Vaccine effectiveness of live attenuated and trivalent inactivated influenza vaccination in 2010/11 to 2015/16

NIHR | National Institute for Health Research

Journals Library

Check for updates

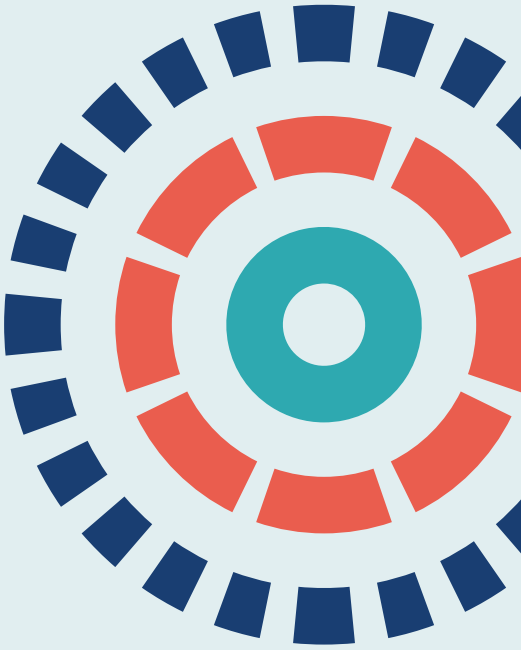
Health Technology Assessment

Volume 24 • Issue 67 • December 2020

ISSN 1366-5278

Vaccine effectiveness of live attenuated and trivalent inactivated influenza vaccination in 2010/11 to 2015/16: the SIVE II record linkage study

Colin R Simpson, Nazir I Lone, Kim Kavanagh, Tanya Englishby, Chris Robertson, Jim McMenamin, Beatrix von Wissman, Eleftheria Vasileiou, Christopher C Butler, Lewis D Ritchie, Rory Gunson, Jürgen Schwarze and Aziz Sheikh



DOI 10.3310/hta24670

Vaccine effectiveness of live attenuated and trivalent inactivated influenza vaccination in 2010/11 to 2015/16: the SIVE II record linkage study

Colin R Simpson,[1,2]* Nazir I Lone,[2] Kim Kavanagh,[3] Tanya Englishby,[3] Chris Robertson,[3,4] Jim McMenamin,[4] Beatrix von Wissman,[4] Eleftheria Vasileiou,[2] Christopher C Butler,[5,6] Lewis D Ritchie,[7] Rory Gunson,[8] Jürgen Schwarze[9] and Aziz Sheikh[2]

[1]School of Health, Faculty of Health, Victoria University of Wellington, Wellington, New Zealand
[2]Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh UK
[3]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK
[4]Health Protection Scotland, Glasgow, UK
[5]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[6]Institute of Primary Care and Public Health, Cardiff University, Cardiff, UK
[7]Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK
[8]West of Scotland Specialist Virology Centre, Glasgow Royal Infirmary, Glasgow, UK
[9]Child Life and Health, Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK

*Corresponding author

Declared competing interests of authors: Christopher C Butler was a member of the Efficacy and Mechanism Evaluation Board. Jürgen Schwarze reports personal fees from the Medical Research Council Infection and Immunity Board. Aziz Sheikh and Chris Robertson report grants from the National Institute for Health Research during the conduct of this study.

Published December 2020
DOI: 10.3310/hta24670

This report should be referenced as follows:

Simpson CR, Lone NI, Kavanagh K, Englishby T, Robertson C, McMenamin J, *et al*. Vaccine effectiveness of live attenuated and trivalent inactivated influenza vaccination in 2010/11 to 2015/16: the SIVE II record linkage study. *Health Technol Assess* 2020;**24**(67).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/34/14. The contractual start date was in October 2014. The draft report began editorial review in May 2018 and was accepted for publication in November 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

Vaccine effectiveness of live attenuated and trivalent inactivated influenza vaccination in 2010/11 to 2015/16: the SIVE II record linkage study

Colin R Simpson,[1,2]* Nazir I Lone,[2] Kim Kavanagh,[3] Tanya Englishby,[3] Chris Robertson,[3,4] Jim McMenamin,[4] Beatrix von Wissman,[4] Eleftheria Vasileiou,[2] Christopher C Butler,[5,6] Lewis D Ritchie,[7] Rory Gunson,[8] Jürgen Schwarze[9] and Aziz Sheikh[2]

[1]School of Health, Faculty of Health, Victoria University of Wellington, Wellington, New Zealand
[2]Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh UK
[3]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK
[4]Health Protection Scotland, Glasgow, UK
[5]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[6]Institute of Primary Care and Public Health, Cardiff University, Cardiff, UK
[7]Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK
[8]West of Scotland Specialist Virology Centre, Glasgow Royal Infirmary, Glasgow, UK
[9]Child Life and Health, Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK

*Corresponding author colin.simpson@vuw.ac.nz

Background: There is good evidence of vaccine effectiveness in healthy individuals but less robust evidence for vaccine effectiveness in the populations targeted for influenza vaccination. The live attenuated influenza vaccine (LAIV) has recently been recommended for children in the UK. The trivalent influenza vaccine (TIV) is recommended for all people aged ≥ 65 years and for those aged < 65 years who are at an increased risk of complications from influenza infection (e.g. people with asthma).

Objective: To examine the vaccine effectiveness of LAIV and TIV.

Design: Cohort study and test-negative designs to estimate vaccine effectiveness. A self-case series study to ascertain adverse events associated with vaccination.

Setting: A national linkage of patient-level general practice (GP) data from 230 Scottish GPs to the Scottish Immunisation & Recall Service, Health Protection Scotland virology database, admissions to Scottish hospitals and the Scottish death register.

Participants: A total of 1,250,000 people.

Interventions: LAIV for 2- to 11-year-olds and TIV for older people (aged ≥ 65 years) and those aged < 65 years who are at risk of diseases, from 2010/11 to 2015/16.

Main outcome measures: The main outcome measures include vaccine effectiveness against laboratory-confirmed influenza using real-time reverse-transcription polymerase chain reaction (RT-PCR), influenza-related morbidity and mortality, and adverse events associated with vaccination.

Results: Two-fifths (40%) of preschool-aged children and three-fifths (60%) of primary school-aged children registered in study practices were vaccinated. Uptake varied among groups [e.g. most affluent vs. most deprived in 2- to 4-year-olds, odds ratio 1.76, 95% confidence interval (CI) 1.70 to 1.82]. LAIV-adjusted vaccine effectiveness among children (aged 2–11 years) for preventing RT-PCR laboratory-confirmed influenza was 21% (95% CI –19% to 47%) in 2014/15 and 58% (95% CI 39% to 71%) in 2015/16. No significant adverse events were associated with LAIV. Among at-risk 18- to 64-year-olds, significant trivalent influenza vaccine effectiveness was found for four of the six seasons, with the highest vaccine effectiveness in 2010/11 (53%, 95% CI 21% to 72%). The seasons with non-significant vaccine effectiveness had low levels of circulating influenza virus (2011/12, 5%; 2013/14, 9%). Among those people aged ≥ 65 years, TIV effectiveness was positive in all six seasons, but in only one of the six seasons (2013/14) was significance achieved (57%, 95% CI 20% to 76%).

Conclusions: The study found that LAIV was safe and effective in decreasing RT-PCR-confirmed influenza in children. TIV was safe and significantly effective in most seasons for 18- to 64-year-olds, with positive vaccine effectiveness in most seasons for those people aged ≥ 65 years (although this was significant in only one season).

Future work: The UK Joint Committee on Vaccination and Immunisation has recommended the use of adjuvanted injectable vaccine for those people aged ≥ 65 years from season 2018/19 onwards. A future study will be required to evaluate this vaccine.

Trial registration: Current Controlled Trials ISRCTN88072400.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 67. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of abbreviations

ARI	acute respiratory infection
BMI	body mass index
CHP	Community Health Partnership
CI	confidence interval
ECOSS	Electronic Communication of Surveillance in Scotland
GP	general practice
HPS	Health Protection Scotland
ICD-10	*International Classification of Diseases,* Tenth Edition
ILI	influenza-like illness
ISD	Information Services Division
LAIV	live attenuated influenza vaccine
NSS	NHS National Services Scotland
OR	odds ratio
PIPER	Pandemic Influenza Primary Care Reporting
RR	risk ratio
RT-PCR	real-time reverse-transcription polymerase chain reaction
SIMD	Scottish Index of Multiple Deprivation
SIVE	Seasonal Influenza Vaccine Effectiveness in the community
SIVE II	Seasonal Influenza Vaccination Effectiveness II
SMR01	Scottish Morbidity Record 01
TIV	trivalent influenza vaccine
TND	test-negative design
TRE	trusted research environment
WoSSVC	West of Scotland Specialist Virology Centre

Plain English summary

In Scotland, a new type of influenza vaccine (live attenuated influenza vaccine), administered via the nose, was introduced in 2014/15 for all children aged between 2 and 11 years. It can be difficult to evaluate any changes in health as a result of new immunisation programmes, given that randomised controlled trials of vaccines are impractical and can also be seen as unethical. These changes are therefore typically not evaluated, making it difficult to inform future policy in this field. Observational studies can be used to assess the effects of health-care interventions without influencing the care that is provided or affecting the people who receive it. An evaluation (effectiveness and safety) of this change in the immunisation programme was conducted. The vaccine programme, an inactivated vaccine administered as an injection, for other groups for whom the evidence available is limited was also evaluated [i.e. for people aged ≥ 65 years and people aged < 65 years who have a medical condition (e.g. asthma) that puts them at risk of severe illness from influenza].

The findings support the view that the intranasal vaccine is effective and safe in preventing influenza in children. The injectable vaccine in people aged < 65 years who are more at risk of complications from flu was safe and effective. Lower effectiveness was found in people aged ≥ 65 years. Both the injectable vaccine and the intranasal vaccine have high levels of uptake in the population offered vaccination. When considering these results, the important limitation of bias in observational study designs should be noted [for instance, residual confounding, whereby it is not possible to measure a characteristic of those people receiving the vaccine (e.g. being healthier)], and this is accounted for in this analysis.

Scientific summary

Background

Globally, there are 90 million new cases of influenza and 1 million cases of influenza-associated severe acute lower respiratory infection per annum among children. National influenza vaccination programmes, delivered by primary care in the community, are important to reduce influenza-related illness, and hence the considerable investment in this approach. Previously, these programmes targeted older people (i.e. those aged ≥ 65 years) and people with chronic disease (e.g. asthma) who are susceptible to serious illness from influenza. Children are also thought to be important in the transmission of influenza to the populations at risk of serious complications from influenza, and diminished circulation of the virus has been predicted to improve herd immunity. Using evidence generated from epidemiological modelling, and following advice from the UK Joint Committee for Vaccination and Immunisation, from September 2013 the seasonal influenza vaccination programme was extended. In addition to the seasonal trivalent influenza vaccine (TIV), the live attenuated influenza vaccine (LAIV) is offered to all children aged 2–11 years (except children clinically severely immunocompromised owing to conditions or immunosuppressive therapy or oral steroids and children with severe asthma), by primary care clinicians in general practice (GP) and in schools in Scotland.

Objectives

Building on prior work, approaches used were further refined as part of three National Institute for Health Research Health Technology Assessment and Health Services and Delivery Research projects [Simpson CR, Ritchie LD, Robertson C, Sheikh A, McMenamin J. Vaccine effectiveness in pandemic influenza – primary care reporting (VIPER): an observational study to assess the effectiveness of the pandemic influenza A (H1N1)v vaccine. *Health Technol Assess* 2010;**14**(34); Simpson CR, Lone N, Kavanagh K, Ritchie LD, Robertson C, Sheikh A, *et al.* Trivalent inactivated seasonal influenza vaccine effectiveness for the prevention of laboratory confirmed influenza in a Scottish population 2000–2009. *Euro Surveill* 2015;**20**:ii–21043; and Simpson CR, Lone N, McMenamin J, Gunson R, Robertson C, Ritchie LD, Sheikh A. Early estimation of pandemic influenza Antiviral and Vaccine Effectiveness (EAVE): use of a unique community and laboratory national data-linked cohort study. *Health Technol Assess* 2015;**19**(79)]. The study determined seasonal influenza vaccine uptake and effectiveness in the Scottish population. This involved the interrogation of data from 230 GPs (a sample of 25% of Scotland's practices) linked to the Health Protection Scotland virology database (Electronic Communication of Surveillance in Scotland), the Information Services Division hospital and mortality records (General Register Office for Scotland Death Certification and Scottish Morbidity Record 01) and the Child Health Services Programme/Scottish Immunisation & Recall Service.

The primary objective was to evaluate:

- early estimates of the uptake and effectiveness of LAIV administered to children (from 2013).

The secondary objectives were to evaluate the:

- vaccine effectiveness of seasonal TIV among older people (aged ≥ 65 years)
- vaccine effectiveness of seasonal TIV among those people with at-risk diseases (e.g. asthma) and aged < 65 years

- validity of using laboratory-confirmed influenza tests from non-Sentinel primary care and secondary care compared with Sentinel primary care practices
- validity of using laboratory-confirmed respiratory syncytial virus as a negative-control outcome
- adverse events associated with vaccination.

Methods

The setting for this project was 230 participating GPs based throughout Scotland.

Data on vaccination and other patient characteristics from GPs were linked using NHS Scotland's unique patient identifier, the Community Health Index number, to the Scottish Morbidity Record catalogue (inpatient hospitalisations) and mortality within Scotland and virological real-time reverse-transcription polymerase chain reaction (RT-PCR) data. Vaccine uptake was derived from the electronic GP record and vaccine effectiveness was calculated using information from linked virological swab data, using a logistic regression model adjusted for the effects of sex, age and socioeconomic status. In addition, the cohort method was used to estimate the proportion of influenza-like illness (ILI), acute respiratory disease and other non-specific clinical outcomes, such as hospitalisation or death from influenza, between vaccinated and unvaccinated cases.

Results

Two-fifths (40%) of preschool-aged children and three-fifths (60%) of primary school-aged children registered in the study's practices were vaccinated. Uptake varied among groups [e.g. most affluent vs. most deprived in 2- to 4-year-olds, odds ratio 1.76, 95% confidence interval (CI) 1.70 to 1.82]. LAIV-adjusted vaccine effectiveness among children (aged 2–11 years) for preventing RT-PCR laboratory-confirmed influenza was 21% (95% CI –19% to 47%) in 2014/15 and 58% (95% CI 39% to 71%) in 2015/16. No significant adverse events were associated with LAIV. Among at-risk 18- to 64-year-olds, significant TIV effectiveness was found for four of the six seasons with the highest vaccine effectiveness in 2010/11 (53%, 95% CI 21% to 72%). The seasons with non-significant vaccine effectiveness had low levels of circulating influenza virus (2011/12, 5%; 2013/14, 9%). For people aged ≥ 65 years, TIV effectiveness was positive in all six seasons, but in only one of the six seasons (2013/14) was significance achieved (57%, 95% CI 20% to 76%). An analysis of age groups found significant vaccine effectiveness for people aged 65–74 years with asthma (53%, 95% CI 13% to 74%) and chronic kidney disease (60%, 95% CI 17% to 81%). Furthermore, significant vaccine effectiveness was found in those aged 75–84 years with chronic respiratory disease against influenza A(H3N2) (52%, 95% CI 11% to 74%) and in those with asthma against influenza B (86%, 95% CI 32% to 97%). Among the oldest age group (i.e. people aged ≥ 85 years), significant vaccine effectiveness was found for those with chronic respiratory disease (20%, 95% CI 2% to 34%), chronic heart disease (27%, 95% CI 3% to 45%), asthma (54%, 95% CI 43% to 62%), diabetes mellitus (34%, 95% CI 9% to 51%) and impaired immune function (42%, 95% CI 3% to 65%). TIV in adults was also found to be safe.

In the cohort analysis for people aged ≥ 65 years, adjusted vaccine effectiveness for reducing primary care consultations for ILIs was not significant in 2012/13 (vaccine effectiveness –64%, 95% CI –72% to –56%) and in 2013/14 (–28%, 95% CI –34% to –23%). However, statistically significant protective vaccine effectiveness was observed in hospitalisation due to influenza and pneumonia, ranging from 17% (95% CI 16% to 19%) in 2010/11 to 28% (95% CI 26% to 29%) in 2013/14. Vaccine effectiveness for death attributable to influenza and pneumonia was statistically significant and ranged from 32% (95% CI 31% to 33%) in 2010/11 to 40% (95% CI 39% to 41%) in 2015/16.

Conclusions

Few countries' health systems allow for the integrated and accessible data recording that made this study possible and made it feasible to centrally collate almost all hospitalisations and deaths attributed to influenza, allowing for completeness of reporting. Using these data, LAIV was found to be safe and effective in decreasing RT-PCR-confirmed influenza in children. TIV was safe and significantly effective (in most seasons) for 18- to 64-year-olds, with positive vaccine effectiveness in most seasons for those aged ≥ 65 years, although this was significant in only one season. Higher vaccine effectiveness was found among younger adults with asthma. This should strengthen the evidence base for health-care practitioners involved in distributing LAIV. TIV immunisation for at-risk adults aged < 65 years in primary health-care settings is effective. The finding of limited vaccine effectiveness in people aged ≥ 65 years supports the recent UK Joint Committee on Vaccination and Immunisation recommendation to introduce adjuvanted vaccine for those in this age group from the 2018/19 season.

Recommendations for research

The monitoring of the LAIV programme with enhanced Sentinel swabbing of preschool- and primary school-aged children should continue. Replication of vaccine effectiveness and safety in LAIV and TIV in other countries that have these influenza vaccine programmes is now required to confirm the results of this study. The Joint Committee on Vaccination and Immunisation has recommended the use of adjuvanted injectable vaccine for those aged ≥ 65 years from season 2018/19 onwards. A future study will be required to evaluate this vaccine.

Trial registration

This trial is registered as ISRCTN88072400.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of the health problem

Globally, it is estimated that seasonal influenza is responsible for 5 million cases of severe illness and 500,000 deaths per year, with, for example, an estimated cost to the USA of US$87B per annum.[1–3] There are also 90 million new cases of influenza and 1 million cases of influenza-associated severe acute lower respiratory infection among children.[4] National influenza vaccination programmes, delivered by primary care in the community, are important to reduce influenza-related illness, and hence the considerable investment in this approach. Previously, these programmes targeted older people (i.e. those aged ≥ 65 years) and people with chronic disease (e.g. asthma) who are susceptible to serious illness from influenza. Children are also thought to be important in the transmission of influenza to the populations at risk of serious complications from influenza, and diminished circulation of the virus has been predicted to improve herd immunity.[5] Using evidence generated from epidemiological modelling,[6] and following advice from the Joint Committee on Vaccination and Immunisation, from September 2013 the seasonal influenza vaccination programme has been extended.[7] In addition to the seasonal trivalent influenza vaccine (TIV), the live attenuated influenza vaccine (LAIV) is offered to all children aged 2–11 years (except children clinically severely immunocompromised owing to conditions or immunosupressive therapy or oral steroids, and children with severe asthma) by primary care clinicians in general practice (GP) and in schools in Scotland.

Existing evidence

The evidence from clinical trials of the benefits of LAIV are largely confined to healthy children aged < 7 years (mostly for children aged < 3 years).[8,9] Efforts to estimate seasonal TIV effectiveness have been largely confined to younger healthier adults (e.g. with no randomised controlled trials showing efficacy of TIV in adults aged ≥ 65 years).[9,10] Recent observational studies have attempted to estimate the vaccine effectiveness in preventing influenza-related illness in GP patients.[3,11] Further studies have examined vaccine effectiveness with hospitalisation or death; however, these studies have suffered from bias when using non-specific outcomes,[8] or have been underpowered when using more specific end points (e.g. laboratory-confirmed influenza), in particular for subgroups being targeted for vaccination (e.g. older people aged ≥ 65 years, people with at-risk disease such as asthma and pregnant women).[12] Cohort studies (with nested case–control studies) or data linkage-derived estimates of vaccine effectiveness have been undertaken, with measures taken to overcome many of the confounding issues that otherwise have limited estimations of effectiveness.[13–15] There is also a need to add to the growing body of evidence with regard to the safety of these vaccines.[16] Given the ongoing controversy regarding vaccine effectiveness and, in particular, in relation to at-risk groups (e.g. those with asthma),[7] there is further need for information to help evaluate new seasonal vaccine strategies.

Chapter 2 Research questions

This research aimed to examine the vaccine effectiveness and safety of the seasonal influenza vaccines, including LAIV and TIV. The research team had access to a unique set of linked databases within a trusted research environment (TRE), which contained individual patient-level data relating to primary health care, acute hospital care data, school immunisation data, virological real-time reverse-transcription polymerase chain reaction (RT-PCR) laboratory tests and mortality.[3]

In contrast to previous observational studies, these rich data sources provide information on a large number of potential confounders and highly specific laboratory outcome measures in a study cohort sampled from the general population. This assessment of the vaccine effectiveness and the public health impact of a new seasonal influenza vaccination programme seeks to clarify whether or not such a programme leads to societal benefits, therefore advancing the international evidence base.

The research questions were:

- What was the uptake and vaccine effectiveness of LAIV administered to children (introduced to the national vaccination programme in 2013)?
- What was the uptake and vaccine effectiveness of TIV administered to at-risk groups (e.g. those people aged ≥ 65 years and people aged < 65 years with asthma)?
- Are laboratory-confirmed influenza tests from non-Sentinel primary care and secondary care valid (vs. Sentinel primary care practices)?
- What was the validity of using laboratory-confirmed respiratory syncytial virus as a negative-control outcome?
- What adverse events are associated with vaccination?

Chapter 3 Methods

Study design and population

Vaccine uptake is reported from a cross-sectional survey of all six influenza seasons. The test-negative design (TND) was used to measure vaccine effectiveness for the RT-PCR outcomes and a cohort study design was used for non-specific clinical outcomes (e.g. hospitalisation or death from influenza or pneumonia).[17]

All practices in Scotland ($n = 998$) were invited to participate and 230 (self-selected) practices were recruited These represented 29 (65.9%) of 44 of the Community Health Partnership (CHP) areas in Scotland. Data were extracted on 1.25 million patients in Scotland into our study. Each patient contributed person-time to each influenza season while alive and fully registered with a participating GP (i.e. a person was included in the study if they were on a participating practice's list of patients, including those who may have died or deregistered during the study period).

