

Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results

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The 2014/15 influenza season in the United Kingdom (UK) was characterised by circulation of predominantly antigenically and genetically drifted influenza A(H3N2) and B viruses. A universal paediatric influenza vaccination programme using a quadrivalent live attenuated influenza vaccine (LAIV) has recently been introduced in the UK. This study aims to measure the end-of-season influenza vaccine effectiveness (VE), including for LAIV, using the test negative case-control design. The overall adjusted VE against all influenza was 34.3% (95% confidence interval (CI) 17.8 to 47.5); for A(H3N2) 29.3% (95% CI: 8.6 to 45.3) and for B 46.3% (95% CI: 13.9 to 66.5). For those aged under 18 years, influenza A(H3N2) LAIV VE was 35% (95% CI: -29.9 to 67.5), whereas for influenza B the LAIV VE was 100% (95% CI: 17.0 to 100.0). Although the VE against influenza A(H3N2) infection was low, there was still evidence of significant protection, together with moderate, significant protection against drifted circulating influenza B viruses. LAIV provided non-significant positive protection against influenza A, with significant protection against B. Further work to assess the population impact of the vaccine programme across the UK is underway.

Introduction

The United Kingdom (UK) has a longstanding selective influenza vaccination programme targeting individuals at an increased risk of developing severe disease following infection. This has been undertaken with a wide range of inactivated influenza vaccines that are available on the UK market. In 2013/14, the phased

roll-out of a universal childhood influenza vaccination programme with a newly licensed live attenuated influenza vaccine (LAIV) commenced. In 2014/15, all two, three and four year olds, children of school age (see below for details across the countries of the UK) and children aged from six months to 18 years of age in a clinical risk group, who did not have any contraindications to receive LAIV, were offered a quadrivalent LAIV. Influenza vaccine is offered to those groups older than six months of age with underlying clinical disease such as chronic heart or respiratory disease that put the patient at increased risk of serious illness from influenza or where influenza may exacerbate the underlying disease itself. For healthy school age children, different parts of the UK targeted different groups [1]: all primary school age children in Scotland and Northern Ireland; primary school and secondary school age children (11–13 years) in pilot areas in England and children aged 11–12 years in Wales. Adults in a target group are offered one of the inactivated vaccines available in the UK. In February 2014, northern hemisphere 2014/15 influenza vaccines were recommended by the World Health Organization (WHO) to contain the following components: an A/California/7/2009 (H1N1)pdm09-like virus; an A/Texas/50/2012 (H3N2)-like virus and a B/Massachusetts/2/2012-like B/Yamagata-lineage virus, plus a B/Brisbane/60/2008-like B/Victoria-lineage virus for quadrivalent vaccines [2].

Moderate levels of influenza activity circulated in the community in the UK in 2014/15, with influenza A(H3N2) the dominant strain for the majority of the

TABLE 1

Details of influenza A(H3N2) haemagglutinin sequences obtained from GISAID used in the phylogenetic analysis

Virus isolate	Segment ID/ Accession number	Country	Collection date (year- month-day)	Originating laboratory	Submitting laboratory
A/Hong Kong/5738/2014	EPI539806	China	2014-04-30	Government Virus Unit, Hong Kong (SAR)	National Institute for Medical Research, London, UK
A/Switzerland/9715293/2013	EPI530687	Switzerland	2013-12-06	Hopital Cantonal Universitaire de Geneves, Switzerland	National Institute for Medical Research, London, UK
A/Samara/73/2013	EPI460558	Russian Federation	2013-03-12	WHO National Influenza Centre, Saint Petersburg, Russian Federation	National Institute for Medical Research, London, UK
A/Texas/50/2012	EPI391247	United States	2012-04-15	Texas Department of State Health Services, Austin, USA	Centers for Disease Control and Prevention, Atlanta, USA
A/AthensGR/112/2012	EPI358885	Greece	2012-02-01	Hellenic Pasteur Institute, Athens, Greece	National Institute for Medical Research, London, UK
A/Stockholm/18/2011	EPI326139	Sweden	2011-03-28	Swedish Institute for Infectious Disease Control, Solna, Sweden	National Institute for Medical Research, London, UK
A/Perth/16/2009	EPI211334	Australia/ Western Australia	2009 (month and day unknown)	WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia	Centers for Disease Control and Prevention, Atlanta, USA
A/Glasgow/400003/2015	EPI175027	United Kingdom	2015-01-02	Gart Naval General Hospital, Glasgow, UK	National Institute for Medical Research, London, UK
A/Glasgow/400097/2015	EPI175028		2015-01-02		
A/Glasgow/400580/2014	EPI175029		2014-12-26		
A/Glasgow/401673/2014	EPI175030		2014-12-29		
A/Glasgow/401674/2015	EPI175031		2015-01-01		
A/Glasgow/401678/2015	EPI175032		2015-01-07		
A/Glasgow/431929/2014	EPI175077		2014-11-23		

GISAID: Global Initiative on Sharing All Influenza Data; UK: United Kingdom; USA: United States of America; WHO: World Health Organization.

season from December 2014, and influenza B from February to April 2015 [3]. The community impact of influenza A(H3N2) virus was predominantly seen in the elderly, with numerous outbreaks in care homes [3]. Admissions to hospital and intensive care units (ICU) were also observed though with some evidence of variation across the UK, with peak ICU numbers higher in England than in recent seasons and levels of excess mortality, particularly in the elderly, higher in England than the influenza season of 2008/09 when A(H3N2) was also the dominant subtype [3].

