

# Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study

Eleftheria Vasileiou,<sup>1</sup> Aziz Sheikh,<sup>1</sup> Chris C. Butler,<sup>2</sup> Chris Robertson,<sup>3</sup> Kimberley Kavanagh,<sup>4</sup> Tanya Englishby,<sup>4</sup> Nazir I. Lone,<sup>1</sup> Beatrix von Wissmann,<sup>5</sup> Jim McMenamin,<sup>5</sup> Lewis D. Ritchie,<sup>6</sup> Jürgen Schwarze,<sup>7</sup> Rory Gunson,<sup>8</sup> and Colin R. Simpson<sup>1,9</sup>

<sup>1</sup>Asthma UK Centre for Applied Research, Usher Institute, The University of Edinburgh, Edinburgh, United Kingdom, <sup>2</sup>Nuffield Department of Primary Care Health Sciences, Oxford University, New Radcliffe House, Radcliffe Observatory Quarter, Oxford, United Kingdom and Cardiff University, Institute of Primary Care and Public Health, Cardiff, United Kingdom, <sup>3</sup>Department of Mathematics and Statistics, University of Strathclyde, Glasgow, United Kingdom and Health Protection Scotland, Glasgow, United Kingdom, <sup>4</sup>Department of Mathematics and Statistics, University of Strathclyde, Glasgow, United Kingdom, <sup>5</sup>Health Protection Scotland, National Health Service (NHS) National Services Scotland, Glasgow, United Kingdom, <sup>6</sup>Centre of Academic Primary Care, University of Aberdeen, Aberdeen, United Kingdom, <sup>7</sup>Centre for Inflammation Research, Queen's Medical Research Institute, Child Life and Health, The University of Edinburgh, Edinburgh, United Kingdom, <sup>8</sup>West of Scotland Specialist Virology Centre, Glasgow, United Kingdom, and <sup>9</sup>School of Health, Faculty of Health, Victoria University of Wellington, Wellington, New Zealand and Asthma UK Centre for Applied Research, Usher Institute, The University of Edinburgh, Edinburgh, United Kingdom

**Background.** Influenza infection is a trigger of asthma attacks. Influenza vaccination can potentially reduce the incidence of influenza in people with asthma, but uptake remains persistently low, partially reflecting concerns about vaccine effectiveness (VE).

**Methods.** We conducted a test-negative designed case-control study to estimate the effectiveness of influenza vaccine in people with asthma in Scotland over 6 seasons (2010/2011 to 2015/2016). We used individual patient-level data from 223 practices, which yielded 1 830 772 patient-years of data that were linked with virological ( $n = 5910$  swabs) data.

**Results.** Vaccination was associated with an overall 55.0% (95% confidence interval [CI], 45.8–62.7) risk reduction of laboratory-confirmed influenza infections in people with asthma over 6 seasons. There were substantial variations in VE between seasons, influenza strains, and age groups. The highest VE (76.1%; 95% CI, 55.6–87.1) was found in the 2010/2011 season, when the A(H1N1) strain dominated and there was a good antigenic vaccine match. High protection was observed against the A(H1N1) (eg, 2010/2011; 70.7%; 95% CI, 32.5–87.3) and B strains (eg, 2010/2011; 83.2%; 95% CI, 44.3–94.9), but there was lower protection for the A(H3N2) strain (eg, 2014/2015; 26.4%; 95% CI, –12.0 to 51.6). The highest VE against all viral strains was observed in adults aged 18–54 years (57.0%; 95% CI, 42.3–68.0).

**Conclusions.** Influenza vaccination gave meaningful protection against laboratory-confirmed influenza in people with asthma across all seasons. Strategies to boost influenza vaccine uptake have the potential to substantially reduce influenza-triggered asthma attacks.

**Keywords.** influenza; vaccination; asthma; laboratory-confirmed influenza.

Seasonal influenza results in substantial global morbidity and mortality each year [1, 2]. In people with asthma, influenza infection can exacerbate asthma symptoms, which may result in asthma attacks that necessitate medical attention and, in many cases, hospital admission [3]. The World Health Organization (WHO) and national immunization programs recommend annual influenza vaccination in people with asthma as the main prophylactic measure against influenza [4–6]. In the United

Kingdom, however, vaccination rates in asthma remain well below the 75% uptake target set by the WHO [7]. This suboptimal vaccine uptake is due, at least in part, to uncertainty among people with asthma and healthcare providers around the effectiveness of influenza vaccines [8]. In the United Kingdom, suboptimal vaccine protection is partly addressed with the introduction of new vaccine formulations. Specifically, in season 2018/2019, younger adults aged 18–64 years who belonged to an at-risk group were offered a quadrivalent inactivated vaccine (QIV) and people aged >65 years were offered an adjuvanted trivalent inactivated vaccine (TIV) [9]. The QIV aims to provide better protection by including 2 influenza B subtypes given that influenza B affects younger age groups. The adjuvanted TIV aims to enhance the immune response in older people and improve the current suboptimal vaccine effectiveness (VE) observed from traditional TIVs [9].

Our recent systematic review suggested that the vaccine is effective against influenza infection in asthma [8]. However, the

Received 29 July 2019; editorial decision 27 October 2019; accepted 4 November 2019; published online November 5, 2019.

Correspondence: E. Vasileiou, Asthma UK Centre for Applied Research, Usher Institute, The University of Edinburgh, Edinburgh, UK (eleftheria.vasileiou@ed.ac.uk)

Clinical Infectious Diseases® 2020;71(7):e94–e104

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)  
DOI: 10.1093/cid/ciz1086

conclusions of that review were based mainly on studies in which the overall quality was rated as low due to methodological issues related to the study design and conduct [8]. Two case-control studies published after the search date of the literature review assessed VE in individuals with asthma [10]. The first study compared the VE between asthma and non-asthma hospitalized patients for laboratory-confirmed influenza [10]. However, there were too few patients with asthma and, thus, the study was underpowered to determine the effectiveness of the influenza vaccine [10]. In the second study, the VE was assessed in children aged 6–59 months during 4 seasons by various characteristics including asthma [11]. VE of 43.3% was found in the asthma subgroup. However, no further analyses in relation to other demographics or other characteristics related to influenza infection or the vaccination were performed for the asthma subgroup [11].

Most national immunization committees assess VE based on evidence from observational studies rather than placebo randomized controlled trials, which are no longer conducted in asthma since the vaccination is now a public health recommendation for all at-risk groups such as people with asthma [12]. Thus, we used a test-negative design (TND), case-control study to best determine the VE for each influenza season since it is now seen as the gold standard for generating unbiased VE estimates [13–16]. In addition, the large sample size of our TND study using swab samples from multiple seasons enabled us to assess various factors that affect VE in observational studies, such as asthma population characteristics and influenza circulating types and subtypes, which were not assessed in previous studies due to sample size limitations [8].

Our aim in this study was to assess VE in children and adults with asthma. More specifically, our objectives were to evaluate seasonal influenza VE across and in single seasons, evaluate VE against common seasonal circulating viral strains, and provide VE estimates by age groups.

