Severe influenza infection in England: assessing the impact and estimating vaccine effectiveness

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Declaration

I, Nicola Boddington, 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.

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Abstract

One of the groups at increased risk of severe influenza illness is children, particularly young children aged five years and below. A national vaccination programme was introduced in England in 2013 to vaccinate children against influenza. Protection against clinically important outcomes is needed to justify resources and can be estimated using observational studies.

Analysis of national surveillance data on laboratory-confirmed influenza hospitalisations demonstrated a high and ongoing burden of influenza infection in under five-year-olds in England. It also showed varying severity of influenza by age and influenza subtype and an increase in overall cumulative hospitalisation incidence rates from the 2015/2016 influenza season onwards.

In a meta-analysis of influenza vaccine effectiveness studies, influenza vaccination was found to give moderate overall protection to children against hospitalisation. Higher protection was seen with inactivated influenza vaccine, although the difference was not statistically significant, and estimates were higher in seasons when the circulating influenza strains were antigenically matched to the vaccine strains.

Two observational study designs often employed to estimate influenza vaccine effectiveness are the test-negative design and the screening method. The strengths and limitations of the two methods were explored through a critical review of the literature. These two methods were then used to estimate vaccine effectiveness against hospitalisation in children in England in the 2013/2014 to 2015/2016 seasons. Both found that the influenza vaccine offered moderately good protection against hospitalisation to children in these seasons.

This Research Project provides some key insights into the impact of influenza in children in England and contributes further to the literature on the effectiveness of influenza vaccination against important clinical outcomes in children. It provides useful evidence for other settings considering vaccinating children against influenza as well as methodological insights for assessments of the effectiveness of other vaccines such as COVID-19.

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Firstly, I would like to thank my two supervisors, Professor Punam Mangtani and Dr Richard Pebody for the unwavering support they have given to me throughout the Doctor of Public Health (DrPH) programme and without whom it would not have been possible.

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DrPH Integrating Statement

The Doctorate of Public Health (DrPH) programme is comprised of three components:

1. The taught component comprising of two modules (Evidence Based Public Health Policy (EBPHP) and Understanding Leadership, Management and Organisation (ULMO))
2. The Organisational and Policy Analysis (OPA)
3. The Research Project

My DrPH journey started in 2013 when I embarked on the first of the three components, the taught modules. One of the most rewarding aspects of this part of the programme was the shared learning experience with the other members of the DrPH cohort. Each member had a variety and wealth of experience, enriching the lectures and learning with practical experiences. The first assignment for EBPHP was to write an Influence and Knowledge Strategy for which I wrote a strategy paper for a non-governmental organisation providing recommendations on how to get influenza vaccination in pregnant women onto the Kenyan government's policy agenda. Applying theories learned from the taught module, the paper provided possible techniques and models for influencing the decision-making process of introducing a new vaccine.

The second assignment for EBPHP was a literature review on the effects of alcohol warning labels on the consumption of alcohol during pregnancy. This in combination with the lectures given, provided an excellent platform to carry out the systematic literature review and meta-analysis I completed as part of the Research Project. The ULMO assignment, a strategic analysis of Public Health England (PHE), my current employer, was a useful exercise, particularly in preparation for the next part of the programme, OPA.

The second component of the DrPH programme is the OPA which provides students with an opportunity to observe and analyse the operations of a public health organisation and how it might shape policy on a particular aspect of public health. For my OPA I carried out a qualitative case study looking at the inception, process and organisational context of developing a national strategy for tuberculosis (TB) by PHE. This was done through semi-structured interviews, observation and document review. I thoroughly enjoyed this project and the opportunity to develop my qualitative research skills and the final report was well received by PHE and other contributors.

The final component of the DrPH programme is the Research Project. Much of the work included in my Research Project evolved through my experiences at PHE with monitoring severe influenza in England. My role included the day-to-day management of the UK Severe Influenza Surveillance System (USISS) and using the data collected I was able to assess the impact of severe influenza in England and extend this to explore the direct impact of vaccination against severe influenza and the methods by which this can be assessed.

In summary, the DrPH programme has been a rewarding and enriching experience and I am sincerely grateful to all those who have supported me and enabled me to complete the programme. It has not been without its challenges; working full-time for large portions of it, including supporting a number of national public health incidents (MERS-CoV, Ebola, COVID-19), having two children, as well as the

COVID-19 pandemic challenges faced by so many of working from home and home-schooling. The experience has taught me valuable life lessons which I will carry forward in my career and the programme has undoubtedly improved my skills as a researcher and a public health professional and I look forward to applying these skills and knowledge in the future.

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List of Abbreviations

ACIP	Advisory Committee on Immunisation Practice
ARI	Acute Respiratory Illness
CAIV-T	Cold-adapted influenza vaccine – trivalent
CCG	Clinical Commissioning Group
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DNA	Deoxyribonucleic acid
ECDC	European Centre for Disease Prevention and Control
EISN	European Influenza Surveillance Network
EUPHO	Eastern Region Public Health Observatory
EU	European Union
GISRS	Global Influenza Surveillance and Response System
GP	General Practitioner
HA	Haemagglutinin
HDU	High Dependency Unit
HES	Hospital Episode Statistics
Hib	Haemophilus influenzae
hMPV	Human Metapneumovirus
ICU	Intensive Care Unit
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
IMD	Index of Multiple Deprivation
ImmForm	Influenza Immunization Uptake Monitoring Programme
I-MOVE	Influenza – Monitoring Vaccine Effectiveness in Europe
IQR	Interquartile Range
IT	Information Technology
IVE	Influenza Vaccine Effectiveness
JCVI	Joint Committee on Vaccination and Immunisation
LA	Local Authority
LAIV	Live Attenuated Influenza Vaccine
LSOA	Lower Super Output Area
MSOA	Middle Super Output Area
NA	Neuraminidase
NHS	National Health Service
NIMS	NHS Immunisation Management Service
NPI	Non-pharmaceutical interventions
ONS	Office for National Statistics
OR	Odds Ratio
P&I	Pneumonia and influenza
PCV7	Seven-valent Pneumococcal Conjugate Vaccination
PCV	Proportion of cases vaccinated
PDS	Patient Demographic Service
PHE	Public Health England
PICU	Paediatric Intensive Care Unit
PII	Personal Identifiable Information
PPV	Proportion of population vaccinated

QIV	Quadrivalent Influenza Vaccine
RCT	Randomised Controlled Trial
RDMS	Respiratory Datamart System
RIDT	Rapid Influenza Diagnostic Test
RNA	Ribonucleic Acid
ROBINS-I	Risk of Bias In Non-Randomised Studies-of Interventions
RT-PCR	Reverse Transcription Polymerase Chain Reaction
rRT-PCR	Real-time Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
TIV	Trivalent Influenza Vaccine
TNCC	Test-Negative Case-Control
TND	Test Negative Design
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency
US	United States
USISS	UK Severe Influenza Surveillance System
VE	Vaccine Effectiveness
WER	Weekly Epidemiological Records
WHO	World Health Organization

Chapter 1
Background

1.1 Introduction

1.1.1 Influenza

Influenza is an acute viral infection of the respiratory tract. The influenza virus is a member of the Orthomyxoviridae family and is a single-stranded, negative sense ribonucleic acid (RNA) virus. Influenza viruses are classified into three genera: A, B and C, although influenza A and B are the two main types which cause clinical illness in humans (1). The influenza A virus is further classified into subtypes according to antigenic differences between the two surface antigens: haemagglutinin (HA) and neuraminidase (NA). Fifteen HA subtypes (H1-H15) and nine NA subtypes (N1-N9) have been identified for influenza A viruses (2). The main subtypes with established lineages in the human population are H1, H2 and H3 and N1 and N2. Influenza B viruses are further classified as belonging to two antigenically distinct lineages, Yamagata and Victoria.

Being an RNA virus, which often lack the proofreading abilities of DNA (deoxyribonucleic acid), influenza viruses are unstable (3). Minor changes, termed antigenic drift, occur through mutations in the genes of the surface antigens, HA and NA. These changes can occur from season to season hence the need for annual vaccination against influenza. The new strains that result are antigenic variants related to those that have circulated in preceding epidemics (2). Major changes, resulting in a novel HA or NA, are termed antigenic shift and result in the emergence of a new subtype for which the population may have little or no immunity, and thus can cause pandemics (2).

Influenza typically circulates in the winter months in the temperate climates of the northern and southern hemispheres, and in the tropics, influenza may circulate all year round. The influenza virus is transmitted via large droplets which are expelled during coughing and sneezing, tiny droplets (aerosols) and fomites (2, 4). Infection with influenza causes a spectrum of clinical illness from symptomless infection (20-50% of infections) through to various respiratory syndromes and disorders, to primary and secondary pneumonia (2, 5, 6). The likelihood of disease progression will vary according to the individual such as the individual's age, degree of pre-existing immunity and comorbidities.

1.1.2 Public health importance of influenza in children

Influenza can affect all age groups with infection being most common in the young, although the extreme end of the age spectrum tends to be most vulnerable to complications from influenza, as well as those with underlying clinical risk factors (7-9).

It has been estimated that between 10 to 30% of children are infected with influenza annually (10-12) and that globally, influenza is the second most commonly identified pathogen in children with acute lower respiratory infection after Respiratory Syncytial Virus (RSV) (13). Childhood influenza infection is generally self-limiting, however, complications leading to hospitalisation can occur and children with underlying clinical risk factors, as well as those under five years, are particularly vulnerable to complications. Young children, particularly those under five years, are thought to experience more severe disease compared to older children and adults.

Severe influenza is usually defined as influenza with a severe symptom or accompanying severe complication and studies often use hospitalisations due to influenza as a marker of severity (14, 15). Early suggestions of the severity of influenza in children, particularly those in the youngest age groups, came from two studies which found that during the influenza season, hospitalisation rates, along with outpatient visits and antibiotic consumption, for respiratory infections significantly increased in younger healthy children (16, 17). Several studies have shown that younger children compared to other ages, even if healthy, have the highest risk of hospitalisation and the highest proportion of severe respiratory cases (18-28). During the 2009 influenza pandemic children, particularly younger children, were also at high risk of clinical influenza (19, 24).

A meta-analysis, carried out in 2010, of global data for disease incidence and case fatality in developed countries found the rate of severe influenza-attributable acute lower respiratory infection was 1/1000 children under five years in 2008 (13). The increase in capacity for laboratory confirmation of influenza infection, along with the 2009 influenza pandemic, has led to increased recognition of severe influenza-related illness in children and adults (13) and many countries now perform hospital-based influenza surveillance (29-32). In a more recent systematic review, Lafond *et al.,* (2016) noted that influenza was associated with 10% of respiratory hospitalisation in children under 18 years of age globally (29).

In England, the youngest children have the highest influenza-attributable hospital admission rates (33-35). In a study using regression modelling to estimate the proportion of acute respiratory illness (ARI) outcomes attributable to laboratory-confirmed influenza, healthy children under five years of age had the highest influenza-attributable hospital admission rates of all age groups (1.9/1,000), over five-fold

higher than in the 65-year-olds (34). In addition, nearly 40% of the influenza-attributable hospital admissions and General Practitioner (GP) consultations in England were estimated to be in children under 15 years of age (34).

1.1.3 Influenza vaccine types and indications for use

There are two main types of influenza vaccines available globally: inactivated influenza vaccines (IIV) and live attenuated influenza vaccines (LAIV). IIVs are generally approved in persons aged six months and older, including pregnant women and persons with underlying clinical risk factors, although some are restricted for use in particular age groups. There are several different types of IIVs including quadrivalent IIVs (QIV) which are either egg-grown, cell-based or recombinant. There are also adjuvanted and high-dose IIVs. Quadrivalent vaccines contain two influenza A strains and two influenza B strains, rather than one influenza B strain which trivalent IIVs contain. Trivalent inactivated influenza vaccines (TIV) are generally being replaced now by QIVs and in the United Kingdom (UK) they were not recommended for any age group or clinical risk group for the 2021/2022 influenza season (36).

IIVs are typically manufactured using viral propagation in embryonated eggs. However, since these vaccines cannot be given to egg-allergic individuals, a few manufacturers have developed cell-based influenza vaccines. Initially, the production of these vaccines also began with egg-grown candidate vaccine viruses, however, cell-grown candidate vaccine viruses have also been approved (37). These cell-grown candidate vaccine viruses are inoculated into cultured cells of mammalian origin instead of fertilised chicken eggs and can be given to severely egg-allergic individuals. They may also have an improved match to circulating influenza strains as they can be used to reduce egg-adaptation issues i.e. changes that can be introduced when growing influenza viruses in eggs. This has been a particular issue contributing to the reduced vaccine effectiveness (VE) in the last decade especially for the influenza A(H3N2) virus (36-40).

Another way of manufacturing IIVs is by using recombinant technology. Recombinant vaccines are created synthetically using the gene for making the HA which is then combined with a baculovirus, a virus that infects invertebrates, resulting in a “recombinant” virus (37). This then produces HA antigens that are harvested in bioreactors. This method therefore does not require the use or growth of the influenza virus and so the vaccine virus cannot adapt or mutate (36). These vaccines also contain a greater amount of influenza virus antigen to enhance the immune response to it (36). Recombinant QIV, known as Flublok, has been widely used in the United States (US) since 2016. It was first used in the UK as part of the 2020/2021 seasonal influenza vaccination programme when authorisation was

granted for temporary supply. Since the 2021/2022 season, it has been licenced as Supemtek and included as part of the routine programme for those aged 65 and over and adults with underlying clinical risk factors (36).

Other IIVs include a high-dose vaccine which is generally approved for people 65 years and over. This vaccine contains four times the amount of antigen compared with standard-dose IIVs to give a better immune response (39). However no high-dose vaccine is available in the UK (36). Influenza vaccines have also been improved by adding immune-stimulating compounds such as adjuvants including MF59 (squalene) and AS03 (squalene and α-tocopherol) which are approved in the European Union (EU), Canada and the US (38). These help to create a stronger immune response to vaccination (39) and are approved for people 65 years and over. An adjuvanted trivalent vaccine was widely used in the UK for three influenza seasons from 2017 in those aged 65 and over, although this has now been replaced by a quadrivalent one for the 2021/2022 season (36).

LAIVs are cold-adapted vaccines in which the live virus in the vaccine can only multiply in the cooler nasal passages, hence they are administered intranasally. LAIVs are approved for use only in persons aged 2 to 49 years who do not have underlying medical conditions and should not be given to pregnant women. Nasal application of LAIV has been used successfully in the Russian Federation for the last 50 years (40). The Russian LAIV has two cold-adapted master donor viruses as a backbone: A/Lenigrad/134/17/57 (H2N) and B/USSR/60/69 (40). In 2003, a trivalent live attenuated, cold-adapted influenza vaccine (CAIV-T) was licensed in the US for the first time (FluMist) (41) and in 2011 LAIV for intranasal use was approved in the EU for children and adolescents (2-17 years of age) (Fluenz) (38). This LAIV, in contrast to the Russian LAIV, is based on the Ann-Arbor backbone (40).

The composition of influenza vaccines is reviewed annually and is often updated due to antigenic drift of the influenza virus to ensure that the vaccine reflects the most frequent and recent circulating strains. In addition, influenza vaccines induce protection of relatively short duration, with significant declines in VE within the first six months following vaccination, particularly in the elderly (42, 43). The process of strain selection for the vaccines for the forthcoming season is managed by the World Health Organization (WHO) based on information gathered from the Global Influenza Surveillance and Response System (GISRS) and through the WHO influenza strain selection meeting. This occurs twice yearly, once for the strain selection for the northern hemisphere vaccine and once for the southern hemisphere vaccine. The composition of each vaccine may differ for each hemisphere or may remain the same. The vaccines are produced at two different times of the year and are usually distributed in September in the northern hemisphere and in March in the southern hemisphere (44, 45).

In general, how well vaccines work is measured by either randomised control trials (RCT) or observational studies such as cohort or case-control studies. RCTs (usually clinical trials) measure vaccine efficacy i.e. how well a vaccine works under optimal conditions. Observational studies measure vaccine effectiveness i.e. how well a vaccine works in real-world conditions (46).

1.1.4 Background to the universal childhood influenza vaccination programme in England

England has had a long-standing selective influenza vaccination programme that targets the populations at higher risk of severe disease due to influenza. An annual influenza immunisation programme was recommended in the late 1960s with the aim of directly protecting those with underlying clinical risk factors at higher risk of influenza-associated morbidity and mortality. In 2000, the programme was extended to include all people aged 65 years and over and in 2010, pregnancy was added as a clinical risk category for routine influenza immunisation (1). In 2012, a major review of the national influenza programme resulted in a recommendation by the Joint Committee on Vaccination and Immunisation (JCVI) that the seasonal influenza programme should be extended to all children aged two years to 16 years (47). The rationale for the extension of the programme is detailed below. The programme began in 2013 and is being delivered through a phased roll out across England with the ultimate goal of targeting all healthy children aged two to 16 years annually (Figure 1).

Vaccination was initially offered to all two and three-year-olds by GP practices at the start of the 2013/2014 season. Further age groups have been added incrementally each season to the programme including school age children for whom vaccination takes place in schools. Alongside the national roll-out a number of geographical pilot areas have vaccinated school aged children that were not being vaccinated as part of the national roll-out in those seasons (Figure 1). These geographical pilots aimed to test different delivery models for the programme and informed the future delivery of the programme by schools (48). They also permitted analysis of the overall and indirect effects (see Section 1.1.6) of the programme for instance by comparing influenza activity in pilot areas compared with non-pilot i.e. non-vaccinated, control areas (48-51).

For the first time in the 2019/2020 season, all primary school aged children were included in the national programme and in 2020/2021 children in the first year of secondary school were added (Year 7, 11-year-olds). The 2021/2022 season saw the biggest expansion of the programme when it was extended by an additional four age cohorts in secondary school so that children up to and including Year 11 (15-year-olds) were offered vaccination. This expansion was a temporary measure introduced to mitigate the impact of possible circulation of both influenza and COVID-19 (49). In the forthcoming

season, 2022/2023, it is planned to scale back the programme and vaccinate primary school aged children only (36, 52).

In the first year of the programme, 2013/2014, the trivalent LAIV vaccine, Fluenz, was used, however in subsequent seasons, the quadrivalent LAIV vaccine, Fluenz Tetra, was used. Whilst acknowledging that children who have not been vaccinated against influenza previously should be given two doses of the vaccine, JCVI recommended that most children should be offered a single dose of vaccine in order to vaccinate as many children as possible. However, two doses should be offered to children in clinical risk groups aged two to less than nine years who have not received the vaccine before (53).

Figure 1: Timetable of the introduction of the childhood influenza vaccination programme in England

The rationale for extending the vaccination programme to include children was multifactorial. In particular the ongoing and considerable burden of disease due to influenza in the general population, especially in young children, despite the longstanding selective vaccination programme, was a key consideration. This was in part due to the limited effectiveness of the vaccine as well as the inability to raise uptake further in targeted groups, despite considerable efforts (54). Some of the other main considerations and evidence used that were available at the time are summarised below:

- One of the key considerations was that healthy children, particularly younger children, have a high burden of influenza. Healthy children under the age of five years were found to have the highest influenza admission rate in England (34).

- Children are also recognised to play a key role in the transmission of influenza viruses (55, 56). In a household-based cohort study in France, households with one member with medically attended influenza-like illness (ILI) were followed up to identify secondary cases amongst household contacts (55). Risk of transmission was highest where contacts were exposed to preschool and school age children (55). In another French study, researchers showed that when using mathematical models fitted to surveillance data, holidays lead to a 20-29% reduction in influenza transmission to children (56). A systematic literature review of influenza outbreak data also demonstrated school closures reduce influenza transmission (57).

- Other mathematical models predicted that influenza vaccination of children would not only reduce the risk of infection in the immunised children themselves but also reduce transmission in the general population and thus reduce influenza-related disease in other non-targeted age groups, including the elderly and individuals in high-risk groups (58-62).

- Evidence from other countries indicated the indirect effects of vaccinating children including the experience in Japan where routine vaccination of school aged children between 1962 and 1994 occurred. Monthly all-cause death and pneumonia and influenza (P&I) deaths were used to estimate the number of deaths in excess of a calculated baseline level per month. The analysis suggested the programme prevented 10,000 – 12,000 P&I deaths for all ages annually (63). In 1994 the programme was discontinued, due to concerns regarding the ethics of vaccinating children and doubts about its effectiveness. Subsequently, excess mortality rates rose to levels similar to those seen prior to the introduction of the programme (63). Other studies have shown significant reductions in ILI incidence in the general population following vaccination of school aged children (64-67).

- The availability of a newly licensed LAIV provided an additional opportunity for extending the programme to children. RCTs in high income settings found LAIV gave high protection in children, as well as cross-protection to other strains (68-70). In addition, LAIV was understood to be more acceptable than traditional injectable vaccines for both children and their parents (69, 71).
- An economic evaluation of various strategies suggested that offering such a LAIV to all children was likely to be highly cost-effective (72).

1.1.5 Childhood influenza vaccination programmes in other countries

Several other countries have also begun to include vaccination of children against influenza to their national immunisation programmes (Table 1). In Europe, these include Austria, Finland, Ireland, Latvia and Slovakia (73). Poland and Slovenia also recommend vaccination of children however their programmes are not funded (73). Several other countries in Europe vaccinate children with underlying clinical risk factors including Belgium, Croatia, Cyprus, Czech Republic, Germany, Greece, Italy, Malta, Norway and Sweden.

In the US, the Centers for Disease Control and Prevention (CDC) recommends annual influenza vaccination for everyone six months and older (74). Likewise in Canada, the National Advisory Committee on Immunization (ACIP) recommends vaccination for all children six months and older (75). In Australia, influenza vaccination is provided for free under the National Immunisation Program for all children aged six months to under five years. Children over five years who have underlying clinical risk factors are also eligible for vaccination (76). In New Zealand, children four years and under who have been hospitalised with a respiratory illness or have a history of significant respiratory illness are recommended to be vaccinated (77).

Table 1: Childhood influenza vaccination programmes in other countries

Country	Vaccination programme	Vaccine offered
Austria	6-23 months 2-15 years	IIV IIV/LAIV
Finland	6 months – 6 years	IIV/LAIV
Ireland	2-17 years	IIV4/LAIV
Latvia	6 months – 6 years (mandatory)	IIV3
Slovakia	6 months – 12 years	IIV3

Poland	6 months – 18 years (not funded)	IIV3
Slovenia	6 months – 23 months (not funded)	IIV4
United States	6 months+ (not funded)	IIV/LAIV4
Canada	6 months+ (not funded)	IIV/LAIV
Australia	6 months to <5 years	IIV4
New Zealand	6 months to <5 years	IIV

1.1.6 Measuring protection from and impact of influenza vaccination programmes

Various study types can be employed to assess the different levels of protection or impact of vaccination (Figure 2) (78, 79). There are two components of the protective effect of a vaccine:

1. The direct protection of the individual by vaccination. The direct effect of vaccination is usually assessed through the difference in outcomes between vaccinated and unvaccinated individuals, all other things being equal. This is often assessed through vaccine efficacy studies pre-licensure through clinical trials or alternatively through post-licensure observational studies once a vaccine is in use and under normal public health conditions of the programme.

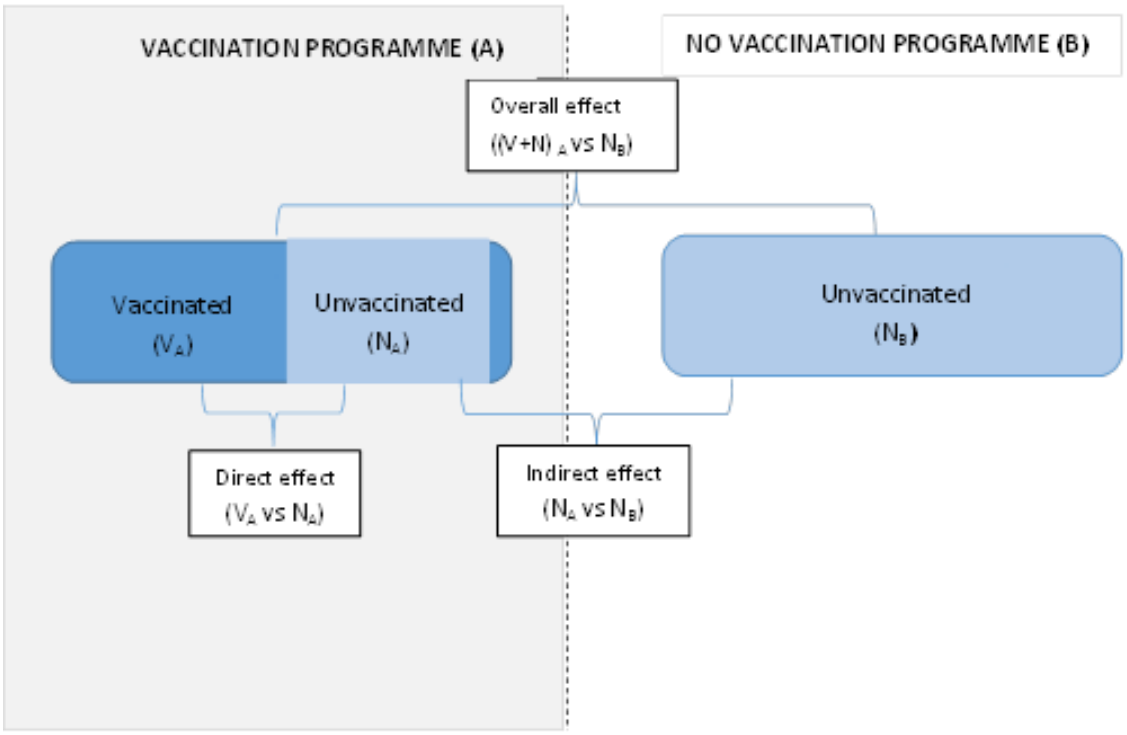
2. The indirect or herd effect. The protection of unvaccinated (or vaccinated but unimmunised) individuals in the population by reducing the number of cases and therefore the amount of transmission of the infectious agent. The indirect effect can be assessed at the individual level by comparing observations in unvaccinated contacts of those vaccinated to unvaccinated contacts of those who have remained unvaccinated, or at the population level by comparing influenza activity in non-targeted age groups in vaccinated areas to comparable age groups in non-vaccinated control areas.

The *overall effect or impact* of a vaccination programme can be measured at the population level by assessing the reduction in risk of infection in a community with the vaccination programme compared to a comparable population without the vaccination programme such as different geographical areas or before and after the introduction of a programme.

Indirect and overall effects of a vaccination programme can be assessed using aggregate population-level data available through routine surveillance sources over several years. With trial data it is theoretically possible to assess separately the direct, indirect and overall effects of vaccination (Figure 2). However, the influenza vaccination programme in England was introduced through a phased delivery model, with the ultimate goal of vaccinating all two to 17-year-olds in England. Part of the

rationale for this was to test different delivery models. Influenza activity in the same population could be compared before and after the introduction of the programme. However, variability in the severity of influenza epidemics and affected age groups each year, as well as secular trends (for example in admission and diagnostic patterns), make this challenging.

In addition to the national roll-out of LAIV vaccination of children aged two to four year olds, the roll-out to older children was initially implemented through a series of geographical pilots. This provides an opportunity to assess the effects of the programme (overall and indirect) by comparing influenza activity in vaccinated areas (i.e. pilot areas) with non-vaccinated, control areas. Some assessment of the indirect effect may be assessed by comparing activity in non-targeted age groups in vaccinated pilot areas to control areas and overall impact assessed by comparing average activity in vaccinated pilot areas relative to control areas.



*V = vaccinated, N = unvaccinated, A = vaccination programme, B = no vaccination programme.

Figure 2: Study designs for the evaluation of vaccine impact, adapted from Halloran ME *et al.* (78)

It is worth noting that the impact of a programme is distinct from disease impact (or burden). The impact of a vaccination programme is measured as described above. The disease impact of influenza will be explored in the second chapter of this Research Project. Disease impact describes how an influenza epidemic/pandemic affects society such as the impact on healthcare through hospitalisation

and Intensive Care Unit (ICU) admissions for example (80). Disease impact is influenced by the transmissibility of the virus and the seriousness of the disease.

1.1.7 Influenza vaccine efficacy and effectiveness

Estimates of influenza vaccine efficacy and effectiveness for influenza will vary according to the match of the vaccine strain to the circulating strain, the intervals between vaccination and influenza epidemics, vaccine product, population characteristics such as age in addition to the outcomes being examined (81). As such it is quite unusual compared with the efficacy and effectiveness of other vaccines as it will vary from season to season, by age group from season to season and with vaccination history (82). Estimates are often calculated against different influenza endpoints including deaths, severe disease, symptomatic disease, infection and transmission.

Generally, the protective effect of influenza vaccination against morbidity and mortality is modest. For example in a meta-analysis of ten RCTs, the pooled efficacy of TIV against laboratory-confirmed clinical influenza infection in adults aged 18-65, and hence pre-licensure, was 59% (95% confidence interval (CI) 51-67) (83).

Numerous RCTs have described the efficacy of LAIV against laboratory-confirmed clinical influenza infection in children, compared with placebo and IIV. Many suggested that LAIV provides good protection against influenza, with some suggesting higher efficacy of LAIV than IIV in children. Some of the results from key systematic reviews and meta-analyses are summarised in Table 2.

It is worth noting here that there are no formal thresholds for determining whether the protective effect of an influenza vaccine is low, modest or high for instance. This is largely subjective and based on interpretation in the context of other studies and on the outcome of interest.

Table 2: Summary of systematic reviews and meta-analyses of studies assessing the efficacy of LAIV in children

Author	Target groups	No. of studies/participants	Outcome	Search period	Findings for LAIV efficacy in children
Osterholm *et al.,* (2012) (83)	Adults and children	17 RCTs, 14 observational studies	Efficacy and effectiveness (medically attended, laboratory-confirmed influenza (RT-PCR and culture-confirmed)).	1 January 1967 – 15 February 2011	Pooled efficacy of LAIV from six RCTs was 83% (95% CI 69-91) in children aged 6 months to 7 years
Lukšić *et al.,* (2013) (84)	Children (<18 years)	30 studies (19 RCTs, 9 cohort and 2 case-control)	Efficacy and effectiveness (against ILI, laboratory-confirmed influenza + hospitalisations).	1910/1947 - 31 December 2011	Pooled efficacy of LAIV was between 76.4% (95% CI 68.7-85.0) and 83.4% (95% CI 78.3-88.8).
Jefferson *et al.,* (2018) (85)	Children (2 to <16 years)	41 clinical trials	Efficacy and effectiveness (against laboratory-confirmed influenza, ILI, otitis media, lower respiratory tract infection, hospitalisation due to otitis media, deaths).	1966/inception - 31 December 2016	Good efficacy of LAIV against confirmed influenza infection (up to 80%). Lower efficacy of IIV (59%). Low effectiveness of LAIV (around 33%) and IIV (around 36%) against ILI.
Ambrose *et al.,* (2012) (86)	Children (2-17 years)	Eight RCT studies	Efficacy against culture-confirmed symptomatic influenza illness.	Meta-analysis was based on all available RCTs relevant to the study. Trials included were conducted	Year one efficacy of 2 doses of LAIV was 83% (95% CI 78-87) against antigenically similar strains compared with placebo. Year 2 efficacy was 87% (95% CI 82-91) against similar strains. Compared with TIV, LAIV recipients experienced 44% (95% CI 28-56)

				between 1996 and 2005.	and 48% (95% CI 38-57) fewer cases of influenza illness caused by similar strains and all strains respectively.
Rhorer *et al.,* (2009) (87)	Children aged 6-71 months and 6-17 years	Nine RCT studies	Efficacy against culture-confirmed symptomatic influenza illness.	Meta-analysis was based on all studies that evaluated LAIV formulations approved for use in the US. Studies included were conducted between 1996 and 2005.	Efficacy 77% (95% CI 73-80%) for two doses in vaccine naïve children, 60% for one dose compared to placebo. When compared with IIV, those who received two doses of LAIV experienced 46% fewer cases of influenza illness.

In observational studies, influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza infection tends to be lower than efficacy estimates from clinical trials. Generally IVE is not higher than 60% and may be as low as 30% (45), although can be around 70-90% in healthy adults when the vaccine is well matched to the circulating strain (41, 84, 88). As noted earlier, age in particular is a known confounder of VE estimates since both vaccine coverage and the risk of illness from influenza infection vary considerably with age (45, 83, 87, 89). Effect modification by age may also be an issue. Together with the other known factors contributing to diversity in VE: virus factors such as the virus type and match with the vaccine strain; vaccine factors such as the vaccine type and mechanism of action; vaccinee factors such as underlying health status of vaccinees and previous exposure/vaccination, a person's first exposure to influenza virus is important; a concept known as original antigenic sin or imprinting (90). Original antigenic sin/imprinting is a term used to describe how the first exposure to influenza virus impacts lifelong immunity and hence the outcome of subsequent exposures. It is closely related to the concept of antigenic seniority where rather than just the first exposure, repeated lifetime influenza exposures create a hierarchy of antibody responses (91).

Recent observational studies of LAIV in children have provided mixed results with VE varying widely across seasons and countries (92-107). In the UK, recent adjusted VE estimates for LAIV against laboratory-confirmed medically attended influenza in children (two to 17 year olds) using the test-negative design (TND) have been mixed over the past several seasons (Table 3).

Table 3: Recent influenza vaccine effectiveness estimates for LAIV against laboratory-confirmed medically attended influenza in children aged 2 – 17 years in the UK

Author (year of publication), study season	Overall (95% CI)	A (95% CI)	A/H1N1pdm09 (95% CI)	A/H3N2 (95% CI)	B (95% CI)
Pebody (2015), 2014/15 (95)		31.2% (-29.5 to 63.4)		35.0% (-29.9 to 67.5)	100% (17.0 to 100.0)
Pebody (2016), 2015/16 (96)	57.6% (25.1 to 76.0)		41.5% (-8.5 to 68.5)		81.4% (39.6 to 94.3)
Pebody (2017), 2016/17 (97)	65.8% (30.3 to 83.2)	63.3% (22.0 to 82.7)		57.0% (7.7 to 80.0)	78.6% (-86.0 to 97.5)
Pebody (2019), 2017/18 (98)	26.9% (-32.6 to 59.7)	-1.8% (-108.1 to 50.2)	90.3% (16.4 to 98.9)	-75.5% (-289.6 to 21)	60.8% (8.2 to 83.3)
PHE (2019) 2018/19 (99)	48.6% (-4.4 to 74.7)		49.9% (-14.3 to 78.0)	27.1% (-130.5 to 77.0)	

PHE (2020) 2019/20 (100)	45.4% (12.6 to 65.9)		NA	30.5% (-18.5 to 59.2)	

A number of issues have been reported in recent seasons regarding the effectiveness of LAIV. In particular, conflicting IVE results across countries were observed in the 2015/2016 influenza season. Studies from the UK, Finland and Canada showed good overall effectiveness of LAIV in children although effectiveness was generally lower, specifically for the influenza A(H1N1)pdm09 component of the vaccine, compared with IIV (96, 103, 107). In contrast, the US reported an unexpected finding of no significant protection of LAIV. Studies carried out by the Flu VE Network demonstrated a lack of protection of LAIV against influenza A(H1N1)pdm09 in the 2013/2014 and 2015/2016 seasons (93, 106, 108). Meanwhile, significant effectiveness of IIV was shown in the same age group (109). Based on this evidence, the US ACIP recommended against the use of LAIV in the 2016/2017 and 2017/2018 seasons (102, 109, 110) although it was reinstated for the 2018/2019 season (111). Other countries continued to recommend LAIV during this period although in Canada they removed the preferential recommendation for LAIV in the 2016/2017 season (112). The US reintroduced the use of LAIV for the 2018/2019 season based on evaluations of previous seasons' data plus a systematic review and meta-analysis, which indicated that LAIV was effective against influenza B and that there was not a significant difference in the effectiveness of LAIV and IIV against influenza A(H3N2) (111). Vaccine manufacturer data also suggested improved replicative fitness (defined as the ability of a virus to produce infectious progeny in a given environment (113)) of a new (H1N1)pdm09-like virus included in the LAIV (111).

There are several hypothesised reasons for the discrepancy between the findings (107, 114). These include prior vaccination since this is more common in North America compared with Europe (115) and viral interference between the A/H1N1pdm09 vaccine strain and other LAIV vaccine viruses (116). Other possible reasons include a reduction in fitness in the vaccine strain and reduced ability of the A/H1N1pdm09 vaccine virus to replicate in the mammalian host (117), problems with vaccine production (117), and mismatches between the vaccine and circulating strain (118). After the 2013/2014 results in the US, the LAIV3 A/H1N1pdm09 A/California strain was replaced with an A/Bolivia/559/2013 strain which was intended to be more thermostable than the A/California strain (114). Despite this change concerns remained regarding the replicative fitness of the A/Bolivia strain and LAIV VE was still low relative to IIV in 2015/2016 (107). More recent studies have been able to demonstrate the reduced fitness of the A/Bolivia strain (119, 120). Dibben *et al.,* (2021) demonstrated

in vitro the reduced fitness of A/Bolivia in ferrets and showed that the vaccine strain was outcompeted in trivalent and quadrivalent formulations of LAIV (119).

Issues with the effectiveness of LAIV, as well as IIV, against influenza A(H3N2), strains have also been reported with estimates consistently lower than VE against other strains (107, 121). Suggested reasons include the rapid evolution of wild A(H3N2) viruses, egg-based manufacturing of vaccines increasing the chance of antigenic mismatch due to egg adaption, and the complexity of human immune responses such as the imprinting effect of the first encountered infection (104, 121). Whilst there are several potential reasons, egg adaptation has been linked to reduced IVE in a number of seasons including the 2012/2013, 2014/2015, 2016/2017 and 2017/2018 seasons (122-126). Egg-adaptation occurs when virus propagation in eggs causes selective pressure, driving the selection for variants that contain mutations that are better adapted for propagation in eggs and thus causing differences between the viruses in the vaccine and circulating ones (127).

1.2 Aims and objectives of the research project

1.2.1 Aims

The overall aims of this research project are to estimate the case-severity and disease impact of influenza infection in England, to systematically review the literature on, and estimate, the effectiveness of influenza vaccination against hospitalisation in children and to critically appraise the methodology used to produce such estimates.

