

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

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***National Institute for
Health Research***

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Abstract

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

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Background: Globally, seasonal influenza is responsible for an estimated 3 to 5 million cases of severe illness and 250,000 to 500,000 deaths per year. It is uncertain to what extent national vaccination programmes can prevent this morbidity and mortality.

Objective: To determine the effectiveness of the seasonal trivalent inactivated influenza vaccine.

Design: We undertook a retrospective observational cohort study. A propensity score model was constructed and adjusted odds ratios (ORs) were calculated to assess differences in vaccine uptake according to a number of patient characteristics. Adjusted illness and mortality hazard ratios (HRs) were estimated from a Cox proportional hazards model adjusted for sex, age, socioeconomic status, smoking status, urban/rural location, clinical at-risk groups (i.e. patients with chronic respiratory, heart, kidney, liver or neurological disease, immunosuppression and diabetes), Charlson comorbidity index, previous pneumococcal and influenza vaccination, and number of previous primary care consultations, prescribed drugs and hospital admissions. We also included nursing home residence and social care support. Vaccine effectiveness (VE) was expressed as a percentage, and represents a reduction in risk provided by the vaccine for a given outcome (e.g. laboratory-confirmed influenza). This was calculated as $1 - HR$, where HR is that of the measured clinical outcome in vaccinated compared with unvaccinated individuals. For estimates of VE derived from linked virological swab data, we carried out a nested case-control study design.

Setting: A national linkage of patient-level primary care, hospital, death certification and virological swab-linked data across nine influenza seasons (2000–9).

Participants: A nationally representative sample of the Scottish population during 1,767,919 person-seasons of observation. Cases of influenza were confirmed using reverse transcription-polymerase chain reaction (RT-PCR) in a subset of the population ($n = 3323$).

Interventions: Trivalent inactivated seasonal influenza vaccination ($n = 274,071$).

Main outcome measures: VE, pooled across seasons and adjusting for confounders, was estimated by determining laboratory-confirmed influenza, influenza-related morbidity and mortality including primary care influenza-like illnesses, hospitalisation and death from influenza and pneumonia.

Results: Most vaccines (93.6%; $n = 256,474$ vaccines) were administered to at-risk patients targeted for vaccination, with a 69.3% uptake among those aged ≥ 65 years (178,754 vaccinations during 258,100 person-seasons). For at-risk patients aged < 65 years there was a 26.2% uptake (77,264 vaccinations during 295,116 person-seasons). VE in preventing RT-PCR laboratory-confirmed influenza was 57.1% [95% confidence interval (CI) 31.3% to 73.3%]. VE was 18.8% (95% CI -103.7% to 67.6%) in patients aged ≥ 65 years and 59.6% (95% CI 21.9% to 79.1%) in those aged < 65 years at risk of serious complications from influenza. In the matched analysis (156,096 person-seasons), adjusted VE for reducing primary care consultations for influenza-like illnesses was 16.3% (95% CI 5.7% to 26.0%). VE in reducing hospitalisations was 19.3% for influenza and pneumonia (95% CI 8.3% to 29.1%) and 26.7% for pneumonia and chronic obstructive pulmonary disease (95% CI 19.8% to 32.9%). VE in reducing death due to influenza and pneumonia was 37.9% (95% CI 29.5% to 45.4%).

Conclusions: Few countries' health systems allow for the integrated and accessible data recording that made this study possible and made it feasible to collate centrally almost all hospitalisations and deaths attributed to influenza, thereby allowing completeness of reporting. Using these data, we found most influenza vaccines were administered to those at risk of serious complications from influenza. In a nationally representative cohort we found that the vaccine was associated with a significant decrease in the risk of RT-PCR-confirmed influenza (the decrease was substantial particularly for at-risk patients aged < 65 years) and complications arising from influenza (where more modest decreases were found). Although the modest size of our cohort made it possible to collate centrally almost all cases of influenza-related disease, analysis of subgroups (in particular older age groups) or by individual season resulted in poorer precision and wide CIs. Any future work should therefore aim to address this issue by ensuring adequate power to test VE in these subgroups of patients, while minimising the effect of bias, such as health-seeking behaviour.

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List of abbreviations

CHI	Community Health Index	PCCIU	Primary Care Clinical Informatics Unit
CI	confidence interval		
COPD	chronic obstructive pulmonary disease	ROC _{AUC}	receiver operating characteristic – area under the curve
GP	general practitioner	RR	rate ratio
GROS	General Register Office for Scotland	RT-PCR	reverse transcription-polymerase chain reaction
HPS	Health Protection Scotland	SIVE	Seasonal Influenza Vaccine Effectiveness
HR	hazard ratio	SMR	Scottish Morbidity Record
ISD	Information Services Division	VE	vaccine effectiveness
OR	odds ratio		

Scientific summary

Background

Each year, influenza causes substantial morbidity and mortality, particularly in people aged ≥ 65 years and those with underlying serious comorbidities. In the USA, for example, it has been estimated that influenza is responsible for 186,000 excess hospitalisations and 44,000 excess deaths at a cost of \$87B per year. In England, influenza-related mortality is estimated to be as high as 8600 deaths per year. National vaccination strategies represent a potentially important approach to reducing both influenza-related illness and death, hence the considerable investment in this preventative strategy in many parts of the world. In populations at risk of developing influenza-related complications (for example, adults aged ≥ 65 years and people with medical conditions such as diabetes, heart or respiratory disease or immune deficiency), there is a paucity of reliable estimates of efficacy from randomised controlled trials, which offer the best opportunity to produce unbiased estimates of vaccine effectiveness (VE). This measure is expressed as a percentage, and represents a reduction in risk provided by the vaccine for a given outcome (e.g. laboratory-confirmed influenza). Furthermore, it is thought that influenza vaccine is less effective in the oldest age groups owing to immune senescence.

Quasi-experimental studies are an alternative to randomised controlled trials and can be used to investigate the effectiveness of vaccine programmes. However, very few have estimated VE in reducing medically confirmed influenza using reliable methods such as viral culture or reverse transcription-polymerase chain reaction (RT-PCR) testing. Given the ongoing controversy regarding VE and, in particular, influenza vaccination in at-risk groups, there is a need for further research at the population level before current policies regarding seasonal vaccine strategies can be altered. We therefore undertook an observational cohort study to determine uptake and VE of the trivalent inactivated influenza vaccine in a quarter of a million people from across Scotland, registered with a sentinel surveillance network of primary care practices.

Objectives

We aimed to examine the effectiveness of the seasonal influenza vaccination in individuals registered with a national sample of general practices in Scotland. More specifically, our three objectives were to evaluate:

1. uptake of the influenza vaccine by the relevant at-risk populations, i.e. patients with relevant comorbidities and those aged ≥ 65 years, as well as by the general population
2. the reduction in the expected incidence of influenza-related morbidity and mortality in these at-risk groups, as this is the major rationale behind current immunisation policies
3. the effectiveness of the influenza vaccine in the population as a whole.

Methods

We used a retrospective cohort design and a nested case-control design. A database was used containing a cohort of patients registered with a sentinel surveillance network of primary care practices. This provided a representative sample constituting 5% of general practices in Scotland. Using the unique Community Health Index (CHI) number, general practice patient-level data were extracted and then linked to the Scottish Morbidity Record (SMR) catalogue, which has details of all inpatient hospital admissions within Scotland as well as information on death certification linked from the General Register Office for Scotland

(GROS). Additionally, we linked these databases to the Health Protection Scotland (HPS) virology data set, which contains information relating to laboratory-confirmed cases of influenza.

We established key characteristics of each identified patient in the cohort, including sex; age; socioeconomic status; smoking status; urban/rural location; whether or not the patient belonged to any clinical at-risk groups (i.e. patients suffering from chronic respiratory, heart, kidney, liver or neurological disease, immunosuppression or diabetes); comorbidity; previous pneumococcal and influenza vaccination; and number of previous primary care consultations, prescribed drugs and hospital admissions. We also included nursing home residence and social care support.

The four primary outcomes that we used to determine influenza VE were primary care consultations for influenza-like illness, hospitalisation due to pneumonia or influenza, death due to pneumonia or influenza and laboratory-confirmed influenza infection. We also assessed VE in reducing numbers of hospitalisations and deaths due to cerebrovascular and cardiovascular disease as secondary outcomes.

We established whether a person had been vaccinated and the date this occurred using the primary care electronic record. Data from 1 September 2000 to 31 August 2009 were used. This allowed for the analysis of nine influenza seasons (2000/1 to 2008/9), yielding a total of 1,767,919 person-seasons for analysis. We allowed for the same individuals being represented in multiple seasons using robust standard errors.

For estimates of laboratory VE derived from linked virological swab data, we carried out a nested case-control study design. A generalised additive logistic regression model was fitted adjusting for the effects of week during the study period, age, sex, deprivation, number of previous primary care consultations and being in a clinical at-risk group. We therefore measured VE by comparing swabs taken after vaccination with those from patients who were not vaccinated at the time the swabs were taken.

We used advanced statistical methods to determine the effectiveness of the influenza vaccine for the three non-laboratory (clinical) outcomes. We used multivariable methods to adjust for potential confounders. In addition, we constructed a propensity score, which included a wide range of factors that might have influenced the propensity to be vaccinated. This propensity score was allocated to each individual in the cohort. VE estimates were produced adjusting for the propensity score as well as matching individuals with similar propensity scores. This was done to ensure that we included individuals who were as similar as possible in all respects other than being vaccinated.

We assessed the robustness of our results by modelling the effect of an unmeasured confounder (such as frailty) on our VE estimates in sensitivity analyses. We varied three factors: the prevalence of the confounder in the vaccinated population, its prevalence in the unvaccinated population and the increased risk of the outcome attributable to the confounder.

We undertook analyses using the whole cohort and also stratified our analysis to produce separate VE estimates for those aged ≥ 65 years and those aged < 65 years in an at-risk group.

Results

Vaccine uptake

In total, during the 1,767,705 person-seasons of observation over nine influenza seasons, 274,071 seasonal influenza vaccinations were administered to the whole population, of which most (93.6%; $n = 256,474$) were given to at-risk patients targeted for vaccination. There was 69.3% uptake of the vaccine among those aged ≥ 65 years (178,754 vaccinations during 258,100 person-seasons). For at-risk patients aged < 65 years there was a 26.2% uptake (77,264 vaccinations during 295,116 person-seasons).

High vaccine uptake was found among the oldest age group (≥ 75 years), care home residents, those previously vaccinated, patients with chronic diseases (except for chronic respiratory disease) and those being issued many prescriptions. After adjustment, the odds ratio (OR) for uptake was lower for individuals who smoked and those with no recorded smoking status, and for those with five or more comorbidities when compared with those with no comorbidities. There were similar findings for at-risk patients and those aged > 65 years, although for the latter group, an OR [with 95% confidence interval (CI)] < 1 was also found among people whose contacts with primary care were by home consultation only (unadjusted OR 0.53, 95% CI 0.50 to 0.56) and, after adjustment for covariates, among those who were admitted multiple times to hospital when compared with those who were not admitted (> 10 hospitalisations: adjusted OR 0.71, 95% CI 0.53 to 0.95).

Vaccine effectiveness

Laboratory outcome

A total of 3323 swabs were taken from 3016 patients over the nine seasons and then tested with RT-PCR. Although all subgroups were represented, patients from whom swabs were taken were more likely to be younger (aged < 75 years), female and relatively affluent. During our study, 13.9% of all swabs tested positive for influenza. Male patients and the socioeconomically deprived were less likely to test positive. One-quarter of school-age children tested were positive for influenza.

For the population as a whole in receipt of trivalent inactivated vaccine, VE in preventing laboratory-confirmed influenza was 57.1% (95% CI 31.3% to 73.3%). VE was 59.6% (95% CI 22.0% to 79.1%) for at-risk patients aged < 65 years and 18.8% (95% CI -103.7% to 67.6%) for patients aged ≥ 65 years.

Clinical outcomes

In the matched propensity score analysis, we found that the influenza vaccine was effective in reducing the rate of primary care consultations for influenza-like illness (VE 16.3%, 95% CI 5.7% to 26.0%) and in reducing the risk of hospitalisation (VE 19.3%, 95% CI 8.3% to 29.1%) and death due to influenza or pneumonia (VE 37.9%, 95% CI 29.5% to 45.4%).

In at-risk patients aged < 65 years, we did not find a significant effect of the vaccine on the risk of either hospitalisation (VE 6.6%, 95% CI -20.5% to 27.6%) or death (VE 34.1%, 95% CI -7.5% to 59.6%) due to influenza or pneumonia. The VE estimates for these outcomes were imprecise owing to the relatively low event rates in this subgroup. In those aged ≥ 65 years, VE for the four outcomes was similar to VE for the whole cohort.

Other outcomes

We found that the influenza vaccine reduced both the rate of hospitalisation (VE 19.3%, 95% CI 8.3% to 29.1%) and the risk of death (VE 41.1%, 95% CI 35.6% to 46.2%) due to cardiovascular and cerebrovascular diseases in the propensity score-matched analysis.

Sensitivity analyses

Our VE estimates were robust to varying the prevalence of the unmeasured confounder and its effect on outcome. The influenza vaccine remained effective in reducing the risk of death due to influenza or pneumonia even when the prevalence of the confounder in the vaccinated population was 20% and the confounder was associated with a doubling of risk of the outcome.

Implications for practice and research recommendations

Using VE estimates for our most specific outcome, that of RT-PCR-confirmed influenza over a 9-year period, the seasonal influenza programme was found to be effective, particularly in preventing influenza in

younger, clinically at-risk groups of patients. However, although the modest size of our cohort made it feasible to collate centrally almost all cases of influenza-related disease, thereby allowing completeness of reporting, analysis of subgroups (in particular, older age groups) or by individual season resulted in poorer precision and wide CIs. Any future work should therefore aim to address this issue by ensuring adequate power to test VE in these subgroups of patients, while minimising the effect of bias, such as health-seeking behaviour. While work is being undertaken to produce better vaccines, continued monitoring and a strong international evidence base for the effectiveness of seasonal influenza vaccination programmes is necessary.

Conclusions

During nine influenza seasons, most influenza vaccines were administered to those at risk of serious complications from influenza, with a high uptake of the vaccine among those aged ≥ 65 years. The trivalent inactivated influenza vaccine was effective in reducing RT-PCR laboratory-confirmed influenza, primary care consultations for influenza-like illness, and hospitalisations and deaths from influenza or pneumonia. We found no clear evidence that the effectiveness of the influenza vaccine varied by age group, although our study was possibly underpowered to assess for effect modification for these outcomes. Our findings were robust to the modelling of unmeasured confounding in sensitivity analyses. This study therefore adds to the evidence base indicating that the influenza vaccine is effective in reducing both laboratory and clinically important outcomes.

Funding

Funding for this study was provided by the Health Services and Delivery Research programme of the National Institute for Health Research.

