Protection provided by influenza vaccine against influenza-related hospitalisation in >=65 year olds: early experience of introduction of a newly licensed adjuvanted vaccine in England in 2018/19

Richard Pebody[1]*, Heather Whitaker[1], Hongxin Zhao[1], Nick Andrews[1], Joanna Ellis[1], Matthew Donati[2], Maria Zambon[1]

1. Public Health England, London, UK
2. Public Health England, Bristol, UK

***Corresponding Author**

Dr Richard Pebody, Immunisation and Countermeasures Division, National Infection Service, Public Health England, London, UK

Abstract

2018/19 was the first season of introduction in England of a newly licensed adjuvanted influenza vaccine (aTIV) for adults 65 years or older , who were previously offered standard-dose, non-adjuvanted vaccine, achieving uptake levels >70%, often with poor effectiveness. This paper presents the end-of-season adjusted vaccine effectiveness (aVE) against laboratory confirmed influenza hospitalisation in this population. A frequency-matched test negative case control approach was used to estimate aVE by influenza A subtype and vaccine type. Cases were influenza confirmed hospitalisations and controls influenza negative hospitalisations who were 65 years or more. Cases and controls were selected from a sentinel laboratory surveillance system which collates details of inpatients and outpatients routinely tested on clinical advice for influenza infection with reverse-transcription polymerase chain reaction (RT-PCR) on respiratory samples. Vaccine and clinical history was obtained from the general practitioners of study participants. A total of 428 cases and 1013 controls were included in the analysis. End-of-season any-influenza aVE against hospitalisation was 53.4% (95% CI: 39.9, 63.9). By influenza A subtype, aVE was 64.8% (95% CI: 49.6, 75.3) against influenza A(H1N1)pdm09 and 39.3% (95% CI: 6.5, 60.6) against influenza A(H3N2). There was insufficient data to estimate influenza B VE. aVE estimates for all influenza, influenza A(H1N1)pdm09 and influenza A(H3N2) for aTIV were 53.8% (39.8, 64.5); 65.9% (50.6, 76.4) and 39.5% (4.8, 61.5) respectively. We provide evidence of significant influenza VE in the elderly, most notably against influenza A(H1N1)pdm09, but also against A(H3N2) for aTIV.

Key words: Elderly, influenza, adjuvanted vaccine, effectiveness

Introduction

The United Kingdom (UK) has had a longstanding influenza vaccine programme with high coverage with normal dose, egg-grown, inactivated vaccines for all those >=65 years of age for almost two decades. In recent years apparent poor vaccine effectiveness (VE) in older people against laboratory confirmed infection in primary care, particularly against the A(H3N2) sub-type has been observed in the UK and elsewhere [1,2]. Influenza A(H3N2) infection in older persons is linked to poorer outcomes such as increased risk of hospitalisation and excess mortality [2]. Several potential explanations for reduced VE in this population have been hypothesised: immunosenescence, with an age-related decline in immune response following vaccination; intra-seasonal waning in effectiveness; antigenic mismatch between the dominant circulating influenza virus strain and the vaccine virus as was seen in 2014/15; mismatch due to changes in egg-grown vaccine strains compared to the wild-type strain and finally repeated prior season vaccination potentially based on the antigenic distance hypothesis [2,3][16].

Following the recent licensure of an adjuvanted trivalent influenza vaccine (aTIV) for those >=65 years of age in the UK, England recommended aTIV use for all those over 65 years of age in the 2018/19 influenza season [4]. Although there is some limited published evidence of superior immunogenicity and effectiveness of adjuvanted influenza vaccine in this population compared to standard non-adjuvanted vaccines [5,6], there remain considerable uncertainties as to how well adjuvanted, normal dose trivalent influenza vaccine protects against influenza-related hospitalisation in older persons. This study, undertaken as part of a service evaluation aims to estimate the effectiveness of influenza vaccination in preventing laboratory-confirmed influenza infection resulting in hospitalisation in adults aged >=65 years in England during the 2018/19 season, where influenza A(H1N1)pdm09 and A(H3N2) co-circulated.

