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Special edition:

Influenza vaccine effectiveness

November 2016

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- Importance of timely monitoring of seasonal influenza vaccine effectiveness

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Decreased effectiveness of the influenza A(H1N1) pdm09 strain in live attenuated influenza vaccines: an observational bias or a technical challenge?

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Citation style for this article:
Penttinen PM, Friede MH. Decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines: an observational bias or a technical challenge?. Euro Surveill. 2016;21(38):pii=30350. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.38.30350

Article submitted on 19 September 2016 / accepted on 22 September 2016 / published on 22 September 2016

There are currently two types of approved influenza vaccines: inactivated or recombinant vaccines, and live attenuated vaccines. The live attenuated influenza vaccines (LAIV) constructed on a backbone of an A/Leningrad virus strain into which the seasonal haemagglutinin (HA) and neuraminidase (NA) selected for the vaccine were inserted by reassortment, were used in the former Soviet Union for over 50 years [1]. Since the early 2000s, a different attenuated virus strain based on the A/Ann Arbor strain, has been approved for vaccine manufacturing in the United States (US) and more recently in the European Union/European Economic Area (EU/EEA) [2,3]. The proposed advantages of the LAIV were that they had superior efficacy compared to inactivated vaccines in young children [4], they were programmatically more suited to immunisation of children [5] and improved cost-effectiveness could potentially be achieved with childhood LAIV programmes [5-7]. LAIV have also been shown to be of great use in pandemic response since the production yield (doses per egg) is much greater than for inactivated vaccines, and the time between production and release is shorter. In addition, the nasal route of delivery could facilitate rapid population-wide immunisation during pandemics.

The technology to produce pandemic LAIV based on the A/Leningrad backbone has been licensed to the World Health Organization (WHO) for manufacture and use in developing countries. It is estimated that a total production capacity of pandemic LAIV will be ca 500 million doses by 2018 (data not shown). A loss of seasonal LAIV production capacity would impact this pandemic response capacity, and is therefore of global concern.

The US Advisory Committee on Immunization Practices (ACIP) has recently withdrawn the recommendation for use of LAIV in the US for the season 2016/17 following an earlier withdrawal of a preferential recommendation [2]. These decisions were made mainly taking into account the lack of demonstrated vaccine effectiveness (VE) against influenza A(H1N1)pdm09 in observational studies conducted. The studies by the US Centers for Disease Control and Prevention (CDC), and the US Department of Defence, suggested a lower relative effectiveness in comparison to the inactivated influenza vaccine (IIV) [2]. However, two VE studies conducted in Europe and published in this issue of *Eurosurveillance*, reported moderate and reasonable, statistically significant VE in children aged two years and older [8,9]. Furthermore, data from a study funded by the manufacturer of FluMist (US)/Fluenz (Europe) showed similar effectiveness for LAIV in the 2015/16 season [2]. These data were also considered by the ACIP.

In Europe, two EU countries, Finland and the United Kingdom (UK), have introduced LAIV into their publicly-funded routine paediatric vaccination programmes [10]. The two National Immunization Technical Advisory Groups, the UK Joint Committee on Vaccination and Immunisation and the Finnish National Expert Group on Vaccines, considered the available evidence of effectiveness as sufficient to continue the roll-out of vaccination programmes in their countries [11], (personal communication, H Nohynek, September 2016).

Any issues related to LAIV effectiveness or future availability may impact seriously on the roll-out of current and future paediatric and adolescent influenza vaccine and they have potential to affect global pandemic preparedness.

The results from VE studies by Pebody et al. and Nohynek et al. done during the 2015/16 influenza season in the two EU/EEA countries rolling out paediatric and adolescent vaccination programmes including LAIV, document moderate effectiveness of LAIV against influenza

Table

Comparison of study designs and populations assessing vaccine effectiveness of live attenuated influenza vaccine, northern hemisphere countries, United States, United Kingdom and Finland, influenza season 2015/16

	CDC United States	DoD United States	ICICLE United States	PHE United Kingdom	THL Finland
VE against A(H1N1)pdm09 (95%CI)	**–21% (–108% to 30%)**	**15% (–48% to 51%)***	**50% (–2% to 75%)***	**41.5% (–8.5% to 68.5%)***	**47.9% (21.6–65.4%)**
Study design	Test-negative case–control	Test-negative case–control	Test-negative case–control	Test-negative case–control	Cohort
Source population / inclusion criteria	Children and adolescents aged 2–17 years*	Children and adolescents (Military dependents) aged 2–17 years presenting to participating facilities	Children and adolescents aged 2–17 years	Children and adolescents 2–17 years of age	Children 24–35 months of age
Inclusion criteria	MAARI, including cough, and onset of illness ≤ 7 days before enrolment	ILI (fever ≥ 38 °C AND cough and/or sore throat of < 72 hours duration)	ARI with fever ≥ 100.0°F (37.8 °C), duration < 5 days	ILI	Laboratory-confirmed influenza
Assessment of vaccination status	Current-season vaccination (at least one vaccine dose ≥ 14 days before illness onset; vaccine records obtained from electronic medical records and immunisation registries for children aged 2–8 years; with addition of reported vaccination for patients aged 9–17 years)*	Electronic medical records	Vaccination status was ascertained by medical record review and/or state or regional vaccine registries	Self-reported by patients to general practitioners	National immunisation registry
Case definition	RT-PCR-positive subjects*	RT-PCR-positive subjects	RT-PCR positive subjects	RT-PCR positive subjects	RT-PCR, multiplex RT-PCR, culture and/or antigen detection test
Final sample size (number of vaccinated with LAIV / number of non-vaccinated)*	133/1,078*	93/338*	101/594	111/514*	8,323/46,119
Adjusted for	Study site, age, self-rated general health status, race/hispanic ethnicity, interval (days) from onset to enrolment, and calendar time	Age groups, three time periods	Site, age group, visit date, outpatient visits in past 6 months, health insurance, and sex	Age group, sex, month, pilot area and surveillance scheme	Propensity scores, and adjusted by their quintiles
Source	ACIP presentation 22 June 2016 also cited in [2] and personal communication (J Clippard, September 2016)*	ACIP presentation 22 June 2016 also cited in [2] and personal communication (S Federinko, September 2016)*	ACIP presentation 22 June 2016 also cited in [2] and personal communication (H Caspard, September 2016)*	Pebody 2016 [9]	Nohynek 2016 [8]

ACIP: Advisory Committee on Immunization Practices; ARI: acute respiratory infection; CDC: Centers for Disease Control and Prevention; DoD: Department of Defence; ICICLE: Influenza Vaccine Effectiveness Influenza Clinical Investigation for Children; ILI: influenza-like illness; MAARI: medically attended acute respiratory infection; PHE: Public Health England; THL: Terveyden ja hyvinvoinnin laitos (National Institute for Health and Welfare).

A(H1N1)pdm09 in the UK (estimated VE: 41.5%*) and influenza A in Finland (estimated VE: 47.9%) (Table). Results from ongoing analysis of VE studies in Scotland are consistent with these results (personal communication, J McMenamin, September 2016). This contrasts with results from the US CDC studies which found no significant effectiveness against this strain. All the studies showed effectiveness against antigenically matched B viruses (even though numbers of influenza B cases were very low in the Finnish study) and in all of them low level circulation limited assessment of VE against influenza A(H3N2). Each of the studies report a lower effectiveness for LAIV against influenza A(H1N1) pdm09 in comparison with inactivated influenza vaccines, which was not the case in randomised controlled trials when FluMist/Fluenz was authorised.

All studies, with the exception of the Finnish one, use the test-negative case–control study methodology which has the potential to control for many of the

biases inherent with observational studies (Table) but lacks power when stratifying e.g. in strata with small sample sizes. This methodology was extensively evaluated in the past and can be considered the gold standard for observational VE studies [12-16]. Therefore the observed discrepancies between the conducted studies are surprising and deserve careful assessment.

Potential explanations for the discrepancies in the VE study results for LAIV during the 2015/16 influenza season could be related to study design, analytical methods to calculate the adjusted VE, or true differences in effectiveness due to properties of the virus or the target populations. Methodological and analytical differences should affect the effectiveness results for influenza B viruses and inactivated influenza vaccines in the same way. All of the studies agree on some LAIV effectiveness against B viruses. LAIV used in Europe and North America are produced in the same factory, therefore it is unlikely that differences in the composition of the vaccine explain the differences in VE.

The factors driving the lower effectiveness observed in the US over the past five years compared to that seen in the European studies are likely to be related to population or programme-specific effects. In this regard, the comparatively high coverage of influenza vaccination in children 6 months to 2 years of age in the US, before the age at which LAIV is given as part of the vaccination programme, may be a contributing factor. Other factors could include environmental issues such as storage and administration temperature particularly since an early formulation of this vaccine was shown to be thermolabile [17].

Nonetheless, a lower comparative (compared to IIV) effectiveness against the influenza A(H1N1) strains was observed in all the studies. The comparatively lower effectiveness is most likely related to the biological properties of the influenza A(H1N1)pdm09 strain used in the vaccines. Potential explanations include (i) the transition to quadrivalent formulations which occurred 5 years ago, and a potential competition between the B strains and the A(H1N1)pdm09 strain and (ii) a lower fitness of the A(H1N1)pdm09 strain in terms of sialic acid binding specificity, rate of cell entry, replication and budding.

Following the ACIP decision, the European Centre for Disease Prevention and Control (ECDC) and WHO have facilitated a series of discussions between relevant public health research groups in order to review available data and generate hypotheses to explain the differences in VE results and to develop a framework to test these hypotheses. To complement this, WHO organised a global consultation in Geneva on 20–21 September 2016 to discuss potential explanations for recent evidence of decreased performance of LAIV compared with IIV. At this meeting, the potential explanations outlined above were discussed and apart from the methodological constraints of observational studies, they were considered to be likely but requiring research to confirm. Gathering more data, testing the hypotheses and identifying corrective actions will require dedicated resources The manufacturer of the LAIV used in Europe and North America has embarked on a comprehensive virological research programme to study many of these hypotheses to improve and optimise the effectiveness of the 2017/18 vaccine formulation (personal communication, M Downham, 20 September 2016). The involved public health agencies are seeking to enhance their VE studies and have embarked upon better understanding drivers of the variability in the effectiveness estimates. Unfortunately, additional national or supranational funding sources do not appear to be available to rapidly fund adequately scaled operational public health research during the upcoming 2016/17 season.

The US Vaccines for Children Programme had ordered 14 million doses of LAIV for the upcoming 2016/17 influenza season, representing roughly two thirds of the global sales for 2016 [18]. They will now not be used due to the June ACIP decision. Difficult commercial decisions will now need to be taken in the coming months regarding the production for the 2017/18 northern hemisphere season. In a situation where all influenza vaccines used in Europe are produced by commercial manufacturers EU/EEA countries depend on commercial decisions by the manufacturers for availability of LAIV for continued immunisation programmes.

In addition to the LAIV currently used in Europe and North America, several manufacturers in developing countries have started the production of LAIV using the A/Leningrad backbone, and one Indian manufacturer produces pandemic and nationally approved seasonal LAIV vaccines. No data regarding the 2015/16 VE are available from these manufacturers. The policy decisions made in Europe and in the US have an impact on commercial decisions by all manufacturers and as mentioned above, on the global capacity to respond to influenza.

The US Food and Drug Authority (FDA) and the European Medicines Agency (EMA) consider that the benefit–risk ratio of the LAIVs licenced by them remains positive and no changes in market authorisation are envisaged [17]. In the coming months, EMA will introduce a new guideline requiring manufacturers to provide annual VE estimates as part of the market authorisation [19].

The VE results for LAIV 2015/16 clearly show the necessity of assessing VE on an annual basis. With core funding from ECDC, the European Influenza Monitoring Vaccine Effectiveness (I–MOVE) network has established a methodology and an EU/EEA-wide network to estimate seasonal VE [20]. The challenge of conducting these studies is to find study sites with sufficiently high uptake of influenza vaccines and the resources to recruit large enough sample sizes. The European Innovative Medicines Initiative has called for a proposal to prepare for a platform to enable these

studies, in particular to establish a governance model where such studies could be undertaken in a public-private partnership. Such partnership should include public health agencies recommending and assessing vaccination programmes and manufacturers producing the vaccines in an atmosphere of transparency and scientific independence [21].

The European seasonal influenza immunisation programmes of children are based on estimated healthcare cost savings (Finland) [7] and estimated reductions of transmission of influenza and indirect protection of the elderly and risk groups (UK) [22]. Both programmes are currently being rolled out, especially in the UK, in a step-wise fashion. Therefore full assessments of the impact of these programmes are only awaited within the next few years. Now these programmes are faced with two immediate risks, before such assessments can be made; on the one hand a low (or non-existent as in the US) effectiveness which would decrease the impact of the programmes and on the other hand the dependence on the commercial decisions of the manufacturers.

Virological, epidemiological and immunological studies are urgently needed to understand the reasons behind the decrease of the influenza A(H1N1)pdm09 component of LAIV to inform the vaccine strain selection decision for the northern hemisphere in February 2017, the public health decisions on the vaccines to be recommended for the 2017/18 season and to support sound commercial decisions by the vaccine manufacturers.

*Author's correction

The VE for 2-17 year-olds in the UK was corrected on request of the authors on 22 and 29 September 2016. In addition, figures for the final sample sizes for CDC, DoD and PHE and case definition for CDC were corrected in the Table on 29 September 2016.

Following publication, the exact confidence intervals for VE in DoD and ICICLE were provided to the authors in personal communications and specified in the Table on 29 September 2016. Exact age groups for the source population and information on vaccination status in the CDC study were provided to the authors in personal communications and specified in the Table on 29 September 2016.

Acknowledgements

Kari Johansen and Justin Ortiz are acknowledged for their indispensable support in ongoing discussions on this topic.

Conflict of interest

None declared.

Authors' contributions

Both authors contributed equally to conception and writing of this editorial.

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Importance of timely monitoring of seasonal influenza vaccine effectiveness

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Citation style for this article:
Pebody RG, Mølbak K. Importance of timely monitoring of seasonal influenza vaccine effectiveness. Euro Surveill. 2016;21(16):pii=30209. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.16.30209

Article submitted on 13 April 2016 / accepted on 20 April 2016 / published on 21 April 2016

Seasonal influenza vaccination programmes represent one the largest components of national immunisation programmes in many industrialised countries with a wide range of target groups in the population. These programmes target groups at higher risk of severe disease including the elderly, those with underlying clinical risk factors and pregnant women in many European countries [1]. Additionally many countries offer vaccines to healthcare workers and some to healthy children [1]. The rationale for vaccinating the latter is to both directly protect the vaccinated persons themselves by reducing the spread of infection and indirectly protect other groups at higher risk of severe disease whether that is in the local community or the hospital where they work.

Due to changes in the dominant circulating strains each season and the limited length of protection [2] afforded by the current generation of influenza vaccines, countries undertake annual vaccination campaigns. These time-limited programmes are usually conducted in the period just prior to the start of the influenza season to maximise population protection. Annual public health monitoring of the effectiveness of seasonal influenza vaccine has now become well established in North America, Europe and Australasia to complement existing virological surveillance and characterisation of circulating strains. Countries use the test-negative case-control approach through established sentinel primary care swabbing networks or comparable data sources, with many countries undertaking mid-season vaccine effectiveness (VE) estimates [3]. These early-season estimates are important for several reasons. Firstly, together with available virus characterisation data, they provide an early indication of how well the current season's vaccine is (or is not) matched to the circulating strains: this enables public health measures to be refined if necessary e.g. the use of antivirals to further reduce the health impact of influenza. VE measures combined with estimates and projections of number of hospital admissions related to influenza are also important for healthcare service planning and situational awareness. Finally, the information from these mid-season VE estimates is provided to the World Health Organization (WHO) twice-yearly convened influenza vaccine composition meeting by the Global Influenza Vaccine Effectiveness collaboration together with virological characterisation and serological data [4]. This group recommends the content of the seasonal influenza vaccine for the northern and southern hemispheres that vaccine manufacturers need to produce ready for the vaccine campaigns six months later. These estimates are importantly provided independent of the vaccine manufacturers, who are required to submit safety and effectiveness data as part of recently introduced European Medicines Agency requirements [5].

Two papers in this week's edition of *Eurosurveillance* highlight further the importance of this timely seasonal influenza VE monitoring in optimising seasonal influenza vaccination strategies [6,7,] while a third addresses pandemic vaccination strategies in the Nordic countries, 2009 [8]. The more ready availability of epidemiological VE data has provided the WHO committee with further and timelier insights into the match between circulating and vaccine strains and enhances its ability to make the best recommendations possible about the vaccine strain composition for the forthcoming season using epidemiological, virological and serological data. The first paper by Leung et al., a systematic review over almost a decade, reinforces this point, with the article demonstrating the usual reliability of these early-season VE estimates when compared to the final end-of-season estimates. The authors also demonstrate that in the majority of studies, the mid-season VE estimates were within 10% of the final end-of-season estimate, with the vast bulk of the interim estimates provided ahead of the WHO influenza vaccine composition meeting. The paper also highlights

the importance of ensuring a standard approach to enhance the comparability between mid- and end-of-season VE, and that protocols need to meet this aim.

The second paper by Kissling et al. from the European I-MOVE network examines the important question of whether there is any evidence of intra-seasonal waning of VE over the period from 2010/11 to 2014/15. They demonstrate evidence of consistent reductions in VE against A(H3N2) to 0% by >three months after vaccination across all seasons examined; with smaller reductions for influenza B and a stable VE against A(H1N1) pdm09 throughout the season. They discuss potential explanations for these observations in particular disentangling intra-seasonal waning of vaccine-derived immunity versus changes in circulating strains which may be antigenically mismatched later in the season. Interestingly the waning findings are mainly restricted to A(H3N2). This subtype is recognised to be challenging as a vaccine target, and which mainly results in health impact in the elderly. From the paper by Leung et al. [6], the overall population impact of this 'waning' of VE can be seen when comparing the mid and end-of-season estimates, reinforcing the findings from Kissling et al. [7]. The reductions in VE on the population level are likely to be more apparent when A(H3N2) circulates later in the season, as was the case in 2013/14, when a number of countries reported evidence of reductions in A(H3N2) VE later in the season.

Whatever the explanation for these observations, the findings of intra-seasonal waning raise important questions about what the optimal intervention strategy is. The authors propose undertaking campaigns later in the season. Practically, this would be a challenging policy to implement, particularly in larger temperate countries. With the timing of influenza activity so variable each year and the season usually lasting at least 6 to 8 weeks; campaigns in the northern hemisphere need to be largely completed by end of December before the season starts. As vaccine is only available usually from October onwards and the delivery of the annual campaign requires several weeks of intensive vaccination activity (including two weeks for protection to be acquired), there is little flexibility in timing, without taking real risks of not providing the population protection required before influenza circulation starts. What strategies might be employed otherwise? Even in an optimal scenario with a good match between the circulating influenza strain and the vaccine, and with a timing of the season in favour of the vaccine, the effectiveness is less than other vaccines offered in the childhood vaccination programmes. Although there is a clear need for new and better influenza vaccines, possibly targeting conserved antigens; there is also a need to identify which of the existing available influenza vaccines e.g. adjuvanted and high dose inactivated or quadrivalent versus trivalent, might provide optimal protection in key target groups, particularly the elderly where the impact of A(H3N2) is usually greatest. How these vaccines might be used better should also be considered as highlighted by Kissling et al., VE depends on age, and although the sample size of their study was not big enough to determine if there was waning immunity in smaller age strata, one question might be if waning vaccine-derived immunity against influenza A(H3N2) is less of a problem in the younger age groups. This would be supportive of another intervention strategy, where the primary focus would be preventing the spread of influenza to groups at higher risk of severe disease by vaccinating children. This approach of trying to provide both direct and indirect population protection is currently being introduced in the United Kingdom through a new vaccination programme of healthy children with live attenuated influenza vaccine. As also mentioned by Kissling et al., the current season influenza VE may vary by prior influenza vaccine history, and there is a need to understand this better to ensure optimal intervention strategies are developed. This strategy is also supported in a third paper by Gil Cuesta et al. [8] also published in this issue, that demonstrates lower cumulative rates of influenza A(H1N1)pdm09 infection in the influenza season following the 2009 pandemic in the four of five Nordic countries with higher pandemic vaccine coverage in the wider general population, including children. This indicates that in the assessment of impact of vaccination strategy, it may be important to look at more than one season, possibly taking type of vaccine and age-group targeted into account.

It is also important to note that there are other interventions than vaccines. Public health authorities need to consider how the use of antiviral drugs might be optimised to further reduce morbidity and mortality particularly when influenza seasons are unusually late. Finally, behavioural measures such as hand hygiene, avoiding close contact to sick persons, staying home when sick and cough etiquette are measures that can contribute to prevention of the spread of influenza throughout the influenza season [9,10].

Conflict of interest

Richard Pebody and Kåre Mølbak are both members of the I-MOVE+ network. KM is a co-author on one of the published papers highlighted.

Authors' contributions

Both authors contributed to writing this editorial.

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Influenza vaccine effectiveness in adults 65 years and older, Denmark, 2015/16 – a rapid epidemiological and virological assessment

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Citation style for this article:
Emborg H, Krause TG, Nielsen L, Thomsen MK, Christiansen CB, Skov MN, Nielsen XC, Weinreich LS, Fischer TK, Rønn J, Trebbien R. Influenza vaccine effectiveness in adults 65 years and older, Denmark, 2015/16 – a rapid epidemiological and virological assessment. Euro Surveill. 2016;21(14):pii=30189. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.14.30189

Article submitted on 16 March 2016 / accepted on 07 April 2016 / published on 07 April 2016

In Denmark, both influenza A(H1N1)pdm09 and influenza B co-circulated in the 2015/16 season. We estimated the vaccine effectiveness (VE) of the trivalent influenza vaccine in patients 65 years and older using the test-negative case–control design. The adjusted VE against influenza A(H1N1)pdm09 was 35.0% (95% confidence interval (CI): 11.1–52.4) and against influenza B 4.1% (95% CI: –22.0 to 24.7). The majority of influenza A(H1N1)pdm09 circulating in 2015/16 belonged to the new genetic subgroup subclade 6B.1.

In Denmark, both influenza A(H1N1)pdm09 and influenza B co-circulated in the 2015/16 season. The trivalent influenza vaccine (TIV) did not include the circulating influenza B Victoria lineage and there is evidence in Europe for genetic evolution of the circulating influenza A(H1N1)pdm09 virus [1]. We estimated the influenza vaccine effectiveness (VE) in people aged 65 years and older. In addition, we describe the genetic and antigenic characteristics of the influenza A(H1N1) pdm09 variant and the influenza B strain circulating in Denmark.

Data for vaccine effectiveness estimation

In the Danish Microbiology Database, all patients swabbed at the general practitioner's (GP) or at hospital and tested for influenza A and B viruses by PCR are registered in real time [2]. During the influenza season, national guidelines recommend that patients belonging to risk groups, including the elderly who present with influenza symptoms at GPs and hospitals are swabbed and tested for influenza. At hospitals, all patients with lower respiratory infections are also recommended to be swabbed. All diagnostic influenza tests from patients aged 65 years and older were included in this study.

Influenza symptoms were defined as sudden onset of fever, muscle ache and upper airway symptoms. The trivalent influenza vaccine (TIV) is offered free of charge to Danish citizens 65 and older between week 40 and week 53, and date of vaccination is registered in the Danish Vaccination Register [3]. In The Danish National Hospital Register, data on all hospital admissions are collected [4]. Comorbidities that can lead to severe influenza disease and were diagnosed between October 2010 and October 2015 were extracted from the Danish National Hospital Register.

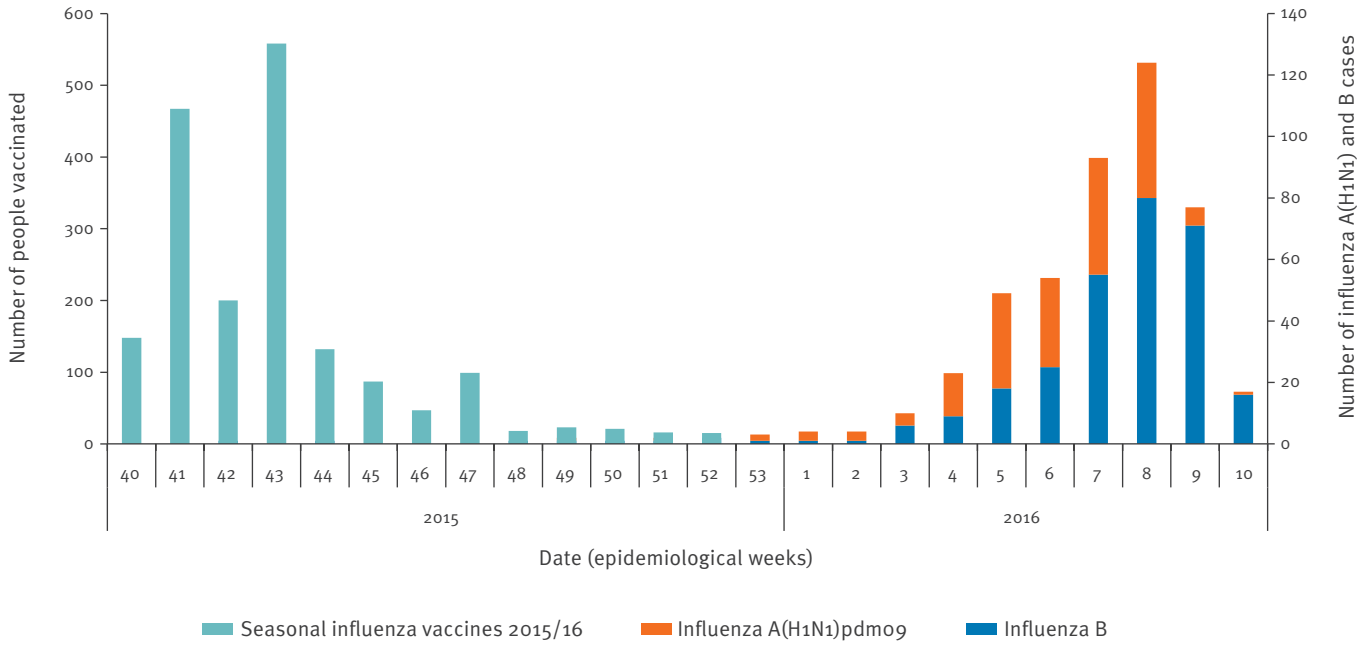
Data from the Danish Microbiology Database, the Danish Vaccination Register and the Danish National Hospital Register were linked using unique identifiers.