Chapter 1 Introduction

Each year, influenza causes substantial morbidity and mortality, particularly in people aged ≥ 65 years and in those with underlying serious comorbidities. In the USA for example, it has been estimated that influenza is responsible for 186,000 excess hospitalisations and 44,000 excess deaths at a cost of \$87B per year.^{1,2} In England, influenza-related mortality is estimated to be as high as 8600 deaths per year.³ National vaccination strategies represent a potentially important approach to reducing both influenza-related illness and death, hence the considerable investment in this preventative strategy in many parts of the world. There is good evidence of the benefits of the vaccine in young healthy adults and children.⁴ However, in populations at risk of developing influenza-related complications (e.g. adults aged ≥ 65 years and people with medical conditions such as diabetes, heart or respiratory disease or immune deficiency) there is a paucity of reliable estimates of efficacy from randomised controlled trials, which offer the best opportunity to produce unbiased estimates of vaccine efficacy. This is of particular concern as it is thought that influenza vaccine may be less effective in the oldest age groups due to immune senescence.⁵ However, given that influenza vaccination programmes now exist in most developed countries, the randomised controlled trial as a form of study design (for evaluating influenza vaccine effectiveness) is now impractical and, moreover, is viewed by many in the medical community as unethical.⁶

Observational studies are an alternative means of investigating the effectiveness of vaccine programmes. However, an individual's decision to attend his or her local general practice surgery for vaccination may be a marker of healthier behaviour generally, as well as identifying more highly educated individuals who are more aware of, and more likely to act on, recommendations for their own health. These individuals may be less likely to die from any cause or be admitted to hospital, thus inducing a spurious relationship between vaccination status and outcome (i.e. positive confounding). Similarly, a 'healthy vaccine effect' may occur, whereby patients who are very frail and unable to attend the general practice surgery may be less likely to be vaccinated, but much more likely to die or be admitted to hospital.⁷ Standard methods of adjustment for confounders are likely to be inadequate to control for confounding due to the healthy vaccine effect. This can result in excessive estimates of vaccine effectiveness (VE) in observational studies using non-influenza-specific outcomes due to residual confounding, in particular for all-cause mortality where VE greater than the total 5% estimated risk of death during winter has been found.^{8,9} A number of methods can be used to try and address this problem including quasi-experimental study designs and advanced statistical methods. In addition, an analysis framework has been proposed to identify residual confounding when undertaking VE studies using observational methods.⁵

Quasi-experimental studies are an alternative that can be used to investigate the effectiveness of vaccine programmes, but very few have estimated VE in reducing medically confirmed influenza using reliable methods such as viral culture or reverse transcription-polymerase chain reaction (RT-PCR) testing.¹⁰ Given the ongoing controversy regarding VE, particularly in relation to influenza vaccination in at-risk groups,¹⁰ there is further need of information before current policies regarding seasonal vaccine strategies can be altered. We therefore undertook an observational cohort study to determine uptake and VE of the trivalent inactivated influenza vaccine in a quarter of a million people from across Scotland, registered with a sentinel surveillance network of primary care practices. This builds on related work to estimate the effectiveness of the 2009 monovalent pandemic (H1N1) influenza vaccine.^{11,12}

Objectives

The aim of the Seasonal Influenza Vaccine Effectiveness (SIVE) study was to examine the effectiveness of the seasonal influenza vaccination in individuals registered with a national sample of general practices in Scotland. Our three specific objectives were to evaluate:

1. uptake of the influenza vaccine by the relevant at-risk populations, i.e. patients with relevant comorbidities and those aged ≥ 65 years, as well as by the general population
2. the reduction in the expected incidence of influenza-related morbidity and mortality in these at-risk groups, as this is the major rationale behind current immunisation policies
3. the effectiveness of the influenza vaccine in the population as a whole.

Chapter 2 Methods

Study design

Almost all individuals resident in Scotland are registered with a general practice, which provides a comprehensive array of health-care services, including the issuing of prescriptions for medications. Specialist hospital care services are typically accessed through referral from primary care or, in emergency situations, through patients attending accident and emergency. General practitioners (GPs) also provide and co-ordinate much of the care of patients discharged back into the community after a hospital admission. The Practice Team Information network practices included in this study are a representative sample constituting 5% of Scottish practices. These practices receive an annual financial incentive to electronically record all face-to-face contacts with patients.¹³ Data from practices within Scotland are of high quality (the completeness of capture of contacts and accuracy of clinical event coding in primary care has been found to be > 90%¹⁴) and their value for epidemiological research has been repeatedly demonstrated.¹⁵ Using each patient's unique Community Health Index (CHI) number, general practice patient-level data were extracted and then linked to the Scottish Morbidity Record (SMR) catalogue, which has information on all inpatient hospital admissions within Scotland as well as information on death certification linked from the General Register Office for Scotland (GROS)¹⁶ (Figure 1). Hospital data from 1981 onwards have been shown to be reliable, with completeness and accuracy rates > 90%.¹⁷ Additionally, we used the Health Protection Scotland (HPS) virology data set, which records all laboratory-confirmed cases of influenza in Scotland.

We established the following key characteristics of each identified patient in the cohort: sex; age (0–4, 5–14, 15–44, 45–64, 65–74 or ≥ 75 years); socioeconomic status [Scottish Index of Multiple Deprivation scores¹⁸ expressed as quintiles: 1 (most affluent) to 5 (most deprived)]; smoking status (current smoker, ex-smoker, non-smoker or not recorded); urban/rural location (one large urban and six remote rural locations were included in the study); whether or not the patient belonged to any clinical at-risk groups (i.e. those suffering from chronic respiratory, heart, kidney, liver or neurological disease, immunosuppression or diabetes); pregnancy status; Charlson comorbidity index;¹⁹ previous pneumococcal and influenza vaccination; and number of previous primary care consultations, prescribed drugs and hospital admissions (e.g. in the year prior to 1 September 2000). No direct measure of functional status existed within the database; to allow this to be taken into account, home consultations by a GP only (vs. practice attendance by the patient) and nursing home residence (including social care support) were also included in our propensity score.

Procedures

Clinical conditions (consultations for influenza and other acute respiratory infections), risk group information and prescribing data (e.g. seasonal influenza vaccination and pneumococcal polysaccharide status) were extracted from primary care records. Influenza primarily infects the respiratory tract, which can often result in pneumonia and influenza being grouped together in data recording.²⁰ We therefore extracted from the SMR and the GROS details on the primary diagnosis of hospitalisation and cause of death from influenza grouped with pneumonia. Furthermore, we also analysed chronic obstructive pulmonary disease (COPD) grouped with influenza and pneumonia, as influenza can account for a significant proportion of COPD exacerbations resulting in hospitalisation and death.²¹

A number of secondary analyses were undertaken using other outcomes. The effect of vaccination status on hospital admissions and deaths relating to cardiovascular and cerebrovascular events as a composite outcome was analysed. In addition, exploratory analyses were undertaken to assess the effect of vaccination status on outcomes for which it would not be expected to have an effect, for example

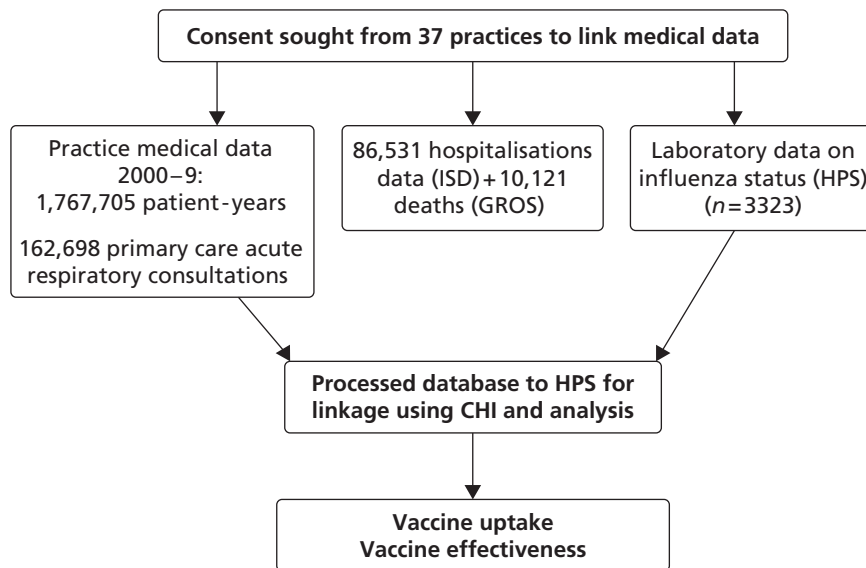


FIGURE 1 Flow diagram for the SIVE study. ISD, Information Services Division.

appendicitis or trauma. This approach of using an alternative outcome as a negative control has been shown to be a useful method for detecting residual bias.²²

Data from 1 September 2000 to 31 August 2009 were used. This allowed for the analysis of nine influenza seasons (2000/1 to 2008/9), yielding a total of 1,767,919 person-seasons for analysis. The influenza season was defined as the period from the date of the first influenza isolate reported by HPS for each year, in or post week 40 of that year, until the date of the last influenza isolate, pre or in week 20 of the subsequent year (i.e. the period of peak influenza) (*Figure 2*).

Vaccination was used to define exposure status if it was given at a time point between the start of the pre-influenza season (e.g. 1 September) and the end of the influenza season. An individual was defined as vaccinated 14 days after the seasonal influenza vaccine was administered. 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'. A detailed description of our methods has previously been published.²³

The earliest influenza season began on 26 September and the latest began on 25 November (*Table 1*). All seasons finished in May.

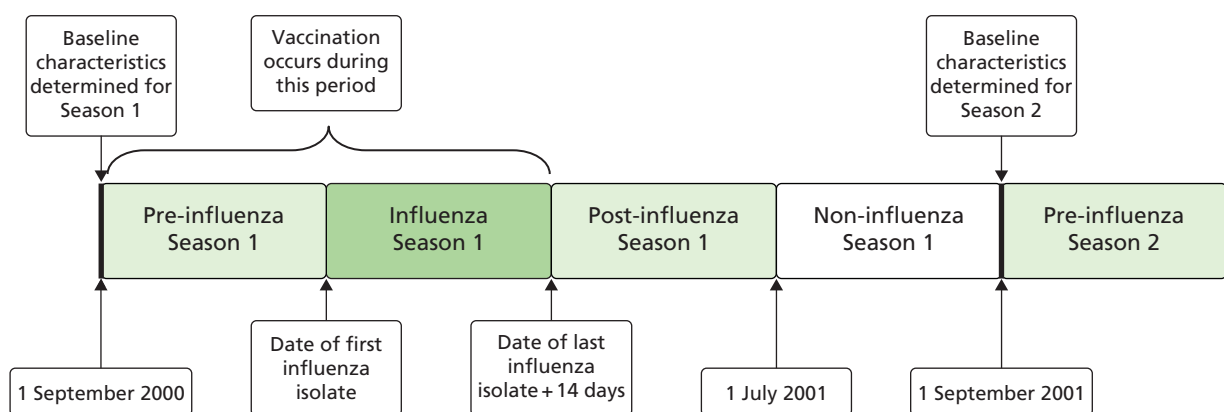


FIGURE 2 Relationship of first influenza season (2000/1) to pre-, post- and non-influenza season periods. Influenza season was defined as the period from the date of the first isolate \geq week 40 until that of the last isolate \leq week 20.

TABLE 1 Influenza season start and end dates

Year	Start date	End date
2000/1	5 October 2000	14 May 2001
2001/2	18 October 2001	17 May 2002
2002/3	25 November 2002	15 May 2003
2003/4	26 September 2003	7 May 2004
2004/5	22 October 2004	19 May 2005
2005/6	6 October 2005	16 May 2006
2006/7	19 October 2006	9 May 2007
2007/8	2 October 2007	13 May 2008
2008/9	13 November 2008	5 May 2009

General practitioners in this study were also involved in the HPS sentinel swabbing scheme, whereby practices are encouraged to obtain nasal/throat swabs from patients of all ages who have symptoms suggestive of influenza. Each general practice is requested to submit five swab samples per week to the West of Scotland Specialist Virology Centre in Glasgow, a World Health Organization-accredited National Influenza Centre which participates in a quality assurance programme to maintain this status. Here, RT-PCR testing for a range of respiratory pathogens is carried out. Swabs should be obtained from any patient presenting for consultation with influenza symptoms, across all age groups and regardless of whether the patient has or has not been vaccinated. We also included results for the patients in our study from swabbing carried out for routine diagnostic purposes in primary and secondary care outside the sentinel scheme.

Vaccine effectiveness is expressed as a percentage, and represents a reduction in risk provided by the vaccine for a given outcome. To calculate VE, each patient's swab data were linked using his or her CHI number, allowing patient characteristics such as vaccination status to be established from general practice and hospital admission data.

Framework for detecting residual confounding

We undertook additional analyses to identify the presence of residual confounding. This has been recommended as part of an analytical framework when reporting VE using observational study designs.⁹ We assessed the variation in VE using the following criteria:

1. *Seasonality.* Stratification by season is more important when VE is measured using non-specific outcomes. Each year of observation was partitioned into four periods: the non-influenza period, pre-influenza season, influenza season (when influenza virus is circulating) and post-influenza season (see *Figure 2*). Maximal VE should be seen during the influenza season. The vaccine should have no effect on outcome in the pre-influenza and non-influenza seasons. The non-influenza season used vaccination status from the previous influenza season. This was to minimise the bias that might occur when vaccination status is applied retrospectively. This retrospective application of vaccine status included patients who died during the preceding non-influenza season as unvaccinated, despite the fact that they would not have survived long enough to be eligible for vaccination.
2. *Vaccine match.* VE should be lower in years during which the influenza vaccine was a poor match for the circulating virus.

3. *Severity of influenza season.* VE should be greater in years during which the circulating virus caused a large excess mortality during the influenza season.
4. *Age.* It is thought that influenza vaccine is less effective in the oldest age groups owing to immune senescence.¹⁰ If this assumption is correct, VE should be lowest in the oldest subgroup. A stratified analysis of age groups was undertaken to assess for this effect.
5. *Specificity of outcome measure.* VE should be greatest for the most specific outcome (laboratory-confirmed influenza infection) and lowest for the least specific outcome (all-cause mortality). In addition to the primary analysis, in the three non-laboratory databases (primary care, acute hospital discharge and death register) we undertook analyses using the more influenza-specific outcomes (influenza-coded deaths, hospital admissions and primary care attendances) and less specific outcomes (any emergency hospital admissions, all-cause deaths and any primary care attendances).