Methods

This study is based upon a frequency matched test-negative case-control (TNCC) study design. Cases and controls were identified from the Respiratory Data Mart laboratory surveillance (RDS) system [7]. This is a national sentinel laboratory surveillance system which collates details of individuals tested for influenza infection with reverse-transcription polymerase chain reaction (RT-PCR) on respiratory tract samples (including both positive and negative results) from 13 laboratories located across England.

The study population was defined as residents in England >=65 years of age (at August 31st 2018) who were admitted to hospital and who had a respiratory swab taken between week 40 2018 and week 20 2019 which was tested for influenza with RT-PCR by one of the RDS laboratories. Those who were swabbed more than seven days after onset were excluded (when onset was known). A case was defined as a person with laboratory confirmed influenza infection (confirmed with RT-PCR). A control was defined as a person who was negative for influenza infection. An adult who was not identifiable by the national patient demographic surveillance system as being registered with a general practitioner (GP) or was not resident in England was excluded. Controls were group-matched to cases by age group (65-74, 75-84, 85+ years) and week of sample (+/- 1 week) with up to 3 controls randomly selected per case within these groups.

Details of cases and controls from RDS were used to identify the GP of these persons and the postcode of the person's residential address, which was used to identify the index of multiple deprivation (IMD) quintile. PHE wrote to the identified GP to collect key epidemiological and clinical information including details of date of onset of symptoms; hospitalisation; influenza vaccination in 2017/18 and 2018/19 and underlying clinical risk factor. Data from returned questionnaires was entered into a secure database held at the Public Health England (PHE) Centre for Infectious Disease Surveillance and Control.

Stata 15 (StataCorp, College Station, TX, USA) was used for this data analysis. Case and controls were described by key co-variables with differences between groups tested using Chi-squared or Fisher's exact test, as appropriate. Logistic regression was used to calculate the unadjusted odds ratios for influenza vaccination in cases compared to controls, with a 95% confidence interval. This was used to calculate an unadjusted VE as VE=1-OR. Logistic regression was used to calculate the odds ratio for vaccination, adjusted for relevant confounders which changed vaccine effect by 3% or more overall, and by month of event and age-group [20]. When estimating VE, age-group, sex, time period (defined by month of sample collection), PHE region and risk group were adjusted for in a multivariable logistic regression model.

Sensitivity analyses were undertaken to include those with onset > 7 days, to exclude those with missing vaccination date and to exclude those with missing onset date. A multiple imputation approach was used for missing vaccination dates by sampling known vaccination dates from individuals whose event occurred in the same week.

Relative effectiveness (rVE) was defined as the odds of influenza comparing aTIV to IIV as the baseline based on the same model as used to estimate aVE.

This project was an evaluation of a vaccination programme. Public Health England (PHE) holds permissions under section 251 of the 2006 NHS Act and the 2002 Health Service (Control of Patient Information) Regulations, to process patient information for such purposes.

Results

A total of 4090 questionnaires were sent to GPs representing 1058 flu cases and 3032 controls. Responses were received for 3001 patients (73% response rate). A total of 750 individuals were excluded (16 not resident in England; 23 <65 years of age on 31/08/2018; 115 unknown vaccination status; 446 with period from onset of illness to sampling > 7 days; 49 vaccinated within 14 days before onset of illness and 1 with vaccination recorded before 01/09/2018. After exclusions, 1712 controls and 639 cases remained of whom 1013 controls and 428 cases were reported to have been hospitalised due to their acute respiratory illness during the study period.

The details of the hospitalised participants stratified according to the swab result and by key co-variables are described in Table 1. Of the 428 hospitalised cases, 182 were due to A(H1N1)pdm09; 123 were A(H3N2); 121 were influenza A(subtype not known), and 2 were influenza B. Therefore, there was inadequate data to provide influenza B VE estimates and this is not further discussed. Of the 1013 hospitalised controls, 85% had no other respiratory virus detected, with RSV the main virus detected in the remainder (57 controls).

