Near real-time vaccine safety surveillance using United Kingdom electronic health records

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DECLARATION

I, Andreia Leite, 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.

Andreia Leite
July 2018

ABSTRACT

This thesis describes the feasibility of implementing a near real-time vaccine safety surveillance system (NRTVSS) using data from the Clinical Practice Research Datalink (CPRD), a United Kingdom (UK) research-level primary care database.

NRTVSS is one method in the vaccine safety post-licensure toolkit, used since 2005. To understand how NRTVSS has been applied I conducted a systematic review of studies using NRTVSS. I identified 31 systems, mainly in the USA. Several sequential tests were in use, most commonly the Poisson-based maximized sequential probability ratio test (PMaxSPRT, 44%) and its binomial version (BMaxSPRT, 24%). Only 75% of studies addressed confounding, mainly by adjusting the expected rate. Delays in data availability may hinder the feasibility of implementing a system; some studies delayed the analysis, whilst others adjusted for delays and partially accrued periods.

In CPRD, delays in recording outcomes are particularly relevant. Hence, I assessed those delays for selected outcomes of interest for vaccine safety (Bell's palsy, Guillain-Barré syndrome (GBS), optic neuritis, and febrile seizures (FS)) by comparing the deemed date of diagnosis to the date the event was recorded in the system. Three-quarters of the records accrued during the first month, considered as sufficient to implement NRTVSS.

I thus trialled the implementation of a system using previously collected CPRD data, for seasonal influenza/GBS and measles-mumps-rubella/FS. This included power calculations for detecting a signal. I used PMaxSPRT for both vaccine/outcome pairs and BMaxSPRT for measles-mumps-rubella/FS. Both tests were adjusted for delays in recording outcomes, based on the previous analysis. It was possible to implement a system, but power was <80% to detect less than a four-fold increase in the risk of GBS following influenza vaccine. For this pair, I re-evaluated power after removing delays in data availability, with no significant improvement.

This work establishes the foundation of a NRTVSS using CPRD for potential application in the UK. Future research could assess further vaccine/outcome pairs and explore the use of other statistical tests. Overall, this project contributes to UK vaccine pharmacovigilance.

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LIST OF ABBREVIATIONS

#	number
95%CI	95% Confidence Interval
A&E	Accident and Emergency
AE	Adverse Event
AEFI	Adverse Events Following Immunisation
AID	Auto-immune disorders
AR	Adverse Reaction
BMaxSPRT	Binomial-based Maximized Sequential Probability Ratio Test
BP	Bell's palsy
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CDC	Centers for Disease Control and Prevention
CIOMS	Council for International Organization of Medical Sciences
CL	Critical Limit
CMaxSPRT	Conditional Maximized Sequential Probability Ratio Test
CND	Cranial nerve disorders
CPRD	Clinical Practice Research Datalink
DD	Demyelinating disorders
DID	Difference-in-difference
DMSS	Defense Medical Surveillance System
DoD	Department of Defense
DPNSN	Disorders of the peripheral nervous system and neuropathy
DT	Diphtheria-tetanus vaccine

DTaP	Acellular diphtheria-tetanus-pertussis vaccine
DTwP	Whole cell diphtheria-tetanus-pertussis vaccine
EHR	Electronic Health Records
EMIS	Egton Medical Information System
EV	Expected Events
FDA	Food and Drug Administration
FS	Febrile Seizures
GBS	Guillain-Barré syndrome
GBMV	Group-B meningococcal conjugate vaccine
GP	General Practitioner
GPRD	General Practice Research Database
GS	Group sequential
HES	Hospital Episode Statistics
HES APC	Hospital Episode Statistics Admitted Patient Care
Hib	Haemophilus influenza type B
HMO	Health Maintenance Organizations
HPS	Health Protection Scotland
HPV	Human Papillomavirus
HPV2	Bivalent human papillomavirus vaccine
HPV4	Quadrivalent human papillomavirus vaccine
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IHS	Indian Health Service
IMD	Index of Multiple Deprivation

IMPACT	Canadian Immunisation Monitoring Program
IPV	Inactivated poliovirus vaccine
ISAC	Independent Scientific Advisory Committee
ITP	Immune thrombocytopenia purpura
KD	Kawasaki Disease
LAIV	Seasonal trivalent live attenuated vaccine
LAMV	H1N1 monovalent live attenuated vaccine
lcd	Last collection date
LL	Lower Limit
LLR	Log-likelihood ratio
LR	Likelihood ratio
LSHTM	London School of Hygiene & Tropical Medicine
MAF	Medically attended fever
MaxSPRT	Maximized Probability Ratio Test
MCV	Meningococcal conjugate vaccine
MHRA	Medicines and Healthcare products Regulatory Agency
MIV	H1N1 monovalent inactivated vaccine
MLE	Maximum Likelihood Estimate
MMR	Measles-Mumps-Rubella
MMRV	Mumps-measles-rubella-varicella vaccine
mo	Months
MoH	Ministry of Health
NHS	National Health Service
NRTVSS	Near real-time vaccine safety surveillance

NVPO	National Vaccine Program Office
OCND	Other Cranial Nerve Disorders
ODD	Other Demyelinating disorders
O-E	Observed-to-expected
ON	Optic neuritis
ONS	Office for Nacional Statistics
PAEDS	Paediatric Active Enhanced Disease Surveillance
PCV13	13-valent pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PHE	Public Health England
PMaxSPRT	Poisson-based Maximized Sequential Probability Ratio Test
PPV	Positive Predictive Value
PRISM	Post-Licensure Rapid Immunization Monitoring System
PY	Persons-year
QIV	Seasonal quadrivalent inactivated vaccine
QOF	Quality Outcomes Framework
RCA	Rapid cycle analysis
RCGP RSC	The Royal College of General Practitioners Research and Surveillance Centre
RR	Relative Risk
RRR	Relative Reporting Ratio
RRV	Rhesus-Rotavirus vaccine
RV	Rotavirus vaccine
RV5	Pentavalent rotavirus virus
SCCS	Self-controlled case series

SCRI	Self-controlled risk interval
SID	Sudden infant death
SJS	Stevens-Johnson syndrome
SMS	Short message service
SPC	Statistical Process Control
SPRT	Sequential Probability Ratio Test
TCP	Thrombocytopenia TIV
TIV	Seasonal trivalent inactivated vaccine
THIN	The Health Improvement Network
UK	United Kingdom
UL	Upper Limit
USA	United States of America
USPRT	Updating Sequential Probability Ratio Test
VA	Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VAMP	Value Added Medical Products
VSD	Vaccine Safety Datalink
w	Weeks
WHO	World Health Organization
WHO-UMC	Uppsala Monitoring Center
yr	Years

1 INTRODUCTION

Vaccination is one of the most effective public health interventions.[1-3] However, the success of vaccination itself poses challenges. As vaccine-preventable diseases have been dramatically reduced, the possibility of adverse reactions has gained relevance. The concerns regarding the safety of vaccines led some to decide against vaccination, which has contributed to the resurgence of some of these diseases.[4,5]

Vaccine safety is studied throughout the vaccine lifecycle. This starts with the assessment of a vaccine candidate, during clinical trials. If the vaccine candidate meets the requirements and is approved the safety continues to be studied using post-licensure studies. At this stage, the main focus is to detect rare adverse events which might have been missed by pre-licensure studies. Several methods are available, including passive and active surveillance.[2] Passive surveillance is mainly represented by spontaneous reports, used worldwide. Active surveillance includes a variety of methods and has benefitted from the advent of electronic health records. Such records allow the study of large volumes of data, which are essential to detect rare adverse events.[6] Given that vaccines are administered to a large number of individuals, it is important to identify these events as soon as feasibly possible. Most available studies do not incorporate a timeliness dimension; to address this issue in 2005 a new method to assess vaccine safety was introduced in the United States of America (USA).[7] This method, initially known as rapid cycle analysis (RCA), and then as near real-time vaccine safety surveillance (NRTVSS) uses electronic health records and sequential tests to identify safety signals in a timely manner. NRTVSS is started very soon after vaccine delivery and data are examined at regular points in time.[8] It is now used routinely in the USA, where it has allowed the identification of several safety signals.[9]

In the United Kingdom (UK), vaccine pharmacovigilance has relied largely on spontaneous reports and on epidemiologic studies aimed at testing hypotheses generated by a variety of sources. NRVTSS has been implemented using spontaneous reports to obtain the number of observed events.[10] However, spontaneous reports suffer from under-reporting and are subject to biases, while hypothesis-testing studies are generally designed in response to suspicions raised some time after the vaccine's introduction. Electronic health records are required for a new UK NRTVSS that relies fully on routinely collected data; such research-level data are available, such as the Clinical Practice Research Datalink (CPRD),[11] The Health Improvement Network (THIN),[12] The Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) network,[13] and ResearchOne.[14] Given the availability of data

that are potentially suitable to implement NRTVSS, it is then necessary to determine which methods are available, their characteristics, and whether available electronic health records are adequate to perform this kind of surveillance.

This thesis reviews the methods available for NRTVSS and explores the feasibility of using CPRD, as an example of a general practice dataset, to perform NRTVSS. In Chapter 2, the main concepts in the field of vaccine safety are summarised, with a particular focus on methods available to assess vaccine safety. The use of near-real time vaccine safety surveillance is introduced. The Chapter finishes with the objectives of the thesis. Chapter 3 provides information on the methods used in this thesis. It starts with information on the data sources used and further explanation of the tests available to perform near real-time vaccine safety surveillance. The remaining Chapters provide an explanation of the work conducted to address the objectives of the thesis. Chapter 4 presents a systematic review undertaken to assess the worldwide use of near real-time vaccine safety surveillance. This work was published as a paper in *Pharmacoepidemiology and Drug Safety*, which is reproduced in Chapter 4 (Paper 1). Chapters 5 and 6 establish the foundation of the feasibility assessment. This assessment includes a trial implementation of near real-time methods using CPRD data (Chapter 7). Chapter 5 details the framework used to establish the feasibility of using CPRD to implement a near-real time system. It starts with information on the process used to select the outcomes and the vaccines to include in the trial implementation, followed by aspects of the data which were considered as essential to implement a near real-time system. One of the key aspects was delays in recording data, and an in-depth analysis of these delays is presented. This analysis was also published as a paper in *Pharmacoepidemiology and Drug Safety*, reproduced in Chapter 5 (Paper 2). The Chapter ends with the explanation of the decision about which vaccine/outcome pairs were considered for the feasibility study. Chapter 6 focuses on how the format and availability of CPRD data limited the design of the trial implementation study, and how these issues were addressed. This is followed by the implementation study itself, which is presented in Chapter 7. This work has been written as a paper published in *Vaccine* (Paper 3). One of the issues identified during this work was lack of power to identify a signal for rare outcomes. Knowing that delays in recording and receiving data for analysis can influence power, this issue was further explored and is reported in a fourth paper, accepted for publication in *Pharmacoepidemiology and Drug Safety.* Finally, Chapter 8 summarises and provides an overall discussion of the findings, and presents the implications of the work.

2 BACKGROUND

2.1 Vaccine safety overview

Vaccines are considered one of the most cost-effective public health interventions.[1-3] The exact number of cases of disease prevented since their introduction is unknown, but estimates for the USA indicate that 103.1 million cases of polio, measles, rubella, mumps, hepatitis A, diphtheria and pertussis might have been prevented from 1924 to 2011.[15] The value of vaccines seems certain.

Vaccine are administered to healthy individuals, often children, and thus the standard for vaccine safety is particularly high. However, not all events following administration of a vaccine will be due to the vaccine itself. The Council for International Organization of Medical Sciences (CIOMS) defines adverse events following immunisation (AEFI) as "any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine".[16 p39-40] AEFI can be: (i) vaccine product-related (related to vaccine components); (ii) vaccine quality-related (due to defects in the product); (iii) immunisation error-related (owing to errors in the handling, prescribing, and administration process); (iv) immunisation anxiety-related (including reactions such as vasovagal syncope); and (v) coincidental events (unrelated to the vaccination process and that would have occurred regardless of the vaccine administration). It is important to make a clear distinction between these different causes of AEFI whenever possible, to avoid undue concerns. Adverse events (AE) and Adverse Reactions (AR) are related concepts: AE is similar to AEFI but are applied more broadly to drugs in general.[17] On the other hand, AR does require a causal association. It is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man".[17] Vaccine pharmacovigilance activities try to detect AR quickly in order to minimise their impact.[16]

Public concerns with the safety of vaccines started with their introduction, due initially to events arising from production methods and subsequently due to other safety concerns.[18] These concerns can undermine the success of immunisation programmes as suggested by Chen and colleagues,[4] who have described the evolution of these programmes (Figure 2.1). They emphasise how vaccine coverage, disease incidence, and the perception/incidence of AE are interlinked. As more people are vaccinated and the disease is controlled (stage 1) disease consequences are less evident and the perception of AE increases (stage 2). This can lead to loss of confidence and decreasing coverage resulting in outbreaks (stage 3). Public

health authorities might be able to restore confidence, with resumption of high coverage and low incidence of the vaccine-preventable disease (stage 4). In special cases, eradication might be achievable and the vaccine can be stopped, as well as its related AE (stage 5).

One example of this evolution started in 1998 with a suggested association between measles-mumps-rubella (MMR) vaccine and gastrointestinal disease and autism.[19] In the UK, MMR coverage by two years of age dropped from 92.5% (1995) to 78.9% (2003) with increasing incidence of measles by 2006-07.[5] Several measles outbreaks have occurred subsequently in Europe and USA.[20]

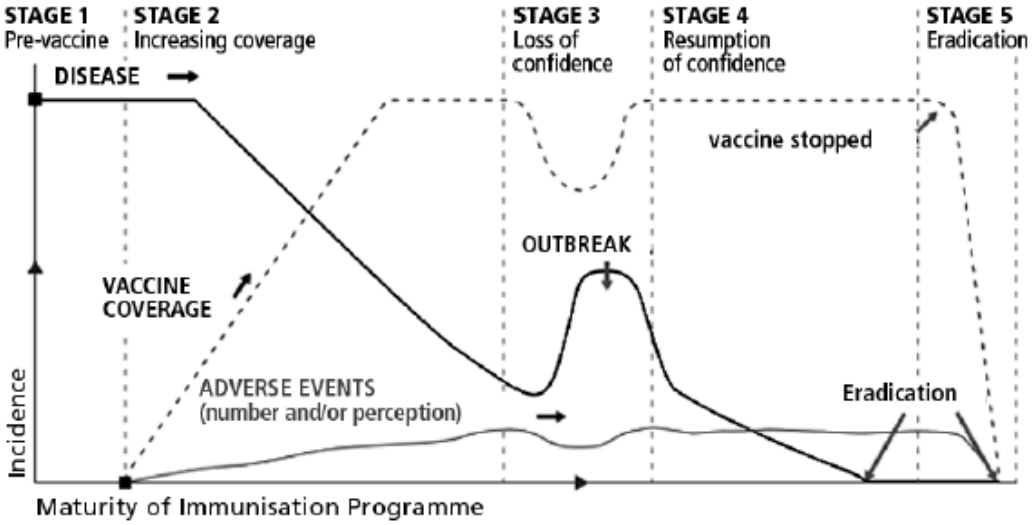

Figure 2.1. Potential stages in the evolution of an immunisation programme.[4,21]

Vaccines can cause AR but, overall, benefits are considered to outweigh the risks. For example, measles-related serious complications/death risk can be up to 1/20 while vaccine-related encephalitis risk is around 1/1,000,000.[22,23] Vaccine safety is assessed at several stages, broadly divided into pre-licensure studies (before vaccine approval) and post-licensure (after approval), as outlined in Sections 2.2 and 2.3.

2.2 Pre-licensure studies

Vaccines are studied extensively in-vitro and in animals before the human tests start. At that stage, clinical trials are the first step in demonstrating a vaccine candidate is safe and efficacious. These trials are conducted in three phases with progressively bigger samples. In

phase I clinical trials the vaccine candidate is tested in a small sample of healthy individuals. For phase II trials a larger sample size is evaluated, allowing identification of common AE and providing important information on the best dosage and schedule. Finally, during Phase III trials a bigger sample is assessed, to ensure precise estimation of vaccine efficacy and enabling detection of less common events.[2,21,24] As mentioned above vaccine safety standards are particularly high and thus phase III vaccine trials tend to enrol more subjects than other drugs trials. At this stage, the sample usually includes between 5,000 to 10,000 individuals but this number can be larger if rare adverse events are anticipated, as in the case of rotavirus vaccine.[24] Following withdrawal of a rotavirus vaccine after approval due to an increased risk of intussusception (estimated to be 1 excess case/10,000 vaccinated children), a new vaccine was required to demonstrate safety regarding intussusception and thus phase III trials included 70,000 children.[2,25] Nevertheless, sample size considerations tend to focus on vaccine efficacy rather than vaccine safety.

If a vaccine candidate meets the efficacy and safety requirements it can be approved. Nevertheless, clinical trials follow strict enrolment criteria (resulting in highly selected populations), do not give information on long-term AE, and they can miss rare AE.[2,26] It is thus important to continue surveillance after vaccine approval. In the European Union, companies are required to submit a risk management plan when applying for approval.[27] This should include information on (i) safety profile; (ii) plans to gain further insight into the safety and efficacy profile; and (ii) risk minimisation activities if required. Risk management plans ensure that any potential safety concerns arising from but not confirmed during clinical trials are followed during the post-licensure stage.

2.3 Post-licensure safety surveillance

Post-licensure safety surveillance aims to identify safety signals. CIOMS defines a signal as "information that arises from one or multiple sources (…), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event (…), that is judged to be of sufficient likelihood to justify verificatory action".[28] In the context of vaccine pharmacovigilance, the intervention is the vaccine and the event the suspected AR. Throughout this work, these will be referred to as the vaccine/outcome pair or pair of interest.

Identifying a safety signal is not the end of surveillance but rather an initial step in a multi-stage process. Several authors have described the process, but concepts have been applied

loosely, with no clear definition.[1,26,29] It is generally agreed that an initial step is to find a signal – the signal identification or detection phase. Nelson et al. defines this phase as the stage to detect unknown AE.[26] Traditionally, this has relied on the use of spontaneous reports (passive surveillance) and employment of a set of techniques known as data mining. Active surveillance approaches have complemented the use of spontaneous reports and include hospital-based surveillance, cohort recruitment, large population-based datasets and internet-related data.[1] Signal strengthening or refinement is an intermediate stage which addresses previously suspected events but does not provides a final confirmation of a potential signal. Ecological studies, observed-to-expected calculations and near real-time surveillance using electronic health records are included in this stage. Signals emerging from both the signal detection and signal strengthening stages need to be confirmed, generally using traditional epidemiological designs, which provide a more rigorous assessment than the methods previously mentioned. Results from confirmatory studies should be interpreted in light of additional considerations such as biological plausibility. Figure 2.2 summarises the approaches used at each stage.[1]

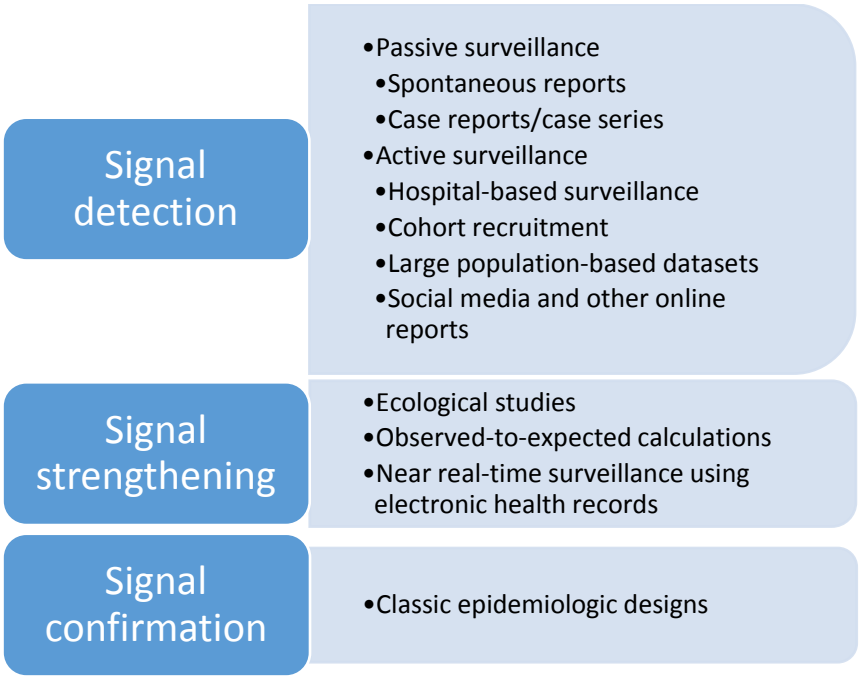

Figure 2.2. Stages in the post-licensure safety surveillance. Adapted from Bonhoeffer et al.[1]

These stages should not be regarded in a linear way: for a given vaccine/outcome pair the assessment might start with a signal strengthening activity (with no explicit signal detection) or a confirmatory study may follow a signal detection (with no signal strengthening stage). The approach should be tailored to the characteristics and existing knowledge for the specific

pair of interest. These methods are briefly explained below with a particular focus on their use for evaluation of vaccine safety. The approach used in this thesis, near real-time surveillance using electronic health records, is presented in more detail.

2.3.1 Signal detection

2.3.1.1 Spontaneous reporting

Post-licensure surveillance has relied on spontaneous reports, which are widely implemented. These systems require that health-care workers or others suspecting an AE to report it, hence they are described as passive systems.[30] Spontaneous reporting systems are considered to be simple, low-cost, represent an opportunity for the public to report, and have a broad scope.[2,30] They are useful for detecting new, extremely rare, and/or unanticipated AE but have limitations. These include report quality/completeness, under/over-reporting, and lack of population denominators.[2] These issues are briefly presented below.

Each case report is carefully reviewed by a clinical analyst in order to assess a possible association between the drug and the AE being studied. This assessment considers several aspects of the report (see below) and is limited when there is incomplete or poor quality information. Spontaneous reports rely on voluntary systems and therefore result in an undetermined level of under-reporting, which differs for each AE. Hence, it is not possible to calculate the denominators that are needed for calculating AE rates in the population. Moreover, temporal reporting trends are non-uniform and may not follow the frequency of the AE/drug in the population. Previous studies have shown that the frequency of reports for a given AE is higher in the first years after approval and declines thereafter. Other factors, such as strong media attention or a newly suspected AE, also affect the reporting behaviour leading to over-reporting.[2,29,30] Despite these limitations several analysis can be performed, including review of case reports, reporting ratios, and data mining.[30]

Review of case reports is a descriptive approach in which cases fulfilling a specified case definition are systematically reviewed and a possible causal relationship is ascertained (case causality assessment). For drugs, the temporal association, biological plausibility, and information on de-challenge (drug withdrawal) and re-challenge (drug re-introduction) are the aspects considered.[30] Vaccines' characteristics make this process more complex.[28] There is usually no information on re-challenge (vaccines are administered once or with long intervals) or de-challenge (due to long-lasting immunological effects). Furthermore,

concomitant vaccine administration is common, making it difficult to attribute the AE to a specific vaccine. This issue also complicates other methods, such as those used for signal strengthening. Finally, live vaccines may cause the vaccine-preventable disease, which can be the source of the event, adding extra complexity.

Several systems have attempted to standardise case causality assessment.[31] The system proposed by the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring (also known as the Uppsala Monitoring Center, WHO-UMC) and the Naranjo probability scale are the most widely used.[31] WHO-UMC uses information on the temporal association, objective confirmation of the event, biological plausibility, de-challenge, and re-challenge, and based on the presence/absence of these classifies reports as 'certain', 'probable/likely', 'possible', 'unlikely', 'conditional/unclassified', and 'unassessable/ unclassifiable'.[32] The Naranjo scale includes questions on the same aspects of the WHO-UMC assessment criteria plus existence of previous reports and dose-response relationships. Each question is scored and a total score obtained.[33] These systems have been criticised as neither produces a reliable quantitative estimate of the likelihood of a causal association between the outcome and the drug being assessed.[31] However, they are considered to be useful as they decrease disagreement between assessors and facilitate report processing.

Even with no denominators it is possible to calculate a relative measure, the reporting ratio:

$$Reporting\ ratio = \frac{Number\ of\ AE/AR}{Drug\ utilization\ measure}.$$

Drug utilization measures try to capture the number of individuals at risk and include dispensing data, the number of persons receiving the drug, or a combination of these with duration of treatment. Reporting ratios are not true incidence/prevalence measures but can be compared with background rates when the event is serious. Alternatively, reporting ratios for other drugs used for the same indication or from the same class can be used as comparators. Given the limitations of spontaneous reports and reporting ratios these comparisons should be made carefully.[30]

Data mining techniques have become a popular option to analyse spontaneous reports and other data sources.[29] These techniques try to identify patterns in existing data, mainly using disproportionality methods. The underlying principle is that any association between a drug and an event will lead to the occurrence of the drug-event pair disproportionately in the data, compared to what would be expected assuming no association. As all reports refer to a specific drug, for the purposes of these analyses the comparator is all other drugs (either

all drugs in the same drug class or simply all other drugs in the data). Disproportionality analysis includes frequentist and Bayesian measures and is based on a simple 2x2 contingency table.[26,29,30,34] Table 2.1 presents the structure commonly used. For frequentist measures, it is possible to calculate a hypothesis test of independence (χ^2 or Fisher's test) and confidence intervals. Nevertheless, these methods tend to become unstable with small number of events, leading to false positives. Bayesian measures were developed to address this issue, as they 'shrink' the measure of association towards the null, depending on the data variability. The most commonly used measures are briefly defined on Table 2.2.

Table 2.1. Contingency table commonly used for signal detection

	Adverse event		
Target drug	**Yes**	**No**	**Total**
Yes	a	b	n = a+b
No	c	d	z = c+d
Total	m = a+c	b+d	t = a+b+c+d

Table 2.2. Measures commonly used for signal detection

Measure	Definition (notation on Table 2.1)	Type
Relative Reporting Ratio (RRR)	(t.a)/(m.n)	Frequentist
Proportional Reporting Ratio	(a.z)/(c.n)	Frequentist
Reporting Odds Ratio	(a.d)/(c.b)	Frequentist
Information Component	$\log_2$(RRR)	Frequentist
Bayesian Confidence Propagation Neural Network	Bayesian version of the information component	Bayesian
Multi-item Gamma Poisson Shrinker	Posterior expectation of the relative reporting ratio distribution	Bayesian

The simplicity of 2x2 tables and the measures presented implies loss of information and makes it impossible to study drug-to-drug interactions or adjust for potential confounders. Other methods exist, such as extensions of disproportionality measures for 3-dimensional tables, logistic regression-based approaches and unsupervised machine learning.[34] An in-depth presentation of these techniques is beyond the scope of this text but is summarised in Harpaz et al.[34]

Spontaneous reports systems are managed at the country level but some databases are aggregated worldwide/regionally. International spontaneous reports databases include: VigiBase – WHO-UMC and EudraVigilance – the European Union Drug Regulating Authorities Pharmacovigilance database.[29] These receive reports for both vaccines and therapeutic

drugs. In the UK, the spontaneous reporting system is known as the Yellow Card system and, as the examples before, receives reports from vaccines and therapeutic drugs.[35] Other systems focus on vaccines, such as the Vaccine Adverse Event Reporting System (VAERS, USA system, run in partnership by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA)), and the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS).[35,36] In 1999, VAERS allowed the identification of a safety signal following a tetravalent rotavirus vaccine, later confirmed by epidemiologic studies, leading to the vaccine withdrawal.[36] CAEFISS has the particularity of including specific case definitions (see 2.3.3) in its reporting structure.[35] For analysis, WHO uses the Bayesian Confidence Propagation Neural Network, while in the UK the Multi-item Gamma Poisson Shrinker has been preferred (Table 2.2).[34]

2.3.1.2 Case reports/case series

Case reports/case series are often reported in the literature and can be used for pharmacovigilance purposes. Case reports simply describe a patient who experienced a given outcome following a certain exposure. Case series are similar but there are several patients either with the same exposure and whose outcomes are described or with the same outcome and whose exposures are investigated.[37] These designs are useful to generate hypotheses about previously unknown or unsuspected events. It is noteworthy that the use of case-series assembled to support a pre-existing hypothesis is not hypothesis-generating and can have detrimental consequences, such as in the case of the suggested association between MMR and autism in the late 1990's.[19] This led to a loss of confidence in the vaccination programmes and decreasing coverage (see Section 2.1).

Case series can also be used to determine the incidence of a suspected outcome following introduction of a new drug. This can be done by recruiting physicians who report cases of the disease. Both case reports and case series are easy to conduct but they are limited by the absence of a control group. Hypotheses generated by these designs should be further tested using a more robust design. Alternatively, and in specific circumstances, data from a case series can be used to conduct a self-controlled case series. This design is presented in detail in Section 2.3.3.3.

2.3.1.3 Active surveillance methods

Active surveillance attempts to identify all AEFI of interest within a defined population and aims to overcome some of the limitations of spontaneous reports. Different approaches to

active surveillance have been proposed.[38,39] The approaches used in the context of signal detection are briefly described.

2.3.1.3.1 Targeted hospital-based surveillance

This approach identifies conditions of interest that are retrieved daily from electronic health records and by contacting key clinicians at participant centres. Trained nurses assess whether the case meets the case definition criteria (previously decided) and can collect further information from relevant sources. Data generated by this process at each centre are then sent for central processing and analyses. Countries adopting this approach include Canada (the Canadian Immunisation Monitoring Program – IMPACT), Australia (the Paediatric Active Enhanced Disease Surveillance – PAEDS), and New Zealand.[39,40] Important features of these systems include their ability to identify cases not identified by other sources, and collecting relevant data on them in a standardised way with regular updates.[40] These initiatives investigate new safety concerns but also other vaccine-related aspects such as effectiveness.[41] Relevant findings include a decrease in febrile seizures and hypotonic episodes with the replacement of diphtheria-tetanus-whole pertussis vaccine by diphtheria-tetanus-acellular pertussis vaccine in 2003, and the increase in cases of acute thrombocytopenia following measles-containing vaccines in 2003.[41]

2.3.1.3.2 Cohort recruitment after vaccination

After administrating a vaccine, it is possible to recruit vaccinated individuals and follow them up with enquiries about AEFI. This approach requires setting up a study for each vaccine of interest but it allows surveillance of virtually any event following a certain vaccine. This contrasts with the previous approach (see 2.3.1.3.1) where the focus is on a previously defined outcome of interest. As with any cohort, detection of rare events requires the recruitment of a very large number of vaccinees, making this a costly option.

There are different options when recruiting/contacting individuals, including: face-to-face interviews,[42] short message service (SMS),[43,44] e-mail,[45] interactive voice response system,[46] computer-assisted telephone interviewing,[46,47] and home telemonitoring.[48] These options will not be presented in detail except for the studies using SMS/e-mail.

The system using SMS and/or e-mail is one of the existing surveillance systems aimed at providing (near) real-time signals and makes use of specific statistical methods to look at data at repeated points in time. This is also the case for the method used throughout the project described in this thesis – near real-time vaccine safety surveillance. However, these two systems differ in the source of data used. Given the specificities in the use of electronic

health records data, throughout this work the expression near real-time vaccine safety surveillance refers to surveillance efforts using electronic health records and thus does not include the use of SMS/e-mail, which is explained below.

Vaccine surveillance using SMS/e-mail has been led by Australia, where a system has been in place since 2011.[44] After receipt of a vaccine, patients or their parents receive a SMS asking if they/their children have experienced any reaction and requesting a Yes/No reply via SMS. If there is an affirmative reply, patients are subsequently contacted by staff asking further details of the reaction. The system is mostly automated as the software retrieves vaccination information and automatically sends SMS to the number on the patient's record. It also records replies received via SMS.[44] The initial tool using SMS has evolved and it was adapted to send e-mails and to perform an on-line based survey instead of a phone survey. Currently, the two systems (using SMS and e-mail) run in parallel.[45] An evaluation of this system showed that over 70% of patients responded to the initial SMS and over 80% of those who responded did so within 2 hours.[44] It is thus distinct from other forms of cohort recruitment as it is less costly, enables a wide reach and allows near real-time information. Systems using SMS have also been implemented in low and middle-income countries.[43]

2.3.1.3.3 Large population-based datasets

Different sources of routinely collected data have been used to study vaccine safety, including information from hospital and/or primary care linked with vaccination history. These electronic health records are readily available and can achieve big sample sizes, thus having the power to detect rare adverse events. Furthermore, they have the potential to be population-based, ensuring representativeness not achieved during clinical trials.[6] In the context of pharmacovigilance, electronic health records have been mainly used for signal strengthening and signal confirmation (see Sections 2.3.2 and 2.3.3) but a few studies have also explored applications for signal detection. Some use text mining techniques,[49] while others have adapted existing disproportionality measures (see 2.3.1.1) for use in a longitudinal context.[50-52] Examples include the Longitudinal Gamma Poisson Shrinker, adapted from the multi-Item Gamma Poisson Shrinker, which considers person-time instead of case counts to estimate the expected number of events[52] and the Temporal Pattern Discovery which adapted the information component using a Bayesian approach and looks at the disproportionality measure at different times around the prescription.[51] Both measures have been validated and the latter has been applied to MMR and a range of adverse events, with results consistent with previous knowledge.[53] Mining electronic health

records has not received much attention for pharmacovigilance. One of the reasons might be the concern of using the same data to generate and confirm a signal. It remains unclear if this can lead to biased results.[54]

2.3.1.3.4 Social media and other online reports

Information generated by internet-related activities has started to be used for public health purposes.[55] Pharmacovigilance is no exception and social media, web-search queries, and data from health forums have been suggested as real-time, low-cost sources of new safety signals.[56] In the last few years, there has been an increasing number of publications in this area, mainly trying to explore how to make use of these data.[56] Progress has been made and there are several options available to extract and use these data with the aim of identifying safety signals. Previous studies have also tried to validate their results by comparing them with data from spontaneous reporting systems. Results have shown a good agreement for Twitter and web-search queries data.[57,58] These studies have mainly focused on therapeutic drugs but have also looked at some vaccines, for example influenza,[58] human papillomavirus (HPV),[57,58] tetanus-diphtheria-pertussis,[57,58] and hepatitis B.[57,58] Overall, they have identified mild AE such as injection site pain, fever and malaise.[57,58] Nevertheless, challenges in identifying adverse events remain, related to the way people report the events and the drugs, but also with the need for human supervision for some of the existing techniques. In addition, multiple ethical questions have been raised, with no clear answers.[56]

To clarify some of the existing questions, a 3-year project, Web-Radr, was launched in 2014. One of its work packages, led by WHO-UMC, aims at identifying new analytical tools for using social media in pharmacovigilance.[59] Despite the progress made in technical terms to harness social media data, the latest publicly available information still questions the role of this data source in terms of signal detection. In particular, there have been discussions on whether it should be considered as a tool to support signal detection or whether it can be used on its own.[60] The place of this data source for pharmacovigilance is yet to be determined.

2.3.2 Signal strengthening

2.3.2.1 Ecological studies

The main feature of ecological studies is the use of aggregate data instead of individual level data. These studies can be conducted in several ways. One option is to perform a before-after comparison, where the overall rate of an outcome of interest is compared before and after the introduction of the vaccine being assessed. This design was used to assess chronic

fatigue syndrome among girls aged 12-20 following introduction of HPV vaccine.[10] Changes in diagnostic patterns and in the outcome incidence for other reasons can affect this type of analysis.

A special case of this comparison is the one used in mass vaccination campaigns where by comparing incidence before, during, and after the campaign it may be possible to further assess a possible causal association. If a causal association exists, a marked increased incidence of the outcome should be observed. This was the case in Brazil where an increase in aseptic meningitis was detected following a mass campaign with a Urabe-containing MMR vaccine.[61]

A less common situation where this design may be used is when there are changes in the vaccination schedule age and there is a causal association between the vaccine and the outcome. In those circumstances, the incidence of the outcome will decrease in the age group in which the vaccine was previously administered and will increase in the new age group.[62]

Ecological studies usually provide quick results but there is limited ability to adjust for potential confounding factors. This study type is thus considered to provide less strong evidence compared to other epidemiologic designs (see 2.3.3).

2.3.2.2 Observed-to-expected (O-E) analysis

These analyses compare rates of observed events to what would be expected, based on rates of the adverse event in the absence of the vaccine. This tries to capture what would have been observed if the vaccine had not been administered and thus helps determine if events are indeed related with the vaccine or are coincidental. O-E analyses have been used to monitor safety concerns identified from signal detection methods where the magnitude of a possible risk is still unclear and rapid results are required.

To identify the number of observed events one might use data from spontaneous reports[63] or prospectively collected data.[64] Using spontaneous reports as a measure of the observed number of events is affected by limitations in spontaneous reports systems (see 2.3.1.1), particularly by underreporting. Different scenarios of underreporting can be assessed in sensitivity analyses.

Expected events are based on a combination of information from background rates of the event and the person-time at risk. The former might be obtained from existing electronic health records or publications and should be drawn from a population as similar to the one

in which the events were observed. The latter should be determined based on the hypothesised period of risk following the vaccine and a measure of the number of doses administered. If there is no information on the doses given, the number of doses sold can be used.[63]

Regardless of the data source used, the analysis is simply the ratio of the number of observed and expected events and it is possible to calculate a 95% Poisson exact confidence interval (95%CI). The disproportionality analysis presented in Section 2.3.1.1 is also a comparison of observed-to-expected events. It differs from the one presented here in the data used, as it only utilizes information from a single spontaneous reporting system, and also in the way it is used, as disproportionality analyses are usually applied for signal generation.[63] O-E analysis is also the basis for some of the near real-time surveillance analysis presented in 2.3.2.3.

2.3.2.3 Near real-time surveillance

In 2005 the Vaccine Safety Datalink (VSD) proposed the use of sequential tests for timely detection of signals, accounting for repeated testing. VSD receives electronic data from 8 participating centres in the USA, corresponding to a population of 9.2 million. Unlike most of the existing methods this type of surveillance usually starts shortly after a new vaccine has been introduced and data are examined at repeated points in time. To adjust for multiple testing, VSD uses sequential tests, initially the maximized probability ratio test (MaxSPRT) and then extensions of this test. In fact, the group developed new statistical tests to address some challenges in vaccine safety and also contributed to a deeper understanding of the properties of existing and new statistical tests. The method has been used to assess several vaccine/outcome pairs, and has allowed the identification of several safety signals, resulting in change of policy. It is now used routinely in the USA.[9]

In the UK, NRVTSS has been implemented using spontaneous reports for observed events and electronic health records to calculate the number expected events.[10] This approach inherits the limitations of spontaneous reports systems, as presented in 2.3.1.1. Given the availability of electronic health records in the country and country-specific vaccination schedules, it would be desirable to implement a system that allows for quick signal identification and that does not rely on spontaneous reports. This thesis thus focuses on assessing the feasibility of implementing a NRTVSS using UK electronic health records.

Given that the vaccine/outcome pairs to study need to be set in advance, NRTVSS is best suited to study a set of events of special interest. These can be selected based on information from clinical trials, signals seen with previous versions of the vaccine (e.g. seasonal influenza

and Guillain-Barré syndrome (GBS), rotavirus vaccine and intussusception), or biological knowledge of the vaccine characteristics. As it does not allow for confirmation of a signal, it is considered under the signal strengthening approach.

The method was initially known as rapid cycle analysis, due to the file structure used in VSD.[65] Considering this designation is specific to the VSD structure and not self-explanatory, other terms were considered. For the purposes of this work the term near real-time vaccine safety surveillance using electronic health records, or simply near real-time vaccine safety surveillance, will be used as this was considered to better illustrate the type of surveillance conducted.

This is not the only tool available to produce (near) real-time results. Other methods include the recruitment of cohorts via SMS/e-mail and the use of internet-related data; see Sections 2.3.1.3.2 and 2.3.1.3.4, respectively, for a description of these other types of (near) real-time surveillance efforts. Unlike cohort recruitment, NTRVSS can be implemented if electronic health records are available with no need for additional data collection, but it is limited by the quality of these records. Furthermore, NRTVSS is a more robust and well-established method compared to the analysis of internet-related data, which is still being explored for this purpose. These two other methods also occupy a different place – they are both in the signal generation sphere, while NRTVSS is used for signal strengthening. NRTVSS is the focus of this thesis and thus more detail on its use is provided throughout this work. In particular, the statistical details of the tests used for this type of surveillance are presented in Section 3.3.

2.3.3 Signal confirmation

Signals identified by a variety of sources usually require confirmation from a rigorous, well-conducted epidemiological study.[66] The increasing availability of electronic health records and their characteristics (in terms of size and representativeness, see 2.3.1.3.3) have become an attractive data source to perform such hypothesis-testing studies. The USA, Denmark and the UK are examples of countries using this data source.[39] Despite its attractiveness, it is important to be aware of issues with data completeness and quality – both vaccination status and outcomes should be well captured. There should also be information regarding potential confounders of interest.[66]

When trying to identify outcomes it is important to know the coding system in use and to identify all the relevant codes. These might be a mixture of diagnostic, symptom and drug codes. In the case of UK primary care data, involving a practising general practitioner (GP)

might be helpful to guide this choice. Code-lists developed will never be perfect and will capture cases with different levels of sensitivity/specificity. The issue of imperfect validity might thus be assessed by using code-lists with varying levels of sensitivity/specificity and comparing the results. Alternatively, new or pre-existing studies assessing the validity of these algorithms might be used.[66,67] Validity assessment for CPRD data is explained in more detail in Section 3.1.1.4.

In some cases, it is possible to access case notes for confirmation of a case identified using the method abovementioned. When inspecting these notes it is important to use standard definitions to ensure comparability of different studies. The Brighton Collaboration has had a fundamental role in guiding the development of such standard definitions. By bringing together professionals interested in vaccine safety and applying a systematic method, this collaboration has contributed to the development of several standard case definitions. Currently, definitions for 47 events of interest are available.[68]

Additionally, information on the time of the vaccination and event are essential, as it is necessary to define a risk-window (time at risk of developing the adverse event).[66] Defining a risk-window depends on the vaccine, the event itself and existing knowledge.

Below, the main designs used in this context are explained, including the main advantages and disadvantages of each one. These confirmatory studies may also rely on other sources of data, such as data retrieved from targeted hospital surveillance or cohorts recruited following vaccination (see 2.3.1.3.1 and 2.3.1.3.2, respectively). As this thesis focuses on the use of electronic health records this Section briefly presents the main designs to conduct epidemiologic studies with a special focus on issues while using electronic health records. Figure 2.3 presents a comparison of the three designs covered (cohort, case-control, and self-controlled case series) for six individuals (3 with the outcome of interest and 3 without the outcome).

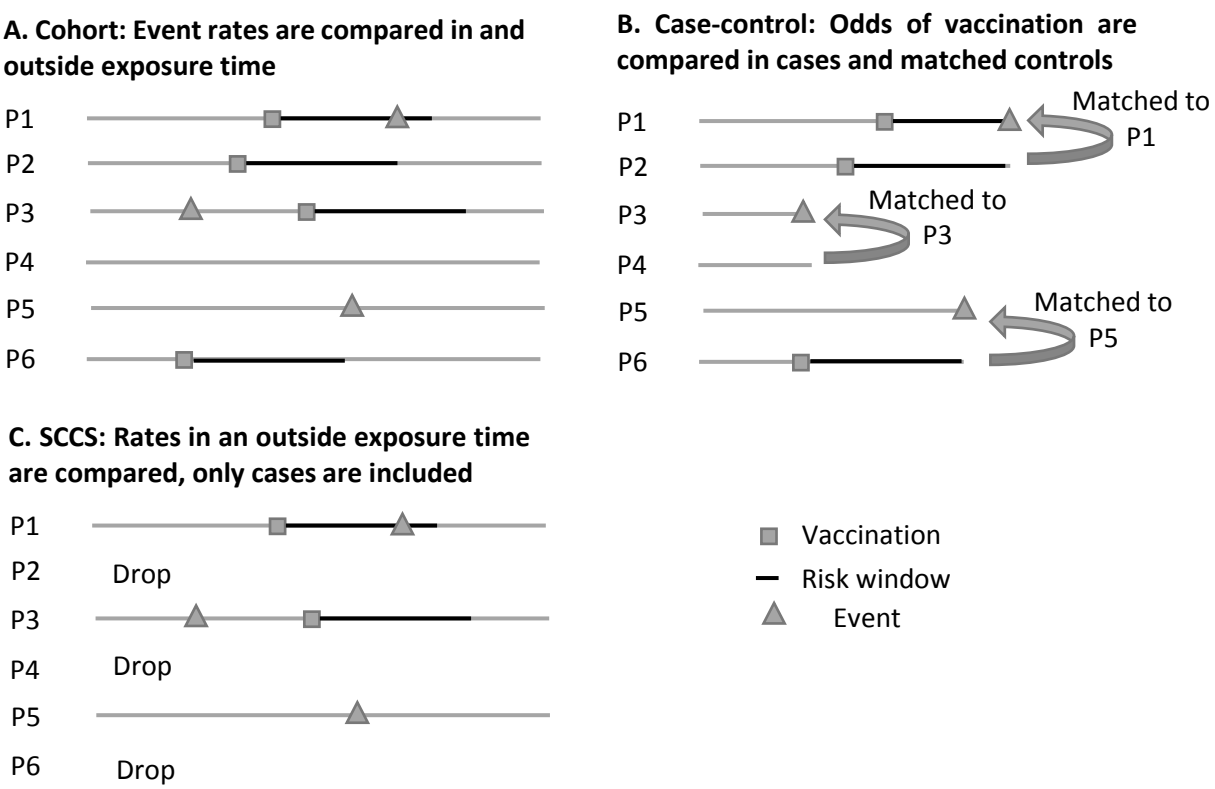

Figure 2.3. Comparison of a cohort, case-control and self-controlled case-series (SCCS) for 6 individuals (3 cases and 3 non-cases). Adapted from Nick A.[66]

2.3.3.1 Cohort studies

For this design, a cohort of individuals is established and cases occurring within and outside the exposure period are identified. The risk of developing the outcome is compared among the exposed and unexposed (Figure 2.3 A). Being a cohort, person-time is available and it is thus possible to obtain direct estimates of risk and attributable risk. Misclassification of the outcome can lead to biased results. The analysis is usually done using Poisson regression. While having person-time is the main advantage of this design, for rare events it requires large amounts of data and if these data is available, the analysis may be computationally intensive.[66,67] For vaccine safety, an example of this design was the assessment of adverse pregnancy outcomes following the HPV vaccine, in Denmark.[69]

2.3.3.2 Case-control studies

For this design, cases of the disease are identified, followed by selection of suitable controls, and odds of exposure (vaccination) is compared in cases and controls. Controls can be matched to controls and exposure assessed based on a reference date/age at the event. It is also possible to use multiple controls per case (Figure 2.3 B). This design requires inclusion of a smaller number of individuals (as compared to a cohort study), which eases the data collection process or, in the case of electronic health records, reduces computational power.

This is of particular relevance for rare outcomes, as it is often the case for vaccine safety. As it does not consider follow-up time, in a case-control study data can be analysed as they become available. This is only an advantage if the comparison is made with a prospective cohort, as use of electronic health records data with an historical cohort design can also be analysed as soon as the data become available. The analysis is usually done using logistic regression. As with other case-control studies, selecting a control group might prove difficult. When using electronic health records this issue may be less problematic as it is always possible to establish a cohort and a case-control study is in fact nested within the cohort.[66,67]

Case-control studies are generally considered to provide weaker evidence than cohort studies but if well conducted they can provide evidence as robust as cohort studies. One issue particularly relevant for case-control studies using electronic health records is identifying cases and controls. Cases are selected based on registered information, including codes on diagnosis and symptoms or drugs prescribed (see 2.3.3). However, absence of a relevant code might not mean absence of the disease of interest. This problem is the same as that of outcome ascertainment in cohort studies that use electronic health data. The issue of imperfect positive predictive value (PPV) of diagnostic codes is considered in Section 3.1.1.4. Nevertheless, for rare outcomes, this will have little impact when estimating odds ratios.[66,67] Smeeth et al. used a case-control study in 2004 to assess a potential increase in autism following MMR.[70]

2.3.3.3 Self-controlled case series studies

The self-controlled case series (SCCS) method was developed by Prof. Farrington, at the Public Health Laboratory Service (now Public Health England), to assess suspected associations between a vaccine and an acute adverse event when only information from cases is available.[66,71,72]

For a given study period, individuals experiencing the outcome of interest are identified and their vaccination histories are retrieved. Based on vaccination date, risk-windows are defined and the remaining of the study period is included as control period for a given individual (serving as the baseline risk). This is equivalent to a retrospective cohort design, conditioning on experiencing the event (Figure 2.3 C). The analysis is thus performed using conditional Poisson regression. The main advantages for this design include: (i) it only requires cases, while keeping similar power to a cohort study, and (ii) it intrinsically adjusts for time-invariant confounding (such as gender or ethnicity). While the method does not intrinsically adjust for time-variant confounders, such as age, it is still often possible to allow for these in the model.

Potential disadvantages follow from the assumptions of the method. First, the probability of the exposure should not depend on the occurrence of the event. For vaccine safety this will matter if (i) the event is a contra-indication for the vaccine (e.g. intussusception and rotavirus vaccine); (ii) the individual is more or less likely to be vaccinated after experiencing the event (e.g. Guillain-Barré syndrome and seasonal influenza); (iii) vaccination is delayed after the event (e.g. after a seizure episode).[66,71,72] For (i) is it possible to use a pseudo-likelihood method, for (ii) using a SCCS will produced biased estimates only if the probability of vaccinations changes considerably while for (iii) the issue might be addressed by considering a low-risk period during the time before vaccinations.[66,71] This assumption (event-independent exposure) is also problematic when the outcome is death, as after dying there is no possible exposure. SCCS can still be used if the deaths are rare and time from exposure to the end of the planned observation period is considered. Secondly, this method is best suited to study events with short risk periods. It can be used for longer periods as in studies assessing the risk of autism following MMR[73,74] but it is more prone to collinearity with age, reducing power.[71] Thirdly, this method does not allow the estimation of absolute incidence, only relative incidence. Finally, it requires variability in the time or age at which the event occurs.

While this method has been developed to study vaccine safety it has been widely applied, particularly in pharmacoepidemiologic studies.[71] For vaccine safety, a review identified 40 studies using SCCS until the end of 2010, looking at a variety of vaccines and adverse events.[72] Examples include autism following MMR vaccine,[73,74] febrile convulsions and MMR[75] and intussusception and rotavirus vaccine.[76] For the former no association was shown while for the two last pairs an increased risk was observed. SCCS is a reference method in vaccine safety confirmatory studies.

2.4 Thesis rationale, aim and objectives

2.4.1 Thesis rationale

In the UK, vaccine pharmacovigilance has relied largely on spontaneous reports and on epidemiologic studies aimed at confirming hypotheses generated by a variety of sources. NRVTSS has been implemented using spontaneous reports for observed events.[10] As outlined in Sections 2.3.1.1 and 2.3.3, spontaneous reports under-report AE and are subject to biases, while hypothesis-testing studies are generally designed in response to suspicions raised some time after the vaccine's introduction. In contrast, NRTVSS is usually started very soon

after vaccine delivery and its sequential nature ensures timely identification of signals. Electronic health records are required for a new UK NRTVSS that relies fully on routinely collected data; in the UK such research-level primary care electronic health records data are available, such as the CPRD,[11] THIN,[12] the RCGP RSC,[13] and ResearchOne.[14] It is then necessary to determine the NRTVSS methods available, their characteristics, and whether available electronic health records are adequate to perform this kind of surveillance. This PhD project explores these aspects, using CPRD as the main data source.

2.4.2 Aim and objectives

The overarching aim of this thesis is to assess the feasibility of implementing a near real-time vaccine safety surveillance system using CPRD data. Specific objectives include to:

1. Review the methods currently used to perform NRTVSS using electronic health records ('Systematic review');
2. Examine recording delays in CPRD for selected conditions, due to practices receiving and recording diagnosis made at secondary care ('Recording delays');
3. Trial the implementation of NRTVSS using previously collected CPRD data ('Trial implementation');
4. Assess how delays in recording outcomes and receiving data influence the power and time to detect a safety signal ('Power').

