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

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ISRCTN registration (if applicable): N/A
1. Aims/Objectives:

We aim to examine the effectiveness of the seasonal influenza vaccination in individuals registered with a national sample of general practices in Scotland. More specifically, the objectives of this study are to: (1) report vaccine uptake in the relevant at-risk populations for whom vaccination is recommended in the UK; (2) evaluate Vaccine Effectiveness (VE) measured in terms of the following outcomes: rate of hospital admissions due to respiratory illness (primary outcome), rate of primary care consultations due to respiratory illness, risk of death due to respiratory illness, and risk of laboratory confirmed influenza infection; and (3) assess the degree of and adjust for residual confounding in our estimates using analyses incorporating propensity scores, instrumental variables and the effect of a hypothetical unknown confounder.

2. Background:

Each year, influenza causes substantial morbidity and mortality, particularly in people aged 65 and over and those with underlying serious comorbidities. In the United States (US), it has been estimated that influenza is responsible for 186,000 excess hospitalisations and 44,000 excess deaths.[1] 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 a reasonable 75.0% (season 2009/10), the rates in at-risk groups under 65 remain low (53.4% in season 2009/10) despite widely promulgated guidelines and incentivised vaccination programmes.[2] There is good evidence of the benefits of the vaccine in young healthy adults and children,[3] but a scarcity of reliable estimates from randomised controlled trials in at-risk populations.[4] There is also limited evidence from observational research, which has only shown effectiveness of vaccination in selected groups of patients, for example those aged over 65,[5] or those in at-
risk groups for single influenza seasons.[6] Furthermore, these studies may have been prone to bias and residual confounding.[4, 7] This may explain, in part, the reason for lower vaccine uptake rates.

3. Need:

Randomised controlled trials offer the best opportunity to produce unbiased estimates of VE. However, given that influenza vaccination programmes exist in most developed countries, this form of study design is now impractical and is viewed by many in the medical community as unethical.[8] Observational studies are an alternative to investigate vaccine effectiveness. However, an individual’s decision to attend the 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 the outcome (i.e. positive confounding). Similarly, 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.[9] This phenomenon is also known as the ‘healthy vaccine effect’.

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 VE in observational studies using non-influenza specific outcomes due to residual confounding. 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 vaccine effectiveness studies using observational methods.[10]

This research aims to examine the effectiveness of the seasonal influenza vaccine, whilst addressing the methodological challenges outlined above of using observational data. We will have access to a unique set of linked databases, which contain individual patient level data relating to primary health
care, acute hospital care, virological laboratory tests and mortality. In contrast to previous observational studies, these rich data sources provide information on a large number of potential confounders and highly specific laboratory outcome measures in a study cohort sampled from the general population. Our assessment of the effectiveness and impact of the seasonal influenza vaccination programme therefore offers potentially large societal benefits both for Scotland, UK and for advancing the international evidence-base.

4. Methods:

a. Setting
Data extracted from 35 general practices of the sentinel surveillance network in Scotland, the Practice Team Information network (PTI) will be used. Participating practices cover a 4% sample of the Scottish population (n=209,452 registered alive in 2009). The population targeted for influenza vaccination comprises all patients aged 65 and older (approximately 15% of the general population, n=28,241 in the sample), and those aged under 65 defined as being in an at-risk group on the basis pre-existing illness (n=33,000, 18% of under 65 year olds).[11] The estimates for proportion of patients under 65 in an at-risk group were taken from our recent VIPER study investigating the effectiveness of the 2009 H1N1 pandemic influenza vaccine.[12] Each patient will contribute person-time to each influenza season whilst alive and registered with a participating general practice. The primary care database was linked to the Scottish acute hospital discharge database and Scottish death register as part of the VIPER project.[12] In addition, a linkage of these datasets to the Health Protection Scotland virology database to determine laboratory confirmed influenza infection is underway (due to be completed 1st February 2012).

b. Design
A cohort study design will be used to assess VE. Vaccine uptake will be reported using serial cross-sectional surveys.