1.2.2 Objectives

The specific objectives of this research project are as follows:

Objective 1: To estimate the case-severity and disease impact of influenza infection in England and to assess for an early signal of the impact of the childhood influenza vaccination programme on the burden of severe influenza in children (Chapter 2).

Objective 2: To critically review the literature on two observational study designs used to evaluate influenza vaccination programmes in high-income settings, the TND and the screening method (Chapter 3).

Objective 3: To systematically review the literature on the effectiveness of influenza vaccination against hospitalisation due to influenza infection in children (Chapter 4).

Objective 4: To estimate the vaccine effectiveness of influenza vaccination against laboratory-confirmed severe influenza infection in children in England, 2015/2016, using a TND study (Chapter 5).

Objective 5: To estimate the vaccine effectiveness of influenza vaccination against laboratory-confirmed severe influenza infection in children in England, 2013-2015, using the screening method (Chapter 6).

1.3 Data sources and data management

1.3.1 Data sources

Several different sources of surveillance data are used throughout this research project (Table 4).

The **UK Severe Influenza Surveillance System (USISS)** was established in 2010 following recommendations from WHO and European Centre for Disease Prevention and Control (ECDC) on the importance of establishing systems to monitor severe influenza (25, 32, 128). It is a routine hospital-based surveillance system for severe seasonal influenza consisting of two schemes: the mandatory and the sentinel system. The mandatory system provides information at aggregate level on weekly numbers of laboratory-confirmed ICU/High Dependency Unit (HDU) admissions in England, although these data were not used in this research project.

The USISS sentinel system data are used in this research project. The USISS sentinel system is a network of 26 to 36 acute National Health Service (NHS) trusts (covering an estimated population size of between 7,500,000 and 12,500,000, 14-24% of NHS acute trusts in England) across England. Initially, trusts were recruited using stratified random sampling according to size (small (<500) and large (>500 beds)), trust type (acute or teaching) and region (10 regions in England). Three trusts were randomly chosen from each region (one small, one large and one teaching), apart from London and the North-West where six were chosen due to the population being higher. This stratified random sampling was done in an attempt to make the recruited hospitals representative of those in England.

From the 2011/2012 influenza season (week 40 – 20) trusts have reported the aggregate weekly number of hospital admissions (at any level of care) due to laboratory-confirmed influenza by sub-

type and age-group. In the 2011/2012 – 2012/2013 seasons, detailed information on individual confirmed influenza cases of all ages admitted to ICU/HDU was also collected through the system. However, since the introduction of the childhood influenza programme, the system was modified to collect individual level information on children under 17 years of age hospitalised with confirmed influenza infection instead.

The **Influenza Immunization Uptake Monitoring Programme (ImmForm)** is the routine vaccine uptake monitoring system used in England (129). ImmForm is a UK Health Security Agency (UKHSA), formally Public Health England (PHE), website used to collect aggregated data on vaccine uptake at the vaccine provider level for immunisation programmes, as well as providing vaccine ordering facilities. In England, national influenza vaccine uptake data has been collected since the national vaccination programme was introduced in 2000. In 2004 the collection moved from a paper-based survey to a web-based reporting system, collected from GP practices via ImmForm.

The ImmForm system collects cumulative weekly, monthly and end-of-season aggregated uptake data from the registered GP population in England between 1 September and 31 January each influenza season, the period of time during which English GPs implement the seasonal influenza vaccination programme. It collects the aggregate number of patients vaccinated against influenza by the different target vaccination groups.

The weekly collection is an automated collection from a sentinel group of GP practices in England, with over 90% of all GPs reporting weekly. Automated data returns are submitted directly to ImmForm from GP software system suppliers on behalf of GP practices.

The monthly and end-of-season collections of GP level aggregated data are part automated, part manual collections of all GPs in England. Manual uploads are required for GP practices that do not have automated extractions set up or where they have had a failed automatic upload.

The weekly, monthly and end-of-season collections are available by Clinical Commissioning Group (CCG) for pre-school children (aged 2, 3 and 4 years) and those in clinical risk groups. CCGs are statutory NHS bodies responsible for the planning and commissioning of healthcare services for their local area.

For the school aged programme, uptake is collected via a separate monthly reporting system and is manually submitted onto Immform monthly and at the end of the season. Aggregate Local Authority (LA) level data is used to populate the ImmForm monthly data collection and is submitted by data providers and/or screening and immunisation coordinators at LA level.

The **Respiratory Datamart System (RDMS)** is a national sentinel laboratory surveillance system which collects details of individuals tested for suspect influenza infection by 14 laboratories located across England (130). Datamart was set up in response to the 2009 influenza pandemic as part of strengthening respiratory virus surveillance initially to collect both positive and negative results for influenza A(H1N1)pdm09. It was later extended to monitor other major respiratory viruses, including RSV, human metapneumovirus (hMPV), rhinovirus, parainfluenza viruses and adenovirus (130). Participating laboratories include all the major PHE/UKHSA regional laboratories, the national reference laboratory (the PHE/UKHSA Respiratory Virus unit of the Virus Reference Department, Colindale, London) and four local NHS laboratories.

Table 4: Summary of data sources

Data source	Used for objectives:	Description	Data available
USISS (Sentinel)	1 (case-severity and disease-impact – Chapter 2) 5 (VE screening method – Chapter 6)	Through the sentinel network of NHS acute trusts (20 – 36 trusts), aggregate and detailed information on confirmed influenza cases admitted to hospital is collected.	Individual level data on confirmed influenza hospital admissions (on those admitted to ICU/HDU in 2011/2012-2012/2013 and in children <17 years of age in 2013/2014 to date). Aggregate data on the number of influenza admissions by week, age group and type.
Respiratory Datamart	4 (VE TND – Chapter 5)	Datamart is a sentinel network of laboratories (n=14) in England that submit laboratory test results (positive and negative) for a range of respiratory viruses.	Laboratory test result data from 2010/11 including patient identifiers which are used to obtain vaccine uptake information.
ImmForm	5 (VE screening method – Chapter 6)	ImmForm is the system used to collect influenza vaccine uptake data at GP level.	Weekly, monthly and end-of-season aggregate-level data on reported

			influenza vaccine uptake by GPs by age-group and clinical risk groups.

1.3.2 Data management

This Research Project uses quantitative data from existing surveillance data collected by PHE, now known as the UKHSA. Most of the data used was collected and analysed under PHE/UKHSA's permissions under Section 251 of the NHS Act 2006 and the 2002 Health Service (Control of Patient Information) Regulations. No additional ethical approval was required. Data used in this project was stored in Microsoft Excel and analysed in STATA, on secure PHE network drives with controlled and restricted access. Data are stored according to the PHE Data Retention policy. This is usually for 30 years for data sets that don't include personal identifiable information (PII), but data sets containing PII may have to be deleted sooner.

Chapter 2

The severity and impact of influenza infection in England

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Student ID Number	194536	**Title**	Mrs
First Name(s)	Nicola Louise		
Surname/Family Name	Boddington		
Thesis Title	Severe influenza infection in England: assessing the impact and estimating vaccine effectiveness		
Primary Supervisor	Punam Mangtani		

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SECTION E

Student Signature	
Date	27/06/2022

Supervisor Signature	
Date	28/06/2022

Overview of Chapter

This chapter addresses objective 1 of this Research Project: To estimate the case-severity and disease impact of influenza infection in England and to assess for an early signal of the impact of the childhood influenza vaccination programme on the burden of severe influenza in children.

Copyright statement

2.1 Research paper 1

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Developing a system to estimate the severity of influenza infection in England: findings from a hospital-based surveillance system between 2010/2011 and 2014/2015

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SUMMARY

The UK Severe Influenza Surveillance System (USISS) was established following the 2009 influenza pandemic to monitor severe seasonal influenza. This article describes the severity of influenza observed in five post-2009 pandemic seasons in England. Two key measures were used to assess severity: impact measured through the cumulative incidence of laboratory-confirmed hospitalised influenza and case severity through the proportion of confirmed hospitalised cases admitted into intensive care units (ICU)/high dependency units (HDU). The impact of influenza varied by subtype and age group across the five seasons with the highest crude cumulative hospitalisation incidence for influenza A/H1N1pdm09 cases in 2010/2011 and in 0–4 year olds each season for all-subtypes. Case severity also varied by subtype and season with a higher hospitalisation: ICU ratio for A/H1N1pdm09 and older age groups (older than 45 years). The USISS system provides a tool for measuring severity of influenza each year. Such seasonal surveillance can provide robust baseline estimates to allow for rapid assessment of the severity of seasonal and emerging influenza viruses.

Key words: Influenza, Hospitalisation, Severity.

INTRODUCTION

Prior to the influenza pandemic in 2009, surveillance of severe respiratory infection in the UK resulting in hospitalisation was limited. New hospital-based surveillance systems for influenza were rapidly developed during the pandemic in order to fill this recognised gap [1, 2] and after, the UK, along with a number of other countries, implemented on-going seasonal influenza severe disease surveillance. The intention was that these systems, besides being utilised for seasonal influenza, would also be available during a future pandemic, following guidance from the WHO (World Health Organization) and the European Centre for Disease Prevention and Control (ECDC) [3, 4]. ECDC now coordinate the collection of case-based data on hospitalised severe influenza cases through the EISN (European Influenza Surveillance Network), although the systems employed for the surveillance of hospitalised cases vary significantly across Europe [5]. The UK Severe Influenza Surveillance System (USISS) is a web-based reporting scheme established in 2010 to collect surveillance data on hospitalised laboratory-confirmed influenza cases. It consists of a sentinel network of acute National Health

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Service (NHS) Hospital Trusts in England and aims to describe the epidemiology of severe influenza in time, place and person, to measure case severity and monitor the impact of influenza on the population.

Since the 2009 pandemic, a range of seasonal influenza subtypes have circulated in England. During the 2010/2011 season, the UK experienced a severe first post-pandemic season primarily due to influenza A/H1N1pdm09 mainly in young adults [6]. In contrast, the 2011/2012 season was characterised by low and late influenza activity, predominantly influenza A/H3N2. In 2012/2013 activity rose to higher levels than those seen in the previous season, with activity mainly due to A/H3N2 [7]. In 2013/2014, a season dominated by A/H1N1pdm09 with a higher peak compared with 2012/2013 [8]. In 2014/2015 moderate levels of influenza activity was seen with circulation of a drifted A(H3N2) strain that resulted in significant excess mortality, particularly in the elderly [9].

The severity of seasonal influenza is known to vary by subtype, with influenza B generally affecting younger age groups, influenza A/H3N2 causing severe disease in the elderly [10–12] and the new A/H1N1pdm09 affecting rather younger adults and children. A rapid understanding of the epidemiology of severe influenza each season is important to guide local and national public health planning on an annual basis and provide a baseline for future seasons. Obtaining a rapid assessment of the severity of a new emerging pandemic influenza virus is critical to inform evolving public health interventions. Three key indicators have been identified to measure severity – case severity (the likelihood that an individual who acquires an influenza infection will be hospitalised, be admitted to intensive care or die due to that infection); transmissibility (the likelihood that an infection will spread in the population as measured by parameters such as the household secondary attack rate or indirectly such as the GP (general practice) ILI (influenza-like illness) consultation rate) and population impact, which is a function of the two previous indicators (as measured by indicators such as cumulative hospitalisation incidence and excess mortality).

This paper investigates how the new USISS hospital-based surveillance system can potentially contribute to severity assessment by measuring the case severity and impact of seasonal influenza in the post-pandemic era over five influenza seasons from 2010 to 2015 using two severity measures and explores how this might be utilised for pandemic severity assessment.

METHODS

The USISS sentinel hospital network was initially piloted in the 2010/2011 season and ran in full during the following 2011/2012, 2012/2013, 2013/2014 and 2014/2015 influenza seasons in England.

Method of sampling

NHS Hospital Trusts were recruited using stratified random sampling in order to obtain a representative sample of contributors. A NHS Hospital Trust is an organisation that provides secondary health services within the English NHS. Trusts were stratified according to size (small (<500) and large (>500 beds)), trust type (acute [NHS Acute Trusts manage the hospitals in a particular area in England.] or teaching [Teaching hospitals/trusts are trusts which are affiliated to a medical school and provide clinical education and training to future health professionals.]) and region (there are 10 regions in England). Speciality trusts [Speciality trusts are regional or national centres for more specialised care.] were excluded. Three trusts from each English region (one small acute trust, one large acute trust and one teaching trust) were randomly chosen to participate. In London and the North West, where the population is higher, six trusts, i.e. two of each type were recruited instead of three. Voluntary enrolment of NHS Trusts in each season commenced approximately 1 month prior to the start of the collection (week 40). If a trust chose not to participate, then another was randomly selected from the same group of trusts, i.e. region and size. Trusts that were recruited after week 40 were asked to retrospectively submit their data from week 40 onwards. Trusts who participated in the previous season were asked to re-participate in the scheme the following season.

In total, 23 of 166 (15%) eligible acute hospital trusts from across England were successfully recruited and submitted weekly data during the 2010/2011 season. In the 2011/2012 season, 34 of 148 (23%) trusts were recruited, in 2012/2013, 31 of 143 (22%) trusts, in 2013/2014, 34 of 142 (24%) and in 2014/2015, 32 of 138 (23%) trusts participated. Of the trusts participating in 2010/2011, 13 were re-recruited to participate in 2011/2012, 12 in 2012/2013, 12 in 2013/2014 and 9 in 2014/2015. In each season the representativeness of trusts varied (12 large, 2 teaching and 9 small in 2010/2011; 16 large, 9 teaching and 9 small in 2011/2012, 15 large, 9 teaching and 7 small in 2012/2013, 18

large, 9 teaching and 7 small in 2013/2014 and 20 large, 8 teaching and 4 small in 2014/2015). A disproportionate number of large trusts were recruited since not all regions had hospitals which met the small trust category. In those cases, trusts with the smallest number of beds within that region were invited to participate.

Case definition

Trusts were asked to undertake respiratory sampling and laboratory investigation for influenza on all suspect influenza cases who presented in hospital with:

(a) Fever ($\geqslant$38 °C) or history of fever in the previous 7 days; and
(b) Two or more of the following symptoms: cough, sore throat, headache, rhinorrhoea, limb or joint pain, vomiting or diarrhoea.

A laboratory-confirmed case was defined as any person who was hospitalised and had laboratory-confirmed influenza A (H1N1pdm09, H3N2 or unknown) or B infection. For the purposes of intensive care units (ICU)/high dependency units (HDU) surveillance, a confirmed case was defined as any person who was admitted to ICU/HDU and had laboratory-confirmed influenza A (H1N1pdm09, H3N2 or unknown) or B infection. These case definitions remained consistent throughout the time period of this study. An HDU provides more extensive care to patients than a normal ward but not to the extent of an ICU.

Data collected

Consultant microbiologists or infection control teams at each participating hospital trust submitted a weekly aggregate report of all laboratory-confirmed cases admitted the previous week, by age group (<1, 1–4, 5–14, 15–44, 45–64 and 65+ year olds) and influenza subtype, at any level of care. In 2011/2012 and 2012/2013, each trust also submitted individual-level data on all cases admitted to ICU/HDU, although only aggregate data was used for this analysis.

Data was collected on cases through a web-based, secure IT (Information technology) platform. Transport-layer encryption is used for this web-tool and trust-based users are only able to access the data within their own hospital trust. The tool is not accessible through standard public internet connections. Data downloaded from the tool are stored on a secure Public Health England (PHE) server protected by a firewall and is only accessible to a minimum number of specific authorised users within the PHE network.

Sampling frame

Data collected between weeks 40 and 20 for the 2011/2012, 2012/2013, 2013/2014 and 2014/2015 seasons were used for this study apart from the 2010/2011 pilot season when data were only collected between weeks 40 and 13. Although the time frames for each period of influenza circulation were not identical in length, they were taken to be equal for the purposes of this study, since a seasonal (or annual) cumulative population risk of hospitalisation was being calculated.

Key indicators examined

Two measures were used to examine severity each season and are described below:
The impact was measured through:

- Risk (cumulative hospitalisation incidence) of hospitalisation was calculated from the number of laboratory-confirmed influenza hospitalisations overall, by age group and by influenza subtype over the season for the acute trust catchment population of all participating NHS Trusts in that corresponding season. The participating trust catchment population estimates were calculated by the ERPHO (Eastern Region Public Health Observatory) derived using Hospital Episode Statistics (HES) data on admissions between 2006/2007 and 2008/2009 and 2009 Office for National Statistics (ONS) mid-year estimates for LSOA (lower super output areas). The proportional flow method was used through which district populations are allocated, pro rata, to a provider based on the proportion of admissions from that district to that provider [13].

The case severity was measured through:

- The proportion of hospitalised-confirmed cases that were reportedly admitted into ICU/HDU, each season stratified by influenza subtype and age group.

Statistical methods

Regression analyses were performed to investigate variation in hospitalisation and ICU/HDU admissions between different subgroups. For each of the analyses the baselines were set as 2011/2012 for year, 15–44 year olds for age group and influenza B for

influenza subtype. Influenza A unsubtyped results were included as a separate subgroup.

Impact:

- Mixed-effects ordinal logistic regression was used for the analysis where the outcome was the weekly number of hospitalised cases for each trust grouped into three categories (0, 1, 2 or more). Season, age group, influenza subtype and logarithm of the population were the fixed-effect explanatory variables, while week and trust were included by means of a joint random effect. The main model consisted of the random effect, the logarithm of the population and all the two-way interactions between the remaining fixed effects. The P values for the interactions were obtained by means of a χ^2 test on the difference of χ^2 values of the main model and a model without the interaction being tested. Three separate models were then fitted with just one interaction and the other fixed effects as main effects only, with the resulting odds ratios (ORs) of larger counts of hospitalisation and 95% confidence intervals presented in the results section.

Case severity:

- For the analysis of ICU/HDU admissions, the outcome was a binary variable (admitted to ICU or not), no population variable and a mixed-effects logistic regression was used. Season, age group and influenza subtype were the fixed-effect explanatory variables, with reference groups of age group 15–44, influenza B and 2011/2012 respectively, while week and trust were included by means of a joint random effect. Highly non-significant interactions were removed one at a time in a backwards stepwise procedure, with the significance level chosen to be 5%. This analysis was restricted to the 2011/2012 and 2012/2013 seasons.

Laboratory methods

Influenza laboratory confirmation was carried out at a local level by NHS Hospital Trusts. Subtyping either took place locally or at the national PHE Influenza Reference Laboratory.

Ethics

Ethical approval was not sought for this scheme as it is undertaken as part of routine national surveillance under Section 3 of the Health Service (Control of Patient Information) Regulations 2002, Regulation 3 which provides statutory support for disclosure of such data by the NHS, and their processing by PHE, for the purposes of diagnosing communicable diseases and other risks to public health and recognising trends in such diseases and risks.

RESULTS

Impact: descriptive analysis

In 2010/2011, the dominant subtype was influenza A H1N1pdm09 – with 1242 of 1651 total hospitalised cases (75·2% of influenza hospital admissions) due to this subtype, with influenza B co-circulation. The 2011/2012 season was dominated by influenza A (485 of 551 total hospitalised cases, 88·0%) specifically influenza A/H3N2 (196/551, 35·6%) or influenza A not subtyped (281/551, 51·0%). The 2012/2013 season was dominated by influenza B (494/1400, 35·3%) and influenza A/H3N2 (375/1400, 26·5%). The 2013/2014 season was dominated by influenza A/H1N1pdm09 (543/907, 59·9%) and the 2014/2015 season by influenza A/H3N2 (887/1736, 51·1%).

The crude cumulative hospitalisation incidence risk for all influenza types in the 2010/2011 season was 22·0/100 000 in the trust catchment population compared with a cumulative incidence of 4·4/100 000 catchment population in 2011/2012, 12·1/100 000 in 2012/2013, 7·1/100 000 in 2013/2014 and 13·8/100 000 in 2014/2015 (Fig. 1).

By season overall, the age-specific cumulative hospitalisation incidence for all influenza types were highest in the 0–4 year olds each season (65·9/100 000 in 2010/2011, 19·4/100 000 in 2011/2012, 43·5/100 000 in 2012/2013, 23·0/100 000 in 2013/2014 and 30·7/100 000 in 2014/2015). By influenza subtype, the age-specific cumulative hospitalisation incidence for influenza A/H1N1pdm09 were highest in the 0–4 year olds followed by the 15–44 year olds, whereas for influenza A/H3N2 the rates were highest in the 0–4 year olds followed by the 65+ year olds. The median age for all cases in 2010/2011 was 33 years (interquartile range (IQR) 16–51) compared with 27 years in 2011/2012 (IQR 4–60), 33 years in 2012/2013 (IQR 6–58), 34 years in 2013/2014 (IQR 13–55) and 49 years in 2014/2015 (IQR 19–73).

Impact: statistical analysis

All the three two-way interactions were highly significant ($P < 0{\cdot}001$ in all cases (season–age group,

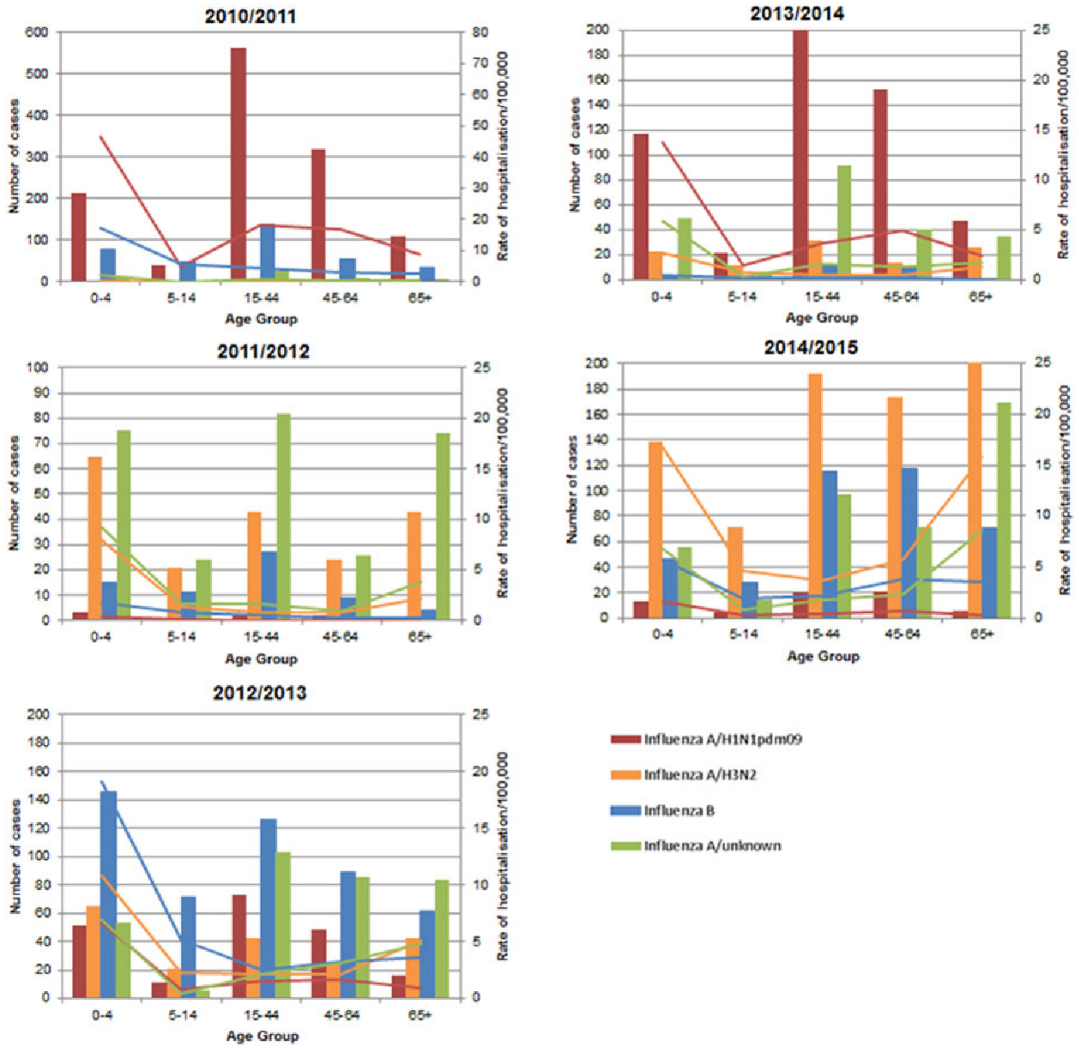

Fig. 1. Cumulative number of hospitalisations in participating trusts by age group and subtype during the 2010/2011–2014/2015 influenza seasons and cumulative hospitalisation incidence per 100 000 catchment population, England. Legend: Bars represent number of hospitalised cases and lines represent rate of hospitalisation per 100 000 catchment population in England.

season–influenza subtype and influenza–subtype-age group)).

By age group, the impact was highest in the under-5 year olds: overall the adjusted ORs of larger counts of hospitalisation were highest in each of the five seasons for 0–4 year olds compared with other age groups (Table 1). The over 65+ year olds were, in three of five seasons, the age group with the second highest OR of hospitalisation. The highest OR of hospitalisation overall by age and season was seen in the 0–4 year olds in the 2010/2011 season (OR 33·7).

The impact by influenza subtype varied across the seasons (Table 2). In 2010/2011 and 2013/2014 the highest OR of hospitalisation by influenza subtype by season were seen in those admitted with influenza A/N1N1pdm09 (OR 47·7 in 2010/2011, 6·9 in 2013/2014) (Table 2). For the remaining seasons, the OR were highest for those admitted with influenza A/unknown in 2011/2012 (OR 3·4), influenza B in 2012/2013 (OR 7·0) and influenza A/H3N2 in 2014/2015 (OR 10·4).

As with season, impact was highest in the 0–4 year old age group regardless of the influenza subtype

Table 1. *Adjusted ORs of hospitalisation by season and age group*

Age group	OR (95% CI) (2010/2011)	OR (95% CI) (2011/2012)	OR (95% CI) (2012/2013)	OR (95% CI) (2013/2014)	OR (95% CI) (2014/2015)
0–4	33·7 (23·1–49·2)	6·6 (4·6–9·5)	13·8 (9·8–19·3)	7·2 (5·1–10·3)	10·3 (7·2–14·6)
5–14	8·7 (6·0–12·7)	1·5 (1·0–2·2)	2·6 (1·8–3·6)	1·1 (0·7–1·6)	2·7 (1·9–3·7)
15–44	10·2 (7·7–13·3)	1·00	2·7 (2·13–3·48)	2·0 (1·5–2·5)	2·9 (2·3–3·7)
45–64	10·0 (7·4–13·4)	0·9 (0·6–1·2)	3·5 (2·7–4·5)	2·4 (1·8–3·2)	5·1 (3·9–6·6)
65+	6·1 (4·3–8·8)	1·8 (1·3–2·7)	4·6 (3·4–6·2)	2·1 (1·5–3·0)	7·5 (5·7–10·0)

OR, odds ratio; CI, confidence interval.

Table 2. *Adjusted ORs of hospitalisation by season and influenza subtype*

Influenza subtype	OR (95% CI) (2010/2011)	OR (95% CI) (2011/2012)	OR (95% CI) (2012/2013)	OR (95% CI) (2013/2014)	OR (95% CI) (2014/2015)
A/H1N1pdm09	47·7 (35·0–65·1)	0·1 (0·1–0·3)	2·6 (1·9–3·6)	6·9 (5·1–9·2)	1·1 (0·8–1·6)
A/H3N2	0·2 (0·1–0·6)	2·7 (1·9–3·7)	4·5 (3·3–6·1)	1·3 (1·0–1·9)	10·4 (7·7–14·0)
A/unknown	2·2 (1·5–3·4)	3·4 (2·5–4·7)	3·9 (2·9–5·3)	2·7 (2·0–3·7)	4·9 (3·6–6·7)
B	16·7 (12·0–23·0)	1·00	7·0 (5·2–9·3)	0·5 (0·3–0·7)	6·0 (4·4–8·1)

OR, odds ratio; CI, confidence interval.

Table 3. *Adjusted ORs of hospitalisation by influenza subtype and age group*

Age group	OR (95% CI) (A/H1N1pdm09)	OR (95% CI) (A/H3N2)	OR (95% CI) (A/unknown)	OR (95% CI) (B)
0–4	4·5 (3·3–6·1)	3·8 (2·8–5·2)	3·5 (2·6–4·7)	4·1 (3·0–5·5)
5–14	0·7 (0·5–0·9)	1·0 (0·7–1·3)	0·4 (0·3–0·6)	1·4 (1·1–1·8)
15–44	1·3 (1·1–1·6)	0·8 (0·6–0·9)	0·9 (0·8–1·1)	1·00
45–64	1·8 (1·4–2·1)	1·1 (0·9–1·3)	1·0 (0·8–1·2)	1·3 (1·0–1·6)
65+	1·0 (0·7–1·3)	2·1 (1·6–2·6)	1·9 (1·5–2·4)	1·12 (0·9–1·5)

OR, odds ratio; CI, confidence interval.

(Table 3). The odds amongst other age groups after 0–4 year olds however varied with the subtype with influenza A/H1N1pdm09 higher in younger adults, i.e. 15–64 year olds, whereas influenza A/H3N2 and A/unknown was higher in the 65+ year olds and influenza B was higher in school-age children (5–14 year olds) and middle-aged adults (45–64 year olds).

Case severity: descriptive analysis

The proportions of hospitalised cases that were admitted to ICU/HDU are presented in Table 4. In 2010/2011, overall 14·1% (237/1681) of hospitalised cases were admitted to ICU/HDU, 8·3% (46/551) in 2011/2012 and 11·8% (165/1400) in 2012/2013. Case severity varied by influenza subtype and age group. In 2010/2011 the highest proportion of hospitalised cases admitted to ICU/HDU were influenza A/unknown cases, although the numbers were small, followed by A/H1N1pdm09 cases, the main circulating strain that season. Only 46 cases were admitted into ICU/HDU in 2011/2012 with the highest proportion of ICU/HDU admissions being for A/H3N2 and B cases at 11·7% and 10·6%, respectively. In 2012/2013 the highest proportion of ICU/HDU admissions were influenza A/H1N1pdm09 cases (20·6%) and by age group, in those aged 15 years and older.

Case severity: statistical analysis

Neither the season–influenza subtype nor season–age group interaction were significant ($P = 0·5$ and 0·2, respectively). While the age group–influenza subtype was not significant, it was nevertheless retained as it

Table 4. *Proportion of hospitalised cases admitted to ICU/HDU in participating trusts by age group and influenza subtype*

Season	Age group	Number of influenza A/H1N1pdm09 ICU/HDU cases	Proportion of A/H1N1pdm09 cases admitted to ICU/HDU (%)	Number of Influenza A/H3N2 ICU/ HDU cases	Proportion of A/H3N2 cases admitted to ICU/HDU (%)	Number of influenza B ICU/HDU cases	Proportion of influenza B cases admitted to ICU/HDU (%)	Number of influenza A/unknown ICU/HDU cases	Proportion of A/unknown cases admitted to ICU/HDU (%)	Total number of ICU/ HDU cases	Overall proportion of hospitalised cases admitted to ICU/HDU (%)
2010/2011	0–4	9	4·2	0	0·0	0	0·0	1	10·0	10	3·3
	5–14	3	7·7	0	–	2	4·2	0	0·0	5	5·7
	15–44	103	18·3	0	0·0	5	3·6	6	24·0	114	15·7
	45–64	81	25·4	0	0·0	10	18·2	4	40·0	95	24·7
	65+	10	9·3	0	0·0	3	9·1	0	0·0	13	8·8
	All ages	206	16·6	0	0·0	20	5·7	11	21·2	237	14·4
2011/2012	0–4	0	0·0	5	7·7	0	0·0	75	4·0	8	5·1
	5–14	0	0·0	3	14·3	3	27·3	24	4·2	7	12·3
	15–44	0	0·0	4	9·3	0	0·0	82	7·3	10	6·5
	45–64	1	50·0	1	4·2	4	44·4	26	3·8	7	11·5
	65+	0	–	10	23·3	0	0·0	74	5·4	14	11·6
	All ages	1	12·5	23	11·7	7	10·6	281	5·3	46	8·3
2012/2013	0–4	6	11·8	10	12·0	8	5·5	53	3·8	26	7·8
	5–14	2	18·2	2	6·5	5	7·0	6	0·0	9	7·6
	15–44	17	23·3	10	8·8	7	5·6	103	7·8	42	10·1
	45–64	13	27·1	4	6·6	18	20·2	86	12·8	46	16·2
	65+	3	18·8	14	16·1	14	22·6	84	13·1	42	16·9
	All ages	41	20·6	40	10·7	52	10·5	332	9·6	165	11·8

ICU, intensive care units; HDU, high dependency units.

Table 5. *Adjusted ORs of ICU/HDU admission in 2011/2012 and 2012/2013 by influenza subtype and age group*

Influenza subtype	Age group	ORs	95% CI	*P* value
A/H1N1pdm09	0–4	2·43	0·73–8·09	
	5–14	3·27	0·53–20·36	
	15–44	5·72	2·11–15·52	
	45–64	8·97	3·09–25·99	
	65+	5·49	1·13–26·70	
A/H3N2	0–4	2·16	0·81–5·80	
	5–14	2·00	0·56–7·09	
	15–44	1·78	0·66–4·80	
	45–64	1·12	0·32–3·85	
	65+	4·47	1·73–11·50	
A/unknown	0–4	0·85	0·25–2·93	
	5–14	0·92	0·10–8·50	
	15–44	1·91	0·71–5·15	
	45–64	2·93	1·05–8·15	
	65+	2·72	1·01–7·38	
B	0–4	0·96	0·33–2·85	
	5–14	1·89	0·62–5·80	
	15–44	1·00		0·03
	45–64	5·94	2·30–15·36	
	65+	7·08	2·50–20·01	
Season	2011/2012	1·00		0·9
	2012/2013	1·03	0·68–1·58	

ICU, intensive care units; HDU, high dependency units; ORs, odds ratios; CI, confidence interval.

was close to statistical significance and the likelihood ratio test suggested it significantly improved the fit of the model.

The adjusted odds that a case admitted to hospital with influenza infection will be admitted to ICU/HDU are given in Table 5. Overall the odds of being admitted to ICU/HDU were consistently higher in the older age groups (45 years and above) for each of the subtypes. The highest odds of admission to ICU/HDU overall was in 45–64 year olds admitted with influenza A/H1N1pdm09 (OR 8·97). The odds of admission to ICU/HDU were generally highest following influenza A/H1N1pdm09 infection, followed by influenza A/H3N2 and then influenza B for each age group, except for those >65 years of age, where the highest odds were seen for influenza B (Table 5).

DISCUSSION

The value of USISS sentinel surveillance

The USISS sentinel system has now run successfully for five seasons up until 2014/2015 and has been able to provide measures of the severity of influenza each season on a weekly and end of season basis. Data collected over these seasons has allowed for inter-seasonal comparisons of influenza and has provided a unique opportunity to describe the epidemiology of severe influenza in England in the post-2009 influenza pandemic era.

Estimates of severity

Two measures were used to assess influenza case severity and impact. In this study each provided valuable information by influenza subtype and age group which can have important public health implications and inform healthcare resource allocation.

We clearly show that the case severity, i.e. the proportion of cases admitted to hospital with confirmed influenza infection being admitted to ICU/HDU were consistently higher in the older age groups (45+) for each influenza subtype. Furthermore, the OR of ICU/HDU admission were generally higher for influenza A/H1N1pdm09 cases compared with the other seasonal strains.

However, we also show that the impact, as measured by the cumulative incidence of hospitalisation varied by influenza subtype and age group across the five seasons. By age group, the greatest impact was consistently observed in the paediatric population <5 years of age thus supporting the rationale for the introduction of universal childhood influenza vaccine programme in 2013/2014, which was initially offered to those 2 and 3 years of age to provide direct protection to this group [14]. However, in seasons during which influenza A/H3N2 was the dominant circulating subtype, the impact was also high in the older age groups, confirming that influenza A/H3N2 can cause considerable impact in older age groups. This variation in impact presumably reflects both the underlying immunity profile of the population due to previous exposure to infection and vaccination; the amount of influenza that circulates and the likelihood that a person will develop severe disease following infection (case severity). Thus for influenza A/H1N1pdm09, although the case severity is highest in the elderly, the impact is mainly seen in younger adults and children, due to underlying cross-protective immunity in the elderly [15], which limits the impact in this age group. This age-specific variation in impact of circulating strains can have important local public health consequences with influenza A/H3N2 often resulting in outbreaks in care homes, resulting in

notable mortality [10, 11, 16, 17], whereas influenza B often results in outbreaks in schools [7]. Rapidly estimating the severity of influenza is very important to determine the morbidity and mortality impact in different segments of the population, to guide anti-viral strategy and vaccination programmes and plan for seasonal epidemics and future pandemics. Such measures of severity have also been suggested as parameters for defining pandemic scenarios [18].

Limitations of the study

There are a number of limitations of this study. Firstly, across all seasons a large proportion of influenza cases with no subtyping information were reported. In 2010/2011 and 2013/2014 due to the predominance of influenza A/H1N1pdm09, it is likely that the majority of these cases were A/H1N1pdm09, and in 2014/2015 to influenza A/H3N2. However, during the other seasons more than one strain circulated.

Inter-seasonal comparisons are limited within this study, particularly for the hospitalisation incidence analysis, since the same trusts did not participate each season and there was a different mix across the recruitment stratum in each season. Under-ascertainment of cases within the system may have occurred, as although guidance on who to test was provided to minimise differential testing and ensure standardisation, trusts may still have applied local testing criteria to hospital admissions. Other studies have shown underdetection to vary by age, site and season and have attempted to correct surveillance data for under-detection [19]. In addition, the trust's target population data used to calculate hospitalisation rates were based on the latest available 2009 ONS data for all years and HES data from 2006/2007 and 2008/2009 and it was assumed that there have not been any major changes with trust populations over this period. However, the availability of these catchments areas allowed for age-specific estimates of hospitalisation rates. While censoring may have occurred during the season, when some severe events resulting from infections to date have yet to occur, this is less likely to be an issue in a retrospective analysis such as this where data was updated throughout the seasons. Real-time monitoring will require statistical adjustment to take into account these reporting delays.

In addition, the higher impact in children may be because children shed more virus and for longer and are therefore more likely to be correctly ascertained as influenza cases, compared with the elderly who shed less and are less likely to fit the case definition as they do not always have fever with influenza [20].