Statistical methods

We constructed a propensity score model and calculated adjusted odds ratios (ORs) to assess differences in vaccine uptake by patients with each of the characteristics outlined previously. The model was non-parsimonious in order to include a wide range of factors that influence propensity to be vaccinated.²⁴ Using this model, a probability of receipt of the influenza vaccination was assigned to each individual in the cohort. Unadjusted illness and mortality rate ratios (RRs) were calculated as the ratios of the rate of emergency admission to hospital or death in vaccinated patients to the rate of emergency admission to hospital or death among those who did not receive the vaccine. The unadjusted estimate of VE was $(1 - RR) \times 100$. Adjusted illness and mortality hazard ratios (HRs) were estimated from a Cox proportional hazards model adjusted for all patient characteristics, and the propensity score (as deciles) and VE were calculated as $1 - HR$ where HR was that of the measured outcome in vaccinated compared with unvaccinated individuals.

For our analysis we pooled data from all nine seasons. This a priori approach gave a more powerful analysis and increased precision, particularly for the less common outcomes (with some patients represented for multiple seasons). In this pooled analysis, we accounted for the within-person correlation resulting from repeated measures on the same individual in different influenza seasons by making an adjustment for clustering using robust standard errors in the model. The effect of time was implicitly considered in the model by using the Cox proportional hazards approach and the inclusion of year as a fixed effect allowed for variation between seasons. In our propensity score matched analysis, only patients with similarly matched propensity to be vaccinated were included. To test the validity of the pooled analysis, heterogeneity between years was determined by testing for interaction between vaccine status and year for the outcomes. Where significant heterogeneity occurred, the pooled analysis was restricted.

For estimates of VE derived from linked virological swab data, we carried out a nested case-control study design. A generalised additive logistic regression model²⁵ was fitted adjusting for the effects of week during the study period, age, sex, deprivation, previous number of primary care consultations and being in a clinical at-risk group. Some of these patients did not receive the influenza vaccine; some received the vaccine, but after they were tested; and others received the vaccine before they were tested. We therefore measured VE by comparing swabs taken after vaccination from individuals who were vaccinated with swabs taken from all those who were not vaccinated at the time the swab was taken (people who were unvaccinated at the time of the swab and who were then subsequently vaccinated counted as unvaccinated in our analysis, as did people who were never vaccinated). We assessed only the first dose when two doses were given. We also stratified our analysis based on patients aged ≥ 65 years and those aged < 65 years who were classified as at risk. Using the 'epitools' library in R version 2.14.1 (the R Foundation for Statistical Computing, Vienna, Austria), we calculated 95% confidence intervals (CIs) for the OR and RR by median-unbiased estimation using the 'odds ratio' and 'rateratio' functions.²⁶ Tests of the differences were performed using the 'rate2by2.test' function.

Further statistical methods to adjust for confounding

Instrumental variable analysis

An instrumental variable is a factor related to exposure status (i.e. vaccination status), which does not have an independent effect on outcome other than by ways mediated through the exposure.²⁷ Furthermore, an 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 an instrumental variable fulfils these criteria, it can be used in analyses to produce unbiased estimates of VE by accounting for unmeasured confounding.²⁷ We assessed the suitability of five potential instrumental variables to estimate VE: antacid prescription, thyroxine prescription, depression, gout and participation in any health screening programme.

Modelling an unmeasured confounder

Hospital admission and death rates are likely to be highest in the frailest members of the study population. As these patients are less likely to seek vaccination, it has been suggested that inadequately measured frailty may explain some of the VE measured in observational studies.^{7,28} As we may not have fully accounted for frailty, which has been defined in recent studies,^{29,30} we used estimates from published data to model this potentially inadequately measured confounder in a sensitivity analysis.³¹ We assumed that prevalence of frailty varied from 5–20% in those aged ≥ 65 years, that frail individuals were two to four times more likely to be hospitalised or die³² and that frail individuals had a 50% lower probability of being vaccinated.³³

Chapter 3 Results

Vaccine uptake

In total, during the 1,767,705 person-seasons of observation over nine influenza seasons, 274,071 seasonal influenza vaccinations were administered to the whole population, of which most (93.6%; $n = 256,474$) were distributed to at-risk patients targeted for vaccination. There was 69.3% uptake of the vaccine among those aged ≥ 65 years (178,754 vaccinations during 258,100 person-seasons). For at-risk patients aged < 65 years there was a 26.2% uptake (77,264 vaccinations during 295,116 person-seasons).

High vaccine uptake was found among the oldest age group (≥ 75 years), care home residents, those previously vaccinated (*Table 2*), those with chronic diseases (except for chronic respiratory disease) and those being issued many prescriptions (*Table 3*). After adjustment, the OR for uptake was lower for individuals who smoked and those with no recorded smoking status (see *Table 2*) and for those with five or more comorbidities when compared with those with no comorbidities (see *Table 3*). There were similar findings for at-risk patients and those aged ≥ 65 years, although for the latter, an OR (with 95% CI) < 1 was also found among people whose contacts with primary care were by home consultation only (unadjusted OR 0.53; 95% CI 0.50 to 0.56) and, after adjustment for covariates, among those admitted multiple times to hospital when compared with those not admitted (> 10 hospitalisations: adjusted OR 0.71; 95% CI 0.53 to 0.95).

For our propensity score, our prediction model showed a high discriminatory power to identify patients who did and did not receive influenza vaccine (see *Appendix 1*) [all patients: receiver operating characteristic – area under the curve (ROC_{AUC}) = 0.97; patients aged ≥ 65 years: ROC_{AUC} = 0.88; at-risk patients aged < 65 years: ROC_{AUC} = 0.90].

Laboratory-confirmed influenza

A total of 3323 swabs were taken from 3016 patients over the nine seasons and then tested with RT-PCR for evidence of influenza infection. Although all subgroups were represented, patients from whom swabs were taken were more likely to be younger (aged < 75 years), female and relatively affluent (*Table 4*). During our study, male patients and the socioeconomically affluent were more likely to test positive for influenza. Of all swabs taken, 13.9% tested positive for RT-PCR-confirmed influenza. This included one-quarter of swabs from school-aged children.

Vaccine effectiveness for the trivalent inactivated influenza vaccine was 57.1% (95% CI 31.3% to 73.3%) (*Table 5*). VE was 59.6% (95% CI 22.0% to 79.1%) for at-risk patients aged < 65 years and 18.8% (95% CI -103.7% to 67.6%) for patients aged ≥ 65 years. Peak VE was found in the 2007/8 influenza season.

Clinical outcomes

In total, during the nine influenza seasons, 5591 of 162,698 (3.4%) primary care acute respiratory consultations (acute respiratory infections including influenza-like illnesses) were for influenza-like illnesses, 3096 of 86,531 (3.6%) emergency hospitalisations (all cause) were due to influenza and pneumonia and 2096 of 10,121 (20.7%) deaths (all cause) were due to influenza and pneumonia. One-fifth of hospitalisations due to influenza or pneumonia that occurred during the nine influenza seasons were in at-risk patients aged < 65 years ($n = 502/2835$ hospitalisations; 17.7%) and most occurred in older patients aged ≥ 65 years ($n = 1700/2835$; 60.0%). Almost all deaths from influenza or pneumonia occurred in

TABLE 2 Baseline characteristics and distribution of vaccine by demographic covariates

Characteristic	Vaccinated (% total) (<i>n</i> = 274,071 seasons)	Unvaccinated (% total) (<i>n</i> = 1,493,634 seasons)	Uptake (%)	Uptake adjusted OR (95% CI)
Sex				
Female	55.69	49.22	17.19	1.00
Male	44.31	50.78	13.80	1.03 (1.01 to 1.06)
Age group (years)				
0–4	0.23	5.36	0.80	1.00
5–14	1.59	13.49	2.12	1.39 (1.23 to 1.56)
15–44	9.21	49.84	3.28	1.21 (1.07 to 1.36)
45–64	23.59	26.02	14.26	2.59 (2.30 to 2.91)
65–74	35.74	3.04	68.36	16.10 (14.28 to 18.15)
75+	29.63	2.25	70.72	10.54 (9.33 to 11.89)
Deprivation quintile				
1 ^a	24.91	23.71	16.16	1.00
2	24.51	22.38	16.73	0.97 (0.94 to 1.01)
3	20.17	19.23	16.14	1.00 (0.97 to 1.04)
4	16.97	18.72	14.26	1.00 (0.96 to 1.03)
5	13.43	15.95	13.38	1.08 (1.04 to 1.12)
Urban/rural score				
1	13.83	18.39	13.80	1.00
2	57.31	56.72	18.54	1.07 (1.04 to 1.11)
3	10.49	9.08	21.20	1.27 (1.22 to 1.33)
4	2.11	1.73	22.44	1.53 (1.41 to 1.66)
5	10.72	9.82	20.03	1.29 (1.24 to 1.35)
6 ^b	5.52	4.25	23.85	1.19 (1.12 to 1.26)
Care home resident	0.66	0.05	70.05	2.10 (1.69 to 2.60)
Primary care home consultations only	2.48	0.77	37.28	1.01 (0.87 to 1.17)
Pneumococcal vaccine	43.82	1.41	85.08	1.61 (1.56 to 1.67)
Previous influenza vaccine	76.89	2.04	87.38	24.14 (23.48 to 24.81)
Smoking status				
Non-smoker	44.37	37.93	17.67	1.00
Ex-smoker	30.44	9.31	37.50	1.06 (1.03 to 1.09)
Current smoker	22.07	23.57	14.66	0.87 (0.85 to 0.90)
Not recorded	3.12	29.20	1.92	0.44 (0.46 to 0.48)

a Most socioeconomically deprived.

b Remote rural areas.

TABLE 3 Baseline characteristics and distribution of vaccine by comorbidities

Characteristic	Vaccinated (% total) (n = 274,071 seasons)	Unvaccinated (% total) (n = 1,493,634 seasons)	Uptake (%)	Uptake adjusted OR (95% CI)
Chronic kidney disease	6.35	0.38	75.59	0.96 (0.90 to 1.04)
Chronic respiratory disease	19.71	9.00	28.68	1.74 (1.68 to 1.80)
Chronic heart disease	27.71	2.43	67.68	1.32 (1.27 to 1.37)
Dementia	2.67	0.24	67.36	0.93 (0.84 to 1.03)
Diabetes	15.33	1.30	68.43	1.98 (1.88 to 2.08)
Impaired immune function	1.62	0.21	58.49	2.98 (2.59 to 3.43)
Liver disease	1.36	0.36	41.22	1.25 (1.12 to 1.40)
Neurological disease	12.66	1.62	58.90	1.08 (1.03 to 1.14)
Charlson comorbidity				
0	28.49	80.15	6.12	1.00
1–2	51.21	18.26	33.97	1.65 (1.60 to 1.70)
> 5	5.03	0.29	75.87	0.79 (0.71 to 0.87)
Primary care consultations				
0	9.67	36.98	4.58	1.00
1	8.01	14.60	9.14	1.17 (1.03 to 1.34)
2	7.67	11.06	11.29	1.26 (1.11 to 1.44)
3	7.32	8.11	14.21	1.35 (1.18 to 1.53)
4	6.91	6.23	16.92	1.35 (1.18 to 1.53)
5	6.53	4.76	20.10	1.40 (1.23 to 1.60)
> 5	53.90	18.26	35.13	1.54 (1.36 to 1.75)
Prescriptions				
0	10.03	70.85	2.53	1.00
1	7.41	11.03	10.97	1.91 (1.85 to 1.97)
2	9.66	6.59	21.20	2.67 (2.58 to 2.77)
3	9.70	3.77	32.08	3.12 (3.00 to 3.24)
4	9.63	2.33	43.11	3.35 (3.21 to 3.49)
5	9.04	1.54	51.83	3.75 (3.58 to 3.93)
11–15	10.61	0.62	75.71	3.79 (3.55 to 4.03)
> 15	3.68	0.19	77.83	3.46 (3.12 to 3.84)
Hospital consultations				
0	76.48	90.92	13.37	1.00
1	12.84	6.52	26.56	1.11 (1.08 to 1.15)
2	5.16	1.44	39.67	1.12 (1.06 to 1.18)
3	2.23	0.51	44.77	0.98 (0.90 to 1.07)
4	1.18	0.23	48.90	1.01 (0.88 to 1.15)

continued

TABLE 3 Baseline characteristics and distribution of vaccine by comorbidities (*continued*)

Characteristic	Vaccinated (% total) (<i>n</i> = 274,071 seasons)	Unvaccinated (% total) (<i>n</i> = 1,493,634 seasons)	Uptake (%)	Uptake adjusted OR (95% CI)
5	0.71	0.12	51.68	1.05 (0.88 to 1.26)
6–10	1.04	0.20	48.96	1.04 (0.90 to 1.20)
> 10	0.34	0.07	48.05	1.17 (0.91 to 1.51)

TABLE 4 Adjusted OR of having influenza confirmed by RT-PCR (*n*=3323 swabs)

Description	Total samples (rate per 1000 person-seasons)	No. vaccinated at test (% of total)	No. of positive swabs (% of total)	Swab-positive adjusted OR ^a	Adjusted OR 95% CI
Gender					
Female	1995 (2.25)	310 (15.54)	248 (12.43)	1.00	–
Male	1328 (1.51)	188 (14.16)	214 (16.11)	1.35	1.07 to 1.69
Age group (years)					
0–4	390 (4.83)	5 (1.28)	60 (15.38)	1.00	–
5–14	433 (2.10)	15 (3.46)	104 (24.02)	1.56	1.05 to 2.32
15–44	1405 (1.82)	69 (4.91)	196 (13.95)	0.89	0.63 to 1.27
45–64	741 (1.63)	174 (23.48)	79 (10.66)	0.71	0.47 to 1.06
65–74	244 (1.70)	154 (63.11)	18 (7.38)	0.67	0.36 to 1.28
75+	110 (0.96)	81 (73.64)	5 (4.55)	0.41	0.15 to 1.13
Deprivation quintile					
1 ^b	961 (3.49)	189 (19.67)	100 (10.41)	1.00	–
2	789 (2.42)	135 (17.11)	97 (12.29)	1.18	0.85 to 1.63
3	735 (2.15)	79 (10.75)	116 (15.78)	1.55	1.13 to 2.12
4	519 (1.92)	59 (11.37)	96 (18.50)	1.94	1.39 to 2.71
5	309 (0.73)	36 (11.65)	51 (16.50)	1.86	1.24 to 2.79
Primary care consultations					
0–2	1133 (1.13)	42 (3.71)	206 (18.18)	1.00	–
3–4	785 (3.10)	63 (8.03)	103 (13.12)	0.69	0.52 to 0.92
≥ 5	1405 (2.76)	393 (27.97)	153 (10.89)	0.87	0.66 to 1.15

a Adjusted for age, sex and socioeconomic deprivation.

b Most socioeconomically deprived.