As in many northern hemisphere countries, the 2014/15 season was characterised by the emergence of A(H3N2) strains that were antigenically and genetically drifted from the 2014/15 H3N2 vaccine strain, A/Texas/50/2012 and more closely related to the A/Switzerland/9715293/2013 virus, the vaccine strain recommended for the forthcoming 2015/16 season [4]. Indeed, an interim mid-season UK estimate of seasonal influenza vaccine effectiveness (VE) calculated in January 2015 showed a low effectiveness of 3.4% (95% CI: -44.8 to 35.5) against laboratory-confirmed influenza infection in primary care [5]. Later in the

season, influenza B viruses circulated, with the majority antigenically and genetically distinguishable from the northern hemisphere 2014/15 B/Yamagata-lineage vaccine strain [3].

This study reports the final end-of-season VE findings for the 2014/15 seasonal influenza vaccine in preventing medically attended laboratory confirmed influenza A(H3N2) and B using the established primary care sentinel swabbing surveillance schemes across the UK by sub-type and age group [5,6]. In addition, the study examines the potential protective effect of vaccination of children (<18 years of age) using the newly licensed intranasally administered LAIV compared with the inactivated, injectable influenza vaccines, in a season when drifted strains circulated.

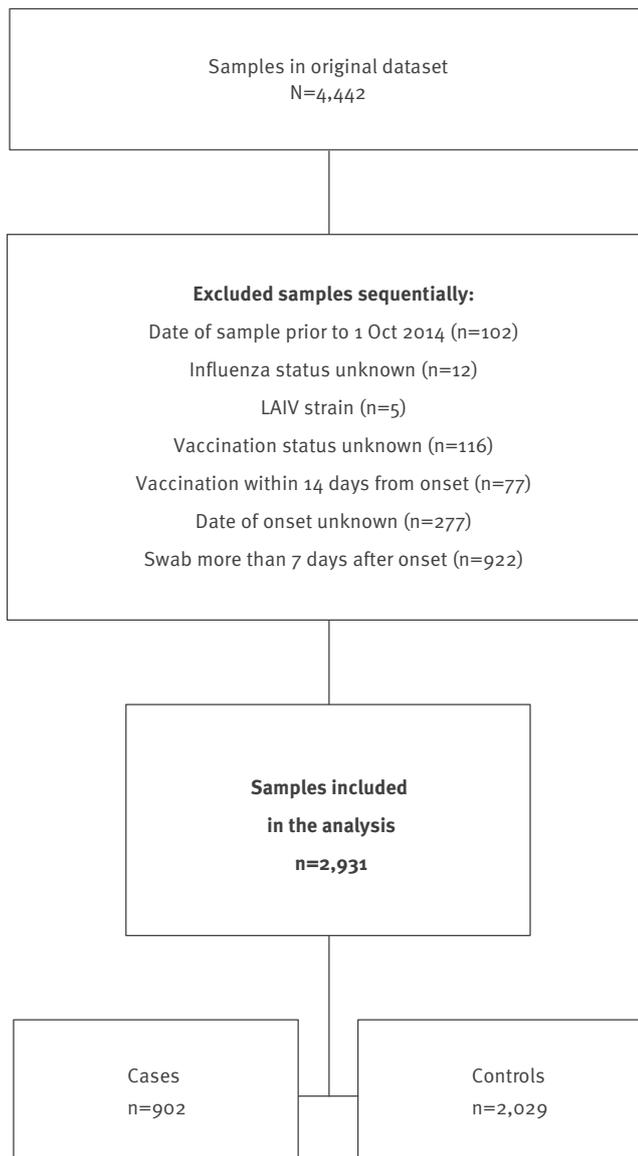
Methods

Study population and period

Data were obtained from five primary care influenza sentinel swabbing surveillance schemes in the UK from England (two schemes), Scotland, Wales and Northern Ireland. Details of the Royal College of

FIGURE 1

Swabbing results of ILI patients in primary care in the United Kingdom, October 2014 to April 2015 (n=4,442)



ILI: influenza-like illness; LAIV: live attenuated influenza vaccine.

General Practitioners (RCGP), Public Health England (PHE) Specialist Microbiology Network (SMN), Public Health Wales, Public Health Agency (PHA) of Northern Ireland and Health Protection Scotland (HPS) swabbing schemes have been published previously [6].

The study period ran from 1 October 2014 to 17 April 2015. A convenience sample of patients presenting with an influenza-like illness (ILI) were swabbed as part of clinical care, after having given verbal consent. Cases were defined as persons presenting during the study period in a participating General Practitioner (GP) practice with an ILI, who were swabbed and then tested positive for influenza A or B. ILI was clinically defined as an individual presenting in primary care with an acute respiratory illness with physician-diagnosed fever or complaint of feverishness in the previous

seven days. Controls were individuals presenting with ILI in the same period that were swabbed and tested negative for influenza.

A standardised questionnaire was completed by the GP while swabbing the patient during the consultation. Demographic, clinical and epidemiological information was collected 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 the 2014/15 season with vaccination dates. Information was collected on whether the vaccine was administered by injection or intranasally, with injection a proxy for inactivated influenza vaccine (IIV) and intranasal administration, a proxy for LAIV.