CONCLUSIONS

This study has highlighted the value in using a variety of severity measures to compare between seasons, age groups and influenza subtypes. The study has demonstrated the varying severity of influenza by age and influenza subtype. In particular, we demonstrate the severity of influenza A/H3N2 and the impact of hospitalisations in children. With the start of the introduction of universal paediatric influenza vaccination ultimately for all 2–16 year olds with LAIV (live attenuated influenza vaccine), it will be important to monitor the performance of the vaccine programme in terms of reducing hospitalisations in children and indirectly through reducing transmission in the population, reducing infection across all groups and thus severe disease in adults. This study will provide baseline rates to enable this over the coming seasons.

The USISS system provides a consistent and timely tool for estimating case severity and impact during seasonal influenza epidemics and provides baseline data to evaluate and to guide rapid severity assessment during future influenza pandemics.

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DECLARATION OF INTEREST

None.

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2.2 The severity and impact of influenza infection in England – updated data and analysis

2.2.1 Background

In the published article included in Section 2.1 of this Chapter, data from a sentinel hospital influenza surveillance system were used to describe the severity of seasonal influenza over five influenza seasons from 2010 to 2015 (33). The study demonstrated the varying severity of influenza by age and influenza subtype and provided baseline rates of hospitalisation prior to the introduction of the childhood influenza vaccination programme in 2013/2014 and for use in future influenza pandemics. It also demonstrated the utility of the sentinel UK Severe Influenza Surveillance System (USISS) in providing a consistent and timely tool for these estimations.

With further data now available, this study has been updated to include the influenza seasons from 2015/2016 to 2019/2020 to further assess the disease impact of seasonal influenza overall and by age group and influenza subtype. The additional data also provides an opportunity to assess the impact of the childhood influenza vaccination programme in England. The programme has been rolled out incrementally by vaccinating additional age cohorts each season as described in the Background Chapter. Since reducing severe outcomes is one of the priorities of the programme it is important to examine whether reductions in hospitalisations due to influenza are observed.

2.2.2 Methods

The annual disease impact of influenza was measured through risk (cumulative hospitalisation incidence) of hospitalisation by calculating the number of laboratory-confirmed influenza hospitalisations over each season (week 40 to week 20) for the acute trust catchment population of all participating National Health Service (NHS) Trusts in England in each corresponding season. It was not possible to assess the case-severity of hospitalisations, i.e. the risk of Intensive Care Unit/High Dependency Unit (ICU/HDU) admission amongst hospitalised cases, for these subsequent seasons since the data collection on ICU/HDU cases ceased before the 2013/14 season.

In the published article, participating trust catchment population estimates were calculated by the Eastern Region Public Health Observatory (ERPHO) and derived using Hospital Episode Statistics (HES) data on admissions between 2006/2007 and 2008/2009 and 2009 Office for National Statistics (ONS)

mid-year estimates for Lower Super Output Areas (LSOA) (131). For this updated analysis, more recently estimated catchment populations by Public Health England (PHE) have been used (132). The estimates were similarly derived using the proportional flow method, where the proportion of admissions to the selected Trust for a Middle Super Output Area (MSOA) is applied to the total population estimate for that MSOA. The resulting figures are then summed to give the trust catchment population. Data through the PHE tool is available from 2011 to 2018 (132). Data is provided by age group (19 groups) including the following age groups for the paediatric ages: 0-4 years, 5-9 years, 10-14 years and 15-19 years.

NHS hospital trusts were originally recruited to the USISS sentinel system using stratified random sampling according to size, trust type and geographical region. In subsequent seasons, recruitment was predominantly based on convenience sampling to replace any trusts that had left the scheme. Attempts were made to recruit 'similar' trusts (based on size, trust type and region) to the ones that had left, however, in many instances, this was not possible as there were not enough trusts left to select from. Over the study period, the recruited NHS trusts covered a population of 14.2% of the population in England in 2010/2011 and 23.7% of the population in 2013/14 (Table 1). All geographical regions were represented in four out of the ten study seasons. In the remaining seasons, the 2010/11 season and from 2015/16, either one or two regions from England were not represented (Table 1).

Data collected through the USISS sentinel system comprises weekly aggregate number of laboratory-confirmed influenza admissions by age group and influenza subtype. In the first few seasons, data were collected by the following age groups: under 1 year, 1-4 years, 5-14 years, 15-64 years and 65+ years. The age groups were disaggregated in the later seasons in line with the roll-out of the childhood influenza vaccination programme. By the 2016/17 influenza season, USISS data were collected by individual age year groups for 0-16-year-olds. The age groups used for this analysis were 0-4 years, 5-14 years, 15-64 years and 65+ year-olds since both numerator and denominator data were only available by these age groups for all seasons.

A mixed-effects ordinal logistic regression was performed to investigate variation in hospitalisation between different subgroups. All seasons were included, including those from the previous analysis, and the baselines were set as 2012/2013 for season, 15-44 year-olds for age group and influenza A(H3N2) for influenza subtype. These differ from those used in the original analysis (previously 2011/2012, 15-44 year-olds and influenza B). The baseline year was changed to 2012/2013 since 2011/2012 was a relatively low influenza activity season whereas 2012/2013 saw moderate influenza activity and was before the introduction of the childhood vaccination programme. Influenza B as the baseline was changed to influenza A(H3N2) since it occurred more frequently across the study

seasons. The outcome for the model was the weekly number of hospitalised cases for each trust grouped into three categories (0, 1, 2 or more). Season, age group and influenza subtype were the fixed explanatory variables, whilst week and trust were included by means of a joint random effect. The main model consisted of the random effect, the logarithm of the population and a three-way interaction between the fixed effects. The resulting odds ratios (ORs) of larger counts of hospitalisation and 95% confidence intervals (CIs) are presented in the results section.

Table 1: Population coverage of UK Severe Influenza Surveillance System (USISS) participating trusts in England, 2010/11 – 2019/20

Season	England population mid-year estimate	No. of participating USISS trusts	Total population of participating trusts	% of England population	No. of geographical regions (N=10) represented by USISS trusts
2010/11	52,642,500	23	7,493,064	14.2%	8
2011/12	53,107,200	36	12,468,055	23.5%	10
2012/13	53,493,700	32	11,588,467	21.7%	10
2013/14	53,865,800	35	12,747,747	23.7%	10
2014/15	54,316,600	32	12,598,255	23.2%	10
2015/16	54,786,300	25	10,464,197	19.1%	9
2016/17	55,268,100	26	10,670,527	19.3%	8
2017/18	55,619,400	25	11,803,147	21.2%	9
2018/19	55,977,200	23	10,418,297	18.6%	8
2019/20	56,287,000	22	10,565,694	18.8%	8

2.2.3 Results

- **Impact of influenza: descriptive analysis**

The dominant influenza types/subtypes amongst USISS hospitalised cases have continued to vary since the 2014/2015 season, the last season included in the published article. The 2015/2016 season was dominated by influenza A(H1N1)pdm09 and influenza B (Table 2). The 2016/2017 season was dominated by influenza A(H3N2) and the 2017/18 season by influenza B and influenza A(H3N2) although both seasons had a large proportion of cases with influenza A not subtyped (Table 2). The 2018/2019 season was dominated by influenza A(H1N1)pdm09 and influenza A not subtyped and the 2019/2020 season by influenza A(H3N2) and influenza A not subtyped (Table 2).

Table 2: Cumulative number of hospitalisations in participating USISS sentinel trusts by influenza subtype during the 2010/2011 – 2019/2020 influenza seasons

	Influenza A(H1N1)pdm09 (%)	Influenza A(H3N2) (%)	Influenza B (%)	Influenza A not subtyped (%)	Total number of hospitalised cases
2010/11	1242 (75.2)	4 (0.2)	353 (21.4)	52 (3.1)	1651
2011/12	8 (1.5)	196 (35.6)	66 (12.0)	281 (51.0)	551
2012/13	199 (14.2)	375 (26.8)	494 (35.3)	332 (23.7)	1400
2013/14	543 (59.8)	108 (11.9)	32 (3.5)	225 (24.8)	908
2014/15	67 (3.7)	891 (49.8)	385 (21.5)	445 (24.9)	1788
2015/16	1554 (55.2)	38 (1.4)	819 (29.1)	403 (14.3)	2814
2016/17	27 (1.7)	1043 (66.3)	87 (5.5)	415 (26.4)	1572
2017/18	675 (6.6)	2158 (21.1)	4983 (48.8)	2399 (23.5)	10215
2018/19	1865 (32.9)	849 (15.0)	43 (0.8)	2918 (51.4)	5675
2019/20	253 (5.1)	1479 (30.1)	361 (7.3)	2826 (57.5)	4919

The crude yearly hospitalisation incidence risk for all influenza types for all ages and by age group are shown in Table 3 and Figure 2. Apart from the 2016/2017 season, the cumulative hospitalisation incidence risks were all higher in the more recent seasons (from 2015/2016) compared with those included in the published paper (2010/2011 to 2014/2015) (Table 3, Figure 1).

By season, the age-specific cumulative hospitalisation incidence for all influenza types were highest in children 0-4 years of age in the majority of seasons. The exceptions were the 2016/2017 and 2017/2018 seasons when the rates were highest in the over 65-year-olds and the 2014/2015 and

2019/2020 seasons when rates were comparable between 0-4 year-olds and the over 65-year-olds (Table 3, Figure 1).

By influenza subtype, the age-specific cumulative hospitalisation incidence for influenza A(H1N1)pdm09 was highest in the 0-4 year-olds with lower impact in all the other age groups over the study seasons. For influenza A(H3N2), rates were highest in the 0-4 year-olds and the 65+ year-olds. The impact of influenza B was also mainly seen in the 0-4 year-olds, with the notable exception of the 2017/2018 season when influenza B was one of the main circulating types and the impact was seen across all age groups. Rates by age group and influenza sub-type for each of the seasons from 2010/2011 to 2019/2020 are shown in Table 3 and Figure 2.

Table 3: Cumulative number of hospitalisations in participating trusts by age group and subtype, and cumulative hospitalisation incidence per 100,000 catchment population, during the 2010/2011 – 2019/2020 influenza seasons, England

Season	Age Group	Population trust catchment areas	Cumulative hospitalisation incidence of A/H1N1pdm09 /100,000	Cumulative hospitalisation incidence of A/H3N2 /100,000	Cumulative hospitalisation incidence of influenza B /100,000	Cumulative hospitalisation incidence of A/unknown /100,000	Total number of hospitalised cases	Cumulative hospitalisation incidence /100,000
2010/11	0-4	461,482	46.4	0.2	17.1	2.2	304	65.9
	5-14	810,731	4.8	0.0	5.9	0.1	88	10.9
	15-44	3,095,523	18.2	0.0	4.5	0.8	726	23.5
	45-64	1,902,669	16.8	0.1	2.9	0.5	385	20.2
	65+	1,222,659	8.8	0.1	2.7	0.5	148	12.1
	All ages	**7,493,064**	**16.6**	**0.1**	**4.7**	**0.7**	**1651**	**22.0**
2011/12	0-4	938,096	0.3	6.9	1.6	8.0	158	16.8
	5-14	1,686,444	0.1	1.2	0.7	1.4	57	3.4
	15-44	5,856,677	0.0	0.7	0.5	1.4	154	2.6
	45-64	3,498,226	0.1	0.7	0.3	0.7	61	1.7
	65+	2,193,103	0.0	2.0	0.2	3.4	121	5.5
	All ages	**14,172,546**	**0.1**	**1.4**	**0.5**	**2.0**	**551**	**3.9**
2012/13	0-4	884,604	5.8	9.4	16.5	6.0	333	37.6
	5-14	1,553,708	0.7	2.0	4.6	0.4	119	7.7
	15-44	5,446,116	1.3	2.1	2.3	1.9	415	7.6
	45-64	3,041,565	1.6	2.0	2.9	2.8	284	9.3
	65+	1,902,563	0.8	4.6	3.3	4.4	249	13.1
	All ages	**12,828,556**	**1.6**	**2.9**	**3.9**	**2.6**	**1400**	**10.9**
2013/14	0-4	970,220	12.1	2.4	0.4	5.3	195	20.1
	5-14	1,703,793	1.3	0.7	0.2	0.4	43	2.5
	15-44	5,851,269	3.5	0.5	0.2	1.6	340	5.8
	45-64	3,281,610	4.7	0.4	0.3	1.2	218	6.6
	65+	2,098,571	2.3	1.3	0.1	1.7	112	5.3
	All ages	**13,905,463**	**3.9**	**0.8**	**0.2**	**1.6**	**908**	**6.5**

2014/15	0-4	874,917	1.5	15.8	5.4	6.5	255	29.1
	5-14	1,580,273	0.3	4.4	1.7	0.9	115	7.3
	15-44	5,044,762	0.4	3.9	2.3	2.0	433	8.6
	45-64	3,099,836	0.7	5.6	3.8	2.9	405	13.1
	65+	2,150,379	0.3	14.6	3.5	8.6	580	27.0
	All ages	**12,750,167**	**0.5**	**7.0**	**3.0**	**3.5**	**1788**	**14.0**
2015/16	0-4	727,064	46.5	0.8	18.7	7.4	534	73.4
	5-14	1,335,317	5.1	0.1	6.5	0.6	165	12.4
	15-44	4,090,638	10.7	0.3	8.0	3.3	910	22.2
	45-64	2,532,458	16.6	0.3	4.6	4.8	665	26.3
	65+	1,778,720	16.3	0.6	8.6	4.8	540	30.4
	All ages	**10,464,197**	**14.9**	**0.4**	**7.8**	**3.9**	**2814**	**26.9**
2016/17	0-4	725,425	0.3	7.4	1.4	1.1	74	10.2
	5-14	1,376,173	0.0	2.8	0.3	0.5	50	3.6
	15-44	4,120,649	0.1	5.0	0.3	3.3	357	8.7
	45-64	2,607,940	0.2	7.3	0.8	2.5	285	10.9
	65+	1,840,340	0.7	30.2	2.1	10.8	806	43.8
	All ages	**10,670,527**	**0.3**	**9.8**	**0.8**	**3.9**	**1572**	**14.7**
2017/18	0-4	755,999	21.2	22.9	28.3	16.9	675	89.3
	5-14	1,525,942	2.6	5.8	15.3	2.9	407	26.7
	15-44	4,501,888	3.7	7.9	18.8	10.2	1830	40.6
	45-64	2,914,372	4.6	13.2	37.1	15.5	2052	70.4
	65+	2,104,946	8.2	54.9	123.9	62.5	5251	249.5
	All ages	**11,803,147**	**5.7**	**18.3**	**42.2**	**20.3**	**10215**	**86.5**
2018/19	0-4	644,783	70.4	19.4	2.8	61.3	992	153.9
	5-14	1,396,285	10.4	3.3	0.4	11.2	354	25.4
	15-44	3,928,933	10.6	4.5	0.3	17.8	1309	33.3
	45-64	2,578,144	16.9	5.5	0.1	26.9	1274	49.4
	65+	1,870,152	22.0	19.2	0.2	52.0	1746	93.4
	All ages	**10,418,297**	**17.9**	**8.1**	**0.4**	**28.0**	**5675**	**54.5**
2019/20	0-4	650,558	6.9	41.3	10.6	47.5	692	106.4
	5-14	1,416,026	0.7	13.2	4.9	12.2	440	31.1
	15-44	3,975,806	1.7	8.5	3.4	14.9	1132	28.5
	45-64	2,611,623	3.1	8.8	1.4	19.7	859	32.9
	65+	1,911,681	2.6	23.9	2.7	64.8	1796	93.9
	All ages	**10,565,694**	**2.4**	**14.0**	**3.4**	**26.7**	**4919**	**46.6**

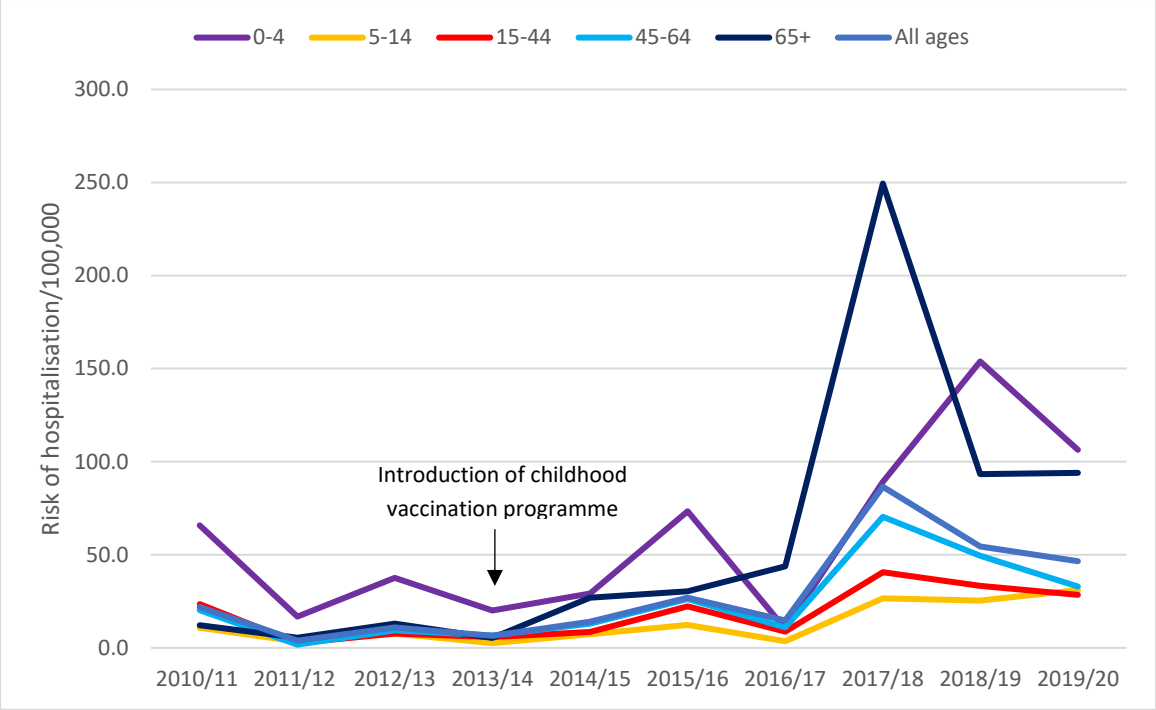

Figure 1: Crude cumulative hospitalisation incidence overall and by age group for all influenza types, 2010/2011 – 2019/2020

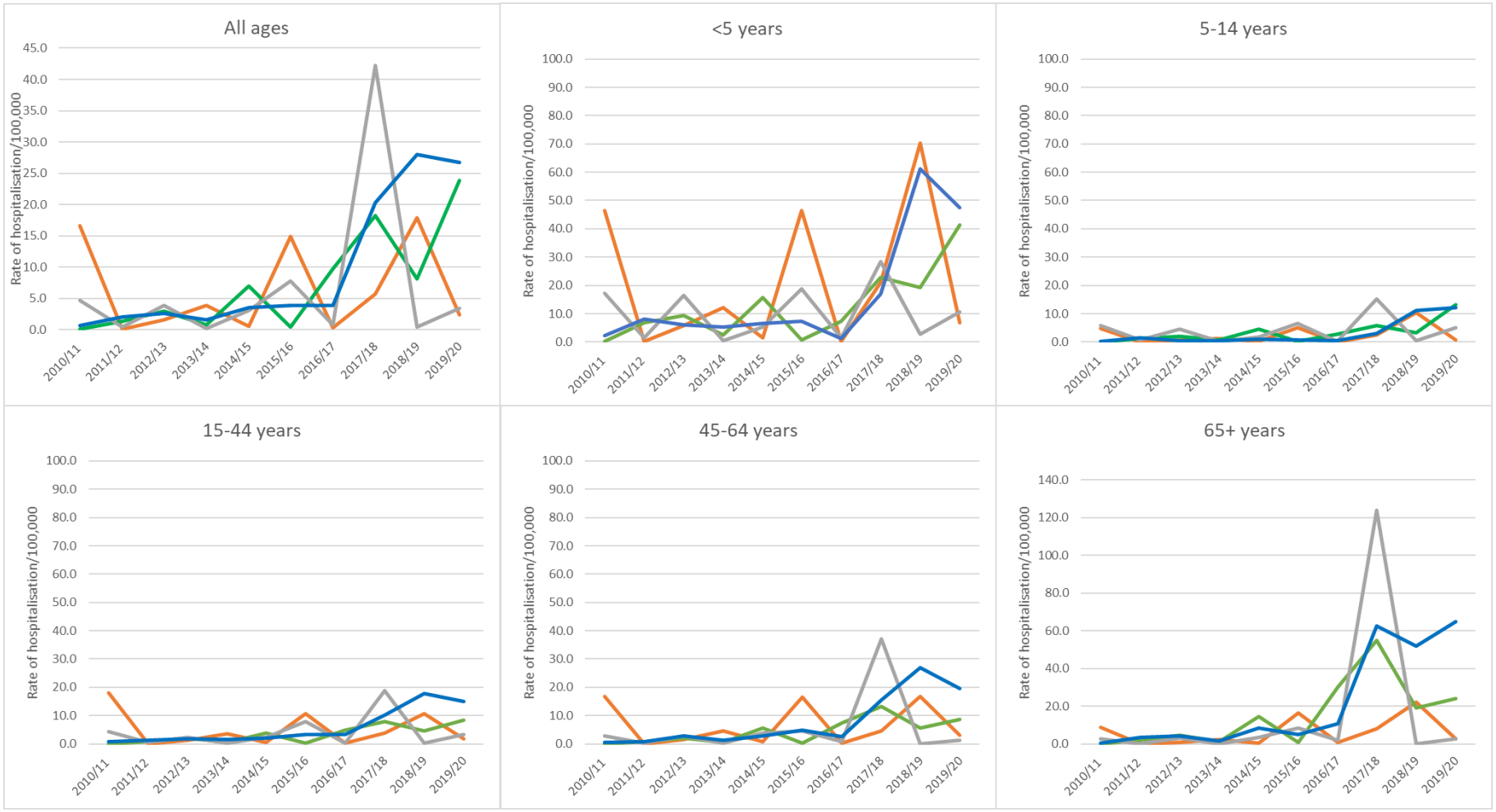

Figure 2: Crude cumulative hospitalisation incidence risk by influenza types, overall and by age group, 2010/2011 – 2019/2020

- **Impact of influenza: statistical analysis**

For this ordinal logistic regression analysis, the outcome was the weekly number of hospitalised cases for each trust were grouped into categories (0, 1, 2 or more). The three-way interaction (season-age group-influenza subtype) in the model was significant ($p<0.001$) suggesting the pattern of change over the seasons differs by age group which differs by influenza type. Overall, the adjusted ORs of higher counts of hospitalisation were highest in the under five-year-olds compared with other age groups by each influenza subtype in the majority of seasons (Tables 4-7). This was particularly true for influenza A(H1N1)pdm09 for which the ORs of higher counts of hospitalisation were highest in the 0-4 year-olds in almost all seasons in the study period (Table 4).

The age groups with higher ORs of hospitalisation with influenza A(H3N2) were the 0-4 year-olds and the 65+ year-olds (Table 5). In particular, the ORs of hospitalisation were higher in the 65+ year-olds in the 2016/2017 and 2017/2018 seasons, both of which saw moderate influenza activity with influenza A(H3N2) as either the main or co-circulating type/subtype.

A mixed picture was observed with influenza A not subtyped with higher ORs in the 0-4 year-olds in the 2010/2011, 2011/2012 and 2013/2014 seasons and higher ORs of hospitalisation in the 2016/2017 and 2017/2018 seasons in the 65+ year-olds (Table 6). Higher ORs of hospitalisation were observed in the 2018/2019 and 2019/2020 seasons compared to earlier seasons (Table 6).

For influenza B, higher ORs of hospitalisation for all age groups in the 2017/2018 season were observed compared with other seasons, in particular for the 65+ year-olds (Table 7). In the majority of other seasons, higher ORs were observed in the 0-4 year-olds.

Table 4: Adjusted odds ratios of hospitalisation due to influenza A(H1N1)pdm09 by season and age group (baseline influenza A(H3N2), 2012/2013, 15-44 year-olds, adjusted for season, age group, influenza subtype and logarithm of the population, week and trust)

	OR (95% CI) 0-4 years	OR (95% CI) 5-14 years	OR (95% CI) 15-44 years	OR (95% CI) 45-64 years	OR (95% CI) 65+ years
2010/2011	49.4 (31.9, 76.5)	6.5 (3.9, 10.9)	19.0 (13.0, 27.6)	18.8 (12.8, 27.6)	8.0 (5.1, 12.6)
2011/2012	0.2 (0.0, 0.8)	0.1 (0.0, 0.4)	0.0 (0.0, 0.1)	0.0 (0.0, 0.2)	0.0 (0.0, -)
2012/2013	3.6 (2.3, 5.6)	0.4 (0.2, 0.7)	0.8 (0.5, 1.1)	0.9 (0.5, 1.3)	0.5 (0.3, 1.0)
2013/2014	7.3 (4.9, 11.0)	0.9 (0.5, 1.5)	2.1 (1.5, 3.0)	3.1 (2.1, 4.4)	1.6 (1.0, 2.4)
2014/2015	0.1 (0.6, 2.1)	0.2 (0.1, 0.5)	0.3 (0.2, 0.5)	0.6 (0.3, 0.9)	0.3 (0.1, 0.6)

2015/2016	23.1 (15.7, 33.9)	3.2 (2.1, 4.9)	7.7 (5.5, 10.7)	11.2 (8.0, 15.6)	9.2 (6.5, 13.2)
2016/2017	0.2 (0.0, 1.4)	0.00 (0.0, -)	0.1 (0.1, 0.4)	0.2 (0.1, 0.6)	0.3 (0.1, 0.8)
2017/2018	14.9 (9.9, 22.5)	1.9 (1.2, 3.1)	3.2 (2.2, 4.6)	3.9 (2.7, 5.7)	5.9 (4.1, 8.5)
2018/2019	34.1 (22.9, 50.8)	7.5 (5.0, 11.2)	5.5 (3.8, 7.8)	8.6 (6.0, 12.2)	10.0 (6.9, 14.5)
2019/2020	8.4 (5.1, 13.7)	0.8 (0.4, 1.7)	2.1 (1.4, 3.2)	3.3 (2.1, 5.0)	3.1 (1.9, 4.9)

Table 5: Adjusted odds ratios of hospitalisation due to influenza A(H3N2) by season and age group (baseline influenza A(H3N2), 2012/2013, 15-44 year-olds, adjusted for season, age group, influenza subtype and logarithm of the population, week and trust)

	OR (95% CI) 0-4 years	**OR (95% CI) 5-14 years**	**OR (95% CI) 15-44 years**	**OR (95% CI) 45-64 years**	**OR (95% CI) 65+ years**
2010/2011	0.3 (0.0, 2.2)	0.0 (0.0, -)	0.0 (0.0, 0.3)	0.1 (0.0, 0.5)	0.1 (0.0, 0.8)
2011/2012	4.7 (3.0, 7.5)	0.9 (0.5, 1.6)	0.5 (0.3, 0.7)	0.5 (0.3, 0.9)	1.3 (0.8, 2.1)
2012/2013	5.0 (3.2, 7.7)	1.1 (0.6, 1.8)	1.0	1.1 (0.7, 1.6)	2.3 (1.5, 3.4)
2013/2014	1.6 (0.9, 2.8)	0.4 (0.2, 0.8)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	0.6 (0.4, 1.1)
2014/2015	7.4 (4.9, 11.3)	2.1 (1.4, 3.4)	1.8 (1.3, 2.6)	3.5 (2.4, 5.0)	6.2 (4.3, 9.0)
2015/2016	0.5 (0.2, 1.4)	0.1 (0.0, 0.4)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)	0.4 (0.2, 0.9)
2016/2017	6.2 (3.7, 10.4)	2.1 (1.2, 3.6)	5.1 (3.5, 7.3)	6.3 (4.3, 9.3)	16.2 (11.2, 23.4)
2017/2018	17.6 (11.8, 26.4)	4.6 (3.1, 7.0)	5.8 (4.1, 8.2)	8.5 (6.0, 12.0)	25.2 (18.0, 35.4)
2018/2019	16.0 (10.4, 24.7)	3.3 (2.1, 5.2)	3.6 (2.5, 5.3)	4.8 (3.3, 7.0)	12.9 (9.0, 18.5)
2019/2020	19.5 (12.5, 30.3)	8.3 (5.4, 12.6)	4.7 (3.2, 6.8)	6.5 (4.4, 9.5)	11.6 (7.9, 17.1)

Table 6: Adjusted odds ratios of hospitalisation due to influenza A not subtyped by season and age group (baseline influenza A(H3N2), 2012/2013, 15-44 year-olds, adjusted for season, age group, influenza subtype and logarithm of the population, week and trust)

	OR (95% CI) 0-4 years	OR (95% CI) 5-14 years	OR (95% CI) 15-44 years	OR (95% CI) 45-64 years	OR (95% CI) 65+ years
2010/2011	2.6 (1.2, 5.7)	0.2 (0.0, 1.2)	0.8 (0.4, 1.5)	0.7 (0.4, 1.5)	0.6 (0.2, 1.5)
2011/2012	5.3 (3.4, 8.2)	1.0 (0.6, 1.7)	0.8 (0.5, 1.2)	0.6 (0.3, 1.0)	1.7 (1.1, 2.6)
2012/2013	3.7 (2.4, 5.9)	0.2 (0.1, 0.5)	0.9 (0.6, 1.4)	1.4 (0.9, 2.0)	2.3 (1.5, 3.4)
2013/2014	3.3 (2.0, 5.2)	0.2 (0.1, 0.5)	0.9 (0.6, 1.3)	0.7 (0.4, 1.1)	1.1 (0.7, 1.7)
2014/2015	3.8 (2.4, 6.1)	0.6 (0.3, 1.1)	1.2 (0.8, 1.7)	1.7 (1.2, 2.6)	4.0 (2.7, 5.8)
2015/2016	5.4 (3.5, 8.6)	0.4 (0.2, 0.8)	1.8 (1.2, 2.6)	3.5 (2.4, 5.1)	3.2 (2.1, 4.8)
2016/2017	1.6 (0.7, 3.4)	0.6 (0.2, 1.4)	3.6 (2.4, 5.3)	2.8 (1.8, 4.3)	8.6 (5.8, 12.8)
2017/2018	12.0 (7.9, 18.3)	2.4 (1.5, 3.9)	7.7 (5.5, 10.7)	13.1 (9.4, 18.4)	31.3 (22.4, 43.8)
2018/2019	42.7 (28.8, 63.1)	8.5 (5.7, 12.6)	14.3 (10.2, 19.9)	21.3 (15.2, 29.9)	38.6 (27.4, 54.3)
2019/2020	55.2 (37.0, 82.5)	15.7 (10.6, 23.3)	25.6 (18.2, 36.0)	33.2 (23.5, 46.8)	72.0 (50.9, 101.8)

Table 7: Adjusted odds ratios of hospitalisation due to influenza B season and age group (baseline influenza A(H3N2), 2012/2013, 15-44 year-olds, adjusted for season, age group, influenza subtype and logarithm of the population, week and trust)

	OR (95% CI) 0-4 years	OR (95% CI) 5-14 years	OR (95% CI) 15-44 years	OR (95% CI) 45-64 years	OR (95% CI) 65+ years
2010/2011	21.2 (13.2, 34.1)	9.3 (5.8, 14.9)	4.9 (3.2, 7.3)	3.6 (2.2, 5.7)	2.7 (1.6, 4.8)
2011/2012	1.1 (0.6, 2.2)	0.5 (0.2, 1.0)	0.3 (0.2, 0.5)	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)
2012/2013	9.4 (6.3, 14.0)	2.5 (1.6, 3.8)	1.4 (1.0, 2.0)	1.9 (1.3, 2.8)	2.0 (1.3, 3.0)
2013/2014	0.3 (0.1, 0.8)	0.1 (0.0, 0.4)	0.1 (0.1, 0.3)	0.2 (0.1, 0.4)	0.1 (0.1, 0.3)
2014/2015	4.3 (2.7, 6.8)	1.1 (0.6, 1.8)	1.5 (1.0, 2.2)	2.7 (1.8, 3.9)	2.3 (1.5, 3.4)

2015/2016	10.8 (7.2, 16.3)	3.4 (2.2, 5.3)	4.8 (3.4, 6.8)	3.0 (2.1, 4.4)	4.6 (3.1, 6.7)
2016/2017	2.0 (1.0, 4.0)	0.4 (0.1, 1.1)	0.4 (0.2, 0.8)	1.1 (0.7, 2.0)	2.6 (1.6, 4.3)
2017/2018	26.0 (17.6, 38.4)	13.1 (9.1, 18.9)	18.7 (13.6, 25.8)	29.5 (21.3, 40.7)	66.8 (48.1, 92.8)
2018/2019	3.0 (1.6, 5.5)	0.5 (0.2, 1.1)	0.4 (0.2, 0.7)	0.1 (0.0, 0.4)	0.2 (0.1, 0.6)
2019/2020	10.6 (6.6, 17.1)	5.9 (3.8, 9.1)	4.8 (3.3, 6.9)	2.1 (1.3, 3.3)	3.7 (2.4, 5.8)

2.2.4 Discussion

This study presents an updated analysis of the severity of influenza infection in England using a national hospital-based surveillance system. The epidemiology and disease impact of severe influenza in England over ten influenza seasons, 2010/2011 to 2019/2020, are described.

During the study period, a higher disease impact of influenza was consistently observed in the paediatric population less than five years of age compared to older children and adults. Cumulative hospitalisation rates were consistently higher in the under five-year-olds over the ten seasons included in the study, although in some seasons rates were highest in the over 65-year-olds. These tended to be seasons during which influenza A(H3N2) was the dominant circulating subtype. This age-specific variation in the impact of the circulating subtype was observed in the previous analysis and has continued to be seen in the later seasons included in this study.

The impact of influenza A(H1N1)pdm09 was observed in children but less so in the other age groups. Influenza A(H3N2) impact was observed in both the youngest and oldest age groups; the under-fives and over 65-year-olds. The impact of influenza B was mainly observed in the under-five year-old age group although in 2017/2018 there was a particularly large impact of influenza B in the over 65-year-olds, with some impact also seen in the other age groups.

The results of this study, using the currently available data, show that overall cumulative hospitalisation incidence rates were larger in several of the seasons following the introduction of the childhood vaccination programme, with particularly large increases in risk in 2017/2018 onwards. It is unclear whether these are true increases in hospitalisation rates or whether they could be due to other factors such as increases in testing and improved case ascertainment and reporting in the latter

seasons. Furthermore, over this period, a number of concerns have emerged in relation to vaccine effectiveness (VE) (98). In 2015/2016, VE from live attenuated influenza vaccine (LAIV) in children was found to be moderately good against influenza-confirmed primary care consultations overall in England, however that protection was lower against influenza A(H1N1)pdm09 despite no suggestion of waning of overall vaccine-derived protection or mismatch between the circulating and vaccine strain (96). Congruently in this study, we see high rates of influenza-related hospitalisation due to influenza A(H1N1)pdm09 in under five-year-olds. Other countries have observed a more substantial reduction in effectiveness of LAIV against influenza A(H1N1)pdm09 (114). It has been hypothesised that this reduction in effectiveness may be related to reduced replicative ability of the A(Bolivia/559/2013) H1N1pdm09 vaccine strain in the quadrivalent LAIV (117). In the 2017/2018 and 2018/2019 seasons VE was found to be low against influenza-confirmed primary care consultations due to influenza A(H3N2) in children and adults regardless of vaccine type in England (98). Correspondingly high rates of hospitalisation due to influenza A(H3N2) were observed in both older adults and children in this study, particularly in the 2017/2018 season. During these two seasons, a number of influenza A(H3N2) variants circulated and there was also evidence of possible egg-adaptation of vaccine viruses affecting their antigenicity (122, 133). Additionally, in the 2017/2018 season, low VE against primary care consultations was observed against influenza B due to a B-lineage mismatch between the predominant circulating influenza B virus lineage and the strain included in the trivalent vaccine (98). As such this was mainly an issue in adults, rather than children who received quadrivalent LAIV and is consistent with the results from this study in which we found high rates of hospitalisation due to influenza B in the over 65-year-olds.

In the two most recent seasons (2018/2019 and 2019/2020), a high proportion of the reported hospitalised influenza cases were not subtyped (51% and 58% of hospitalised cases respectively) and the cumulative hospitalisation rates for all ages with influenza A not subtyped were higher than other subtypes. Over the study period, the hospitalisation rates generally matched the pattern of the dominant influenza A subtype seen in each season, suggesting the non-subtyped results were likely to be the main circulating subtype. Given the increasing incidence of influenza hospitalisations over time and the high proportion of results not subtyped in recent seasons, it is possible at least part of the increase is due to increased testing of suspect cases, possibly in line with the advent of rapid tests for influenza.

At the end of both the 2017/2018 and 2018/2019 influenza seasons, a questionnaire was sent by PHE to all NHS trusts in England to understand more about how rapid influenza molecular tests are being used in secondary care (134). Although the response rate was low (22%), the findings suggested a

large proportion of trusts were using rapid influenza molecular tests, either alone or in combination with other testing (42% of responding trusts in 2017/2018 and 55% of responding trusts in 2018/2019) and many had plans to increase their usage in future seasons (134). Of the rapid tests used by trusts, the majority did not provide the results by subtype and limited follow-up testing was carried out, thus suggesting that the increasing use of rapid tests may have contributed to the high proportion of unsubtyped results reported in recent seasons through the USISS system. Such challenges of rapid tests from a surveillance perspective have been documented elsewhere (135, 136). Rapid tests were introduced in Scotland in 2017/2018 when moderate to high levels of influenza activity were putting pressure on bed occupancy within the hospital system. Whilst the introduction was found to have a positive impact on local bed occupancy, treatment and infection control measures, due to a lack of provision to enable the results of the rapid tests to be captured by the Scottish national surveillance system, there was a loss of data to the national surveillance system (135). In the 2018/2019 season, most positive rapid test results were believed to be captured by the national system, however, a sizable proportion of negative results were still not captured by the national system (135).

