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Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A(H1N1) 2009 vaccines in preventing influenza in the United Kingdom

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SUMMARY

An analysis was undertaken to measure age-specific vaccine effectiveness (VE) of 2010/11 trivalent seasonal influenza vaccine (TIV) and monovalent 2009 pandemic influenza vaccine (PIV) administered in 2009/2010. The test-negative case-control study design was employed based on patients consulting primary care. Overall TIV effectiveness, adjusted for age and month, against confirmed influenza A(H1N1)pdm 2009 infection was 56% (95% CI 42–66); age-specific adjusted VE was 87% (95% CI 45–97) in <5-year-olds and 84% (95% CI 27–97) in 5- to 14-year-olds. Adjusted VE for PIV was only 28% (95% CI −6 to 51) overall and 72% (95% CI 15–91) in <5-year-olds. For confirmed influenza B infection, TIV effectiveness was 57% (95% CI 42–68) and in 5- to 14-year-olds 75% (95% CI 32–91). TIV provided moderate protection against the main circulating strains in 2010/2011, with higher protection in children. PIV administered during the previous season provided residual protection after 1 year, particularly in the <5 years age group.

Key words: Influenza, influenza vaccines, vaccine-preventable diseases.

INTRODUCTION

The emergence of the 2009 pandemic influenza virus led to the development and manufacture of a new generation of monovalent influenza vaccines – some of which employed new adjuvants. Many countries implemented pandemic vaccine programmes targeted at new risk groups, in particular children [1–3]. A number of observational studies have since shown the pandemic influenza vaccines (PIV) administered during the pandemic had high levels of vaccine effectiveness (VE) against various end-points [4]. Early mid-season analyses from 2010/11, including from the UK, have suggested some residual protection from the adjuvanted pandemic vaccine 12 months later in a number of settings [5] as have some end-of-season analyses [6].

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A number of countries are considering the potential introduction of routine childhood seasonal influenza vaccine programmes. Uncertainties continue regarding the potential effectiveness of seasonal influenza vaccines in this particular age group – such information will be critical to inform estimates of the potential future impact and cost-effectiveness of implementing such vaccine programmes.

The 2010/11 influenza season was characterized by the re-introduction of the normal, unadjuvanted trivalent seasonal influenza vaccine (TIV) after the 2009 pandemic. The 2010/11 unadjuvanted TIV, as recommended by WHO, included the influenza A(H1N1)pdm 2009 strain [7], with the UK 2010/11 vaccination programme starting in autumn 2010 and reaching a final uptake of 50·4% in clinical at-risk groups aged 6 months to 65 years.

The UK experienced intense influenza A(H1N1)pdm 2009 transmission during the 2010/11 season, with later co-circulation of influenza B. This provided the opportunity to undertake mid-season estimate for VE using the established swab-negative case-control approach [8, 9]. These mid-season estimates against influenza A (H1N1)pdm 2009 infection up to January 2011 have been published [5], demonstrating an effectiveness of 34% for monovalent vaccine only given in 2009/10, 46% for trivalent 2010/11 vaccine only and 63% if vaccinated with both vaccines.

This present study presents the end-of-season VE for the 2010/11 TIV in preventing confirmed influenza A(H1N1)pdm 2009 and influenza B infection in both children and adults. It also examines in further detail the potential protection from vaccination with monovalent A(H1N1)2009 vaccine administered the previous season and finally the potential accuracy of mid-season VE estimates.

METHODS

Study population and period

Data was derived from five primary-care influenza sentinel surveillance schemes in England (two schemes), Northern Ireland, Scotland and Wales. Details of the Royal College of General Practitioners (RCGP), Health Protection Agency (HPA) Regional Microbiology Network (RMN), Public Health Wales and Health Protection Scotland (HPS) swabbing schemes have been presented previously [3]. The Public Health Agency of Northern Ireland operated a scheme with 37 practices in 2010/11, covering 11·6% of the registered population.

The study period ran from 1 September 2010 to 17 March 2011. Cases were defined as persons presenting during the study period in a participating practice with an acute influenza-like illness (ILI) who were swabbed and then tested positive for influenza A(H1N1)pdm 2009 or influenza B. ILI was defined as an acute respiratory illness with fever or complaint of feverishness. Controls were individuals presenting with ILI in the same period that were swabbed and tested negative for influenza. Individuals testing positive for other influenza A types were dropped.

A standardized questionnaire collected demographic, clinical and epidemiological information from cases and controls including date of birth, sex, underlying clinical risk group, date of onset of respiratory illness, date of specimen and influenza vaccination status for 2010/11 and previous season with vaccination dates was completed by the GP during the patient consultation for their respiratory illness. Vaccination data were derived from the patient's medical record.

