease resulting in wasting syndrome
B227	hiv dis resulting in multiple diseases classif elsewhere
B23	human immunodef virus dis resulting in other conditions
B230	acute hiv infection syndrome
B231	hiv dis result (persistent) generalized lymphadenopathy
B232	hiv dis result haematologic / immunologic abnorm nec
B238	hiv disease resulting in other specified conditions
B24	unspecified human immunodeficiency virus [hiv] disease
F024	dementia in human immunodef virus [hiv] disease
R75	laboratory evidence of human immunodeficiency virus [hiv]
Z114	spec screening exam for human immunodeficiency virus [hiv]
Z206	contact with and exposure to human immunodef virus [hiv]
Z21	asymptomatic human immunodef virus [hiv] infect status
P350	congenital rubella syndrome
P352	congenital herpesviral [herpes simplex] infection
P351	congenital cytomegalovirus infection
P371	congenital toxoplasmosis



## Appendix 6 – Code lists used for influenza vaccination

### Read codes

Where a code describes the “administration” of a vaccine, this does not mean the vaccine was given to the patient but rather that some administrative task relating to vaccination was carried out. This could include sending reminders to patients, for example. Such codes were classified as “advised”.

Read Code	Read Term	Seasonal vaccine	Pandemic vaccine	Unspecified influenza vaccine	Received	Refused	Advised	Given Elsewhere	Not indicated	Adverse
68NV000	Consent given for seasonal influenza vaccination	1			1					
65ED.00	Seasonal influenza vaccination	1			1					
9N4q100	DNA first intranasal seasonal influenza vaccination	1				1				
812F000	Seasonal influenza vaccination contraindicated	1				1				
90X5600	Second intranasal seasonal influenza vaccination declined	1				1				
90X5100	Seasonal influenza vaccination declined	1				1				
68NE000	No consent for seasonal influenza vaccination	1				1				
90X5200	First intranasal influenza vaccination declined	1				1				
90X5300	Second intranasal influenza vaccination declined	1				1				
90X5400	First intranasal seasonal influenza vaccination declined	1				1				
65EE100	Administration of second intranasal influenza vaccination	1					1			
65EE.00	Administration of intranasal influenza vaccination	1					1			
65ED100	Administration of first intranasal seasonal influenza vacc	1					1			
65ED400	Administration of first inactivated seasonal influenza vacc	1					1			
65ED300	Administration of second intranasal	1					1			

Read Code	Read Term	Seasonal vaccine	Pandemic vaccine	Unspecific influenza vaccine	Received	Refused	Advised	Given Elsewhere	Not indicated	Adverse
	seasonal influenza vacc									
65EE000	Administration of first intranasal influenza vaccination	1					1			
8BQ1.00	Long term indication for seasonal influenza vaccination	1					1			
65ED200	Seasonal influenza vaccination given while hospital inpt	1						1		
65E2000	Seasonal influenza vaccin given by other healthcare provider	1						1		
65E2100	First intranasal seasonal flu vacc gvn by othr hlthcare prov	1						1		
65E2400	1st intramuscular seasonal influenza vacc given by other HCP	1						1		
65E2300	2nd intramuscular seasonal influenza vacc given by other HCP	1						1		
65E2200	Secnd intranasal seasonal flu vacc gvn by othr hlthcare prov	1						1		
65ED000	Seasonal influenza vaccination given by pharmacist	1						1		
8I6D000	Seasonal influenza vaccination not indicated	1							1	
65E6.00	CELVAPAN - second influenza A (H1N1v) 2009 vaccination given		1		1					
65E0.00	First pandemic influenza vaccination		1		1					
65E1.00	Second pandemic influenza vaccination		1		1					
65E5.00	CELVAPAN - first influenza A (H1N1v) 2009 vaccination given		1		1					
65E9.00	PANDEMRIX - first influenza A (H1N1v) 2009 vaccination given		1		1					
65EA.00	PANDEMRIX - second influenza A (H1N1v) 2009 vaccination give		1		1					
68Nr.00	Consent given for pandemic influenza vaccination		1		1					