TABLE 5 Percentage vaccinated by case-control status and adjusted VE for RT-PCR-confirmed influenza

Description	Influenza-positive (cases)		Influenza-negative (controls)		% total positive	Adjusted VE (95% CI)
	No. vaccinated/total	% vaccinated	No. vaccinated/total	% vaccinated		
Age group (years)						
All ages	27/462	5.84	471/2861	16.46	13.90	57.13 (31.26 to 73.26)
< 65	14/439	3.19	249/2530	9.84	14.79	66.23 (39.29 to 81.21)
< 65 at risk	14/117	11.97	209/788	26.52	12.93	59.60 (21.95 to 79.08)
≥ 65	13/23	56.52	222/331	67.07	6.50	18.82 (- 103.66 to 67.64)
Season						
2000/1	0/59	0.00	53/404	13.12	12.93	NA
2001/2	1/55	1.82	25/310	8.06	7.67	77.26 (- 116.76 to 97.61)
2002/3	1/21	4.76	22/220	10.00	10.55	68.19 (- 310.30 to 97.53)
2003/4	4/56	7.14	12/269	4.46	5.18	49.14 (- 57.81 to 83.61)
2004/5	5/49	10.20	60/351	17.09	19.40	43.59 (- 66.17 to 80.85)
2005/6	6/141	4.26	52/470	11.06	10.49	28.68 (- 108.83 to 75.64)
2006/7	2/26	7.69	23/228	10.09	10.92	22.29 (- 374.58 to 87.28)
2007/8	3/43	6.98	55/214	25.70	29.15	80.19 (20.64 to 95.06)
2008/9	4/40	10.00	50/254	19.69	22.50	38.04 (- 135.74 to 83.71)
NA, not applicable.						

those groups targeted for vaccination ($n = 2001/2096$; 95.5%); most occurred in people aged ≥ 65 years ($n = 1860/2096$; 88.7%).

In *Tables 6* and *7*, we report the incidence rate of clinical outcomes (and unadjusted rates) for unvaccinated versus vaccinated individuals as well as VEs for the whole cohort. In *Table 8* we report results for one subgroup, clinically at-risk patients aged < 65 years; *Table 9* presents the results for people who are aged ≥ 65 years. In *Tables 6* and *7*, where results for the whole population are reported, it should be noted that unadjusted rates among the vaccinated are far higher than among the unvaccinated. This is largely due to the majority of the vaccinated being older people (aged ≥ 65 years) who are more likely to have clinical outcomes (particularly hospitalisation and death) than younger, unvaccinated individuals.

After adjustment for confounding factors (including age in the model), recipients of influenza vaccine were less likely to have acute respiratory illnesses, less likely to require hospitalisation for influenza, pneumonia, COPD or cardiovascular disease, and less likely to die from all outcomes studied in the whole population (see *Tables 6* and *7*). In the at-risk population aged < 65 years, analyses were less precise due to lower

TABLE 6 Clinical primary care and hospitalisation outcomes and VE: all patients

Outcomes of interest	Vaccination status	Events (rate per 1000 person-seasons)	Unadjusted RR (95% CI)	Adjusted VE (95% CI) ^a	Matched VE (95% CI) ^b
Primary care ILI	No	2998 (2.60)	1.00	–	–
	Yes	599 (2.69)	1.03 (0.95 to 1.13)	9.96 (–3.81 to 21.90)	16.44 (5.70 to 25.96)
Primary care ARI	No	62,751 (54.40)	1.00	–	–
	Yes	22,434 (100.67)	1.95 (1.92 to 1.98)	2.73 (0.20 to 5.19)	–33.00 (–39.90 to –26.40)
Hospitalisation IP	No	1188 (1.03)	1.00	–	–
	Yes	1090 (4.89)	4.77 (4.39 to 5.18)	8.53 (–3.59 to 19.24)	19.32 (8.25 to 29.05)
Hospitalisation IPC	No	2251 (1.95)	1.00	–	–
	Yes	3289 (14.76)	7.66 (7.26 to 8.08)	12.22 (4.36 to 19.44)	26.66 (19.82 to 32.92)
Hospitalisation CVD	No	3659 (3.17)	1.00	–	–
	Yes	5944 (26.67)	8.61 (8.26 to 8.98)	9.26 (3.71 to 14.49)	22.60 (17.53 to 27.35)
Hospitalisation all	No	32,598 (28.26)	1.00	–	–
	Yes	17,672 (79.29)	2.96 (2.91 to 3.02)	7.08 (4.14 to 9.94)	12.39 (9.10 to 15.57)
Hospitalisation trauma	No	5427 (4.70)	1.00	–	–
	Yes	2115 (9.49)	2.03 (1.93 to 2.13)	11.35 (3.74 to 18.37)	18.10 (10.10 to 25.39)
Hospitalisation appendicitis and hernia	No	700 (0.61)	1.00	–	–
	Yes	402 (1.80)	2.98 (2.63 to 3.36)	0.70 (–21.27 to 18.69)	–4.20 (–21.40 to 10.61)

ARI, acute respiratory infections; CVD, cerebrovascular and cardiovascular disease; ILI, influenza-like illness; IP, influenza, pneumonia; IPC, influenza, pneumonia, COPD.

a Includes propensity score as a covariate – vaccinated seasons at risk (2002–9): yes = 222,854; no = 1,153,455.

b Matched on propensity score – vaccinated seasons at risk (2002–9): yes = 78,048; no = 78,048.

event rates for most of the outcomes. However, significant VE was found for hospitalisations and deaths from cardiovascular disease and deaths due to influenza, pneumonia or COPD (see *Table 8*). Significant VE was found for most hospitalisation and death outcomes in the population aged ≥ 65 years (see *Table 9*).

Significant heterogeneity was found in 2000/1 and 2001/2 when compared with other years (test for interaction: $p < 0.0001$) and these years were excluded from the final pooled analysis. After propensity score matching was performed (for seven seasons from 2002/3 to 2008/9) there were 78,048 matched pairs of patients. Influenza vaccine recipients were less likely to be hospitalised or to die from influenza, pneumonia, COPD or cardiovascular disease (see *Tables 6* and *7*).

In our sensitivity analysis using negative controls, we found significant VE for trauma hospitalisation with the exception of at-risk patients aged < 65 years. However, further sensitivity analyses (see *Table 10*) revealed that VE for trauma during the post season was greater than that during peak influenza season, and this suggests that it may be a poor choice of negative control. No significant VE was found for appendicitis and hernia hospitalisation.

TABLE 7 Clinical outcomes, deaths and VE: all patients

Outcomes of interest	Vaccination status	Events (rate per 1000 person-seasons)	Unadjusted RR (95% CI)	Adjusted VE (95% CI) ^a	Matched VE (95% CI) ^b
Deaths IP	No	789 (0.68)	1.00	–	–
	Yes	833 (3.74)	5.48 (4.97 to 6.04)	29.86 (19.47 to 38.91)	37.91 (29.47 to 45.35)
Deaths IPC	No	1228 (1.06)	1.00	–	–
	Yes	1385 (6.21)	5.87 (5.43 to 6.34)	19.47 (22.00 to 37.50)	41.78 (33.94 to 48.70)
Deaths CVD	No	1832 (1.59)	1.00	–	–
	Yes	2110 (9.47)	6.01 (5.64 to 6.40)	32.96 (26.55 to 38.81)	41.13 (35.60 to 46.19)
Deaths all	No	3961 (3.43)	1.00	–	–
	Yes	3807 (17.08)	5.04 (4.82 to 5.27)	33.60 (29.00 to 37.90)	41.63 (31.10 to 45.83)

CVD, cerebrovascular and cardiovascular disease; IP, influenza, pneumonia; IPC, influenza, pneumonia, COPD.

a Vaccinated seasons at risk, whole population (2002–9): yes = 222,854; no = 1,153,455.

b Vaccinated seasons at risk, matched analysis (2002–9): yes = 78,048; no = 78,048.

Sensitivity analyses

Seasonality

Analyses performed to identify residual confounding found that, with the exception of all-cause hospitalisations, maximal VE for our clinical outcomes were found during the influenza season (*Table 10*). However, pre-season VEs were higher for primary care acute respiratory disease. In the post-season analysis, positive estimates of VE were found for hospitalisation due to trauma and all causes. In the non-influenza season, positive estimates of VE were found for all-cause hospitalisation and for hospitalisation due to influenza, pneumonia or COPD. In addition, the influenza-positive estimates were found for all-cause mortality and cerebrovascular and cardiovascular disease-related mortality during the non-influenza season period.

Vaccine match and severity of influenza season

Poor precision resulted in difficulty comparing VE by season. Using the laboratory-confirmed influenza data (see *Table 5*) the most severe season was 2007/8, with 29.15% of positive tests. This year (2007/8) also had the highest VE in our clinical outcomes (*Figure 3*: deaths from influenza and pneumonia for people aged ≥ 65 years are shown here as an example). During the season 2005/6, where the influenza B component of the vaccine was regarded as poorly matched, VE was the second lowest for laboratory-confirmed influenza in the nine seasons (see *Table 5*). However, no obvious decline in VE for this poorly matched year was found in our clinical outcomes.

Where all-cause death was used as an outcome, VE was similar between seasons (*Figure 4*).

Specificity of outcome measure

The highest VE was for our most specific outcome, laboratory-confirmed influenza (see *Table 5*). For primary care clinical outcomes, VE for acute respiratory diseases was lower than for the more specific influenza-like illnesses (see *Table 6*). For hospitalisation and death, however, VE was lower in the most specific outcome, influenza and pneumonia (see *Tables 6 and 7*).

TABLE 8 Clinical outcomes and VE in at-risk patients aged <65 years

Outcomes of interest	Vaccination status	Events	Rate per 1000 person-seasons ^a	Unadjusted RR (95% CI)	Adjusted VE (95% CI)
Primary care ILI	No	600	3.51	1.00	–
	Yes	215	3.32	0.94 (0.81 to 1.10)	6.39 (–15.00 to 23.81)
Primary care ARI	No	20,127	117.81	1.00	–
	Yes	9858	152.01	1.34 (1.31 to 1.38)	–0.69 (–2.76 to 4.02)
Hospitalisation IP	No	247	1.45	1.00	–
	Yes	167	2.58	1.78 (1.46 to 2.17)	6.56 (–20.53 to 27.55)
Hospitalisation IPC	No	539	3.16	1.00	–
	Yes	574	8.85	2.82 (2.51 to 3.17)	9.81 (–7.60 to 24.40)
Hospitalisation CVD	No	1211	7.09	1.00	–
	Yes	1031	15.90	2.26 (2.08 to 2.46)	13.15 (2.76 to 22.43)
Hospitalisation all	No	7691	45.02	1.00	–
	Yes	4030	61.14	1.41 (1.35 to 1.46)	9.54 (4.31 to 14.47)
Deaths IP	No	67	0.39	1.00	–
	Yes	43	0.66	1.69 (1.15 to 2.48)	34.14 (–7.50 to 59.63)
Deaths IPC	No	144	0.84	1.00	–
	Yes	103	1.59	1.89 (1.46 to 2.43)	35.68 (9.52 to 54.27)
Deaths CVD	No	211	1.24	1.00	–
	Yes	146	2.25	1.82 (1.48 to 2.25)	30.04 (7.19 to 47.26)
Deaths all	No	549	3.21	1.00	–
	Yes	307	4.73	1.48 (1.28 to 1.70)	33.02 (18.78 to 44.77)
Hospitalisation trauma	No	964	5.64	1.00	–
	Yes	372	5.74	1.02 (0.90 to 1.15)	6.36 (–10.28 to 20.50)
Hospitalisation appendicitis and hernia	No	134	0.78	1.00	–
	Yes	62	0.96	1.22 (0.90 to 1.65)	24.36 (–12.80 to 49.26)

ARI, acute respiratory infections; CVD, cerebrovascular and cardiovascular disease; ILI, influenza-like illness; IP, influenza, pneumonia; IPC, influenza, pneumonia, COPD.

^a Vaccinated seasons at risk (2002–9): yes = 64,853; no = 170,836.

Presence of immune senescence by age

Vaccine effectiveness was higher for our clinical outcomes in people aged ≥ 65 years compared with younger at-risk patients (see *Tables 8* and *9*).

Instrumental variable analysis

Participation in a screening programme was the variable most closely correlated with influenza vaccination (correlation coefficient 0.71) and was also associated with one of the main study outcomes (death due to influenza or pneumonia; HR 2.6, 95% CI 2.4 to 2.9, $p < 0.001$). However, this association with outcome was not exclusively mediated through vaccination status (HR adjusted for vaccination status 1.4, 95% CI 1.3 to 1.6, $p < 0.001$). Furthermore, participation in a screening programme was also strongly associated with a number of confounding variables (e.g. number of previous hospital admissions, comorbidity, age,

TABLE 9 Clinical outcomes and VE in patients aged ≥ 65 years

Outcomes of interest	Vaccination status	Events	Rate per 1000 person seasons ^a	Unadjusted RR (95% CI)	Adjusted VE (95% CI)
Primary care ILI	No	103	1.79	1.00	–
	Yes	348	2.40	1.35 (1.08 to 1.68)	19.29 (– 3.25 to 36.91)
Primary care ARI	No	2558	44.43	1.00	–
	Yes	11,927	82.43	1.93 (1.85 to 2.02)	4.17 (– 0.33 to 8.46)
Hospitalisation IP	No	453	7.87	1.00	–
	Yes	905	6.25	0.79 (0.71 to 0.89)	11.57 (– 2.42 to 23.65)
Hospitalisation IPC	No	1130	19.62	1.00	–
	Yes	2687	18.57	0.95 (0.88 to 1.01)	15.85 (7.04 to 23.83)
Hospitalisation CVD	No	1888	32.79	1.00	–
	Yes	4883	33.75	1.03 (0.98 to 1.09)	12.77 (6.45 to 18.67)
Hospitalisation all	No	5716	99.27	1.00	–
	Yes	13,114	90.63	0.90 (0.88 to 0.93)	13.14 (9.51 to 16.62)
Deaths IP	No	657	11.41	1.00	–
	Yes	781	5.40	0.47 (0.42 to 0.52)	32.50 (21.94 to 41.63)
Deaths IPC	No	991	17.21	1.00	–
	Yes	1270	8.78	0.51 (0.47 to 0.55)	32.75 (24.38 to 40.20)
Deaths CVD	No	1428	24.80	1.00	–
	Yes	1955	13.51	0.54 (0.50 to 0.58)	34.35 (27.65 to 40.42)
Deaths all	No	2749	47.74	1.00	–
	Yes	3437	23.75	0.49 (0.46 to 0.51)	36.93 (32.25 to 41.30)
Hospitalisation trauma	No	841	14.60	1.00	–
	Yes	1681	11.62	0.79 (0.73 to 0.86)	19.27 (10.15 to 27.46)
Hospitalisation appendicitis and hernia	No	116	2.01	1.00	–
	Yes	333	2.30	1.14 (0.92 to 1.41)	– 16.22 (– 51.24 to 10.69)

ARI, acute respiratory infections; CVD, cerebrovascular and cardiovascular disease; ILI, influenza-like illness; IP, influenza, pneumonia; IPC, influenza, pneumonia, COPD.

a Vaccinated seasons at risk (2002–9): yes = 144,700; no = 57,578.

sex and socioeconomic status). Similarly, each of the remaining four variables was unlikely to fulfil criteria for use as an instrumental variable to produce unbiased estimates of VE. Our findings are in keeping with those of other investigators who have attempted to assess influenza VE using instrumental variables in routine health-care data.³⁴ We were therefore unable to use this method to estimate VE accounting for unmeasured confounding.