Laboratory methods

Laboratory confirmation was undertaken using real-time polymerase chain reaction (RT–PCR) assays for circulating influenza A viruses, influenza B viruses and other respiratory viruses [10, 11]. Samples in England were sent to the HPA Microbiology Services, Colindale (RCGP scheme) or one of the regional HPA microbiology laboratories (RMN scheme). Samples in Wales were sent to the Public Health Wales Specialist Virology Centre and in Scotland to the West of Scotland Specialist Virology Centre (HPS scheme) for molecular testing. In Northern Ireland samples were sent to the Regional Virus Laboratory, Belfast.

Statistical methods

To assess VE based on monovalent H1N1 2009 vaccine and 2010/11 TIV status, a four-level variable was defined as previously [5] with the following categories:

(1) unvaccinated in both years;
(2) receipt of monovalent 2009 PIV in 2009/10 but not in receipt of 2010/11 TIV;

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(3) receipt of either PIV in 2010/11 (provided to certain risk groups) or TIV in 2010/11 or both, but not vaccinated in 2009/10;
(4) receipt of PIV in 2009/10 and TIV in 2010/11, or received first dose of PIV in 2009/10 and second dose of PIV in 2010/11.

As numbers were low (five persons had two doses), those that had received two doses of PIV in 2009/10 were not analysed separately from those who received only one dose. Persons were defined as vaccinated if date of vaccination with 2010/11 TIV or PIV was $\geqslant$14 days before onset of illness. Those in whom the period between vaccination and onset of illness was $<$14 days were excluded, as immunity is unknown. When assessing VE of PIV or combination of PIV and 2010/11 TIV, only those with known vaccination status were included. To assess VE of just 2010/11 TIV, individuals could still be included if PIV status was not known. If the date of vaccination was missing, as the 2010/11 campaign occurred before influenza circulation, it was assumed that 2010/11 TIV vaccination was $\geqslant$14 days before onset date. For PIV, if date of vaccination was missing, it was assumed the person was vaccinated in 2009/10. If date of onset of symptoms was missing then the date was assumed to have been 4 days prior to the date the swab was taken (the median interval based on the observed data). Respiratory samples with a delay of $>$29 days between onset of illness and sample collection were excluded as the sensitivity of the PCR test is less effective for long intervals between onset and sampling. A sensitivity analysis was also undertaken censoring at 7 days between onset of illness and sample collection.

VE was estimated as 1 – (odds ratio) using multivariable logistic regression models with influenza A(H1N1)pdm 2009 or influenza B PCR results as outcomes and seasonal or pandemic vaccination status as the linear predictor. In the analyses evaluating VE in preventing influenza A(H1N1)pdm 2009 infection, samples positive for influenza B were excluded and vice versa. Age (coded into five standard age groups: $<$5, 5–14, 15–44, 45–64, $\geqslant$65 years), gender, clinical risk group, surveillance scheme (HPS, RCGP, RMN, NI, Wales) and date of sample collection (month) were investigated as potential confounding variables.

To assess the impact of missing vaccination history (or date of vaccination) and to allow inclusion of the risk group variable without dropping many individuals, multiple imputation was used in a sensitivity analysis. The analysis, which also imputed missing data for gender and age, was performed using the multiple imputations chained equation (MICE) package in R (R version 2.13.0, R Foundation for Statistical Computing, 2011). Additional variables, which had no missing data, used in the imputation were flu virology status, month swab was collected and surveillance scheme. All variables were included as possible predictors of the missing data and logistic regression was the model for gender and risk group, proportional odds regression for age group, and polytomous logistic regression for the combined seasonal/pandemic vaccine status. Five separate imputation datasets were imputed and the model estates combined [12].

All other statistical analyses were performed in Stata version 10 (StataCorp, USA).

RESULTS

A total of 7797 individuals were swabbed during the study period. Thirty-nine were dropped as they were positive for influenza H3 or influenza A but not influenza A(H1N1)pdm 2009. Of the rest, 4418 (56·9%) were collected from the RCGP scheme, 1902 (24·5%) from the HPS scheme, 884 (11·4%) from the RMN scheme, 190 (2·4%) from the Public Health Wales Scheme and 364 (4·7%) from the PHA Northern Ireland Scheme. Table 1 summarizes those individuals excluded because of missing information. Vaccine date was unknown for 25 individuals given TIV and 45 given PIV. Although date of onset was missing for 801 (10·3%) individuals, these were included with onset date defined as swab date minus 4 days.

The demographic and epidemiological characteristics of cases and controls are summarized in Table 2. A total of 848 individuals had received 2010/11 TIV and 616 monovalent PIV. Whereas very few children received 2010/11 TIV (14 aged $<$5 years and 27 aged 5–14 years).

Model fitting for VE estimation

When estimating vaccine effects, age group, gender, time period and surveillance scheme were adjusted for in a multivariable logistic regression model. Although all these variables were significantly associated with having a positive swab, only age group and time period were confounders for the vaccine effects.