## METHODS

### Study Design

We undertook a retrospective, observational, TND, case-control study to evaluate influenza VE in patients who seek care for acute respiratory infection. In a TND study, cases are those who test positive for influenza and controls are those who test negative for influenza. This study included children (aged >6 months) and adults who were recommended by UK immunization guidelines to receive influenza vaccination, that is, those treated for asthma who require continuous or repeated use of inhaled or systemic corticosteroids and/or with previous exacerbations that required hospital admission. The study participants were identified from 223 general practices (sentinel and nonsentinel) and hospitals for acute respiratory illness from influenza season 2010/2011 to 2015/2016 in Scotland. Patients were swabbed and tested for influenza using the multiplex real-time polymerase chain reaction

(RT-PCR) assay [17]. Patients with a positive test for influenza were classified as cases, while those with a negative test were classified as controls. In patients with more than 1 positive test for influenza, only the first positive test was counted as a single case. VE was estimated by comparing positivity proportions between the vaccinated and unvaccinated patients [16].

The VE assessment in the asthma population was an objective of the Seasonal Influenza Vaccine Effectiveness (SIVE) II project [18] (see included datasets in Figure 1). See [Supplementary Material 1](#) for details.

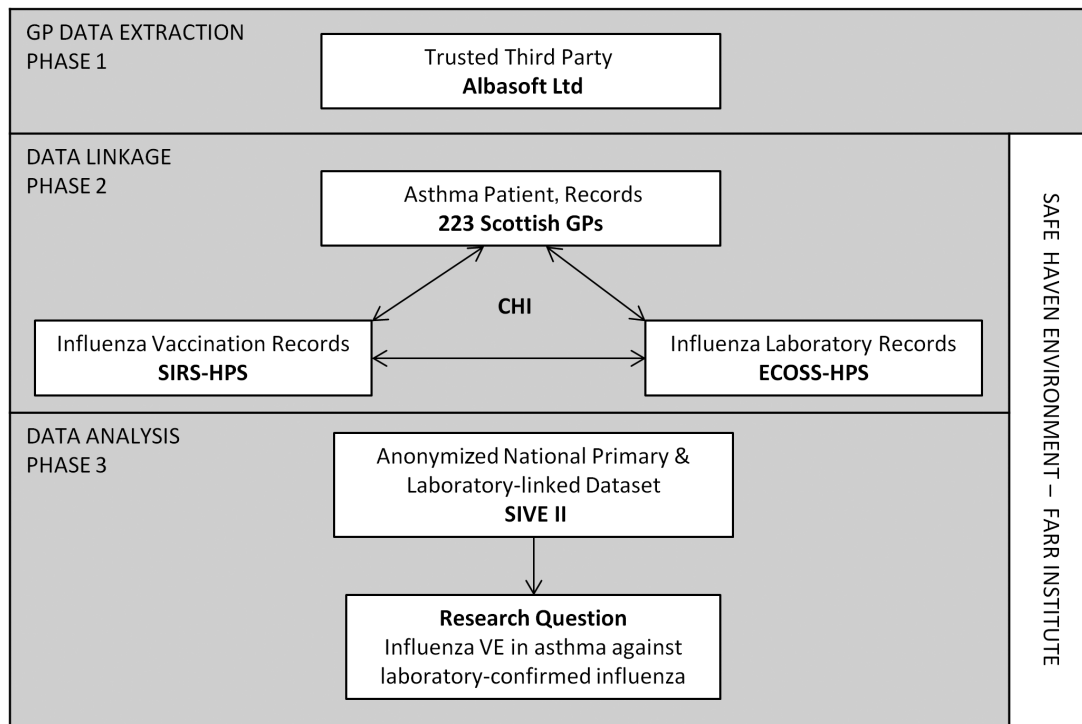
### Exposure and Outcome Assessment

The exposure status was based on vaccination administered between the preinfluenza season and the end of the influenza season. Individuals vaccinated from 1 September until the end of the influenza season defined the “exposed” group. Individuals with no vaccination record, vaccinated after being tested for influenza, or vaccinated within 14 days prior to testing were classified as the “unexposed” group [18].

General practitioners who were part of the sentinel scheme obtained nasal or nasopharyngeal swabs from patients with influenza-like illness (ILI) symptoms. General practitioners usually collected swab samples from patients who presented with ILI symptoms (independent of whether the patient had or had not been vaccinated) within 7 days of the date of onset of those symptoms. Each general practitioner collected up to 5 samples per week and submitted those to the West of Scotland Specialist Virology Centre (WoSSVC) [18]. Each swab sample collected in general practice sentinel settings was tested at the WoSSVC using the multiplex RT-PCR test for a range of respiratory pathogens, including influenza [18]. For non-sentinel practices or secondary care, other laboratories were involved in testing. Subtype and genetic characterization was performed for positive influenza sentinel samples and most of the nonsentinel general practice and hospital samples. Data on laboratory tests carried out in nonsentinel primary and secondary healthcare facilities were also collected by the Electronic Communication of Surveillance in Scotland database. See [Supplementary Material 2](#) for baseline characteristics description.

### Statistical Analyses

Baseline characteristics of study participants were described. The relation between vaccination status and baseline characteristics was also provided for cases and controls. Proportions and odds ratios (ORs) were used to describe differences between study groups depending on the nature of each variable. All baseline population characteristics were presented as categorical variables, and the  $\chi^2$  test was used to describe any association in relation to exposure or outcome. Any missing data were reported. All tests were 2-tailed, and results were considered significant if  $P < .05$ . See [Supplementary Materials 3 and 4](#) for details on unit of analysis and metaanalysis.



**Figure 1.** Phases of data extraction, linkage, and analysis in a secured environment. Abbreviations: CHI, Community Health Index; ECOSS-HPS, Electronic Communication of Surveillance in Scotland-Health Protection Scotland; GP, general practitioners; SIRS, Scottish Immunisation & Recall System-Health Protection Scotland; SIVE II, Seasonal Influenza Vaccine Effectiveness II project; VE, vaccine effectiveness.

### Primary and Secondary Analyses

Prespecified subgroup analyses as per our published protocol included the provision of VE for influenza A and B strains per season [18]. Post hoc analysis not specified in our protocol was also carried out in this study. Specifically, we stratified the VE by age groups in order to investigate the age when immunosenescence begins in adults.

### Vaccine Effectiveness

VE and the 95% confidence intervals (CIs) were estimated using the formula,  $VE = (1 - aOR) \times 100$  based on adjusted ORs (aORs) [18]. ORs were calculated by the regression coefficients of vaccine status in the model. A generalized additive logistic regression model was used to explain the relationship between influenza infection and influenza vaccine in the presence of other confounding covariates. The model provided VE estimates adjusted for the effects of the following covariates: time, age, underlying medical conditions, and the source of swab sample collection, which were either statistically or epidemiologically associated with the outcome. Adjustment for time was performed for all VE estimates. Time was measured in days from the beginning of October each season. It was included as a spline function to account for bias related to time differences between influenza circulation and vaccine administration during each season [18].

