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C R Simpson (c.simpson@ed.ac.uk)[1], N I Lone[1], K Kavanagh[2], L D Ritchie[3], C Robertson[2,4,5], Aziz Sheikh[1,6], J McMenamin[4]

1. Allergy and Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, United Kingdom
2. Department of Mathematics and Statistics, University of Strathclyde, Glasgow, United Kingdom
3. Centre of Academic Primary Care, University of Aberdeen, Aberdeen, United Kingdom
4. Health Protection Scotland, Glasgow, United Kingdom
5. International Prevention Research Institute, Lyon, France
6. Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston MA, United States

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To evaluate seasonal trivalent inactivated influenza vaccine effectiveness (VE) in Scotland, we performed a Scotland-wide linkage of patient-level primary care, hospital and virological swab data from 3,323 swabs (pooling data over nine influenza seasons: 2000/01 to 2008/09). We estimated the VE for reducing real-time RT-PCR-confirmed influenza using a test-negative study design. Vaccination was associated with a 57% (95% confidence interval (CI): 31–73) reduction in the risk of PCR-confirmed influenza. VE was 60% (95% CI: 22–79) for patients younger than 65 years and clinically at risk of serious complications from influenza, and 19% (95% CI: –104 to 68) for any individual 65 years and older. Vaccination was associated with substantial, sustained reductions in laboratory-confirmed influenza in the general population and younger patients in clinical at-risk groups.

Introduction

Each year, influenza causes substantial morbidity and mortality, particularly in people aged 65 years and older and those with underlying serious comorbidities [1]. Globally, for example, it is estimated that influenza is responsible for 5 million cases of severe illness and 250,000 to 500,000 deaths per year; the 186,000 excess hospitalisations and 44,000 excess deaths in the United States (US) have been estimated to cost USD 87 billion (EUR 77 billion) per year [2-4]. Annual costs of influenza epidemics for the European Union are estimated to be EUR 27 billion [5]. National vaccination strategies represent a potentially important approach to reduce both influenza-related illness and death, hence the considerable investment in this preventive approach in many parts of the world. In Scotland, the influenza vaccination programme has been successful with high rates of uptake for targeted individuals such as adults aged over 65 years and those clinically at risk of serious influenza-like illness [6]. There is evidence of the benefits of the seasonal influenza vaccine in healthy children and younger adults (16 to 65 years) [7,8]. However, in populations at highest risk of developing influenza-related complications (e.g. adults 65 years and older, people with medical conditions such as diabetes, heart or respiratory disease, and people with immunodeficiency), the populations particularly targeted by many countries' vaccination programmes including in Scotland, there is a paucity of reliable estimates of efficacy from randomised controlled trials [9]. This is of concern, as it has been suggested that influenza vaccine is less effective in older people due to immunosenescence [10]. Given that influenza vaccination programmes now exist in most developed countries, randomised controlled trials of the vaccine are impractical; these are also viewed as unethical by some sections of the medical community [11]. Observational studies are a study design that can be used to investigate the effectiveness of vaccine programmes.

Since 2005, the test-negative study design, using real-time RT-PCR testing, has become more commonly used for evaluating influenza vaccine effectiveness (VE) [12]. Most, however, have been carried out on single influenza seasons [13] and the three which have pooled data from multiple seasons only reported VE for limited age groups [14-16]. Building on related work [17,18], we undertook a data linkage study and used detailed electronic health record data over nine consecutive seasons 2000/01 to 2008/09 to determine VE of the trivalent inactivated influenza vaccine in reducing laboratory-confirmed influenza.

Methods

Study databases and population characteristics

Almost all individuals resident in Scotland are registered with primary care, which provides a comprehensive array of healthcare services (free at the point of care), including prescriptions for medications. We used the Practice Team Information network, which covers a 5% representative sample of Scottish practices [19]. Using the unique Community Health Index (CHI) number, specific patient-level data approved for use in this project were extracted and then linked to the Health Protection Scotland virology dataset, which consists of all laboratory-confirmed cases of influenza in Scotland. Once linkage had been completed, the analysis file was anonymised by replacing the unique CHI number with a study identifier.

