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

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This study provides mid-season estimates of the effectiveness of 2010/11 trivalent influenza vaccine and previous vaccination with monovalent influenza A(H1N1)2009 vaccine in preventing confirmed influenza A(H1N1)2009 infection in the United Kingdom in the 2010/11 season. The adjusted vaccine effectiveness was 34% (95% CI: -10 - 60%) if vaccinated only with monovalent vaccine in the 2009/10 season; 46% (95% CI: 7 - 69%) if vaccinated only with trivalent influenza vaccine in the 2010/11 season and 63% (95% CI: 37 - 78%) if vaccinated in both seasons.

Introduction

Following the emergence of pandemic influenza A(H1N1)2009 virus and the development of several monovalent pandemic influenza A(H1N1)2009 vaccines, a number of observational studies have since demonstrated the clinical effectiveness of these vaccines in various settings during the 2009/10 influenza A(H1N1)2009 pandemic [1-3]. Uncertainty exists, however, about their duration of protection.

Vaccination with the 2010/11 northern hemisphere seasonal trivalent influenza vaccine, which includes the influenza A(H1N1)2009 strain, was started in autumn 2010. The United Kingdom (UK) target populations for vaccination were individuals aged six months to under 65 years in clinical risk groups at elevated risk of severe disease (including pregnant women) and individuals aged 65 years and over [4]. Approximately 35% of those under 65 years of age in a clinical risk group had already received monovalent pandemic influenza vaccine in 2009/10 [4].

In the period December 2010-January 2011, the UK experienced widespread influenza A(H1N1)2009 transmission. Using the established swab-negative case-control approach in primary care [5,6], this study sets out to provide in-season interim estimates of the effectiveness of the 2010/11 seasonal influenza vaccine in preventing confirmed influenza infection in the UK in 2010/11 and the potential effect of previous vaccination with monovalent A(H1N1)2009 vaccine.

Methods

Study population and period

This study uses data from four influenza sentinel surveillance schemes in England, Scotland and Wales. Details of the Royal College of General Practitioners (RCGP), Health Protection Agency (HPA) Regional Microbiology Network (RMN) and Health Protection Scotland (HPS) swabbing schemes have been described previously [3]. Public Health Wales operates a sentinel general practitioner (GP) swabbing scheme with 44 practices covering a population of 355,705, 12 per cent of the population in Wales.

This study covers samples collected in the period from 1 September 2010 to 11 January 2011. Cases were individuals presenting with an acute influenza-like illness (ILI) in a participating practice in the study period who were swabbed and tested positive for influenza regardless of type or subtype. 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. A standard specimen request form provided demographic and clinical information on cases and controls including date of birth, sex, risk

group, date of onset of illness, date of specimen collection, influenza vaccination status for the current and previous season and vaccination dates.

Laboratory methods

Samples in England were sent to the HPA Microbiology Services (RCGP scheme) or one of the local HPA Regional 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. Laboratory confirmation was undertaken using reverse transcription polymerase chain reaction (RT-PCR) assays for circulating influenza A viruses, influenza B viruses and other respiratory viruses [7,8].

Statistical methods

In order to assess vaccine effectiveness (VE) against influenza A(H1N1)2009 infection, a four-level variable was defined with the following four categories:

1. Unvaccinated in both years (not in receipt of either pandemic influenza A(H1N1)2009 vaccine in 2009/10 or trivalent vaccine in 2010/11);
2. Receipt of pandemic influenza A(H1N1)2009 vaccine in 2009/10 but not in receipt of 2010/11 trivalent vaccine;
3. Receipt of either pandemic influenza A(H1N1)2009 vaccine in 2010/11 (provided to certain risk groups) or trivalent vaccine in 2010/11 or both, but not vaccinated in 2009/10;
4. Receipt of pandemic influenza A(H1N1)2009 vaccine in 2009/10 and trivalent vaccine in 2010/11, or received first dose of pandemic influenza A(H1N1)2009 vaccine in 2009/10 and second dose in 2010/11.

Persons who had received two doses of pandemic influenza A(H1N1)2009 vaccine in 2009/10 were not analysed separately from those who received only one dose as the numbers were low.

Individuals were considered vaccinated if their date of seasonal or pandemic influenza A(H1N1)2009 vaccination was 14 days or more before the date of onset of illness. Persons for whom the interval between vaccination and onset of illness was less than 14 days were excluded, as their immunity status was considered unknown. If a person's trivalent vaccination status was known but not their pandemic influenza A(H1N1)2009 vaccination status or vice versa, they were excluded from the estimation of VE for influenza A(H1N1)2009 vaccine. For the estimation of VE for influenza A(H3) or B, pandemic vaccination status was not considered of interest. If the date of trivalent vaccination was missing, it was assumed that the person was vaccinated more than 14 days before the onset date, and for pandemic influenza A(H1N1)2009 vaccine it was assumed the person was vaccinated in 2009/10.