Modelling an unmeasured confounder

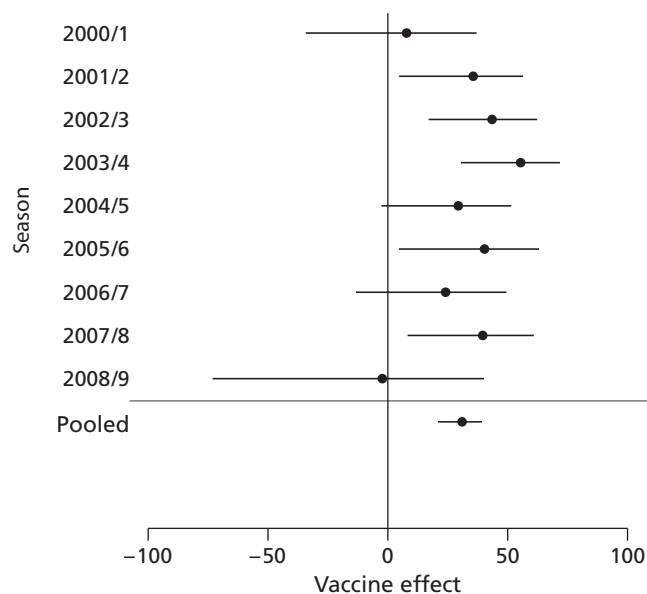
We used estimates from published data to model the effect of inadequately measured confounders on VE in our matched population.

TABLE 10 Pre- and post-season analysis for matched analysis

Outcomes of interest	Pre-season adjusted VE (95% CI)	Post-season adjusted VE (95% CI)	Non-season adjusted VE (95% CI)
Primary care ILI	-36.05 (-169.04 to 31.21)	-18.14 (-100.95 to 30.53)	17.75 (-33.81 to 49.44)
Primary care ARI	13.07 (3.56 to 21.65)	-38.41 (-46.48 to -30.79)	-26.46 (-33.67 to -19.64)
Hospitalisation IP	-26.22 (-129.43 to 30.56)	11.64 (-10.18 to 16.07)	12.59 (-13.82 to 32.88)
Hospitalisation IPC	-21.38 (-129.43 to 30.56)	-12.11 (-31.66 to 4.53)	16.35 (1.00 to 29.33)
Hospitalisation CVD	-7.46 (-34.87 to 14.38)	1.15 (-10.58 to 11.64)	5.84 (-4.51 to 15.16)
Hospitalisation all	-16.83 (-170.93 to 49.64)	6.42 (0.74 to 11.78)	8.12 (3.01 to 12.96)
Deaths IP	- ^a	2.22 (-34.59 to 28.96)	-12.57 (-52.28 to 16.24)
Deaths IPC	- ^a	-9.62 (-42.19 to 15.47)	-4.04 (-31.14 to 17.46)
Deaths CVD	- ^a	10.07 (-9.49 to 26.13)	18.71 (2.70 to 32.09)
Deaths all	- ^a	8.91 (-5.62 to 21.43)	13.35 (1.65 to 23.66)
Hospitalisation trauma	4.73 (-40.53 to 35.41)	20.61 (5.34 to 33.42)	6.56 (-9.42 to 20.22)
Hospitalisation appendicitis and hernia	-16.81 (-170.93 to 49.64)	2.91 (-42.43 to 33.82)	11.90 (-24.45 to 37.63)

ARI, acute respiratory infections; CVD, cerebrovascular and cardiovascular disease; ILI, influenza-like illness; IP, influenza, pneumonia; IPC, influenza, pneumonia, COPD.

^a Only two deaths occurred in the unvaccinated pre-season.

**FIGURE 3** Death from influenza and pneumonia by season in patients aged ≥ 65 years.

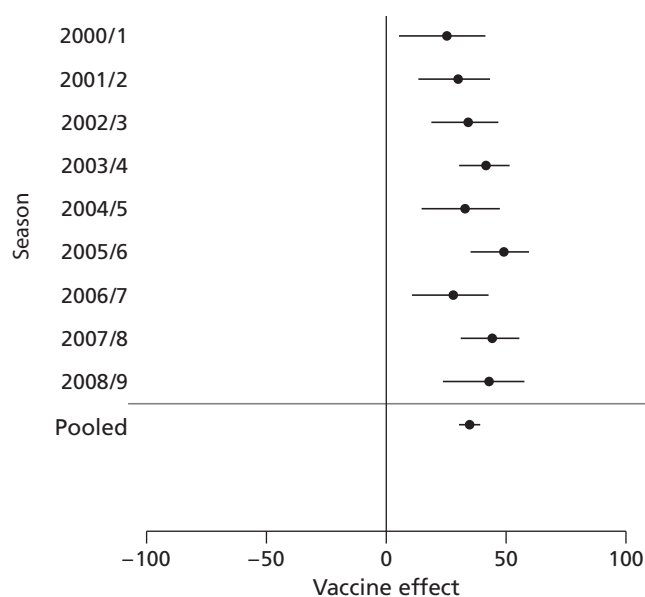


FIGURE 4 All-cause death by season in patients aged ≥ 65 years.

We found that for one outcome, death due to influenza or pneumonia, a scenario of 20% prevalence of frailty among unvaccinated individuals resulted in the vaccine no longer being effective (VE 13.2%, 95% CI 2.2% to 22.3%).⁹ Frailty resulted in a twofold increase in the risk of death and was not present in the vaccinated population. By varying the prevalence of frailty and its risk on outcome, we modelled the change in VE estimates for a number of scenarios (*Table 11*). We also found that this model can be displayed effectively in graphical form (*Figures 5 and 6*). In *Figures 5 and 6* the VE 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 both unvaccinated and vaccinated individuals, the baseline result is achieved, as there is no difference in the level of the unmeasured variable in the two groups.

TABLE 11 Sensitivity analysis to quantify the effects of a hypothetical unmeasured confounder on the matched analysis results

Increase in the risk of outcome on account of the confounder	Prevalence of confounder		Death from pneumonia or influenza: adjusted VE (95% CI)
	In unvaccinated individuals (%)	In vaccinated individuals (%)	
–	0	0	27.63 (18.51 to 35.73)
Doubled	5	0	24.01 (14.43 to 32.51)
Doubled	15	5	20.73 (10.74 to 29.61)
Doubled	20	5	17.29 (6.86 to 26.55)
Quadrupled	5	0	16.77 (6.28 to 26.09)
Quadrupled	15	5	8.75 (–2.75 to 18.96)
Quadrupled	20	5	–0.69 (–13.38 to 10.58)

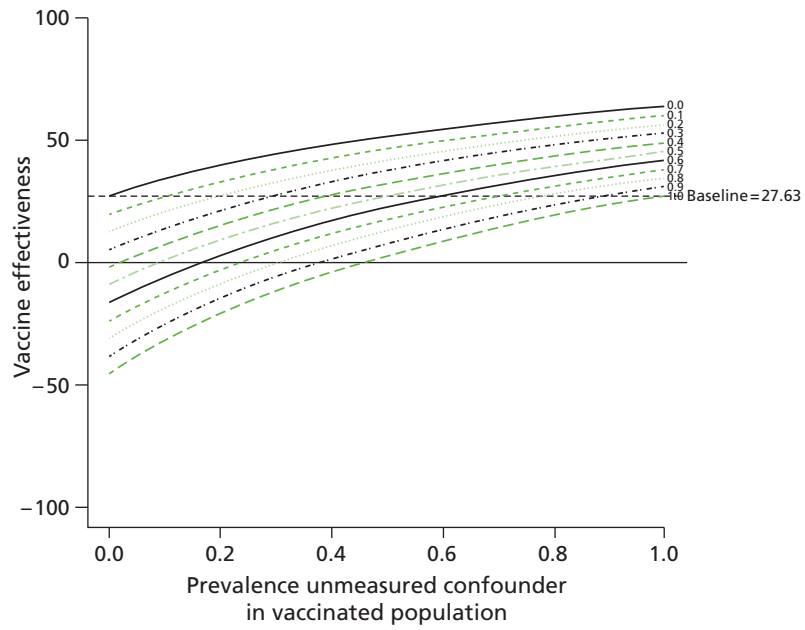


FIGURE 5 Unmeasured residual confounding and VE (doubling of risk of death from influenza and pneumonia).

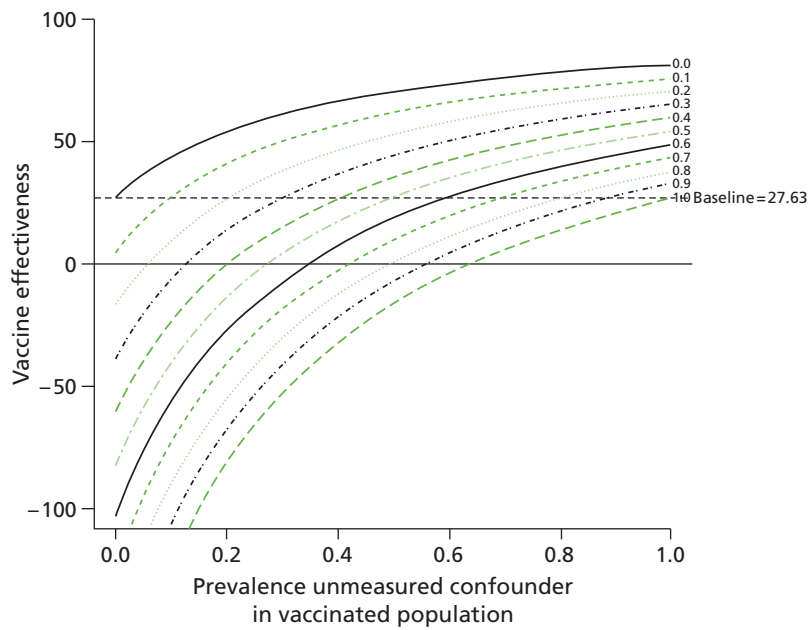


FIGURE 6 Unmeasured residual confounding and VE (quadrupling of risk of death from influenza and pneumonia).

Chapter 4 Discussion

The majority of the trivalent inactivated influenza vaccines were distributed to at-risk patients targeted for vaccination. There was high uptake of the vaccine among those aged ≥ 65 years. However, during the nine seasons, only one-quarter of at-risk patients aged < 65 years received the vaccine. The trivalent inactivated influenza vaccine was effective in reducing RT-PCR laboratory-confirmed influenza, as well as hospitalisations and deaths from influenza and pneumonia.

The modest vaccine uptake among at-risk patients aged < 65 years was similar to that found using the QRESEARCH database (2000/1: 20.6%; 2004/5: 29.3%),³⁵ but lower than that found using questionnaire surveys carried out in a more recent year (2007/8: 56.0%).³⁶

Our finding of 57.1% trivalent influenza VE, using RT-PCR in symptomatic medical attenders of all ages presenting over nine seasons, is similar to the pooled efficacy of 59% found in a meta-analysis of randomised studies (albeit in a younger, healthier population). In the 2007/8 season, when vaccine and circulating virus were well matched (A/H1N1 Solomon Islands virus), our VE for laboratory-confirmed influenza was higher than that of a US study which used a study design similar to ours (80% vs. 52%).³⁷ We also compared our results with those of two case-control effectiveness studies in older age groups which used a similar study design to ours.^{38,39} One of these, carried out in the USA in 2010/11 using RT-PCR, found a VE of 36% (95% CI – 22% to 62%) but suffered from poor precision due to low numbers of cases.³⁸ The other was a pilot using RT-PCR and culture in Spain in 2008/9, which found a very high effectiveness (78%; 95% CI 26% to 93%) but with very low numbers of unvaccinated control subjects.³⁹

Rates of hospitalisation for influenza and pneumonia were identical to those reported for people aged ≥ 65 years in the USA (0.7% in unvaccinated and 0.6% in vaccinated individuals).³² However, our all-cause death rates were higher (4.6% vs. 1.6% in unvaccinated and 2.4% vs. 1.0% in vaccinated patients) although our rates of death for influenza and pneumonia were lower (1.0% in unvaccinated and 0.5% in vaccinated individuals; no comparative figures available from Nichol *et al.*³²). This may be partly attributable to differences between the Scottish and US health-care systems.

Although criticised for bias,²⁸ previous observational studies have found a high VE for preventing clinical outcomes such as hospitalisation for influenza and pneumonia (27%) and all-cause death (48%) in people aged > 65 years.³² More recently, estimates made during periods when influenza was not circulating estimated far lower VE.^{40,41} Our study, which included detailed patient information from the primary care electronic health record linked to other health-care data sources, found that in people aged ≥ 65 years, VE estimates were higher than those reported by Fireman *et al.*⁴⁰ for emergency admissions for influenza and pneumonia (4.6%) and all-cause death (8.5%).

Quasi-experimental studies can be used to assess the effects of health-care interventions without influencing the care provided or the patients who receive it.⁴ When used in the assessment of vaccination programmes they therefore have high external validity and broad generalisability. However, the non-randomised nature of studies such as this are limited by the extent to which there may be dissimilarities between vaccinated and unvaccinated individuals, in both their likelihood of receiving vaccination and in their subsequent care and follow-up, leading to overestimated mortality benefits. The retrospective ascertainment of vaccination status is necessarily less reliable than prospective clarification, but our use of data derived from health records has been found to be more reliable than self-reporting methods,⁴² as is the electronic recording of uptake rates in this sample of the Scottish population.