When fitting the final model, deprivation was not adjusted for as it changed the overall estimates by less than 1%, whereas gender, PHE region and risk group each changed the overall estimates by more than 3% so were considered confounders for the vaccine effect.

The crude and adjusted VE (aVE) estimates against all influenza, influenza A(H1N1)pdm09 and influenza A(H3N2) are shown in Table 2. For all influenza-confirmed hospitalisations, the aVE was 53.4% (95% CI: 39.9, 63.9). By influenza A subtype, aVE was 64.8% (95% CI: 49.6, 75.3) against influenza A(H1N1)pdm09 and 39.3% (95% CI: 6.5, 60.6) against influenza A(H3N2).

We can report < 5% difference to all main estimates (including A+B, all A, H3, H1) for all of the sensitivity analyses (see supplementary tables). There were no large changes in VE estimate when missing vaccination date was imputed.

The aVE estimates against all influenza, influenza A(H1N1)pdm09 and influenza A(H3N2) stratified by age-group are shown in Table 3. The results are similar to the all-age estimates for the 65-74 and 85+ year age groups influenza VE estimates, though there was a suggestion of lower, non-significant, A(H3N2) VE for the 75-84 year age-group. The aVE estimates against all influenza, influenza A(H1N1)pdm09 and influenza A(H3N2) stratified by

risk group are shown in Table 3, with aVE non-significantly different when comparing aVE in those with and without a risk factor by influenza sub-type.

The aVE estimates against all influenza, influenza A(H1N1)pdm09 and influenza A(H3N2) stratified by vaccine type are shown in Table 3. The majority of vaccinated controls had received aTIV rather than non-adjuvanted vaccine (IIV), with aVE estimates for aTIV non-significantly higher compared to IIV for both all influenza and specifically for A(H3N2). There was no significant difference in aVE estimates by vaccine type for A(H1N1)pdm09. The relative VE was non-significantly higher when comparing aTIV against IIV for all influenza and A(H3N2), but very similar for A(H1N1)pdm (Table 2). However, as so few patients were IIV vaccinated, the confidence intervals are extremely wide and non-significant.

The aVE estimates against all influenza, influenza A(H1N1)pdm09 and influenza A(H3N2) by prior vaccine history are shown in Table 4. The lowest aVE was observed for those who had been vaccinated only in 2017/18. The highest aVE was observed, both overall and by subtype, for those who had been vaccinated in both 2017/18 and 2018/19.

Discussion

In summary, we firstly demonstrate that the influenza vaccine programme for people65 years and older in 2018/19 provided significant protection against influenza-confirmed hospitalisation. Secondly, we found that this protection extended to those >85 years of age. Thirdly, we found significant effectiveness against both the circulating A(H1N1)pdm09 and A(H3N2) strains. Finally, influenza vaccination in 2018/19 generally provided evidence of significant protection against influenza related hospitalisation regardless of prior vaccine history during the 2017/18 season.

The study had a number of strengths and potential weaknesses. The study uses the well - established test-negative case control design which has been used extensively to estimate influenza VE including against hospitalisation [8]. It does use routine laboratory detections to obtain these cases and controls which raises the question of potential selection bias. We attempted to control for this by restricting to those who had been hospitalised for their illness. Encouragingly, the proportion of vaccinated controls (71%), was very similar to that in the community in this age-group from routine uptake monitoring (72%) [9]. Those patients without a registered GP were excluded as it was not possible to collect relevant information if it was unclear if they were resident in the UK. If these persons were less likely to be vaccinated, their exclusion could lead to an underestimate of VE though numbers were small. Laboratory testing for influenza infection in the age group studied tends to occur mainly among those presenting to secondary care. This will have a limited effect on the estimate of VE as cases and (test-negative) controls presenting to hospital are likely to have similar severity of illness in order to be tested. A series of sensitivity analyses were undertaken which led to only small differences in the adjusted estimates. Finally, the rVE results for aTIV were non-significantly higher compared to IIV for all influenza and for A(H3N2) due to the small numbers of individuals who received IIV. Despite this uncertainty, our findings, as discussed later, do triangulate with other information.

