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

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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

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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 administrated 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 χ^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.

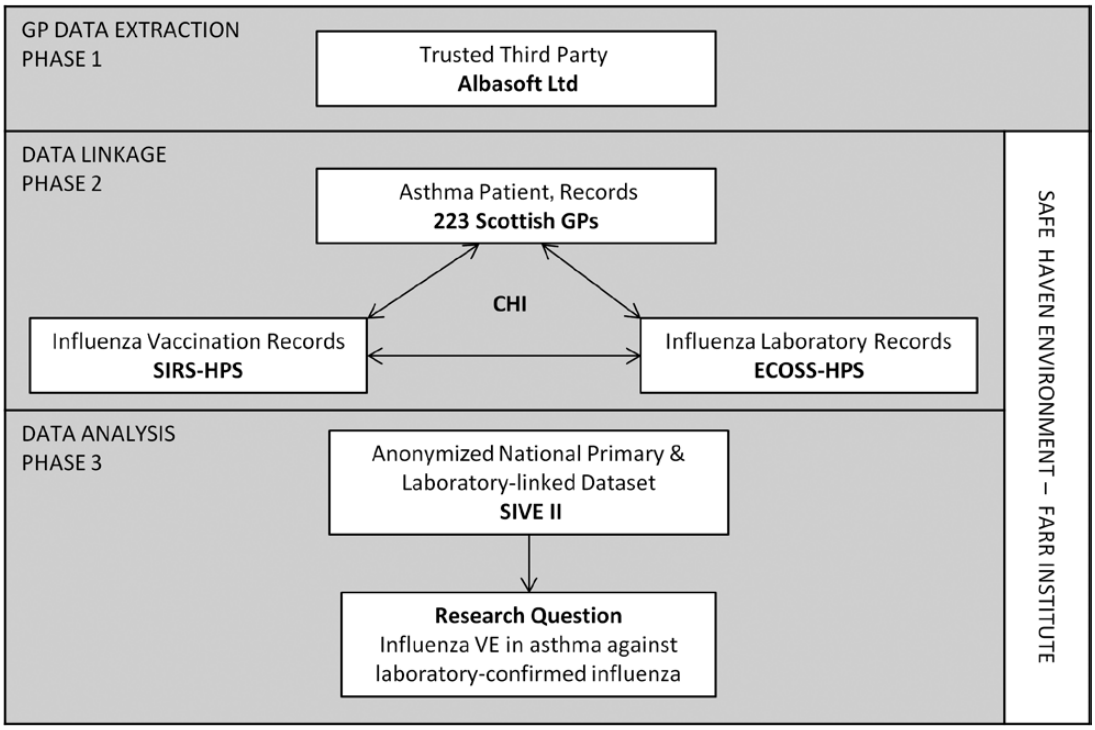

Figure 1. Phases of data extraction, linkage, and analysis in a secured environment. Abbreviations: CHI, Community Health Index; ECOSS-HPS, Electronic Communication of Surveillance in Scotland-Health Protection Scotland; GP, general practitioners; SIRS, Scottish Immunisation & Recall System-Health Protection 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) × 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*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*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].

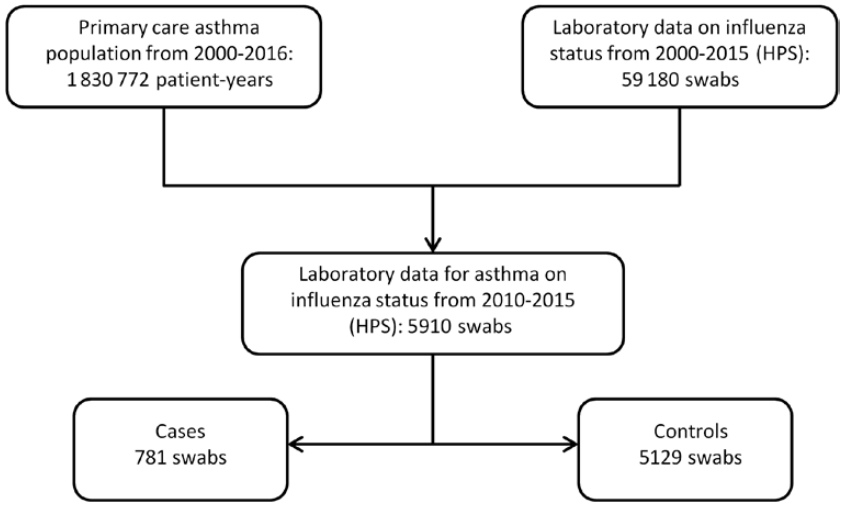

Figure 2. Flow diagram for the test-negative design, case-control study for an asthma population for the influenza seasons 2010/2011 to 2015/2016, Scotland. Abbreviation: HPS, Health Protection Scotland.