The work conducted to address these objectives has been written as four papers, numbered 1 to 4, in accordance to the corresponding objective number. The papers are presented in this thesis and Table 2.3 indicates the Chapter in which each paper can be found. This table also includes the secondary objectives for **objectives 2** and **3**, as well as the outcomes and vaccines considered for each main objective. Further information on the work conducted but not included in the papers has been placed alongside each paper and in intervening Chapters. This additional work is intended to provide the reader with a deeper understanding of the choices made regarding the work described in the papers. Before explaining the work conducted to address each of these objectives, in the next Chapter the data sources used (CPRD and Hospital Episode Statistics - HES) are presented, as well as how they were used to select the study population. The Chapter ends with a detailed presentation of the sequential tests used to perform NRTVSS.

Table 2.3. Thesis objectives

Objective	Chapter	Secondary objectives	Outcome(s)	Vaccine(s)
1. Systematic review	4	-	Any	Any
2. Recording delays	5	To evaluate completeness of recording of diagnoses in CPRD	• GBS • Bell's palsy • Optic neuritis • Febrile seizures	No specific vaccines considered
3. Trial implementation	7	To assess: • the statistical test to use; • how to adjust for delays; • power to detect a signal.	• GBS • Febrile seizures	• Seasonal influenza • MMR
4. Power	7	-	• GBS	• Seasonal influenza

GBS – Guillain-Barré syndrome, MMR – Measles-mumps-rubella vaccine

3 RESEARCH METHODS

3.1 Data sources

3.1.1 CPRD

In the UK, over 98% of the population is registered with a GP, who manages a variety of health conditions and acts as a gatekeeper for further care, including referring patients for secondary care when necessary. Following these assessments at secondary care, results are communicated back to GPs. GPs and other practice staff register information on their patients (including feedback from secondary care) onto dedicated software, where the information is stored for future reference.[77,78] The main GP software systems include EMIS (Egton Medical Information System), SystmOne and Vision.[78]

CPRD collects data from participating practices in the UK that use Vision software and it is one of the largest primary care databases in the world.[77,78] It started in 1987, under the name of Value Added Medical Products (VAMP), and was initially restricted to London. It then expanded in 1993 when it was renamed the General Practice Research Database (GPRD) and again in 2012, when it received its current name, CPRD. As of July 2013, CPRD contained information on 4.4 million patients (6.9% of the UK population), with its population broadly following the UK population in age, sex, and ethnicity distributions. CPRD has been extensively used for research purposes, with almost 1800 research papers published[79] on a wide range of topics, including (pharmaco)epidemiologic studies, health economics, health services research and pragmatic trials.[77] Knowing the content and structure of these data as well as the data available is required in order to understand the findings from studies that use them.

3.1.1.1 Data content

CPRD data contain anonymised information on health-related diagnosis, tests, referrals, lifestyle factors, and prescriptions. Practice staff may enter information into GP systems using coded and free text. In Vision, information is coded with Read codes, a hierarchical thesaurus of clinical terms used in the National Health Service (NHS) since 1985.[80] Free text can be added to these coded terms as a way to provide additional information. Alternatively, letters or e-mails can be attached. These usually document communication with other levels of care (to and from GPs) and are considered a distinctive type of free text.[78] In the past, anonymised free text was available for purchase upon request, and was mainly used for

validation purposes and in some cases for improving diagnostic algorithms. CPRD also explored the use of natural processing language techniques to improve the usability of free text for research and, in 2012, there were plans to develop free text tools as a way to maximise the utility of this data source.[78] However, due to changes in the information governance environment in the UK, in April 2016 CPRD stopped making free text data available to researchers (CPRD Knowledge Centre, personal communication). Prescriptions are identified in a different way from the remaining information. They receive a unique CPRD product code and information on the BNF (British National Formulary) code is also included.[81,82] In addition to Read codes and product codes, immunisation information can also be recorded using specific information in a dedicated file. This includes two main variables, the immunisation type, which contains information on the vaccine type, and immunisation status, which indicates if the vaccine has been administered, advised or refused. CPRD data also comprise structured data fields, used to register test results and clinical information. This information is recorded using 'entity types' and CPRD provides information on what is recorded in each entity type together with look-up tables detailing what is recorded under each code.

As CPRD diagnoses, tests, referrals, vaccinations and therapies are coded, when ascertaining cases of disease/drug exposure it is necessary to develop appropriate code-lists covering the codes that might have been used to identify the disease of interest/drug exposure. To facilitate identification of relevant Read codes and product codes CPRD provides customers with browsing tools. Section 3.2 details how these browsers were used to develop code-lists.

3.1.1.2 Data structure

CPRD contains medical information from patients in participating practices. This information is held in different files depending on its content, as presented in Table 3.1.[82,83] These files can be linked to provide the entire medical history from a given patient. For the purposes of this work patient, practice, clinical, test, referral, immunisation and therapy files were used. Data from these files allowed identification of diagnoses and vaccinations of interest. Further details are provided in Section 3.2.

Table 3.1. Content of each CPRD file type[82,83]

File	Content
Patient	Patient demographics and registration details.
Practice	Practice information (including when information was last collected).
Staff	Practice staff details.
Consultation	Information on the type of consultation.
Clinical	All medical history, including symptoms, signs and diagnoses. Data are coded using Read codes.
Additional Clinical details	Information entered in structured data areas in the GP's software using entity types.
Test	Information on test data (e.g. results from blood tests).
Referral	Information on referrals to external care (e.g. hospital).
Immunisation	Information on vaccinations coded using Read codes and special immunisation information.
Therapy	Details of all prescriptions (including vaccines and therapeutic drugs).

GP – General Practitioner

To understand the medical history of a patient it is also important to know for which time period we have information available for. This is done using key dates, both at the practice and patient level, summarised in Table 3.2. For a given patient, information can be used from the time that the practice in which s/he is registered is deemed to be of research quality (up-to-standard date, see 3.1.1.4) and from when the patient registered with that practice (current registration date). It has been demonstrated that in the first few months after a patient registers with a new practice GPs tend to record not only new diagnoses but also retrospectively record past diagnoses.[84] It was therefore suggested that up to the first year after the current registration date should be excluded to avoid capturing retrospective recording.[84] Data from a patient can thus be used for a study starting at the latest of up-to-standard date and current registration date plus up to one year (depending on the specific condition). Data are available until they were last collected from the practice (last collection date), the patient transferred out of the practice (transfer out date) or the patient died (death date). Follow-up thus ends at the earliest of last collection date, transfer out date and death date. These beginning and end of follow-up are then adapted for each study depending on the design and study period. Records also contain specific dates which might be of interest. These include the system date, the date when a record was entered into the system, which is automatically assigned by the practice software and the event date, entered by the practice staff and which is deemed to represent the date the clinical event happened. The importance of these record-level dates is explained in more detail when assessed recording delays in Section 5.3 (**Objective 2**).

Table 3.2. Relevant dates in CPRD

Date	Content
Practice level	
Up-to-standard date	When the practice met certain quality requirements.
Last collection date	When the practice last uploaded data to CPRD. Available for each monthly release of CPRD.
Patient level	
Current registration date	When the patient registered with the practice.
Transfer out date	When the patient was transferred to another practice.
Death date	When the patient died.
Record level	
Event date	When the event is deemed to have occurred. Entered by the practice staff. Ideally represents the correct date of diagnosis or the date when the patient re-consulted for on-going or past events. However, can also be the date when the record of a past diagnosis was entered retrospectively into the GP system.
System date	When the record was entered into the system (automatically assigned by the software).

CPRD – Clinical Practice Research Datalink, GP – General Practitioner

3.1.1.3 Data available for analysis

The London School of Hygiene and Tropical Medicine (LSHTM) holds a CPRD license and receives a new data release every 6 months. For these data, it is possible to search for eligible patients both on the basis of recorded Read codes or other characteristics in any of the file types. CPRD data are released on a monthly basis and it is also possible to access data from these monthly versions of the data. There is online access for licence holders and patients' data can be extracted based on specific Read and therapy codes. Vaccination information is coded using a combination of Read, therapy and special immunisation codes (including the vaccine type and vaccination status, see 3.1.1.1). Therefore, it is not possible to use the online access provided to identify patients on the basis of their vaccination status. The study reported in this thesis required identification of vaccinated individuals and the current online search tool allows only limited identification of eligible patients because of the inability to search for the totality of immunisation coding. This limitation and the solutions applied to address it are presented in further detail and discussed in Section 6.2.

3.1.1.4 Data quality

CPRD size, information on medical history and long follow-up time make this data an attractive source. However, CPRD data are not collected for research purposes and, as with

any routine data source, it is important to understand the data available and their possible limitations.

CPRD uses data quality markers both at the patient and practice level. For patients, CPRD includes an 'acceptability flag', based on indicators of potentially poor recording or discontinuous follow-up. Patients are considered acceptable if: (i) they have information on year of birth, (ii) there are no events registered before their birth year, (iii) gender is male, female or indeterminate, (iv) age is ≤ 115 years at last collection date or transfer out date, (v) first registration date is on or after the month/year of birth, (vi) current registration date is valid, on/after the month/year of birth and first registration date, and for permanent registration, (vii) the transfer out date exists when there is a reason for transfer out, and it is on/after the first and the current registration dates, (viii) there is at least one valid event date.[78,83] At the practice level, each practice is assigned an up-to-standard date, which indicates when the practice was deemed as being of research quality. This date is established based on mortality rates and practice recording behaviour. For the former, CPRD compares the number of deaths in the practice to an expected range given the UK's mortality rate and the practice size. The latter involves a practice-level assessment of recording gaps, considering the median number of events in the clinical, consultation and therapy files. Each practice should not have any significant gaps of low recording, i.e. five consecutive weeks in which there were less than 30% of the median number of events.[78,83]

While the data quality markers help ensure that the data available are of good quality, further aspects need to be considered, including validity, timeliness, and secular trends. When ascertaining outcomes and exposures, the general principles outlined in 2.3.3 should be followed. A 2010 systematic review looking at studies attempting to validate diagnosis in CPRD identified 357 validations assessing 183 diagnosis.[85] Validation studies were either internal (using only data from CPRD, for example by reviewing anonymised free text) or external (e.g. by contacting GPs to confirm a patient coded as a case did indeed have the condition identified, or by comparing measures of frequency with those obtained from another data source). Studies reporting quantitative measures of validity most often reported PPV, i.e. the proportion of cases identified from CPRD that were confirmed as true positives. Other measures of validity, such as sensitivity, specificity, and negative predictive value were usually not assessed. In general, diagnoses based on CPRD data were confirmed based on either internal or external information (median PPV of 89%). Despite assessment of validity relying mainly on PPV, CPRD has been extensively used for research purposes.

Completeness of recording of diagnoses is typically regarded as an aspect of validity (encompassing sensitivity and negative predictive value). Nevertheless, some authors examine completeness of diagnostic recording separately, as a distinct issue. For example, a previous study looking at myocardial infarction showed that using CPRD only identified 75% of all cases, as compared to linking several data sources (CPRD primary health care records, hospital records, disease registers and death certificates).[86] This is highly dependent on the place of diagnosis and management of the condition of interest but also on its severity; conditions generally diagnosed and/or managed by GPs are likely to be well captured in CPRD. The same applies to vaccination information. Vaccines administered in GP practices (e.g. most childhood vaccines) are expected to have high levels of completeness while the remaining (e.g. HPV vaccine, administered in schools) may have lower levels of completeness or be recorded after long delays. Furthermore, completeness might change throughout time leading to secular trends. These changes may be due to modification in clinical practice or recording behaviour. One well-known reason for changes in recording behaviour is the Quality and Outcomes Framework (QOF), introduced in April 2004. This scheme provides financial incentives to record specific outcomes as a way to achieve certain indicators. Recording behaviour is likely to change depending on the specific indicators incentivised at specific periods, and thus increase/decrease completeness.[87] Alternatively, secular trends might be due to patients' health service use or changing epidemiology of the condition of interest. When using CPRD it is thus important to reflect on whether the condition(s) of interest are likely to be well captured and consider implications of incomplete recording over time.

An issue that is less often discussed is timeliness. Delays in CPRD data might happen for several reasons: (i) delays in having a final diagnosis after patient presentation, (ii) delays in receiving or recording feedback from other levels of care (e.g. hospital), (iii) delays in practices uploading files to CPRD, (iv) delays in researchers receiving the latest updated data from CPRD. A previous study used THIN, another UK primary care database, to compare two successive releases of the dataset. In particular, the authors compared the number of events available in the later version of the data but not in the earlier version and assessed how these entries varied as function of time since the last collection date. This work showed that using a later version of the same data would capture more events, particularly in the month previous to the last collection date (9.6% additional events captured).[88] This is particularly relevant for incidence/prevalence studies as not considering delays in receiving data from practices (reason (iii), above) would lead to underestimation of rates. For the purposes of

the work presented in this thesis, timeliness is of particular relevance as a near real-time time system relies on timely data. To assess timeliness, it is important to know how quickly data accrue in CPRD. The approach in the work by Sammon et al.[88] is an initial step in recognizing the issue of delays in recording outcomes but it does not provide quantification of how long it takes for data to accrue. As a central aspect of a near real-time system implementation, timeliness was explored as part of this project and is reported in Section 5.3.

3.1.1.5 Data linkage

CPRD data provide comprehensive information on the medical history of a patient but additional information might be only found or be better recorded in other databases. Hence, linked data from other data sources are available as a way to complement CPRD data. Linkage is performed by a Trusted Third Party (NHS Digital) in order to preserve anonymity of records. At the moment, CPRD is linked to hospital data (HES, only for 75% of the English practices), mortality data (from the Office for National Statistics - ONS), cancer registration data (from Public Health England - PHE), mental health data and deprivation data (Index of Multiple Deprivation - IMD). Further linkages are being planned.[89]

For the purposes of the work presented in this thesis the information required is mainly on vaccines administered and possible outcomes of interest for vaccine safety. Most vaccines are administered in primary care and thus CPRD is a good data source to capture this information. As for events of interest, some are likely to be well captured in CPRD. For others, that are more serious and require hospitalisation (e.g. GBS), hospital data might provide additional records. Hospital data would thus be relevant to complement information available in CPRD. However, data are linked too infrequently to allow implementation of a near-real time system based on linked data (see 3.1.2.3). As such, I envisaged a system solely based on CPRD, and stand-alone CPRD data were used for most of the work presented. The exception is the work presented in Section 5.3, looking at completeness of records initially diagnosed in hospital. For that work, linked CPRD-HES data were used; HES data are thus reviewed below.

3.1.2 HES

Information from hospital activity in England is collected in several HES datasets: (i) HES Admitted Patient Care (HES APC), which collates information on hospital admissions; (ii) HES outpatient data, which contain information on outpatient appointments; (iii) HES Accident and Emergency (A&E), where details on A&E attendances are collected; and (iv) HES

Diagnostic Imaging Dataset, where details from diagnostic imaging tests (x-rays, magnetic resonance imaging, etc.) are maintained. These data are maintained by NHS Digital and anonymised for research use.[89,90] Only a small proportion of diagnoses in HES Outpatient data and HES A&E are coded, limiting their use (Rachael Williams, CPRD, personal communication). For this work only HES APC was used and is explained in more depth below. It will be simply referred as HES.

HES data started to be collected in 1987 and national coverage was attained in the financial year 1989/1990. It was initiated to inform management and planning of services and since 2004/05 is the basis of a payment-for-performance system in place in the NHS. CPRD linkages with HES data only cover the period from 1997 onwards as this corresponds to the date when NHS numbers became a mandated return from hospitals and thus could be used in the linkage by the third trusted party.[91] Given the universal coverage of these data, the long period of data collection and the possibility to follow-up individuals, HES has also been used for research purposes, including: disease incidence, vaccine safety, treatment patterns by different hospitals, impact of clinical guidelines and policies, therapy outcomes and factors associated with these outcomes, and risk prediction models.[90] What follows is an explanation of the data characteristics with implications for this work.

3.1.2.1 Data content

HES contains clinical, demographic, and provider information for each hospital admission. This includes a unique CPRD identifier (to allow linkage with CPRD data) and information on the quality of linkage between HES and CPRD data. Hospital information collected includes coded diagnosis and relevant dates (e.g. admission and discharge dates). HES data are coded using the International Classification of Diseases, Tenth Revision (ICD-10). ICD-10 is a hierarchical coding system including diseases, disorders, injuries, and health-related conditions. It has been used worldwide to monitor disease incidence and prevalence, reasons of death, to evaluate guidelines implementation, and for reimbursement purposes.[92]

3.1.2.2 Data structure

In HES, each admission (an uninterrupted stay in a hospital) is known as a 'spell'. For each spell there may be several Finished Consultant Episodes, i.e. periods during which a patient was under the care of a single consultant. Each episode has one primary diagnosis and may have up to 20 diagnoses in total; the episode must have at least one primary diagnosis, and the maximum number of diagnoses that can be recorded has changed over time (from seven

diagnoses until April 2002, to 14 between April 2002-March 2007, and 20 diagnoses ever then).

As in CPRD, HES data are stored in multiple files. Files available in the linked data are presented in Table 3.3. For the purposes of this work, only the patient, hospitalisations, episodes and diagnosis files were used.

Table 3.3. Content of Hospital Episode Statistics Admitted Patient Care (HES APC) file (linked data)[89,90,93]

File	Content
Patient	Patient demographics and linkage quality.
Hospitalisations	Admission, stay and discharge details (dates, duration, etc.).
Episodes	Episode characteristics (dates, speciality, duration).
Diagnosis	Details of diagnoses (including ICD-10 codes), available by episode for each hospitalisation, including the primary diagnosis.
Procedures	Details of procedures received. Can be linked with episode or spell.
Augmented care	Specific information on time spent on intensive and/or high dependency levels of care.
Critical	Information on patients receiving critical care (type and duration).
Maternity	Birth and delivery information.
Health Resource Group	Information on the Healthcare Resource Group (and thus unit of cost) the episode was linked to.

ICD-10 - International Classification of Diseases, Tenth Revision.

3.1.2.3 Data available

After a patient discharge, a physician responsible for the patient's care fills in a discharge summary for the specific episode (including diagnosis and procedures). These summaries are then sent to a hospital coding department where they are entered in an electronic database. These data are extracted from each hospital on a monthly basis and sent to NHS Digital. NHS Digital performs data checks and cleaning procedures, and generates HES identifiers for each episode. Hospitals can submit an updated version of the data to correct data quality issues at the end of the financial year. NHS Digital thus produces a provisional annual HES extract, which is reviewed by the hospital, and after this a final revision is made available.

CPRD-HES linked data are made available in sets which are released too infrequently to allow the implementation of a near real-time surveillance system. These datasets also suffer from delays in data received from the hospitals. For example, the linked data released in January 2015 (Set 10) included HES hospitalisations only up to 31st March 2014. The subsequent release (Set 11) was made available to researchers in December 2015 and contained HES data up to 31st March 2015. Despite some improvement in this regard (for example, Set 12 was released in March 2016 and included HES data up to 30th September 2015) a more timely

updating of the linkage is not envisioned in the near future. As such, CPRD-HES linked data were not considered an adequate data source for NRTVSS implementation. Instead, I used them to assess aspects of CPRD stand-alone data quality, as explained in Section 5.3.

3.1.2.4 Data quality

As with CPRD data, one of the main issues when using HES data is the quality of coding. Coders are trained to follow standardised rules when transcribing information from discharge summaries. However, the quality and completeness of these summaries may vary thus limiting the ability to apply the existing rules, particularly for comorbidities. Additionally, changes in financial incentives to improve coding depth may have led to an increase in the number of codes used and improvement in coding. This will affect validity of research findings in general. In particular it may bias time trend comparisons and comparability of studies conducted at different time periods, as validity of recording may not be constant over time.[90]

HES collects data on admitted patients but admission thresholds might vary between hospitals or over time. For example, in 2004 the A&E waiting time target in England changed to a maximum of 4 hours, which might have triggered an increase in the number of admissions as a way to meet this target. This might influence characteristics of patients admitted and influence comparisons over time.[90]

3.2 Identifying eligible individuals: development of code-lists

As explained above, CPRD and HES contain coded information using Read codes or ICD-10 codes, respectively. Analysis using these data require a prior identification of code-lists which allow ascertainment of cases and exposures. Analyses performed to address each of the study objectives included different study populations and had distinct inclusion and exclusion criteria. These are explained in the Chapters where the specific analyses are reported. In this Section, details are provided on how the code-lists were developed to identify eligible patients and how data were extracted.

As explained in 3.1.1.1, CPRD provides browsers to facilitate the search of Read and product codes. I carried out searches in a two-stage process. First, a free-text search with terms relating to the condition of interest was performed. The results of the search were assessed individually and a decision made whether to include them. After selecting the codes to include, the relevant Read code hierarchies were identified and searched to identify further terms. Immunisation information also requires the identification of dedicated codes and is

detailed in Section 3.1.1.2 and below. A similar procedure was followed when developing code-lists to identify cases in HES but using ICD-10.

For **objective 2** of this project (examine recording delays in CPRD, due to practices receiving and recording diagnosis made at secondary care, for selected conditions) eligible patients had at least one of four outcomes: Bell's palsy (BP), GBS, optic neuritis (ON) and febrile seizures (FS). The rationale for selection of these outcomes is presented in Section 5.2. Table 3.4 presents searches conducted for both Read terms (initial searches) and Read codes (based on the initial search). Prof. Sara Thomas developed an initial code-list for BP. Prof. Sara Thomas and Prof. Nick Andrews shared with me existing code-lists for FS. For both BP and FS, I conducted searches to update existing code-lists. I developed initial searches and code-lists using data (and thus browsers) released in July 2015. I conducted new searches in July 2016 with the view of updating these lists; no further codes were identified. The codes included in the code-lists were classified as being specific or not for the condition of interest. All codes were used in the main analysis, and then the sub-set of codes classified as specific were used to conduct a sensitivity analysis. This additional analysis was performed to assess the imperfect validity of diagnosis records, as suggested by previous studies and explained in Section 2.3.3. Final code-lists are available in Section 5.4.

Table 3.4. Searchers performed to develop and/or update code-lists using Read codes

Outcome	Read terms	Read codes
BP[†]	*bell*, *facial*	14*, 2BR*, F31*
GBS	*guillian*, *neuritis*, *neuropath*, *demyelin*	F17*, F21*, F36*, F37*, Fyu*, N24*
ON	*optic*, *visual*, *demyelination*, *neuritis*	F4H*, F21*, Fyu*
FS[†]	*seizure*, *convulsion*, *fit*	1B2*, 1B6*, 282*, F13*, F25*, Fyu*, Q48*, R00*, Ryu*, Eu4*

*Any term is allowed, [†]Only for updating purposes**.** BP – Bell's palsy, GBS – Guillain-Barré syndrome, ON – Optic neuritis, FS – Febrile seizures.

Data from patients with a relevant code in the clinical, test, referral, or immunisation file during the study period (January 2005-July 2014) were extracted using data released in July 2015. First-ever codes were used to capture incident cases and avoid counting the same events multiple times. After extraction, eligibility was further assessed by looking at beginning and end of follow-up dates. Beginning of follow-up was the latest of up-to standard date, current registration date plus one year (see 3.1.1.2) and the beginning of study period (specific to each study question), and end of follow-up was the earliest of date

of death, transfer out date, last collection date (see 3.1.1.2) or end of study period (also specific to each study question). Patients were included if they had at least a day of follow-up. Further details and other eligibility criteria are available in the Section where each specific study is reported.

Work conducted to address **objective 2** (assessing recording delays in CPRD data) also included the analysis of linked CPRD-HES data. When analysing these linked data, individuals with one of the four outcomes of interest in HES were included, which thus required outcome ascertainment using HES data. Searches conducted in ICD-10 to identify relevant codes are available in Table 3.5. Final code-lists are available in Section 5.4. Patients with a first-ever code recorded in any diagnosis field during the study period (January 2005-March 2014) were included. First-ever code was used for both delay and completeness to simplify interpretation of the completeness analysis. Patients with no previous record of that outcome in CPRD were followed-up from the hospital episode date in which the outcome was first recorded until they had an outcome in CPRD or were censored (earliest of date of death, transfer out date, last collection date or July 2015). For patients in this cohort, recording in CPRD was then assessed using the code-lists developed for the main analysis.

Table 3.5. Searches performed to develop code-lists using ICD-10

Outcome	Free text	ICD-10 code
BP	Bell, bell	G51
GBS	Guillain, demyelination	G36, G61
ON	Optic, optic, bulbar	G36, H46, H47
FS	seiz, convulsi, fit	F44, R56

BP – Bell's palsy, GBS – Guillain-Barré syndrome, ON – Optic neuritis, FS – Febrile seizures.

For **objective 3** (trialling the implementation of a near real-time system using historical CPRD data) and **objective 4** (assessing how delays influence the power and time to detect a safety signal) it was necessary to identify a cohort of vaccinated individuals. This included patients aged 65 years or older who were vaccinated against seasonal influenza, and children aged 12-23 months receiving a first MMR dose. The rationale for the choice of these vaccines and the rationale for inclusion of only vaccinated individuals is presented in Section 5.6 and Section 8.3.2, respectively.

As outlined in Section 3.1.1.1, immunisation information can be found in multiple files, using different fields: (i) in the clinical, referral, test, and immunisation files using Read codes; (ii) in the therapy file using therapy codes; and (iii) in the immunisation file using a combination

of specific vaccine codes (immunisation type) and codes indicating whether the vaccine was administered, simply advised or the patient refused it (immunisation status). Information contained in these files can be conflicting, for example with one code indicating the vaccine was administered and another one stating the vaccine was refused. It is thus necessary to first identify relevant codes for each of these scenarios and then develop a decision algorithm to determine whether to consider that an individual received the vaccine during the study period.

Code-lists for seasonal influenza vaccine were based on an existing code-list, previously developed by Prof. Sara Thomas and Dr. Elizabeth Millett. I conducted a search to update this code-list, presented in Table 3.6. Read terms and Read codes search terms were used to identify relevant Read codes and the remaining terms were used to identify therapy codes.

Table 3.6. Search terms used to identify relevant terms for influenza vaccine

Coding system	Search terms
Read terms	*flu*vac*
Read codes	9OX*, 9N4*, 68N*, 65E*, 8I2*, 14LJ*, 8IA*, 8I6*, U60*, ZV0*
Drug substance name	*influen*, *agrippal*, *fluvirin*, *imuvac*, *influvac*, *optaflu*, *begrivac*, *fluarix*
BNF code	14040200

BNF – British National Formulary

For the immunisation files the look-up for the entity immunisation type was consulted. Relevant codes for each vaccine were selected based on visual inspection of these codes. This information was used in conjunction with the immunisation status variable. Following this search, relevant codes were divided into codes indicating the vaccine had been administered or not.

After finalising these code-lists, I extracted data from the following potentially eligible individuals: (i) individuals with a given Read code in the clinical, referral, test, and immunisation files; (ii) individuals with a product code in the therapy file; and (iii) individuals with one of the immunisation types for seasonal influenza and a status ‘given’.

Following data extraction from potentially eligible individuals, I assessed the beginning and end of follow-up time (see above and Section 7.1 for further details). If they were eligible and had potentially received the vaccine during the study period, were aged 65 years or above, I applied a decision algorithm and made a final selection of vaccinated individuals.

The algorithm used is presented in Section 7.2.1.1.5. The code-lists were developed initially using data released in July 2015 and then updated using data released in July 2016. No further codes were identified.

For MMR, code-lists were based on previous work by Prof. Sara Thomas and Dr. Jemma Walker, who kindly shared their code-lists. The procedure for data extraction was similar to the one described above. The algorithm used is presented in Section 7.2.1.2.5.

To identify observed cases of GBS and FS, following seasonal influenza vaccine or MMR respectively, the code-lists presented Sections 5.4.1.1 and 5.4.4.1 were used. GBS was considered a 'once only' event and hence the first ever code was used (subsequent codes were deemed to represent retrospective recording of a past event). In contrast, in this analysis more than one episode for FS was allowed (see Sections 7.1 and 7.2.3 for details). Further inclusion and exclusion criteria are presented in Section 7.1.

3.3 Sequential tests

Near real-time vaccine safety surveillance makes use of sequential tests. In this Section the statistical aspects of sequential tests that are relevant for vaccine surveillance are presented. The first sequential test was proposed by Wald in the 1940's and was known as the sequential probability ratio test (SPRT). He defined a sequential test as any statistical test that allowed one of three decisions at each observation of a given experiment: (i) accept the null hypothesis; (ii) reject the null hypothesis; or (iii) continue the experiment (make more observations). The sequential nature of these tests results in a fundamental difference in comparison to a non-sequential approach: the number of observations required is not fixed, but is a random variable, depending on the results of previous observations. This feature results in a reduction of the number of observations required before making a decision ((i) or (ii), above) and it intrinsically accounts for multiple testing. In the case of SPRT, Wald argued that for the same α (or type I error, the probability of rejecting H_0 when H_0 is true) and β (or type II error, the probability of accepting H_0 when it is false) it allowed a reduction of about 50% in the number of observations required compared to a non-sequential test.[94]

SPRT was originally developed for quality control in manufacturing[94,95] but has been extended in several ways and applied in multiple contexts. One of its extensions, the family of group sequential tests, has been extensively used in the context of clinical trials.[96,97] For vaccine safety it is important to detect a signal as early as possible. This need was emphasised in the late 1990's, after the discovery of an increased risk of intussuception following

RotaShield® vaccine after its approval and licensure. In response to this discovery, several USA institutions came together and decided to build the capacity to detect adverse events during the post-licensure phase more rapidly. As stated in Section 2.3.2.3, this work has been led by VSD which started using sequential tests in 2005, as a way to reduce the number of observations required until a decision is made about whether to reject the null hypothesis.[7] Below is an explanation of SPRT, with a particular focus on vaccine safety.

Consider p, the probability of an AE to the vaccine under study. Define $H_0: p = p_0$, $H_1: p = p_1$, α, the probability of rejecting H_0 when H_0 is true, and β, the probability of accepting H_0 when it is false. Define C_t as the random variable representing the number of adverse events occurring within D days after the vaccine (risk window), administered in the period $[0, t]$. For the t-th observation, where c_t events have been observed, the likelihood ratio (LR_t) is the test statistic, given by:[7,8,94]

$$LR_t = \frac{P(C_t = c_t|H_1)}{P(C_t = c_t|H_0)} = \frac{p_1^{c_t}(1-p_1)^{t-c_t}}{p_0^{c_t}(1-p_0)^{t-c_t}}, (t = 1, 2, \dots)$$

More often the log-likelihood ratio (LLR) is calculated as data accumulate; it can be calculated considering the last test result.[7]

$$LLR_t = LLR_{t-1} + \log\left(\frac{L(Data_t, p_1)}{L(Data_t, p_0)}\right)$$

The calculations above assume a binomial distribution but SPRT can also be used assuming a Poisson distribution. In this case consider RR, the relative risk, and μ_t, the expected events, $H_0: RR = RR_0$, $H_1: RR = RR_1$. For this situation the test statistic, LR_t, is defined as:

$$LR_t = \frac{P(C_t = c_t|H_1)}{P(C_t = c_t|H_0)} = \frac{e^{-RR\mu_t}(RR\mu_t)^{c_t}/c_t!}{e^{-\mu_t}\mu_t^{c_t}/c_t!} = e^{(1-RR)\mu_t}(RR)^{c_t},$$

and its log version by:

$$LLR_t = \ln(LR_t) = (1 - RR)\mu_t + c_t \ln(RR).$$

Given the sequential nature of the test, based on the LLR_t, at each time point it is possible to evaluate if there is evidence to accept/reject H_0 or if it is necessary to continue surveillance. A decision is made by comparing LLR_t to the previously defined upper (UL) and lower limits (LL). For SPRT, UL is defined as:

$$UL = \frac{1-\beta}{\alpha},$$

and LL as:

$$LL = \frac{\beta}{1-\alpha}.$$

Possible scenarios and associated decisions include:

$$\begin{cases} LLR_t < \ln(LL) \rightarrow Accept\ H_0 \\ \ln(UL) < LLR_t < \ln(LL) \rightarrow Continue\ surveilance \\ LLR_t > \ln(UL) \rightarrow Reject\ H_0\ (signal\ detected) \end{cases}$$

Figure 3 exemplifies the use of SPRT for a known signal (intussusception following rotavirus vaccine). The surveillance period started in January 1999 and there was no signal until 2nd April 1999 (10th week of surveillance). At that time, LLR_t surpassed the upper limit, thus generating a signal. It is important to observe the decrease in the LLR_t following that time point. A signal should be raised irrespective of a subsequent decrease bringing the LLR_t down to the surveillance range.[7]

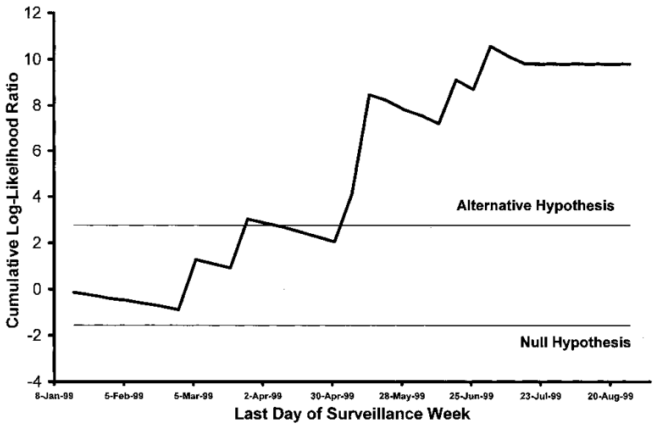

Figure 3.1. Use of Sequential Probability Ratio Test to detect a signal (intussusception) after introduction of rotavirus vaccine. The upper limit is crossed after 10 weeks of surveillance and the null hypothesis rejected[7]

SPRT requires a pre-specified probability/RR of the AE. [7,8,94] Previous knowledge regarding the AE and its public health importance can guide the choice.[32] However, the final test result depends highly on this choice: if H_1 is too far from the real value the signal might be missed (accepting H_0). Being conservative might delay signal detection. These characteristics limit the applicability of SPRT to NRTVSS, where timely identification of signals is crucial. An alternative version of this test has thus been formulated – the maximized sequential probability ratio test (MaxSPRT).[96] MaxSPRT uses a composite alternative hypothesis ($H_1: RR > 1$) thus requiring only one critical limit (CL). This test was developed for two

distributions – the Poisson (PMaxSPRT) and the binomial (BMaxSPRT), as presented in Sections 3.3.1 and 3.3.2.[96]

3.3.1 PMaxSPRT

When assuming a Poisson distribution and the notation previously used, the LR_t is given by:[8,96]

$$LR_t = \max_{H_1} \frac{P(C_t = c_t|H_1)}{P(C_t = c_t|H_0)} = \max_{RR>1} \frac{e^{-RR\mu_t}(RR\mu_t)^{c_t}/c_t!}{e^{-\mu_t}\mu_t^{c_t}/c_t!} = \max_{RR>1} e^{(1-RR)\mu_t}(RR)^{c_t},$$

and the LLR_t is

$$LLR_t = \ln(LR_t) = \max_{RR>1}[(1-RR)\mu_t + c_t \ln(RR)] = (\mu_t - c_t) + c_t \ln\left(\frac{c_t}{\mu_t}\right),$$

as the maximum likelihood estimate of RR is c_t/μ_t and $c_t \geq \mu_t$.

For PMaxSPRT, there is no lower limit to decide when to stop surveillance; this happens when a predetermined number of expected events (EV) is reached. Figure 3.2 exemplifies the use of PMaxSPRT to study seizures following concomitant use of inactivated influenza vaccine/23-valent pneumococcal conjugate vaccine in 6-23 month old children. Only one critical limit is used and a signal was detected on the seventh test.[98]

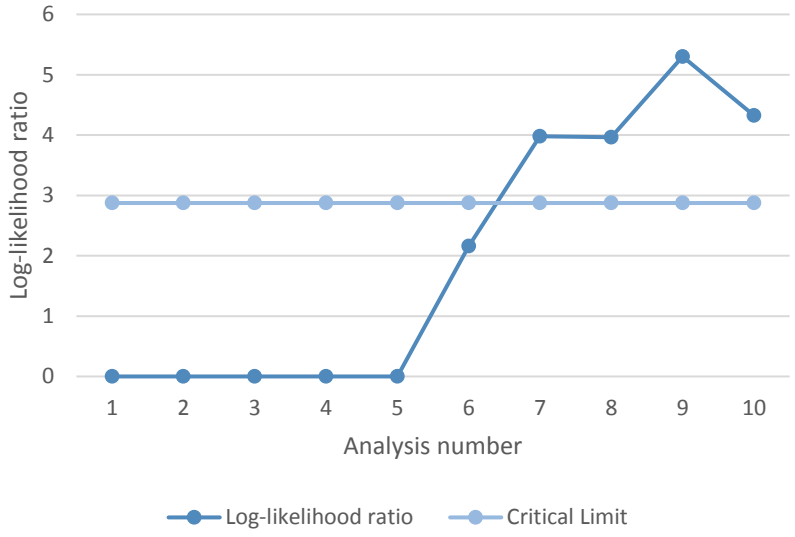

Figure 3.2. Use of Poisson-based maximized sequential probability ratio test to study seizures following inactivated influenza vaccine/23-valent pneumococcal conjugate vaccine in 6-23 month olds (adapted from Yih et al. [98])

To implement a PMaxSPRT it is necessary to calculate a CL. There are several options but Kulldorff et al.[96] proposed to calculate the CL based on the probability of rejecting H_0 if H_0 is

true (α) at the end of surveillance, when at least n events have occurred. Consider the log-likelihood ratio, calculated at the latest possible time when H_0 can be rejected, after n adverse events, denoted as s_n. The log-likelihood at s_n, LLR_{s_n}, is given by:

$$LLR_{s_n} = (\mu_{s_n} - n) + nln\left(\frac{n}{\mu_{s_n}}\right) = CL$$

LLR_{s_n} also gives our CL of interest. Given that we stop surveillance when $s_n > EV$ and n gives us the number of adverse events required to reject H_0, we can thus determine the probability of rejecting H_0 based on the probability of having n or more events at EV. As we run tests at repeated points in time, the probability of having n or more events at EV is conditional on the probabilities observed at s_{n-1}. The diagram below (Figure 3.3) illustrates this for $n = 3$. At s_3 we can only have three or more events if we had observed zero events at s_1 and zero or one events at s_2.The probability of having three or more events at s_3 (and thus rejecting H_0) is thus given by that same probability, conditional on having zero events at s_1 and zero or one events at s_2. As we assume a Poisson distribution to represent our variable of interest, we can calculate this same distribution to calculate these probabilities. To do that we need to know the mean of the Poisson distribution of interest (μ_{s_3} in this particular example, μ_{s_n} for any n of interest). This mean can be obtained by re-arranging the equation above:

$$\mu_{s_n} = -nW(-e^{-1-CL/n})$$

W is known as Lambert's function, which solves the equation $y = xe^x$ for x. In other words, $W(xe^x) = x$.

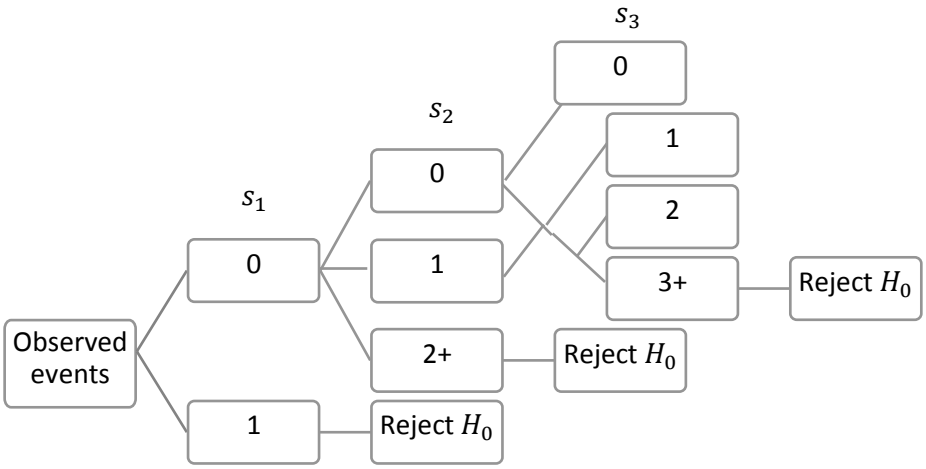

Figure 3.3. Probability tree for rejection of H_0 after we have observed three events

The approach just described would allow us to calculate α but given that α is previously set, we can use these principles to determine the critical limit using an iterative process based on two initial CL (CL_i and CL_{i-1}) and their corresponding α ($\alpha(CL_i)$ and $\alpha(CL_{i-1})$). This process is followed until it converges to the desired precision.

$$CL_{i+1} = CL_i - (CL_i - CL_{i-1})\frac{\alpha(CL_i) - 0.05}{\alpha(CL_i) - \alpha(CL_{i-1})}$$

Using this method our critical limit only depends on the expected number of events and α.

It is also possible to use this same reasoning to determine the existing power to detect an increased RR at the end of surveillance. For power, we are interested in β, in this case the probability of having less than n events at s_n considering a Poisson with a mean of $\mu_{s_n} * RR$.

3.3.2 BMaxSPRT

If one decides to use the BMaxSPRT, a comparison of the exposed to unexposed period is assumed. Both a self-controlled and a matched cohort design can be used. Considering the observed number of events at a given moment as n (exposed plus unexposed), c_n the number of events among the exposed, and z the length of the unexposed to exposed matched time periods, then the LR of a number of events, LR_n is given by:

$$LR_n = \max_{H_1}\frac{P(C_n = c_n|H_1)}{P(C_n = c_n|H_0)} = \max_{RR>1}\frac{[RR/(z+RR)]^{c_n}[z/(z+RR)]^{n-c_n}}{[1/(z+1)]^{c_n}[z/(z+1)]^{n-c_n}},$$

and the LLR_n is given by:

$$LLR_n = \ln(LR_n)$$
$$= c_n ln\left(\frac{c_n}{n}\right) + (n-c_n)\ln\left(\frac{n-c_n}{n}\right) - c_n\ln\left(\frac{1}{z+1}\right) - (n-c_n)\ln\left(\frac{z}{z+1}\right),$$

with $zc_n/(n-c_n)$ being the maximum likelihood estimate of RR. The formula only applies when $zc_n/(n-c_n) > 1$, otherwise LLR_n will be zero. Figure 3.4 presents an example of BMaxSPRT. This used the same data as that used in Figure 3.2, to study seizures following concomitant use of inactivated influenza vaccine/23-valent pneumococcal conjugate vaccine in 6-23 month old children, but considering a self-controlled design. Unlike PMaxSPRT, BMaxSPRT did not signal.[98]

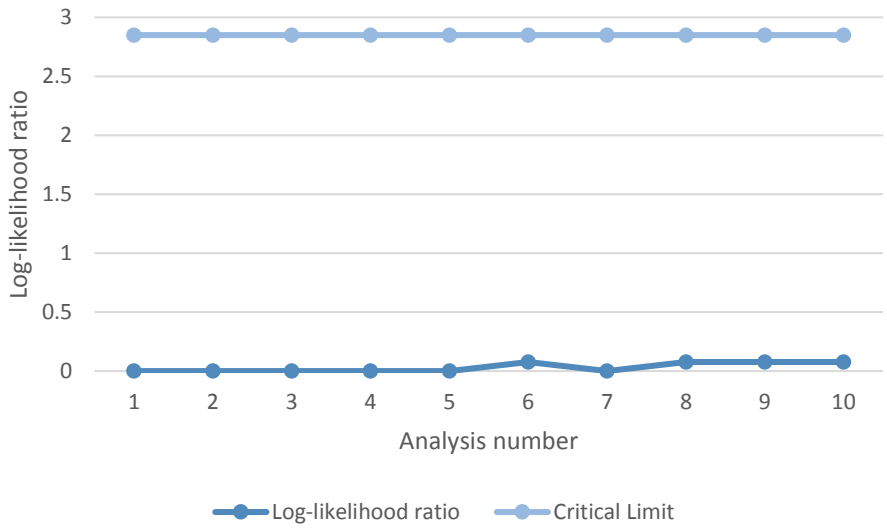

Figure 3.4. Use of binomial-based maximized sequential probability ratio (BMaxSPRT) test to study seizures following inactivated influenza vaccine/23-valent pneumococcal conjugate vaccine in 6-23 month olds (adapted from Yih et al.[98])

When using BMaxSPRT, the CL is calculated as detailed above (considering the last possible point at which the null might be rejected) but using an iterative Markov chain approach (instead of a Poisson distribution). The critical limit depends on the matching ratio, the observed number of events, and α.

Tables with CL for commonly used values have been published[96] and exact calculations are available in the package *Sequential,*[99] R software.[100]

3.3.3 Other tests

Near real-time vaccine safety surveillance was initiated in the USA in 2005 using SPRT and then its maximized version. Further methodological work was conducted to develop new versions of these tests. An example is the development of a conditional test to account for uncertainty in the use of historical data, which the PMaxSPRT is sensitive to. Another area of methodological research has been the assessment of the properties of the methods employed. For example, Maro et al.[101] assessed how outcome misclassification impacted timeliness of signal detection. Overall, this work has been led by VSD and NRTVSS use has grown since its introduction.[9] Further tests, their characteristics and use are presented in the next Chapter.

3.4 Statistical software

Data were extracted, cleaned and analysed using STATA/MP™ 14,[102] except for analyses involving the use of sequential tests. For these, the R package Sequential was used (version 2.3.1).[99] Sequential includes several functions which allow implementation of a system and evaluation of a system performance. The functions that I used during the course of this work are summarised in Table 3.7.

During the first attempts to code my analyses I identified bugs in the CV.Poisson and AnalyzeSetUp.Poisson functions. When running these functions with a small number of expected events there were error messages indicating programming errors (intermediate values not specified). I explored the reasons behind these by carefully looking at the R code running behind the functions. I then contacted the authors of the package detailing the issues identified and their possible reasons. The authors corrected the bugs identified and I was able to use the corrected functions for all the analyses performed.

I also attempted to verify the results obtained when using the package, as the package has been recently developed and includes non-standard functions. In particular, I calculated the log-likelihood ratio test for PMaxSPRT using the formula presented in Section 3.3.1 and compared my results with the ones obtained from the function Analyze.Poisson. Additionally, I used the values published in Lieu et al.[65] (which include the critical limit considered in their analysis) to confirm the calculation of critical limits using the function CV.Poisson yielded the same numbers as reported in the original publication. For BMaxSPRT, I also verified the results from Analyze.Binomial using the formula presented in Section 3.3.2, for a situation with a constant matching ratio.

Table 3.7. Description of the functions in the package Sequential used for the analysis of the project[99]

Function	General description	Inputs	Outputs	Relevant thesis sections/references
Analyze.Binominal	Allows the implementation of a system based on the observed number of cases and controls, and the matching ratio (using BMaxSPRT). The results of a test run are automatically stored and can be used for a subsequent test, helping to facilitate the implementation of a system. Requires the set-up of the parameters to be considered through AnalyzeSetUp.Binominal	Name of the analysis (should match the one given when setting the parameters), test number, number of controls matched to each case or the probability of a case under the null hypothesis, number of cases, number of controls, alpha spending function (if different from the one specified in the set-up).	Summary table and plots including information on: the test number, number of cases and controls (by test and cumulative), estimated relative risk by test, log-likelihood by test, target alpha spent for each test, actual alpha spent for each test, number of cases required to reject the null hypothesis at each test, decision on the null hypothesis (reject or not).	3.3.2, 7.1[8,99]
AnalyzeSetUp.Binominal	Used to set up the parameters when using Analyze.Binominal	Name of the analysis, level of significance, minimum number of events before rejecting the null, type and shape of alpha spending function	No specific output; parameters are stored for later use.	3.3.2, 7.1[8,99]
Analyze.Poisson	Similar to the Analyze.Binomial function but using the PMaxSPRT and thus based on the number of observed and expected events at each test. It also requires an initial set-up using the function AnalyzeSetUp.Poisson.	Name of the analysis (should match the one given when setting the parameters), test number, expected number of events under the null, number of observed events, alpha spending function (if different from the one specified in the set-up).	Summary table and plots including in-formation on: the test number, number of expected and observed events (by test and cumulative), estimated relative risk by test, log-likelihood, target alpha spent for each test, actual alpha spent for each test, number of events required to reject the null hypothesis at each test, decision on the null hypothesis (reject or not).	3.3.1, 7.1[8,99]

(Continues)

Table 3.7. (Continued)

Function	General description	Inputs	Outputs	Relevant thesis sections/references
AnalyzeSetUp.Poisson	Used to set up the parameters when utilising Analyze.Poisson	Name of the analysis, level of significance, minimum number of events before rejecting the null, type and shape of alpha spending function	No specific output; parameters are stored for later use.	3.3.1, 7.1[8,99]
CV.Binomial	Used to calculate the critical limit of a continuous BMaxSPRT.	Level of significance, expected sample size, number of events before rejecting the null hypothesis, and matching ratio or probability of having a case under the null hypothesis.	Critical value, type I error given the critical value. When there is not a critical value corresponding to the type I error established in the input (level of significance) the largest conservative value is returned.	3.3.2, 7.1[8,99]
CV.Poisson	Used to calculate the critical limit of a continuous PMaxSPRT.	Level of significance, expected sample size, number of events before rejecting the null and number of expected events before the first look at the data.	Critical value. When there is not a critical value corresponding to the type I error established in the input (level of significance) the largest conservative value is returned.	3.3.1, 7.1, 7.4[8,99]
Performance.Binominal	Allows assessment of the performance of a system based on a continuous BMaxSPRT.	Number of events at the end of the surveillance period, number of events before rejecting the null hypothesis, the critical limit (calculated using CV.Binomial), matching ratio or probability of having a case under the null hypothesis and the relative risk to detect.	Power, expected time to signal if the null hypothesis is rejected, expected sample size at the end of surveillance (whether the null hypothesis is rejected or not).	3.3.2, 7.1[8,99]

(Continues)

Table 3.7. (Continued)

Function	General description	Inputs	Outputs	Relevant thesis sections/references
Performance.Poisson	Similar to Performance.Binomial to assess the performance of a system based on continuous PMaxSPRT.	Expected number of events at the end of the surveillance period, number of events before rejecting the null hypothesis, expected number of events under the null at the first look at the data, the critical limit (calculated using CV.Poisson), and the relative risk to detect.	Power, expected time to signal if the null hypothesis is rejected, expected sample size at the end of surveillance (whether the null hypothesis is rejected or not).	3.3.1, 7.1, 7.4 [8,99]

BMaxSPRT – Binomial-based Maximized Probability Ratio Test, PMaxSPRT – Poisson-based Maximized Probability Ratio Test

3.5 Ethics

Approval for this project was obtained from the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (MHRA) (ISAC number: 15_230) and from the Ethics Committee of the London School of Hygiene & Tropical Medicine (LSHTM reference: 10421).

When considering the development of the existing methods to perform near real-time vaccine safety surveillance, it is important to understand not only their statistical properties but also how to best apply them in practice. Such understanding is crucial when deciding how to approach the implementation of a system using a new data source. The next Chapter presents a systematic review conducted to ascertain existing methods to perform near real-time vaccine safety surveillance and how they have been applied.

4 METHODS AVAILABLE TO PERFORM NEAR REAL-TIME VACCINE SAFETY SURVEILLANCE

4.1 Introduction to Paper 1

This paper was published in *Pharmacoepidemiology and Drug Safety* in January 2016 and reports the results of a systematic review I conducted to identify methods currently used worldwide to perform near real-time vaccine safety surveillance.

To assess existing methods, I conducted searches to identify both published and unpublished studies. For the former, I developed a search strategy for use in Medline and EMBASE. The search strategy was also used in Web of Science to identify conference abstracts. Further conference abstracts were ascertained by searches of relevant conferences abstract books. Unpublished studies were identified through contacts with vaccine safety experts. For this step, I developed an on-line questionnaire which was sent via e-mail to a list of experts. In this questionnaire, I asked if the expert had been involved or was aware of any relevant studies. If the answer was yes, the questionnaire included several questions to capture the details of those studies.

This review identified 31 near real-time systems (i.e. a combination of a data source and statistical methods used to analyse it and produce results in near real-time), mainly from the USA, spanning from May 2005 to April 2015. These systems focussed mainly on influenza vaccine, particularly the 2009 H1N1 vaccine. The review allowed the identification of several statistical tests. The choice of statistical test changed over time but it was generally guided by the frequency of electronic health records and the adverse event studied. PMaxSPRT was the test that was most often selected, followed by BMaxSPRT and a conditional version of MaxSPRT. The review also revealed only limited strategies to account for confounding factors. Studies adjusting for potential confounders used mainly an adjusted expected rate. Despite the development of these methods, NRTVSS is not yet widely used outside the USA.