Three basic data sets for analysis were created:

1. all patients with a RT-PCR test
2. patients by age group (e.g. 2–4, 5–11, 12–17, 18–64 and $\geq$ 65 years)
3. patients at risk of serious influenza-like illnesses (ILIs) (e.g. asthma).

Databases

Data fields extracted from the following databases (*Figure 1*) were linked deterministically using the Community Health Index number; a unique identifier used by the NHS for the Scottish population.[3] The database linkage and analysis was carried out within the NHS National Services Scotland (NSS) TRE by the electronic Data Research and Innovation Service (eDRIS).

General practice

Almost all individuals resident in Scotland are registered with a GP, which provides health-care services free of charge. Virtually all specialist hospital care services are also free of charge, usually obtained through referral from primary care or, in emergency situations, through patients attending an accident and emergency department. Primary care-based physicians co-ordinate the influenza vaccination programme for their patients and provide much of the care of patients discharged back into the community by secondary and tertiary care services. Completeness of capture of contacts and accuracy of clinical event coding (using Read codes) has been found to be > 91% among practices in Scotland.[18,19] The electronic recording of long-term prescribing information by primary care has also been found to be both accurate and complete.[20]

Child Health Services Programme/Scottish Immunisation & Recall System

The Child Health Services Programme/Scottish Immunisation & Recall System database has a record of all children (used nationally from 2002) with scheduled vaccinations. Data on vaccination administration for all children in Scotland are also recorded here.[21] These data were used to determine influenza vaccinations that have been administered in schools rather than in primary care.

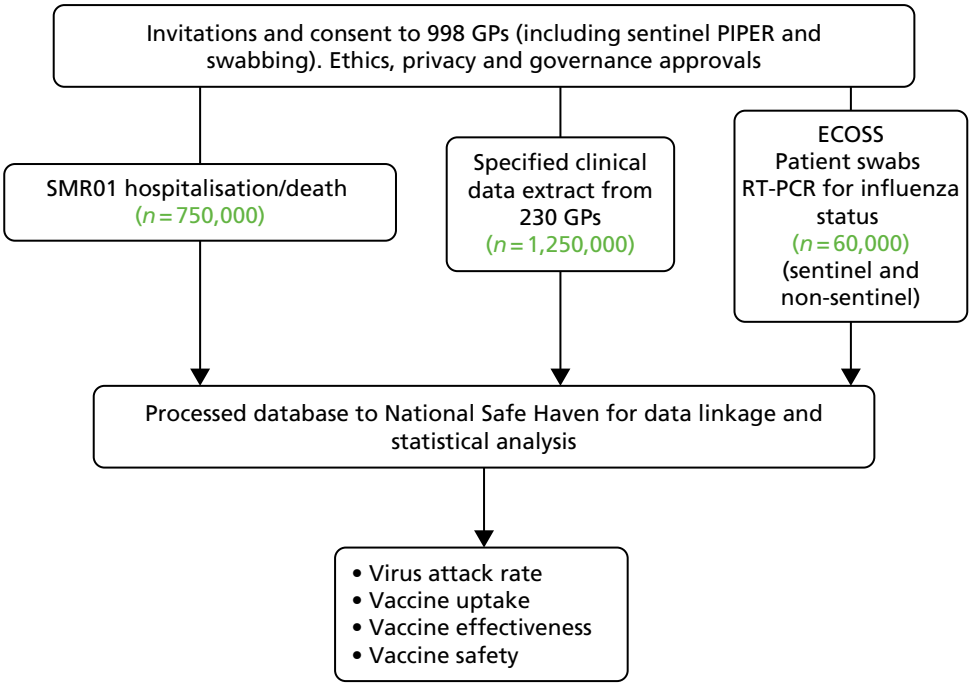


FIGURE 1 Flow diagram for the Seasonal Influenza Vaccination Effectiveness II project. ECOSS, Electronic Communication of Surveillance in Scotland; PIPER, Pandemic Influenza Primary Care Reporting; SMR01, Scottish Morbidity Record 01.

Electronic Communication of Surveillance in Scotland

Data on > 60,000 RT-PCR tests (including an additional 1500 tests per season funded to target 2- and 3-year-olds), collated into the Electronic Communication of Surveillance in Scotland (ECOSS) database, were used for the identification of severe disease, outbreaks and long-term trends in the incidence of laboratory-reported infections.[22]

Scottish Morbidity Record

The Information Services Division (ISD) NSS maintains a database of all acute hospital discharges and deaths in Scotland, known as the Scottish Morbidity Record 01 (SMR01). All inpatient and day-case episodes of care for acute hospitals since 1981 have been recorded in the database. The database is subject to regular validation checks and the most recent quality assurance report indicated good levels of accuracy (i.e. > 90%) for the fields used in this study.[23] Diagnostic information is recorded using the *International Classification of Diseases,* Tenth Edition (ICD-10). There are up to six fields that can be used to record diagnoses, with one field allocated as the main reason for admission. SMR01 is linked routinely by the ISD to the Scottish death register using patient characteristics in a probabilistic matching algorithm, with a high degree of accuracy.[24] Details from death certificates issued for all deaths in Scotland are recorded in the death register, maintained by the National Records of Scotland.[25] Cause of death has been routinely coded, using ICD-10, since 2000.[3]

Study period

Data from 1 September 2010 to 31 August 2016 were used. These allowed an analysis of six influenza seasons (from 2010/11 to 2015/16). Each patient contributed person-time to each influenza season while alive and registered with a participating GP. For the non-pandemic seasons, each year (i.e. 1 September to 31 August) was divided in to four periods (*Figure 2*). The influenza season was defined for each year using national influenza surveillance data.[26] The other periods include a pre-influenza season (starting on 1 September), a post-influenza period (which ends on 31 May each year) and a 'non-influenza' period (from 1 June to 31 August) (see *Figure 2*). Because there was a phased roll-out arrangement for influenza

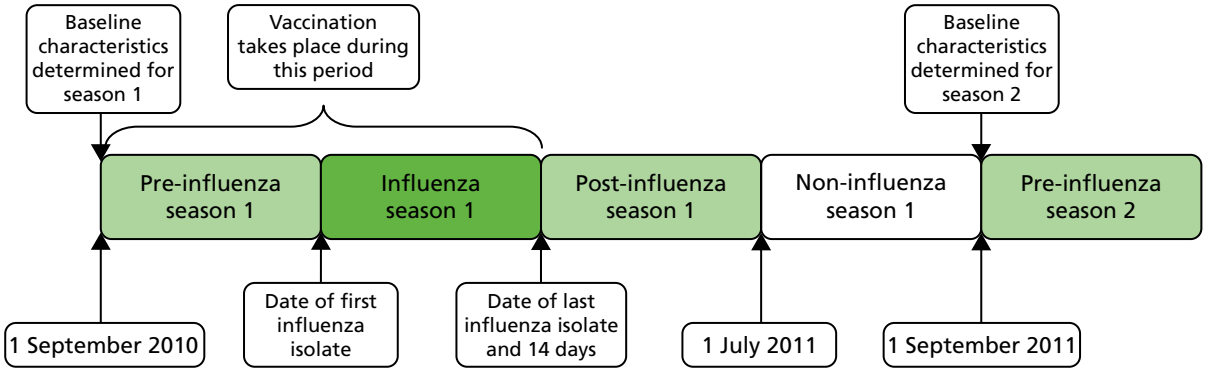


FIGURE 2 Relationship of the first influenza season (2010–11) to pre-, post- and non-influenza season periods. Reproduced from Simpson *et al.*[3] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

vaccination among children, children aged 2–3 years and primary school-aged children (for which pilots were taking place) in season 2013/14, and all preschool children aged 2–4 years and all primary school-aged children (i.e. all children aged 2–11 years) in seasons 2014/15 and 2015/16 were analysed.

Baseline characteristics for each patient was determined on 1 September each year. The earliest date of influenza vaccination varied for each influenza season, but always took place after 1 September.

Exposure definition

For people in at-risk groups, influenza vaccinations (TIV and LAIV for preschool children aged ≥ 2 years) are free and administered by general practitioners (*Table 1*).[28] Data on influenza vaccination carried out in GP (including Community Health Index number and date of administration) are recorded to enable reimbursement. Information on individuals receiving LAIV in schools is collated in the Child Health Services Programme/Scottish Immunisation & Recall Service database and was extracted for this analysis.[21] Vaccination was used to define exposure status when it was given at a time point between 1 September and the end of the influenza season (see *Figure 2*). An individual was defined as vaccinated 14 days after the seasonal influenza vaccine had been administered.[29] The time period from the first day of the influenza season to day 14 post vaccination was defined as 'unexposed' and the period from day 14 post vaccination until the end of the influenza season was defined as 'exposed'. Therefore, those people vaccinated between the start of the pre-influenza period up until 14 days before the influenza season were defined as 'exposed' for the duration of the influenza season.[30]

Study outcomes

Real-time reverse-transcription polymerase chain reaction

Data are collated by Health Protection Scotland (HPS) on patients having had swab samples RT-PCR tested in primary and secondary care for routine diagnostic purposes outside the Sentinel scheme. All RT-PCR data on both positive and negative tests are held by HPS in the national laboratory database (the ECOSS database). From 1999, the RT-PCR testing used to confirm respiratory virus type has been found to be highly sensitive for influenza A (H3, H1) and B diagnosis.[3,31] Improvements to RT-PCR, since 2003, include the development of multiplex testing, which increases the number of pathogens tested per assay. However, the high sensitivity of these tests remains unchanged.[32]

TABLE 1 Seasonal Influenza Vaccination Effectiveness II specification

Variable	Data: Item	Source
Age, sex		SMR01[27] and GP[27]
Hospital admission type: emergency/routine admission		SMR01[27]
Date of first admission		
Length of stay		
Clinical condition coding[a]	Influenza vaccination	GP[27]
Recorded given	Influenza vaccination	ISD Scotland[21]
Clinical condition coding[a]	Pneumococcal vaccination	GP[27]
SIMD: rural/urban[b]		GP[27]
Prescription	Antiviral prescriptions	GP[27]
Prescription	Asthma- and COPD-related prescriptions	GP[27]
Clinical condition coding[a]	Clinical at-risk groups (chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, immunosuppression, diabetes mellitus, pregnancy)	GP[27]
Diagnosis fields	Charlson Comorbidity Index comorbidities	SMR01[27]
Prescription, clinical attendance	Number of previous GP consultations, prescribed drugs	GP[27]
Clinical condition coding[a]	Smoking,[b] exercise status[b]	GP[27]
Number of previous hospital admissions		SMR01[27]
Clinical condition coding[a]	Pregnancy	GP[27]
Quality and Outcomes Framework exception reported (patient unsuitable, etc.)		GP[27]
Clinical condition coding[a]	Home oxygen	GP[27]
Clinical condition coding,[a] diagnosis	Trauma	SMR01[27] and GP[27]
Clinical condition coding,[a] diagnosis	ILI	SMR01,[27] GP[27] and death records[27]
Clinical condition coding,[a] diagnosis	Asthma and COPD symptoms and exacerbations	SMR01[27] and GP[27]
RT-PCR swab results		ECOSS virology database

COPD, chronic obstructive pulmonary disease; SIMD, Scottish Index of Multiple Deprivation.
a Clinician condition coding: Read/ICD-10 codes.
b Variable with possible missing data.

Primary care practices involved in the HPS Sentinel swabbing scheme are encouraged to obtain nasal/throat swabs from patients of all ages who have symptoms suggestive of influenza. Each GP was requested to submit five swab samples per week (seven in season 2015/16) to the West of Scotland Specialist Virology Centre (WoSSVC), Glasgow Royal Infirmary, for RT-PCR testing for a range of respiratory pathogens on any patient presenting for consultation in the practice with influenza symptoms across all ages, independent of whether the patient has or has not been vaccinated. The WoSSVC is a World Health Organization-accredited national influenza centre, which participates in the quality assurance programme to maintain this status.

Non-specific clinical outcomes

To determine the effect of vaccination status on influenza-related primary care consultations, hospital admissions and deaths, secondary analyses were undertaken using non-specific clinical outcomes derived from primary and secondary care. Data on ILI consultation were derived from the GP database. Data on hospitalisation and cause of death from influenza or pneumonia were derived from SMR01.

Confounding factors

Key characteristics of each identified patient characteristics present in each season of the cohort were included as confounders in the analyses. These were defined in each year on the first day of the pre-influenza season (i.e. on 1 September).

Demographics

Sex, age band and socioeconomic status were included in all analyses; socioeconomic status was measured using quintiles of the Scottish Index of Multiple Deprivation (SIMD). SIMD is an area-based measure of deprivation derived from seven domains, including income, employment and education.[3,33] SIMD identifies small-area concentrations of multiple deprivation across all of Scotland in a consistent way. SIMD ranks small areas (called data zones) from the most deprived (ranked 1) to the least deprived (ranked 6976), and this was mapped onto postcode and then split into quintiles of socioeconomic status. For this project, SIMD was derived from an individual patient's full postcode. Rurality in terms of urban/rural location (one large urban and eight remote rural areas) was also included in the analysis, and this was classified in this project using an individual patient's postcode.[34]

At-risk groups

At-risk patients are those with certain comorbidities for whom seasonal influenza vaccination is indicated. Patients were defined as high risk according to national guidance if they had one or more of the following conditions:[28]

- asthma
- chronic heart disease
- chronic kidney disease (including renal transplantation), stages 1 and 2 and 3–5
- chronic liver disease
- chronic neurological diseases
- chronic respiratory diseases
- conditions or drugs causing impaired immune function
- diabetes mellitus.

Chronic diseases

This was included for our non-specific clinical outcomes and adverse events. Comorbidity was defined by the 17 disease categories that constituted the Charlson Comorbidity Index.[35] This index has been validated in a number of different databases using codes from health-care databases.[36] A study has mapped Read codes from a UK GP database to the relevant Charlson Comorbidity Index comorbid disease groups, resulting in a model that performed well in the prediction of 5-year mortality.[37] These codes were used to identify comorbidities that are present in a patent's record prior to the start of each pre-influenza season (i.e. on 1 September).

Smoking status

Smoking status was derived from primary care data (current smoker, ex-smoker, non-smoker) and determined on 1 September each year.

Previous vaccinations

A variable was included for patients who have received seasonal influenza vaccination in previous seasons to account for the possibility of persisting vaccine effectiveness in the subsequent year.[38,39] Adjustment for previous pneumococcal vaccination at any time in the primary care record prior to 1 September each year was also undertaken.

Previous health-care utilisation

Measures of previous health-care resource use was used to capture other aspects of chronic health status and included previous years' GP consultations, prescriptions (repeat) and number of admissions to hospital.

Functional status

There is no direct measure of functional status made in any of these national databases. However, individuals who were resident in some form of institutional care setting were identified from the primary care database. This was used as an indicator of more severe functional limitation.

Sensitivity analyses

Simonsen *et al.*'s[40] framework was used to consider the role of confounding.

Seasonality

Vaccine effectiveness should be highest during the influenza season and lower pre and post season (see *Figure 2*).

Vaccine match

Vaccine effectiveness should be lower in years during which the influenza vaccine was a poor match for the circulating virus.

Severity of influenza season

Vaccine effectiveness should be greater in years during which the circulating virus caused a large excess mortality during the influenza season.

Age

It is thought that influenza vaccine is less effective in the oldest age groups because of immune senescence.

Specificity of outcome measure

Vaccine effectiveness should be greatest for the most specific outcome (i.e. laboratory-confirmed influenza infection) and lowest for the less specific outcomes [e.g. general practice acute respiratory infection (ARI) consultations].

Unmeasured confounding

The robustness of the results were assessed by modelling the effect of an unmeasured confounder, such as frailty, on the vaccine effectiveness estimates in a sensitivity analysis; an approach adopted to help explain the role of unknown confounding in observational analyses.[40] Three factors were varied: (1) the prevalence of the confounder in the vaccinated population, (2) its prevalence in the unvaccinated population and (3) the increased risk of the outcome attributable to the confounder.[41]

Instrumental variable analyses

The use of influenza vaccine coverage by geographical area has been found to be a strong and valid instrumental variable, which can be used to account for confounding.[3,42] Rather than comparing patients with respect to whether or not they received influenza vaccination, this instrumental variable behaves like natural randomisation of patients to regional vaccination groups that differ in their likelihood of receiving influenza vaccination. The NSS TRE is an important development in this respect, and permissions were received to extract granular postcode/geocoding data required to test the validity of this instrumental variable analysis in the Seasonal Influenza Vaccination Effectiveness II (SIVE II) database. Therefore, the use of vaccination uptake in geographically distinct CHP areas or other suitable health board areas as a suitable instrumental variable was explored. Because there are only 14 health boards and > 30 CHPs, the latter was used as the geographical area. To be valid, this instrumental variable needed to be related to exposure status (i.e. vaccination status) and not have an independent effect on outcome other than by ways mediated through the exposure.[43] Furthermore, the instrumental variable should not be related to any variables that confound the relationship between exposure and outcome. If an association with confounders is demonstrated, it is assumed that the instrumental variable is associated with unmeasured confounders and is therefore not valid. If the instrumental variable fulfils these criteria, it can be used in analyses to produce unbiased estimates of vaccine effectiveness by accounting for unmeasured confounding.

Adverse events associated with vaccination

A self-controlled study design was used to estimate the risk of adverse events associated with influenza vaccination.[44] The assumption underlying this design is that in the situation in which the adverse event is related to vaccination, the occurrence of an adverse event in the period after vaccination is greater than periods in the same patient that are temporally unrelated to vaccination.[45] This method has the advantage of controlling for all fixed individual-level confounders as comparisons are within the same individual, rather than between vaccinated and unvaccinated populations. The time period at risk for an adverse event (risk interval) and time period not at risk (control interval) were determined separately for each outcome.[46] For virtually all adverse events, the at-risk period was 14 days following receipt of the vaccination and the pre-risk period was the 90-day period prior to the 14 days before the vaccine (i.e. days 104 to 15 before receipt of the vaccine). The post-risk period was also 90 days and began on day 15 following vaccination. The main comparisons are with the rate of adverse events in the risk period compared with (1) the pre-risk period and (2) the post-risk period.

The self-controlled case series design uses data from only those with the adverse event and who are vaccinated. For some of the adverse events, there is the possibility of a temporal change in the risk over the ≥ 200 days of observation periods. To take this into account, data were also included from unvaccinated individuals who experienced the adverse event. These individuals were assigned a pseudo date of vaccination based on the median date of vaccination for the age and season. Interaction tests were then used to compare the rates of adverse events in (1) the risk period compared with the pre-risk period, and (2) the risk period compared with the post-risk period, among vaccinated and unvaccinated individuals. If there is evidence of a significant interaction with a higher risk ratio among vaccinated individuals, then this suggests that there is a potential adverse event associated with vaccination. Because there were a large number of adverse events being tested, the Benjamini–Hochberg false discovery rate was used to adjust for multiple testing.

The analysis of the self-controlled case series was undertaken using a stratified analysis in which the comparisons of the different risk periods were made within individuals. This was achieved by using matched logistic regression, with an offset for the length of the risk period. To avoid biases, the risk periods were not censored at death or when an individual left a practice.

Statistical analysis

A 5% significance level was used for hypothesis tests for the primary outcome. All *p*-values were two sided. All analyses were undertaken in R, version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). Ninety-five per cent confidence intervals (CIs) were also calculated. Logistic regression was used to investigate vaccine uptake. A generalised additive model was used to estimate the vaccine effect within the TND. Splines were used to model the effect of age and time within the season. A time-dependent Cox model was used to estimate the effect of vaccination on the consultation, hospitalisation and mortality end points. The receipt of vaccination was a time-dependent covariate. Summary statistics for this analysis are based on the person-time at risk.

Annual and pooled analyses

The study initially analysed each of the six influenza seasons separately for the primary outcome. However, a pooled analysis was carried out, in which increased precision was required (particularly for analysing subgroups of patients). In the TND, the pooled analysis used a separate spline term for days within each season.

Vaccine uptake and vaccine effectiveness

Vaccine uptake was calculated for all age groups per season as a percentage uptake.

Real-time reverse-transcription polymerase chain reaction outcomes

For vaccine effectiveness, using information from linked virological RT-PCR swab data (a binary event), a nested case test-negative control study was carried out.[47] Influenza positivity was compared with no influenza among patients who had influenza-like symptoms. The primary analysis utilised a logistic generalised additive model, in which the effects of sex, age, socioeconomic status (via the SIMD) and being in an at-risk morbidity group were adjusted for (TND study).[3,33] A spline function for time during each season was included to model the background rate of influenza and correct for any potential bias associated with the proportions of test-negative and test-positive patients in different periods. Vaccine effectiveness was measured by comparing the results from swabs taken after vaccination among those patients vaccinated, with swabs taken from those unvaccinated patients at the time the swab was collected. Vaccination was used to define exposure status if it was given at a time point between 1 September and the end of the influenza season (see *Figure 2*). The adjusted estimate of vaccine effectiveness was calculated using (1 – OR) × 100, in which the odds ratio (OR) was derived from the coefficient of vaccine status in the model. In the main analysis, the first dose was assessed only when two doses were given. An analysis, stratified by influenza A (H1, including pandemic influenza and H3 subtype where recorded) and influenza B, was carried out.

In addition, a number of sensitivity analyses for the primary end point were carried out.

Non-Sentinel versus Sentinel

We explored the validity of using laboratory-confirmed influenza tests from non-Sentinel primary care and secondary care sources compared with Sentinel primary care practices. Patient characteristics of individuals swabbed in non-Sentinel primary care practices and secondary care were described and any interaction between the source of the swab and the outcome was tested.

Negative controls

The use of laboratory-confirmed infections (currently 10 respiratory viruses and an infection, including rhinovirus and adenovirus) was explored using multiplex RT-PCR at the same time as the influenza RT-PCR.

Non-specific clinical outcomes

Vaccine effectiveness was estimated for non-specific clinical outcomes: primary care consultations for ILI and ARI; and emergency hospitalisation and death due to influenza/pneumonia. Hospital admissions and consultations can have multiple events and each event was counted.

Methods that were found in previous studies to be optimal for measuring vaccine effectiveness and accounting for bias and confounding were adopted.[30,47,48] Adjusted risk ratios (RRs) of vaccine effectiveness for prevention of hospitalisation/death/GP consultation were derived from time-dependent Cox models, taking into account the time at risk and the possibility of multiple events (not for death). Models did not include a cluster term to account for intrapractice correlation, as a practice code was not available in the analysis. Practice code not being available ensures that the identity of the practices in the study is hidden from the researchers. The models adjusted for sex, age, deprivation and clinical risk group, and exposure to vaccination in each season was included as a time-dependent covariate. For each season, individuals began in the unvaccinated group (and accumulated time at risk) until 14 days after the receipt of the vaccine, and then they switched to the vaccinated group.