Sensitivity analysis framework

There are two types of confounding which have a role when estimating VE: (i) confounding by indication, or negative confounding, which will underestimate VE and will include people with underlying chronic diseases who are more likely to be vaccinated (and are at greater risk of disease and only moderately elevated risk of death); and (ii) positive confounding, which will overestimate VE and will include healthier individuals who are more readily vaccinated (as they may be more mobile and actively seek the vaccine) and, conversely, very frail people who are less likely to be vaccinated and may die soon thereafter.⁴³

First, to try and account for residual confounding, we used the most detailed electronic health information available (in particular that from primary care, which uses the granular Read coding system⁴⁴) to include in our model a score determining propensity to be vaccinated. We found variation in uptake between groups. Among care home residents, for instance, uptake was high and this reflects what is a common practice in the UK of vaccinating residents en masse by visiting nursing home facilities. We also found that with increased use of primary care, uptake increased and this may be due to the increased opportunity to vaccinate. We did, however, find a curvilinear relationship between vaccination and Charlson comorbidity. In particular, for patients aged ≥ 65 years, there were higher ORs for uptake in the presence of at least one Charlson comorbidity or hospitalisation, but lower ORs (than in those with no morbidity) were found among those with a Charlson score of five or more and > 10 hospitalisations. By matching individuals in our cohort on a propensity score we were able to effectively compare people with a similar propensity to be vaccinated. This should have limited the effect of positive confounding, which will overestimate VE. We feel that the use of our propensity score has reduced bias for our estimates of VE. However, our VE for all-cause deaths was still higher than the estimated excess mortality attributed to influenza of 5–10%.⁹

We also attempted to explore and account for residual confounding using the framework suggested by Simonsen *et al.*⁸ The influenza vaccine should be not be effective for outcomes unrelated to infection with seasonal influenza and reassuringly no VE was found for hospitalisation due to appendicitis and hernia. A positive VE (which continued in the post-influenza season), however, was found for hospitalisation due to trauma (e.g. for wounds and fractures). However, further sensitivity analyses revealed that VE for trauma during the post-influenza season was greater than during peak influenza seasons, and this suggests that it may be a poor choice of negative control. It is of interest though that the unvaccinated group was more likely to be hospitalised than the vaccinated group for this type of admission. When analysing VEs stratified by the four periods of each year (influenza season and non-, pre- and post-influenza season), maximal VE, determined by use of viral surveillance information, was generally seen for most of our clinical outcomes during the influenza season. VEs outside the influenza season were usually close to zero with wide 95% CIs owing to the relatively small exposure periods outside the main influenza season (at most 2.5 months) and a lack of influenza/pneumonia outcomes. Positive VEs were, however, found for less specific outcomes such as hospitalisations and deaths for any cause, or for outcomes that can be exacerbated or caused by factors other than influenza, for example, acute respiratory disease, COPD hospitalisation or death from cerebrovascular and cardiovascular disease. Our VE for less specific outcomes, however, was found to continue during post- and non-influenza seasons when influenza was not circulating, suggesting some residual bias still exists. Sophisticated seasonality techniques such as case-centred logistic regression, which attempt to account for deaths that take place when influenza is not circulating, have found that without vaccination, excess mortality during influenza season would be 9.8%, and estimated VE 4.6% (half of all deaths being prevented by vaccine).⁴⁰

Our unique cohort allowed VE to be derived for a range of outcomes in the same population over multiple influenza seasons. However, although the modest size of our cohort made it feasible to collate centrally almost all cases of influenza-related disease, allowing for completeness of reporting, any analysis by subgroups or by individual season resulted in poorer precision and wide CIs. It was therefore less than straightforward to draw conclusions regarding the validity of our VE estimates using Simonsen's framework.⁸ However, we were able to determine that during the most severe season for our cohort

(2007/8, as determined from swabs), VE was highest for our outcomes. Although there was no protective effect for the outcome appendicitis and hernia, a protective effect was found for trauma, which is unrelated to influenza. The significant heterogeneity in the matched analysis for the years 2000/1 and 2001/2 may have been caused by accuracy and completeness issues (found in 2000), which were resolved by the Information Services Division (ISD) in subsequent years.⁴⁵

We attempted to use further methods to assess the degree of bias in our VE estimates. We were unable to use instrumental variables for this purpose as none were found to be valid. However, we modelled the effect of an unmeasured confounder, such as frailty, on our VE estimates. We found that VE for our primary outcome, death due to influenza or pneumonia, was robust to modelling a high prevalence of unmeasured frailty. This is despite the fact that we included a number of variables in our models which would have captured some degree of frailty, such as residence in a nursing home, provision of social care, number of previous hospital admissions, number of GP consultations and number of repeat prescriptions.

Implications for practice

Using VE estimates for our most specific outcome, RT-PCR-confirmed influenza over a 9-year period, the seasonal influenza programme was found to be effective, particularly in preventing influenza in younger, clinically at-risk groups of patients.

Research recommendations

Although the modest size of our cohort made it feasible to collate centrally almost all cases of influenza-related disease, allowing for completeness of reporting, the analysis of subgroups (in particular, older age groups) or analysis by individual season resulted in poorer precision and wide CIs. Any future work should therefore aim to address this issue by ensuring adequate power to test VE in these subgroups of patients, while minimising the effect of bias, such as health-seeking behaviour. While work is being undertaken to produce better vaccines, continued monitoring and a strong international evidence base for the effectiveness of seasonal influenza vaccination programmes is necessary.

Chapter 5 Conclusions

Few countries' health systems allow for the integrated and accessible data recording that made this study possible and made it feasible to collate centrally almost all hospitalisations and deaths attributed to influenza, allowing for completeness of reporting. By making best use of the integrated and accessible Scottish data available to us, we found most influenza vaccines were distributed to those at risk of serious complications from influenza. Influenza vaccination was associated with a significant decrease in the risk of laboratory-confirmed influenza and complications arising from influenza in a nationally representative cohort.

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Contributions of authors

Dr Colin Simpson (Reader in Population Health Sciences) and **Dr Nazir Lone** (Clinical Fellow, Intensive Care) were principal investigators and led the writing of this report.

Professor Lewis Ritchie (Professor of Primary Care), **Professor Aziz Sheikh** (Professor of Primary Care Research & Development) and **Dr Jim McMenamin** (Consultant Epidemiologist) helped design the study and commented on drafts of the paper.

Professor Chris Robertson (Professor of Statistics) and **Dr Kim Kavanagh** (Research Fellow, Statistics) helped to design the study, carry out the analyses and write the paper.

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Appendix 1 Propensity scores

All people

Cohort split into two to create model ($n = 1,179,201$) and test predictions ($n = 588,718$). From the model output a propensity score based on the model coefficients is created and a score is assigned to each individual in the cohort.

Model output

```

Call:
svyglm(formula = flu.vacc ~ factor(sex) + factor(Age.gp) + factor(flu.vacc.ly) +
  factor(UR6) + factor(SIMD5) + factor(charlson.gp) + factor(smoke.status) +
  factor(remote_cons_only) + factor(nCons_hosp) + factor(nDays_Encounter_Gp) +
  factor(CareHome_Social) + factor(Dementia) + factor(resp) +
  factor(cardiac) + factor(renal) + factor(liver) + factor(neuro) +
  factor(immuno) + factor(diab) + factor(repeat.pres.ly_gp) +
  factor(pneumo.ever), design = cohort.training.svy, family = binomial)

Survey design:
svydesign(~UniquePatientId, data = cohort.training)

Coefficients:

```

	Estimate	Std. Error	t value	Pr(> t)	
(Intercept)	-5.163396	0.089081	-57.963	< 2e-16	***
factor(sex)Male	0.032294	0.011342	2.847	0.004410	**
factor(Age.gp) 5-14	0.325973	0.059112	5.514	3.50e-08	***
factor(Age.gp) 15-44	0.187020	0.059994	3.117	0.001825	**
factor(Age.gp) 45-64	0.951544	0.060094	15.834	< 2e-16	***
factor(Age.gp) 65-74	2.778910	0.061131	45.458	< 2e-16	***
factor(Age.gp) 75+	2.354741	0.061891	38.046	< 2e-16	***
factor(flu.vacc.ly) Yes	3.183722	0.014071	226.266	< 2e-16	***
factor(UR6) 2	0.069301	0.015972	4.339	1.43e-05	***
factor(UR6) 3	0.242218	0.022836	10.607	< 2e-16	***
factor(UR6) 4	0.424048	0.040620	10.439	< 2e-16	***
factor(UR6) 5	0.255765	0.022653	11.291	< 2e-16	***
factor(UR6) 6	0.175151	0.029596	5.918	3.26e-09	***
factor(SIMD5) 2	-0.027190	0.016198	-1.679	0.093231	.
factor(SIMD5) 3	0.001886	0.017108	0.110	0.912207	
factor(SIMD5) 4	-0.005225	0.017947	-0.291	0.770947	
factor(SIMD5) 5	0.080094	0.018669	4.290	1.79e-05	***
factor(charlson.gp) 1-2	0.501041	0.015800	31.712	< 2e-16	***
factor(charlson.gp) 3-4	0.153466	0.028607	5.365	8.12e-08	***
factor(charlson.gp) >5	-0.242651	0.050073	-4.846	1.26e-06	***
factor(smoke.status) Ex	0.056231	0.014858	3.785	0.000154	***
factor(smoke.status) Non	-0.136418	0.013520	-10.090	< 2e-16	***
factor(smoke.status) Unknown	-0.778736	0.024544	-31.728	< 2e-16	***
factor(remote_cons_only) No consultations	-0.138234	0.065581	-2.108	0.035046	*
factor(remote_cons_only) Remote Cons only	0.008292	0.074263	0.112	0.911099	
factor(nCons_hosp) 1	0.106073	0.016377	6.477	9.36e-11	***
factor(nCons_hosp) 2	0.110790	0.028753	3.853	0.000117	***
factor(nCons_hosp) 3	-0.018769	0.045639	-0.411	0.680899	
factor(nCons_hosp) 4	0.005948	0.066145	0.090	0.928347	
factor(nCons_hosp) 5	0.053042	0.089938	0.590	0.555350	
factor(nCons_hosp) 6-10	0.037076	0.072040	0.515	0.606795	
factor(nCons_hosp) >10	0.155130	0.129528	1.198	0.231053	
factor(nDays_Encounter_Gp) 1	0.160636	0.065726	2.444	0.014525	*
factor(nDays_Encounter_Gp) 2	0.231544	0.066011	3.508	0.000452	***
factor(nDays_Encounter_Gp) 3	0.297805	0.066347	4.489	7.17e-06	***
factor(nDays_Encounter_Gp) 4	0.296494	0.066513	4.458	8.29e-06	***
factor(nDays_Encounter_Gp) 5	0.335880	0.066917	5.019	5.19e-07	***
factor(nDays_Encounter_Gp) >5	0.430833	0.064938	6.634	3.26e-11	***
factor(CareHome_Social) 1	0.741180	0.109467	6.771	1.28e-11	***
factor(Dementia) 1	-0.073691	0.051375	-1.434	0.151471	
factor(resp) 1	0.554444	0.017424	31.822	< 2e-16	***
factor(cardiac) 1	0.277502	0.020332	13.648	< 2e-16	***
factor(renal) 1	-0.036640	0.038149	-0.960	0.336823	
factor(liver) 1	0.225042	0.055754	4.036	5.43e-05	***
factor(neuro) 1	0.076495	0.025617	2.986	0.002826	**
factor(immuno) 1	1.092630	0.071349	15.314	< 2e-16	***
factor(diab) 1	0.681164	0.026429	25.773	< 2e-16	***
factor(repeat.pres.ly_gp) 1	0.645068	0.016714	38.595	< 2e-16	***
factor(repeat.pres.ly_gp) 2	0.983606	0.017648	55.734	< 2e-16	***
factor(repeat.pres.ly_gp) 3	1.138363	0.019586	58.121	< 2e-16	***
factor(repeat.pres.ly_gp) 4	1.208559	0.021634	55.865	< 2e-16	***
factor(repeat.pres.ly_gp) 5	1.321132	0.023860	55.371	< 2e-16	***
factor(repeat.pres.ly_gp) 6	1.361947	0.026786	50.845	< 2e-16	***
factor(repeat.pres.ly_gp) 7	1.309643	0.029916	43.777	< 2e-16	***
factor(repeat.pres.ly_gp) 8	1.348675	0.033608	40.130	< 2e-16	***
factor(repeat.pres.ly_gp) 9	1.363557	0.037257	36.598	< 2e-16	***
factor(repeat.pres.ly_gp) 10	1.352909	0.042095	32.140	< 2e-16	***
factor(repeat.pres.ly_gp) 11-15	1.331225	0.032323	41.185	< 2e-16	***
factor(repeat.pres.ly_gp) >15	1.241235	0.053467	23.215	< 2e-16	***
factor(pneumo.ever) 1	0.478901	0.017438	27.463	< 2e-16	***

```

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 0.7060592)

Number of Fisher Scoring iterations: 7

```

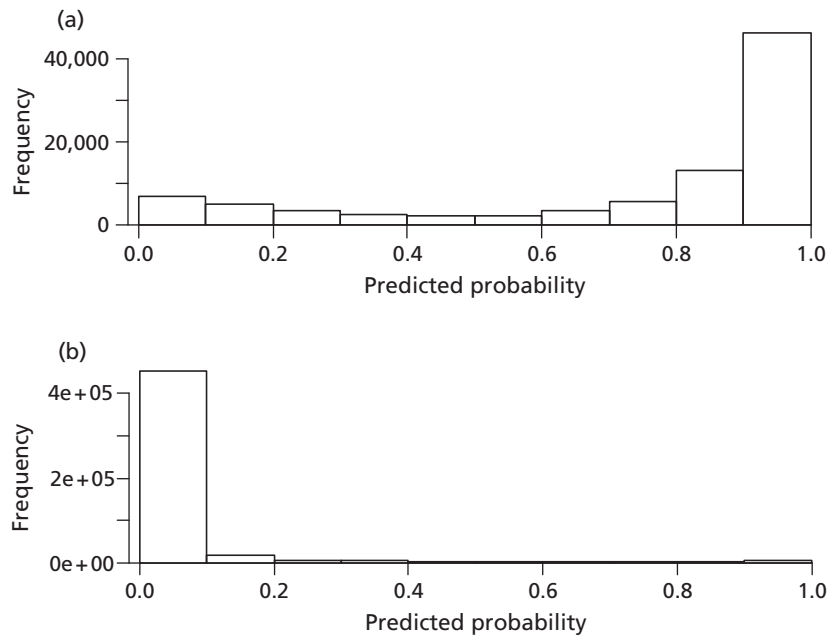


FIGURE 7 Propensity to be vaccinated score in deciles. (a) Vaccinated; and (b) unvaccinated.

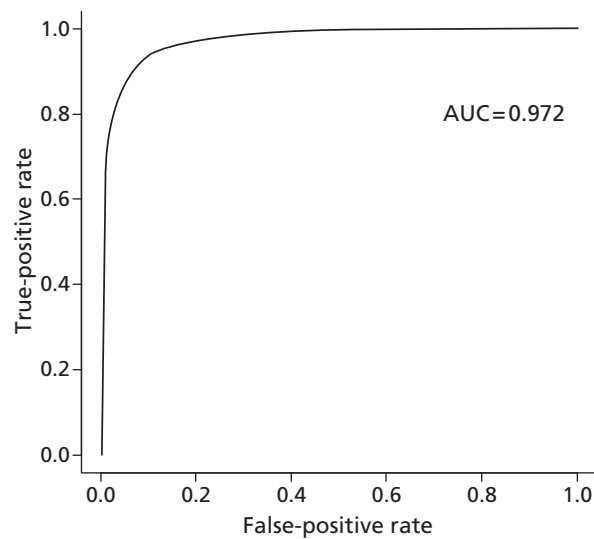


FIGURE 8 Receiver operating characteristic curve for all individuals. AUC, area under the curve.