### Sample Size

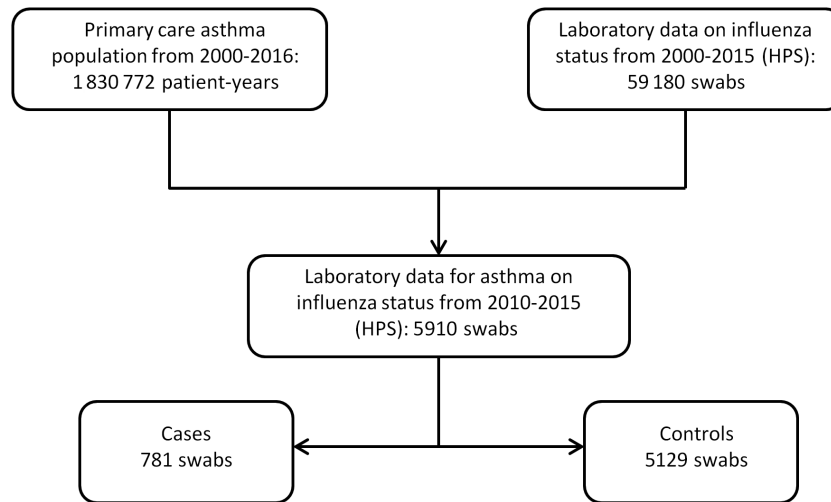
Using data from a previous study [18], we anticipated 1454 asthma patients would be swabbed over the 2 seasons 2014–2016. We assumed that 582 or 40.0% ( $1454 \times 0.40$ ) of asthma patients had been vaccinated for influenza and that the number of tests positive for influenza was 218 or 15.0% ( $1454 \times 0.15$ ), which gave an 80.0% power to detect a VE of 33.0% [18]. The study recruited 1413 patients swabbed in 2014/2015 and 1670 swabbed in 2015/2016. Sample size details are provided in [Supplementary Material 5](#). Statistical analyses were carried out using R Version 3.4.2 and RStudio (Version 1.0.143) [19] within the National Health Service Scotland data safe haven.

### Ethical Considerations

The Information Services Division, National Services Scotland, Privacy Advisory Committee approved the linkage and the statistical analysis of the anonymized data used in this study.

### Reporting

We used the Strengthening the Reporting of Observational studies in Epidemiology and REporting of studies Conducted using Observational Routinely collected Data checklists to guide transparent reporting of this TND, case-control study (see [Supplementary Materials 6 and 7](#)) [20, 21].



**Figure 2.** Flow diagram for the test-negative design, case-control study for an asthma population for the influenza seasons 2010/2011 to 2015/2016, Scotland. Abbreviation: HPS, Health Protection Scotland.

## RESULTS

A total registered primary care asthma population of 1 830 772 person-years out of 194 319 people with asthma was recruited in this study over a 16-year period. These data were collected as part of the SIVE II study [18] and included 5910 swab samples taken from 5022 asthma patients from 2010/2011 to 2015/2016 (Figure 2). These swabs were collected in primary or secondary care settings from people with asthma and tested for influenza with the RT-PCR test. There were 781 of 5910 (13.2%) swabs that tested positive for influenza and were classified as cases (Table 1); 86.8% tested negative for influenza and were classified as controls (Figure 2). Patients more likely to test positive for influenza were aged 45–64 years (15.1%), lived in remote small towns (>10%), had not received previous seasonal influenza vaccine (15.2%), and had a swab sample collected in a primary care setting (16.7%; Table 2).

### Vaccine Effectiveness by Season and Influenza Type and Subtype

The VE for the common influenza circulating strains was estimated for each strain in each influenza season. In 2010/2011, the overall VE was high (76.1%; 95% CI, 55.6 to 87.1), with A/H1N1 and B predominating (Table 3). In 2011/2012, the overall VE was lower and imprecise (45.1%; 95% CI, –35.1 to 77.7), with A/H3N2 predominating. Slightly higher and more precise overall VE of 45.2% (95% CI, 13.8 to 65.1) was observed in the 2012/2013 season when all influenza A subtypes codominated. The overall VE in 2013/2014 (when the predominant strain was A/H1N1) was 52.3% (95% CI, 6.5 to 75.6). In 2014/2015, an overall VE of 48.6% (95% CI, 27.8 to 63.4) was found with a high swab positivity (16.4%) and predominant strains H3N2 and B. In the 2015/2016 season, the overall VE of 57.8% (95% CI, 40.1 to 70.3) was higher compared with previous seasons (except for 2010/2011); the predominant strains were A/H1N1 and B, and the swab positivity was 12.0%.

In 2010/2011, we found high VE for the influenza A(H1N1) subtype and B, with estimates of 70.7% (95% CI, 32.5 to 87.3) and 83.2% (95% CI, 44.3 to 94.9), respectively (Table 3). In the 2011/2012 season, a small number of cases of influenza A(H3) subtype and B resulted in low and imprecise VE estimates of 3.7% (95% CI, –240.5 to 75.0) and 71.8% (95% CI, –358.1 to 98.3), respectively. In the 2012/2013 season when all influenza A subtypes codominated, a particularly high VE of 77.5% (95% CI, 9.8 to 94.4) was observed for A(H1N1), but lower VE was found for the cocirculating influenza A(H3) and B strains. In 2013/2014, a VE of 32.0% (95% CI, –52.2 to 69.6) was observed for the influenza A(H1N1) subtype; imprecision in the VE estimate was due to low swab positivity. In 2014/2015, a high VE of 77.0% (95% CI, 53.9 to 88.5) for influenza B was found. In 2015/2016, the swab positivity was 12.0% and a VE estimate of 54.7% (95% CI, 19.5 to 74.5) was observed for influenza B.

### Pooled Vaccine Effectiveness by Influenza Type and Subtype

The overall VE estimate was 54.9% (95% CI, 44.4 to 63.4) against influenza A and B types as it is shown by the OR provided in the random effect model (Figure 3). Heterogeneity for this pooled estimate was detected but it was small. A substantially

**Table 1. Number of Influenza (Sub)Types Out of the 781 Influenza-Positive Cases**

Influenza (Sub)Type	Number of Influenza (Sub)Types per Number of Cases (%)
Influenza A	581/781 (74.4)
A(H1N1)	240/781 (30.7)
A(H3)	208/781 (26.6)
A(unknown)	133/781 (17.0)
Influenza B	205/781 (26.2)
Influenza A and B	5/781 (0.6)