Other studies give a mixed picture when examining the impact of the childhood influenza programme in reducing influenza admissions in children. Hardelid *et al.,* (2018) used data on influenza-related admissions to paediatric intensive care units (PICU) in England to undertake a before-after analysis to estimate influenza-associated PICU admission rates. They compared the rates in the seasons since the introduction of the programme to the 2011/2012 and 2012/2013 seasons, the two seasons before the introduction of the programme (137). They were unable to identify any significant decreases in admission rates in the period since the introduction of the programme in any age group and found admissions rates to be significantly higher in children under five years of age (137).

Results have generally been different when comparing rates of laboratory-confirmed influenza hospitalisations and ICU admissions between selected areas of England which had piloted different vaccination programmes with more evidence to support an impact of the programme (48-51). In these studies, the cumulative incidence of laboratory-confirmed influenza hospitalisations per 100,000 population were compared between pilot and non-pilot areas in targeted and non-targeted age groups. These studies were carried out within the same influenza season, thus avoiding some of the potential temporal biases that may exist within a longitudinal study. In the 2013/2014 season analysis, cumulative incidence rates were found to be non-significantly lower in pilot areas compared with non-pilot areas in target (four to 11-year-olds) and non-target (under four-year-olds) age groups (48). In the 2014/2015 season analysis, significant reductions in cumulative incidence were seen in target age groups (five to 10-year-olds) (93% reduction, p=0.012) in pilot areas compared with non-pilot areas.

Indirect reductions, although non-significant, were also seen in under five-year-olds (61% reduction, p=0.324) and individuals 17-years-old and over (34%, p=0.434) in pilot compared with non-pilot areas (49). In the 2015/2016 and 2016/2017 seasons, non-significant reductions were observed in target and non-target age groups comparing pilot to non-pilot areas (50, 51). Furthermore, in the 2015/2016 analysis, cumulative incidence rates for pilot and non-pilot areas were observed for two seasons prior to the introduction of the programme up to the 2015/2016 season (50). They showed that, in the two seasons before the programme, hospitalisation rates for influenza were similar between the pilot and non-pilot areas, however, there was a divergence of rates between areas from 2013/2014 with a relative reduction in hospitalisations in pilot areas compared with non-pilot areas (50). This was also seen for some age groups in the 2016/2017 analysis (51).

This study has several strengths. The USISS system has continued to show its ability to measure the impact of influenza in England and allowed for inter-seasonal comparisons. This study uniquely presents a 10-year time series of influenza hospitalisation data and benefits from updated and more accurate trust catchment population estimates. A further strength of the USISS data is that, since the initiation of the scheme, standardised testing protocols have been provided to participating trusts to help ensure that those admitted with respiratory symptoms are tested for influenza. As part of the testing protocols trusts were encouraged to carry out subtyping of positive influenza samples and report the subtyping results as part of their weekly submissions to USISS. The reporting system allowed trusts to update influenza A not subtyped results in subsequent reporting weeks in case the subtyping result was not available at the time of reporting.

There are a number of limitations to this study. Similar to the findings of the initial analysis, there remains a high proportion of influenza cases with no subtyping information reported. In particular, the most recent two seasons had high proportions of cases with no subtyping information which appears to coincide with the increase in the use of rapid diagnostic tests for influenza within hospital settings and hence greater ascertainment of cases. Studies looking at trends in invasive pneumococcal disease following the introduction of the 13-valent pneumococcal conjugate vaccination programme have attempted to address similar challenges in surveillance sensitivity over time by increasing the incidence of disease before the surveillance of invasive pneumococcal disease becoming mandatory (138). As the use of rapid tests for influenza becomes more embedded in clinical practice within secondary care, particularly following the COVID-19 pandemic, it may be possible to adjust for changes in surveillance sensitivity over time using USISS data, by potentially inflating the incidence of influenza hospitalisations prior to the advent of rapid tests, to ensure that the impact of the childhood vaccination programme is not underestimated. Work also needs to be done with trusts to ensure that

rapid tests are followed up with additional sampling for subtyping purposes, as well as reinforcing the importance of contributing samples and data for public health surveillance, alongside the development and use of rapid tests that have the ability to identify influenza A virus subtypes.

This study is also limited by the lack of more granular age groups in the trust catchment populations, the denominator data, and to some extent the USISS age groups, the numerator data. The restricted age groups meant that it was not possible to look at the rates in the under two-year-olds, who have higher rates of influenza-related hospitalisation than over two-year-olds and are not eligible for vaccination unless in a clinical risk group (139). It also limited the ability to look more closely at the targeted age groups of the vaccination programme and identify any impact of the programme within these targeted age groups. Trust catchment populations in single-year age groups would be preferable, at least for the youngest ages such as the under five-year-olds.

The number of trusts participating in the scheme each season varied and decreased in the later seasons. The main reasons given for trusts dropping out of the scheme were usually due to lack of resources and staff time to participate. The study also only included three seasons prior to the introduction of the programme, two of which had low-moderate influenza activity (2011/2012 and 2012/2013), and one had high levels of activity (2010/2011). A longer pre-programme period may enable these findings to be explored further, however, the USISS system was only established in the 2010/2011 season. HES may provide an alternative source of data for a longer pre-programme period, particularly if linked with national laboratory surveillance data since influenza diagnoses within HES do not rely on laboratory confirmation. This study did not include the 2020/2021 influenza season however this season very low levels of influenza activity were observed due to the ongoing COVID-19 pandemic (140).

In summary, this study demonstrates the continuing impact of influenza hospitalisations overall and in children as well as the varying impact of influenza by age and influenza subtype. Monitoring hospitalisations due to influenza enables the burden of clinically important influenza to be estimated as well as the impact of vaccination. Generally, the impact of influenza A(H1N1)pdm09 was concentrated in younger children, influenza A(H3N2) in younger children and older adults and a mixed impact from influenza B. The study identifies an increase in influenza-related hospital admission rates in England particularly since 2017/2018. This increase in admission rates is likely related to a number of factors including improved testing of patients presenting to hospital with severe ARI using rapid diagnostic tests which have become more widespread in usage in recent influenza seasons. Furthermore, it is also likely to be related to varying protection from the vaccines over this period; including previously documented higher rates of hospitalisation seen in years with greater antigenic

variation between vaccine strains and circulating viruses (141, 142), issues with egg-adaptation of influenza A(H3N2) vaccine viruses and reduced replicative ability of the A(Bolivia) H1N1pdm09 vaccine strain. Monitoring of influenza admission rates should continue as part of the evaluation of the childhood influenza vaccination programme. Availability of admission rates and corresponding denominator data by single year of age, in those under the age of five years especially, would enable further trends to be explored more precisely in the targeted age groups and those at higher risk.

Chapter 3

Critical literature review on the use of the test-negative design and screening method for estimating influenza vaccine effectiveness in high-income settings

3.1 Background

The focus of this critical literature review is how to assess influenza vaccine effectiveness (IVE) using observational studies after the introduction of a vaccine into the population in high-income settings. The review aims to provide a critical evaluation of two approaches to measuring IVE, the test-negative design (TND) and the screening method (Objective 2 of the Research Project).

IVE is an important component of assessing the impact of influenza vaccination programmes. Information on the direct effect of vaccines such as the efficacy in clinical trials or effectiveness measured by post-licensure observational studies, as well as the impact or overall effect (i.e. the reduction in risk of infection in a community with the vaccination programme compared to a comparable population without the programme), help to justify the resources required to set up and maintain vaccine programmes, as well as to assess how well a programme is working and whether changes are required to the mode of delivery and schedules for instance. The introduction and expansion of vaccination programmes for rotavirus, *Haemophilus influenzae* type B (Hib) and *S.pneumoniae* have led to well-established guidance for evaluating both the effectiveness of vaccines and the impact of vaccination programmes (45).

Post-licensure IVE estimations are required on an annual basis due to the heterogeneity of viral strains circulating in influenza seasons. They help to evaluate IVE in real-world conditions, input into models of outcomes averted by vaccination, to inform policy decisions and to inform optimal vaccine composition in subsequent seasons. IVE estimates generated from surveillance data using the TND have been presented at the World Health Organization's (WHO) twice-annual influenza vaccine strain selection meeting since 2013 and are considered as part of the package reviewed, providing information on vaccine performance in previous influenza seasons (143). These are reviewed alongside other data from the WHO Global Influenza Surveillance and Response System (GISRS) including surveillance data, genetic and antigenic characterisation of viruses, human serology studies, virus fitness forecasting, antiviral resistance and availability of candidate vaccine viruses (144). A recent example of the use of IVE studies influencing policy decisions was in the United States (US) in 2015 when the decision to use live attenuated influenza vaccine (LAIV) was reversed for the

2015/2016 season based on VE studies from previous seasons which showed low effectiveness against influenza A(H1N1)pdm09 (102).

IVE is generally modest as discussed in the Background Chapter. IVE against laboratory-confirmed influenza infection is generally not higher than 60% and may be as low as 30% (45), although can be around 70-90% in healthy adults when the vaccine is well matched to the circulating strain (41).

Estimates of IVE can vary according to many different factors:

- Virus factors such as the virus type. Influenza viruses undergo frequent changes to their surface antigens and so considerable heterogeneity of circulating influenza viruses is seen on an annual basis (41, 81). IVE will vary according to how well matched the vaccine is to the circulating influenza strains and so is routinely assessed by type and subtype.

- Vaccine factors such as the vaccine type and mechanism of action. Influenza vaccines are either trivalent (containing antigens of influenza A(H1N1), influenza A(H3N2) and one influenza B strain) or quadrivalent which contain two influenza A strains and two influenza B strains (Victoria and Yamagata lineages) (45). The antigenic composition of influenza vaccines is adjusted each year, in an attempt to match the predicted circulating strain for that season. The degree to which the vaccine matches the circulating viruses will affect the IVE as mentioned above (measured through antigenic characterisation, serology tests and genetic sequencing). There are also inactivated and live attenuated influenza vaccines, as well as recombinant, adjuvanted and high-dose inactivated influenza vaccines (IIV) (although these are mainly used for people 65 years and over), and VE varies across these vaccine products.

- Vaccinee factors such as age, the underlying health status of vaccinees, the health outcomes investigated and previous exposure or vaccination (45, 145). Age in particular is a known confounder, and possible effect modifier, of IVE estimates since both vaccine coverage (146) and the risk of illness from influenza infection vary considerably with age (45, 83, 87, 89). IVE will also vary according to the underlying health status of vaccinees, varying potentially by specific underlying medical condition as well as with multimorbidity. With regards to previous exposure or vaccination, IVE can differ between groups that have residual immunity from either past exposure or prior vaccination to those who are naïve to circulating viruses. IVE can also vary with the time interval between vaccination and influenza epidemics.

Given their role in assessing the impact of influenza vaccination programmes, having a critical understanding of the strengths, limitations and validity of such observational studies to assess the

effectiveness of influenza vaccines is important. This critical review aims to review the two observational study designs: the TND and the screening method.

3.2 The test-negative design

3.2.1 The history of the study design

The TND was initially developed out of the 'indirect cohort' study design used to study pneumococcal vaccine effectiveness (VE) (147). It was used to compare the odds of vaccination in those infected with non-vaccine serotype with those with vaccine-type disease (147). The pneumococcal vaccine consists of 23 serotypes which protects against 80-90% of the serotypes causing disease (148). This method was found to be advantageous since it was less likely to exaggerate the protective effect of the vaccine because the unvaccinated cases also have pneumococcal bacteraemia. It showed that pneumococcal vaccination did not affect the risk of non-vaccine-type pneumococcal infections among those vaccinated (147, 149).

The method was first used to estimate IVE in 2005 in Canada and has since been used extensively in IVE studies and has also been applied to rotavirus, cholera and COVID-19 vaccines (150-153).

3.2.2 Overall design

The TND is a special instance of a case-only design whereby cases are those that fit the clinical case definition and test positive for the infection in question. Those that meet the clinical case definition but test negative are used as "controls". Controls are intended to be representative of the exposure of interest for the population that gave rise to the cases. Using this approach, both cases and test-negative controls are usually selected from a population of persons presenting to healthcare, either primary or, more recently, secondary health care services (for instance in the United Kingdom (UK), their general practice (GP) or hospital) for a defined set of symptoms such as influenza-like illness (ILI) or acute respiratory illness (ARI). Study participants are either selected exhaustively or systematically (for example patients every second day, or the first two ILI cases seen each week per GP) (154, 155). Those fulfilling a certain clinical case definition are swabbed and tested for influenza virus. Figure 1, taken from Sullivan *et al.,* illustrates well how cases and test-negative controls enter a TND study to estimate IVE (89).

Using this method, VE is calculated by comparing the odds of vaccination in those that test positive (O_{pos}) compared with the odds of vaccination in those that test negative (O_{neg}) as follows:

VE = 100 * (1- O_{pos}/O_{neg})

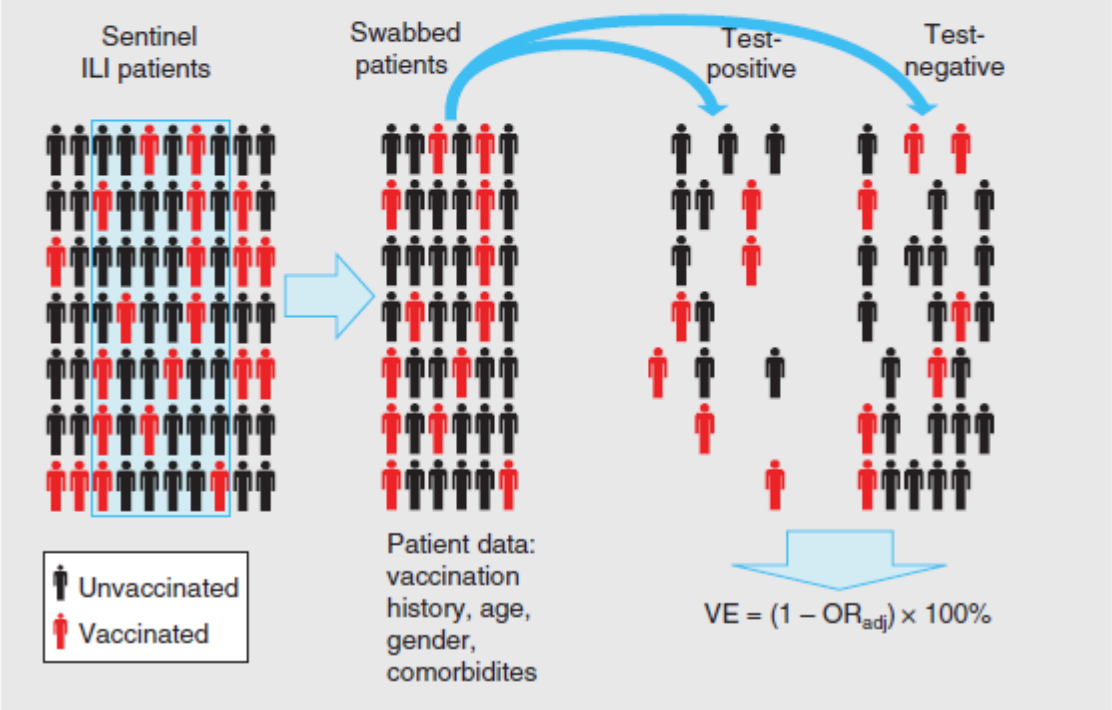

Figure 1: The test-negative design for estimating influenza vaccine effectiveness (taken from Sullivan *et al*., 2014 (89))

The design was also previously referred to as the "test-negative case-control" design. Whilst similar to a case-control study, the TND is distinctly different since individuals enter a TND study before their case status is known. In contrast, in a case-control study, sampling into the study population depends upon case or control status (156).

3.2.3 Measurement of exposure (i.e. vaccination)

Data on vaccine receipt as well as the timing of vaccination is collected on the identified individuals both testing positive and testing negative for influenza. Vaccine history can be ascertained in a number of ways including:

- administrative records such as vaccination cards
- national registries
- by asking the study subjects

Each method has potential limitations. Administrative records, such as those created as part of a vaccination programme such as 'red books' and the accompanying child health information systems, as in the case in England for childhood vaccinations or vaccination cards (157). Most countries are able

to keep vaccination records, such as through vaccination cards, particularly for children. However, adults are not usually given vaccination cards, and in countries without any further established infrastructure, vaccination may not be routinely recorded in clinical records (45). This may lead to a reliance on self-reporting and possible underestimation of vaccine uptake, as discussed below (45).

National registries which record vaccine uptake may also be incomplete and inaccurate and there may be limited ability in some cases to link study subjects with the registry (45). National registries may be incomplete due to vaccination taking place in alternative settings such as occupational settings or privately by pharmacies and the record of vaccination not being transferred to GP health records or the national registry. In England, most influenza vaccinations for the main targeted groups take place in GP settings. School aged children, however, are vaccinated via schools which presents a similar challenge with the transfer of vaccine receipt information into the GP health records. With both administrative records and national registries, where there is no record of vaccination having taken place, this will likely be a mixture of those where vaccination has occurred but has not been recorded and those where vaccination has not occurred. This can create differential exposure misclassification and limit accurate measurement of IVE.

Adult subject's recall of influenza vaccine receipt has been shown to be accurate in some settings, although it has been shown to be inaccurate for parental recall of a child's vaccine history and uptake tends to be overestimated when derived via patient recall (158). As such it is generally not the preferred method for obtaining vaccine history (159-162). In some instances, a combination of these methods is used such as in the US (93, 108).

Despite each method having potential limitations, one advantage of the TND is that it allows for the collection or linkage to this exposure information before ascertaining the outcome, which limits some of the sources of differential exposure misclassification (89).

3.2.4 Measurement of outcomes (i.e. confirmed influenza infection)

Laboratory confirmation of cases is important since non-specific outcomes may bias IVE estimates towards the null therefore underestimating the true IVE (163). Many other respiratory pathogens cause similar ILI symptoms (i.e. non-specific ILI) which, if not caused by influenza, may be distributed similarly amongst the vaccinated and non-vaccinated (164). Simulation studies of the TND have also been carried out showing that test specificity (reducing the number of false negatives), to a greater extent than test sensitivity, will lower VE estimates compared to the true value, hence the importance of a specific endpoint (164). Misclassification of true influenza cases as controls (i.e. lower sensitivity) is less important as a source of bias (164).

The type of laboratory confirmation may also influence VE estimates. Issues with the use of serological confirmation of infection have been well-documented (165-168). Using serological confirmation, rises in antibody titres are used to identify infections (based on a fourfold rise in antibodies for example). However, antibody titres also rise after vaccination, particularly following vaccination with IIV, and it is often not possible to disentangle influenza vaccine and naturally derived immunity with serology. It is only possible for a small number of infections, such as hepatitis B and to some extent COVID-19, to differentiate vaccine from natural immunity. Furthermore, antibody titres may also not rise further after infection – a hypothesised reason for this is the "antibody ceiling" concept whereby once antibody titres rise in response to vaccination, they cannot rise any further in response to infection making it difficult to confirm influenza infection in those vaccinated compared to those unvaccinated, hence leading to an overestimation of VE (83, 168-170).

Reverse transcription polymerase chain reaction (RT-PCR) is increasingly used as the gold standard for influenza confirmation given its high sensitivity and specificity for influenza diagnosis, meaning there is only a very small chance of outcome misclassification (171). Studies that have compared detection rates of respiratory viruses found that RT-PCR increases the yield of viral identification when compared with serology and culture (171, 172). Furthermore, the sensitivity and specificity using RT-PCR testing can be further optimised by restricting cases and controls to those swabbed within seven days of onset, since viral titres decrease with time since onset thus reducing sensitivity (5).

Different laboratory end points used to determine efficacy were compared in a placebo-controlled trial of IIV and LAIV (168). They found that whilst all influenza A (H3N2) and B cases isolated in cell culture were also identified by RT-PCT, just under 70% of influenza A cases identified by RT-PCR were identified by cell culture. Only 23% of IIV recipients demonstrated serological confirmation of infection (influenza A(H3N2)), in contrast, 90% of placebo and 87% of LAIV recipients demonstrated serological confirmation (168). The difference seen with the LAIV as opposed to IIV might be in part because LAIV does not produce major serologic antibody responses therefore an increase in antibodies produced by infection is more easily demonstrated (168). Other studies have also shown RT-PCR to be more sensitive than conventional viral culture (171-173).

Rapid influenza diagnostic tests (RIDT) are another alternative testing method for influenza. Despite issues with the quality of RIDTs, notably the low sensitivity, lack of subtyping for some tests and lack of virus for further characterisation, their use is becoming more widespread. As such some VE studies are based on the results of RITDs (174-177). However, their use in VE studies is suboptimal when compared with RT-PCR and could lead to biased estimates due to outcome misclassification when using the TND.

Generally using the TND, patients who test positive for influenza are compared with those that test negative, however, some studies have used comparison groups of patients who test negative for influenza but positive for other respiratory viruses. Part of the rationale for using different comparison groups in many of these studies was to assess the hypothesis that virus interference can affect VE estimates using the TND (178). Virus interference is a phenomenon whereby infection by one virus alters the susceptibility to infection by another virus (178). The underlying mechanism by which it may occur is unclear but may involve both nonspecific and influenza-specific immunity (178, 179). Theoretically, it may be an issue since when influenza infection is prevented by vaccination, non-specific immunity is not induced and so the vaccinee is more susceptible than usual to infection by co-circulating viruses (178). This in turn might bias VE estimates since there would be higher vaccination coverage in controls with other respiratory viruses compared with those with no other virus detected. A systematic review of studies however suggested that in practice using different control groups (such as test negative only for influenza, test positive for viruses other than influenza or test negative for all viruses) made little difference in VE estimates (178). Twelve studies were identified from seven countries that looked across all age groups between 2003/2004 to 2013/2014. Pooled estimates of the difference in VE were very similar between groups. The pooled estimates of the difference between using controls testing negative for influenza and those positive for other/another respiratory virus was -4% (95% CI -10, 2), -1% for those testing negative for influenza and those testing negative for all other viruses in the panel (95% CI -8, 5) and 5% (95% CI -2, 12) for those positive for other/another respiratory virus and those negative for all viruses in the panel (178).

3.2.5 Aspects of the TND study design to reduce threats to validity

Several studies have attempted to assess the overall validity of the TND either through re-analyses using randomised control trial (RCT) data or by using simulation models. For instance, the values obtained using a TND have been obtained by re-analyses of data from RCTs of influenza (180) and rotavirus (181) vaccines. These produced similar effectiveness estimates to the efficacy measured by the original trials and the point estimates and surrounding confidence intervals (CI) were found to be very similar. However, it is worth noting that the participants included in the RCTs had been randomised i.e. measures were applied so that differences between vaccinated and unvaccinated participants are minimised. In contrast, this may not be true of a TND study based on observational studies.

As discussed in Section 4.2.4, the choice of laboratory confirmation for outcome classification can influence the validity of the TND. Orenstein *et al.,* (2007) developed a mathematical model to assess the impact of test sensitivity and specificity on IVE for a number of different study designs, including

the TND (164). Using a model with five input parameters (true IVE, attack rates of influenza-ILI and non-influenza ILI and the sensitivity and specificity of the diagnostic test), they found that the use of an imperfect test will bias IVE estimates towards the null. Test specificity was a major determinant of bias and resulted in an underestimation of the true VE. This bias increases as the attack rates of influenza-ILI relative to non-influenza ILI decreases i.e. as the positive predictive value falls (164).

Another important issue with regards to the validity of the TND design is the need to control for calendar time and hence the timing of influenza activity. This is important since the probability of vaccination and risk of infection change over time (156, 182). A study on rotavirus vaccination compared VE estimates calculated using an RCT design with a TND and found that when the analyses were restricted to the rotavirus season, the difference between the VE estimates using the two methods became smaller. This restriction was in addition to matching or adjusting the analyses by month and year. Limiting the time period also helps to avoid the inclusion of false positives, although this is less of an issue if specific tests are used.

In a recent systematic review, Okoli *et al.,* (2020), examined the influence of study characteristics on seasonal IVE estimates from TND studies (183). Among the study characteristics examined were the source of vaccine information, respiratory specimen swab time, and covariate adjustment on VE. The authors found that whilst IVE estimates did vary by these study characteristics, the differences were not significant. They found a 5% higher pooled IVE against all influenza types for self-reported vaccine reports (VE 48%, 95% CI 31-61) compared with confirmation via medical records (43%, 95% CI 35-79), an 8% higher VE for swab collection within seven days of symptom onset (46%, 95% CI 41-51) compared within four days (38%, 95% CI 15, 55) and 4% higher VE for studies that only included age (47%, 95% CI 42-52) as a covariate compared with those that included both age and medical conditions (43%, 95% CI 34-51). Despite the lack of statistical significance of the findings, the authors did conclude that these factors should be considered in the design and evaluation of TND studies (183).

3.2.6 Strengths of the design

A key strength of the TND is that it reduces selection bias due to confounding by healthcare seeking behaviour since both the cases and test-negative controls will have sought care for similar sets of symptoms (Table 1a). This is important since it is known that healthcare seeking behaviour is driven by similar attributes to vaccine uptake e.g. individuals with a propensity to seek care when ill may be more likely to receive vaccination as well as have behaviour that reduces the risk of infection (184, 185). Usually, healthcare seeking behaviour is hard to adjust for in other studies such as cohort studies

since measuring it is difficult. Possible bias due to differential healthcare seeking behaviour among the vaccinated and unvaccinated can also be further reduced by strict clinical criteria for testing and case definitions for enrolment and testing (186).

Another key strength of the TND is that it can be applied to routine and existing surveillance systems and cases and test-negative controls can be taken from the same surveillance systems, thus reducing administrative burden and costs (89). Since they are taken from the same system, cases and test-negative controls should have a high degree of comparability, since the controls would have been recruited as cases should they have had the outcome of interest; a key general guideline for reducing selection bias in case-control studies. In addition, the controls are recruited at the same time as the cases independently of exposure status, therefore further reducing the risk of selection bias.

When the study population is also restricted to those who have sought care for respiratory illness at the same sorts of facility or stratified by facility, cases and test-negative controls will have generally come from the same communities thus reducing further the potential confounding that could be introduced from community-level variations in vaccine coverage and risk of infection (153). Heterogeneity in vaccine coverage and intensity of influenza season can also be further mitigated by matching cases and test-negative controls on week of the season, as described in Section 6.2.5 above (156).

As mentioned in Section 6.2.3, an additional strength of the TND is that exposure information can be collected before or independently of ascertaining the outcome, therefore limiting the likelihood of differential exposure misclassification (Table 1a) (89).

3.2.7 Limitations of the design

Despite several strengths of the design, there are some potential weaknesses that need consideration (Table 1b). Firstly, as discussed earlier, studies have shown that when using imperfect tests for influenza, the TND tends to bias results towards the null and therefore underestimate the true VE (164). Whilst this is less of an issue when using RT-PCR, it is also important that cases should be limited to those diagnosed within a short time frame from symptom onset (for example swabbed within seven days of onset) to reduce the risk of false negatives since viral shedding is limited to a few days (5, 187).

Using the TND it may not be possible to control for all possible confounders such as disease severity. Disease severity affects the probability of seeking healthcare which is also associated with vaccination status. Using a hypothetical case TND, Foppa *et al.,* (2013) found that when severity does differ between aetiologies, and healthcare seeking behaviour is driven by disease severity as well as the attributes that drive vaccination uptake, then these associations can lead to the confounding of VE

estimates and will overestimate VE (184). However, they showed that by stratifying by disease severity valid VE estimates could be obtained (184, 188).

Similarly, whilst the design has been validated against certain outcomes such as outpatient illness, it has not been validated as well in studies using hospitalisation outcomes. A potential source of confounding in this instance is that many underlying diseases increase the risk of hospitalisation for respiratory symptoms (at possibly to varying degrees depending on the underlying disease itself, and presence of multiple underlying diseases), but at the same time some of these diseases are indication for vaccination, known as confounding by indication. As such hospital based test-negative controls may be different from the source population in their uptake of vaccination (188). Specifically, if the symptoms used to identify study subjects in a hospital-based study are too broad and non-specific, the test-negative controls could be biased towards people with acute exacerbations of chronic respiratory conditions, with symptoms that mimic acute respiratory symptoms but are more likely to test negative for influenza and may be more likely to seek medical care. These controls may also be more likely to receive influenza vaccination thus introducing selection bias and potentially overestimating VE estimates unless adjustment for underlying risk factors is carried out (45, 188). Despite this, simulation models suggest that, in most situations, selection bias is unlikely to meaningfully impact TND VE estimates (189). Using mathematical expressions and numerical simulations to verify theoretical results, Foppa *et al*., (2016) found that if chronic cardiopulmonary individuals are enrolled as controls due to non-influenza illness, VE estimates will be overestimated, since these individuals tend to be highly vaccinated (188). However, they demonstrated that if these chronic conditions are adequately adjusted for, or excluded from the analysis, and both influenza infection and vaccination status are measured accurately, unbiased VE estimated can be obtained from inpatient TND studies (188).

Feng et al., (2016) compared IVE estimates derived using the TND in outpatient settings compared with inpatient settings (190). They focused on comparisons of VE estimates from the same location, same influenza season and similar age groups. Across 25 pairs of VE estimates, no substantial statistical differences in the VE estimates from different settings were found. They did however find that influenza positivity was generally lower amongst hospitalised patients which is likely due to inpatient studies including more false test-negatives due to more time between illness onset and admission. In contrast, vaccination coverage amongst controls was found to be higher amongst inpatients. This is likely due to the high-risk status of hospitalised patients and therefore being in a group indicated for vaccination (190).

As indicated above, studies using severe end-points may be of limited use if a large proportion of patients are hospitalised due to complications of influenza that occur after the virus is no longer detectable (188). Since proof of active infection is required for the case definition, these late complications of influenza leading to hospitalisation will be missed by inpatient TND studies. As such VE estimates may underestimate the level of protection from complications of influenza due to a greater number of false negatives leading to a reduction in sensitivity (188).

Another possible limitation of the design is that it assumes that the incidence of non-influenza respiratory illness is the same in the vaccinated as in the unvaccinated groups i.e. vaccination against influenza has no effect on the immunity to non-influenza respiratory viruses (156). This issue was first highlighted by an Australian study which found that, when evaluating VE against trivalent IIV in young children, vaccination rates were higher in controls positive for other respiratory viruses compared with those negative for all respiratory viruses (191). Similarly, a small RCT suggested the rate of ARI due to detectable non-influenza viruses may differ between vaccinated and unvaccinated subjects. They found more ARI due to non-influenza in the vaccinated subjects (192). One hypothesised explanation for this difference is possible temporary non-specific immunity after influenza infection which the vaccinated do not benefit from and hence have a higher risk of non-influenza ARI (156, 192). However viral interference was only short, making it unlikely to be an issue and it has not been confirmed in further studies. One simulation study found that the degree of bias from viral interference was only marginal in typical seasons and most of the time during pandemics. However, the bias could become larger when the incidence of influenza is very high (influenza attack rate greater than 50%) and the duration of non-specific immunity is long (at least half the influenza season) (193). This was corroborated by a more recent study by Ainslie *et al.,* (2018) who evaluated bias of VE estimates from observational studies using a dynamic mathematical probability model. They found that when the assumption that vaccination does not influence the probability of developing non-influenza ARI is violated then VE estimates will be biased, however, the bias will generally not be severe (194).

The mechanism of immunity from vaccination may also be an issue in TND studies. In a recent study, the mathematical relationship between the estimated test-negative odds ratio to the true VE was used to assess the quantitative impact of potential biases of the TND (186). One of the key findings was that bias may result using the design unless protection from vaccination follows an “all or nothing” mechanism of action whereby some individuals have perfect protection and others have no protection. This however is an issue since unvaccinated people become immune via natural infection faster than vaccinated people, which causes these two groups to become more similar over time (186). However, it is difficult to know to what extent a vaccine confers “all-or-nothing” or “leaky” protection

(when a vaccine prevents development of disease symptoms but does not prevent infection). The authors propose that biases due to "leaky" vaccines may be reduced in populations that are less exposed to transmission and as such early-season VE estimates might be more reliable (186).

Another possible limitation of the TND is that it might lead to collider bias since both healthcare seeking behaviour and infection lead to testing. Since the study design conditions on testing it may not eliminate bias due to healthcare seeking behaviour (185, 195). As such, by only including patients tested for influenza, selection bias is induced by conditioning/restricting on the collider, testing (195). It is however thought to be less of an issue in studies looking at severe disease (153).

Unmeasured or residual confounding may also be an issue in TND studies if information on known confounders is not collected or inadequately collected, or there is a lack of data on an unrecognised or unknown confounder. For example immunity from prior natural infections or history of past vaccination are likely to be important but difficult to assess using routine surveillance data (82). Several studies have shown VE to vary according to vaccine history with reduced effectiveness in more vaccinated groups or those with past and current season vaccination, although the mechanisms by which this may occur are not well understood (82, 196-199). Lewnard and Cobey (2018) state that a TND study would ideally stratify VE according to past vaccination, exposure, and infection history (82). In certain settings, these variables could possibly be collected from routine records.

Despite many TND studies following a broadly similar basic design, there can be considerable variation in the study design and analytical approach of TND studies which may limit comparability and pooling of data (89, 182, 183). For instance, there may be variation in the case definitions for recruitment, ascertainment of vaccination status, laboratory influenza diagnostic test and restrictions placed on the data for analysis such as period of surveillance, and variables included in the analysis. Studies have shown that many of these design features have limited impact on VE estimates, although others do such as the method of ascertainment for vaccination status (89, 183). There is also considerable variation in the analytical approaches between TND studies (89). Shared protocols such as those developed by the Influenza – Monitoring Vaccine Effectiveness in Europe (I-MOVE) collaborative network in Europe may help reduce variations in study design (200).

3.3 The screening method

3.3.1 History of the design

The screening method was developed in the early 1980s and was originally described for estimating VE against measles (158, 201). It has since been used to measure effectiveness of vaccines against Hib (202), pertussis (203), measles (204), meningococcus (205), mumps (206), influenza (207-211) and pneumococcal disease (212). It was termed the 'screening method' as it was designed to give rapid, preliminary estimates of VE prior to other data such as incidence data being available and to determine if the number of vaccine breakthrough cases is within the expected range (153, 212). The screening method has generally been more successfully used for diseases where the population vaccine coverage is stable, and a good proportion of the population remains unvaccinated. It generally works less well in instances where the vaccination coverage has risen quickly such as with the seven-valent pneumococcal conjugate vaccination (PCV7) in the US (212).

3.3.2 Overall design

The screening method is a simple and rapid method for estimating VE using routinely available data especially when there is a lack of suitable controls (211, 213-216). As such this method is often used as a first step to establish whether further evaluation is warranted (217). It is a pseudo-ecologic design which uses individual level data on vaccination history from cases, and ecologic data on vaccination coverage in the population from which the cases came from. Using this method only three data points are required (stratified by key confounders where possible): (1) the number of cases, (2) the number of cases vaccinated and (3) the percentage of the population vaccinated (212). VE is then calculated as follows:

$$VE = 1 - [(PCV/(1-PCV)) \times ((1-PPV)/PPV)]$$

where PCV is the proportion of cases who are vaccinated and PPV is the proportion of persons vaccinated in the population from which the cases are drawn.

3.3.3 Case ascertainment and measurement of exposure

Using the screening method, cases are generally identified through existing surveillance systems making it less resource-intensive and cheaper than some methods. As with the TND, a specific outcome should be used such as laboratory-confirmed influenza cases as this outcome provides the highest specificity for estimating the true VE. Outcomes such as ILI are non-specific and will underestimate VE as many cases of ILI will not be influenza. Furthermore, tests with high sensitivity and specificity such as RT-PCR should be used to confirm the outcome and reduce outcome

misclassification. Exposure information may already be known or proactively collected on the cases as discussed in Section 2.3. As with the TND, misclassification of vaccination status will bias VE estimates. Where exposure information is derived from patient recall, vaccine coverage tends to be overestimated, whereas studies that verify vaccine coverage using written records tend to underestimate it due to failure to record vaccine receipt (158). It is also preferential to collect exposure information independently of the outcome.

3.3.4 Measurement of population vaccination coverage

The reference group i.e. population vaccination coverage is generally obtained from sources external to the study such as national vaccination coverage records. Accurate and valid estimates of population vaccine coverage are key to the validity of the screening method. Falchi *et al.* assessed VE values during the 2010/2011 influenza season in France using three sources of population vaccine coverage. These included social security scheme administrative data, a cross-sectional national telephone survey and a one-day GP consultation population survey. They found that the screening method generates differing VE estimates depending on the choice of the source of vaccination coverage estimates (210).

Another important factor concerning the population vaccination coverage is that the vaccination status of cases needs to be compared with the population vaccine coverage during the period when the cases occurred (158). If there is a large temporal difference between the two then VE may be overestimated (158, 210). This is because as time goes on a greater proportion of the reference group is likely to become vaccinated. Alternatively, this can be adjusted for if vaccination coverage is available by time. Like other VE studies, it is also important to be able to adjust for other important confounders such as age group, underlying risk factors and geography.

In England, influenza vaccine uptake is primarily collected at the aggregate level through GP reporting systems via a system called Immform, as described in the Background Chapter. Data is collected from all GP practices providing the immunisation programme and it collects cumulative weekly, monthly and end-of-season aggregated uptake data using manual and automated methods (129). High levels of returns are received for both the weekly and monthly collections with over 99% of practices returning data for the monthly collections and on average over 93% for the weekly collections in 2019/2020 (218). As such where vaccination takes place at GP practices, for instance for pre-school children, under 65-year-olds with an underlying condition and the over 65s, vaccination coverage records are high. Where vaccination takes place in other settings, such as for the school programme, it is encouraged that a record of vaccination is passed back to the patient's GP. Data for the school programme is collected by providers and submitted manually to Immform monthly. High levels of

return are received for the monthly school collections, with often 100% of providers returning data (219). The transfer of this information to GP records, however, tends not to be very efficient, therefore GP vaccination coverage records for vaccinations given outside GP practices in healthy school aged children are often lower and the separate monthly direct returns to Immform are used instead.

3.3.5 Strengths

A key strength of the screening method is its simplicity given the fact that it does not require detailed data collection on non-cases and thus can be used in scenarios where only data on the vaccination status of cases is available (Table 1a). This saves costs and time, meaning it can often be used to provide quick, in-season estimates, particularly at the early stages of the epidemic period allowing for public health measures to be implemented (220). The screening method can also be used to monitor changes in VE over time, assuming that any biases remain reasonably constant over time (221).