Case definitions and statistical analysis

Cases were defined as patients who tested positive for influenza A(H1N1)pdm09 or influenza B, and a patient was only included the first time a test was positive for either type. Controls were patients who tested negative for both influenza A and B. Patients were considered vaccinated if they had received the TIV at least two weeks before the sample was taken. A logistic regression model was used to estimate VE against influenza A(H1N1)pdm09 and influenza B using the test-negative case–control design (1-OR) × 100%. The

Figure 1

Trivalent influenza vaccines received (n = 1,831) and laboratory-confirmed influenza A(H1N1)pdm09 and B cases among tested patients ≥ 65 years (n = 468), Denmark, 28 September 2015–9 March 2016



Influenza vaccines are given free of charge to the elderly 65 years and older from 1 October to 31 December. Due to delay in registration of vaccinations, data from week 53 were not available at the time this analysis was performed.

In weeks 40 to 53, between 0 and two influenza A(H1N1) and B cases were registered per week (not visible at presented range of the y-axis).

estimates were adjusted for sex and co-morbidities diagnosed within a five-year period before the 2015/16 influenza season. Among 195 subtyped influenza A isolates from patients aged 65 years and older, less than 10% (n = 18) were A(H3N2) and VE against this subtype was not estimated.

The statistical programme SAS version 9.4 was used for the descriptive and statistical analyses (SAS Institute, Cary, United States).

Influenza virus characterisation

All influenza samples received at The National Influenza Center in Denmark (NIC) were screened for influenza virus by an in-house multiplex real-time reverse-transcriptase PCR (qRT-PCR), with primers and probes detecting influenza A and B virus as well as subtypes of H3 haemagglutinin (HA) and N1pdm09 neuraminidase. Subtyping of influenza B virus is also performed by an in-house duplex qRT-PCR which differentiates between the Yamagata and Victoria lineage on a fragment of the HA gene.

Sequencing of the HA gene of influenza A(H1N1)pdm09 and influenza B viruses was performed on extracted viral RNA from 62 and 20 samples, respectively. Total nucleic acid was extracted using 200 µl of sample material and the MagNA Pure LC Total Nucleic Acid Isolation Kit on the MagNa Pure 96/32 (Roche). RT-PCR of the complete HA gene was performed using in-house primers and an in-house one-step RT-PCR programme on a TRIO cycler (Biometra). Sequencing was performed by using Big Dye chemistry on an ABI3500 capillary sequencer (Thermo Fisher). Assembly of contigs was done in Bionumerics version 6.6 (Applied maths) and alignment and phylogenetic analysis were conducted with MEGA version 6 [5]. For alignment, the Muscle algorithm was used and phylogenetic trees were created by the maximum likelihood method using 1,000 bootstrap replicates. Sequences were also analysed by BLAST at NCBI GenBank, the Global Initiative on Sharing All Influenza Data (GISAID) and at the FLUSERVER [6]. The authors gratefully acknowledge the 59 originating and submitting laboratories who contributed sequences used in the phylogenetic analysis to GISAID (www.gisaid.org).

Virus isolation was successful for 32 influenza A(H1N1) pdm09 and 13 influenza B samples by standard procedures in confluent monolayers of MDCK and/or MDCK-SIAT cells [7]. Several samples were shipped in E-swab medium which is cytotoxic and therefore is challenging for virus isolation [8]. Antigenic characterisation was performed by HA inhibition (HAI) test [7] using reference ferret antiserum against A/California/07/2009 (H1N1pdm09), B/Brisbane/60/2008 (Victoria lineage) and B/Phuket/3073/2013 (Yamagata lineage) provided

Figure 2

Phylogenetic tree of the haemagglutinin gene with reference viruses for the different phylogenetic clades of H1N1pdm09 influenza A viruses (n = 40)

The Danish viruses are indicated with a black circle. A subclade formed by viruses with the amino acid substitutions S101N, S179N and I233T, subclade 6B.1, is indicated as well as the subclade formed by viruses with the V169T, V190I, E508G and D518E substitutions, subclade 6B.2. The authors gratefully acknowledge the 59 originating and submitting laboratories who contributed sequences used in the phylogenetic analysis to GISAID (www.gisaid.org).

Table

Laboratory-confirmed influenza A(H1N1)pdm09 and B cases (n = 468) and influenza A and B test-negative controls (n = 3,363) aged ≥ 65 years by trivalent influenza vaccination status, age group and sex, and vaccination coverage among influenza cases and controls by age group and sex, Denmark, 28 September 2015–9 March 2016

Characteristic	Influenza A(H1N1)pdm09			Influenza B			Controls		
	Vaccinated (n)	Not vaccinated (n)	Vaccination coverage (%)	Vaccinated (n)	Not vaccinated (n)	Vaccination coverage (%)	Vaccinated (n)	Not vaccinated (n)	Vaccination coverage (%)
Age group									
65–69	16	42	27.6	37	42	46.8	337	488	40.8
70–74	20	29	40.8	37	41	47.4	385	458	45.7
75–79	18	22	45.0	27	34	44.3	363	323	52.9
≥ 80	13	17	43.3	34	39	46.6	544	466	53.9
Comorbidities									
No	15	34	30.6	36	66	35.3	347	480	42.0
Yes	52	76	40.6	99	90	52.4	1,282	1,255	50.5
Sex									
Female	28	45	38.4	70	79	50.0	780	865	47.4
Male	39	65	37.5	65	77	45.8	849	869	49.4
Total	67	110	37.8	135	156	46.4	1,629	1,734[a]	48.3

[a] Sex was not known for one person.

by the World Health Organization (WHO) Collaboration Centre, Mill Hill, London.

Vaccine effectiveness results

By 9 March 2016, 3,831 patients 65 years and older were tested for influenza A(H1N1)pdm09 and B, and 65% of them were swabbed at a hospital. In total, 177 patients were positive for influenza A(H1N1)pdm09 and 291 for influenza B. In total, 1,505 (82%) of 1,831 study participants had received the TIV before 2 November in 2015 (Figure 1).

Vaccine coverage in cases diagnosed with influenza A(H1N1)pdm09 was 37.8%, which is lower than the coverage in controls (48.3%), cases diagnosed with influenza B (46.4%) (Table) and the estimated national coverage of 44% (data not shown). The coverage, for both cases and controls, was higher among patients with comorbidities compared with patients without comorbidities (Table).

Adjusted interim VE among those aged 65 years and older against influenza A(H1N1)pdm09 was 35.0% (95% confidence interval (CI): 11.1–52.4) and against influenza B 4.1% (95% CI: –22.0 to 24.7).

Virus characterisation results

Full gene sequencing of the HA gene from 62 influenza A(H1N1)pdm09 samples revealed in 46 of them an amino acid substitution at position 179 (H1 complete open reading frame numbering) from serine to asparagine, which leads to a potential glycosylation site formed by positions 179–181 with the amino acid motif asparagine–glutamine–serine (NQS) (Table). Additional substitutions were revealed at amino acid position S101N and I233T in the 46 samples having the S179N. Two of the patient samples had an additional substitution at H155Y. Nine samples had a different amino acid motif with substitutions at positions V169T, V190I, E508G and D518E.

Phylogentic analysis revealed that all 62 sequenced HA genes of A(H1N1)pdm09 viruses belonged to genetic clade 6B (Figure 2), however, the 46 viruses with the S101N, S179N, and I233T substitutions formed their own subclade which now is categorised by the WHO as subclade 6B.1. In addition, the nine V169T, V190I, E508G and D518E viruses clustered together with the A/Minnesota/32/2015(H1N1pdm09) virus (Figure 2) and are now categorised as subclade 6B.2.

Of the 32 A(H1N1)pdm09 viruses isolated in cell culture, 25 belonged to subclade 6B.1, three belonged to subclade 6B.2, and four belonged to clade 6B. Antigenic characterisation showed all 32 virus isolates to be equally inhibited or inhibited to a lesser extent (two- to fourfold decrease in HAI titre), by ferret antiserum against A/California/07/2009 (H1N1pdm09) compared with the A/California/07/2009 (H1N1pdm09) reference virus HAI titres.

Of 447 influenza B virus samples from all age groups received for the national influenza surveillance programme at NIC Denmark by mid-March 2016, 350 were subtyped; 307 (88%) belonged to the B-Victoria lineage and 43 (12%) belonged to the B-Yamagata lineage. The HA genes of 15 B-Victoria viruses were sequenced and all belonged to clade 1A, corresponding to the

strain included in the quadrivalent vaccine but not included in the trivalent vaccine used in Denmark in the current season. Antigenic characterisation by HAI test of 13 virus isolates showed a two- to fourfold decrease in HAI-titre using the ferret antiserum against B/Brisbane/60/2008 compared with the vaccine reference virus B/Brisbane/60/2008. None of the B-Victoria viruses was inhibited by the B-Yamagata reference antiserum B/Phuket/3073/2013.

Discussion

Due to the late start of the influenza season in Europe only few interim VE estimates have been published [9,10] and in particular, little information is available on the VE in those aged 65 years and older, an important target group for influenza vaccination. Furthermore, a mismatch was observed between the circulating B-Victoria lineage and the B-Yamagata lineage included in the TIV for the northern hemisphere.

We found no effect of the TIV against influenza B 4.1% (95% CI: −22.0 to 24.7), which accounted for 62% of the influenza detections in patients aged 65 years and older in Denmark until 9 March 2016. This can be explained by the mismatch because 88% of the B infections were Victoria lineage. This is in line with findings from Hong Kong in 2011/12 where B-Victoria was included in the vaccine and VE against paediatric influenza B-Yamagata hospitalisation was estimated at 9.5% (95% CI: −240.4 to 76.0) [11]. However, in the same season, a study from the United States estimated a VE of 66% (95%CI: 38–81) against B-Yamagata although only the B-Victoria lineage was included in the vaccine [12], which could suggest cross-protection between lineages. Antigenic characterisation at the Danish NIC supports a lack of cross-reactivity between B-Yamagata and B-Victoria when using the current season's vaccine antiserum against B/Brisbane/60/2008 and B/Phuket/3073/2013 in the HAI test which is also reported in the study from Hong Kong [11]. Influenza B lineage-specific TIV VEs have earlier been estimated in seasons with both mismatch and/or cocirculation of two influenza B lineages. Some VE studies have suggested cross-protection between lineages and others not. The reasons for these differences are not known but may be explained by methodological issues or by differences in population immunity due to variations in vaccination strategies or differences in circulating lineages between regions [13].

It is likely that immunity against influenza B Victoria in the Danish population is low, as only few isolates from this lineage have been detected in Denmark since 2010/11 and have not been included in the vaccine since 2011/12. Influenza B-Victoria also dominates over B-Yamagata in the rest of Europe [14], and if the quadrivalent vaccine had been used instead of TIV during the current season morbidity due to influenza B might have been lower.

We found a moderate to low VE against influenza A(H1N1)pdm09 of 35.0% (95% CI: 11.1–52.4) in patients aged 65 years and older, although the majority of influenza A(H1N1)pdm09 circulating in Denmark in the 2015/16 season belonged to the new genetic subclade 6B.1. VE against influenza A(H1N1)pdm09 in the current season was similar to the VE against influenza A(H1N1)pdm09 in the 2014/15 season in Denmark of 31% (95% CI: −0.7 to 52.7) where 114 patients were positive for influenza A(H1N1)pdm09 and 3,351 patients tested negative (data not shown). This estimate also corresponds to the estimated VE of 22% (95% CI: −44.4 to 58.4) against influenza A(H1N1)pdm09 in the same age group in season 2014/15 reported by I-Move following a multicentre case–control study [15].

Conclusion

We estimated similar VE against influenza A(H1N1)pdm09 in season 2014/15 and 2015/16 in those aged 65 years and older in spite of the occurrence of the new subclade 6B.1. This is reassuring as the WHO recommendations for the influenza A(H1N1)pdm09 component in the 2016/17 vaccine for the northern hemisphere remained the same as in previous years, while the influenza B component changed from Yamagata to Victoria [16].

Acknowledgement

Test results for influenza virus were obtained from the Danish Microbiology Database (MiBa, http://miba.ssi.dk), which contains all electronic reports from departments of clinical microbiology in Denmark since 2010, and we acknowledge the collaboration with the MiBa Board of Representatives.

The authors gratefully acknowledge the 59 originating and submitting laboratories who contributed sequences used in the phylogenetic analysis to GISAID (www.gisaid.org).

We also acknowledge for the laboratory work, Dennis Jelsbak Schmidt and Bente Andersen, National Influenza Center Denmark, Statens Serum Institut, Copenhagen, Denmark.

Statens Serum Institut would also like to acknowledge the participation in the I-MOVE+ (Integrated Monitoring of Vaccines in Europe) project that has received funding from the European Union´s Horizon 2020 research and innovation programme under grant agreement Nº 634446.

Conflict of interest

None declared.

Authors' contributions

Hanne-Dorthe Emborg led the writing of the paper. Ramona Trebbien was responsible for the virological characterization and Jesper Rønn for the laboratory work. Lene Nielsen, Marianne Kragh Thomsen, Claus Bohn Christiansen, Marianne Nielsine Skov, Xiaohui Chen Nielsen and Lenette Sandborg Weinreich performed the initial diagnostics of influenza positive samples. Tyra Grove Krause and Thea Kølsen Fischer conceptualised the study together with Hanne-Dorthe Emborg and Ramona Trebbien and discussed

the data and perspectives. All authors provided contributions to the paper and approved the final version.

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Effectiveness of seasonal influenza vaccine in preventing influenza primary care visits and hospitalisation in Auckland, New Zealand in 2015: interim estimates

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Citation style for this article:
Bissielo A, Pierse N, Huang Q, Thompson M, Kelly H, Mishin V, Turner N, SHIVERS. Effectiveness of seasonal influenza vaccine in preventing influenza primary care visits and hospitalisation in Auckland, New Zealand in 2015: interim estimates. Euro Surveill. 2016;21(1):pii=30101. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.1.30101

Article submitted on 01 December 2015 / accepted on 22 December 2015 / published on 07 January 2016

Preliminary results for influenza vaccine effectiveness (VE) against acute respiratory illness with circulating laboratory-confirmed influenza viruses in New Zealand from 27 April to 26 September 2015, using a case test-negative design were 36% (95% confidence interval (CI): 11–54) for general practice encounters and 50% (95% CI: 20–68) for hospitalisations. VE against hospitalised influenza A(H3N2) illnesses was moderate at 53% (95% CI: 6–76) but improved compared with previous seasons.

Introduction

Seasonal influenza vaccines are used widely to reduce the burden of influenza, but effectiveness measures vary by a range of factors including season, age and underlying co-morbidities [1,2]. The Southern Hemisphere Influenza and Vaccine Effectiveness, Research and Surveillance (SHIVERS) study [3], running since 2012, allows estimation of vaccine effectiveness (VE) against patients presenting with influenza illness to general practice (primary care) and against influenza requiring hospitalisation. Reports were published for 2012, 2013 and 2014 [4–6]. Here we report the preliminary VE results for the 2015 influenza season in New Zealand.

Methods

We used the case test-negative design, as previously described [4], to estimate VE of southern hemisphere trivalent inactivated influenza vaccine (IIV3) against laboratory-confirmed influenza in patients presenting during the 2015 winter season. We included patients who had presented to selected general practices with an influenza-like illness (ILI) or who had been hospitalised with a severe acute respiratory infection (SARI). Both syndromes were defined as onset of an acute illness with a cough and a history of fever or measured temperature ≥ 38 °C; illnesses with onset within the past seven days before presentation were included in this report.

Ethics approval was obtained from the Northern A Health and Disability Ethics Committee (11/11/102/AM02). The analysis was done on data collected between 27 April and 26 September 2015. The study population for both ILI and SARI came from the Central, South and East Auckland city districts with a population of ca 900,000.

ILI patients were recruited from 16 sentinel general practices that serve ca 100,000 enrolled patients. All identified ILI patients were screened for influenza by a general practitioner or practice nurse, and data were entered through an electronic form into the practice management system. SARI patients were recruited by a research nurse screening all patients admitted overnight with a respiratory illness, and data were collected on a case report form and completed with information from electronic hospital records. All consenting patients had a nasopharyngeal or throat swab collected for influenza virus testing.

Confirmed cases of influenza were defined as those with a positive laboratory result for any influenza virus detected by real-time reverse transcription PCR (rRT-PCR). As per previous years, all swabs were tested using the United States Centers for Disease Control and Prevention (CDC) protocol [7] or the AusDiagnostic PCR protocol [8]. The assays detected influenza virus types A and B, A subtypes and B lineages. A screening

Figure 1

Study participants with influenza-like illness (n = 1,197) and severe acute respiratory infection (n = 754) who were influenza virus-positive or -negative, by week, Auckland, New Zealand, 27 April–26 September 2015

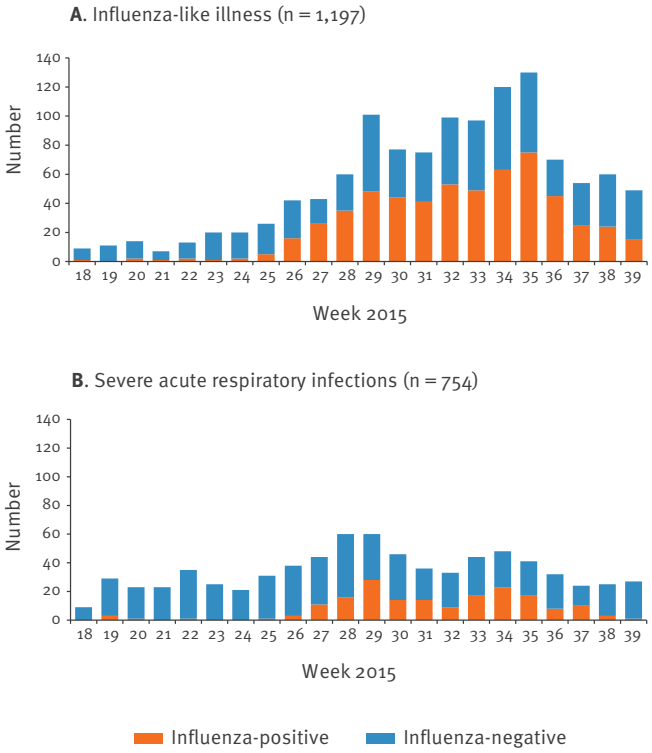
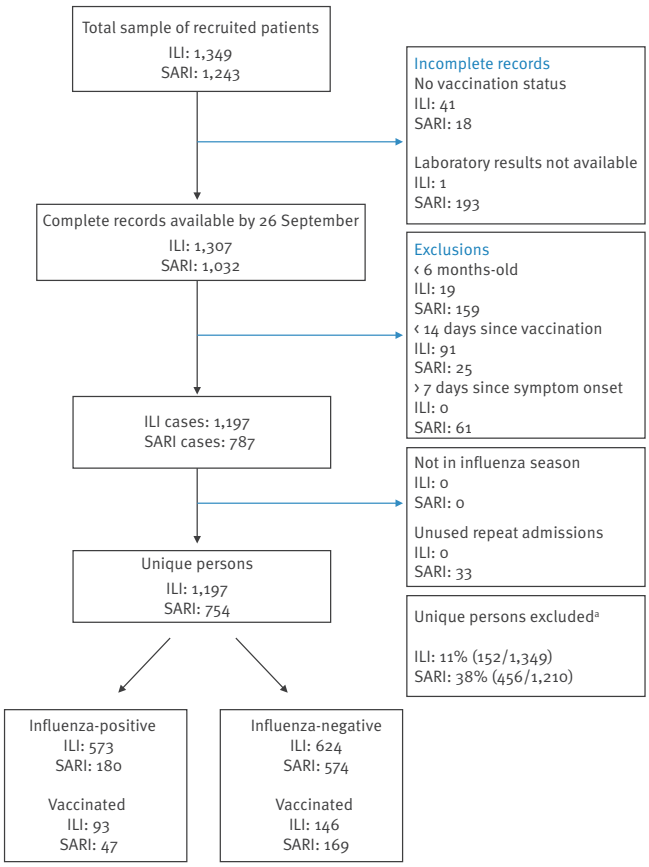


Figure 2

Flowchart of all patients with influenza-like illness (n = 1,197) and severe acute respiratory infection (n = 754) selected, recruited and tested for influenza vaccine effectiveness analysis, Auckland, New Zealand, 27 April–26 September 2015



ILI: Influenza-like illness; SARI: severe acute respiratory infection.

a A number of SARI patients are admitted to hospital multiple times. The total of 1,243 included multiple admissions, which were removed in this box.

of A(H3N2) viruses for genetic markers associated with six major haemagglutinin (HA) genetic groups (3C.2, 3C.2a, 3C.2b, 3C.3, 3C.3a, and 3C.3b) was done with a pyrosequencing assay. The detailed protocol for the H3 genetic groups pyrosequencing assay is available upon request (fluantiviral@cdc.gov).

Vaccination status for ILI patients was ascertained from electronic documentation in the general practice records. For SARI patients, vaccination status was based on self-report. A patient was considered fully vaccinated if they had received at least one self-reported or documented dose of the 2015 influenza vaccine.

We excluded infants younger than six months, those vaccinated less than 14 days before illness onset and those with symptom onset more than seven days before presentation. For patients with multiple illness presentations, the first influenza virus-positive episode was used for the analysis or, when there was no influenza virus-positive episode, the first illness episode.

VE was analysed for all influenza viruses, subtypes and clades. Unconditional logistic regression was used to compare the odds of vaccination among influenza virus-positive vs influenza virus-negative participants for both ILI and SARI datasets, with VE estimated as 100% x (1–OR). VE estimates were adjusted for age group, calendar week, any underlying health condition and days since illness onset at swab collection.

Results

In total, 1,197 ILI and 754 SARI patients were included for analysis (Figure 1 and Figure 2).

Of these, 573 (47.9%) of the ILI and 180 (23.9%) of the SARI were influenza virus-positive (Figure 2). Of all influenza infections, 399 were with influenza A viruses (285 ILI and 114 SARI); 281 were influenza A(H3N2), one was A/California/7/2009(H1N1) and 117 were not subtyped at the time of reporting. All 101 pyrosequenced influenza A(H3N2) samples were identified as clade 3C.2a (86 ILI and 15 SARI), which is like the vaccine component. There were 354 influenza B viruses (288 ILI and 66 SARI); 140 were B/Yamagata (including 95 B/Phuket/3073/2013 lineage), 159 were B/Victoria (including 52 B/Brisbane/60/2008 lineage) and 55 were not genotyped at the time of reporting.

Table

Crude and adjusted estimated influenza vaccine effectiveness by age group and influenza virus type and subtype, Auckland, New Zealand, 27 April–26 September 2015

Influenza type or	Influenza-positive			Influenza-negative			Unadjusted		Adjusted[a]	
Age groups	Number vaccinated	Total	%	Number vaccinated	Total	%	VE %	95% CI	VE %	95% CI
ILI										
Overall	93	573	16	146	624	23	37	15 to 52	36	11 to 54
6 months–17 years	15	260	6	26	258	10	45	−6 to 72	50	1 to 75
18-64 years	59	287	21	89	331	27	30	−2 to 52	27	−8 to 51
≥ 65 years	19	26	73	31	35	89	65	−36 to 91	67	−41 to 92
Influenza A	54	285	19	146	624	23	23	−9 to 46	24	−15 to 50
A(H3N2)	45	216	21	146	624	23	14	−26 to 41	22	−23 to 51
Influenza B	39	288	14	146	624	23	49	25to 65	46	17 to 65
B/Yamagata	18	131	14	146	624	23	48	11 to 69	35	−18 to 64
B/Victoria	19	145	13	146	624	23	56	22 to 75	56	22 to 75
SARI										
Overall	47	180	26	169	574	29	15	−24 to 42	50	20 to 68
6 months–17 years	3	55	5	30	312	10	NA	NA	NA	NA
18-64 years	25	92	27	61	154	40	43	0 to 68	46	1 to 70
≥ 65 years	19	33	58	78	108	72	48	−17 to 77	52	−14 to 79
Influenza A	33	114	29	169	574	29	2	−52 to 37	54	21 to 73
A(H3N2)	19	65	29	169	574	29	1	−74 to 44	53	6 to 76
Influenza B	14	65	22	169	574	29	34	−22 to 65	40	−24 to 71

CI: Confidence interval; ILI: Influenza-like illness; NA: not applicable; SARI: severe acute respiratory infections; VE: vaccine effectiveness.