The same approach was used if date of onset was missing in a vaccinated individual. Respiratory samples with a delay greater than 29 days between onset of illness and sample collection were excluded as the sensitivity of the PCR test reduces for long intervals between onset and sampling. A sensitivity analysis was undertaken censoring at seven days between onset of illness and sample collection.

Vaccine effectiveness was estimated as 1-[odds ratio] using multivariable logistic regression models with influenza A(H1N1)2009 or influenza B PCR results as outcomes and seasonal or pandemic vaccination status

Table 1

Inclusion and exclusion criteria of participants for specimens submitted, United Kingdom, 1 September 2010 –11 January 2011

Criteria	Excluded	Included
1. Original participants		4,554
- Excluded as no PCR results available	538	
- Remaining participants		4,016
2. Influenza A(H1N1)2009 endpoint		
- Excluded as confirmed influenza B or A(H3)	535	
-Excluded as no result for influenza A(H1N1) 2009	1	
- Excluded as missing vaccination history	553[a]	
Interval between onset of illness and sample longer than 29 days	36	
- Final remaining study participants		*2,891*
3. Influenza A(H3)/B endpoint		
- Excluded as confirmed A(H1N1)2009	1,251	
-Excluded as not tested/no result for influenza B	8	
- Excluded as missing vaccination history	236	
Interval between onset of illness and sample longer than 29 days	34	
- Final remaining study participants		*2,487*

[a] Including eight people with sample taken later than 29 days after onset of illness.
PCR: Polymerase chain reaction.

Table 2

Details for pandemic influenza A(H1N1)2009 cases and controls, United Kingdom, September 2010 – January 2011 (n=3,480)[a]

	Number of controls (%) (n=2,229)	Number of cases (%) (n=1,251)
Age group (years)		
<5	224 (10.0)	93 (7.4)
5-14	217 (9.7)	130 (10.3)
15-44	1,030 (46.2)	734 (58.7)
45-64	526 (23.6)	272 (21.7)
≥65	215 (9.6)	16 (1.3)
Missing	17 (0.8)	6 (0.5)
Sex		
Male	843 (37.8)	514 (41.1)
Female	1,324 (59.4)	668 (53.4)
Missing	62 (2.8)	69 (5.5)
Month of sample collection		
September 2010	67 (3.0)	0 (0)
October 2010	436 (19.6)	24 (1.9)
November 2010	629 (28.2)	51 (4.1)
December 2010	934 (41.9)	1,096 (87.6)
January 2011	163 (7.3)	80 (6.4)
Missing	0 (0)	0 (0)
Interval from onset of illness to sampling (days)		
0-1	245 (11.0)	193 (15.4)
2-4	847 (38.0)	598 (47.8)
5-7	462 (20.7)	197 (15.7)
8-14	283 (12.7)	97 (7.8)
15-29	85 (3.8)	18 (1.4)
>29	36 (1.6)	8 (0.6)
Missing	271 (12.2)	140 (11.2)
Vaccination status		
Unvaccinated	1,567 (70.3)	1,022 (81.7)
Vaccinated 2009/10 season only	105 (6.7)	26 (2.1)
Vaccinated 2010/11 season only	78 (3.5)	22 (1.8)
Vaccinated in both seasons	86 (3.9)	21 (1.7)
Vaccination status missing (either 2009/10 season, 2010/11 season or both)	393 (17.6)	160 (12.8)
Surveillance scheme		
RCGP	1,529 (68.6)	775 (34.8)
RMN	239 (10.7)	171 (7.7)
HPS	410 (18.4)	250 (11.2)
Wales	51 (2.3)	55 (2.5)
Missing	0 (0)	0 (0)

HPS: Health Protection Scotland; RCGP: Royal College of General Practitioners' surveillance scheme; RMN: Health Protection Agency Regional Microbiology Network.

[a] Includes those with missing vaccination history and/or interval from onset of illness to sample longer than 29 days.

as the linear predictor. Age (coded into five standard age groups, <5 years, 5-14 years, 15-44 years, 45-64 years and ≥65 years), surveillance scheme (HPS, RCGP or RMN) and date of sample collection (month) were investigated as potential confounding variables.

All statistical analyses were carried out in R version 2.10.1.

Results

This report has information on 4,554 individuals from whom samples were collected during the study period. Of these, 3,204 samples were collected through the RCGP surveillance scheme, 469 through the RMN scheme, 743 through the HPS scheme and 138 through the Public Health Wales scheme.