Read Code	Read Term	Seasonal vaccine	Pandemic vaccine	Unspecific influenza vaccine	Received	Refused	Advised	Given Elsewhere	Not indicated	Adverse
68Nt.00	Consent given for influenza A subtype H1N1 vaccination		1		1					
68Ns.00	No consent for influenza A (H1N1v) 2009 vaccination		1			1				
812d.00	Pandemic influenza vaccination contraindicated		1			1				
81AG.00	Pandemic influenza vaccination declined		1			1				
90X5500	First intranasal pandemic influenza vaccination declined		1			1				
90X5000	Influenza A virus subtype H1N1 vaccination declined		1			1				
9N4q000	Did not attend influenza A virus subtype H1N1 vaccination		1			1				
6.50E+01	Administration of first intranasal pandemic influenza vacc		1				1			
65E1000	Administration of second intranasal pandemic influenza vacc		1				1			
2J63.00	High priority for influenza A subtype H1N1 vaccination		1				1			
90XC000	Influenza A virus subtype H1N1 vaccination SMS text message sent		1				1			
65E3.00	1st pandemic influenza vaccination given by other healthcare provider		1					1		
65E3000	First intranasal pandemic influenza vaccination given by other healthcare provider		1					1		
65EB.00	PANDEMRIX - 1st influenza A (H1N1v) 2009 vaccination by other healthcare provider		1					1		
65EC.00	PANDEMRIX - 2nd influenza A (H1N1v) 2009 vaccination by other healthcare provider		1					1		
65E7.00	CELVAPAN - 1st influenza A (H1N1v) 2009 vaccination by other healthcare provider		1					1		
65E4.00	2nd pandemic influenza vaccination given by other healthcare provider		1					1		
65E8.00	CELVAPAN - 2nd influenza A (H1N1v) 2009 vaccination by other healthcare provider		1					1		

Read Code	Read Term	Seasonal vaccine	Pandemic vaccine	Unspecified flu vaccine	Received	Refused	Advised	Given Elsewhere	Not indicated	Adverse
816g.00	Pandemic influenza vaccination not indicated		1						1	
68NV.00	Influenza vaccination consent given			1	1					
65E..00	Influenza vaccination			1	1					
ZV04811	[V]Flu - influenza vaccination			1	1					
ZV04800	[V]Influenza vaccination			1	1					
68Nu.00	No response to influenza vaccination invitation			1		1				
812F.00	Influenza vaccination contraindicated			1		1				
90X5.00	Influenza vaccination declined			1		1				
68NE.00	No consent - influenza imm.			1		1				
9N4q.00	Did not attend flu vaccination appointment			1		1				
90X7200	Influenza vaccination third telephone invitation			1			1			
90XD.00	Influenza vaccination verbal invitation			1			1			
90XC200	Influenza vaccination invitation 2nd SMS text message sent			1			1			
90XD000	Influenza vaccination first verbal invitation			1			1			
90XC300	Influenza vaccination invitation 3rd SMS text message sent			1			1			
90X4.00	Needs influenza immunisation			1			1			
90XB.00	Influenza vaccination invitation third letter sent			1			1			
9k7..00	Influenza immunisation - enhanced services administration			1			1			
90XE100	Influenza vaccination invitation second email			1			1			
90XA.00	Influenza vaccination invitation second letter sent			1			1			

