Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection

R G Pebody (richard.pebody@hpa.org.uk)[1], N Andrews[1], J McMenamin[2], H Durnall[3], J Ellis[4], C I Thompson[4], C Robertson[5,6], S Cottrell[7], B Smyth[8], M Zambon[4], C Moore[7], D M Fleming[3], J M Watson[1]

1. Health Protection Agency Health Protection Services – Colindale, London, United Kingdom
2. Health Protection Scotland, Glasgow, United Kingdom
3. Royal College of General Practitioners Research and Surveillance Centre, Birmingham, United Kingdom
4. Health Protection Agency Microbiology Services – Colindale, London, United Kingdom
5. University of Strathclyde, Glasgow, United Kingdom
6. International Prevention Research Institute, Lyon, France
7. Public Health Wales, Cardiff, United Kingdom
8. Public Health Agency Northern Ireland, Belfast, United Kingdom

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The 2011/12 season was characterised by unusually late influenza A (H3N2) activity in the United Kingdom (UK). We measured vaccine effectiveness (VE) of the 2011/12 trivalent seasonal influenza vaccine (TIV) in a test-negative case–control study in primary care. Overall VE against confirmed influenza A (H3N2) infection, adjusted for age, surveillance scheme and month, was 23% (95% confidence interval (CI): -10 to 47). Stratified analysis by time period gave an adjusted VE of 43% (95% CI: -34 to 75) for October 2011 to January 2012 and 17% (95% CI: -24 to 45) for February 2012 to April 2012. Stratified analysis by time since vaccination gave an adjusted VE of 53% (95% CI: 0 to 78) for those vaccinated less than three months, and 12% (95% CI: -31 to 41) for those vaccinated three months or more before onset of symptoms (test for trend: p=0.02). For confirmed influenza B infection, adjusted VE was 92% (95% CI: 38 to 99). A proportion (20.6%) of UK influenza A(H3N2) viruses circulating in 2011/12 showed reduced reactivity (fourfold difference in haemagglutination inhibition assays) to the A/Perth/16/2009 2011/12 vaccine component, with no significant change in proportion over the season. Overall TIV protection against influenza A(H3N2) infection was low, with significant intraseasonal waning.

Introduction

Following the 2009 influenza pandemic and the first post-pandemic influenza season which was dominated by influenza A(H1N1)pdm09 virus activity, the United Kingdom (UK) experienced unusually late influenza activity in 2011/12, peaking only in week 8/2012 [1]. The dominant circulating influenza virus in 2011/12 was influenza A(H3N2), with the disease burden falling particularly on the elderly population, as evidenced by an increase in excess all-cause mortality and influenza outbreaks in nursing home settings. A number of these end-of-season outbreaks occurred in populations highly vaccinated with influenza vaccine [1]. Influenza B also circulated throughout the 2011/12 season, particularly in January and February 2012.

In 2011/12, the UK, like many other countries, utilised non-adjuvanted trivalent seasonal influenza vaccines (TIV) targeted at all those over 65 years of age and at those under the age of 65 years falling into a clinical risk group. The 2011/12 TIV contained the three influenza strains A/California/7/2009 (H1N1) pdm09-like virus, A/Perth/16/2009 (H3N2)-like virus, B/Brisbane/60/2008-like virus, as recommended by the World Health Organization (WHO) for the 2011/12 winter season in the northern hemisphere [1]. The vaccination programme started in September 2011 and reached an uptake of 74% in those over 65 years of age and 51.6% in those under 65 years of age falling into a clinical at-risk group by the end of January 2012 in England [2]. Early 2011/12 season estimates suggested a low to moderate VE against influenza A(H3) of 43% (95% CI: -0.4 to 67.7). The occurrence of late season outbreaks led to questions about whether protection had waned following the 2011/12 vaccination programme earlier in the season [3,4].

This study presents the end-of-season vaccine effectiveness (VE) for the 2011/12 seasonal TIV in preventing medically attended confirmed influenza A(H3N2) and B infection. It also examines the protective effect of vaccination at different points during the season and by time since vaccination, to determine if there is any evidence of intraseasonal waning protection. The results

are put into context with available antigenic data for circulating A(H3N2) viruses.