The results presented in the paper are based on a search I conducted on 6th January 2015. In order to update these results I re-ran the search on 14th June 2017. The new results are presented in Section 4.3.

The search terms, a detailed explanation of the search strategy used to review abstract books of selected conferences, the online questionnaire I designed to identify unpublished studies and the table with detailed characterization of the studies were all published as supporting

information for the paper (Appendix A to D). In this thesis appendices A to C (search terms, a detailed explanation of the search strategy to review abstract books, and the online questionnaire) are included immediately after the paper, in Section 4.2. Appendix D (a table with detailed characterization of the studies) is presented in Section 4.4 after the results from the systematic review update, as the studies identified in the update were added to this table.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Andreia Leite
Principal Supervisor	Prof. Sara Thomas
Thesis Title	Near real-time vaccine safety surveillance using United Kingdom electronic health records

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?	Pharmacoepidemiology and Drug Safety		
When was the work published?	2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**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?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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)	I defined inclusion and exclusion criteria and developed the search strategy, with advice from Prof. S Thomas and Prof. N Andrews. I conducted the search, screened the results, and extracted data. Each co-author screened a random sample of 5% of results. I drafted the survey and e-mail to contact vaccine safety experts and revised them

	following comments from both co-authors. Prof. N Andrews provided the contacts from vaccine safety experts and sent some e-mails on my behalf. I drafted the initial manuscript and made changes according to comments from Prof. S Thomas and Prof. N Andrews. I incorporated suggestions from peer-reviewers, after discussion with Prof. S Thomas and Prof. N Andrews.

Student Signature: [redacted] **Date:** 05/10/17

Supervisor Signature: [redacted] **Date:** 05/10/17

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REVIEW

Near real-time vaccine safety surveillance using electronic health records—a systematic review of the application of statistical methods†

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ABSTRACT

Purpose Pre-licensure studies have limited ability to detect rare adverse events (AEs) to vaccines, requiring timely post-licensure studies. With the increasing availability of electronic health records (EHR) near real-time vaccine safety surveillance using these data has emerged as an option. We reviewed methods currently used to inform development of similar systems for countries considering their introduction.
Methods Medline, EMBASE and Web of Science were searched, with additional searches of conference abstract books. Questionnaires were sent to organizations worldwide to ascertain unpublished studies. Eligible studies used EHR and regularly assessed pre-specified AE to vaccine(s). Key features of studies were compared descriptively.
Results From 2779 studies, 31 were included from the USA (23), UK (6), and Taiwan and New Zealand (1 each). These were published/conducted between May 2005 and April 2015. Thirty-eight different vaccines were studied, focusing mainly on influenza (47.4%), especially 2009 H1N1 vaccines. Forty-six analytic approaches were used, reflecting frequency of EHR updates and the AE studied. Poisson-based maximized sequential probability ratio test was the most common (43.5%), followed by its binomial (23.9%) and conditional versions (10.9%). Thirty-seven of 49 analyses (75.5%) mentioned control for confounding, using an adjusted expected rate (51.4% of those adjusting), stratification (16.2%) or a combination of a self-controlled design and stratification (13.5%). Guillain-Barré syndrome (11.9%), meningitis/encephalitis/myelitis (11.9%) and seizures (10.8%) were studied most often.
Conclusions Near real-time vaccine safety surveillance using EHR has developed over the past decade but is not yet widely used. As more countries have access to EHR, it will be important that appropriate methods are selected, considering the data available and AE of interest.

KEY WORDS—electronic health records; safety; sequential tests; statistical process control; vaccines; pharmacoepidemiology

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INTRODUCTION

Vaccines are considered to be one of the most cost-effective interventions in public health.[1,2] As with other drugs, vaccines are not totally safe,[3] but safety requirements are particularly high as vaccines are given to healthy individuals, most often children.[4] All vaccines go through extensive safety assessment before licensure; however, pre-licensure studies have limited ability to detect rare adverse events (AEs) to vaccines (with frequency $<1/10\,000$-$1/100\,000$)[5], AE occurring among specific sub-populations who were not included in clinical trials, and long-term AE.[6] To overcome these limitations, timely post-licensure studies are required. These can be broadly divided into passive (spontaneous reports) and active studies and should be followed by confirmatory epidemiologic studies. While spontaneous reporting of AE is widely implemented worldwide as a simple and low-cost method, useful to detect new, unanticipated AE, it has limitations.[2] These include difficulties in denominator calculation, potential reporting biases (e.g. over-reporting of potential AE receiving extensive media coverage) and incomplete reporting. In contrast, active surveillance tries to identify all those experiencing (or at least seeking medical attention for) a potential AE to vaccines. This approach includes analyses of large population datasets (using electronic health records (EHR)), targeted hospital-based surveillance

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† Prior postings and presentations statement: This work has not been submitted or accepted elsewhere. Preliminary results have been presented at the NIHR Health Protection Research Unit on Immunisation annual meeting in March 2015 and have been presented as a poster presentation to the 31st International Conference on Pharmacoepidemiology & Therapeutic Risk Management.

(where trained health workers daily seek potential cases of conditions of interest) and recruitment of vaccinated cohorts for detection of AE (using face-to-face interviews, phone interviews, short-message services or web-based tools).[7,8] With the increased availability of large population datasets, near real-time vaccine safety surveillance (NRTVSS) has emerged as an option.[9]

Near real-time vaccine safety surveillance, also known as rapid cycle analysis, involves regular interrogation of EHR to investigate pre-specified AE to vaccines.[2] By testing these AE on a regular basis after introduction of a new vaccine, these methods ensure a timely detection of possible safety problems.[10] When a signal is detected by this approach, it needs to be further analysed, including a signal refinement stage and eventual confirmatory analyses. These steps should be predetermined and will lead to the decision of whether to validate or invalidate the signal. NRTVSS is thus part of a systematic approach to signal detection, with a dual role of signalling possible AE to vaccines and reassuring authorities and populations that events are being monitored.[11] For a given vaccine, NRTVSS only considers a small number of suspected AE (e.g. 5 to 10); complementary information is provided by existing methods such as spontaneous reports.[12]

The growing use of NRTVSS methods, along with the increasing availability of EHR, highlights the need to review studies using this approach. Such a review can provide crucial information on the development of systems for vaccine safety surveillance for countries considering their introduction.

OBJECTIVE

The aim of this study was to carry out a systematic review of published and unpublished data on the methods used for NRTVSS using EHR.

METHODS

Studies were included in the review if they (i) used routinely collected health data (at least for the expected number of events); (ii) studied pre-specified outcome(s) to assess the safety of one or more vaccines; and (iii) regularly tested the outcomes. Studies (i) including only information based on spontaneous reporting systems, (ii) aimed at testing hypothesis/confirming previously generated/suspected signals or (iii) aimed at developing new methods for NRTVSS (unless a specific application of the new method was given) were excluded. No limits were imposed in terms of language or year.

Medline and EMBASE were searched for studies published until 6 January 2015, using a combination of thesaurus and free-text terms (search strategy is provided in Supporting Information Appendix A). Titles and abstracts were reviewed to determine eligibility status, followed by the full text for those considered potentially eligible. References from the papers collected were also reviewed. Reviews of the topic were selected for reference mining. A.L. was responsible for evaluating eligibility of the identified studies. To ensure quality, eligibility of a random sample of 10% of the results was evaluated by S.T. and N.A. When eligibility was unclear, the study was discussed among the authors until a consensus was reached.

To complement the database searches, a citation search was conducted. To the best of our knowledge, the methods under study were first applied to the field of vaccine safety by the Vaccine Safety Datalink (VSD). Two key VSD papers that describe the testing and implementation of rapid cycle analysis using routinely collected health data were selected to perform a citation search.[9,13]

The same search strategy was used in the Web of Science Core Collection to cover meetings and conferences, restricting the search to meeting abstracts or proceedings papers. Also, the Annual Conference on Vaccine Research and the Vaccine and ISV Congress abstract book and programme, respectively, were analysed (Supporting Information Appendix B). The Brighton Collaboration newsletter was also searched as a potential source of relevant new studies or contacts.[14]

A second stage of the review included contacting experts in vaccine safety, as follows:

- Specialists in vaccine safety (from the Global Advisory Committee on Vaccine Safety (GACVS),[15] Brighton Collaboration[16] and Accelerated Development of Vaccine benefit–risk collaboration in Europe (ADVANCE) [17]) were asked if they were aware of work being conducted in the area and fulfilling our inclusion criteria.
- Authors with known work using routinely collected data and the potential to have implemented/conducted eligible studies were contacted (Medicines and Healthcare products Regulatory Agency (MHRA),[18] VSD[19] and Statens Serum Institute[20]). Further contacts were also asked for at this stage.
- Finally, authors with a previous published work but incomplete information, and those suggested by other experts, were contacted to ask for further information to characterize the methods.

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An online questionnaire was used to capture information on studies conducted (Supporting Information Appendix C). When other sources of information (e.g. reports) were available and shared by the contacts these were used. Expert contacts took place from February to March 2015.

The information identified was extracted using a standardized extraction form. Data extracted included timeline, country/institutions where the study was conducted, vaccines studied, study population, outcomes assessed and their method of ascertainment, methods used to perform the analyses, frequency of assessment, confounding, data-accrual lag (i.e. delays in the data available to perform surveillance, which may affect the results), assessment of the validity of the outcomes of interest (e.g. chart review) and main results. A descriptive summary of country/institution, vaccines, outcomes studied, confounding and data-accrual lag handling was drawn up.

RESULTS

A total of 29 reports were included for data extraction (including information provided by expert contacts),[9,13,21–45] representing 31 studies/systems (Figure 1). A brief description of the studies/systems included by country, methods used and adjustment for confounding strategies is given in Table 1. A detailed characterization of the studies is provided in Supporting Information Appendix D.

Near real-time vaccine safety surveillance using EHRs was first reported by Davis *et al.* in 2005, when a retrospective study assessing the feasibility of implementing such methods was published. Since this time, we identified a further 13 studies conducted by the VSD and 17 other studies in three countries (Figure 2). The first study conducted outside the VSD was conducted in New Zealand and published in 2007. The report from the last study included was published online in 2015. Four studies (all in the USA) were conducted completely or partially in a retrospective manner, to test the feasibility of implementing this kind of system (Table 1). Two of these studies attempted to replicate known signals (rotavirus vaccine and intussusception and acellular diphtheria-tetanus-pertussis (DTaP)/whole cell diphtheria-tetanus-pertussis vaccine and febrile seizures). Of the prospective studies, most were conducted in the USA ($n=20$), with studies also conducted in the UK ($n=6$), and Taiwan and New Zealand ($n=1$ for each). The prospective studies looked mainly at influenza vaccines ($n=16$), especially the 2009 H1N1 pandemic influenza vaccine ($n=7$). Rotavirus ($n=5$), DTaP-based ($n=3$) and human papillomavirus vaccines ($n=3$) also received attention.

The outcomes studied were most often neurological (58.5%). Looking at specific outcomes, Guillain-Barré syndrome (GBS) (11.9% of studied known outcomes), meningitis/encephalitis/myelitis (11.9%) and seizures (10.8%) were the most often included. Outcome ascertainment for the near real-time analysis was, in most cases, based on automated data (with no *a priori* confirmation of the diagnosis). In these cases, chart review and confirmation were used whenever a potential AE was signalled. Only two studies performed this kind of confirmation for the near real-time analysis,[21,35] and one compared the analysis considering the chart-reviewed and non-reviewed outcome for GBS.[33] From the outcomes studied, 11 signals were identified, but only three confirmed (measles-mumps-rubella-varicella combination vaccine and febrile seizures,[27] 2010–2011 trivalent inactivated influenza vaccine and febrile seizures,[37] and monovalent rotavirus vaccine and intussusception[41]).

Table 2 summarizes the methods used by the studies included in this review. These can be broadly divided into continuous sequential testing, which allows examination of the data as often as desired ($n=25$),[9,13,22–34,37,38,40–43,45] group sequential testing ($n=4$)[35,36,38,39] and statistical process control (SPC; $n=3$).[21,44] The choice of the group of methods has been determined by the frequency of updates to the EHR data used (Table 2).

When considering specific versions of the tests available, the choice has been guided by the increasing availability of new methods and knowledge of these methods over time, as shown in Figure 2, as well as the frequency of AE studied. In VSD, the sequential probability ratio test (SPRT) was first applied[9] being subsequently replaced by its maximized version (MaxSPRT) with the advantage of not having to specify a single alternative hypothesis.[13] The use of MaxSPRT and its variations also evolved over time. While in the beginning the Poisson and binomial versions were simultaneously used for the same outcome,[13] from 2010, a targeted selection of the test version and its extensions, based on the strengths of each method (Table 2) and the characteristics of the outcome under study, was preferred.[24,33,34,42,43] In particular, Poisson-based MaxSPRT (PMaxSPRT) has been used when less than 50 events were anticipated and the conditional version when the ratio of observed historical events to upper limit was ≤ 2.5. Outside VSD, a pattern in the use of continuous sequential methods was less clear. Overall, these tests were the most often employed—PMaxSPRT (45.7%),[10,50]

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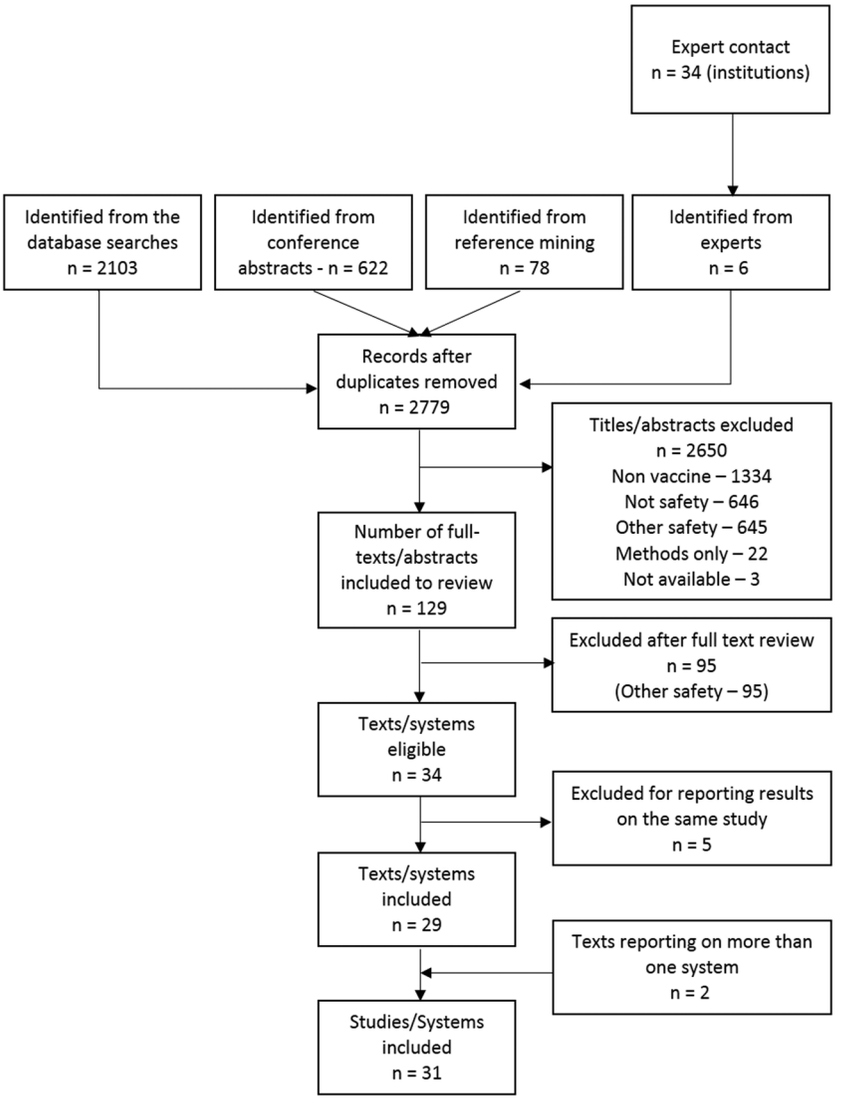

Figure 1. Flowchart of included studies. Studies were excluded for (i) not considering vaccines (nonvaccine), (ii) not analysing the safety of a vaccine (not safety), (iii) considering safety issues but not applying the methods of interest (other safety), (iv) only developing new methods (methods only) and (v) having no abstract available (not available)

followed by the binomial (BMaxSPRT—23.9%)[10,50] and conditional (10.9%) versions.[51]

More recently, four studies used group sequential testing. Two of these used an alpha-spending approach,[38,39] (a function controlling how much of the alpha will be 'spent' every time a new analysis is run[52]), one the Updating Sequential Probability Ratio Test[53] and other the Abt's modification of SPRT.[54] An alpha-spending approach was thus preferred over the two other tests employed in a group sequential way. Both the Pocock-type and O'Brien–Fleming-type functions have been used.[12,55] The remaining methods did not follow a clear evolution and include use of SPC[56] at different times by two non-USA institutions (New Zealand Ministry of Health, Health Protection Scotland).[21,44]

Thirty-seven of 49 analyses (75.5%) mentioned control for confounding. Strategies chosen were often design-based and included (alone or in combination) the following: (i) using a self-controlled design, which automatically addresses time-invariant confounders; (ii) matching baseline confounders, through a concurrent comparator design; (iii) adjusting the expected rate obtained from a historical comparison group based on the confounders' distribution in the study cohort (iv) stratifying the results according to relevant confounder categories. Analyses adjusting for potential confounders used mainly an expected rate adjusted

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Table 1. Included studies according to the country, methods used and control for confounding strategies (see Supporting Information Appendix D for further details)

Study	Country, organization	Method	Confounding	Data-accrual lag or underreporting adjustment
Retrospective				
Davis[9]	USA, VSD	SPRT	Risk adjustment* (site, age, time, season, sex)	Retrospective
Lieu[13†]	USA, VSD	PMaxSPRT	Unclear	Retrospective
Brown[22]	USA, i3 Drug Safety	PMaxSPRT	Expected counts (sex, age, region, month, concomitant vaccination)	Retrospective; data lags assessed during the study
Greene[24†]	USA, VSD	PMaxSPRT	Expected rates (age and site)	Retrospective—data assumed to accrue without delay
		BMaxSPRT[‡]	SC; stratification (age, season)	
Prospective				
Lieu[13]	USA, VSD	PMaxSPRT	No adjustment	Analyses waited at least 6 weeks from the vaccination or preventive visit
		BMaxSPRT	Matching (age, week, site)	
McNicholas[21]	New Zealand, MoH	SPC	Stratification (age)	Daily review of databases, medical charts, discharge letters and laboratory records
Yih[23]	USA, VSD	PMaxSPRT	Expected counts (GBS/seizures—age; other AE—age, sex)	Analysis started at least 8 weeks from the date of vaccination[46] and redone at the end of the study
Belongia[25†]	USA, VSD	PMaxSPRT	Expected rates (intussusception—trend, age, site by Poisson regression; other AE—site)	Analysis started at least 8 weeks from the date of vaccination[46]
Bryan[28]	UK, MHRA	PMaxSPRT	Expected rates (age and gender)	Adjusted for underreporting (yellow-card data)
Huang[30†]	Taiwan, CDC	PMaxSPRT	Stratification (age)	Database updated daily
		BMaxSPRT[‡]	SC	
Enger[29]	USA, i3 Drug Safety	Unclear	Unclear	Unclear
DMSS[26,32,47,48]	USA, DoD	PMaxSPRT	Unclear	Unclear
VA[26,32,48]	USA, VA	PMaxSPRT	Unclear	Unclear
IHS[26,32,48.49]	USA, IHS/ FDA	PMaxSPRT	Unclear	Unclear
PRISM[26,32,48]	USA, FDA/ NVPO	PMaxSPRT	Unclear	Unclear
		BMaxSPRT[‡]		
Klein[27†]	USA, VSD	BMaxSPRT	Matching (age group, site, calendar year and respiratory virus season)	Analysis delayed at least 8 weeks from date of vaccination[46]
Gee[34]	USA, VSD	PMaxSPRT	Expected rates (age, site)	Unclear
		BMaxSPRT[§]	Matching (age, site, vaccination date)	
Lee[33]	USA, VSD	PMaxSPRT[¶]	Expected rates (age and site)	Adjusted for partially elapsed risk interval and delay in the arrival of inpatient data
		BMaxSPRT[‡]	SC	
		Both	Stratification** (age)	
Bryan[31†]	MHRA, UK	PMaxSPRT	Expected rates (age)	Adjusted for underreporting (yellow-card data)
Burwen[36]	USA, FDA	USPRT	No	Critical limits adjusted for delays in the claims (based on previous seasons)
Loughlin[35†]	USA, OptumInsight	Abt's modification of SPRT	No	No

(*Continues*)

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Table 1. (Continued)

Study	Country, organization	Method	Confounding	Data-accrual lag or underreporting adjustment
Tse[37]	USA, VSD	PMaxSPRT[¶]	Stratification (age, site)	Adjusted for partially elapsed risk interval and delay in the arrival of inpatient data
		BMaxSPRT[‡]	SC	
Donegan[40†]	UK, MHRA	PMaxSPRT	Stratification (age)—first year of surveillance	Sensitivity analyses assuming various degrees of underreporting (yellow-card data)
Nelson[38]	USA, VSD	GS	Expected counts (site, gender, age group, site × age—Poisson regression)	No[††]
		PMaxSPRT		
Tseng[39]	USA, VSD	GS	Stratification (age, dose number—only for febrile seizures, urticaria/angioneurotic oedema, asthma)	No[††]
Daley[42†]	USA, VSD	PMaxSPRT[¶]	Expected rates (site—except for GBS and SJS—weighted average used)	Exclusion of the most recent 14 weeks of data[11]
Kawai[43]	USA, VSD	PMaxSPRT[¶]	Expected rates adjusted (age, site)	Delayed analysis until estimated data lag accrual and follow-up time was completed
		BMaxSPRT[‡]	SC, stratification (age)	
Weintraub[41†]	USA, VSD	PMaxSPRT	Expected rates (age, site)	Analysis delayed 2 weeks
Murdoch[44†]	UK, HPS	SPC	Stratification (age, site)	No
Yih[45]	USA, FDA	PMaxSPRT[¶]	Expected rates (age for anaphylaxis and seizures and data partner for seizures)	Adjusted for partially elapsed risk interval and delay in the arrival of inpatient data
		BMaxSPRT[‡]	SC, stratification (seizures—age, concomitant PCV13 6–23 months)	
HPS[†] (unpublished)	UK, HPS	SPC	Stratification (age, sex for herpes zoster, site)	No
MHRA[†] (unpublished)	MHRA, UK	PMaxSPRT	Expected rates (age)	Adjusted for underreporting (yellow-card data)

Studies in italic are the ones identified from expert contacts.
AE-Adverse event; BMaxSPRT, binomial-based maximized sequential probability ratio test; CDC, Centers for Disease Control and Prevention; DMSS, Defense Medical Surveillance System; DoD, Department of Defense; FDA, Food and Drug Administration; HPS, Health Protection Scotland; IHS, Indian Health Service; MHRA, Medicines and Healthcare products Regulatory Agency; MoH, Ministry of Health; NVPO, National Vaccine Program Office; PCV13, 13-valent pneumococcal conjugate vaccine; PMaxSPRT, Poisson-based maximized sequential probability ratio test; PRISM, Post-Licensure Rapid Immunization Safety Monitoring; SC, self-controlled design; SJS, Stevens–Johnson syndrome; SPC, statistical process control; SPRT, sequential probability ratio test; USPRT, updating sequential probability ratio test; VA, Veterans Affairs; VSD, Vaccine Safety Datalink.
*Each unique combination of potential confounders is identified, forming a stratum, and a baseline risk is calculated. For each stratum, a test statistic is calculated, and the test statistics are combined.
†Additional information obtained from the authors.
‡Uses a self-controlled design.
§Uses an exact version of the test, with flexible matching.
¶Uses the conditional version of the test.
**Only for inactivated vaccines and specific outcomes (demyelinating disease of the central nervous system, disorders of the peripheral nervous system and neuropathy, seizures, Bell's palsy and other cranial nerve disorders).
††Analysis based on the number of doses might minimize delays for initial periods of surveillance.

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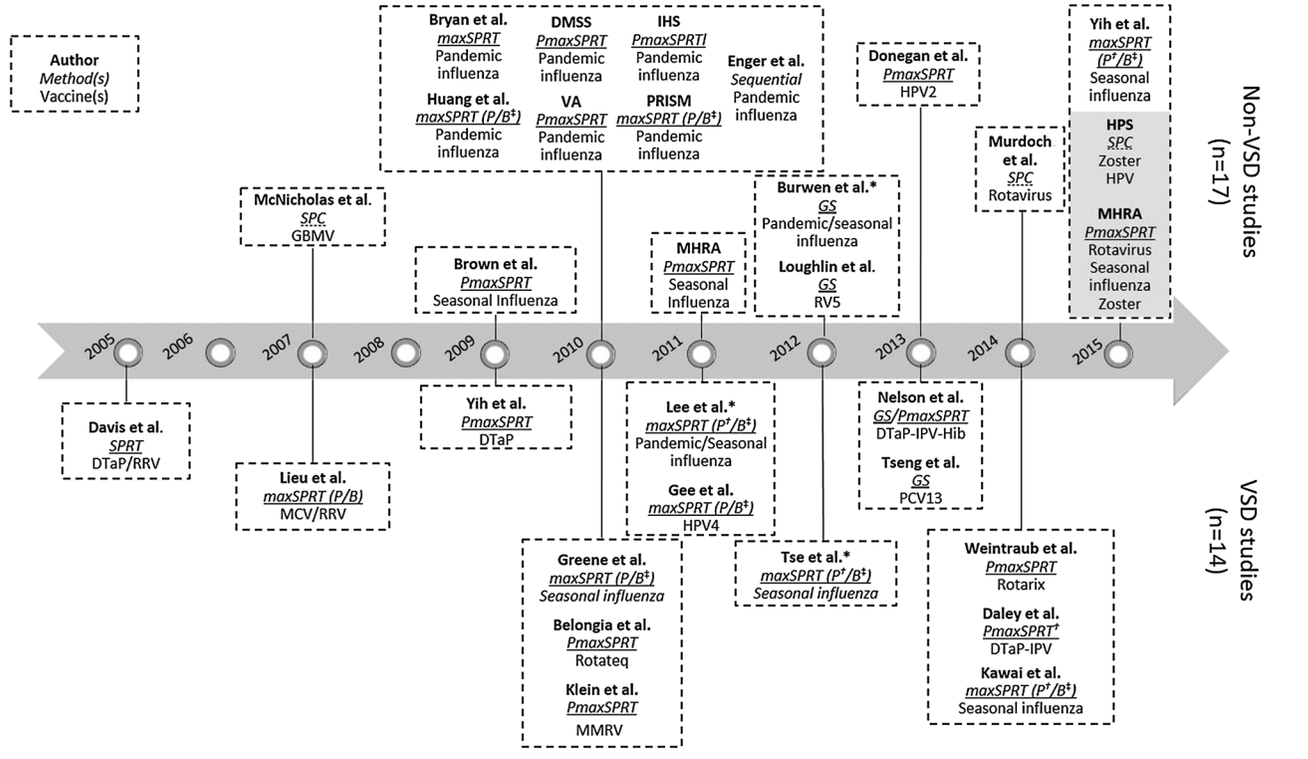

Figure 2. Studies included in the review, ordered by the year of publication. Continuous sequential test are underlined with single line, group sequential with bold line, and statistical process control with dashed line. Grey background indicates non-published studies. *Results with previous published results. maxSPRT – Maximized Sequential Probability Ratio Test, P – Poisson version (†use of the conditional version), B – binomial version (‡use of self-controlled case-series or extensions of the test). DMSS – Defense Medical Surveillance System, DTaP – acellular diphtheria-tetanus-pertussis vaccine, DTwP – whole cell diphtheria-tetanus-pertussis vaccine, GBMV – Group-B Meningococcal Vaccine, HPS – Health Protection Scotland, HPV2 – bivalent human papillomavirus vaccine, HPV4 – quadrivalent human papillomavirus vaccine, IHS – (US) Indian Health Service, IPV – inactivated poliovirus vaccine, MCV – meningococcal conjugate vaccine, MHRA – Medicines and Healthcare products Regulatory Agency, MMRV – Measles-Mumps-Rubella-Varicella combination vaccine, PCV13 – 13-valent pneumococcal conjugate vaccine, PRISM – Post-Licensure Rapid Immunization Safety Monitoring, RRV – Rhesus-Rotavirus vaccine, RV5 – pentavalent rotavirus vaccine, VA – Veteran's Affaires, VSD – Vaccine Safety Datalink

for potential confounders (51.4% of those adjusting), stratification (16.2%) or a combination of a self-controlled design and stratification (13.5%). The choice of approaches also depended on the analytical method selected. For group sequential methods and SPC, strategies to deal with confounders were even more limited. When employing group sequential methods, only expected rate calculations based on the confounders' distribution and stratification were considered. For SPC, only stratification was used. Potential confounders considered include age, sex, geographic site, concomitant vaccine administration, season and trend (Table 1).

Some of the prospective studies considered data-accrual lags in their analysis. Most often, the analysis was delayed by some weeks ($n=7$). Others adjusted for partially elapsed risk intervals and delays in the arrival of inpatient data ($n=3$).[46] For studies using spontaneous report for the observed number of events (and EHR for the expected number of events), sensitivity analyses with several degrees of underreporting were conducted ($n=4$).[28,31,40] Updates to the previous datasets already analysed were not considered a specific strategy to adjust for data-accrual lags as they would not reduce the time to signal. The majority of studies did not mention ways or did not adjust for data-accrual lags ($n=11$).

DISCUSSION

Our comprehensive systematic review has identified an increasing number of studies and systems implementing NRTVSS. All the studies identified were performed in high-income countries/regions with most in the USA. This might reflect limited capacity in many settings to provide registry data in a timely fashion and the infra-structure required to set up the system.

A clear effort was put into using these methods to assess pandemic influenza vaccine safety. This vaccine

Table 2. Methods and respective extensions used by the eligible studies. Main advantages and challenges of each method are provided

Generic method	Version	General description	Comparator	Advantages and disadvantages	Confounding
Continuous sequential—allow examination of the data as often as desired, the various versions are described later (SPRT and MaxSPRT)					
Wald's SPRT	General description	This is the generic method proposed by Wald in the 1940s.	For vaccine safety, a Poisson model would typically be used with the observed count compared with a fixed expected count.[9;50]	Advantage—Easy implementation of the Poisson model. Disadvantage (compared with MaxSPRT)—Fixed single alternative hypothesis (e.g. RR = 3) whose choice will usually be arbitrary.[50]	Covariate adjusted expected levels can be obtained to allow for possible confounding.[9]
MaxSPRT	General description	This generically describes all SPRT methods that have a composite alternative hypothesis (RR > 1).	Depends on the version of the test (refer to succeeding data).	No need to specify a single alternative.[50]	Depends on the version of the test (refer to succeeding data).
	Poisson	—	This implementation assumes a Poisson distribution for observed counts and compares to a fixed expected mean.[50]	Advantage—Simple to implement. The use of a fixed expected level increases power.[10] Disadvantage—Relies on accurate data for the expected level, which may not be the case if data are limited or only historical.[51]	Covariate adjusted expected levels can be obtained to allow for possible confounding. Potential for confounding due to seasonal or temporal changes in disease incidence or coding.[10]
	Binomial	—	Based on a binomial distribution events occurring among vaccine exposed individuals/periods versus comparison (unexposed individuals/periods).[50]	Advantage—Does not rely on a fixed expected value and can match on confounders or compare to other periods within individuals.[50] Disadvantage—Less powerful than Poisson unless multiple unvaccinated available per vaccinated.[50] The use of a self-controlled design with post-exposure comparison intervals might result in delays.[46]	Can be used in different versions—matching controls (fixed or flexible matching ratio—exact sequential analysis[57]) or self-controlled design (SCCS or SCRI) or considering previous seasons, avoiding the healthy vaccinee effect (DID[24]). Potential for confounding depends on the version of the test used.
	Conditional	—	Assumes a Poisson process for the cumulative person-time to observe a number of adverse events.[51]	Advantage—Does not assume the expected number of cases is known (as the Poisson-based MaxSPRT). Accounts for uncertainty in historical data.[51] Disadvantage—Assumes constant event rates are in historical and surveillance data.[51]	Same as Poisson
Group sequential testing	General description	Data are examined at discrete points in time.[10]	Several approaches used a group sequential way (PMaxSPRT, Abt's modification of SPRT, USPRT) often implementing an alpha-spending approach (using a function to determine how to 'spend' the alpha in the different tests).[12]	Advantage—Requires less frequent updates. Disadvantage—Continuous tests are more powerful.[58] Less explored (compared with continuous tests) in the observational setting, including adjustment for confounders. More complex designs.[12]	Depends on the specific version used.

(*Continues*)

Table 2. (Continued)

Generic method	Version	General description	Comparator	Advantages and disadvantages	Confounding
Statistical process control	General description	Graphical approach where the number of events is compared with an upper limit (the threshold is typically—mean + a certain number of SD).[56]	Expected count.	Advantage—Easy to implement. Disadvantage—Less methodological work on applications to vaccine safety. No formal way to control for multiple test.	Stratification can be used to handle confounding.

AE, adverse event; DID, difference-in-difference; (P)MaxSPRT, (Poisson-based) maximized probability ratio test; RR, relative risk; SCCS, self-controlled case series; SCRI, self-controlled risk interval; SD, standard deviation; SPRT, sequential probability ratio test; USPRT, updating sequential probability ratio test; UL, upper limit.

is a good example of the importance of post-licensure surveillance due to potential safety concerns.[32] Meningococcal group B vaccine in New Zealand[21] represents a similar situation, where NRTVSS, along with enhanced passive surveillance and other active methods, was implemented after the vaccine was approved without phase III trials. Other situations where these methods have been particularly useful include vaccines/AE of concern due to experiences with previous versions of the vaccine—for example, rotavirus/intussusception[25] and influenza/GBS.[32] For previously suspected AE, the set of methods here reviewed has the advantage of informing in a timely manner the existence of a safety concern or reassuring regulatory authorities and the public about vaccine safety.

In this review, we have identified different methods to perform NRTVSS using EHR and the way these have been applied, both by VSD and by other institutions. All the methods identified are derived from Wald's sequential test.[50,59,60] When choosing a particular method, it is important to be aware of its properties. Properties of the continuous and group sequential methods have been studied in the context of drug safety.[12] Group sequential methods were deemed to be more appropriate when data updates are less frequent,[12] but more recent work comparing these methods has found that for any group sequential design, there is a better continuous method and recommended that the data are looked at as frequently as possible.[58] After selecting the methodological approach, it is necessary to choose the specific test to employ. For example, using the PMaxSPRT and BMaxSPRT simultaneously might be a more robust approach owing to complementary strengths. However, as previously suggested, BMaxSPRT might fail to identify a signal when investigating very rare events. Hence, an alternative is to use PMaxSPRT when less than 50 events are anticipated and the conditional version when the ratio of observed historical events to upper limit is ≤ 2.5. The use of a targeted approach has been considered in VSD's more recent work.[24,33,34,42,43]

On the other hand, the properties of SPC-based methods applied to vaccine safety have not been extensively studied. Both Kulldorff *et al.*[50] and Musonda *et al.*[61] have argued that SPC-based methods such as cumulative sum are not appropriate to perform surveillance for newly introduced products as the aim is to detect a safety problem that is already present and not a sudden change. These authors defend the use of such methods in the context of surveillance for batch-related problems (problems arising at the time

of manufacture rather than related to the product itself). However, we should consider that at the time of introduction, if there is a safety problem with that specific vaccine and an appropriate comparison group is used, a sudden change would be observable as well. Given its ease of implantation, SPC is attractive, but recommendations on the use of SPC are deferred until further research on their properties is available.

Control for potential confounders has been limited in both the strategies employed and factors adjusted for. This observation is in agreement with Nelson *et al.*,[12] who have argued for better methods for confounder adjustment, in particular at the analysis stage. Recent work has been performed in this area, adapting group sequential methods with regression adjustment and comparing this to existing approaches.[62,63] To the best of our knowledge, these promising approaches are still at the development stage and have not yet been applied to new studies. As pointed out by Yih,[11] it might not be possible to adjust for all possible confounders in this setting, which can lead to spurious signals. However, it should be noted that, as a near real-time analysis, aimed at quickly identifying/strengthening signals, priority is given to rapid results. As such, confounding adjustment is not deemed as critical—more complete analyses can be performed at confirmatory stages.[11] These might include adjusting for additional confounders or a more detailed adjustment (e.g. using finer categorization of a variable) to avoid residual confounding. The specific confounders to adjust for should be decided on the basis of the vaccine, outcome and age groups studied. In addition to those factors considered by studies, adjustments for day-of-the-week effects or co-morbidities might be required.[11] Nevertheless, 12 studies[13,24–27,29,30,35,36] did not refer to potential confounding in at least one of the analyses reported in their published texts.

Best practice using EHR apply equally to NRTVSS as to any study using these kind of data. For example, Lanes *et al.* provide an approach to identify outcomes in healthcare databases.[64] One of the aspects to consider while doing so is misclassification. In some occasions, manual review of individual medical records can be used, particularly if a signal is found. In this review, only two studies[21,35] performed this confirmation before running the NRTVSS analysis, as doing so might delay the surveillance process. Alternatively, multiple algorithms might be developed, providing a trade-off between sensitivity and positive predictive values (PPV). In the NRTVSS, an algorithm with higher sensitivity and moderate PPV is generally considered to be timelier than algorithms with moderate sensitivity algorithm and high PPV. This should be considered for the specific outcome under study, its seriousness and the data available.[65] Misclassification of the exposure might also be problematic. A possible approach is to restrict the analysis to vaccinated individuals, avoiding potential biases.[11]

A key aspect to consider while using these methods is the availability of timely data. 'Real-time' analyses are difficult to achieve, and thus, the expression 'near real-time' is preferred. In fact, delays can occur at various stages, including delays in diagnosis (e.g. for conditions with more insidious onset), recording (e.g. retrospective recording of vaccination administration or diagnosis), receiving the data for analysis (due to either incomplete data accrual or partially accrued risk windows) and reporting. The timeliness of data should thus be considered. Some studies have delayed the analysis for some weeks.[13,23,25,27,41–43] While this approach gives time for data to accrue, it will not reduce the time to signal. The use of group sequential methods with less frequent testing portrays a similar situation where more time has been given for data to accrue.[35,38,39] Nevertheless, for events occurring closer to the time of testing, data-accrual lags may still be problematic. Finally, adjustments for partially elapsed risk interval and delays in the arrival of inpatient data have been proposed (through the expected number of events)[46] or integrated in the critical limits calculation[36]. These can decrease the time to signal, based on previously observed data-accrual patterns. They have been applied in a few, influenza vaccine, studies. Influenza vaccines pose particular challenges when using delayed data as failure to detect a signal before the season ends will impede adequate action. Strategies proposed so far do not specifically address delays between illness onset and diagnosis.

Only three of the 11 outcomes identified in the prospective studies were confirmed as true signals. In addition to issues already raised (confounding factors that have not been considered, misclassification of the outcome), unconfirmed signals were due to (i) changes in the true incidence or coding practices; (ii) inappropriate comparison groups; (iii) uncertainty in background rates; and (iv) type I errors.[11,33] For type I errors, additional strategies to reduce the false discovery rate are available at the planning stage: these include delaying the first test,[66] requiring a minimum number of events to occur before rejecting the null hypothesis[67] or, in the case of group sequential tests, selecting an O'Brien–Fleming threshold. The latter spends less alpha in earlier tests and was used by Nelson *et al.*[38] During the surveillance period, it is important to update the critical limits as data arrive, as the

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observed data might differ from those planned.[66] As in the case of outcome identification, these considerations should be balanced against the importance of detecting signals in a timely manner. Even after careful consideration of all these aspects before and during surveillance, possible spurious signals may still arise. This emphasizes the need for a predetermined plan of action for signal refinement if a signal is found.[11] The plan should include a careful decision on the data source to use to test the hypothesis in subsequent analyses if needed, owing to potential biases with the use of the same data to identify and test the signals. NRTVSS is thus not a stand-alone method but part of the signal detection and evaluation process.

This review aimed at capturing studies and systems worldwide using EHR to perform NRTVSS. Our rigorous search strategy and further contacts with many experts on vaccine safety from different countries and institutions (with a satisfactory response rate, 70.6%) should have minimized the risk of missing systems currently in use. However, we cannot exclude the existence of similar systems elsewhere. Furthermore, some information was missing from the studies included, which we have tried to reduce by contacting the authors. The missing information most often related to confounding control strategies and the data-accrual lag adjustment employed. This might reflect the limited options to address these issues, especially for the earlier studies.

Countries considering introduction of these methods should benefit from the work developed so far and from strategies under development. There should be a cautious reflection on the availability of timely data and their characteristics (including discussion with the data providers), the vaccine(s) and outcome(s) to be studied and the infra-structure needed in case a signal is detected. Future directions for research might include further development and application of strategies for adjustment for confounding and data-accrual lag, as well as consideration of other methods not yet applied to observational settings but in use in clinical trials, for example, Bayesian approaches to group sequential tests.[68] Bayesian methods can incorporate previous information (such as the data generated by pre-licensure studies) and potentially provide a more flexible approach.

In conclusion, NRTVSS using EHR to assess the safety of newly introduced vaccines is being increasingly used in the USA, with limited introduction in a few other countries. These methods ensure timely detection of safety signals. New methods have been integrated over time, but strategies to account for potential confounders and data-accrual lags have received less attention. As new vaccines are expected to be introduced and the public questions vaccine safety, the demand for strong post-licensure surveillance systems will increase.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Near real-time vaccine safety surveillance using electronic health records (EHR) is one of the options available to identify vaccine safety signals.
- Use of near real-time vaccine safety surveillance using EHR has been increasing in the USA but to date has only been considered in a few other countries.
- Methods available have developed over time and have been integrated into systems using this kind of surveillance. Continuous sequential testing has been the preferred approach.
- Strategies to address potential confounding factors are currently limited, but further developments may address this in the near future.
- Timeliness and allowing for data-accrual lag are important factors for consideration when implementing near real-time surveillance using EHR. Lags have only been addressed in a few studies.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

4.2 Supporting information

4.2.1 Search strategy

4.2.1.1 Medline

1. Vaccin* or Immuni#ation

2. exp Vaccination/ or exp Vaccines/ or exp Immunization/ or Immunization Programs/

3. 1 or 2

4. safety or monitor* or Postauthori#ation or Post authori#ation or Post-authori#ation or Post-licensure or Postlicensure or Post licensure or Post-market or Postmarket or Post market or adverse event* or adverse effect* or assessment or risk

5. exp Product Surveillance, Postmarketing/ or exp Adverse Drug Reaction Reporting Systems/ or "Drug-Related Side Effects and Adverse Reactions"/ or exp Population Surveillance/ or Risk/ or Risk assessment/

6. 4 or 5

7. ("Sequential test*" or "sequential analys*" or (sequential adj4 method*) or "sequential monitor*" or "Rapid cycle analys*" or "rapid risk assessment" or ((Active or Real-time) adj4 surveillance) or (real-time adj4 monitor*) or "early detection" or "sequential probability ratio test*" or maxSPRT or SPRT or "cumulative sum chart*" or "Sequential case series" or "signal refinement" or "signal adjudication" or "signal strengthening" or "signal identification" or "signal generation" or "observed-expected" or "observed-to-expected" or "observed vs. expected" or "observed vs expected" or "observed versus expected" or "observed-vs.-expected" or "observed-vs-expected" or "current-historical" or "current versus historical" or "current-vs-historical" or "current-vs.-historical" or "current vs. historical" or "current vs historical" or "standardi#ed incidence ratio" or "vaccine safety datalink" or "Post-Licensure Rapid Immunization Safety Monitoring" or "Canadian Immunisation Monitoring Program" or "Paediatric Active Enhanced Disease Surveillance")

8. Poisson Distribution/

9. 7 or 8

10. 3 and 6 and 9

4.2.1.2 Embase

1. Vaccin* or Immuni#ation

2. exp vaccination/ or exp vaccine/ or exp immunization/ or exp preventive health service/

3. 1 or 2

4. safety or monitor* or Postauthori#ation or Post authori#ation or Post-authori#ation or Post-licensure or Postlicensure or Post licensure or Post-market or Postmarket or Post market or adverse event* or adverse effect* or assessment or risk

5. exp adverse drug reaction/ or exp postmarketing surveillance/ or risk/ or risk assessment/ or exp health survey/

6. 4 or 5

7. ("Sequential test*" or "sequential analys*" or (sequential adj4 method*) or "sequential monitor*" or "Rapid cycle analys*" or "rapid risk assessment" or ((Active or Real-time) adj4 surveillance) or (real-time adj4 monitor*) or "early detection" or "sequential probability ratio test*" or maxSPRT or SPRT or "cumulative sum chart*" or "Sequential case series" or "signal refinement" or "signal adjudication" or "signal strengthening" or "signal identification" or "signal generation" or "observed-expected" or "observed-to-expected" or "observed vs. expected" or "observed vs expected" or "observed versus expected" or "observed-vs.-expected" or "observed-vs-expected" or "current-historical" or "current versus historical" or "current-vs-historical" or "current-vs.-historical" or "current vs. historical" or "current vs historical" or "standardi#ed incidence ratio" or "vaccine safety datalink" or "Post-Licensure Rapid Immunization Safety Monitoring" or "Canadian Immunisation Monitoring Program" or "Paediatric Active Enhanced Disease Surveillance")

8. Poisson distribution/

9. 7 or 8

10. 3 and 6 and 9

4.2.1.3 Web of Science core collection

#11 #9 AND #6 AND #3

Refined by: DOCUMENT TYPES: (MEETING ABSTRACT OR PROCEEDINGS PAPER)

DocType=All document types; Language=All languages;

#10 #9 AND #6 AND #3

DocType=All document types; Language=All languages;

#9 #8 OR #7

DocType=All document types; Language=All languages;

#8 TS=(((Sequential testing or sequential analys* or (sequential NEAR/4 method*) or sequential monitor* or Rapid cycle analys* or rapid risk assessment or ((Active or Real-time) NEAR/4 surveillance) or (real-time NEAR/4 monitor*) or early detection or sequential probability ratio test* or maxSPRT or SPRT or cumulative sum chart* or Sequential case series or signal refinement or signal adjudication or signal strengthening or signal identification or signal generation or "observed-expected" or "observed-to-expected" or "observed vs. expected" or "observed vs expected" or "observed versus expected" or "observed-vs.-expected" or "observed-vs-expected" or "current-historical" or "current versus historical" or "current-vs-historical" or "current-vs.-historical" or "current vs. historical" or "current vs historical" or standardi?ed incidence ratio or vaccine safety datalink or Post-Licensure Rapid Immunization Safety Monitoring or Canadian Immunisation Monitoring Program or Paediatric Active Enhanced Disease Surveillance)))

DocType=All document types; Language=All languages;

#7 TS=(Poisson Distribution/)

DocType=All document types; Language=All languages;

#6 #5 OR #4

DocType=All document types; Language=All languages;

#5 TS=(exp Product Surveillance, Postmarketing/ or exp Adverse Drug Reaction Reporting Systems/ or "Drug-Related Side Effects and Adverse Reactions"/ or exp Population Surveillance/ or Risk/ or Risk assessment/)

DocType=All document types; Language=All languages;

#4 TS=(safety or monitor* or Postauthori?ation or Post authori?ation or Post-authori?ation or Post-licensure or Postlicensure or Post licensure or Post-market or Postmarket or Post market or adverse event* or adverse effect* or assessment or risk)

DocType=All document types; Language=All languages;

#3 #2 OR #1

DocType=All document types; Language=All languages;

#2 TS=(Vaccin* or Immuni?ation)

DocType=All document types; Language=All languages;

#1 TS=(exp Vaccination/ or exp Vaccines/ or exp Immunization/ or Immunization Programs/)

DocType=All document types; Language=All languages;

4.2.2 Search strategy followed while reviewing abstract books of selected conferences

Annual Conference on Vaccine Research (ACVR) abstracts books are available online[103] under different formats. For the first to third ACVR, titles were searched using the browser search engine for words (only title) 'safety', 'risk', 'adverse', 'real-time', 'monitor', 'surveillance', 'rapid cycle', and 'AEFI' and results checked for eligibility. For the fourth ACVR, abstract book titles were manually read, followed by revision of the abstract if considered as potentially relevant. Fifth to 16th ACVR abstracts books were searched using the pdf search engine for the words (title and abstract) abovementioned, followed by manual revision of the results.

Vaccine & ISV Congress provides the Congress history including the list of oral communications and posters presented each year.[104] For each pdf file (one file for communications and another for posters, for each year, totalising 14 files) a search was conducted using the built-in pdf function. Terms searched included safety', 'risk', 'adverse', 'real-time', 'monitor', 'surveillance', 'rapid cycle', and 'AEFI'. Titles including any of these terms were considered. If a title was considered as relevant a further online search was conducted using that same title, trying to identify publication of a full manuscript. When that

same search did not produce any compatible result the first author's last name was searched together with relevant terms of the title (such as the name of the vaccine evaluated and safety). Finally if no result was obtained, authors discussed the relevance of the result, which was either discarded or added to the contacts list.

4.2.3 On-line questionnaire

Near "real-time" vaccine safety surveillance

As part of a partnership between Public Health England and London School of Hygiene and Tropical Medicine we are carrying out a systematic review of methods used to assess postlicensure vaccine safety. We are looking specifically at studies that are conducting near "real-time" vaccine safety surveillance for early detection of adverse events associated with vaccination. To clarify,

we are NOT looking for…

- Anything based solely on passive pharmacovigilance data (for example, the UK yellow card system);
- Methods that have been developed but never actually used in near "real-time";
- Data mining methods.

We ARE looking for systems/studies that have the following attributes:

- They use routinely collected health data (electronic health record/administrative claims) at least for the expected number of events;
- They use pre-specified outcome(s) of interest;
- They regularly look for an excess in the observed number of events;
- They have been used or are in the process of being implemented.

So far, reviewing the published literature, we have identified studies conducted in the USA (Vaccine Safety Datalink), UK (Medicines and Healthcare products Regulatory Agency), and Taiwan (Taiwan Centers for Disease Control). We are contacting you because of your area of expertise to ask if you have information on any other eligible studies that you might have conducted or be aware of.

We kindly ask you to fill in the questionnaire provided (even if you have not done any studies). It should take no more than 5-10 minutes (or 1 minute if you have no studies). Please press the submit button when you have finalised entering your responses. If you have any documents describing the work you have conducted and you prefer to share these documents (rather than completing the form) please send them to Andreia Leite (andreia.leite@lshtm.ac.uk). Please use also this contact if you have any queries regarding the study or this form.

Thank you for your time.

Andreia Leite

on behalf of London School of Hygiene & Tropical Medicine/Public Health England Health Protection Research Unit on Immunisation

*Required

1. Please provide your name. *

.....

2. Which institution are you affiliated to? *

.....

3. Please provide your e-mail *

.....

4 Have you ever been involved in a study using routinely collected health data to assess the safety of one or more vaccines regarding pre-specified outcome(s) [potential adverse events] and regularly tested the outcomes? * Mark only one oval.

- ◯ Yes Skip to question 5.
- ◯ No Skip to question 26.

Stop filling out this form.

Eligible studies

5. Are you willing to share information on the design of the study to be included in a systematic review? *

The level of detail reported in the final review will be agreed with each author of unpublished data. Please contact Andreia Leite (andreia.leite@lshtm.ac.uk) for further questions.
Mark only one oval.

- ◯ Yes Skip to question 6.
- ◯ No Skip to question 26.

Studies details

If you have conducted more than one study please give the answers considering all the studies you have been involved with unless stated otherwise.

6. What was/were the age groups included in your study(ies)? *

.....

7. Which sex(es) did you include? * Mark only one oval.

- ◯ Male
- ◯ Female
- ◯ Both

8. If your study(ies) population(s) included any other relevant characteristics apart from age and sex please provide details. Relevant characteristics might include specific morbidities, health plans, geographic regions, etc.