Overall: includes any influenza and all ages ≥ 6 months; B/Yamagata: B/Yamagata lineage + B/Phuket/3073/2013-like; B/Victoria: B/Victoria lineage + B/Brisbane/60/2008-like.

[a]Adjusted for six age groups (<6, 6–17, 18–45, 46–64, 65–79 and ≥80 years), week in season, any underlying health condition and days since illness onset at swab collection.

Data source: SHIVERS 27 April to 26 September 2015 (week 18–week 39).

Among ILI patients of all ages, 93 of 573 (16%) influenza virus-positive persons and 146 of 624 (23%) influenza virus-negative persons were vaccinated, resulting in a crude VE against all circulating influenza strains of 37% (95% confidence interval (CI): 15–52); VE adjusted for variables listed in the methodology was 36% (95% CI: 11–54). Adjusted VE point estimates by age group were 50%, 27% and 67% for patients aged 6 months to 17 years, 18–64 years and ≥ 65 years, respectively, but with wide confidence intervals (Table).

For all ages, the adjusted VE against ILI with influenza A(H3N2) viruses was 22% (95% CI: −23 to 51), but the VE point estimate, though not statistically significant, was slightly higher for the subset identified as Clade 3C.2a: 27% (95% CI: −46 to 63). For all ages, the adjusted VE against ILI with any influenza B virus was 46% (95% CI: 17–65), but the VE point estimate, though not statistically significant, was slightly higher for the B/Victoria than for B/Yamagata lineage.

Among hospitalised SARI patients of all ages, 47 of 180 (26%) influenza-positive persons and 169 of 574 (29%) influenza-negative persons were vaccinated, resulting in a crude VE of 15% (95% CI: −24 to 42) against circulating influenza viruses. VE adjusted for age, week, underlying conditions and days since onset was higher at 50% (95% CI: 20–68). Adjusted VE point estimates against SARI influenza by age were 49%, 46% and 52% for patients aged 6 months to 17 years, 18–64 years and ≥ 65 years, respectively, but with wide confidence intervals (Table) (p interaction = 0.99). Age-adjusted VE for influenza A(H3N2) virus-associated SARI was 53% (95% CI: 6–76); we did not have a sufficient number of Clade 3C.2a identified viruses to date to do a clade-specific SARI VE estimate. Finally, for SARI associated with influenza B (of either lineage), adjusted VE was 40% (95% CI: −24 to 71).

Background

In New Zealand, the influenza season occurs between March and September, and southern hemisphere IIV3 is offered annually free of charge from early March to all those older than six months with high risk medical conditions, to pregnant women and to those 65 years and older. The influenza strains in the 2015 trivalent vaccine were A/California/7/2009 (H1N1)-like virus, A/Switzerland/9715293/2013 (H3N2)-like virus and B/Phuket/3073/2013-like virus.

Discussion

The 2015 New Zealand influenza season was dominated by influenza A(H3N2) and B viruses (including both B/Victoria and B/Yamagata lineages). Our interim results suggest that IIV3 was ca 37–50% effective at preventing influenza-associated acute respiratory illnesses (with fever and cough) that resulted in general practice visits or hospitalisation. If this trend continues, the overall VE observed in 2015 will be similar to the moderate VE reported during the previous three influenza seasons in New Zealand, even though the virus mix was different. VE point estimates have been consistently around 50% with minimal differences between ambulatory and inpatient medical care [4-6].

In 2014, although influenza A(H1N1)pdm09 was the predominant circulating strain, A(H3N2) viruses were also in circulation. During 2014, we observed no measureable protection of southern hemisphere IIV3 against influenza A(H3N2) virus-associated ILI or SARI [9]. This was consistent with reports from the northern hemisphere during the 2014/15 season, when the A/Texas/50/2012 (H3N2)-like component of the vaccine was not a good match to the circulating strains [10-13]. The influenza A(H3N2) IIV3 component was subsequently changed to A/Switzerland/9715293/2013 (H3N2)-like virus. In this interim 2015 report, all influenza A(H3N2) viruses with pyrosequencing performed to date belonged to the genetic clade 3C.2a, which is antigenically related to the vaccine clade 3C.3a.

We are encouraged by our interim observation of positive VE point estimates for influenza A(H3N2) virus-associated ILI (22%; 95% CI: –23 to 51) and SARI (53%; 95% CI: 6–76), which may indicate that VE improved with the change in vaccine strain.

The precision of our interim estimates was limited by relatively small numbers of observations for some ages and outcomes. Large differences in vaccination uptake and influenza positivity between age groups also resulted in substantial differences between our crude and adjusted VE estimates for SARI. Specifically, when we combined the data across ages, the lower vaccination coverage among children and greater likelihood of older age groups testing positive for influenza virus biased the crude VE estimate towards the null (i.e. Simpson's paradox which occurs because vaccination and the likelihood of testing positive are both correlated with age [14]).

Our interim results are subject to at least four other limitations. Firstly, the hospitalised patient results are based on self-reported vaccination status. However self-reporting has been shown to be generally accurate, especially among hospitalised elderly patients [15], and when comparing self-reporting with documented vaccination status, VE estimates have been shown to be very similar [16]. Secondly, the precision of our age and (sub)type-specific estimates was low given the use of preliminary data with few observations in many categories. Thirdly, we adjusted for covariates included in prior VE analyses, but a complete examination of potential confounders, including confirmation of chronic medical conditions must await our final report. Finally, we examined VE for a single dose only and because of pending vaccination records and small numbers of children enrolled to date we could not examine VE for the two-dose regimen recommended for children under the age of nine years.

Similar to previous SHIVERS studies, this study suggests that inactivated influenza vaccines provided moderate protection against laboratory-confirmed influenza virus illness in general practice and hospital settings.

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Acknowledgements

The SHIVERS (Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance) project is funded by the United States Department of Health and Human Services, Centers for Disease Control and Prevention (CDC) (1U01IP000480).

The SHIVERS project is a multiagency and multidisciplinary collaboration: Institute of Environmental Science and Research, Auckland District Health Board, Counties Manukau District Health Board, University of Auckland, University of Otago, the US Centres for Disease Control and Prevention and WHO Collaborating Centre at St Jude Children's Research Hospital in Memphis, United States.

WHO Collaborating Centre for Research and Surveillance of Influenza, Melbourne and US Centres for Disease Control and Prevention for supplying antigenic typing reagents and some results for influenza isolates.

The 16 participating sentinel general practices from Auckland PHO, East Tamaki Health Care and ProCare.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention.

Conflict of interest

None declared.

Authors' contributions

Ange Bissielo: involved in study design, data collection and analysis, interpretation and manuscript development. Nevil Pierse: involved in study design, methodological design, data analysis, interpretation and manuscript development. Q Sue Huang: principal investigator for the larger SHIVERS study, involved in study design, implementation, and manuscript development. Mark Thompson: involved in study design, interpretation and manuscript development. Heath Kelly: involved in study design, methodological analysis, data analysis and interpretation, manuscript development and editing. Vasiliy Mishin: involved in methodological and data analysis analysis, Nikki Turner: involved in study design, implementation, analysis, manuscript development.

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Effectiveness of the live attenuated and the inactivated influenza vaccine in two-year-olds – a nationwide cohort study Finland, influenza season 2015/16

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Citation style for this article:
Nohynek H, Baum U, Syrjänen R, Ikonen N, Sundman J, Jokinen J. Effectiveness of the live attenuated and the inactivated influenza vaccine in two-year-olds – a nationwide cohort study Finland, influenza season 2015/16. Euro Surveill. 2016;21(38):pii=30346. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.38.30346

Article submitted on 19 July 2016 / accepted on 03 September 2016 / published on 22 September 2016

Although widely recommended, influenza vaccination of children is part of the national vaccination programme only in few countries. In addition to Canada and the United States (US), in Europe Finland and the United Kingdom have introduced live attenuated influenza vaccine (LAIV) for healthy children in their programmes. On 22 June 2016, the US Advisory Committee on Immunizations Practices, voted against further use of LAIV due to no observed vaccine effectiveness (VE) over three consecutive influenza seasons (2013/14 to 2015/16). We summarise the results of a nationwide, register-based cohort study (N=55,258 of whom 8,086 received LAIV and 4,297 TIV); all outcome (laboratory-confirmed influenza), exposure (vaccination) and confounding variable data were retrieved from four computerised national health registers, which were linked via a unique personal identity code assigned to all permanent Finnish residents regardless of nationality. Our study provides evidence of moderate effectiveness against any laboratory-confirmed influenza of the quadrivalent LAIV vaccine (VE: 51%; 95% confidence interval (CI): 28–66%) as well as the inactivated trivalent vaccine (VE: 61%; 95% CI: 31–78%) among two-year-olds during the influenza season 2015/16 in Finland. Based on these data, Finland will continue using LAIV for young children in its National Immunisation Programme this coming influenza season.

Introduction

Influenza causes mild to severe symptoms among one in three young children. Vaccination is considered the best available intervention to prevent influenza in children and its spread from children to other age groups reducing the disease burden in the entire population [1]. Many European countries recommend to vaccinate the elderly, medical risk groups and healthcare workers but only nine countries recommend vaccination of healthy children, i.e. Austria, Estonia, Finland, Latvia, Malta, Poland, Slovakia, Slovenia, and the United Kingdom (UK) [2].

Since 2007, influenza vaccine has been given free of charge to all children aged 6 to 35 months as part of the National Vaccination Programme of Finland (NVP) [3], following a formal cost effectiveness analysis [4] requested by the National Immunization Technical Advisory Group and favourable decision by the government. For young healthy children and those above three but under nine years of age with medical risk conditions, the recommended schedule has included two doses for those vaccinated for the first time ever and one dose if they were already vaccinated during previous seasons.

Different types of influenza vaccines have been available for large scale use since early 1970s. Inactivated influenza vaccines have been commonly used. The live attenuated influenza vaccine (LAIV) was developed already in the 1960s but it has been available for large scale use in the United States (US) since 2003 (FluMist) and in Europe since 2011 (Fluenz). Prior to season 2015/2016, in Europe, only the UK had introduced LAIV for healthy children in their programme.

During the influenza season 2015/16, for the first time in Finland, two-year-olds (i.e. children aged 24 to 35 months) were offered either one or two doses of trivalent inactivated influenza vaccine (TIV; Vaxigrip) or one dose of LAIV (FluenzTetra). No preference for either was made in the national recommendation. Both vaccines were scheduled to be given in November and December 2015, although TIV could also be used from 6 January 2016 onwards after LAIV doses available in NVP had expired.

On 22 June 2016, the US Advisory Committee of Immunization Practices (ACIP) discussed the effectiveness of LAIV given to children from 2 to 17 years of age over three consecutive seasons in the US. Due to no observed vaccine effectiveness using the test negative design methodology, the ACIP voted against the use of LAIV in children during the coming season 2016/17 [5]. However, mid-season data from both Finland and the UK made available to the ACIP via CDC demonstrated reasonable effectiveness of the LAIV vaccine produced in the same plant [6,7].

As part of its statutory tasks, the Finnish National Institute for Health and Welfare (THL) is obliged to monitor the effectiveness and safety of vaccines used, in order to measure the impact of the NVP, and to give evidence-based vaccination recommendations [3]. Finland recently established a nationwide, computerised, real-time vaccination register (NVR) [8]. Linking NVR with disease register data in real time allows comprehensive effectiveness studies in timely manner. We present the end-of-season estimate of the influenza vaccine effectiveness (VE) among all two-year-old children residing permanently in Finland during the influenza season 2015/16 using national register data.

Methods

Study design and follow-up period

This nationwide register-based cohort study retrospectively assessed influenza VE in two-year-old children, i.e. the birth cohort of 2013, during the influenza season 2015/16, defined as lasting from week 40 (28 September 2015) to week 20 (22 May 2016). All outcome, exposure and confounding variable data were retrieved from four computerised national health registers maintained by THL, which were linked via a unique personal identity code assigned to all permanent Finnish residents regardless of nationality.

Study population

The study population, i.e. the birth cohort of 2013, was defined based on the Finnish Population Register, which contains an up-to-date information of all permanent residents in Finland.

Exposure

Vaccination status was defined by the NVR, which contains individual-level vaccination records comprising the vaccinee's personal identity code, the administered vaccine (including brand name) and the date of vaccination. The NVR covers records of vaccinations given from 2009 onwards in public primary healthcare, which is responsible for the delivery of the NVP. However, small regional and temporal information gaps are assumed, mainly due to data dispatch problems [8]. Every individual within the study population and with at least one recorded influenza vaccination in the NVR in 2015/16 was considered vaccinated since the day of vaccination. For purposes of sensitivity analysis, children were also considered vaccinated only after a two-week-period following vaccination allowing them to develop a sufficiently protective immunity. Consecutive vaccinations within the same season are rare among two-year-olds, and observed in less than 1% of those vaccinated. They were not considered in the analysis.

Outcome

The outcome of interest was any laboratory-confirmed influenza (LCI) registered in the National Infectious Disease Register (NIDR). The NIDR covers nationwide data about LCI cases, diagnosed in both public and private primary and secondary care. No universal recommendation exists when a suspected case should be tested for influenza. In Finland, influenza suspected patients are tested for influenza by RT-PCR, multiplex RT-PCR, culture and/or antigen detection and all influenza-positive cases from all laboratories are reported to the NIDR, where the patient's personal identity code, the influenza type, and the date of laboratory confirmation is recorded. In this report, LCI was defined as influenza finding in RT-PCR, multiplex RT-PCR, culture and/or antigen detection test, and further stratified to LCI type A and LCI type B.

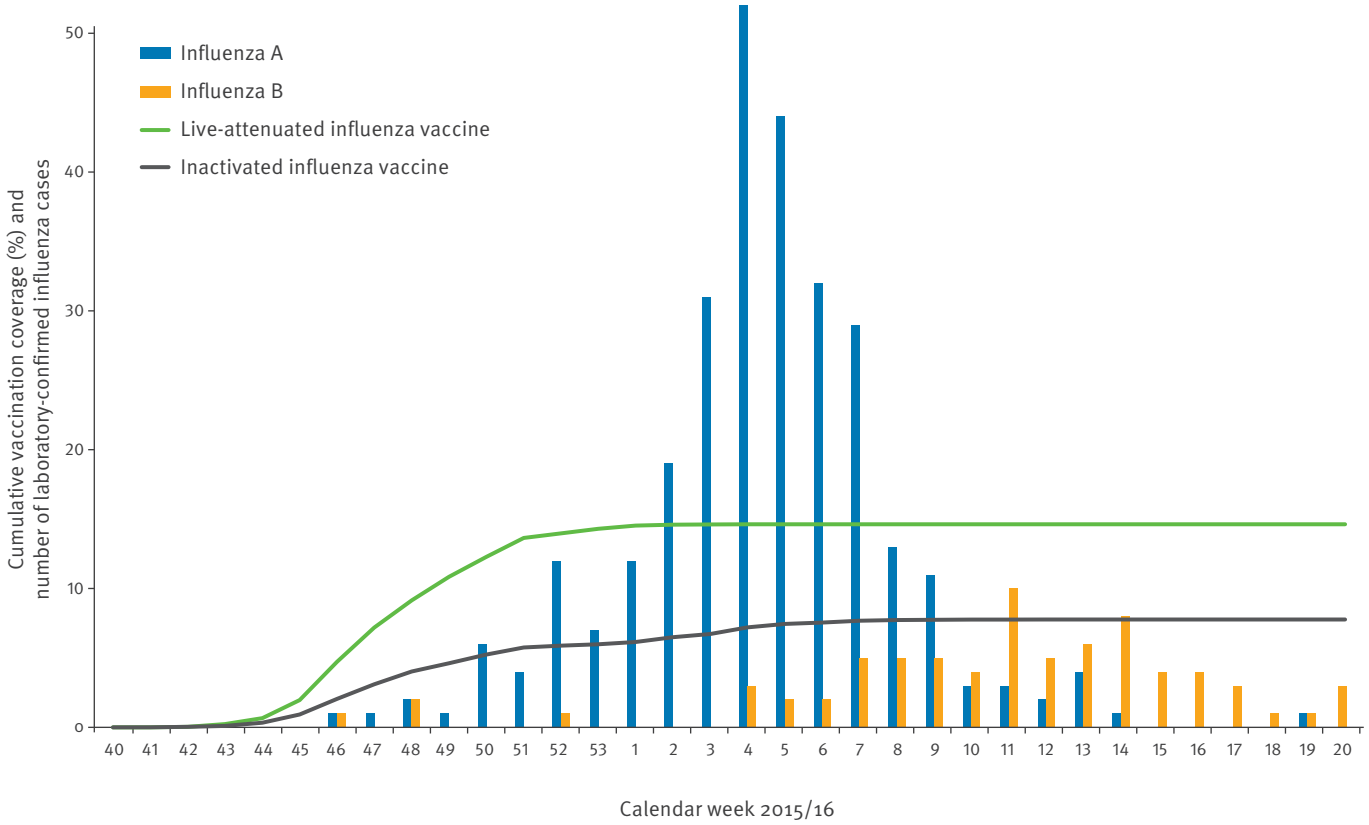
Confounders

In order to control for potential confounders, several variables describing the characteristics of the study population were included in the analysis. Background information was collected from the Finnish National Medical Birth Register (NMBR), which contains data about the status of the child and the mother at the time of child's birth [9]. The following 12 categorical variables (levels given in Table 1) were considered in the analysis: mother's age at birth in years (<20, 20–24, 25–29, 30–34, 35–39, ≥40), socio-economic status (based on mother´s profession), marital status and smoking behaviour, as well as child's birth weight in grams (<1,500, 1,500-2,499, ≥2,500), gestational age at birth in weeks, number of siblings at birth, month of birth (January–June, July–December) as indicator for the eligibility to previous seasonal influenza vaccinations, sex, nationality, place of residence, and BCG (Bacillus Calmette–Guérin) vaccination status.

Acute and chronic diagnoses made in hospitals were extracted from the National Register of Health Care (NRHC), which covers diagnosis information of all outpatient and inpatient healthcare provided in Finnish hospitals [10]. The following three acute diseases diagnosed within 6 months before the vaccination campaign (weeks 14–39 in 2015) and 13 chronic disease entities from birth until the end of 2015 were selected based on their International Statistical Classification of Diseases and Related Health Problems tenth Revision (ICD-10) codes [11]: acute bacterial and viral infections (A30–A49, A85–A89), acute diseases of the middle ear (H65–H75, H92), acute respiratory infections (J00–J06, J10–J22), HIV (B20–B24), malignant neoplasms (C69–C97), diseases of the blood and blood forming organs (D55–D89), diabetes mellitus and obesity (E10–E14,

Figure

Cumulative seasonal influenza vaccination coverage and number of laboratory-confirmed influenza in two-year-old children by calendar week, Finland, influenza season 2015/16 (n=55,258)



E65–E68), mental retardation (F71–F73, F79.1), diseases of the nervous system (G31, G40–G41, G70–G73, G80–G83), heart diseases (I34–I37, I42, I50), diseases of the respiratory system (J35, J40–J47), atopic dermatitis (L20), diseases of the musculoskeletal system and connective tissue (M02–M07, M13, M30–M36), diseases of the kidney (N00–N19), congenital malformations of the circulatory and respiratory system and Down syndrome (Q20–Q39, Q90) and undergone organ transplantations (Z94.0–Z94.6).

In contrast to the NVR and the NIDR, the NRHC does not accumulate in real time and is currently updated once a year. At the time this study was conducted, the NRHC covered patient encounters until the end of 2015, with preliminary data for 2015.

Statistical analysis

VE was defined as one minus the hazard rate ratio, estimated using Cox regression [12] with the time since the first day of week 40 as underlying time scale. Influenza vaccination was treated as time-dependent variable. VE was estimated for LAIV and TIV separately, using the unvaccinated cohort as a reference for both. Each individual of the study population was followed till the date of LCI, the date of receiving either (i) TIV (when analysing LAIV effectiveness) or (ii) LAIV (when analysing TIV effectiveness), the last day of week 20 or death, whatever occurred first. The validity of the proportional hazards assumption was evaluated using Schoenfeld residuals, and no notable deviation from proportionality was found.

The propensity score method [13] was used to account for potential confounders. In order to include also children with partially missing confounder information, missing values observed in five NMBR variables (Table 1 footnotes d and e; socio-economic status based on mother's occupation, mother's marital status, mother's smoking behaviour, birth weight, gestational age at birth) were imputed using hot deck imputation [14]. Altogether 29 variables, 12 categorical variables derived from NMBR plus one categorical (i.e. number of hospitalisations in 2015, irrespective of the ICD-10 code) and 16 binary variables derived from NRHC, were included into two separate propensity score models estimating each child's probability of being vaccinated (i) with LAIV and (ii) with TIV conditional on the covariates by applying logistic regression.

The VE estimates were adjusted for (i) LAIV propensity score quintiles in LAIV analysis and (ii) TIV propensity score quintiles in TIV analysis. In addition, further population and outcome subgroup-stratified analyses were conducted according to the child's seasonal influenza vaccination status in 2013/14 and 2014/15, as well as according to LCI type A and LCI type B.

Table 1

Baseline characteristics of two-year-old children by seasonal influenza vaccination status, Finland, influenza season 2015/16 (n= 55,258)

	Not vaccinated (N=42,875)	LAIV vaccinated (N=8,086)	TIV vaccinated (N=4,297)	p-value[a]
Mother's age at birth[b]				
Years	30 (5.3)	31 (5.0)	31 (5.0)	<0.001
Socio-economic status based on mother's occupation[c,e]				
Higher white-collar workers	8,596 (20.0)	2,158 (26.7)	1,145 (26.6)	<0.001
Lower white-collar workers	18,375 (42.9)	3,329 (41.2)	1,760 (41.0)	
Blue-collar workers	7,069 (16.5)	934 (11.6)	516 (12.0)	
Others	8,835 (20.6)	1,665 (20.6)	876 (20.4)	
Mother's marital status[d]				
Single or divorced	4,202 (9.8)	620 (7.7)	334 (7.8)	<0.001
Cohabiting	14,830 (34.6)	2,408 (29.8)	1,210 (28.2)	
Married	23,843 (55.6)	5,058 (62.6)	2,753 (64.1)	
Mother's smoking behaviour[d]				
No	35,303 (82.3)	7,284 (90.1)	3,867 (90.0)	<0.001
Quitted during first trimester	3,232 (7.5)	427 (5.3)	210 (4.9)	
Continued after first trimester	4,340 (10.1)	375 (4.6)	220 (5.1)	
Birth weight[b,d]				
Grams	3,514 (541.8)	3,470 (579.7)	3,459 (595.1)	<0.001
Gestational age at birth[d]				
<28 weeks	68 (0.2)	35 (0.4)	30 (0.7)	<0.001
≥28 and <37 weeks	4,173 (9.7)	903 (11.2)	504 (11.7)	
≥37 weeks	38,634 (90.1)	7,148 (88.4)	3,763 (87.6)	
Number of siblings at birth[c]				
0	16,156 (37.7)	4,057 (50.2)	1,830 (42.6)	<0.001
1	15,116 (35.3)	2,465 (30.5)	1,509 (35.1)	
>1	11,603 (27.1)	1,564 (19.3)	958 (22.3)	
Month of birth[c]				
January–June	22,169 (51.7)	3,424 (42.3)	1,967 (45.8)	<0.001
July–December	20,706 (48.3)	4,662 (57.7)	2,330 (54.2)	
Sex[c]				
Male	21,870 (51.0)	4,225 (52.3)	2,302 (53.6)	0.001
Female	21,005 (49.0)	3,861 (47.7)	1,995 (46.4)	
Nationality[c]				
Finnish	39,483 (92.1)	7,682 (95.0)	4,013 (93.4)	<0.001
Non-Finnish	3,392 (7.9)	404 (5.0)	284 (6.6)	
Place of residence[c]				
Urban	29,709 (69.3)	6,220 (76.9)	3,368 (78.4)	<0.001
Semi-urban	7,713 (18.0)	1,125 (13.9)	517 (12.0)	
Rural	5,453 (12.7)	741 (9.2)	412 (9.6)	
BCG vaccination status[c]				
Not vaccinated	39,403 (91.9)	7,618 (94.2)	3,988 (92.8)	<0.001
Vaccinated	3,472 (8.1)	468 (5.8)	309 (7.2)	
Presence of underlying chronic conditions[c]				
No	37,734 (88.0)	7,032 (87.0)	3,510 (81.7)	<0.001
Yes	5,141 (12.0)	1,054 (13.0)	787 (18.3)	
Presence of an acute disease between week 14–39, 2015[c]				
No	39,766 (92.7)	7,354 (90.9)	3,791 (88.2)	<0.001
Yes	3,109 (7.3)	732 (9.1)	506 (11.8)	
SIV vaccination status in2013/14 and 2014/15[c,f]				
Not vaccinated	38,288 (89.3)	3,470 (42.9)	1,386 (32.3)	<0.001
Vaccinated	4,587 (10.7)	4,616 (57.1)	2,911 (67.7)	

BCG: Bacillus Calmette–Guérin vaccine: LAIV: live attenuated influenza vaccine; TIV: trivalent inactivated influenza vaccine; SIV: seasonal influenza vaccine.