At-risk patients aged under 65 years

Call:

```
svyglm(formula = flu.vacc ~ factor(sex) + factor(Age.gp) + factor(flu.vacc.ly) +
  factor(UR6) + factor(SIMD5) + factor(charlson.gp) + factor(smoke.status) +
  factor(remote_cons_only) + factor(nCons_hosp) + factor(nDays_Encounter_Gp) +
  factor(CareHome_Social) + factor(Dementia) + factor(resp) +
  factor(cardiac) + factor(renal) + factor(liver) + factor(neuro) +
  factor(immuno) + factor(diab) + factor(pneumo.ever) + factor(repeat.pres.ly_gp),
  design = cohort.training.svy, family = binomial)
```

Survey design:

```
svydesign(~UniquePatientId, data = cohort.training)
```

Coefficients:

	Estimate	Std. Error	t value	Pr(> t)	
(Intercept)	-3.3877796	0.1528964	-22.157	< 2e-16	***
factor(sex)Male	-0.0261893	0.0164878	-1.588	0.112202	
factor(Age.gp)5-14	-0.1247681	0.0658102	-1.896	0.057982	.
factor(Age.gp)15-44	-0.2606412	0.0682763	-3.817	0.000135	***
factor(Age.gp)45-64	0.1589972	0.0691151	2.300	0.021426	*
factor(flu.vacc.ly)Yes	2.6471869	0.0198894	133.095	< 2e-16	***
factor(UR6)2	-0.0111673	0.0232101	-0.481	0.630418	
factor(UR6)3	0.1641901	0.0335993	4.887	1.03e-06	***
factor(UR6)4	0.2273729	0.0590656	3.849	0.000119	***
factor(UR6)5	0.1037367	0.0342128	3.032	0.002430	**
factor(UR6)6	0.1237899	0.0400289	3.093	0.001986	**
factor(SIMD5)2	-0.0192896	0.0225339	-0.856	0.391987	
factor(SIMD5)3	-0.0005527	0.0239671	-0.023	0.981600	
factor(SIMD5)4	-0.0259018	0.0258887	-1.001	0.317071	
factor(SIMD5)5	0.0302439	0.0276954	1.092	0.274830	
factor(charlson.gp)1-2	0.0540785	0.0327161	1.653	0.098345	.
factor(charlson.gp)3-4	0.0738406	0.0444261	1.662	0.096499	.
factor(charlson.gp)>5	-0.0943108	0.0778472	-1.211	0.225714	
factor(smoke.status)Ex	0.2892964	0.0231059	12.520	< 2e-16	***
factor(smoke.status)Non	0.0837808	0.0191914	4.366	1.27e-05	***
factor(smoke.status)Unknown	-0.5460049	0.0397413	-13.739	< 2e-16	***
factor(remote_cons_only)No consultations	-0.1596681	0.1308625	-1.220	0.222425	
factor(remote_cons_only)Remote Cons only	0.0781530	0.1655805	0.472	0.636933	
factor(nCons_hosp)1	0.1220508	0.0237041	5.149	2.63e-07	***
factor(nCons_hosp)2	0.2292434	0.0407926	5.620	1.92e-08	***
factor(nCons_hosp)3	0.1516443	0.0630117	2.407	0.016105	*
factor(nCons_hosp)4	0.2880628	0.0907633	3.174	0.001506	**
factor(nCons_hosp)5	0.4180132	0.1165371	3.587	0.000335	***
factor(nCons_hosp)6-10	0.3038334	0.0861925	3.525	0.000424	***
factor(nCons_hosp)>10	0.1539335	0.1497340	1.028	0.303933	
factor(nDays_Encounter_Gp)1	0.1279984	0.1305848	0.980	0.326995	
factor(nDays_Encounter_Gp)2	0.1912552	0.1305391	1.465	0.142895	
factor(nDays_Encounter_Gp)3	0.2695948	0.1306673	2.063	0.039097	*
factor(nDays_Encounter_Gp)4	0.2951549	0.1312182	2.249	0.024495	*
factor(nDays_Encounter_Gp)5	0.3104337	0.1315971	2.359	0.018329	*
factor(nDays_Encounter_Gp)>5	0.4488306	0.1292770	3.472	0.000517	***
factor(CareHome_Social)1	1.0429837	0.3435107	3.036	0.002397	**
factor(Dementia)1	0.3507086	0.2136598	1.641	0.100713	
factor(resp)1	0.0434330	0.0299227	1.452	0.146645	
factor(cardiac)1	0.3031314	0.0288685	10.500	< 2e-16	***
factor(renal)1	0.0168211	0.0554083	0.304	0.761446	
factor(liver)1	-0.1707315	0.0530366	-3.219	0.001287	**
factor(neuro)1	-0.0129488	0.0331292	-0.391	0.695903	
factor(immuno)1	0.8048622	0.0632314	12.729	< 2e-16	***
factor(diab)1	0.5068088	0.0333058	15.217	< 2e-16	***
factor(pneumo.ever)1	0.6732317	0.0251089	26.812	< 2e-16	***
factor(repeat.pres.ly_gp)1	0.6405762	0.0293578	21.820	< 2e-16	***
factor(repeat.pres.ly_gp)2	1.0452760	0.0275866	37.891	< 2e-16	***
factor(repeat.pres.ly_gp)3	1.1815649	0.0296732	39.819	< 2e-16	***
factor(repeat.pres.ly_gp)4	1.2748749	0.0322148	39.574	< 2e-16	***
factor(repeat.pres.ly_gp)5	1.4110980	0.0349799	40.340	< 2e-16	***
factor(repeat.pres.ly_gp)6	1.4978584	0.0372578	40.203	< 2e-16	***
factor(repeat.pres.ly_gp)7	1.4753375	0.0413652	35.666	< 2e-16	***
factor(repeat.pres.ly_gp)8	1.5789070	0.0451223	34.992	< 2e-16	***
factor(repeat.pres.ly_gp)9	1.6253275	0.0499929	32.511	< 2e-16	***
factor(repeat.pres.ly_gp)10	1.5720306	0.0566597	27.745	< 2e-16	***
factor(repeat.pres.ly_gp)11-15	1.5739549	0.0437484	35.977	< 2e-16	***
factor(repeat.pres.ly_gp)>15	1.6586168	0.0675987	24.536	< 2e-16	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 0.9461439)

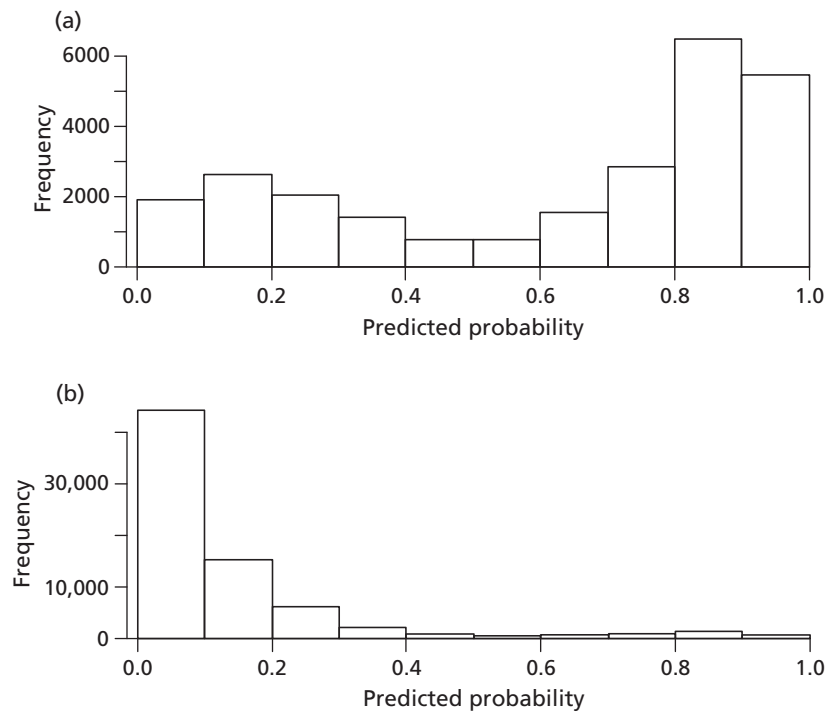


FIGURE 9 Propensity to be vaccinated score in deciles for age < 65 years. (a) Vaccinated; and (b) unvaccinated.

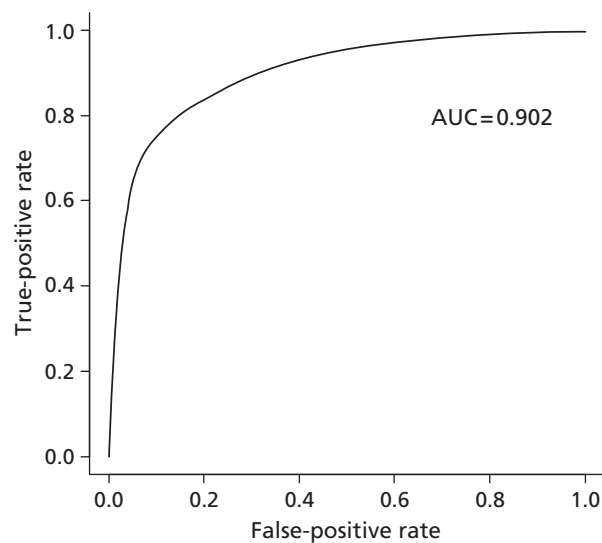


FIGURE 10 Receiver operating characteristic curve for at-risk patients aged < 65 years. AUC, area under the curve.

Patients aged 65 years and over

```
Call:
svyglm(formula = flu.vacc ~ factor(sex) + factor(Age.gp) + factor(flu.vacc.ly) +
  factor(UR6) + factor(SIMD5) + factor(charlson.gp) + factor(smoke.status) +
  factor(remote_cons_only) + factor(nCons_hosp) + factor(nDays_Encounter_Gp) +
  factor(CareHome_Social) + factor(Dementia) + factor(resp) +
  factor(cardiac) + factor(renal) + factor(liver) + factor(neuro) +
  factor(immuno) + factor(diab) + factor(pneumo.ever) + factor(repeat.pres.ly_gp),
  design = cohort.training.svy, family = binomial)
```

```
Survey design:
svydesign(~UniquePatientId, data = cohort.training)
```

Coefficients:

	Estimate	Std. Error	t value	Pr(> t)	
(Intercept)	-1.5179874	0.0776853	-19.540	< 2e-16	***
factor(sex)Male	0.1485459	0.0176219	8.430	< 2e-16	***
factor(Age.gp)75+	-0.1883190	0.0173753	-10.838	< 2e-16	***
factor(flu.vacc.ly)Yes	2.7287886	0.0189534	143.973	< 2e-16	***
factor(UR6)2	-0.0003488	0.0248319	-0.014	0.988794	
factor(UR6)3	0.1796824	0.0351519	5.112	3.21e-07	***
factor(UR6)4	0.4186948	0.0711164	5.887	3.95e-09	***
factor(UR6)5	0.0866038	0.0345185	2.509	0.012114	*
factor(UR6)6	0.0704938	0.0433095	1.628	0.103601	
factor(SIMD5)2	-0.0275423	0.0232964	-1.182	0.237110	
factor(SIMD5)3	0.0643746	0.0260672	2.470	0.013531	*
factor(SIMD5)4	0.1125077	0.0274506	4.099	4.16e-05	***
factor(SIMD5)5	0.3251502	0.0309261	10.514	< 2e-16	***
factor(charlson.gp)1-2	0.0460915	0.0215096	2.143	0.032131	*
factor(charlson.gp)3-4	-0.0071160	0.0326422	-0.218	0.827431	
factor(charlson.gp)>5	-0.0818053	0.0510756	-1.602	0.109240	
factor(smoke.status)Ex	0.2088681	0.0239945	8.705	< 2e-16	***
factor(smoke.status)Non	0.2020169	0.0221952	9.102	< 2e-16	***
factor(smoke.status)Unknown	-0.5561789	0.0345225	-16.111	< 2e-16	***
factor(remote_cons_only)No consultations	-0.3423499	0.0699230	-4.896	9.81e-07	***
factor(remote_cons_only)Remote Cons only	0.0688971	0.0752623	0.915	0.359973	
factor(nCons_hosp)1	0.0130555	0.0229428	0.569	0.569329	
factor(nCons_hosp)2	-0.0475919	0.0346102	-1.375	0.169112	
factor(nCons_hosp)3	-0.1935549	0.0512100	-3.780	0.000157	***
factor(nCons_hosp)4	-0.2930959	0.0689741	-4.249	2.15e-05	***
factor(nCons_hosp)5	-0.2462326	0.0973869	-2.528	0.011462	*
factor(nCons_hosp)6-10	-0.4850885	0.0773022	-6.275	3.52e-10	***
factor(nCons_hosp)>10	-0.3463081	0.1520802	-2.277	0.022782	*
factor(nDays_Encounter_Gp)1	0.1342878	0.0707345	1.898	0.057640	.
factor(nDays_Encounter_Gp)2	0.2268462	0.0712868	3.182	0.001463	**
factor(nDays_Encounter_Gp)3	0.3038609	0.0720357	4.218	2.47e-05	***
factor(nDays_Encounter_Gp)4	0.3026107	0.0727502	4.160	3.19e-05	***
factor(nDays_Encounter_Gp)5	0.2835812	0.0732797	3.870	0.000109	***
factor(nDays_Encounter_Gp)>5	0.4126031	0.0685629	6.018	1.78e-09	***
factor(CareHome_Social)1	0.5049023	0.0995785	5.070	3.99e-07	***
factor(Dementia)1	0.1232917	0.0458161	2.691	0.007126	**
factor(resp)1	0.0547617	0.0234632	2.334	0.019603	*
factor(cardiac)1	0.0438433	0.0219782	1.995	0.046065	*
factor(renal)1	-0.0991812	0.0352614	-2.813	0.004914	**
factor(liver)1	-0.1190626	0.0819474	-1.453	0.146254	
factor(neuro)1	-0.0641870	0.0261420	-2.455	0.014080	*
factor(immuno)1	0.0471494	0.0882068	0.535	0.592976	
factor(diab)1	-0.0013419	0.0309242	-0.043	0.965388	
factor(pneumo.ever)1	0.4163173	0.0198186	21.006	< 2e-16	***
factor(repeat.pres.ly_gp)1	0.4151060	0.0312791	13.271	< 2e-16	***
factor(repeat.pres.ly_gp)2	0.4318936	0.0307731	14.035	< 2e-16	***
factor(repeat.pres.ly_gp)3	0.5131569	0.0312764	16.407	< 2e-16	***
factor(repeat.pres.ly_gp)4	0.5281653	0.0318044	16.607	< 2e-16	***
factor(repeat.pres.ly_gp)5	0.5938531	0.0332666	17.851	< 2e-16	***
factor(repeat.pres.ly_gp)6	0.6434007	0.0354502	18.149	< 2e-16	***
factor(repeat.pres.ly_gp)7	0.6114186	0.0382691	15.977	< 2e-16	***
factor(repeat.pres.ly_gp)8	0.6891470	0.0418299	16.475	< 2e-16	***
factor(repeat.pres.ly_gp)9	0.6406019	0.0447252	14.323	< 2e-16	***
factor(repeat.pres.ly_gp)10	0.6801670	0.0480301	14.161	< 2e-16	***
factor(repeat.pres.ly_gp)11-15	0.7433502	0.0393074	18.911	< 2e-16	***
factor(repeat.pres.ly_gp)>15	0.6991537	0.0577734	12.102	< 2e-16	***

```
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(Dispersion parameter for binomial family taken to be 0.9911984)
```

```
Number of Fisher Scoring iterations: 5
```