Laboratory methods

Samples in England were sent to the PHE Microbiology Services, Colindale (RCGP scheme) or one of the specialist PHE microbiology laboratories (SMN scheme). Samples in Northern Ireland were sent to the Regional Virus Laboratory, Belfast, in Scotland to the West of Scotland Specialist Virology Centre, Glasgow (HPS scheme), and in Wales to the Public Health Wales Specialist Virology Centre, Cardiff. All these laboratories participate in the UK Influenza Testing Laboratory Network and undertake testing annually of PHE molecular influenza detection external quality assurance scheme panels [7]. Laboratory confirmation of study samples was undertaken using comparable methods with real-time PCR (RT-PCR) assays capable of detecting circulating influenza A and influenza B viruses and other respiratory viruses [8,9]. Further strain characterisation was also performed; influenza viruses were isolated in MDCK or MDCK-SIAT₁ cells from RT-PCR positive samples from England as previously described [10,11]. Influenza virus isolates with a haemagglutination titre ≥ 40 were characterised antigenically using post-infection ferret antisera in haemagglutination inhibition (HI) assays, with guinea pig or turkey red blood cells [12].

Nucleotide sequencing of the haemagglutinin (HA) gene of a subset of influenza A(H3N2) viruses with H3 subtype PCR detection cycle threshold (Ct) values ≤ 32 , was undertaken. The samples selected were representative of vaccination status, date of sample collection, geographical location and antigenic characterisation (when available) across the study period. Sequencing was performed using an influenza A full genome amplification protocol [13] for sequencing on an Illumina MiSeq sequencer.

A phylogenetic tree was constructed with a neighbour-joining algorithm available in the Mega 6 software (<http://www.megasoftware.net>) [10]. HA sequences from reference strains used in the phylogenetic analysis were obtained from the EpiFlu database of the Global Initiative on Sharing Avian Influenza Data (GISAI) (Table 1).

TABLE 2

Details for influenza A and B cases (n=902) and controls (n=2,029), United Kingdom, October 2014 to April 2015

	Controls (n = 2,029)	B (n = 184)	A(H1N1) (n = 60)	A(H3N2) (n = 629)	A (untyped) (n = 31)	P value ^a
	n (%)	n (%)	n (%)	n (%)	n (%)	
Age group (years)						0.062
<18	507 (72.3)	33 (4.7)	16 (2.3)	142 (20.3)	4 (0.6)	
18–44	770 (69.1)	60 (5.4)	27 (2.4)	244 (21.9)	16 (1.4)	
45–64	502 (66.1)	79 (10.4)	16 (2.1)	157 (20.7)	6 (0.8)	
≥65	250 (71)	12 (3.4)	1 (0.3)	84 (23.9)	5 (1.4)	
Missing information	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	
Sex						0.077
Female	1,198 (70.6)	101 (5.9)	34 (2)	352 (20.7)	14 (0.8)	
Male	822 (67.5)	83 (6.8)	26 (2.1)	271 (22.2)	17 (1.4)	
Missing	9 (60)	0 (0)	0 (0)	6 (40)	0 (0)	
Surveillance scheme						<0.001
Northern Ireland	67 (55.4)	9 (7.4)	2 (1.7)	28 (23.1)	15 (12.4)	
RCGP	832 (65.5)	100 (7.9)	40 (3.1)	300 (23.6)	0 (0)	
SMN	235 (75.1)	15 (4.8)	3 (1)	54 (17.3)	6 (1.9)	
Scotland	867 (74)	60 (5.1)	15 (1.3)	221 (18.9)	10 (0.9)	
Wales	28 (51.9)	0 (0)	0 (0)	26 (48.1)	0 (0)	
Risk group^b						0.473
No	1,376 (68.7)	149 (7.4)	48 (2.4)	416 (20.8)	17 (0.8)	
Yes	479 (70.1)	28 (4.1)	6 (0.9)	158 (23.1)	12 (1.8)	
Missing	174 (71.3)	7 (2.9)	6 (2.5)	55 (22.5)	2 (0.8)	
Interval onset-swab (days)						<0.001
0–1	275 (67.1)	22 (5.4)	9 (2.2)	100 (24.4)	4 (1)	
2–4	975 (64.4)	108 (7.1)	34 (2.2)	380 (25.1)	20 (1.3)	
5–7	779 (77.4)	54 (5.4)	17 (1.7)	149 (14.8)	7 (0.7)	
Month						<0.001
October	222 (94.9)	2 (0.9)	2 (0.9)	7 (3)	1 (0.4)	
November	354 (94.4)	6 (1.6)	0 (0)	15 (4)	0 (0)	
December	417 (65.1)	4 (0.6)	6 (0.9)	209 (32.6)	5 (0.8)	
January	476 (61.7)	20 (2.6)	19 (2.5)	251 (32.5)	7 (0.9)	
February	311 (59.7)	51 (9.8)	17 (3.3)	128 (24.6)	14 (2.7)	
March	198 (64.1)	77 (24.9)	14 (4.5)	17 (5.5)	4 (1.3)	
April	51 (64.6)	24 (30.4)	2 (2.5)	2 (2.5)	0 (0)	
Vaccination status						0.104
Unvaccinated	1,507 (68.5)	151 (6.9)	53 (2.4)	469 (21.3)	21 (1)	
Vaccinated (14–91 days ago)	293 (73.8)	6 (1.5)	1 (0.3)	93 (23.4)	4 (1)	
Vaccinated (>91 days ago)	229 (68.4)	27 (8.1)	6 (1.8)	67 (20)	6 (1.8)	
Pilot area						0.002
No	725 (65.8)	91 (8.3)	28 (2.5)	253 (23)	6 (0.5)	
Yes	1,272(71.2)	91 (5.1)	32 (1.8)	368 (20.6)	25 (1.4)	
Missing	32(76.2)	2 (4.8)	0 (0)	8 (19)	0 (0)	
Vaccine administration method (under 18 only)						0.022
Injection	11 (55)	2 (10)	0 (0)	6 (30)	1 (5)	
Intranasal	66 (80.5)	0 (0)	3 (3.7)	13 (15.9)	0 (0)	
Missing	5 (62.5)	1 (12.5)	0 (0)	2 (25)	0 (0)	

RCGP: Royal College of General Practitioners; SMN: Specialist Microbiology Network.