Commented [RP1]: Comment on sensitivity analyses

The 2018/19 influenza season in England was characterised by the initial circulation of A(H1N1)pdm09, followed by A(H3N2)[9]. Overall we found evidence of significant protection against influenza-confirmed hospitalisation in those over 65 years of age, in a season when the circulating A(H1N1)pdm09 and A(H3N2) strains were genetically matched to the 2018/19 vaccine virus strains [9], but also with the introduction of aTIV for the first time for all those >=65 years of age. Our overall aVE estimate of 53% for protection against influenza in secondary care is encouragingly similar to what was measured for the same age-group in primary care of 49% (95% CI -13.7, 77.9) in 2018/19 [9]. It is higher than seen in a recently published meta-analysis of prevention of severe disease by influenza vaccine (VE= 37%;

(95%CI: 30, 44) among ≥65 years) [8]; what has been reported previously in the UK [2] and from 2018/19 mid-season estimates from elsewhere in Europe and the United States [17,18]. It is similar to the 2018/19 mid-season estimate reported from Canada, where A(H1N1)pdm09 was the dominant circulating influenza A subtype [19]. In addition, we report effectiveness of 62% in those >84 years of age – a group in whom in the UK, there has been little evidence of effectiveness of non-adjuvanted, standard-dose IIV in preventing laboratory confirmed primary care consultations in recent seasons [2]. Some caution should be exercised in interpreting this result due to potential biases related to reduced propensity to hospitalise this age-group.

On estimation of influenza A subtype specific protection, we found a significant effectiveness against hospital associated A(H1N1)pdm09 infection of 64.8%, which compares favourably to the published pooled VE estimate of 54% (95%CI: 26; 82) [8] for influenza hospitalisation in the elderly. Furthermore, we observed a lower, but still significant, VE against A(H3N2) of 39.3%, similar to the published pooled IVE estimate of 33% (95%CI: 21;45) for A(H3N2) seen in the period of the meta-analysis of 2009-2016 [8] and similar to what was observed in primary care this season in the UK [9]. There was some suggestion of reduction in aVE against A(H3N2) in older age-groups. Lower VE of the egg-based, standard-dose, non-adjuvanted influenza vaccine has been observed in more recent seasons in the elderly in seasons dominated by A(H3N2) [10]. The reasons for this lower effectiveness seems to be multifactorial. The available published literature suggests some evidence of improved immunogenicity of adjuvanted influenza vaccine [5,11,12], with more limited studies of superior effectiveness compared to traditional non-adjuvanted influenza vaccine [5,6,13]. In this article, we add to the evidence base, showing that in a season with co-circulation of A(H1N1)pdm09 and A(H3N2), aTIV has provided significant effectiveness for those over 65 years of age, with higher, albeit non-significant, relative effectiveness compared to non-adjuvanted IIV. The aTIV rVE estimate of 29.6% is similar to that seen in a recent meta-analysis of 25% [5]. Our findings highlight that further work is required to compare aTIV against both traditional and other enhanced vaccines for the elderly as they become licensed in Europe, in particular high-dose influenza vaccine and cell-based vaccines. This will build on the head-to-head evidence of the comparative performance of these vaccines now starting to emerge from elsewhere, most notably the United States [14].

Although some studies have suggested prior vaccination may be responsible for negative vaccine interference [15], we found no such evidence in this particular season, which is unsurprising in that the UK saw mainly A(H3N2) viruses of genetic subclade 3C.2a predominate in both 2017/18 (with mainly 3C.2a2) and 2018/19 (with mainly 3C.2a1b), with an associated change in the H3N2 vaccine virus component. Vaccination in 2017/18 did not

reduce effectiveness for those vaccinated in 2018/19 either overall or by influenza A subtype. Indeed, for those vaccinated only in 2017/18, VE levels were suboptimal the following season, highlighting that vaccination in the current season was required, regardless of prior season's vaccine exposure, to ensure optimal protection against hospitalised influenza.