In all models used to estimate the vaccine effectiveness, variables associated with the receipt of a vaccination and effect modifiers, such as vaccinations, consultations and hospitalisation in the previous influenza season, SIMD, urban/rural status, smoking status and Charlson Comorbidity Index score, were adjusted for. The main analysis for the non-specific clinical outcomes was a covariate adjustment.

Sample size

A final total sample size of up to 1.25 million people, from 230 practices, was expected. Using data from the Pandemic Influenza Primary Care Reporting (PIPER) 2014/15 study cohort, which had 263,000 individuals (of whom 16% were aged 2–17 years and 18% were aged ≥ 65 years),[49] vaccine uptake among children aged 3–12 years was 60% and vaccine uptake among people aged ≥ 65 years was 70%. Linked to this PIPER cohort from all virology tests in Scotland were, overall, 1745 RT-PCR tests, comprising 331 RT-PCR tests among 2- to 17-year-olds and 366 RT-PCR tests among people aged ≥ 65 years. This gave a multiplier ratio of around 5 : 1 from the PIPER cohort to the SIVE II cohort, and this was used to estimate the number of RT-PCR tests expected each year. This study expected 1800 RT-PCR tests per year among people aged ≥ 65 years and 1650 laboratory tests per year among children aged 2–17 years. The study expected 630 (i.e. 1745/12 × 5) asthma patients swabbed per year, because approximately 12% of the population was treated for asthma.

Using data generated from the Seasonal Influenza Vaccine Effectiveness in the community (SIVE) project, the study estimated a vaccination rate of 60% among children targeted for receipt of LAIV and a swab positivity rate of 20% among unvaccinated children.[13] This gave 90% power to detect a vaccine effectiveness of 31% based on 1650 swabs in one season. Pooling data over two seasons gave an estimated 3300 swabs in children eligible for vaccination and a 90% power to detect a vaccine effectiveness of 22%.

For those people aged ≥ 65 years targeted for receipt of TIV, for whom there was a vaccination rate of 70% and a swab positivity rate of 10%, among the unvaccinated individuals the study anticipated an 80% power to detect a vaccine effectiveness of 39%. It was estimated that there would be a need for 1800 swabs each year in the later years. During the peak influenza activity, when swab positivity might have increased to 20%, there is a 90% power to detect a vaccine effectiveness of 31%. Approximately 1 in 12 of the population is treated for asthma and it is anticipated that 1260 swabs are needed among patients with asthma in the final two seasons.[50] Assuming that 40% are vaccinated and that the swab positivity is around 15% gives 80% power for a vaccine effectiveness of 35%. These powers do not take into account design effects for the clustering of patients within GPs. Analyses of the historic PIPER cohorts has revealed a design effect of < 7% and this serves to increase the detectable vaccine effectiveness by about 2 percentage points.

Ethics and governance processes

Permissions were obtained from the Privacy Advisory Committee (NSS) (68/14), the National Research Ethics Committee West Midlands – Edgbaston (15/WM/0035), the National Caldicott Guardian and General Practice Data Custodians. Ms Elisabeth Ehrlich was the study's public and patient involvement lead and helped with the grant application. From a lay perspective, Ms Ehrlich helped to guide the team, ensuring

that the work was relevant to the interests and needs of the public and patients. The study was supported by members of the Asthma UK Centre for Applied Research Patient Advisory Group, which comprises > 60 people (including parents of children). This group helped advise on, and contribute to, study materials and it was invited to comment on the study from the patient and family perspective. An Independent Steering Group was convened, with public and patient involvement, to oversee this work, which comprised Neil Kelly (Chairperson, General Practitioner), Jonathan Van Tam (Professor of Health Protection), Punam Mangtani (Associate Professor Clinical) and Elisabeth Ehrlich (Public and Patient Involvement Representative).

Chapter 4 Results

Vaccine uptake

The uptake of LAIV among the children registered with the 230 practices taking part in this project increased over the study period (*Table 2*), with nearly two-thirds of primary school-aged children vaccinated by 2015/16. TIV uptake among at-risk patients aged 12–65 years was highest in those aged 55–64 years, with nearly two-thirds being vaccinated. Among those aged ≥ 65 years, vaccine uptake was highest in the 75–84 years age group.

In all but two age groups (i.e. 2–4 and ≥ 85 years), more females than males received the influenza vaccine. High levels of vaccine uptake were found among the least deprived children, people living in remote and rural areas of Scotland, people with chronic diseases, people with an emergency hospital admission in the past year (specifically for preschool-aged children and 11- to 17-year-olds), and people with a prior ARI GP consultation in the past year (*Table 3*). The least deprived at-risk 18- to 55-year-olds were less likely to receive the vaccine. For all those people aged ≥ 65 years and eligible to receive TIV, levels of uptake were similar to levels among children, with higher levels of uptake among the least deprived groups, those people living in rural and remote areas, those people with comorbidities and a prior ARI GP consultation. Those people with an emergency hospitalisation in the last year were less likely to receive the vaccine.

Laboratory-confirmed influenza

Live attenuated influenza vaccine effectiveness

A statistically significant adjusted vaccine effectiveness among children (aged 2–11 years) for preventing RT-PCR laboratory-confirmed influenza was found in 2015/16 [for all influenza, influenza A, influenza B and the significant dominant influenza A(H1N1) subtypes]. This was not, however, evident in 2014/15 (*Table 4*). Vaccine effectiveness was higher for influenza B than for influenza A subtypes. There were insufficient numbers of children receiving a second dose of LAIV to include in the statistical model.

TABLE 2 Vaccine uptake (%) by age group

	Age group (years)							
Season	2–4[a]	5–11[a]	12–17[b]	18–54[b]	55–64[b]	65–74	75–84	≥ 85
2010/11	–	–	21.74	29.97	62.78	60.40	66.20	62.62
2011/12	–	–	21.64	30.29	63.19	60.65	66.93	63.65
2012/13	–	–	22.32	30.69	63.48	61.40	67.74	64.90
2013/14	32.20[c]	–	23.55	30.62	63.53	61.87	68.54	65.98
2014/15	39.33	58.76	24.94	29.52	61.70	61.16	67.95	65.25
2015/16	40.12	59.61	23.84	28.15	59.90	59.26	67.06	65.33

a LAIV percentage uptake.
b Percentage uptake for age group with at-risk morbidity.
c Only 2- to 3-year-olds were targeted for vaccination.

TABLE 3 Adjusted ORs of differences in vaccine uptake by patient characteristics by age group (2010–16)

	Age group (years), OR (95% CI)							
Variable	2–4	5–11	11–17[a]	18–54[a]	55–64[a]	65–74	75–84	≥ 85
Males (vs. females)	1.01 (0.98 to 1.03)	0.96 (0.95 to 0.97)	0.90 (0.86 to 0.95)	0.59 (0.58 to 0.59)	0.85 (0.83 to 0.87)	0.87 (0.86 to 0.88)	0.95 (0.94 to 0.97)	1.03 (1.00 to 1.06)
SIMD quintile								
2 (vs. 1)	1.10 (1.06 to 1.14)	1.07 (1.05 to 1.09)	1.10 (1.02 to 1.19)	0.96 (0.94 to 0.98)	1.01 (0.98 to 1.05)	0.95 (0.93 to 0.97)	0.96 (0.93 to 0.98)	0.97 (0.93 to 1.02)
3 (vs. 1)	1.25 (1.21 to 1.30)	1.17 (1.14 to 1.19)	1.02 (0.94 to 1.10)	0.92 (0.90 to 0.94)	1.01 (0.98 to 1.05)	1.00 (0.98 to 1.02)	0.96 (0.93 to 0.99)	0.92 (0.88 to 0.97)
4 (vs. 1)	1.42 (1.37 to 1.47)	1.23 (1.21 to 1.26)	1.22 (1.13 to 1.32)	0.91 (0.89 to 0.93)	1.00 (0.97 to 1.04)	1.03 (1.01 to 1.06)	1.08 (1.04 to 1.11)	1.02 (0.98 to 1.07)
5 (vs. 1)[b]	1.76 (1.70 to 1.82)	1.46 (1.43 to 1.49)	1.36 (1.26 to 1.47)	0.86 (0.84 to 0.88)	1.00 (0.96 to 1.03)	1.13 (1.11 to 1.16)	1.19 (1.16 to 1.23)	1.22 (1.17 to 1.27)
UR8FOLD								
UR8FOLD 2 (vs. 1)[c]	1.01 (0.99 to 1.04)	1.24 (1.22 to 1.26)	0.79 (0.75 to 0.84)	0.84 (0.82 to 0.85)	0.84 (0.81 to 0.87)	1.10 (1.09 to 1.12)	1.00 (0.98 to 1.02)	1.02 (0.99 to 1.05)
factor(UR8FOLD)3 (vs. 1)	1.03 (0.98 to 1.07)	1.32 (1.29 to 1.36)	0.82 (0.75 to 0.89)	0.90 (0.88 to 0.93)	0.88 (0.85 to 0.92)	1.07 (1.05 to 1.10)	0.94 (0.91 to 0.97)	0.79 (0.76 to 0.83)
factor(UR8FOLD)4 (vs. 1)	0.89 (0.83 to 0.95)	1.22 (1.17 to 1.27)	0.92 (0.79 to 1.06)	0.74 (0.70 to 0.78)	0.59 (0.55 to 0.63)	0.86 (0.83 to 0.89)	0.92 (0.88 to 0.96)	0.89 (0.83 to 0.95)
factor(UR8FOLD)5 (vs. 1)	1.09 (0.99 to 1.20)	1.64 (1.55 to 1.75)	1.12 (0.92 to 1.35)	0.98 (0.92 to 1.05)	1.00 (0.91 to 1.10)	0.67 (0.64 to 0.70)	0.68 (0.64 to 0.72)	0.72 (0.66 to 0.79)
factor(UR8FOLD)6 (vs. 1)	1.15 (1.10 to 1.20)	1.27 (1.24 to 1.30)	0.93 (0.85 to 1.01)	0.90 (0.87 to 0.92)	0.84 (0.81 to 0.87)	1.19 (1.17 to 1.22)	1.30 (1.26 to 1.34)	1.50 (1.42 to 1.58)
factor(UR8FOLD)7 (vs. 1)	1.18 (1.10 to 1.28)	1.26 (1.20 to 1.32)	1.24 (1.08 to 1.42)	0.99 (0.94 to 1.04)	0.78 (0.73 to 0.83)	1.10 (1.07 to 1.14)	1.17 (1.11 to 1.23)	1.48 (1.36 to 1.61)
factor(UR8FOLD)8 (vs. 1)	1.54 (1.43 to 1.65)	1.74 (1.66 to 1.81)	1.17 (1.03 to 1.33)	1.17 (1.12 to 1.23)	1.05 (0.99 to 1.12)	1.34 (1.30 to 1.38)	1.27 (1.21 to 1.33)	1.26 (1.18 to 1.36)

Variable	Age group (years), OR (95% CI)							
	2–4	5–11	11–17[a]	18–54[a]	55–64[a]	65–74	75–84	≥ 85
Asthma vs. no asthma	1.94 (1.76 to 2.15)	1.69 (1.64 to 1.74)	1.92 (1.65 to 2.23)	1.35 (1.31 to 1.39)	1.33 (1.29 to 1.37)	2.70 (2.63 to 2.77)	2.73 (2.63 to 2.84)	2.33 (2.19 to 2.47)
Chronic heart disease vs. no chronic heart disease	1.68 (1.49 to 1.90)	1.70 (1.58 to 1.84)	2.48 (2.13 to 2.89)	2.64 (2.55 to 2.73)	2.31 (2.24 to 2.39)	2.99 (2.92 to 3.06)	3.14 (3.06 to 3.22)	2.77 (2.68 to 2.87)
Chronic liver disease vs. no chronic liver disease	2.45 (0.53 to 11.24)	1.74 (0.97 to 3.12)	9.35 (4.98 to 17.54)	1.78 (1.69 to 1.88)	1.48 (1.38 to 1.58)	1.90 (1.75 to 2.06)	2.08 (1.84 to 2.35)	1.30 (1.03 to 1.64)
Chronic neurological disease vs. no chronic neurological disease	2.03 (1.29 to 3.20)	1.84 (1.43 to 2.36)	2.19 (1.66 to 2.89)	2.08 (1.99 to 2.18)	1.57 (1.51 to 1.64)	2.09 (2.03 to 2.15)	2.24 (2.17 to 2.31)	2.14 (2.05 to 2.22)
COPD vs. no COPD	1.02 (0.06 to 16.41)	0.70 (0.33 to 1.46)	0.93 (0.80 to 1.10)	0.78 (0.76 to 0.81)	0.79 (0.76 to 0.82)	1.18 (1.13 to 1.24)	1.10 (1.04 to 1.15)	0.95 (0.87 to 1.03)
Diabetes mellitus vs. no diabetes mellitus	2.73 (1.64 to 4.55)	2.53 (2.13 to 2.99)	0.58 (0.23 to 1.43)	2.36 (2.23 to 2.49)	2.02 (1.93 to 2.12)	3.14 (3.06 to 3.21)	2.85 (2.77 to 2.94)	2.24 (2.13 to 2.35)
Immunosuppression vs. no immunosuppression	1.54 (0.45 to 5.25)	1.40 (0.99 to 1.98)	8.71 (7.33 to 10.35)	5.06 (4.90 to 5.22)	3.00 (2.91 to 3.10)	2.96 (2.71 to 3.25)	2.67 (2.39 to 2.97)	2.02 (1.73 to 2.37)
Total number of emergency hospitalisations per year[d]	1.10 (1.06 to 1.14)	1.02 (0.98 to 1.06)	3.75 (2.67 to 5.27)	2.57 (2.42 to 2.74)	2.01 (1.84 to 2.19)	0.81 (0.79 to 0.82)	0.73 (0.72 to 0.74)	0.75 (0.74 to 0.77)
Total number of ARI GP consultations per year[d]	1.16 (1.13 to 1.19)	1.10 (1.07 to 1.12)	1.24 (1.15 to 1.35)	1.11 (1.09 to 1.13)	0.98 (0.95 to 1.00)	1.37 (1.33 to 1.40)	1.36 (1.31 to 1.41)	1.32 (1.25 to 1.39)

COPD, chronic obstructive pulmonary disease; UR8FOLD, Urban Rural Score.
a At-risk group.
b 5 = least deprived.
c 1 = large urban; 8 = remote rural.
d More than one vs. zero events.

TABLE 4 Vaccine effectiveness for laboratory-confirmed influenza for LAIV in 2- to 11-year-olds

	Laboratory-confirmed influenza					Vaccine effectiveness (95% CI)	
	Influenza-positive cases		Influenza-negative controls				
Influenza type and subtype	Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)	Total positive (%)	Unadjusted[a]	Adjusted[b]
Season: 2014/15							
Influenza A[c]	44/131	33.59	342/1272	26.89	9.34	11.09 (–33.87 to 40.95)	11.36 (–35.31 to 41.93)
A(H1N1)	3/4	75.00	383/1399	27.38	0.29	–474.59 (–5469.42 to 40.72)	–468.38 (–5949.37 to 46.60)
A(H3)	33/109	30.28	353/1294	27.28	7.77	27.04 (–14.77 to 53.62)	30.67 (–10.95 to 56.68)
Influenza B	3/18	16.67	383/1385	27.65	1.28	62.50 (–31.42 to 89.30)	69.56 (–9.04 to 91.50)
Influenza positive[d]	47/149	31.54	339/1254	27.03	10.62	18.72 (–19.91 to 44.91)	20.54 (–18.53 to 46.73)
Season: 2015/16							
Influenza A[c]	42/176	23.86	410/1513	27.10	10.42	51.62 (28.95 to 67.06)	46.38 (19.77 to 64.16)
A(H1N1)	36/143	25.17	416/1546	26.91	8.47	46.27 (18.90 to 64.40)	40.39 (8.21 to 61.29)
A(H3)	1/5	20.00	451/1684	26.78	0.30	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
Influenza B	5/43	11.63	447/1646	27.16	2.55	82.86 (50.51 to 94.07)	88.27 (63.86 to 96.19)
Influenza positive[d]	46/217	21.20	406/1472	27.58	12.85	57.71 (39.45 to 70.46)	58.09 (39.08 to 71.17)

–inf, infinity.
a Adjusted for time (days) only.
b Adjusted for time (days), age, clinical risk groups and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.

Trivalent influenza vaccine effectiveness

Among at-risk 18- to 64-year-olds, a significant TIV effectiveness was found for four of the six seasons (*Table 5*). For the two seasons with no significant vaccine effectiveness, low levels of circulating influenza virus were present (2011/12, 5%; 2013/14, 9%). Unlike the pattern in children, there was an inconsistent observation of vaccine effectiveness being greater against B subtypes of influenza than against A subtypes of influenza. Among those people aged ≥ 65 years, significant vaccine effectiveness of 57% was found for the 2013/14 season (*Table 6*); however, no other season had significant vaccine effectiveness. No obvious pattern of vaccine effectiveness by influenza subtype was evident between the seasons.

At-risk comorbidity vaccine effectiveness

A pooled analysis over six seasons found a significant positive vaccine effectiveness for preventing RT-PCR laboratory-confirmed influenza for those aged people ≥ 65 years with asthma (*Table 7*). Significant positive vaccine effectiveness was found for preventing laboratory-confirmed influenza A among those people aged ≥ 65 years with chronic heart disease. Generally, vaccine effectiveness was non-statistically higher against influenza B than against influenza A.

An analysis of age groups found significant vaccine effectiveness for (1) 18- to 54-year-olds with asthma, impaired immune function and a body mass index (BMI) of > 25 kg/m^2 (*Table 8*); (2) 55- to 64-year-olds with asthma (*Table 9*); (3) 65- to 74-year-olds with asthma and chronic kidney disease (overall and for influenza A) (*Table 10*); and (4) 75- to 84-year-olds with chronic respiratory disease [against influenza A(H3N2)] and asthma (against influenza B) (*Table 11*). Among the oldest age group (i.e. those people aged ≥ 85 years), significant vaccine effectiveness was found for those with chronic respiratory disease (overall and for influenza A and B), chronic heart disease (overall), asthma [overall, for influenza A and B, and for influenza A (H3N2)], diabetes mellitus (overall and for influenza A) and impaired immune function (overall) (*Table 12*).

Swabbing setting

No significant difference was found in vaccine effectiveness between laboratory-confirmed influenza tests from Sentinel GPs, non-Sentinel GPs and hospital care sources (*Table 13*). No interaction was found between the source of the swab and the outcome.

Negative controls

The study explored the use of laboratory-confirmed infections, tested using multiplex RT-PCR at the same time as the influenza RT-PCR, and found no significant vaccine effectiveness for non-influenza viruses (*Table 14*).

Clinical outcomes

After adjustment for confounding, including age in the model, significant negative vaccine effectiveness was found for GP outcomes, ARI and ILI for people aged ≥ 65 years (*Table 15*). Significant positive vaccine effectiveness was found for emergency hospitalisation or death from influenza and pneumonia (see *Table 15*). Rates and relative risks can be found in *Table 16*.

In the sensitivity analysis, and according to Simonsen *et al.*'s framework,[40] vaccine effectiveness during the pre- and post-influenza season was similar to that during peak influenza season (*Table 17*). Little variation was found between the seasons with different poorly or well-matched vaccines, severity, or by specificity of outcome (all-cause mortality had higher vaccine effectiveness than hospitalisation for influenza and pneumonia).[37]

Instrumental variable analysis

Vaccine uptake did vary by the proposed instrumental variable community CHP areas (*Table 18*). However, the correlation with individual vaccine uptake and our outcome was low and, therefore, this is considered a weak instrument. Therefore, it was not possible to use this method to estimate vaccine effectiveness accounting for unmeasured confounding.