[a] One-way analysis of variance for continuous and chi-squared test of independence for categorical variables.

[b] Mean (standard deviation).

[c] Absolute frequency (relative frequency in %). Because of rounding, percentages may not total 100.

[d] Proportion of data imputed by hot deck imputation: <0.2%.

[e] Proportion of data imputed by hot deck imputation: 31.5%.

[f] Vaccinated group contains those vaccinated either in the 2013/14, 2014/15 season or both.

Table 2

Influenza vaccine effectiveness against laboratory-confirmed influenza in two-year-old children, stratified by influenza type, Finland, influenza season 2015/16 (n=55,258)[a]

Laboratory-confirmed influenza	Cases			Person-years			Crude effectiveness (95% confidence intervals)		Adjusted effectiveness (95% confidence intervals)	
Type	Not vaccinated	LAIV	TIV	Not vaccinated	LAIV	TIV	LAIV	TIV	LAIV	TIV
A and B	317	31	12	29,984	3,965	1,954	46.5% (22.7%–63.0%)	58.2% (25.6%–76.5%)	50.7% (28.4%–66.1%)	61.2% (30.7%–78.3%)
A	260	26	5	29,994	3,967	1,955	45.4% (18.2%–63.5%)	78.2% (47.3%–91.0%)	47.9% (21.6%–65.4%)	79.5% (50.3%–91.6%)
B	62	6	7	30,063	3,972	1,957	47.1% (-22.5%–77.1%)	-14.1% (-149.3%–47.8%)	57.2% (-0.0%–81.7%)	-1.0% (-122.8%–54.2%)

LAIV: live attenuated influenza vaccine; TIV: trivalent inactivated influenza vaccine.

[a] Crude and adjusted for propensity score quintiles.

When stratified by previous exposure to influenza vaccinations, there was a tendency towards higher effectiveness among those previously vaccinated (Table 3), although due to a small number of cases in each stratum, these differences were not statistically significant.

Results

Epidemiology of the 2015/16 influenza season in Finland

The Finnish sentinel surveillance [15] covering a representative sample of all age groups, demonstrated that the influenza season started earlier than usual (in week 47) and spread almost simultaneously all over the country. During the first wave of the season, influenza A(H1N1)pdm09 viruses predominated and all characterized A(H1N1)pdm09 viruses represented the new genetic subclade 6B.1. The second wave was caused by influenza B/Victoria viruses that genetically fell into the B/Brisbane/60/2008 clade. Influenza A(H3N2) viruses belonging to clades 3C.2a and 3C.3a were detected only sporadically. No B/Yamagata viruses were detected in 462 samples tested in the frame of the sentinel surveillance.

Influenza vaccine effectiveness in two-year-olds

The study population for the VE estimation comprised all permanent residents of Finland eligible for both LAIV and TIV vaccination, i.e. the birth cohort of 2013. Due to small regional and temporal information gaps in the NVR, 5% of the birth cohort 2013 were excluded because of presumably incomplete vaccination records. In addition, 2% that were not found in the NMBR were excluded, leaving 93% of the birth cohort for analysis. The final study population thus comprised 55,258 two-year-old children. The total influenza vaccination coverage was 22%; about two thirds were vaccinated with LAIV and one third with TIV. The characteristics of those included in the analyses are described in Table 1. Among the 55,258 children, a total 360 LCI were registered in the NIDR. Influenza A cases peaked in week 4 and caused 291 laboratory-confirmed infections. Influenza B mainly circulated between weeks 11 and 14 and caused 69 LCI cases in the study population (Figure). The majority of vaccinations was given before the epidemic (Figure).

The combined influenza A and B effectiveness estimates adjusted for potential confounders were similar among the LAIV and TIV recipients (51% and 61%, respectively) with widely overlapping confidence intervals (95%CI 28–66 vs. 31–78, respectively), as described in Table 2. The highest effectiveness (80%, 95%CI 50–92) was observed against influenza A among those vaccinated with TIV. Due to small numbers, the influenza B analysis yielded statistically borderline non-significant point estimates (Table 2). The results were practically the same when children were considered vaccinated only after a two-week-period following vaccination (data not shown).

When stratified by previous exposure to influenza vaccinations, there was a tendency towards higher effectiveness among those previously vaccinated (Table 3), although due to a small number of cases in each stratum, these differences were not statistically significant.

Discussion

In Finland, the overall influenza vaccine uptake during the influenza season 2015/16 among two-year-old children was low (22%) but sufficient for a meaningful effectiveness analysis using a nationwide cohort approach. The end-of-season effectiveness estimates were moderately good for both LAIV and TIV with generally slightly higher point estimates for TIV, although the confidence intervals were wide and overlapping. This is in contrast to the findings reported from the US where unlike TIV, LAIV yielded no effectiveness already for the third consecutive season [5]. The LAIV, however, was produced in the same plant for both North American and European markets. The results from the US were based on a test-negative case–control design (TND), and covered children aged 2 to 17 years, in contrast to

Table 3

Influenza vaccine effectiveness against laboratory-confirmed influenza in two-year-old children, stratified by influenza type and seasonal influenza vaccination status in the 2013/14 and 2014/15 seasons, Finland, influenza season 2015/16 (n=55,258)

Laboratory-confirmed influenza		Cases			Person-years			Crude effectiveness (95% confidence intervals)		Adjusted effectiveness (95% confidence intervals)	
Type		Not vaccinated	LAIV	TIV	Not vaccinated	LAIV	TIV	LAIV	TIV	LAIV	TIV
A and B	NPV	272	17	5	25,750	1,691	588	29.3% (-15.4%–56.7%)	40.1% (-45.1%–75.3%)	34.0% (-8.1%–59.7%)	44.1% (-35.7%–76.9%)
	PV	45	14	7	4,234	2,274	1,366	66.2% (38.4%–81.5%)	73.1% (40.4%–87.9%)	69.7% (44.0%–83.6%)	73.3% (40.4%–88.1%)
A	NPV	221	15	2	25,759	1,691	589	23.1% (-29.8%–54.4%)	69.3% (-23.4%–92.4%)	24.6% (-27.8%–55.5%)	70.6% (-18.6%–92.7%)
	PV	39	11	3	4,235	2,275	1,367	70.1% (41.6%–84.7%)	86.4% (56.0%–95.8%)	74.0% (48.5%–86.9%)	87.1% (57.9%–96.0%)
B	NPV	56	2	3	25,817	1,695	590	60.1% (-63.4%–90.3%)	-51.4% (-383.7%–52.6%)	68.5% (-29.8%–92.4%)	-29.3% (-315.5%–59.8%)
	PV	6	4	4	4,246	2,277	1,367	15.3% (-211.9%–77.0%)	-5.5% (-273.9%–70.2%)	16.7% (-213.7%–77.9%)	-25.1% (-352.0%–65.4%)

LAIV: live attenuated influenza vaccine; NPV: not previously vaccinated; PV: previously vaccinated; TIV: trivalent inactivated influenza vaccine.
[a] Crude and adjusted for propensity score quintiles.

this study's cohort design, focusing only on two-year-olds. Our findings are in agreement with those from the UK, where VE in the 2015/16 season was also moderate for influenza A and even good for influenza B [6,16,17] in children and adolescents younger than 18 years and based on a TND.

The particular strength of our study is that by utilising population-based registers, we were able to cover the whole population eligible for LAIV and TIV vaccination; monitoring VE by using routine health registers is particularly suitable for measuring the public health impact of vaccination programmes. Furthermore, the non-preferential national recommendation of influenza vaccinations for two-year-olds for the season 2015/16 allowed us to investigate the effectiveness of LAIV and TIV in parallel within the same cohort.

When using routine registers for defining the exposure, data completeness is a special concern. Therefore the quality and completeness of the NVR is constantly monitored [8] and geographic areas not fulfilling quality criteria are omitted from any cohort analysis. Based on a recent validation study [8] on childhood vaccinations – using MMR vaccination at the age of 12 months as a proxy – the register covers 96% of influenza vaccination records, translating to misclassification of approximately 500 vaccinated in our study cohort. Some LAIV doses may also have been given in the private primary care, which is not currently covered by NVR. However, since all NVP vaccinations are given in public primary care and free of charge, it is anticipated that private primary care uptake in our study cohort was negligible. This is supported by the national pharmaceutical distribution figures in 2015 of 2,120 LAIV doses distributed for the whole eligible age group of 2–17-year-olds. Finally, since lack of data completeness leads to misclassifying a subgroup of those vaccinated to the group of unvaccinated, our VE estimates can be considered conservative, i.e. an underestimation of the real VE.

As with any observational study, the VE estimates may be biased due to unobserved confounders or other types of unknown selection processes in the uptake of vaccinations or care seeking or access to care captured by routine register data. In order to account for potential biases, we adjusted our estimates with several background variables at birth and data of hospital visits prior to the 2015/16 seasonal influenza vaccination campaign. Information on baseline characteristics helps to understand the possible sources of bias in the analysis. The statistically significant differences observed between the three groups, i.e. not vaccinated, LAIV and TIV vaccinated, may not necessarily have clinical significance but underscore the need to perform adjusted analyses. Many of the characteristics thought to increase infection risk, such as siblings, non-Finnish nationality, non-urban residence, low socio-economic status, single mothers and smoking mothers, were more common among the non-vaccinated. Therefore it is somewhat surprising that the adjusted estimates are generally higher than the crude

estimates. This may be explained by healthcare-seeking behavior so that parents who get their children vaccinated are possibly also more likely to seek healthcare e.g. for acute respiratory infections like influenza. This is supported by the observation that diagnoses of both chronic and acute diseases prior to the vaccination campaign were more common among the vaccinated. In addition, parents e.g. with higher socio-economic status may predominantly use private primary care, in which the threshold for obtaining laboratory confirmation is presumably lower than in public primary care. Even after adjustment, some residual confounding may still be present.

The role of exposure to previous influenza vaccine doses in the immunological response to subsequent doses has been debated [18]. In young children, two doses have been recommended as necessary for the first time exposure to secure proper priming and maturation of sufficient protection. For LAIV, however, the difference in protection provided by first time one or two doses is marginal [19]. The NVR with vaccination data since year 2009 allows stratified analyses of effectiveness by previously received seasonal influenza vaccine doses; past exposure to influenza vaccines appears to contribute to increased effectiveness in the two-year-old children during the season 2015/16, but due to the relatively small sample size, this difference did not reach statistical significance.

A good antigen match was expected for the quadrivalent LAIV before the start of the 2015/16 influenza epidemic, because the World Health Organization had recommended to change the influenza vaccine composition for both the A(H3N2)- and B-components. Also, the A(H1N1) strain of LAIV was changed due to concerns over its heat instability. Since subtype specific identification of viruses is seldom done in routine clinical practice, our study can reliably address only overall and influenza A VE. The numbers of observations of influenza B viruses were few in this age group and there was not sufficient power to detect VE.

Conclusion

During the influenza season 2015/16, both LAIV and TIV were effective against laboratory-confirmed influenza among two-year-old children. Finland will continue using LAIV as an alternative intervention to TIV without any official statement on preference. Our study also demonstrates that population-based national health registers are extremely valuable to generate routine data for measuring vaccine impact in a timely manner.

Conflict of interest

None declared.

Authors' contributions

Hanna Nohynek: conceptualised the paper, participated in the analysis of the data, wrote the first draft and finalised the manuscript.

Ulrike Baum: planned and performed the statistical analyses, participated in the writing of the paper.

Ritva Syrjänen: participated in the analysis of the data and reviewed the manuscript.

Niina Ikonen: performed the virological analyses and participated in the writing of the paper.

Jonas Sundman: was in charge of the data management and reviewed the manuscript.

Jukka Jokinen: conceptualised the design and data sources to be used for the study, supervised the statistical analyses, participated in the writing of the paper.

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Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results

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Citation style for this article:
Pebody R, Warburton F, Ellis J, Andrews N, Potts A, Cottrell S, Johnston J, Reynolds A, Gunson R, Thompson C, Galiano M, Robertson C, Byford R, Gallagher N, Sinnathamby M, Yonova I, Pathirannehelage S, Donati M, Moore C, de Lusignan S, McMenamin J, Zambon M. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. Euro Surveill. 2016;21(38):pii=30348. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.38.30348

Article submitted on 15 July 2016 / accepted on 30 August 2016 / published on 22 September 2016

The United Kingdom (UK) is in the third season of introducing universal paediatric influenza vaccination with a quadrivalent live attenuated influenza vaccine (LAIV). The 2015/16 season in the UK was initially dominated by influenza A(H1N1)pdm09 and then influenza of B/Victoria lineage, not contained in that season's adult trivalent inactivated influenza vaccine (IIV). Overall adjusted end-of-season vaccine effectiveness (VE) was 52.4% (95% confidence interval (CI): 41.0–61.6) against influenza-confirmed primary care consultation, 54.5% (95% CI: 41.6–64.5) against influenza A(H1N1)pdm09 and 54.2% (95% CI: 33.1–68.6) against influenza B. In 2–17 year-olds, adjusted VE for LAIV was 57.6% (95% CI: 25.1 to 76.0) against any influenza, 81.4% (95% CI: 39.6–94.3) against influenza B and 41.5% (95% CI: –8.5 to 68.5) against influenza A(H1N1)pdm09. These estimates demonstrate moderate to good levels of protection, particularly against influenza B in children, but relatively less against influenza A(H1N1)pdm09. Despite lineage mismatch in the trivalent IIV, adults younger than 65 years were still protected against influenza B. These results provide reassurance for the UK to continue its influenza immunisation programme planned for 2016/17.

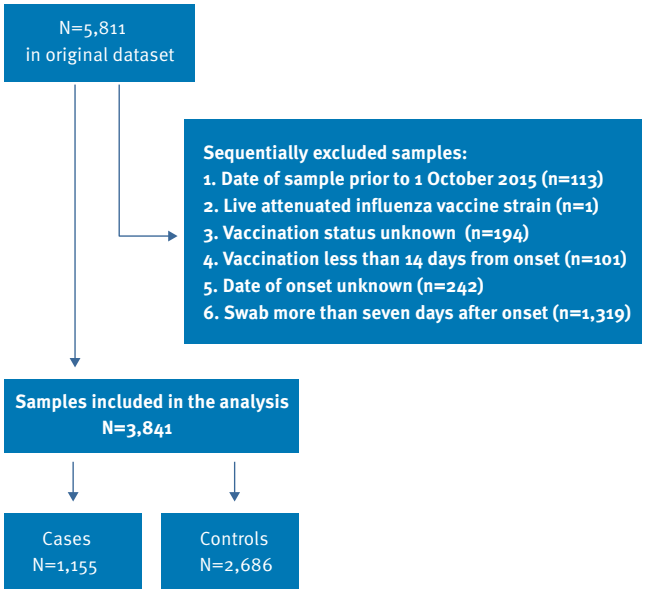
Introduction

The United Kingdom (UK) has had a long-standing selective inactivated influenza vaccination programme targeted at individuals at higher risk of severe disease such as the elderly, those with an underlying clinical risk condition and pregnant women. Following recommendations from the Joint Committee of Vaccination and Immunisation (JCVI) in 2012, the decision was taken for a phased introduction of a newly licensed live attenuated influenza vaccine (LAIV), ultimately offered LAIV in each season to all healthy children aged two to 16 years [1]. 2015/16 is the third season of the introduction of this new influenza vaccination programme; all healthy children aged two to four years and in school years 1 and 2 were offered a single dose of LAIV [2]. In Northern Ireland and Scotland and in selected pilot areas in England, all other older children of primary school age were also offered LAIV in 2015/16. Children aged two to 17 years in a clinical risk group were also offered LAIV, while children with a risk factor, in whom LAIV is contraindicated, were offered quadrivalent inactivated influenza vaccine (IIV). All children in a clinical risk group aged six to 23 months were offered IIV. The United States Centers for Disease Control and Prevention (US CDC) recently reported the observation that LAIV did not provide protection in children against circulating influenza strains in North America in the 2015/16 season [3]. This raised a question about the effectiveness of LAIV in children in the UK.

In the UK, the 2015/16 season started late, peaking in week 11 of 2016, with circulation initially dominated by influenza A(H1N1)pdm09 viruses. Impact mainly fell on younger adults resulting in large numbers of hospitalisations and admissions to intensive care units (ICU) [4].

Figure 1

Specimen inclusion and exclusion criteria, end-of-season 2015/16 influenza vaccine effectiveness evaluation, United Kingdom, 1 October 2015–1 May 2016 (n = 5,811)



Genetically, the haemagglutinin (HA) genes of A(H1N1) pdm09 viruses all belonged in subgroup 6B, the predominant clade circulating in the 2014/15 season. The later stages of the 2015/16 season were dominated by influenza B circulation, with the majority of viruses antigenically similar to B/Brisbane/60/2008, the influenza B/Victoria lineage component included in the 2015/16 northern hemisphere quadrivalent vaccine but not in the trivalent vaccine [4]. This raised questions about the protection provided by the 2015/16 trivalent vaccine, the main influenza vaccine offered to adults, and about the potential added value of switching to quadrivalent vaccine as the main vaccine of choice.

Following the mid-2015/16 season report of influenza vaccination effectiveness (VE) [5], this article presents the end-of-season estimates of influenza VE using well established systems across the four countries of the UK [6,7]. The aims of the investigation were to measure VE against laboratory-confirmed influenza by type, subtype and clade/lineage, and to determine the effectiveness of the vaccine in children two to 17 years of age according to type of vaccine, particularly in relation to LAIV, but also IIV. In addition, we estimated the effectiveness of both LAIV and IIV in children two to 17 years of age over the three seasons since the UK introduced the LAIV programme.

Methods

Study population and period

The test-negative case–control (TNCC) design was used to estimate VE. The study was undertaken in five sentinel general practice surveillance networks across the UK, details of which have been outlined previously [7]. The surveillance schemes were: Royal College of General Practitioners (RCGP), Research and Surveillance Centre (RSC), Specialist Microbiology Network (SMN) England and Wales, Northern Ireland and Scotland.

The main study took place from 1 October 2015 until 1 May 2016. The study population were patients presenting to their general practitioner (GP) during the study period with an acute influenza-like illness (ILI), who the physician consented verbally to be swabbed during the consultation. A patient with ILI was defined as an individual presenting in primary care with an acute respiratory illness with physician-diagnosed fever or complaint of feverishness. GPs were asked to swab a random sample of cases up to a total of 10 per week in any one practice. Cases were patients who tested positive for influenza A or B virus by real-time PCR. Controls were patients with the same symptoms who tested negative for influenza A and B. Further details of the laboratory methods are provided below.

During the consultation, the GP completed a standard questionnaire. It collected demographic, clinical and epidemiological information from patients including potential confounders such as sex, date of birth, underlying clinical risk factors, date of onset of ILI, date of sample collection (recommended within seven days of onset) and influenza vaccination history for the 2015/16 season including date of vaccination and route of administration (intranasal/injection). In England, residence in an area where a primary school LAIV immunisation programme took place was also recorded.

A further specific sub-analysis was undertaken among children two to 17 years of age for the period 1 October 2013 until 1 May 2016. This covered the period since the introduction of LAIV in the UK. All aspects of data collection, testing and analysis were comparable over this period and are as described above.

Laboratory methods

Sentinel GP surveillance networks sent the respiratory samples to the national laboratories as previously outlined [7]. Laboratory confirmation was made using comparable real-time PCR methods able to detect circulating influenza A and B viruses [8,9]. Positive samples were sent to the reference laboratories for genetic characterisation. Isolation of influenza viruses was tried from all PCR-positive samples using Madin-Darby canine kidney epithelial (MDCK) cells or MDCK cells containing the cDNA of human 2,6-sialtransferase (SIAT1) cells as described previously [10,11].

Antigenic characterisation was only undertaken at the PHE reference laboratory. Post-infection ferret antisera were used in haemagglutination inhibition (HI) assays with turkey red blood cells to antigenically characterise influenza A(H1N1)pdm09 and influenza B virus isolates with a haemagglutination titre ≥ 40 [12]. Reference virus strains used for HI assays for A(H1N1)pdm09

Figure 2

Phylogenetic tree of the haemagglutinin genes of sentinel influenza B isolates, United Kingdom, October 2015–May 2016 (n = 324)

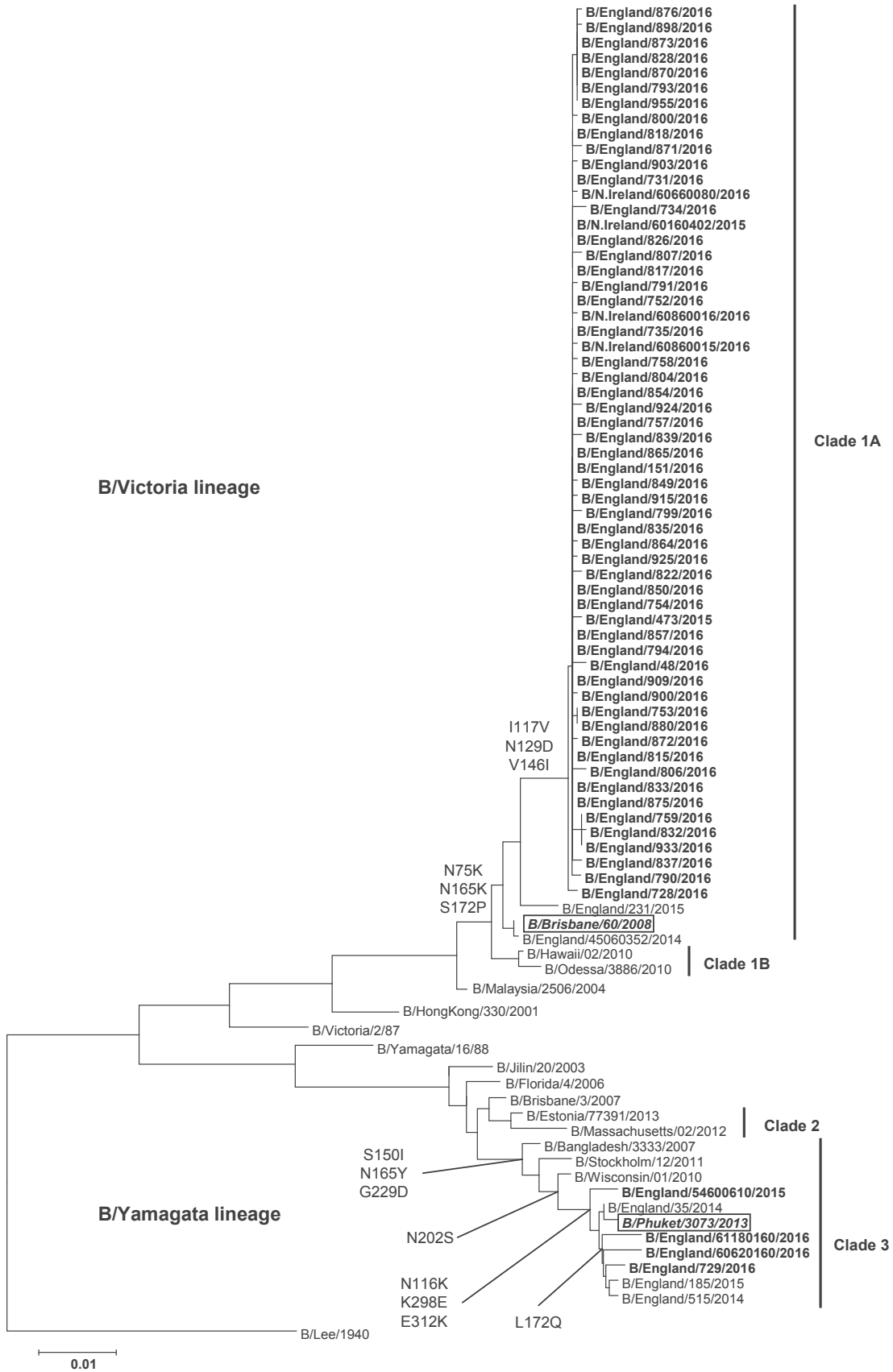


Table 1

Influenza B haemagglutinin sequences obtained from GISAID used in the phylogenetic analysis

Influenza virus isolate	Segment ID/ Accession number	Country	Collection date (year-month-day)	Originating laboratory	Submitting laboratory
B/Brisbane/3/2007	EPI154537	Australia	2007-Jan-01	Queensland Health Scientific Services, Queensland, Australia	WHO Collaborating Centre for Reference and Research on Influenza, Victoria, Australia
B/Stockholm/12/2011	EPI346827	Sweden	2011-Mar-28	Swedish Institute for Infectious Disease Control, Solna, Sweden	National Institute for Medical Research, London, UK
B/England/515/2014	EPI555201	United Kingdom	2014-Oct-22	Public Health England, London, UK	National Institute for Medical Research, London, UK
B/Estonia/77391/2013	EPI467120	Estonia	2013-Apr-08	Health Protection Inspectorate, Tallin, Estonia	National Institute for Medical Research, London, UK
B/Odessa/3886/2010	EPI271913	Ukraine	2010-Mar-19	Ministry of Health of Ukraine, Kiev, Ukraine	National Institute for Medical Research, London, UK
B/Phuket/3073/2013	EPI540675	Australia	2013-Nov-21	WHO Collaborating Centre for Reference and Research on Influenza, Victoria, Australia	National Institute for Medical Research, London, UK
B/Massachusetts/02/2012	EPI438406	United States	2012-Jan-01	New York Medical College, New York, US	Centers for Disease Control and Prevention, Atlanta, US
B/Wisconsin/01/2010	EPI271545	United States	2010-Feb-20	Wisconsin State Laboratory of Hygiene, Madison, US	Centers for Disease Control and Prevention, Atlanta, US
B/Hawaii/02/2010	EPI271558	United States	2010-Mar-25	State of Hawaii Department of Health, Pearl City, US	Centers for Disease Control and Prevention, Atlanta, US
B/Brisbane/60/2008	EPI172555	Australia	2008-Aug-04		Centers for Disease Control and Prevention, Atlanta, US
B/Florida/4/2006	EPI134356	United States	2006-Nov-01		Centers for Disease Control and Prevention, Atlanta, US
B/Bangladesh/3333/2007	EPI156050	Bangladesh	2007-Aug-18		Centers for Disease Control and Prevention, Atlanta, US

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

viruses included A/California/7/2009 (vaccine strain) grown in embryonated chicken eggs and other A(H1N1) pdm09 England strains grown in embryonated chicken eggs or tissue culture cells. Reference virus strains used for HI assays for influenza B viruses included B/Phuket/3073/2013 (trivalent and quadrivalent vaccine strain) and B/Brisbane/60/2008 (quadrivalent vaccine strain) together with a panel of other egg- and tissue culture-grown influenza B viruses from both the B/Yamagata/16/88-lineage and the B/Victoria/2/87 lineage. The fold difference between the homologous HI titre for the corresponding vaccine strain 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 was undertaken (primer sequences available on request) for a subset of influenza A(H1N1)pdm09 and B viruses selected to be representative of the range of the patients' age, date of sample collection, geographical location and, if performed, antigenic characterisation of the virus isolate, and phylogenetic trees were constructed with a neighbour-joining algorithm available in the Mega 6 software (http://www.megasoftware.net) [13]. The A(H1N1)pdm09 results have been previously presented [5]. HA sequences from reference strains used in the phylogenetic analysis for influenza B in this paper were obtained from GenBank: B/Malaysia/2506/2004 (CY038287), B/Jilin/20/2003 (CY033828), B/Yamagata/16/88 (CY018765), B/Victoria/2/87 (M58428), B/HongKong/330/2001 (AF532549) and from the EpiFlu database of the Global

Initiative on Sharing All Influenza Data (GISAID) (Table 1).