In conclusion, we demonstrate encouraging levels of protection provided by the newly implemented adjuvanted influenza vaccine for those over 65 years of age in England. This is only a single season and it will be critical to continue to evaluate the impact and effectiveness of this vaccine plus other newly licensed vaccines that may be offered to this age-group in future seasons, most notably cell-based and high-dose vaccines.

Declarations of Interests

MD received lecturing fee from Sanofi Pasteur MSD; SpeeDx provided partial financial support for an educational meeting and UK Clinical Virology Network (UK CVN) which he chairs is a registered charity which includes a number of commercial partners. No other co-authors had conflicts to declare

Acknowledgements

We would like to acknowledge all the participating laboratories of the Respiratory DataMart surveillance system and all the GPs who responded to requests for information on their patients.

Contributions

RP and NA conceived and designed the study; HZ co-ordinated the acquisition of data; HW and NA undertook the statistical analysis; all co-authors were involved in the interpretation of data; RP wrote the first draft and all co-authors contributed to critical revision; all co-authors provided final approval of the submitted version.

Tables and figures

Table 1. Details for hospitalised influenza A cases and controls in the elderly, England, 1 October 2018– 8 April 2019 Numbers and row percentages (to indicate positivity rates [a]) are shown (N=1439)

	Negative (n=1013)	A/H1 (n=182)	A/H3 (n=123)	A not known (n=121)	X^2 p-value
Age					0.434
65-74	450 (69%)	101 (49%)	46 (44%)	58 (45%)	
74-84	378 (72%)	60 (40%)	50 (56%)	39 (35%)	
85+	185 (72%)	21 (29%)	27 (52%)	24 (25%)	
Sex					0.162
Female	552 (72%)	89 (41%)	54 (43%)	73 (50%)	
Male	461 (68%)	93 (44%)	69 (58%)	48 (41%)	
IMD quintile					0.824
1	201 (70%)	33 (38%)	24 (45%)	28 (28%)	
2	186 (69%)	39 (46%)	23 (51%)	22 (24%)	
3	216 (69%)	43 (44%)	26 (47%)	29 (30%)	
4	207 (71%)	33 (39%)	25 (49%)	25 (26%)	
5	203 (73%)	34 (45%)	25 (60%)	17 (19%)	
Risk group					0.014
No	117 (63%)	21 (30%)	28 (58%)	20 (24%)	
Yes	859 (72%)	150 (44%)	91 (48%)	95 (56%)	
Missing	37 (64%)	11 (52%)	4 (40%)	6 (9%)	
Onset to swab					0.184
0 to 1 days	232 (69%)	34 (33%)	32 (46%)	38 (36%)	
2 to 4 days	244 (73%)	37 (42%)	22 (42%)	29 (28%)	
5 to 7 days	117 (66%)	27 (44%)	18 (53%)	15 (18%)	
onset missing	420 (71%)	84 (48%)	51 (57%)	39 (35%)	
Vaccination status					<0.001
Unvaccinated	272 (59%)	90 (48%)	45 (46%)	51 (46%)	
Vaccinated (>14 days ago)	723 (75%)	91 (38%)	77 (53%)	68 (47%)	
Vaccinated (date missing)	18 (82%)	1 (25%)	1 (33%)	2 (2%)	
Previous 2017/18 vaccination					<0.001
No	237 (61%)	75 (50%)	36 (47%)	40 (40%)	
Yes	744 (74%)	102 (38%)	85 (52%)	78 (51%)	
unknown	32 (76%)	5 (50%)	2 (40%)	3 (4%)	
Month of event					0.551
October	11 (55%)	1 (11%)	3 (38%)	3 (5%)	
November	35 (69%)	5 (31%)	5 (45%)	6 (8%)	
December	251 (69%)	44 (39%)	37 (54%)	32 (32%)	