TABLE 5 Vaccine effectiveness for laboratory-confirmed influenza for TIV in 18- to 64-year-olds

Dominant circulating strain(s)	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Season: 2010–11								
A/California/07/ 2009 (H1N1) pdm2009 B/Brisbane/60/ 2008	Influenza A[c]	39/118	33.05	156/380	41.05	23.69	46.03 (7.66 to 68.45)	45.34 (1.37 to 69.71)
	A(H1N1)	33/104	31.73	162/394	41.12	20.88	51.25 (14.27 to 72.28)	49.01 (5.67 to 72.44)
	A(H3)	0/0	NA	195/498	39.16	0.00	–1.62E^{-12} (–inf to 100.00)	0.00 (–inf to 100.00)
	Influenza B	6/26	23.08	189/472	40.04	5.22	73.38 (29.90 to 89.89)	71.17 (22.61 to 89.26)
	Influenza positive[d]	45/144	31.25	150/354	42.37	28.92	54.74 (26.91 to 71.98)	53.04 (21.41 to 71.94)
Season: 2011–12								
A/Victoria/208/ 2009 (H3N2)[a]	Influenza A[c]	12/22	54.55	131/379	34.56	5.49	–34.00 (–236.15 to 46.58)	–65.86 (–333.81 to 36.59)
	A(H1N1)	0/0	NA	143/401	35.66	0.00	–4.66E^{-13} (–inf to 100.00)	0.00 (–inf to 100.00)
	A(H3)	7/12	58.33	136/389	34.96	2.99	–47.99 (–401.76 to 56.35)	–103.89 (–645.92 to 44.27)
	Influenza B	0/0	NA	143/401	35.66	0.00	–2.52E^{-11} (–inf to 100.00)	0.00 (–inf to 100.00)
	Influenza positive[d]	12/22	54.55	131/379	34.56	5.49	–34.00 (–236.15 to 46.58)	–65.86 (–333.81 to 36.59)

Dominant circulating strain(s)	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Season: 2012–13								
B/Wisconsin/1/ 2010	Influenza A[c]	32/91	35.16	238/562	42.35	13.94	46.14 (12.98 to 66.66)	45.82 (10.59 to 67.16)
	A(H1N1)	1/15	6.67	269/638	42.16	2.30	92.18 (39.64 to 98.99)	89.53 (17.41 to 98.67)
	A(H3)	21/49	42.86	249/604	41.23	7.50	15.71 (–54.02 to 53.87)	22.60 (–46.92 to 59.23)
	Influenza B	16/43	37.21	254/610	41.64	6.58	42.47 (–10.78 to 70.12)	33.19 (–31.48 to 66.05)
	Influenza positive[d]	48/134	35.82	222/519	42.77	20.52	46.43 (19.06 to 64.55)	43.50 (13.16 to 63.24)
Season: 2013–14								
A/California/07/ 2009 (H1N1) pdm09	Influenza A[c]	25/55	45.45	262/608	43.09	8.30	31.29 (–24.55 to 62.10)	25.41 (–42.75 to 61.02)
	A(H1N1)	18/39	46.15	269/624	43.11	5.88	27.25 (–43.77 to 63.19)	37.50 (–27.22 to 69.29)
	A(H3)	2/7	28.57	285/656	43.45	1.06	68.90 (–64.61 to 94.12)	46.91 (–205.10 to 90.76)
	Influenza B	1/2	50.00	286/661	43.27	0.30	5.11 (–1482.68 to 94.31)	66.91 (–641.63 to 98.52)
	Influenza positive[d]	26/57	45.61	261/606	43.07	8.60	29.88 (–25.65 to 60.87)	31.07 (–26.85 to 62.54)

continued

TABLE 5 Vaccine effectiveness for laboratory-confirmed influenza for TIV in 18- to 64-year-olds (*continued*)

Dominant circulating strain(s)	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Season: 2014–15								
A/Texas/50/2012 (H3N2)[a]	Influenza A[c]	82/180	45.56	407/887	45.89	16.87	27.06 (–3.77 to 48.73)	31.47 (1.31 to 52.42)
	A(H1N1)	5/9	55.56	484/1058	45.75	0.84	18.53 (–232.68 to 80.05)	23.21 (–219.16 to 81.53)
B/Yamagata/ 16/88	A(H3)	62/140	44.29	427/927	46.06	13.12	28.57 (–5.27 to 51.54)	29.84 (–4.80 to 53.03)
	Influenza B	14/39	35.90	475/1028	46.21	3.66	62.08 (22.19 to 81.52)	64.95 (26.82 to 83.21)
	Influenza positive[d]	95/217	43.78	394/850	46.35	20.34	33.75 (8.91 to 51.82)	38.75 (14.88 to 55.92)
Season: 2015–16								
A/California/07/ 2009 (H1N1) pdm09	Influenza A[c]	55/149	36.91	434/1101	39.42	11.92	39.11 (11.26 to 58.21)	42.27 (14.87 to 60.84)
	A(H1N1)	44/111	39.64	445/1139	39.07	8.88	30.00 (–6.47 to 53.97)	32.85 (–3.26 to 56.33)
B/Victoria/2/87	A(H3)	2/4	50.00	487/1246	39.09	0.32	–227.57 (–12,600.90 to 91.55)	–195,334.91 (–3.78E^{+26} to 100.00)
	Influenza B	16/47	34.04	473/1203	39.32	3.76	54.53 (11.05 to 76.76)	41.12 (–19.54 to 70.99)
	Influenza positive[d]	69/193	35.75	420/1057	39.74	15.44	41.51 (18.16 to 58.20)	40.88 (16.43 to 58.17)

–inf, infinity; NA, not applicable.
a Adjusted for time (days) only.
b Adjusted for time (days), age and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.

TABLE 6 Vaccine effectiveness for laboratory-confirmed influenza for TIV in people aged ≥ 65 years

Dominant circulating strain(s)	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Season: 2010–11								
A/California/07/ 2009 (H1N1) pdm2009 B/Brisbane/60/ 2008	Influenza A[c]	25/53	47.17	234/458	51.09	10.37	31.84 (–24.33 to 62.63)	42.76 (–13.13 to 71.03)
	A(H1N1)	19/39	48.72	240/472	50.85	7.63	28.99 (–43.07 to 64.75)	28.18 (–53.73 to 66.45)
	A(H3)	0/0	NA	259/511	50.68	0.00	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	Influenza B	14/28	50.00	245/483	50.72	5.48	41.79 (–33.29 to 74.58)	35.01 (–64.89 to 74.46)
	Influenza positive[d]	37/78	47.44	222/433	51.27	15.26	36.20 (–5.77 to 61.52)	43.38 (–0.15 to 67.99)
Season: 2011–12								
A/Victoria/208/ 2009 (H3N2)[a]	Influenza A[c]	15/23	65.22	280/475	58.95	4.62	–3.28 (–157.62 to 58.60)	–6.80 (–187.75 to 60.89)
	A(H1N1)	0/0	NA	295/498	59.24	0.00	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	A(H3)	8/12	80.00	287/488	58.81	2.01	–104.95 (–892.87 to 57.70)	–87.17 (–867.16 to 63.78)
	Influenza B	0/2	0.00	295/496	59.48	0.40	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza positive[d]	15/24	62.50	280/474	59.07	4.82	9.08 (–120.05 to 62.44)	6.50 (–136.90 to 63.10)

continued

TABLE 6 Vaccine effectiveness for laboratory-confirmed influenza for TIV in people aged ≥ 65 years (*continued*)

Dominant circulating strain(s)	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Season: 2012–13								
B/Wisconsin/1/ 2010	Influenza A[c]	78/134	58.21	450/818	55.01	0.48	–2.29 (–50.49 to 30.47)	13.95 (–31.48 to 43.68)
	A(H1N1)	8/8	37.50	525/944	55.61	5.25	60.32 (–69.43 to 90.71)	64.10 (–69.39 to 92.39)
	A(H3)	50/78	64.10	478/874	54.69	0.00	–38.27 (–126.17 to 15.47)	–23.86 (–111.01 to 27.30)
	Influenza B	29/53	54.72	499/899	55.51	2.02	14.98 (–51.13 to 52.17)	15.03 (–59.74 to 54.80)
	Influenza positive[d]	107/186	57.53	421/766	54.96	8.57	4.41 (–34.24 to 31.93)	15.67 (–21.76 to 41.60)
Season: 2013–14								
A/California/07/ 2009 (H1N1) pdm09	Influenza A[c]	31/53	58.49	618/1058	58.41	4.77	31.18 (–22.14 to 61.22)	55.47 (17.53 to 75.96)
	A(H1N1)	24/39	61.54	625/1072	58.30	3.51	16.92 (–61.47 to 57.25)	39.51 (–22.62 to 70.16)
	A(H3)	2/5	40.00	647/1106	58.50	0.45	69.14 (–89.40 to 94.97)	100.00 (–1187.54 to 100.00)
	Influenza B	0/1	0.00	649/1110	58.47	0.09	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza positive[d]	31/54	57.41	618/1057	58.47	4.86	33.06 (–18.01 to 62.03)	56.63 (20.26 to 76.42)

Dominant circulating strain(s)	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Season: 2014–15								
A/Texas/50/2012 (H3N2)[a]	Influenza A[c]	282/488	57.79	1127/2037	55.33	19.33	12.11 (–9.10 to 29.21)	13.58 (–8.92 to 31.43)
B/Yamagata/ 16/88	A(H1N1)	9/12	75.00	1400/2513	55.71	0.48	–124.89 (–754.55 to 40.82)	–145.32 (–1171.67 to 52.68)
	A(H3)	224/393	57.00	1185/2132	55.58	15.56	15.96 (–6.05 to 33.39)	15.84 (–8.03 to 34.43)
	Influenza B	54/84	64.29	1355/2441	55.51	3.33	–14.76 (–86.81 to 29.50)	–1.82 (–76.04 to 41.11)
	Influenza positive[d]	335/568	58.98	1074/1957	54.88	22.50	8.39 (–11.93 to 25.02)	11.90 (–9.24 to 28.96)
Season: 2015–16								
A/California/07/ 2009 (H1N1) pdm09	Influenza A[c]	113/183	61.75	1264/2350	53.79	7.22	–5.26 (–44.95 to 23.57)	7.61 (–30.39 to 34.53)
B/Victoria/2/87	A(H1N1)	81/133	60.90	1296/2400	54.00	5.25	1.47 (–42.04 to 31.66)	10.21 (–33.15 to 39.45)
	A(H3)	2/3	66.67	1375/2530	54.35	0.12	–179.37 (–4614.03 to 83.44)	–34.41 (–2046.34 to 91.58)
	Influenza B	47/82	57.32	1330/2451	54.26	3.24	11.48 (–40.96 to 44.42)	4.02 (–57.78 to 41.61)
	Influenza positive[d]	159/263	60.46	1218/2270	53.66	10.38	0.76 (–30.05 to 24.28)	7.31 (–23.73 to 30.57)

–inf, infinity; NA, not applicable.
a Adjusted for time (days) only.
b Adjusted for time (days), age and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.

TABLE 7 At-risk comorbidities: pooled vaccine effectiveness for laboratory-confirmed influenza in people aged ≥ 65 years (2010–16)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic respiratory disease	Influenza A[c]	178/287	62.02	1332/2209	60.30	11.50	13.60 (–13.84 to 13.21)	13.21 (–14.46 to 34.19)
	A(H1N1)	62/92	67.39	1448/2404	60.23	3.69	–0.92 (–61.95 to 37.11)	–2.93 (–66.33 to 32.29)
	A(H3)	79/132	59.85	1431/2364	60.53	5.29	12.09 (–31.45 to 41.21)	12.48 (–30.89 to 41.48)
	Influenza B	39/62	62.90	1471/2434	60.44	2.48	15.38 (–48.88 to 51.91)	19.04 (–43.25 to 54.24)
	Influenza positive[d]	217/347	62.54	1293/2149	60.17	13.90	15.06 (–9.15 to 33.90)	15.72 (–8.43 to 34.50)
Chronic heart disease	Influenza A[c]	193/256	75.39	1249/1688	73.99	13.17	31.95 (4.22 to 51.65)	33.12 (5.72 to 52.56)
	A(H1N1)	51/60	85.00	1391/1884	73.83	3.09	–33.65 (–182.87 to 6.86)	–31.91 (–181.45 to 38.18)
	A(H3)	94/128	73.44	1348/1816	74.23	6.58	36.47 (–1.44 to 60.21)	35.74 (–2.79 to 59.82)
	Influenza B	42/50	84.00	1400/1894	73.92	2.57	1.58 (–122.38 to 56.44)	8.34 (–110.18 to 60.03)
	Influenza positive[d]	232/303	76.57	1210/1641	73.74	15.59	28.71 (1.78 to 48.25)	30.88 (–4.45 to 49.94)
Asthma	Influenza A[c]	114/148	77.03	748/998	74.95	12.91	43.06 (6.27 to 65.41)	44.93 (8.73 to 66.77)
	A(H1N1)	40/49	81.63	822/1097	74.93	4.28	12.72 (–95.99 to 61.13)	12.70 (–100.41 to 61.97)
	A(H3)	54/65	83.08	808/1081	74.75	5.67	–14.47 (148.84 to 47.34)	–3.95 (–128.44 to 52.69)
	Influenza B	24/34	70.59	838/1112	75.36	3.06	65.33 (19.31 to 85.10)	66.34 (19.99 to 85.84)
	Influenza positive[d]	137/181	75.69	725/965	75.13	7.07	48.77 (20.91 to 66.81)	50.69 (23.26 to 68.31)

a Adjusted for time (days) only.
b Adjusted for time (days), age and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.

TABLE 8 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged 18–54 years in Scotland (2010–16) in various at-risk groups

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic respiratory disease	Influenza A[c]	27/74	36.49	182/496	36.69	12.98	20.12 (–45.75 to 56.22)	24.43 (–41.03 to 59.51)
	A(H1N1)	11/32	34.38	198/538	36.80	5.61	31.01 (–84.47 to 74.20)	26.50 (–87.95 to 71.25)
	A(H3)	9/26	34.62	200/544	36.76	4.56	30.75 (–86.64 to 74.30)	38.10 (–83.17 to 79.08)
	Influenza B	6/20	30.00	203/550	36.91	3.51	61.28 (–24.82 to 87.99)	62.37 (–23.32 to 88.52)
	Influenza positive[d]	33/94	35.11	176/476	36.97	16.49	27.59 (–22.60 to 57.24)	29.70 (–20.53 to 59.00)
Chronic heart disease	Influenza A[c]	12/29	41.38	86/204	42.16	12.45	24.83 (–104.11 to 72.31)	32.86 (–85.58 to 75.71)
	A(H1N1)	5/14	35.71	93/219	42.47	6.01	–158.96 (–4645.69 to 85.87)	90.67 (–13,107.43 to 99.99)
	A(H3)	5/10	50.00	93/223	41.70	4.29	18.20 (–1897.24 to 96.65)	100.00 (–7.08E^{+11} to 100.00)
	Influenza B	6/10	60.00	92/223	41.26	4.29	31.84 (–430.94 to 91.25)	100.00 (–inf to 100.00)
	Influenza positive[d]	16/37	43.24	82/196	41.84	15.88	4.15 (–116.09 to 57.49)	7.83 (–108.90 to 59.33)
Asthma	Influenza A[c]	72/280	25.71	546/1600	34.13	14.89	50.88 (32.30 to 64.36)	52.42 (33.50 to 65.95)
	A(H1N1)	33/141	23.40	585/1739	33.64	7.50	49.47 (19.92 to 68.12)	55.98 (28.33 to 72.97)
	A(H3)	22/83	26.51	596/1797	33.17	4.41	59.78 (29.76 to 76.97)	53.36 (17.59 to 73.61)
	Influenza B	21/82	25.61	597/1798	33.20	4.36	58.40 (28.08 to 75.93)	62.41 (33.79 to 78.66)
	Influenza positive[d]	92/361	25.48	526/1519	34.63	19.20	52.21 (36.38 to 64.10)	54.74 (38.97 to 66.43)

continued

TABLE 8 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged 18–54 years in Scotland (2010–16) in various at-risk groups (*continued*)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic liver disease	Influenza A[c]	5/15	33.33	53/145	36.55	9.38	32.90 (–140.51 to 81.28)	37.88 (–130.17 to 83.24)
	A(H1N1)	2/6	33.33	56/154	36.36	3.75	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	A(H3)	1/5	20.00	57/155	36.77	3.13	19.06 (–inf to 100.00)	0.00 (–inf to 100.00)
	Influenza B	3/5	60.00	55/155	35.48	3.13	0.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza positive[d]	8/20	40.00	50/140	35.71	12.50	22.92 (–130.59 to 74.23)	32.61 (–109.70 to 78.34)
Chronic neurological disease	Influenza A[c]	12/14	64.29	52/109	47.71	11.38	–267.18 (–12,633.70 to 89.41)	$-4.24E^{+5}$ (–inf to 100.00)
	A(H1N1)	4/9	44.44	57/114	50.00	7.32	79.30 (–52.98 to 97.20)	100.00 (–inf to 100.00)
	A(H3)	1/1	100.00	60/122	49.18	0.81	$-2.8E^{+11}$ (–inf to 100.00)	0.00 (–inf to 100.00)
	Influenza B	0/2	0.00	61/121	50.41	1.63	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza positive[d]	9/16	56.25	52/107	48.60	13.01	60.34 (–74.89 to 91.00)	59.10 (–182.08 to 94.07)
Diabetes mellitus	Influenza A[c]	29/56	51.79	206/379	54.35	12.87	27.04 (–34.28 to 60.36)	30.00 (–30.15 to 62.35)
	A(H1N1)	13/23	56.52	222/412	53.88	5.29	–3.30 (–171.77 to 60.73)	11.16 (–182.82 to 72.09)
	A(H3)	11/19	57.89	224/416	53.85	4.37	–45.50 (–420.43 to 59.32)	–48.82 (–447.01 to 59.51)
	Influenza B	9/17	52.94	226/418	54.07	3.91	79.64 (11.24 to 95.33)	80.48 (–9.48 to 96.52)
	Influenza positive[d]	38/73	52.05	197/362	54.42	16.78	33.74 (–13.99 to 61.49)	33.87 (–14.78 to 61.90)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Impaired immune function	Influenza A[c]	6/20	30.00	88/234	37.61	7.87	80.71 (–25.42 to 97.03)	100.00 (–2.4E^{+10} to 100.00)
	A(H1N1)	1/5	20.00	93/249	37.35	1.97	99.09 (–6.4E^{+8} to 100.00)	100.00 (–1.85E^{+13} to 100.00)
	A(H3)	4/10	40.00	90/244	36.89	3.94	70.38 (–81.40 to 95.16)	64.44 (–121.43 to 94.29)
	Influenza B	5/12	41.67	89/242	36.78	4.72	64.12 (92.08 to 4.72)	67.42 (–57.79 to 93.27)
	Influenza positive[d]	11/32	34.38	83/222	37.39	12.60	66.46 (13.45 to 87.00)	67.51 (15.08 to 87.57)
Chronic kidney disease	Influenza A[c]	10/26	38.46	80/157	50.96	14.21	98.42 (74.77 to 99.90)	100.00 (–262E^{+23} to 100.00)
	A(H1N1)	3/10	30.00	87/173	50.29	5.46	100.00 (–2.25E^{+25} to 100.00)	100.00 (–1.29E^{+30} to 100.00)
	A(H3)	6/12	50.00	84/171	49.12	6.56	49.55 (–239.03 to 92.49)	92.70 (–182.86 to 99.81)
	Influenza B	4/4	100.00	86/179	48.04	2.19	–1.26E^{+22} (–inf to 100.00)	–1.21E^{+30} (–inf to 100.00)
	Influenza positive[d]	14/30	46.67	76/153	49.67	16.39	52.28 (–30.13 to 82.50)	69.12 (–45.74 to 93.46)
[e]BMI > 25 kg/m^2	Influenza A[c]	6/45	15.56	75/267	28.09	14.42	70.94 (25.87 to 88.61)	78.52 (39.16 to 92.42)
	A(H1N1)	6/31	19.35	76/281	27.05	9.94	60.15 (–10.00 to 85.56)	64.10 (–12.07 to 88.50)
	A(H3)	1/1	100.00	81/311	26.05	0.32	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	Influenza B	3/14	21.43	79/298	26.51	4.49	65.65 (–63.58 to 92.79)	49.38 (–200.13 to 91.46)
	Influenza positive[d]	9/58	15.52	73/254	28.74	18.59	65.04 (23.95 to 83.93)	68.35 (24.52 to 86.72)

–inf, infinity.
a Adjusted for time (days) only.
b Adjusted for time (days), season, age and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.
e BMI is for 2015/16 season only.

TABLE 9 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged 55–64 years in Scotland (2010–16) in various at-risk groups

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic respiratory disease	Influenza A[c]	60/102	58.82	283/583	48.54	14.89	–7.33 (–73.60 to 33.65)	–12.43 (–83.74 to 31.20)
	A(H1N1)	26/44	59.09	317/641	49.45	6.42	–11.59 (–127.76 to 45.21)	–22.93 (–157.48 to 41.31)
	A(H3)	21/37	56.76	322/648	49.69	5.40	23.85 (–71.39 to 66.16)	–5.09 (–142.55 to 54.47)
	Influenza B	7/14	50.00	336/671	50.07	2.04	55.98 (–46.59 to 86.78)	60.06 (–35.65 to 88.24)
	Influenza positive[d]	67/116	57.76	276/569	48.51	16.93	1.56 (–54.40 to 37.24)	–1.72 (–60.85 to 35.67)
Chronic heart disease	Influenza A[c]	27/44	61.36	184/297	61.95	12.90	49.15 (–9.49 to 76.39)	49.09 (–9.66 to 76.37)
	A(H1N1)	12/21	57.14	199/320	62.19	6.16	58.83 (–19.25 to 85.79)	61.84 (–16.59 to 87.51)
	A(H3)	8/14	57.14	203/327	62.08	4.11	47.05 (–76.42 to 84.11)	47.66 (–77.55 to 84.57)
	Influenza B	5/7	71.43	206/334	61.68	2.05	7.37 (–573.80 to 87.27)	–2157.56 (–209,967.00 to 75.74)
	Influenza positive[d]	32/51	62.75	179/290	61.72	14.96	41.64 (–18.00 to 71.14)	39.89 (–21.35 to 70.23)
Asthma	Influenza A[c]	42/75	56.00	265/494	53.64	13.18	30.80 (–19.82 to 60.03)	35.62 (–13.78 to 63.57)
	A(H1N1)	17/32	53.13	290/537	54.00	5.62	35.26 (–63.07 to 74.29)	35.68 (–68.54 to 75.45)
	A(H3)	18/29	62.07	289/540	53.52	5.10	8.52 (–138.11 to 64.85)	16.28 (–130.89 to 69.64)
	Influenza B	12/15	13.33	305/554	55.05	2.64	92.95 (66.23 to 98.53)	94.77 (71.65 to 99.04)
	Influenza positive[d]	44/90	48.89	263/479	54.91	15.82	51.21 (19.24 to 70.52)	55.48 (24.93 to 73.60)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic liver disease	Influenza A[c]	5/12	41.67	32/60	53.33	16.67	82.66 (–140.51 to 81.28)	100.00 (–inf to 100.00)
	A(H1N1)	1/4	25.00	36/68	52.94	5.56	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	A(H3)	4/7	57.14	33/65	50.77	9.72	61.95 (–737.95 to 98.27)	100.00 (–inf to 100.00)
	Influenza B	0/2	0.00	37/70	52.86	2.78	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza positive[d]	5/13	38.46	32/59	54.24	18.06	88.74 (–81.98 to 99.30)	100.00 (–inf to 100.00)
Chronic neurological disease	Influenza A[c]	19/28	67.86	83/159	52.20	14.97	$-2.2E^{+17}$ ($-2.16E^{+17}$ to 99.78)	$-6.7E^{+6}$ ($-3.67E^{+17}$ to 100.00)
	A(H1N1)	8/10	80.00	94/177	53.11	5.35	$-8.3E^{+14}$ ($-1.10E^{+10}$ to 100.00)	$-2.53E^{+12}$ (–inf to 100.00)
	A(H3)	9/13	69.23	93/174	53.45	6.95	–1227.12 (–23,294.75 to 24.72)	$-1.43E^{+34}$ (–inf to 100.00)
	Influenza B	2/3	66.67	100/184	54.35	1.60	–285.94 (–15,731.02 to 90.59)	$-2.65E^{+5}$ ($-1.34E^{+29}$ to 100.00)
	Influenza positive[d]	21/31	67.74	81/156	51.92	16.58	–524.31 (–2945.94 to 27.96)	–1007.43 (–6944.49 to –74.09)
Diabetes mellitus	Influenza A[c]	39/59	66.10	187/306	61.11	16.16	32.65 (–45.22 to 68.77)	34.65 (–46.44 to 70.84)
	A(H1N1)	14/24	58.33	212/341	62.17	6.58	–24.77 (478.667 to 73.10)	26.51 (–179.83 to 80.70)
	A(H3)	16/23	69.57	210/342	61.40	6.30	0.04 (–233.25 to 70.02)	23.17 (–188.28 to 79.52)
	Influenza B	3/6	50.00	223/359	62.12	1.64	100.00 (–inf to 100.00)	55.39 (–397.51 to 96.00)
	Influenza positive[d]	42/64	65.63	184/301	61.13	17.53	32.92 (–31.24 to 65.72)	36.40 (–29.72 to 68.82)

continued

TABLE 9 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged 55–64 years in Scotland (2010–16) in various at-risk groups (*continued*)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Impaired immune function	Influenza A[c]	12/16	75.00	65/138	47.10	10.39	–106.35 (–807.45 to 53.08)	–97.56 (–860.25 to 59.36)
	A(H1N1)	3/4	75.00	74/150	49.33	2.60	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	A(H3)	7/8	87.50	70/146	47.95	5.19	$-3.67E^{+82}$ (–inf to 100.00)	$-2.25E^{+68}$ (–inf to 100.00)
	Influenza B	0/3	0.00	77/151	50.99	1.95	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza positive[d]	12/19	63.16	65/135	48.15	12.34	28.43 (–165.04 to 80.68)	27.79 (–193.54 to 82.24)
Chronic kidney disease	Influenza A[c]	20/29	68.97	110/158	69.62	15.51	32.90 (–79.79 to 74.96)	22.56 (–114.57 to 72.05)
	A(H1N1)	6/10	60.00	124/177	70.06	5.35	67.92 (–553.88 to 98.43)	$-4.5E^{+19}$ (–inf to 100.00)
	A(H3)	10/14	71.43	120/173	69.36	7.49	26.65 (–546.44 to 91.68)	–8.52 (–901.07 to 88.24)
	Influenza B	3/5	60.00	127/182	69.78	2.67	100.00 (–inf to 100.00)	$-1.6E^{+14}$ (–inf to 100.00)
	Influenza positive[d]	23/33	69.70	107/154	69.48	17.65	74.94 (–21.45 to 94.83)	67.38 (–77.57 to 94.01)
[e]BMI > 25 kg/m^2	Influenza A[c]	9/20	45.00	72/134	53.73	12.99	62.18 (–7.14 to 86.65)	61.62 (–27.75 to 88.47)
	A(H1N1)	6/13	46.15	75/141	53.19	8.44	56.94 (–55.13 to 88.05)	69.12 (–43.86 to 93.37)
	A(H3)	1/1	100.00	80/153	52.29	0.65	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	Influenza B	2/2	100.00	79/152	51.97	1.30	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	Influenza positive[d]	11/22	50.00	70/132	53.03	14.29	57.20 (–19.30 to 84.65)	57.81 (–34.78 to 86.79)

–inf, infinity.
a Adjusted for time (days) only.
b Adjusted for time (days), season, age and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.
e BMI is for 2015/16 season only.