**Table 2. Baseline Characteristics for Cases and Controls With Asthma During 6 Seasons, Scotland, 2010–2016**

Covariate	Total Samples (% of Total)	Number of Vaccinated at Test (% of Total)	PValue	Number of Positive Swabs (% of Total)	PValue	Swab-Positive Adjusted Odds Ratio <sup>a</sup>	Adjusted 95% Confidence Interval
<b>Gender</b>							
Female (reference)	3575 (60.5)	1777 (49.7)	.04	469 (13.1)	.79	NA	NA
Male	2335 (39.5)	1097 (47.0)		312 (13.4)		1.02	.88–1.19
<b>Age group, y<sup>b</sup></b>							
0–1	5 (0.1)	3 (60.0)	<.001	0 (0.0)	.0004	8.688845e-06	1.320726e-209 to 5.716258e+198
2–4	169 (2.9)	64 (37.9)		11 (6.5)		0.47	.25–.90
5–11	530 (9.0)	213 (40.2)		45 (8.5)		0.63	.44–.91
12–17	371 (6.3)	119 (32.1)		45 (12.1)		0.94	.65–1.35
18–44	1615 (27.3)	436 (27.0)		234 (14.5)		1.15	.90–1.47
45–64	1625 (27.5)	826 (50.8)		246 (15.1)		1.21	.95–1.54
65–74	747 (12.6)	549 (73.5)		91 (12.2)		0.94	.70–1.27
≥75 (reference)	847 (14.3)	663 (78.3)		109 (12.9)		NA	NA
<b>Deprivation quintile<sup>c</sup></b>							
1 <sup>d</sup> (reference)	1350 (22.8)	620 (45.9)	.06	178 (13.2)	.69	NA	NA
2	1486 (25.1)	732 (49.3)		184 (12.4)		0.93	.75–1.16
3	1035 (17.5)	531 (51.3)		147 (14.2)		1.09	.86–1.38
4	976 (16.5)	465 (47.6)		130 (13.3)		1.01	.79–1.29
5	938 (15.9)	475 (50.6)		116 (12.4)		0.93	.72–1.19
<b>Urban/rural score<sup>e</sup></b>							
1 (reference)	3210 (54.3)	1573 (49.0)	.003	352 (11.0)	<.001	NA	NA
2	1459 (24.7)	676 (46.3)		228 (15.6)		1.50	1.26–1.80
3	381 (6.4)	183 (48.0)		63 (16.5)		1.61	1.19–2.14
4	91 (1.5)	40 (44.0)		16 (17.6)		1.73	.97–2.93
5	54 (0.9)	22 (40.7)		14 (25.9)		2.84	1.48–5.15
6	448 (7.6)	253 (56.5)		57 (12.7)		1.18	.87–1.58
7	63 (1.1)	24 (38.1)		16 (25.4)		2.76	1.51–4.82
8 <sup>f</sup>	118 (2.0)	65 (55.1)		17 (14.4)		1.37	.78–2.25
Chronic obstructive pulmonary disease	775 (13.1)	522 (67.4)	<.001	95 (12.3)	.40	0.91	.72–1.13
Chronic heart disease	722 (12.2)	527 (73.0)	<.001	92 (12.7)	.69	0.95	.75–1.20
Chronic liver disease	112 (1.9)	56 (50.0)	.77	15 (13.4)	.96	1.02	.56–1.70
Chronic neurological disease	357 (6.0)	251 (70.3)	<.001	45 (12.6)	.73	0.94	.68–1.29
Diabetes	597 (10.1)	417 (69.8)	<.001	75 (12.6)	.62	0.94	.72–1.20
Immunosuppression	166 (2.8)	85 (51.2)	.5	18 (10.8)	.36	0.79	.47–1.27
<b>Number of risk groups (comorbidities)</b>							
1 (reference)	3693 (62.5)	1440 (39.0)	<.001	490 (13.3)	.71	NA	NA
2	1042 (17.6)	632 (60.7)		141 (13.5)		1.02	.83–1.25
3	705 (11.9)	461 (65.4)		95 (13.5)		1.02	.80–1.28
4	333 (5.6)	241 (72.4)		39 (11.7)		0.87	.60–1.21
5	112 (1.2)	81 (72.3)		11 (9.8)		0.71	.36–1.28
6	25 (0.4)	19 (76.0)		5 (20.0)		1.63	.54–4.06
<b>Influenza vaccine in previous season</b>							
Yes	3352 (56.7)	2417 (72.1)	<.001	392 (11.7)	<.001	0.74	.64–.86
No (reference)	2558 (43.3)	457 (17.9)		389 (15.2)		NA	NA
<b>Swab samples taken in general practices or hospitals</b>							
General practice (reference)	873 (14.8)	359 (41.1)	<.001	146 (16.7)	.0005	NA	NA
Hospital	5010 (84.8)	2494 (49.8)		628 (12.5)		0.71	.59–.87
Unknown	27 (0.5)	21 (77.8)		7 (25.9)		1.74	.67–4.02

All P values were estimated using the  $\chi^2$  test.

Abbreviation: NA, not applicable.

<sup>a</sup>Adjusted for gender, age, and socioeconomic deprivation.

<sup>b</sup>Age group available for 5909 swabs.

<sup>c</sup>Deprivation score only available for 5785 swabs.

<sup>d</sup>Most socioeconomically deprived.

<sup>e</sup>Urban/rural score only available for 5824 swabs.

<sup>f</sup>Remote rural areas.

**Table 3. Vaccine Effectiveness for Laboratory-Confirmed Influenza Type and Subtype by Season, Scotland, 2010–2016**

Dominant Circulating Strain(s) for Each Influenza Season	Influenza Type and Subtype	Influenza-Positive (Cases)		Influenza-Negative (Controls)		Total Positive (%)	Unadjusted Vaccine Effectiveness <sup>a</sup> (95% CI)	Adjusted Vaccine Effectiveness <sup>b</sup> (95% CI)
		Vaccinated/ Total (n)	Vaccinated (%)	Vaccinated/ Total (n)	Vaccinated (%)			
Season: 2010–2011 A/California/07/2009 (H1N1)pdm2009 B/Brisbane/60/2008	Influenza A and B	29/123	23.6	176/364	48.4	25.3	70.1 (49.5 to 82.3)	76.1 (55.6 to 87.1)
	A(H3)	0/0	0.0	205/487	42.1	0.0	0.0 (–Inf to 100)	0.0 (–Inf to 100)
	A(H1N1)	17/79	21.5	188/408	46.1	16.2	68.8 (37.9 to 84.3)	70.7 (32.5 to 87.3)
	Influenza B	5/26	19.2	200/461	43.4	5.3	78.0 (37.3 to 92.3)	83.2 (44.3 to 94.9)
Season: 2011–2012 A/Victoria/208/2009 (H3N2)	Influenza A and B	14/28	50.0	241/546	44.1	4.9	34.4 (–44.3 to 70.1)	45.1 (–35.1 to 77.7)
	A(H3)	6/11	54.6	249/563	44.2	1.9	20.1 (–173.0 to 76.6)	3.7 (–240.5 to 75.0)
	A(H1N1)	0/0	0.0	255/574	44.4	0.0	0.0 (–Inf to 100)	0.0 (–Inf to 100)
	Influenza B	2/5	40.0	253/569	44.5	0.9	57.1 (–186.7 to 93.6)	71.8 (–358.1 to 98.3)
Season: 2012–2013 A/Victoria/208/2009 (H3N2) A/St Petersburg/27/2011 (H1N1) B/Brisbane/60/2008 B/Brisbane/3/2007 B/Massachusetts/02/2012	Influenza A and B	50/143	35.0	323/691	46.7	17.2	48.2 (22.2 to 65.5)	45.2 (13.8 to 65.1)
	A(H3)	17/45	37.8	356/789	45.1	5.4	27.9 (–36.3 to 61.9)	38.0 (–25.7 to 69.4)
	A(H1N1)	3/17	17.7	370/817	45.3	2.0	79.8 (28.3 to 94.3)	77.5 (9.8 to 94.4)
	Influenza B	18/53	34.0	355/781	45.5	6.4	40.0 (–9.8 to 67.3)	11.7 (–70.7 to 54.3)
Season: 2013–2014 A/California/07/2009 (H1N1)pdm09	Influenza A and B	26/54	48.2	457/878	52.1	5.8	37.7 (–10.7 to 64.9)	52.3 (6.5 to 75.6)
	A(H3)	2/6	33.3	481/926	51.9	0.6	65.9 (–105.0 to 94.3)	–3.9 (–1304.5 to 92.3)
	A(H1N1)	18/34	52.9	465/898	51.8	3.7	21.4 (–59.2 to 61.2)	32.0 (–52.2 to 69.6)
	Influenza B	2/5	40.0	481/927	51.9	0.5	45.2 (–259.1 to 91.7)	100 (0 to 100)
Season: 2014–2015 A/Texas/50/2012 (H3N2) B/Yamagata/16/88	Influenza A and B	122/232	52.6	605/1181	51.2	16.4	36.3 (13.3 to 53.2)	48.6 (27.8 to 63.4)
	A(H3)	79/140	56.4	648/1273	50.9	9.9	21.1 (–16.0 to 46.4)	26.4 (–12.0 to 51.6)
	A(H1N1)	5/6	83.3	722/1407	51.3	0.4	–290.9 (–3301.3 to 55.1)	–157.0 (–2565.5 to 75.2)
	Influenza B	20/49	40.8	707/1364	51.8	3.5	62.0 (30.3 to 79.3)	77.0 (53.9 to 88.5)
Season: 2015–2016 A/California/07/2009 (H1N1)pdm09 B/Brisbane/60/2008	Influenza A and B	85/201	42.3	746/1469	50.8	12.0	54.8 (37.8 to 67.1)	57.8 (40.1 to 70.3)
	A(H3)	2/6	33.3	829/1664	49.8	0.4	39.0 (–294.0 to 90.5)	78.1 (–102.6 to 97.6)
	A(H1N1)	51/104	49.0	780/1566	49.8	6.2	32.8 (–2.0 to 55.7)	36.7 (–6 to 60.2)
	Influenza B	26/67	38.8	805/1603	50.2	4.0	60.9 (33.9 to 76.8)	54.7 (19.5 to 74.5)