c. Data collection
Acute hospital discharge database: The Information Services Division, National Services Scotland maintains a database of all acute hospital
discharges in Scotland, known as the Scottish Morbidity Record 1 (SMR01). All inpatient and day case episodes of care for acute hospitals since 1981 have been recorded in the database. The database is subject to regular validation checks, and the most recent quality assurance report indicated good levels of accuracy (>90%) for the fields used in this study.[13] Diagnostic information is recorded using International Classification of Disease version 10 (ICD-10). There are up to six fields the can be used to record diagnoses, with one allocated as the main reason for admission. SMR01 is linked routinely by Information Services Division to the Scottish death register using patient characteristics in a probabilistic matching algorithm with a high degree of accuracy.[14, 15]

_Death register:_ Details from death certificates issued for all deaths in Scotland are recorded in the death register, maintained by National Records Scotland (NRS).[16] Cause of death has been routinely coded using ICD-10 since 2000.

_Primary care database:_ Almost all individuals resident in Scotland are registered with a primary care practice, which provides health care services free of charge. Virtually all specialist hospital care services are also free of charge, usually obtained through referral from primary care or, in emergency situations, through patients attending an emergency department. Primary care-based physicians provide or coordinate much of the care of patients discharged back into the community by secondary and tertiary care services. The primary care database was linked to the other databases using probabilistic linkage. Linkage accuracy was high due to the high quality and number of patient identifiers available from the primary care database. Completeness of capture of contacts and accuracy of clinical event coding (using Read codes) has been found to be above 91% amongst the study practices.[17, 18] The electronic recording of long-term prescribing information by primary care has also been found to be both accurate and complete.[19]

_Health Protection Scotland virology database:_ The Scotland-wide unique patient identifier, the Community Health Index (CHI) number, is being used to
link records in the virology database to the other databases.

d. Data analysis
Crude and adjusted VE estimates will be reported for each outcome. VE estimates will be calculated for the cohort as a whole, and stratified using the subgroups specified above. We will use the VE outcomes above to calculate numbers needed to vaccinate to prevent one swab-determined influenza infection, hospitalisation, consultation and death. A person-time denominator will be used for general practice consultations, hospital admissions and death. Follow-up time will be censored at death from any cause for consultations and admissions. Hospital admissions and consultations can have multiple events and each event will be counted.

*Hospitalisations and primary care consultations:* The ratio of the number of admissions to hospital per person-time during the post-vaccination period compared to the number of admission to hospital per person-time during the pre-vaccination period will be calculated. The unadjusted estimate of VE will be calculated as $(1-RR)^*100\%$. Adjusted RRs of VE for prevention of hospitalisation will be derived from Poisson regression models, adjusting for the confounders listed above. Similar methods will be used to estimate VE for primary care consultations.

*Deaths:* The odds ratio of deaths in the vaccinated group to deaths in the unvaccinated group will be calculated; these will be both unadjusted and adjusted for the confounders listed above. VE will be calculated as $(1-OR)^*100\%$.

*Laboratory-confirmed infection:* For VE, using information from linked virological swab data, a logistic regression model will be fitted adjusting for the confounders listed above. 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. VE will be calculated as $(1-OR)^*100\%$. 

[HSR 09/2000/37] [Simpson] protocol version: 1 [09.02.2012] 6
5. Contribution of existing research:

VE has 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) [20], limited analysis to only a few seasons [21] or to specific groups only (such as >65 years) [22], and were unable to distinguish whether subjects were at-risk of complications from influenza-like illness [21,22]; 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 [23], 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 [24].