.....

9. What vaccine(s) was/were included in your study(ies)? *

.....

10 Which data source(s) did you use to identify the vaccination status? *

.....

11. Which outcome(s) did you look for? *

.....

12. Which data source(s) did you use to identify the outcome(s)? *

.....

13. How were the outcomes defined? *
Tick all that apply.

- [ ] ICD-9 codes
- [ ] ICD-10 codes
- [ ] Read codes
- [ ] Algorithm (combination of diagnosis, codes, and/or tests)
- [ ] Other: .....

14. Which statistical method(s) did you use to analyse the data? * Tick all that apply.

- [ ] SPRT (Sequential Probability Ratio Test)
- [ ] Poisson-based maxSPRT (Maximized Sequential Probability Ratio Test)
- [ ] Binomial-based maxSPRT (Maximized Sequential Probability Ratio Test)
- [ ] Group sequential testing
- [ ] Statistical Process Control
- [ ] Other: .....

15. Please provide details regarding the reasons to chose the methods used. * Please also include details on any extensions to the method(s) you used to analyse the data

.....

.....

.....

.....

.....

Skip to question 16.

Comparison group

16 Did you use a comparison group? (e.g. historical comparator, concurrent comparator) *

Mark only one oval.

- ◯ Yes, between-person comparison Skip to question 17.
- ◯ Yes, within-person comparison Skip to question 19.
- ◯ No Skip to question 19.

Comparison group details

17. Which kind of comparison group did you considered? *

Tick all that apply.

- [ ] Historical comparison group
- [ ] Concurrent comparison group
- [ ] Other: .....

18. Please briefly state who the comparison group was. *

.....

Confounding

19. Did you consider potential confounding factors? * Mark only one oval.

- ◯ Yes Skip to question 20.
- ◯ No Skip to question 22.

Confounding details

20. How did you account for potential confounders? * Please consider the study design used for signal detection. Tick all that apply.

- [ ] Stratification
- [ ] Matching
- [ ] Self-controlled case series
- [ ] Other: .....

21. Which factor(s) did you account for? * Tick all that apply.

- [ ] Age
- [ ] Sex
- [ ] Geographic site
- [ ] Concomitant vaccine administration
- [ ] Time-invariant factors (Self-controlled case-series)
- [ ] Other: .....

Safety signal

22. Did you find any evidence of a safety signal? * Mark only one oval.

- ◯ Yes Skip to question 23.
- ◯ No Skip to question 26.
- ◯ Study ongoing Skip to question 26.

Skip to question 26.

Safety signal details I

23. For which combination vaccine/outcome was the signal identified? *

.....

24. Did you perform (or are you performing) further analyses to confirm the signal identified? *

Mark only one oval.

- ◯ Yes Skip to question 25.
- ◯ No Skip to question 26.

Skip to question 26.

Safety signal details II

25. Was the signal confirmed with these analyses? * Mark only one oval.

- ◯ Yes Skip to question 26.
- ◯ The analyses are not yet completed Skip to question 26.
- ◯ No Skip to question 26.

Further contacts

26. Are you aware of anyone else who has conducted such a study? *

Eligible studies include those using routinely collected health data to assess the safety of one or more vaccines regarding pre-specified outcome(s) and regularly tested the outcome(s). We are already aware of the work in the USA by the Vaccine Safety Datalink, in the UK by the Medicines and Healthcare products Regulatory Agency, and in Taiwan by the Taiwan Centers for Disease Control. Mark only one oval.

- ◯ Yes Skip to question 27.
- ◯ No Stop filling out this form.

Skip to question 27.

Providing contacts

27. Please provide any contact or publication details about the work you are familiar with in the space provided. *

.....

4.3 Systematic review update

With the view to identifying more recent studies that were not included in the initial systematic review, I re-ran the search strategy drawn up to identify studies in Medline and EMBASE on 14th June 2017. After deduplication, the search yielded 513 results. After title/abstract screening, six papers where selected for full-text review. Two studies were excluded as they were aimed at confirming hypotheses previously generated (see inclusion and exclusion criteria in 4.1). Of the four eligible results, two[105,106] reported results of the same study, which had been included in the original systematic review (through a report identified from contacts with vaccine safety experts). An updated flowchart, with the results from both the initial search and the update conducted, is presented in Figure 4.1. The two new studies are briefly reviewed below.[107,108] In the next Section (4.4), a table with the details of all eligible studies is presented. This table corresponds to Appendix D of the supporting information of Paper 1, which was updated to include the characteristics of the two new studies identified.

Both studies were conducted in the USA (using VSD[107] and Medicare[108] data) and assessed Guillain-Barré syndrome following seasonal influenza vaccine (Sandhu et al.[108] for seasons 2010/11 to 2013/14 and Li et al.[107] for season 2013/14 and 2014/15). Additionally, Li et al.[107] monitored six other outcomes in relation to seasonal influenza vaccine: acute disseminated encephalomyelitis, anaphylaxis, Bell's palsy, encephalitis, febrile seizures, and transverse myelitis. With regards to the specific methods, Li et al.[107] used PMaxSPRT and BMaxSPRT simultaneously and adjusted for delays and partially accrued risk windows. Analyses using PMaxSPRT were also adjusted for age and geographical site. Sandhu et al.[108] used the Updating Sequential Probability Ratio Test (USPRT), which includes an adjustment for delays in the critical limit calculation. Both studies identified a signal: Li et al.[107] for febrile seizures during the 2014/15 season in children aged 6-23 months, and Sandhu et al.[108] for GBS in the season 2010/11. The former was confirmed in a subsequent confirmatory study but not the latter.[107,108]

The new studies I identified from the updated search are in accordance with the results presented in the original systematic review. No new methods or aspects of their utilisation were identified, which suggests that within USA institutions, the methods presented and explored in depth in the systematic review became a standard; they are routinely used, particularly to assess seasonal influenza vaccine. It is noteworthy that Li et al. used PMaxSPRT and BMaxSPRT simultaneously, owing to their complementary strengths. The issue of

deciding between these two tests has been discussed in the original systematic review and approaches have been shown to change over time. As referred in Section 4.1 and mentioned by Li et al. the simultaneous use of both tests might provide a more robust option than deciding on one specific test.[107]

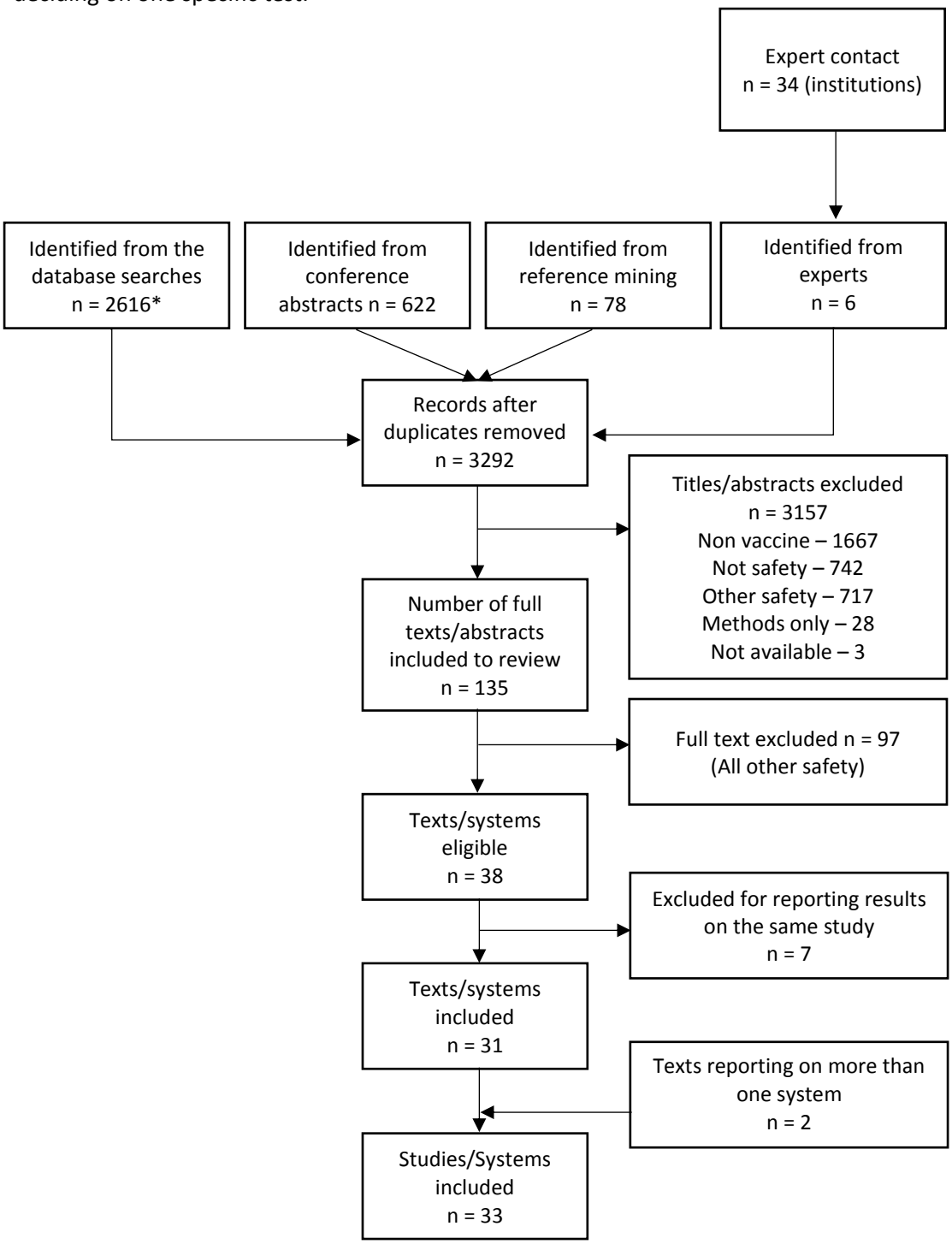

*Figure 4.1. Updated flowchart of included studies. *Includes 513 additional studies identified from the search conducted on 14th June 2017.*

The results of this update point out the importance of having included grey literature and unpublished studies in the original systematic review, as shown by the subsequent identification of published studies that were previously identified and included through contact with vaccine safety experts. Searches for unpublished studies and requests for information from vaccine safety experts allowed not only identification of work that had not yet been disseminated through formal publications but also the most recent studies. Overall, the main conclusions from the original systematic review remain valid.

The systematic review allowed the identification of methods currently under use to perform NRTVSS and how they have been selected and applied. This information is crucial when envisaging implementation of a NRTVSS, as in the case of this thesis. Yet, before proceeding to the actual implementation of a system, is important to select which vaccine/outcome pairs to include in the trial implementation and to reflect on how the data characteristics of CPRD are likely to influence implementation. These aspects are explored in the next two Chapters, starting in the next Chapter with details of the framework used to select vaccine/outcome pairs to include in the implementation study.

4.4 Details of studies included in the systematic review

Table 4.1. Studies included in the systematic review

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
Davis, 2005[7]	USA, VSD	Children from 4 HMO	DTaP and RRV; Vaccine administration data	DTaP – 63,367 doses, 52w, 1997-2000; RRV – 26,069 doses, 43w, 1999	DTaP – DTwP (1995-96) Background rate (1995-99)	DTaP – fever, FS, other neurologic outcomes. RRV – intussusception. ICD-9 codes	SPRT	Risk-adjustment - site, age, time, season, and sex	Weekly	Conducted retrospectively	Known associations verified after varying numbers of weeks.
Lieu, 2007[65]¶	USA, VSD	11-17.99yr from 8 geographically diverse HMO	MCV; counts of MCV administration preventive visits; Rotashield®	MCV – 119,972 doses, 106w, 2005-06; Rotashiled® – 36w, 1999	MCV – Non exposed controls (going to preventive visit) or background rates; Rotashield® – background rates	MCV – GBS, BP, seizures, TCP. Rotashield® – intussusception. ICD-9 codes	MCV – BMaxSPRT (all outcomes) PMaxSPRT (all but seizures); Rotashield - PMaxSPRT	BMaxSPRT – Matching by age, week, and geography; PMaxSPRT – none; Unclear for Rotasheild	Weekly	MCV – Analyses waited at least 6 weeks from the vaccination or preventive visit; Intussusception used as example and conducted retrospectively.	No signal identified for MCV; known intussusception signal verified
McNicholas, 2007[109]	New Zealand, MoH	<19yr from 3 hospitals (Auckland City, Middlemore, and Whangarei) serving the regions where the vaccine was implemented	Meningococcal Group B; immunisation registry	719,790, c. 70w, 2004-05	Background rates (Acute flaccid paralysis and encephalopathy – 1998-2002, for the remaining – published data)	Acute flaccid paralysis, encephalopathy, seizures, TCP (all confirmed by trained nurses). ICD-9 codes	SPC	Stratification for age	Weekly	Daily review of databases, medical charts, discharge letters and laboratory records	No signal identified

(Continues)

Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
Brown, 2009[110] (and Moore[111])	USA, i3 Drug Safety/FDA	>10 m old from a 13.5 million, multistate, health insurance plan – excluded if sex or year of birth missing or multiple claims for influenza vaccination on the same day	2006-07 Influenza season (TIV+LAIV); only 2nd dose if 2; procedure codes	897,229 doses, 26w, 2006-07 season	2005-06 seasonal influenza	Anaphylaxis, urticaria, allergic reactions, angioneurotic edema, DD, GBS, seizures, DPNSN, meningoen-cephalitis, ataxia, paralytic syn-dromes, CND. ICD-9 codes	PMaxSPRT	Expected # adjusted for sex, age, region, month, and concomitant vaccination	Monthly	Conducted retrospectively; lags assessed at the end of the study	Signal detected for urticaria but not confirmed after chart-review
Yih, 2009[112]	USA, VSD	10 to 64 yr old from 7 HMO (3.3 million enrolled during the study period)	DTaP; immunisation status	660,000 doses, 145w, 2005-08	2000-04 TD recipients except in GBS (overall rates used)	Encephalopathy/ encephalitis/ meningitis, GBS, paralytic syndromes, seizures, CND (including BP). ICD-9 codes	PMaxSPRT	Expected # adjusted for: - Age (GBS/ seizures) - Age/sex (remaining)	Weekly	Analysis started ≥ 8 weeks from the date of vaccination[113] and redone at the end of the study	No signal identified
Belongia, 2010[114]¶	USA, VSD	4 to 48 w old from 8 HMO with 8.8 million members and an annual birth cohort of 95000	RotaTeq® (Pentavalent rotavirus vaccine); immunisation data	207,621 doses, 104w, 2006-08	Background rates (1991-2004 for intussusception, myocarditis and Gram- sepsis, 2000-04 for the remaining)	Intussusception, seizures, meningitis/ encephalitis, myocarditis, Gram- sepsis. ICD-9 codes	PMaxSPRT	Intussuscep-tion expected # adjusted for trend/age/ site (Poisson regression); others for site	Weekly	Analysis started at least 8 weeks from the date of vaccination[113]	No signal identified

(Continues)

Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
Bryan, 2010[115] (and Seabroke, 2010[116])	UK, MRHA	Numerator – potentially all vaccinees, CPRD for denominator	H1N1; cases based on spontaneous AE reports	>4 million, 2009-10 season	CPRD age, gender specific rates	GBS, facial palsy, ITP, epilepsy, transverse myelitis, ON, stillbirth. Read codes	PmaxSPRT	Age-gender adjusted expected #	Weekly	Adjusted for underreporting (yellow-card data)	No signal identified
Enger, 2010[117]	USA, i3 Drug Safety	Large US insurance health plan	H1N1 vaccine	982,352 doses, 2009-10 season	Same season seasonal flu and 4 previous seasons	GBS+13 outcomes not listed. Not available	SPRT (specific test unclear)	Unclear	Weekly	Unclear	No signal identified
Greene, 2010[118]¶	USA, VSD	≥6 m old from 8 HMO* with more than 9 million	TIV; vaccine administration	5,969,508 doses, 35w in each season (2005-06 to 2007-08)	Background rates for Poisson-based analysis (previous seasons – from 2000-01).	Seizures, meningoen-cephalitis, BP, OCND, DD, DPNSN, ataxia, anaphylaxis, allergic reactions other than anaphylaxis, GBS. ICD-9 codes	SCCS and DID with BMaxSPRT for all outcomes except GBS; PMaxSPRT for GBS	BMaxSPRT – stratified for age/season; SCCS – time-invariant confounders; PMaxSPRT – expected # adjusted for age/site	Weekly	Data assumed to accrue without delay	No signal identified
Huang, 2010[119]¶	Taiwan, Taiwan CDC	Taiwanese population (≥6m)	LAMV, MIV; vaccination registry	5,667,176 doses, 22w, 2009-10 season	Background rates among ≥6m (2004-08)	Group 1 – GBS, ODD (6m-17yr), encephalitis/ myelitis, anaphylaxis. Group 2 – ODD (≥18yr), seizures, BP (≥18yr). ICD-9 codes	Group 1 – PMaxSPRT; Group 2 – SCCS BMaxSPRT	SCCS – Time-invariant; stratification for age	Weekly	Database updated daily	No signal identified

(Continues)

Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
DMSS[120-123]	USA, DoD	17-64yr, military personnel (around 1.4 million people monitored)	H1N1; vaccination history	1,288,353 (as of April 24, 2010), 2009-10 season	Background rates (2004-08)	GBS, ON, BP, myelitis/en-cephalomyelitis/ encephalitis, anaphylaxis, TCP. ICD-9 codes	PMaxSPRT	Unclear	Weekly	Unclear	Weak signal found for thrombocy-topenia (not confirmed after review)
VA[121-123]	USA, VA	Veterans (Northeastern and Western States – around 2 million people monitored)	H1N1; VA immunisation package	334,897 (as of April 24, 2010), 2009-10 season	Background rates for 2007, 2008 and 2009	GBS, ON, BP, myelitis/en-cephalomyelitis/ encephalitis, anaphylaxis, TCP. ICD-9 codes	PMaxSPRT	Unclear	Unclear	Unclear	Weak signal found for thrombocy-topenia (not confirmed after review)
IHS[121-124]	USA, IHS/FDA	IHS user population (around 1.4 million people monitored)	H1N1; vaccination history	321,305 (as of April 15, 2010), 2009-10 season	Unclear	All flu vaccines – GBS, ON, BP, myelitis/en-cephalomyelitis/ encephalitis, anaphylaxis, TCP; LAMV – asthma/ wheezing. ICD-9 codes	PMaxSPRT	Unclear	Unclear	Unclear	Weak signal found for thrombocytope nia and Bell's palsy (not confirmed after review)

(Continues)

Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
PRISM[121-123]	USA, FDA/NVPO	Members of several health plans (total membership – 38 million)	H1N1; immunisation registries	2,555,639 (as of April 17, 2010), 2009-10 season	Background rates, 2007-08/2008-09 seasons	Group 1 – GBS, DD (including ON), DPNSN, seizures, BP, OCND, ataxia, myelitis/en-cephalomyelitis/ encephalitis, anaphylaxis; Group 2 – abortion, stillborn, (pre-) eclampsia; Group 3 – myocarditis, pericarditis. ICD-9 codes	Group 1 and 3 – PmaxSPRT, CmaxSPRT and SCCS BmaxSPRT; Group 2 – only counts monitored	Unclear	Biweekly	Unclear	No signal identified
Klein[125]¶	USA, VSD	12 to 23 m from 7 HMO† (belonging to a group of 8 HMO with over 9 million members in total)	MMRV	430,00 during c. 79w (2006-07)	MMR and varicella vaccine administered separately (2000-06)	Seizures, TCP, encephalitis/ meningitis, ataxia, allergic reactions, and arthritis. ICD-9 codes	BmaxSPRT	Matching on age group, site, calendar year, and respiratory virus season	Weekly	Analysis delayed for ≥ 8 weeks from date of vaccination[113]	Signal found for seizures (febrile) and confirmed

(Continues)

Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
Gee, 2011[126]	USA, VSD	9 to 26 yr old females from 7 HMO†	HPV4; vaccination status	600,558, 79-164w (depending on the outcome), 2006-08	Background rates for Poisson based analysis and non-vaccinated individuals going to preventive visits (2000-06)	Group 1 – anaphylaxis; Group 2 – allergic reactions, seizures, first ever seizures, syncope; Group 3 – appendicitis, GBS, stroke, VTE. ICD-9 codes	Group 1 – not formally tested due to low counts; Group 2 – exact sequential analysis, Group 3 – PMaxSPRT	Group 2 – matching on age, site and vaccination date; Group 3 – expected # adjusted for age and site	Weekly	Unclear	Signal for appendicitis but it was not confirmed after review
Lee, 2011[127] (and CDC, 2009[128])	USA, VSD	≥ 6 m (for MIV, TIV, and LAIV) or 2 to 49 years old (LAMV) from 8 HMO* (around 9.2 million in total)	2009-10 seasonal influenza and H1N1 (analysis by specific type – MIV, TIV, LAIV, LAMV); ascertained from the claims	4,512,366 doses, 26w	Background rates for Poisson-based analysis (2000-01/2008-09 seasons after TIV or overall rate)	Group 1 – GBS, encephalomyeli-tis, ataxia, anaphylaxis, allergic reactions other than anaphylaxis; Group 2 – DD (central nervous system), DPNSN, BP, OCND, seizures; myocarditis/ pericarditis for LAIV and LAMV. ICD-9 codes	SCRI, BMaxSPRT if ≥ 50 AE anticipated; PMaxSPRT if < 50 AE anticipated; CMaxSPRT when observed historical AE:upper limit ≤ 2.5.	SCRI – time invariant; PMaxSPRT and CMaxSPRT– expected # (age and site). For MIV and TIV and outcomes in group 2 stratification by age group	Weekly	Adjusted for partially elapsed risk interval and delays in the arrival of inpatient data	Signal for Bell's palsy not confirmed

(Continues)

Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
Bryan, 2011¶	UK, MRHA	Numerator - potentially all vaccines, CPRD for denominator (Only <5 years)	Seasonal influenza (2010/11); cases based on spontaneous AE reports	72,000, c. 23w	CPRD data (age-specific rates, 2000-10)	FS. Read codes	PmaxSPRT	Age adjusted expected #	Weekly	Adjusted for underreporting (yellow-card data)	No signal identified
Burwen, 2012[129] (and Burwen, 2010[130])	USA, FDA/ Centers for Medicare and Medicaid Services	Medicare population (38.8 million >64 yr and 7.8 million disabled or end-stage renal disease)	2009-10 seasonal influenza and H1N1; ascertained from the claims	14 million doses for seasonal and 3.3 million for H1N1	Seasonal influenza recipients in the 5 previous seasons	GBS. ICD-9 codes	USPRT	No	Weekly after the 100,000 vaccines	Critical limits adjusted for delays in the claims (based on previous seasons)	No signal identified
Loughlin, 2012[131]¶	USA, OptumInsight/Merck	<1yr from large geographically diverse health plan	RV5; ascertained from the claims	>210,000 doses, 2006-07	DTaP recipients, 2000-05	Intussusception and KD (chart-confirmed). ICD-9 codes	Group sequential (Abt's modification of SPRT)	No	Infants identified quarterly	No	No signal identified
Tse, 2012[132] (and replaces Tse, 2012[133])	USA, VSD	6w-17yr from 8 HMO* (belonging to a 10 HMO group with around 9.2 million people)	TIV; immunisation information	590,272, 27w, 2010-11	Background rates during previous 5 seasons (2005-06 to 2009-10)	FS. ICD-9 codes	SCRI - BMaxSPRT, CMaxSPRT	SCRI – Time-invariant, CMaxSPRT - stratification (age and site)	Weekly	Adjusted for partially elapsed risk interval and delays in arrival of inpatient data	Signal identified and confirmed
Donegan, 2013[10]¶	UK, MHRA	Numerator – potentially all vaccinees, CPRD for denominator (only females 12 to 18 yr old)	HPV2; cases based on spontaneous AE reports	1,536,995 doses, 104w, 2008-10	Background rates (10 previous year CPRD)	Fatigue syndromes, GBS, facial palsy, encephalitis. Read codes	PMaxSPRT	Stratification for age in the 1st yr of surveillance (fatigue syn-dromes).	Weekly	Sensitivity analyses assuming various degrees of underreporting	No signal identified

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Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
Nelson, 2013[134]	USA, VSD	6w-2yr from 7 HMO‡ (belonging to a 10 HMO group with around 9.2 million people)	DTaP-IPV-Hib (combination); vaccination history	149,337 (c. 78w for MAF and seizures and c. 116w for the remaining), 2008-10	DTaP-containing vaccine recipients background rates (2007-09 or 2005-09 for very rare outcomes)	MAF, seizure, meningitis/encephalitis/myelitis, serious nonanaphylactic allergic reaction; Not formally tested – invasive Hib disease, GBS, anaphylaxis, all hospitalizations. ICD-9 codes	Group sequential testing (Pocock boundary) and PMaxSPRT	Expected # adjusted by site, gender, age group, and interaction site-age (Poisson regression).	GS – 1st test after 1yr of introduction and then 11 evenly spaced tests based on # of vaccines given; PMaxSPRT – weekly	Analysis based on the number of doses	No signal identified
Tseng, 2013[135]	USA, VSD	1mo-2yr from 8 HMO*	PCV13; vaccination records	599,229 doses, 90w, 2010-12	PCV7 recipients background rates (2007-09 or 2005-09 for anaphylaxis and encephalopathy)	Encephalopathy, urticaria and angioneurotic edema, asthma, anaphylaxis, TCP, FS, KD. ICD-9 codes, platelet counts.	Group sequential analysis (O'Brien-Fleming boundary)	For urticaria/ angioneurotic edema, FS and asthma stratification by age/dose number. None for the remaining	GS – 12 evenly spaced tests based on # of vaccines given.	Analysis based on the number of doses	Signal identified for encephalopathy and KD but not confirmed. No more signals identified.
Daley, 2014[136]¶	USA, VSD	4-6yr from 4 HMO	DTaP-IPV (combination)	201,116 doses, 176w, 2009-12	Background rates in DT and IPV recipients separately on the same day (group 1) or all children (group 2), (2005-08 or 2000-08 for GBS)	Group 1 – Meningitis/encephalitis, seizures, stroke Group 2 – GBS, SJS, anaphylaxis, serious allergic reactions, serious local reactions. ICD-9 codes	PMaxSPRT for all but serious allergic and local reactions (CMaxSPRT used)	Expected # adjusted for site (except GBS and SJS – weighted average used)	Weekly	Exclusion of the most recent 14 weeks of data[9]	No signal identified

(Continues)

Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
Kawai, 2014[137]	USA, VSD	6mo-17yr (TIV) and 2-49yr (LAIV) old from 8 HMO* (belonging to a 9 HMO group with over 9 million people)	TIV, LAIV (first-dose vaccine)	>3.5 million doses IIV, 256,406 doses LAIV, 19w, 2012-13 influenza season	Historical controls	Seizures, GBS, encephalitis, anaphylaxis. ICD-9 codes	Seizures – SCRI BMaxSPRT; GBS – PMaxSPRT; Encephali-tis and ana-phylaxis – CMaxSPRT	SCRI – time-invariant, stratification – age; for the remaining – expected # adjusted for age and site	Weekly	Delayed analysis until estimated data lag accrual and follow-up time was completed	No signal identified
Weintraub, 2014[138]¶	USA, VSD	4-34w from 6 HMO§	Rotarix; vaccination information	207,955 doses, 260w, 2008-13	Background rates 2001-05	Intussusception	PMaxSPRT	Expected # adjusted for age and site	Weekly	Analyses delayed 2 weeks	Signal identified after 156660 doses and confirmed
Murdoch, 2014[139]¶	UK, HPS	Rotavirus - < 2 years	Rotavirus; Scottish Immunisation Recall System	Rotavirus – 9,000 vaccines administered /month	Background rates	Intussusception, KD, anaphylaxis, haematochezia. ICD-10 codes.	SPC	Stratification – age, sex, geographical site	Monthly	No	Rotavirus – signal for haematochezia, not confirmed
Yih, 2015[98]	USA, FDA	≥6 m (TIV) and 2-49yr (LAIV) members from 3 geographically diverse health plans (with up to 110 million individuals)	Seasonal influenza (2012-13 - pilot and 2013-14 seasons, TIV and LAIV separately); data partners and immunisation information systems	7,464,461 doses	Background rates previous seasons	Anaphylaxis, FS. ICD-9 codes	SCRI BMaxSPRT (only seizures) and PMaxSPRT	PMaxSPRT – expected # adjusted by age and data partner (seizures); SCRI – time-invariant; Seizures – stratification by age and concomitant PCV13 in the 6-23m group	Bimonthly	Adjusted for partially elapsed risk interval and delays in the arrival of inpatient data	Signal for seizures following concomitant PCV13 and TIV.

(Continues)

Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
HPS¶	UK, HPS	HPV – Female adolescents; Herpes zoster - >70 years	HPV2, HPV4, and Herpes zoster; Scottish Immunisation Recall System	HPV – 62,000 doses/year Herpes zoster – 47,000 doses in 2013-14	Background rates (HPV – 2004-08, Herpes zoster – 5 years before introduction)	HPV – >60 outcomes, from TCP to juvenile onset of diabetes. Shingles – zoster, ataxia, GBS, anaphylaxis, meningitis, encephalitis, encephalopathy, events: cardiovascular, cerebrovascular and respiratory. ICD-10 codes.	SPC	Stratification – age, sex (not for HPV), geographical site	Monthly for Herpes zoster, annually for HPV	No	HPV – signal for Bell's palsy, not confirmed
MHRA¶	UK, MRHA	Numerator – potentially all vaccinees, CPRD for denominator	Rotavirus, LAIV (2013-14), Herpes zoster; cases based on spontaneous AE reports	First year of the programme evaluated (introduced in 2013)	CPRD age-specific rates	Rotavirus – SID, intussusception. LAIV – AID, BP narcolepsy, FS, respiratory events. Herpes zoster – death, GBS, BP. Read codes	PmaxSPRT	Expected # adjusted by age; Rotavirus – stratification by dose	Weekly	Adjusted for underreporting (yellow-card data)	No signal identified
Li, 2016[107]	USA, VSD	≥6m old from 6 integrated healthcare organizations§	Influenza vaccines (TIV, QIV, LAIV4); Immunisation history	Doses 2013-14: 4,029,951; Doses 2014-15: 3,988,644; c. 41w each season	Background rates for Poisson-based analysis based on TIV vaccinees in prior seasons (2005–06 to 2012–13)	Acute disseminated encephalomyelitis, anaphylaxis, BP, encephalitis, GBS, FS, transverse myelitis. ICD-9 codes	SCRI BMaxSPRT and PMaxSPRT	Expected # adjusted by age and site;	Weekly	Adjusted for partially elapsed risk interval and delays in the arrival of inpatient data	Signal identified for FS following TIV (children 6-23mo, season 2014-15) and confirmed with concomitant PCV13.

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Table 4.1. (Continued)

First author, year published	Location (Country, institution)	Study population	Vaccine studied; ascertainment if available	Doses, weeks and time frame evaluated	Comparison group (for between-person analyses)	Outcomes studied and method of ascertainment	Method used	Confounding: method and factors	Frequency of assessment	Adjustment for data-accrual lag	Main findings
Sandhu, 2017[108]	USA, FDA and Centers for Medicare and Medicaid Services	Medicare population (individuals aged ≥65yr those with disability or end-stage renal disease; c. 50 million individuals each season)	Influenza vaccine; procedure codes	Doses • 2010-11: 15,460,544; • 2011-12: 15,474,830; • 2012-13: 16,220,362; • 2013-14: 16,189,893; c. 46w each season	Prior seasons • 2010-11: 2005-06 to 2009-10; • 2011-12: 2006-07 to 2009-10 • 2012-13: 2006-07 to 2009-10 • 2013-14: 2010-11 to 2012-13	GBS	USPRT	Unclear	20 consecutive weekly tests, 5 ad hoc tests, and a 26th final end of season test	Test statistic adjusted for delays in receiving the claims and partially elapsed risk interval	Signal identified for GBS in the season 2010/11 but not confirmed

AE – Adverse Event, AID – Auto-immune disorders, BMaxSPRT – Binomial-based Maximized Sequential Probability Ratio Test, BP – Bell's palsy, CDC – Centers for Disease Control and Prevention, CMaxSPRT – Conditional Maximized Sequential Probability Ratio Test, CND – Cranial nerve disorders, CPRD – Clinical Practice Research Datalink, DD – Demyelinating disorders, DID – Difference-in-difference, DMSS – Defense Medical Surveillance System, DoD – Department of Defense, DPNSN – Disorders of the peripheral nervous system and neuropathy, DT – diphtheria-tetanus vaccine, DTaP – acellular diphtheria-tetanus-pertussis vaccine, DTwP – whole cell diphtheria-tetanus-pertussis vaccine, FDA – Food and Drug Administration, FS – Febrile seizures, GBS – Guillain-Barré syndrome, GS – Group sequential, Hib – *Haemophilus influenza* type B, HMO – Health Maintenance Organizations, HPS – Health Protection Scotland, HPV2 – Bivalent human papillomavirus vaccine, HPV4 – Quadrivalent human papillomavirus vaccine, ICD-9 – International Classification of Diseases Ninth Revision, ICD-10 – International Classification of Diseases Tenth Revision, IHS – Indian Health Service, IPV – inactivated poliovirus vaccine, ITP – Immune thrombocytopenia purpura, KD – Kawasaki Disease, LAIV – seasonal trivalent live attenuated vaccine, LAMV – H1N1 monovalent live attenuated vaccine, MAF – medically attended fever, MCV – meningococcal conjugate vaccine, MHRA – Medicines and Healthcare products Regulatory Agency, MIV – H1N1 monovalent inactivated vaccine, MMRV – Mumps-measles-rubella-varicella vaccine, mo – months, MoH – Ministry of Health, NVPO – National Vaccine Program Office, OCND – Other Cranial Nerve Disorders, ODD – Other Demyelinating disorders, ON – Optic neuritis, PCV7 – 7-valent pneumococcal conjugate vaccine, PCV13 – 13-valent pneumococcal conjugate vaccine, PMaxSPRT – Poisson-based Maximized Sequential Probability Ratio Test, PRISM – Post-Licensure Rapid Immunization Monitoring System, QIV – Seasonal quadrivalent inactivated vaccine, RRV – Rhesus-Rotavirus vaccine, RV5 – Pentavalent rotavirus virus, SCCS – Self-controlled case series, SCRI – Self-controlled risk interval, SID – Sudden infant death, SJS – Stevens-Johnson syndrome, SPC – Statistical Process Control, SPRT – Sequential Probability Ratio Test, TCP – Thrombocytopenia, TIV – Seasonal trivalent inactivated vaccine, UK – United Kingdom, USA – United States of America, USPRT – Updating Sequential Probability Ratio Test, VA – Veteran's Affairs, VSD – Vaccine Safety Datalink, w – weeks, yr – years, # – number. *Geographic location: Seattle - Washington, Boston - Massachusetts, Minneapolis - Minnesota, Denver - Colorado, Oakland - California, Pasadena - California, Marshfield - Wisconsin, Portland – Oregon. †Geographic location: Seattle - Washington, Boston - Massachusetts, Minneapolis - Minnesota, Denver - Colorado, Oakland - California, Marshfield - Wisconsin, Portland – Oregon. ‡Geographic location: Seattle - Washington, Boston - Massachusetts, Denver - Colorado, Oakland - California, Southern California, Marshfield - Wisconsin, Portland – Oregon. §Geographic location: Seattle - Washington, Denver - Colorado, Oakland - California, Southern California, Marshfield - Wisconsin, Portland – Oregon. ¶ Additional information obtained from the authors.

5 IMPLEMENTING A SYSTEM – PREPARATORY STEPS

This Chapter details the process used to select the vaccine/outcome pairs to assess in the trial implementation study. It does not include the actual implementation of the new system, which is presented in Chapter 7. Rather, it establishes the foundation of the actual implementation. Chapter 6 complements the current Chapter, by presenting data-related aspects of implementing a system using previously collected data.

Timeliness is a key feature of a data source envisaged to implement NRTVSS. However, it is also necessary that a data source has certain electronic health record characteristics, including that it is population-based, has appropriate size, and has good validity for both exposure and outcomes. Data sources meeting these requirements would be considered ideal for NRTVSS implementation. These characteristics were used as a starting point to guide the feasibility study, and together with the results from the systematic review, to support the decision of which vaccines/outcome pairs to select for the implementation study (Chapter 7). The current Chapter starts with an overview of the framework used to select pairs to study, followed by an in-depth assessment of data accrual delays for selected outcomes. The latter has been written as a paper, included here. The Chapter finishes with a discussion of the findings and conclusion on the vaccine/outcome pairs to assess in the implementation step (Chapter 7).

5.1 Framework

As stated above, a data source to implement NRTVSS should be population-based, have appropriate size, have good validity for both exposure and outcomes, and be timely. As presented in 3.1.1, CPRD data are known to be population-based, but it is important to evaluate the remaining characteristics in this context.

When implementing NRTVSS, outcomes can be selected based on previous information, expert opinion, and/or biological plausibility.[134] As this thesis aims to provide general information on the use of CPRD to perform NRTVSS, a selection of pairs based on vaccine/outcome characteristics that influenced implementation of a system (for example, the frequency of the outcome) seemed more appropriate. Furthermore, it would not be possible to assess all potential vaccine/outcome pairs of interest within the time frame of this project. It was thus necessary to perform an initial feasibility assessment for a range of possible outcomes of interest, followed by a more detailed feasibility assessment and

implementation of a NRTVSS for the selected vaccine/outcome pairs (identified by the initial assessment), as summarised in Figure 5.1.

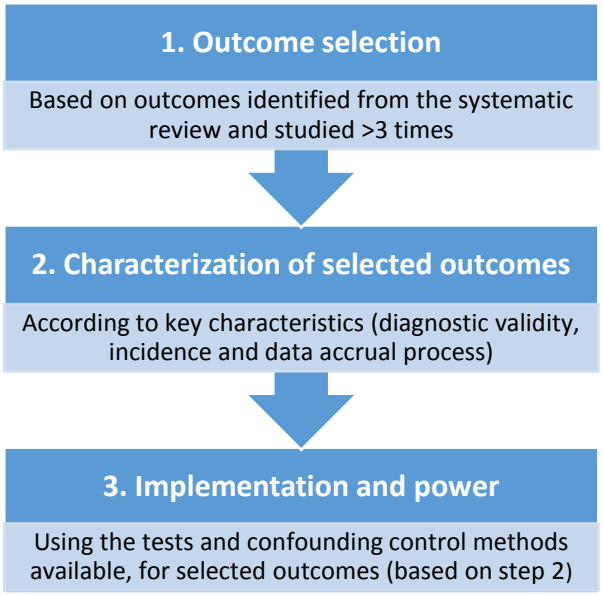

Figure 5.1. Workflow to study the feasibility of implementing a near real-time system.

The steps included:

1. For the initial assessment a list of outcomes was generated from the studies identified in the systematic review (presented in Section 4.1). Those studied more than 3 times were selected. This criterion was used as outcomes studied more often were more likely to be events of interest for the implementation of a future system. As mentioned, when implementing a near real-time system in practice this choice should be guided by previous knowledge of the vaccine under study (e.g. results from clinical trials, previous versions of the vaccine, biological plausibility).[134]
2. Outcomes selected were characterized in terms of their diagnostic validity in CPRD, incidence, and the data accrual process in CPRD, as follows:
    a. Validity – Studies validating the selected outcomes in CPRD were identified, using a previous systematic review of the topic[85] and the CPRD bibliography.[79] The authors from the systematic review on validity kindly shared the data they extracted and the list of outcomes was inspected to allow identification of the outcomes of interest for the current project. Subsequently, I conducted searches in the CPRD bibliography to identify studies that had validated the diagnosis of one or more outcome from the

list generated from step 1 but that had not been included in the 2010 systematic review. These searches were based on searching the publication title as this was the only information available in the bibliography. As discussed in 3.1.1.4, studies attempting to validate diagnosis of outcomes in CPRD and that provided quantitative measures often only calculate the positive predictive value of a diagnostic code or diagnostic algorithm.[85] This measure provides limited assessment of validity but given it is the most often used it was the aspect of validity extracted, when provided in the publication. 95% confidence intervals for proportions were calculated if not provided by the original publication. When positive predictive value was not calculated, information on other forms of validation (e.g. comparison of rates obtained from CPRD to those from other sources) was extracted. The results are presented in Section 5.2.

b. Incidence – Even when large volumes of data are available there might be not enough power to detect a signal for rare outcomes or exposures with short risk windows. It was not possible to assess power for all outcomes in the list obtained from step 1 as such assessment required the full implementation of a system (including decision of which pairs to assess, statistical tests, and control for confounding strategies). Therefore, power was only assessed for pairs included in the trial implementation (see step 3). The concerns regarding power to detect a signal for rare outcomes guided my decision to include at least one uncommon outcome in the trial implementation. Hence, I used incidence as a proxy for power and to guide the choice of pairs to assess during the trial implementation. Information on incidence was not required to be CPRD-specific as it was used as an indication of the outcome frequency. Nevertheless, priority was given to information generated from CPRD data, following by other UK data and then from other sources if neither CPRD nor other UK data were identified. The results are presented in Section 5.2.

c. Data accrual process (delays) – Delays in recording outcomes in the GP data were assessed in a two-stage process. The initial stage considered the characteristics of the outcome as a proxy of the data accrual process. Characteristics were based on factors likely to affect data accrual, including place of diagnosis (GP vs. hospital) and onset of symptoms (acute vs.

insidious). For example, a condition diagnosed in hospital might be less well captured in CPRD or recording might be more delayed than a GP-diagnosed condition. Similarly, outcomes with more insidious onset might take longer to be diagnosed and thus captured. All the outcomes identified from step 1 were classified according to these categories. Results from this first assessment are presented in Section 5.2.

Based on results from the validity and initial stage of assessing delays, a subset of outcomes were selected to conduct an in-depth analysis of delays. This selection considered outcomes deemed to represent broadly a range of characteristics (in terms of onset and place of diagnosis). Outcomes selected for this assessment included GBS, Bell's palsy, optic neuritis, and febrile seizures. Further explanation of the selection of these outcomes is provided in Section 5.2; the in-depth delays assessment was published as a paper, presented in Section 5.3.

After the initial assessment, outcomes were considered potentially suitable/not suitable for NRTVSS in CPRD. In particular, those with low diagnostic PPV and/or very delayed data accrual were deemed non-suitable. In the event of having many suitable outcomes, a selection was made encompassing a variety of characteristics and additional considerations (e.g. the relevance of the outcome for vaccines that are well captured in CPRD data). For outcomes deemed to be not feasible, changes necessary to allow future feasibility were discussed. A final choice on the vaccine/outcome pairs to include in the implementation step was then made and rationale for this is provided in Section 5.6.

3. Trial implementation was performed for the selected vaccine/outcomes pairs. This included definition of the details of the system for the pairs selected (e.g. which statistical test to use, adjustment for delays, control for confounding strategies) and calculation of power to detect a signal. Just as in step 2, for outcomes deemed as not being feasible (those that had issues with implementation or low power), the changes necessary to allow feasibility are discussed. This work in presented in Chapter 7.

5.2 Initial feasibility assessment: results

Studies included in the systematic review analysed 218 outcomes. Table S 1 (Appendix A) lists the outcomes considered ≤3 times and thus excluded. The remaining outcomes, along with their main characteristics, are presented in Table 5.1. These outcomes have been investigated in association with different vaccines. All outcomes except for intussusception have been studied following influenza vaccines, highlighting the importance of near real-time vaccine safety surveillance to assess influenza vaccine. Conversely, the remaining vaccines have been assessed for fewer outcomes, which might be due to these methods having been used less often to assess other vaccines or an interest only on specific outcomes following these vaccines. A particular example is rotavirus vaccine which has only been studied to date in relation to intussusception.

Regarding the outcomes, demyelinating disease and disorders of the peripheral nervous system/neuropathy were examined exclusively for influenza vaccines, others such as allergic reactions, encephalitis and seizures have been considered for several vaccines, including childhood vaccines. In addition, a variety of outcomes was included – both acute and insidious events, and outcomes potentially diagnosed by GPs and in hospital.

Overall, CPRD data have been used to assess all the outcomes of interest listed in Table 5.1, except for ataxia. I identified several studies that validated the recorded diagnosis of some of these outcomes in CPRD and that provided a quantitative measure, namely PPV. For outcomes with this information, PPV was generally high, the exception being idiopathic peripheral neuropathy which had an estimated PPV of 41%. This outcome was therefore deemed as non-suitable for inclusion in later stages of the study. For allergic reactions, ataxia, cranial nerve disorders, encephalitis/encephalopathy/meningitis/myelitis, Guillain-Barré syndrome, and thrombocytopenia, no studies were identified that validated the diagnosis in the GP data and that provided a quantitative validation measure. It was possible to identify validation studies using external data (i.e. comparing the rates of the outcome based on CPRD data to the rates from other sources) for trigeminal neuralgia (a type of cranial nerve disorder) and Guillain-Barré syndrome. No validation studies of the diagnosis of allergic reactions, encephalitis and thrombocytopenia were identified.

For most outcomes, data on incidence was identified. Polyneuritis, GBS, and transverse myelitis were the rarest conditions. Some of the studies estimating incidence of these outcomes used CPRD data.[115,140] As stated above, this was not considered an essential requirement as information on incidence was merely used as an indication of the outcome

Table 5.1. Analysis of outcome/vaccine pairs of potential interest according to selected characteristics

Requirements / Outcome	Vaccines	Validity (in CPRD)	Volume of data (incidence/100,000 PY, unless indicated otherwise)	Factors affecting data accrual (onset, place of diagnosis)
Serious allergic reactions (including anaphylaxis)	DTaP-IPV, DTaP-IPV-Hib, pandemic and seasonal influenza, HPV, MCV, GBMV, MMRV, PCV13, RV, zoster	No studies found. CPRD previously used to estimate anaphylaxis incidence.[141]	Increase in anaphylaxis incidence.[142] UK: 21.28 (10-79 yr)[143]; Spain: 313.58 and 74.43 among the 0-4 and 5-9 yr[144]	Acute, GP/hospital
Ataxia	Pandemic and seasonal influenza, MMRV, zoster	No studies found.	UK (HES): 45.95 diagnosis/100,000 admissions* in 2014/2015[145]	Acute/insidious, GP/hospital
Bell's palsy/Facial palsy	pandemic and seasonal influenza, HPV, MCV, zoster	PPV: 77% (95%CI: 67-85)[146]	**Bell's palsy[140]** 0–17 years: 11.98 18–44 years: 28.92 45–65 years: 36.28 >65 years: 44.91	Usually acute, GP/hospital
Cranial nerve disorders	Pandemic and seasonal influenza, TDaP	Trigeminal neuralgia: incidence in CPRD higher than other studies[147]	Age- and sex-adjusted incidence in London: 6.00.	Acute/insidious (depending on the cause), GP/hospital
Demyelinating disease	Pandemic and seasonal influenza	PPV for multiple sclerosis (incident and prevalent cases): 82% (95%CI: 79-85)[148]	**Multiple sclerosis[149]** *Female* / *Male* 0–19 years: 0.54 / 0.40 20–39 years: 19.86 / 6.57 40–59 years: 23.57 / 9.74 ≥60 years: 10.60 / 7.06 **Optic neuritis[115]** *Female* / *Male* 0–15 years: 0.85 / 0.54 16–64 years: 8.26 / 3.13 ≥65 years: 2.18 / 2.40	Insidious, hospital

(Continues)

Table 5.1. (Continued)

Requirements / Outcome	Vaccines	Validity (in CPRD)	Volume of data (incidence/100,000 PY, unless indicated otherwise)			Factors affecting data accrual (onset, place of diagnosis)
Disorders of the peripheral nervous system and neuropathy	Pandemic and seasonal influenza	PPV for idiopathic peripheral neuropathy: 41% (95%CI: 21-63)[150]	**Acute infectious and post-infectious polyneuritis[140]**			Acute/insidious, hospital
				Female	*Male*	
			0–17 years	0.79	0.70	
			18–44 years	1.57	1.63	
			45–65 years	2.07	2.50	
			>65 years	2.52	4.57	
Encephalitis/ encephalopathy/ meningitis/ myelitis	DTaP-IPV, DTaP-IPV-Hib, pandemic and seasonal influenza, HPV, GBMV, MMRV, PCV13, RV, zoster, Tdap	CPRD previously used to estimate transverse myelitis incidence.[115]	**Encephalitis[151]**			Acute/insidious, hospital
			<1 year	11.63		
			1-4 years	6.06		
			5-19 years	2.86		
			20–44 years	3.23		
			45–64 years	4.46		
			≥65 years	6.06		
			Transverse myelitis[115]			
				Female	*Male*	
			0–15 years	0.22	0.12	
			16–64 years	1.55	0.88	
			≥65 years	0.46	0.83	
Guillain-Barré Syndrome	DTaP-IPV, DTaP-IPV-Hib, pandemic and seasonal influenza, HPV, MCV, zoster, DTaP	Similar incidence reported in CPRD and external sources.[85] CPRD previously used to study GBS as a possible AE to vaccines[115,152,153]	**Guillain-Barré Syndrome[115]**			Acute, hospital
				Female	*Male*	
			0–15 years	0.65	0.70	
			16–64 years	1.66	1.79	
			≥65 years	2.31	4.30	

(Continues)

Table 5.1. (Continued)

Requirements / Outcome	Vaccines	Validity (in CPRD)	Volume of data (incidence/100,000 PY, unless indicated otherwise)			Factors affecting data accrual (onset, place of diagnosis)
Intussusception	RV	PPV: 88% (95%CI: 82-93)[154,155]	UK: 24.8 cases/100,000 live births[156]			Acute, hospital
Seizures (including febrile)	DTaP-IPV, DTaP-IPV-Hib, pandemic and seasonal influenza, HPV, MCV, GBMV, MMRV, PCV13, RV, DTaP	PPV: 80% (95%CI: 68-94)[157]	Age- and sex-adjusted incidence in London for single seizures: 11.00[158]			Acute, GP/hospital
Thrombocytopenia/ ITP	Pandemic influenza, HPV, MCV, GBMV, MMRV, PCV13	No studies found. CPRD previously used to study ITP as a possible AE to vaccines[159]	**Autoimmune thrombocytopenia[140]**			Acute, GP/hospital
				Female	*Male*	
			<18 years	3.7	4.7	
			18–64 years	3.8	2.0	
			≥65 years	7.1	7.8	

*Diagnosis for "Ataxia, unspecified" and "Other and unspecified lack of coordination". AE – Adverse Event, CPRD – Clinical Practice Research Datalink, DTaP – acellular diphtheria-tetanus-pertussis vaccine, GBMV – Group-B meningococcal conjugate vaccine, GP – General Practitioner, HES – Hospital Episode Statistics, HPV – human papillomavirus, IPV – inactivated poliovirus vaccine, ITP – Immune thrombocytopenic purpura, MCV – meningococcal conjugate vaccine, MMRV - Measles-Mumps-Rubella-Varicella vaccine, PCV13 – 13-valent pneumococcal conjugate vaccine, PPV – Positive Predictive Value, PY – Persons-year, RV – Rotavirus vaccine, UK - United Kingdom, yr - years.

frequency and exact figures were not required at this stage. Nevertheless, the use of CPRD in this context illustrates how widely these data have been used.

For the in-depth delays assessment, only a few outcomes were selected in an attempt to cover different characteristics that might influence delays (i.e. onset of symptoms and place of diagnosis). Bell's palsy was selected as an example of an acute condition, generally diagnosed and managed by GPs. Guillain-Barré syndrome was deemed to exemplify a condition generally diagnosed and managed in hospital, with an acute presentation. Optic neuritis was one of the few conditions with an insidious onset and was thus selected to represent this group of outcomes. Finally, febrile seizures were included as an example of an acute condition that can present in both hospital and general practice. This outcome was also selected as it is of particular importance following childhood vaccines.

The next Section (5.3) comprises Paper 2, published in *Pharmacoepidemiology and Drug Safety*. This paper presents the methods and results of the in-depth delays assessment.

5.3 In-depth delays assessment (Paper 2)

This paper was published in *Pharmacoepidemiology and Drug Safety* in February 2017 and reports the results of the in-depth delays analysis.