Using this method it is possible to adjust for some of the key confounders if they are available for both cases and the population vaccinated. This is done by matching the appropriate population group's vaccine coverage for a particular confounder to the individual cases in the same group (213-215).

3.3.6 Limitations

As mentioned earlier, it is important that accurate and valid estimates of population vaccine coverage are used for the screening method. It is possible that the source population for the cases may differ from the general population (e.g. if the values for PCV and PPV are drawn from different populations) and so it is important that the source population is correctly identified. The screening method has been shown to be sensitive to errors in the input estimates such as the estimated population coverage. For instance, VE will be overestimated if the population vaccination coverage is overestimated (Table 1c) (212, 217).

Another limitation of this method is that the information relating to the population vaccine coverage can often be limited which restricts the possibility of controlling for confounding factors (158, 216). The number of confounders will be limited to those that are available for both the cases and reference population (often just age, time and location).

Farrington (1993) explored the screening method in a methodological framework and showed that due to a cohort effect, data needs to be stratified by confounding variables using the screening method (216). Specifically, if cohorts with different vaccine coverage are pooled, the resulting VE will be confounded. As such vaccine status of the cases should be compared to the vaccine coverage of

the reference group stratified by possible confounding variables such as age, location, time period, and at-risk groups.

Another possible issue with the screening method is that the cases included in the study are those that present to healthcare, and it is not possible to control for the propensity to consult. However, in the instance of using hospitalisation as the outcome, this is less likely to be an issue since hospital admission is a serious outcome that it is unlikely to be influenced by access to healthcare.

Furthermore, if case ascertainment is not independent of vaccination status, bias will be introduced. This can occur in vaccine studies in which access to healthcare influences both the ascertainment of the outcome and the chances of being vaccinated. For example, negative confounding may be introduced if those more likely to develop severe complications are more likely to be vaccinated, thus leading to a reduced estimate of VE, often known as confounding by indication or 'channelling' as mentioned earlier (222). Positive confounding may be introduced due to the 'healthy vaccine effect', if those with a healthy lifestyle are more likely to accept/request vaccination, this will lead to an increase in measured VE since healthy individuals may be less likely to die from any cause or be admitted to hospital thus further confounding the relationship between vaccination status and outcome (158). Positive confounding may also be explained by people being in a state of "extreme frailty" not being offered or refusing vaccination. As such frail individuals may be less likely to be vaccinated, thus resulting in an overestimation of VE (223).

3.4 Conclusions

Observational studies are required to evaluate the real-world performance of vaccines, address gaps in evidence from clinical trials and provide input into impact models (153). However, due to the nature of observational studies and the non-randomisation of vaccination in real-world settings, they are subject to confounding and biases.

The TND and the screening method are two observational study designs that have been widely used in IVE studies. Each design has strengths and weaknesses, summarised in Table 1, and may be appropriate ways to monitor IVE in certain populations and settings possibly in a stepwise manner or as alternates depending on the question and the data available.

Increasingly the data required for TND studies are being incorporated into existing surveillance systems making them relatively easy to perform. The TND might be more appropriate in these

instances and in settings that have existing surveillance systems that can be used or adapted to collect the data required, such as vaccine receipt in non-cases, for the study design.

On the other hand, the screening method is a rapid and quick way of assessing VE when information on non-cases is lacking but population vaccine coverage is available. It thus provides a useful method for calculating early/mid-season IVE estimates to give early indications of how a vaccine might be performing. It may also be useful in determining whether the number of breakthrough cases is within the expected range. The method is generally most appropriate in settings, or with routine infant vaccines, where accurate and stable population coverage is available and where the population coverage corresponds to the population from which the cases arose. Since it relies on stable and valid population coverage estimates it may not be a valid method in the early stages of a new vaccine programme, such as COVID-19, where coverage is increasing rapidly.

There are several key principles that can be applied to both designs to minimise bias and increase the robustness of the studies such as:

- the use of laboratory-confirmed outcomes such as RT-PCR
- the use of a strict standardised clinical case definition for enrolment
- only consider cases to be fully vaccinated if symptom onset occurred 14 days after receipt of vaccination (since on average it takes 10 to 14 days following vaccination before an immune response and protection develops (224))
- the use of documented vaccination records rather than self-report
- collect exposure information independently to the outcome
- collect data by key covariates to control for confounding in the analysis
- For the screening method specifically, population uptake data should be for the same population and target group and time period in which the cases were identified.

In summary, the validity of IVE estimates is important given their role in impacting policy decisions, vaccine development and assessing vaccination programmes. This critical review has attempted to summarise some of the key features, strengths, and weaknesses of the two study designs used to measure IVE. Chapters 5 and 6 of this Research Project put these two methods into practice to estimate IVE against hospitalisation in children in England.

Tables 1a-c: A comparison of the strengths and weaknesses of the TND and the screening method

Table 1a: Strengths of the test-negative design and the screening method

Test-negative design strengths	Screening method strengths
Can be applied to routine and existing surveillance systems, reducing administrative burden and cost.	Can be applied to routine and existing surveillance systems, reducing administrative burden and cost.
Both cases and controls have sought care for similar sets of symptoms, reducing differences in healthcare seeking behaviour.	Can be carried out easily and rapidly, providing early and in-season estimations of IVE allowing for public health measures to be implemented.
Cases and controls can be identified from the same surveillance system, giving a high degree of comparability, helping to ensure controls are representative of the population cases arise from and reducing selection bias.	Can be carried out when there is a lack of suitable controls since it only requires population denominator data.
Controls are recruited at the same time as the cases and prior to ascertaining outcome.	Easily reproducible each year; possibility of inter-year comparisons.
Strict clinical criteria for testing and case definitions for enrolment also reduce bias due to differential healthcare seeking behaviour among the vaccinated and unvaccinated.	Able to adjust for potential confounding factors if available for both cases and population coverage estimates.
The study population can be restricted to those who have sought care at the same/similar facilities, reducing possible confounding from community-level variations in vaccine coverage and risk of infection.	
Exposure information can be collected prior to/independent of outcome, reducing differential exposure misclassification.	

Table 1b: Limitations of the test-negative design

Test-negative design limitations	Magnitude of limitation	Direction of effect
May be subject to exposure misclassification depending on the method used to obtain vaccination uptake information.	Large	Varies
May be subject to outcome misclassification if non-specific outcome measures are used. May also be affected by the type of laboratory confirmation used.	Moderate	Underestimate
Confounding may exist if disease severity is not controlled for. Disease severity may affect probability of seeking healthcare which is associated with vaccination.	Low, but may vary with high/low VE estimates	Overestimate
Confounding may exist in studies using severe outcomes since many underlying diseases increase the risk of hospitalisation and are also associated with vaccination uptake (confounding by indication).	Low - moderate	Overestimate
It assumes the rate of non-influenza respiratory illness is the same in vaccinated and unvaccinated groups.	Low	
Unmeasured or residual confounding may exist if information on known confounders is not/inadequately collected such as immunity from prior infections.	Unknown	Unknown
Design features and statistical approaches may vary across TND studies, limiting comparability and pooling of data.	Unknown	Unknown
Bias may occur if the protection from vaccination does not follow an “all or nothing” mechanism of action.	Impact increases with time since start of vaccination campaign	Decreases
Collider bias may exist whereby healthcare seeking behaviour and infection lead to testing	Unknown	Unknown

Table 1c: Limitations of the screening method

Screening method limitations	Magnitude of limitation	Direction of effect
May be subject to exposure misclassification depending on the method used to obtain vaccination uptake information on cases.	Large	Varies
May be subject to outcome misclassification if non-specific outcome measures are used. May also be affected by the type of laboratory confirmation used.	Moderate	Underestimate
VE estimation could be inaccurate if the values for PCV and PPV are drawn from different populations, at different times, as well as if there are inaccuracies in these estimates.	Large	Varies
Estimates may be restricted by the amount of information available on the population coverage, therefore ability to control for confounders is limited.	Unknown	Unknown
Bias can occur if case ascertainment is not independent of vaccination status. Specifically, if access to healthcare influences both ascertainment of outcome and chances of being vaccinated (confounding by indication).	Moderate	Varies

Chapter 4

Effectiveness of influenza vaccination in preventing hospitalisation due to influenza in children: a systematic review and meta-analysis

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Surname/Family Name	Boddington		
Thesis Title	Severe influenza infection in England: assessing the impact and estimating vaccine effectiveness		
Primary Supervisor	Punam Mangtani		

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Where was the work published?	Clinical Infectious Diseases		
When was the work published?	27 March 2021 (early access). 01 November 2021 (in print)		
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SECTION E

Student Signature	
Date	27/06/2022

Supervisor Signature	
Date	28/06/2022

Overview of Chapter

This chapter addresses objective 3 of this Research Project: To systematically review the literature on the effectiveness of influenza vaccination against hospitalisation due to influenza infection in children.

Copyright statement

The Supplementary Material from the Research paper are included in Appendix 3.

4.1 Research paper 2

Effectiveness of influenza vaccination in preventing hospitalisation due to influenza in children: a systematic review and meta-analysis

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Key words: Vaccine effectiveness, children, hospitalisation, influenza, systematic review

Running title: Influenza vaccine effectiveness in children

Key points: This study provides a complete and up-to-date review of the literature and highlights that influenza vaccination provides good protection against any influenza-associated hospitalisation in children and provides continued support for annual vaccination in children. Effectiveness varies by subtype and vaccine type.

Abstract

This systematic review assesses the literature for estimates of influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza-associated hospitalisation in children.

Studies of any design to 08 June 2020 were included if the outcome was hospitalisation, participants were 17 years old or less and influenza infection was laboratory-confirmed.

A random-effects meta-analysis of 37 studies that used a test-negative design gave a pooled seasonal IVE against hospitalisation of 53.3% (47.2-58.8) for any influenza. IVE was higher against influenza A/H1N1pdm09 (68.7%, 56.9-77.2) and lowest against influenza A/H3N2 (35.8%, 23.4-46.3). Estimates by vaccine type ranged from 44.3% (30.1-55.7) for LAIV to 68.9% (53.6-79.2) for inactivated vaccines. IVE estimates were higher in seasons when the circulating influenza strains were antigenically matched to vaccine strains (59.3%, 48.3-68.0).

Influenza vaccination gives moderate overall protection against influenza-associated hospitalisation in children supporting annual vaccination. IVE varies by influenza subtype and vaccine type.

Introduction

It is estimated that influenza causes 3-5 million severe infections annually (1). One of the groups at elevated risk of severe influenza illness are younger children, particularly younger children under two years, as well as children with chronic medical conditions (2).

Influenza vaccination remains the most effective method of preventing influenza illness in the population and reducing its burden. The World Health Organization (WHO) recommends annual influenza vaccination to individuals at increased risk of severe disease (disease resulting in hospitalisation or death) including healthy children aged 6 to 59 months (3). A number of countries have begun to adopt programmes to vaccinate children or are considering vaccination (4-6). Monitoring the effectiveness of the influenza vaccine in children is important both from an annual perspective to inform how well matched the vaccine might be to the main circulating strain and from a longer-term perspective to inform resource allocation including for future adoption in other settings. Globally there are two broad types of influenza vaccines available: inactivated influenza vaccines (IIV) and live-attenuated influenza vaccines (LAIV). In early randomised control trials (RCT) in high income settings LAIV was found to offer high protection to children, often higher than IIV (7-9), and with higher levels of acceptability than traditional injectable vaccines, LAIV has, in some countries, been preferentially recommended in children (10). However, vaccine-effectiveness studies post-licensure have shown mixed effectiveness of LAIV with estimates ranging from 0% to 57.6% (11-17).

One of the main study designs used to estimate influenza vaccine effectiveness (IVE) is the test-negative study design (TND). The method was first developed to measure IVE against medically-attended outcomes (18), however it has become increasingly used for hospital admissions with influenza (19, 20). Using this approach, the cases are those that fit the clinical case definition and test positive for influenza and those that meet the clinical case definition, but test negative are used as controls.

However, there are limitations to single season studies given the year-to-year variability of influenza, and thus meta-analyses of data from separate studies and over several seasons can be used to provide more robust VE estimates. A recent, industry sponsored, systematic review and meta-analysis of the effectiveness of influenza vaccination in preventing severe illness in children (6 months to 17 years old) found that influenza vaccination provided moderately good protection against influenza-associated hospitalisation of over 50% pooled over all seasons, but there was also considerable heterogeneity (21). The heterogeneity across studies especially given issues such as egg adaptation with influenza A/H3N2 or blunting of LAIV effectiveness against influenza A/H1N1pdm09 (22, 23)

suggest that further disaggregation by season, subtype and vaccine match would be useful to inform future vaccine use.

In this study we review and summarise the literature of all study types estimating IVE against laboratory-confirmed influenza-associated hospitalisation up to June 2020. We aim to provide updated estimates of overall IVE against laboratory-confirmed influenza-associated hospitalisations, and for the first time, by vaccine type (IIV and LAIV) as well as by influenza subtype and vaccine match.

Methods

We conducted a systematic review and meta-analysis of extracted IVE estimates. We restricted the meta-analysis to studies that used a TND to reduce heterogeneity due to study design across studies.

Search strategy and selection criteria

A search strategy was developed using the PICOST (population, intervention, comparison, outcome, situation and type of study) framework. All study designs were included except case series/reports and systematic/critical reviews.

Databases, search construct, screening and study selection

The following databases were used to conduct a comprehensive literature search: MEDLINE, Embase, Global Health, Web of Science and SCOPUS from inception to 02 May 2019 and updated on 08 June 2020. We developed a unique search strategy for each database, the main search terms included "influenza/flu", "immunisation/vaccination", "effectiveness" and "hospitalisation/intensive care/death" (full searches in Supplementary Material). No language restrictions were placed on the searches. Reference lists were searched to identify additional studies. The study protocol was registered on Prospero (CRD42019149315).

After removal of duplicates, two reviewers independently screened titles and abstracts of studies identified through the initial search. Identified studies were retrieved in full text and independently assessed for inclusion using an adapted Cochrane ERC data collection form. Any disagreements were solved by discussion.

Studies were considered eligible for inclusion if they met all the following criteria: (i) outcome was hospitalisation, (ii) study participants were children (17 years and less), (iii) influenza infection was laboratory confirmed (by any method).

The following studies were excluded: (i) studies conducted in an outpatient setting, (ii) studies containing exclusively adult data (or mixed adult and children data which could not be separated, or where estimates for children were non-estimable), (iii) interim estimates superseded by a final report, and (iv) studies that assessed the monovalent 2009 pandemic vaccine. Studies that assessed influenza VE against intensive care admission or death were also excluded due to the small number (n=2) that assessed these outcomes (24, 25).

Data collection and extraction

We used a structured electronic collection tool to extract data from the studies reviewed. For each article, one author extracted the information and another one checked the extracted data. When necessary corresponding authors were contacted for clarification of data.

Data analysis

TND studies were grouped by influenza season, and we performed a random effects meta-analysis to estimate the IVE against any type of influenza-related hospitalisation in children.

Secondary analyses were carried out by stratifying the data by influenza type (influenza A and B), age group (less than 5 years old, 6-17 years old) and vaccine type (IIV, QIV, TIV, LAIV). Where possible influenza type A was further sub-grouped by subtype (A/H1N1pdm09 and A/H3N2) and influenza B by vaccine type (IIV, QIV, TIV, LAIV). A sensitivity analysis was undertaken, restricting the overall analysis to only studies which used molecular testing. Studies that used multiple types of tests were excluded.

Throughout the study VE estimates by individual influenza season were used in preference to multiple seasons estimates, including for sub-group analyses, unless only multiple season estimates were available.

For the VE estimates by season, estimates from the southern hemisphere were grouped with those from the subsequent northern hemisphere season, apart from in seasons when the vaccine compositions were different. In this case they were grouped with the previous northern hemisphere season estimates when the vaccine compositions matched.

Where given, adjusted VE estimates were included in the meta-analysis and no minimum criteria were established for adjustment.

Where studies specified vaccination status (i.e. partially or fully vaccinated) we used fully vaccinated VE estimates which was usually defined by authors as children vaccinated in line with the recommended vaccination schedule.

For the overall meta-analysis, estimates for any age groups within 6 months to 17 years were included. For the sub-group analysis by age, any estimate that fell within the age band of interest was included.

The analysis by vaccine match was restricted to studies that presented VE estimates against hospitalisation by single seasons. In the first instance, authors conclusions about the similarity between circulating and vaccine strains were used. In the absence of this information, the WHO Weekly Epidemiological Records (WER) (26) and other relevant public health body websites were used to determine antigenic characterisation of circulating virus strains and the WHO recommendations on the composition of influenza virus vaccines (27). VE estimates by subtype were used if available otherwise overall VE estimates for all influenza were used. A match between the circulating strain and vaccine was considered if either all the vaccine components belonged to the same influenza A subtypes and B lineages, or if at least one vaccine strain was similar to the predominant virus circulating.

Heterogeneity among studies and subgroups was assessed using the χ^2 -based Q test (Cochran's Q) and the I^2 statistic. Studies were assessed for risk of bias using the Risk Of Bias In Non-randomised Studies-of Interventions (ROBINS-I) tool (28).

Stata v16.1 (Stata Corporation, College Station, TX) was used to perform the statistical analysis.

Results

After removing duplicates, we identified 2,592 potential studies. Following title and abstract screening, 305 studies were identified for full text review. Of these 262 were excluded leaving a total of 45 studies, of which 37 studies used the TND (Figure 1).

Six studies used a non-TND and are summarised in Table 1. Four were case-control studies (29-32), one used the screening method (33) and one was a prospective, non-randomised observational study (34) (Table 1). Excluding the case-control study by Joshi *et al.,* (2012) (30), all non-TND studies showed good protection against influenza-associated hospitalisation with estimates ranging between 54% and 83%.

Among the 37 TND studies, the study years ranged from 2005/2006 to 2018/2019 (Table 2). The majority were from the Northern Hemisphere (n=26), 10 studies were from the Southern Hemisphere and there was one global study.

- Estimates of overall IVE against hospitalisation (by season) (Figure 2)

Thirty-four studies provided IVE estimates in children against any type of influenza-associated hospitalisation. Among them six studies provided estimates over multiple seasons (35-40). The overall pooled IVE against hospitalisation in children due to any influenza across the seasons was 53.3% (95% CI 47.2-58.8) with moderate heterogeneity (I^2 = 62.7%, p=0.000) (Figure 2). Heterogeneity by season was much lower than the overall heterogeneity, though it was still moderate to high across studies in the 2016/17 and 2018/19 seasons. In a sensitivity analysis, the overall results were similar (52% (95% CI 41.7, 60.5)) when restricted to studies which used molecular testing.

- Estimates of IVE against hospitalisation by type/subtype (Figure 3)

Twenty-two studies provided IVE estimates against influenza A hospitalisations (Figure 3). Overall IVE against influenza A hospitalisation was 58.0% (95% CI 49.8, 64.8) with moderate heterogeneity (I^2 = 62.1%, p=0.000). Eight studies assessed IVE against influenza A only which gave a IVE of 59.7% (95% CI 46.3, 69.8) with moderate heterogeneity (I^2 = 54.0%, p=0.043). Fourteen studies assessed subtype specific IVE. The IVE against influenza A/H1N1pdm09 was 68.7% (95% CI 56.9, 77.2), with moderate heterogeneity (I^2 = 65.87%, p=0.001) and against influenza A/H3N2 was 35.8% (95% CI 23.4, 46.3), with low heterogeneity (I^2 = 0%, p=0.893).

Nineteen studies provided IVE estimates against influenza B hospitalisation (Supplement Figure 1). Overall IVE against influenza B hospitalisation was 47.6% (95% CI 38.0, 55.7) with low heterogeneity (I^2 = 17.9%, p=0.346).

- Estimates of IVE against hospitalisation by vaccine type (Figure 4)

Thirty-five studies provided IVE estimates against influenza-associated hospitalisation by vaccine type (Figure 4). For LAIV, based on a small number of studies (n=3), IVE was 44.3% (95% CI 30.1, 55.7). IVE for inactivated influenza vaccine was 67.1% (95% CI 53.5, 76.8). For TIV specifically the IVE was 47.5% (95% CI 39.5, 54.4) and for QIV 50.2% (10.7, 72.3). For influenza B specifically, the IVE estimate for quadrivalent vaccine was higher, 48.0% (95% CI -7.9, 74.9), than the trivalent vaccine with an IVE of 42.9% (95% CI 25.1, 56.5) although with wide and overlapping confidence intervals (Supplement Figure 1).

- Estimates of IVE against hospitalisation by age group (Supplement Figure 2+3)

Fifteen studies provided IVE estimates against influenza-associated hospitalisation in children aged 6 months to 5 years. The pooled VE estimate was 61.7% (95% CI 54.1, 68.1) with moderate

heterogeneity (I^2 = 58.6%, p=0.000). For children aged 6 years to 17 years, influenza VE was 51.7% (95% CI 42.9, 59.1) with low heterogeneity (I^2 = 0.66%, p=0.8567).

- Estimates of IVE against hospitalisation by vaccine match (Figure 5)

Information on whether the vaccine matched the circulating virus strains during the study periods were ascertained for twenty studies. IVE estimates were highest in seasons where the circulating influenza strains were antigenically matched to those strains included in the vaccine (IVE=59.3%, 95% CI 48.3-68.0), and in seasons where there was a mixed match with the vaccine (IVE= 58.4%, 95% CI 34.0-73.7) i.e. good match for some but not all the circulating strains. In seasons when there was a mismatch between circulating and vaccine strains, IVE was 33.6% (95% CI -2.4-57.0).

- Risk of bias assessments

Studies were either assessed as having moderate (n=37) or severe risk of bias (n=16). Most studies appeared to provide useful evidence although biases inherent with non-randomised studies remained such as selection bias. Generally, this is lower in TND studies since cases and controls are selected from a population of persons presenting with a defined set of symptoms, and in this review, these persons were hospitalised, reducing the scope for ascertainment bias. In two studies however controls were not hospitalised, introducing more serious risk of bias. A further source of bias was the lack of adjustment for underlying medical conditions in the analysis.

Discussion

In this paper we present an updated and independent review of the literature on the effectiveness of influenza vaccination in preventing hospitalisations due to influenza in children. The review includes all study designs to provide a more complete picture of the evidence. We also present the results of an updated meta-analysis that provides pooled estimates of IVE against influenza-associated hospitalisation in children by vaccine type, influenza type/subtype, age group and vaccine match.

Overall, we found that influenza vaccination provided good protection against any influenza-associated hospitalisation in children aged 6 months to 17 years old (53.2%, 95% CI 47.1-58.6). Overall heterogeneity was present but reduced when the data was split by season. This is unsurprising given the variability in the main circulating strains and vaccine match each season, as well as antigenic changes that might require attention such as egg-adaptation (22). The meta-analysis was restricted to TND studies and excluded ICU admissions and deaths to reduce heterogeneity.

To the best of our knowledge, this is the first study that looks at the effectiveness of influenza vaccination in preventing hospitalisation in children by vaccine type and vaccine match. The IVE estimates by vaccine type ranged from 44.3% (95% CI 30.1-55.7) for LAIV to 68.9% (53.6-79.2) for IIV although with overlapping confidence intervals. Whilst early RCTs suggested that LAIV may have superior efficacy compared with IIV in children (7-9), more recent observational studies have shown mixed effectiveness of LAIV against medically-attended influenza in children, particularly against influenza A(H1N1)pdm09 (11-17, 41, 42). Effectiveness estimates have also varied geographically with studies from the United States showing low LAIV effectiveness during the 2013-2016 seasons (12-14, 41, 43, 44). Hypothesised reasons for the recent lower LAIV estimates include a reduction in fitness in the vaccine strain (45), problems with vaccine production (46), mismatch between vaccine and circulating strains, or negative interference (when a vaccine's immunogenicity may be affected by pre-existing immunity) (10). Further studies are required to assess the difference of effectiveness between LAIV and IIV against more severe outcomes including hospitalisations in children.

By influenza type, IVE was slightly higher against influenza A compared to influenza B although the confidence intervals overlapped and by influenza A subtype, IVE was slightly higher against influenza A/H1N1pdm09 compared with influenza A/H3N2. Poor VE has often been seen against influenza A(H3N2), including against severe influenza in adults (47). This is thought to be related vaccine mismatch as well as to egg adaptation of A(H3N2) vaccine viruses during the vaccine production process (22, 48).

By age, IVE was higher in younger children, 6 months to 5 years, compared to those 6 years to 17 years although the confidence intervals overlapped. IVE estimates were also higher in seasons where the circulating influenza strains were antigenically matched to the vaccine strains and in seasons where there was a mixed match with the vaccine.

The majority of studies used molecular testing, specifically RT-PCR, for influenza confirmation. Overall IVE estimates were similar when restricted to studies using only molecular tests. Molecular diagnostic tests are highly sensitive and specific for detecting influenza viruses (49). Other methods, such as rapid antigen tests, are often found to be less sensitive and/or specific and can lead to biased VE estimates (49, 50).

Other sources of bias, common to many studies included in the review, was the lack of inclusion of underlying medical conditions as a confounder in their analyses. This is an important confounder since many underlying conditions can increase the risk of hospitalisation for respiratory symptoms, as well as being indications for vaccination (20).

The IVE estimates of this study are consistent with, although slightly lower than, a similar meta-analysis of IVE against hospitalisation in children carried out up to November 2019 (21). This study identified 28 studies compared with the 37 studies included in this meta-analysis. This study did not assess IVE by vaccine type. Our estimates were generally lower, although we had smaller confidence intervals and thus greater precision around our estimates. In contrast, our estimates were higher than a similar meta-analysis of IVE against hospitalisation in adults rather than children (47). The authors in this study showed that vaccination provided moderate protection against influenza-associated hospitalisation (47).

Meta-analyses of studies reporting IVE against medically-attended influenza illness using the TND show a consistent pattern in terms of higher VE against A(H1N1)pdm09 and lowest against A(H3N2) (51, 52). This is in-line with the conclusions from a meta-analysis that inpatient and outpatient IVE estimates were consistent with each other most of the time (19).

The meta-analysis was limited by the number of observations for some sub-group analyses such as influenza B lineage specific IVE estimates, and we did not look at prior vaccination or the effect of full versus partial vaccination. Previous studies in the outpatient setting have shown the potential benefit of full vaccination, particularly in younger children (under 5 years), which can be considered as two doses in children aged 6 months to 8 years depending on past vaccination status (53-56). Whilst we did restrict the meta-analysis to TND studies, we did not apply any further restriction to other methodological features. Only a small number of studies included in this review reported the match between the vaccine and the antigenic characterisation of circulating virus strains. We therefore made use of WHO publications and other relevant public health body websites.

In conclusion, this study demonstrates that influenza vaccination offers moderate protection against any influenza-associated hospitalisation in children aged 6 months to 17 years old. It also highlights variable protection over seasons as well as by influenza type/subtype and vaccine type although further evidence is required.

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There are no funding sources to declare or conflicts of interests from any authors.

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Tables and Figures

Table 1: Characteristics and overall vaccine effectiveness estimates of non-Test Negative Design (TND) studies identified in the systematic review

Author and year of publication	Country	Study design	Influenza season	Vaccine type	Diagnostic test used	Age groups	Clinical inclusion criteria	Vaccine ascertainment	Overall VE estimates against all influenza types (95% CI)
Dixon, 2010 (29)	Australia	Case-control	2008	TIV	Multiple	6 months – 59 months	Laboratory confirmed influenza for cases; acute non-ARI as controls	Parental report: validated by vaccine provided/Australian Childhood Immunisation Registry (for 87% of participants)	▪ 87% (-11, 98) (crude) ▪ 83% (-54, 98) (adjusted)
Joshi, 2012 (30)	United States	Case-control	1999-2006	TIV	Multiple	6 months – 18 years	Medically-attended influenza illness (cases laboratory confirmed influenza; controls laboratory confirmed influenza but not hospitalised)	Medical records	-267% (-740, -60) (OR = 3.67 (1.6, 8.4) (crude)
Katayose, 2011 (34)	Japan	Prospective, non-randomised, observational	2002/03 – 2007/08	TIV	Rapid tests	6 months – 5 years	ARI	Medical records	71% (59, 80) (against influenza A) (crude)

Pebody, 2017 (33)	England	Screening	2015/16	LAIV	RT-PCR	2 years – 6 years	Hospitalised, laboratory confirmed influenza for cases	Medical records	▪ 58.3% (38.8, 72.4) (crude) ▪ 54.5% (31.5, 68.4) (adjusted)
Wang, 2019 (31)	Taiwan	Case-control	2012/13 – 2015/16	Not stated	Multiple	6 months – 5 years	Hospitalised, laboratory confirmed influenza for cases; matched controls seeking medical services in same facility	Vaccination cards	57.3% (40.6, 69.4) (OR 0.427, 0.306-0.594) (adjusted)
Sugaya, 2018 (32)	Japan	Case-control + TND*	2013/14 – 2015/16	QIV	Rapid tests	6 months – 15 years	ILI (cases laboratory confirmed influenza, controls were outpatients with ILI irrespective of whether they were positive/negative for influenza.	Multiple	45% (36, 54) (adjusted)

*Results from the TND study reported in Table 2

Table 2: Characteristics of Test Negative Design (TND) studies identified in the systematic review and included in the meta-analysis

Author and year of publication	Country(ies)	Influenza season(s)	Vaccine type	Diagnostic test used	Clinical inclusion criteria	Vaccine ascertainment	Relevant child age group included	ROBINS-I Risk of Bias
Arriola, 2019	South America	2013 - 2017	Inactivated trivalent	RT-PCR	SARI	Multiple	6 months - 24 months	Moderate
Baselga-Moreno, 2019	Multiple	2016/17	Not stated	RT-PCR	ILI for patients >5 years	Multiple	0 months - 17 years	Severe
Bissielo, 2016	New Zealand	2015	Inactivated trivalent	RT-PCR	SARI	Self-report	6 months - 17 years	Moderate
Blyth, 2015	Australia	2008, 2010 - 2013	Inactivated trivalent	RT-PCR	ARI	Medical records	6 months - 17 years	Moderate
Blyth, 2016	Australia	2014	Inactivated trivalent	RT-PCR	ARI	Multiple	6 months - 15 years	Severe
Blyth, 2019	Australia	2017	Inactivated quadrivalent	RT-PCR	ARI	Multiple	6 months - 16 years	Moderate
Blyth, 2020	Australia	2018	Inactivated quadrivalent	RT-PCR	ARI	Multiple	6 months - 16 years	Moderate

Boddington, 2019	England	2015/16	Multiple	RT-PCR	Suspect influenza	Medical records	2 years - 16 years	Moderate
Buchan, 2017	Canada	2010/11 - 2013/14	TIV or LAIV	Multiple	Individuals hospitalised + respiratory specimen collected within 3 days of admission	Billing claims records	6 months - 59 months	Moderate
Buchan, 2018	Canada	2012/13 - 2015/16	LAIV or IIV	RT-PCR	Hospitalised + tested for influenza	Multiple	2 years - 17 years	Moderate
Campbell, 2019	US	2016/17, 2017/18	Not stated	Molecular assay	ARI	Multiple	6 months - 17 years	Moderate
Chiu, 2016	Hong Kong	2009/10 - 2013/14	Inactivated trivalent	Multiple	ARI	Parental report	6 months - 17 years	Severe
Chiu, 2018a	Hong Kong	2016/17	Inactivated trivalent + quadrivalent	RT-PCR	ARI	Multiple	6 months - 17 years	Severe
Chiu, 2018b	Hong Kong	2017/18	Inactivated trivalent + quadrivalent	Multiple	ARI	Multiple	6 months - 17 years	Severe
Chiu, 2019	Hong Kong	2018/19	Inactivated trivalent +	RT-PCR	ARI	Multiple	6 months - 17 years	Severe

			quadrivalent					
Chua, 2019	Hong Kong	2011 - 2019	Inactivated trivalent + quadrivalent	Multiple	ARI	Multiple	6 months - 8 years	Severe
Cowling, 2014	Hong Kong	2009 - 2012	Inactivated trivalent	Multiple	ARI	Parental report	6 months - 17 years	Severe
Cowling, 2017	Hong Kong	2015/16	Inactivated trivalent + quadrivalent	Multiple	ARI	Parental report	6 months - 17 years	Severe
Feldstein, 2020	US	2015/16	Multiple	Molecular assay	ARI	Multiple	6 months - 17 years	Moderate
Feng, 2018	Hong Kong	2012 - 2016	Multiple	Multiple	ARI	Multiple	6 months - 17 years	Severe
Fowlkes, 2017	US	2013 - 2016	Multiple	RT-PCR	SARI	Vaccine register	6 months - 12 years	Moderate
Menniti-Ippolito, 2014	Italy	2011/12, 2012/13	Not stated	RT-PCR	ILI	Parental report	6 months - 16 years	Severe
Omeiri, 2018	Latin America	2013	Inactivated trivalent	RT-PCR	SARI	Multiple	6 months - 5 years	Moderate

Pebody, 2020	England	2018/19	LAIV + inactivated quadrivalen	RT-PCR	Hospitalised + tested for influenza	Medical records	2 years - 17 years	Moderate
Pierse, 2016	New Zealand	2014	Inactivated trivalent	RT-PCR	SARI	Self-report	6 months - 17 years	Moderate
Qin, 2016	China	2013/14, 2014/15	Inactivated trivalent	RT-PCR	Inpatients with diagnosis potentially associated with influenza + ILI for patients >5 years	Vaccine register	6 months - 17 years	Moderate
Segaloff, 2019	Israel	2015/16 - 2017/18	Inactivated trivalent	RT-PCR	Hospitalised + tested for influenza (as part of clinical care)	Medical records	6 months - 8 years	Severe
Shinjoh, 2015	Japan	2013/14	Inactivated trivalent	Rapid tests	Fever of 38^{o}C or over	Medical records	6 months - 15 years	Severe
Shinjoh, 2018	Japan	2016/17	Inactivated quadrivalent	Rapid tests	Fever of 38^{o}C or over	Multiple	6 months - 15 years	Moderate
Staat, 2011	US	2005/06, 2006/07	Inactivated trivalent	RT-PCR	ARI	Multiple	6 months - 59 months	Moderate

Sugaya, 2016	Japan	2014/15	Inactivated trivalent	Rapid tests	Fever 38^{o}C or more and cough and/or rhinorrhoea	Multiple	6 months - 15 years	Severe
Sugaya, 2018	Japan	2013/14 - 2015/16	Multiple	Rapid tests	Fever 38^{o}C or more and cough and/or rhinorrhoea	Multiple	6 months - 15 years	Moderate
Turner, 2014a	New Zealand	2013	Inactivated trivalent	RT-PCR	SARI	Self-report	6 months - 17 years	Severe
Turner, 2014b	New Zealand	2012	Inactivated trivalent	Multiple	SARI	Self-report	6 months - 17 years	Severe
Wang, 2016	China	2011/12	Not stated	RT-PCR	SARI	Vaccine register	6 months - 59 months	Moderate
Yeung, 2018	Hong Kong	2014/15, 2015/16	Multiple	Multiple	Febrile/respiratory-associated admissions	Multiple	6 months - 72 months	Severe
Zhang, 2017	China	2015/16	Inactivated trivalent	RT-PCR	Hospitalised with diagnosis from list of conditions	Vaccine register	6 month - 4 years	Moderate

Figure Legends

Figure 1: Flowchart of the selection of studies

Figure 2: Seasonal influenza vaccine effectiveness against any influenza hospitalisation by season

Figure 3: Influenza vaccine effectiveness estimates against hospitalisation by influenza A

Figure 4: Influenza vaccine effectiveness estimates against hospitalisation by vaccine type

Figure 5: Influenza vaccine effectiveness against hospitalisation in children by vaccine match