There are cases with unknown influenza A subtype, which explains why the total influenza A(H3) and A(H1N1) samples do not add up exactly to the total influenza A samples.

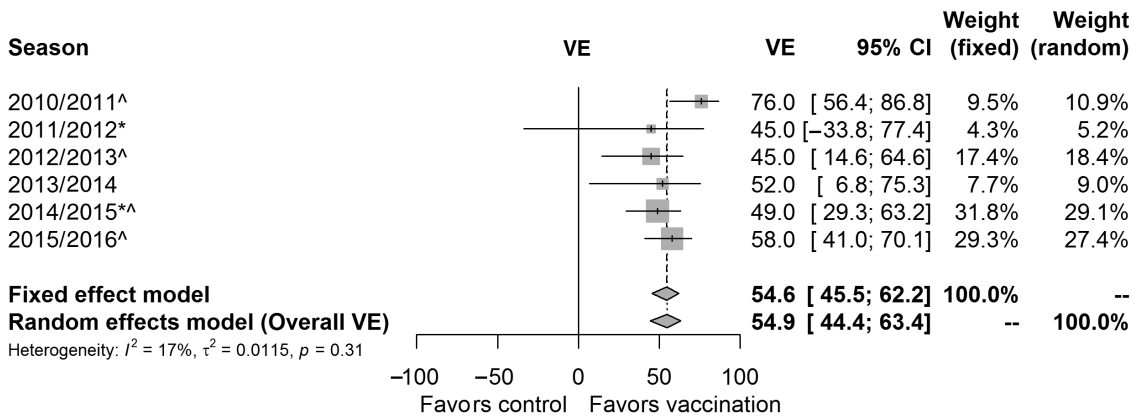
Abbreviation: CI, confidence interval; Inf, Infinite.

<sup>a</sup>Adjusted for time (ie, days) only.

<sup>b</sup>Adjusted for time (ie, days), age, number of risk groups, and swab location (ie, general practice or hospital).

low VE estimate of 29.3% (95% CI, 1.0 to 49.4) was detected for influenza A(H3), but no heterogeneity was found (Figure 4). A higher pooled VE of 48.4% (95% CI, 19.4 to 66.9) was found against influenza A(H1N1) compared with influenza

A(H3). Low-to-moderate heterogeneity was observed across seasons (Figure 5). The highest pooled VE of 60.8% (95% CI, 31.6 to 77.5) was detected for influenza B. Higher heterogeneity was also observed for influenza B compared with other strains



**Figure 3.** Vaccine effectiveness against laboratory-confirmed overall influenza (influenza A and B) by season. \*Season with poorly matched vaccine. <sup>^</sup>Season with high influenza attack rate. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

but it was nonsignificant. An unadjusted OR was used for the 2013/2014 season due to zero adjusted OR. This happened due to low circulating levels of influenza B strains resulting in small to zero OR, which would have prohibited the provision of any meaningful OR in the meta-analysis and a subsequent VE estimation (Figure 6).

#### Vaccine Effectiveness by Age Group

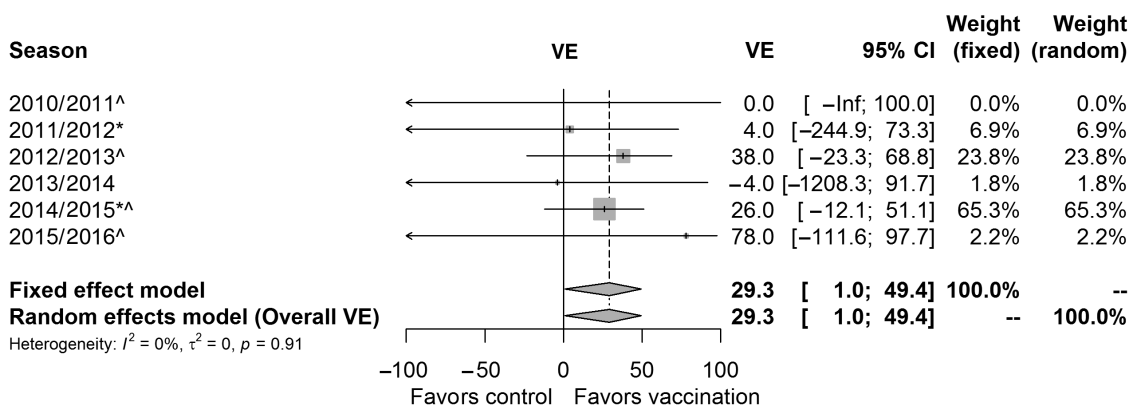
This analysis showed that in those aged  $\geq 55$  years the VE was low against influenza A subtypes, except those aged 65–74 years for A(H1N1), while high VEs for influenza B were found. VE was high in children (aged <18 years), with a VE of 90.5% against A(H1N1) (Table 4).

#### DISCUSSION

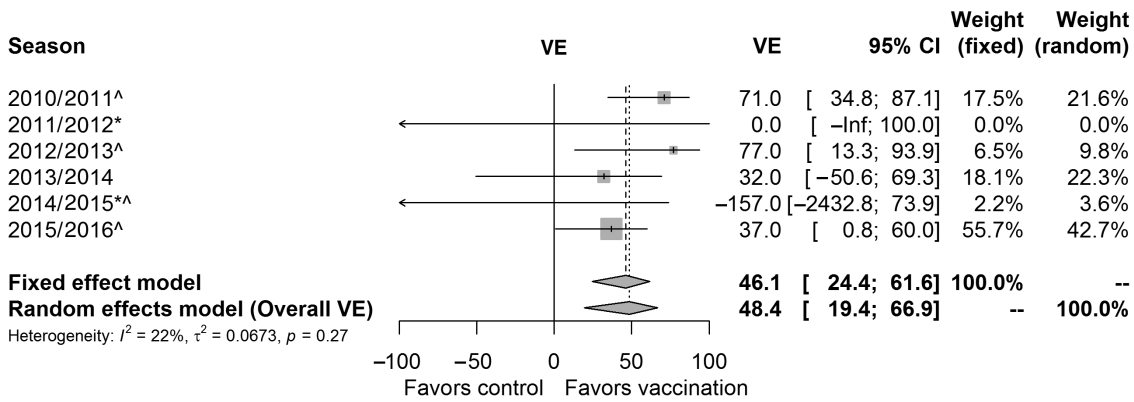
During 6 influenza seasons, influenza vaccination effectiveness was greater than 50% for laboratory-confirmed influenza in people with asthma. Better protection was observed during

seasons with good antigenic match and against the A(H1N1) and B strains. Moderate VE was found against influenza A(H1N1) (47%) and influenza B (62%), and VE was low for influenza A(H3N2) (34%). In younger adults (aged 18–54 years), the seasonal influenza vaccine provided protection against influenza A(H1N1), influenza A(H3) subtypes, and influenza B.