Statistical methods

Patients were defined as vaccinated if they had received the 2015/16 seasonal vaccine at least 14 days before first onset of ILI. Patients were excluded if they were vaccinated less than 14 days before symptom onset. If vaccinated, but date of vaccination was unknown, the median date of vaccination of those with known dates was taken instead. Patients with date of onset not known or onset more than seven days before swabbing were also excluded. A similar approach was used to undertake a pooled analysis for the 2013/14, 2014/15 and 2015/16 seasons.

The odds ratios (OR) obtained from multivariable logistic regression models were used to calculate VE with influenza laboratory results as the outcome and influenza vaccination status as the linear predictor. Influenza A(H1N1)pdm09- and influenza B-specific VE was also calculated. Samples positive for other subtypes were excluded as the numbers were too small, except for the three-season pooled analysis, which also included influenza A(H3N2). The adjusted estimates were set based on past seasons as age (age groups: 0–4, 5–17, 18–44, 45–64, ≥ 65 years), month of sample collection, residence in area where a primary school programme was in place, sex and surveillance scheme. We also explored whether being in a risk group for whom vaccination is recommended provided any evidence of confounding. For the three-year pooled analysis, year was also included in the model. All statistical analyses were carried out in Stata version 13 (StataCorp, College Station, Texas).

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: EPI679258, EPI811543, EPI811551, EPI811554, EPI811562, EPI811570, EPI811578, EPI811586, EPI811594, EPI811598, EPI811606, EPI811614, EPI811622, EPI811626, EPI811629, EPI811637, EPI811645, EPI811648, EPI811656, EPI811664, EPI811671, EPI811675, EPI811683, EPI811691, EPI811699, EPI811707, EPI811715, EPI811723, EPI811726, EPI811734, EPI811742, EPI811750, EPI811758, EPI811766, EPI811774, EPI811782, EPI811788, EPI811796, EPI811799, EPI811807, EPI811815, EPI811823, EPI811831, EPI811839, EPI811842, EPI811845, EPI811853, EPI811856, EPI811864, EPI811868, EPI811876, EPI811884, EPI811891, EPI811894, EPI811898, EPI811906, EPI811909, EPI811915, EPI811916, EPI811924, EPI811932, EPI811940, EPI811944, EPI811952, EPI811958.

Results

Of the 5,811 swabbed individuals potentially eligible, 3,841 individuals were confirmed eligible and included in the study (Figure 1). The details of those included in the study are provided by swab result in Table 2, including those with missing data. There were a total of 2,686 controls, 351 (9.1%) influenza B detections, 770 A(H1N1)pdm09 detections (20.0%), 24 influenza A(H3N2) detections (0.6%) and 15 influenza A(untyped) detections (0.4%). Four samples tested positive for both A(H1N1)pdm09 and influenza B and one sample was positive for both A(H1N1)pdm09 and A(H3N2). Positivity rates differed significantly by age group, sex, risk group, month, scheme, vaccination status and area of primary school programme in England (Table 2).

Influenza A(H1N1)pdm09 and B strain characterisation from sentinel samples

Since week 40 in 2015, a total of 730 influenza viruses from this study have been characterised by the PHE Respiratory Virus Unit and the West of Scotland Virology Centre: 128 antigenically, 293 genetically and 309 through both methods. Only the PHE Respiratory Virus Unit undertook the antigenic analysis.

A total of 482 influenza A(H1N1)pdm09 viruses were characterised. All belonged in the genetic subgroup 6B, which had been the predominant genetic subgroup in the 2014/15 season. Some heterogeneity was seen in the HA of the current season's A(H1N1)pdm09 viruses, with some newly emerging genetic subgroups: the HA genes of the majority (93%) 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 6% 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 into a third minor cluster with substitutions N129D, R450K and E491G. A few viruses from this season did not have any of these changes or had only the substitution S84N, and clustered with A(H1N1)pdm09 viruses from season 2014/15 (6B subgroup). A tree showing the phylogenetic relationships for the A(H1N1)pdm09 has already been published [5]. Of 123 A(H1N1)pdm09 viruses isolated from sentinel samples between December 2015 and April 2016 and analysed by HI assay using an extended panel of ferret post-infection sera including a ferret post-infection antiserum to A/California/7/2009 (NIBSC, UK), 100% were antigenically similar to the A/California/7/2009 northern hemisphere 2015/16 A(H1N1)pdm09 vaccine strain. Using this extended panel of ferret post-infection antisera, no antigenic low reactors to A/California/7/2009 antisera were observed.

A total of 324 influenza B viruses were characterised: more than 96% of them belonged to the B/Victoria lineage in clade 1A, represented by B/Brisbane/60/2008 (the 2015/16 quadrivalent vaccine strain) (Figure 2). Viruses in this clade have N75K, N165K and S172P in their HA compared with the previous vaccine virus. Additional amino acid substitutions seen this season were I117V, N129D and V146I. A few (‹ 3%) UK 2015/16 B/Yamagata lineage viruses were detected, all belonging to genetic clade 3, with amino acid substitutions S150I, N165Y and G229D relative to a previous vaccine

Table 2

	Controls		Influenza B[a]		Influenza A(H1N1)[a]		Influenza A(H3N2)		Influenza A(untyped)		Total[a]	p value[b]
Age group (years)												
0–4	273	71.3	19	5.0	91	23.8	1	0.3	1	0.3	383	<0.0001
5–17	392	69.3	92	16.3	78	13.8	5	0.9	1	0.2	566	
18–44	1,022	65.9	170	11.0	348	22.4	7	0.5	5	0.3	1,551	
45–64	636	70.0	47	5.2	211	23.2	7	0.8	7	0.8	908	
≥ 65	346	84.6	19	4.6	39	9.5	4	1.0	1	0.2	409	
Missing	17	70.8	4	16.7	3	12.5	0	0	0	0	24	
Sex												
Female	1,627	72.4	188	8.4	417	18.5	12	0.5	8	0.4	2,248	<0.0001
Male	1,046	66.4	162	10.3	350	22.2	12	0.8	7	0.4	1,576	
Missing	13	76.5	1	5.9	3	17.6	0	0	0	0	17	
Surveillance scheme												
Northern Ireland	76	49.0	22	14.2	51	32.9	0	0	6	3.9	155	<0.0001
RCGP	1,148	64.0	179	10.0	449	25.0	19	1.1	0	0	1,793	
SMN	138	67.0	12	5.8	50	24.3	1	0.5	5	2.4	206	
Scotland	1,242	81.8	101	6.6	172	11.3	3	0.2	4	0.3	1,519	
Wales	82	48.8	37	22.0	48	28.6	1	0.6	0	0	168	
Risk group												
No	1,794	66.5	276	10.2	607	22.5	14	0.5	9	0.3	2,697	<0.0001
Yes	817	79.7	53	5.2	141	13.8	9	0.9	6	0.6	1,025	
Missing	75	63.0	22	18.5	22	18.5	1	0.8	0	0	119	
Interval onset–sample (days)												
0–1	292	67.6	41	9.5	95	22.0	2	0.5	2	0.5	432	<0.0001
2–4	1,351	66.1	216	10.6	463	22.6	14	0.7	5	0.2	2,045	
5–7	1,043	76.5	94	6.9	212	15.5	8	0.6	8	0.6	1,364	
Month												
October	304	98.7	1	0.3	1	0.3	1	0.3	1	0.3	308	<0.0001
November	396	96.1	6	1.5	8	1.9	2	0.5	0	0	412	
December	463	86.4	5	0.9	67	12.5	0	0	1	0.2	536	
January	541	68.7	26	3.3	217	27.6	3	0.4	2	0.3	787	
February	445	56.1	67	8.4	275	34.7	4	0.5	3	0.4	793	
March	366	48.0	197	25.8	190	24.9	7	0.9	5	0.7	763	
April	171	70.7	49	20.2	12	5.0	7	2.9	3	1.2	242	
Vaccination status (all ages)												
Unvaccinated	1,959	66.4	308	10.4	658	22.3	15	0.5	13	0.4	2,949	<0.0001
Vaccinated (14–91 days ago)	377	89.8	6	1.4	33	7.9	3	0.7	1	0.2	420	
Vaccinated (>91 days ago)	350	74.2	37	7.8	79	16.7	6	1.3	1	0.2	472	
Pilot area (SMN and RCGP only)												
No	1,185	63.8	181	9.7	470	25.3	20	1.1	2	0.1	1,858	0.057
Yes	91	72.2	9	7.1	24	19.0	0	0	2	1.6	126	
Missing	11	64.7	1	5.9	4	23.5	0	0	1	5.9	17	
Vaccine status (by route) (2–17 years)												
Not vaccinated	402	65.5	94	15.5	112	18.2	6	1.0	1	0.2	614	0.01
Injection	16	84.2	3	15.8	0	0	0	0	0	0	19	
Intranasal	89	77.4	4	3.5	22	19.1	0	0	0	0	115	
Missing	12	70.6	1	5.9	4	23.5	0	0	0	0	17	

RCGP: Royal College of General Practitioners Research and Surveillance Centre; SMN: Specialist Microbiology Network.
Note: Differences between cases and controls for all variables in this table were statistically significant.
[a] Four positive for influenza A(H1N1) and B; one positive for influenza A(H1N1) and A(H3N2). Duplicates are not included in row totals.
[b] Positive vs negative for influenza.

Table 3

Samples positive (cases; n = 1,155) and negative (controls; n = 2,686) for influenza A and B according to vaccination status and vaccine effectiveness estimates, United Kingdom, October 2015–May 2016

	Cases		Controls		Crude VE (95% CI)	Adjusted[a] VE (95% CI)
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		
Influenza A or B	165	990	727	1,959	55.1 (45.9–62.7)	52.4 (41.0–61.6)
Influenza A(H1N1)	112	658	727	1,959	54.1 (43–63.1)	54.5 (41.6–64.5)
Influenza A/6B1[b]	45	232	651	1,739	48.2 (28.8–62.8)	48.9 (26.4–64.5)
Influenza B	43	308	727	1,959	62.4 (47.7–73.0)	54.2 (33.1–68.6)
Influenza B/ Victoria[b]	21	161	651	1,739	65.2 (44.6–78.1)	57.3 (28.4–74.6)

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

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

[b] Based only on data from RCGP and Scotland only.

Table 3 shows that the adjusted VE was 54.5% (95% CI: 41.6–64.5) against influenza A(H1N1)pdm09 and specifically 48.9% (95% CI: 26.4–64.5) for clade 6B1 viruses. The age-specific VE against influenza A(H1N1)pdm09 ranged from 48.5% (95% CI: 8.5–71.0) in those aged two to 17 years to 59.8% (95% CI: 35.8–74.8) in those aged 18 to 44 years (Table 4). There was no significant difference in VE against influenza A(H1N1) pdm09 by time since vaccination or period of vaccination (Table 4), overall or by age (adult/child).

strain. More recent substitutions observed this season included N116K, K298E, E312K and also L172Q seen in the majority of B/Yamagata clade 3 viruses.

Of 99 influenza B viruses isolated from sentinel sources between December 2015 and May 2016 and analysed by HI assay, 98 (99%) were characterised as belonging to the B/Victoria/2/87 lineage and were antigenically similar to B/Brisbane/60/2008, the influenza B/Victoria-lineage component of the 2015/16 northern hemisphere quadrivalent vaccines. One virus (1%) was characterised as belonging to the B/Yamagata/16/88-lineage and was antigenically similar to B/Phuket/3073/2013, the influenza B/Yamagata-lineage component of the 2015/16 northern hemisphere trivalent and quadrivalent vaccines.

Model fitting for vaccine effectiveness estimation

The variables incorporated in the multivariable model (month of sample collection, age group, sex, surveillance scheme and primary school programme area) were all significantly associated with swab positivity, and all except primary school programme area and sex were confounders for the vaccine effects (changed estimates by more than 5%). As with previous seasons' analyses [5-7], risk group was not included in the final model as it was not a confounder and data were missing for 119 samples (3.1%).

The crude and adjusted VE estimates against all confirmed influenza, influenza A(H1N1)pdm09 and influenza B for the 2015/16 season are given in Table 3. There were inadequate numbers to estimate VE against influenza A(H3N2). The adjusted VE was 52.4% (95% confidence interval (CI): 41.0–61.6) against all laboratory-confirmed influenza for all ages.

Table 3 shows that the adjusted VE was 54.5% (95% CI: 41.6–64.5) against influenza A(H1N1)pdm09 and specifically 48.9% (95% CI: 26.4–64.5) for clade 6B1 viruses. The age-specific VE against influenza A(H1N1) pdm09 ranged from 48.5% (95% CI: 8.5–71.0) in those aged two to 17 years to 59.8% (95% CI: 35.8–74.8) in those aged 18 to 44 years (Table 4). There was no significant difference in VE against influenza A(H1N1) pdm09 by time since vaccination or period of vaccination (Table 4), overall or by age (adult/child).

Table 3 also shows that the adjusted VE was 54.2% (95% CI: 33.1–68.6) against influenza B and specifically 57.3% (95% CI: 28.4–74.6) for viruses of the B/Victoria lineage. The age-specific VE against influenza B ranged from 76.5% (95% CI: 41.9–90.5) in those aged two to 17 years to −20.0% (95% CI: −259.1 to 59.8) in those aged 65 years and older (Table 4), although these age-specific differences in VE were not significant. There was no significant difference in influenza B VE by time since vaccination or by period of vaccination (Table 4).

The VE results by type of vaccine in children two to 17 years of age are given in Table 5. For children receiving LAIV, the overall VE against all laboratory-confirmed influenza was 57.6% (95% CI: 25.1–76) and specifically 81.4% (95% CI: 39.6–94.3) for influenza B and 41.5% (95% CI: −8.5 to 68.5) for influenza A(H1N1)pdm09. This compares to an overall VE of 77.8% (95% CI: 7.3–94.7) for children receiving IIV and a specific VE of 56.3% (95%CI: −121.6 to 91.4) against influenza B and 100% (95%CI: 13.3–100) against influenza A(H1N1)pdm09. By age group, overall LAIV VE in two to eight year-olds was

Table 4

Adjusted vaccine effectiveness estimates for influenza by age, time since vaccination, vaccination period and risk group, United Kingdom, October 2015–May 2016 (n = 3,841)

Factor	Level	Adjusted VE[a] by type % (95% CI)		
		A+B	A(H1N1) pdm09	B
Age (years)[b]	2–17	60.6 (34.4–76.3)	48.5 (8.5–71.0)	76.5 (41.9–90.5)
	18–44	55.3 (34.2–69.6)	59.8 (35.8–74.8)	45.9 (1.0–70.4)
	45–64	55.4 (34.6–69.5)	58.6 (36.9–72.8)	65.0 (15.1–85.6)
	≥65	29.1 (–34.1 to 61.8)	56.1 (7.2–79.3)	-20.2 (–259.1 to 59.8)
Period of vaccination[b]	Oct - Jan	50.0 (27.6–65.4)	54.3 (31.6–69.4)	35.9 (–70.5 to 75.9)
	Feb - April	53.0 (38.7–64.0)	53.6 (36.1–66.3)	56.9 (35.1–71.3)
Time from vaccination to onset[b]	<3 months	51.4 (29.9–66.3)	56.7 (34.9–71.3)	53.1 (–12.1 to 80.3)
	>3 months	52.7 (39.2–63.2)	53.9 (38.1–65.6)	53.4 (30.0–69.0)

CI: confidence interval; VE: vaccine effectiveness.

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

[b] No significant evidence of interaction.

50.2% (95% CI: 1.6–74.8) and 63.9% (95% CI: –20.3 to 89.2) in nine to 17 year olds.

In 2013/14, the dominant circulating strain was influenza A(H1N1)pdm09, whereas in 2014/15, the dominant circulating strain was influenza A(H3N2), which had antigenically and genetically drifted from the vaccine strain, followed by influenza B mainly of the B/Yamagata lineage. Over the three seasons, the overall VE of LAIV was 53.1% (95% CI: 31.4–67.9) against all confirmed influenza, with a VE of 31.5% (95%CI: –50.4–68.8) for IIV (Table 6). The LAIV VE showed evidence of significant VE against laboratory-confirmed influenza B infection, borderline significance against influenza A(H3N2) and moderate, non-significant effectiveness against influenza A(H1N1)pdm09. Over the three-year period, albeit with small numbers, there was no evidence of significant effectiveness of IIV against influenza B or A(H3N2), but effectiveness of 100% (95% CI: 16.2–100) against influenza A(H1N1)pdm09.

Discussion

In the 2015/16 season, the UK completed the third season of the introduction of a universal paediatric LAIV programme. The 2015/16 season was characterised by late, prolonged influenza A(H1N1)pdm09 activity, with predominance of an emerging genetic HA subgroup, which was antigenically well matched to the vaccine strain, followed by circulation of influenza B viruses, predominantly of the B/Victoria lineage which was not represented in the 2015/16 trivalent inactivated influenza vaccine. The end-of-season VE was moderately good in adults for influenza A(H1N1)pdm09 and in adults younger than 65 years for influenza B, despite the B lineage mismatch for the trivalent influenza vaccine, the main vaccine used in adults. Overall VE for LAIV in children was also moderately good and specifically for influenza B, it was very good, although protection was less against influenza A(H1N1)pdm09. There was no evidence to suggest waning vaccine-derived protection or changes in circulating strains over the 2015/16 season.

We found an overall significant VE of 52.4% and specifically of 54.5% against influenza A(H1N1)pdm09, the dominant circulating strain this season. Although 2015/16 has seen the continued emergence of the new genetic subgroups 6B.1 and 6B.2, the antigenic characterisation indicates a good match to the 2015/16 influenza vaccine strain and no measurable differences between these two emerging groups, which reinforces the VE findings in this paper. These levels of effectiveness are consistent with those reported mid-season in 2015/16 [5], but also in earlier A(H1N1)pdm09 seasons, in particular in 2010/11 [14]. The 2015/16 A(H1N1)pdm09 VE results were also similar to the mid-season estimates reported from North America and elsewhere in Europe this season [15,16]. The continuing apparent antigenic and epidemiological match to the vaccine strain remains encouraging and supports the World Health Organization's recommendation that the vaccine for the 2016/17 northern hemisphere winter should include an A/California/7/2009-like vaccine strain [17].

In younger adults under 65 years of age, influenza B VE was over 50%. Almost all vaccinated adults in the UK can be expected to have received the 2015/16 trivalent inactivated (rather than the quadrivalent) influenza vaccine, which contained the B/Yamagata vaccine strain in 2015/16. Our results indicate that despite this lineage mismatch, the 2015/16 IIV in younger adults continued to provide important levels of protection against influenza B, findings which are consistent with earlier published literature [18]. On the other hand, we failed to find evidence of significant VE against influenza B in the elderly, although underpowered with only 19 positive detections and a low positivity of 4.6% in this age group. This is in contrast to the 2014/15 season, when influenza vaccines elsewhere in Europe provided effectiveness of 50.4% (95% CI: 14.6–71.2) against influenza B in those older than 65 years [19]; in that season, the dominant circulating strain was B/Yamagata and belonged to a clade that was antigenically similar to the vaccine virus that season. Evidence of cross-protection, as we seem to have seen in the younger adults this season, might have important implications for the potential incremental cost-effectiveness and recommendations for preferential use of quadrivalent vaccines in adults and highlights the importance of gathering further data in this area to better inform such decisions.

Table 5

Vaccine effectiveness estimates for influenza by type of vaccine in two to 17 year-olds, United Kingdom, October 2015–May 2016 (n = 729)

Type/subtype	Type of vaccine	Cases (unvaccinated; vaccinated)	Controls (unvaccinated; vaccinated)	Crude VE (95% CI)	Adjusted VE[a] (95% CI)
All	Intranasal	212; 26	402; 89	44.6 (11.6–65.3)	57.6 (25.1–76)
	Injectable	212; 3	402; 16	64.4 (–23.4 to 89.8)	77.8 (7.3–94.7)
Influenza A/(H1N1)pdm09	Intranasal	112; 22	402; 89	11.3 (–47.9 to 46.8)	41.5 (–8.5 to 68.5)
	Injectable	112; 0	402; 16	100 (13.3–100)	100 (13.3–100)[b]
Influenza B	Intranasal	95; 4	402; 89	81 (46.9–93.2)	81.4 (39.7–94.3)
	Injectable	95; 3	402; 16	20.7 (–177.8 to 77.3)	56.3 (–121.6 to 91.4)

CI: confidence interval; VE: vaccine effectiveness.

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

[b] Cornfield's unadjusted estimate.

Among children two to 17 years of age, we observed an overall significant VE of 57.6% for the quadrivalent LAIV vaccine this season, specifically 81.4% for influenza B and 41.5% for influenza A(H1N1)pdm09, with a similar picture when examining the previous three seasons. Over the three seasons, the overall effectiveness of LAIV was higher compared with inactivated vaccine in that age group, specifically for influenza A(H3N2) and B, but lower in 2015/16 and specifically for influenza A(H1N1)pdm09. These findings are in contrast to those recently reported by the US CDC who found an overall VE of only 3% for LAIV in two to 17 year-old children with very low VE against influenza A(H1N1)pdm09, while the inactivated vaccine showed significant effectiveness [3]. The US first noted lower VE of LAIV against influenza A(H1N1)pdm09 in 2013/14, which on further investigation was considered related to reduced thermostability of the A/California/7/2009 vaccine strain [20]. This led to the replacement of the A(H1N1)pdm09 LAIV vaccine strain with the more recently emerged A/Bolivia/559/2013 vaccine strain for the 2015/16 season. Based on the 2015/16 VE findings from the CDC, the US Advisory Committee on Immunisation recommended a temporary suspension of use of LAIV for children in the US for the forthcoming 2016/17 season [3]. In addition to the UK findings presented here, Finland, in its first season of use of LAIV in pre-school age children, found overall levels of protection of 51%, similar to the UK [21].

The reasons why the observed levels of overall protection were higher in Europe than in the US, with apparent reduced protection against influenza A(H1N1)pdm09 compared to IIV, remain under investigation. Several hypotheses have been suggested. Firstly, are the observed differences real or the consequence of a methodological difference? If real, viral interference between the A(H1N1)pdm09 vaccine strain and the other influenza vaccine viruses in the quadrivalent LAIV vaccine might provide an explanation; such interference has been discussed previously [22] and might be reinforced by prior vaccination with LAIV and/or IIV in young children (which is at present much more likely in North America than Europe) or by repeat vaccination in-season, with the US offering two doses of influenza vaccine to children compared with one dose for healthy children in Europe. A further explanation is possible antigenic drift between the A/Bolivia/559/2013 vaccine strain in the 2015/16 LAIV vaccine and circulating A(H1N1)pdm09 strains in winter 2015/16, although antigenically, the virus is considered to be well matched. Finally, programmatic or logistical differences, e.g. related to cold chain or vaccine handling might play a role.