Methods

Study population and period

Data were derived from five primary care influenza sentinel surveillance schemes in England (two schemes), Scotland, Wales and Northern Ireland. Details of the Royal College of General Practitioners (RCGP), Health Protection Agency (HPA) Specialist Microbiology Network (SMN), Public Health Wales, Public Health Agency (PHA) of Northern Ireland and Health Protection Scotland (HPS) swabbing schemes have been presented previously [5].

The study period ran from 1 October 2011 to 16 April 2012. Cases were defined, as persons presenting during the study period in a participating GP practice with an acute influenza-like illness (ILI) who were swabbed and then tested positive for influenza A(H3N2) or B. A case of ILI was defined as an individual presenting in primary care with an acute respiratory illness with fever or complaint of feverishness. Patients were swabbed as part of clinical care, with verbal consent. Controls were individuals presenting with ILI in the same period who were swabbed and tested negative for influenza. Individuals testing positive for other influenza A types (including A(H1N1)pdm09) were excluded from the study.

A standardised questionnaire collected demographic, clinical and epidemiological information from cases and controls including date of birth, sex, defined underlying clinical risk group, date of onset of respiratory illness, date of specimen collection, and influenza vaccination status for 2011/12 with vaccination dates completed by the patient's responsible general practitioner.

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 [6,7]. Samples in England were sent to the HPA Microbiology Services, Colindale (RCGP scheme) or one of the specialist HPA microbiology laboratories (SMN 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. Influenza viruses were isolated in MDCK or MDCK-SIAT1 cells from RT-PCR positive samples as previously described [8]. Virus isolates were characterised antigenically using post-infection ferret antisera in haemagglutination inhibition (HI) assays, with guinea pig red blood cells [9]

Statistical methods

Persons were defined as vaccinated if date of vaccination with the 2011/12 TIV was 14 or more days before onset of illness. Those in whom the period between vaccination and onset of illness was less than 14 days were excluded, as their immune status was unclear. If the date of vaccination was missing, as the 2011/12 campaign occurred before influenza circulation, it was assumed that TIV vaccination was more than14 days before onset date. If date of onset of symptoms was missing then the date was assumed to have been four days before the swab was taken (the median interval based on the observed data). 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 decreases for long intervals between onset and sampling. A sensitivity analysis was also undertaken, censoring at seven days between onset of illness and sample collection.

VE was estimated as 1-(odds ratio) using multivariable logistic regression models with influenza A(H3N2) or influenza B PCR results as outcomes and seasonal vaccination status as the linear predictor. In the analyses evaluating VE in preventing influenza A(H3N2) infection, samples positive for influenza B were excluded, and vice versa. Age (coded into five standard age groups, <5 years, 5–14 years, 15–44 years, 45–64 years and ≥65 years), sex, clinical risk group, surveillance

Table 1

Inclusion and exclusion criteria of participants for specimens submitted, United Kingdom, October 2011–April 2012

Criteria	N Excluded	N Included
1. Original participants		**3,869**
Excluded as interval from onset to sampling >29 days	81	
Remaining participants		3,788
2. Analysis of TIV 2010/11		
Excluded as missing vaccination history	166	
Excluded as vaccinated 0–14 before onset	62	
Final remaining study participants		*3,560*
Final for assessment of influenza A(H3N2)		*3,517*
Final for assessment of influenza B		*3,184*

TIV: trivalent seasonal influenza vaccine.

Table 2

Details for influenza A(H3N2) and B cases and controls, United Kingdom, October 2011–April 2012 (n=3,869)