We established key population characteristics: sex, age (0–4, 5–14, 15–44, 45–64, 65–74, and ≥ 75 years), socioeconomic status (Scottish Index of Multiple Deprivation scores [20] expressed as quintiles: 1 = most deprived to 5 = most affluent), receipt of pneumococcal and influenza vaccination in the previous year, smoking status (current, ex, non, not recorded), urban/rural residence (1 = large urban to 6 = remote rural), whether a patient was in a clinical group at risk of serious illness from influenza (i.e. chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, immunosuppression or diabetes), Charlson co-morbidity index [21], number of previous primary care consultations, prescribed drugs and hospital admissions (in the year before 1 September).

Study design

In order to estimate VE derived from linked virological swab data, we carried out a test-negative study similar to that used by I-MOVE [22], pooling data from nine influenza seasons (2000/01 to 2008/09). Influenza A(H1N1) subtype was dominant in 2007/8 (A/Solomon Island/3/2006) and H3N2 subtype was dominant in 2001/2 (A/Panama/2007/99), 2003/4 (A/Fujian/411/2002), 2006/7 (A/Wisconsin/67/05) and 2008/9 (A/Brisbane/10/2007). Influenza B was dominant in 2005/6 (B/Malaysia/2506/2004). Influenza A(H1N1) (A/New Caledonia/20/99) and influenza B (B/Beijing/184/93) were co-dominant in 2000/1. Influenza A(H3N2) and influenza B were co-dominant 2002/3 (A/Panama/2007/99, B/HongKong/330/01) and 2004/5 (A/Wellington/01/2004, B/Shanghai/361/2002). We carried out an individual patient-level pooled analysis and adjusted for year. The influenza season was defined as the period from the date of the first influenza isolate reported by Health Protection Scotland for each year, in or after week 40 and the date of the last influenza isolate before or in week 20 (during the period of peak influenza). Vaccination was used to define exposure status if it was given at a time point between the start of the pre-influenza season (i.e. 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'. The earliest influenza season began on 26 September and the latest began on 25 November, and all seasons finished in May (Table 1). A protocol of the study methods has been previously published [23].

Study outcomes

General practitioners in this study were also involved in the Health Protection Scotland sentinel-swabbing scheme, whereby practices are encouraged to obtain nasal or throat swabs from patients of all ages who have presented with symptoms suggestive of influenza. This is independent of whether or not the patient has been vaccinated. Each general practice is requested to submit five swab samples per week to the West of Scotland Specialist Virology Centre, Glasgow, UK for PCR testing for a range of respiratory pathogens. We also included results from swabbing carried out in primary and secondary care for routine diagnostic purposes in symptomatic patients outside the sentinel scheme. As a post-hoc sensitivity analysis, we excluded patients recruited from non-sentinel sources (n = 542; 16.3%) and those presenting symptoms less than 14 days after vaccination (n = 47; 1.4%). The West of Scotland Specialist Virology Centre is a World Health Organization-accredited National Influenza Center, which participates in the Quality Assurance programme to maintain this status. To calculate VE, patient swab data were linked with the unique patient identifier CHI, allowing characteristics of patients such as vaccination status to be established from general practice and hospital admission data. In 2005/06 when influenza B (B/Malaysia/2506/2004) was the predominant circulating virus type, tests were performed in sufficient numbers to estimate VE against influenza B in that season.

Table 1

Influenza seasons start and end dates, Scotland, 2000–09

Season	Start date	End date
2000/01	5 Oct 2000	14 May 2001
2001/02	18 Oct 2001	17 May 2002
2002/03	25 Nov 2002	15 May 2003
2003/04	26 Sep 2003	07 May 2004
2004/05	22 Oct 2004	19 May 2005
2005/06	06 Oct 2005	16 May 2006
2006/07	19 Oct 2006	09 May 2007
2007/08	02 Oct 2007	13 May 2008
2008/09	13 Nov 2008	05 May 2009

The Privacy Advisory Committee of the Information Services Division, National Services Scotland, approved the linkage and analysis of the anonymised datasets for this project.

