Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 mid-season results

R Pebody 1, F Warburton 1, J Ellis 1, N Andrews 1, A Potts 2, S Cottrell 3, J Johnston 1, A Reynolds 2, R Gunson 5, C Thompson 1, M Galiano 1, C Robertson 4, D Mullett 7, N Gallagher 4, M Sinnathamby 1, I Yonova 8, C Moore 3, J McMenamin 2, S de Lusignan 7, M Zambon 1

1. Public Health England, London, United Kingdom
2. Health Protection Scotland, Glasgow, United Kingdom
3. Public Health Wales, Cardiff, United Kingdom
4. Public Health Agency Northern Ireland, Belfast, United Kingdom
5. West of Scotland Specialist Virology Centre, Glasgow, United Kingdom
6. University of Strathclyde, Glasgow, United Kingdom
7. University of Surrey, Guildford, United Kingdom
8. Royal College of General Practitioners, Research and Surveillance Centre, London, United Kingdom

Correspondence: Richard Pebody (richard.pebody@phe.gov.uk)


In 2015/16, the influenza season in the United Kingdom was dominated by influenza A(H1N1)pdm09 circulation. Virus characterisation indicated the emergence of genetic clusters, with the majority antigenically similar to the current influenza A(H1N1)pdm09 vaccine strain. Mid-season vaccine effectiveness (VE) estimates show an adjusted VE of 41.5% (95% confidence interval (CI): 3.0–64.7) against influenza-confirmed primary care consultations and of 49.1% (95% CI: 9.3–71.5) against influenza A(H1N1)pdm09. These estimates show levels of protection similar to the 2010/11 season, when this strain was first used in the seasonal vaccine.

Introduction

The United Kingdom (UK) has had for many years an influenza vaccination programme using inactivated influenza vaccine targeted at individuals at higher risk of severe disease such as the elderly and under 65-year-olds in a clinical risk group. The 2015/16 influenza season is the third where an intranasally administered live attenuated influenza vaccine was provided to children [1]. This winter has been characterised by circulation of mainly influenza A(H1N1)pdm09, with evidence of hospitalisations and admissions to the intensive care unit (ICU) particularly in younger adults 15 to 64 years of age [2]. Influenza A(H1N1)pdm09 previously circulated in the UK in 2013/14, 2012/13 and particularly in 2010/11, the first post-pandemic season where particular impact was seen in younger adults. The 2015/16 season has also seen a large number of school and hospital outbreaks with evidence of excess all-cause mortality in 15 to 64 year-olds using the EuroMoMo standard algorithm [2].

The UK has long-standing systems to measure influenza vaccine effectiveness (VE) in the middle and at the end of the season [3,4]. The aims of the present study were to provide early season estimates of influenza VE to inform influenza prevention and control measures both for the remainder of this season and for the World Health Organization (WHO) northern hemisphere meeting that was held in February 2016 to decide influenza vaccine composition for the forthcoming 2016/17 season.

Methods

Study population and period

Five primary care influenza sentinel swabbing surveillance schemes from England (two schemes), Scotland, Wales and Northern Ireland provided data. Information on the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), Public Health England (PHE) Specialist Microbiology Network (SMN), Public Health Wales, Public Health Agency (PHA) of Northern Ireland and Health Protection Scotland (HPS) schemes have been provided in earlier publications [4].

The time of investigation ran from 1 October 2015 to 22 January 2016. Patients were swabbed during their consultation, with verbal consent. Cases were defined as patients presenting to a general practitioner (GP) in a participating practice with an acute influenza-like
illness (ILI) who tested positive for influenza A or B viruses by real-time PCR. Controls were individuals presenting with ILI in the same period who tested negative for influenza. ILI was defined as an individual presenting in primary care with an acute respiratory illness with physician-diagnosed fever or complaint of feverishness.

A standardised form was completed by the GP during the consultation. Demographic, epidemiological and clinical information was collected from participants, including date of birth, sex, defined underlying clinical risk group, date of specimen collection, date of onset of respiratory illness, and influenza vaccination status for the 2015/16 season with vaccination dates and route of administration (injection/intranasal). It was also recorded (in England, Scotland and Northern Ireland) whether the patient was resident in an area where a primary school-age programme was in operation.