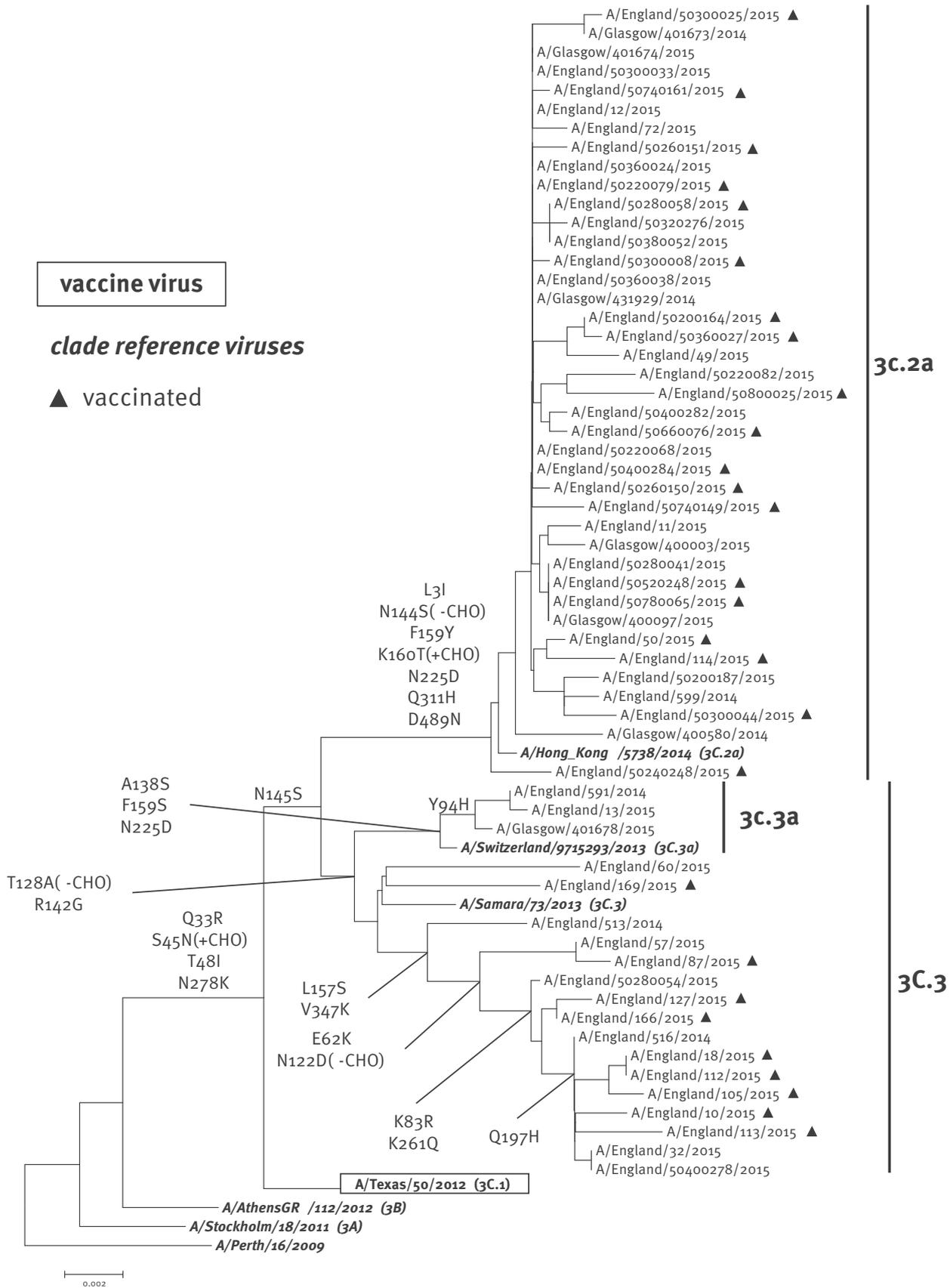
Two people were positive for both influenza B and influenza A (one H1N1, one H3N2).

^a Positive versus negative for influenza.

^b Individuals older than six months of age with underlying clinical disease such as chronic heart or respiratory disease that put the patient at increased risk of serious illness from influenza or where influenza may exacerbate the underlying disease itself.

FIGURE 2

Phylogenetic analysis of representative haemagglutinin sequences from United Kingdom influenza A(H3N2) 2014/15 viruses with reference viruses obtained from the GISAID EpiFlu database



Branch lengths are drawn to scale. Amino acid changes characteristic of genetic clades/subclades are marked on the tree.