For the main analysis presented in the paper, I used stand-alone CPRD data from individuals with an outcome of interest (Guillain-Barré syndrome, Bell's palsy, optic neuritis and febrile seizures) and compared the event date (deemed to represent when the event occurred) and the system date (date when the record was entered in the general practice records). The difference between these dates allowed the description of the data accrual process in CPRD for the outcomes of interest. The results showed that most diagnoses examined were recorded with delays of 30 days or less. Furthermore, and as a secondary objective, I conducted an analysis of completeness of recording of diagnosis in the CPRD data and further analysis of delays, using CPRD-HES linked data. For this analysis, I considered a cohort of individuals with an outcome of interest first recorded in HES and followed them up until they had the same outcome recorded in CPRD or until they were censored. This analysis showed that less than 50% of individuals with a record in HES had a corresponding record in CPRD after 1 year, indicating low completeness of records in CPRD.

Despite low completeness of recording, the results indicate that CPRD data are timely enough to implement a near real-time vaccine safety surveillance system. The material published as supporting information is reproduced in this thesis in Sections 5.4 (Appendix A from the supporting information) and 5.5.

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SECTION A – Student Details

Student	Andreia Leite
Principal Supervisor	Prof Sara Thomas
Thesis Title	Near real-time vaccine safety surveillance using United Kingdom electronic health records

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?	Pharmacoepidemiology and Drug Safety		
When was the work published?	2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**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?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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)	I designed the study with detailed advice from Prof. S Thomas and Prof. N Andrews. Prof. S Thomas developed an initial code-list for Bell's palsy and Prof. N Andrews shared an existing code-list for febrile seizures. I developed the remanining code-lists and updated the existing lists, under Prof. S Thomas supervision. I extracted the data

	(under Prof. S Thomas supervision) and analysed the data following discussion with both co-authors. In particular, the method for identifying updated system dates was developed following several discussions with Prof. S Thomas and Prof. N Andrews. I drafted the initial manuscript and made changes according to comments from Prof. S Thomas and Prof. N Andrews. I incorporated suggestions from peer-reviewers, after discussion with Prof. S Thomas and Prof. N Andrews.

Student Signature: [redacted] **Date:** 05/10/17

Supervisor Signature: [redacted] **Date:** 05/10/17

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ORIGINAL REPORT

Assessing recording delays in general practice records to inform near real-time vaccine safety surveillance using the Clinical Practice Research Datalink (CPRD)

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ABSTRACT

Purpose Near real-time vaccine safety surveillance (NRTVSS) is an option for post-licensure vaccine safety assessment. NRTVSS requires timely recording of outcomes in the database used. Our main objective was to examine recording delays in the Clinical Practice Research Datalink (CPRD) for outcomes of interest for vaccine safety to inform the feasibility of NRTVSS using these data. We also evaluated completeness of recording and further assessed reporting delays for hospitalized events in CPRD.

Methods We selected Guillain–Barré syndrome (GBS), Bell's palsy (BP), optic neuritis (ON) and febrile seizures (FS), from January 2005 to June 2014. We assessed recording delays (e.g. due to feedback from specialist referral) in stand-alone CPRD by comparing the event and system dates and excluding delays >1 year. We used linked CPRD-hospitalization data to further evaluate delays and completeness of recording in CPRD.

Results Among 51 220 patients for the stand-alone CPRD analysis (GBS: n = 830; BP: n = 12 602; ON: n = 1720; and FS: n = 36 236), most had a record entered within 1 month of the event date (GBS: 73.6%; BP: 93.4%; ON: 76.2%; and FS: 85.6%). A total of 13 482 patients, with a first record in hospital, were included for the analysis of linked data (GBS: n = 678; BP: n = 4060; ON: n = 485; and FS: n = 8321). Of these, <50% had a record in CPRD after 1 year (GBS: 41.3%; BP: 22.1%; ON: 22.4%; and FS: 41.8%).

Conclusion This work shows that most diagnoses in CPRD for the conditions examined were recorded with delays of ≤30 days, making NRTVSS possible. The pattern of delays was condition-specific and could be used to adjust for delays in the NRTVSS analysis. Despite low sensitivity of recording, implementing NRTVSS in CPRD is worthwhile and could be carried out, at least on a trial basis, for events of interest. © 2017 The Authors. *Pharmacoepidemiology & Drug Safety* Published by John Wiley & Sons Ltd.

KEY WORDS—delay; electronic health records; safety; surveillance; timeliness; vaccines; pharmacoepidemiology

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INTRODUCTION

The Clinical Practice Research Datalink (CPRD) is a UK primary care database widely used for epidemiological research, including monitoring disease rates over time and assessing the post-licensure safety of several vaccines using epidemiological designs.[1–9] Near real-time vaccine safety surveillance (NRTVSS) using electronic health records is a post-licensure vaccine surveillance tool that involves monitoring rates of adverse events over time to identify changes associated with vaccine use. NRTVSS is ideally started at the time a vaccine is introduced in a population by looking at data at repeated time points to ensure timely signal identification. This type of surveillance is now used by the Vaccine Safety Datalink in the USA and has been implemented by a few other countries.[10] In the UK, NRTVSS has been carried out using spontaneous reports to calculate the observed number of events and CPRD data to calculate the expected number of events.[11] However, CPRD data have not been used as the sole data source to perform NRTVSS.

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This work has not been submitted or accepted elsewhere. Preliminary results have been presented at the Public Health England Applied Epidemiology Scientific Conference, Warwick, March 2016, and have been accepted for presentation at the 2016 International Population Data Linkage Conference to take place in August 2016.

The CPRD data are currently updated monthly and are therefore a potential data source for implementing NRTVSS. For near real-time surveillance, timeliness is paramount. One way of dealing with delays is to delay the analysis until sufficient data accrue. A more timely approach[12] is to know how long it takes for data to accrue and then use the pattern of delays to adjust the expected number of events.

Data accrual delays in CPRD can be due to the following: (i) delays in making the diagnosis after an initial consultation, (ii) practices receiving and recording diagnoses made at secondary care and (iii) delays in uploading the data for researchers. Different outcomes of interest might have different sources and levels of delay, depending, for example, on whether the onset of the condition is acute or insidious and the healthcare setting in which it is diagnosed and managed.[13] Given CPRD's structure, it is likely that an acute condition that is usually diagnosed and managed by general practitioners (GPs) will accrue more quickly than a condition diagnosed and managed in hospital. Conversely, a more insidious condition and which tends to be diagnosed in secondary care might take longer to accrue. Understanding recording delays, by knowing the time it takes for data to accrue and how this differs by condition, helps to determine the feasibility of implementing NRTVSS in CPRD. In this paper, we focus on delays in practices recording diagnoses made elsewhere (aforementioned scenario ii).

It is also important to understand the sensitivity of CPRD for capturing outcomes of interest. Feedback from secondary care (e.g. hospital admissions and outpatient consultations) may not be completely captured as coded diagnoses in CPRD, for example, if GPs do not code these events but simply scan in hospital letters without adding diagnostic codes to the patient record. The information from hospital admissions in England is recorded in the Hospital Episode Statistics (HES) database and linked to CPRD for a subset of practices. Previous studies have shown that the use of linked data (including primary and secondary care information) improves sensitivity of diagnoses.[14–16] However, these linkages are currently updated too infrequently to allow their use for surveillance purposes. To the best of our knowledge, no previous studies have investigated completeness of recording for conditions of interest for NRTVSS that are typically diagnosed in secondary care such as Guillain–Barré syndrome (GBS).

Our main objective was thus to examine recording delays for selected conditions, due to practices receiving and recording diagnoses made at secondary care, in stand-alone CPRD, to inform the feasibility of implementing NRTVSS in England using these data. Secondary objectives were to further assess delays and evaluate completeness of recording of diagnoses in CPRD using linked hospitalization data.

METHODS

Data sources

For our main analysis, we used data from CPRD, which comprises anonymized UK primary care health records for >11.3 million patients from 674 general practices, with information on demographics, diagnosis, therapies, vaccines, health-related behaviours and referrals to secondary care.[1] Patient information is recorded using Read codes, and when a new record is entered, the software automatically assigns it the current date, the system date. Practice staff also enters an event date, the date generally considered to represent the time the event has occurred. Monthly updates of CPRD data include the date information was last collected from each practice (last collection date).[13]

Despite being assigned when new records are entered, the system date can be changed when mass transfer of records occurs. These might occur when (Rachael Williams, personal communication) (1) the practice changes software to Vision (and joins CPRD) or updates their version of Vision: previous system dates will be updated for all patients to the date the change has occurred; (2) patients' records are transferred from their previous practice (or an internal transfer of a patient occurs within a practice); the system dates for that patient's records will then all be changed to the date the transfer occurred.

Our secondary analysis used CPRD–HES linked data, which includes patient-level information from 58% of all CPRD practices.[1] HES data are coded using International Classification of Diseases, version 10 (ICD-10), and each hospitalization includes ≥1 episode, corresponding to the time a patient is under the care of a single consultant.[17] Information available includes date of hospital admission and discharge and, for each episode, a starting date (episode date).

Outcomes

We selected four outcomes of interest for NRTVSS[10]: GBS, Bell's palsy (BP), optic neuritis (ON) and febrile seizures (FS). These represent different characteristics that might affect delays; GBS is an acute condition, diagnosed and managed in hospital; BP is typically diagnosed and managed by GPs; ON is a more

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insidious condition, likely to be diagnosed in outpatient hospital settings; and FS can be diagnosed and managed in both primary and secondary care.[10] For each outcome, a specific and a broader (potentially more sensitive but less specific) code lists were considered (Appendix A). These different versions were used to explore the effect of imperfect validity of different code lists to identify the outcomes. It has been previously suggested that for NRTVSS, a more sensitive code list generates more timely signals.[18] We thus considered the broader code list in our main analysis and the specific code list in a sensitivity analysis.

Analysis

System dates and event dates were compared to assess delays in recording. To avoid overestimation of delays because of mass transfers of system dates to later dates, we first studied which records were likely to have been part of such transfers and excluded these from remaining analyses.

We assumed that (i) an unusually high number of records with the same system date was due to a mass transfer; (ii) mass transfers are infrequent, so only a small proportion of patients will have records affected by mass transfers; (iii) there is a threshold number of repeated system dates above which mass transfers can be identified. To identify this threshold, we created a within-patient proportion of records with the same system date used s times (p_{si}), using eligible patient records from the clinical, test, referral and immunization files. p_{si} is given by t_{si}/r_i, where t_{si} is the number of records with a given number of repeat system dates and r_i the total number of records for that patient. For example, if we consider a patient with a total of 300 records and if this patient has four records registered on one shared system date and four others on a different shared system date, p_4 is given by $8/300 \approx 0.03$. This means that 3% of all this patient's records are recorded in blocks of four records.

The patient-level p_{si} was averaged across all patients ($ap_s = \sum_{i=1}^{n} p_{si}/n$). This average proportion of records with the same system date s was displayed graphically, and we selected candidate thresholds, on the basis of our assumptions about mass transfers.

For each threshold, we took a sample of 10 patients with that number of repeated dates (e.g. if threshold = 100, we selected the 100 records with the same system date for 10 patients). We then looked at these records to assess the likelihood that they had been involved in mass transfers. We considered that records with the same system dates that had codes that could feasibly refer to the same condition or a related procedure/test result and which all had the same event date were likely to have been entered on the same day. Conversely, if the codes were unrelated, with varying event dates, this would suggest a mass transfer. To evaluate the influence of the final threshold decision, we calculated the percentage of the outcomes assigned as mass transfers and excluded using the selected threshold.

After excluding system dates likely to have been part of mass transfers, we used a forward approach to assess delays, that is, considering the time from the event date (the assumed date of diagnosis) until the system date (the date the diagnosis was entered in the practice system). Delays were calculated as the difference between the system and event dates (Figure 1(A)). We excluded diagnoses with a delay >1 year as these would be of limited utility for NRTVSS and could be ignored if NRTVSS was only based on events recorded within a year. To give enough time for data to accrue, we considered records with an event data up to June 2014 (using CPRD data released in July 2015). Diagnoses within a year of registration (6 months if aged <1 year) with the practice were excluded to avoid counting past diagnoses recorded retrospectively.[19] We described delays in terms of their cumulative distribution and further described these by year of diagnosis to assess whether this distribution was constant over time.

The secondary analysis focused on completeness and delays in recording for patients with an outcome of interest in HES. We considered a cohort of patients with an outcome first recorded in HES. Patients were followed up from the hospital episode date in which the outcome was first recorded until they had an outcome in CPRD (noting the system date) or were censored (earliest of date of death, date of leaving the practice, last collection date or July 2015) (Figure 1 (B).). We excluded patients with a previous record of the outcome in CPRD, as these would be captured by a system on the basis of CPRD. We conducted a sensitivity analysis to evaluate the effect of adding these patients. Patients with diagnoses within a year of their registration date (6 months if aged <1 year) with the practice were also excluded, unless a relevant diagnosis was made in HES during that period (as the latter is not subject to retrospective recording of this type). Kaplan–Meier analysis of the time until recording the condition in CPRD was used to describe completeness and delays, truncating the curves at 1 year (considered the period of interest for NRTVSS).

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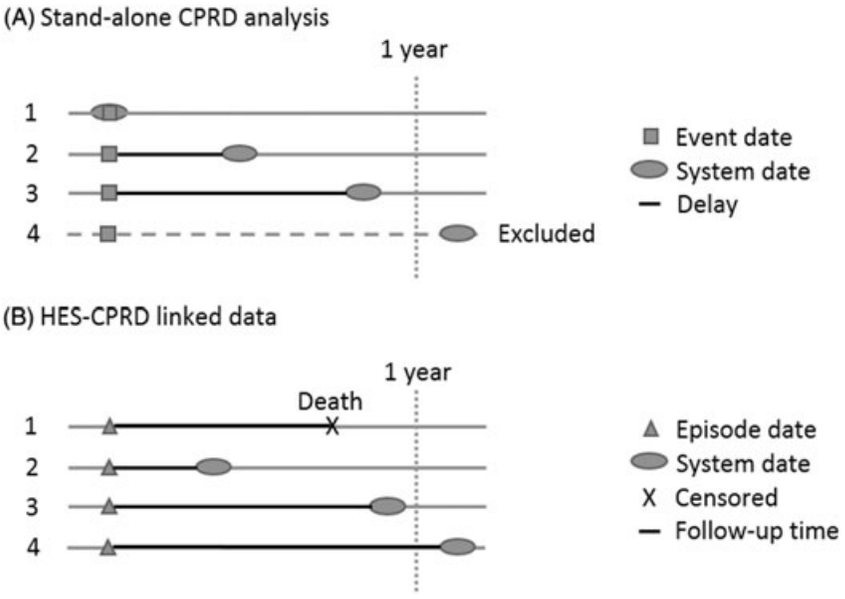

Figure 1. Schematic representation of the analysis undertaken for describing recording delays in CPRD (A) and completeness and delays in HES-CPRD linked data (B). (A) includes patients with no delay (1), varying delays (2 and 3) and those who were excluded because of having a delay of more than a year (4). (B) includes a censored patient because of death (1), patients with varying delays (2 and 3) and a patient with a delay of more than 1 year, included in the analysis but not displayed in the Kaplan–Meier curves. CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics

RESULTS

Analysis of mass transfers

We identified 54 252 eligible patients for the mass transfer analysis, with 24 905 375 records. Repeated system dates ranged from 1 to 3958. Figure 2 shows the proportion (and cumulative proportion) of records with a unique date, ranging from 2 to 3958 on the same date, averaged across patients. The average proportion of records with repeated dates decreased until 50 records, after which it stabilized. The vast majority (Figure 2 bottom) of records were recorded at the same time as <49 other events.

We thus selected 50, 100 and 150 as candidate thresholds, which resulted in losses of 7.7%, 4.5% and 3.1% of records, respectively. Some of the code lists with 50 repeated dates were a mixture of blood tests and diagnosis codes, all with the same event date. These were considered a plausible combination of codes to have been entered on the same system

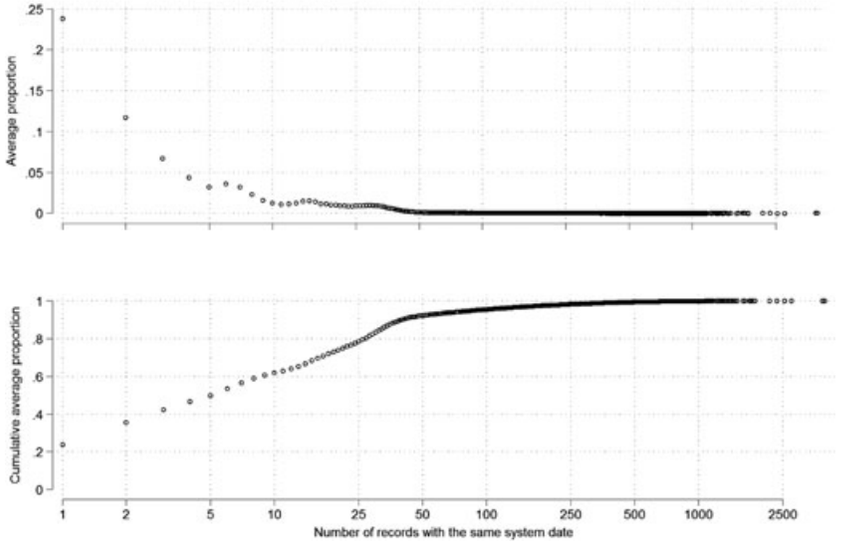

Figure 2. Average proportion (top) and cumulative average proportion of repeated system dates (number of records is represented in the logarithmic scale)

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date. On the other hand, all the lists of 100 and 150 codes were for different conditions, with different event dates. We interpreted this as highly suggestive of a mass transfer and therefore selected 100 as the threshold. This reduced cases by 2.3%, 1.5%, 2.4% and 1.5% for GBS, BP, ON and FS, respectively. After excluding records deemed to be mass transfers, we assessed delays in stand-alone CPRD for 53 414 patients (GBS: n = 905; BP: n = 13 234; ON: n = 1837; and FS: n = 37 625).

Recording delays in stand-alone Clinical Practice Research Datalink

We further excluded records with delays >1 year (% of exclusions: GBS, 8.3%; BP, 4.8%; ON, 6.4%; and FS, 3.7%). Our final analysis included 51 220 patients (GBS: n = 830; BP: n = 12 602; ON: n = 1720; and FS: n = 36 236). Table 1 summarizes gender, age and year of event date for these patients.

Table 2 and Figure 3 present the cumulative distribution of data accrual lags by condition in CPRD, defined as the time from event date to system date. Most diagnoses were recorded within a month (73.6% (GBS); 93.4% (BP)). BP had the highest percentage of records with identical system and event dates (72.0%), while ON had the lowest (27.8%). BP and FS records accrue more quickly than GBS and ON. These differences occur mainly (but not entirely) until 10 weeks after the event date, after which data accrual seemed to stabilize. Using a more specific code list yielded similar patterns (Appendix B). These patterns were constant over time (Appendix C).

Comparison of Hospital Episode Statistics–Clinical Practice Research Datalink

We included 13 482 patients (GBS: n = 678; BP: n = 4060; ON: n = 485; FS: n = 8321) with a first outcome recorded in HES. Table 3 shows the characteristics of included patients and completeness of recording in CPRD. Age and sex distributions for GBS and FS were similar to those observed for the stand-alone data. BP and ON patients in HES were older (mean age: BP: HES—57.4, CPRD—48.2; ON: HES—49.9, CPRD—42.9). BP and ON had the lowest completeness of recording and FS and GBS the highest. Most records accrued within a year. When we added patients with a first record in CPRD, the increase in total completeness was less than 10% (Appendix D).

Figure 4 illustrates data accrual patterns. BP and FS accrued more quickly at initial stages and plateaued sooner than the other outcomes. GBS showed a steadier accrual pattern, plateauing at around 20 weeks after HES recording. Sensitivity analyses using specific code lists showed similar patterns (Appendix E).

DISCUSSION

We have conducted a comprehensive analysis of recording delays and completeness for four outcomes, to inform NRTVSS. Our results showed that data accrual patterns and completeness depend on the conditions studied. Selecting conditions with different characteristics (in clinical presentation, place of diagnosis and management) enabled us to capture these different patterns. BP showed the quickest data accrual and highest agreement between system and event date, consistent with a condition often diagnosed and

Table 1. Gender, age and year of event date of included patients by condition

	GBS (n = 830)	BP (n = 12 602)	ON (n = 1720)	FS (n = 36 236)
Gender, n (%)				
Male	465 (56.0)	6218 (49.3)	569 (33.1)	19 029 (52.5)
Female	365 (44.0)	6384 (50.7)	1151 (66.9)	17 207 (47.5)
Mean age (SD)	53.5 (20.1)	48.2 (20.2)	42.9 (17.8)	35.4 (29.0)
Year of event date, n (%)				
2005	70 (8.4)	1317 (10.5)	187 (10.9)	3605 (9.9)
2006	98 (11.8)	1240 (9.8)	181 (10.5)	3774 (10.4)
2007	76 (9.2)	1275 (10.1)	191 (11.1)	3808 (10.5)
2008	100 (12.0)	1430 (11.3)	162 (9.4)	3989 (11.0)
2009	94 (11.3)	1407 (11.2)	175 (10.2)	3983 (11.0)
2010	84 (10.1)	1376 (10.9)	182 (10.6)	3853 (10.6)
2011	90 (10.8)	1390 (11.0)	196 (11.4)	3844 (10.6)
2012	96 (11.6)	1320 (10.5)	195 (11.3)	3923 (10.8)
2013	83 (10.0)	1251 (9.9)	166 (9.7)	3778 (10.4)
2014	39 (4.7)	596 (4.7)	85 (4.9)	1679 (4.6)

BP, Bell's palsy; FS, febrile seizures; GBS, Guillain–Barré syndrome; ON, optic neuritis; SD, standard deviation.

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Table 2. Cumulative distribution of delays by condition (*n* (%))

Delay*	GBS (*n* = 830)	BP (*n* = 12 602)	ON (*n* = 1720)	FS (*n* = 36 236)
Same day	275 (33.1)	9076 (72.0)	478 (27.8)	14 254 (39.3)
First week	371 (44.7)	10 459 (83.0)	699 (40.6)	22 181 (61.2)
First month	611 (73.6)	11 776 (93.4)	1310 (76.2)	31 031 (85.6)
6 months	790 (95.2)	12 431 (98.6)	1672 (97.2)	35 575 (98.2)
1 year	830 (100.0)	12 602 (100.0)	1720 (100.0)	36 236 (100.0)

BP, Bell's palsy; FS, febrile seizures; GBS, Guillain–Barré syndrome; ON, optic neuritis.
*Defined as the difference between the system and the event date.

managed by GPs. GBS and ON showed the slowest data accrual. GBS is an acute condition usually requiring admission, while ON is typically diagnosed and managed in outpatient settings. We considered FS as an acute condition diagnosed at any level of care, but in most cases not requiring prolonged admission. This is consistent with an intermediate agreement between system and event date (38.1%) and more rapid data accrual than GBS and ON. Overall, our findings indicate that conditions diagnosed by GPs or during short-term hospital admissions tend to accrue more quickly than conditions diagnosed in hospital with longer admission or diagnosed in outpatients. In general, data captured in CPRD accrued within the first month of the diagnosis, making NRTVSS possible using this data source.

Our assessment of completeness showed that a low proportion of diagnoses first recorded in HES subsequently accrued in CPRD. It seems particularly unlikely that GPs are aware of <50% of cases of serious conditions such as GBS. A recent UK study that contacted GPs about patients with a coded GBS diagnosed in HES found that 68.2% (95% confidence interval: 60.7–74.9%) were aware of a GBS diagnosis made in hospital that has been confirmed (Julia Stowe, personal communication). Incomplete diagnostic coding in general practice may occur because GPs instead scan in hospital letters or record diagnoses in free text, neither of which is now available to researchers using CPRD because of changes in the information governance environment in the UK. This might have decreased the ability to assess fully the validity of CPRD data for research purposes. The inclusion of therapy codes might help to capture some incompletely coded diagnoses for conditions requiring treatment, but the conditions we examined do not have unique treatments. On the other hand, HES is itself an imperfect source to capture conditions of interest as it might include unconfirmed cases. If that is the case, our analysis would have underestimated completeness in CPRD. For NRTVSS, if completeness is constant over time, this should not bias the results, but it decreases power. Knowing whether there is enough power is a key aspect when considering a new data source to implement NRTVSS. This goes beyond the scope of our study but should be assessed by future work looking at trial

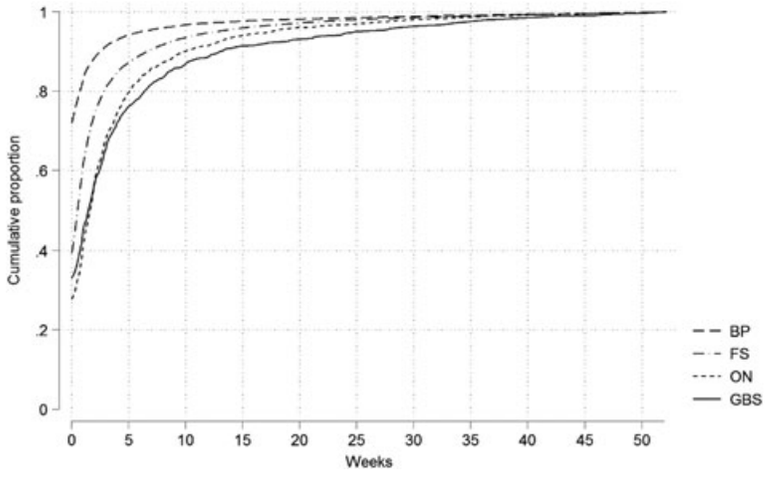

Figure 3. Weekly data accrual in CPRD across 52 weeks considering data accrued during the first year and diagnosis made up to June 2014. BP, Bell's palsy; CPRD, Clinical Practice Research Datalink; FS, febrile seizures; GBS, Guillain–Barré syndrome; ON, optic neuritis

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Table 3. Characteristics of included patients, time of follow-up and completeness of records in Clinical Practice Research Datalink per condition of interest

	GBS (n = 678)	BP (n = 4060)	ON (n = 485)	FS (n = 8321)
Gender, n (%)				
Male	363 (53.5)	1844 (45.4)	155 (32.0)	4662 (56.0)
Female	315 (46.5)	2216 (54.6)	330 (68.0)	3659 (44.0)
Mean age (SD)	55.8 (21.0)	57.4 (24.1)	49.9 (25.2)	34.8 (31.2)
Year of diagnosis,* n (%)				
2005	61 (9.0)	424 (10.4)	56 (11.5)	1264 (15.2)
2006	73 (10.8)	460 (11.3)	45 (9.3)	1108 (13.3)
2007	79 (11.7)	400 (9.9)	47 (9.7)	1103 (13.3)
2008	85 (12.5)	417 (10.3)	47 (9.7)	1055 (12.7)
2009	79 (11.7)	515 (12.7)	56 (11.5)	912 (11.0)
2010	69 (10.2)	545 (13.4)	68 (14.0)	793 (9.5)
2011	76 (11.2)	471 (11.6)	48 (9.9)	702 (8.4)
2012	71 (10.5)	404 (10.0)	56 (11.5)	715 (8.6)
2013	69 (10.2)	358 (8.8)	54 (11.1)	531 (6.4)
2014	16 (2.4)	66 (1.6)	8 (1.6)	138 (1.7)
Median follow-up time (years)	0.9	1.9	2.1	1.4
Completeness, % (95% confidence interval)†				
Maximum	45.9 (41.5–50.5)	26.8 (25.0–28.7)	28.5 (22.9–35.0)	46.0 (44.8–47.2)
At 1 year	41.3 (37.6–45.3)	22.1 (20.8–23.5)	22.4 (18.9–26.5)	41.8 (40.7–42.9)

BP, Bell's palsy; FS, febrile seizures; GBS, Guillain–Barré syndrome; ON, optic neuritis; SD, standard deviation.
*Considering the start of episode date in Hospital Episode Statistics database.
†Kaplan–Meier estimates of individuals with a record in Clinical Practice Research Datalink.

implementation of NRTVSS using CPRD. Results from that work will allow further conclusions on the possibility of implementing NRTVSS using CPRD. A further consideration is that, for conditions which may not always require hospital admission, hospitalized patients may be a particular subset of all cases, for example, those with more severe disease (as highlighted in studies of upper gastrointestinal bleeding and venous thromboembolism[14,20]) or specific patient characteristics (as in our study, which showed that patients with BP and ON captured in HES were older). This will matter if the adverse event is more likely among these specific subgroups.

Previous adjustments for accrual delays when conducting NRTVSS with administrative claims data have focused on delays in processing information for filing and approval.[12] Primary care-based data have different sources of delay, and our work focused on delays in practices documenting feedback from secondary care. Our work thus differs from Greene *et al.*[12] in the reasons for the delays we have considered. In addition, we looked at four outcomes (GBS, BP, ON and FS), while Greene *et al.*[12] have only considered GBS. Other sources of delay include time before data are made available; CPRD data are released to researchers monthly and practices upload

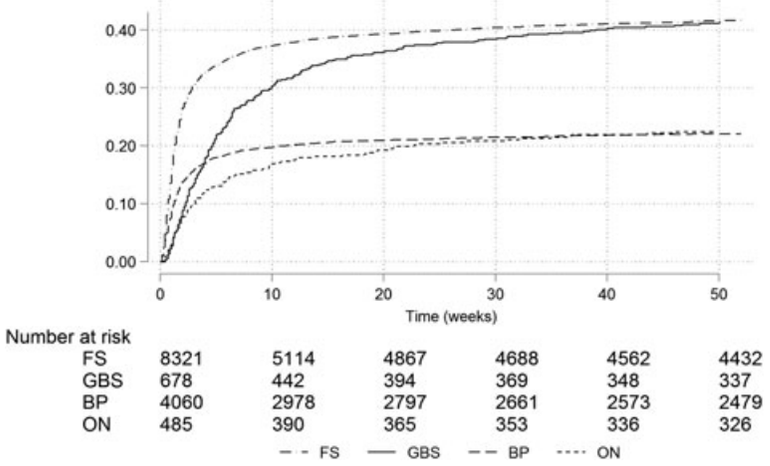

Figure 4. Kaplan–Meier recording estimates considering a first record in HES and a subsequent record in CPRD, truncated at 1 year. BP, Bell's palsy; CPRD, Clinical Practice Research Datalink; FS, febrile seizures; GBS, Guillain–Barré syndrome; HES, Hospital Episode Statistics; ON, optic neuritis

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data some time before each release. These delays could be examined by looking at the time between last collection date and date of release, and adjustments made depending on the patterns of such delays. Delays in making diagnoses could involve identifying early symptom codes, with the extent of delay varying by condition. The results of our study indicate that adjustments for data accrual delays should be tailored for individual conditions and that future studies should consider including setting-specific adjustments, that is, generating delay distributions for diagnoses made in primary care, in-patient and outpatient settings. More broadly, we recommend that researchers reflect on the source of delays in their data and whether these delays are likely to be dependent on the outcomes of interest, to help decide whether to establish condition-specific data accrual patterns.

To the best of our knowledge, this is the first in-depth analysis of recording delays in CPRD. Sammon and Petersen[13] recently examined the number of records lost as a function of last collection date, to inform incidence or prevalence studies. Our study complements and extends this work by quantifying delays for selected conditions and investigating how their characteristics affect delays. Our study is novel in showing the limitations of using system dates, and we have proposed a simple approach to minimize the effects of these limitations that are relevant to those planning surveillance using CPRD. We also provide the first analyses of both completeness and timeliness of recording of these four specific conditions in CPRD.

This study is subject to some limitations. Firstly, measurement error in delays in stand-alone CPRD may have resulted from errors in system and event dates. We addressed misclassification of system dates by excluding dates that were likely to have been part of mass transfers. As we did not take an unduly low threshold, we may have included some transferred system dates and thus overestimated delays. However, our exclusion of delays >1 year should have minimized this issue. Furthermore, if the same criteria are applied to a future NRTVSS, inclusion of these records should not bias results. The event date is also an imperfect measure of the date of diagnosis. When entering diagnoses made elsewhere, GPs might insert the diagnosis date, but alternatively, the date of hospital admission or discharge, the date the hospital letter was received or the date of data entry. For the latter three scenarios, our delays (the difference between system and event dates) would be underestimated. However, if this coding behaviour is constant over time, any adjustments made in the future considering our results would be valid. Furthermore, the choice of code lists affects the validity of cases. We did not validate the code lists directly, but assessed the potential effects of imperfect validity by using code lists with different levels of sensitivity. The use of a more specific code list did not substantially affect our results. When implementing a new system, this should be further assessed; previous analyses suggest that a more sensitive code list might produce more timely results.[18] Finally, we did not quantify the uncertainty around the data accrual estimates in CPRD. However, our sensitivity analysis describing yearly patterns showed stable results, suggesting it is appropriate to use our distributions for future adjustments.

In conclusion, this work shows that most diagnoses recorded in stand-alone CPRD accrued within the first month, making NRTVSS possible. The distribution of delays was condition-specific, and the weekly delay distribution could be used to adjust for delays in the NRTVSS analysis. CPRD can be a viable data source to use in this kind of analysis; next steps will include trial implementation of the system using these data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Near real-time vaccine safety surveillance using electronic health records is one of the methods available to detect vaccine safety signals. It requires timely data.
- The Clinical Practice Research Datalink (CPRD) is a potential data source for this surveillance.
- Delays in recording of events in CPRD will limit its utility, and delays were found to vary by condition. For Bell's palsy and febrile seizures, events were recorded sooner than for Guillain–Barré syndrome and optic neuritis. For all these conditions, most events documented by practices were recorded within the first month of the presumed diagnosis date.
- Records of Guillain–Barré syndrome, Bell's palsy, optic neuritis and febrile seizures diagnosed in hospital have low completeness of recording in CPRD, with less than 50% recorded within a year of the hospital admission date.
- The CPRD is a feasible data source to implement near real-time surveillance, although sensitivity of recording of events first seen at hospital may be low.

ETHICS STATEMENT

All data were anonymized prior to receipt by the authors. Ethics approval for the study was given by the Independent Scientific and Advisory Committee (of CPRD) and the London School of Hygiene and Tropical Medicine Ethics Committee.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

5.4 Code-lists used for the in-depth delays assessment

The code-lists used for the analysis reported in Paper 2 (presented in Section 5.3) are available below. This corresponds to Appendix A of the supporting information of the paper. As explained in the paper, the main analysis used a less specific Read codes list, followed by a sensitivity analysis using a more specific set of Read codes. The lists used in the main analysis are presented and the codes considered for the sensitivity analysis are highlighted in each list. The methods used to obtain these lists are detailed in Section 3.2. Results from the sensitivity analysis are presented in Section 5.5.

5.4.1 Guillain-Barré syndrome

5.4.1.1 CPRD

Read code	Read term
F370000	Guillain-Barre syndrome
F370200	Miller-Fisher syndrome
F370.00	Acute infective polyneuritis
F37X.00	Inflammatory polyneuropathy, unspecified
F37y.00	Other toxic or inflammatory neuropathy
F37z.00	Toxic or inflammatory neuropathy NOS
F370z00	Acute infective polyneuritis NOS
F370100	Postinfectious polyneuritis
F37..00	Inflammatory and toxic neuropathy
Fyu7100	[X]Other inflammatory polyneuropathies
Fyu7B00	[X]Inflammatory polyneuropathy, unspecified
F21X.00	Acute disseminated demyelination, unspecified
Fyu4200	[X]Acute disseminated demyelination, unspecified
Fyu4000	[X]Other specified acute disseminated demyelination

5.4.1.2 HES

ICD-10	Description
G61.0	Guillain-Barré syndrome

5.4.2 Bell’s palsy

5.4.2.1 CPRD

Read code	Read term
1476	H/O: Bell's palsy*
F310.00	Bell's (facial) palsy
F31z.00	Facial nerve disorder NOS
F31..00	Facial nerve disorders
2BR6.00	O/E -cranial nerve 7-palsy-LMN

Read code	Read term
2BR7.00	O/E -cranial 7 -paralysis -LMN

*Patients with a first diagnosis of history of Bell's palsy were excluded to avoid retrospective recording

5.4.2.2 HES

ICD-10	Description
G51.0	Bell's palsy

5.4.3 Optic Neuritis

5.4.3.1 CPRD

Read code	Read term
F210.00	Neuromyelitis optica
F4H3z00	Optic neuritis NOS
F4Hz.00	Disorder of optic nerve or visual pathway NOS
F4H3.00	Optic neuritis
F4H5z00	Optic chiasm disorder NOS
F4H..00	Disorders of optic nerve and visual pathways
F4H4z00	Other optic nerve disorder NOS
F4H4.00	Other optic nerve disorders
F210.11	Devic's disease
F4H5.00	Optic chiasm disorders
F4H3000	Unspecified optic neuritis
F4H6z00	Other visual pathway disorder NOS
FyuJ.00	[X]Disorders of optic nerve and visual pathway
F4H3200	Acute retrobulbar neuritis

5.4.3.2 HES

ICD-10	Description
H46	Optic neuritis

5.4.4 Seizures

5.4.4.1 CPRD

Read code	Read term
R003400	[D]Nocturnal seizure
F25H.00	Generalised seizure
1B27.00	Seizures in response to acute event
1B63.00	Had a fit
1B63.11	Fit - had one, symptom
1B64.00	Had a convulsion
1B64.11	Convulsion - symptom
1B6B.00	Febrile convulsion

Read code	Read term
282..00	O/E - fit/convulsion
282..11	O/E - a convulsion
282..12	O/E - a fit
282..13	O/E - a seizure
2822	O/E - grand mal fit
2823	O/E - petit mal fit
2824	O/E - focal (Jacksonian) fit
2824.11	O/E - Jacksonian fit
2824.12	O/E - focal fit
2825	O/E - psychomotor fit
2827	O/E - febrile convulsion
2828	Absence seizure
282Z.00	O/E - fit/convulsion NOS
F132z12	Myoclonic seizure
F250011	Epileptic absences
F250200	Epileptic seizures - atonic
F250300	Epileptic seizures - akinetic
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251600	Grand mal seizure
F251y00	Other specified generalised convulsive epilepsy
F252.00	Petit mal status
F253.00	Grand mal status
F253.11	Status epilepticus
F254500	Complex partial epileptic seizure
F255600	Simple partial epileptic seizure
F256.00	Infantile spasms
F256.11	Lightning spasms
F256z00	Infantile spasms NOS
F25X.00	Status epilepticus, unspecified
F25y300	Complex partial status epilepticus
F25z.11	Fit (in known epileptic) NOS
Fyu5900	[X]Status epilepticus, unspecified
Fyu5200	[X]Other status epilepticus
Q480.00	Convulsions in newborn
Q480.11	Fits in newborn
Q480.12	Seizures in newborn
R003.00	[D]Convulsions
R003000	[D]Convulsions, febrile
R003011	[D]Pyrexial convulsion
R003100	[D]Convulsions, infantile
R003200	[D]Fit
R003211	[D]Fit (in non epileptic) NOS
R003y00	[D]Other specified convulsion

Read code	Read term
R003z00	[D]Convulsion NOS
R003z11	[D]Seizure NOS
Ryu7100	[X]Other and unspecified convulsions
Eu44511	[x]pseudoseizures

5.4.4.2 HES

ICD-10	Description
R56.0	Febrile convulsions

5.5 In-depth delays assessment: sensitivity analyses

The in-depth delays analysis, presented in Section 5.3, included several sensitivity analyses, published as supporting information, and assessing three aspects of the analyses conducted. The first sensitivity analysis attempted to assess the effect of imperfect validity of the code-lists used for outcome ascertainment. For this analysis, a more specific code-list was used and the results are presented in Section 5.5.1. The second sensitivity analysis assessed trends in recording delays over time (both for the main and secondary analysis) and is presented in Section 5.5.2. The third and final analysis assessed how completeness changed if patients with a prior record in CPRD were included in the cohort (see Section 5.5.3).

5.5.1 Specific code-lists

The code-lists used in this thesis have not been validated. However, it has been previously suggested that using an initial code-list in the main analysis, followed by a sensitivity analysis using another code-list with a different level of specificity, might be used as an indication of the quality of recording.[85] This strategy was used for the Read-code lists; in the main analysis, a broader code-list was used, followed by a sensitivity analysis with a more restricted set of codes. For the secondary analysis (using linked CPRD-HES data) to identify outcomes in CPRD, the strategy described above was followed (a broader code-list in the main analysis and a more specific one in the sensitivity analysis). In contrast, each outcome in HES data was identified using a single ICD-10 code-list that was designed to include only more specific codes. The approach of selecting more specific codes in HES data was deemed to result in a higher positive predictive value (compared to a less specific code-list), allowing capture of less false positive diagnoses (which would not require a subsequent record in CPRD).

Figure 5.2 shows the results of the sensitivity analysis of the data accrual process in CPRD using a more specific set of Read-codes for all the outcomes studied and corresponds to Appendix B of the supporting information. Overall, the patterns were similar to the ones observed in the main analysis using a broader code-list (see Figure 3 in Section 5.3), with a

few noticeable differences for febrile seizures and Guillain-Barré syndrome. For febrile seizures, using a more specific code-list resulted in a more delayed data accrual pattern, with less than 20% of the records being recorded on the same day of the event (compared to around 40% in the main analysis). Nevertheless, this difference seems to be mainly in the first few days after the event and after the second week after the event date the patterns became very similar. For Guillain-Barré syndrome, the use of a more specific code-list led to a more delayed data accrual throughout the analysis period but the extent of the additional delay was minimal. For both outcomes, the differences observed are unlikely to affect the implementation of a near-real time system.

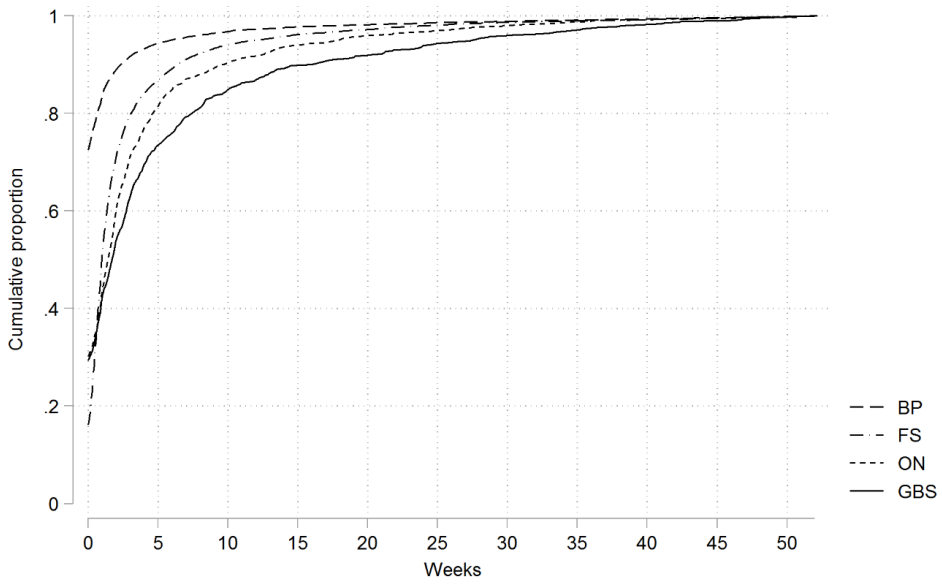


Figure 5.2. Weekly data accrual in CPRD across 52 weeks considering diagnosis made until June 2014 and using a specific set of read-codes. BP – Bell's palsy, FS – Febrile seizures, GBS – Guillain-Barré syndrome, ON – Optic neuritis.

The results of the sensitivity analysis using a more specific set of Read-codes for the completeness analysis using linked CPRD-HES data (Figure 5.3, originally published as Appendix E of the paper's supporting information) are also very consistent with those of the analysis presented in the paper (see Figure 4 in Section 5.3). The overall accrual pattern overlaps with the one observed and completeness at one year is similar. The results of this sensitivity analysis indicate that the use of less specific codes does not affect completeness of recording.

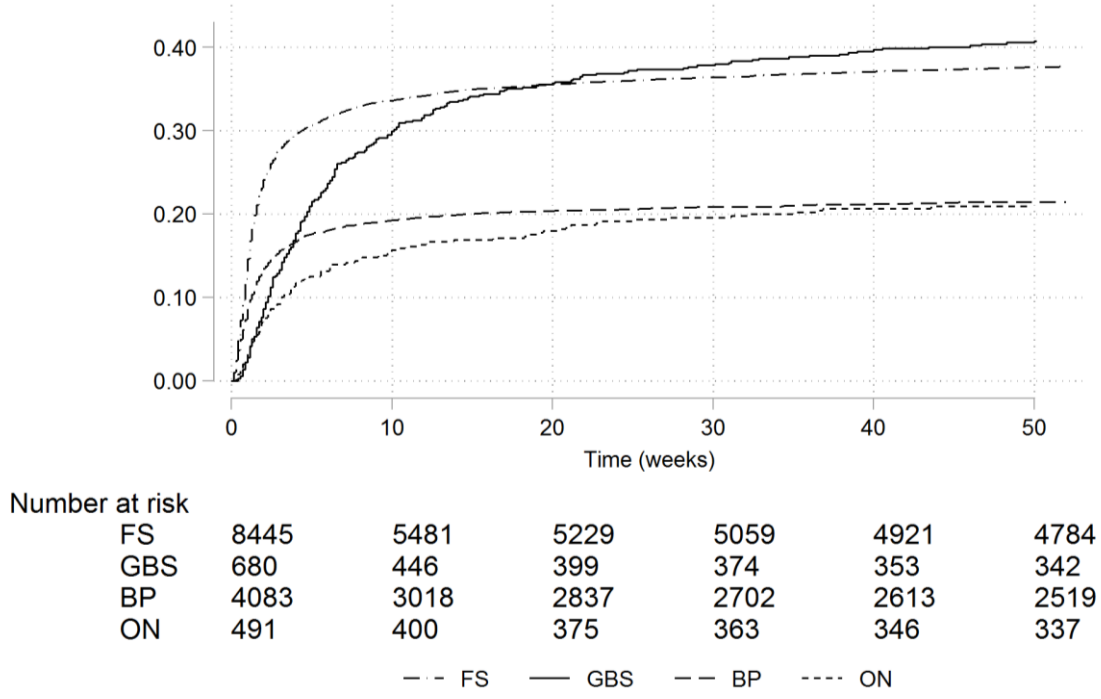


Figure 5.3. Kaplan-Meier recording estimates considering a first record in HES and a subsequent record in CPRD, using a specific set of read-codes. BP – Bell's palsy, FS – Febrile seizures, GBS – Guillain-Barré syndrome, ON – Optic neuritis.

5.5.2 Data accrual per calendar year

The analyses presented in Section 5.3 used ten years of data and assumed that there were no differences in data accrual over time. However, recording behaviours might not be constant throughout time, thus limiting the utilisation of these results in a future system. To assess this issue, I compared data accrual patterns by year. The results for the stand-alone CPRD data are displayed in Figure 5.4 and results for the linked CPRD-HES data are presented in Table 5.2 (results presented in Appendix C of the paper's supporting information). Figure 5.4 shows extremely consistent patterns in each year for Bell's palsy and febrile seizures. Results for Guillain-Barré syndrome and optic neuritis have a good overlap but present more variability. This is likely to be related to the smaller number of records for these two outcomes, particularly for Guillain-Barré syndrome, which showed higher variability. Similar results were observed using linked CPRD-HES data (Table 5.2). These results are reassuring when considering use of the overall data accrual distribution to adjust for delays in the implementation study (see Sections 5.3 and 6.3).

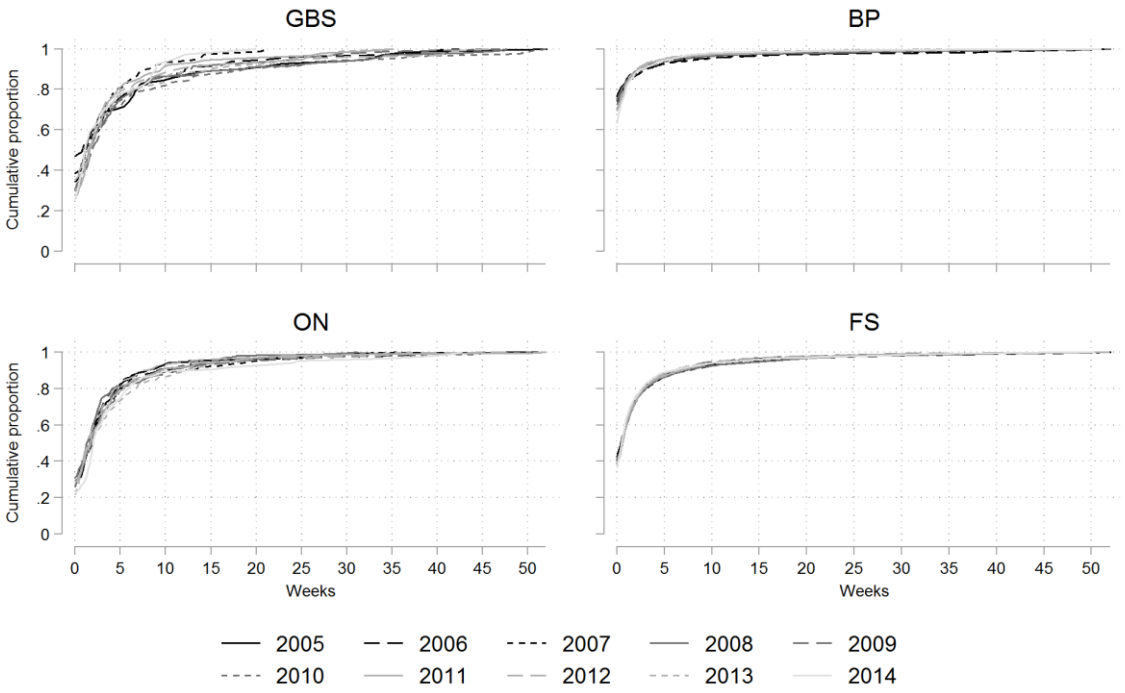


Figure 5.4. Comparison of the data accrual in CPRD per year of diagnosis considering the records made within one year, by condition of interest. BP – Bell's palsy, FS – Febrile seizures, GBS – Guillain-Barré syndrome, ON – Optic neuritis.

Table 5.2. Median (Q1-Q3) number of days of data accrual for the conditions studied and years included.

Year	GBS	Bell's Palsy	Optic Neuritis	FS
2005	8 (0 - 45)	0 (0 - 0)	12 (0 - 28)	3 (0 - 14)
2006	6 (0 - 34)	0 (0 - 1)	12 (0 - 25)	4 (0 - 16)
2007	9 (0 - 28)	0 (0 - 1)	14 (0 - 31)	4 (0 - 16)
2008	12 (0 - 37)	0 (0 - 1)	10 (0 - 21)	4 (0 - 16)
2009	14 (0 - 37)	0 (0 - 2)	12 (0 - 28)	4 (0 - 15)
2010	13 (0 - 41)	0 (0 - 4)	13 (0 - 32)	4 (0 - 15)
2011	12 (0 - 30)	0 (0 - 3)	12 (0 - 30)	5 (0 - 16)
2012	11 (0 - 25)	0 (0 - 3)	10 (0 - 26)	4 (0 - 15)
2013	12 (0 - 31)	0 (0 - 3)	13 (2 - 38)	4 (0 - 14)
2014	9 (0 - 31)	0 (0 - 5)	14 (4 - 36)	4 (0 - 14)

*Considering the start of episode date in the hospital data. FS – Febrile seizures, GBS - Guillain-Barré syndrome.

5.5.3 Inclusion of patients with a previous diagnostic record in CPRD

The last sensitivity analysis assessed the effect of having conducted the completeness analysis only on patients with no previous recording of the outcome of interest in CPRD. The results of this analysis that considered all patients are presented in Figure 5.5 (originally published as Appendix D of the paper's supporting information), with no appreciable differences from Figure 4 of the Section 5.3. When all patients were considered,

completeness at one year decreased for febrile seizures and Guillain-Barré syndrome and increased for Bell's palsy and optic neuritis. For all outcomes, absolute differences were lower than 4%, showing the results are not sensitive to changes in the cohort.