TABLE 10 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged 65–74 years in Scotland (2010–16) in various at-risk groups

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic respiratory disease	Influenza A[c]	90/142	63.38	591/1024	57.71	12.18	5.15 (–41.73 to 36.53)	6.96 (–39.56 to 37.98)
	A(H1N1)	37/58	63.79	644/1108	58.12	4.97	6.54 (–67.71 to 47.92)	10.54 (–61.81 to 50.54)
	A(H3)	35/51	68.63	646/1115	57.94	4.37	–59.82 (–215.67 to 19.09)	–57.72 (–212.17 to 20.31)
	Influenza B	20/30	66.67	661/1136	58.19	2.57	5.29 (–123.24 to 59.82)	12.59 (–110.36 to 63.68)
	Influenza positive[d]	110/172	63.95	571/994	57.44	14.75	6.52 (–36.77 to 36.10)	9.21 (–33.29 to 38.16)
Chronic heart disease	Influenza A[c]	61/78	78.21	436/591	73.77	11.66	18.54 (–53.83 to 56.86)	22.75 (–46.68 to 59.32)
	A(H1N1)	22/29	75.86	475/640	74.22	4.33	18.15 (–119.09 to 69.42)	41.19 (–72.66 to 79.97)
	A(H3)	21/27	77.78	476/642	74.14	4.04	20.35 (–122.69 to 71.51)	21.11 (–121.12 to 71.86)
	Influenza B	15/19	78.95	482/650	74.15	2.84	22.97 (–159.73 to 77.16)	29.22 (–145.98 to 79.64)
	Influenza positive[d]	76/97	78.35	421/572	73.60	14.50	19.97 (–40.43 to 54.39)	23.50 (–34.88 to 56.62)
Asthma	Influenza A[c]	49/71	69.01	343/465	73.76	13.25	51.09 (4.24 to 75.02)	52.41 (6.50 to 75.78)
	A(H1N1)	22/30	73.33	370/506	73.12	5.60	49.37 (–33.86 to 80.85)	51.88 (–32.58 to 82.53)
	A(H3)	18/24	75.00	374/512	73.05	4.48	–3.42 (–225.38 to 67.13)	0.43 (–212.35 to 68.26)
	Influenza B	12/13	61.54	384/523	73.42	2.43	62.96 (–25.05 to 89.03)	58.66 (–41.25 to 87.90)
	Influenza positive[d]	57/84	67.86	335/452	74.12	15.67	52.24 (12.13 to 74.04)	52.82 (12.90 to 74.44)

continued

TABLE 10 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged 65–74 years in Scotland (2010–16) in various at-risk groups (*continued*)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic liver disease	Influenza A[c]	6/8	75.00	41/62	66.13	11.43	23.75 (–1005.13 to 94.74)	–130.96 (–6164.46 to 91.48)
	A(H1N1)	3/4	75.00	44/66	66.67	5.71	–34.53 (–10,492.47 to 98.29)	100.00 (–3.43E^{+53} to 100.00)
	A(H3)	2/2	100.00	45/68	66.18	2.86	–8.41E^{+27} (–inf to 100.00)	–7.33E^{+172} (–inf to 100.00)
	Influenza B	2/2	100.00	45/68	66.18	2.86	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza positive[d]	8/10	80.00	39/60	65.00	14.29	37.22 (–2021.30 to 98.14)	22.24 (–4917.79 to 98.80)
Chronic neurological disease	Influenza A[c]	34/44	77.27	201/298	67.45	12.87	–51.60 (–271.90 to 38.20)	–46.06 (–264.66 to 41.50)
	A(H1N1)	12/15	80.00	223/327	68.20	4.39	–66.92 (–619.06 to 61.25)	–51.30 (–579.46 to 66.31)
	A(H3)	16/19	84.21	219/323	67.80	5.56	–253.35 (–1593.54 to 26.27)	–669.38 (–7677.05 to 23.89)
	Influenza B	10/14	71.43	225/328	68.60	4.09	34.55 (–180.26 to 84.71)	45.60 (–152.01 to 88.26)
	Influenza positive[d]	44/58	75.86	191/284	67.25	16.96	–25.43 (–175.38 to 42.87)	–17.04 (–161.96 to 47.70)
Diabetes mellitus	Influenza A[c]	38/52	73.08	329/429	76.69	10.81	50.02 (–9.24 to 77.13)	49.22 (–11.31 to 76.84)
	A(H1N1)	13/19	68.42	354/462	76.62	3.95	58.44 (–30.95 to 86.81)	59.52 (–30.04 to 87.40)
	A(H3)	16/18	88.89	351/463	75.81	3.74	–37.95 (–624.27 to 73.72)	–43.05 (–651.03 to 72.75)
	Influenza B	14/17	82.35	353/464	76.08	3.53	–66.82 (–808.29 to 69.36)	–61.40 (–886.95 to 73.61)
	Influenza positive[d]	52/68	76.47	315/413	76.27	14.14	36.75 (–23.40 to 67.58)	34.06 (–29.41 to 6.40)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Impaired immune function	Influenza A[c]	6/8	75.00	135/183	73.77	4.19	67.77 (–221.12 to 96.77)	100.00 (–inf to 100.00)
	A(H1N1)	3/3	100.00	138/188	73.40	1.57	92.84 (–inf to 100.00)	$-1.14E^{+138}$ (–inf to 100.00)
	A(H3)	1/1	100.00	140/190	73.68	0.52	$-8E^{+11}$ (–inf to 100.00)	$-2.14E^{+19}$ (–inf to 100.00)
	Influenza B	8/10	80.00	133/181	73.48	5.24	43.45 (–856.17 to 96.66)	34.58 (–1089.97 to 96.40)
	Influenza positive[d]	14/18	77.78	127/173	73.41	9.42	59.57 (–136.58 to 93.09)	61.62 (–148.18 to 94.07)
Chronic kidney disease	Influenza A[c]	31/45	68.89	241/320	75.31	12.33	56.98 (5.23 to 80.47)	60.15 (11.32 to 82.09)
	A(H1N1)	11/18	61.11	261/347	75.22	4.93	67.19 (–14.61 to 90.61)	71.44 (–3.93 to 92.15)
	A(H3)	10/14	71.43	262/351	74.64	3.84	62.85 (–62.04 to 91.48)	71.24 (–37.04 to 93.96)
	Influenza B	10/14	71.43	262/351	74.64	3.84	40.63 (–163.49 to 86.62)	77.23 (–135.16 to 97.79)
	Influenza positive[d]	41/58	70.69	231/307	75.24	15.89	55.71 (10.27 to 78.14)	59.90 (17.23 to 80.57)
[e]BMI > 25 kg/m^2	Influenza A[c]	25/28	89.29	190/239	79.50	10.49	2.39 (–272.14 to 74.39)	–16.90 (–352.53 to 69.80)
	A(H1N1)	19/21	90.48	196/246	79.67	7.87	–17.06 (–465.56 to 75.77)	–25.32 (–526.88 to 74.95)
	A(H3)	1/1	100.00	214/266	80.45	0.37	$-3.2E^{+12}$ (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza B	9/10	90.00	206/257	80.16	3.75	19.89 (–616.34 to 91.04)	32.04 (–238.13 to 68.98)
	Influenza positive[d]	34/38	89.47	181/229	79.04	14.23	6.45 (–204.17 to 71.23)	–2.42 (–238.13 to 68.98)

–inf, infinity.
a Adjusted for time (days) only.
b Adjusted for time (days), season, age and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.
e BMI is for 2015/16 season only.

TABLE 11 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged 75–84 years in Scotland (2010–16) in various at-risk groups

		Laboratory-confirmed influenza					Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
Disease group	Influenza type and subtype	Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)	Total positive (%)	Unadjusted[a]	Adjusted[b]
Chronic respiratory disease	Influenza A[c]	65/111	58.56	522/855	61.05	11.49	23.20 (–19.47 to 50.63)	22.63 (–20.86 to 50.48)
	A(H1N1)	22/29	75.86	565/937	60.30	3.00	–88.16 (–391.61 to 27.98)	–91.64 (–413.21 to 28.44)
	A(H3)	29/59	49.15	558/907	61.52	6.11	53.55 (14.37 to 74.81)	52.02 (11.10 to 74.10)
	Influenza B	9/18	50.00	578/948	60.97	1.86	50.96 (–44.37 to 83.34)	47.97 (–56.81 to 82.74)
	Influenza positive[d]	74/127	58.27	513/839	61.14	13.15	30.83 (–4.20 to 54.09)	29.84 (–6.20 to 53.65)
Chronic heart disease	Influenza A[c]	94/116	81.03	502/693	72.44	14.34	–4.52 (–8186 to 39.93)	–6.93 (–87.95 to 39.17)
	A(H1N1)	21/22	95.45	575/787	73.06	2.72	–520.47 (–4722.90 to 20.18)	–855.25 (–10,783.76 to 16.16)
	A(H3)	50/63	79.37	546/746	73.19	7.79	17.73 (–17.85 to 62.37)	17.25 (–79.69 to 61.89)
	Influenza B	13/15	86.67	583/794	73.43	1.85	–13.32 (–453.61 to 76.80)	–17.24 (–547.17 to 78.76)
	Influenza positive[d]	105/129	81.40	491/680	72.21	15.95	–7.43 (–81.86 to 36.54)	–6.91 (–82.98 to 37.54)
Asthma	Influenza A[c]	47/54	87.04	289/392	73.72	12.11	–2.36 (–160.98 to 59.85)	5.13 (–144.10 to 63.13)
	A(H1N1)	16/17	94.12	320/429	74.59	3.81	–589.17 (–6684.50 to 29.99)	–462.54 (–5311.69 to 41.52)
	A(H3)	23/27	85.19	313/419	74.70	6.05	59.46 (–102.83 to 91.90)	57.84 (–123.12 to 92.03)
	Influenza B	12/17	70.59	324/429	75.52	3.81	82.90 (31.45 to 95.73)	85.67 (32.32 to 96.97)
	Influenza positive[d]	58/70	82.86	278/376	73.94	15.70	34.76 (–42.37 to 70.10)	41.21 (–29.81 to 73.37)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic liver disease	Influenza A[c]	1/3	33.33	21/33	63.64	8.33	–7.33E^{+172} (–inf to 100.00)	–7.33E^{+172} (–inf to 100.00)
	A(H1N1)	0/0	NA	22/36	61.11	0.00	–7.33E^{+172} (–inf to 100.00)	–7.33E^{+172} (–inf to 100.00)
	A(H3)	1/2	50.00	21/34	61.76	5.56	–7.33E^{+172} (–inf to 100.00)	–7.33E^{+172} (–inf to 100.00)
	Influenza B	0/0	NA	22/36	61.11	0.00	–7.33E^{+172} (–inf to 100.00)	–7.33E^{+172} (–inf to 100.00)
	Influenza positive[d]	1/3	33.33	21/33	63.64	8.33	–7.33E^{+172} (–inf to 100.00)	–7.33E^{+172} (–inf to 100.00)
Chronic neurological disease	Influenza A[c]	52/69	75.36	305/411	74.21	14.38	40.38 (–20.90 to 70.60)	41.42 (–20.88 to 1.61)
	A(H1N1)	6/9	66.67	351/471	74.52	1.88	13.08 (–396.56 to 84.78)	–16.11 (–640.71 to 81.80)
	A(H3)	36/44	81.82	321/436	73.62	9.17	24.42 (–96.62 to 70.95)	28.39 (–90.33 to 73.06)
	Influenza B	4/6	66.67	353/474	74.47	1.25	69.59 (–161.12 to 96.46)	80.46 (–108.59 to 98.17)
	Influenza positive[d]	55/74	74.32	302/406	74.38	15.42	43.71 (–9.06 to 70.95)	45.80 (–6.61 to 72.44)
Diabetes mellitus	Influenza A[c]	47/59	79.66	361/470	76.81	11.15	38.36 (–34.39 to 71.73)	41.72 (–33.00 to 74.46)
	A(H1N1)	7/10	70.00	401/519	77.26	1.89	64.10 (–73.55 to 92.57)	71.98 (–147.90 to 96.83)
	A(H3)	27/33	81.82	381/496	76.81	6.24	28.57 (–114.68 to 76.24)	20.23 (–155.69 to 75.11)
	Influenza B	14/15	93.33	394/514	76.65	2.84	–153.11 (2005.78 to 69.58)	–157.16 (–2141.99 to 70.50)
	Influenza positive[d]	61/74	82.43	347/455	76.26	13.99	24.64 (–55.97 to 63.59)	26.73 (–58.00 to 66.02)
Impaired immune function	Influenza A[c]	5/6	83.33	64/94	68.09	6.00	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	A(H1N1)	2/2	100.00	67/98	68.37	2.00	–7.7E^{+14} (–inf to 100.00)	–2.20E^{+57} (–inf to 100.00)
	A(H3)	2/2	100.00	67/98	68.37	2.00	–2.3E^{+18} (–inf to 100.00)	100.00 (–inf to 100.00)
	Influenza B	1/1	100.00	68/99	68.69	1.00	–3.84E^{+60} (–inf to 100.00)	–4.8E^{+15} (–inf to 100.00)
	Influenza positive[d]	6/7	85.71	63/93	67.74	7.00	56.01 (–686.74 to 97.54)	100.00 (–inf to 100.00)

continued

TABLE 11 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged 75–84 years in Scotland (2010–16) in various at-risk groups (*continued*)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic kidney disease	Influenza A[c]	65/79	82.28	418/559	74.78	12.38	–3.69 (–107.95 to 48.30)	–2.72 (–110.53 to 49.89)
	A(H1N1)	14/17	82.35	469/621	75.52	2.66	26.69 (–259.64 to 85.060)	32.97 (–272.50 to 97.94)
	A(H3)	33/39	84.62	450/599	75.13	6.11	–30.70 (–257.36 to 52.20)	–28.59 (–264.90 to 54.68)
	Influenza B	14/15	93.33	469/623	75.28	2.35	–133.50 (–1849.28 to 72.03)	–138.54 (–2232.41 to 75.60)
	Influenza positive[d]	78/93	83.87	405/545	74.31	14.58	–12.78 (–117.03 to 41.40)	–8.23 (–115.20 to 45.57)
[e]BMI > 25 kg/m^2	Influenza A[c]	15/18	83.33	153/192	79.69	8.57	49.07 (–106.34 to 87.43)	68.17 (–60.99 to 93.71)
	A(H1N1)	12/13	84.62	157/197	79.70	6.19	40.82 (–204.51 to 88.50)	67.98 (–110.77 to 95.14)
	A(H3)	0/0	NA	168/210	80.00	0.00	1.36E^{-11} (–inf to 100.00)	2.21E^{-12} (–inf to 100.00)
	Influenza B	4/5	80.00	164/205	80.00	2.38	5.86 (–921.74 to 91.33)	–1024.20 (–46,864.21 to 73.09)
	Influenza positive[d]	19/23	82.61	149/187	79.68	10.95	39.90 (–103.98 to 82.29)	57.17 (–58.87 to 88.45)

–inf, infinity; NA, not applicable.
a Adjusted for time (days) only.
b Adjusted for time (days), season, age and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.
e BMI is for 2015/16 season only.

TABLE 12 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged ≥ 85 years in Scotland (2010–16) in various at-risk groups

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness[a] (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic respiratory disease	Influenza A[c]	249/450	55.33	1708/3274	52.17	12.08	15.43 (–5.18 to 32.00)	15.42 (–5.55 to 32.23)
	A(H1N1)	96/170	56.47	1861/3554	52.36	4.56	10.27 (–26.39 to 36.30)	8.44 (–30.05 to 35.54)
	A(H3)	101/184	54.89	1856/3540	52.43	4.94	15.05 (–18.61 to 39.16)	15.25 (–18.75 to 39.52)
	Influenza B	47/92	51.09	1910/3632	52.59	2.47	37.90 (3.53 to 60.03)	36.34 (0.68 to 59.19)
	Influenza positive[d]	296/540	54.81	1661/3184	52.17	14.50	20.45 (2.88 to 34.84)	19.78 (1.77 to 34.49)
Chronic heart disease	Influenza A[c]	198/289	68.51	1318/2063	63.89	12.29	22.44 (–4.18 to 42.26)	30.75 (5.81 to 49.08)
	A(H1N1)	61/97	62.89	1455/2255	64.52	4.12	34.99 (–4.40 to 59.52)	35.94 (–5.35 to 61.05)
	A(H3)	85/119	71.43	1431/2233	64.08	5.06	12.11 (–38.70 to 44.30)	27.83 (–15.90 to 55.06)
	Influenza B	43/59	72.88	1473/2293	64.24	2.51	20.07 (–48.62 to 57.01)	13.63 (–65.01 to 54.79)
	Influenza positive[d]	237/344	68.90	1279/2008	63.70	14.63	20.26 (–4.54 to 39.17)	26.79 (2.76 to 44.88)
Asthma	Influenza A[c]	223/534	41.76	1669/3622	46.08	12.85	41.37 (28.06 to 52.21)	48.62 (35.56 to 59.03)
	A(H1N1)	89/232	38.36	1803/3924	45.95	5.58	41.73 (20.86 to 57.10)	48.42 (27.19 to 63.45)
	A(H3)	88/188	46.81	1804/3968	45.46	4.52	34.23 (8.81 to 52.57)	36.69 (9.68 to 55.63)
	Influenza B	53/167	31.74	1839/3989	46.10	4.02	66.51 (52.07 to 76.60)	65.46 (49.30 to 76.47)
	Influenza positive[d]	274/696	39.37	1618/3460	46.76	16.75	48.47 (38.18 to 57.04)	53.56 (43.30 to 61.96)

continued

TABLE 12 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged ≥ 85 years in Scotland (2010–16) in various at-risk groups (*continued*)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness[a] (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Chronic liver disease	Influenza A[c]	17/39	43.59	154/312	49.36	11.11	50.22 (–9.54 to 77.38)	54.37 (–6.38 to 80.43)
	A(H1N1)	6/14	42.86	165/337	48.96	3.99	62.62 (–49.99 to 90.68)	59.06 (–72.08 to 90.26)
	A(H3)	5/17	47.06	163/334	48.80	4.84	60.93 (–131.78 to 93.41)	54.38 (–158.14 to 91.94)
	Influenza B	5/9	55.56	166/342	48.54	2.56	–10.94 (–504.25 to 79.63)	–3.23 (–681.43 to 86.36)
	Influenza positive[d]	22/47	46.81	149/304	49.01	13.39	43.28 (–15.18 to 72.07)	48.89 (–7.70 to 75.74)
Chronic neurological disease	Influenza A[c]	120/165	72.73	688/1065	64.60	13.41	4.49 (–42.98 to 36.21)	7.23 (–40.00 to 38.52)
	A(H1N1)	31/45	68.89	777/1185	65.57	3.66	14.78 (–74.67 to 58.42)	9.53 (–88.14 to 56.50)
	A(H3)	64/80	80.00	744/1150	64.70	6.50	–46.06 (–172.98 to 21.84)	–31.40 (–152.54 to 31.63)
	Influenza B	18/28	64.29	790/1202	65.72	2.28	56.39 (–4.76 to 81.85)	54.69 (–12.49 to 81.75)
	Influenza positive[d]	137/192	71.35	671/1038	64.64	15.61	13.67 (–25.79 to 40.74)	15.42 (–24.37 to 42.47)
Diabetes mellitus	Influenza A[c]	156/232	67.24	1119/1643	68.11	12.37	35.42 (9.87 to 53.73)	34.82 (8.00 to 53.82)
	A(H1N1)	49/78	62.82	1226/1797	68.22	4.16	37.49 (–7.04 to 63.49)	34.04 (–15.49 to 62.33)
	A(H3)	71/96	73.96	1204/1779	67.68	5.12	2.54 (–67.55 to 43.31)	1.85 (–72.18 to 4.05)
	Influenza B	41/57	71.93	1234/1818	67.88	3.04	29.19 (–37.35 to 63.50)	23.64 (–52.19 to 61.69)
	Influenza positive[d]	197/287	68.64	1078/1588	67.88	15.31	35.56 (12.88 to 52.33)	33.61 (9.28 to 51.42)