Laboratory methods
Sentinel samples from the GP surveillance networks were sent to the national laboratories as previously described [4]. Laboratory confirmation was undertaken at all sites using comparable real-time PCR methods capable of detecting circulating influenza A and influenza B viruses and other respiratory viruses [5,6]. In addition, hospital diagnostic laboratories submitted samples in which influenza virus had been detected to the reference laboratories from a selection of cases (including severe cases and vaccinated cases) for further strain characterisation. Influenza viruses from all sources (both sentinel and non-sentinel) were isolated from PCR-positive samples in Madin-Darby canine kidney epithelial (MDCK) cells or MDCK cells containing the cDNA of human 2,6-sialtransferase (SIATs) cells as previously described [7,8].

Influenza A(H1N1)pdm09 virus isolates with a haemagglutination titre ≥ 40 were characterised antigenically using post-infection ferret antisera in haemagglutination inhibition (HI) assays, with turkey red blood cells [9]. Reference virus strains used for HI assays included A/California/7/2009 (vaccine strain) grown in embryonated chicken eggs, and other A(H1N1)pdm09 England strains were grown in embryonated chicken eggs or tissue culture cells. The fold difference between the homologous HI titre for egg-grown A/California/7/2009 and the HI titre for each clinical isolate was calculated to determine antigenic similarity of clinical isolates to the vaccine strain.

Nucleotide sequencing of the haemagglutinin (HA) gene of a subset of influenza A(H1N1)pdm09 viruses selected to be representative of the range of the patients’ age, date of sample collection, geographical location and antigenic characterisation of the virus isolate, if performed, was undertaken (primer sequences available on request), and phylogenetic trees were 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 (GISAID) (Table 1).

The HA sequences from England obtained in this study, which were also used in the phylogenetic analysis, were deposited in GISAID under the following accession numbers: EPI679151, EPI679186, EPI679213, EPI679221, EPI679245, EPI679266, EPI679300, EPI679313, EPI711775, EPI711780, EPI711788, EPI711796, EPI711804, EPI711812, EPI711820, EPI711828, EPI711834, EPI711842, EPI711850, EPI711858, EPI711866, EPI711873, EPI711881, EPI711888, EPI711893, EPI711901, EPI711909, EPI711917, EPI711925, EPI711930, EPI711938, EPI711943, EPI711951, EPI711959, EPI711967, EPI711975, EPI711983, EPI711991, EPI711996, EPI712002, EPI712007, EPI712012, EPI712020, EPI712028, EPI712036, EPI712044, EPI712052, EPI712060, EPI712068, EPI712076, EPI712084, EPI712092, EPI712100, EPI712108, EPI712116, EPI712121, EPI712129, EPI712137, EPI712142, EPI712150, EPI712166, EPI712167, EPI712168, EPI712169, EPI712170, EPI712171, EPI712172, EPI712311.
**Figure 2**
Phylogenetic analysis of full length haemagglutinin gene comparing reference sequences from the GISAID EpiFlu database and influenza A(H1N1)pdm09 sequences from patients, United Kingdom, 2015/16 influenza season.

The tree was built using a neighbour-joining algorithm, with vaccine strain A/California/07/2009 selected as the root. Signature amino acid substitutions characterising genetic groups are annotated at the root of each cluster. 2015/16 UK samples are highlighted in bold. Sentinel samples are highlighted in red.
Patients were defined as vaccinated if the date of vaccination with the 2015/16 seasonal vaccine was at least 14 days before onset of illness. Those vaccinated less than 14 days before onset of illness and those with unknown date of vaccination were excluded. Those with unknown date of onset or onset date more than seven days before the swab was taken were also excluded.