TABLE 3

Samples positive (cases, n=902) and negative (controls, n=2,029) for influenza A and B according to vaccination status and VE estimates, United Kingdom, October 2014 to April 2015

	Cases (n=902)		Controls (n=2,029)		Crude VE (95% CI)	Adjusted ^a VE (95% CI)
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		
Influenza A or B	210	692	522	1,507	12.4% (-5.3 to 27.1)	34.3% (17.8 to 47.5)
Influenza A	177	543	522	1,507	5.9% (-14.6 to 22.7)	29.9% (10.5 to 45.1)
Influenza A/H3	160	469	522	1,507	1.5% (-20.9 to 19.8)	29.3% (8.6 to 45.3)
Influenza B	33	151	522	1,507	36.9% (6.9 to 57.3)	46.3% (13.9 to 66.5)

CI: confidence interval; VE: vaccine effectiveness.

^a Adjusted for age group, sex, month, pilot area and surveillance scheme.

The England HA sequences obtained in this study, which were also used in the phylogenetic analysis, were deposited in GISAID under the following accession numbers: EPI607577, EPI607585, EPI607593, EPI607601, EPI607609, EPI607617, EPI607625, EPI607633, EPI607641, EPI607649, EPI607657, EPI607665, EPI607673, EPI607681, EPI607689, EPI607697, EPI607705, EPI607713, EPI607721, EPI607729, EPI607737, EPI607745, EPI607753, EPI607761, EPI607769, EPI607777, EPI607785, EPI607793, EPI607801, EPI607809, EPI607817, EPI607825, EPI607833, EPI607841, EPI607849, EPI607857, EPI607865, EPI607873, EPI607881, EPI607889, EPI607899, EPI607914, EPI607930, EPI607945, EPI607960, EPI607975, EPI607990, EPI608006, EPI608022, EPI608038, EPI608051, EPI608067.

Statistical methods

Persons were defined as vaccinated if the date of vaccination with the 2014/15 influenza vaccine (either inactivated or live attenuated) was 14 or more days before onset of illness. To take into account the time taken for an immune response, those in whom the period between vaccination and onset of illness was less than 14 days, were excluded from the analysis. Those with a missing date of onset or an onset date more than seven days before the swab was taken, were excluded.

VE was estimated by the test-negative case-control (TNCC) design. In this design, VE is calculated as 1-(odds ratio, OR) obtained using multivariable logistic regression models with influenza A and B RT-PCR results as outcomes, and seasonal vaccination status as the linear predictor. No analysis was conducted for influenza A(H1N1)pdm09 because of the small number of cases. In the analyses evaluating VE for a specific type or subtype, those positive for other types/subtypes were excluded. Age (coded into four standard age groups, <18, 18-44, 45-64 and ≥65 years), sex, clinical risk group, surveillance scheme (RCGP, SMN, Scotland, Wales, Northern Ireland), pilot area and date of sample collection (month) were investigated as potential confounding variables. Pilot area was defined as those

parts of the UK where primary school-age vaccination was undertaken (England primary pilot areas, Scotland and Northern Ireland - all primary school age children). To investigate whether the VE changed in relation to time since vaccination, analyses stratifying VE by time since vaccination (less than three months, three months or longer) and by period (October to January, February to April) were undertaken. Where date of vaccination was not given, time since vaccination was estimated based on the assumption that vaccination occurred at the median vaccination date of 15 October 2014, and also treated as missing in a sensitivity analysis. VE was also assessed stratified by age group and scheme with differences in VE assessed by a likelihood ratio test between groups where numbers were not too low for a precise estimate. In addition, an analysis was performed just in those aged ≥18 years (in whom IIV would have been given). Finally, to estimate the VE for LAIV, an estimate was obtained in those aged under 18 years as well as for two, three and four year olds who had received the intranasal vaccine. A sensitivity analysis was undertaken to include all samples dropped from the main analysis due to late sampling (more than seven days after onset). A regression analysis was undertaken to compare the viral load using the Ct values for H3 detection by PCR in vaccinated and unvaccinated A(H3N2) laboratory-confirmed cases in samples from the RCGP scheme in England.

All statistical analyses were carried out in Stata version 13 (StataCorp, College Station, Texas).

Results

A total of 4,442 individuals were swabbed in primary care during the study period. For the VE analysis, 116 were excluded due to missing vaccination status, 277 due to missing date of onset, 922 because they were swabbed more than seven days after onset, 77 because they were vaccinated within 14 days of onset and five because of vaccine (LAIV) contamination of samples (Figure 1).

TABLE 4

Adjusted vaccine effectiveness estimates for influenza by age, surveillance scheme, LAIV pilot area and by risk group in >18 year olds, United Kingdom, October 2014 to April 2015 (n = 2,228)

Factor	Level	Adjusted VE ^a % (95% CI) by type		
		A	A(H3N2)	B
Age (years)	>18	30.4 (8.4 to 47.2)	29.4(5.8 to 47.1)	43.6(5.5 to 66.3),
	18–44	34.5 (–3.0 to 58.4)	30.3 (–12.4 to 56.7)	40.4 (–50.9 to 76.5)
	45–64	32.4 (–1.8 to 55.2)	31.1 (–5.8 to 55.2)	49.2 (–0.4 to 74.3)
	≥65	30.2 (–46.4 to 66.7)	32.6 (–44.5 to 68.6)	–203 (–2,300 to 61.7) ^b
	18–64	33.4 (10.5 to 50.5)	31.2 (6.1 to 49.6)	41.9 (0.1 to 66.1)
Scheme	RCGP	41.5 (19.9 to 57.3)	37.7 (13.5 to 55.1)	24.4 (–30.2 to 56.1)
	SMN	–13 (–152.6 to 49.4)	–23.6 (–192.2 to 47.2)	66.2 (–79.4 to 93.6)
	Scotland	23.1 (–9.4 to 46)	19.2 (–16.2 to 43.8)	81.5 (47.2 to 93.5)
	Wales	–41 (–458.6 to 64.4)	–41 (–458.6 to 64.4)	No influenza B
	Northern Ireland	21.7 (–150.3 to 75.5)	44.5 (–122.6 to 86.2)	–18.7 (–539.4 to 78) ^b
Pilot area	Non-pilot	33.9 (1.5 to 55.7)	32.5 (–2.9 to 55.7)	34.2 (–28.4 to 66.3)
	Pilot	25.4 (–2.3 to 45.6)	24.5 (–5.3 to 45.8)	57.4 (13.8 to 78.9)
Risk group ^c	≥65 or in a risk group	34.8 (3.1 to 56.2)	32.4 (–2.4 to 55.3)	15.5 (–107.6 to 65.6)
	In a risk group	32.5 (–3.4 to 55.9)	30.0 (–9.3 to 55.2)	40.6 (–55.6 to 77.3)