6. Plan of Investigation:

Vaccination will be used to define exposure status if it is given at a time point between the start of the pre-influenza season (1st September) and the end of the influenza season (Figure 1). An individual will be defined as vaccinated 14 days after the seasonal influenza vaccine has been administered.[25] The time period from the first day of the influenza season to day 14 post-vaccination will be defined as ‘unexposed’ and the period from day 14 post-vaccination until the end of the influenza season will be defined as ‘exposed’. Therefore, those vaccinated between the start of the pre-influenza period up until 14 days before the influenza season will be defined as ‘exposed’ for the duration of the influenza season.
Figure 1. Relationship of first influenza season (2000 to 2001) to pre-, post- and non-influenza season periods. Baseline characteristics for each patient are determined on September 1\textsuperscript{st} each year. The earliest date of influenza vaccination varied for each influenza season, but always occurred after September 1\textsuperscript{st}.

VE should ideally be measured using influenza-specific outcomes in each of the databases. However, it is likely that ICD codes or Read codes referring to influenza-specific outcomes are underused by clinicians and coders, thereby reducing the sensitivity and power of the primary analysis. For this reason, codes for acute respiratory diseases were chosen as primary outcome measures as they would capture a substantial proportion of influenza-related events during the influenza season. Laboratory-confirmed influenza infection will be a highly specific outcome, and will be calculated on a subgroup of the study population.

VE will be calculated by subtracting the rate ratio (RR) or odds ratio (OR) of vaccinated compared with unvaccinated patients from 1 (i.e. $VE=[1-\text{OR}]*100\%$ or $VE=[1-\text{RR}]*100\%$) for each of the following outcome measures:

a) Hospital discharge data: rate of emergency hospitalisations with a diagnosis of influenza or pneumonia (primary measure of VE).

b) Primary care data: rate of consultations in primary care for influenza-like illnesses and acute respiratory infection.

c) Death register: deaths due to influenza, pneumonia or COPD.

d) Health Protection Scotland Virology Database: laboratory-confirmed influenza.

Additional sensitivity analyses will be undertaken using less specific outcomes.
(all-cause mortality, emergency admission to hospital for any reason) as well as the influenza-specific outcomes (deaths due to influenza, hospital admissions due to influenza). These analyses will be part of the framework to assess bias.

A number of secondary analyses will be undertaken using other outcomes. The effect of vaccination status on hospital admissions and deaths relating to cardiovascular and cerebrovascular events as a composite outcome will be analysed. In addition, exploratory analyses will be undertaken to assess the effect of vaccination status on outcomes for which it would not be expected to have an effect, for example 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.[26]

7. Project Management:

The University of Edinburgh will sponsor the project and the PCCIU, Health Protection Scotland and Department of Statistics and Modelling Science teams will act on a consultancy basis, invoicing Edinburgh on completion of work. Dr Colin Simpson will be co-ordinating the project, and the co-applicants will also contribute some of their time towards the completion of the project. The PCCIU (University of Aberdeen) will ask for permissions to use the data from the general practices and will pre-process the anonymised dataset, providing a database, which can be used for the appropriate statistical analysis. The Department of Statistics and Modelling Science University of Strathclyde will assist HPS with the linkage of virological swab data, carry out the statistical analyses and help with the write-up of the final report.

Project Timetable:

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<tr>
<th>Milestones</th>
<th>Completion date</th>
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<tbody>
<tr>
<td>Study commencement</td>
<td>1st January 2011</td>
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<tr>
<td>Practice recruitment (by PCCIU (University of Aberdeen) and principle investigator,) 10 practices per week and other regulatory approvals (Research Ethics and Privacy and Advisory</td>
<td>1st February 2011</td>
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[HSR 09/2000/37] [Simpson] protocol version: 1 [09.02.2012]
8. Service users/public involvement:

Dr Neil Kelly, General Practitioner and lead representative of the Scottish Practice Team Information Practices has been asked to lead the independent steering group for this project. The independent steering group will comprise of service users, experts and members of the public. We will be sending the general practices that took part in the original data extraction (VIPER NIHR ref: 09/84/90) results of this project. Results of the study will be distributed through social media channels and a short lay summary of our findings will be made available to patients.

9. References:


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This protocol refers to independent research commissioned by the National Institute  
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the authors and do not necessarily reflect those of the NHS, the NIHR,  
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