Those excluded from the study because of missing information (including PCR results and available vaccination history) are summarised in Table 1. Date of onset of illness was missing for 521 persons (11.4%): these were still included in the analyses. In the analyses evaluating VE in preventing influenza A(H1N1)2009 infection, samples positive for influenza A(H3) or influenza B were excluded and vice versa. There were therefore 2,891 persons for whom data on both vaccination status (for both vaccines) and pandemic influenza A(H1N1)2009 infection was available. Similarly, there were 2,487 persons included in the estimation of trivalent vaccine for prevention of influenza B or A(H3).

Table 2 shows the distribution and completeness of the baseline characteristics of the study participants according to whether they were influenza A (H1N1)2009 cases or controls. Age group, surveillance scheme and time period were found to be significantly associated with a confirmed influenza A(H1N1)2009 infection (Table 2).

Vaccine effectiveness in prevention of influenza A(H1N1)2009 infection

Table 3 shows the number and proportion of samples positive for influenza A(H1N1)2009 virus according to vaccination status (three categories). Crude vaccine effectiveness is also shown.

Age group, time period and surveillance scheme were adjusted for in a multivariable logistic regression model. These were all significantly associated with having a positive swab result. Risk group was missing for 1,316 of 4,554 samples (29%), and this variable was therefore not included in the model. The total number of observations included was 2,872.

The adjusted VE estimates (Table 3) increased from 34% (95% CI: -10 - 60%) for vaccination only in 2009/10 to 46% (95% CI: 7 - 69%) for vaccination only in 2010/11 to 63% (95% CI: 37 - 78%) if vaccinated in both seasons. Persons who had received vaccination in both 2009/10 and 2010/11 seasons did not have a significantly higher VE compared to persons who received vaccine only 2009/10 (Wald test p=0.06). Persons vaccinated only in 2010/11 also did not have a significantly different VE compared to those vaccinated only in 2009/10 (Wald test p=0.45). The VE for 2010/11 trivalent vaccination, irrespective of previous pandemic vaccination status, was 51% (95% CI: 29 - 66%). Censoring samples taken more than seven days after symptom onset did not significantly change the VE estimates: the adjusted VE for those vaccinated last season was 44% (95% CI: 0 - 68%), for those vaccinated only this season was 63% (95% CI: 32 - 79%) and for those vaccinated both seasons was 64% (95% CI: 36 - 80%).

The adjustment for month had a large effect on the VE point estimate for the group vaccinated in 2009/10; it decreased from 62% (crude) to 34% after adjustment. This is because the number of people vaccinated in 2009/10 only decreases across months (whilst influenza A(H1N1)2009 incidence is increasing), whereas the number of people vaccinated in 2010/11 is increasing over time.

There was no evidence of significant effect modification of vaccine by age group (using the same five age groups, likelihood ratio test p=0.21), although some of the vaccine-age sub-groups did not have any PCR positive results among them.

Vaccine effectiveness in prevention of H3 or influenza B infection

Twenty-one of 216 persons vaccinated with trivalent influenza vaccine (9.7%) were positive for influenza B or A(H3) compared to 478 of 2,271 persons unvaccinated with trivalent influenza vaccine (21%). This gives a crude VE of 60% (95% CI: 36 - 75%). If adjusted

Table 3

Number and proportion of samples positive for influenza A(H1N1)2009 according to vaccination status, United Kingdom, September 2010 – January 2011

Vaccination status	Influenza A(H1N1)2009 positive/n (%)[a]	Crude vaccine effectiveness	Adjusted vaccine effectiveness
Unvaccinated	1,014/2,554 (39.7%)	-	-
Vaccinated season 2009/10 only	26/130 (20.0%)	62% (95% CI: 41 - 75%)	34% (95% CI: -10 - 60%)
Vaccinated 2010/11 season only	22/100 (22.0%)	57% (95% CI: 31 - 73%)	46% (95% CI: 7 - 69%)
Vaccinated in both seasons	21/107 (19.6%)	63% (95% CI: 40 - 77%)	63% (95% CI: 37 - 78%)

[a] Chi-square test p<0.001 on three degrees of freedom.

for age group, surveillance scheme and time period (month), adjusted VE was reduced to 50% (95% CI: 17 - 70%). There was no evidence of significant age–vaccine interaction (likelihood ratio test p=0.37).

Discussion

The swab-negative case -control study design is an established approach to estimate influenza vaccine effectiveness. A number of studies have recently been published on the methodology [9,10]. The potential limitations of the approach presented in this paper have been outlined previously and relate to convenience sampling; the potential for selection bias; missing data items and lack of information on risk status. The likely impact of each of these on VE estimates has been addressed earlier [3].