Risk group was missing for 2270 (29%) out of 7758 samples, and was therefore not included in the

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Table 1. *Inclusion and exclusion criteria of participants for specimens submitted, UK, 1 September 2010 to 17 March 2011*

Criteria	Excluded (*n*)	Included (*n*)
1. Original participants		7758
Excluded as interval from onset to sampling >29 days	112	
Remaining participants		7646
2. Analysis of monovalent H1N1 vaccine and 2010/11 TIV		
Excluded as missing vaccination history	1203	
Excluded as vaccinated 0–14 days before onset	70	
Final remaining study participants		6373
Final for assessment of H1H1 (2009)		5372
Final for assessment of Flu B		4825
3. Analysis of 2010/11 TIV only		
Excluded as missing vaccination history	438	
Excluded as vaccinated 0–14 days before onset	87	
Final remaining study participants		7121
Final for assessment of H1H1 (2009)		6004
Final for assessment of Flu B		5419

TIV, Trivalent seasonal influenza vaccine.

final model. If risk group was included, or if multiple imputation was used, the VE estimates remained similar. Tables 3 and 4, as well as Figures 1–3 show VE estimates against influenza A(H1N1)pdm 2009 and influenza B according to vaccination status and, in the figures, by age group and scheme.

VE against influenza A(H1N1)pdm 2009 infection

The adjusted VE estimates against influenza A(H1N1)pdm 2009 increased from 28% [95% confidence interval (CI) −6 to 51] for PIV only in 2009/10; to 55% (95% CI 31–71) for vaccination only in 2010/11 mainly with 2010/11 TIV; to 60% (95% CI 39–73) if vaccinated in both seasons with PIV then mainly with 2010/11 TIV (Table 3). Persons who had received vaccination in both 2009/10 and 2010/11 or just in the 2010/11 season had a significantly higher VE compared to persons who received PIV only in 2009/10 (Wald test $P=0{\cdot}012$, 0·002 for just 2010/11, both respectively). There was no difference in VE between those vaccinated in both seasons (PIV in 2009/10 and mainly TIV in 2010/11) and those just vaccinated (mainly with TIV) in 2010/11 ($P=0{\cdot}58$). The VE for 2010/11 TIV, irrespective of previous PIV status, was 56% (95% CI 42–66) (Table 4).

For 2010/11 TIV, there was no evidence VE differed significantly by age group ($P=0{\cdot}16$). VE was 87% (95% CI 45–97) in the <5 years age group and 84% (27–97) in the 5–14 years age group (Fig. 1*a*). The point estimate was lower in older age groups (Fig. 1*a*). For PIV there was no significant difference in VE estimates by age when using the five age groups ($P=0{\cdot}12$) but a difference was found when splitting age as <5 and ⩾5 years ($P=0{\cdot}04$) (Fig. 2). This age division was chosen due to the different strategy for the <5 years age group who were all recommended the monovalent vaccine during 2009/10. This gave VE estimates of 72% (95% CI 15–91) for the <5 years age group and 10% (95% CI −36 to 41) for the ⩾5 years age group. No significant difference in VE was observed by surveillance scheme (Fig. 3).

In a sensitivity analyses of VE against influenza A(H1N1)pdm 2009, censoring samples taken >7 days after symptom onset gave slightly higher VE estimates with broader confidence intervals: the adjusted VE for those vaccinated in the previous season (2009/10) was 39% (95% CI 5–61); for those vaccinated only in the current season (2010/11) VE was 61% (95% CI 35–77) and for those vaccinated both seasons VE was 65% (95% CI 43–79). The VE for 2010/11 TIV irrespective of PIV status increased to 63% (95% CI 48–73). With multiple imputation, the results were similar to those found without imputation, but did allow adjustment for risk group: the imputed VE for vaccination in both seasons was 59·0% (95% CI 36·4–73·6), which is similar to the VE estimate given in Table 3.

Adjusting for month had a large effect on VE for those vaccinated in 2009/10, decreasing it from 53% (crude) to 36% after adjustment.

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Table 2. *Details for pandemic influenza A(H1N1) 2009 and influenza B cases and controls, UK, September 2010 to March 2011 (n = 7758)*