January	697 (71%)	129 (46%)	76 (49%)	78 (52%)	
February	19 (73%)	3 (43%)	2 (50%)	2 (3%)	
Vaccine Status					<0.001
Unvaccinated	272 (59%)	90 (48%)	45 (46%)	51 (46%)	
aTIV	637 (75%)	80 (38%)	67 (52%)	61 (45%)	
QIV/TIV	14 (67%)	2 (29%)	3 (60%)	2 (3%)	
Vac (unknown)	90 (78%)	10 (40%)	8 (53%)	7 (8%)	
PHE region					<0.001
East Midlands	209 (66%)	58 (53%)	18 (35%)	34 (34%)	
East of England	184 (69%)	57 (70%)	19 (79%)	5 (7%)	
London	118 (84%)	0 (0%)	16 (73%)	5 (6%)	
North East	40 (89%)	0 (0%)	1 (20%)	4 (4%)	
North West	46 (49%)	11 (23%)	17 (46%)	20 (29%)	
South East	21 (81%)	0 (0%)	1 (20%)	4 (5%)	
South West	195 (76%)	10 (17%)	9 (18%)	40 (34%)	
West Midlands	120 (69%)	33 (62%)	19 (95%)	1 (1%)	
Yorkshire and The Humber	80 (65%)	13 (30%)	23 (74%)	8 (11%)	

Table 1 - footnote

[a] p-values relate to a Chi-square test on all influenza positives (A and B) and influenza negatives

[b] missing vaccination dates were set at the median date to calculate frequencies

IMD = Index of Multiple Deprivation

Table 2 Hospitalised cases and controls for influenza A and B according to vaccination status and VE estimates in 65+, England, 1 October 2018 – 8 April 2019 (n = 1441)

Influenza	Cases[a]		Controls[a]		Crude VE (95%CI)	Adjusted[b] VE (95% CI)
	Vac	Unvac	Vac	Unvac		
A and B	241 (56%)	187	741 (73 %)	272	52.6% (40, 62.6)	**53.4% (39.9, 63.9)**
A only	240 (56%)	186	741 (73 %)	272	52.5% (39.9, 62.5)	**53.8% (40.3, 64.2)**
A/H1N1	92 (51%)	90	741 (73 %)	272	62.4% (48.1, 72.7)	**64.8% (49.6, 75.3)**
A/H3N2	78 (63%)	45	741 (73 %)	272	36.2% (5.6, 56.9)	**39.3% (6.5, 60.6)**

CI: confidence interval; VE: vaccine effectiveness; Vac: vaccinated; Unvac: unvaccinated

[a] Frequencies were calculated substituting the median vaccination date where unknown. In the logistic regression model missing vaccination dates were dealt with using multiple imputation.

[b] Adjusted for age-group, gender, month, region and risk group.

Table 3 Adjusted vaccine effectiveness estimates for influenza by sub-type, age-group and vaccine type, England in the elderly, 1 Oct 2018–8 April 2019

	Cases[a]		Controls[a]		Adjusted[b] VE
	Vac	**Unvac**	**Vac**	**Unvac**	**(95% CI)**
A & B					
65-74	92 (47%)	104	320 (73%)	120	68.8% (54.7, 78.5)
74-84	96 (67%)	47	264 (73%)	96	25.8% (-16.1, 52.6)
85+	41 (60%)	27	131 (74%)	45	61.9% (23.2, 81.1)
Risk group (Y)	198 (59%)	140	640 (75%)	219	53.7% (38.6, 65)
Risk group (N)	31 (45%)	38	75 (64%)	42	62.3% (25.9, 80.8)
>65 (aTIV)	199 (53%)	178	619 (53%)	261	53.8% (39.8, 64.5)
>65 (IIV)	7 (4%)	178	14 (4%)	261	34.4% (-72.2, 75)
rVE (aTIV/IIV)					29.6% (-83.4, 73)
A/H1N1pdm09					
65-74	43 (45%)	52	320 (73%)	120	75.8% (59.5, 85.5)
74-84	33 (59%)	23	264 (59%)	96	52.8% (10.5, 75.1)