This study demonstrates three key findings: vaccination with this current season's trivalent influenza vaccine provides protection against both confirmed influenza A(H1N1)2009 and influenza B infection and immunisation with A(H1N1)2009 vaccine in 2009/10 followed by trivalent influenza vaccine this season provides better protection against confirmed influenza A(H1N1)2009 infection. Finally vaccination only last season with A(H1N1)2009 vaccine, seems to provide the least protection against confirmed influenza A(H1N1)2009 infection.

This study provides some of the first evidence that this season's trivalent influenza vaccine is effective in reducing confirmed influenza A(H1N1)2009 and B infection in persons consulting in primary care. This level of protection is consistent with several studies undertaken with trivalent influenza vaccines in the pre-pandemic era and is congruent with moderately good matching between the vaccine and the circulating influenza strain [5,6]. We found no evidence that protection was significantly different by age group; however it is likely that the study size was not sufficiently large to address this point specifically.

Although recently published work has demonstrated in several geographical settings, that the pandemic influenza A(H1N1)2009 vaccine was highly effective last season in preventing confirmed influenza A(H1N1)2009 infection that season [2,3], this study indicates that pandemic vaccine protection may not last across seasons. This corroborates recent findings from a longitudinal sero-epidemiological survey, which suggests that population A(H1N1)2009 antibody levels may start to reduce in the post-pandemic period, particularly in the 5-14-years old age-band [11]. Further work needs to be undertaken in this area. Our paper does suggest that within the data available at present there is a dose-response relationship and, that vaccination with this season's trivalent influenza vaccine of individuals who have already received monovalent A(H1N1)2009 vaccine last season produced the highest effectiveness compared to vaccination only in the 2010/11 season or vaccination with A(H1N1)2009 vaccine alone in the 2009/10 season. This reinforces the importance of the UK policy for vaccination of those who had received the monovalent vaccine in the previous season.

In conclusion, this study undertaken mid-season provides evidence that this season's trivalent influenza vaccine does provide protection against infection to both strains of influenza circulating this season (A(H1N1)2009 and influenza B) in Europe. It is important to note that more precision in this estimate will be available at the end of the season. The findings seem to provide some of the first published evidence that protection might wane following vaccination with influenza A(H1N1)2009 vaccine after 12 months and reinforces the recommendation that annual re-immunisation of target groups is required regardless of vaccination the previous season (including those vaccinated with an adjuvanted vaccine).

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Conflicts of interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that DM 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. All other authors declare they have no conflicts of interest.

References

1. Wichmann O, Stöcker P, Poggensee G, Altmann D, Walter D, Hellenbrand W, Krause G, Eckmanns T. Pandemic influenza A(H1N1) 2009 breakthrough infections and estimates of vaccine effectiveness in Germany 2009-2010. Euro Surveill. 2010;15(18):pii=19561. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19561.
2. Valenciano M, Kissling E, Cohen JM, Oroszi B, Barret AS, Rizzo C 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 Med. 2011;8(1):e1000388.

3. Hardelid P, Fleming DM, McMenamin J, Andrews N, Robertson C, SebastianPillai P, Ellis J, Carman W, Wreghitt T, Watson JM, Pebody RG. Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009-2010. Euro Surveill. 2011;16(2):pii=19763. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19763
4. Health Protection Agency. Department of Health. Pandemic influenza vaccine uptake amongst patient groups in primary in England 2009-10. Available from: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_121014.pdf
5. Skowronski DM, Masaro C, Kwindt TL, Mak A, Petric M, Li Y 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(15):2842-51.
6. Fleming DM, Andrews NJ, Elllis JS, Bermingham A, Sebastianpillai P, Elliot AJ et al. Estimating Influenza vaccine effectiveness using routinely collected laboratory data. J Epidemiol Community Health. 2010;64(12):1062-7
7. Gunson R, Maclean A, Davies E, Bennett S, Miller R, Carman WF. 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. J Virol Methods. 2010;163(2):258-61.
8. Ellis J, Iturriza M, Allen R, Bermingham A, Brown K, Gray J, Brown D. Evaluation of four real-time PCR assays for detection of influenza A(H1N1)v viruses. Euro Surveill. 2009;14(22):pii=19230. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19230.
9. Ferdinands JM, Belongia EA, Nwasike C, Shay DK. Influenza vaccination status is not associated with influenza testing among children: Implications for observational studies of vaccine effectiveness. Vaccine. 2011. [Epub ahead of print]
10. Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. Int J Epidemiol. 2007;36(3):623-31.
11. Hardelid P, Andrews N, Hoschler K, Stanford E, Baguelin M, Waight P et al. Assessment of baseline age-specific antibody prevalence and incidence of infection to novel influenza AH1N1 2009. Health Technol Assess. 2010;14(55):115-92.