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)	*P* Value	Number of Positive Swabs (% of Total)	*P* Value	Swab-Positive Adjusted Odds Ratio[a]	Adjusted 95% Confidence Interval
Gender							
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
Age group, y[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
Deprivation quintile[c]							
1[d] (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
Urban/rural score[e]							
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[f]	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
Number of risk groups (comorbidities)							
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
Influenza vaccine in previous season							
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
Swab samples taken in general practices or hospitals							
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 χ^2 test.

Abbreviation: NA, not applicable.

[a]Adjusted for gender, age, and socioeconomic deprivation.

[b]Age group available for 5909 swabs.

[c]Deprivation score only available for 5785 swabs.

[d]Most socioeconomically deprived.

[e]Urban/rural score only available for 5824 swabs.

[f]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[a] (95% CI)	Adjusted Vaccine Effectiveness[b] (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.

[a]Adjusted for time (ie, days) only.

[b]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

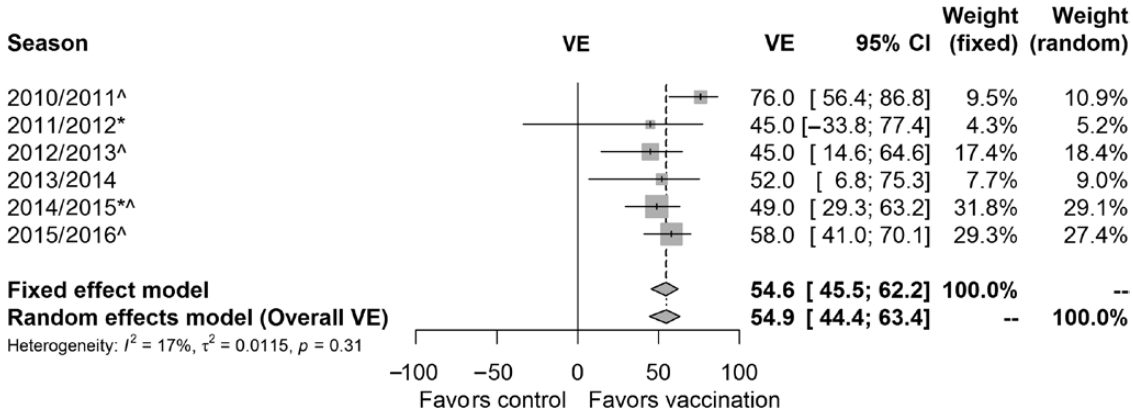

Figure 3. Vaccine effectiveness against laboratory-confirmed overall influenza (influenza A and B) by season. *Season with poorly matched vaccine. ^Season with high influenza attack rate. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

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 ≥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

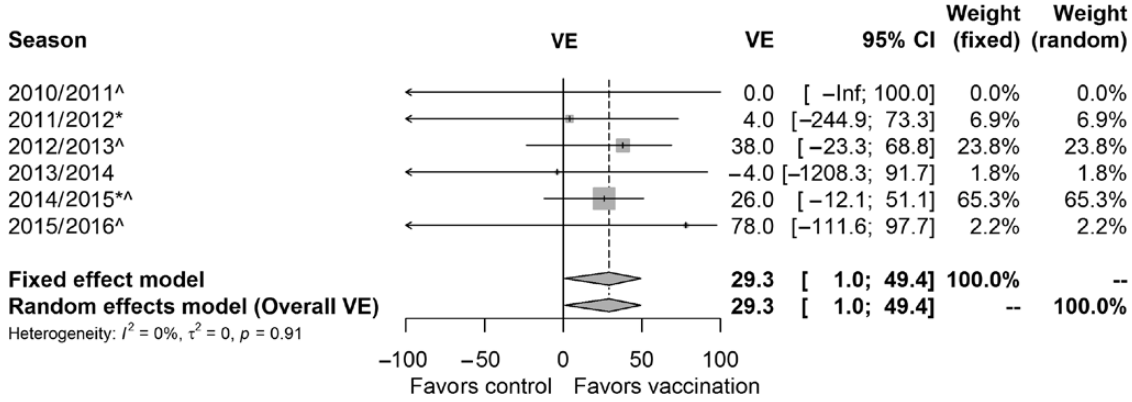

Figure 4. Vaccine effectiveness against laboratory-confirmed influenza A(H3) subtype by season. *Season with poorly matched vaccine. ^Season with high influenza attack rate. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

