# 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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## Scientific summary

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# 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 $\geq 65$ 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 $\geq 65$ 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).





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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 $\geq 65$ 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.

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