	Controls (N=3,428) n (%)	Influenza B cases (N=45) n (%)	Influenza A(H3N2) cases (N=396) n (%)
Age group (years)			
<5	257 (7.5)	3 (6.6)	57 (14.4)
5–14	292 (8.5)	10 (22.2)	65 (16.4)
15–44	1,609 (47.0)	18 (40.0)	160 (40.4)
45–64	834 (24.3)	12 (26.7)	86 (21.7)
65+	423 (12.3)	2 (4.4)	26 (6.6))
Missing	13 (0.4)	0 (0.0)	2 (0.5)
Sex			
Male	1,350 (39.4)	18 (40.0)	190 (48.0)
Female	2,052 (59.9)	27 (60.0)	201 (50.8)
Missing	26 (0.8)	0 (0.0)	5 (1.3)
Month of sample collection			
October	477 (13.9)	0 (0.0)	3 (0.8)
November	735 (21.4)	1 (2.2)	4 (1.0)
December	731 (21.3)	3 (6.7)	14 (3.5)
January	578 (16.9)	6 (13.3)	56 (14.1)
February	470 (13.7)	20 (44.4)	173 (43.7)
March	365 (10.7)	13 (28.9)	137 (34.6)
April	72 (2.1)	2 (4.4)	9 (2.3)
Surveillance scheme			
RCGP	1,748 (51.0)	23 (51.1)	267 (67.4)
SMN	305 (8.9)	12 (26.7)	31 (7.8)
HPS	1,198 (35.0)	9 (20.0)	89 (22.5)
Wales	61 (1.8)	0 (0.0)	0 (0.0)
Northern Ireland	116 (3.4)	1 (2.2)	9 (2.3)
Risk group			
No	2,365 (69.0)	33 (73.3)	301 (76.0)
Yes	709 (20.7)	6 (13.3)	60 (15.2)
Missing	354 (10.3)	6 (13.3)	35 (8.8)
Interval onset to sampling (days)			
0–1	338 (9.9)	4 (8.9)	62 (15.7)
2–4	1,223 (35.7)	22 (48.9)	193 (48.7)
5–7	812 (23.7)	11 (24.4)	80 (20.2)
8–14	506 (14.8)	5 (11.1)	22 (5.6)
15–29	236 (6.9)	1 (2.2)	10 (2.5)
≥29	74 (2.2)	0 (0.0)	7 (1.8)
Missing onset date	239 (7.0)	2 (4.4)	22 (5.6)
Vaccination status (only considering TIV)			
Unvaccinated	2,586 (75.4)	43 (95.6)	325 (82.1)
Vaccinated (0–13 days ago)	62 (1.8)	1 (2.2)	0 (0.0)
Vaccinated (14–91 days ago[a])	402 (11.7)	0 (0.0)	8 (2.0)
Vaccinated (>91 days ago[a])	221 (6.5)	1 (2.2)	50 (12.6)
Missing	157 (4.6)	0 (0.0)	13 (3.3)

HPS: Health Protection Scotland; RCGP: Royal College of General Practitioners' surveillance scheme; SMN: Health Protection Agency (HPA) Specialist Microbiology Network.

Note: Differences between cases and controls for all variables in this table were statistically significant.

[a] Where a date of vaccination was missing this was estimated by assuming vaccination was on 19 October 2011, the median time of vaccination in controls with onset in 2012.

scheme (RCGP, SMN, HPS, Wales, Northern Ireland) and date of sample collection (month) were investigated as potential confounding variables. To investigate whether the VE changed in relation to time since vaccination analyses stratifying influenza A(H3N2) VE by time since vaccination (<3 months, ≥3 months) and by period (October to January, February to April) were undertaken. To test for the significance of changes in VE with the time since vaccination, the multivariable logistic regression was performed in vaccinated individuals with days since vaccination (between vaccination and onset date) included as a continuous variable. As testing for evidence of waning was one of the primary study objectives of the study, multiple testing adjustments were not made.

All statistical analyses were carried out in Stata version 12 (StataCorp, College Station, Texas).

Results

A total of 3,893 individuals were swabbed in primary care during the study period. Six were excluded because they were positive for influenza A(H1N1) pdm09, two because the swab result was inconclusive and 16 because no laboratory result was available. This left 3,869 persons in the analysis. Table 1 summarises which of those individuals were excluded from the analysis of effectiveness.

Of these 3,869, 2,038 (52%) were collected from the RCGP scheme, 1,296 (33%) from the HPS scheme, 348 (9%) from the SMN scheme, 61 (2%) from the Public Health Wales Scheme and 126 (3%) from the Northern Ireland Scheme. The demographic and epidemiological characteristics of cases and controls are summarised in Table 2. There were statistically significant differences between cases and controls for all variables in Table 2. Vaccine date was unknown for 148 individuals who had received TIV. Although date of onset was missing for 263 (7%) individuals, these were included with onset date defined as swab date minus four days.

Model fitting for vaccine effectiveness estimation

When estimating vaccine effects, age group, sex, time period (defined by month of sample collection) 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 month of sample collection were confounders for the vaccine effects. Tables 3, 4 and 5 show vaccine effectiveness estimates against influenza A(H3N2) and B according to vaccination status and time since vaccination and period.