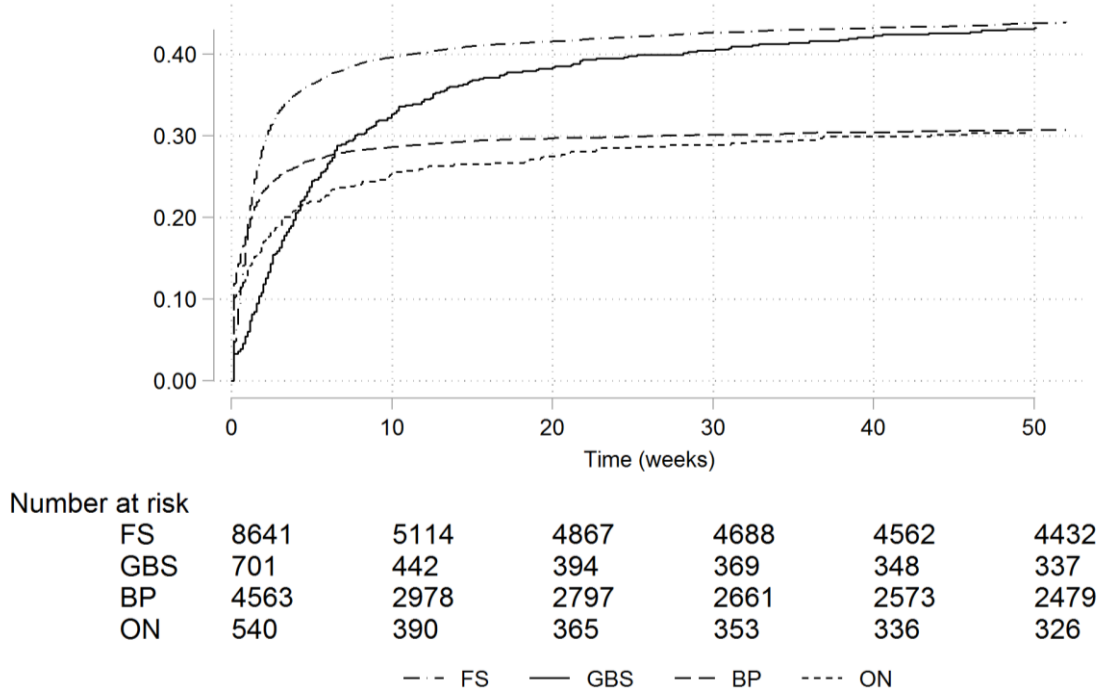


Figure 5.5. Kaplan-Meier recording estimates considering an event as having a record in CPRD at any time. Patients with a record in CPRD prior to HES were considered to have a follow-up of one day. Completeness at one year (%, 95% confidence interval) was: BP - 30.7 (29.4-32.1); FS - 43.9 (42.9-45.0); GBS - 43.3 (39.6-47.1); ON - 30.3 (26.6-34.5). BP – Bell's palsy, FS – Febrile seizures, GBS – Guillain-Barré syndrome, ON – Optic neuritis.

Overall, the three sensitivity analyses indicate that the results from the study assessing delays in recording outcomes in CPRD are robust and can be used when implementing a near real-time system and adjusting for delays. An in-depth explanation of the impact of delays and possible adjustment for delays is presented in the next Chapter.

5.6 Overall discussion and conclusions

The initial feasibility assessment showed CPRD meets some of the conditions necessary to implement near real-time vaccine safety surveillance: it is population-based, has good validity (based on the existing data) and data are timely enough to allow a real-time activity. To proceed with the detailed feasibility assessment, it was necessary to select the vaccine/outcome pairs. Due to the need to prepare all the data and explore the issues arising from the system implementation, only two pairs were selected (seasonal influenza vaccine/Guillain-Barré syndrome and MMR/febrile seizures). The selection was based on

consideration of the outcome characteristics (as explained above in the in-depth delays assessment) but also the existing vaccines and the frequency of the outcome. Having two outcomes with different characteristics allowed the implementation of a system within the time frame available and, at the same time, ensured the implementation study captured a wider diversity of issues. For example, having both a rarer and a more frequent outcome allowed the use of PMaxSPRT and BMaxSPRT (see 4.1 and 7.1).

When selecting the outcomes, only the outcomes included in the in-depth delays assessment were considered. This was to ensure that the delay distribution was known as the system included an adjustment for delays, based on the delay distribution (see Section 6.3). Rare outcomes were also given preference as a way to understand the power available to detect a signal with a small number of events.

For the vaccines, CPRD has been used in several hypothesis-confirmation vaccine safety studies and vaccination records are considered to be complete for vaccines such as MMR[160] (for which general practices are financially incentivised[87]) but it is not anticipated to constitute a good source for vaccines administered outside general practice such as HPV. Thus, only vaccines administered in general practice were included.

After consideration, the pairs selected were seasonal influenza vaccine/Guillain-Barré syndrome and MMR/febrile seizures. Guillain-Barré syndrome was deemed to exemplify a rare outcome, which is often assessed following seasonal influenza vaccine. This vaccine was also considered to be of particular relevance, owing to the specific characteristics of its schedule. As seasonal influenza vaccines change on a yearly basis and administration occurs within a short period of time there is limited time to detect a signal and implement measures should one be identified. For the analysis of this pair, only individuals aged 65 years and above were included as this is the group of adults for which the vaccine is universally recommended and administered in practices. Regarding MMR/febrile seizures, the decision was mainly driven by the known increase in febrile seizures following MMR.[75] This pair thus served as a positive control. It also met other requirements for its selection: MMR is one of the childhood vaccines administered in practices and febrile seizures is a more frequent outcome in the age group of interest than Guillain-Barré syndrome. By selecting these pairs diversity was achieved – a rare outcome following an adult vaccine and a more frequent one following a childhood vaccine, which simultaneously served as a positive control.

The work conducted to trial the implementation of a near real-time system is presented in Chapter 7. Before this, in the next Chapter, data-related aspects of implementing a system

are explained and their implications discussed. These aspects include issues with the data available to conduct the implementation study using previously collected data and implications of delays for the implementation.

6 PRACTICAL ASPECTS FOR IMPLEMENTING A NEAR REAL-TIME SYSTEM USING CPRD DATA

6.1 Introduction

Following the selection of seasonal influenza vaccine/GBS and MMR/febrile seizures as vaccine/outcome pairs to assess, and before performing the actual implementation of NRTVSS in CPRD, it was necessary to reflect on the data available and how that could affect the implementation. This included aspects related to the data that could be used for analysis (i.e. the data stored in-house at LSHTM and/or data potentially extracted online, see 3.1.1.3) and delays in recording and receiving data (explained in Section 5.3). This Chapter starts by expanding on the data availability described in Section 3.1.1.3 and explains how this influenced the implementation study, presented in Chapter 7. Following that, it builds on the delays paper presented in Section 5.3 and discusses the influence of these delays on the implementation of the system, as well as possible adjustments. Overall, this Chapter provides a rationale for the data used in the implementation study.

6.2 Issues with data extraction for the implementation study

The implementation study presented in Chapter 7 used a monthly sequential time-step, as this is the frequency of CPRD data releases. Ideally, it would be possible to extract data monthly, however, at the moment, this is limited by the online search tool used to extract data, which does not allow searches of special immunisation codes in the immunisation file that are required to identify vaccinated individuals (see Sections 3.1.1.3 and 3.2). An alternative to get around this issue would be to extract data online for all individuals targeted by the vaccine of interest (for example, all those aged 65 years older and above) and then apply the algorithms developed to identify vaccinated individuals to this dataset. This option would result in the extraction of large amounts of data and would therefore demand more computational power. It would also require special ethics permission (special permission is required when the number of individuals in a CPRD study is greater than one million).

To overcome these issues the solution was to use the LSHTM in-house version of the data. These data allow for searches of Read codes, therapy codes and specific vaccination information contained in the immunisation file, thus allowing extraction of information on a limited number of individuals (only those potentially vaccinated). However, LSHTM only receives new CPRD data every six months, therefore using these data required the

identification of when each record accrued, i.e. in which monthly version of the data it would be available for the first time. For example, if data released in July 2016 (one of the data releases used, see Section 7.1) are used for analysis it is necessary to identify which data were available in the June 2016 release, in the May 2016 release, and so on (see Figure 6.1). This can be done by using the last collection date for each practice in each monthly version of the data and the dates of each monthly release. Events with a system date and last collection date before the date of each monthly release would be included in a given monthly release of the data. To conduct the implementation study, practice files from each monthly release were thus requested from CPRD to identify the last collection dates. This solution minimised the amount of data to extract and the amount of data requested from CPRD and was considered the most appropriate for the purposes of mimicking a near real-time system in the implementation study. Implications for the use of this system in practice and alternative approaches are presented in the discussion (Section 8.4).

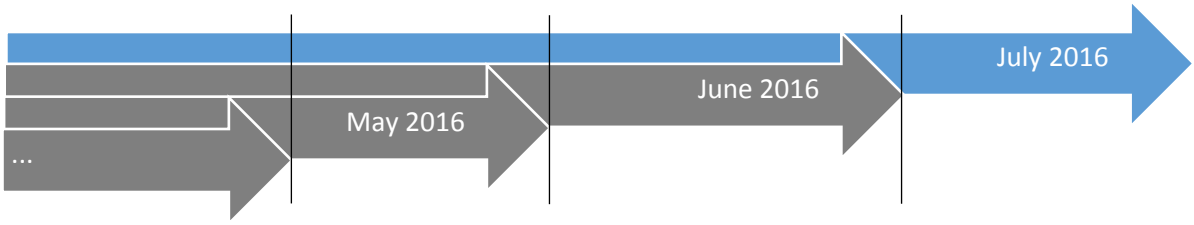


Figure 6.1. Reconstruction of the data accrual process. Arrows in grey represent the data releases not available to LSHTM. Based on the data available (July 2016) it was necessary to identify which data were available in the previous releases

6.3 Options to adjust for delays in CPRD

As previously explained, near real-time vaccine safety surveillance requires timely and readily available data but availability of diagnostic data in CPRD is subject to a variety of different delays: (i) delays in physicians making a diagnosis after an initial consultation; (ii) recording delays; (iii) delays in data being uploaded to data providers; (iv) delays in uploaded data being made available to researchers. These delays might make it difficult or impossible to implement a system, particularly for vaccines requiring a very timely detection of adverse events, such as seasonal influenza. To the best of my knowledge there is no work analysing delays in diagnosing a condition in the context of near real-time vaccine safety surveillance. Such investigation is beyond the scope of a near real-time system but this type of delay is likely to result in random misclassification of the outcome in and outside the risk-window (conditions which started before the risk-window are recorded during the risk-window and vice-versa) thus biasing the analysis towards the null. The systematic review presented in Section 4.1 showed delays in existing systems due to other reasons were dealt with in two

main ways: (a) delaying the analysis for some weeks; (b) adjusting for delays based on a historical delay distribution. The adjustments considered by the systems identified in the review focused on delays due to data being unavailable to researchers and were based on historical data.[113] Site-specific distributions of data accrual were generated and used to adjust the number of expected events when using PMaxSPRT, by applying the proportion of data estimated to be received by a certain time. For example if, based on historical data, the number of expected cases during the first week was ten but only 50% of the data were available after the first week, then the adjusted number of expected cases was five. If no adjustment were implemented, we would consider ten expected cases, thus overestimating the number of expected cases, which in turn would bias the analysis towards no signal. This simple approach is only possible if we assume that an underlying distribution of delays exists and is constant over time.

CPRD data structure differs from the data sources used previously to perform near real-time vaccine safety surveillance. Practices upload data at different times, and information of the time of uploading is available in the data (last collection date) but all data are released to researchers simultaneously. As some of the outcomes of interest are diagnoses made mainly in secondary care (for example Guillain-Barré syndrome) it is also important to consider delays due to recording feedback from other levels of care. The effect of these delays on the implementation of the system depends on the test used. As PMaxSPRT and BMaxSPRT were the tests selected to implement a system (see Section 7.1) an explanation on the effects on delays is provided for these two tests.

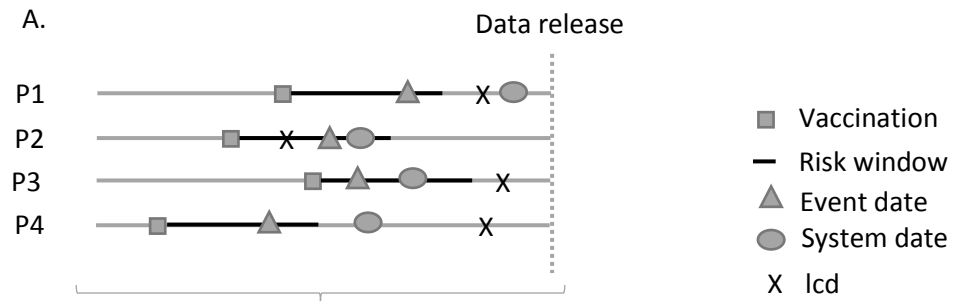
6.3.1 PMaxSPRT

The work presented in Section 5.3 described delays in recording selected conditions of interest for near real-time vaccine safety surveillance. The knowledge generated from these analyses can also be used to adjust for these types of delays. It is thus important to consider different ways to carry out these adjustments and how to best implement them in light of the CPRD structure.

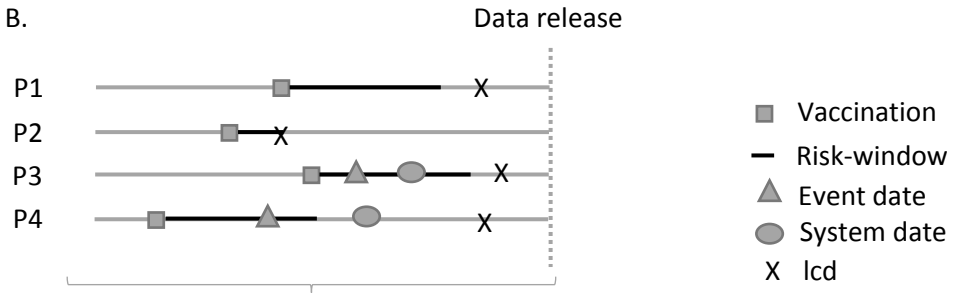
Delays in obtaining data available for analysis are important, due to biases related to differences in the accrual of case and comparator data. In the case of PMaxSPRT the comparison is an observed vs. expected number of cases. Therefore, delays need to be taken into account if there is differential data accrual in the observed and expected cases. As explained in Section 7.1, PMaxSPRT is implemented by applying a historical rate to a follow-up period. As this follow-up period uses the last collection date when calculating rates there

is no differential data accrual due to delays in practices uploading data. Nevertheless, as explored in Section 7.4, this source of delay might lead to a decrease in power.

On the other hand, delays in recording outcomes will lead to biased results if unaccounted for. This happens because the rates calculated to generate the number of expected events are based on historical (stable) data where delays do not affect the rates, whilst the observed number of cases is subject to recording delays because they are obtained closer to the time of the last collection date from the practice and therefore there is less time for data to accrue. Overall, the bias would be towards the null, resulting in loss of power to identify a signal. The issue is represented in Figure 6.2 where four patients with an outcome of interest and different recording patterns are depicted.



4 events:
P1 – Outcome only gets recorded after lcd
P2 – Outcome only happens after lcd
P3 – Outcome happens and is recorded within the risk window and before lcd
P4 – Outcome is recorded after the risk window but before lcd.



Only 2 events will appear in the most recent version of the data as P1 and P2 were only recorded after the last collection date.

Figure 6.2. Potential patterns of recording for four patients experiencing the outcome of interest within the risk window. A. represents what would be observed using stable data and B. what would be observed in recent data. lcd - last collection date

For the purposes of this explanation, it is assumed the system date represents the date the event was entered in the patient's record. Figure 6.2 A shows that the outcome might be

recorded at different times: outside the risk-window and after data have been uploaded for the next data release (P1); during the risk-window but after data have been uploaded for the next release (P2); during the risk-window and before data have been uploaded (P3); or outside the risk-window, before the data are uploaded for the next data release (P4). Figure 6.2 B represents what would be observed in the most recent version of the data: only two of the four events would be captured, given that the remaining two events were recorded after the data were uploaded. The missing events would only be observed in later versions of the data.

From the other two sources of delays (recording outcomes and receiving data) and when using PMaxSPRT, delays in recording are the delays that require adjustment. Below, possible ways to implement this adjustment are presented and discussed.

1. **Apply a single recording delay distribution at the patient level** – Data accrual depends on the outcome of interest as seen in Section 5.3, but also on the time available for data to accrue (the longer the available time, the more data will accrue). When considering observed events in a post-vaccination risk-window the latter will vary from patient to patient depending on the time between the date of vaccination and last collection date. To allow for the delays, the observed number of events could be increased according to the delay distribution, but increasing the number of observed events would artificially inflate power to detect a signal. A better solution is to keep the observed number, but reduce each individual's follow-up time based on the previously generated delay distribution (see Section 5.3). The adjusted follow-up time is then summed and the historical outcome rate is applied to the total adjusted follow-up. This adjustment helps to ensure the comparison of observed vs. expected is unbiased.

   The adjustment using the delay distribution can be done with different levels of complexity. A detailed adjustment would consider, for each individual, the interval between each day of the vaccine risk-window and the end of follow-up time. For each of these intervals, the proportion of records accrued within that number of days (from the delay distribution) is used. These proportions are then summed resulting in a patient-level adjusted follow-up time. For example, consider an outcome with a risk-window of two days and an individual with 60 days between the first day of the risk-window and the end of follow-up time. If the proportion of records accrued within 60 days is 0.80 and the corresponding proportion for 59 days is 0.78, then the adjusted follow-up time for that same patient would be 1.58 days (0.80+0.78)

instead of two. This correction is easy to apply to short risk-windows as illustrated in the example, but would require a huge analytical effort for long risk-windows such as the window considered for Guillain-Barré syndrome (42 days, see Section 7.1). A simpler way to implement the correction is to consider the risk-window mid-point and apply the correction based on the interval between this point and the end of follow-up time. The implementation is then similar to the one explained above but using a single interval and thus a single proportion of records accrued. This is a simplification of the data accrual process because it assumes the event would occur at the risk-window mid-point but does not require successive adjustments for each day. Figure 6.3 provides a representation of this adjustment using the same four hypothetical patients presented in Figure 6.2 and assuming a risk-window of 42 days. The first individual has an initial follow-up time of 42 days (corresponding to the risk-window) and an interval of 30 days between the risk-window mid-point and end of follow-up. If 75% of the records are expected to accrue within 30 days then the adjusted follow-up is 22.5 days. This process is repeated for all patients and each adjusted follow-up is summed yielding the total adjusted follow-up time. The outcome rate is then applied to this follow-up time to obtain the adjusted number of expected events.

A correction based on the mid-point is simple to implement, and relies on the delay distribution generated for the work previously conducted and presented in Section 5.3. For these reasons, this was the adjustment used in the implementation study, reported in Section 7.1. Other options considered are presented below.

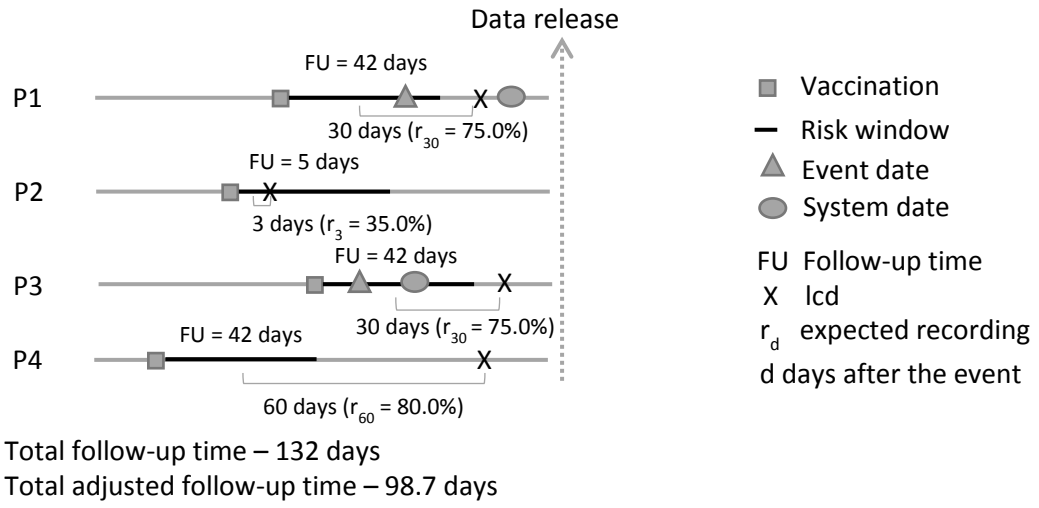
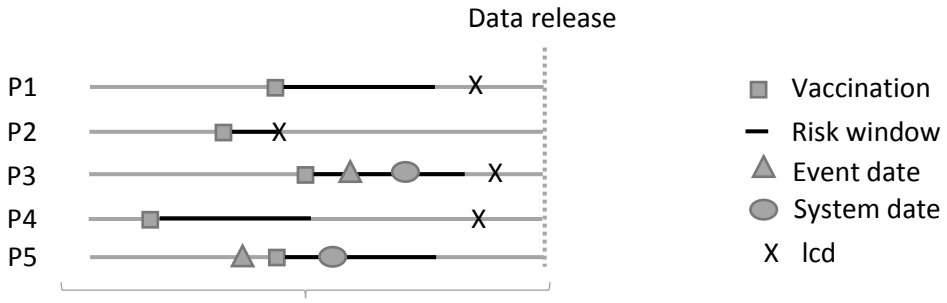


Figure 6.3. Representation of data considered for adjustment of delays at the patient level.

2. **Consider the system date** – Instead of using the event date and adjusting for delays it is possible to generate the outcome rate based on the system date, thus considering a *recorded outcome rate* instead of an outcome rate. Using the system date for outcomes can be done in different ways:
    a. Calculate the outcome rate by considering the events recorded within the historical period. This rate would be applied to the risk-window selected after vaccination, which would give the expected number of recorded cases within the risk-window. The observed and expected number of cases would be equivalent. However, this would capture events occurring before the vaccination but recorded in the risk-window, and would not include some events occurring in the risk period but recorded outside it. This random misclassification would thus give a biased estimate. This option is depicted in Figure 6.4 using the same example from previous Figures. A fifth individual was included to capture the possibility of including events occurring before vaccination.

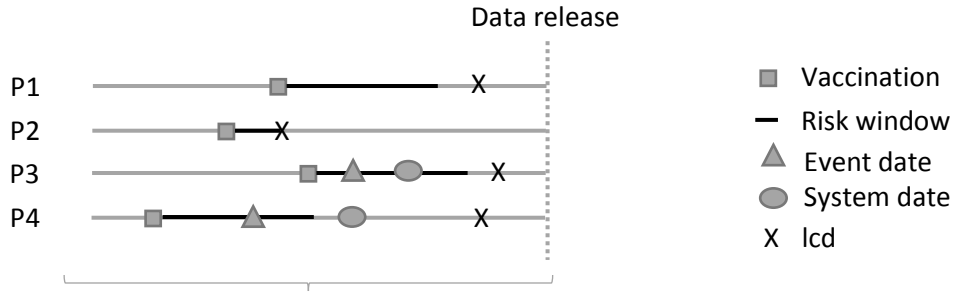


Two events are considered but one occurred outside the risk window. Analysis is biased.

Figure 6.4. Outcomes considered when the adjustment is based on the use of the system date.

    b. To avoid random misclassification it is necessary to consider both the system and event dates. In this case, only outcomes happening during the risk-window and recorded during a season should be included. These are the events considered to calculate the observed number. To generate an equivalent historical rate representing this situation, it is necessary to consider vaccinated individuals in the historical data and then only include those who have had the event date within the risk-window and had an outcome recorded within the season and by the date of the monthly analysis. Additionally, and as explained in Section 6.2, it is important to know at which data release the record first appeared in the data. Figure 6.5

represents the events considered to calculate the historical rate and the observed number of events if the intention is to include events both occurring within the risk-window and being captured in a specific data release. This assessment is based on the last collection date for each data release. It thus assumes that practices upload their data at approximately the same time before each new release. Implementing this adjustment, would require assessment of the vaccination status for the entire historical period as well as information on the last collection date for each monthly release, for both the historical and study period.



Two events are considered in both observed and expected but requires more calculation of rates for vaccinated in historical seasons and lcd for each release of historical data

Figure 6.5. Events considered based on the system date before the next data release

Option 2a was biased, hence not suitable for implementation. Options 1 and 2b are valid but present disadvantages as well as advantages. Option 1 was simple to implement and did not require additional data extraction and analysis as it used data generated for the analysis presented in Section 5.3. Option 2b would require information on vaccinated individuals for the historical period, as well as monthly information on the last collection date for this period. Additionally, it would result in a loss in power as the historical rate would be generated using less data. Hence, Option 1 was selected and used in the implementation study (see Section 7.1).

6.3.2 BMaxSPRT

When implementing a near real-time system the issue of data availability goes beyond delays in recording and receiving data; it is necessary to consider periods (risk or comparison) that are to be included in the analysis but have not yet accrued. When applying PMaxSPRT to CPRD data, the latter issue is not relevant given that follow-up time is considered and therefore partially accrued risk-windows are implicitly accounted for. For BMaxSPRT that is

not the case and so partially accrued periods need attention. Furthermore, delays in data accrual should also be taken into consideration. Below, the issues of partially accrued periods and delays in data availability are presented in the context of BMaxSPRT.

6.3.2.1 Partially accrued periods

BMaxSPRT using a self-controlled approach involves comparing the number of events occurring during the risk period with those occurring during the comparison period. The comparison period might be pre- or post-vaccination. For the former, if the risk-window is long and has not yet accrued, comparing events during the comparison and risk period might result in a biased estimate (underestimating the risk). The partially accrued period might result from an actual time constraint (with the period of interest in the future) or from a delay in receiving data from a practice. Despite being an issue with data delays, the latter is considered in this Section as the mechanism of bias is similar to that resulting from an actual partially accrued period. This is illustrated in Figure 6.6 considering CPRD's data structure, for a vaccinated individual and a specific practice. If the data were uploaded on 28th March and the release occurred on 6th April and this period is within the comparison period, there would be no information regarding that interval.

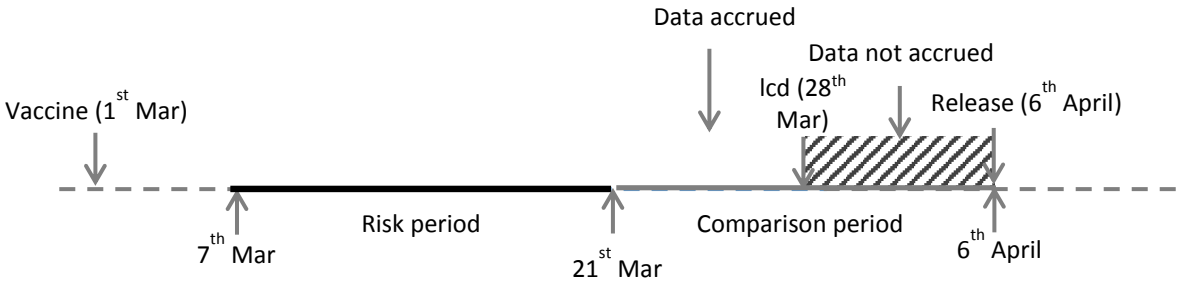
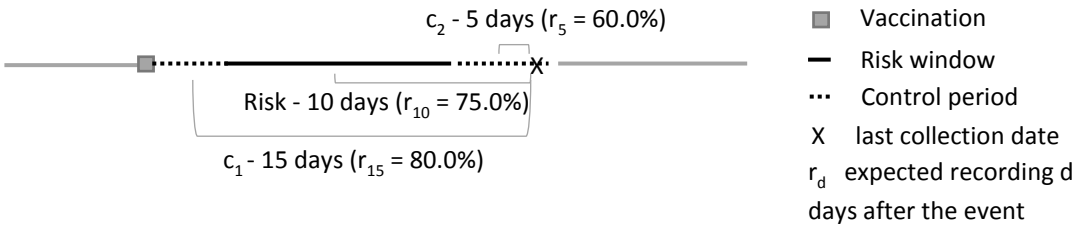


Figure 6.6. Schematic representation of data available for analysis for the risk and comparison periods, for a release and a specific patient. lcd – last collection date

The issue of partially accrued periods in this context might be addressed in several ways, including: (i) shortening the comparison or risk period, (ii) including a pre-vaccination comparison period, and (iii) restricting the comparison to the period that has accrued in the risk/comparison window (e.g. for a pre-vaccination comparison window and a risk-window of 42 days, if only 14 days of the risk-window have elapsed then only the first 14 days of the comparison period are used).[113] Options (i) and (ii) depend on the specific outcome to be studied, as its characteristics determine the period length. For Option (iii), in CPRD, individuals will have different time periods accrued due to practices uploading data at different time points. To take this structure into account and apply Option (iii) it is possible

to calculate the average number of days of the risk/comparison period that have accrued and consider only that time period for the equivalent period (comparison or risk, depending on which one comes first). Alternatively, it is possible to count the number of days accrued in each period for each patient, sum them and calculate the ratio of the comparison period to the risk period. This ratio can be used as a matching ratio in the BMaxSPRT (see Section 3.3.2). As explained in 7.1, BMaxSPRT was used to assess febrile seizures following MMR and the latter adjustment option was preferred as it makes use of all the data available (compared to the use of an average accrued period). Additionally, the comparison period was split into pre- and post risk-window periods. This further minimised the issue of partially accrued periods. Figure 6.7 presents this adjustment together with the adjustment considered for delays in recording outcomes (see Section 6.3.2.2), for a specific individual.



	Data	
	Observed	**Adjusted**
Period	*Period duration (days)*	
Control 1 (c_1)	5	4
Risk	15	11
Control 2 (c_2)	7	4
	Ratio (control/risk)	
Control/Risk	$\frac{5+7}{15} \approx 0.8$	$\frac{4+4}{11} \approx 0.7$

Figure 6.7. Adjustments for delays when using a binomial-based maximized sequential probability ratio test (BMaxSPRT). The number of days in each period is adjusted by the expected recording (r) and the ratio of adjusted days in the control and risk period is calculated for each patient. The patient-level ratios are then averaged and used as a matching ratio in the BMaxSPRT.

6.3.2.2 Data accrual delays

As explained for PMaxSPRT, delays can bias the analysis if the data being compared differ due to these delays. In the case of the previous test this can happen due to potential differences between the expected and observed number of events. In the case of BMaxSPRT the comparison is between periods that are adjacent or close together and involves data which accrued recently. Delays will matter if there are differences in the data accrual for the periods being compared. In the case of febrile seizures, the data accrual curve (see Section

5.3) indicates a rapid change in the accrual rate for the first five weeks, which includes the risk and comparison periods used in the implementation study (see Section 7.1). Therefore, the adjustment used for PMaxSPRT was also applied in this context, for each period considered. In this case, the proportion of data accrued (based on the interval between each period mid-point and last collection date) was applied to the number of days of that period, generating an adjusted number of days. This adjusted number of days was then summed across all individuals for each period (risk and comparison) and the ratio of the two adjusted periods was used to incorporate partially accrued periods as explained above. Figure 6.7 summarizes the overall adjustment (for delays and partially accrued risk windows).

In the next Chapter, the implementation of a near real-time system using CPRD is presented, using the LSHTM version of the data and the adjustments for delays both for PMaxSPRT and BMaxSPRT, as explained above.

7 IMPLEMENTING A NEAR REAL-TIME SYSTEM USING CPRD DATA

Following selection of the vaccine/outcome pairs to include in the trial implementation (seasonal influenza vaccine/GBS and MMR/febrile seizures) and definition of adjustment for delays, I proceeded to perform the abovementioned implementation of a near real-time system using CPRD data. The current Chapter presents the issues related to this implementation. This encompasses assessment of both how to best implement a system and how to improve existing limitations. The Chapter starts by detailing how the trial implementation was performed; in particular, it contains information on the selection of the most appropriate statistical test to identify a signal, adjustment for delays, and calculation of power to detect a signal. This work has been written as a paper (Paper 3), included here. In addition to the work presented in the paper, I provide further information on the use of variable matching ratios when applying BMaxSPRT.

As part of the work performed to trial the implementation of a system, I identified that there was limited power to recognise an increased risk of GBS following seasonal influenza. Existing delays in recording and receiving data for analysis can limit the data available to perform NRTVSS, thus decreasing power to detect a signal in a timely way. Therefore, I re-assessed power in the absence of delays. This work has also been written as a paper (Paper 4), which is included in this Chapter, after the explanation of variable matching ratios. The Chapter finishes with the main conclusions of the work conducted to implement a near real-time system and improve its performance.

7.1 Trial implementation (Paper 3)

This paper was published in *Vaccine* in October 2017. It reports the design and results of the trial implementation of a near real-time system using CPRD data.

As outlined in Section 5.6, I selected two vaccine/outcome pairs to trial the implementation of a system: seasonal influenza vaccine/GBS as an example of a rare outcome and MMR vaccine/febrile seizures as a positive control and an example of a more frequent outcome. In this paper, I detail how implementation was performed (including the choice of the most appropriate statistical test to identify a safety signal and adjustment for delays). The final step to assess the feasibility of implementing a system (assessment of power, see Section 5.1), was also performed at this stage by calculating the power to detect a signal.

For seasonal influenza/GBS I implemented a system for the 2013/2014 and 2014/2015 influenza seasons; for MMR/seizures the surveillance period was July 2014-June 2015. I used the continuous PMaxSPRT for both pairs and the continuous BMaxSPRT for MMR/febrile seizures; power calculations were performed for detecting increases in relative risk (RR) from 1.5-10. The results showed no signal for influenza/GBS in either season. Power to detect a signal was above 80% for detecting 4-fold increases in the risk of GBS following seasonal influenza vaccine. For MMR/seizures, there was a signal with PMaxSPRT but not with BMaxSPRT. Power was ≥80% for detecting 2.5-fold increases in the risk of febrile seizures, for both tests. These results show that CPRD can be used to implement NRTVSS to exclude large increases in the risk of rare outcomes after seasonal influenza and lower increases in risk for more frequent outcomes.

This paper is supported by additional information, including code-lists to identify the outcomes studied, algorithms developed to identify vaccinated individuals, determination of follow-up time, adjustment for delays, and handling of repeated febrile seizure episodes (Appendix A to E in the paper, respectively). These appendices are presented in the thesis in a number of places: Appendix A was previously presented in Section 5.4, as these same code-lists were used for the assessment of delays in recording GBS and febrile seizures (Chapter 5). Appendix D (adjustment for delays) includes the graphical representation of the adjustment for delays considered for PMaxSPRT and BMaxSPRT; it was presented in Chapter 6, in which the issue of delays was explained in detail (Figure 6.3 and Figure 6.7, respectively). The remaining appendices (B. Vaccinated individuals, C. Follow-up time, and E. Repeated febrile seizures episodes) are presented in order after Paper 3, in Section 7.2, below.

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SECTION A – Student Details

Student	Andreia Leite
Principal Supervisor	Dr Sara Thomas
Thesis Title	Near real-time vaccine safety surveillance using United Kingdom electronic health records

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?	Vaccine		
When was the work published?	Accepted for publication		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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)	Prof N Andrews conceived the original idea of the study. I designed the study, I extracted and analysed the data, and interpreted the results, following discussion with both co-authors. Prof. S Thomas contacted CPRD when additional data were required. I drafted the initial manuscript and made changes according to comments from Prof. S

	Thomas and Prof. N Andrews. I incorporated suggestions from peer-reviewers, after discussion with both co-authors.

Student Signature: [redacted] **Date:** 05/10/17

Supervisor Signature: [redacted] **Date:** 05/10/17

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Implementing near real-time vaccine safety surveillance using the Clinical Practice Research Datalink (CPRD)

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ABSTRACT

Introduction: Near real-time vaccine safety surveillance (NRTVSS) using electronic health records is increasingly used to rapidly detect vaccine safety signals. NRTVSS has not been fully implemented in the UK. We assessed the feasibility of implementing this surveillance using the UK Clinical Practice Research Datalink (CPRD).

Methods: We selected seasonal influenza vaccine/Guillain-Barré Syndrome (GBS) as an example of a rare outcome and measles-mumps-rubella (MMR) vaccine/febrile seizures as a positive control. For influenza/GBS we implemented a system for the 2013/2014 and 2014/2015 influenza seasons; for MMR/seizures the surveillance period was July 2014–June 2015. We used the continuous Poisson-based maximized sequential probability ratio test (PMaxSPRT), comparing observed-to-expected events, for both pairs. We calculated an age-sex-adjusted rate using 5 years of historic data and used this rate to calculate the expected number of events in pre-specified post-vaccination risk-window (GBS: 0–42 days, seizures: 6–21 days). For MMR/seizures we also implemented the system using the Binominal-based maximized sequential probability ratio test (BMaxSPRT). For this, we compared seizures in the risk-window (6–21 days) to a control window (0–5 and 22–32 days). Delays in recording outcomes influence the data available, so we adjusted the expected number of events using a historical distribution of delays in recording GBS/febrile seizures. Analyses were run using data up to each CPRD monthly release. We also performed power calculations for detecting increases in relative risk (RR) from 1.5 to 10.

Results: For influenza/GBS we implemented a system in both seasons with no signal. Power to detect a signal was >80% for RR $\geq$ 4. For MMR/seizures we were able to identify a signal with PMaxSPRT but not with BMaxSPRT. Power $\geq$ 80% for RR $\geq$ 2.5 for both tests.

Conclusion: CPRD is a potential data source to implement NRTVSS to exclude large increases in the risk of rare outcomes after seasonal influenza and lower increases in risk for more frequent outcomes.

1. Introduction

Near real-time vaccine safety surveillance (NRTVSS) using electronic health records is amongst the tools available to perform post-licensure vaccine safety surveillance. NRTVSS is usually started shortly after a new vaccine is introduced and data is analysed at repeated points in time. Near real-time surveillance was introduced in the USA in 2005 first using the sequential probability ratio test and later its maximized version. It is now used routinely in this country [1]. It has allowed the identification of several safety signals [2].

In the UK, there are electronic health records available such as the Clinical Practice Research Datalink (CPRD). NRTVSS has been implemented in the UK using spontaneous reports to obtain the observed number of events and CPRD to calculate the expected number of events. This implementation inherits spontaneous reports limitations, including underreporting [3]. A NRTVSS fully relying on electronic health records has not been implemented to date.

When envisaging a new data source to implement NRTVSS timeliness is a key consideration. In CPRD, delays can happen due to: (i) delays in making a diagnosis after an initial consultation; (ii) delays in recording diagnosis made in other levels of care (e.g. hospital); (iii) delays in receiving data for analysis. To the best

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of our knowledge, there has been no work to explore systematically the influence of (i) on recording patterns using CPRD data. For (ii), a previous analysis of CPRD data looking at conditions of interest for vaccine safety has shown that recording delays exist, but the majority of records accrue within a month after the date of the event [4]. Researchers receive CPRD data on a monthly basis (delay (iii)). Thus, from the evidence to date CPRD is a potential source of data to implement NRTVSS.

In addition to delays, several questions regarding the actual implementation of a system using CPRD data remain unaddressed, such as which statistical method to use, how to account for delays, and whether there is enough power to identify safety signals. To address these we sought to trial the implementation of NRTVSS using previously collected CPRD data.

2. Methods

2.1. Data source

We used data from CPRD, a primary health care database with anonymised health records from a broadly representative sample (~6.9%) of the UK population. CPRD includes information on demographics, coded diagnosis, therapies, vaccines, health-related behaviours, and referrals to secondary care [5]. Diagnoses recorded in CPRD include diagnoses made both in primary care and in hospital. Hospital diagnoses are fed back to GPs via letter, which are later coded in the system. Diagnoses are coded using Read-codes, a hierarchical thesaurus of clinical terms used in the UK since 1985 [6].

CPRD contains several relevant dates. For each patient there is information on the patient's current registration with the practice (crd) and the patient left the practice (tod). Each record contains the date when the record was entered into the system (system date) and the date deemed to represent when the event registered took place (event date). At the practice-level, CPRD includes the date when the practice met certain recording quality criteria (up-to-standard date, uts) and the date when data were last collected from the practice before each monthly release (last collection date, lcd) [5].

2.2. Vaccine/outcome pairs

We selected two pairs: seasonal influenza vaccine/Guillain-Barré syndrome (GBS) and Measles-Mumps-Rubella (MMR) vaccine/febrile seizures. NRTVSS is of particular relevance to assess seasonal influenza vaccine due to the short time available for action, and GBS is a rare outcome of interest following influenza vaccine. Influenza vaccine/GBS was thus chosen to assess the potential of CPRD as a data source to implement NRTVSS for rare events. Febrile seizures are a known adverse reaction seen after MMR vaccine, so we selected this pair to represent a positive control and as an example of a somewhat less rare event with a childhood vaccine [7]. Appendix A presents code-lists used to identify GBS/seizures and Appendix B the algorithms used to identify vaccinated individuals.

3. Analysis

3.1. Statistical tests

Choice of the statistical test to use should be guided by the test characteristics (e.g. power and underlying assumptions), frequency of data updates and frequency of the outcome under study. One approach is to select first the general group of tests (continuous or group sequential) and then choose a specific version of the test [2]. For continuous tests, data are looked at as often as desired, and ideally when a new event is observed, while for group sequential tests data are interrogated at discrete points in time [2]. Previous work has shown that continuous sequential tests perform better than group sequential [8] and aggregate data (weekly or monthly) can be used in a continuous way [9]. As CPRD is updated monthly, we considered continuous sequential tests more appropriate.

Poisson-based Maximized Sequential Probability Ratio Test (PMaxSPRT), the Binomial-based Maximized Sequential Probability Ratio Test (BMaxSPRT), and the Conditional Maximized Sequential Probability Ratio Test (CMaxSPRT) are the continuous sequential tests available. PMaxSPRT involves a comparison observed-to-expected and its use has been proposed when less than 50 events are expected, as it is a more powerful test [2]. Disadvantages include limited ability to adjust for confounders and potential bias by secular or coding trends, as it relies on historical data. It also does not allow for uncertainty in the expected count (it is taken as a fixed expected number). BMaxSPRT compares the number of events in exposed-to-unexposed individuals or in periods within individuals. This allows further adjustment for potential confounders but lessens power. Unlike PMaxSPRT, CMaxSPRT was designed to account for uncertainty in the historical data. The comparison is made in terms of the cumulative person-time it took to observe a certain number of adverse events in the historical and surveillance data. It assumes event rates are constant in both versions of the data.

Given the rarity of GBS we selected PMaxSPRT for influenza vaccine/GBS. For seizures/MMR the number of expected events was still lower than 50 (see below), suggesting the use of PMaxSPRT. However, previous works have also considered the simultaneous use of PMaxSPRT and BMaxSPRT owing to their complementary strengths [9]. We preferred this approach as it allowed us to further identify challenges/potential solutions when using CPRD to perform NRTVSS. It has been previously suggested that PMaxSPRT gives biased results when a small sample is used to estimate the number of expected events [10]. To avoid this, we used a long historical period (5 years) to obtain more stable estimates and thus reduce uncertainty to negligible levels relative to uncertainty in the observed data. It has also been suggested as an *ad hoc* guideline that an alternative test (CMaxSPRT) should be used when the number of observed events in the historical data is less than five times the number of expected events in the surveillance data. We thus assessed whether this *ad hoc* rule held in our data.

Below we detail how we obtained the observed and expected numbers of events to implement PMaxSPRT for each pair. We start with an explanation for seasonal influenza/GBS followed by MMR/seizures. For the latter we emphasize aspects that differ from the first pair. For BMaxSPRT we used a case-only design and compared the number of cases during the exposed-to-unexposed periods, also detailed below. Analyses were performed using R package Sequential 2.3.1 [11].

3.2. Influenza/GBS

We studied the 2013/14 and 2014/15 seasons (1st September–31st March), using data released in July 2015 and 2016, respectively. Using these data releases allowed at least a year from the event date for them to be recorded. In all analyses we did not consider the small proportion of events that are recorded with a delay >1 year [4].

3.2.1. Historical rates, expected and observed number of events (PMaxSPRT)

For the historical comparison, we used the general background rate of GBS among individuals aged ≥65 years as this is the age in which seasonal influenza vaccine is routinely recommended and given in GP practices. For each study season, we calculated GBS

historical rates stratified by age (65–74, 75–84, ≥85 years old) and gender for the 5 previous seasons (2008/09–2012/13 and 2009/10–2013/14, respectively). Numerators were first-ever GBS cases for active patients. We have previously demonstrated that when GP systems are updated the system date (the date a record is added to a patient's file, assigned automatically by the general practice software) of some records can be altered to a later date [4]. For those records, it is not possible to estimate accurately the delay in recording the outcome. Hence, these records were identified using the approach proposed in [4] and were excluded. Active patients were defined as contributing follow-up time during each season. Start of follow-up was the latest of uts, crd (plus 1 year to exclude retrospective recording of previous diagnoses when registering with a new practice [12]), or 1st September 2008–13. End of follow-up was the earliest of date of tod, lcd, or 31st March 2009–14. We averaged seasonal GBS rates over the five historical seasons and applied this rate to the vaccine-exposed follow-up time in the study seasons, to obtain an expected number of events (adjusted by age and gender). For the study seasons end of follow-up was the earliest of tod, lcd or 42 days after vaccination (Appendix C) [13]. The observed number of events was the total number recorded in the vaccine risk-window at the time of each analysis.

3.2.2. Delays

For each patient we calculated the time between the risk-window midpoint and lcd (time = d) and then used the previously generated delay distribution [4] to calculate the probability (r_d) that an event that did occur within a year would be recorded by delay d. This was used to adjust the follow-up to obtain an adjusted follow-up. For example, if a patient had 30 days between the risk-window mid-point and lcd and $r_d = 75\%$, then only 75% of this patient follow-up time was considered (Fig. 2 in Appendix D). We assumed no delays in vaccination data.

3.3. MMR/Seizures

The system was implemented for one year (July 2014–June 2015) using data released in July 2016.

3.3.1. Historical rates, expected and observed number of events (PMaxSPRT)

We calculated febrile seizures rates during the second year of life (12–23 months, timing of MMR 1st dose [13]), stratified by age (two weeks periods) and gender, for the five years previous to the study period (July 2009–June 2014). We first identified all febrile seizures events for eligible patients and excluded records likely to be duplicated (Appendix E).

We calculated follow-up time and the expected and observed number of events as described above (Appendix C) for the historical period July 2009–June 2014 and the study period July 2014–June 2015. A previous study looking at the risk of febrile seizures following MMR and using hospital data identified a risk-window of 6–11 days [7]. In this work, we used primary care data, which are likely to capture febrile seizures with some delay. This can happen if parents seek care outside primary care (e.g. emergency services) and GPs only receive and register the information regarding the seizure a few days after it has occurred. We thus allowed extra time, by using a risk window of 6–21 days to capture such events.

3.3.2. BMaxSPRT

To apply BMaxSPRT we used the same risk-window of 6–21 days post-vaccination and used a control period of 1–5 (c_1) and 22–32 (c_2) days post-vaccination, selected to be a period of the same length and close to the risk period.

3.3.3. Delays (BMaxSPRT)

For BMaxSPRT it was necessary to adjust for delays for each of the post-vaccination periods (the risk period and c_1, c_2). This was done by calculating an adjusted follow-up period for each of these intervals as shown in Fig. 3 in Appendix D. For each individual we then calculated a ratio of the corrected follow-up for control period compared to the risk period (see Appendix D for an example) and then obtained an average ratio across individuals. This average ratio was included in the calculations for the BMaxSPRT method as the matching ratio [9]. This final adjustment simultaneously accounted for delays in practices uploading data and partially accrued period.

3.4. Implementation

To mimic a NRTVSS using pre-existing data we first recreated how data accrued. To determine whether a record of interest would have been in each data release we used: release date; lcd (practice-level); event date of the record; and system date of the record. CPRD is released on a monthly basis, on the first Monday of each month. For a particular release we considered the outcome would be captured if the event date, system date, and last collection date all happened before the date of release. For example, an event taking place (event date) on 9/10/2014, with a system date of 10/11/2014, and lcd 28/10/2014 for the November release would not appear in the November. If lcd for the December release was 25/11/2014 then the event would appear in December.

As no signal was expected for influenza/GBS we further tested NRTVSS implementation by adding cases to generate an increase in risk of approximately 4 and 5-fold, which power calculations suggested should be detectable.

Implementation was done graphically by calculating the log-likelihood ratio test at the time of each data release. For PMaxSPRT the log-likelihood is based on the number of observed and expected events while for BMaxSPRT it considers the number of observed events occurring in the control and risk periods. The results from the log-likelihood ratio test were compared with the critical limit. For each vaccine/outcome pair and study period we calculated critical limits considering a minimum number of observed events to reject the null hypothesis of 1, 2, and 4.

3.5. Power and expected time to signal

Post-licensure vaccine safety surveillance aims at detecting signals that might have been missed before vaccine approval, due to the lack of power in the analyses conducted. When considering NRTVSS we thus need to assess power. The R package Sequential includes system performance tools, allowing calculating of power and expected time to signal [11].

Power is affected by several factors: incidence of the outcome (both background incidence and incidence following vaccination), vaccine uptake, vaccine risk-window length, length of the study period, delays in receiving the data, relative risk (RR) to be detected, events in the first look at the data, minimum number of events before rejecting the null, and level of significance. Calculations were performed for a plausible range of RR (1.5–10), considered no events in the first look at the data, and a level of significance of 5% ($\alpha = 0.05$). For PMaxSPRT we also required 1, 2 or 4 events before rejecting the null [14] and the remaining factors were integrated through the expected number of events at the end of the surveillance period. For BMaxSPRT we considered the total number of events at the end of the surveillance period (both from risk-window and control periods).

Expected time to signal is conditional on having identified a signal and is obtained in the units of expected number of events. As CPRD data do not accrue at a constant rate, to know at which

release we would expect a signal we evaluated at which release the number of expected events would have been achieved.

4. Results

Table 1 presents the number of doses identified and the main characteristics of individuals receiving the vaccine of interest.

4.1. Seasonal influenza/GBS

We identified 1.89 and 1.66 expected events for season 2013–14 and 2014–15, respectively. The historical rates used were based on 33 observed events for each season. Hence, the use of CMaxSPRT was not deemed necessary. Fig. 1 presents system implementation. No signal was identified for both seasons. When we added cases to generate an increase in risk of 4- and 5-fold we found, for an increase in risk of 4, the signal would be identified at the beginning of January and February for the season 2013/14 and 2014/15, respectively, if a minimum of 4 events was stipulated. For an increase of 5 times the risk the signals would be detected a month before (Fig. 2).

Table 2 presents power and expected time to signal for seasonal influenza/GBS and both seasons. In general, there was power $\geq$ 80% to detect RR $\geq$ 4. If there was a signal this would be detected at the beginning of December for large increases in risk (6–8 times) and at the beginning of January for lower increases (4–5 times).

Table 1
Main characteristics of individuals receiving the vaccine of interest for the pairs included.

Characteristic	Vaccine/outcome pair		
	Influenza/GBS season 2013–14	Influenza/GBS season 2014–15	MMR/Febrile seizures
Number of doses (n)	533,110	477,454	28,249
Sex – n (%)			
Male	240,884 (45.2)	216,224 (45.3)	14,474 (51.2)
Female	292,226 (54.8)	261,230 (54.7)	13,775 (48.8)
Age (years) – n (%)			
65–74	270,690 (50.8)	242,168 (50.7)	–[a]
75–84	188,423 (35.3)	168,160 (35.2)	–[a]
≥85	73,997 (13.9)	67,126 (14.1)	–[a]
Age (months) – n (%)			
12	–[a]	–[a]	11,460 (40.6)
13	–[a]	–[a]	10,049 (35.6)
14	–[a]	–[a]	3320 (11.8)
≥15	–[a]	–[a]	3420 (12.1)

GBS – Guillain-Barre syndrome.
MMR – Measles-mumps-rubella.
[a] Age (at time of vaccination) is expressed in years for seasonal influenza/GBS and months for MMR/febrile seizures.