85+	11 (55%)	9	131 (55%)	45	68.5% (7.1, 89.3)
Risk group (Y)	77 (51%)	73	640 (51%)	219	67.8% (52.7, 78.1)
Risk group (N)	10 (48%)	11	75 (48%)	42	59.8% (-24.6, 87)
>65 (aTIV)	76 (48%)	84	619 (48%)	261	65.9% (50.6, 76.4)
>65 (IIV)	2 (2%)	84	14 (5%)	261	64.9% (-65.9, 92.6)
rVE (aTIV/IIV)					2.8% (-358.1, 79.4)
A/H3N2					
65-74	22 (50%)	22	320 (73%)	120	60.2% (22.9, 79.5)
74-84	39 (78%)	11	264 (73%)	96	-10.1% (-147.7, 51.1)
85+	14 (56%)	11	131 (74%)	45	66.7% (-5.8, 89.5)
Risk group (Y)	62 (68%)	29	640 (75%)	219	33.5% (-10, 59.8)
Risk group (N)	13 (46%)	15	75 (64%)	42	60.9% (-1.6, 85)
>65 (aTIV)	64 (59%)	44	619 (70%)	261	39.5% (4.8, 61.5)
>65 (IIV)	3 (6%)	44	14 (5%)	261	-5.2% (-336.4, 74.7)
rVE (aTIV/IIV)					42.5% (-133.7, 85.8)

CI: confidence interval; VE: vaccine effectiveness; Vac: vaccinated; Unvac: unvaccinated; aTIV – adjuvanted trivalent inactivated vaccine, QIV – quadrivalent inactivated vaccine.

[a] Frequencies were calculated substituting the median vaccination date where unknown.

[b] adjusted for age-group, gender, month, risk group and region.

rVE – relative vaccine effectiveness

Table 4 Adjusted vaccine effectiveness estimates for influenza hospitalisation by subtype and prior vaccine history, England in the elderly, 1 Oct 2018–8 April 2019

	Cases[a]		Controls[a]		Adjusted[b] VE
	Vac	**Unvac**	**Vac**	**Unvac**	**(95% CI)**
A and B					
2017/18 only	63 (36%)	111	95 (38%)	156	8.2% (-40.2, 39.9)
2018/19 only	30 (21%)	111	74 (32%)	156	44.8% (8.6, 66.7)
Both seasons	195 (64%)	111	624 (80%)	156	57% (41.6, 68.3)
A/H1N1					
2017/18 only	25 (30%)	57	95 (38%)	156	23.3% (-37.5, 57.2)
2018/19 only	11 (16%)	57	74 (32%)	156	65.9% (29, 83.7)
Both seasons	73 (56%)	57	624 (80%)	156	69.5% (53.6, 79.9)
A/H3N2					
2017/18 only	21 (49%)	22	95 (38%)	156	-67.8% (-239.2, 17)
2018/19 only	12 (35%)	22	74 (32%)	156	-16.4% (-160.1, 47.9)
Both seasons	62 (74%)	22	624 (80%)	156	30.2% (-21.5, 59.9)

CI: confidence interval; VE: vaccine effectiveness; Vac: vaccinated; Unvac: unvaccinated

[a] Frequencies were calculated substituting the median vaccination date where unknown.

[b] Adjusted for age-group, gender, month, region, and risk group.

Figure 1: Distribution of Respiratory Datamart sentinel surveillance laboratories