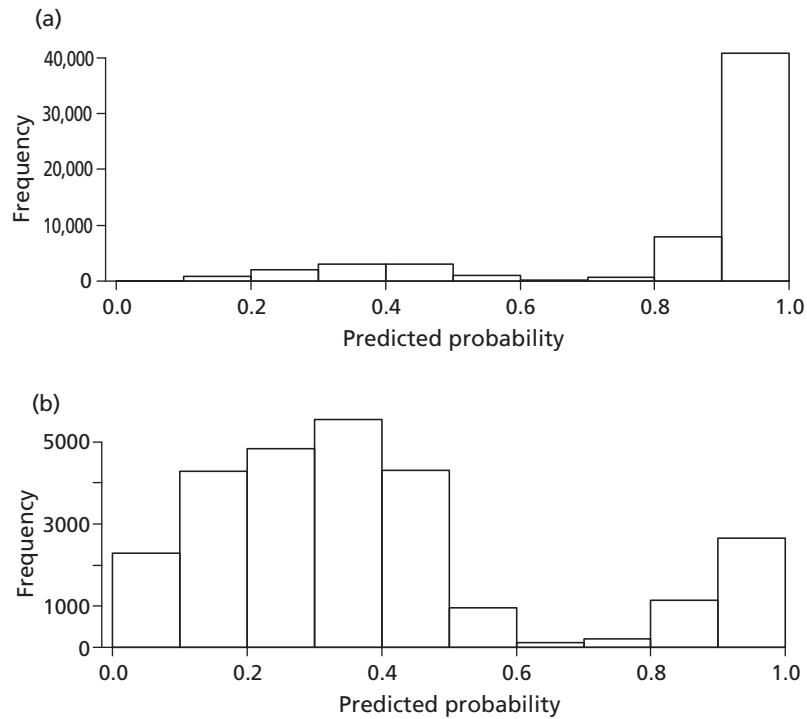


FIGURE 11 Propensity to be vaccinated score in deciles for age ≥ 65 years. (a) Vaccinated; and (b) unvaccinated.

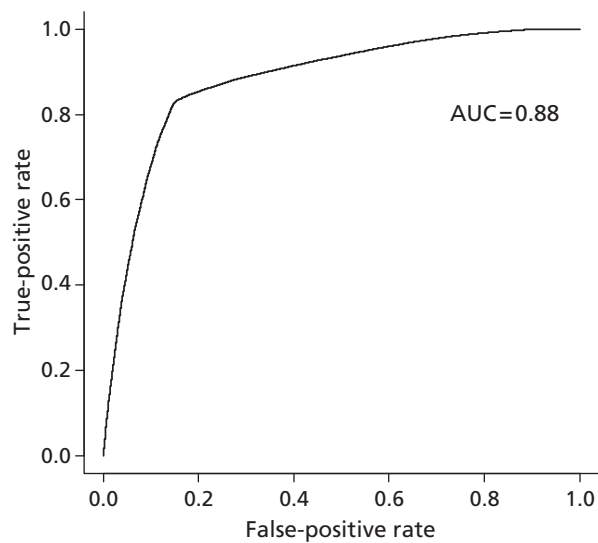


FIGURE 12 Receiver operating characteristic curve for all individuals aged ≥ 65 years. AUC, area under the curve.

Appendix 2 Study protocol

1. PROJECT TITLE

Seasonal Influenza Vaccine Effectiveness (SIVE): exploitation of a unique community-based national linked dataset

2. CHANGES SINCE THE PROTOCOL WAS SUBMITTED

We are now in a position to undertake analysis on individual patient virological swab data, which will be linked to the primary-secondary care dataset. These data will be made available by Health Protection Scotland (HPS) for all eight influenza seasons for which data are potentially available (i.e. 2000-2008). Access to these individual patient data should provide more robust estimates of vaccine effectiveness (VE).

3. PLANNED INVESTIGATION

3.1 Research aims and objectives

Building on prior work [1,2], we aim to use a previously successfully employed approach to determine influenza vaccine uptake and effectiveness over eight influenza seasons in the Scottish population. This will involve interrogation of data from a sentinel surveillance network of 41 general practices (yielding a total of 1,020,000 patient years), the Practice Team Information network (PTI), linked to the Information Services Division (NHS Scotland) hospital and mortality records (Scottish Morbidity Record and General Register of Scotland death certification – SMR01) as part of the National Institute of Health Research VIPER project (Ref: 09/84/90) [2].

Our three specific objectives are to evaluate the:

1. Uptake of the influenza vaccine by the relevant at risk populations i.e. patients with relevant co-morbidities and those aged > 65 years and the general population;
2. Reduction in the expected incidence of influenza-related morbidity and mortality in these at risk groups, since this is the major rationale behind current immunisation policies;
3. Effectiveness of the influenza vaccine in the population as a whole.

3.2 Existing research

Each year, influenza is responsible for considerable potentially avoidable morbidity and mortality; much of this disease burden falls on people aged 65 and over and/or those with a range of pre-existing long-term conditions. In the USA, it has been estimated that influenza is responsible for 186,000 excess hospitalisations and 44,000 excess deaths [3]. National vaccination strategies represent a potentially important approach to reduce both influenza-related illness and death, hence the considerable investment in this approach in many parts of the world. Although vaccination rates in those over 65 in Scotland are reasonable (for example, 76.3% for the 2008/9 season), despite widely promulgated guidelines and incentivised vaccination programmes, the rates of vaccination in 'at risk' groups under 65 remains poor (47.8% in the 2008/9 season). This may partially be due to the scarcity of reliable estimates of the benefits of the vaccine from randomised controlled trials and limited evidence from observational research which has only shown effectiveness of vaccine in selected groups of patients (i.e. those aged over 65) [4] or for those in 'at-risk' groups for single influenza seasons [5]. Furthermore, these studies have been prone to bias, in particular, with confounding from the 'healthy vaccine effect' whereby more healthy individuals have been vaccinated [6].

VE has also been previously estimated using information collected by swabs independent of routinely collected clinical information. However, such studies have been limited in that they have either employed the less reliable 'screening method' (calculated from aggregated as opposed to patient level data) [7], limited analysis to only a few seasons [8] or to specific groups only (such as > 65 years) [9], and were unable to distinguish whether subjects were at risk of complications from influenza-like illness [8,9]; furthermore, many of these studies were unable to determine vaccination status in a large proportion of their subjects. Further evidence using whole population primary care data linked to hospitalisation, swab and death data is therefore clearly required. Also, this project will significantly build on the Pandemic Influenza Primary Care Reporting (PIPeR) project [10], which has been ongoing since 2006 and also VE work using consultations for acute respiratory and influenza like symptoms estimated using the cohort method within the European Union EpiConcept Programme [11]. CR and JM are collaborating on both projects. Information generated from this and ongoing projects will be important for informing policy makers, clinicians and the public of the relative benefits of the vaccination programme.

3.3 Research methods

3.3.1 Design

We plan to undertake a large national retrospective observational cohort study using a unique community-based linked dataset.

3.3.2 Setting

The PTI network of 41 general practices covers a five per cent representative sample of the Scottish population (n = 240,000). These practices have received annual financial incentives since 1998 to record all of their practice data electronically [12]. Data from general practices within Scotland have shown to be of high quality and useful for epidemiological research [13]. The completeness of capture of contacts and accuracy of clinical event coding in primary care (using Read codes) has been found to be above 91% [14]. Using the unique Community Health Index (CHI) number, general practice patient level data were extracted and linked to the Scottish Morbidity Record (SMR) catalogue which has information on all in-patient hospitalisations within Scotland (as well as information on death certification linked from the General Register Office for Scotland (GROS) [15] from 1981. Hospital data are reliable, with completeness and accuracy rates exceeding 90% [14]. We also wish to link general practice information (using CHI) with the HPS virological swab dataset, which consists of all laboratory-confirmed cases of influenza (since 2000) from the general practices.

3.3.3 Target population

240,000 people of all ages registered with participating practices throughout Scotland.

3.3.4 Recruitment

This general practice and hospital linked dataset was previously used to estimate H1N1 influenza A VE [2] and is currently held at the University of Aberdeen and HPS.

3.4 Planned inclusion/exclusion criteria

All registered patients will be studied so there are no exclusion criteria.

3.5 Planned interventions

The study will involve a quantitative evaluation of the winter influenza vaccination programmes implemented through general practice over eight influenza seasons: 2000/1 to 2007/8. Primary care practices are given financial incentives by NHS National Services Scotland to record and code additional data electronically, over and above that routinely recorded for clinical care or as part of the PTI project (e.g. age, out of hours contacts and socioeconomic status), including influenza vaccination status. Virological swab data have been collected from these practices by HPS. Information generated on VE is important for informing policy makers, clinicians and the public of the relative benefits of the vaccination programme throughout the study period.

3.6 Ethical and privacy arrangements

Permission to use the database for research purposes has provisionally been obtained from the PCCIU Research Governance Group. Further permission has been granted by the MREC West of Scotland 2 Ethics Committee. Permissions from the general practices that have contributed data to this project are being sought, but based on previous experiences we do not foresee any major objections.

3.7 Risks and anticipated benefits for trial participants and society, including how benefits justify risks

As this study is seeking to assess VE using previously collected and anonymised data, this work will not add any known additional risks or benefits for the individual patients present in the databases. Informing patients as to the potential risks and benefits of vaccination will remain at the discretion of the appropriate primary care clinician. There are however potentially large societal benefits from assessing the effectiveness and impact of the vaccination programmes for Scotland and the UK as a whole, but also for the international scientific community.

3.8 Proposed sample size

Patient level data from 41 practices with a combined list size of 240,000 patients have been collected. Approximately 15% (n = 36,000) aged over 65 years, and 30% (n = 72,000) under 65 years will be deemed to be in the at-risk category on the basis of existing illnesses.

A power calculation was carried out to determine the numbers needed to detect a difference in the relative risk of death between the vaccinated and unvaccinated groups in one flu season. Among people over 65 the daily death rate from all causes in Scotland is 0.000133. Assuming that 55–75% of the age group are vaccinated against seasonal influenza then this study has a power in excess of 80% to detect a difference of 30% or more in the proportions of vaccinated and unvaccinated individuals dying over a period of three months. Hospitalisation rates among the at risk groups are of the order of 20 per 100,000 per day and over the period of the four month influenza season the whole cohort will have a power of over 95% to detect a difference of 10% in hospitalisation rates between the vaccinated and unvaccinated, assuming that 50% of the at risk groups are vaccinated. Consultation rates for influenza-like illnesses are of the order of 30 per 100,000 per day and over the period of four months the whole cohort will have a power of over 95% to detect a difference of 8% in consultation rates between the vaccinated and unvaccinated. We anticipate therefore that the numbers of individuals being studied through the PTI dataset will provide high power of assessing clinical effectiveness of the seasonal influenza vaccination programmes in each of the flu seasons from 2000/01 to 2007/08.

3.9 Statistical analysis

Odds ratios (adjusted for age, sex and deprivation) will be calculated for differences in vaccine uptake rates between different groups of patients (sex, age, Carstairs deprivation categories and at-risk groups) and for investigating trends in vaccine uptake. For VE using information from linked virological swab data, a logistic regression model will be fitted adjusting for the effects of gender, age, socioeconomic status and being in an at-risk morbidity group. VE will be measured by comparing swabs taken after vaccination with swabs taken before vaccination for all vaccinated individuals, and secondly by comparing swabs taken after vaccination among those vaccinated to swabs taken among those never vaccinated. A delay of fourteen days after vaccination will be used to establish the protective effect of the influenza vaccine. Propensity scores, such as vaccinations, consultations and hospitalisation in the previous flu season, and the effect modifiers will be used to control for the healthy vaccine effect [6]. In addition, using the cohort method the proportion of influenza-like illness, acute respiratory disease, and other adverse outcomes between vaccinated and unvaccinated cases will be ascertained. Confidence intervals for the rate ratio and tests of the differences between two rates will be carried out using the 'midp method' in the 'rate ratio' (RR) function and `rate2by2.test` function respectively using the 'epitools' package in R [17]. For small samples, confidence intervals for the RR will be estimated using the Excel workbook [18].

Illness RRs, i.e. the ratio of the rate of first admission to hospital or general practice (GP) consultation in the vaccinated compared to the rate of first admission to hospital or GP consultation among those who did not receive the vaccine will be calculated in both the 'at-risk' populations and the general population. This is a direct measure of VE. The unadjusted estimate of $VE = (1 - RR) * 100$. Adjusted RRs of VE for prevention of first hospitalisation/GP consultation will be derived from Poisson regression models, adjusting for gender, age, deprivation and clinical risk group.

3.10 Proposed outcome measures

For the eight influenza seasons, we will calculate:

- The vaccination uptake in the relevant 'at risk' populations (patients < 65 with 'at-risk' co-morbidities and those > 65 years) and the general population recorded by general practices;
- Consultation for influenza-related morbidity (e.g. influenza, pneumonia, COPD and cardiac related consultations) from general practice data in vaccinated and unvaccinated patients stratified by 'at-risk' populations, age, sex and socio-economic status;
- Mortality and influenza-related serious morbidity (e.g. influenza, pneumonia, COPD and cardiac related death and hospitalisation from SMR01 records) in vaccinated and unvaccinated patients stratified by 'at-risk' populations, age, sex and socioeconomic status; and
- Influenza positivity from virological swab data in vaccinated and unvaccinated patients stratified by 'at-risk' populations, age, sex and socioeconomic status.

3.11 Research governance

Data are held by HPS and PCCIU. The University of Edinburgh will act as the sponsor for this study. We will, as with previous similar work, convene an Independent Steering Group, comprising of leading academics and policy makers to oversee this work.

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A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

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