Disease group	Influenza type and subtype	Laboratory-confirmed influenza				Total positive (%)	Vaccine effectiveness[a] (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
Impaired immune function	Influenza A[c]	35/57	61.40	392/734	53.41	7.21	52.67 (7.98 to 75.66)	49.52 (–4.19 to 75.54)
	A(H1N1)	10/15	66.67	417/776	53.74	1.90	54.69 (–106.62 to 90.06)	43.43 (–21.36 to 89.72)
	A(H3)	17/24	70.83	410/767	53.46	3.03	7.56 (–147.54 to 65.48)	–26.33 (–257.22 to 55.33)
	Influenza B	18/31	58.06	409/760	53.82	3.92	70.04 (25.45 to 87.96)	46.72 (–20.33 to 76.40)
	Influenza positive[d]	53/88	60.23	374/703	53.20	11.13	48.60 (14.52 to 69.09)	41.87 (2.56 to 65.33)
Chronic kidney disease (stage 3–5)	Influenza A[c]	134/188	71.28	903/1278	70.66	12.82	32.97 (1.01 to 54.62)	33.14 (–0.54 to 55.54)
	A(H1N1)	35/56	62.50	1002/1410	71.06	3.82	60.06 (23.62 to 79.11)	56.31 (14.17 to 77.76)
	A(H3)	64/85	75.29	973/1381	70.46	5.80	12.83 (–58.12 to 51.94)	3.43 (–82.66 to 48.94)
	Influenza B	33/40	82.50	1004/1426	70.41	2.73	–40.33 (–283.72 to 48.68)	–44.59 (–299.58 to 47.69)
	Influenza positive[d]	166/225	73.78	871/1241	70.19	15.35	27.94 (49.89 to 15.35)	27.50 (–6.01 to 50.41)
[e]BMI > 25 kg/m^2	Influenza A[c]	4/5	80.00	80/101	79.21	4.72	81.77 (–257.22 to 99.07)	100.00 (–inf to 100.00)
	A(H1N1)	3/4	75.00	81/102	79.41	3.77	84.24 (–141.32 to 98.97)	100.00 (–inf to 100.00)
	A(H3)	0/0	NA	84/106	79.25	0.00	1.07E^{-11} (–inf to 100.00)	–3.60E^{-12} (–inf to 100.00)
	Influenza B	2/2	100.00	82/104	78.85	1.89	–4.8E^{+16} (–inf to 100.00)	98.52 (–inf to 100.00)
	Influenza positive[d]	5/6	83.33	79/100	79.00	5.66	68.78 (–513.65 to 98.41)	100.00 (–2.31E^{+77} to 100.00)

–inf, infinity; NA, not applicable.
a Adjusted for time (days) only.
b Adjusted for time (days), season, age and swab location (i.e. hospital or GP).
c Influenza A subtyped + unsubtyped.
d Influenza A + B.
e BMI is for 2015/16 season only.

TABLE 13 Overall vaccine effectiveness for laboratory-confirmed influenza for various influenza types and subtypes in people aged ≥ 18 years in Scotland (2010–16), for swabs taken in hospitals vs. swabs taken in Sentinel and non-Sentinel GPs

		Laboratory-confirmed influenza					Vaccine effectiveness (95% CI)	
		Influenza-positive cases		Influenza-negative controls				
Swab location	Influenza type and subtype	Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)	Total positive (%)	Unadjusted[a]	Adjusted[b]
GP Sentinel	Influenza A[c]	71/399	17.79	647/3302	19.59	10.78	29.33 (5.47 to 47.16)	17.62 (–17.24 to 42.12)
	A(H1N1)	17/181	9.39	701/3520	19.91	4.89	71.96 (51.03 to 83.94)	61.13 (27.45 to 79.17)
	A(H3)	52/203	25.62	666/3498	19.04	5.49	–26.25 (–77.00 to 9.94)	–28.19 (–93.94 to 15.27)
	Influenza B	30/220	13.64	688/3481	19.76	5.94	54.39 (29.04 to 70.68)	31.13 (–16.05 to 59.13)
	Influenza positive[d]	98/601	16.31	620/3100	20.00	16.24	36.29 (18.57 to 50.16)	19.14 (–8.80 to 39.91)
GP non-Sentinel	Influenza A[c]	29/104	27.88	73/270	27.04	27.81	36.66 (–31.02 to 69.38)	70.59 (19.97 to 89.19)
	A(H1N1)	3/23	13.04	99/351	28.21	6.15	69.22 (–7.88 to 91.22)	74.75 (–14.91 to 94.45)
	A(H3)	3/5	60.00	99/369	26.83	1.34	–418.03 (–3560.82 to 26.70)	6.05 (–1302.25 to 93.70)
	Influenza B	11/41	26.83	91/333	27.33	10.96	74.67 (0.77 to 93.53)	77.86 (–12.78 to 95.65)
	Influenza positive[d]	37/140	26.43	65/234	27.78	37.43	43.28 (–7.17 to 69.99)	64.01 (16.87 to 84.42)
Hospital	Influenza A[c]	776/2247	34.53	5819/15,439	37.69	12.70	26.21 (18.38 to 33.28)	27.02 (18.13 to 34.94)
	A(H1N1)	259/995	26.03	6336/16,691	37.96	5.63	49.62 (41.54 to 56.58)	34.73 (22.83 to 44.80)
	A(H3)	349/773	45.15	6246/16,913	36.93	4.37	–14.31 (–32.59 to 1.46)	18.42 (3.31 to 31.18)
	Influenza B	174/551	31.58	6421/17,135	37.47	3.12	41.47 (29.17 to 51.63)	35.04 (19.05 to 47.88)
	Influenza positive[d]	948/2789	33.99	5647/14,897	37.91	15.77	29.90 (23.24 to 35.99)	29.51 (21.78 to 36.47)

a Adjusted for time (days) only.
b Adjusted for time (days), age and number of risk groups.
c Influenza A subtyped + unsubtyped.
d Influenza A + B.

TABLE 14 Influenza vaccine effectiveness against non-influenza viruses/infections, as confirmed by RT-PCR (2010–16)

Age group (years)	Virus/infection type	Laboratory-confirmed infections				Total positive (%)	Vaccine effectiveness (95% CI)	
		Virus-positive cases		Virus-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
18–54	Coronavirus	17/124	13.71	294/2624	11.20	4.51	–30.42 (–123.90 to 24.03)	–26.55 (–118.06 to 26.56)
	Mycoplasma pneumoniae	9/70	12.86	305/2699	11.30	2.53	–47.74 (–207.99 to 29.13)	–58.04 (–231.04 to 24.55)
	Parainfluenza type 1	3/25	12.00	310/2743	11.30	0.90	–57.56 (–450.79 to 54.93)	–54.60 (–441.17 to 55.84)
	Parainfluenza type 2	4/22	18.18	310/2747	11.29	0.79	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	Rhinovirus	40/337	11.87	274/2431	11.27	12.17	–25.91 (–82.33 to 13.05)	–33.88 (–94.46 to 7.84)
	Respiratory syncytial virus	9/101	8.91	305/2667	11.44	3.65	18.90 (–64.31 to 59.97)	23.60 (–55.35 to 62.43)
55–64	Coronavirus	13/37	35.14	142/641	22.15	5.46	–74.31 (–264.18 to 16.57)	–64.15 (–246.37 to 22.20)
	Mycoplasma pneumoniae	3/14	21.43	153/668	22.90	2.05	–44.85 (–467.39 to 63.02)	–22.00 (–409.71 to 70.80)
	Parainfluenza type 1	0/9	0.00	156/673	23.18	1.32	100.00 (–inf to 100.00)	100.00 (–inf to 100.00)
	Parainfluenza type 2	1/6	16.67	155/676	22.93	0.88	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	Rhinovirus	14/67	20.90	142/614	23.13	9.84	–35.57 (–165.50 to 30.78)	–39.63 (–175.51 to 29.23)
	Respiratory syncytial virus	6/38	15.79	150/644	23.29	5.57	34.32 (–66.52 to 74.09)	30.06 (–78.52 to 72.60)

continued

TABLE 14 Influenza vaccine effectiveness against non-influenza viruses/infections, as confirmed by RT-PCR (2010–16) (*continued*)

Age group (years)	Virus/infection type	Laboratory-confirmed infections				Total positive (%)	Vaccine effectiveness (95% CI)	
		Virus-positive cases		Virus-negative controls				
		Vaccinated/ total (*n*)	Vaccinated (%)	Vaccinated/ total (*n*)	Vaccinated (%)		Unadjusted[a]	Adjusted[b]
65–74	Coronavirus	25/38	65.79	367/661	55.52	5.44	8.57 (–97.00 to 57.57)	11.27 (–92.39 to 59.08)
	Mycoplasma pneumoniae	5/11	45.45	390/693	56.28	1.56	10.54 (–254.85 to 77.45)	13.31 (–250.11 to 78.53)
	Parainfluenza type 1	4/12	33.33	391/692	56.50	1.70	46.80 (–111.93 to 86.64)	49.03 (–106.45 to 87.42)
	Parainfluenza type 2	4/09	44.44	391/695	56.26	1.28	0.00 (–inf to 100.00)	0.00 (–inf to 100.00)
	Rhinovirus	43/83	51.81	353/622	56.75	11.77	–9.12 (–85.25 to 35.72)	–9.67 (–86.66 to 35.57)
	Respiratory syncytial virus	30/42	71.43	366/662	55.29	5.97	–82.47 (–283.43 to 13.17)	–81.98 (–282.79 to 13.48)

–inf, infinity.
a Adjusted for time (days) only.
b Adjusted for time (days), season and age.

TABLE 15 Clinical primary care and hospitalisation outcomes for people aged ≥ 65 years

Outcome	Season	Vaccine effectiveness (95% CI)
GP consultations		
ARI	2015/16	–47.64 (–49.61 to –45.69)
	2014/15	–59.28 (–61.47 to –57.12)
	2013/14	–55.40 (–57.64 to –53.19)
	2012/13	–53.34 (–55.51 to –51.21)
	2011/12	–59.69 (–61.99 to –57.42)
	2010/11	–46.72 (–49.05 to –44.43)
Influenza or pneumonia	2015/16	–33.66 (–39.61 to –27.97)
	2014/15	–34.90 (–40.49 to –29.54)
	2013/14	–64.02 (–72.41 to –56.05)
	2012/13	–28.70 (–34.41 to –23.22)
	2011/12	–58.01 (–65.39 to –50.95)
	2010/11	–46.43 (–52.98 to –40.16)
Emergency hospitalisations		
Influenza or pneumococcal disease	2015/16	17.28 (15.55 to 18.98)
	2014/15	23.40 (21.81 to 24.95)
	2013/14	22.41 (20.51 to 24.27)
	2012/13	27.56 (25.89 to 29.19)
	2011/12	20.58 (18.69 to 22.44)
	2010/11	21.19 (19.19 to 23.15)
Deaths	2015/16	31.82 (30.78 to 32.84)
	2014/15	38.57 (37.64 to 39.49)
	2013/14	34.57 (33.50 to 35.62)
	2012/13	33.93 (32.90 to 34.93)
	2011/12	34.19 (33.14 to 35.22)
	2010/11	39.78 (38.83 to 40.71)

TABLE 16 Non-specific clinical primary care and hospitalisation outcome rates and relative risk for people aged ≥ 65 years

Outcome	Season	Vaccination status	Rate per 1000 patient-seasons	Relative risk	95% CI
GP					
Influenza or pneumonia consultation	2015/16	Unvaccinated	5.20	1.00	NA
		Vaccinated	5.85	1.13	1.11 to 1.15
	2014/15	Unvaccinated	5.61	1.00	NA
		Vaccinated	5.99	1.07	1.05 to 1.09
	2013/14	Unvaccinated	4.12	1.00	NA
		Vaccinated	4.50	1.09	1.07 to 1.12
	2012/13	Unvaccinated	4.79	1.00	NA
		Vaccinated	4.98	1.04	1.02 to 1.06
	2011/12	Unvaccinated	4.48	1.00	NA
		Vaccinated	4.86	1.08	1.06 to 1.11
	2010/11	Unvaccinated	3.95	1.00	NA
		Vaccinated	4.38	1.11	1.08 to 1.13
ARI consultation	2015/16	Unvaccinated	10.92	1.00	NA
		Vaccinated	22.80	2.09	2.06 to 2.11
	2014/15	Unvaccinated	10.85	1.00	NA
		Vaccinated	23.85	2.20	2.17 to 2.22
	2013/14	Unvaccinated	10.57	1.00	NA
		Vaccinated	22.58	2.14	2.11 to 2.16
	2012/13	Unvaccinated	11.57	1.00	NA
		Vaccinated	22.98	1.99	1.96 to 2.01
	2011/12	Unvaccinated	10.73	1.00	NA
		Vaccinated	22.23	2.07	2.05 to 2.10
	2010/11	Unvaccinated	9.67	1.00	NA
		Vaccinated	16.91	1.75	1.73 to 1.77
Emergency hospitalisations					
Influenza or pneumococcal disease	2015/16	Unvaccinated	1.05	1.00	NA
		Vaccinated	1.82	1.73	1.66 to 1.79
	2014/15	Unvaccinated	1.27	1.00	NA
		Vaccinated	2.22	1.76	1.70 to 1.82
	2013/14	Unvaccinated	0.86	1.00	NA
		Vaccinated	1.70	1.98	1.90 to 2.07
	2012/13	Unvaccinated	1.12	1.00	NA
		Vaccinated	1.97	1.75	1.68 to 1.82
	2011/12	Unvaccinated	1.00	1.00	NA
		Vaccinated	2.15	2.15	2.06 to 2.23
	2010/11	Unvaccinated	1.19	1.00	NA
		Vaccinated	2.13	1.79	1.73 to 1.85

TABLE 16 Non-specific clinical primary care and hospitalisation outcome rates and relative risk for people aged ≥ 65 years (*continued*)

Outcome	Season	Vaccination status	Rate per 1000 patient-seasons	Relative risk	95% CI
Deaths	2015/16	Unvaccinated	11.02	1.00	NA
		Vaccinated	9.60	0.87	0.86 to 0.88
	2014/15	Unvaccinated	11.80	1.00	NA
		Vaccinated	9.78	0.83	0.82 to 0.84
	2013/14	Unvaccinated	10.60	1.00	NA
		Vaccinated	8.98	0.85	0.84 to 0.86
	2012/13	Unvaccinated	11.95	1.00	NA
		Vaccinated	10.11	0.85	0.83 to 0.86
	2011/12	Unvaccinated	11.59	1.00	NA
		Vaccinated	9.55	0.82	0.81 to 0.84
	2010/11	Unvaccinated	10.39	1.00	NA
		Vaccinated	9.71	0.93	0.92 to 0.95

NA, not applicable.

TABLE 17 Influenza and pneumonia emergency hospitalisation and vaccine effectiveness for those aged < 65 years in an at-risk group by season stage

Outcome	Season	Season stage	Start	End	Vaccine effectiveness (95% CI)
Emergency hospitalisations: influenza or pneumococcal disease	2010/11	Pre	1 September 2010	11 October 2010	27.77 (10.80 to 41.51)
	2010/11	Mid	12 December 2010	13 March 2011	22.40 (10.19 to 32.95)
	2010/11	Post	14 March 2011	30 June 2012	15.73 (2.83 to 26.92)
	2011/12	Pre	1 September 2011	19 February 2012	25.97 (16.43 to 34.43)
	2011/12	Mid	20 February 2012	6 May 2012	12.84 (–2.01 to 25.54)
	2011/12	Post	7 May 2012	30 June 2012	21.28 (4.39 to 35.19)
	2012/13	Pre	1 September 2012	9 December 2012	26.40 (9.87 to 39.89)
	2012/13	Mid	10 December 2012	21 April 2013	29.17 (20.97 to 36.53)
	2012/13	Post	22 April 2013	30 June 2013	4.43 (–14.04 to 19.91)
	2013/14	Pre	1 September 2013	2 February 2014	22.71 (11.71 to 32.34)
	2013/14	Mid	3 February 2014	13 April 2014	9.47 (–7.19 to 23.53)
	2013/14	Post	14 April 2014	30 June 2014	24.07 (11.02 to 35.20)
	2014/15	Pre	1 September 2014	14 December 2014	22.71 (7.92 to 35.12)
	2014/15	Mid	15 December 2014	19 April 2015	23.52 (15.48 to 30.80)
	2014/15	Post	20 April 2015	30 June 2015	18.01 (4.61 to 29.53)
	2015/16	Pre	1 September 2015	27 December 2015	11.24 (–3.12 to 23.60)
	2015/16	Mid	28 December 2015	15 May 2016	21.14 (12.88 to 28.61)
	2015/16	Post	16 May 2016	30 June 2016	18.05 (0.77 to 32.33)

TABLE 18 Vaccine uptake in Scotland (2010–16) for people aged ≥ 65 years in each CHP

	Vaccine uptake by season (%)					
CHP	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
S03000001	78.80	77.30	78.30	79.30	80.54	78.11
S03000002	78.35	79.58	80.89	75.28	75.78	76.16
S03000003	78.40	76.98	78.52	73.53	77.14	78.20
S03000004	64.46	67.46	63.64	63.41	62.95	61.53
S03000005	100.00	100.00	NA	NA	NA	NA
S03000006	70.40	61.30	64.94	78.54	77.77	74.89
S03000007	62.49	63.39	63.24	63.61	62.85	61.15
S03000008	55.23	54.74	55.71	56.24	54.75	53.22
S03000009	80.15	80.96	81.00	81.02	80.14	77.10
S03000010	73.25	74.65	74.94	75.78	74.53	73.68
S03000011	77.15	78.12	79.29	79.51	78.88	78.14
S03000013	0.00	0.00	0.00	0.00	50.00	66.67
S03000014	40.00	37.50	33.33	37.50	33.33	20.00
S03000015	76.85	78.67	80.80	79.19	79.54	78.05
S03000017	61.97	63.22	63.77	63.19	61.81	62.60
S03000018	75.04	76.07	81.05	77.22	75.97	74.48
S03000020	77.82	77.25	82.39	79.31	81.06	80.27
S03000023	74.68	76.09	76.91	80.08	79.39	75.83
S03000025	19.47	20.50	19.72	20.24	19.78	19.95
S03000029	65.85	66.77	66.50	73.10	72.63	67.24
S03000030	78.80	79.05	81.38	81.54	79.16	79.40
S03000031	46.85	47.47	47.66	47.25	46.30	44.74
S03000032	56.06	56.65	58.13	57.90	57.29	56.01
S03000035	49.20	50.03	51.11	51.34	50.82	49.99
S03000036	0.00	0.00	0.00	NA	NA	NA
S03000037	76.79	76.67	81.07	78.16	79.32	78.62
S03000038	76.76	76.04	78.10	78.51	77.98	75.19
S03000039	72.21	76.20	76.81	77.54	76.19	76.48
S03000040	73.69	72.60	72.84	75.05	73.79	73.85
S03000041	0.00	0.00	0.00	0.00	NA	100.00
S03000042	57.80	58.75	58.78	58.76	57.94	57.07
S03000043	61.27	61.94	63.53	64.43	63.36	61.82
S03000044	62.66	63.21	63.62	63.41	62.94	60.74

NA, not applicable.

Modelling an unmeasured confounder

Estimates from published data were used to model the effect of inadequately measured confounders on vaccine effectiveness in the cohorts for emergency hospitalisations due to pneumonia or influenza. The baseline vaccine effectiveness is that derived from pooling the estimates for the six seasons in *Table 12*. The pooled estimate, using a random-effects meta-analysis, is 22.9% (95% CI 19.8% to 25.8%).

It was found that a scenario of 15% prevalence for unaccounted frail individuals in the unvaccinated population, with frailty causing a fourfold increase in the risk of emergency hospitalisation and with a 5% presence of frailty among the vaccinated population, resulted in the vaccine no longer being effective (vaccine effectiveness 2.75, 95% CI –1.11 to 6.49).[9] A twofold increase in risk of hospitalisation would have relatively little impact, although it does reduce the magnitude of the vaccine effect estimate. By varying the prevalence of frailty and its risk on outcome, the change in vaccine effectiveness estimates for a number of scenarios (*Table 19*) were modelled.[27] The study also found that this model can be displayed effectively in graphical form (*Figures 3* and *4*). In *Figures 4* and *5*, the vaccine effectiveness is estimated given levels of the unmeasured confounder in the vaccinated population (*x*-axis) and unvaccinated population (each of the lines representing a different prevalence of the unmeasured confounder in the vaccinated population). At points where the prevalence of the unmeasured confounder is the same in the unvaccinated individuals and vaccinated individuals, then the baseline result is achieved, as there is no difference in the level of the unmeasured variable in the two groups.

Vaccine safety

The LAIV was found to be safe in children, with no adverse reactions found (*Figures 5* and *6*). The number of adverse events recorded for children was very small and the CIs are wide. In most cases, fewer adverse events were reported among children who were vaccinated than in those who were unvaccinated, suggesting that relatively healthy children are the ones who received the LAIV.

The TIV was found to be safe, with no association with adverse events (*Figures 7* and *8*). The exception to this finding was a statistically significant increase in allergic reaction (non-anaphylaxis) coded in the GP database; here, the TIV incidence RR (without the interaction term) was 1.33 (96% CI 1.13 to 1.56; $p < 0.001$). The Benjamini–Hochberg-adjusted *p*-value for this interaction test was 0.009 for GP consultations. This is the only adverse event for which there was a suggestion that the TIV was associated with a temporary increase in consultations following vaccination. In a majority of potential adverse events, those people who were vaccinated were at lower risk of GP consultation post vaccination than those people who were unvaccinated.