VE was estimated by the test-negative case control design. In that design, VE is calculated using odds ratios (OR) as 1−(OR) obtained using multivariable logistic regression models with influenza A PCR results (influenza B numbers were too small to examine) and seasonal vaccination status as the linear predictor. VE was also calculated separately for influenza A(H1N1)pdm09. In the analyses evaluating VE for a specific type or strain, those positive for other virus types were excluded from the analysis. For this mid-season analysis, we fixed the variables for adjusted estimates based on past seasons as age (coded into standard age groups, <5, 5–17, 18–44, 45–64 and ≥65 years),

### Table 1
Influenza A(H1N1)pdm09 haemagglutinin sequences obtained from GISAID used in the phylogenetic analysis

<table>
<thead>
<tr>
<th>Virus isolate</th>
<th>Segment ID/Accession number</th>
<th>Country</th>
<th>Collection date (year-month-day)</th>
<th>Originating laboratory</th>
<th>Submitting laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Hong Kong/5659/2012</td>
<td>EPI390473</td>
<td>Hong Kong (SAR)</td>
<td>2012-May–21</td>
<td>Government Virus Unit, Hong Kong (SAR)</td>
<td>National Institute for Medical Research, London, UK</td>
</tr>
<tr>
<td>A/Hong Kong/3934/2011</td>
<td>EPI326206</td>
<td>Hong Kong (SAR)</td>
<td>2011-Mar-29</td>
<td>Government Virus Unit, Hong Kong (SAR)</td>
<td>National Institute for Medical Research, London, UK</td>
</tr>
<tr>
<td>A/Hong Kong/2212/2010</td>
<td>EPI279895</td>
<td>Hong Kong (SAR)</td>
<td>2010-Jul-16</td>
<td>Government Virus Unit, Hong Kong (SAR)</td>
<td>National Institute for Medical Research, London, UK</td>
</tr>
<tr>
<td>A/St. Petersburg/100/2011</td>
<td>EPI316435</td>
<td>Russian Federation</td>
<td>2011-Mar-14</td>
<td>Russian Academy of Medical Sciences, Saint Petersburg, Russian Federation</td>
<td>Centers for Disease Control and Prevention, Atlanta, US</td>
</tr>
<tr>
<td>A/South Africa/3626/2013</td>
<td>EPI577031</td>
<td>South Africa</td>
<td>2013-Jun-06</td>
<td>National Institute for Medical Research, London, UK</td>
<td>Centers for Disease Control and Prevention, Atlanta, US</td>
</tr>
<tr>
<td>A/Christchurch/16/2010</td>
<td>EPI180344</td>
<td>New Zealand</td>
<td>2010-Jul-12</td>
<td>WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia</td>
<td>Centers for Disease Control and Prevention, Atlanta, US</td>
</tr>
<tr>
<td>A/California/07/2009</td>
<td>EPI177294</td>
<td>United States</td>
<td>2009-Apr-09</td>
<td>Naval Health Research Center, San Diego, US</td>
<td>Centers for Disease Control and Prevention, Atlanta, US</td>
</tr>
</tbody>
</table>

GISAID: Global Initiative on Sharing All Influenza Data; SAR: Special Administrative Regions of the People’s Republic of China; UK: United Kingdom; US: United States; WHO: World Health Organization.

Statistical methods
Patients were defined as vaccinated if the date of vaccination with the 2015/16 seasonal vaccine was at least 14 days before onset of illness. Those vaccinated less than 14 days before onset of illness and those with unknown date of vaccination were excluded. Those with unknown date of onset or onset date more than seven days before the swab was taken were also excluded.

VE was estimated by the test-negative case control design. In that design, VE is calculated using odds ratios (OR) as 1−(OR) obtained using multivariable logistic regression models with influenza A PCR results (influenza B numbers were too small to examine) and seasonal vaccination status as the linear predictor. VE was also calculated separately for influenza A(H1N1)pdm09. In the analyses evaluating VE for a specific type or strain, those positive for other virus types were excluded from the analysis. For this mid-season analysis, we fixed the variables for adjusted estimates based on past seasons as age (coded into standard age groups, <5, 5–17, 18–44, 45–64 and ≥65 years),
sex, surveillance scheme (RCGP, SMN, HPS, Wales, Northern Ireland), residence in an area where a primary school-age programme operated and date of sample collection (month). All statistical analyses were carried out in Stata version 13 (StataCorp, College Station, Texas).

Results
The reasons for study inclusion and exclusion are outlined in Figure 1.