Vaccine effectiveness against influenza A(H3N2) infection

The adjusted VE estimate for TIV 2011/12 against influenza A(H3N2) was 23% (95% confidence interval (CI): -10 to 47). Stratifying by time period resulted in an adjusted VE for TIV 2011/12 of 43% (95% CI: -34 to 75) for the period October 2011 to January 2012, compared with 17% (95% CI: -24 to 45) for the period February 2012 to April 2012 (Table 3).

Table 3

Samples positive (cases) and negative (controls) for influenza A(H3N2) according to vaccination status and vaccine effectiveness estimates, United Kingdom, October 2011–April 2012 (n=3,517 for crude, n=3,474 for adjusted analysis)

Period	Vaccination status	Number of cases: controls	Crude VE % (95% CI)	Adjusted VE[a] % (95% CI)
Oct 2011–Apr 2012	Unvaccinated	320:2,531	26 (1 to 45)	23 (-10 to 47)
	Vaccinated	57:609		
Oct 2011–Jan 2012	Unvaccinated	60:1,861	42 (-22 to 73)	43 (-34 to 75)
	Vaccinated	8:430		
Feb 2012–Apr 2012	Unvaccinated	260:670	29 (1 to 50)	17 (-24 to 45)
	Vaccinated	49:179		

CI: confidence interval; VE: vaccine effectiveness.

[a] Adjusted for age group, sex, month and surveillance scheme.

Table 4

Samples positive (cases) and negative (controls) for influenza B according to vaccination status and vaccine effectiveness estimates, United Kingdom, October 2011–April 2012 (n=3,184 for crude, n=3,148 for adjusted analysis)

Period	Vaccination status	Number of cases: controls	Crude VE % (95% CI)	Adjusted VE[a] % (95% CI)
October 2011–April 2012	Unvaccinated	43:2,531	90 (30 to 99)	92 (38 to 99)
	Vaccinated	1:609		

CI: confidence interval; VE: vaccine effectiveness.

[a] Adjusted for age group, sex, month and surveillance scheme.

The adjusted age-specific estimates suggested protection was lower in the middle age groups (15 to 64 years), although the observed differences were not significant. There were significant differences in VE in relation to the interval since vaccination, with an adjusted VE of 53% (95% CI: 0 to 78) if the time from onset to vaccination was less than three months, compared with 12% (95% CI: -31 to 41) if the time was three months or more (test for trend: p=0.02).

The adjusted VE for TIV 2011/12 against influenza A(H3N2) with time since vaccination and interval from onset to swab included in the model is shown in Table 5. There was no significant difference in adjusted VE by scheme or by time from onset to swab (Table 5). Information on risk group was missing for 395 of 3,869 samples (10.2%) and was therefore not included in the final model. If risk group was included, the VE estimates remained unchanged.

Vaccine effectiveness against influenza B infection

The adjusted VE of TIV against influenza B was 92% (95% CI: 38 to 99) adjusted for age group, sex, time period and surveillance scheme. There no evidence that the VE varied by age group, although the numbers were small (with only a single vaccinated influenza B case with a B/Yamagata lineage infection). It was therefore not possible to stratify by time since vaccination, or by time period, to determine if there was reduction in protection.

Antigenic characterisation of circulating A(H3N2) viruses

The majority of the 160 A(H3N2) 2011/12 viruses analysed (79.4%) were antigenically similar to the A/Perth/16/2009 2011/12 H3N2 vaccine component, with some (20.6%) A(H3N2) viruses showing reduced reactivity in antigenic characterisation assays with antiserum

Table 5

Adjusted vaccine effectiveness estimates for influenza A(H3N2) by age, surveillance scheme and by time since vaccination, United Kingdom, October 2011–April 2012 (n=3,478)

Factor	Level	Adjusted VE[a] % (95% CI)	p value for VE varying across factor
Age	<5	52 (-446 to 96)	0.83
	5–14	69 (-172 to 97)	
	15–44	7 (-67 to 48)	
	45–64	11 (-56 to 49)	
	All <65	19 (-19 to 45)	
	≥65	48 (-50 to 82)	
Scheme	RCGP	36 (0 to 60)	0.37
	SMN[b]	-46 (-600 to 45)	
	HPS[b]	-4 (-107 to 48)	
	Wales	N too low	
	Northern Ireland	N too low	
Time since vaccination	<3 months	53 (0 to 78)	0.02[c]
	≥3 months	12 (-31 to 41)	
Interval onset to swab	<7 days	23 (-15 to 50)	0.69
	7 to 29 days or not known	29 (-72 to 70)	

CI: confidence interval; HPS: Health Protection Scotland; RCGP: Royal College of General Practitioners' surveillance scheme; RMN: Health Protection Agency (HPA) Specialist Microbiology Network, VE: vaccine effectiveness.