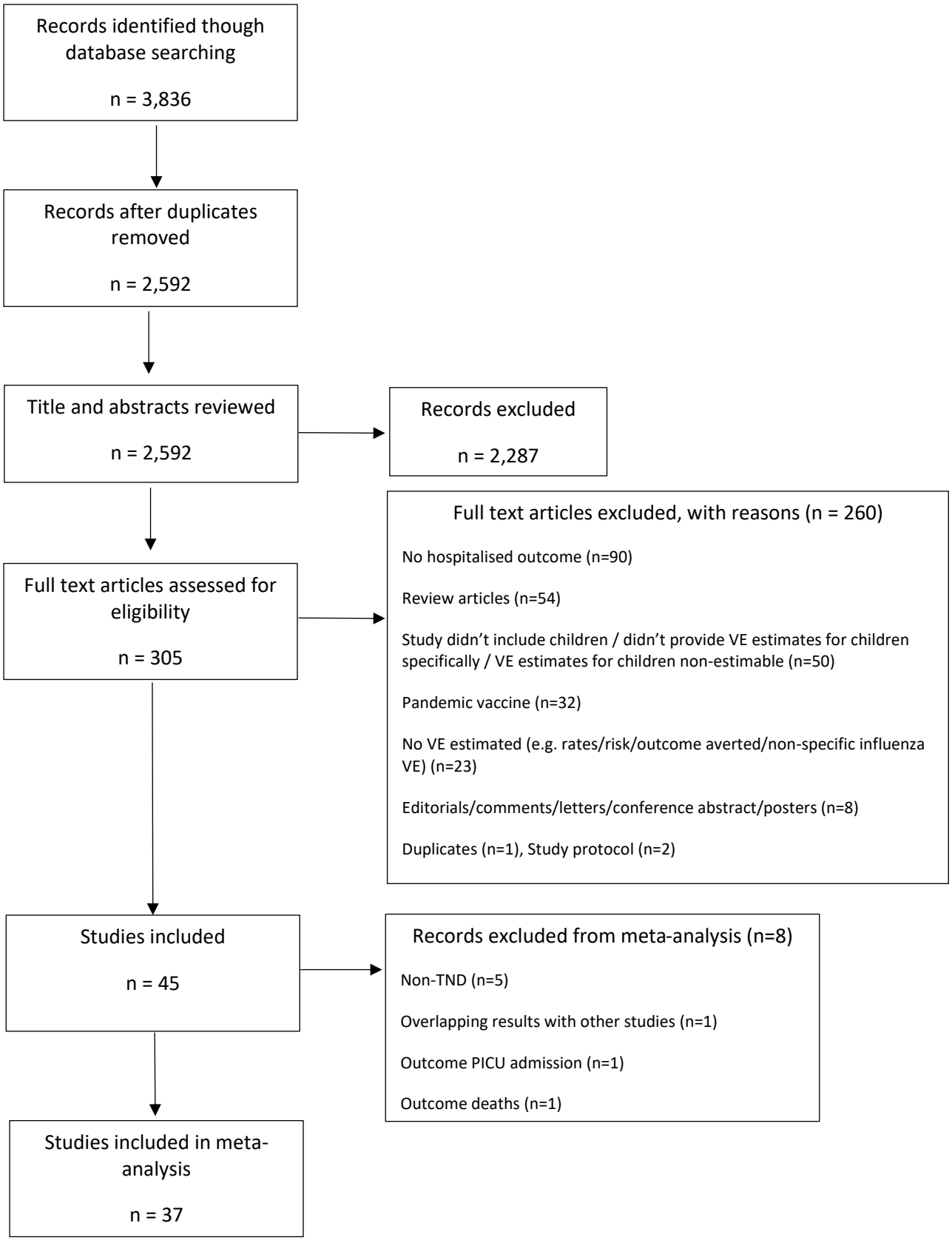

Figure 1: Flowchart of the selection of studies

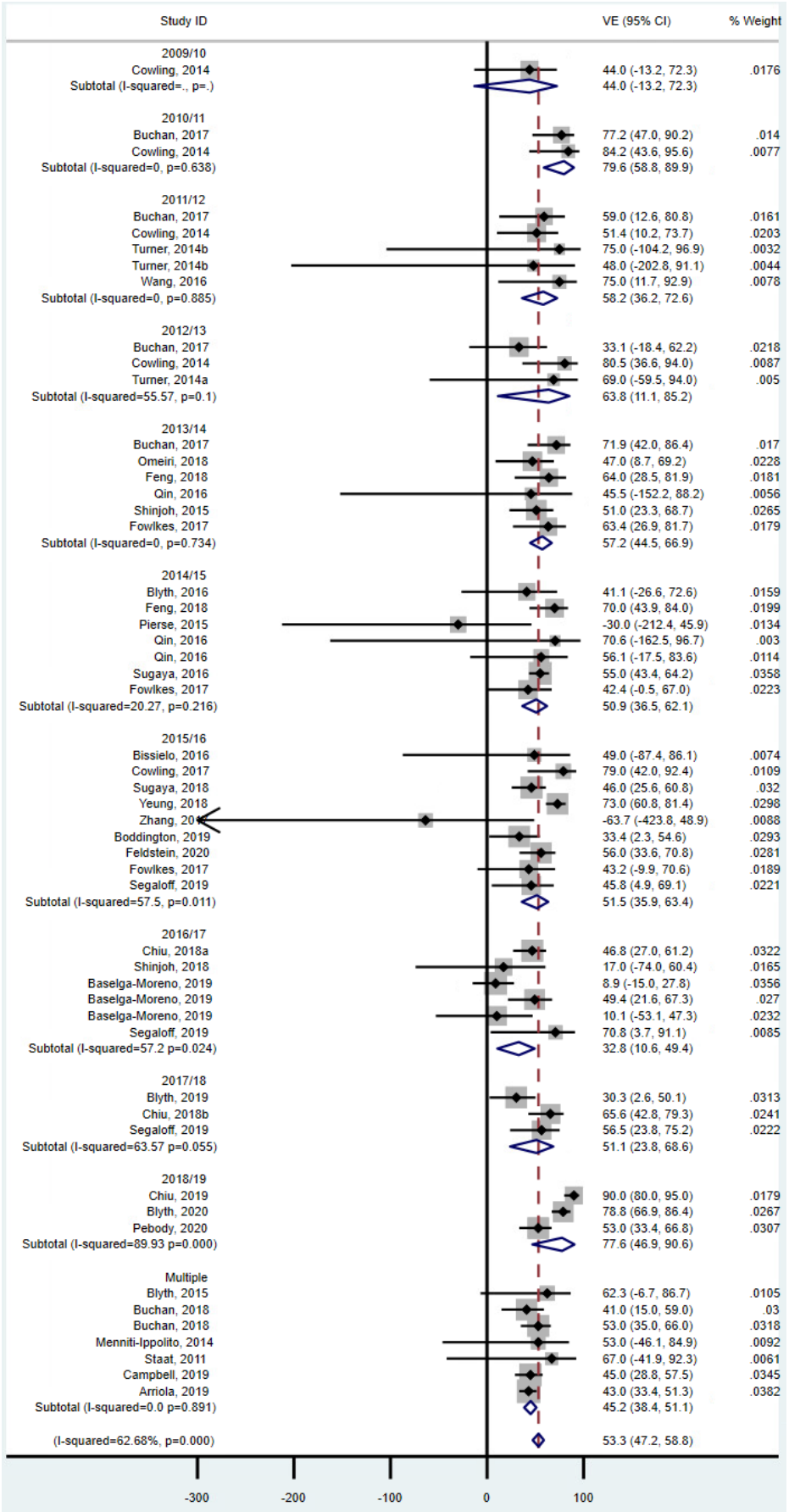

Figure 2: Seasonal influenza vaccine effectiveness against any influenza hospitalisation by season

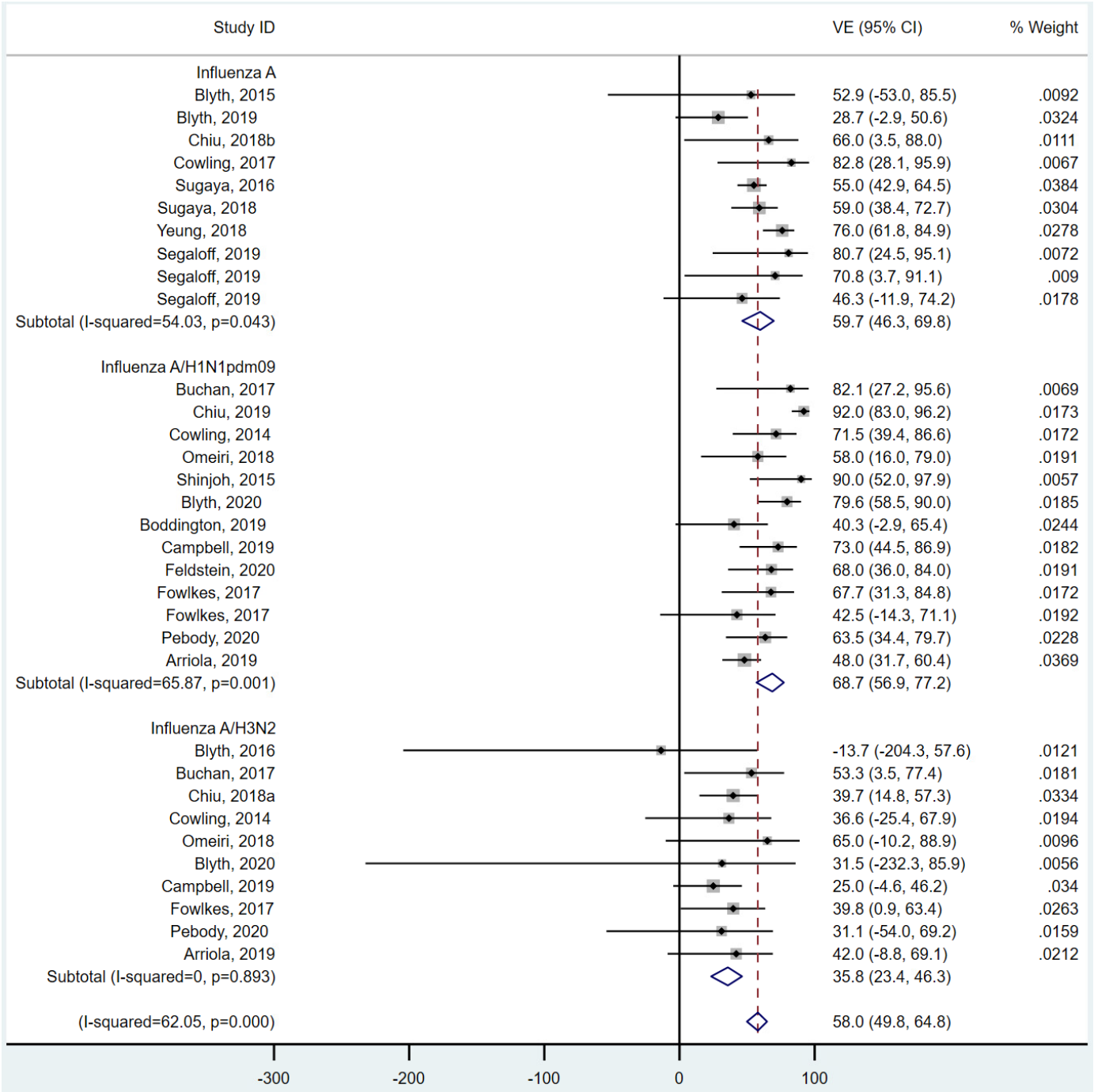

Figure 3: Influenza vaccine effectiveness estimates against hospitalisation by influenza A

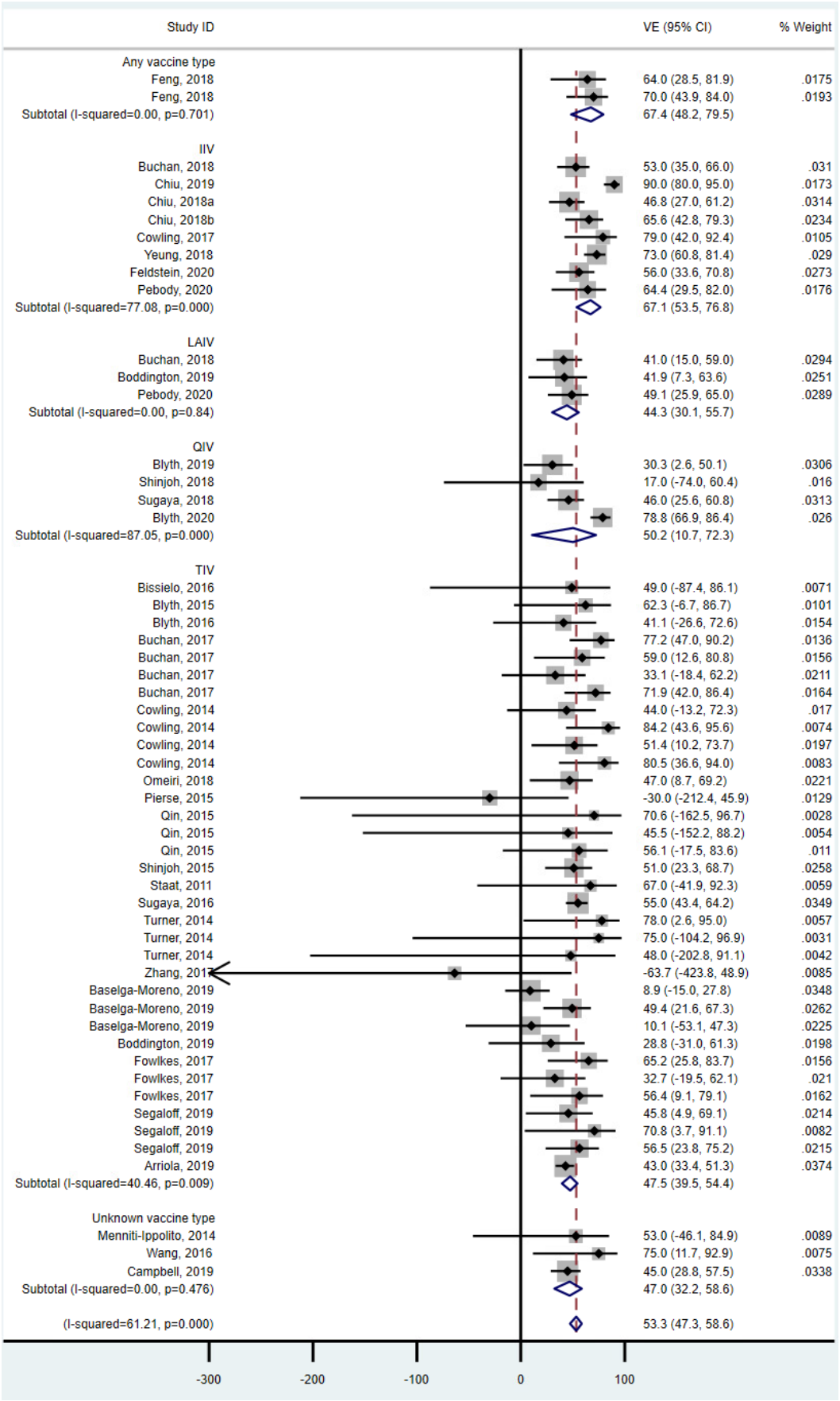

Figure 4: Influenza vaccine effectiveness estimates against hospitalisation by vaccine type

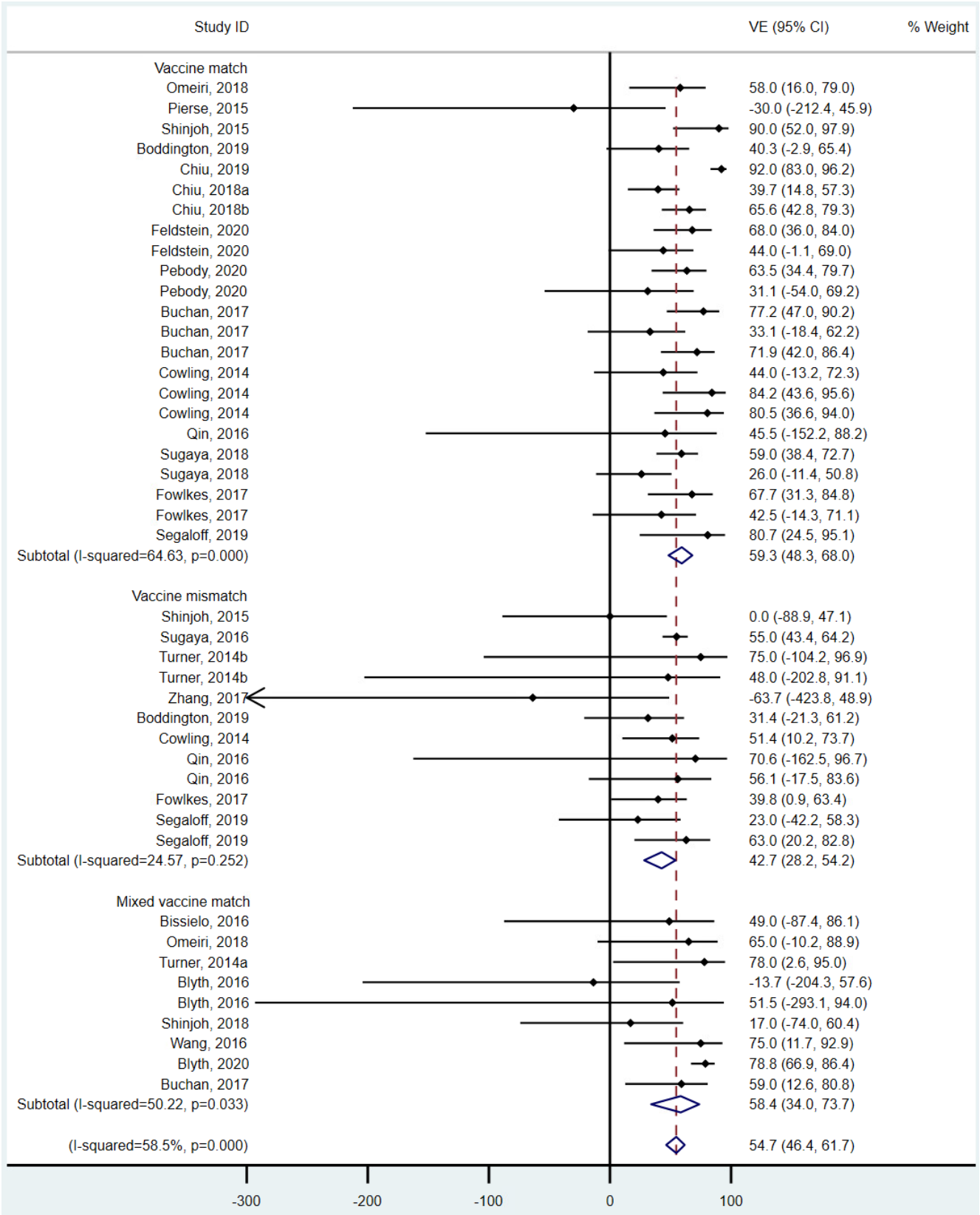

Figure 5: Influenza vaccine effectiveness against hospitalisation in children by vaccine match

Chapter 5

Influenza vaccine effectiveness against hospitalisation in children in England in the 2015/2016 influenza season – a test-negative design study

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Thesis Title	Severe influenza infection in England: assessing the impact and estimating vaccine effectiveness		
Primary Supervisor	Punam Mangtani		

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SECTION E

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Date	27/06/2022

Supervisor Signature	
Date	28/06/2022

Overview of Chapter

This chapter addresses objective 4 of this Research Project: To estimate the vaccine effectiveness of influenza vaccination against laboratory-confirmed severe influenza infection in children in England, 2015/2016, using a TND study.

Copyright statement

5.1 Research paper 3

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Influenza vaccine effectiveness against hospitalisation due to laboratory-confirmed influenza in children in England in the 2015–2016 influenza season – a test-negative case–control study

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Abstract

England has recently started a new paediatric influenza vaccine programme using a live-attenuated influenza vaccine (LAIV). There is uncertainty over how well the vaccine protects against more severe end-points. A test-negative case–control study was used to estimate vaccine effectiveness (VE) in vaccine-eligible children aged 2–16 years of age in preventing laboratory-confirmed influenza hospitalisation in England in the 2015–2016 season using a national sentinel laboratory surveillance system. Logistic regression was used to estimate the VE with adjustment for sex, risk-group, age group, region, ethnicity, deprivation and month of sample collection. A total of 977 individuals were included in the study (348 cases and 629 controls). The overall adjusted VE for all study ages and vaccine types was 33.4% (95% confidence interval (CI) 2.3–54.6) after adjusting for age group, sex, index of multiple deprivation, ethnicity, region, sample month and risk group. Risk group was shown to be an important confounder. The adjusted VE for all influenza types for the live-attenuated vaccine was 41.9% (95% CI 7.3–63.6) and 28.8% (95% CI −31.1 to 61.3) for the inactivated vaccine. The study provides evidence of the effectiveness of influenza vaccination in preventing hospitalisation due to laboratory-confirmed influenza in children in 2015–2016 and continues to support the rollout of the LAIV childhood programme.

Introduction

In 2013, the United Kingdom (UK) started the introduction of a paediatric influenza vaccination programme following recommendations of the Joint Committee on Vaccination and Immunisation (JCVI) in 2012 [1]. The aim of this programme is to ultimately offer annual influenza vaccination to all children 2–11 years of age to both directly protect them, and by reducing their rate of infection, indirectly protect others in the community who may be at higher risk of severe disease following infection [1]. The programme initially targeted all 2 and 3 year olds in 2013/14 and has been incrementally extended in subsequent seasons to further age groups. Once it has been extended to include all 2–11 years olds the programme will be paused and evaluated.

Through this programme, healthy children are offered a single dose live-attenuated influenza vaccine (LAIV) which is administered intranasally. The live-attenuated vaccine was recommended compared with the injectable, inactivated vaccine due to apparent higher effectiveness in children, potential to provide cross-protection against poorly vaccine-virus matched strains, higher acceptability amongst children, their parents and carers and possible longer-term immunological advantages [2].

The 2015–2016 season was the third season of the introduction of this paediatric influenza vaccination programme. All healthy children aged 2–4 years of age, together with children of school years 1 and 2 (ages 5 and 6 years) across England were offered quadrivalent LAIV [3]. In addition, children aged 2–16 years in a clinical risk group were also offered LAIV where not contraindicated, with the remainder offered quadrivalent inactivated vaccine.

The 2015–2016 influenza season started late in England and peaked in week 11 [4]. Comparatively large numbers of hospitalisations and admissions to intensive care units, particularly in younger adults were seen [4]. The season was dominated by circulation of influenza A(H1N1)pdm09, which was well matched to the A(H1N1)pdm09 2015–16 vaccine strain, and later by influenza B, predominantly of the B/Victoria lineage, which was not included in the 2015–2016 trivalent inactivated influenza vaccine [4]. The end-of-season vaccine effectiveness (VE) against laboratory-confirmed influenza infection in primary care in children for LAIV

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was moderately good against all influenza types (57.6%, 95% confidence interval (CI) 25.1–76.0) with moderate, but non-significant VE for influenza A(H1N1)pdm09 (41.5%, 95% CI −8.5 to 68.5) and high VE for influenza B (81.4%, 95% CI 39.6–94.3) [5]. Similar LAIV effectiveness results in children were also seen in the first two seasons of the programme [6]. However these findings for LAIV in children contrast those reported by the US Center for Disease Control and Prevention (CDC) in 2015–2016 who found an overall VE of only 5% (95% CI −47 to 39) in 2–17 years old children with a VE against influenza A(H1N1)pdm09 of −19% (95% CI −113 to 33) [7]. These findings led to the recommendation that LAIV should not be used in the USA by the Advisory Committee on Immunisation Practice (ACIP) [8].

For the first time in 2015–2016, the UK also published data on the effectiveness of LAIV against more severe disease in a study using the screening method [9]. This study found evidence that the LAIV was effective in preventing laboratory-confirmed influenza hospitalisation in children 2–6 years of age in England in 2015–2016 [9]. The screening method can be a useful study design for estimating VE rapidly and inexpensively as it uses routinely available population data when there is a lack of suitable controls. Despite this, the screening method has a number of potential limitations; most notably the cases may arise from a population that differs from that used to determine vaccine uptake rates and the inability to adjust for important but unmeasured confounders.

The aim of this enhanced surveillance project is to evaluate influenza VE in children of 2–16 years in England in 2015–2016 in protecting against laboratory-confirmed infection resulting in hospitalisation using the alternative test-negative case–control (TNCC) design.

Methods

Study design

The test-negative design is a particular type of case–control study. Using this study design participants are recruited if they meet a certain clinical case definition and are tested for the infection in question. The odds of vaccination are then compared between those testing positive *vs.* those testing negative to estimate VE. A TNCC study was used to estimate the VE in vaccine-eligible children aged 2–16 years in preventing laboratory-confirmed influenza hospitalisation in England in the 2015–2016 season.

Setting and participants

Cases and controls were both identified from the Respiratory DataMart System. This is a national sentinel laboratory surveillance system which records details of individuals tested for suspect influenza infection. Suspect cases are tested for influenza, respiratory syncytial virus, rhinovirus, parainfluenza 1–4 and human metapneumovirus using reverse transcription real-time polymerase chain reaction (rRT-PCR), and adenovirus using real-time PCR on respiratory samples by 14 laboratories located across England [10]. The most common sample types are nasopharyngeal aspirate, tracheal secretion and nasal and throat swabs. On average the total number of samples tested each year from these participating laboratories is 70 000 per year. Those testing positive for other respiratory viruses were not excluded from the analysis. Cases and controls were recruited during the 2015–2016 influenza season between week 40 of 2015 and week 20 of 2016.

Participants

Cases

A case was defined as an individual with laboratory-confirmed influenza A or/and B infection (confirmed by RT-PCR) with a specimen date from week 40 of 2015 to week 20 of 2016 aged between 2 and 16 years old (on 31 August 2015) and resident in England.

Controls

A control was defined as an individual who was tested for influenza infection, with a specimen date from week 40 of 2015 to week 20 of 2016 and tested negative for influenza infection (by RT-PCR) aged 2–16 years and resident in England.

Controls were group-matched to cases by age group (2–4, 5–8, 9–11, 12–17) and week of sample with up to three controls randomly selected per case within these groups. If fewer than three controls were available then all available controls were selected in that strata. Estimated population figures by age group and region are provided in Table 1.

Variables

Demographic details of cases and controls from the DataMart system were used to identify the primary care (general) practitioners (GPs) of these children, using the Patient Demographic Service (PDS) system. Any individuals not identifiable by the PDS system as being registered with a GP or as not resident in England were excluded from the study. Postal questionnaires were then sent to the identified GPs to ascertain whether the child had received influenza vaccination during the 2015–2016 season and if so, the vaccination date and whether the vaccine was administered by injection or intranasally and whether they had been vaccinated in the previous season. Information on whether the child was in a clinical risk group for vaccination was also obtained from the GPs.

The outcome of interest was laboratory-confirmed influenza infection (confirmed with RT-PCR through the Respiratory DataMart system) and the exposure was vaccination against influenza during the 2015–2016 influenza season.

Data on a number of potential *a priori* confounders were collected including age group, sex, ethnicity, region, index of multiple deprivation (IMD) and month of sample collection. These have been shown to confound the vaccination-influenza effect [12]. Risk group was also explored as a possible confounder since the presence of certain medical condition may increase a person's risk of severe influenza as well as being an eligibility criterion for free vaccination [12]. Risk groups included were those as defined in the UK Immunisation against Infectious Disease Book ('Green Book') [13] and individuals belonging to one or more of these risk groups were categorised as being in a risk group.

The 2015 IMD decile for the child was based on the place of residence (1–10, where 1 is the most deprived and 10 the least deprived) [14]. Ethnic group was assigned using Onomap software [15]. The Onomap software assigned each study subject into one of the UK 2001 census ethnic groups which were then grouped into the following categories: White, Asian, Black and Other ethnicity.

Statistical methods

A child was considered vaccinated if they received at least one dose of influenza vaccine at least 14 days before the child's date of

Table 1. 2015 mid-year population estimates by age group and region in England [11]

	2–4	5–6	7–8	9–11	12–16
North	289,409	190,150	187,947	264,656	425,787
South	271,116	178,936	177,776	248,677	408,070
Midlands and East	321,320	210,092	207,860	292,570	474,138
London	194,446	119,287	115,522	154,752	236,308

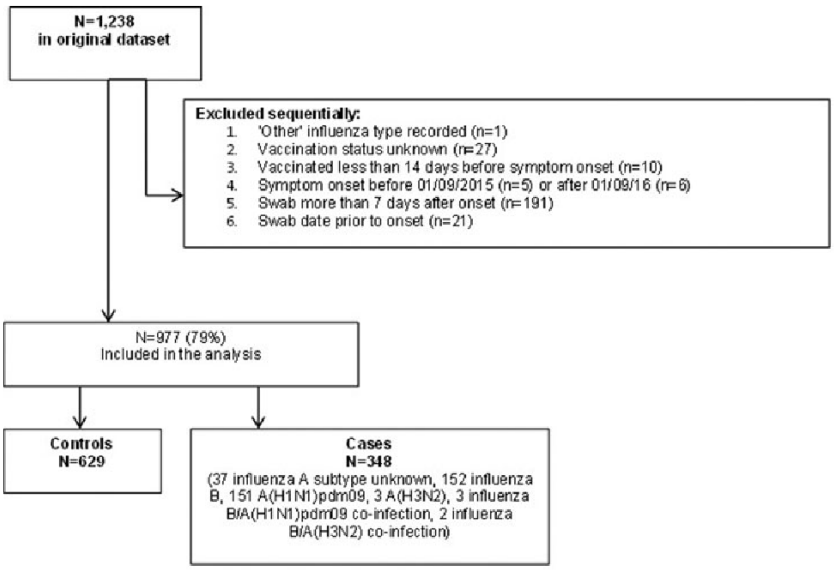

Fig. 1. Patient inclusion and exclusion criteria.

reported symptom onset, the assumed minimum time period for the child to achieve maximum protection. Due to a large proportion of individuals missing the dates of onset, the sample date minus 4 days was taken as a proxy onset date, which was the median time amongst those in whom the information was available.

If the child was vaccinated less than 14 days before onset, had an unknown vaccination record, or the vaccine was given less than 14 days before the onset of symptoms then the child was excluded from the analysis. A child was considered unvaccinated if they were reported to have received no vaccine. Where the date of vaccination was missing, the median date of vaccination amongst the vaccinated cases and controls where known was taken (31 October 2015).

Descriptive analysis

The characteristics of cases and controls are described and compared by baseline characteristics including sex, age, IMD quintile, ethnicity and region of residence, using the χ^2 test or Fisher's exact test as appropriate.

Crude and adjusted vaccine effectiveness

Logistic regression was used to calculate the unadjusted odds ratios (OR) for influenza vaccination in cases compared with controls, with a 95% CI, with influenza test result as the outcome and influenza vaccination status as the predictor. VE is defined as $(1 - \text{OR}) \times 100$.

Adjusted estimates were estimated using sex, age group, region, ethnicity, deprivation and month of sample collection. Risk group was also investigated as a potential confounding variable.

Adjusted VE estimates were calculated overall and also examined by type of influenza (influenza A, influenza A(H1N1)pdm09 and influenza B), type of vaccination (intranasal, intramuscular), age group (2–7 and 8–16) and prior vaccination.

All statistical analyses were carried out in Stata version 13.1 (StataCorp., USA).

Governance

This work was undertaken as a routine public health function to monitor vaccination programmes; Public Health England (PHE) holds permissions under Section 251 (Regulation 3) of the 2002 Health Service (Control of Patient Information) Regulations to process patient identifiable information without patient consent as part of monitoring and evaluation of national vaccination programmes.

Results

Descriptive analysis

There were a total of 1238 children aged between 2 and 16 years (on 31 August 2015) reported to DataMart, who were hospitalised between week 40 of 2015 and week 20 of 2016 and tested for influenza infection. Two-hundred and fifty-six individuals were excluded (20.7%). These individuals were excluded due to having 'other' recorded as the influenza type ($n = 1$), unknown vaccination status ($n = 27$), due to being vaccinated less than 14 days before symptom onset ($n = 10$), symptom onset either before or

after the study period ($n = 11$) and having a swab taken either prior to onset or more than 7 days after onset ($n = 201$). The remaining 977 individuals were selected for analysis (Fig. 1). There were 34 individuals with unknown vaccination dates however the median date of vaccination from those where the information was known was used instead. The median date was 31 October 2015 which was assumed to be valid since influenza activity occurred late during the season, peaking around week 11, as well as the vaccination programme being completed by end of January. It was thus likely cases would have been fully immunised prior to the onset of influenza activity.

Of the 977 included individuals, there were 348 cases and 629 controls. Of the cases, 151 (43.4%) tested positive for influenza A (H1N1)pdm09, 152 for influenza B (43.7%), 37 for influenza A (subtype unspecified) (10.5%), three for influenza A(H3N2) (0.9%) and five were co-infections (1.4%) (Table 2).

The demographic characteristics of the cases and controls are summarised in Table 2. The majority of recruited individuals were between 2 and 4 years of age (47.7%) and there was a roughly equal ratio of males and females included in the study (52.3% and 47.7% respectively). Where known, the majority of the participants were of White ethnicity (77.4%) followed by Asian ethnicity (13.4%). Ethnicity was missing for 14 individuals. Data on the risk group status was unknown or missing for 16.4% of individuals. Where known, a large proportion of all study individuals had a risk factor (53.1%). A greater proportion of controls had a risk factor (52.9%) compared with cases with a risk factor (29.0%).

Almost one-third of the individuals included in the study were vaccinated against influenza in 2015–2016 (30.4%) and the majority of vaccinated individuals (62.2%), where information was known, received the vaccine intranasally (LAIV). Information on the route of vaccination was missing for 19 individuals who were excluded from VE estimates stratified by route.

Positivity rates between cases and controls differed significantly by the ethnic group, month of sample collection, risk group status, region and vaccination status, but not by age group, sex, IMD and route of vaccination (Table 2). Whilst there was no significant difference in positivity rates by IMD deciles ($P = 0.408$), there was an increasing number of individuals included in the study with increasing deprivation.

Vaccine effectiveness estimates

Explanatory variables were added to the model in a step-wise manner (Table 3). Risk factor was the only confounder for the vaccine effects which changed the point estimates by more than 5%, however all *a priori* confounders were incorporated into the final multivariable model (Table 4).

The crude overall VE for all ages was 45.9% (95% CI 26.9–60.0) for all influenza types, which decreased to 33.4% (95% CI 2.3–54.6) after adjusting for age group, sex, IMD, ethnicity, region, month and risk group (Table 3).

Overall by route, the adjusted VE for all influenza types was 41.9% (95% CI 7.3–63.6) when administered intra-nasally (LAIV) and 28.8% (95% CI −31.1 to 61.3) when administered intra-muscularly (IIV) (Table 5).

By influenza sub-type, non-significant VE estimates were seen (Table 5). For influenza A(H1N1)pdm09 the overall estimate was 40.3% (95% CI −2.9 to 65.4), 42.4% (95% CI −7.8 to 69.2) for LAIV and 46.3% (95% CI −40.9 to 79.5) for IIV. For influenza B the overall estimate was 31.4% (95% CI −21.3 to 61.2), 61.0% (95% CI 11.3–82.8) for LAIV and −13.8% (−160.0 to 50.2) for IIV.

By the target age group, non-significant VE estimates were also seen. For the target age group for vaccination in the 2015–2016 season (2–6 year olds) the adjusted VE was 30.0% (95% CI −10.7 to 55.7) and for the non-target age group for vaccination (7–16 year olds) the adjusted VE was 45.6% (95% CI −17.6 to 74.8).

When comparing with no vaccination in both the current or previous influenza seasons, the adjusted VE for being vaccinated in both seasons was 50.8% (95% CI 18.2–84.1) (Table 6).

Discussion

The study assessed VE against hospitalisation during the 2015–2016 influenza season in England and found an overall significant VE of 33.4% against any influenza in children aged 2–16 years. The results indicate intranasal vaccine is likely to be effective. Risk factor was shown to be an important confounder in the analysis, which has often not been the case in studies looking at primary care end points [5, 6].

Overall VE was higher in children who received LAIV compared with IIV. By subtype, LAIV VE was slightly higher against B compared with influenza A(H1N1)pdm09, although these differences were not significant. The results in relation to prior vaccination are limited by small numbers however provide reassurance of the benefit of annual vaccination with evidence of significant protection if vaccinated in both seasons and possible cumulative effect.

Our findings of overall effectiveness against influenza-related hospitalisation in 2015–2016 in children are consistent with other published findings that influenza vaccination in 2015–2016 provided significant protection. In particular our study shows similar, although slightly lower (42% (95% CI 7.3–63.6) for all ages and 30.0% (95% CI −10.7 to 55.7) in the target age group for vaccination), estimates for LAIV to those found using the screening method against laboratory-confirmed influenza hospitalisation (54.5% (95% CI 31.5–68.4%)) [9] and in primary care (57.6% (95% CI 25.1–76.0%)) in England in 2015–2016 [5]. Internationally these results are also similar to those seen in Finland in primary care for 2 year olds in 2015–2016 [16]. They are however discordant with those seen in the United States where they found little evidence of effectiveness of LAIV in protecting children against laboratory-confirmed illness in primary care in 2015–2016 resulting in the removal of the recommendation to use LAIV [7, 8]. The reasons for these findings remain under investigation. Prior season vaccination has been hypothesised as a potential reason since the paediatric programme has been running for almost 10 years in the United States [17], however results from the UK [5] and Finland [16] as well as this study do not support this hypothesis.