CI: confidence interval; RCGP: Royal College of General Practitioners Research and Surveillance Centre; SMN: Specialist Microbiology Network; VE: vaccine effectiveness.

^a Adjusted for age group, sex, month, pilot area and surveillance scheme.

^b Unadjusted 95% confidence interval.

^c Individuals older than six months of age with underlying clinical disease such as chronic heart or respiratory disease that put the patient at increased risk of serious illness from influenza or where influenza may exacerbate the underlying disease itself.

The details of those remaining in the study (n=2,931) are given in Table 2 according to the swab result. Positivity rates differed significantly by surveillance scheme, interval from onset and pilot area.

Strain characterisation

During the 2014/15 season, the PHE Respiratory Virus Unit (RVU) isolated and antigenically characterised 84 A(H3N2) influenza viruses received through the two primary care influenza sentinel swabbing surveillance schemes in England. The majority were antigenically similar to the A/Texas/50/2012 H3N2 northern hemisphere 2014/15 vaccine strain, however 26 showed reduced reactivity in antigenic tests with A/Texas/50/2012 antiserum. These 26 isolates were antigenically similar to A/Switzerland/9715293/2013, the H3N2 virus selected for the 2015/16 northern hemisphere influenza vaccine [2]. A/Switzerland/9715293/2013 is related to, but antigenically and genetically distinguishable, from the A/Texas/50/2012 vaccine virus. One virus isolate was antigenically similar to A/England/507/2014, a reference virus from the 3C.2a genetic clade.

Genetic characterisation of A(H3N2) viruses was performed by both RVU and the West of Scotland laboratory. Of 118 A(H3N2) viruses from samples received through the RCGP scheme in England and characterised genetically by RVU, some of which did not grow sufficiently to be able to be antigenically characterised, and

149 A(H3N2) viruses genetically characterised by the West of Scotland laboratory, the majority (192; 72%) fall into the haemagglutinin (HA) genetic subgroup 3C.2a and 7 (3%) fall into another HA subgroup, 3C.3a; viruses from both of these HA genetic subgroups have been shown to be antigenically distinguishable from the 2014/15 A(H3N2) vaccine virus [4]. The remaining 68 (25%) H3N2 viruses sequenced had HA genes which belong in genetic group 3C.3, which is antigenically similar to the 2014/15 A(H3N2) vaccine virus.

Of 45 influenza B viruses isolated and antigenically characterised as belonging to the B/Yamagata/16/88 lineage by RVU, 41 showed reduced reactivity in antigenic tests (≥four-fold difference) with antiserum to the 2014/15 northern hemisphere B/Yamagata-lineage trivalent and quadrivalent vaccine virus, B/Massachusetts/2/2012, with 29 of these 41 isolates showing significant (>four-fold difference) reduced reactivity, indicative of antigenic drift. These 41 isolates were antigenically similar to B/Phuket/3073/2013, the influenza B/Yamagata lineage virus selected for 2015/16 northern hemisphere influenza vaccines. B/Phuket/3073/2013 is related to, but antigenically and genetically distinguishable, from the B/Massachusetts/2/2012 vaccine virus. Three influenza B viruses have been isolated and antigenically characterised as belonging to the B/Victoria/2/87 lineage, similar to the influenza B/Victoria-lineage component

TABLE 5

Adjusted vaccine effectiveness estimates for influenza by age, type of vaccine and pilot area in <18 year olds, United Kingdom, October 2014 to April 2015 (n = 701)

Factor	Level	Adjusted VE ^a % (95% CI) by type		
		A	A(H3N2)	B
Age	2,3,4 years	58.5 (-31.4 to 86.9)	69.2 (-30.9 to 92.7)	100 (-82.5 to 100) ^b
	2,3,4 years intranasal	52.5 (-54.3 to 85.4)	65.7 (-50.1 to 92.1)	100 (-112.8 to 100) ^b
	<18 years intranasal	31.2 (-29.5 to 63.4)	35.0 (-29.9 to 67.5)	100 (17 to 100) ^b
	<18 years injection	-69.4 (-409.3 to 43.7)	-73.2 (-456.9 to 46.2)	-123.7 (-1,343 to 65.3)
	<18	17.5 (-41.1 to 51.7)	19.1(-44.1 to 54.6)	59.4(-48.1 to 88.8)
Pilot area	Non-pilot	38.1 (-64.7 to 76.7)	37.9 (-77.6 to 78.3)	50 (-205.4 to 91.8)
	Pilot	5.9 (-82 to 51.4)	5.4 (-92.4 to 53.4)	76.9 (-99.4 to 97.3)

CI: confidence interval;; RCGP: Royal College of General Practitioners Royal College of General Practitioners Research and Surveillance Centre; SMN Specialist Microbiology Network; VE: vaccine effectiveness.