The highest VE was observed in 2010/2011, which was characterized by high influenza activity predominated by the influenza A(H1N1) and B strains in the United Kingdom [22, 23]. While low VE was detected in 2011/2012, this is likely due to low and late activity of the predominant A(H3) strain and an antigenic vaccine mismatch [24]. Intraseasonal VE waning and low VE against A(H3N2) was observed in the United Kingdom and the United States [8, 25, 26]. This lower VE has been attributed to antigenic drift [26]. In the 2012/2013 season, good protection was found only against the A(H1N1) strain; this was consistent with the findings from another UK study [27]. Antigenic drift for influenza B and VE decline for influenza A(H3N2), particularly in the second trimester following



**Figure 4.** Vaccine effectiveness against laboratory-confirmed influenza A(H3) subtype by season. \*Season with poorly matched vaccine. <sup>^</sup>Season with high influenza attack rate. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.



**Figure 5.** Vaccine effectiveness against laboratory-confirmed influenza A(H1N1) subtype by season. \*Season with poorly matched vaccine. <sup>^</sup>Season with high influenza attack rate. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

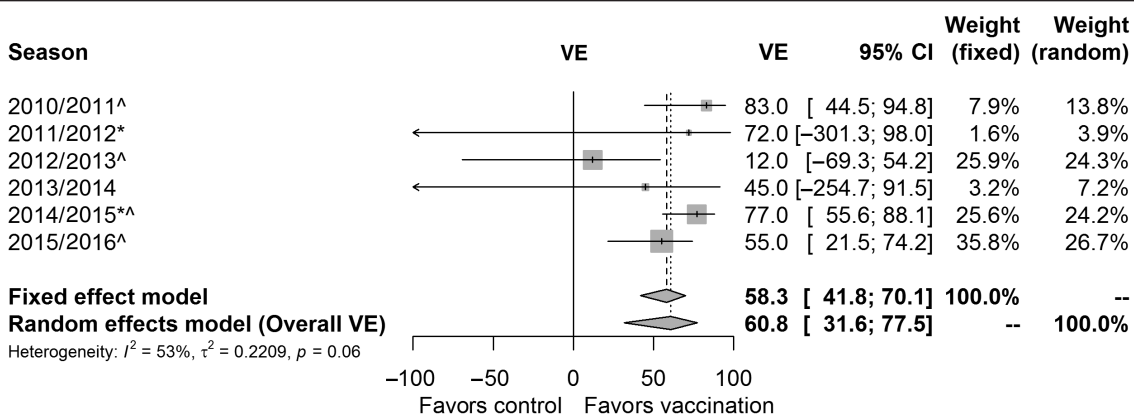
vaccination, was noted during this season [27, 28]. A US study that included 1259 people with asthma reported a moderate VE of 46% in 2012/2013 [8, 29].

We found overall protection against influenza in 2013/2014 when the influenza activity was low and prolonged, influenza A(H1N1) dominated, and the vaccine was well matched [30]. In 2014/2015, there was vaccine strain mismatch for H3N2, and we observed a positive VE for influenza B that was similar to findings in a UK-wide study [31]. In the 2015/2016 season, our finding of an overall positive VE is consistent with the VE of 55% found in a UK study [32]. The influenza A(H1N1) strain predominated, and the vaccine was well matched for this subtype [33]. We also observed a high VE against influenza B despite lineage mismatch with the vaccine, which was also found in another study [32].

The overall VE of 46% in children in this study was similar to a recent TND study in Canada where the VE was 43% in children [11]. However, in our study, protection was found only against the B strain, while previous studies have also shown protection against A(H1N1) [34, 35]. Lower strain-specific protection was observed in older adults (aged  $\geq 55$  years), and no

protection was found against influenza A strains. Nevertheless, the VE decrease in those aged  $\geq 55$  years may only be indicative of immunosenescence, and additional studies that are better powered to investigate this phenomenon are needed. There is evidence that the VE in those aged  $>75$  years may be lower than in those aged 65–74 years [36]. The mechanism for this is uncertain but may be explained by reduced immune responsiveness to historically used influenza antigens in the most elderly individuals [36]. Such evidence has led to the development and introduction of either adjuvanted influenza vaccines or high-dose influenza vaccines in this age group. In addition, the effects of other factors, such as the presence of other underlying conditions in older persons, could explain the decrease in VE estimates in this age group.

The strengths of this study include the influenza diagnosis based on a test with high predictive value and reduction of any recall or misclassification bias due to documentation of vaccination and medical condition status in high-quality electronic medical records [37]. Additionally, the TND study minimized the effects of selection bias due to differential healthcare-seeking behavior between cases and controls by assessing only the



**Figure 6.** Vaccine effectiveness against laboratory-confirmed influenza B subtype by season. \*Season with poorly matched vaccine. <sup>^</sup>Season with high influenza attack rate. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.