[a] Adjusted for age group, sex, month and surveillance scheme.

[b] Note that positive swabs from SMN and HPS were mainly taken after January 2012 with only four and six positive samples by January, respectively. RCGP had 65 positive swabs by January and gave a VE estimate for samples up to January of 50% (95% CI: -25 to 80), and one of 59% (95% CI: 1 to 83) for those vaccinated within three months before symptom onset.

[c] Test for trend using time since vaccination as continuous.

Table 6

Proportion of influenza A/H3N2 isolates with difference in haemagglutination inhibition assay titres compared to the A/Perth/16/2009 2011/12 H3N2 vaccine component, United Kingdom, October 2011–April 2012 (n=160)

Period	<4-fold difference in HI	4-fold difference in HI	>4-fold difference in HI
October 2011–January 2012	86.9% (20/23)	13.0% (3/23)	0% (0/23)
February 2012–April 2012	78.1% (107/137)	21.9% (30/137)	0% (0/137)
October 2011–April 2012	79.4% (127/160)	20.6% (33/160)	0% (0/160)

HI: haemagglutination inhibition.

raised against influenza A/Perth/16/2009 (fourfold difference in HI assays; Table 6). A more than fourfold difference in HI assay titres with reference antiserum is considered to be significant antigenic drift [10]. The proportion with a fourfold difference increased but did not change significantly over the duration of the 2011/12 season (from 13% in the period October 2011 to January 2012 to 21.9% in the period February 2012 to April 2012). Antigenic analysis of A(H3N2) virus isolates from combined sentinel and non-sentinel sources, confirmed the change in proportion over the two time periods to be non-significant (data not shown).

Discussion

This observational study of influenza VE for TIV against laboratory-confirmed influenza infection in primary care in the UK 2011/12 winter season, a late, low intensity influenza season with A(H3N2) as the dominant circulating strain, has several key findings: firstly, the 2011/12 seasonal influenza vaccine was overall poorly protective in preventing influenza A(H3N2) infection; secondly, vaccine protection was moderate in the first three months of the season, but reduced in the second three months; thirdly, there was evidence of waning protection against influenza A(H3N2) three months after vaccination; and finally, the 2011/12 TIV was highly protective against the circulating influenza B strain.

The test-negative case–control study design is becoming an increasingly well established approach to measure influenza vaccine effectiveness [11,12]. One criticism of the method relates to the selected control population (test-negatives). In fact, use of this control group of individuals consulting in primary care with a respiratory illness that is not influenza is believed to overcome differences in health-seeking behaviour between cases and controls. Another criticism relates to the inclusion of individuals who were tested up to 29 days after disease onset, rather than those tested within seven days of onset. It is argued that test sensitivity declines with time from onset to swab and that such an approach may result in misclassification of cases as controls. We demonstrated that restricting samples to those taken within seven days of symptom onset did not significantly change the estimated vaccine effectiveness, although it did lead to loss of power as individuals were discarded. We did not adjust for multiple testing because waning was a priori of interest and was an objective of the study. This study based on surveillance data only had access to limited information on confounders. However, observational VE studies based on routine electronic health data in primary care using RCGP data [13] suggest that the most important confounders have been captured in our analysis. Indeed in our paper, we found risk status was not an important confounding variable, and to maximise power it was not included in the final multivariable analysis.