^a Adjusted for age group, sex, month, pilot area and surveillance scheme.

^b Unadjusted Cornfield 95% confidence interval.

(B/Brisbane/60/2008) of the 2014/15 northern hemisphere quadrivalent vaccine. The West of Scotland laboratory genetically characterised 184 influenza B viruses by real-time PCR; 171 (93%) fell within the B/Yamagata lineage and 13 (7%) within the B/Victoria lineage. Of these, 37 B/Yamagata lineage viruses were sequenced and all genetically characterised as B/Phuket/3073/2013-like, which is antigenically distinguishable from the B/Yamagata vaccine virus. Four B/Victoria lineage viruses were genetically characterised as B/Brisbane/60/2008-like, which matches the B/Victoria lineage component of the quadrivalent vaccine. Figure 2 shows the phylogenetic characteristics of the HA of circulating A(H3N2) strains.

Model fitting for vaccine effectiveness estimation

When estimating vaccine effects, age group, sex, time-period (defined by month of sample collection), pilot area 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 (changed the estimate by more than 5% as previously described [5,6]). Information on risk group was missing for 244 of 2,931 samples (8.3%) and was therefore not included in the final model. If risk group was included, it was found not to be associated with being positive and the VE estimates remained similar.

Tables 3, 4 and 5 show vaccine effectiveness estimates against influenza A (overall), A(H3N2) and B in all ages, ≥18 year olds and <18 year olds. The overall influenza VE was respectively 34.3% (95% CI: 17.8 to 47.5) for all ages; 34.7% (95% CI: 16 to 49.3) for those ≥18 year of age and 25.2% (95% CI: -23.3, 54.7) for those <18 years. Further breakdown by age is shown in Table 4.

Vaccine effectiveness against influenza A virus infection

The adjusted overall VE against influenza A was 29.9% (95% CI: 10.5 to 45.1), very similar to the estimate seen specifically for A(H3N2) of 29.3% (95% CI: 8.6, 45.3) (Table 3) reflecting the dominance of A(H3N2).

The VE for A(H3N2) for the period October 2014 to January 2015 was 23.6% (95% CI: -2.9 to 43.2) compared with 47.8% (95% CI: 10 to 69.7) for the period February to April 2015. VE for A(H3N2) for those vaccinated within three months of onset of illness was 24.6% (95% CI: -2.7 to 44.6) compared with 34.4% (95% CI: 3.5 to 55.4) for those vaccinated more than three months before onset of illness.

For those aged 18 years and over, the influenza A VE was 30.4% (95% CI: 8.4 to 47.2) and for A(H3N2), it was 29.4% (95% CI: 5.8 to 47.1) (Table 4). The results were very similar for 18–44, 45–64 and ≥65 year olds, although with broader CIs for both influenza A and for A(H3N2). The VE against influenza A in the specific inactivated influenza vaccine (IIV) target groups (aged ≥65 or in a clinical risk group) was 34.8% (95% CI: 3.1 to 56.2), with a similar result for A(H3N2). Although the VE showed some variability across the various surveillance schemes, this difference was not significant.

For those aged under 18 years, the influenza A VE was 17.5% (95% CI: -41.1 to 51.7) and for A(H3N2) 19.1% (95% CI: -44.1 to 54.6) (Table 5). There was no evidence of a significant difference in effectiveness in pilot and non-pilot areas. The estimate for vaccines administered by injection (VE = -69.4% (95% CI: -409.3 to 43.7%)) was non-significantly lower than for vaccine administered intranasally (VE = 31.2% (95% CI: -29.5 to 63.4)). The estimates were very similar for A(H3N2) compared with those for influenza A overall. The results were also

similar for the sub-analysis in 2–4 year olds, with more uncertainty.

A regression analysis of the viral load (Ct values) in the A(H3N2) unvaccinated (n=227) and vaccinated (n=73) laboratory-confirmed cases received through the RCGP sentinel scheme in England, taking into account the number of days between onset and swab, found no statistically significant difference (p=0.266) between the two groups. The mean difference in Ct values (not vaccinated – vaccinated) was –0.668 (95% CI: –1.848 to 0.512).

Vaccine effectiveness against influenza B virus infection

The adjusted overall VE against influenza B was 46.3% (95% CI: 13.9 to 66.35 (Table 3). The VE for influenza B for those aged 18 and over was 43.6% (95% CI: 5.5 to 66.3), with similar results for the 18–44 and 45–64 age groups, although with broader confidence intervals.

The VE against influenza B in the vaccine target group (aged ≥65 or in a risk group) was 15.5% (95% CI: –107.6 to 65.6). Influenza B VE also showed some variability across the schemes although this difference was not significant (Table 4).

VE for those aged under 18 years of age for influenza B was 59.4% (95% CI: –48.1 to 88.8), with the estimate for vaccine administered by injection (VE=–123.7% (95% CI: –1,343 to 65.3) lower, but not statistically significant, compared with that for vaccine administered intranasally, which did show evidence of significant protection (VE=100%, 95% CI: 17 to 100.0). The results were similar for the sub-analysis in 2–4 year olds.