**Table 4. Vaccine Effectiveness for Laboratory-Confirmed Influenza by Various Age Groups, Scotland, 2010–2016**

Age, y	Influenza Type and Subtype	Influenza-Positive (Cases)		Influenza-Negative (Controls)		Total Positive (%)	Unadjusted Vaccine Effectiveness <sup>a</sup> (95% CI)	Adjusted Vaccine Effectiveness <sup>b</sup> (95% CI)
		Vaccinated/ Total (n)	Vaccinated (%)	Vaccinated/ Total (n)	Vaccinated (%)			
All ages	Influenza A and B	326/781	41.7	2548/5129	49.7	13.2	48.6 (39.2 to 56.6)	55.0 (45.8 to 62.7)
	A(H3)	106/208	51.0	2768/5701	48.5	3.5	26.0 (−.8 to 45.6)	33.8 (6.7 to 53.1)
	A(H1N1)	94/240	39.2	2780/5670	49.0	4.1	43.2 (23.6 to 57.8)	46.6 (25.4 to 61.8)
	Influenza B	73/205	35.6	2801/5705	49.1	3.5	59.0 (44.2 to 70.0)	61.5 (45.7 to 72.7)
≤17	Influenza A and B	31/101	30.7	368/974	37.8	9.4	52.9 (23.4 to 71.0)	46.0 (11.2 to 67.2)
	A(H3)	8/26	30.8	391/1049	37.3	2.4	55.7 (−11.0 to 82.3)	51.1 (−25.4 to 80.9)
	A(H1N1)	4/15	26.7	395/1060	37.3	1.4	64.9 (−66.8 to 92.6)	90.5 (−45.3 to 99.4)
	Influenza B	12/45	26.7	387/1030	37.6	4.2	69.6 (26.1 to 87.5)	56.3 (3.8 to 80.2)
18–54	Influenza A and B	94/376	25.0	733/2093	35.0	15.2	54.0 (39.2 to 65.2)	57.0 (42.3 to 68.0)
	A(H3)	22/84	26.2	805/2385	33.8	3.4	58.4 (28.4 to 75.8)	53.3 (17.9 to 73.5)
	A(H1N1)	33/143	23.1	794/2326	34.1	5.8	45.7 (14.4 to 65.5)	53.0 (23.8 to 71.1)
	Influenza B	22/89	24.7	805/2380	33.8	3.6	49.9 (15.9 to 70.1)	54.5 (21.1 to 73.7)
55–64	Influenza A and B	51/104	49.0	384/667	57.6	13.5	51.1 (22.0 to 69.4)	57.6 (29.6 to 74.5)
	A(H3)	18/29	62.1	417/742	56.2	3.8	2.6 (−145.9 to 61.4)	2.1 (−178.5 to 65.6)
	A(H1N1)	17/33	51.5	418/738	56.6	4.3	38.0 (−36.3 to 71.8)	38.7 (−43.4 to 73.8)
	Influenza B	7/24	29.2	428/747	57.3	3.1	78.7 (45.0 to 91.8)	88.2 (61.2 to 96.4)
65–74	Influenza A and B	61/91	67.0	488/656	74.4	12.2	54.8 (22.5 to 73.6)	56.8 (24.0 to 74.9)
	A(H3)	18/24	75.0	531/723	73.4	3.2	−13.4 (−249.3 to 63.2)	1.0 (−196.9 to 67.0)
	A(H1N1)	22/30	73.3	527/717	73.5	4.0	57.5 (−37.4 to 86.9)	60.5 (−37.9 to 88.7)
	Influenza B	12/20	60.0	537/727	73.9	2.7	65.3 (9.0 to 86.8)	65.8 (5.2 to 87.6)
≥75	Influenza A and B	89/109	81.7	575/739	77.8	12.9	48.9 (4.8 to 72.5)	51.9 (9.2 to 74.5)
	A(H3)	40/45	88.9	624/803	77.7	5.3	−13.5 (−232.9 to 61.3)	−15.4 (−278.2 to 64.8)
	A(H1N1)	18/19	94.7	646/829	77.9	2.2	−542.3 (−6752.7 to 39.8)	−501.0 (−5639.5 to 37.1)
	Influenza B	20/27	74.1	644/821	78.4	3.2	67.6 (15.1 to 87.6)	70.4 (19.8 to 89.1)

Abbreviation: CI, confidence interval.

<sup>a</sup>Adjusted for time within a season (ie, days).<sup>b</sup>Adjusted for time (ie, days), age, number of risk groups, and swab location (ie, general practitioner or hospital).

prevention of the vaccine against medically attended influenza. The inclusion of 6 seasons increased the power of the study, allowing the provision of VE estimates for different seasons, strains, and patient characteristics. Thus, this study's findings can be generalized to the wider asthma population in Scotland.

Several limitations also need to be considered in this study. The VE in this study assessed only the prevention of influenza. However, vaccinated individuals may have also benefited by having less severe influenza illness and a subsequent lower risk of a severe asthma attack. Thus, vaccine protection provided

by a decrease in influenza severity cannot be quantified in this study [14, 16, 38]. Although the electronic health records from general practices include vaccinations that take place in nongeneral practice settings, there may be some misclassification of vaccination status. Results from the post hoc analyses need careful interpretation since they were not prespecified in this study's protocol. Unmeasured confounders could still have influenced the VE estimates. Future research should assess the confounding effect on VE from TND studies. TND studies offer an elegant way to deal with selection bias related to healthcare-seeking behavior between cases and control. However, bias may occur due to differences in healthcare-seeking behavior between vaccinated and unvaccinated patients, and swab testing may also differ between vaccinated and nonvaccinated patients, particularly in nonsentinel settings [39].

In this study, we showed that vaccination can prevent influenza in individuals with asthma who present with ILI in Scottish primary and secondary care settings. While substantial variation in VE was observed among circulating strains and age groups, protection was still observed in most subgroups. There was significant pooled VE when the A(H1N1) strain dominated, which could be explained by the absence of vaccine mismatch over the 3 seasons [23, 30, 33]. The lower pooled VE when the A(H3) strain dominated could be due to vaccine mismatch in most seasons and the intraseasonal VE waning [27, 30]. Generally, the protection against A(H3N2) is usually lower compared with A(H1N1) and B, which is around 60% or even higher [40]. Thus, evidence from this study reinforces the recommendation for annual seasonal vaccination in asthma patients. Although there are current developments toward universal vaccines with better potency, durability, and wide protection, these vaccines may not be available for another decade [41]. Thus, monitoring of the effectiveness of current vaccines should be continued. Further adequately powered studies will be needed to monitor the effectiveness of these vaccines in population groups that are at risk of severe influenza and complications such as asthma.

The findings of this study can guide research and policy makers for the provision of a more targeted and effective vaccination program, improving the current protection of the asthma population. Specifically, policy makers and clinicians should consider adjuvant vaccine or high-dose influenza vaccine in people with asthma aged  $\geq 55$  years [9]. Healthcare providers and people with asthma will also have a clearer answer regarding the value of influenza vaccination, which is prevention of influenza infection in children and adults with current asthma.

In summary, we provide compelling national evidence over a number of years that influenza vaccination substantially reduces the risk of influenza in people with asthma. There is a need for strategies to boost influenza vaccination uptake in people with asthma.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

**Author contributions.** E. V. conducted and wrote the study. C. R. S., N. I. L., K. K., C. R., J. M., B. V. W., L. D. R., R. G., T. E., J. S., C. C. B., and A. S. contributed to the conception of the study. K. K., C. R., and T. E. helped prepare the data and advised on the statistical analysis. All authors contributed to the design of the study. All authors critically revised earlier drafts of the manuscript. All authors approved the final version of the manuscript to be published.

**Acknowledgments.** The authors thank and acknowledge all colleagues at the Asthma UK Centre for Applied Research for their support in this study.

**Disclaimer.** The funding bodies had no role in the design of the study, review process, analysis, interpretation, or reporting of data. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, National Institute for Health Research (NIHR), National Health Service, or the Department of Health.

**Financial support.** The work was funded by the Chief Scientist Office of the Scottish Government under the grant (AUKCAR/14/03) and the NIHR–Health Technology Assessment (HTA) Programme (13/34/14) for the Seasonal Influenza Vaccination Effectiveness II (SIVE II) study. As principal investigator, C. R. S. received a grant for the SIVE-II project from the NIHR HTA. This work was carried out with the support of the Asthma UK Centre for Applied Research (AUK-AC-2012-01), the Farr Institute (MR/M501633/2), Health Data Research UK (an initiative funded by UK Research and Innovation, Department of Health and Social Care England and the devolved administrations and leading medical research charities), the European Union's Horizon 2020 research and innovation programme (under grant agreement No 634446) and European Centre for Disease Prevention and Control (Influenza-Monitoring Vaccine Effectiveness).