The TNCC methodology has previously been used to assess the effectiveness of influenza vaccine in high-risk groups hospitalised in England against pandemic (H1N1) 2009 infection [18]. The test-negative design has a number of advantages; most notably is that both cases and controls should have a high degree of comparability, since they are recruited at the same time with the clinician not knowing the outcome of testing, thus reducing the risk of selection bias. Selection bias is also reduced by the fact that both cases and controls sought to care for similar sets of symptoms, reducing bias due to healthcare seeking behaviour which is in turn associated with vaccine uptake [19]. Despite this in studies using hospitalisation outcomes, the method may

Table 2. Characteristics of influenza cases ($n = 348$) and controls ($n = 629$)

	Cases (%) ($n = 348$)	Controls (%) ($n = 629$)	Total ($n = 977$)	*P*-value
Age group (years)				
2–4	156 (44.8)	310 (49.3)	466	0.556
5–6	50 (14.4)	81 (12.9)	131	
7–8	46 (13.2)	68 (10.8)	114	
9–11	36 (10.3)	56 (8.9)	92	
12–16	60 (17.2)	114 (18.1)	174	
Sex				
Female	158 (45.4)	308 (49.0)	466	0.285
Male	190 (54.6)	321 (51.0)	511	
Ethnic group				
White	250 (71.8)	495 (78.7)	745	0.028
Asian	57 (16.4)	72 (11.4)	129	
Black	5 (1.4)	15 (2.4)	20	
Other	31 (8.9)	38 (6.0)	69	
Missing	5 (1.4)	9 (1.4)	14	
IMD				
1	64 (18.4)	124 (19.7)	188	0.408
2	57 (16.4)	67 (10.7)	124	
3	41 (11.8)	76 (12.1)	117	
4	38 (10.9)	63 (10.0)	101	
5	23 (6.6)	53 (8.4)	76	
6	17 (4.9)	46 (7.3)	63	
7	29 (8.3)	55 (8.7)	84	
8	28 (8.0)	52 (8.3)	80	
9	24 (6.9)	46(7.3)	70	
10	27 (7.8)	47 (7.5)	74	
Month of sample collection				
October	2 (0.6)	9 (1.4)	11	<0.0001
November	1 (0.3)	18 (2.9)	19	
December	13 (3.7)	77 (12.2)	90	
January	49 (14.1)	96 (15.3)	145	
February	75 (21.6)	152 (24.2)	227	
March	150 (43.1)	170 (27.0)	320	
April	47 (13.5)	72 (11.4)	119	
May	11 (3.2)	35 (5.6)	46	
Risk group				
Yes	101 (29.0)	333 (52.9)	434	<0.0001
No	132 (37.9)	251 (39.9)	383	
Missing	115 (33.0)	45 (7.2)	160	
Regions				
North	143 (41.1)	168 (26.7)	311	<0.0001
South	88 (25.3)	158 (25.1)	246	
Midlands + East	91 (26.1)	211 (33.5)	302	
London	26 (7.5)	92 (14.6)	118	
Vaccination status				
Vaccinated	78 (26.3)	219 (73.7)	297	<0.0001
Not vaccinated	270 (39.7)	410 (60.3)	680	
Vaccination status (by route)				
Intramuscular	27 (7.8)	78 (12.4)	105	0.869
Intranasal	46 (13.2)	127 (20.2)	173	
Missing	5 (1.4)	15 (2.4)	20	
Influenza type/subtype				
Influenza A/ H1N1pdm09	151 (43.4)			
Influenza A/H3N2	3 (0.9)			
Influenza A unknown subtype	37 (10.5)			
Influenza B	152 (43.7)			
Co-infection (3 influenza A(H1N1) pdm09–B, 2 influenza A (H3N2)–B)	5 (1.4)			

Table 3. Stepwise addition of explanatory variables and respective adjusted VE estimates

Possible confounding variable	VE estimate (95% CI)
Unadjusted	45.9 (26.9–60.0)
+ Age group	45.5 (26.3–59.7)
+ Age group and sex	46.1 (27.0–60.1)
+ Age group, sex and IMD	45.5 (26.1–59.8)
+ Age group, sex, IMD and ethnicity	45.8 (26.4–60.1)
+ Age group, sex, IMD, ethnicity and region	47.3 (28.0–61.4)
+ Age group, sex, IMD, ethnicity, region and month	46.6 (26.4–61.3)
+ Age group, sex, IMD, ethnicity, region, month and risk group (final model)	33.4 (2.3–54.6)

be subject to bias due to the fact that many underlying diseases increase the risk of hospitalisation for respiratory symptoms, but at the same time some of these diseases are indication for vaccination [20]. This is likely to explain the important confounding effect of risk-group when looking at severe end-points. The difference in the proportion of cases and controls that have a risk factor in this study is noteworthy. The limitations of this study include the fact that it had had limited power for the various stratifications. In addition, laboratory testing for influenza infection in the hospitalised age group studied tends to occur mainly among those presenting to secondary care. This will have a limited effect on the estimate of VE as cases and (test-negative) controls are

Table 4. Vaccine uptake in cases and controls by explanatory variables

	Cases (%) (n = 348)		Controls (%) (n = 629)		
	Vacc (%)	Unvacc (%)	Vacc (%)	Unvacc (%)	Total (n = 977)
Age Group					
2–4	43 (27.6)	113 (72.4)	111 (35.8)	199 (64.2)	466
5–6	13 (26.0)	37 (74.0)	35 (43.2)	46 (56.8)	131
7–8	4 (8.7)	42 (91.3)	19 (27.9)	49 (72.1)	114
9–11	7 (19.4)	29 (80.6)	15 (26.8)	41 (73.2)	92
12–16	11 (18.3)	49 (81.7)	39 (34.2)	75 (65.8)	174
Sex					
Female	34 (21.5)	124 (78.5)	96 (31.2)	212 (68.8)	466
Male	44 (23.2)	146 (76.8)	123 (38.3)	198 (61.7)	511
Ethnic Group					
White	14 (24.6)	43 (75.4)	25 (34.7)	47 (65.3)	129
Asian	3 (60.0)	2 (40.0)	5 (33.3)	10 (66.7)	20
Black	8 (25.8)	23 (74.2)	14 (36.8)	24 (63.2)	69
Other	53 (21.2)	197 (78.8)	174 (35.2)	321 (64.8)	745
Missing	0 (0.0)	5 (100.0)	1 (11.1)	8 (88.9)	14
IMD					
1	12 (18.8)	52 (81.3)	40 (32.3)	84 (67.7)	188
2	18 (31.6)	39 (68.4)	17 (25.4)	50 (74.6)	124
3	10 (24.4)	31 (75.6)	25 (32.9)	51 (67.1)	117
4	6 (15.8)	32 (84.2)	21 (33.3)	42 (66.7)	101
5	3 (13.0)	20 (87.0)	22 (41.5)	31 (58.5)	76
6	4 (23.5)	13 (76.5)	20 (43.5)	26 (56.5)	63
7	6 (20.7)	23 (79.3)	24 (43.6)	31 (56.4)	84
8	9 (32.1)	19 (67.9)	16 (30.8)	36 (69.2)	80
9	5 (20.8)	19 (79.2)	18 (39.1)	28 (60.9)	70
10	5 (18.5)	22 (81.5)	16 (34.0)	31 (66.0)	74
Month of sample collection					
October	1 (50.0)	1 (50.0)	0 (0.0)	9 (100.0)	11
November	0 (0.0)	1 (100.0)	9 (50.0)	9 (50.0)	19
December	2 (15.4)	11 (84.6)	22 (28.6)	55 (71.4)	90
January	9 (18.4)	40 (81.6)	45 (46.9)	51 (53.1)	145
February	18 (24.0)	57 (76.0)	50 (32.9)	102 (67.1)	227
March	32 (21.3)	118 (78.7)	56 (32.9)	114 (67.1)	320
April	10 (21.3)	37 (78.7)	21 (29.2)	51 (70.8)	119
May	6 (54.5)	5 (45.5)	16 (45.7)	19 (54.3)	46
Risk group					
Yes	34 (33.7)	67 (66.3)	156 (46.8)	177 (53.2)	434
No	21 (15.9)	111 (84.1)	46 (18.3)	205 (81.7)	383
Missing	23 (20.0)	92 (80.0)	17 (37.8)	28 (62.2)	160
Regions					
North	28 (19.6)	115 (80.4)	62 (36.9)	106 (63.1)	311

(*Continued*)

Table 4. (*Continued.*)

	Cases (%) (*n* = 348)		Controls (%) (*n* = 629)		
	Vacc (%)	Unvacc (%)	Vacc (%)	Unvacc (%)	Total (*n* = 977)
South	19 (21.6)	69 (78.4)	58 (36.7)	100 (63.3)	246
Midlands + East	25 (27.5)	66 (72.5)	76 (36.0)	135 (64.0)	302
London	6 (23.1)	20 (76.9)	23 (25.0)	69 (75.0)	118

Table 5. Number of hospitalised individuals positive (cases) and negative (controls) for influenza, by vaccination status and VE estimates by subtype and route in 2–16 year olds in 2015–2016, England

Influenza type	Cases (vac/unvac)	Controls (vac/unvac)	Crude VE (95% CI)	Adjusted VE[a] (95% CI)
Any influenza				
Overall	78/270	219/410	45.9 (26.9–60.0)	33.4 (2.3–54.6)
Intra-nasal	46/270	127/410	45.0 (20.3–62.0)	41.9 (7.3–63.6)
Intra-muscular	27/270	78/410	47.4 (16.4–66.9)	28.8 (−31.1 to 61.3)
Influenza A				
Overall	48/148	219/410	39.3 (12.6–57.8)	31.3 (−9.9 to 57.1)
Intra-nasal	33/148	127/410	28.0 (−10.3 to 53.0)	27.9 (−22.6 to 57.6)
Intra-muscular	13/148	78/410	53.8 (14.5–75.1)	50.6 (−15.4 to 78.8)
Influenza B				
Overall	33/124	219/410	53.1 (28.2–69.3)	31.4 (−21.3 to 61.2)
Intra-nasal	14/124	127/410	63.6 (34.4–79.7)	61.0 (11.3–82.8)
Intra-muscular	16/124	78/410	32.2 (−20.4 to 61.8)	−13.8 (−160.0 to 50.2)
Influenza A(H1N1)pdm09				
Overall	34/120	219/410	47.0 (19.7–65.0)	40.3 (−2.9 to 65.4)
Intra-nasal	23/120	127/410	38.1 (−0.9 to 62.0)	42.4 (−7.8 to 69.2)
Intra-muscular	9/120	78/410	60.6 (19.1–80.8)	46.3 (−40.9 to 79.5)

[a]Adjusted VE by age group, sex, IMD, ethnicity, region, month and risk group.

Table 6. Number of individuals positive (cases) and negative (controls) and VE estimates by prior vaccination history in 2–16 year olds in 2015–2016, England

Previous vaccination, any influenza type	Cases	Controls	Crude VE (95% CI)	Adjusted VE[a] (95% CI)
Not vaccinated in either season	129	326	Baseline	Baseline
Vaccinated in 2014–2015, not 2015–2016	9	73	68.8 (35.9–84.9)	63.9 (18.2–84.1)
Vaccinated in 2015–2016, not 2014–2015	24	75	19.1 (−33.79 to 51.1)	2.6 (−73.3 to 45.2)
Vaccinated in both seasons	22	134	58.5 (31.9–74.7)	50.8 (18.2–84.1)
Missing	164	21		

[a]Adjusted VE by age group, sex, IMD, ethnicity, region, month and risk group.

likely to have similar severity of illness in order to be tested. Positivity rates between cases and controls differed significantly by month of sample collection despite group matching the controls to cases on week of sample. This is likely due to remaining differences from the return rates and missing data, as well as the fact the matching was carried out on the entire dataset prior to making any exclusions. As such age group and month were still included in the analysis.

This study provides evidence for the effectiveness of influenza vaccination in preventing hospitalisations due to influenza in children in 2015–2016 and continues to support the rollout of the LAIV childhood programme in England. The test-negative design is becoming increasingly popular for use in hospital-based studies adding to evidence of influenza VE in preventing severe influenza illness which is important to inform current vaccination strategies.

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Chapter 6

Live attenuated influenza vaccine effectiveness against hospitalisation in children in England in the 2013/2014 to 2015/2016 influenza seasons using the screening method

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Overview of Chapter

This chapter addresses objective 5 of this Research Project: To estimate the vaccine effectiveness of influenza vaccination against laboratory-confirmed severe influenza infection in children in England, 2013-2015, using the screening method.

Copyright statement

6.1 Research paper 4

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ORIGINAL ARTICLE

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Live-attenuated influenza vaccine effectiveness against hospitalization in children aged 2–6 years, the first three seasons of the childhood influenza vaccination program in England, 2013/14–2015/16

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Abstract

Introduction: In 2013, the United Kingdom began to roll-out a universal annual influenza vaccination program for children. An important component of any new vaccination program is measuring its effectiveness. Live-attenuated influenza vaccines (LAIVs) have since shown mixed results with vaccine effectiveness (VE) varying across seasons and countries elsewhere. This study aims to assess the effectiveness of influenza vaccination in children against severe disease during the first three seasons of the LAIV program in England.

Methods: Using the screening method, LAIV vaccination coverage in children hospitalized with laboratory-confirmed influenza infection was compared with vaccination coverage in 2–6-year-olds in the general population to estimate VE in 2013/14–2015/16.

Results: The overall LAIV VE, adjusted for age group, week/month and geographical area, for all influenza types pooled over the three influenza seasons was 50.1% (95% confidence interval [CI] 31.2, 63.8). By age, there was evidence of protection against hospitalization from influenza vaccination in both the pre-school (2–4-year-olds) (48.1%, 95% CI 27.2, 63.1) and school-aged children (5–6-year-olds) (62.6%, 95% CI 2.6, 85.6) over the three seasons.

Conclusion: LAIV vaccination in children provided moderate annual protection against laboratory-confirmed influenza-related hospitalization in England over the three influenza seasons. This study contributes further to the limited literature to date on influenza VE against severe disease in children.

KEYWORDS
children, influenza, influenza vaccine effectiveness, LAIV, screening method

1 | INTRODUCTION

The United Kingdom previously had a long-standing selective influenza vaccination program that targeted populations at higher risk of severe disease due to influenza. Historically, this approach had been targeted at those 65 years of age and over, and those less than 65 years of age in clinical risk groups, including pregnant women, and healthcare workers, and aimed to directly protect these groups.[1] Despite the program, there was recognized to still remain a considerable burden of disease, both in the targeted groups, largely due to limited effectiveness of vaccination, and, prior to the COVID-19 pandemic, no substantial increases in uptake for many years, as well as on-going burden and transmission in the non-targeted groups, such as children.[1]

It is estimated that between 10% and 30% of children are infected with influenza annually[2–4] and, although most often influenza infection is self-limiting, complications leading to hospitalization can occur, particularly in those under 5 years of age and in children with chronic medical conditions. In the United Kingdom, the youngest children have the highest influenza-related admission rates of all ages.[5–7] In addition, children are recognized to play a key role in the transmission of the influenza virus in the wider community.[8–10]

In 2012, the Joint Committee on Vaccination and Immunisation (JCVI) considered the evidence for extending influenza immunization to healthy children using the newly licensed live-attenuated influenza vaccine (LAIV) and recommended universal annual vaccination of all children aged 2–16 years for influenza with LAIV in England.[11] The program was introduced incrementally from the start of the 2013/2014 influenza season, during which initially children aged 2–3 years were targeted nationally through general practice, as well as primary school aged children in seven geographical pilot areas in England. Since then, the program has been rolled out incrementally by adding additional age cohorts each season.

An important component of any new vaccination program is measuring how effective it is. The direct effect of a vaccine can be assessed after introduction in the targeted population using observational vaccine effectiveness (VE) studies.[12] LAIVs have been previously shown to provide good protection against influenza illness, although more recent observational studies have provided mixed results, with VE varying widely across seasons and other countries.[13–16] In particular, in the United States, studies demonstrated reduced protection of LAIV against influenza A/H1N1pdm09 infection in the 2013/14 and 2015/16 seasons.[15,17,18] Studies from the United Kingdom, Finland and Canada have shown good overall effectiveness of LAIV in children, although effectiveness was generally lower, specifically for the influenza A/H1N1pdm09 component of the vaccine, compared with injected inactivated vaccine (IIV).[13,14,19] This was despite a new component, A/Bolivia/559/2013 strain, being introduced to the vaccine in 2015/16. These findings resulted in a temporary suspension of the use of LAIV and greater reliance on IIVs in the United States in 2016/17 and 2017/18.[20–22]

Despite these findings, other studies conducted in England have shown maintained protection against more severe disease (i.e., hospitalization) due to influenza A/H1N1pdm09 in 2015/16.[23,24] Using the screening method, Pebody et al. estimated LAIV VE against laboratory-confirmed hospitalization in 2–6-year-olds to be 48.3% when adjusted for age, geography, and month for influenza A/H1N1pdm09.[24] Boddington et al. estimated LAIV VE against laboratory-confirmed hospitalization due to influenza A/H1N1pdm09 in 2–16-year-olds to be 42.4% when adjusted for sex, risk-group, age group, region, ethnicity, deprivation, and month of sample collection using the test-negative design.[23]

This study aims to extend the findings of these studies by assessing the effectiveness of influenza vaccination in children during the first three seasons of the LAIV program and to assess if protection against hospitalization was maintained in the seasons prior to 2015/16 when the influenza A/California/7/2009(H1N1)pdm09 strain was used in the LAIV, and in 2015/16, when the new vaccine strain was introduced (A/Bolivia/559/2013).

Using three seasons gives a greater amount of data to provide more robust evidence for the continued rollout of the childhood influenza vaccination program in England. The study also provides an opportunity to assess the utility of the screening method in assessing VE against hospitalization; the findings for which might be relevant for other vaccination programs such as the COVID-19 VE studies.

The objective of this study was to estimate VE of influenza vaccination in preventing hospital admissions of laboratory-confirmed influenza infection in children aged 2–6 years during the 2013/14, 2014/15, and 2015/16 influenza seasons using the screening method.

2 | METHODS

Using the screening method, vaccination coverage in children hospitalized with laboratory-confirmed influenza infection was compared with vaccination coverage in children in the general population, adjusted for age group, week/month, and geographical area.

2.1 | Details of the data collection

2.1.1 | Cases

Cases of severe influenza admitted to hospital were identified from the sentinel UK Severe Influenza Surveillance System (USISS): a national surveillance system that collects data on hospitalized laboratory-confirmed influenza cases from a sentinel network of acute NHS hospital Trusts in England.[7] A confirmed case was defined as an individual admitted to a USISS sentinel hospital with a laboratory-confirmed influenza infection during the influenza surveillance periods of the 2013/14, 2014/15, and 2015/16 influenza seasons (i.e., between Week 40 and Week 20 of the respective seasons) that were of target age for vaccination during those seasons (described below). Hospital trusts were provided with testing criteria to ensure that all patients admitted to hospital with clinical signs or suspicion of influenza were tested for influenza.

TABLE 1 Target childhood vaccination groups in England, 2013–15, setting of vaccine delivery and method of vaccine uptake data collection

Target group	Vaccine delivery	Vaccine offered	Denominator	Vaccine uptake	Data available
Pre-school children (aged 2, 3, and 4 years[a]	Via primary care (GPs)	LAIV[c]	Number of patients registered with GP (healthy + those with clinical risk factors)	Immform[d]	Cumulative weekly, monthly and end-of-season uptake data aggregated by CCG and presence/absence of clinical risk group
School-aged children (school years 1 and 2, i.e., children aged 5 rising to 6 years and aged 6 rising to 7 years)[b]	Via schools (but some areas chose to vaccinate via pharmacies/GPs)	LAIV[c]	Total number of children eligible for influenza vaccination in the LA geography AND children educated out of school in the LA geography, using local education authority population figures (healthy + those with clinical risk factors)	Immform[d] via a separate monthly reporting system	Cumulative monthly and end-of-season uptake data aggregated by local authority

Abbreviation: LAIV, live-attenuated influenza vaccine.
[a]Pre-school children aged 2–3 years were vaccinated in 2013/14, and in 2014/15 and 2015/16, pre-school children aged 2–4 years were vaccinated.
[b]School-aged children were included in the program from the 2015/16 season,
[c]Unless medically contraindicated in which case IIV is offered, although this data was not captured for the school program.
[d]Immform is the routine national vaccine uptake monitoring system, Influenza Immunisation Uptake Monitoring Programme.

For each case, data on age, sex, geography, date of onset of influenza-like illness, date of hospitalization, and specific clinical risk group status were extracted from the USISS system. The target groups for vaccination that were included in the study were 2–3-year-olds in the 2013/14 season, 2–4-year-olds in the 2014/15 season and 2–6-year-olds in the 2015/16 season (Table 1).

2.1.2 | Vaccination uptake of cases

Vaccination history of cases was obtained by sending a standard data collection proforma by post to the cases' General Practitioner in England. The date of administration and whether the vaccine was administered by injection or intranasally were also collected. This information was used to determine the proportion of cases vaccinated (PCV). This data collection was limited to the seasons included in this study.

A case was considered vaccinated if they received at least one dose of influenza vaccine (LAIV) in the relevant influenza season more than 14 days before disease onset, as this was considered the minimum time period to achieve maximum protection. When onset date was missing, the sample date minus 2 days was used as a proxy (based on the median time among those cases in whom the information was available) and if sample date was unknown then the test date minus 3 days was used (again based on the median time among those cases in whom the information was available).

Cases vaccinated by injection (i.e., by IIV) were excluded since population vaccine uptake is not available by vaccine type. All of the children in the school aged cohort will have been offered LAIV; however, a small number of 2–4-year-olds may have received IIV if they were contraindicated to recieve LAIV (due to severe immunodeficiency, those receiving salicylate therapy, those who have active wheezing at the time of vaccination or severe asthma and some with egg allergy[1]).

Cases where the vaccination history was unknown, or they were vaccinated less than 14 days before onset of symptoms, were also excluded from the analysis. When the date of vaccination was missing, cases who were hospitalized after mid-January in the respective seasons were assumed to be vaccinated at more than 14 days before onset, because the vast majority of vaccinations are completed by mid-January. In addition, cases where the interval between onset of illness and swab date exceeded 7 days were also excluded due to well documented reduced test sensitivity for longer time periods between these two-time points.[25–28]

2.1.3 | Reference population vaccine uptake

Data on population vaccination coverage was obtained from ImmForm: the routine national vaccine uptake monitoring system in England.[29]

For the pre-school ages, weekly data were extracted from ImmForm on the number of children registered in primary care and the number of children who received seasonal influenza vaccination during the study seasons. Data were available by age group, week, geographical area (CCG), and presence/absence of a clinical risk factor. Data were not available by vaccine type.

For vaccinations in school-aged children, data were extracted from ImmForm on the number of children of school age and the number of school-aged children who received seasonal influenza vaccination during the study seasons. Data were available by year group, geographical area (local authority [LA]) and month.

This information was used to determine the proportion of the population vaccinated (PPV).

2.2 | Statistical analysis

Data were analyzed using Stata v. 13.1 (StataCorp., USA).

For the crude analysis, VE can be calculated as 1− the odds of vaccination in cases/odds of vaccination in the population, or as below:

$$VE = 1 - (PCV/(1 - PCV))$$

$$(PPV/(1 - PPV))$$

where PPV is the proportion of the reference group vaccinated, and PCV is the proportion of the influenza cases vaccinated.

End-of-season vaccine uptake figures by target group were used for the crude PPV estimates. These crude estimates can be stratified according to the availability of vaccination coverage in the reference group such as by age group.

For the adjusted analysis, each case was matched to the appropriate PPV that best matched that case according to key confounding variables. For this analysis, PPV was available by age group/year group (2–4-year-olds, school years 1 and 2), geographical area (CCG/LA) and by week/month. To take into account the 14 days required to develop immunity, vaccine coverage data were offset by 14 days to provide an estimate of weekly effective influenza vaccine uptake.

The VE, controlling for age group, week/month, and geographical area, was then estimated using logistic regression with vaccination status of the case as the outcome variable, a constant fitted and the logit of the individually matched vaccine coverage as an offset according to the method of Farringdon.[30]

The presence/absence of risk group was collected on all hospitalized cases although population vaccine uptake by presence/absence of risk group was only available for the pre-school age groups (2–4-year-olds). In a subgroup analysis for 2–4-year-olds, where risk factor information was available, PPV was assigned to cases that matched to each case by presence/absence of risk factor, as well as age group, geographical area, and week used above. Separately, because data completion on risk factor information was poor, a sensitivity analysis was also undertaken for the above group. In the first instance, all cases aged 2–4 years were assumed to have a risk factor, then second, they were all assumed not to have a risk factor. Stratified VE estimates were also estimated for those with/without a risk factor.

This work was undertaken as a routine public health function to monitor vaccination programs. Public Health England (PHE), now the UK Health Security Agency (UKHSA), holds permissions to collect data under Section 251 of the National Health Service Act 2006 and the 2002 Health Service (Control of Patient Information) regulations, as part of the monitoring of the performance of national vaccination programs.

3 | RESULTS

3.1 | Description of cases

Three hundred and ninety-seven cases eligible for vaccination were reported to the USISS scheme during the 2013/14, 2014/15, and 2015/16 influenza seasons. Of these 227 were eligible for inclusion in the study, and the remaining 170 cases were excluded (Figure 1). These cases were excluded for reasons including cases not being in a target group for vaccination in the study seasons ($n = 106$),

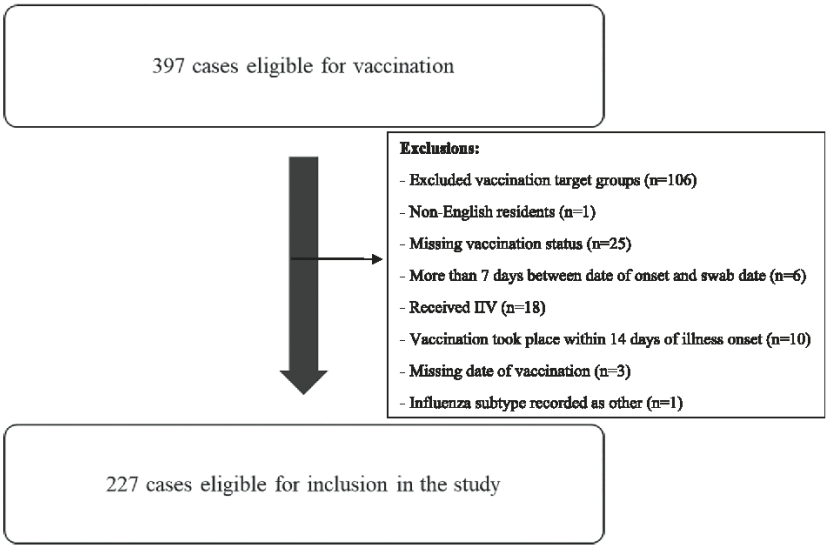

FIGURE 1 Case inclusion and exclusion flowchart

non-English residents ($n = 1$), missing vaccination status ($n = 25$), more than 7 days between date of onset and swab date ($n = 6$), received IIV ($n = 18$), vaccination took place within 14 days of illness onset ($n = 10$), missing date of vaccination ($n = 3$), and influenza subtype recorded as other ($n = 1$) (Figure 1).

Of the 227 included cases, 69.6% occurred in the 2015/16 influenza season ($n = 157$), 21.6% in the 2014/15 season ($n = 49$), and the remaining 8.8% ($n = 20$) in the 2013/14 season (Table 2). 50.7% were due to influenza A(H1N1pdm09) ($n = 115$), 15.4% due to influenza A(H3N2) ($n = 33$), 23.8% due to influenza B ($n = 54$), and 10.1% due to influenza A unknown subtype ($n = 23$).

Fifty-five of the 227 cases included (24.2%) were vaccinated. Of these, all cases were vaccinated with the LAIV ($n = 53$), apart from two cases with vaccine type unknown ($n = 2$).

TABLE 2 Characteristics of influenza cases ($n = 227$)

	Number (column %)	Number vaccinated (row %)	Number unvaccinated (row %)
Season			
2013/14	20 (8.8)	6 (30.0)	14 (70.0)
2014/15	49 (21.6)	11 (22.4)	38 (77.6)
2015/16	158 (69.6)	38 (24.1)	120 (75.9)
Age group			
2 years	79 (34.8)	18 (22.8)	61 (77.2)
3 years	65 (28.6)	17 (26.2)	48 (73.8)
4 years	58 (25.6)	14 (24.1)	44 (75.9)
Year 1 (aged 5 rising to 6 years)	14 (6.2)	1 (7.1)	13 (92.9)
Year 2 (aged 6 rising to 7 years)	11 (4.8)	5 (45.5)	6 (54.5)
Sex			
Male	135 (59.5)	31 (23.0)	104 (77.0)
Female	92 (40.5)	24 (26.1)	68 (73.9)
PHE region			
North of England	109 (48.0)	26 (23.9)	83 (76.1)
South of England	48 (21.1)	12 (25.0)	36 (75.0)
Midlands and East of England	37 (16.3)	8 (21.6)	29 (78.4)
London	31 (13.7)	8 (25.8)	23 (74.2)
Unknown	2 (0.9)	1 (50.0)	1 (50.0)

Abbreviation: PHE, Public Health England.

TABLE 3 Vaccination status in cases reported to UK Severe Influenza Surveillance System (USISS) compared with national cumulative influenza vaccine uptake and crude and adjusted influenza vaccine effectiveness by age group and season, England

	Percentage of cases vaccinated (PCV)[a]	Percentage of reference population vaccinated (PPV)[b]	Crude VE (95% CI)	Adjusted VE[c] (95% CI)
2013/14				
2–3 years	30.0 (6/20)	41.1 (594 610/447 303)	38.5 (−70.2, 80.6)	50.5 (−39.0, 82.3)
2014/15				
2–4 years	22.4 (11/49)	37.6 (828 663/204 408)	51.9 (4.1, 77.8)	43.3 (−12.1, 71.3)
2015/16				
2–4 years	24.1 (32/133)	34.4 (728 066/119 123)	39.5 (9.1, 60.7)	49.4 (22.8, 66.9)
Year 1 + 2 combined (5–6-year-olds)	24.0 (6/25)	53.6 (716 928/336 603)	46.1 (25.2, 61.8)	62.6 (2.6, 85.6)

Abbreviations: CI, confidence interval; PPV, proportion of the population vaccinated; VE, vaccine effectiveness.
[a]At least 14 days prior to symptom onset.
[b]% vaccinated by January 31.
[c]Adjusted VE matched by CCG/local authority, age in years, week/month of infection.

3.2 | Description of reference population

The population vaccine coverage for England for the population groups eligible for vaccination in the study seasons are shown in Table 3. Uptake was generally higher in all population groups compared with the PCV (Table 3).

TABLE 4 Crude and adjusted influenza vaccine effectiveness estimates overall, by age group and influenza type, 2013/14–2015/16

	Crude VE (95% CI)	Adjusted VE[a] (95% CI)
Overall (2013/14–2015/16)	52.7 (35.6, 65.8)	50.1 (31.2, 63.8)
By season (main circulating strain)		
2013/14 (influenza A/H1N1pdm09)	38.5 (−70.2, 80.6)	50.5 (−39.0, 82.3)
2014/15 (influenza A/H3N2 & B)	51.9 (4.1, 77.8)	43.3 (−12.1, 71.3)
2015/16 (influenza A/H1N1pdm09 & B)	55.9 (36.1, 70.2)	52.0 (29.2, 67.5)
By age group		
2–4-year-olds	46.1 (25.2, 61.8)	48.1 (27.2, 63.1)
Year 1 + 2 combined (5–6-year-olds)	72.7 (28.9, 91.1)	62.6 (2.6, 85.6)
By flu type		
Influenza A (all subtypes)	49.6 (28.5, 65.0)	45.0 (21.3, 61.6)
Influenza A/H1N1pdm09	47.8 (20.1, 66.6)	44.0 (13.8, 63.5)
Influenza A/H3N2	48.8 (−12.7, 78.9)	49.7 (−17.4, 78.5)
Influenza A unknown subtype	58.9 (−14.7, 88.1)	43.8 (−54.5, 79.5)
Influenza B	62.2 (25.4, 82.4)	65.0 (27.3, 83.1)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.
[a]Adjusted VE by CCG/local authority, age in years (where appropriate), week/month of infection.

3.3 | VE estimates

The crude and adjusted VE estimates for preventing influenza-hospitalized cases in children by season and age group, for all influenza types, are shown in Tables 3 and 4.

The overall adjusted LAIV VE for all influenza types pooled over the three influenza seasons and all age groups was 50.1% (95% confidence interval [CI] 31.2, 63.8) (Table 4). By age, there was good evidence of protection against hospitalization from LAIV in both the pre-school age group (2–4-year-olds) (48.1, 95% CI 27.2, 63.1, $p < 0.000$) and in school aged children (Years 1 and 2) (62.6%, 95% CI 2.6, 85.6, $p = 0.044$) over the three influenza seasons. Results after stratifying by influenza type gave an adjusted VE in children (pre-school and Years 1 and 2) of 44.0% against influenza A/H1N1pdm09, 49.7% against influenza A/H3N2, 43.8% against influenza unknown subtype, and 65.0% against influenza B (Table 4).

Adjusted VE estimates were varied by age group and season. The LAIV vaccine showed good protection against hospitalization in 2015/16 in children in both the pre-school (49.4%, 95% CI 22.8, 66.9) and school cohort (62.6, 95% CI 2.6, 85.6) (Table 3). Good point estimates of protection were also seen for 2–3-year-olds in 2013/14 (50.5, 95% CI −39.0, 82.3) and 2–4-year-olds in 2014/15 (43.3, 95% CI −12.1, 71.3), although with wide CIs overlapping zero (Table 3).

A high proportion of 2- to 4-year-old cases had missing information on risk group status (66.8%). A slightly greater proportion of unvaccinated cases had missing information on risk group status compared with vaccinated cases (69.9% compared with 57.1%). When stratified by risk group, the adjusted VE for those with a risk factor was −8.0% (95% CI −117.6, 46.4) and for those with no risk factor, VE was 50.7% (95% CI −22.5, 80.2).

In a further subgroup analysis restricted to 2–4-year-olds on whom risk factor status was known, VE estimates were also adjusted for presence/absence of a risk factor (Table 5). The combined VE for 2–4-year-olds with known risk factor after adjusting for risk factor, as well as geography, week, and age was 44.2%. (95% CI 3.3, 67.8) compared with 48.1% (95% CI 27.2, 63.1) without adjusting for underlying risk factor (Table 5).

In a sensitivity analysis, cases where risk group status was unknown were assumed to have a risk factor, and the appropriate

TABLE 5 Vaccine effectiveness estimates adjusted for risk group status for children aged 2–4 years, and sensitivity analysis

Age group	Adjusted VE (all cases, no adjustment for risk group)	Adjusted VE* (restricted to cases with known risk group status) (95% CI)	Adjusted VE (cases with unknown risk group status assumed to have risk factor) (95% CI)	Adjusted VE (cases with unknown risk group status assumed to have no risk factor) (95% CI)
2–4-year-olds	48.1 (27.2, 63.1)	44.2 (3.3, 67.8)	69.9 (57.6, 78.6)	57.6 (34.1, 72.7)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.
*Adjusted for risk factor in addition to CCG, week, and age.

vaccine uptake for presence of a risk group was used. The adjusted VE in this instance was 69.9% (95% CI 57.6, 78.6) for all 2–4-year-olds (Table 5). Alternatively, the adjusted VE when cases with missing risk group status were assumed to have no risk factor was 57.6% (95% CI 34.1, 72.7) in all 2–4-year-olds (Table 5).

4 | CONCLUSIONS

In this study, the screening method was used to evaluate the effectiveness of influenza vaccination in preventing influenza-associated hospitalizations in children during the 2013/14–2015/16 influenza seasons in England: the first three seasons following the introduction of the childhood influenza vaccination program. Overall adjusted LAIV effectiveness against hospitalization in children over the three seasons was 50.1%.

Using the screening method, vaccination coverage for confirmed influenza hospitalizations was collected through a severe disease surveillance system and compared with population vaccination coverage obtained through a national vaccine uptake monitoring system. Overall LAIV vaccine uptake among the hospitalized cases was 24.2%. Adjusted influenza VE against hospitalization showed good evidence of protection against hospitalization in both pre-school children (48.1%) and school-aged children (62.6%) over the three seasons. By season, good protection was seen in the 2015/16 season, when influenza A/H1N1pdm09 and influenza B dominated and the A/Bolivia strain was the vaccine strain.[31] This provides reassurance that the vaccine continued to provide protection against severe disease over these seasons.

VE was good against influenza B (65.0%) and influenza A/H1N1pdm09 (44.0%), although non-significant results were seen against influenza A/H3N2 subtype, the dominant circulating subtype in 2014/15. This was likely due to mismatch between the strains included in the vaccine and the circulating influenza A/H3N2 strain in the 2014/15 season.[32]

Recent studies have found mixed results regarding inclusion of the presence/absence of underlying medical risk factors as a confounder of VE estimates.[19,23,32,33] It is, theoretically, a possible important confounder of the vaccination–influenza effect, because the presence of certain medical conditions may increase a person's risk of severe influenza, as well as being an eligibility criterion for free vaccination in certain countries.[34]

For the reference population uptake, risk factor status was only available for the 2- to 4-year-old group, although it was missing for 66.8% of 2- to 4-year-old hospitalized cases. When restricting the analysis to 2–4-year-olds with known risk factor status, the overall adjusted VE for 2–4-year-olds reduced slightly from 48.1% to 44.2%. To assess the robustness of the conclusions, a sensitivity analysis was performed to explore the effects of missing risk factor information further. Assuming all those to have an underlying risk factor or all assumed not to have an underlying risk factor made only a small difference to the VE estimate (69.9% compared to 57.6%) for 2–4-year-olds.

Our findings are consistent with a similar study that used the screening method to assess VE against hospitalization in 2–6-year-olds in England in the 2015/16 influenza season.[24] The overall adjusted VE in this study was similar to our estimate for 2015/16 (54.5% compared with 52.0%) with overlapping CIs. Our 2015/16 season findings are also consistent, although slightly higher, with a test negative design (TND) study that also assessed LAIV VE against hospitalization in children in 2015/16 in England.[23] This TND study found an overall adjusted VE against hospitalization in children aged 2–16 years of 41.9%.[23] In this study, risk factor was controlled for along with age, sex, risk group, region, and sample month, as well as index of multiple deprivation and ethnicity.

There are several strengths and limitations to our study. This study utilised an established severe disease surveillance system to identify hospitalized cases that allowed key variables to be collected on the cases. In addition, a write back to the case's GPs was conducted and provided a rapid and cheap method of obtaining vaccine uptake status on the cases while achieving high levels of completion of vaccine information. This study also benefitted from an existing, national vaccine uptake monitoring system, Immform, to provide population vaccine uptake figures. A strength of this national uptake data is that it is available by some of the key potential confounding variables in examining associations between vaccination and hospitalization for influenza.

One of the main limitations of the screening method is that VE estimates may be biased if cases arise from a population that differs from the population used to determine vaccine coverage rates. We have attempted to address this by comparing the vaccine coverage among cases to the uptake in the general population to the same age in the local area where cases lived. Where possible we also compared uptake by risk group status, however, this was poorly completed on cases and not available for all population vaccination groups, specifically the school-based groups. A second potential limitation of the screening method is the inability to adjust for important confounders, particularly due to lack of detail on key confounders on the population coverage. In this study, we were able to adjust for age, time of infection, place of residence and, for some age groups, risk group status; however, vaccine type was not available, so it was not possible to assess if VE differed by vaccine type. Another limitation of this study specifically was that illness onset dates were missing for a proportion of cases; however, we were able to use alternative dates as a proxy for onset date. Okoli et al. suggest that accurate reporting of symptom onset is crucial for TND studies and, specifically, that symptom onset should be restricted to 7 days or less, which is likely to also be applicable to the screening method.[35]

In summary, we have found that vaccination with LAIV provided good protection against laboratory-confirmed influenza infection resulting in hospitalization in England over the 2013–2015 influenza seasons. The screening method provides a rapid and cheap method to estimate influenza vaccination effectiveness overall and by influenza subtype. The study highlights the importance of having clinical risk factor information available for both cases and the reference population. Optimizing the completeness of data such as swab dates,

vaccination status and dates, and risk factor status could improve the validity of VE estimates using this method. The results of this study of VE against hospitalization with influenza support the roll-out of the childhood influenza vaccination program in the United Kingdom. These findings are of importance as this current influenza season sees the further expansion of the program to secondary school children in England and of relevance to other countries considering introducing childhood influenza vaccination programs.

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AUTHOR CONTRIBUTIONS

Nicki Boddington: Data curation; formal analysis; methodology; project administration. **Punam Mangtani:** Methodology; supervision. **Hongxin Zhao:** Data curation; project administration. **Neville Verlander:** Formal analysis. **Joanna Ellis:** Data curation. **Nick Andrews:** Formal analysis. **Richard Pebody:** Conceptualization; data curation; methodology; supervision.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Chapter 7
Discussion

This chapter provides an overview of the key findings of this Research Project according to the key objectives. It includes a summary of the strengths and limitations of the approaches used in this Research Project and discusses the contribution of the Research Project to the literature as well possible future areas of work.

7.1 Key findings

This section summarises the key findings arising from the objectives of the Research Project as outlined in Chapter 1.

Objective 1: To estimate the case-severity and disease impact of influenza infection in England and to assess for an early signal of the impact of the childhood influenza vaccination programme on severe influenza in children.