Read Code	Read Term	Seasonal vaccine	Pandemic vaccine	Unspecified flu vaccine	Received	Refused	Advised	Given Elsewhere	Not indicated	Adverse
90X7000	Influenza vaccination first telephone invitation			1			1			
90X..00	Influenza vacc. administratn.			1			1			
90XC100	Influenza vaccination invitation 1st SMS text message sent			1			1			
90XE.00	Influenza vaccination invitation email			1			1			
6797000	Education about influenza vaccination			1			1			
90XE200	Influenza vaccination invitation third email			1			1			
90XE000	Influenza vaccination invitation first email			1			1			
8ME..00	Influenza vaccination requested			1			1			
90X7100	Influenza vaccination second telephone invitation			1			1			
90XD200	Influenza vaccination third verbal invitation			1			1			
90XD100	Influenza vaccination second verbal invitation			1			1			
90X..11	Flu vaccination administration			1			1			
68NN.11	Influenza immunization advised			1			1			
68NO.00	Influenza imm.advised at home			1			1			
90X9.00	Influenza vaccination invitation first letter sent			1			1			
90X6.00	Influenza vaccination invitation letter sent			1			1			
90XC.00	Influenza vaccination invitation SMS text message sent			1			1			
90X7.00	Influenza vaccination telephone invite			1			1			
90XZ.00	Influenza vacc.administrat.NOS			1			1			
90X1.00	Has 'flu vaccination at home			1				1		
90X3.00	Has 'flu vaccination at hosp.			1				1		

Read Code	Read Term	Seasonal vaccine	Pandemic vaccine	Unspecified flu vaccine	Received	Refused	Advised	Given Elsewhere	Not indicated	Adverse
65E2.00	Influenza vaccination given by other healthcare provider			1				1		
90X8.00	Has influenza vaccination at work			1				1		
90X2.00	Has'flu vaccination at surgery			1				1		
816D.00	Influenza vaccination not indicated			1					1	
F034G00	Post influenza vaccination encephalitis			1						1
U60K400	[X]Influenza vaccine causing adverse effects therapeutic use			1						1

### Immunisation codes

Immunisation codes cannot be categorized as indicating vaccine receipt, refusal or advice. Whether a vaccine is received, refused or advised is available under a different variable in the immunisation file and must be used in conjunction with the immunisation codes.

Immunisation code	Immunisation type	Pandemic vaccine	Seasonal vaccine	Unspecified vaccine	Vaccine Given Elsewhere
4	FLU			1	
71	PFLUGEN	1			
72	PFLUGSK	1			
73	PFLUGSKO	1			1
74	PFLUGS	1			
75	PFLUBAXO	1			1
76	PFLUBAX	1			
78	PFLUGENO	1			1
84	FLUSOHP		1		1
85	FLUSPHARMA		1		1
89	FLUSIN		1		
97	FLUSINOHP		1		1
100	FLUSIMOHP		1		1

### Product codes

Records in the therapy file are created when a prescription is generated. Therefore, all codes are thought to indicate that the vaccine has been received.

Product code	Product name	Pandemic vaccine	Seasonal vaccine
41150	Pandemrix vaccine emulsion and suspension for emulsion for injection (GlaxoSmithKline UK Ltd)	1	
41240	Influenza H1N1 vaccine (whole virion, Vero cell derived, inactivated) suspension for injection	1	
41168	Influenza H1N1 vaccine (split virion, inactivated, adjuvanted) emulsion and suspension for emulsion for injection	1	

41925	Celvapan (H1N1) vaccine (whole virion, Vero cell derived, inactivated) suspension for injection (Baxter Healthcare Ltd)	1	
44759	INFLUENZA PRE-FILLED SYRINGE		1
9710	Agrippal vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)		1
43827	Intanza 9microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd)		1
61792	Fluenz Tetra vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)		1
27407	Imuvac vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)		1
57401	Influvac Desu vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)		1
51289	Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose		1
48085	Influenza inactivated split virion Vaccination (Chiron UK Ltd)		1
16585	Viroflu vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd)		1
48658	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd)		1
1329	Fluvirin vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)		1
48740	Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes		1
54677	Preflucel vaccine suspension for injection 0.5ml pre-filled syringes (Baxter Healthcare Ltd)		1
57140	Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose		1
11824	Enzira vaccine suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)		1
834	Begrivac vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)		1
47932	Fluenz vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)		1
61580	Influenza vaccine (split virion, inactivated) suspension for injection 0.25ml pre-filled syringes		1
30156	Invivac vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)		1
40876	Influenza vaccine (split virion, inactivated) 9microgram strain suspension for injection 0.1ml pre-filled syringes		1
2552	Influvac Sub-unit vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)		1
63690	Inflexal V suspension for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd)		1
51087	Optaflu vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)		1
49716	Influenza vaccine (surface antigen, inactivated, virosome) suspension for injection 0.5ml pre-filled syringes		1
398	Influenza inactivated split virion Vaccination (Aventis Pasteur MSD)		1
7951	FLUVIRIN AQUEOUS ML VAC		1
65205	FluMist Quadrivalent vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)		1
43825	Intanza 15microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd)		1
57917	Fluarix Tetra vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)		1
18612	Mastaflu vaccine suspension for injection 0.5ml pre-filled syringes (Masta Ltd)		1
2139	Fluarix vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)		1
45661	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)		1
32391	Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)		1