Of the 2,666 swabbed individuals, 1,548 individuals were included in the study. Their details were stratified according to the swab result. There were a total of 1,366 controls, 20 influenza B detections, 152 influenza A(H1N1)pdm09 detections, 3 influenza A(H3N2) detections and nine influenza A(unknown) detections. Influenza A(H1N1)pdm09 positivity rates were highest by age in younger than five years (16.8%) and in 18 to 44 year-olds (10.9%), by vaccine status in those who were unvaccinated (11.1%) compared with vaccinated (5.6%), and in non-pilot (14.1%) compared with pilot areas (6.3%). Overall positivity rates differed significantly by age group (highest in 15 year-olds), sex (higher in males), risk group (higher in those without a risk factor), month (highest in January), scheme, vaccination status (highest in unvaccinated) and area of primary school-age programme (highest in non-pilot areas) (Table 2). Numbers and row percentages (to indicate positivity rates) are shown.

Influenza A(H1N1)pdm09 strain characterisation from sentinel and non-sentinel samples
Since the start of the 2015/16 winter influenza season in week 40 2015, the PHE Respiratory Virus Unit has characterised a total of 274 influenza A(H1N1)pdm09 viruses from all sources; 103 genetically (of which nine (9%) from sentinel sources), 210 antigenically (of which 46 (22%) sentinel sources) and 39 both antigenically and genetically (of which three (8%) from sentinel sources).

The A(H1N1)pdm09 viruses genetically characterised to date all belonged in the genetic subgroup 6B (Figure 2), which had been the predominant genetic subgroup in the 2014/15 season. Some heterogeneity has been seen in HA of the current season’s A(H1N1)pdm09 viruses, with some genetic subgroups becoming evident: the HA genes of more than 85% of A(H1N1)pdm09 viruses fell into genetic cluster 6B.1, characterised by the amino acid changes S84N, S162N (with gain of a potential glycosylation site) and I216T, with a subset in this cluster having the substitution A215G. Less than 10% of viruses fell into a second emerging cluster (6B.2), and had the amino acid substitutions V152T, V173I, E491G and D501E in the HA gene, or a third minor cluster with substitutions N129D, R450K and E491G. A few viruses from this season did not show any of these changes or have substitution S84N alone, and clustered with A(H1N1)pdm09 viruses from season 2014/15 (6B subgroup).

Of 210 viruses analysed by HI assay using ferret post-infection sera, more than 90% were antigenically similar to the A/California/7/2009 northern hemisphere 2015/16 A(H1N1)pdm09 vaccine strain. In the period 1 October to 30 November 2015, 6% (2/32) of isolates had an eightfold or greater reduction in reactivity to antiserum raised to egg-grown A/California/7/2009 virus, compared with 11% (19/178) that had an eightfold or greater reduction in the period 1 December 2015 to 22 January 2016.

Model fitting for vaccine effectiveness estimation
The variables included in the multivariable model (age group, sex, month of sample collection, surveillance scheme and primary school-age programme area) were all significantly associated with swab positivity and were confounders for the vaccine effects (changed estimates by more than 5%) with the exception of primary school-age programme area. Information on risk group was missing for 53 samples (3.4%) and as in previous seasons’ analyses [4] was not included in the final model.

Vaccine effectiveness estimates against influenza A(H1N1)pdm09, influenza A (all types) and all influenza are shown in Table 3. It was not possible to estimate effectiveness against influenza A(H3N2) or influenza B due to inadequate sample number. The adjusted VE of influenza vaccine against any influenza was 41.5% (95% confidence interval (CI): 30.0–64.7) and was very similar for A(H1N1)pdm09 at 49.1% (95% CI: 9.3–71.5).

Discussion
In a season dominated by circulation of influenza A(H1N1)pdm09, we found an overall VE of 41.5% in preventing laboratory-confirmed influenza infection resulting in a primary care consultation; it was 49.1% specifically against A(H1N1)pdm09, reflecting the fact that A(H1N1)pdm09 was the dominant circulating strain at this stage of the season. We also found some early evidence of circulation of A(H1N1)pdm09 genetic variants, but with no evidence of loss of effectiveness of the 2015/16 vaccine.

The UK, together with other European Union Member States, the United States, Canada and Australia has well established systems to generate interim estimates of seasonal influenza VE. These early results are used to optimise in-season control and prevention measures, to inform other countries before their influenza season and to contribute to the WHO deliberations on the influenza vaccine composition for the northern hemisphere. The UK, as other countries in Europe, has experienced a season dominated by circulation of influenza A(H1N1)pdm09 with reports of increases in hospitalisations and ICU admissions mainly in younger adults [11]. Although concerns have been expressed
about a possible increase in virulence, the epidemiological observations are consistent with earlier seasons in the UK dominated by circulation of A(H1N1)pdm09, in particular in 2010/11, the first post-pandemic season, but also to a lesser extent in 2012/13 and 2013/14.