The first objective of this Research Project was to estimate the case-severity and disease impact of influenza in England and to assess for an early signal of the impact of the childhood influenza vaccination programme on severe influenza in children. Data were collected through a national hospitalisation surveillance system, the sentinel UK Severe Influenza Surveillance System (USISS) system. Case-severity was estimated as the proportion of confirmed hospitalised cases admitted to Intensive Care Unit (ICU)/High Dependency Unit (HDU). Disease impact was measured through risk (cumulative hospitalisation incidence) of hospitalisation by calculating the number of laboratory-confirmed influenza hospitalisations over each season for the acute trust catchment population of all participating National Health Service (NHS) Trusts in England in each corresponding season. Initially, the analysis included data from the 2010/2011 to 2014/2015 influenza seasons, but this was extended to include the period up to the 2019/2020 season. Both analyses demonstrated the varying disease impact of influenza by age and influenza type/subtype in England. In particular, the results showed the high disease impact of influenza in children less than five years of age, each season and for all subtypes, as well as high impact in older age groups in seasons during which influenza A(H3N2) was the dominant circulating subtype. The first analysis (Chapter 2, Section 2.1) also assessed case-severity, which varied by influenza subtype and season, with a higher hospitalisation: ICU/HDU ratio for influenza A(H1N1)pdm09 and older age groups (older than 45 years) for all subtypes.

The updated analysis (Chapter 2, Section 2.2) which included six influenza seasons (2015/2016 – 2019/2020) following the introduction of the childhood influenza vaccination programme was unable

to demonstrate any significant impact of the programme either directly in children or indirectly when looking at changes in hospitalisation rates in non-targeted age groups over the same period. The analysis showed increasing overall cumulative hospitalisation incidence rates, particularly since the 2017/2018 season. This is likely due to a range of factors including those which might lead to reduced before-after effect size such as temporal changes with improvements in case ascertainment and reporting for instance due to increasing availability and use of rapid diagnostic tests. The lack of apparent vaccine impact could also relate to a potential reduction in vaccine effectiveness (VE) – though separate analyses provided evidence of significant effectiveness against severe disease. Higher rates of hospitalisation in this analysis also corresponded with seasons with known greater antigenic variation between vaccine strains and circulating viruses.

Objective 2: To critically review the literature on two observational study designs used to evaluate influenza vaccination programmes in high-income settings, the TND and the screening method

The critical review chapter provided an opportunity to assess the strengths and limitations of the two VE study designs employed in this Research Project. Observational studies such as the test-negative design (TND) and the screening method have the potential to be biased due to issues such as confounding, misclassification and selection bias.

Through this critical review, the strengths and limitations of both methods were discussed in detail, and it was evident that the two methods may have roles to play in accessing IVE in different scenarios, possibly in a stepwise manner or as alternates depending on the question and the data available. The screening method can be applied rapidly and with relative ease when population vaccine coverage is available, thus providing a useful method to provide early-mid season IVE estimates to give early indications of how a vaccine might be performing. It may also be useful in determining whether the number of breakthrough cases is within the expected range and in settings where data are not available on controls. That said the method relies on stable and valid population coverage estimates so it might not be an appropriate method in the early stages of a new vaccine programme, such as COVID-19, where coverage is increasing rapidly. Often this method can be limited by the availability of population vaccine coverage by different population subgroups thus restricting the possibility of controlling for important confounding factors. The TND might be more appropriate in these instances and in settings that have existing surveillance systems that can be used or adapted to collect the data required, such as vaccine receipt in non-cases, for the study design. One of the key strengths of the TND is that cases and test-negative controls will have both sought care for similar symptoms, therefore reducing selection bias due to confounding by healthcare seeking behaviour. Selection bias is further minimised using the TND as both cases and test-negative controls are selected from the same

surveillance system and should have a high degree of comparability since the controls would have been recruited as cases should they have had the outcome of interest thus helping to ensure the controls represent the population from which the cases arose.

Several key principles can be applied to both designs to minimise bias and increase their robustness including, but not exhaustively, the use of laboratory-confirmed outcomes, strict clinical case definitions, obtaining vaccine status from a reliable and documented source and independently to the outcome, ensuring cases and reference groups or controls are drawn from the same population and collection of data by key covariates to adjust for confounders in the analysis.

Objective 3: To systematically review the literature on the effectiveness of influenza vaccination against hospitalisation due to influenza infection in children.

Influenza vaccination remains one of the most effective methods of preventing influenza illness in the population and reducing its clinical burden. Given the variable protection of influenza vaccination on an annual basis and the need to inform optimal vaccine composition as part of the annual vaccine composition meeting, ongoing assessment of the effectiveness of vaccination is required. In addition, knowledge of its effectiveness against severe disease helps justify resource allocation to a childhood influenza vaccination programme; a topic of increasing relevance as several countries have begun to adopt programmes to vaccinate children. As such a systematic literature review and meta-analysis were carried out to estimate the effectiveness of influenza vaccination against hospitalisation in children.

In this systematic review, studies of any design (except case series/reports and systematic/critical reviews) that assessed IVE against laboratory-confirmed influenza-associated hospitalisation in children were included to provide a complete picture of the evidence. A total of 45 studies were identified with 37 studies contributing to a random-effects meta-analysis. The meta-analysis provided estimates of overall IVE against laboratory-confirmed influenza-associated hospitalisation and for the first time by vaccine type as well as by influenza subtype and vaccine match. The meta-analysis found that influenza vaccination provided good overall protection against any influenza-associated hospitalisation in children aged six months to 17 years old (53.3%, 95% CI 47.2-58.8). The results suggested that inactivated influenza vaccine (IIV) may give slightly greater protection (68.9%, 95% CI 53.6-79.2) against hospitalisation than live attenuated influenza vaccine (LAIV) (44.3%, 95% CI 30.1-55.7), although with overlapping confidence intervals, and that protection was greater in seasons in which the circulating influenza strains were antigenically matched to the vaccines strains. Results also varied by influenza type with the highest effectiveness against influenza A(H1N1)pdm09 (68.7%, 95%

CI 56.9, 77.2). The variability of estimates by vaccine type and influenza type, particularly given issues such as egg adaptation with influenza A(H3N2) seen for both IIV and LAIV and reduced effectiveness of LAIV against influenza A(H1N1)pdm09 in some instances, highlight the importance of disaggregated estimates.

Objectives 4 and 5: To estimate the vaccine effectiveness of influenza vaccination against laboratory-confirmed severe influenza infection in children in England, 2013-2016, using two different methods (the screening method and the test-negative design).

Following the introduction of the childhood influenza vaccination programme at the start of the 2013/2014 season in England and the documented disease impact of influenza in children, monitoring VE in children was of high importance. In the 2015/2016 season, the LAIV programme was extended to offer vaccination to all healthy children aged two to four years of age, together with children of school years 1 and 2 (age 5 and 6 years). Two studies using different methodologies were carried out as part of this Research Project to assess the effectiveness of influenza vaccination against hospitalisation in children in the 2015/2016 season to assess protection against severe disease. They were both methods being used at the time by Public Health England (PHE) and it provided an opportunity to critique and evaluate the study designs in practice following the critical review of these methods in Chapter 3.

The first study used the test-negative design (TND) using cases and test-negative controls identified from a national sentinel laboratory surveillance system, Respiratory Datamart. Using this method, participants were recruited if they met a certain clinical case definition and were tested for influenza. The odds of vaccination were compared between those testing positive to those testing negative to estimate VE. In this study influenza vaccination was found to provide moderately good protection against hospitalisation due to influenza in children aged 2 – 16 years of age in England in 2015/2016 (33.4%, 95% CI 2.3-54.6). Overall VE was higher in children who received LAIV compared with IIV although with overlapping confidence intervals. The presence of underlying clinical risk factors was found to be an important confounder, in contrast to the findings of studies assessing IVE against primary care end points.

The screening method was used for the second study to estimate the effectiveness of LAIV against hospitalisation due to laboratory-confirmed influenza in children in England in the first three seasons following the introduction of the childhood influenza vaccination programme (2013/2014 – 2015/2016). Three seasons were used to give a greater amount of data to provide robust evidence as well as to enable assessment of whether protection against hospitalisation was maintained in the

seasons before 2015/2016 when the influenza A/California/7/2009(H1N1)pdm09 vaccine strain was used, and in 2015/2016 when the new vaccine strain was introduced (A/Bolivia/559/2013). Vaccination uptake of cases, who were identified through a severe disease surveillance system, USISS, were compared with population vaccination coverage obtained through a national vaccine uptake monitoring system. Overall adjusted IVE against hospitalisation in children aged 2 to 6 years over the three seasons was moderately good (50.1%, 95% CI 31.2, 63.8). Good evidence of protection against hospitalisation in both pre-school children (48.1%) and school aged children (62.6%) over the three seasons was observed. The study also showed good protection of LAIV against influenza A(H1N1)pdm09 and influenza B. It highlighted that the screening method is a feasible observational study in this setting, providing consistent results with the TND study. Like the TND study, it highlighted the importance of having clinical risk factor information available for both cases and the reference population. The VE estimate for the 2015/2016 in this study was consistent with, albeit slightly higher, than the overall estimate from the TND study in Chapter 5.

Both studies provided evidence to support the ongoing roll-out of the childhood influenza vaccination programme in England and contributed to the limited literature to date on IVE against hospitalisation in children.

7.2 Strengths and limitations of the Research Project approach

The strengths and limitations of the methodological and analytical approaches are discussed in detail in each of the respective chapters of this Research Project, however, the overarching strengths and limitations of each of the key studies are discussed in this section according to the Research Project objectives.

Objective 1: The national hospitalisation data collected by the USISS sentinel system used in this chapter provided robust surveillance data and a unique time series of disease burden based on hospitalisation data spanning ten influenza seasons in England. This enabled a detailed analysis of the epidemiology of hospitalisations due to influenza in England. The main limitations of this study were the high proportion of reported hospitalised influenza cases lacking subtyping information, particularly in the more recent seasons, which may have been due to the increasing use of rapid influenza diagnostic testing. In addition, the study was unable to look at the rates of hospitalisation in the under two-year-olds, and other more specific age groups such as those targeted by the LAIV programme, due to the limited age groups available in the denominator data. It is also worth noting the possible impact that the criteria for testing used by participating trusts might have. Studies have

previously demonstrated differences in the presentation of influenza in young and older adults, in particular a reduced febrile response in the elderly (139). Further work could be initiated to examine differences between the clinical presentation of different age groups to participating trusts and possible need for different clinical criteria for testing.

Objective 3: The systematic literature review provides a comprehensive review of studies, of any observational design, used to assess IVE in preventing hospitalisation in children. The meta-analysis also uniquely assessed IVE against severe disease by vaccine type and vaccine match. The meta-analysis was limited by the number of observations for some sub-group analyses such as vaccine type and was also unable to assess the effect of prior vaccination or full or partial vaccination on IVE estimates.

Objective 4: The strengths of the TND study included in this Research Project were that the cases and test-negative controls were recruited at the same time using an existing surveillance system. They also sought care for similar symptoms and exposure status was unknown at the time of recruitment. Some of the limitations include the limited power of the study for various stratifications, such as more granular age breakdowns by flu type and vaccine type.

Objective 5: The screening method study benefitted from robust hospitalisation data from the USISS sentinel system and reliable national vaccine uptake data which was available by some of the key confounders. The study was limited by the lack of availability of population vaccine uptake data by additional confounders such as vaccine type and underlying clinical risk factor (for the school aged children). Additionally, a large proportion of cases had missing data on underlying risk factors, limiting the ability to control for underlying clinical risk factor.

7.3 Contribution to knowledge and relevance to other countries and other vaccination programmes

This Research Project contributes to the existing knowledge base on severe influenza in three key areas with the main findings described above. The three key areas include:

i. The disease impact of influenza infection in England.
ii. How effective influenza vaccines are in preventing severe influenza in children.
iii. The strengths and weaknesses of the methodological approaches used to monitor IVE against severe outcomes.

These areas of contribution can be used to inform both the design of the ongoing influenza vaccination programme in England and other countries considering a vaccination programme for children as well as informing vaccination programmes against other diseases such as COVID-19 by applying the methodological and design findings, as described below.

7.3.1 Applying the findings to the influenza vaccination programme in the UK and other countries

The findings of this Research Project can be used to inform the continued roll-out of the influenza vaccination programme in England as well as in other countries which have introduced or are considering introducing similar programmes. In terms of the programme in England, this Research Project highlights, from the systematic literature review and the two IVE studies, that influenza vaccination generally provides moderate protection against influenza hospitalisation in children. The effectiveness varies according to several factors such as season, age group, and match between the vaccine and circulating strain. The results of these studies were suggestive that IVE also varies by vaccine type although further work is required to substantiate this finding further. Despite this, the disease impact of severe influenza continues to be observed in the paediatric population in England. Further work is required to monitor the impact of the vaccination programme on preventing hospitalisations due to influenza and to better understand the recent surveillance trends of increasing rates of hospitalisations.

This Research Project also provides a critical appraisal of the strengths and limitations of the two observational VE study designs which are useful for those embarking on such studies and those interpreting and applying the results of such studies. It highlights some of the limitations of the designs and how they can lead to biased VE estimates, but also how these limitations can be mitigated against.

During the most recent influenza season, the 2021/2022 season, all children aged two to 15 years in England were offered the influenza vaccine and children aged 12 years and above were offered the COVID-19 vaccine (225). This was a large expansion of the childhood influenza programme which has, in previous seasons, only been expanded by one year group per season with the intention of pausing the programme for an evaluation once all primary school aged children had been included. However, as a temporary measure for the 2021/2022 season, the programme was extended by four additional cohorts in secondary school so that all those from year 7 to year 11 were offered vaccination (225). The rationale for this was to mitigate the potential impact of a combined influenza and COVID-19 season and to help ease potential pressure on the health system in dealing with this (226).

Since the COVID-19 pandemic started, high influenza vaccine coverage has been seen in England. In the 2020/2021 season, high coverage was achieved with record levels of uptake seen in many of the target groups (227). High targets were set for the 2021/2022 season, including a target of 70% in school aged children and two to three year-olds, to build on the momentum of the previous season and reflect the importance of protecting against influenza. The latest figures for the 2021/2022 season to date indeed show high levels of uptake in certain target groups (228). For children, provisional uptake to 28 February 2022 was slightly lower than the previous season with an uptake of 48.7% in 2-year-olds, 51.4% in 3-year-olds and 51.5% in school aged children (228).

The monitoring and evaluation of the LAIV programme will therefore be of continued importance this season and on an ongoing basis. This will include monitoring the impact of the programme in preventing hospitalisations in children and indirectly in other age groups, as well as assessing the effectiveness of vaccination in these groups, particularly in secondary school children, who have not been widely vaccinated before. Continuous monitoring is important to justify resource allocation to the programme.

A recent modelling study evaluated the cost-effectiveness of vaccinating different age groups within the 2-16 year-old age range in England (229). Economic evaluations compared the influenza vaccination programme from 1995/1996 to 2013/2014 to seven different vaccination strategies based on pre-school and school-based age divisions. The authors suggest that the current LAIV programme could be improved by focussing only on the school-based programme for primary and secondary school children and halting vaccination of two to four year-olds as a way of mitigating some of the implementation challenges of the programme (229). However, the study does not consider other factors related to successful implementation such as public confidence in the programme which may decline should the programme, or parts of it, be withdrawn. Furthermore, the highest burden of disease continues to be observed in the pre-school age group (i.e. under five-year-olds), therefore most of the direct effect of the programme will be in that group, making it difficult to justify removing this age group from the programme from a public health perspective. Another recent study examined the impact and cost-effectiveness of different vaccination strategies across Europe (230). They found that moving the elderly to either a high-dose or adjuvanted trivalent vaccine along with adopting mass paediatric programmes brought about the most benefit and likelihood of being cost-effective across all settings and paediatric vaccine coverage levels (230).

7.3.2 Measuring VE against COVID-19 and other diseases: applying the learning from assessing IVE

This section discusses possible lessons that could be applied from this Research Project to the COVID-19 vaccine response. The COVID-19 pandemic has, until more recently, largely been controlled by using non-pharmaceutical interventions (NPI) such as school closures, mask-wearing, physical distancing, hospitality closures and stay-at-home orders/lockdowns. However, in December 2020, the first COVID-19 vaccine was granted regulatory approval in the UK. Since then there has been a rapid roll-out of the vaccination programme with over 90% of the population aged 12 years and over having been vaccinated with at least one dose to date (231). The programme was rolled out incrementally based on the risk of COVID-19-specific mortality in phase one of the programme and then based on the prevention of hospitalisation in the second phase (157). Children were latterly added to the programme with those aged 16-17 years at higher risk being targeted first followed by those aged 16-17 years not in a risk group. The programme was recently extended to all children aged 12-15 years for the 2021/2022 season. The burden of COVID-19 in children and young people is low with the risk of severe disease and death due to SARS-CoV-2 being very low compared to adults (232). Despite this, the programme was extended to children 12 years and over predominantly to avoid school absences and disruption to education and has most recently been extended to include everyone aged 5 and over (233, 234).

Understanding COVID-19 VE in real-world settings is essential post-introduction of the vaccine. In many countries, vaccine programmes for COVID-19 were rolled out very quickly following accelerated clinical trials. As programmes continue to be rolled out further there is an ongoing need to evaluate VE for COVID-19 to monitor the duration of effectiveness and possible waning immunity, to assess the effectiveness in different groups such as by age or clinical risk factor and against specific outcomes, assess protection by natural infection and against different variants as they emerge.

As with influenza vaccination, there are a number of possible observational study designs available to assess COVID-19 VE including the TND, cohort studies, case-control studies, and the screening method. These can be used to assess effectiveness against several outcomes including death, severe disease, symptomatic disease, infection and transmission. When assessing COVID-19 VE, many studies have benefited from existing influenza surveillance platforms making these studies more feasible and simplifying the logistics. Many of these existing platforms exist at primary and secondary care levels allowing the different levels of disease severity to be assessed.

The COVID-19 VE guidance in England draws heavily on the influenza VE guidance due to similarity in clinical presentation and epidemiology. Nonetheless, several distinct features of COVID-19 epidemiology and vaccines create unique challenges and approaches to evaluation, including the high levels of vaccination coverage that were reached quickly in many target groups. It is worth noting, in

the context of COVID-19 given the very rapid roll-out, that VE studies with either very low (for example under 10%) or very high coverage (for example over 90%) are likely to be more prone to biases (153). This is because those who get vaccinated first or do not get vaccinated when coverage is high, are likely to have different levels of risk of exposure and/or disease (153). It is also worth noting that the main objective of the COVID-19 vaccination programme in England is protection against severe disease.

The World Health Organization (WHO) COVID-19 VE guidance states that the TND design is "probably the most efficient and least biased study design for VE studies of COVID-19 disease in most settings" (153). This is due to many of the strengths of the design that have been discussed throughout this Research Project when using the design to assess IVE. In particular, these include the reduction in selection bias as cases and test-negative controls are taken from the same system and sought care for similar sets of symptoms, reducing selection bias due to healthcare seeking behaviour. Many of the limitations found when using the TND to assess IVE however will still be an issue including possible false-negative misclassification (although likely to be minimal given the high specificity of PCR testing for COVID-19 and longer duration of shedding), not removing confounding from predictors of vaccination and exposure to infection (such as occupation or being in a priority group for vaccination) and limited ability to control for confounding by indication (153). Additionally, if the symptoms used to identify study subjects are too broad and non-specific then test-negative controls could be more likely to be tested for exacerbation of an underlying illness whilst also being more likely to receive COVID-19 vaccination. This could potentially overestimate VE estimates unless adjustment for underlying risk factors is carried out. Another challenge that might present itself when using the TND for COVID-19 VE is that there might be insufficient controls if the burden of COVID-19 is high at the time, and rates of other respiratory viruses are low.

The screening method is another proposed study design for assessing COVID-19 VE however it is likely to be most useful when vaccine coverage rates are stable rather than in the early phases of the vaccine roll-out when vaccine coverage is rapidly changing (153). This is because the method relies on accurate population vaccination coverage. Furthermore, the use of repeated boosters for COVID-19 may make it challenging to get the numerators and denominators correct. As discussed in this Research Project the screening method may also be limited by the availability of coverage data by potential confounders. The screening method may however have a role in assessing vaccine breakthrough cases and in assessing whether a vaccine is performing as expected, including against new variants, due to its ease and ability to produce estimates rapidly when population vaccination coverage is available (235). Breakthrough infections are infections of SARS-CoV-2 that occur after the completion of all

recommended doses of the vaccine. New variants of SARS-CoV-2 have the potential to reduce the effectiveness of public health interventions such as vaccination, as observed already with the emergence of the Omicron variant in late 2021 (236). Vaccine breakthrough cases may give an early warning of reduced VE against emerging variants and the screening method has been proposed as a possible method to assess this (235). The crude VE can be estimated using the percentage of total cases occurring in fully vaccinated persons (i.e. breakthrough cases as a proportion of all cases) and the vaccination coverage in the population (235). Once calculated, the crude VE can be compared to vaccine efficacy estimates from clinical trials or VE estimates from observational studies conducted in similar settings, with similar populations and a similar outcome. The estimates can also be compared over time to detect changes (235). If these estimates are suggestive of reduced VE against a new variant, then further studies could be triggered such as the TND.

7.4 Future work

Several areas of this Research Project could be expanded in the future to further strengthen and expand on the findings, as discussed below.

- Future studies assessing the disease impact of influenza on hospitalisations should consider the possibility of trying to adjust for changes in surveillance sensitivity over time, as the use of rapid influenza testing becomes more widespread and embedded into clinical practice within secondary care. Alongside this, systems need to work towards integrating typing/subtyping results and follow-up results from rapid influenza testing.

- The work looking at the impact of the LAIV programme in preventing hospitalisation could be expanded to explore further the overall effect of the programme. This could be done by assessing hospital admissions attributable to influenza before and after the introduction of the programme in targeted and non-targeted age-groups using time series methods. Hospital Episode Statistics (HES) data linked to national laboratory reports would enable the number of hospital admissions attributable to influenza to be calculated. HES data would provide a greater pre-programme time series however there would likely still be issues such as those we have seen with the USISS data such as increased ascertainment, although this may be less of an issue with syndromic data.

- Further approaches should also be explored, given the challenges with before-after vaccine impact studies with influenza, including those that compare different geographical areas at the same time for instance areas of high and low coverage.

- A future iteration of the systematic literature review and meta-analysis would be helpful once more studies become available. This would allow further assessment of the effectiveness of LAIV and IIV separately against severe outcomes and by type and subtype. Additional studies would also enable more sub-group analyses to be carried out including assessing prior vaccination and the effect of full/partial vaccination.

- At the end of the 2021/2022 season, it will be important to assess VE against hospitalisation in secondary school aged children. Whilst hospitalisation rates are generally lower in this age group, it has previously been shown that VE against hospitalisation is also lower in this age group than in younger children (237, 238). Updated estimates for this age group will be important to inform and justify the future roll-out of the programme in England, although the decision has been made to exclude them from the programme in the 2022/2023 season (239).

- Following the introduction of the NHS Immunisation Management Service (NIMS) in England, a centralised service for the management of the COVID-19 and seasonal influenza vaccination programmes, alternative ways of carrying out VE studies in England are now possible, particularly the TND, with opportunities of data linkage between NIMS and national influenza surveillance systems being explored and piloted in the 2021/2022 season.

- Since the COVID-19 pandemic, globally very little influenza activity has been detected. As a result, decision-making on future vaccine strain selection has been challenging. Given the low levels of activity, it is likely that there may well exist limited immunity to influenza within the population now, a possible immunity debt (240, 241). In particular, this may exist in cohorts of children who may not have been exposed to influenza before, as well as in the wider population who have experienced limited immune-boosting by infection in the recent seasons. It therefore, remains critically important in the forthcoming seasons to have strong systems in place to continue to monitor the performance of the influenza vaccination programme.

7.5 Conclusions

This Research Project provides important insights into the disease impact of influenza in children in England and contributes further to the literature on the effectiveness of influenza vaccination against important clinical outcomes in children. It provides important learning for other countries and settings considering introducing vaccination of children against influenza as well as some methodological insights for public health assessments of the effectiveness of influenza vaccines and other vaccines such as for COVID-19 against severe outcomes.

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Appendix 3: Chapter 4: Research Paper 2 - Supplementary tables and figures

Supplement Table 1: Systematic literature review search strategies

Medline search strategy:

	Free text	**Subject headings**
#1	influenza.tw OR flu.tw OR human influenza.tw	exp Influenza, Human/
#2	vaccin*.tw OR immuni*.tw OR innocula*.tw	exp Immunization/ exp Vaccination/
#3	efficacy.tw OR effectiveness.tw	
#4	hospital*.tw OR secondary care.tw OR patient.tw OR inpatient.tw OR life-threatening.tw OR intensive care.tw OR critical care.tw OR death.tw	exp Hospitalization/ exp Secondary care/ exp Patients/ exp Critical care/ exp death/
#5	Child*.tw OR infant*.tw OR p?ediat*.tw OR preschool*.tw OR school*.tw OR young.tw OR adolescent*.tw OR toddler*.tw	exp infant/ exp child/ exp adolescent/ exp pediatrics/
#6	1 AND 2 AND 3 AND 4 AND 5	

Embase search strategy:

	Free text	**Subject headings**
#1	influenza.tw OR flu.tw OR human influenza.tw	exp influenza/
#2	vaccin*.tw OR immuni*.tw OR innocula*.tw	exp immunization/ exp Vaccination/
#3	efficacy.tw OR effectiveness.tw	

#4	hospital.tw OR hospitali*.tw OR secondary care.tw OR patient.tw OR inpatient.tw OR life-threatening.tw OR intensive care.tw OR critical care.tw OR death.tw	exp hospitalization/ exp secondary health care/ exp patient/ exp intensive care/ exp death/
#5	Child*.tw OR infant.tw OR p?ediat*.tw OR preschool*.tw OR school*.tw OR young.tw OR adolescent*.tw OR toddler*.tw	exp juvenile
#6	1 AND 2 AND 3 AND 4 AND 5	

Global Health search strategy:

	Free text	**Subject headings**
#1	influenza.tw OR flu.tw OR human influenza.tw	exp influenza/
#2	vaccin*.tw OR immuni*.tw OR innocula*.tw	exp immunization/ exp vaccines/
#3	efficacy.tw OR effectiveness.tw	exp efficacy/
#4	hospital.tw OR hospitali*.tw OR secondary care.tw OR patient.tw OR inpatient.tw OR life-threatening.tw OR intensive care.tw OR critical care.tw OR death.tw	exp hospitals/ exp patients/ exp intensive care/ exp death/
#5	Child*.tw OR infant.tw OR p?ediat*.tw OR preschool*.tw OR school*.tw OR young.tw OR adolescent*.tw OR toddler*.tw	exp children/ exp infants/ exp adolescents/ exp paediatrics/
#6	1 AND 2 AND 3 AND 4 AND 5	

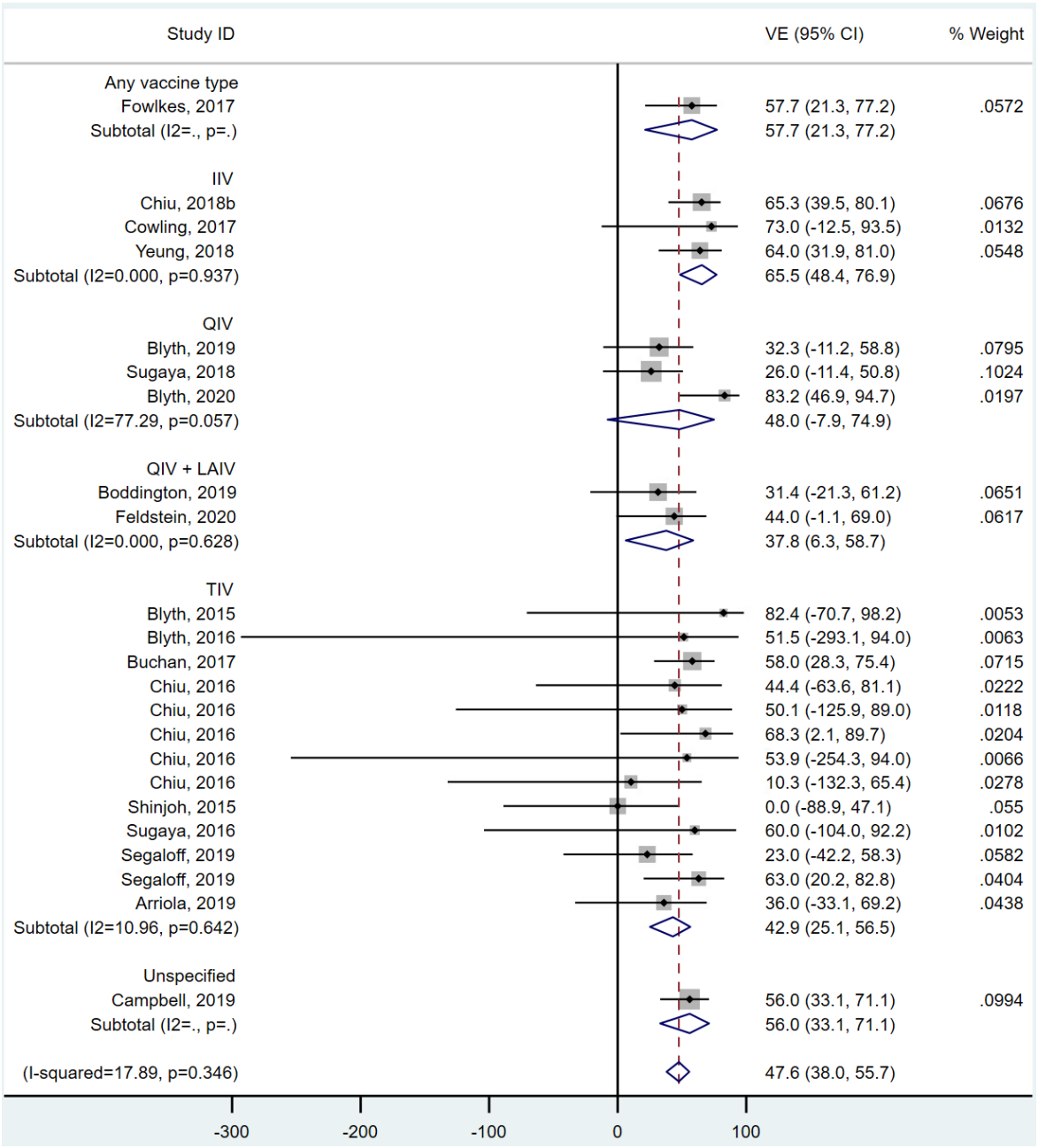
Web of Science search strategy: NB no subject headings in web of science. Note: a 'Topic Search' will return results from the title, abstract and keywords/keywords plus fields.

	Free text
#1	TS=(influenza OR flu OR human influenza)
#2	TS=(vaccin* OR immuni* OR innocula*)
#3	TS=(efficacy OR effectiveness)
#4	TS=(hospital OR hospitali* OR secondary care OR patient OR inpatient OR life-threatening OR intensive care OR critical care OR death)
#5	TS=(Child* OR infant OR p$ediat* OR preschool OR school* OR young OR adolescent* OR toddler*)
#6	1 AND 2 AND 3 AND 4 AND 5

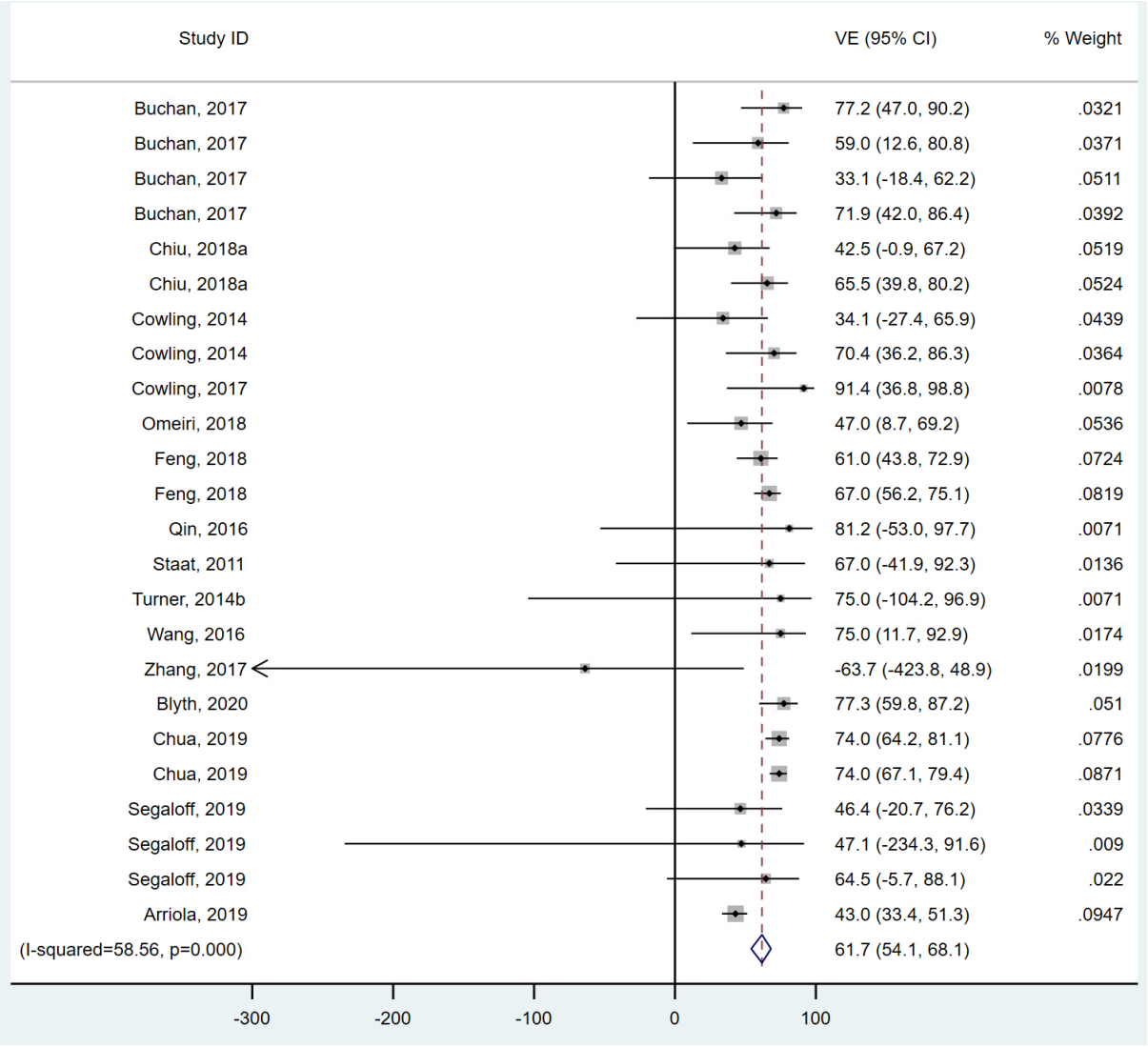
SCOPUS search strategy:

(TITLE-ABS-KEY (infuenza OR flu OR human AND influenza) AND TITLE-ABS-KEY (vaccin* OR immune* OR innocula*) AND TITLE-ABS-KEY (efficacy OR effectiveness) AND TITLE-ABS-KEY (hospital OR hospitali* OR secondary AND care OR patient OR inpatient OR life-threatening OR intensive AND care OR critical AND care OR death) AND TITLE-ABS-KEY (child* OR infant OR p*ediat* OR preschool OR school* OR young OR adolescent* OR toddler*))

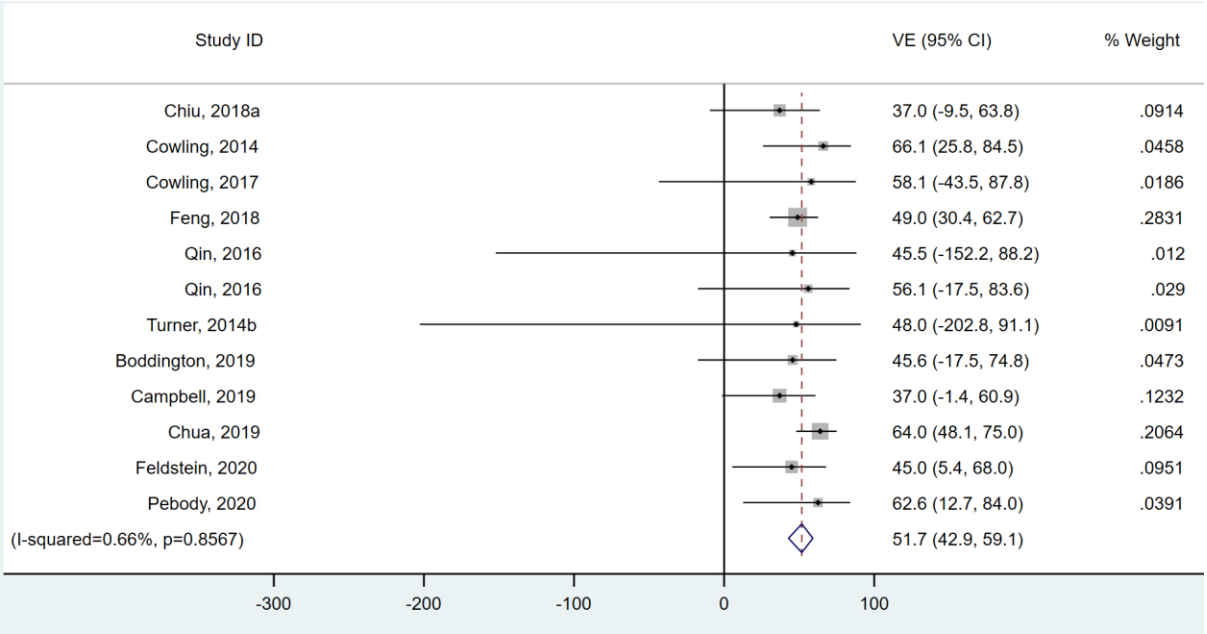
Supplement Figure 1: Influenza vaccine effectiveness estimates against hospitalisation by influenza B



Supplement Figure 2: Influenza vaccine effectiveness against hospitalisation in children aged 6 months to five years old



Supplement Figure 3: Influenza vaccine effectiveness against hospitalisation in children aged 6 years to 17 years old



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