Statistical methods

A generalised additive logistic regression model [24] was fitted, adjusting for the effects of week during season (through a separate spline model each season) and age, sex, deprivation, smoking status, number of primary care and hospital consultations in the previous 12 months, influenza vaccination in the previous season, and being in a clinical group at risk of serious complications from influenza. Some of these patients did not receive the influenza vaccine; some received the vaccine, but after they were tested; and others had 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 swab and who were then subsequently vaccinated counted as unvaccinated in our analysis as did people who were never vaccinated). When two doses were given we used the date of the first vaccine dose in our analysis. We stratified our analysis by people 65 years and older vs people younger than 65 years and at risk, and also tested for any heterogeneity between seasons. We also tested for any heterogeneity or collinearity between receipt of current and previous season's influenza vaccination.

Using data from previous studies, we estimated that with 400 swabs per year, an effectiveness of 20% would be detected with 79% power for our primary outcome of PCR-confirmed influenza (assuming that 15% of the population would be vaccinated, 30% swab-positive and adjusting for clustering within each primary care practice [25,26]). All statistical analysis was conducted using R (version 2.14.1).

Results

A total of 3,323 swabs were taken from 3,016 patients with influenza symptoms over the nine seasons (of a total registered primary care population of 1,767,705 person-seasons) and then tested with RT-PCR for evidence of influenza infection. Some 489 swabs (14.7%) were performed on individuals who were vaccinated at the time of the swab. Although all subgroups were represented, proportionately more young, female, and socioeconomically deprived patients were swabbed (Table 2). Furthermore, a large proportion of the virological tests (42.3%) were carried out on patients that had presented more than five times to primary care in the previous year. During our study, 13.9% of swabs were positive for RT-PCR-confirmed influenza, with male patients and the socioeconomically affluent being more likely to test positive for influenza (Table 2). One quarter of the swabs from school-aged children (5–14 years) tested positive for RT-PCR-confirmed influenza. Pooled over nine seasons, VE for the trivalent inactivated influenza vaccine in the whole population was 57% (95% confidence interval (CI): 31–73) (Table 3). VE for at-risk patients under 65 years was 60% (95% CI: 22–79) and 19% (95% CI: −104 to 68) for 65 years and older. Although there was variability between seasons, no significant heterogeneity was found ($p < 0.05$); there were no positive tests among vaccinated people in 2000/01 and the highest VE was found in season 2007/08 (Table 4). In 2005/06 for influenza B, there were 44 positive tests in 426 unvaccinated and three in 137 vaccinated individuals. In that season, VE against influenza B was 79% (95% CI: 32–96).

Table 2

Number of swabs vs laboratory-confirmed influenza, by population group, Scotland, 2000–09 (n = 3,323)

Description	Total samples	Swab-positive (number and % positive)	Swab-positive AOR[a]	AOR 95% CI
Sex				
Female	1,995	248 (12.4)	1.00	NA
Male	1,328	214 (16.1)	1.35	1.07–1.69
Age group (years)				
0–4	390	60 (15.4)	1.00	
5–14	433	104 (24.0)	1.56	1.05–2.32
15–44	1,405	196 (14.0)	0.89	0.63–1.27
45–64	741	79 (10.7)	0.71	0.47–1.06
65–74	244	18 (7.4)	0.70	0.36–1.36
≥75	110	5 (4.6)	0.43	0.15–1.24
Deprivation quintile[b]				
1[c]	961	100 (10.4)	1.00	NA
2	789	97 (12.3)	1.18	0.85–1.63
3	735	116 (15.8)	1.55	1.13–2.12
4	519	96 (18.5)	1.94	1.39–2.71
5	309	51 (16.5)	1.86	1.24–2.79
Influenza vaccine in previous season				
No	2,817	426 (15.1)	1.00	NA
Yes	506	36 (7.1)	0.90	0.53–1.52
Primary care consultations				
0–2	1,133	206 (18.2)	1.00	NA
3–4	785	103 (13.1)	0.69	0.52–0.92
≥5	1,405	153 (10.9)	0.87	0.66–1.15
Secondary care consultations				
0	2,728	400 (14.7)	1.00	NA
1–2	456	47 (10.3)	0.73	0.51–1.04
≥3	139	15 (10.8)	0.78	0.42–1.45