Further work is required to investigate these hypotheses, although UK programme evaluation results from 2013/14 and 2014/15 already suggest that the UK LAIV paediatric programme reduced influenza circulation when comparing pilot areas where children of primary school age were offered vaccine to those areas where they were not [23,24]. The UK VE results presented in this paper have been reviewed by the JCVI who strongly recommended not to change the current influenza immunisation strategy planned for 2016/17, but further work is required to better understand these recent observations in the light of the US findings and to potentially optimise vaccine composition.

Although waning protection post vaccination has recently been noted [25] and although 2015/16 was a particularly late influenza season with significant activity until late into the spring, there was no evidence to suggest either waning protection by time since

Table 6

Three-season vaccine effectiveness estimates for influenza by type of vaccine in two to 17 year-olds, United Kingdom, October 2013–May 2016 (n = 1,655)

Type/subtype	Type of vaccine	Cases (unvaccinated; vaccinated)	Controls (unvaccinated; vaccinated)	Crude VE (95% CI)	Adjusted VE[a] (95% CI)
All	Intranasal	414; 49	1,003; 189	37.2 (12.2–55)	53.1 (31.4–67.9)
	Injectable	414; 11	1,003; 29	8.1 (–85.7 to 54.5))	31.5 (–50.4 to 68.8)
Influenza A(H3N2)	Intranasal	129; 13	1,003; 189	46.5 (3.4–70.4)	46.7 (–6.9 to 73.4)
	Injectable	129; 5	1,003; 29	-34.1 (–252.4 to 49)	-22.0 (–274.8 to 60.3)
Influenza A/(H1N1)pdm09	Intranasal	159; 32	1,003; 189	-6.8 (–61 to 29.1)	35.6 (–4.4 to 60.3)
	Injectable	159; 0	1,003; 29	100 (16.2–100)	100 (16.2–100)[b]
Influenza B	Intranasal	125; 4	1,003; 189	83 (63.5–93.8)	86.9 (61.0–95.6)
	Injectable	125; 5	1,003; 29	-38.3 (–263.9 to 47.4)	24.8 (–153.3 to 77.7)

CI: confidence interval; VE: vaccine effectiveness.

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

[b] Cornfield's unadjusted estimate.

vaccination or changes in effectiveness by vaccination period due to the emergence of new clades or lineages over the course of the season in the UK. Our findings are congruent with recent work which suggests that intra-seasonal waning is of lesser importance with influenza A(H1N1)pdm09 and influenza B compared with influenza A(H3N2) [25].

The paper has a number of strengths. It uses a well-established methodology, the TNCC, the results of which approximate well to more traditional case–control approaches [26]. Data completeness was very high and the integration of genetic characterisation data has allowed the estimation of clade- and lineage-specific VE. Caution is needed in the interpretation of the results in children two to 17 years of age owing to the small sample size, particularly in relation to IIV where only a small proportion of the paediatric control population with available information (16/507, 3%) were reported to be vaccinated, while for LAIV, 18% of controls were reported vaccinated.

Conclusion

In summary, notwithstanding the limitation of the small sample size, our findings together with those from Finland confirm encouraging overall levels of protection for LAIV. This protection is particularly effective against influenza B, though less against influenza A(H1N1)pdm09, a finding which in the light of observations in the US requires further investigation.

Acknowledgements

We are grateful to the 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 RSC, 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 Filipa Ferreira, Ana Correa, David Mullett from RCGP RSC/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

MD declares lecture fees and travel grant/ conference fees from Sanofi-Pasteur MSD in 2016; SdeL declares no direct conflict of interest, however University of Surrey has received grant funding from two Innovative Medicine Initiatives programmes ADVANCE (SdeL is a work package lead) and FLUCOP. Surrey has also received grant funding from GSK to explore the feasibility of collecting European Medicine Agency listed influenza brand-specific side effects in near real time, SdeL is PI.

Authors' contributions

RGP led the drafting; FW, CR 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 drafts and approved the final version.

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Interim estimates of 2015/16 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, February 2016

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Citation style for this article:
Chambers C, Skowronski D, Sabaiduc S, Winter A, Dickinson J, De Serres G, Gubbay J, Drews S, Martineau C, Eshaghi A, Krajden M, Bastien N, Li Y. Interim estimates of 2015/16 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, February 2016. Euro Surveill. 2016;21(11):pii=30168. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.11.30168

Article submitted on 25 February 2016 / accepted on 17 March 2016 / published on 17 March 2016

Using a test-negative design, the Canadian Sentinel Practitioner Surveillance Network (SPSN) assessed interim 2015/16 vaccine effectiveness (VE) against influenza A(H1N1)pdm09 viruses. Adjusted VE showed significant protection of 64% (95% confidence interval (CI): 44–77%) overall and 56% (95%CI: 26–73%) for adults between 20 and 64 years-old against medically attended, laboratory-confirmed A(H1N1)pdm09 illness. Among the 67 A(H1N1)pdm09-positive specimens that were successfully sequenced, 62 (>90%) belonged to the emerging genetic 6B.1 subclade, defined by S162N (potential gain of glycosylation) and I216T mutations in the haemagglutinin protein. Findings from the Canadian SPSN indicate that the 2015/16 northern hemisphere vaccine provided significant protection against A(H1N1)pdm09 illness despite genetic evolution in circulating viruses.

Introduction

In contrast to the early and intense 2014/15 influenza season dominated by A(H3N2) viruses that were mismatched to vaccine [1,2], the beginning of the 2015/16 northern hemisphere season had low-level, mixed circulation of influenza A and B viruses. Notable influenza activity in North America and some European countries did not start until December 2015 and A(H1N1)pdm09 viruses predominated among influenza A detections, with some regional variation observed [3-5]. An increasing proportion of A(H1N1)pdm09 viruses belonging to the newly emerging 6B.1 subclade, defined by S162N (conferring a potential gain of glycosylation) and I216T mutations in the haemagglutinin (HA) protein, has been identified since October 2015 [5-7].

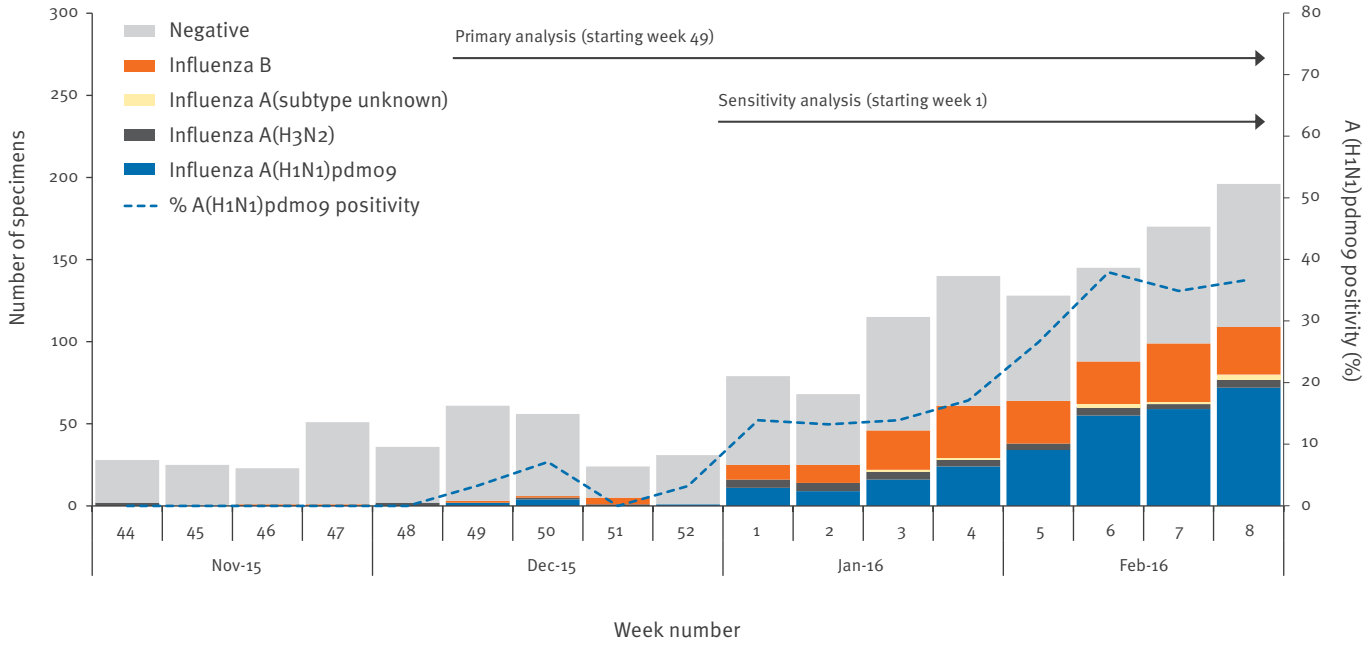
In February 2016, the Influenza – Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case–control study was published reporting early estimates of 2015/16 vaccine effectiveness (VE) against A(H1N1)pdm09 of<50% based on a test-negative study design [8]. This finding raised possible concerns about reduced protection conferred by the A/California/07/2009(H1N1)pdm09 vaccine component that has been recommended for the northern hemisphere seasonal influenza vaccine since the 2009 pandemic, including for the forthcoming 2016/17 season [7,9,10]. Here we present interim VE findings for A(H1N1)pdm09 viruses collected through the Canadian Sentinel Practitioner Surveillance Network (SPSN) also using a test-negative study design. Detailed genetic characterisation of sentinel viruses was undertaken to assess the contribution of the emerging 6B.1 subclade in Canada and its potential impact on measured VE.

Methods

Patients ≥ 1-year-old presenting within seven days of influenza-like illness (ILI) onset to community-based sentinel sites in four provinces (Alberta, British Columbia, Ontario, and Quebec) were eligible for study inclusion. ILI was defined as acute onset of respiratory illness with fever (based on physician's assessment

Figure 1

Influenza detections by type/subtype and week of specimen collection, Canadian Sentinel Practitioner Surveillance Network (SPSN), 1 November 2015–27 February 2016 (n = 1,375)[a]



[a] Includes specimens collected from week 44 2015 (starting 1 November) to week 8 2016 (ending 27 February). Specimens were included in the epidemic curve if the patient met the influenza-like illness case definition, had specimen collection within 7 days of illness onset, was ≥1 year-old at time of illness onset, had valid laboratory results, and had known information for all covariates assessed in vaccine effectiveness analysis (age, comorbidity, influenza-like illness onset date, province, and specimen collection date); specimens were included regardless of the patient's vaccination status or timing of vaccination. Missing collection dates were imputed as the laboratory accession date minus two days.

or self reported by the patient) and cough and one or more of the following symptoms: arthralgia, myalgia, prostration or sore throat. Fever was not required for patients ≥ 65-years-old. Epidemiological information was collected from consenting patients/guardians using a standard questionnaire at the time of specimen collection. Ethics review boards in each participating province provided study approval.

Nasal/nasopharyngeal specimens were tested for influenza viruses by real-time, reverse-transcription polymerase chain reaction (RT-PCR) at provincial reference laboratories.

Sequencing of the HA1 region was attempted on a subset of original patient specimens that tested RT-PCR-positive for A(H1N1)pdm09 and contributed to VE analysis to identify mutations in established antigenic sites (Sa, Sb, Ca1, Ca2, and Cb) [11,12].

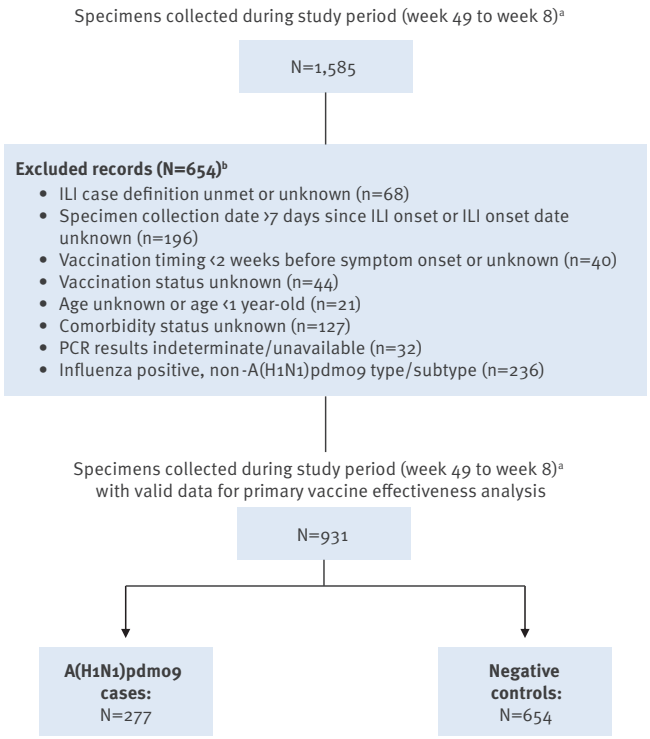
A subset of A(H1N1)pdm09-positive specimens were cultured in Madin-Darby canine kidney (MDCK) or rhesus monkey kidney cells and submitted to Canada's National Microbiology Laboratory for antigenic characterisation by haemagglutination inhibition (HI) assay using turkey erythrocytes, as previously described [12-14].

Specimens collected from week 49 2015 (starting 6 December), corresponding to the first week of A(H1N1)pdm09 detection (Figure 1), to week 8 2016 (ending 27 February) were included in the primary VE analysis. In sensitivity analyses, the study period was restricted to specimens collected from week 1 2016 (starting 3 January) onwards, corresponding to the first week when A(H1N1)pdm09 positivity exceeded 10% (Figure 1).

Patients received 2015/16 influenza vaccine as part of the seasonal vaccination campaign, typically commencing in October in each province. Patients who self-reported receiving at least one dose of influenza vaccine ≥ 2 weeks before ILI onset were considered vaccinated; those vaccinated < 2 weeks before ILI onset were excluded. Odds ratios (OR) for laboratory-confirmed, medically attended A(H1N1)pdm09 illness in vaccinated compared to unvaccinated participants were derived using logisitic regression. VE (expressed as a percentage) was calculated as 1 – OR. ORs were adjusted for age group, comorbidity, province, interval from specimen collection to ILI onset, and calendar time (based on 2-week interval for specimen collection). All analyses were conducted using SAS version 9.3 (SAS Inc., Cary, NC).

Figure 2

Study exclusions, interim influenza A(H1N1)pdm09 vaccine effectiveness (VE) evaluation, Canadian Sentinel Practitioner Surveillance Network (SPSN), 6 December 2015–27 February 2016 (n = 1,585)



ILI: influenza-like illness; PCR: polymerase chain reaction.

[a] Includes specimens collected from week 49 2015 (starting 6 December) to week 8 2016 (ending 27 February).

[b] Exclusions are not mutually exclusive; specimens may have >1 exclusion criterion that applies. Counts for each criterion will sum to more than the total number of specimens excluded.

Results

From 6 December 2015 to 27 February 2016, 1,585 specimens were collected, of which 1,167 (74%) met study inclusion criteria (Figure 2). Influenza viruses were detected in 513 (44%) specimens, including 321 (63%) influenza A, 191 (37%) influenza B, and one influenza A/B co-infection. Of the 314 of 322 (98%) influenza A viruses with known subtype, 277 (88%) were A(H1N1) pdm09.

Overall 14% (n=40) of cases and 31% (n=200) of controls were considered vaccinated (p < 0.01) (Table 1).

Among vaccinated participants who had available data for prior vaccination history, 89% (198/222) of participants ≥ 2 years-old had also received the prior season's 2014/15 vaccine, 83% (172/207) ≥ 3 years-old had received both the 2014/15 and 2013/14 seasonal vaccines, and 79% (132/168) ≥ 7 years-old had received the 2009 monovalent A(H1N1)pdm09 pandemic vaccine, for which ca 95% of the product distributed in Canada was AS03-adjuvanted [15]. Among the 38 vaccinated cases with available data, 37 (97%) had received prior 2014/15 vaccine, 95% (35/37) had received both 2014/15 and 2013/14 vaccines, and 81% (22/27) had received 2009 monovalent A(H1N1)pdm09 vaccine.

After adjustment for relevant covariates, VE against A(H1N1)pdm09 was 64% (95% confidence interval (CI): 44–77%) for the primary analysis and 62% (95%CI: 41–76%) when restricted to specimens collected from week 1 2016 onwards (Table 2). Adjusted VE was 56% (95%CI: 26–73%) and 59% (95%CI: 21–79%) among adults between 20 and 64 years-old, and 20 and 49 years-old, respectively.

Sequencing was attempted on 102 A(H1N1)pdm09-positive specimens collected up to 15 February 2016. Amplification was successful for 67 (66%) of these viruses. All 67 sequenced viruses (100%) had the antigenic site mutation K163Q (Sa) and the non-antigenic site mutations A256T and K283E in HA1 associated with clade 6B, along with antigenic site mutations S185T (Sb) and S203T (Ca1) present in all clade 6 viruses [6]. Sixty-two (93%) viruses had the additional mutations S162N (Sa), conferring a potential gain of glycosylation at residues 162–164, and I216T (non-antigenic) defining the emerging 6B.1 subclade. Two (3%) viruses had the additional mutation V152T within the receptor binding site (RBS) associated with the emerging 6B.2 subclade. One 6B.1 subclade virus had a V152I mutation in addition to S162N and I216T mutations.

Of the 30 sentinel viruses collected in December and January characterised by HI assay, all were considered antigenically similar to the A/California/07/2009(H1N1) pdm09 reference strain.

Discussion

In this interim analysis, we measured statistically significant VE of 64% (95%CI: 44–77%) against circulating A(H1N1)pdm09 viruses largely belonging to the emerging 6B.1 subclade. This point estimate is slightly lower than but comparable to the significant VE measured by our network in 2013/14 mid-season (74%; 95%CI: 58–83%) [13] and end-of-season (71%; 95%CI: 58–80%) [12] analyses against dominant clade 6B A(H1N1)pdm09 viruses. In 2013/14, clade 6B viruses had the antigenic site K163Q mutation but had not yet acquired the adjacent S162N mutation associated with the newly emerging 6B.1 subclade. Despite some genetic evolution in A(H1N1)pdm09 viruses, our 2015/16 VE estimate remains closely aligned with a recent meta-analysis of test-negative studies globally for which pooled VE for seasonal vaccine against A(H1N1)pdm09 since 2010 was 61% (95%CI: 57–65%) [16].

Our point estimates of VE against A(H1N1)pdm09 are higher (but with overlapping confidence intervals) compared with those reported in similar mid-season analysis from the European I-MOVE multicentre case–control

Table 1

Characteristics of participants included in interim influenza A(H1N1)pdm09 vaccine effectiveness (VE) evaluation, Canadian Sentinel Practitioner Surveillance Network (SPSN), 6 December 2015–27 February 2016 (n = 931)

Characteristic	Overall n (column %)[a]	Distribution by case status n (column %)[a]			Vaccination coverage n (row %)	
		A(H1N1)pdm09 cases	Negative controls	P value[b]	Vaccinated	P value[b]
N (row %)	931 (100)	277 (30)	654 (70)	–	240 (26)	–
Age group in years						
1–8	132 (14)	35 (13)	97 (15)	<0.01	23 (17)	<0.01
9–19	113 (12)	25 (9)	88 (13)		14 (12)	
20–49	411 (44)	142 (51)	269 (41)		74 (18)	
50–64	179 (19)	57 (21)	122 (19)		64 (36)	
≥65	96 (10)	18 (7)	78 (12)		65 (68)	
Median (range)	36 (1–92)	37 (1–83)	35 (1–92)	0.62	53 (1–92)	<0.01
Sex[c]						
Female	571 (62)	164 (60)	407 (63)	0.37	156 (27)	0.19
Male	346 (38)	109 (40)	237 (37)		81 (23)	
Unknown	14	4	10		3	
Comorbidity[d]						
No	746 (80)	239 (86)	507 (78)	<0.01	152 (20)	<0.01
Yes	185 (20)	38 (14)	147 (22)		88 (48)	
Province						
Alberta	243 (26)	84 (30)	159 (24)	<0.01	70 (29)	0.14
British Columbia	241 (26)	47 (17)	194 (30)		65 (27)	
Ontario	323 (35)	95 (34)	228 (35)		83 (26)	
Quebec	124 (13)	51 (18)	73 (11)		22 (18)	
Collection interval in days						
≤4	697 (75)	229 (83)	468 (72)	<0.01	169 (24)	0.07
5–7	234 (25)	48 (17)	186 (28)		71 (30)	
Median (range)	3 (0–7)	3 (0–7)	3 (0–7)	<0.01	3 (0–7)	0.01
Month of specimen collection[e]						
December	152 (16)	7 (3)	145 (22)	<0.01	38 (25)	0.96
January	298 (32)	56 (20)	242 (37)		78 (26)	
February	481 (52)	214 (77)	267 (41)		124 (26)	
Vaccination status						
Any vaccination[f]	261/952 (27)	43/280 (15)	218/672 (32)	<0.01	NE	–
≥2 weeks before ILI onset	240 (26)	40 (14)	200 (31)	<0.01	NE	–
LAIV[g]	11/128 (9)	1/22 (5)	10/106 (9)	0.69	NE	–
QIV[h]	33/140 (24)	5/22 (23)	28/118 (24)	0.92	NE	–
Adjuvanted[i]	16/35 (46)	4/5 (80)	12/30 (40)	0.16	NE	–
Prior vaccination history						
2014/15 vaccine[j]	308/858 (36)	68/252 (27)	240/606 (40)	<0.01	198/308 (64)	<0.01
2013/14 vaccine[k]	301/811 (37)	74/240 (31)	227/571 (40)	0.02	185/301 (61)	<0.01
2009 monovalent vaccine[l]	296/673 (44)	79/199 (40)	217/474 (46)	0.15	132/296 (45)	<0.01

ILI: influenza-like illness; LAIV: live attenuated influenza vaccine; NE: not estimated; QIV: quadrivalent influenza vaccine.

[a] Unless otherwise specified, the values presented in this column are the number of specimens per category and percentage relative to the total. Where the denominator for the percentages differs from the total, fractions supporting the calculation of percentages are shown.

[b] Differences between cases and controls and vaccinated and unvaccinated participants were compared using the chi-squared test, Fisher's exact test or Wilcoxon rank-sum test.

[c] The percentage was only calculated among the total patients whose sex was known.

[d] Includes chronic comorbidities that place individuals at higher risk of serious complications from influenza as defined by Canada's National Advisory Committee on Immunization (NACI) including: heart, pulmonary (including asthma), renal, metabolic (such as diabetes), blood, cancer, or immune comprising conditions; conditions that compromise management of respiratory secretions and increase risk of aspiration; or morbid obesity (body mass index ≥40) [29].

[e] Missing collection dates were imputed as the laboratory accession date minus two days.

[f] Participants who received seasonal 2015/16 influenza vaccine <2 weeks before ILI onset or for whom vaccination timing was unknown were excluded from the primary analysis. They were included for assessing 'any' vaccination, regardless of timing, for comparison with other sources of vaccination coverage.

[g] Among participants between two and 59 years-old who received 2015/16 influenza vaccine ≥2 weeks before ILI onset and had known information for type of vaccine. Among participants between two and 17 years-old for whom LAIV is recommended by NACI [29], 44% (11/25, including one case) with known information had received LAIV. Among participants between two and five years-old for whom LAIV is preferentially recommended by NACI [29], 36% (5/14, including one case) with known information had received LAIV.

[h] Among participants who had known information for trivalent vs. quadrivalent vaccine. QIV includes both inactivated influenza vaccine (IIV4) and live-attenuated influenza vaccine (LAIV4) products.

[i] Among participants ≥65 years-old who received 2015/16 influenza vaccine ≥2 weeks before ILI onset and had known information for adjuvanted vaccine receipt.

[j] Children <2 years-old in 2015/16 were excluded from 2014/15 vaccine uptake analysis as they may not have been eligible for vaccination during the autumn 2014 vaccination campaign.

[k] Children <3 years-old in 2015/16 were excluded from 2013/14 vaccine uptake analysis as they may not have been eligible for vaccination during the autumn 2013 vaccination campaign.

[l] Children <7 years-old in 2015/16 were excluded from 2009 monovalent A(H1N1)pdm09 vaccine uptake analysis as they may not have been eligible for vaccination during the autumn 2009 vaccination campaign.