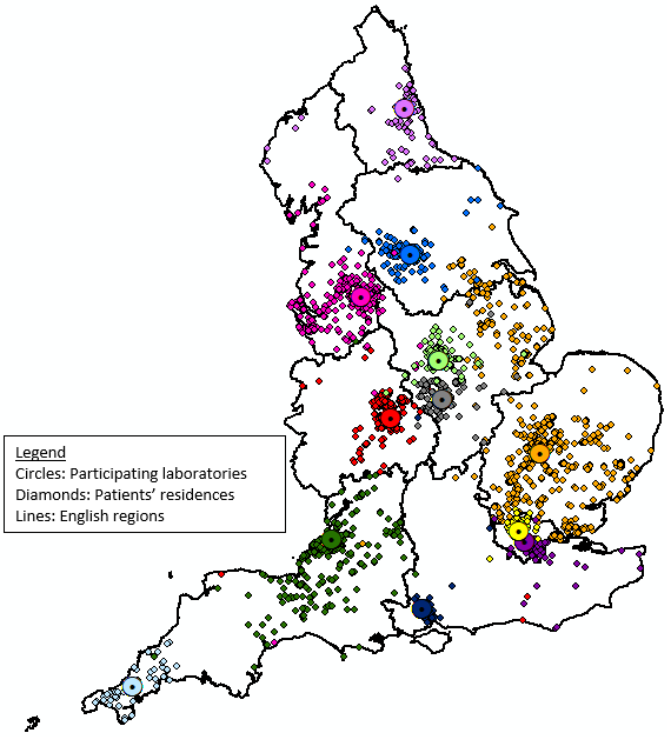
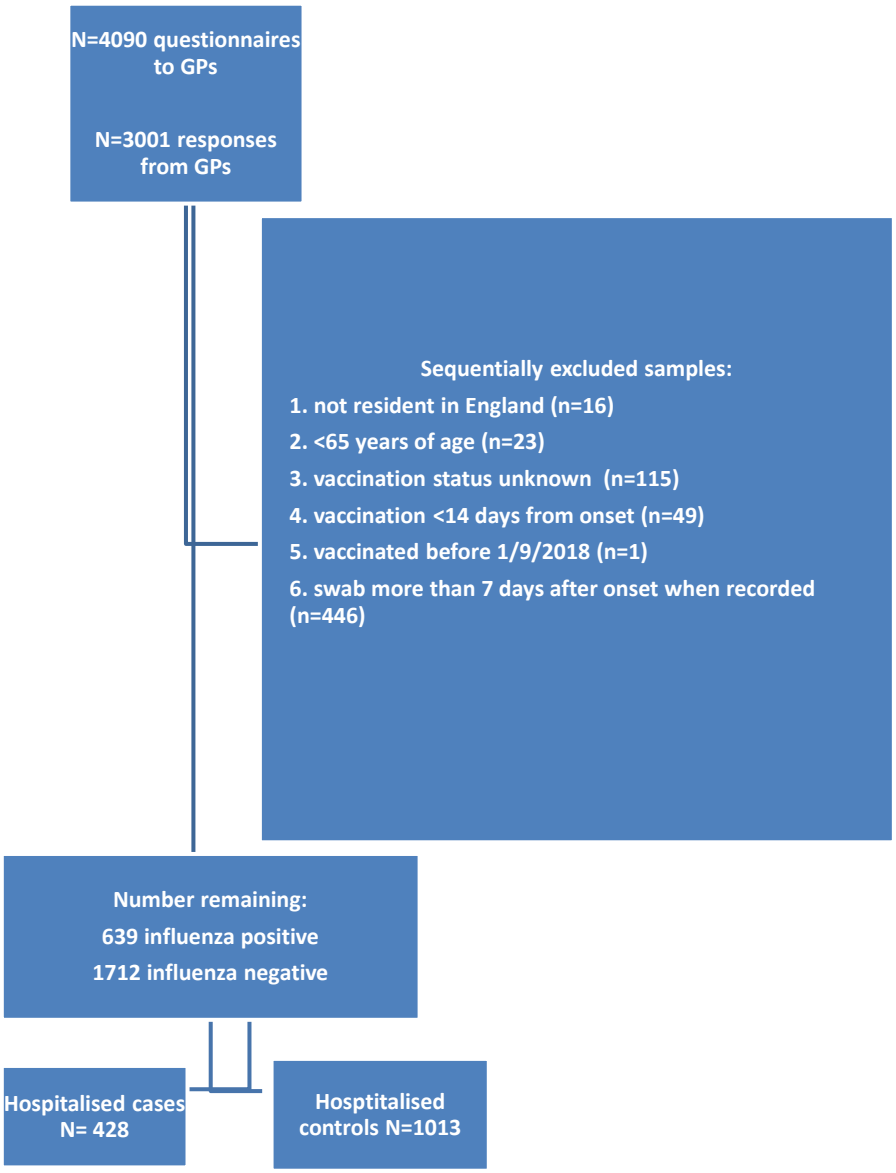


Figure 1: Swabbing results of patients in secondary care in England, October 2018 to April 2019



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