**Potential conflicts of interest.** The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

- Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011; 378:1917–30.
- Centers for Disease Control and Prevention. Flu season. <http://www.cdc.gov/flu/about/season/flu-season.htm>. Accessed 10 March 2015.
- Schwarze J, Openshaw P, Jha A, et al. Influenza burden, prevention, and treatment in asthma—A scoping review by the EACCI Influenza in Asthma Task Force. *Allergy* 2018; 73:1151–81.
- Background Paper on Influenza Vaccination and Immunization, SAGE Working Group. [http://www.who.int/immunization/sage/meetings/2012/april/1\\_Background\\_Paper\\_Mar26\\_v13\\_cleaned.pdf](http://www.who.int/immunization/sage/meetings/2012/april/1_Background_Paper_Mar26_v13_cleaned.pdf). Accessed 14 September 2015.
- Public Health England. Influenza: the green book. Chapter 19. [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/663694/Greenbook\\_chapter\\_19\\_Influenza.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/663694/Greenbook_chapter_19_Influenza.pdf). Accessed 28 March 2018.
- Centers for Disease Control and Prevention. Influenza (Flu). Get Vaccinated. <https://www.cdc.gov/flu/consumer/vaccinations.htm>. Accessed 01 April 2018.
- Commission of the European Communities. Proposal for a council recommendation on seasonal influenza vaccination 2009. [http://ec.europa.eu/health/ph\\_threats/com/Influenza/docs/seasonflu\\_rec2009\\_en.pdf](http://ec.europa.eu/health/ph_threats/com/Influenza/docs/seasonflu_rec2009_en.pdf). Accessed 11 May 2018.
- Vasileiou E, Sheikh A, Butler C, et al. Effectiveness of influenza vaccines in asthma: a systematic review and meta-analysis. *Clin Infect Dis* 2017; 65:1388–95.
- NHS England. Vaccine ordering for 2018–19 influenza season. <https://www.england.nhs.uk/wp-content/uploads/2018/02/vaccine-ordering-18-19-influenza-season-gp-pharm.pdf>. Accessed 13 July 2018.
- Suarez-Varela MM, Llopis A, Fernandez-Fabrellas E, et al. Asthma and influenza vaccination in elderly hospitalized patients: matched case-control study in Spain. *J Asthma* 2017; 55:391–401.

11. Buchan SA, Chung H, Campitelli MA, et al. Vaccine effectiveness against laboratory-confirmed influenza hospitalizations among young children during the 2010–11 to 2013–14 influenza seasons in Ontario, Canada. *PLoS One* **2017**; 12:e0187834.
12. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* **2012**; 12:36–44.
13. De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. *Euro Surveill* **2013**; 18:pii=20585.
14. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* **2013**; 31:2165–8.
15. Foppa IM, Haber M, Ferdinands JM, Shay DK. The case test-negative design for studies of the effectiveness of influenza vaccine. *Vaccine* **2013**; 31:3104–9.
16. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. *Expert Rev Vaccines* **2014**; 13:1571–91.
17. Boivin G, Côté S, Déry P, De Serres G, Bergeron MG. Multiplex real-time PCR assay for detection of influenza and human respiratory syncytial viruses. *J Clin Microbiol* **2004**; 42:45–51.
18. Simpson CR, Lone NI, Kavanagh K, et al. Evaluating the effectiveness, impact and safety of live attenuated and seasonal inactivated influenza vaccination: protocol for the Seasonal Influenza Vaccination Effectiveness II (SIVE II) study. *BMJ Open* **2017**; 7:e014200.
19. RStudio Team (2016). *RStudio: Integrated Development for R*. RStudio, Inc., Boston, MA URL. <http://www.rstudio.com/>. Accessed 03 January 2018.
20. STROBE Statement. Strengthening the reporting of observational studies in epidemiology. <https://www.strobe-statement.org/index.php?id=available-checklists>. Accessed 13 July 2018.
21. RECORD Checklist. Reporting of studies Conducted using Observational Routinely-collected Data. <http://www.record-statement.org/checklist.php>. Accessed 13 July 2018.
22. Pebody R, Hardelid P, Fleming DM, et al. Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: mid-season analysis 2010/11. *Euro Surveill* **2011**; 16:pii=19791.
23. Health Protection Agency (HPA). Surveillance of influenza and other respiratory viruses in the UK 2010/11. London: HPA; **2011**. [http://webarchive.nationalarchives.gov.uk/20140629102627/http://hpa.org.uk/webc/HPAwebFile/HPAweb\\_C/1296687414154](http://webarchive.nationalarchives.gov.uk/20140629102627/http://hpa.org.uk/webc/HPAwebFile/HPAweb_C/1296687414154). Accessed 14 June 2017.
24. Health Protection Agency (HPA). Surveillance of influenza and other respiratory pathogens in the UK 2011/12. London: HPA; **2012**. [http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb\\_C/1317134705939](http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317134705939). Accessed 14 June 2017.
25. Pebody R, Andrews N, McMenamin J, et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection. *Euro Surveill* **2013**; 18:pii=20389.
26. Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011–2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. *Clin Infect Dis* **2014**; 58:319–27.
27. Andrews N, McMenamin J, Durnall H, et al. Effectiveness of trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2012/13 end of season results. *Euro Surveill* **2014**; 19:pii=20851.
28. Public Health England. *Surveillance of influenza and other respiratory viruses, including novel respiratory viruses, in the United Kingdom: Winter 2012/13*. London, **2013**. [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/325217/Annual\\_flu\\_report\\_winter\\_2012\\_to\\_2013.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/325217/Annual_flu_report_winter_2012_to_2013.pdf). Accessed 14 June 2017.
29. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012–2013: variable protection by age and virus type. *J Infect Dis* **2015**; 211:1529–40.
30. Public Health England. *Surveillance of influenza and other respiratory viruses in the United Kingdom: Winter 2013/14*. London, **2014**. [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/325203/Flu\\_annual\\_report\\_June\\_2014.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/325203/Flu_annual_report_June_2014.pdf). Accessed 14 June 2017.
31. Pebody R, Warburton F, Andrews N, et al. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. *Euro Surveill* **2015**; 20:pii=30013.
32. Pebody R, Warburton F, Ellis J, et al. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. *Euro Surveill* **2016**; 21:pii=30348.
33. Public Health England. *Surveillance of influenza and other respiratory viruses in the United Kingdom: Winter 2015/16*. London, **2016**. [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/526405/Flu\\_Annual\\_Report\\_2015\\_2016.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/526405/Flu_Annual_Report_2015_2016.pdf). Accessed 14 June 2017.
34. Miyazaki C, Nakayama M, Tanaka Y, et al. Immunization of institutionalized asthmatic children and patients with psychomotor retardation using live attenuated cold-adapted reassortment influenza A H1N1, H3N2 and B vaccines. *Vaccine* **1993**; 11:853–8.
35. Tanaka Y, Ueda K, Miyazaki C, et al. Trivalent cold recombinant influenza live vaccine in institutionalized children with bronchial asthma and patients with psychomotor retardation. *Pediatr Infect Dis J* **1993**; 12:600–5.
36. Pebody RG, Warburton F, Andrews N, et al. Uptake and effectiveness of influenza vaccine in those aged 65 years and older in the United Kingdom, influenza seasons 2010/11 to 2016/17. *Euro Surveill* **2018**; 23:pii=1800092.
37. Jhund PS, MacIntyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population survey of 5.1 million people. *Circulation* **2009**; 119:515–23.
38. Simpson CR, Lone NI, Kavanagh K, et al. Trivalent inactivated seasonal influenza vaccine effectiveness for the prevention of laboratory-confirmed influenza in a Scottish population 2000 to 2009. *Euro Surveill* **2015**; 20:pii=21043.
39. Lewnard JA, Tedijanto C, Cowling BJ, Lipsitch M. Measurement of vaccine direct effects under the test-negative design. *Am J Epidemiol* **2018**; 187:2686–97.
40. Monto AS. Moving toward improved influenza vaccines. *J Infect Dis* **2017**; 215:500–2.
41. Berlanda Scorza F, Tsvetnitsky V, Donnelly JJ. Universal influenza vaccines: shifting to better vaccines. *Vaccine* **2016**; 34:2926–33.