AOR: adjusted odds ratio; CI: confidence interval; NA: not applicable.

[a] Adjusted for season, week during season (through a separate spline model each season), age, sex, previous season's influenza vaccination, consultations and socioeconomic deprivation.

[b] Deprivation score only available for 3,313 swabs.

[c] 1 = most socioeconomically deprived.

Table 3

Proportion of vaccinated by case/control status and adjusted vaccine effectiveness for laboratory-confirmed influenza, Scotland, 2000–09 (n = 3,323)

Age group	Influenza-positive (cases)		Influenza-negative (controls)		% total positive	Adjusted vaccination effectiveness % (95% CI)[a]
	Vaccinated/ total (n)	Vaccinated (%)	Vaccinated/ total (n)	Vaccinated (%)		
<65 years[b]	14/439	3.2	249/2,530	9.8	14.8	66 (39 to 81)
<65 years clinically at risk	14/117	12.0	209/788	26.5	12.9	60 (22 to 79)
≥65 years	13/23	56.5	222/331	67.1	6.5	19 (–104 to 68)
All ages	27/462	5.8	471/2,861	16.5	13.9	57 (31 to 73)

CI: confidence interval.

[a] Adjusted for season, week during season, sex, number of hospital and primary care consultations, socioeconomic deprivation and being in a clinical at-risk group (where appropriate).

[b] All patients including clinically at risk.

Table 4

Vaccine effectiveness for laboratory-confirmed influenza and predominant circulating influenza by season, Scotland, 2000–09 (n = 3,323)

Season	Influenza-positive (cases)		Influenza-negative (controls)		% total positive	Adjusted vaccination effectiveness (95% CI) [a]	Dominant types circulating
	Vaccinated/ total (n)	Vaccinated (%)	Vaccinated/ total (n)	Vaccinated (%)			
2000/01	0/59	0.0	53/404	13.1	12.9	NA	A/New Caledonia/20/99 (H1N1) B/Beijing/184/93
2001/02	1/55	1.8	25/310	8.1	7.7	77 (–117 to 98)	A/Panama/2007/99 (H3N2)
2002/03	1/21	4.8	22/220	10.0	10.6	68 (–310 to 98)	A/Panama/2007/99 (H3N2) B/HongKong/330/01
2003/04	4/56	7.1	12/269	4.5	5.2	49 (–58 to 84)	A/Fujian/411/2002 (H3N2)[a]
2004/05	5/49	10.2	60/351	17.1	19.4	44 (–66 to 81)	A/Wellington/01/2004 (H3N2)[a] B/Shanghai/361/2002
2005/06	6/141	4.3	52/470	11.1	10.5	29 (–109 to 76)	B/Malaysia/2506/2004[a]
2006/07	2/26	7.7	23/228	10.1	10.9	22 (–375 to 87)	A/Wisconsin/67/05 (H3N2)
2007/08	3/43	7.0	55/214	25.7	29.2	80 (21 to 95)	A/Solomon Island/3/2006 (H1N1)
2008/09	4/40	10.0	50/254	19.7	22.5	38 (–136 to 84)	A/Brisbane/10/2007 (H3N2)

CI: confidence interval; NA: not applicable.

[a] Poorly matched vaccine.