TABLE 19 Sensitivity analysis to quantify the effects of a hypothetical unmeasured confounder on the cohort analysis results

Increase in the risk of outcome on account of the confounder	Prevalence of confounder (%)		Emergency hospitalisation for pneumonia or influenza, adjusted vaccine effectiveness (95% CI)
	In unvaccinated population	In vaccinated population	
–	0	0	22.88 (19.81 to 25.84)
Doubled	5	0	19.03 (15.80 to 22.13)
Doubled	10	5	19.21 (15.99 to 22.31)
Doubled	215	5	15.54 (12.17 to 18.77)
Quadrupled	5	0	11.31 (7.78 to 14.71)
Quadrupled	10	5	12.82 (–9.35 to 16.16)
Quadrupled	15	5	2.75 (–1.11 to 6.49)

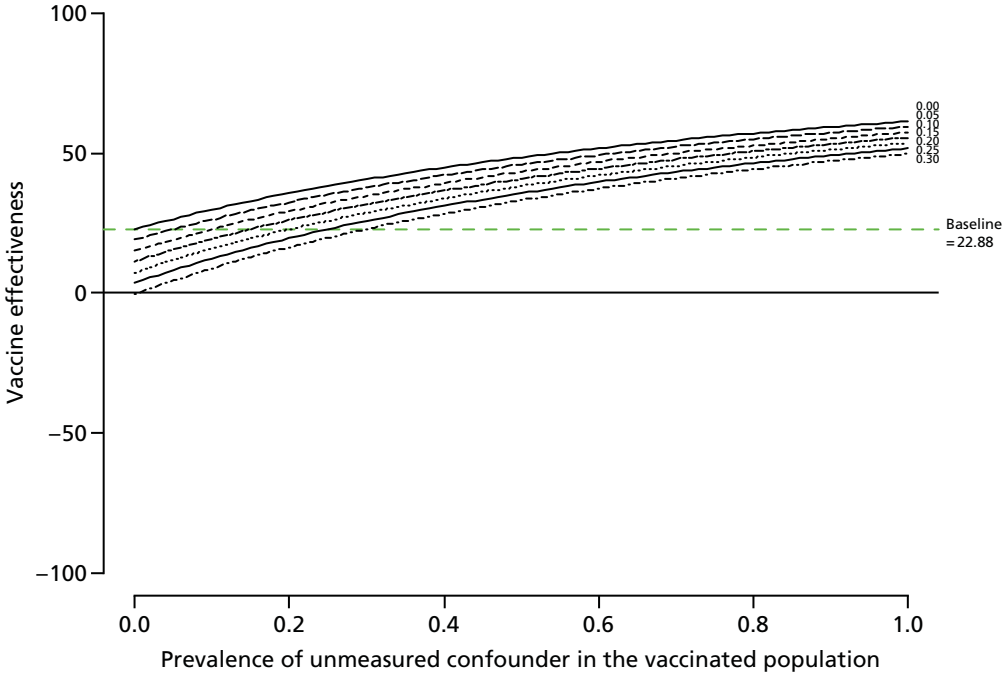


FIGURE 3 Unmeasured residual confounding and vaccine effectiveness (doubling of risk in emergency hospitalisations for influenza and pneumonia).

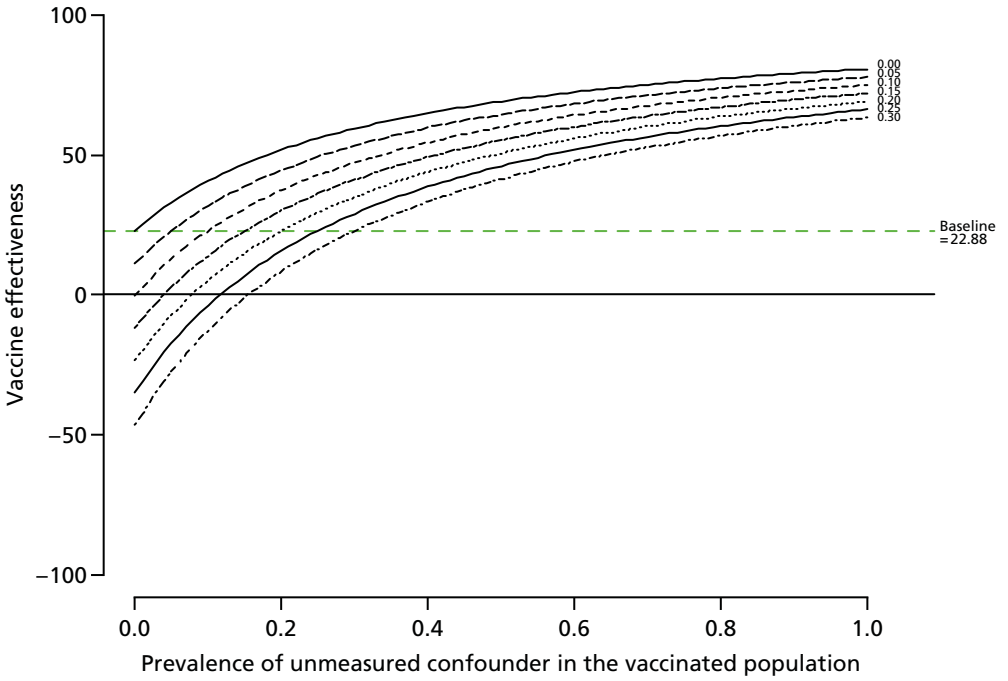


FIGURE 4 Unmeasured residual confounding and vaccine effectiveness (quadrupling of risk in emergency hospitalisations for influenza and pneumonia).

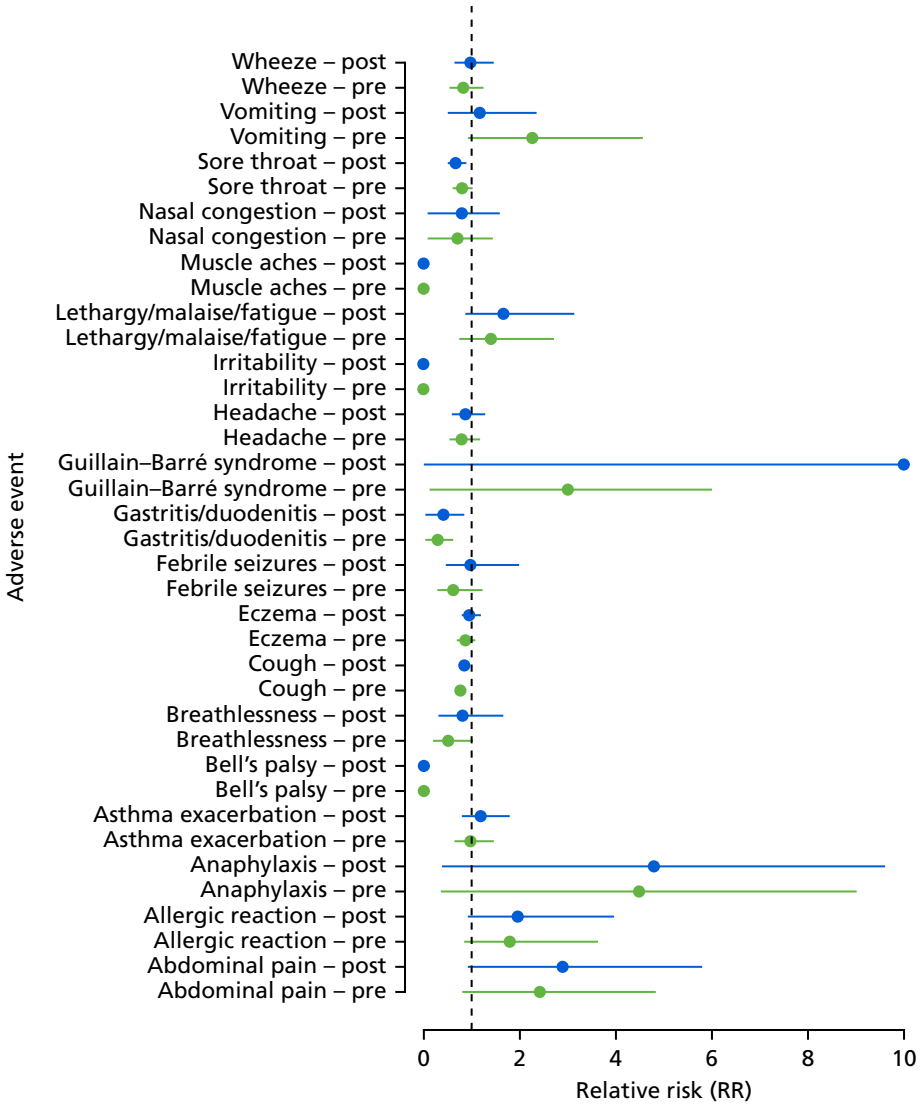


FIGURE 5 General practice consultations: adverse events in children with LAIV interactions. Note that dots to the left of the vertical dashed line at 1 correspond to adverse events where the RR comparing the risk period with the pre- or post-risk period is lower among those children vaccinated than in those children unvaccinated. Dots to the right of the vertical dashed line at 1, and where all of the horizontal line corresponding to the 95% CI is above 1, indicate adverse events where there is a potential association with receipt of the vaccine. Some of the estimates are based on very small numbers and the right-hand side of the plot is truncated at 10.

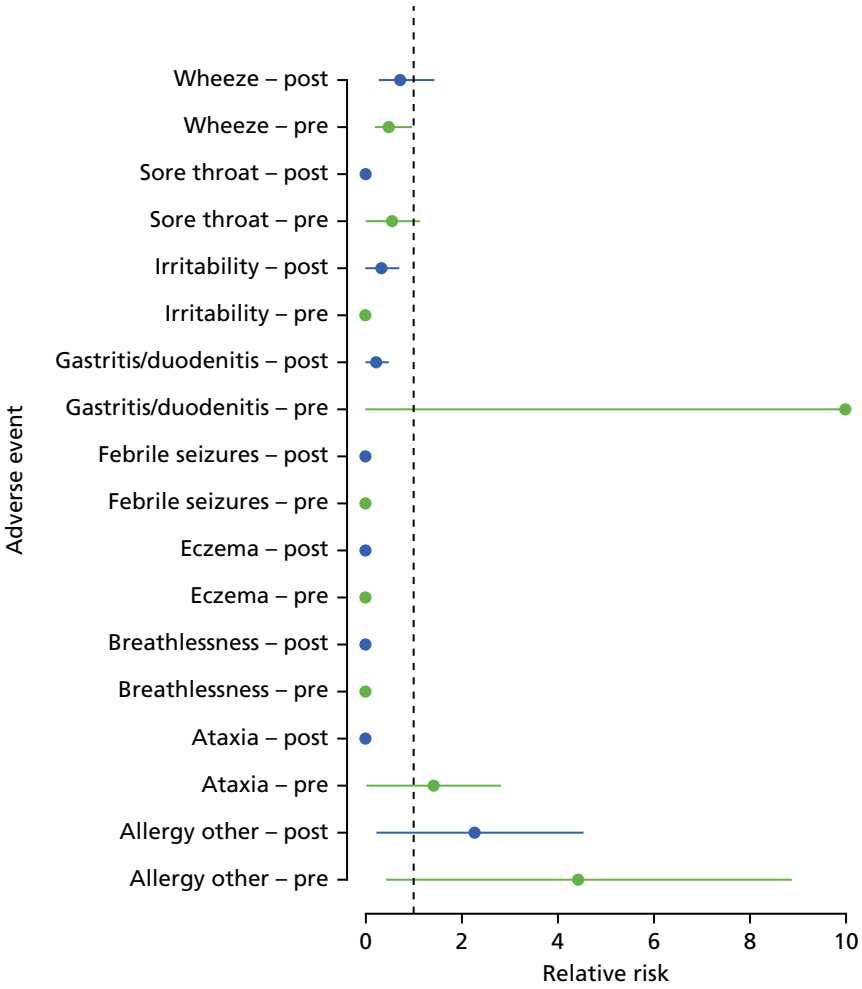


FIGURE 6 Hospitalisation: adverse events in children with LAIV interactions.

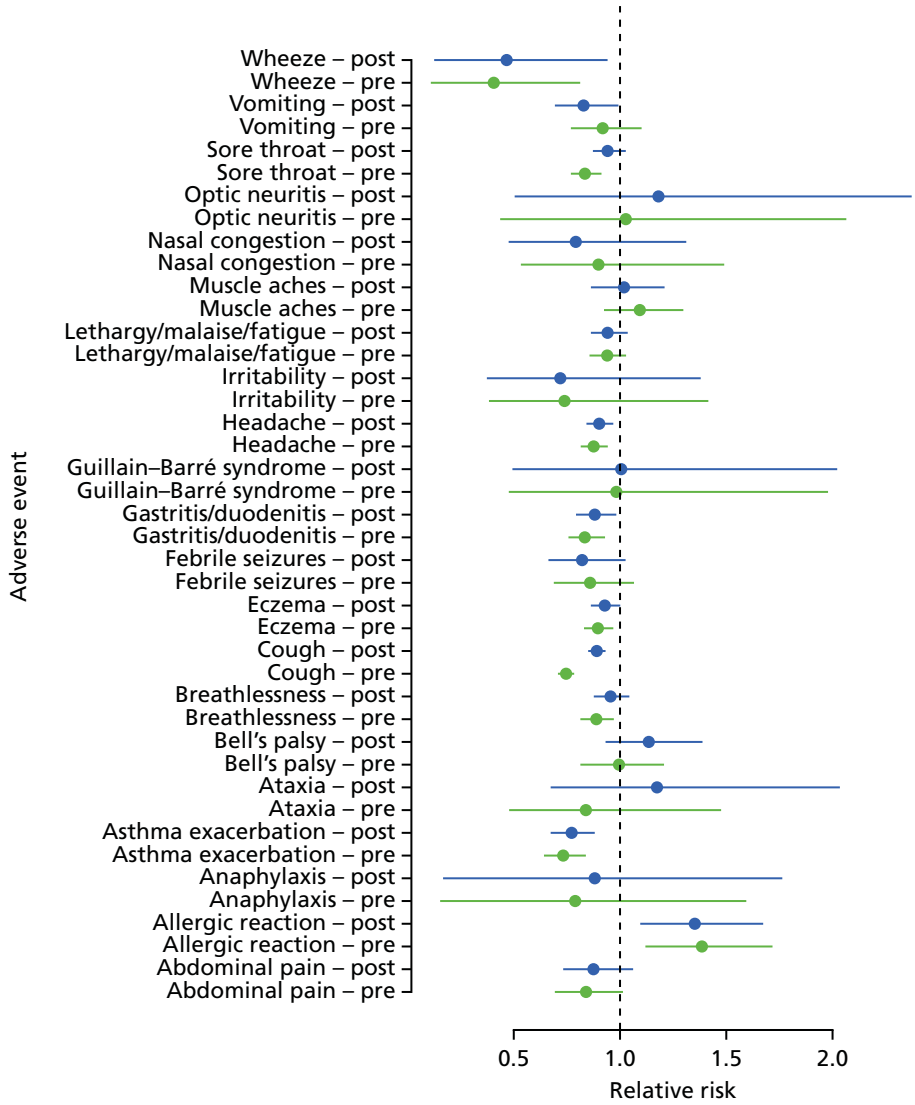


FIGURE 7 General practice consultations: adverse events in adults with TIV interactions.

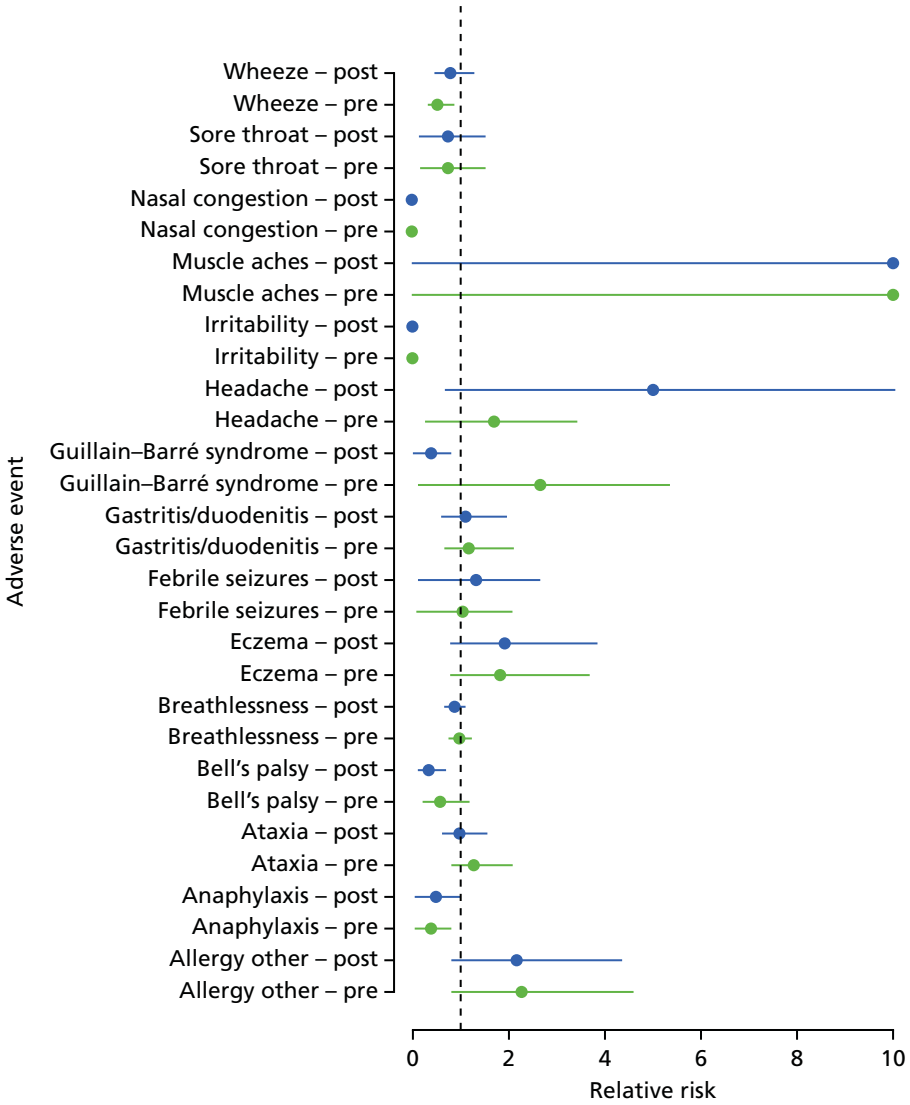


FIGURE 8 Hospitalisation: adverse events in adults with TIV interactions.

Chapter 5 Discussion

In the first year of full rollout of LAIV to all preschool-aged and primary school-aged children in 2014/15 [an influenza season with circulating influenza A(H3N2)], vaccine effectiveness was positive (but non-significant) against RT-PCR laboratory-confirmed influenza. Highly significant vaccine effectiveness was found for season 2015/16, in which influenza A(H1N1) predominated. The LAIV was found to be safe among children, with no increased adverse reactions.

For those people considered at risk and who were aged < 65 years, TIV conferred significant protection against influenza for four of the six seasons. The two seasons in which no statistically significant vaccine effectiveness could be demonstrated coincided with seasons in which there was low levels of circulating influenza virus.

Positive significant vaccine effectiveness was found among those people aged ≥ 65 years for one season (2013/14), a less severe season in which one predominate strain [influenza A(H1N1)] circulated. TIV was found to be safe overall. The finding of increased GP consultation for (non-anaphylaxis) allergic reaction may be related to common TIV issues at the injection site (e.g. arm soreness and redness).[10]

The acceptability of the LAIV programme among children registered with our practices was evidenced by high initial and then increasing uptake in both preschool- and primary school-aged children. There were also high levels of uptake of the TIV among those people aged ≥ 65 years, all of whom were able to receive the vaccine for free as part of the programme. High levels of TIV uptake was found for adults with at-risk diseases and who were aged 55–64 years. Uptake of the vaccine varied among different groups. Vaccine effectiveness, measured using hospital and GP non-specific clinical outcomes, was assessed using the Simonsen *et al.*[40] framework and was found to suffer from bias. The chosen instrumental variable, vaccine uptake by geographically determined health area, was determined not to be valid.

The LAIV uptake among 2- to 4-year-olds in the SIVE II practices in the 2014/15 season (39.3%) was similar to uptake in England and Wales (38.7%).[51] The modest uptake that was found among at-risk patients (particularly those aged between 18 and 55 years) has been found previously in our SIVE study and in other data sets (e.g. QResearch and questionnaire surveys).[52,53] The uptake in this study for older adults was lower than that found using GP routine reporting in Scotland [e.g. 59.2–67.1% vs. 74.5% (for those aged ≥ 65 years) in 2015–16].[54]

When comparing different groups of patients stratified by age band, there was greater power in this study than in the SIVE study to determine if uptake differed among groups of patients.[47] This study found, for example, that children in the least deprived quintile were more likely to receive influenza vaccine than those in the most deprived quintile; a similar pattern was found in uptake across deprivation groups using England and Wales GP data.[51] As in the SIVE study, it was also found that older people who had an emergency admission were less likely to be vaccinated;[47] however, this may be an example of the healthy vaccine effect bias in which less sick older people are more likely to be vaccinated.[40]

The findings of positive vaccine effectiveness (against RT-PCR-confirmed influenza) for LAIV in the two seasons for which there was full vaccination rollout to primary school-aged and preschool-aged children (significantly positive in 2015/16) have been found elsewhere. For example, this study's 2015/16 results confirm those of a UK study (which included Scottish GPs) [overall vaccine effectiveness 58.1% vs. 57.6%; influenza B 88.3% vs. 81.4%; and influenza A(H1N1) 40.4% vs. 41.5%, respectively].[55] However, the study's results were in contrast to those from the US Centers for Disease Control and Prevention, which found that no protection was conveyed to children vaccinated with LAIV in 2014/15 (21% vs. −3%) and in 2015/16 (58% vs. 3%).[56,57]

Trivalent influenza vaccine effectiveness among adults was the lowest when the predominant circulating subtype of influenza was H3N2 and highest when the predominant circulating subtype of influenza was H1N1. This was found for the pre-2009/10 seasons in the SIVE study.[47] Low vaccine effectiveness for H3N2 has been found elsewhere.[58] Reasons for poor vaccine effectiveness for H3N2 seasons have been postulated. Chicken eggs are used for culturing clinical isolates and for large-scale production of vaccines. However, influenza virus can mutate while being grown in chicken eggs, which could have an influence on antigenicity and lead to decreasing vaccine effectiveness.[59] Others have suggested that low H3N2 vaccine effectiveness in adults may not be due to egg adaptation, but rather caused by low vaccine immunogenicity in a subset of the population.[60] The finding of reduced TIV effectiveness in those people aged ≥ 65 years reinforces the evidence base on which the Joint Committee on Vaccination and Immunisation has made a recommendation of the preferential use of an adjuvanted seasonal influenza vaccine for the 2018/19 season.[61]

When compared with vaccine effectiveness in other vaccines administered to children and adults, influenza vaccine effectiveness was found to be lower. For example, rotavirus vaccination among young children was 90% effective in children aged > 12 months;[62] vaccination for measles, mumps, rubella and varicella was 85% effective against varicella;[63] and herpes zoster vaccine was 69% effective in adults aged ≥ 60 years.[64]

In contrast to Wong *et al.*,[42] who determined that geographical zones could be used as an instrumental variable, this study's use of the geographical area – CHP – did not result in a strong instrumental variable.[43]

The well-known safety profile of the TIV has been confirmed in this study using a novel observational study design to reduce bias.[9,10,46] However, there is less evidence regarding the safety of LAIV in children.[8] Previously reported short-term adverse effects of LAIV from clinical trials include bronchospasm, headache, nausea, vomiting and diarrhoea. Serious adverse events include pneumonia, bronchopneumonia, bronchiolitis and bronchitis. This study found no increase in adverse harms (mild and serious) from the LAIV used.