10030	Inflexal V vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd)		1
13595	Fluzone Vaccination (Aventis Pasteur MSD)		1
639	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes		1
40760	Influenza vaccine (split virion, inactivated) 15microgram strain suspension for injection 0.1ml pre-filled syringes		1
61898	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (A A H Pharmaceuticals Ltd)		1
30198	Influenza inactivated split virion Vaccination (sanofi pasteur MSD Ltd)		1
922	Influenza inactivated surface antigen Vaccination		1
23251	FLUVIRIN PRE-FILLED SYRINGE		1
2601	Mfv-ject Vaccination (Aventis Pasteur MSD)		1
38421	Influenza inactivated split virion Vaccination (Evans Vaccines Ltd)		1
57678	Fluenz vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)		1



## Appendix 7 – Read codes used in the published THIN study

Read codes used in the published THIN study<sup>195</sup> to identify major congenital malformations but not used in the algorithm developed as part of this thesis.

Read Code	Read Term
7L0F000	REDUCTION OF GIGANTISM OF HAND
7L0K200	REDUCTION OF GIGANTISM OF FOOT
7L0G111	ALBEE OSTEOTOMY OF PELVIS
7L0G116	PEMBERTON OSTEOTOMY OF ILIUM
7L0G117	SALTER OSTEOTOMY OF PELVIS
7L0G118	SHELF PROCEDURE FOR STABILISATION OF HIP JOINT
7L0K000	OSTEOTOMY OF BODY OF OS CALCIS
7L0K012	DWYER OSTEOTOMY OF BODY OF OS CALCIS
7L0H112	MCFARLAND BONE GRAFT PSEUDOARTHROSIS OF TIBIA
7L0G115	GILL OSTEOTOMY OF PELVIS
7L0L311	LAPIDUS TRANSPLANTATION OF TENDON OF FIFTH TOE
7L0L000	RELEASE OF STREETER(CONSTRICTION) BAND
7L0K111	ELMSLIE WEDGE TARSECTOMY
7L0H600	COVENTRY TIBIAL OSTEOTOMY
7L0G211	COLONNA ARTHROPLASTY OF HIP
7L0F900	RELEASE OF THUMB-IN-PALM DEFORMITY
7L0K011	BAKER OSTEOTOMY OF BODY OF OS CALCIS
7L0H200	EXCISION OF ANLAGE OF FIBULA
7043000	FREEING OF SPINAL TETHER
7L0N400	FRONTAL ADVANCEMENT - FIXED
7L0G11A	SUTHERLAND OSTEOTOMY OF PELVIS
7L0H700	GRUCA TIBIAL BIFURCATION PROCEDURE
7L0H511	VAN NES ROTATIONPLASTY FOR CONGENITAL DEFORMITY
7L0H500	REVERSAL ROTATION PLASTY ANKLE CORRECT CONGENITAL DEFORM LEG
7L0H100	CORRECTION OF PSEUDARTHROSIS OF TIBIA
7L0H300	EXCISION OF ANLAGE OF TIBIA