Although evidence of heterogeneity has been seen in the HA gene of A(H1N1)pdm09 viruses genetically characterised from all sources to date this season, more than 90% of the 210 viruses analysed by HI assays were antigenically similar to the A/California/7/2009 northern hemisphere 2015/16 (H1N1)pdm09 vaccine strain, suggesting little change in the antigenic properties.
In support of the antigenic characterisation findings, we demonstrate that the influenza vaccine has been effective in preventing laboratory-confirmed primary care consultations this season. The adjusted VE against all influenza for all age groups was very similar to that against influenza A(H1N1)pdm09 reflecting the fact that A(H1N1)pdm09 has been the dominant circulating virus strain this season. Indeed, the result is not significantly different to that observed for the UK mid-season estimate in 2010/11, when A(H1N1)pdm09 was the dominant circulating strain with an estimate against A(H1N1)pdm09 of 51% (95% CI 29 to 66%) [12], and in 2012/13 with an end of season estimate of 73% (95% CI: 37 to 89) [4]. The results were also not significantly different from the VE against influenza A(H1N1)pdm09 of 44.2% (95% CI: −3.1 to 69.8%) recently reported for the current season by the European I-MOVE network [13] and the recent estimate from Canada of 64% (95% CI 44–77%) [14]. The lack of apparent antigenic and epidemiological vaccine mismatch at this stage is encouraging.

Nonetheless, it is important to highlight lack of precision in our estimate: the lower 95% CI was 3% and the upper CI was 65%, indicating a large range of uncertainty, although we can say with confidence that the influenza vaccine has been effective so far this season. Furthermore, this mid-season analysis was done at a time when activity was still increasing and does not preclude the possibility to that there may be changes in the dominant circulating strain, with potential implications for the vaccine effectiveness. These limitations will be addressed in the end-of-season analysis which will also include stratification by age group and type of vaccine, in particular for children.

Finally, the results outlined in this paper have contributed to the recent global assessment for the coming season’s influenza vaccine composition: the WHO recommended that the vaccine for the 2016/17 northern hemisphere winter should continue to include the A/California/7/2009 vaccine strain [15].

Acknowledgements

We are grateful many patients of participating practices who consent to virology swabs being taken; to the practices in the participating in the surveillance schemes in England, Wales, Northern Ireland and Scotland who supplied the clinical information on their patients; to the staff of the PHE Respiratory Virus Unit, the PHE Specialist Microbiology Laboratories, Public Health Wales Molecular Diagnostics Unit, the West of Scotland Specialist Virology Centre and the Regional Virus Laboratory, Belfast who undertook analysis of specimens. We thank the staff of PHE, RCGP, Public Health Wales, Public Health Agency Northern Ireland and Health Protection Scotland teams who coordinate the GP schemes, in particular Praveen SebastianPillai and Nisha Oppilamany from PHE; Richard Lewis and Ember Hilvers from PHW; Chris Nugent and Cathriona Kearns from the PHA Catherine Frew, Alasdair MacLean, Samantha Shepherd and Celia Aitken from WoSSVC and Diogo Marques, Robert Seremani, Naoma William, Louise Primrose-Shaw and Amanda Burridge from HPS for overseeing data collection, and Sameera Pathirannehelage, Filipa Ferreira, Ana Correa, Rachel Byford from RCGP/University of Surrey. We acknowledge the originating and submitting laboratories of the sequences from GISAID’s EpiFlu Database on which some of the analyses are based (see Table 1). All submitters of data may be contacted directly via the GISAID website www.gisaid.org

Conflict of interest

None declared.

Authors’ contributions

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

References


License and copyright

This is an open-access article distributed under the terms of the Creative Commons Attribution (CC BY 4.0) Licence. You may share and adapt the material, but must give appropriate credit to the source, provide a link to the licence, and indicate if changes were made.

This article is copyright of the authors, 2016.