	Controls, *n* (%) (*N* = 4730)	B cases, *n* (%) (*N* = 1211)	H1N1 (2009) cases, *n* (%) (*N* = 1817)*
Age group (years)			
< 5	502 (10·6)	93 (7·7)	146 (8)
5–14	459 (9·7)	352 (29·1)	198 (10·9)
15–44	2161 (45·7)	577 (47·6)	1035 (57)
45–64	1148 (24·3)	154 (12·7)	406 (22·3)
⩾65	431 (9·1)	31 (2·6)	22 (1·2)
Missing	29 (0·6)	4 (0·3)	10 (0·6)
Sex			
Male	1859 (39·3)	551 (45·5)	774 (42·6)
Female	2836 (60)	646 (53·3)	1027 (56·5)
Missing	35 (0·7)	14 (1·2)	16 (0·9)
Month of sample collection			
September	123 (2·6)	1 (0·1)	0 (0)
October	534 (11·3)	9 (0·7)	34 (1·9)
November	661 (14)	56 (4·6)	73 (4)
December	1358 (28·7)	543 (44·8)	1356 (74·6)
January	1473 (31·1)	472 (39)	342 (18·8)
February	532 (11·2)	117 (9·7)	11 (0·6)
March	49 (1)	13 (1·1)	1 (0·1)
Surveillance scheme			
RCGP	2771 (58·6)	643 (53·1)	1004 (55·3)
RMN	510 (10·8)	130 (10·7)	244 (13·4)
HPS	1135 (24)	359 (29·6)	408 (22·5)
Wales	85 (1·8)	43 (3·6)	62 (3·4)
Northern Ireland	229 (4·8)	36 (3)	99 (5·4)
Risk group			
No	2626 (55·5)	750 (61·9)	1097 (60·4)
Yes	716 (15·1)	120 (9·9)	179 (9·9)
Missing	1388 (29·3)	341 (28·2)	541 (29·8)
Interval onset sampling (days)			
0–1	531 (11·2)	139 (11·5)	260 (14·3)
2–4	1755 (37·1)	605 (50)	849 (46·7)
5–7	955 (20·2)	260 (21·5)	310 (17·1)
8–14	666 (14·1)	65 (5·4)	153 (8·4)
15–29	247 (5·2)	17 (1·4)	33 (1·8)
⩾29	93 (2)	7 (0·6)	12 (0·7)
Missing onset date†	483 (10·2)	118 (9·7)	200 (11)
Vaccination status (monovalent – TIV combinations)			
Unvaccinated	3223 (68·1)	917 (75·7)	1457 (80·2)
TIV only	240 (5·1)	22 (1·8)	31 (1·7)
TIV only (0–13 days)	32 (0·7)	2 (0·2)	9 (0·5)
Monovalent only	196 (4·1)	41 (3·4)	43 (2·4)
Both	236 (5)	26 (2·1)	31 (1·7)
Both (TIV 0–13 days)	24 (0·5)	2 (0·2)	4 (0·2)
Missing (either year)	779 (16·5)	201 (16·6)	242 (13·3)
Vaccination status (only considering TIV)			
Unvaccinated	3767 (79·6)	1065 (87·9)	1637 (90·1)
Vaccinated	618 (13·1)	58 (4·8)	82 (4·5)
Vaccinated (0–13 days)	72 (1·5)	5 (0·4)	13 (0·7)
Missing	273 (5·8)	83 (6·9)	85 (4·7)

HPS, Health Protection Scotland; RCGP, Royal College of General Practitioners' surveillance scheme; RMN, Health Protection Agency (HPA) Regional Microbiology Network; TIV, trivalent seasonal influenza vaccine.

* Five cases positive by both H1N1 (2009) and influenza B are shown in this column.

† Missing onset date was calculated as 4 days prior to sample date.

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Table 3. *Number and proportion of samples positive for influenza A(H1N1) 2009 and influenza B according to vaccination status and vaccine effectiveness (VE) (crude and adjusted*) estimates, UK, September 2010 to March 2011*

Vaccination status	No. H1N1 positive/*N* (%)	Crude VE (95% CI)	Adjusted VE (95% CI) [5212 obs.]	No. flu B positive/*N* (%)	Crude VE (95% CI)	Adjusted VE (95% CI) [4673 obs.]
Unvaccinated	1450/4610 (31·4%)	—	—	916/4076 (22·5%)	—	—
2009/10 monovalent	42/235 (17·9%)	53% (33–66)	28% (−6 to 51)	42/235 (17·9%)	25% (−6 to 47)	−4% (−51 to 29)
2010/11 TIV only	30/267 (11·2%)	72% (59–81)	55% (31 to 71)	22/259 (8·5%)	68% (50 to 79)	56% (29 to 73)
Vaccinated in both seasons	31/260 (11·9%)	70% (53–80)	60% (39 to 73)	26/255 (10·2%)	61% (41 to 74)	53% (27 to 70)

CI, Confidence interval; TIV, trivalent seasonal influenza vaccine.
* Adjusted for age group, gender, time period and surveillance scheme.