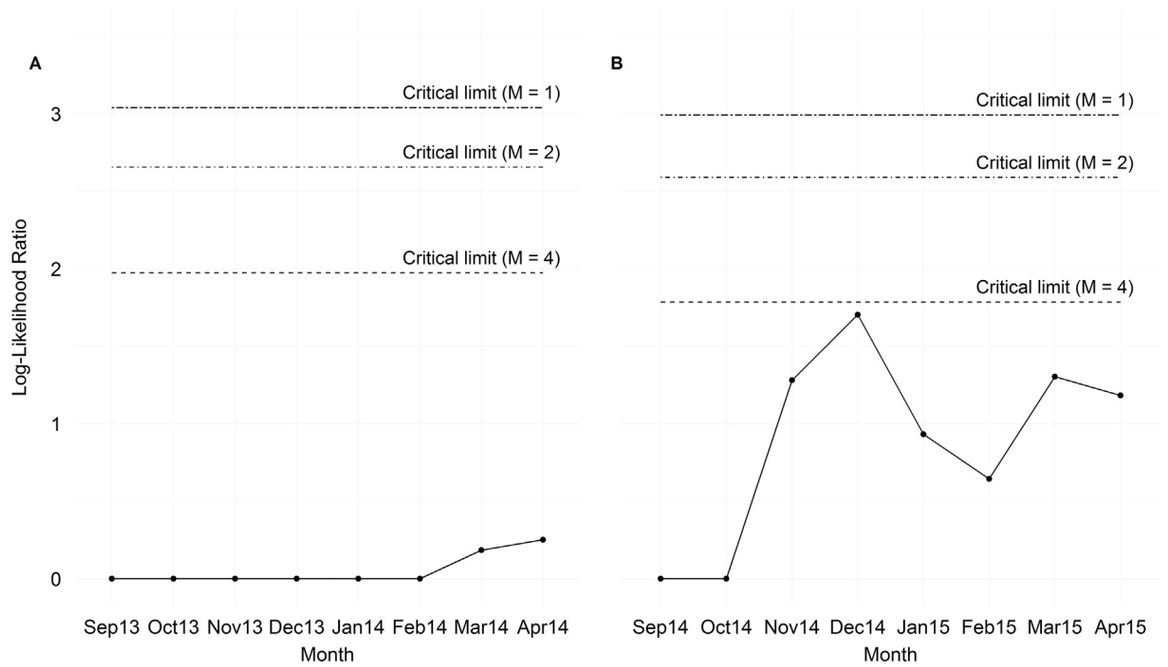

Fig. 1. Implementation of a system for influenza vaccine/GBS for season 2013–14 (A) and season 2014–15 (B). No signal is detected in any of the seasons.

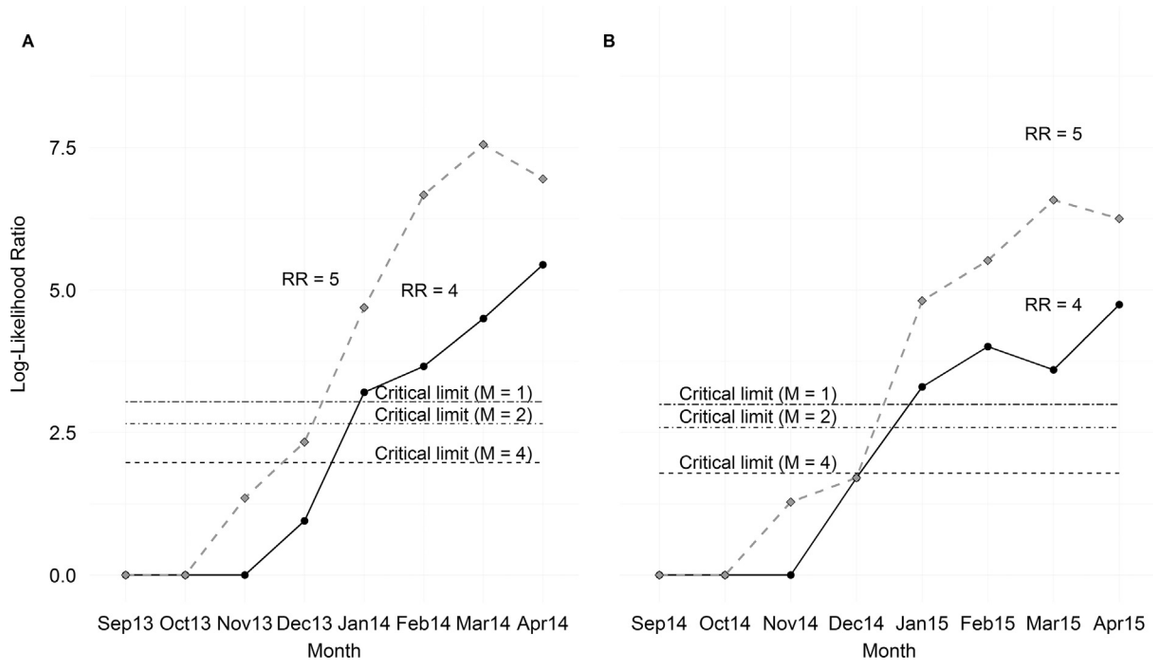

Fig. 2. Implementation of a system for influenza vaccine/GBS for season 2013–14 (A) and season 2014–15 (B), assuming an increase in risk of 4 and 5 times. A signal is detected at different points in time depending on critical limits considered.

Table 2
Power and expected time to signal for seasonal influenza/GBS (seasons 2013–14 and 2014–15) using Poisson-based Maximized Sequential Probability Ratio.

Minimum events	Season	Data available at	Power (time to signal in months from beginning of surveillance)[a] Relative risk								
			1.5	2	2.5	3	4	5	6	8	10
1	2013–14	07–04-2014	13	25	40	55 (4)	78 (4)	**91 (3)**	**97 (3)**	**100 (3)**	**100 (3)**
	2014–15	06–04-2015	12	23	37	51 (4)	74 (4)	**88 (4)**	**95 (4)**	**99 (3)**	**100 (3)**
2	2013–14	07–04-2014	14	28	44	60 (4)	**82 (4)**	**93 (3)**	**98 (3)**	**100 (3)**	**100 (3)**
	2014–15	06–04-2015	14	26	41	55 (4)	77 (4)	**90 (4)**	**96 (4)**	**100 (3)**	**100 (3)**
4	2013–14	07–04-2014	16	33	50	65 (4)	**86 (4)**	**95 (4)**	**98 (4)**	**100 (3)**	**100 (3)**
	2014–15	06–04-2015	16	31	47	62 (4)	**83 (4)**	**93 (4)**	**98 (4)**	**100 (4)**	**100 (4)**

Cells in bold refer to power ≥80%.
PMaxSPRT - Poisson-based Maximized Sequential Probability Ratio.
[a] Time to signal is only displayed for cells where equivalent power≥50%.

4.2. MMR/seizures

After investigation of duplicated records of febrile seizures we decided to exclude those occurring with three days of one another (Appendix E). We identified 11.3 expected episodes in the study period and the historical rates were based on 2693 observed events. Fig. 3 presents NRTVSS implementation. We identified a signal using PMaxSPRT. For BMaxSPRT the signal was just missed.

Table 3 presents power and expected time to signal for febrile seizures/MMR based on a one-year surveillance period. We observed power ≥ 80% to detect RR ≥ 2.5. If there was a signal this would be detected at the beginning of September (2 months after beginning of surveillance) using PMaxSPRT for RR of ≥5, and in subsequent months for lower increases in risk. Power for BMaxSPRT was lower but would still allow detection of an RR of ≥2.5.

5. Discussion

We systematically assessed the feasibility of implementing a NRTVSS using data from CPRD. Our study shows that it is feasible to use CPRD and it would enable detection of medium/large increases in risk of GBS following seasonal influenza vaccine among individuals aged ≥65 years, and smaller increases in the risk of febrile seizures following first dose of MMR.

For influenza/GBS, CPRD would only enable detection of large increases in risk. In addition, the signal would only be detected around mid-season (beginning of January) which might be late, as the vaccine is recommended early in the season [15]. Despite limited power to detect an increased risk, our finding of no increased risk of GBS following seasonal influenza vaccine seems consistent with the existing literature. For example, a recent work assessing GBS following influenza vaccine in the USA between 2010/11 and 2013/14 found no signal for the season 2013/14, the season we also assessed as part of our work [16]. Overall, we believe the system now proposed addresses some of the limitations of the existing system, which is based on spontaneous reports and thus is limited by underreporting [3].

We were able to replicate a known signal for febrile seizures following MMR based a one-year surveillance period. This signal was identified only with PMaxSPRT (after 3 months of surveillance, if a minimum events of 2 events was stipulated). Although BMaxSPRT did not quite signal as it is a less powerful test, it has the advantage

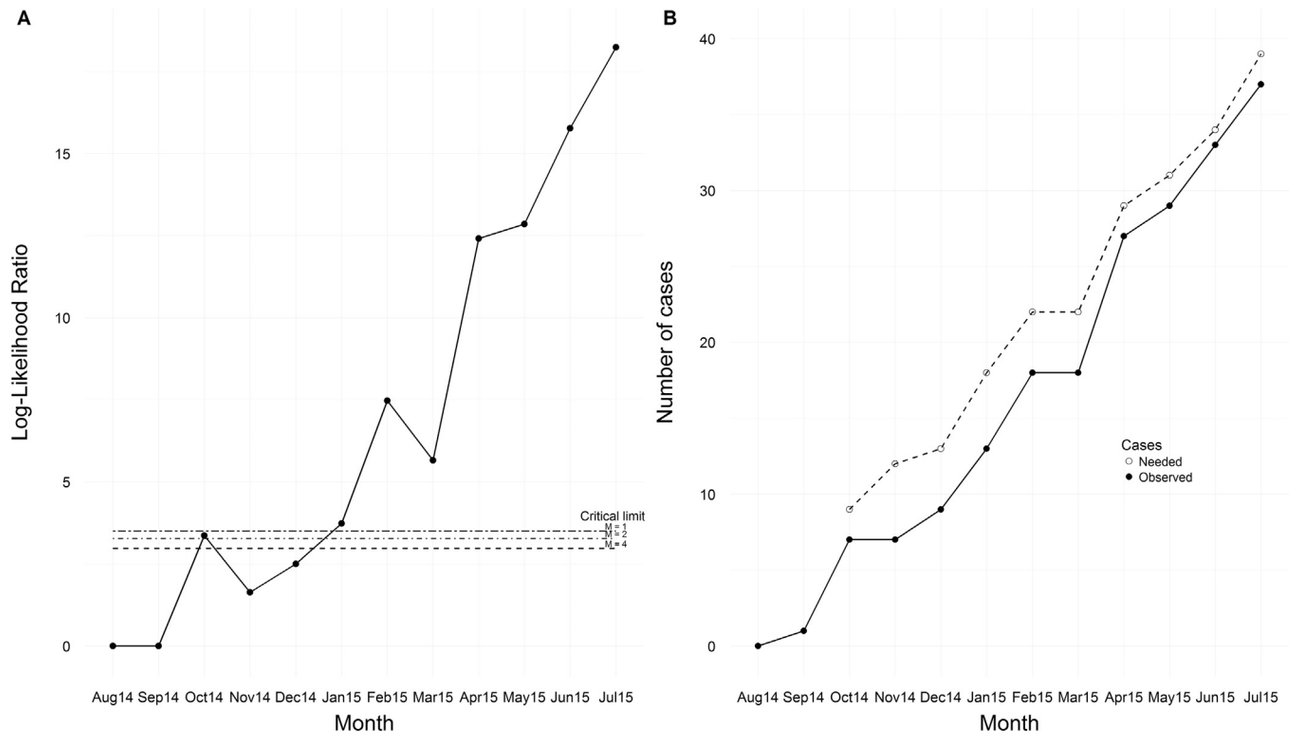

Fig. 3. Implementation of a system for MMR/febrile seizures using PMaxSPRT (right) and BMaxSPRT (left). Only for PMaxSPRT a signal is detected.

Table 3
Power and expected time to signal for MMR/febrile seizures after, using Poisson and Binomial-based Maximized Sequential Probability Ratio.

Minimum events	Test	Data available at	Power (time to signal in months from beginning of surveillance)[a] Relative risk								
			1.5	2	2.5	3	4	5	6	8	10
1	PMaxSPRT	06–07-2015	30	73 (5)	**95 (4)**	**99 (3)**	**100 (2)**	**100 (1)**	**100 (1)**	**100 (1)**	**100 (1)**
	BMaxSPRT	06–07-2015	28	63 (6)	**85 (6)**	**95 (5)**	**99 (5)**	**100 (4)**	**100 (3)**	**100 (3)**	**100 (3)**
2	PMaxSPRT	06–07-2015	33	76 (5)	**96 (4)**	**100 (3)**	**100 (2)**	**100 (1)**	**100 (1)**	**100 (1)**	**100 (1)**
4	PMaxSPRT	06–07-2015	36	79 (5)	**96 (4)**	**100 (3)**	**100 (2)**	**100 (1)**	**100 (1)**	**100 (1)**	**100 (1)**

Cells in bold refer to power≥80%.
BMaxSPRT - Binomial-based Maximized Sequential Probability Ratio.
PMaxSPRT - Poisson-based Maximized Sequential Probability Ratio Test.
[a] Time to signal is only displayed for cells where equivalent power≥50%.

of having a much more relevant comparator period that should be less prone to bias and would likely have signalled with an extended surveillance period. We would therefore suggest that despite the low number of expected events (11) it is still worthwhile using this method in addition to PMaxSPRT to make the signal more robust. Others have suggested a minimum number of expected events of 50 [2].

A further aspect is the minimum number of events required to reject the null hypothesis. As previous work has suggested, rejecting the null hypothesis only after a certain number of events increases power [14]. Given we have limited power for seasonal influenza/GBS we would recommend implementing a system with a requirement of 4 events before rejecting the null.

Vaccine safety studies require careful specification of risk-windows and, if applicable, comparator windows. This includes not only knowledge of the characteristics of the vaccine/outcome pair under study but also the data available for analysis. In the case of MMR/seizures we decided to use a longer risk-window than previously suggested (6–21 days instead of 6–11 days) to account for delayed recording of seizures in the primary care data. If our choice resulted in an unduly long risk-window the result would be an underestimation of the risk and thus a reduction in the power to detect a signal. In practice, a way to address uncertainty in the specification of risk-windows is to conduct a sensitivity analysis using an alternative risk/comparator window. Alternatively, this uncertainty can be addressed at the confirmatory stage by looking at the distribution of cases within the risk-window.

Data quality should also be considered. Our previous assessment of completeness of records first diagnosed in hospital showed that CPRD had low sensitivity to capture GBS. However, if this suboptimal sensitivity is constant over time, for the purposes of the current system the effect would be a decrease in power to detect an event [2]. We know of no studies assessing the positive predictive value of the outcomes included. As for the vaccination data, the vaccines we selected are administered in general practices and GPs are financially incentivised to achieve certain thresholds of vaccine uptake. It is thus expected that individuals classified as vaccinated are indeed so.

Our study presents several limitations. The use of PMaxSPRT is susceptible to uncertainty in historical rates and a conditional test

was proposed to address this issue. We tried to minimize this by using data from the 5 previous seasons/years to estimate historical rates. Given the amount of observed events in the historical data is substantial larger (more than five times) than the number of expected events in the study period we considered that the use of a conditional test was not necessary. Secondly, for our study period we considered only vaccinated individuals while for historical rates we included both vaccinated and non-vaccinated. Including vaccinated individuals in historical periods could have led to a slight overestimate of the background rate and underestimate of the RR and thus miss a signal. However, even if there were increases in risk in the historical periods due to the vaccine, the increase in the attributable risk would be small, thus minimizing this issue. Nevertheless, we were able to detect a signal for seizures/MMR, which is reassuring. Finally, our study is limited by assumptions of the method used, including homogenous distribution of a potential risk during the risk-window and throughout the study period and that if there is an increase in risk these additional cases would be also recorded in CPRD.

We proposed a new adjustment for delays but it might still not fully capture existing delays [17]. We only considered a mid-point for adjustment, which simplifies the data accrual process. Furthermore, we considered a delay distribution based on historical data and recording patterns might have changed, although previous work looking at ten years' worth of data shows consistent recording patterns [4]. Overall, we believe our adjustment reduces bias due to data availability and enables an earlier start of surveillance.

As previously pointed out there are few strategies available to deal with potential confounding factors [2]. For influenza/GBS we were able to account for gender and partially for age. If there is a signal, further adjustment for confounders is one of the initial steps [1], potentially including more detailed adjustment for age (we only considered 10-year age groups) and for other potential confounders. Influenza incidence may be one of these potential confounders, as GBS is known to be associated with influenza-like illness [18]. Rapid yearly estimates are provided for influenza incidence and could potentially be used in this context. For seizures/MMR, we were able to account for age and gender in the PMaxSPRT analysis but we did not explicitly account for age in the BMaxSPRT. Febrile seizure rates are known to change rapidly with age [19] but the use of a control period before and after the risk period should have helped to limit potential confounding due to age.

Our study made use of previously collected data to mimic a new system. However, CPRD is expanding, to include practices using different softwares [20]. While this can be seen as an opportunity to increase power to detect lower increases in risk for rare outcomes, there might be differences in coding systems and behaviour that could limit the applicability of the results of our previous studies. Alternatively, these new practices could be used for signal confirmation should a signal be identified. This strategy would be a way to avoid using the same data for signal identification and confirmation.

As we have further knowledge on NRTVSS and its application using CPRD next steps include application to new vaccines. In addition, there is the need to define which steps to undertake if a signal is detected. Yih et al. [1] proposed a series of steps in case a signal is found, broadly including: to check data and code, to examine descriptive statistics for patterns in time between the exposure and outcome, to adjust for additional confounders, to conduct a non-sequential analysis with a different comparator, to conduct a review of records, to compare the results with similar outcomes or other existing data, to analyse new data or to design a new study. All steps can be conducted using CPRD data. However, there is limited ability to perform a timely confirmation of the patient's recorded diagnoses. Currently, when GPs are asked to validate diagnoses identified from coded information this process may take several months. Future discussions with data providers and medicines regulatory authorities may help to facilitate the process of data validation. An in-depth presentation of the steps required following a signal is beyond the scope of this work.

In conclusion, our results suggest the implementation of NRTVSS using CPRD as a way to complement existing methods, by allowing timely identification of signals for more frequent outcomes and by excluding large increases in risk for less frequent outcomes.

Ethics statement

All data were anonymised prior to receipt by the authors. Approval for the study was obtained from the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (ISAC number: 15_230) and from the Ethics Committee of the London School of Hygiene & Tropical Medicine (LSHTM reference: 10421). The procotol for the overall programme of work was made available for reviewers.

Author contributions

NA conceived the idea for the study. All authors contributed to the design of the study. AL analysed the data and wrote the first and final drafts of the manuscript, with input from NA and ST. All authors contributed to and approved the final manuscript.

Conflict of interest

The authors state no conflict of interest.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.09.022.

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7.2 Supporting information

As stated in Section 7.1, some of the supporting information of Paper 3 was previously presented in this thesis: for code-lists used to identify GBS and febrile seizures (Appendix A) see Section 5.4 and for the graphical representation of the adjustment for delays considered for PMaxSPRT and BMaxSPRT (Appendix D) see Chapter 6 (Figure 6.3 and Figure 6.7). The remaining appendices (B. Vaccinated individuals, C. Follow-up time, and E. Repeated febrile seizures episodes) are presented below.

7.2.1 Identification of vaccinated individuals (Appendix B)

As outlined in Sections 3.1.1.1 and 3.2, information regarding the vaccination of a patient is provided in different files within their electronic health records and it is not always consistent. It is thus necessary to create algorithms to identify vaccinated individuals. Section 3.2 presented the methods followed to develop these algorithms for seasonal influenza and for MMR vaccines. In this Section, I provide information on the resulting algorithm. For each vaccine, this included use of the relevant code-lists and how these were combined to ascertain vaccination status. The relevant code-lists included: (i) a list of Read codes indicating that influenza vaccine had been administered (designated as *Read codes indicating vaccination*); (ii) a list of codes indicating that the vaccine had not been administered (designated as *Read codes indicating the vaccine has not been given*), and (iii) a list of therapy codes indicating a prescription for the vaccine of interest (entitled *Therapy codes*). Lists (i) and (ii) were used to identify records in the clinical, referral, test, and immunisation files. List (iii) was used to search the therapy file. The immunisation file contains additional coded information on vaccines, comprising 'immunisation type' codes (indicating the type of vaccine) and 'immunisation status' codes (indicating vaccination status). I thus selected codes indicating that the record was related to the vaccine of interest (seasonal influenza or MMR, see *Codes in the immunisation file*), and the status codes that indicated that the vaccine was administered; the remaining immunisation status codes (advised or refused) did not provide evidence of vaccine administration.

7.2.1.1 Seasonal influenza vaccine

The lists drawn up for seasonal influenza vaccine are presented below, followed by the algorithm developed to identify individuals vaccinated against seasonal influenza.

7.2.1.1.1 Read codes indicating vaccination

Read code	Read term
65ED100	Administration of first intranasal seasonal influenza vacc
65EE.00	Administration of intranasal influenza vaccination
65ED000	Seasonal influenza vaccination given by pharmacist
ZV04800	[V]Influenza vaccination
65EE000	Administration of first intranasal influenza vaccination
65ED200	Seasonal influenza vaccination given while hospital inpt
65ED300	Administration of second intranasal seasonal influenza vacc
65EE100	Administration of second intranasal influenza vaccination
65ED.00	Seasonal influenza vaccination
65E2.00	Influenza vaccination given by other healthcare provider
65E..00	Influenza vaccination
ZV04811	[V]Flu - influenza vaccination
65E2000	Seasonal influenza vaccin given by other healthcare provider
65E2100	First intranasal seasonal flu vacc gvn by othr hlthcare prov
65E2200	Secnd intranasal seasonal flu vacc gvn by othr hlthcare prov

7.2.1.1.2 Read codes indicating the vaccine has not been given

Read code	Read term
9N4q100	DNA first intranasal seasonal influenza vaccination
8I2F000	Seasonal influenza vaccination contraindicated
14LJ.00	H/O: influenza vaccine allergy
9OX5600	Second intranasal seasonal influenza vaccination declined
9OX5400	First intranasal seasonal influenza vaccination declined
8I6D000	Seasonal influenza vaccination not indicated
9OX5.00	Influenza vaccination declined
9OX5300	Second intranasal influenza vaccination declined
9OX5200	First intranasal influenza vaccination declined
8I2F.00	Influenza vaccination contraindicated
68NE000	No consent for seasonal influenza vaccination
9OX5100	Seasonal influenza vaccination declined
ZV14F00	[V]Personal history of influenza vaccine allergy
8I6D.00	Influenza vaccination not indicated
9N4q.00	Did not attend flu vaccination appointment

7.2.1.1.3 Therapy codes

Product code	Product name
11824	Enzira vaccine suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)
1329	Fluvirin vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)
7951	FLUVIRIN AQUEOUS ML VAC

Product code	Product name
23251	FLUVIRIN PRE-FILLED SYRINGE
9710	Agrippal vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)
27407	Imuvac vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)
2552	Influvac Sub-unit vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)
57401	Influvac Desu vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)
51087	Optaflu vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)
2139	Fluarix vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)
57917	Fluarix Tetra vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)
43827	Intanza 9microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd)
43825	Intanza 15microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd)
47932	Fluenz vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)
57678	Fluenz vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)
398	Influenza inactivated split virion Vaccination (Aventis Pasteur MSD)
38421	Influenza inactivated split virion Vaccination (Evans Vaccines Ltd)
44759	INFLUENZA PRE-FILLED SYRINGE
40876	Influenza vaccine (split virion, inactivated) 9microgram strain suspension for injection 0.1ml pre-filled syringes
61580	Influenza vaccine (split virion, inactivated) suspension for injection 0.25ml pre-filled syringes
24779	Influenza inactivated split virion Paediatric vaccination
639	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes
61898	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (A A H Pharmaceuticals Ltd)
45661	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)
922	Influenza inactivated surface antigen Vaccination
48658	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd)
48740	Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes
51289	Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose
32391	Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)
30198	Influenza inactivated split virion Vaccination (sanofi pasteur MSD Ltd)
61792	Fluenz Tetra vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)
48085	Influenza inactivated split virion Vaccination (Chiron UK Ltd)
57140	Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose
40760	Influenza vaccine (split virion, inactivated) 15microgram strain suspension for injection 0.1ml pre-filled syringes
49716	Influenza vaccine (surface antigen, inactivated, virosome) suspension for injection 0.5ml pre-filled syringes
2601	Mfv-ject Vaccination (Aventis Pasteur MSD)

Product code	Product name
13595	Fluzone Vaccination (Aventis Pasteur MSD)
16585	Viroflu vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd)
10030	Inflexal V vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd)
834	Begrivac vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)
18612	Mastaflu vaccine suspension for injection 0.5ml pre-filled syringes (Masta Ltd)
30156	Invivac vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)
54677	Preflucel vaccine suspension for injection 0.5ml pre-filled syringes (Baxter Healthcare Ltd)
63690	Inflexal V suspension for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd)
65205	FluMist Quadrivalent vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)

7.2.1.1.4 Codes in the immunisation file

Immunisation type

Code	Description
4	FLU
84	FLUSOHP
85	FLUSPHARMA
89	FLUSIN
97	FLUSINOHP
100	FLUSIMOHP

Immunisation status

Code	Immunisation Status
1	Given
4	Refusal to start or complete course
9	Advised

7.2.1.1.5 Algorithm

Based on the lists above, I developed the algorithm presented in Figure 7.1. Priority was given to information on the immunisation file as this contains specific information on vaccines, followed by information from the therapy file, as the latter indicates a prescription was issued.

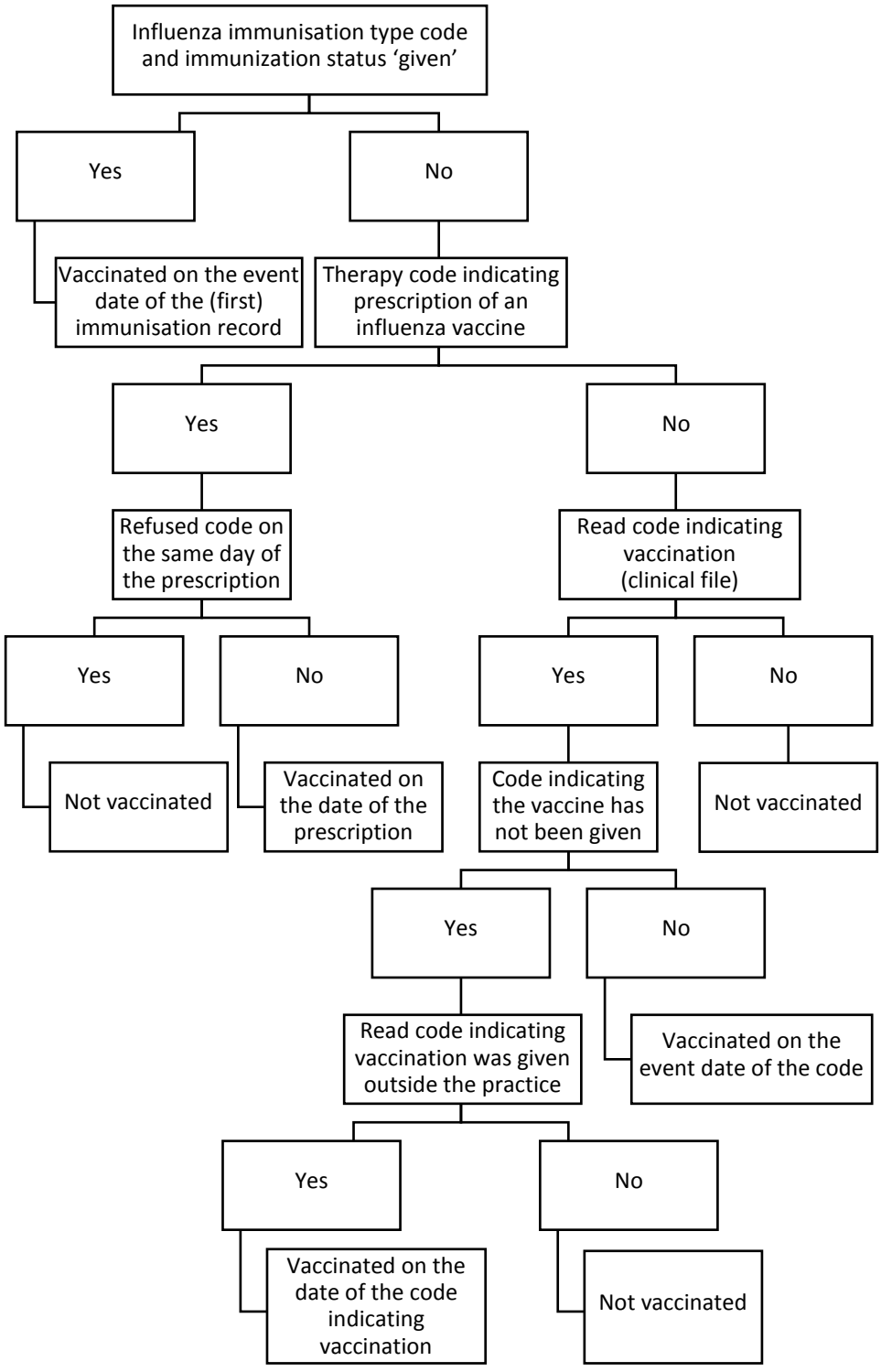

Figure 7.1. Algorithm utilised to identify individuals vaccinated against influenza vaccine.

7.2.1.2 Measles-Mumps-Rubella vaccine

MMR is a combined vaccine and thus for an individual to be considered vaccinated I required evidence that s(he) had received all the components of the vaccine. To assess this, each vaccine code included in the list that was developed was assigned as having one of more components of the vaccine. The components each specific code corresponds to are denoted in the list below as '1' in the respective column of the lists. When assessing specific information from the immunisation file, the component assessment was carried out by considering an additional variable in this file which indicates which compound of the vaccine had been administered. The code-lists and respective components are presented below, followed by the algorithm that was developed.

7.2.1.2.1 Read codes indicating vaccination

Read code	Readterm	MMR	measles	mumps	rubella
ZV04200	[V]Measles vaccination		1		
ZV06400	[V]Measles-mumps-rubella (MMR) vaccination	1			
ZV04600	[V]Mumps vaccination			1	
ZV04300	[V]Rubella vaccination				1
U60K014	[X] Adverse reaction to measles vaccine		1		
U60K016	[X] Adverse reaction to mumps vaccine			1	
U60K017	[X] Adverse reaction to rubella vaccine				1
TJK4.00	Adverse reaction to measles vaccine		1		
TJK6000	Adverse reaction to mumps vaccine			1	
TJK6100	Adverse reaction to rubella vaccine				1
65B..11	German measles vaccination				1
65MA.00	Measles mumps and rubella booster vaccination	1			
9ki1.11	Measles mumps rubella catch-up vaccination	1			
65A2.00	Measles vaccin.+immunoglobulin		1		
65A..00	Measles vaccination		1		
65A1.00	Measles vaccination		1		
SLK4.00	Measles vaccine poisoning		1		
65M1.00	Measles/mumps/rubella vaccn.	1			
65M2.00	Measles/rubella vaccination		1		1
65MB.00	MMR pre-school booster vaccination	1			
65MC.00	MMR vaccination - 2nd dose	1			
65M2.11	MR - Measles/rubella vaccination		1		1
65F5.00	Mumps vaccination			1	
SLK6000	Mumps vaccine poisoning			1	
F034C00	Post measles vaccination encephalitis		1		
F034E00	Post mumps vaccination encephalitis			1	
F034F00	Post rubella vaccination encephalitis				1
65B..00	Rubella vaccination				1

7.2.1.2.2 Therapy codes

Product code	productname	MMR	measles	mumps	rubella
18912	Immravax Vaccination (Aventis Pasteur MSD)	1			
12711	Measles live Vaccination		1		
18172	Measles, Mumps and Rubella vaccine (live) powder and solvent for solution for injection 0.5ml vials	1			
20845	Measles, Mumps and Rubella vaccine (live) powder and solvent for suspension for injection 0.5ml pre-filled syringes	1			
4189	MEASLES SCHWARZ STRAIN VAC		1		
9089	MEASLES EDMONSTON STRAIN VAC		1		
25157	Mumpsvax Vaccination (Aventis Pasteur MSD)			1	
4190	Mumps Vaccination			1	
11016	MUMPSVAX ML VAC			1	
2244	Rubella Vaccine				1
49697	Rubella vaccine powder and solvent for solution for injection 0.5ml vials				1
10348	Almevax rubella Vaccination (Celltech Pharma Europe Ltd)				1
12005	Attenuvax Vaccination (MSD Thomas Morson Pharmaceuticals)		1		
11714	Priorix vaccine powder and solvent for solution for injection 0.5ml vials (GlaxoSmithKline UK Ltd)	1			
15473	Mevillin-l Vaccination (Manufacturer unknown)		1		
38476	M-M-RVAXPRO vaccine powder and solvent for suspension for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd)	1			
10333	Pluserix Vaccination (GlaxoSmithKline Consumer Healthcare)	1			
3906	M-M-R II vaccine powder and solvent for solution for injection 0.5ml vials (sanofi pasteur MSD Ltd)	1			
30506	Meruvax ii Vaccination (MSD Thomas Morson Pharmaceuticals)				1
10335	Rubavax Vaccination (Aventis Pasteur MSD)				1
3468	Ervevax vaccine powder and solvent for solution for injection 0.5ml vials (GlaxoSmithKline UK Ltd)				1

7.2.1.2.3 Read Codes indicating the vaccine has not been given

Read code	Read term
9ki0.11	Did not attend for MMR catch-up vaccination
9N4z000	Did not attend measles mumps and rubella vaccination
9N4z400	Did not attend second measles mumps and rubella vaccination
9N4c.00	DNA - DTaP, polio and MMR booster

Read code	Read term
9ki0.00	DNA MMR catch-up vaccination - ESA
9ki2.00	MMR catch-up vacc declind - enhanced services administration
68NT.00	MMR not given
8I3x.00	MMR vaccination declined
68NI.11	MMR vaccine contra-indicated.
68NB.00	No consent - measles imm.
68NC.00	No consent - rubella imm.
68NM.00	No consent for MMR
68Na.00	No consent for MMR1
68Nb.00	No consent for MMR2
68NY.00	No consent for MR - Measles/rubella vaccine

7.2.1.2.4 Codes in the immunisation file

Code	Immunisation Type	MMR	measles	mumps	rubella
7	MEASLES		1		
8	RUBELLA				1
9	MUMPS			1	
50	MR		1		1
51	MMR	1			

7.2.1.2.5 Algorithm

Based on the lists above, I developed the algorithm presented in Figure 7.2.

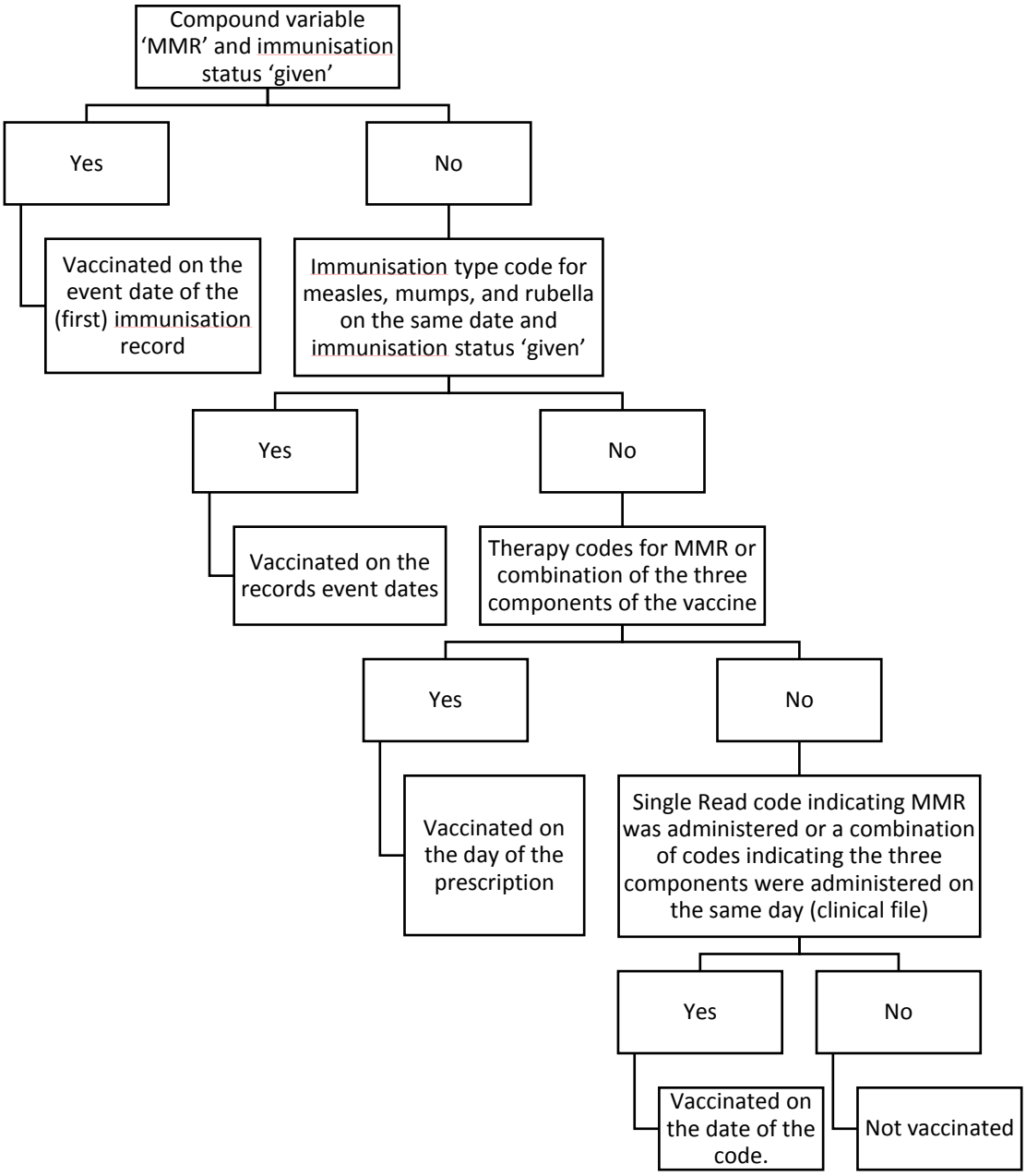

Figure 7.2. Algorithm used to identify children vaccinated with measles-mumps-rubella vaccine (MMR).

7.2.2 Follow-up time (Appendix C)

Figure 7.3 summaries the follow-up time included to calculate the historical GBS rate (the background rate) and the follow-up time during the study period. When calculating the GBS rate for each of the historical seasons, all active patients aged 65 years or older were included. Their follow-up time started at the latest of the practice's up-to-standard date, the patient's current registration date plus one year and 1st September of each season. The follow-up ended at the earliest of the last collection date from the practice, the date the patient transferred out of the practice or died, and 31st March of each season. For the seasons under study (2013/14 and 2014/15), only individuals aged 65 years or older who had received an influenza vaccine were included. For these individuals, follow-up began at the latest of the practice up-to-standard date, the patient's current registration date plus one year, 1st September of each season and the date of vaccination. Follow-up terminated at the earliest of the last collection date from the practice, the date the patient transferred out of the practice or died, 31st March of each season, and the end of the risk-window (42 days in the case of GBS).

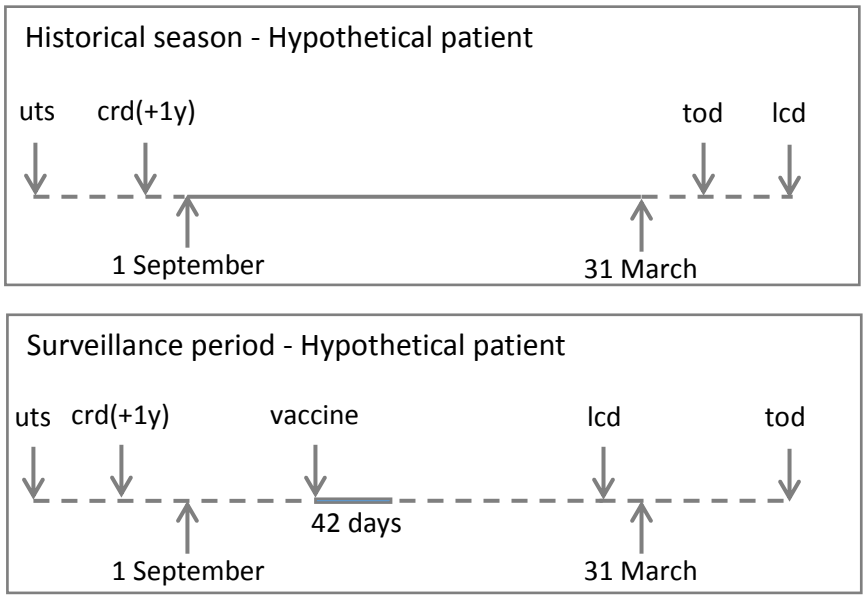

Figure 7.3. Included follow-up time for hypothetical patients for historical influenza vaccination seasons, used to calculate background rates (top) and for the surveillance period (bottom). Dashed lines indicate time not considered for the current analysis, the solid line indicate the follow-up time considered. uts – Date at which practice reached research-level quality, crd – current registration date of the patient with the practice, tod – date the patient transferred out of the practice, lcd – last data collection date (for the practice).

7.2.3 Repeated consultations for febrile seizures (Appendix E)

7.2.3.1 Methods

After an initial febrile seizure episode, GPs may ask parents to come back in a few days to reassess the child and the GP may then code the second consultation as a febrile seizure. Counting all the seizure-coded consultations would thus overestimate the incidence of seizures. To avoid this, I first investigated which records were likely to refer to the same episode, so that non-incident consultations could be excluded. I looked at the cumulative distribution of the time difference between subsequent records. For this initial step, an extra month at the beginning and end of the historical period was included to ensure inclusion of consultations starting before and finishing after the first and final eligible consultations.

7.2.3.2 Results

During the historical period studied for this analysis (June 2009 - July 2014) I identified 3,263 children with at least one seizure recorded, with a total of 4,084 seizure records. Among those children, 2,309 had a single seizure recorded and 954 had two or more seizures recorded within the study period; the maximum number of seizure records per child was 14. The difference between two adjacent seizure records had a median of 13 days (Q_1-Q_3:1-68 days) and the cumulative distribution is depicted in Figure 7.4. A steep gradient was observed in the few days following an initial seizure-coded consultation, after which the steepness decreased and was constant until approximately 100 days after the initial consultation. Looking at consultations occurring only 30 days after a previous record (Figure 7.5) we can see that the steep line occurs within three days of a previous record. This indicates that records registered within three days of a previous record refer to the same seizure rather than to a different occurrence of seizures. I thus decided to exclude any record within three days of a previous one, which resulted in the exclusion of 447 seizure-coded consultations. After exclusion, differences between remaining records were recalculated and no remaining records had a difference of three or less days.

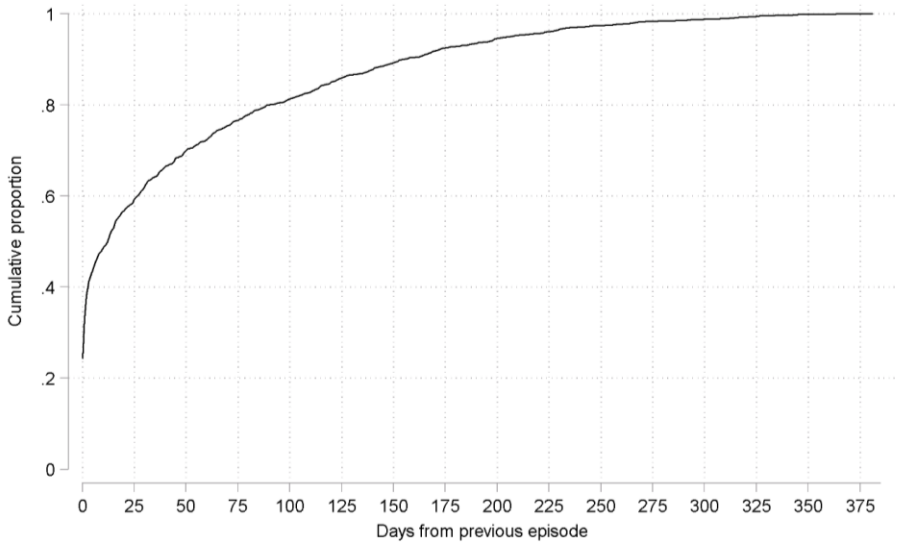

Figure 7.4. Cumulative distribution of the time difference for two subsequent records of seizures within the same patient.

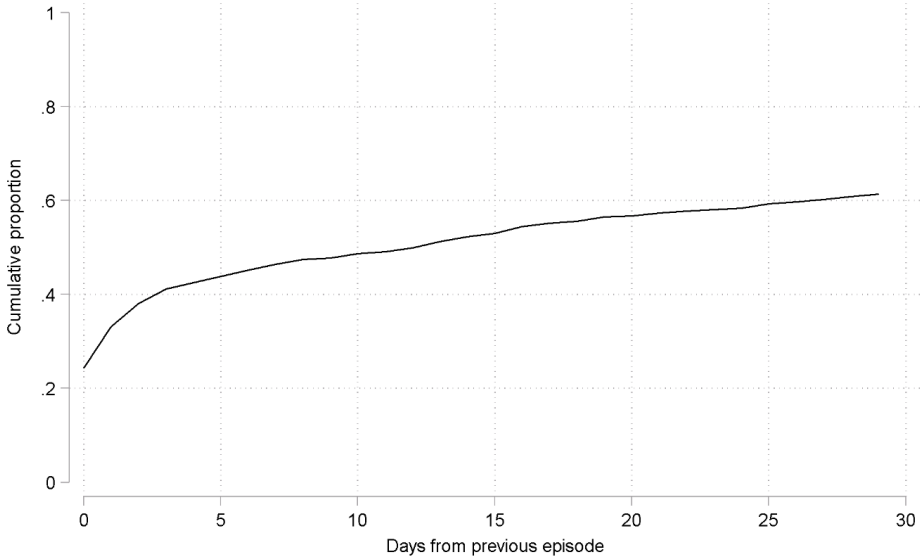

Figure 7.5. Cumulative distribution of the time difference for two subsequent records of seizures within the same patient considering differences of 30 days or less

7.3 Variable matching ratios

As outlined in Section 7.1, I investigated the use of BMaxSPRT to assess febrile seizures following MMR vaccine. In this particular example, I used matching ratios as a way to account for delays in recording outcomes and receiving data, as well as partially accrued periods. In this Section I provide further information on the matching ratios obtained as part of the analyses, together with information on the use of variable (as opposed to fixed) matching ratios.

The calculation of matching ratios was presented in Figure 6.7 and explained in detail in Section 6.3.2. In brief, these ratios were calculated as the quotient of the number of days in the control period to the number of days in the risk period. The number of days considered in the ratio was adjusted for delays in recording outcomes, using the delay distribution presented in Section 5.3. This was calculated for all the children included at each data release. Table 7.1 provides the matching ratios obtained and used to generate the test statistics provided in Figure 3 from Section 7.1. Overall, the matching ratios are lower at the beginning and get closer to one as surveillance progresses. This can be explained by the fact that as time passes, data have had more time to accrue and therefore we have data from both the control and risk periods for the individuals identified in the early releases. Hence, this adjustment is more relevant early in the surveillance period.

Table 7.1. Matching ratios used to adjust for delays and partially accrued periods in the binomial-based maximized probability ratio test

Release number	Ratio unexposed to exposed
1	0.84
2	0.81
3	0.91
4	0.94
5	0.95
6	0.96
7	0.98
8	0.97
9	0.98
10	0.98
11	0.98
12	0.98

The matching ratios obtained by this approach are variable which meant that the log-likelihood ratio (LLR_n), as presented in Section 3.3.2 and reproduced below, could not be used. As a reminder, the observed number of events at a given moment is denoted as n (exposed plus unexposed), c_n denotes the number of events among the exposed at a given point and z the matching ratio.

$$LLR_n = \ln(LR_n)$$
$$= c_n ln\left(\frac{c_n}{n}\right) + (n - c_n)\ln\left(\frac{n - c_n}{n}\right) - c_n \ln\left(\frac{1}{z+1}\right) - (n - c_n)\ln\left(\frac{z}{z+1}\right)$$

The use of this formula assuming several different matching ratios (z_n) would result in the estimation of different RR. In the package Sequential.[99] Kulldorff and Silva addressed this issue by using an alternative formula to estimate the log-likelihood (Ivair Silva, personal communication). For n tests, all with different matching ratios, the log-likelihood to estimate RR would be:

$$LLR(RR) \propto c_1 ln\frac{RR}{RR+z_1} - (n_1 - c_1) l\, n(RR + z_1) + \ldots + c_n ln\frac{RR}{RR+z_n} - (n_n - x_n) l\, n(RR + z_n)$$

This formula incorporates the assumption of a single RR thus allowing the use of variable matching ratios. This is the log-likelihood implemented in the function used to implement the system (*Analyze.Binomial*, see Section 3.4). Work by Silva showed that violating the assumption of constant ratios still gives accurate results.[161] Nevertheless, the extent of variability in the matching ratios that can be assumed as constant remains unknown. As a general message, I would recommend researchers to reflect on the need to using matching ratios (variable or fixed) and then decide on the most appropriate method to estimate the log-likelihood. In any case, the use of both approaches is straightforward as they can be implemented easily using the functions in R.

7.4 Influence of delays in the performance of a system (Paper 4)

This paper was accepted for publication in Pharmacoepidemiology and Drug Safety in October 2017. It reports the work conducted to assess the influence of delays in the performance of a near real-time system.

When I implemented a system using CPRD data the results showed that implementation is feasible but there was limited power to detect an increased risk of GBS following seasonal influenza vaccine (power ≥ 80% to detect a RR of four or more). Given that existing delays in receiving data and recording outcomes can affect the amount of data available, thus reducing power, I assessed how these sources of delays influence power and the expected time to signal. I utilised the same data and study period used to implement a system for seasonal influenza vaccine/Guillain-Barre Syndrome (GBS) (2013-2014/2014-2015 seasons, see Section 7.1). I used PMaxSPRT and calculated power and time to detect a signal, under different combinations of the presence/absence of delays in recording outcomes and in receiving data. For each combination, calculations were performed for a range of RRs (1.5-10).

The results showed there was power of 80% or more to detect a four-fold increase in risk of GBS. Removing delays did not substantially improved power (a maximum increase of 4% in the absence of delays) or timeliness. Therefore, removing delays in CPRD will not significantly improve the performance of a near real-time system; expansion of the data is required.

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SECTION A – Student Details

Student	Andreia Leite
Principal Supervisor	Prof Sara Thomas
Thesis Title	Near real-time vaccine safety surveillance using United Kingdom electronic health records

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?	Pharmacoepidemiology and Drug Safety		
When was the work published?	Accepted for publication		
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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)	I designed the study with detailed advice from Prof. S Thomas and Prof. N Andrews. I analysed the data following discussion with both co-authors. I drafted the initial manuscript and made changes according to comments from Prof. S Thomas and Prof. N Andrews. I incorporated suggestions from peer-reviewers, after discussion with Prof. S

	Thomas and Prof. N Andrews.

Student Signature: [redacted] **Date:** 05/10/17

Supervisor Signature: [redacted] **Date:** 05/10/17

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WILEY

BRIEF REPORT

Do delays in data availability limit the implementation of near real-time vaccine safety surveillance using the Clinical Practice Research Datalink?

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Abstract

Purpose: Near real-time vaccine safety surveillance (NRTVSS) using electronic health records has been used to detect timely vaccine safety signals. Trial implementation of NRTVSS using the Clinical Practice Research Datalink (CPRD) has shown that there is limited power to detect safety signals for rare events. Delays in recording outcomes and receiving data influence the power and timeliness to identify a signal. Our work aimed to compare how different sources of delays influence power and expected time to signal to implement NRTVSS using CPRD.

Methods: We studied seasonal influenza vaccine/Guillain-Barré syndrome and performed power and expected time to signal calculations for the 2013-2014/2014-2015 seasons. We used the Poisson-based maximised sequential probability ratio test, which compares observed-to-expected events. For each study season, we obtained an average Guillain-Barré syndrome/seizures age-sex–adjusted rate from the 5 previous seasons and then used this rate to calculate the expected number of events, assuming a 42-day risk-window. Calculations were performed for detecting rate ratios of 1.5 to 10. We compared power and timeliness considering combinations of the presence/absence of delays in recording outcomes and in receiving data. The R-package Sequential was used.