Table 2

Interim vaccine effectiveness (VE) estimates against influenza A(H1N1)pdm09, Canadian Sentinel Practitioner Surveillance Network (SPSN), 6 December 2015–27 February 2016 (n = 931)

Covariates	VE % (95%CI)	N total Cases: n (n vac, % vac); Controls: n (n vac, % vac)
Primary analysis[a,b]		
Unadjusted	62 (44–74)	**Total: 931** Cases: 277 (40, 14%); Controls: 654 (200, 31%)
Age group (1–8, 9–19, 20–49, 50–64, ≥65 years)	62 (43–74)	
Comorbidity (no, yes)	58 (39–72)	
Province (AB, BC, ON, QC)	62 (44–74)	
Interval from specimen collection to ILI onset (≤4, 5–7 days)	61 (43–73)	
Calendar time (2-week interval)[c]	66 (49–77)	
Age group, comorbidity, province, interval, calendar time	64 (44–77)	
Restricted to specimens collected from week 1 to week 8, 2016[b]		
Unadjusted	63 (45–75)	**Total: 776** Cases: 270 (40, 15%); Controls: 506 (161, 32%)
Age group (1–8, 9–19, 20–49, 50–64, ≥65 years)	63 (44–75)	
Comorbidity (no, yes)	60 (40–73)	
Province (AB, BC, ON, QC)	62 (44–75)	
Interval from specimen collection to ILI onset (≤4, 5–7 days)	62 (44–74)	
Calendar time (2-week interval)[c]	65 (48–76)	
Age group, comorbidity, province, interval, calendar time	62 (41–76)	
Restricted to adults 20–64 years-old[a,b]		
Unadjusted	58 (34–73)	**Total: 590** Cases: 199 (28, 14%); Controls: 391 (110, 28%)
Age group (20–49, 50–64 years)	58 (34–74)	
Comorbidity (no, yes)	56 (30–72)	
Province (AB, BC, ON, QC)	58 (33–73)	
Interval from specimen collection to ILI onset (≤4, 5–7 days)	57 (33–73)	
Calendar time (2-week interval)[c]	56 (28–73)	
Age group, comorbidity, province, interval, calendar time	56 (26–73)	
Restricted to adults 20–49 years-old[a,b]		
Unadjusted	62 (29–80)	**Total: 411** Cases: 142 (14, 10%); Controls: 269 (60, 22%)
Comorbidity (no, yes)	61 (28–79)	
Province (AB, BC, ON, QC)	63 (31–80)	
Interval from specimen collection to ILI onset (≤4, 5–7 days)	61 (27–79)	
Calendar time (2-week interval)[c]	59 (23–79)	
Comorbidity, province, interval, calendar time	59 (21–79)	

AB: Alberta; BC: British Columbia; CI: confidence interval; ILI: influenza-like illness; ON: Ontario; QC: Quebec; vac: vaccinated; VE: vaccine effectiveness.

[a] Restricted to specimens collected from week 49 2015 (starting 6 December) to week 8 2016 (ending 27 February).

[b] Patient specimens were included in VE analysis if the patient met the ILI case definition, had specimen collection within 7 days of ILI onset, was ≥1 year-old at time of ILI onset (based on age eligibility of ≥6 months for influenza vaccine during the autumn 2015 vaccination campaign), received 2015/16 influenza vaccine ≥2 weeks before ILI onset, had valid laboratory results, and had known information for all covariates assessed in VE analysis (age, comorbidity, ILI onset date, province, and specimen collection date).

[c] Based on date of specimen collection; missing collection dates were imputed as the laboratory accession date minus two days.

study, which indicated VE against A(H1N1)pdm09 of 44% (95%CI: -3 to 70%) overall and 41% (95%CI: -25 to 72%) in adults between 18 and 64 years-old, although estimates were not statistically significant [8]. Because of the low vaccination coverage in Europe (<15% among controls) and late start to the 2015/16 influenza season, the I-MOVE study likely had limited statistical power to measure stable or significant VE in mid-season analysis [8]. Their findings are, however, comparable to their previously published estimates against A(H1N1)pdm09 from the 2013/14 and 2014/15 seasons (ranging from 48 to 54%) [17,18]. Our estimates are also slightly higher than the point estimate of 51% reported for A(H1N1)pdm09 by the United States (US) Flu VE Network for the current 2015/16 season [19], although this US estimate is also not substantially different from their recently published estimate of 54% (95%CI: 46–61%) for the A(H1N1)pdm09-dominant 2013/14 season [20]. The lack of further epidemiological and genomic detail in interim findings from elsewhere prevents direct comparison to our Canadian SPSN results. In addition to possible virologic differences in the mix of circulating strains contributing to VE analysis, differences in study methods, patient

populations, and vaccination programmes, including the use of AS03-adjuvanted vaccine during the 2009 pandemic in Canada [15], should be taken into account in comparing VE estimates across settings or seasons [16].

As seen in prior SPSN analyses [12-14], the largest proportion of specimens in the current analysis was collected from younger, non-elderly adults between 20 and 49 years-old (44%), more notable among cases than controls (51% vs 41%) (Table 1). Adjusted VE estimates in age-stratified analyses were comparable to, but slightly lower than, our primary analysis at 59% (95%CI: 21–79%) when restricted to adults aged between 20 and 49 years-old, and 56% (95%CI: 26–73%) when broadened to include all adults between 20 and 64 years-old. This may reflect random variation owing to the smaller sample size in age-stratified analyses or unmeasured residual confounding across patient age groups. Variation by age could also reflect cohort effects resulting from different immunological priming/boosting as well as varying responses to vaccination by age or other patient factors. Over 80% of vaccinated participants in our study had received prior 2014/15 and 2013/14 seasonal vaccines; however, repeat vaccination effects could not be assessed in interim analyses because of the small number of participants who were vaccinated in the current, but not prior, season. These considerations warrant further evaluation in end-of-season VE or serological analyses and should also be taken into account in comparing VE estimates across studies or seasons with different participant age-distribution or immunological profiles.

Consistent with virus circulation globally [5,6], all sentinel A(H1N1)pdm09 viruses sequenced in our study belonged to clade 6B, with 62 of 67 (93%) more specifically falling within the emerging 6B.1 subclade. Information on genetic characterisation was not provided in the I-MOVE study [8], but separately published surveillance data for Europe report that about 80% of 6B viruses contain the S162N and I216T mutations [6]. The S162N mutation is located in antigenic site Sa close to the RBS and adjacent to the clade-defining K163Q mutation that other investigators have hypothesised to have facilitated resurgent A(H1N1) pdm09 activity disproportionately affecting middle-aged adults in 2013/14 [12,21]. The S162N mutation confers a potential gain of glycosylation at residues 162–164 that may mask K163Q and other epitopes relevant for neutralising antibody binding [6,22,23]. Despite genetic evolution, most circulating 6B viruses characterised globally, including the sentinel viruses assessed in this study, remain antigenically similar to the A/California/07/2009(H1N1)pdm09 reference strain (belonging to clade 1) based on HI and virus neutralisation assays [3-7]. Interim VE estimates from the Canadian SPSN were also not markedly affected by recent molecular changes in circulating A(H1N1) pdm09 viruses and are consistent with the recent World Health Organization (WHO) decision to retain the A/California/07/2009(H1N1)pdm09 vaccine strain for the forthcoming 2016/17 season [7]. Our interim VE estimates were submitted alongside other estimates from the Global Influenza Vaccine Effectiveness (GIVE) Collaboration and contributed to the February 2016 WHO consultation meeting on the composition of influenza vaccines for the 2016/17 northern hemisphere season [24].

Limitations of this analysis include the small number of cases available for interim analysis and resulting wide 95% CIs, particularly in stratified analyses. Although the validity of the test-negative design for deriving VE estimates has been demonstrated relative to randomised controlled trials and simulation studies [25-27], residual bias and confounding due to the observational study design cannot be ruled out. VE was measured against medically attended outpatient illness and may not be generalisable to more severe outcomes, although a recent meta-analysis suggests that VE estimates derived using the test-negative design do not substantially differ between outpatient and inpatient settings [28]. Interim estimates are only presented for A(H1N1)pdm09 viruses; where possible, VE for other types/subtypes, including clade- and lineage-specific estimates, will be explored in end-of-season analyses.

Interim VE analyses from the Canadian SPSN suggest that the 2015/16 northern hemisphere vaccine has provided significant protection against A(H1N1)pdm09 viruses belonging to the emerging 6B.1 subclade. Due to considerations such as the late start of the 2015/16 influenza season and smaller number of accrued cases, estimates may vary in end-of-season analyses and should be interpreted with caution. Further investigation into the impact of evolving antigenic site mutations, including the role of S162N and its potential glycosylation effects, on vaccine protection is required.

Acknowledgements

The authors gratefully acknowledge the contribution of sentinel sites whose regular submission of specimens and data provide the basis of our analyses. We wish to acknowledge the coordination and technical support provided by epidemiological and laboratory staff in all participating provinces. We wish to thank the following for network coordination and data entry activities in each province including: Lisan Kwindt for the British Columbia Centre for Disease Control; Elaine Douglas, Kinza Rizvi and Virginia Goetz for TARRANT in Alberta; Romy Olsha for Public Health Ontario; and Sophie Auger and Isabelle Petillot for the Institut national de santé publique du Québec. We thank those who provided laboratory support in each of the British Columbia Centre for Disease Control Public Health Laboratory, the Alberta Provincial Laboratory for Public Health (ProvLab), the Public Health Ontario Laboratory, and the Laboratoire de santé publique du Québec. We further acknowledge the virus sequencing support provided by Aimin Li, Janet Obando, and Narisha Shakuralli at the Public Health Ontario Laboratory. Funding was provided by the British Columbia Centre for Disease Control, Alberta Health and Wellness, Public Health Ontario, Ministère de la santé et des services sociaux du Québec,

l'Institut national de santé publique du Québec, and the Public Health Agency of Canada.

Conflict of interest

Within 36 months of manuscript submission, GDS received research grants and compensation for travel costs to attend an ad hoc advisory board meeting from GlaxoSmithKline (GSK), a research grant from Pfizer for unrelated studies, and separate compensation for participation as expert witness in a legal challenge of enforced healthcare worker influenza vaccination. JBG has received a research grant from Pfizer. MK has received research grants from Roche, Merck, Hologic, Boerhinger Ingelheim and Siemens. The other authors declare that they have no competing interests to report.

Authors' contributions

Principal investigators (epidemiological): DMS (National and British Columbia); JAD (Alberta); ALW (Ontario); and GDS (Québec). Principal investigator (laboratory): MK (British Columbia); SD (Alberta); JBG (Ontario); CM (Québec); and YL and NB (National Microbiology Laboratory). Virus sequencing: SS, JBG and AE. Data analysis: CC and DMS (epidemiological); SS (molecular). Preparation of first draft: CC and DMS. Draft revision and approval: all.

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Research article

Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN)

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Citation style for this article:
Blyth CC, Macartney KK, Hewagama S, Senenayake S, Friedman ND, Simpson G, Upham J, Kotsimbos T, Kelly P, Cheng AC. Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN). Euro Surveill. 2016;21(30):pii=30301. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.30.30301

Article submitted on 29 May 2015/ accepted on 06 November 2015 / published on 28 July 2016

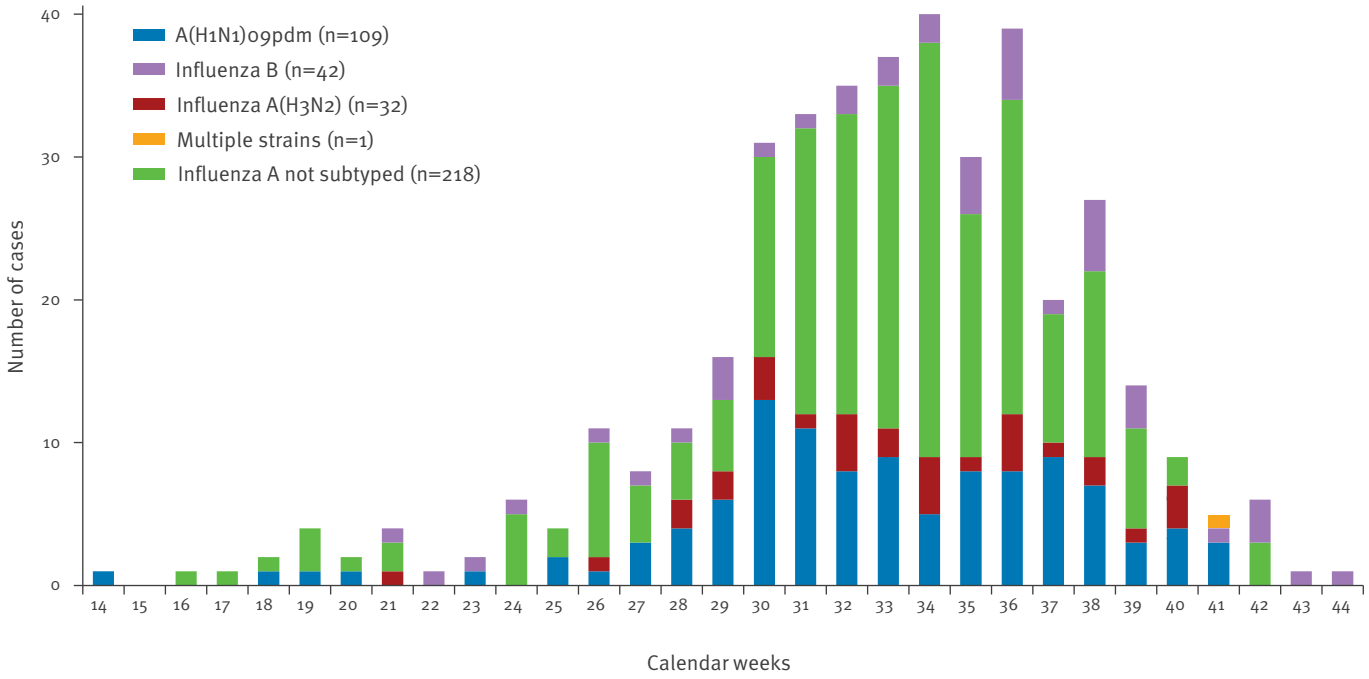
The Influenza Complications Alert Network (FluCAN) is a sentinel hospital-based surveillance programme operating in all states and territories in Australia. We summarise the epidemiology of children hospitalised with laboratory-confirmed influenza in 2014 and reports on the effectiveness of inactivated trivalent inactivated vaccine (TIV) in children. In this observational study, cases were defined as children admitted with acute respiratory illness (ARI) with influenza confirmed by PCR. Controls were hospitalised children with ARI testing negative for influenza. Vaccine effectiveness (VE) was estimated as 1 minus the odds ratio of vaccination in influenza positive cases compared with test-negative controls using conditional logistic regression models. From April until October 2014, 402 children were admitted with PCR-confirmed influenza. Of these, 28% were aged < 1 year, 16% were Indigenous, and 39% had underlying conditions predisposing to severe influenza. Influenza A was detected in 90% of cases of influenza; influenza A(H1N1)pdm09 was the most frequent subtype (109/141 of subtyped cases) followed by A(H3N2) (32/141). Only 15% of children with influenza received antiviral therapy. The adjusted VE of one or more doses of TIV for preventing hospitalised influenza was estimated at 55.5% (95% confidence intervals (CI): 11.6–77.6%). Effectiveness against influenza A(H1N1)pdm09 was high (91.6% , 95% CI: 36.0–98.9%) yet appeared poor against H3N2. In summary, the 2014 southern hemisphere TIV was moderately effective against severe influenza in children. Significant VE was observed against influenza A(H1N1)pdm09.

Introduction

Influenza is a common respiratory viral infection that affects up to 5–10% of the population each year [1]. Previous studies demonstrate that young children have the highest rate of hospitalisation [2]. A national sentinel surveillance programme for severe influenza was established in Australia in 2009, primarily to monitor hospitalisations in adults with confirmed influenza: the Influenza Complications Alert Network (FluCAN). Given the significant burden of disease in young children and the important role that children play in introducing and spreading influenza virus in the household and the community [3], paediatric influenza surveillance provides public health authorities with important and timely information on disease severity in the early phase of the winter respiratory virus season. Hospital-based sentinel surveillance enables

Figure 1

Date of admission in children hospitalised with confirmed influenza, epidemiological cohort, Influenza Complications Alert Network, Australia, April to October 2014 (n=402)



detailed information on the severity of illness to be collected, and complements community- and primary care-based surveillance systems. Comprehensive nationwide clinical data were collected from Australian children admitted to six tertiary paediatric hospitals during the pandemic in 2009 [4]. However, from 2010 to 2013, insufficient numbers of children were prospectively enrolled in existing surveillance programs to ascertain paediatric seasonal influenza activity and severity in Australia. Two tertiary paediatric hospitals (from the separate Paediatric Active Enhanced Disease Surveillance network (PAEDS) [5]) were included in the existing FluCAN sentinel system in 2014.

The Australian Technical Advisory Group on Immunisation (ATAGI) recommends influenza vaccination in all children 6 months and older, yet in 2014, influenza vaccine was only provided free of charge under the National Immunisation Programme (NIP) for children with comorbidities that predispose them to severe outcomes following influenza infection [6]. In Western Australia, a state funded programme has provided free influenza vaccine to all children between 6 months and 5 years of age from 2008 [7-9]. Four brands of inactivated unadjuvanted trivalent influenza vaccine (TIV) were available for use in Australian children: more than 80% of vaccine administered to children in Australia was Vaxigrip or Vaxigrip junior (Sanofi-Pasteur Pty Ltd; personal communication, Brynley Hull, October 2015). Live attenuated and quadrivalent influenza vaccines were not available in Australia in 2014.

Previous studies have demonstrated that inactivated influenza vaccine is protective against influenza [10, 11], yet have concluded that insufficient evidence exists to confirm the effectiveness in the very young. The Western Australian Influenza Vaccine Effectiveness (WAIVE) study has previously estimated vaccine effectiveness (VE) of TIV in children aged 6 to 59 months attending a paediatric emergency department against any laboratory-confirmed influenza at 64.7% (95% confidence interval (CI): 33.7–81.2%) [7]. Insufficient numbers of hospitalised children have been enrolled in this and similar paediatric VE studies to generate robust estimates against hospitalisation. Cowling et al. estimated VE against hospitalisation with laboratory-confirmed influenza to be 61.7% (95% CI: 43.0–74.2%) in Hong Kong (2009–2013) [12].

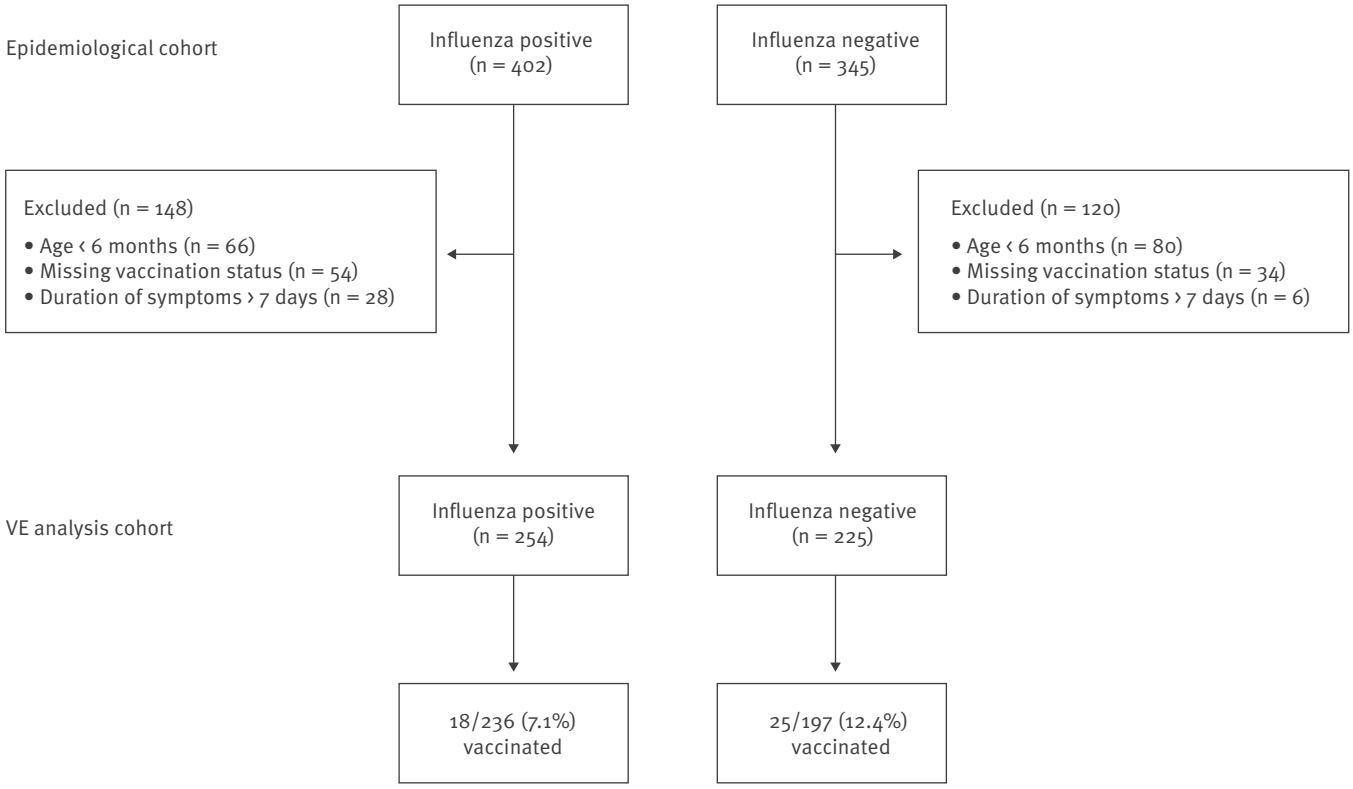
With nearly 70,000 notifications of laboratory-confirmed influenza, the incidence of disease in 2014 was high compared with previous seasons [13]. Virological surveillance of circulating strains suggested influenza A(H1N1)pdm09 predominated across most jurisdictions throughout the season, but influenza A(H3N2) was predominant in New South Wales and the Australian Capital Territory [14]. In this report, we describe the epidemiology of hospitalisation in children with confirmed influenza and report on VE estimates for the 2014 southern hemisphere inactivated TIV.

Methods

FluCAN is a national hospital-based sentinel surveillance system [15]. In 2014, surveillance was expanded to include two large specialty paediatric hospitals:

Figure 2

Flowchart of children included in epidemiological and vaccine effectiveness cohorts, Influenza Complications Alert Network, Australia, April to October 2014 (n=747)



VE: vaccine effectiveness.

Children's Hospital at Westmead (New South Wales) and the Princess Margaret Hospital for Children (Western Australia). In addition, paediatric cases from the other 15 participating sites were also included: Canberra Hospital (ACT), University Hospital Geelong (VIC), Princess Alexandra Hospital (QLD), Cairns Base Hospital (QLD), and Alice Springs Hospital (NT) contributed cases. Ethics approval has been obtained at all participating sites, at Monash University and the Australian National University.

An influenza case was defined as a paediatric patient (<16 years) admitted to hospital with an acute respiratory illness (ARI) and with influenza confirmed by PCR. Influenza testing was initiated by clinicians based on clinical indications and local guidelines. All influenza cases were confirmed using real-time reverse transcriptase PCR assays using standard primers. All tests were performed in local or referral laboratories accredited by the National Association of Testing Authorities. An ARI was defined by the presence of new respiratory symptoms including cough and rhinorrhoea. A hospital admission was defined as requiring inpatient care outside of the emergency department.

Under FluCAN, surveillance is conducted during the southern hemisphere influenza season (i.e. April to October with follow up continuing to the end of November each year). Admission to an intensive care unit (ICU), including high dependency unit (HDU), was also recorded. The presence of risk factors predisposing to severe outcomes following influenza infection including ethnicity (Indigenous or non-Indigenous Australian) and the presence of underlying conditions (hereafter referred to as comorbidities) was ascertained from the patient's medical record [6]. Comorbidities assessed included congenital heart disease, chronic respiratory and neurological disorders, immunocompromising conditions or immunosuppression, Down syndrome and chronic illnesses such as diabetes mellitus and renal failure [6].

We examined factors associated with ICU admission and the length of hospital stay (LOS) using multivariable regression. Factors associated with ICU admission were determined using a logistic regression model, with factors retained in the multivariable model if $p<0.20$. Factors associated with LOS were modelled using a linear regression, as the mean duration of stay was the parameter of interest. Standard errors were estimated using bootstrapping (1,000 replicates) to correct for heteroskedasticity.

Table 1

Demographic characteristics of children hospitalised with confirmed influenza, epidemiological cohort, Influenza Complications Alert Network, Australia, April to October 2014 (n=402)

	Influenza type				Total influenza positive cases
	A(H1N1A(H1N1)09pdm	A(H3N2)	A not subtyped	B	
Number of children	109	32	218	42	402[a]
Age group					
Neonate<28 days	2 (1.8%)	0 (0.0%)	5 (2.3%)	0 (0.0%)	7 (1.7%)
Infant 28 days to 1 year	29 (26.6%)	9 (28.1%)	60 (27.5%)	8 (19.0%)	107 (26.6%)
1–5 years	40 (36.7%)	16 (50.0%)	94 (43.1%)	15 (35.7%)	165 (41.0%)
5–9 years	23 (21.1%)	5 (15.6%)	34 (15.6%)	12 (28.6%)	74 (18.4%)
10–16 years	15 (13.8%)	2 (6.3%)	25 (11.5%)	7 (16.7%)	49 (12.2%)
Male	62 (56.9%)	16 (50.0%)	107 (49.1%)	24 (57.1%)	209 (52.0%)
Indigenous	9 (8.3%)	3 (9.4%)	48 (22.0%)	3 (7.1%)	63 (15.7%)
Hospital					
Alice Springs	0 (0.0%)	0 (0.0%)	43 (19.7%)	5 (11.9%)	48 (11.9%)
Canberra	15 (13.8%)	14 (43.8%)	0 (0.0%)	2 (4.8%)	31 (7.7%)
Cairns Base	4 (3.7%)	0 (0.0%)	10 (4.6%)	3 (7.1%)	17 (4.2%)
Children›s Hospital, Westmead	0 (0.0%)	0 (0.0%)	135 (61.9%)	16 (38.1%)	151 (37.6%)
Geelong Hospital	0 (0.0%)	0 (0.0%)	21 (9.6%)	0 (0.0%)	22 (5.5%)
Princess Alexandra	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.2%)
Princess Margaret	90 (82.6%)	18 (56.3%)	9 (4.1%)	15 (35.7%)	132 (32.8%)

[a] One child with disease due to multiple subtypes included in total

Estimation of vaccination coverage and effectiveness

Vaccination status was obtained from the medical record, by parental report and confirmed, in children<7 years of age, on the Australian Childhood Immunisation Register (ACIR). In those 10 years and older, 'fully immunised' was defined by receipt of one dose of 2014 TIV more than 2 weeks before presentation. In children age<10 years, 'fully immunised' was defined as either (i) two doses of TIV at least 21 days apart and at least 2 weeks before presentation or (ii) one dose of TIV at least 2 weeks before presentation and receipt of at least one TIV dose in a previous year [6]. 'Partially vaccinated' children were those aged<10 years receiving only one dose of vaccination in 2014 without receipt of TIV in previous years. 'Unvaccinated' children where those not receiving TIV in 2014 or receiving the vaccine less than 2 weeks before presentation.