Table 4. *Number and proportion of samples positive for influenza A(H1N1) 2009 and influenza B according to 2010/11 TIV status and vaccine effectiveness (VE) (crude and adjusted*) estimates, UK, September 2010 to March 2011*

Vaccination status	No. H1N1 positive/*N* (%)	Crude VE (95% CI)	Adjusted VE (95% CI) [5820 obs.]	No. flu B positive/*N* (%)	Crude VE (95% CI)	Adjusted VE (95% CI) [5244 obs.]
Unvaccinated	1626/5319 (30·6%)	—	—	1064/4757 (22·4%)	—	—
Vaccinated	81/685 (11·8%)	70% (61–76)	56% (42–66)	58/662 (8·8%)	67% (56–75)	57% (42–68)

CI, Confidence interval; TIV, trivalent seasonal influenza vaccine.
* Adjusted for age group, gender, time period and surveillance scheme.

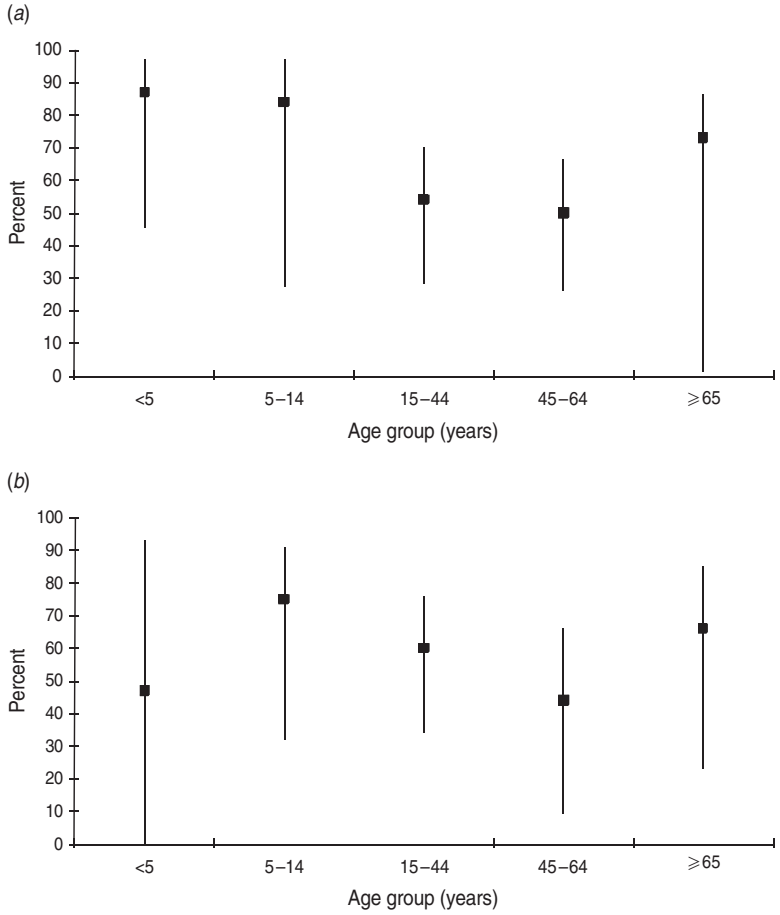

Fig. 1. Trivalent influenza vaccine effectiveness 2010/11 against (*a*) H1N1 (2009) and (*b*) flu B by age group UK, 2010–11.

VE against influenza B infection

There was no evidence of any VE of PIV against influenza B (Table 3). The VE analysis therefore only considers 2010/11 vaccination status. The adjusted VE was 57% (95% CI 42–68). Censoring samples taken >7 days after symptom onset increased VE to 61% (95% CI 45–72).

There was no evidence VE varied by age group (no significant age–vaccine interaction, likelihood ratio test, $P=0{\cdot}46$). VE in the <5 years age group was 47% (95% CI −337 to 93) and in 5–14 years age group it was 75% (95% CI 32–91) (Fig. 1*b*). There was, however, evidence that VE against B infection varied for both surveillance scheme (Fig. 3) and strain (B/Victoria and B/Yamagata). The majority (93%) of B viruses circulating in England and Scotland in 2010/11 were of B/Victoria lineage. Of these B/Victoria isolates, 7/268 cases had been vaccinated with 2010/11 TIV giving an adjusted VE of 78% (95% CI 51–91). This compared to 3/15 B/Yamagata isolates, giving an adjusted VE of −34% (95% CI −448 to 68).

DISCUSSION

This observational study of influenza VE in the UK has several key findings: first, vaccination with the 2010/11 TIV provided significant protection against laboratory-confirmed infection for both influenza A(H1N1)pdm 2009 and influenza B; second, there was evidence of significant protection with 2010/11 TIV for school children for both influenza A(H1N1)pdm 2009 and B infections; third, immunization with A(H1N1)2009 vaccine in 2009/10 followed by TIV in the 2010/11 season provided similar protection against confirmed influenza A(H1N1)pdm 2009 infection to just receiving TIV in 2010/11; fourth, protection against influenza A(H1N1)pdm 2009 infection in 2010/11 following vaccination with PIV 1 year previously in 2009/10 was reduced, although for children aged <5 years VE was maintained; fifth, there was evidence of strain-specific variation in VE for confirmed influenza B infection and finally the findings reinforce earlier published mid-season estimates of VE [5].