A sensitivity analysis for influenza A and B including all discarded samples (n=922) due to late sampling (more than seven days after onset) did not lead to large changes in these point estimates, but slightly narrowed confidence intervals (data not shown).

Discussion

This study presents the end of season VE results for the 2014/15 season, when the UK experienced circulation of both a drifted influenza A(H3N2) strain, followed by a drifted influenza B strain. This occurred in a season with a newly introduced universal paediatric influenza vaccination programme with a recently licensed live attenuated influenza vaccine. Our analysis finds that influenza A(H3N2) VE, unlike that for influenza B, was low, though nonetheless effective, in key target groups. Influenza B effectiveness was preserved despite the apparent drift of the main circulating B strains from the associated vaccine strain. Finally, there was a suggestion of effectiveness of LAIV in children against both influenza A and B.

The UK, as several other northern hemisphere countries, experienced circulation of an antigenically and genetically drifted A(H3N2) strain, which was associated in particular with impact in the elderly, with

levels of excess mortality higher than seen in the last substantial A(H3N2) season in 2008/09 [1,4]. The VE results presented in this paper indicate an overall effectiveness against medically attended laboratory-confirmed influenza in primary care of ca 30%, which although lower than would be anticipated for a well- or moderately matched influenza vaccine, still indicates some clinically beneficial protection against the drifted strain. The age-specific estimates in the over 18 year olds (which will represent the effect of IIV) were broadly similar in the elderly and clinical at-risk groups. These end-of-season VE results, although low, are non-significantly higher than the mid-season point-estimate (of 3.4%) undertaken in January 2015 had suggested [5], and which had mirrored the findings elsewhere, in particular in Canada and North America [14,15]. Previous interim, mid-season estimates have usually provided a good indication of the final end-of-season measure, albeit with more uncertainty as they are based on a smaller sample size. The apparent difference this season could be due to a range of potential factors. The higher overall VE will be partially explained by the higher VE against influenza B which circulated later in the season, though this will not explain the difference in the point estimate for influenza A. One explanation for this observation might be changes in the circulation of A(H3N2) genetic sub-groups over the season, however there was no significant change in the monthly proportion of A(H3N2) for genetic groups 3C.3 and 3C.2a (data not shown) over the season, and random variation seems to provide the most likely explanation for our observed non-significant difference between VE at the middle and the end of the season. The mid-season estimates, with all their uncertainty, did nonetheless provide an early indication of lower effectiveness of the A(H3N2) component of the seasonal influenza vaccine and was important for public health action purposes to highlight the value of other interventions, in particular use of antivirals for treatment and prophylaxis.

Influenza A(H3N2) is generally considered to be associated with more severe disease in the elderly and the lower VE seen this season is likely to have been a contributory factor to the relatively severe impact of influenza observed this year. The last intense H3N2 season was in 2008/09, where even in a season with a moderately matched H3N2 vaccine component with high coverage in the elderly, significant levels of excess mortality in the >65 year olds was still seen [16]. These observations highlight the limitations of the traditional, selective influenza vaccination policy of targeting groups at higher risk of severe disease such as the elderly and were part of the rationale for the introduction of the live attenuated influenza vaccination programme for healthy children, which attempts to not only provide direct protection to the children themselves, but to also reduce transmission of influenza and thus provide indirect protection to the rest of the population.

The main circulating influenza B strain this season was also drifted, with the dominant circulating B strain being of the B/Yamagata/16/88 lineage, but with reduced antigenicity to the 2014/15 northern hemisphere B/Yamagata-lineage vaccine virus, B/Massachusetts/2/2012 [1]. However, despite this virological finding, the overall influenza B VE was still moderately high at almost 50% effectiveness against the main circulating B strains and highlights the importance of observational VE studies to fully understand the clinical impact of drift when it occurs, and also the fact that tri/quadrivalent influenza vaccines provide potential protection against all these seasonal influenza types and subtypes. It is also important to note that the B viruses circulating this season are also antigenically similar to B/Phuket/3073/2013, the influenza B/Yamagata lineage virus selected for 2015/16 northern hemisphere influenza vaccines [17].

It is important to note that several of the sub-analyses, particularly stratifying VE by age, pilot area and scheme, result in estimates with lower precision. There were no significant differences in VE by these co-variables although the point estimates for VE against influenza A were different. These differences are likely to be chance fluctuations due to small numbers and highlight the need for large numbers of swabs to improve the power of such subgroup analyses.

Despite these limitations, for the under 18 year olds, our results provide evidence of significant effectiveness for the live attenuated intranasally administered vaccine for influenza B, albeit based on limited numbers. The LAIV VE estimate for influenza A indicated non-significant protection and is congruent with the published literature indicating that LAIV can provide cross-protection against drifted strains [18-20]. Although the US [18], has dropped its preferential recommendation for the use of LAIV in children, the UK findings are particularly encouraging for this season, with the circulation of both A(H3N2) and B drifted strains and support the rationale for the introduction of the universal paediatric programme. Further work is underway to examine the population impact of the childhood influenza vaccine programme by comparing pilot and non-pilot school age programme areas in England and across the UK to investigate in particular the presence and size of any indirect effects of the programme.

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Conflict of interest

Dr Matthew Donati received lecture fees from Sanofi-Pasteur MSD which produces influenza vaccines. None of the other co-authors have any conflicts of interest to declare.

Authors' contributions

RGP wrote the first draft; FW and NA led on the statistical analysis; all co-authors contributed epidemiological and/or virological data, contributed to the interpretation of the results, reviewed the early draft and approved the final version.

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