Study limitations

The estimates of vaccine uptake (particularly for those people aged ≥ 65 years) are lower relative to those reported by HPS, which are based on vaccine claim counts by all GPs in Scotland. SIVE II study practices may have been located in areas with a low level of vaccine uptake (e.g. more deprived areas). However, in this study it was not possible to check this as the study did not have practice identifiers. In similar, previous studies with smaller numbers of practices,[30,47,65,66] but using similar data sets, vaccine uptake among those people aged ≥ 65 years was closer to national estimates of 75%. If SIVE II practices have actual lower levels of vaccine uptake, then this study's estimates of vaccine effectiveness will be unbiased. If this study has missing data on vaccination, then the effect of the misclassification of some vaccinated individuals as unvaccinated will have moved the estimates of vaccine effectiveness towards zero, and so the vaccine effectiveness reported in this study may be too low. However, the estimates of vaccine effectiveness are unlikely to be substantially lower, as the pooled estimates for the TND for any influenza among those people aged ≥ 65 years over the six seasons is 17.9% (95% CI 5.2% to 28.7%), whereas from the cohort for emergency hospitalisation for pneumonia or influenza the vaccine effectiveness is 22.9% (95% CI 19.8% to 25.8%). Therefore, there was little scope for big increases in the estimated vaccine effectiveness, assuming that all of the misclassified unvaccinated individuals did not experience an event. The study was unable to calculate whether or not there was any indirect effect of the LAIV. The indirect impact of LAIV, defined as reduction in cumulative disease incidence over the same period between pilot and non-pilot areas in non-target age groups (< 4 years of age and > 11 years of age), was measured in England; however, no statistically significant indirect protection to other age groups was found.[67] The work of other groups exploring this issue will continue to be monitored. Owing to the observational nature of this study, which uses routinely collected data, residual confounding may be present or unaccounted for.

A no-cost extension to this project was granted: this was due to the complexity of extracting and linking data from a number of disparate data sets (challenging in terms of putting the necessary governance

permissions in place and technical processes required for data extraction and linkage). Future projects requiring data linkage should build adequate time to address governance and technical challenges.

The study recruited 230 practices, which was fewer than the 500 practices (of a total of 998 Scottish GPs) originally stated in the grant application. Substantial resource was committed to the process of recruitment (e.g. presentation to GP national users groups, GP newsletter advertisements, e-mail and telephone recruitment, and several reminders). Despite the lower than expected final number of GPs participating in this project, to date this is one of the largest individual patient-level primary care recruitment and data extractions to take place in Scotland (with one-fifth of practices participating). Only a small number of practices responded to turn down the offer to participate (almost all with no explanation). With the introduction of national strategies to use primary care data for research purposes [e.g. the Scottish Primary Care Information Resource; URL: www.spire.scot (accessed 1 October 2018)], it is hoped that ambitious recruitment targets, such as in this study, will be seen as more feasible.

Recommendations for further research

The monitoring of the LAIV programme with enhanced Sentinel swabbing of preschool- and primary school-aged children should continue. Future studies should be planned to further monitor the seasonal influenza vaccine in at-risk patients and such studies will continue to require expertise in data linkage and advanced analyses of these complex data sets. Replication of vaccine effectiveness and safety in LAIV and TIV in other countries (that have these influenza vaccine programmes) is also needed to confirm this study's results. A future study will be required to monitor the safety and effectiveness of the adjuvanted TIV available to older people for the 2018/19 season.[61] Any future evaluation work should contain a health economics analysis to help understand at what level of vaccine effectiveness it becomes cost-effective to recommend vaccination or continue to vaccinate.

Conclusions

Using these data, it was found that LAIV was safe and effective in decreasing RT-PCR-confirmed influenza in children. TIV was safe and significantly effective (in most seasons) for those people aged 18–64 years with positive vaccine effectiveness and in most seasons for those people aged $\geq$ 65 years (although this was statistically significant in only one season). Higher vaccine effectiveness was found among younger adults with asthma. Few countries' health systems allow for the integrated and accessible data recording that made this study possible and which made it feasible to centrally collate almost all hospitalisations and deaths attributed to influenza, allowing for completeness of reporting. LAIV was found to be safe, with vaccine effectiveness comparable to that found for TIV. TIV immunisation for at-risk adults in primary health-care settings is effective.

Acknowledgements

The authors would like to thank staff at Albasoft Ltd, HPS, the WoSSVC, the Asthma UK Centre for Applied Research and the ISD electronic Data Research and Innovation Service team, and would also like to thank the GPs contributing data to the study and members of the Independent Steering Committee and Asthma UK Centre for Applied Research patient and public involvement team for overseeing this work.

Contributions of authors

Colin R Simpson (Professor of Population Health) was the principal investigator and led the writing of this report.

Nazir I Lone (Senior Clinical Fellow, Intensive Care) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Kim Kavanagh (Senior Lecturer) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Tanya Englishby (Research Fellow) carried out the analyses and helped to design the study and write the report.

Chris Robertson (Professor of Statistics) carried out the analyses and helped to design the study and write the report.

Jim McMenamin (Consultant Epidemiologist) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Beatrix von Wissman (Specialist Trainee in Public Health) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Eleftheria Vasileiou (PhD student) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Christopher C Butler (Professor of Primary Care) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Lewis D Ritchie (Professor of Primary Care) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Rory Gunson (Consultant Clinical Scientist) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Jürgen Schwarze (Edward Clark Chair of Child Life and Health) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Aziz Sheikh (Professor of Primary Care Research and Development) helped design the study, draft and write the project protocol and revise the report for important intellectual content.

Publications

Simpson CR, Lone NI, Kavanagh K, Robertson C, McMenamin J, von Wissman B, *et al.* Evaluating the effectiveness, impact and safety of live attenuated and seasonal inactivated influenza vaccination: protocol for the Seasonal Influenza Vaccination Effectiveness II (SIVE II) study. *BMJ Open* 2017;**7**:e014200.

Vasileiou E, Sheikh A, Butler CC, Robertson C, Kavanagh K, Englishby T, *et al.* Seasonal influenza vaccine effectiveness in people with asthma: a national test-negative design case-control study. *Clin Infect Dis* 2020;**71**:e94–e104.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

References

1. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, Fukuda K. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;**289**:179–86. https://doi.org/10.1001/jama.289.2.179
2. Molinari NA, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, Bridges CB. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007;**25**:5086–96. https://doi.org/10.1016/j.vaccine.2007.03.046
3. Simpson CR, Lone NI, Kavanagh K, Robertson C, McMenamin J, von Wissman B, *et al.* Evaluating the effectiveness, impact and safety of live attenuated and seasonal inactivated influenza vaccination: protocol for the Seasonal Influenza Vaccination Effectiveness II (SIVE II) study. *BMJ Open* 2017;**7**:e014200 https://doi.org/10.1136/bmjopen-2016-014200
4. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, *et al.* Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011;**378**:1917–30. https://doi.org/10.1016/S0140-6736(11)61051-9
5. Cauchemez S, Valleron AJ, Boëlle PY, Flahault A, Ferguson NM. Estimating the impact of school closure on influenza transmission from Sentinel data. *Nature* 2008;**452**:750–4. https://doi.org/10.1038/nature06732
6. Baguelin M, Flasche S, Camacho A, Demiris N, Miller E, Edmunds WJ. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. *PLOS Med* 2013;**10**:e1001527. https://doi.org/10.1371/journal.pmed.1001527
7. Department of Health and Social Care. *CVI Statement on the Routine Annual Influenza Vaccination Programme*. London: Department of Health and Social Care. URL: www.gov.uk/government/publications/jcvi-statement-on-the-routine-annual-influenza-vaccination-programme (accessed 17 June 2015).
8. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:36–44. https://doi.org/10.1016/S1473-3099(11)70295-X
9. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev* 2012;**8**:CD004879. https://doi.org/10.1002/14651858.CD004879.pub4
10. Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer GA, Al-Ansary LA, Ferroni E. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2010;**7**:CD001269. https://doi.org/10.1002/14651858.CD001269.pub4
11. Valenciano M, Ciancio B, I-MOVE study team. I-MOVE: a European network to measure the effectiveness of influenza vaccines. *Euro Surveill* 2012;**17**:20281. https://doi.org/10.2807/ese.17.39.20281-en
12. Doshi P. Influenza: marketing vaccine by marketing disease. *BMJ* 2013;**346**:f3037. https://doi.org/10.1136/bmj.f3037
13. Simpson CR, Lone N, Kavanagh K, Ritchie LD, Robertson C, Sheikh A, *et al.* Trivalent inactivated seasonal influenza vaccine effectiveness for the prevention of laboratory confirmed influenza in a Scottish population 2000–2009. *Euro Surveill* 2015;**20**:ii–21043. https://doi.org/10.2807/1560-7917.ES2015.20.8.21043

14. Kavanagh K, Robertson C, McMenamin J. Assessment of the variability in influenza A(H1N1) vaccine effectiveness estimates dependent on outcome and methodological approach. *PLOS ONE* 2011;**6**:e28743. https://doi.org/10.1371/journal.pone.0028743

15. Kavanagh K, Robertson C, McMenamin J. Estimates of influenza vaccine effectiveness in primary care in Scotland vary with clinical or laboratory endpoint and method – experience across the 2010/11 season. *Vaccine* 2013;**31**:4556–63. https://doi.org/10.1016/j.vaccine.2013.07.056

16. Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M, SNIFFLE Study Investigators. Safety of live attenuated influenza vaccine in atopic children with egg allergy. *J Allergy Clin Immunol* 2015;**136**:376–81. https://doi.org/10.1016/j.jaci.2014.12.1925

17. De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. *Euro Surveill* 2013;**18**:20585. https://doi.org/10.2807/1560-7917.ES2013.18.37.20585

18. Information Services Division. *Practice Team Information (PTI) Statistics*. Edinburgh: National Services Scotland; 2010.

19. McAlister FA, Murphy NF, Simpson CR, Stewart S, MacIntyre K, Kirkpatrick M, *et al.* Influence of socioeconomic deprivation on the primary care burden and treatment of patients with a diagnosis of heart failure in general practice in Scotland: population-based study. *BMJ* 2004;**328**:1110. https://doi.org/10.1136/bmj.38043.414074.EE

20. Whitelaw FG, Nevin SL, Milne RM, Taylor RJ, Taylor MW, Watt AH. Completeness and accuracy of morbidity and repeat prescribing records held on general practice computers in Scotland. *Br J Gen Pract* 1996;**46**:181–6.

21. Information Services Division. *Scottish Immunisation & Recall System*. URL: www.isdscotland.org/Health-Topics/Child-Health/Child-Health-Programme/Scottish-Immunisation-Recall-System.asp (accessed 25 November 2015).

22. Health Protection Scotland. *Surveillance Data and Systems*. Glasgow: Health Protection Scotland. URL: https://hpspubsrepo.blob.core.windows.net/hps-website/nss/2104/documents/1_2012-05-17.pdf (accessed 17 June 2015).

23. Information Services Division. *NHS Hospital Data Quality: Towards Better Data from Scottish Hospitals*. Edinburgh: ISD Publications Scotland; 2007.

24. Kendrick S, Clarke J. The Scottish Record Linkage System. *Health Bull* 1993;**51**:72–9.

25. Scottish Public Health Observatory. *Overview of Key Data Sources: ISD Linked Database*. Edinburgh: National Services Scotland; 2010.

26. Health Protection Scotland. *Influenza Surveillance Systems*. Glasgow: Health Protection Scotland. URL: https://hpspubsrepo.blob.core.windows.net/hps-website/nss/2524/documents/1_2009-05-19.pdf (accessed 23 November 2015).

27. Simpson CR, Lone N, McMenamin J, Gunson R, Robertson C, Ritchie LD, Sheikh A. Early estimation of pandemic influenza Antiviral and Vaccine Effectiveness (EAVE): use of a unique community and laboratory national data-linked cohort study. *Health Technol Assess* 2015;**19**(79). https://doi.org/10.3310/hta19790

28. Chief Medical Officer. *Seasonal Influenza Vaccination Programme 2015–16*. Edinburgh: National Services Scotland; 2015.

29. Influenza (updated November 2011). In Salisbury D, Ramsay M, Noakes K, editors. *Immunisation Against Infections Disease*. London: The Stationery Office; 2006. pp. 185–204.

30. Lone NI, Simpson C, Ritchie LD, Robertson C, Sheikh A, McMenamin J, *et al.* Seasonal Influenza Vaccine Effectiveness in the community (SIVE): exploitation of a unique national linked dataset. *BMJ Open* 2012;**15**:e001019. https://doi.org/10.1136/bmjopen-2012-001019

31. Wallace LA, McAulay KA, Douglas JD, Elder AG, Stott DJ, Carman WF. Influenza diagnosis: from dark isolation into the molecular light. West of Scotland Respiratory Virus Study Group. *J Infect* 1999;**39**:221–6. https://doi.org/10.1016/S0163-4453(99)90053-1

32. Gunson RN, Bennett S, Maclean A, Carman WF. Using multiplex real time PCR in order to streamline a routine diagnostic service. *J Clin Virol* 2008;**43**:372–5. https://doi.org/10.1016/j.jcv.2008.08.020

33. National Statistics. *Scottish Index of Multiple Deprivation: 2009 General Report*. Edinburgh: Scottish Government National Statistics Publications; 2009.

34. Scottish Government. *Scottish Government Urban Rural Classification*. Edinburgh: Scottish Government. URL: www.gov.scot/Topics/Statistics/About/Methodology/UrbanRuralClassification (accessed 14 August 2018).

35. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83. https://doi.org/10.1016/0021-9681(87)90171-8

36. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. *Int J Epidemiol* 2000;**29**:891–8. https://doi.org/10.1093/ije/29.5.891

37. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Fam Pract* 2010;**11**:1. https://doi.org/10.1186/1471-2296-11-1

38. McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, Belongia EA. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. *Clin Infect Dis* 2014;**59**:1375–85. https://doi.org/10.1093/cid/ciu680

39. Skowronski DM, Chambers C, Sabaiduc S, De Serres G, Winter AL, Dickinson JA, *et al.* A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014–15 season. *Clin Infect Dis* 2016;**63**:21–32 https://doi.org/10.1093/cid/ciw176

40. Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. *Lancet Infect Dis* 2007;**7**:658–66. https://doi.org/10.1016/S1473-3099(07)70236-0

41. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 1998;**54**:948–63. https://doi.org/10.2307/2533848

42. Wong K, Campitelli MA, Stukel TA, Kwong JC. Estimating influenza vaccine effectiveness in community-dwelling elderly patients using the instrumental variable analysis method. *Arch Intern Med* 2012;**172**:484–91. https://doi.org/10.1001/archinternmed.2011.2038

43. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol* 2000;**29**:722–9. https://doi.org/10.1093/ije/29.4.722

44. Glanz JM, McClure DL, Xu S, Hambidge SJ, Lee M, Kolczak MS, *et al.* Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. *J Clin Epidemiol* 2006;**59**:808–18. https://doi.org/10.1016/j.jclinepi.2005.11.012

45. Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. *Vaccine* 2004;**22**:2064–70. https://doi.org/10.1016/j.vaccine.2004.01.017

46. Vellozzi C, Burwen DR, Dobardzic A, Ball R, Walton K, Haber P. Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring. *Vaccine* 2009;**27**:2114–20. https://doi.org/10.1016/j.vaccine.2009.01.125

47. Simpson CR, Lone N, Kavanagh K, Ritchie LD, Robertson C, Sheikh A, *et al.* Seasonal Influenza Vaccine Effectiveness (SIVE): an observational retrospective cohort study – exploitation of a unique community-based national-linked database to determine the effectiveness of the seasonal trivalent influenza vaccine. *Health Serv Deliv Res* 2013;**1**(10).

48. Kotz D, Viechtbauer W, Simpson C, van Schayck OC, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. *Lancet Respir Med* 2015;**3**:761–8. https://doi.org/10.1016/S2213-2600(15)00320-3

49. Health Protection Scotland. *Influenza Surveillance Systems*. Glasgow: Health Protection Scotland. URL: www.hps.scot.nhs.uk/a-to-z-of-topics/influenza (accessed 1 April 2016).

50. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med* 2010;**103**:98–106. https://doi.org/10.1258/jrsm.2009.090348

51. Hardelid P, Rait G, Gilbert R, Petersen I. Factors associated with influenza vaccine uptake during a universal vaccination programme of preschool children in England and Wales: a cohort study. *J Epidemiol Community Health* 2016;**70**:1082–7. https://doi.org/10.1136/jech-2015-207014

52. Coupland C, Harcourt S, Vinogradova Y, Smith G, Joseph C, Pringle M, Hippisley-Cox J. Inequalities in uptake of influenza vaccine by deprivation and risk group: time trends analysis. *Vaccine* 2007;**25**:7363–71. https://doi.org/10.1016/j.vaccine.2007.08.032

53. Blank PR, Schwenkglenks M, Szucs TD. Vaccination coverage rates in eleven European countries during two consecutive influenza seasons. *J Infect* 2009;**58**:446–58. https://doi.org/10.1016/j.jinf.2009.04.001

54. Health Protection Scotland. *Monthly National Influenza Report Week Ending 8 May 2016*. Glasgow: Health Protection Scotland. URL: www.hps.scot.nhs.uk/resourcedocument.aspx?id=4356 (accessed 17 June 2018).

55. Pebody R, Warburton F, Ellis J, Andrews N, Potts A, Cottrell S, *et al.* Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. *Euro Surveill* 2016;**21**:pii–30348. https://doi.org/10.2807/1560-7917.ES.2016.21.38.30348

56. Zimmerman RK, Nowalk MP, Chung J, Jackson ML, Jackson LA, Petrie JG, *et al.* 2014–2015 influenza vaccine effectiveness in the United States by vaccine type. *Clin Infect Dis* 2016;**63**:1564–73. https://doi.org/10.1093/cid/ciw635

57. Centers for Disease Control and Prevention (CDC). *ACIP Votes Down Use of LAIV for 2016–2017 Flu Season. Media Statement*. Atlanta, GA: CDC; 2016. URL: www.cdc.gov/media/releases/2016/s0622-laiv-flu.html (accessed 17 June 2018).

58. Belongia EA, Simpson MD, King JP, Sundaram ME, Kelley NS, Osterholm MT, McLean HQ. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis* 2016;**16**:942–51. https://doi.org/10.1016/S1473-3099(16)00129-8

59. Wu NC, Zost SJ, Thompson AJ, Oyen D, Nycholat CM, McBride R, *et al.* A structural explanation for the low effectiveness of the seasonal influenza H3N2 vaccine. *PLOS Pathog* 2017;**13**:e1006682. https://doi.org/10.1371/journal.ppat.1006682

60. Cobey S, Gouma S, Parkhouse K, Chambers BS, Ertl HC, Schmader KE, *et al.* Poor immunogenicity, not vaccine strain egg adaptation, may explain the low H3N2 influenza vaccine effectiveness in 2012–13. *Clin Infect Dis* 2018;**67**:327–33. https://doi.org/10.1093/cid/ciy097

61. Joint Centre for Vaccination and Immunisation. *Draft Minute of the Meeting on 7 February 2018*. URL: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/284102495624 (accessed 29 May 2018).

62. Braeckman T, Van Herck K, Meyer N, Pirçon JY, Soriano-Gabarró M, Heylen E, *et al.* Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. *BMJ* 2012;**345**:e4752. https://doi.org/10.1136/bmj.e4752

63. Seward JF, Marin M, Vázquez M. Varicella vaccine effectiveness in the US vaccination program: a review. *J Infect Dis* 2008;**197**(Suppl. 2):82–9. https://doi.org/10.1086/522145

64. Tseng HF, Harpaz R, Luo Y, Hales CM, Sy LS, Tartof SY, *et al.* Declining effectiveness of herpes zoster vaccine in adults aged ≥60 years. *J Infect Dis* 2016;**213**:1872–5. https://doi.org/10.1093/infdis/jiw047

65. Simpson CR, Ritchie LD, Robertson C, Sheikh A, McMenamin J. Vaccine effectiveness in pandemic influenza – primary care reporting (VIPER): an observational study to assess the effectiveness of the pandemic influenza A (H1N1)v vaccine. *Health Technol Assess* 2010;**14**(34). https://doi.org/10.3310/hta14340-05

66. Simpson CR, Ritchie LD, Robertson C, Sheikh A, McMenamin J. Effectiveness of H1N1 vaccine for the prevention of pandemic influenza in Scotland, UK: a retrospective observational cohort study. *Lancet Infect Dis* 2012;**12**:696–702. https://doi.org/10.1016/S1473-3099(12)70133-0

67. Pebody RG, Green HK, Andrews N, Zhao H, Boddington N, Bawa Z, *et al.* Uptake and impact of a new live attenuated influenza vaccine programme in England: early results of a pilot in primary school-age children, 2013/14 influenza season. *Euro Surveill* 2014;**19**:20823. https://doi.org/10.2807/1560-7917.ES2014.19.22.20823

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library