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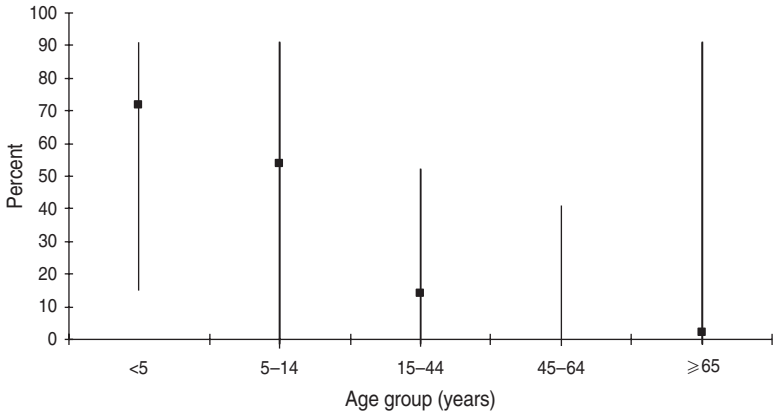

Fig. 2. Pandemic influenza vaccine 2009 effectiveness against H1N1 (2009) by age group UK, 2010–11.

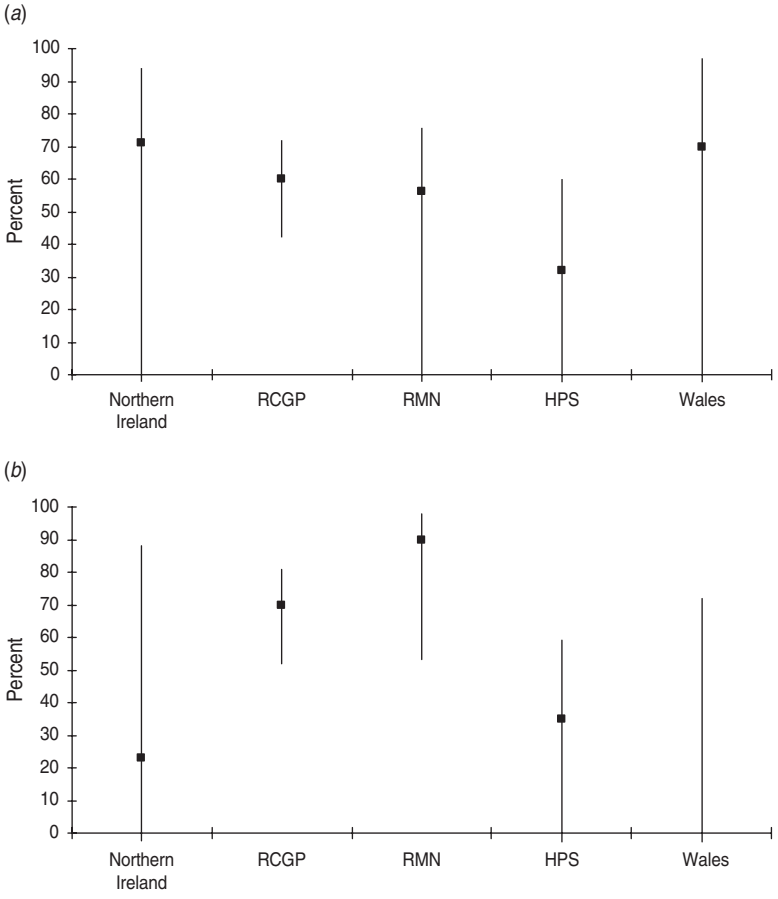

Fig. 3. Trivalent influenza vaccine effectiveness 2010/11 against (*a*) influenza H1N1 (2009) and (*b*) flu B by surveillance scheme, 2010/11, UK. RCGP, Royal College of General Practitioners' surveillance scheme; RMN, Health Protection Agency (HPA) Regional Microbiology Network; HPS, Health Protection Scotland.

The swab-negative case-control study design is now a well established approach to estimate influenza VE, with several studies published on the methodology [13, 14]. The potential limitations presented in this paper have been outlined previously and relate to convenience sampling of biological specimens resulting in the potential for selection bias; missing data items and lack of information on risk status [3]. Furthermore, for children aged <13 years the analysis is based on having received one or more doses of vaccines, as we were not able to disentangle those who had received the recommended two doses from

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those who only received one dose. This could potentially underestimate the VE of the recommended two-dose schedule in this age group. We have presented various sensitivity analyses to attempt to address the potential impact on VE of missing data items. In addition, we have applied multiple imputation methods, which have allowed us to adjust for risk status and demonstrate that this was not an important confounding variable in this particular analysis.