When including influenza vaccination in the previous season (for all nine seasons), the vaccine effect in the current year was 55% (95% CI: 22–74) and there was no significant effect of the vaccination in the previous year (OR = 0.89; 95% CI: 0.53–1.52). A post-hoc interaction test showed a significant (p = 0.01) interaction between receipt of the previous season's and the current season influenza vaccination and VE but no major collinearity. Table 5 presents the VEs of three possible combinations of vaccinated or unvaccinated in the current or previous season (combining all the seasons studied) compared with people with no vaccination in either season. Significant positive VEs were found for subgroups vaccinated in the current and previous season and those vaccinated in the current but not the previous season. A non-significant positive VE was found for people vaccinated in the previous season but not the current.

VE was similar to our primary analysis when excluding virological tests from non-sentinel sources (60%; 95% CI: 31–77) or patients with onset of symptoms less than 14 days after vaccination (VE = 61%; 95% CI: 36–76).

Discussion

Our trivalent influenza VE using RT-PCR in symptomatic patients presenting over nine seasons was similar to the efficacy found in healthy adults younger than 65 years in controlled trials (66% vs 75%) [8]. Our findings were also similar to other observational studies which pooled data across several seasons and estimated a VE of 61% for adults 50 years and older [15]

Table 5

Vaccine effectiveness for the combined influenza vaccinations in the previous and current season, Scotland, for all seasons (n = 3,323)

Previous season	Current season	Vaccination effectiveness	95% CI	p compared with unvaccinated in both seasons
Unvaccinated	Unvaccinated	0.0	0.0 to 0.0	NA
Vaccinated	Unvaccinated	47.6	−6.1 to 74.1	0.072
Unvaccinated	Vaccinated	85.2	51.5 to 95.5	0.002
Vaccinated	Vaccinated	50.4	15.6 to 70.8	0.010

CI: confidence interval.

and 62% for 20–64 year-olds [14]. In a single season (2012/13) in which genetic drift of the predominant influenza A(H3N2) strain had occurred, the VE estimate for people 65 years and older was −11% against influenza A [27]. This is lower than our pooled estimate of 19% VE for this age group over nine seasons with different circulating strains. In the 2007/08 season when vaccine and circulating virus were well matched and influenza A/Solomon Island/3/2006 (H1N1) was the main circulating virus, our VE was higher for laboratory-confirmed influenza than in a US study in the same season which used a study design similar to ours (80% vs 52%) [28]. In the 2005/06 season when influenza B/Malaysia/2506/2004 was the predominant strain, our estimate of 29% was similar to a US study (21%) [29], but lower than reported in Canada (63%) [30]. These differences in VE are likely to be due to between-country variation in the distribution of vaccine types, dominant circulating influenza types, subtypes, and lineages, and antigenic (mis)match between vaccine virus and circulating virus [31]. Although there was poor precision, we found variations in VE over the seasons. In the two seasons when influenza A(H1N1) co-dominated or dominated and the vaccine was well matched (2000/01 and 2007/08, respectively), VE was high (≥ 80%). In 2003/04 and 2004/05 when vaccine mismatch occurred in the A(H3N2) component of the vaccine, VEs of 49% and 44% were found. In 2005/06 when there was vaccine mismatch for influenza B, a 79% VE for influenza B was found. This was similar to findings in a well-powered study in the same season on influenza B in England (67%; 95% CI: 31–85). In all other seasons, influenza A(H3N2) was the predominant influenza A subtype and VE varied from 22% (2006/07) to 77% (2001/02) [32].

Our finding of an interaction, whereby prior influenza vaccination interfered with current vaccine effectiveness, has been described previously in a community-based study [33]. Similar to that study, we were limited by a relatively small number of cases and were only able to dichotomise prior and current season vaccination status (yes or no). However, this simplified approach has been criticised and a more in-depth analysis has been suggested which includes the number, nature and antigenic distance specified by virus mutations across sequential circulating variants and vaccine components [34]. This is a potential avenue for further work.