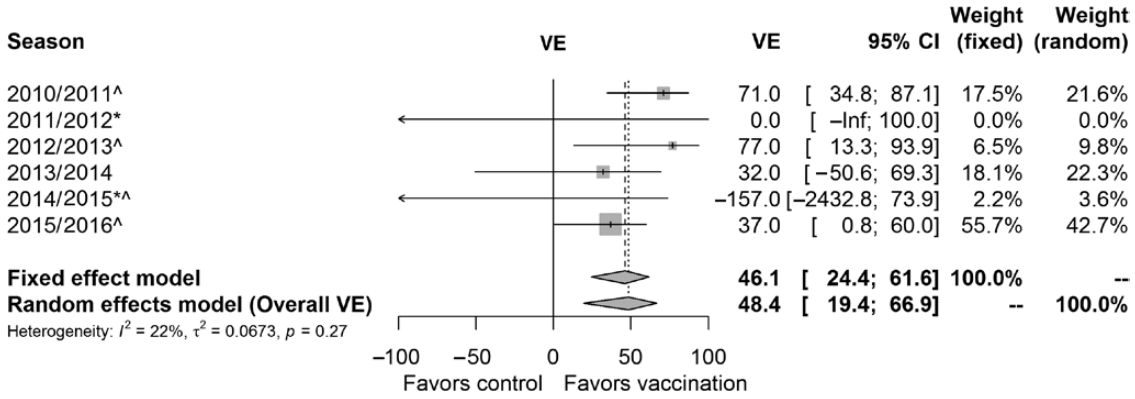

Figure 5. Vaccine effectiveness against laboratory-confirmed influenza A(H1N1) subtype by season. *Season with poorly matched vaccine. ^Season with high influenza attack rate. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

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 ≥55 years), and no protection was found against influenza A strains. Nevertheless, the VE decrease in those aged ≥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

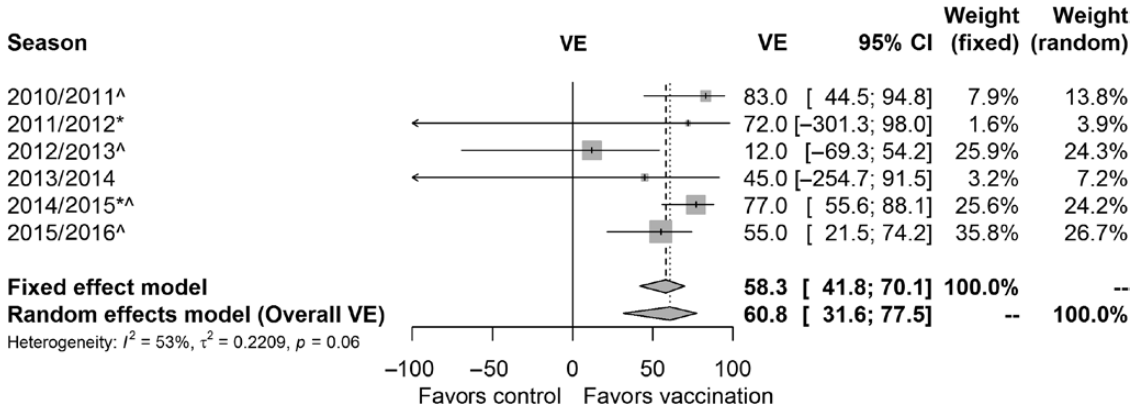

Figure 6. Vaccine effectiveness against laboratory-confirmed influenza B subtype by season. *Season with poorly matched vaccine. ^Season with high influenza attack rate. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

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[a] (95% CI)	Adjusted Vaccine Effectiveness[b] (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.

[a]Adjusted for time within a season (ie, days).

[b]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 ≥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.

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