This study confirms that 2010/11 TIV was effective in protecting against both confirmed influenza A(H1N1)pdm 2009 and influenza B infection in people consulting their GP with an acute respiratory illness. This also confirms published findings from several settings including an earlier mid-season UK analysis. These all demonstrated that the 2010/11 seasonal influenza vaccine provided moderate protection against influenza A(H1N1)pdm 2009 infection [5, 15–18]. This VE is consistent with studies on the effectiveness of TIV in the pre-pandemic era, which suggests that the vaccine is protective against the circulating influenza strains [8, 9].

Among children we found that 2010/11 TIV was significantly effective in both the <5 and 5–14 years age groups in preventing influenza A(H1N1)pdm 2009 infection and in the 5–14 years age group only for protecting against confirmed influenza B infection. Only a small number of studies have been published on the effectiveness of unadjuvanted seasonal influenza vaccines mainly in pre-school children [19–21] and this current study provides further useful evidence of the effectiveness of unadjuvanted seasonal TIV in children of all ages. This will be helpful in informing decisions around possible introduction of seasonal influenza vaccines into childhood – particularly for school-aged children.

Although recently published work has demonstrated that the pandemic influenza A(H1N1) 2009 vaccine had good effectiveness in 2009/10 in preventing confirmed influenza A(H1N1)pdm 2009 infection during the pandemic period in a wide range of geographical settings [2, 3], this present study indicates that overall adjuvanted pandemic vaccine protection does not last across the season to the following year. This corroborates findings from our earlier mid-season analysis in the UK [5] and Spain [17]. There was, however, evidence in the current study that PIV protection was maintained in children aged <5 years. It is important to note that this particular target group was broader compared to the older age groups. In the UK all healthy children up to age 5 years, not just those in a clinical risk group, were targeted with PIV in 2009/10 reaching an uptake of 23·6%. Furthermore, this part of the pandemic vaccine programme was delivered later in the 2009/10 season with most vaccine given in the spring of 2010 compared to those with an underlying clinical risk factor aged <65 years, where the programme was started in autumn 2009 and reached an uptake of 35·4%. Both these factors may explain why protection is maintained in this age group compared to older age groups. Our study is also congruent with other studies that have suggested pandemic influenza vaccine protection is lower in older children and adults in the 2009/10 season [22], with others suggesting that antibodies persist after 1 year in children after vaccination with adjuvanted PIV [23].

The lower VE estimate against influenza B for the Yamagata lineage strain is also of some interest. In any season there may be several B variants within the main influenza types/subtypes co-circulating. It would be expected that the calculated VE would vary dependent on how well the circulating strains match the vaccine components. The trivalent seasonal vaccine, however, contained only a single influenza B strain in 2010/11; a B/Brisbane/60/2008-like virus. During 2010/11, both Victoria lineage (B/Brisbane/60/2008-like viruses) and Yamagata lineage (B/Bangladesh/3333/2007-like viruses) influenza B viruses were identified as circulating by molecular analysis or antigenic typing. There is evidence of some variation within the UK in the relative contribution of each of these influenza B lineage strains; in England 7% of influenza B viruses from any source were characterized as B/Bangladesh/3333/2007-like, while in Scotland although this figure was higher (21%), it is based on a much smaller number of samples submitted for molecular typing rather than antigenic typing.

Although the earlier published mid-2010/11 season UK estimates were reasonably accurate, one of the main changes [5] in this end-of-season analysis is that the possible dose–response relationship that persons who received vaccination in both 2009/10 and 2010/11 seasons had a non-significantly higher VE compared to persons who received vaccine only 2009/10 is now significant in the current study. This highlights the importance of annual re-vaccination with influenza vaccine.

The current estimates are also now more precise than the mid-season analysis, in particular for VE against influenza B. Thus, although the mid-season

estimate provided some important early findings, this end-of-season study provides the definitive results and also allows an age-specific analysis.

In conclusion, this end-of-season study provides important evidence that the 2010/11 season's TIV provided protection against infection to both strains of influenza circulating in the 2010/11 season [influenza A(H1N1)pdm 2009 and influenza B] in the UK. In particular, the study provides evidence of TIV effectiveness in school-aged children, which will be an important finding in consideration of potential extension of the national programme to children. The findings also provide evidence that PIV protection wanes after 1 year except for those aged <5 years. The study reinforces the recommendation that annual re-immunization of target groups is required regardless of vaccination the previous season (including those vaccinated with an adjuvanted vaccine). Furthermore, the study confirms the potential value of undertaking a mid-season analysis to provide an early estimate of protection. This can provide key information to assist decision-making, e.g. the WHO vaccine strain selection for the following season.