Clinical data collected by these sentinel practices are of high quality (90% completeness and accuracy [25]) and their value for epidemiological research has been repeatedly demonstrated [26]. Observational studies can be used to assess the effects of healthcare interventions without influencing the care provided or the patients who receive it. When used in the assessment of vaccination programmes they therefore have high external validity and can be broadly generalised. Furthermore, by pooling data from nine seasons from the same population, we were able to generate sufficient power to provide a precise VE estimate. The test-negative design offers an elegant way to deal with selection bias that may arise if there is a strong association between vaccination status and subject recruitment. However, this design only measures the protection provided by the vaccine to individuals seeking medical attention, rather than VE against influenza, because for some persons (e.g. people with co-morbidities and at risk of serious complications from influenza), vaccination may not truly prevent influenza, but may reduce illness severity, preventing death or hospitalisation or reducing severity below their care-seeking threshold [35]. If possible, one should therefore assess the likely impact of VE on disease severity [36] and the influence of non-influenza acute respiratory infections by restricting controls to those who tested negative for influenza and positive for a different respiratory pathogen (e.g. parainfluenza or respiratory syncytial viruses) [35,37]. Swabs from symptomatic patients outside the systematically collected subset were included in our study, and this may have led to some selection bias, although physicians swabbing in secondary care (where the majority of non-sentinel swabbing took place) were unlikely to know the patient's vaccine status unless self-reported and a sensitivity analysis found no change to our VE estimates (but decreased their precision). However, even with the inclusion of these additional tests from non-sentinel sources, there was an over-representation of swabs from working-age adults and therefore we had lower power to measure VE among children and older people. There was also inadequate power to measure pooled estimates of

VE for types or subtypes of influenza (e.g. A(H3N2), A(H1N1) and B), most individual seasons, patients with chronic diseases (e.g. asthma) or pregnancy (which was not included as a risk factor for this analysis) or for those given a second dose of the vaccine. A much larger study is therefore required to perform these stratified analyses. In our primary analysis, we considered that the vaccine effect was random over seasons rather than the seasons having random effect. In this pooled model we found that there was already a different intercept and seasonal trend each year and that this permitted more differences among the seasons compared with a random effects model. The random effects meta-analysis estimate was 51%, close to the pooled estimate reported in this paper (57%). Furthermore, treating each season equally gave a VE estimate of 65%. Some of the patients were found to have contributed with more than one swab in different seasons, with 231 people with swabs in two seasons, 27 with swabs in three seasons and six with swabs in more than three seasons. We therefore performed post-hoc sensitivity analyses using a generalised estimating equation (GEE) model and a clustered regression model. Both of these models were found to inflate the variance of the vaccine effect, but did not have a major impact on the conclusions.

Our primary objective was to make use of the best integrated and accessible Scottish data available to us to evaluate a new national influenza vaccination programme introduced in Scotland in September 2000. During the period 2000 to 2009, seasonal influenza vaccination was provided to at-risk groups (at no cost to the patient) through primary care. This targeted approach resulted in high vaccine uptake rates of 66 to 76% in older people and 38 to 49% in at-risk groups [6]. We found that during the period when the programme was implemented (and before pandemic influenza), which included seasons with poor vaccination match and severe influenza, there was strong evidence for the effectiveness of vaccination in preventing laboratory-confirmed influenza, particularly for younger people and people susceptible to severe influenza-like illness. This information should reassure countries considering the implementation of a similar programme. However, while work is being undertaken to produce better vaccines and new vaccines are introduced, the continued development of a strong international evidence base is required to monitor the effectiveness of seasonal influenza vaccination programmes, particularly among subgroups of patients at risk of serious complications from influenza such as older people.

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Conflict of interest

None declared

Authors' contributions

Dr Colin Simpson (Senior Lecturer in Population Health Sciences) and Dr Nazir Lone (Senior Clinical Lecturer) were Principal Investigators and led the project and the writing of this paper. 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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