Our study demonstrates that during the 2011/12 influenza season, the 2011/12 TIV was overall poorly effective (with a non-significant adjusted VE of 23%) in protecting against confirmed influenza A(H3N2) infection for persons consulting their general practitioner (GP) with an ILI. Early estimates from the 2011/12 season have been published by several other countries – including a pooled case–control study from several European countries [3] and a study from Spain [4], demonstrating a low to moderate VE (43% and 55% respectively). It has been postulated in these studies that this could be due to a combination of a poor match between the 2011/12 TIV A(H3N2) virus strain (A/Perth/16/2009) and the circulating A(H3N2) virus, and a waning protection. In the UK we found that the majority of characterised A(H3N2) viruses were antigenically similar to the vaccine component, with a notable proportion of A(H3N2) viruses showing some reduced reactivity in antigenic characterisation assays, but no significant change in that proportion over the duration of the 2011/12 season. Thus a certain degree of mismatch may explain the initial moderate protection, but does not seem to provide a complete explanation for the observed reduction in vaccine effectiveness over the course of the season and with increasing time since vaccination. These observations could challenge our current view on how mismatch is to be defined – an issue highlighted by Skowronski et al. [14]

An alternative explanation may be waning immunity. Our study demonstrates that influenza A(H3N2) vaccine effectiveness was higher in the first three months of the 2011/12 season compared to the last three months. In addition, TIV VE was moderate and significantly higher when disease onset was within three months of vaccination compared to three months or more. The UK, indeed, experienced an extremely late and mild influenza season in 2011/12, with influenza A(H3N2) activity not peaking until week 8 in 2012, such as has rarely been observed in previous GP weekly consultation data from RCGP (for example activity peaked in week 11 in 1993 when the dominant circulating strains were A(H1N1) and B, with both strains included in the vaccine). This present observation was accompanied by reports of outbreaks of influenza A(H3N2) in nursing home settings, which frequently had a high proportion of vaccinated persons [1]. Waning intraseasonal vaccine protection would provide an explanation for these observations. At least two published studies have demonstrated intraseasonal waning in antibody titre following seasonal influenza vaccination [15,16]. Bothshowed a significant reduction in antibody titre in elderly populations 20 to 22 weeks after vaccination. This would provide a biological explanation for our observed reduction in vaccine effectiveness over this particularly late season, where the median time from vaccination to disease onset was approximately three months. There are few reports of this in the literature: a large summertime outbreak due to circulation of a drifted A/Sydney/05/97-like (H3N2) virus reported in elderly tourists in Alaska was reported to have been

due to a combination of drift and waning immunity [17]. Our study was not adequately powered to be able to examine age-specific differences in waning and to determine if the effect was particularly marked in the elderly.

The 2011/12 TIV VE estimate against influenza B demonstrates high protection. This corresponds only partially with the virological data, which shows that in 2011/12, both B/Yamagata-lineage and B/Victoria-lineage influenza B viruses co-circulated in the UK. Furthermore the majority of influenza B circulated late in the season, like the A(H3N2) virus [1]. Thus although we were not able to formally examine if there had been a reduction in protection connected to either time in the season or time since vaccination, effectiveness against influenza B was still high at the end of the season, with single vaccine failure occurring in a person infected with the B/Yamagata-lineage non-vaccine strain.

In conclusion, this end of season study provides important evidence that the 2011/12 season's TIV provided good protection against influenza B, but overall poor protection against the dominant circulating influenza A(H3N2) virus. This observation seems to be at least partially related to waning protection. The relative contributions of waning immunity and vaccine mismatch are unclear. This highlights the importance of future work to examine this phenomenon further. The study, however, reinforces the recommendation that annual re-immunisation of target groups is required regardless of TIV vaccination the previous season. The concept that vaccine protection can be so short-lived provides a challenge for public health policy. Influenza immunisations are given before the start of the influenza season when vaccine becomes available. In many winters, protection will therefore be optimal when the peak period of activity occurs in the first half of the winter. Influenza activity, however, can occur in the second half of the winter season, when protection may be waning. This highlights the pressing need for the development of influenza vaccines which provide better and longer-lasting protection, whether in terms of antigen content or formulation, e.g. through the use of adjuvants. In the interval, until such vaccines become available, this poses a policy question about whether there is a role for a second dose of seasonal influenza vaccine in certain circumstances: for example, when faced with late season outbreaks particularly in the groups most at risk of complications.

Our findings reinforce the need for annual revaccination and for early intraseasonal estimates of vaccine effectiveness to provide information for public health action, in particular to inform the annual WHO recommendation for composition of the vaccine for the following season. The identification of low or moderate vaccine effectiveness may allow communication of public health messages to clinicians to suspect influenza infection even in their highly vaccinated populations and have a lower threshold for prescribing of antiviral drugs to prevent the worst complications of influenza.

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Conflict 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 three 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.

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