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DECLARATION OF INTEREST

D. M. Fleming has received funding to attend influenza-related meetings and has received consultancy fees from influenza vaccine manufacturers who might have an interest in the submitted work in the previous 3 years. In addition, The Virus Reference Department of the Health Protection Agency receives funding from a variety of vaccine manufacturers who might have an interest in the submitted work.

REFERENCES

1. **Wichmann O, *et al.*** Pandemic influenza A(H1N1) 2009 breakthrough infections and estimates of vaccine effectiveness in Germany 2009–2010. *Eurosurveillance* 2010; **15**.
2. **Valenciano M, *et al.*** Estimates of pandemic influenza vaccine effectiveness in Europe, 2009–2010: results of influenza monitoring vaccine effectiveness in Europe (I-MOVE) multicentre case-control study. *PLoS Medicine* 2011; **8**: e1000388.
3. **Hardelid P, *et al.*** Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009–2010. *Eurosurveillance* 2011; **16**.
4. **Andrews N, *et al.*** Age-specific effectiveness of an oil-in-water adjuvanted pandemic (H1N1) 2009 vaccine against confirmed infection in high risk groups in England. *Journal of Infectious Diseases* 2011; **203**: 32–39.
5. **Pebody R, *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. *Eurosurveillance* 2011; **16**.
6. **Jimenez-Jorge S, *et al.*** Effectiveness of the 2010–11 seasonal trivalent influenza vaccine in Spain: cycEVA study. *Vaccine* 2012; **30**: 3595–3602.
7. **Department of Health.** Seasonal influenza vaccine uptake amongst GP patient groups in England, 2010/11 (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_129856.pdf).
8. **Skowronski DM, *et al.*** Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: results from the 2005–2006 season of dual A and B vaccine mismatch in Canada. *Vaccine* 2007; **25**: 2842–2851.
9. **Fleming DM, *et al.*** Estimating Influenza vaccine effectiveness using routinely collected laboratory data. *Journal of Epidemiology and Community Health* 2010; **64**: 1062–1067.
10. **Ellis J, *et al.*** Evaluation of four real-time PCR assays for detection of influenza A(H1N1)v viruses. *Eurosurveillance* 2009; **14**: pii = 19230.
11. **Gunson R, *et al.*** Development of a multiplex real-time RT-PCR that allows universal detection of influenza A viruses and simultaneous typing of influenza A/H1N1/2009 virus. *Journal of Virological Methods* 2010; **163**: 258–261.
12. **van Buuren S, Groothuis-Oudshoorn K.** mice: multivariate imputation by chained equations. *Journal of Statistical Software* 2011; **45**: 1–67.

13. **Ferdinands JM, *et al.*** Influenza vaccination status is not associated with influenza testing among children: implications for observational studies of vaccine effectiveness. *Vaccine* 2011; **29**: 1935–1940.
14. **Orenstein EW, *et al.*** Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *International Journal of Epidemiology* 2007; **36**: 623–631.
15. **Kissling E, Valenciano M.** Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010/11: I-MOVE, a multicentre case-control study. *Eurosurveillance* 2011; **16**.
16. **Fielding JE, *et al.*** Effectiveness of seasonal influenza vaccine against pandemic (H1N1) 2009 virus, Australia, 2010. *Emerging Infectious Diseases* 2011; **17**: 1181–1187.
17. **Castilla J, *et al.*** Effectiveness of trivalent seasonal and monovalent influenza A(H1N1)2009 vaccines in population with major chronic conditions of Navarre, Spain: 2010/11 mid-season analysis. *Eurosurveillance* 2011; **16**.
18. **Skowronski DM, *et al.*** A sentinel platform to evaluate influenza vaccine effectiveness and new variant circulation, Canada 2010–11 season. *Clinical Infectious Diseases*. Published online: 21 May 2012. PMID no.: 22539661.
19. **Szilagyi PG, *et al.*** Influenza vaccine effectiveness among children 6 to 59 months of age during 2 influenza seasons: a case-cohort study. *Archives of Pediatrics & Adolescent Medicine* 2008; **162**: 943–951.
20. **Heinonen S, *et al.*** Effectiveness of inactivated influenza vaccine in children aged 9 months to 3 years: an observational cohort study. *Lancet Infectious Diseases* 2011; **11**: 23–29.
21. **Eisenberg KW, *et al.*** Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003–2004 and 2004–2005 influenza seasons. *Pediatrics* 2008; **122**: 911–919.
22. **Griffin MR, *et al.*** Effectiveness of non-adjuvanted pandemic influenza A vaccines for preventing pandemic influenza acute respiratory illness visits in 4 U.S. communities. *PLoS One* 2011; **6**: e23085.
23. **Walker WT, *et al.*** H1N1 antibody persistence 1 year after immunization with an adjuvanted or whole-virion pandemic vaccine and immunogenicity and reactogenicity of subsequent seasonal influenza vaccine: a multicenter follow-on study. *Clinical Infectious Diseases* 2012; **54**: 661–669.