Results: In general, there was ≥80% power to detect increases in risk of ≥4 at the end of the season. Assuming absence of delays slightly improved power (a maximum increase of 4%) but did not noticeably reduce time to detect a signal.

Conclusion: Removing delays in data availability is insufficient to significantly improve the performance of a NRTVSS system using CPRD. Expansion of CPRD data is required.

KEYWORDS

delay, electronic health records, pharmacoepidemiology, power, safety, surveillance, vaccines

1 | INTRODUCTION

Near real-time vaccine safety surveillance (NRTVSS) is an option in the post-licensure vaccine safety toolkit. Near real-time vaccine safety surveillance is usually initiated soon after a new vaccine is introduced, and data from electronic heath records are examined at regular points in time. This helps with timely detection of safety signals.[1]

Near real-time vaccine safety surveillance has not been fully implemented in the UK, but our recent study trialling NRTVSS implementation using data from the Clinical Practice Research Datalink (CPRD) showed it is possible to implement a system.[2] Nevertheless,

This work has not been submitted or accepted elsewhere. Preliminary results have been presented at the 2017 International Society for Pharmacoepidemiology mid-year meeting, London, April, 2017.

system performance (including power and expected time to signal) to identify a rare outcome (Guillain-Barré syndrome, GBS) following seasonal influenza was not optimal. In particular, using the most powerful test (Poisson-based maximised probability ratio test, PMaxSPRT), there was power of ≥80% to identify a fourfold increase in risk, and a signal would be detected 3 months after the start of surveillance. It is thus important to understand what factors affect power and expected time to signal and what changes to currently available data might improve the ability to identify signals rapidly using CPRD.

If PMaxSPRT is used, the expected number of events at the end of the surveillance period dictates power and expected time to signal. The expected number of events is a function of the data available, depending on both the number of individuals contributing data (the volume of data) and on delays in data availability. Clinical Practice Research Datalink is a primary care database, and the volume of data is determined by the number of practices and patients contributing data. Delays can occur in (i) identifying a condition after the initial consultation, (ii) recording a condition diagnosed outside the practice (e.g. in hospital), (iii) practices uploading their data to CPRD, and (iv) researchers receiving data for analysis. Previous work assessing delays due to (ii) showed that, for selected conditions of interest regarding vaccine safety, records accrue within a month of the deemed date of diagnosis.[3] Regarding (iii) and (iv), CPRD data are made available to researchers monthly and practices upload data prior to this, with the last collection date from each practice recorded in CPRD.

Clinical Practice Research Datalink is a dynamic database, and new practices may start contributing data. Additionally, changes to the mode of data collection from practices and frequency of data releases could reduce delays. Both expansion and reduction of delays could improve NRTVSS system performance. We sought to assess how delays influenced power and expected time to signal, to inform data providers on how decreasing delays could improve performance of a NRTVSS system. As a secondary objective, we further assessed the performance of a system based on data available around the middle of the surveillance period for a short vaccine programme of fixed length, to understand what could be detected at a time when it would still be possible to implement measures to minimise risks.

2 | METHODS

We used data from our previous study that evaluated the feasibility of implementing a NRTVSS system. Here, we provide a brief summary of the methods used to obtain those data (for further information see Leite et al[2]). Additionally, we explain how we assessed the influence of delays on power and expected time to signal, the main focus of this report.

2.1 | Data source

We used CPRD, a UK database containing anonymised primary care records from individuals registered with participating practices (6.9% of the population). Information is Read-coded, including demographics, diagnoses, therapies, vaccinations, health-related behaviours, and referrals to and feedback from hospital.[4] Clinical Practice Research Datalink also contains information of when a patient joined and left a practice (current registration date and transfer out date, respectively), when a practice met certain requirements necessary for it to be considered of research quality (up-to-standard) and when information was last collected from each practice (last collection date, available in each monthly update).[4]

KEY POINTS

- The Clinical Practice Research Datalink (CPRD) can be used to implement near real-time vaccine safety surveillance, but there is limited power to detect signals for rare outcomes.
- Delays in recording outcomes and in receiving data might limit power and timeliness of a system. We assessed the influence of these sources of delays to inform data providers of the steps required to improve a system using CPRD data.
- Removing delays in recording outcomes and receiving data is unlikely to significantly improve the performance of a system using CPRD data. Expansion of the data available is needed.

2.2 | Vaccine/outcome pairs and study period

Our original study evaluated seasonal influenza vaccine/GBS and mumps-measles-rubella vaccine/seizures. As there was sufficient power to detect a twofold increase in risk for mumps-measles-rubella vaccine/seizures, we considered the performance of the system for this pair was satisfactory. We thus only assessed the influence of delays for seasonal influenza/GBS. We included individuals aged ≥65 years and studied seasons 2013/2014 and 2014/2015, using data released in July 2015 and 2016, respectively.

2.3 | Analysis

We used continuous PMaxSPRT as it is the most powerful test, and CPRD provides data in a near-continuous fashion (monthly).[5] The number of expected events was obtained based on the average GBS age-sex–specific rate from the 5 seasons prior to the study seasons (2008-2013 and 2009-2014), considering a 42-day post-vaccination risk-window.

We applied the historical rates to the follow-up time in the study periods to obtain the expected number of events. Start of follow-up time was the latest of the up-to-standard date, current registration date (plus 1 year to exclude retrospective recording of events when registering with a new practice[6]), the beginning of the study period, and the start of the risk-window. End of follow-up was the earliest of the patient's transfer out date, the practice's last collection date, end of the study period, or end of the risk-window.

The number of expected events was calculated in slightly different ways, to consider different delay scenarios (see below). Based on these numbers, we calculated power and expected time to signal (performance measures), assuming a range of plausible rate ratios (1.5-10),

TABLE 1 Combination of delays assessed under each scenario

Scenario—Source of Delays	Delays		End of Surveillance	Comments
	Recording	Receiving		
Recording/receiving (reference)	+	+	April data release (end of season)	Corresponds to the way NRTVSS was implemented using CPRD data. Reference scenario
1. None	−	−	April data release (end of season)	Ideal scenario; events are recorded as they happen and data are available immediately
2. Recording	+	−	April data release (end of study period)	Mimics a situation where CPRD receives data on a daily basis and makes it available straight away
3. Recording/receiving	+	+	December data release	Corresponds to the reference scenario but considering data available until December

Abbreviations: CPRD, Clinical Practice Research Datalink; NRTVSS, near real-time vaccine safety surveillance.

a level of significance of 5%, and stipulating a minimum of 1, 2, or 4 events before raising a signal. Calculations were performed using the R package Sequential.[7]

We assessed the influence of delays on system performance by calculating follow-up time (hence, the expected number of events) assuming the system had different combinations of presence/absence of delays in recording outcomes and in receiving data. Additionally, we looked at performance measures assuming analyses ended at the mid-season (December release). Ending surveillance earlier might increase power as less sequential tests are performed, but the number of expected events is likely to be lower (due to less data available), thus reducing power. The delay scenarios assessed are presented in Table 1. The scenario considering both sources of delays was used as a reference, as this corresponded to what we did for the test implementation.[2]

For delays in recording outcomes, we considered the follow-up time for the patients as explained above (absence of delays) and then adjusted this follow-up time to account for delays, by reducing the expected number of events based on the historical delays' distribution (presence of delays).

For delays in receiving data, we included all data available for the study period regardless of when these data were received (absence of delays) and then included only data received by the end of the surveillance period (presence of delays). We identified data received by the end of surveillance by using the last collection date in that data release. For the reference scenario, we considered the last collection dates available in the April 2014 and April 2015 releases for season 2013/2014 and 2014/2015, respectively. Similarly, we used the last collection dates available in the December releases (2013 and 2014 for season 2013/2014 and 2014/2015, respectively) when assessing performance at the mid-season (scenario 3).

3 | RESULTS

Table 2 presents the results of our calculations. In general, there was ≥80% power to detect increases in risk of ≥4 at the end of the season. Removing sources of delays improved power by 1% to 4% and would allow detection of a signal at the same release of the implementation scenario. Stopping surveillance around mid-season (scenario 3) resulted in substantial reductions in power, particularly to detect medium (3-6 fold) increases in risk. For this scenario, there was ≥80% power to detect an increase in risk of 8 to 10. If there was a signal, this would be detected by early December.

4 | DISCUSSION

We analysed the impact of delays in data availability on NRTVSS implementation using CPRD as a way to inform data providers about measures that could improve performance of a NRTVSS system. Our results showed that delays affect power, but only slightly. There were almost no differences observed in the expected time to signal, even when there were improvements in power. Removing delays would thus be insufficient to improve the performance of a system using CPRD data, as the main limiting factor is the volume of data available.

The small differences between each scenario are probably related to the performance measures being calculated on the basis of expected events at the end of the surveillance period. Most individuals are vaccinated at the beginning of the season, and by its end, data have had enough time to accrue. This applies to both sources of delays.

Assessment of the performance at mid-season revealed that we would be able to detect only very large increases in risk at the beginning of December. This raises the issue of timeliness, as by then most individuals would have been vaccinated and any intervention might have limited reach.

Clinical Practice Research Datalink currently collects data from practices using VISION software, but it is expanding to include practices using EMIS software.[8] Presently, there are data from 4.4 million active patients. Initial analysis of EMIS practices indicates an additional 2.6 million active patients (Rachel Williams, personal communication). Assuming this would translate to a similar number of expected events, the new data would amount to approximately 3 expected events, which would be sufficient to detect increases of threefold or more in the risk of GBS following seasonal influenza vaccination. This might not be enough to detect small increases in risk, particularly for rare events. Furthermore, including data from practices using a different software may pose new challenges. For example, the adjustment for delays we proposed is based on the delay distribution observed using data from VISION practices, and it might not be applicable for EMIS practices.[3] Including EMIS practices in a NRTVSS will thus require additional exploration of these data.

In our work, we considered a power of ≥80% as a satisfactory performance. However, GBS can be a severe condition, and when implementing a system, it may be necessary to require higher power level to detect more serious conditions (such as 90%). For existing CPRD data, requirement of 90% power would mean that we could only accurately identify increases in risk ≥5.

TABLE 2 Expected number of events, power, and expected time to signal under different combination of delays

Minimum events	RR	Delay Scenario			
		Reference	Scenario 1	Scenario 2	Scenario 3
Season 2013-2014					
Expected number of events					
—	—	1.89	2.09	1.94	0.62
Power (expected time to signal in terms of data release)					
1	**1.5**	13	13	13	10
	2	25	26	25	16
	2.5	40	42	40	22
	3	55 (J)	58 (J)	55 (J)	30
	4	78 (J)	81 (J)	79 (J)	44
	5	91 (D)	93 (J)	92 (D)	58 (D)
	6	97 (D)	98 (D)	97 (D)	69 (D)
	8	100 (D)	100 (D)	100 (D)	85 (D)
	10	100 (D)	100 (D)	100 (D)	93 (D)
2	**1.5**	14	15	15	11
	2	28	30	29	18
	2.5	44	46	45	27
	3	60 (J)	62 (J)	61 (J)	35
	4	82 (J)	84 (J)	83 (J)	52 (D)
	5	93 (D)	95 (D)	94 (D)	65 (D)
	6	98 (D)	98 (D)	98 (D)	76 (D)
	8	100 (D)	100 (D)	100 (D)	89 (D)
	10	100 (D)	100 (D)	100 (D)	96 (D)
4	**1.5**	16	17	16	
	2	33	34	33	
	2.5	50 (J)	52 (J)	50 (J)	
	3	65 (J)	68 (J)	66 (J)	
	4	86 (J)	88 (J)	86 (J)	[a]
	5	95 (J)	96 (J)	95 (J)	
	6	98 (J)	99 (J)	99 (J)	
	8	100 (D)	100 (D)	100 (D)	
	10	100 (D)	100 (D)	100 (D)	
Season 2014-2015					
Expected number of events					
—	—	1.66	1.84	1.69	0.38
Power (expected time to signal in terms of data release)					
1	**1.5**	12	13	12	9
	2	23	25	24	13
	2.5	37	40	37	18
	3	51 (J)	55 (J)	52 (J)	23
	4	74 (J)	78 (J)	75 (J)	34
	5	88 (J)	91 (J)	89 (J)	44
	6	95 (J)	97 (J)	96 (J)	54 (D)
	8	99 (D)	100 (D)	100 (D)	70 (D)
	10	100 (D)	100 (D)	100 (D)	81 (D)
2	**1.5**	14	14	14	10
	2	26	28	26	16
	2.5	41	43	41	22
	3	55 (J)	59 (J)	56 (J)	29
	4	77 (J)	81 (J)	78 (J)	42
	5	90 (J)	93 (J)	91 (J)	53 (D)
	6	96 (J)	98 (J)	96 (J)	63 (D)
	8	100 (D)	100 (D)	100 (D)	78 (D)
	10	100 (D)	100 (D)	100 (D)	87 (D)
4	**1.5**	16	16	16	
	2	31	33	31	
	2.5	47	50 (J)	48	
	3	62 (J)	65 (J)	63 (J)	
	4	83 (J)	86 (J)	84 (J)	[a]
	5	93 (J)	95 (J)	94 (J)	
	6	98 (J)	98 (J)	98 (J)	
	8	100 (J)	100 (J)	100 (J)	
	10	100 (J)	100 (J)	100 (J)	

Abbreviations: D, December; J, January; RR, rate ratio.

[a]Number of expected events is too small to calculate performance measures.

Our work is subject to some limitations. Our adjustment for recording delays was based on a simplification of the data accrual process and on a historical distribution of delays. Nevertheless, previous work has shown constant recording delay patterns during a 10-year period, which is reassuring.[3] Furthermore, while absence of delays in recording and receiving data is the ideal scenario, it is unlikely that delays in recording can be changed as result of direct action by data providers. Finally, this work is based on a single vaccine/outcome pair. Nevertheless, results for other vaccine/outcome pairs are likely to be similar to the ones observed for seasonal influenza/GBS. The reason for this is twofold: first and as explained above, the lack of improvement in the system's performance is probably related to the fact that the performance is assessed at the end of the surveillance period (when most of the data have already accrued); second, delays in receiving data are fixed and similar for all outcomes. Regarding delays in recording outcomes, GBS is likely to have longer delays than other conditions due to prolonged hospitalisation. Therefore, removing delays in recording these other outcomes would result in even less improvement on power.

In conclusion, minimising delays in data availability are unlikely to substantially improve the performance of a system using CPRD data. Expansion of the data is required.

ETHICS STATEMENT

All data were anonymised prior to receipt by the authors. Approval for the study was obtained from the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (ISAC number: 15_230) and from the Ethics Committee of the London School of Hygiene and Tropical Medicine (LSHTM reference: 10421). The protocol for the overall programme of work was made available for reviewers.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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7.5 Conclusions

This Chapter reports the main work conducted to achieve the overarching aim of this thesis: assessing the feasibility of implementing a near real-time system using CPRD data. Together with the results presented in the remaining Chapters, the trial implementation showed that CPRD can be used to implement such a system but with limited power to identify small increases in the risk of GBS following seasonal influenza. Therefore, I complemented the implementation work by assessing how limitations in power to detect a signal could be addressed. This latter work showed that to improve the performance of the system expansion of the data is needed. The information contained in this Chapter can thus be used by those wishing to implement a system as well as by data providers as a means to guide their policy regarding data availability and expansion.

The next Chapter presents an overall discussion of the work conducted as part of this thesis, together with its main conclusions.

8 DISCUSSION

In this thesis I have sought to assess the feasibility of implementing near real-time vaccine safety surveillance using CPRD data through four main objectives (2.4.2): to review the methods currently used to perform NRTVSS using electronic health records (Chapter 4); to examine recording delays in CPRD for selected conditions, due to practices receiving and recording diagnosis made at secondary care (Chapter 5); to trial the implementation of NRTVSS using previously collected CPRD data (Chapter 7); and to assess how delays in recording outcomes and receiving data influence the power and time to detect a safety signal (Chapter 7). This chapter provides a review of the main findings, discusses the main strengths and limitations of the overall project, and points out implications for both research and practice.

8.1 Summary of the main findings

8.1.1 Methods currently under use to perform NRTVSS

8.1.1.1 What was known

In 2005, the Vaccine Safety Datalink in the USA proposed the use of a sequential test, SPRT, as a way to generate quickly vaccine safety signals.[7] It was later shown that the use of SPRT was challenging because it requires the probability/RR of the adverse event to be selected in advance: if the RR/probability specified is too high, the test may not lead to rejection of the null hypothesis (even if there is an increased risk); conversely, the selection of an unduly low RR/probability may result in a delayed signal.[96] A maximized version of the test was then proposed (MaxSPRT), with a composite alternative hypothesis; it is available based on two distributions for events, Poisson (PMaxSPRT) and binomial (BMaxSPRT).[96] Further tests have been developed to address other limitations identified while using MaxSPRT. For example, PMaxSPRT requires a reliable estimate of the expected number of events using sufficient past data whereas the conditional version (CMaxSPRT) was developed for use when these estimates are based on few data.[162] Group sequential tests were also applied in this context.[163] Near-real time vaccine safety surveillance is conducted routinely in the USA[9] but there was limited information on its use elsewhere. Previous publications reviewed the use of these methods but focused on the statistical aspects of existing tests[8,164] and on the work conducted by VSD.[9]

8.1.1.2 What this study adds

This study identified several methods to perform NRTVSS using electronic health records and the way these have been applied. It identified 31 systems in 2015 when it was first conducted and 2 additional studies in 2017 at the time of its update. The review showed that NRTVSS has been increasingly used in the USA but also in a few other places, such as the UK, Taiwan and New Zealand. The main vaccine that had been assessed is influenza vaccine (both seasonal and pandemic). The systems identified used three main groups of statistical tests: continuous sequential tests, which allow testing as often as desired; group sequential tests, where testing is conducted at discrete points in time; and statistical process control, which uses a graphical representation to compare the number of observed events to an expected mean plus a number of standard deviations. The most common tests were the Poisson-based maximized sequential probability ratio test (PMaxSPRT, used by 44% of the systems identified) and its binomial version (BMaxSPRT, used by 24%). The test selected for use in the studies depended on the frequency of data updates and the adverse event of interest. Only 75% of studies addressed confounding, mainly by adjusting the expected rate (carried out by 51% of studies that adjusted). Delays in data availability were considered in some studies, either by delaying the analysis or adjusting for delays and partially accrued periods. Overall, this review provided a broad overview of existing studies (including both VSD and non-VSD studies) and from a more applied perspective than the previously published literature on the topic. It summarised the main characteristics of systems performing NRTVSS. Therefore, it can be used to inform those wishing to implement similar systems.

8.1.2 Recording delays

8.1.2.1 What was known

When considering a new data source to implement a near real-time vaccine safety surveillance system it is necessary to know what type of delays these data are subject to. In the case of CPRD data, delays occur for a variety of reasons: (i) delays in physicians making a diagnosis following an initial consultation; (ii) delays in recording outcomes diagnosed in other levels of care (e.g. hospital); (iii) delays in practices uploading data to CPRD; and (iv) delays in researchers receiving uploaded data for analysis (from CPRD). Previous studies using NRTVSS considered delays either by postponing the analysis or by adjusting the number of expected events. This adjustment only considered delays in receiving data for analysis (corresponding to reasons (iii) and (iv)) and was based on a historical distribution of delays.[113] CPRD data are made available on a monthly basis and there is information (the last collection

date) on when practices last uploaded their data. A previous study using THIN, a related primary care data source, examined the number of records lost as function of the last collection date (delays due to reason (iii)), to inform incidence/prevalence studies. This study showed that not accounting for delays in uploading data results in underestimation of incidence/prevalence.[88] There was no known work assessing delays due to other reasons (reasons (i) and (ii)). Furthermore, there was no known work using the system date (the date when a record is entered in the GP system) to assess delays.

Several outcomes of interest for vaccine safety are diagnosed mainly in secondary care (e.g. GBS) and may not be fully captured in CPRD. This can happen if GPs only scan the hospital letters without adding a diagnostic code to the patient's record. Previous studies have shown that the use of CPRD linked data improves the sensitivity of diagnosis[86,165] but existing linkages with hospital data are updated too infrequently to allow the use of these data in a NRTVSS. I was not aware of previous studies evaluating the completeness of recording diagnoses of interest for vaccine safety and made mainly in secondary care (e.g. GBS). This information is relevant to understand the extent to which diagnoses are not captured in CPRD.

8.1.2.2 What this study adds

This study included a comprehensive analysis of recording delays in CPRD for selected conditions of interest for vaccine safety surveillance (GBS, Bell's palsy, optic neuritis, and febrile seizures), both using stand-alone CPRD data and CPRD-hospitalisation linked data.

The assessment of delays in stand-alone data was done by calculating the difference between the event date (the purported date of diagnosis of the condition) and the system date (as outlined in Section 8.1.2.1, the date the record was added to the patient's medical file). As a preparatory step, I also investigated how system dates can be altered, due to data updates by general practices. The analysis showed that mass transfers of data do indeed occur in general practice, and these transfers need to be identified before system dates can be used to assess recording delays. The study highlights this hitherto unrecognised problem, and suggests one methodological approach for addressing this. Following removal of updated system dates, the main analysis of stand-alone CPRD data showed that data accrual in CPRD varies with the condition of interest and in general, over 70% of all records in CPRD data accrue within the first month.

While the analysis of stand-alone CPRD data showed that records of selected conditions accrue with an acceptable delay, it does not provide any information on how completely

these conditions are recorded in CPRD. Hence, I analysed linked CPRD-hospitalisation data, which demonstrated that CPRD has low sensitivity to capture coded diagnoses for selected conditions first recorded in hospital. However, for the diagnoses that were subsequently captured in CPRD, data accrual occurred within the ten weeks of their hospitalisation for GBS, and within the first month for the remaining conditions.

Overall, this study shows that recording delays in CPRD are compatible with the implementation of a near real-time vaccine safety surveillance and the delay distribution can be used to adjust for delays when implementing a near real-time system.

8.1.3 Implementation of a near real-time system using CPRD data

8.1.3.1 What was known

In the UK, two near real-time systems using electronic health records had been previously implemented.[10,139] One was UK-wide and used sequential tests; it relied on spontaneous reports to obtain the observed number of events and CPRD to obtain the expected number of events.[10] The second system was implemented in Scotland, used hospital data and applied statistical process control to identify new signals.[139] Statistical process control does not formally control for multiple testing and has been considered more appropriate to identify issues with vaccine quality rather than identify new adverse events.[96] There was no known implementation relying fully on electronic health records and using sequential tests. CPRD is a population-based data source used extensively for research purposes. It is released monthly and practices upload their data some time before that. My work conducted to examine recording delays in CPRD showed that records are indeed registered with some delay but these delays are compatible with NRTVSS. From this regard, CPRD data could potentially be used to implement a NRTVSS. However, additional questions remained unaddressed, such as what is the most appropriate statistical test to use, how to account for delays and whether there is enough power to detect a signal.

8.1.3.2 What this study adds

This study showed that it is possible to implement a NRTVSS using CPRD, for at least two selected vaccine/outcome pairs: seasonal influenza vaccine/GBS and MMR/febrile seizures. For seasonal influenza vaccine/GBS, PMaxSPRT was deemed as the most appropriate test while for MMR/febrile seizures both the PMaxSPRT and the BMaxSPRT could be used. For MMR/febrile seizures, I was able to replicate a known safety signal, and showed that there was sufficient power to detect a signal of an increased risk of 2.5 times or more. For seasonal influenza/GBS there was more limited power to identify a safety signal; at its current size,

use of CPRD would enable exclusion of large increases in risk (over four times) of this rare outcome following seasonal influenza. This work proposes an adjustment for delays adapted to CPRD's data structure and based on the delays analysis reported in Section 5.3.

This work will inform any future decision-making by UK regulatory authorities about how best to implement this type of surveillance, including awareness of both the strengths and limitations of using CPRD data in this context. Additionally, these results are useful to researchers or practitioners who are developing near real-time surveillance activities using related electronic health record data.

8.1.4 Power to detect a signal and delays

8.1.4.1 What was known

The work conducted as part of the third objective of this thesis (Section 7.1) showed it is possible to implement a near real-time vaccine safety surveillance system using data from CPRD but there is limited power to identify a rare outcome (GBS) following seasonal influenza vaccine (power was ≥80% to identify a 4-fold increase in risk). For MMR/febrile seizures there was sufficient power to detect a 2.5-fold increase in risk. When using PMaxSPRT the number of expected events at the end of the surveillance determines power. This number is a function of the data available, depending on both the number of individuals contributing data (the volume of data) and on delays in data availability (both in practice staff recording outcomes and CPRD receiving data from participating practices). CPRD is a dynamic database and the number of individuals can increase (by including data from new practices and/or existing practices increasing in size) and delays can be reduced (by changing the way data are collected from practices and the regularity of data releases). The performance of a near real-time system could therefore improve by expanding the database and/or reducing delays.

8.1.4.2 What this study adds

This study explored the effect of delays in recording outcomes and receiving data on the performance (the power to detect a signal and the expected time to signal) of a system assessing GBS following seasonal influenza vaccine. Additionally, it assessed the system performance based on data available around the middle of the surveillance period, to understand what could be detected at a time when it would still be possible to implement some measures.

The results showed that absence of delays produced only limited improvements in power (with a maximum improvement of 4%). Timeliness in the absence of delays was similar to that observed when assuming delays. Assessment of power at mid-influenza season (early December) showed a substantial reduction in power (compared to end of the season), and would only allow detection of very large increases in risk (relative risks of more than eight). Removing delays would thus not be sufficient to improve the performance of a near real-time vaccine safety surveillance system for rare outcomes; expansion of CPRD is required. The results of this study can be used to inform any future decision-making by data providers about how best to improve the data available to support near real-time surveillance. More widely, the study provides a framework on how to consider delays and their effect on near real-time surveillance activities when using electronic health record data.

8.2 Strengths

The strengths of each study were discussed in the Chapters in which they are reported. Here, I provide an overview of the strengths of the project as a whole. These include the use of large, population-based electronic health records, careful consideration of data-related aspects and the implementation of a new vaccine safety surveillance system.

8.2.1 Use of large, population-based data

This work used CPRD, a large, population-based database, used extensively for epidemiologic research. Post-licensure vaccine safety studies require large databases as the main concern is the detection of rare adverse events. The use of CPRD in this context enables the detection of signals for rare events (at least for large increases in the relative risk, see Section 7.1). In general, collecting primary data to identify such rare events would be costly, time-consuming and would not generate timely results. Additionally, a population-based data resource is important to ensure that the results obtained are indeed representative of what is happening in the population. In practice, if the system is applied and no signals are detected, the results will be important to reassure the population that the vaccine under study is safe; on the other hand, if a signal is identified and then confirmed the results will help deciding which measures should be taken.

8.2.2 Careful consideration of data-related aspects

Throughout this project, I have carefully considered data-related aspects that could potentially affect the work conducted. First, I used rigorous methods to develop code-lists, and used wider and narrower definitions when evaluating delays in recording outcomes to

assess the effect of imperfect validity of diagnostic code-lists. I then assessed delays in stand-alone CPRD by using the system date, the date a record has been entered into the patient's file. As part of this work, I also investigated how system dates can be changed due to software and patient record updates, and proposed a method to investigate and exclude these. To the best of my knowledge the system date had not been previously used in this context and the mass transfer of records had not been investigated up to now. Finally, I proposed adjustments to account for delays in recording outcomes (for PMaxSPRT and BMaxSPRT) and receiving data (for BMaxSPRT), as well as partially accrued periods (for BMaxSPRT). These adjustments were based on previous work[113] but I adapted them to the structure of CPRD data. Overall, these aspects should be considered when envisaging the use of a data source to implement near real-time vaccine safety surveillance; my work can also be used by others looking at similar systems and related electronic health data.

8.2.3 Implementation of a surveillance system

The project reported in this thesis establishes the main features of a system that can be implemented in the UK. As such, I sought to provide results for vaccine/outcome pairs encompassing a range of characteristics, including a rare (GBS) and a more frequent outcome (febrile seizures), as well as an adult (influenza vaccine) and a childhood vaccine (MMR). I have also proposed an implementation for two tests (PMaxSPRT and BMaxSPRT) which further maximised the range of issues explored as part of my work. Time requirements to implement a system were not formally assessed but are discussed in Section 8.4. In addition to proposing the main aspects of a system relying solely on CPRD data, I assessed what needs to change to address existing limitations. In particular, I identified limited power to detect small increases in the risk of GBS following influenza vaccine (see Section 7.1) and, therefore I re-assessed power in the absence of delays for influenza vaccine/GBS. This particular work can be used to inform discussion with data providers about the way forward to improve data to be used in the context of a near real-time system. In summary, my work provides information not only on how a near real-time vaccine surveillance system can be implemented but also on how to address some of the existing limitations with currently available data.

8.3 Potential limitations

The specific limitations of each study were presented in Chapters 4, 5, and 7. In this section, I present the overarching limitations of the thesis in terms of my own work, limitations of

the data used and intrinsic limitations of the methods available. Issues related to the generalisability of the results are also presented here.

8.3.1 Limitations of my work

Due to the limited time in which to conduct this work, I selected two vaccine/outcome pairs to trial the implementation of a system using CPRD data. Systems run in routine practice generally assess five to ten pairs.[8] The tests selected were deemed to be the most appropriate to assess the pairs included. However, the inclusion of new pairs might require the use of tests not selected for the purposes of this work. For example, if there are limited data to estimate the historical rate of the outcome of interest CMaxSPRT might be required. Nevertheless, I tried to capture a range of issues to provide a broad overview of the challenges faced when implementing a system using CPRD data (see Section 8.2.3). These should be regarded as an initial step towards the implementation of a system as routine practice.

A key issue when using CPRD data is the validity of diagnostic codes used to ascertain outcomes and vaccines. Time constraints also prevented carrying out a full validation study of the code-lists used as part of this study. However, I assessed the effect of imperfect validity on delays by using a broader and more specific set of codes and the completeness of diagnostic codes in CPRD. The use of two lists with different levels of specificity yielded no significant effect on the delay distribution, which indicates that outcome misclassification does not impact the distribution generated.

8.3.2 Limitations of the data used

CPRD data have not been collected for research purposes. As such, researchers using these data should be aware of their limitations. As outlined in Section 8.3.1, I assessed the effect of imperfect validity of codes by using two lists with different levels of specificity with no appreciable effect in the delay distribution. On the other hand, my work assessing the completeness of diagnoses captured in CPRD (i.e. sensitivity, see Section 5.3) showed appreciable underreporting, even for serious conditions (e.g. GBS). In the context of near real-time surveillance, if underreporting is constant over time it decreases power to detect a signal, but it may have wider implications for research in general. The need to use linked data to improve completeness of diagnostic records has been previously recognized.[86,165] However, present linkages with hospital data are not timely enough to be used in a near real-time system. If this changes in the future the use of linked data would be an important improvement to a near real-time system. With regards to vaccination information, I am not

aware of a study that formally assesses the validity of vaccination information for the vaccines assessed as part of this study. However, both MMR for young children and seasonal influenza vaccine for individuals aged 65 years or more are administered in GP practices. Administration of these vaccines is part of the services practices should deliver[166] and practices are paid based on the records entered into the system.[167] It is thus expected that this information is well recorded. Moreover, the inclusion of only vaccinated individuals with careful development of algorithms to identify these individuals should have contributed to minimising further potential misclassification.

Delays in recording outcomes and in receiving data for analysis can also limit the feasibility of a near real-time system. I extensively considered delays in the context of this project, both by characterizing them and by adjusting for delays during the trial implementation analyses. These efforts ensured the analyses conducted were feasible and unbiased (as far as delays are concerned) but they did not remove existing delays. Outcomes diagnosed in hospital are only recorded after GPs receive feedback from hospital-based physicians, therefore, as discussed above, using readily available linked CPRD-hospital data would likely minimise this source of delays. Uploading data from practices more frequently (e.g. daily, weekly) and make them available to researchers would also reduce delays further. CPRD is now trialling new data collection from practices using EMIS software (see below), with daily uploads. As this system progresses towards implementation, discussion with data providers will be important to anticipate these improvements and to decide how to best integrate them into the surveillance system. Nevertheless, my work assessing the influence of power on delays for influenza vaccine/GBS showed that removing delays only results in limited improvements in power to detect a signal.

I have also shown that there is limited power to detect a signal for a rare outcome (GBS) following seasonal influenza (see Section 7.1) and suggested that data expansion is required to improve power. Such improvement should be possible as CPRD is about to release data that are substantially larger due to the inclusion of practices using EMIS software. EMIS is one of the main software in the UK[78] and this will be an important addition for future CPRD expansion. CPRD is now assessing data from EMIS practices and the current plan is to include data from these practices in the Spring of 2018 (with test usage for selected studies from the Autumn of 2017) (Dan Dedman, CPRD, personal communication). In the future, CPRD is also planning to include practices using TPP SystmOne software (Helen Booth, CPRD, personal communication). Only after data are released will it be possible to assess what improvement results from these additional data.

8.3.3 Limitations of the methods

As pointed out in my systematic review of existing methods to perform near real-time vaccine safety surveillance (see Section 4.1), there were limited strategies to account for confounders and, in general, only a few confounding variables were considered. In 2015, Cook et al. proposed a group sequential test using generalized estimating equations to allow for more flexible control for confounding than previously existing methods.[168] To the best of my knowledge, this new method has not been subsequently applied, and confounding has been addressed at the confirmation stage, after a signal is found. This might be related to the fact that near real-time surveillance is regarded as a simple and quick signal strengthening method, which requires a full confirmatory study afterwards when a signal is found. As such, it should not be over-complex, and more complete and robust approaches are left to the confirmatory stage.

8.3.4 Generalisability

This work aimed to assess the feasibility of using CPRD to implement a near real-time vaccine safety surveillance system. Therefore, the issue of generalisability is discussed from the perspective of applying the existing results to new CPRD data releases. This is particularly important as CPRD is undergoing substantial changes that may limit the use of the results generated as part of this project. The issues presented in this section should also be considered if implementation using other primary care databases is envisaged (e.g. ResearchOne, THIN, RCGP RSC).

The main change, as highlighted in Section 8.3.2 above, is the addition of practices using EMIS software. The inclusion of EMIS practices brings additional challenges to the implementation of a system, including: (i) the use of system date; (ii) GPs' recording behaviour; (iii) mode of data collection; and (iii) a different coding system. These aspects are reviewed. As explained in Section 5.3, in Vision practices' data, the date when a record was added to a patient's file (the system date) can be changed when the software version is updated. My work included investigation of which records have been included in such updates, followed by their exclusion. Currently, it is not known if this is also an issue for data from EMIS practices. Release of these data and conversations with data providers will be important to gain a deeper insight of the relevant issues for EMIS data. The need to exclude records due to mass transfers for EMIS data should thus be assessed in light of that information. Similarly, the delay distribution generated using Vision practices data may not be generalizable for EMIS practices data. Previous CPRD work looking at Huntington's disease

suggested a slightly lower prevalence for the disease as estimated from EMIS practices in comparison to Vision practices (Dan Dedman, CPRD, personal communication). This may be due to the EMIS system not requiring GPs to enter a code when adding information to a patient's file (Dan Dedman, CPRD, personal communication). Further differences between the two systems may lead to a different delay distribution. If EMIS data contain information on the date each record was entered (an equivalent to system date) both the issue of mass transfer of records and delays in recording outcomes can be assessed using the programme files I developed. The use of my files would reduce the workload required to conduct a new assessment, as only data extraction and minor adaptions of the files to the new data would be required.

Data collection will also differ between EMIS and Vision practices. CPRD is likely to receive daily data extracts from EMIS data, which has potential to reduce delays in practices uploading their data. If CPRD data releases start to be provided more often than monthly, frequency of testing might be increased accordingly. Nevertheless, my work assessing the effect of reducing delays on power (Section 7.4) showed that removing delays will only slightly improve the performance of a system.

All the work developed was based on Read codes version 2 lists while EMIS codes information using Read codes version 3. All GPs systems will be required to adopt SNOMED CT codes by April 2018.[169] Therefore, in the future, implementation will require the mapping of existing lists to SNOMED CT codes.

Future changes that can limit the application of the proposed implementation include changes in the way data are captured from hospital (for example, automatic capture of hospital-coded data by the GP system) and/or expansion of CPRD data to include other data sources (for example linkage of child health records from all settings). This would improve the validity of diagnostic codes (by improving the sensitivity) but would also lead to changes in the delay distribution (used for adjustment of delays), thus requiring data re-analysis. Overall, the effect of changes affecting the data used for implementation should be carefully considered and adaptions should be adopted as required.

8.4 Implications for practice

This work establishes the main aspects of a near real-time vaccine safety system using CPRD data. However, full implementation will require further considerations. To start with, a fully functioning system will require monitoring of more than one or two outcomes (generally five

to ten[8]). Additionally, the implementation of this system will require the establishment of further steps should a signal be identified. VSD has proposed several steps after a signal is identified, including: checking the data and code, examining descriptive statistics for patterns in time between the exposure and outcome, adjusting for additional confounders, conducting a non-sequential analysis with a different comparator, conducting a review of records, comparing the results with similar outcomes or other existing data, analysing new data or designing a new study.[9] When using CPRD, it is no longer possible to access GPs' free-text, and it may not be feasible to obtain medical records of cases identified and validate them in a timely manner. However, the remaining steps can be applied. A debated issue is the use of the same dataset to identify and confirm a signal.[34] Some authors claim this should be avoided due to possible biases. I am not aware of a formal study showing and quantifying these biases in the context of signal identification and confirmation. However, a related issue has been extensively discussed in the field of prognostic models,[170] and it is recommended that a model is fitted and validated in separate datasets, preferably from different patient centres. If we consider the same approach in the context of signal identification and confirmation, there are further primary care datasets available in the UK such as THIN and RCGP. Within CPRD, in the future it would be possible to use Vision practices for system implementation and EMIS practices for signal confirmation. Nevertheless, this approach would remove the power gain of adding EMIS practices to the data used to implement a system. Furthermore, these concerns arose in the context of data mining studies.[34] Unlike data mining, NRTVSS is hypothesis driven and there is a rationale for selection of the vaccine/outcome pairs to assess. In epidemiologic terms, particularly regarding confounding factors, NRTVSS also provides an initial analysis and (as highlighted above) there is room for more robust and rigorous analysis following a signal, even if the same data are used. Hence, I would propose the application of the steps previously mentioned (e.g. more detailed adjustment for confounders in a formal epidemiological study) using CPRD data. This is also the approach followed by VSD, in which the same data are used for NRTVSS and signal confirmation. Authors defending this approach claim that analyses at the confirmation stage should be 'statistically independent' or 'orthogonal' from the ones used at the identification stage, i.e. they should look at aspects of the data that are distinct from each other.[171,172] Nevertheless, further research on the use of the same data for identifying and confirming a signal would be useful.

One of the challenges when implementing this system in practice is data availability. As explained in Section 6.2, for the purposes of this work it was not possible to use the monthly

release of the data to mimic a near real-time system. Instead, I used the 6-month releases available to LSHTM, which were deemed appropriate within the scope of this project. If the system is implemented in practice, monthly data releases should be used. The MHRA is one of the possible implementers of this system and they can access and extract data without the restrictions of the online extraction tool. As such, the issues relating to identifying individuals with immunisation codes would not be relevant. If others wish to proceed towards implementation of this type of system, one option is to discuss with data providers the possibility of searching for immunisation codes in the online extraction tool.

The issue of timeliness regarding data has been discussed extensively. However, it is also necessary to consider the time required to perform the analysis. Having produced several programs to conduct these analyses I can make them available to those who wish to pursue this type of surveillance using CPRD data. That would greatly reduce the time required to conduct the analysis. It is difficult to give a precise estimate of the time required to set up and run a system as this depends greatly on the knowledge of the data and methods used, as well as on the number of events to study for each vaccine. Nevertheless, in Table 8.1, I provide a breakdown of the tasks required to implement a system, alongside an estimate of the time required to perform each task. The most time-consuming work can be done before the beginning of the surveillance period, preventing unnecessary delays at this stage. The R package Sequential also helps to reduce the time required for analysis; for example, Sequential stores the results from one analysis to the next, thus simplifying the analysis process. Overall, I estimate that two full-days of work are required to perform the analysis of each data release for a specific vaccine/outcome pair. It is noteworthy that adding more outcomes will not increase the workload in a linear way, as several tasks will take approximately the same time for one or more outcomes. However, those implementing a system should consider the additional workload from implementing a system and whether it is necessary to have a dedicated person to perform the entire analysis. I would recommend that a specific person is assigned to perform the several stages of the analysis, with further support from a team with a wide set of skills. Having a dedicated person would diminish the time required to acquire the specific skills needed to implement the system (e.g. familiarisation with the package Sequential). However, I do not think a full-time dedicated person would be required. In the future, the work can be further automated by the development of dedicated programs, and the use of R Markdown to produce standard reports.[173] R Markdown allows the development of dynamic documents with R, embedding R code and text in the same file. Such files are particularly useful when one wishes to run and

report similar analyses at repeated points in time such as in the case of sequential analyses. Developing an R Markdown file to generate a standard report for each sequential analysis would therefore reduce the workload required to report each new analysis.

Table 8.1. Tasks required to implement a system and estimate of time commitment, for a specific vaccine/outcome pair

Task	**Time (hours)**
Prior to surveillance	
Development of code-lists (per outcome)	1 to 2
Development of algorithm to identify vaccinated individuals (per vaccine)	6 to 8
Sub-total (prior to surveillance)	**7 to 10**
PMaxSPRT - Before surveillance starts	
Definition of the comparator period	1
Data extraction	2 to 3
Data cleaning and management	3 to 4*
Calculation of an appropriate historical rate	3
Generation of delay distribution	3
Calculation of expected number of events at end of surveillance based on historical data	2
Sub-total (PMaxSPRT - Before surveillance starts)	**14 to 16**
BMaxSPRT - Before surveillance starts	
Calculation of the observed number of events at end of surveillance based on historical data	2**
After surveillance starts (task required at each data release) – similar for PMaxSPRT and BMaxSPRT	
Data extraction	2 to 3
Data cleaning and management	3 to 4*
Identification of vaccinated individuals and their follow-up time (includes refinement of algorithm to identify vaccinated individuals)	4 to 6
Calculation of the expected number of events (PMaxSPRT only) and identification of the observed number of events (PMaxSPRT and BMaxSPRT)	2
Calculation of the test statistics	1
Sub-total (After surveillance starts)	**12 to 16**

*Assuming adaption of pre-existing programme files. **Assuming use of the same historical data as PMaxSPRT

8.5 Implications for future research

As outlined above, a fully functioning system will require the assessment of more than two vaccine/outcome pairs. New outcomes might require the use of other tests that were not

studied as part of this project, such as the conditional maximized sequential probability ratio test. Furthermore, the assessment of vaccines other than seasonal influenza and MMR may require the use of further tests or their combination. For example, when assessing newly introduced vaccines, it may be necessary to allow some time for initial uptake. A possible strategy in this context is to initiate the sequential analysis only after a pre-determined number of doses have been given.[163] The specific tests to apply to each vaccine/outcome pair should be decided on a case-by-case basis.

Other areas of research include comparison of the system proposed in this thesis with other systems. For example, NRTVSS had been previously implemented using spontaneous reports to generate the observed number of events and CPRD to calculate the expected number of events, while I am now proposing to implement the system relying exclusively on CPRD data. The properties of both systems could be assessed as a way to understand how to best use them in practice (using one or both systems).

As outlined in Section 2.3.1.3.4, it has been shown that it is possible to identify mild AE to vaccines (e.g. injection site pain, fever and malaise) using social media and other online reports but their place in pharmacovigilance is still unclear.[57,58] In particular, it is not known if social media should be considered as a tool to support signal detection or if it can be used on its own. As with electronic health records, these data contain a vast amount of records and may seem appealing to identify rare adverse events, however, there are additional issues that need to be explored. For example, it may be difficult to capture conditions less familiar to the general public such as GBS and there might be issues regarding representativeness of the data. Addressing these questions could inform how to best use these two (near) real-time systems in practice. Additionally, it would be important to know how the two systems (NRTVSS and social media) perform in terms of their timeliness.

The work conducted also has implications for other researchers using these data sources. First, to the best of my knowledge, this is the first work to recognize objectively that general practice records are subject to mass transfers, which also update the date a record was entered in the patient's file. More importantly, the work using linked data to assess completeness showed low sensitivity of coded records in CPRD for some diagnoses. For the implementation of a near real-time system, if recording is constant over time this would decrease the number of existing records, thus diminishing power to detect a signal. However, this has implications for researchers in general, who should be aware that even serious conditions such as GBS might not be coded by GPs. Overall, these issues highlight that

researchers need to have a deep understanding of existing data to be able to use them in an appropriate manner.

8.6 Personal development

The work developed as part of my PhD allowed me to acquire a range of skills. Firstly, I learned in detail the specific methods used to perform near real-time vaccine safety surveillance. Secondly, I made enormous progress in my understanding of the complex CPRD structure and how it can be use to perform epidemiological research. I learnt how to create and use code-lists and how to extract data. I have also developed my knowledge of the potential and limitations of using CPRD (and other electronic health records) to perform epidemiological research. Thirdly, I developed my command of both STATA and R. When I first started this project, my STATA knowledge was limited; I have thus greatly expanded it, not only by using new commands to perform data cleaning, management and analysis, but also by learning how to best use STATA to analyse very large datasets, trying to maximise the efficiency of my commands and thus reduce computational time. Being already fluent in R before the start of my PhD, I learnt how to use the specific functions required to implement a NRTVSS and to assess the performance of a system (Sequential package). Finally, I have greatly developed my writing skills. This is probably the area where I feel I benefitted the most from my PhD experience. Having received detailed feedback on my written documents has enabled me to improve my writing and the way I communicate my work. Overall, these skills will be vital in my future career as a researcher.

In addition to the work around my PhD project, the time spent at LSHTM has given good opportunities to understand the daily functioning of an academic institution with a vibrant research environment. There is a wealth of research seminars given by a wide range of resident and invited speakers, and my regular attendance at these has enabled me to make contact with other researchers working on a variety of public health topics. Furthermore, I was able to develop my teaching skills. At LSTHM, I taught on several Masters-level modules (Statistics for Epidemiology and Population Health, Extended Epidemiology and Statistical Methods in Epidemiology), focusing on the application of statistical methods in epidemiology and development of epidemiological concepts. In these modules, I led practical sessions, supporting students with the use of STATA, and for some, I also assessed final assignments.

The progress made was achieved with the invaluable support of my supervisors, bridging academic and public health practice. Throughout the course of my project I have also

collaborated with the MHRA, by sharing results and discussing the steps of my project. This collaboration has been beneficial for me as I was able to improve my project using MHRA experts' knowledge but also benefited the MHRA, as my work provided them with valuable information. Furthermore, I had the opportunity to present my work at several national and international conferences, where I received feedback from experts in the area of vaccine safety. For a full list of presentations see Appendix B of this thesis.

8.7 Conclusions

Near real-time vaccine safety surveillance using electronic health records is one of the methods available to assess vaccine safety after approval. It started to be used in 2005 in the USA and it has been increasingly used worldwide ever since. Several statistical approaches have been considered to conduct this type of surveillance, including continuous sequential tests, group sequential tests, and statistical process control. PMaxSPRT and BMaxSPRT were the tests most commonly used. There were limited strategies to account for confounding factors and it is possible to account for delays in receiving and recording data as part of the implementation of a system. In the UK, this type of surveillance had been implemented using spontaneous reports to obtain the number of observed events and CPRD to calculate the number of expected events. Research-level primary data sources are available in the country.

For a data source to be considered for use in a near real-time vaccine safety surveillance system it should be population-based, have a good validity of both vaccination and outcome information, be available in a timely manner and have enough power to detect signals. CPRD data are known to be population-based and it is generally considered to have good validity for vaccines administered in general practices and outcomes of interest for vaccine safety. As part of this work, I have shown that outcomes of interest for vaccine safety are recorded with some delay but this is compatible with the implementation of a near real-time system.

Trial implementation of a system using CPRD data was successfully carried out. PMaxSPRT was deemed as the most appropriate test to use for rare events while both PMaxSPRT and BMaxSPRT can be used for more frequent events. Adjustment for delays was possible and should be considered when implementing a system. There was good power to detect a signal for more frequent events such as febrile seizures following MMR vaccine but limited power to detect a signal for rare events. Further exploration of this issue showed that removing delays was not sufficient to improve power in this context and CPRD data expansion is therefore required.

Overall, it is possible to implement NRTVSS using CPRD data and further expansion of CPRD (both in terms of size and data available) might help addressing some of the currently existing limitations. The work reported here will support and strengthen pharmacovigilance activities.

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APPENDIX A: OUTCOMES NOT INCLUDED IN THE FEASIBILITY ASSESSMENT

Table S 1. Outcomes not included in the feasibility assessment.

Outcome	Number of times studied
Acute flaccid paralysis	1
All hospitalization	1
Appendicitis	1
Arthritis	1
Asthma/wheezing	2
Auto-immune disorders	1
Cardiovascular events	1
Cerebrovascular events	1
Death	1
Epilepsy	1
Fatigue syndromes	1
Fever	2
Gram negative sepsis	1
Haematochezia	1
Invasive *Haemophilus influenzae* type b disease	1
Juvenile onset of diabetes	1
Kawasaki disease	3
Myocarditis (±pericarditis)	2
Narcolepsy	1
Other neurologic outcomes	1
Paralytic syndromes	2
Respiratory events	2
Serious local reactions	1
Stevens-Johnson syndrome	1
Stillbirth	1
Stroke	2
Sudden infant death	1
Syncope	1
Varicella zoster	1
Venous Thromboembolism	1
Herpes zoster	1

APPENDIX B: LIST OF PRESENTATIONS

Below I provide a list of presentations (oral and posters) performed as part of my PhD project.

1. Near-real time vaccine safety surveillance – a systematic review of statistical methods. Health Protection Research Unit in Immunisation Annual Scientific Meeting. London: 30 March 2015 (oral presentation);
2. Near-real time vaccine safety surveillance using the Clinical Practice Research Datalink: a feasibility study – LSHTM Vaccine Centre Research Degree Students meeting. London: 21 July 2015 (oral presentation);
3. Near-real time vaccine safety surveillance – a systematic review of statistical methods. 31st International Conference on Pharmacoepidemiology and Therapeutic Risk Management: Boston: 24 August 2016 (poster);
4. Assessing recording delays in the Clinical Practice Research Datalink (CPRD) to inform near real-time vaccine safety surveillance. LSHTM Vaccine Centre Retreat. Windsor: 11 February 2016 (oral presentation);
5. Assessing recording delays in the Clinical Practice Research Datalink (CPRD) to inform near real-time vaccine safety surveillance. Public Health England Applied Epidemiology Scientific Conference. Warwick: 22 March 2016 (oral presentation);
6. Assessing recording delays in the Clinical Practice Research Datalink (CPRD) to inform near real-time vaccine safety surveillance. International Population Data Linkage Conference. Swansea: 25 August 2016 (oral presentation);
7. Near real-time vaccine safety surveillance using electronic health records. Uppsala Monitoring Centre. Uppsala Monitoring Centre Seminar. Uppsala: 26 October 2016. Available from: https://www.youtube.com/watch?v=dCq50ydl_FY (accessed 2017-07-07) (oral presentation);
8. Implementing near-real time vaccine safety surveillance using the Clinical Practice Research Datalink - Is there enough power? International Society for Pharmacoepidemiology Mid-Year Meeting. London: 3 April 2017 (poster);
9. Vigilância de segurança de vacinas em tempo quase real [Near real-time vaccine safety surveillance]. II Encontro da Rede de Bioestatísticos Portugueses e da Secção de Biometria da Sociedade Portuguesa de Estatística [2nd meeting from the Portuguese Biostatisticians Network and Biometrics Section from the Portuguese Society of Statistics]. Lisbon: 6 January 2017. Available from:

https://www.youtube.com/watch?v=FoGgiR5mNrE (accessed 2017-07-07) [Portuguese] (oral presentation);

10. Implementing near-real time vaccine safety surveillance using the Clinical Practice Research Datalink (CPRD). Public Health England Applied Epidemiology Scientific Conference. Warwick: 22 March 2017 (oral presentation);
11. Implementing Near-Real Time Vaccine Safety Surveillance Using the Clinical Practice Research Datalink. 33rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management: Montreal: 28 August 2017 (oral presentation).