Vaccination coverage was estimated in patients›6 months of age admitted with ARI who tested negative to influenza by PCR. We used an incidence density test negative design to estimate VE, where controls were selected from influenza-test negative subjects with ARI tested contemporaneously with a case: controls could be test-negative for all pathogens or have an alternative pathogen detected [16-18]. VE was estimated as 1 minus the odds ratio (OR) of vaccination in influenza-positive cases compared with test-negative control patients using methods previously described [15,19]. Only children›6 months of age and tested within 7 days of admission were included in VE estimates. A conditional logistic regression model using influenza case status as the dependent outcome was constructed from influenza vaccination and adjusted for potential confounders (age group<2 years and comorbidities). The regression was stratified on site, except for the models that considered VE against H1N1 due to small numbers. Models that included more age groups (<1 year, 1–4 years, 5–9 years and≥10 years,) and Indigenous status as adjusting variables were considered in sensitivity analyses. In addition, VE estimates excluding children with duration of symptoms of›7 days (as opposed to restriction the analysis to who underwent testing within 7 days) were performed. These adjustments had minimal effect (<3%) on VE estimates and thus were dropped from the final model. Analyses were performed using Stata 13 for Windows (College Station, Texas, US).

Results

During the period 3 April to 31 October 2014, 402 children were admitted with PCR-confirmed influenza to seven of 17 sentinel hospitals, including 283 admissions to the two specialist paediatric hospitals, and 119 admissions to five non-specialist hospitals (Table 1). The peak rate of admission was in late August (Figure 1). Of these 402 children, 114 (28%) were<1 year of age, 63 (16%) were Indigenous Australians, and 155 (39%) had underlying comorbidities (Table 1; Table 2).

Table 2

Risk factors, severity and outcomes in children hospitalised with confirmed influenza, epidemiological cohort, Influenza Complications Alert Network, Australia, April to October 2014 (n=402)

	Not admitted to ICU	Admitted to ICU	Total
Total	**356**	**46**	**402**
Age group			
Neonate<28 days	5 (1.4%)	2 (4.3%)	7 (1.7%)
Infant 28d - 1 year	93 (26.1%)	14 (30.4%)	107 (26.6%)
1–4 years	147 (41.3%)	18 (39.1%)	165 (41.0%)
5–9 years	68 (19.1%)	6 (13.0%)	74 (18.4%)
10–15 years	43 (12.1%)	6 (13.0%)	49 (12.2%)
Smoking	4 (1.1%)	2 (4.3%)	6 (1.5%)
Others smoking in the household	21 (5.9%)	5 (10.9%)	26 (6.5%)
Chronic medical comorbidities	127 (35.7%)	28 (60.9%)	155 (38.6%)
Chronic respiratory disease	38 (10.7%)	12 (26.1%)	50 (12.4%)
Prematurity	33 (9.3%)	12 (26.1%)	45 (11.2%)
Chronic cardiac disease	21 (5.9%)	3 (6.5%)	24 (6.0%)
Diabetes	4 (1.1%)	1 (2.2%)	5 (1.2%)
Chronic neurological disease	26 (7.3%)	7 (15.2%)	33 (8.2%)
Chronic renal disease	10 (2.8%)	4 (8.7%)	14 (3.5%)
Immunosuppressed	35 (9.8%)	4 (8.7%)	39 (9.7%)
Chronic liver disease	7 (2.0%)	3 (6.5%)	10 (2.5%)
Genetic abnormality	28 (7.9%)	10 (21.7%)	38 (9.5%)
Inborn error of metabolism	4 (1.1%)	3 (6.5%)	7 (1.7%)
Chronic aspirin use	4 (1.1%)	0 (0.0%)	4 (1.0%)
Residential care	1 (0.3%)	1 (2.2%)	2 (0.5%)
Influenza vaccination	11/242 (4.5%)	4/35 (11.4%)	15/277 (5.4%)
Influenza subtype			
A(H1N1)09pdm	92 (25.8%)	17 (37.0%)	109 (27.1%)
A(H3N2)	24 (6.7%)	8 (17.4%)	32 (8.0%)
A not subtyped	199 (55.9%)	19 (41.3%)	218 (54.2%)
B	40 (11.2%)	2 (4.3%)	42 (10.4%)
multiple strains	1 (0.3%)	0 (0.0%)	1 (0.2%)
Mortality	0/317 (0.0%)	1/41 (2.4%)	1/358 (0.3%)

Presentation and treatment

In 395 patients with influenza where the duration of symptoms was known, the median duration of symptoms before admission was 3 days (interquartile range (IQR): 2, 5 days). Only 64 (15%) of patients with influenza, received oseltamivir; of these, 24 patients were known to have received oseltamivir within 48 hours of symptom onset.

Admission to intensive care

Of all influenza cases, 40 (10%) were initially admitted to intensive care (ICU) and a further six (1%) patients were subsequently transferred to ICU after initial admission to a general ward. The presence of comorbidities was associated with intensive care admission: OR 2.80 (95% CI: 1.49–5.27, p=0.001). Influenza B appeared associated with a lower risk of admission to ICU but this difference was not statistically significant: OR 0.36 (95% CI: 0.08–1.53, p=0.16). In a multivariate model, only the presence of one or more comorbidity was associated with ICU admission (Table 3).

Outcome

The mean LOS of all patients was 3.7 days. The presence of comorbidities was associated with an increase in mean hospital length of stay of 2.6 days. Other factors associated with prolonged length of stay included ICU admission and being Indigenous but these differences were not statistically significant (data not shown). The duration of hospital stay was similar in patients that received antivirals within 48 hours of symptom onset (median: 2.5 days; IQR: 2, 6 days), compared with those who received antivirals more than 48 hours after symptom onset (median: 4 days; IQR: 1, 7 days) and who did not receive antivirals (median: 2 days; IQR: 1, 3 days).

One in-hospital death was reported, in a 13-year-old boy with no known comorbidities.

Table 3

Factors associated with admission to intensive care in patients hospitalised with confirmed influenza, epidemiological cohort, Influenza Complications Alert Network, Australia, April to October 2014 (n=402)

Variable	Crude OR (95% CI)	p value	AOR (95% CI)	p value
Infant<12 months	1.40 (0.73, 2.69)	0.306	1.86 (0.94, 3.69)	0.076
Medical comorbidities	2.80 (1.49, 5.27)	0.001	3.20 (1.66, 6.16)	0.001
Indigenous Australian	0.79 (0.32, 1.94)	0.603	NI	NA
Influenza type				
Influenza A	1 (referent)		1 (referent)	
Influenza B	0.36 (0.08, 1.53)	0.166	NI	NA

AOR: adjusted odds ratio; CI: confidence interval; NA: not applicable; NI: not included in final model; OR: odds ratio.

Vaccine coverage

Vaccine coverage for all children>6 months of age, as shown in Figure 2, was low. Of the 225 children who tested negative for influenza within 7 days of onset of illness, 28 children had received at least one dose of vaccine in 2014 (estimated full or partial vaccine coverage: 12.4%). Eighteen children were regarded as fully vaccinated (estimated full coverage: 8.0%) Of those with comorbidities (eligible to receive influenza vaccine under the NIP), only 16 of 89 children had received at least one dose of vaccine in 2014 (estimated full or partial coverage: 18.0%), of whom only nine children were regarded as fully vaccinated (estimated full coverage: 10.1%).

Vaccine effectiveness

In children aged>6 months, the crude VE of full or partial vaccination (i.e. children who received at least one dose of vaccine in 2014) was estimated as 48.8% (95% CI: 1.1–73.5%; Table 4). After adjusting for age group and comorbidities, the adjusted full/partial VE was estimated as 55.5% (95% CI: 11.6–77.6%). VE differed by infecting strain (Table 4) with poor VE against circulating influenza A(H3N2) noted. Only one child with A(H1N1) infection was partially vaccinated with no vaccine breakthrough cases in fully vaccinated children identified: adjusted fully/partial VE estimate for A(H1N1) was 91.6% (95% CI: 36.0–98.9%).

In children aged>6 months, the crude VE based on children who were regarded as fully vaccinated in 2014 was estimated as 30.5% (95%CI -45.7 to 66.8%). After adjusting for age group (age<2 years), and chronic medical comorbidities, the adjusted VE was estimated as 41.1% (95% CI: -26.7 to 72.6%).

Discussion

Inclusion of two tertiary paediatric hospitals (from the separate Paediatric Active Enhanced Disease Surveillance network; PAEDS [5]) into the existing FluCAN sentinel system has allowed us to report on influenza in 3,400 hospitalised children and adults in 2014 (unpublished data), inclusive of metropolitan and regional hospitals, specialist paediatric and adult hospitals and hospitals in tropical and subtropical regions. By collecting data on control patients with ARI who tested negative for influenza, vaccine coverage (particularly in vulnerable patients) and VE against severe influenza can also be accurately estimated [20]. Here we report the first significant VE estimate against hospitalised influenza in Australian children.

In 2014, we recorded over 400 paediatric admissions in the FluCAN system. When compared with children with influenza requiring hospitalisation in 2009 (n=601 across six paediatric hospitals), a number of similarities and differences were identified. In both cohorts, more than 50% of children did not have any underlying comorbidities, highlighting that healthy children form a significant proportion of those requiring hospital admission. Indigenous Australians are at increased risk of hospital admission with influenza; national hospitalisation discharge data indicate that indigenous children aged <5 years are hospitalised more than twice as frequently with influenza compared with their non-indigenous peers [21]. This finding has prompted the inclusion of Indigenous children<5 years of age as eligible for NIP-funded influenza vaccination from 2015 onwards. The higher proportion of indigenous children enrolled in this study in 2014 (16.0% vs 4.5% in 2009) needs to be interpreted with caution as recruitment from sites with sizable indigenous populations (e.g. Alice Springs Hospital) occurred in 2014 and not in 2009. The proportion of Indigenous children with influenza in the study (excluding those admitted to Alice Springs Hospital) was 6.5% (23/354). This is compared with the national average of 4.4% [22].

For all children, similar outcomes were observed in 2014 compared with 2009, respectively: 11.4% and 9.9% of children were admitted to ICU, and mortality was 0.3% and 0.9% respectively. Despite the availability of free vaccine through the NIP for children with comorbidities from 2010, uptake of seasonal TIV in those at greatest risk has not significantly changed since 2009: in 2014 only 21.0% of controls with comorbidities were vaccinated compared with 18.4% in 2009 [4]. Another striking difference is the infrequent use of antiviral medications in 2014 compared with the pandemic year, 2009 (15% vs 47%). The effectiveness of

Table 4

Estimated vaccine effectiveness against hospitalisation with influenza in children aged > 6 months (vaccine effectiveness cohort), Influenza Complications Alert Network, Australia, April to October 2014

Strains	Number of cases and controls				Unadjusted VE (95% CI)	Adjusted VE[a] (95% CI)
	Vaccinated cases	Unvaccinated cases	Vaccinated controls	Unvaccinated controls		
Vaccinated cases inclusive of fully and partially vaccinated children						
All strains[b]	18	236	28	197	48.8% (1.1%, 73.5%)	55.5% (11.6%, 77.6%)
H1N1	1	72	28	197	90.2% (26.9%, 98.7%)	91.6%[c] (36.0%, 98.9%)
H3N2	13	90	28	197	6.2% (-110.7%, 58.2%)	-4.0% (-138.9%, 54.7%)
B	2	22	28	197	66.0% (-163.3%, 95.6%)	65.0% (-179.4%, 95.6%)
Vaccinated cases inclusive of fully vaccinated cases only						
All strains[b]	15	236	18	197	30.5% (-45.7%, 66.8%)	41.1% (-26.7%, 72.6%)
H1N1	0	72	18	197	100%	100%[c]
H3N2	11	90	18	197	3.5% (-154.1%, 63.4%)	-13.6% (-204.1%, 57.6%)
B	2	22	18	197	47.3% (-317.0%, 93.3%)	51.5% (-294.4%, 94.0%)

CI: confidence intervals; VE: vaccine effectiveness.

[a] adjusted for age›2 years, and comorbidities

[b] Inclusive of patients with untyped influenza A infection, H1N1, H3N2 and influenza B.

[c] 1 patient with A(H1N1) was partially vaccinated and none fully vaccinated. Non-conditional logistic regression used

oseltamivir in children and adults with influenza has recently been debated following meta-analyses by Jefferson et al. and Dobson et al. with conflicting methods, results and conclusions [23,24]. Data pooled by Jefferson et al. demonstrates that oseltamivir reduces the length of symptoms by 29 hours (95% CI: 12 to 47 hours; p=0.001) at the expense of increased rates of vomiting in children [23]. Despite no appreciable difference in complications or hospitalisation being noted, the numbers of children in both the intervention and control arms of these analyses are very small. Given the current evidence, oseltamivir is most likely to benefit patients at high risk of hospitalisation and patient with influenza requiring hospitalisation [25]. Future work should focus on ways to improve both vaccine uptake and antiviral use, particularly among children with comorbidities or other risk factors for severe influenza.

VE estimates are now generated using test-negative design in multiple populations to guide vaccine strain choice. Existing southern-hemisphere systems and VE studies have either focused on children (and adults) presenting for outpatient or emergency care [7,26,27] or enrolled insufficient numbers of children to generate robust estimates for hospitalised influenza in children, particularly in any single influenza seasons [9,26,27]. The addition of large paediatric sites to the FluCAN network, has enabled calculation of VE estimates against hospitalised influenza for children aged‹16 years in a single season. Moreover, the VE point estimate (55.5% (95% CI: 11.6–77.6%)) is comparable to that observed in hospitalised adults (51.5% (95% CI: 41.6–59.7%), unpublished data), albeit with less precision. Restricting the estimate to those fully vaccinated resulted in a lower point estimate (41.1% (95% CI: -26.7–72.6%)) but given the small numbers of vaccinated cases and controls and wide confidence intervals, this result needs to be interpreted with caution, Similar differences in VE between different influenza strains were also observed (data not shown). The addition of data from more paediatric hospitals, or over subsequent seasons, would assist in providing VE estimates against specific influenza strains and in subgroups of interest, for example the children aged 6 months to 2 years in whom data on VE is sparse.

There are a number of limitations to this study. The decision to test was left to the treating clinician using local guidelines. The impact of this is expected to be small as influenza tests are routinely recommended for infection control purposes in children requiring hospital admission with acute respiratory symptoms. It remains possible that the decision to test might have been influenced by vaccination status. As in all observational studies, a biased estimate of VE may result from unmeasured confounding or misascertainment of vaccination status or outcome. Case ascertainment was likely incomplete due to the underutilisation of influenza laboratory testing by treating clinicians, despite the diagnosis of influenza having implications for infection control and antiviral use in hospitals.

Delayed presentations or secondary bacterial pneumonia may be associated with false negative influenza tests as the influenza infection may be cleared at the time of presentation. Influenza subtyping was not available for the majority (55%) of patients, thereby limiting our ability to determine the relative burden of influenza A types and calculate accurate VE estimates by strain. Furthermore, the antigenic characteristics of influenza viruses from cases was not performed and as such we are unable to determine the relatedness of circulating strains with influenza strains included in the 2014 seasonal vaccine. The inability to determine vaccination status in all children was a limitation although no significant differences were noted when influenza status and risk factors of those with known vaccination status were compared with children with unknown vaccination status (data not shown). Low vaccine uptake was a major limitation impacting on our ability to more precisely calculate VE.

In summary, we describe more than 400 children hospitalised with seasonal influenza in Australia, of whom 10% required ICU admission. Influenza A was detected in 90% of cases with influenza A(H1N109)pdm the most frequent subtype. Vaccine uptake in those with and without comorbidities remains poor. Use of influenza antivirals in children is infrequent. TIV appeared moderately effective against hospitalisation with any influenza in 2014, but was more effective against the influenza A(H1N109)pdm subtype.

The FluCAN network and PAEDS group

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FluCAN and PAEDS are funded by the Australian Department of Health.

Acknowledgements

We thank Sue Dixon, Sue Richmond (Cairns Base Hospital), Tina Collins, Michelle Collins (Princess Alexandra Hospital), Wendy Beckingham, Sammy Xu (The Canberra Hospital), Amber Smith, Lorissa Hopkins, Douglas Dorahy (John Hunter Hospital), Susan Wagg (Royal Hobart Hospital), Janine Roney, Leah Christie, Jill Garlick (The Alfred), Kate Ellis (University Hospital Geelong), Jocelynne McRae, Helen Knight, Sue Low, Sharon Tan, Laura Rost, Jean Li-Kim-Moy (Children's Hospital at Westmead), Carolyn Finucane, Jackie Connell, (Princess Margaret Hospital). We also thank the members of the FluCAN network and the PAEDS group, whose additional investigators are listed below.

Conflict of interest

Dr Blyth has received salary supported from a WA Health / Raine Medical Clinical Research Fellowship.

Authors' contributions

Drs Blyth, Macartney, Hewagama, Senenayake, Friedman, Simpson and Upham supervised recruitment of children at their respective sites. Drs Cheng, Kotsimbos and Kelly established the FluCAN network. Drs Blyth and Cheng undertook the analysis and drafted the manuscript. All authors reviewed the manuscript prior to submission.

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Research article

I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?

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Citation style for this article:
Kissling E, Nunes B, Robertson C, Valenciano M, Reuss A, Larrauri A, Cohen JM, Oroszi B, Rizzo C, Machado A, Pitigoi D, Domegan L, Paradowska-Stankiewicz I, Buchholz U, Gherasim A, Daviaud I, Horváth JK, Bella A, Lupulescu E, O´Donnell J, Korczyńska M, Moren A, I-MOVE case–control study team. I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination? . Euro Surveill. 2016;21(16):pii=30201. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.16.30201

Article submitted on 03 December 2015 / accepted on 10 February 2016 / published on 21 April 2016

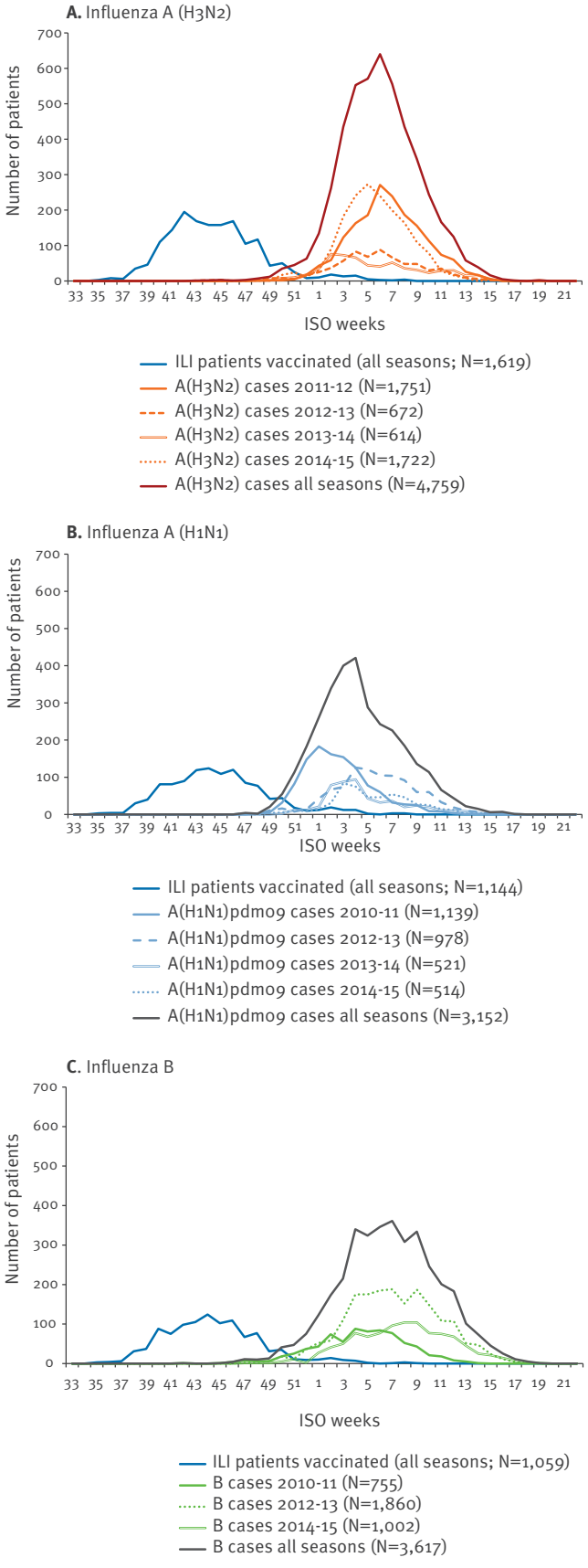
Since the 2008/9 influenza season, the I-MOVE multicentre case–control study measures influenza vaccine effectiveness (VE) against medically-attended influenza-like-illness (ILI) laboratory confirmed as influenza. In 2011/12, European studies reported a decline in VE against influenza A(H3N2) within the season. Using combined I-MOVE data from 2010/11 to 2014/15 we studied the effects of time since vaccination on influenza type/subtype-specific VE. We modelled influenza type/subtype-specific VE by time since vaccination using a restricted cubic spline, controlling for potential confounders (age, sex, time of onset, chronic conditions). Over 10,000 ILI cases were included in each analysis of influenza A(H3N2), A(H1N1)pdm09 and B; with 4,759, 3,152 and 3,617 influenza positive cases respectively. VE against influenza A(H3N2) reached 50.6% (95% CI: 30.0–65.1) 38 days after vaccination, declined to 0% (95% CI: -18.1–15.2) from 111 days onwards. At day 54 VE against influenza A(H1N1)pdm09 reached 55.3% (95% CI: 37.9–67.9) and remained between this value and 50.3% (95% CI: 34.8–62.1) until season end. VE against influenza B declined from 70.7% (95% CI: 51.3–82.4) 44 days after vaccination to 21.4% (95% CI: -57.4–60.8) at season end. To assess if vaccination campaign strategies need revising more evidence on VE by time since vaccination is urgently needed.

Introduction

Influenza vaccination is currently the best measure available to prevent seasonal influenza infection. In most European countries one dose (or two doses for children) of seasonal vaccine is recommended from late September/October to November/December for target groups for vaccination, which may include the elderly (either ≥55, ≥60 or ≥65 years of age), clinical risk groups, pregnant women, healthcare workers, other occupational groups and other groups depending on country [1]. In Europe, influenza seasons can last until mid-May [2], and it is expected that vaccination confers protection to the individual for the duration of the season. In thirteen of fifteen reviewed studies on the length of vaccine-induced protection among the elderly, using anti-haemagglutination antibody titres as a proxy for seroprotection levels, seroprotection rates lasted at least 4 months after vaccination [3].

Figure 1

Onset of influenza-like illness (ILI) among (A) influenza A(H3N2), (B) A(H1N1)pdm09 and (C) B cases, by season and pooled, and dates of vaccination[a] of ILI patients, by ISO week, I-MOVE multicentre case–control study, influenza seasons 2010/11–2014/15



ILI: influenza-like illness; ISO: International Organisation for Standardisation a Patients vaccinated include those vaccinated <15 days before symptom onset.

However, in the 2011/12 influenza season various studies in Europe reported a decrease in influenza vaccine effectiveness (VE) against A(H3N2) over time within the season [4-7]. In the United States (US), a decrease in VE against A(H3N2) with time since vaccination was also observed in the 2007/08 influenza season [8].

The observed decrease of VE over time may be explained by viral change (notably antigenic drift) occurring in the season. Drift in B viruses may be slower than in A viruses [9], and A(H3N2) viruses have a higher rate of nucleotide substitutions than A(H1N1) pdm09 viruses [10].

The decrease of VE over time can also be explained by a waning of the immunity conferred by the vaccine independently from viral changes. If vaccine-induced protection wanes during the season, then depending on the start and duration of the influenza season, the decline of VE may cause increases in overall incidence, outbreaks, particularly in residential care facilities, as well as hospitalisations and deaths. Changes to vaccination strategies i.e. timing and/or boosters, may be needed.

As anti-haemagglutination antibody titres are not well defined as a correlate of protection [11,12], vaccine efficacy, as measured in trials, or VE measured in observational studies may be one way to measure vaccine-induced protection. These studies require a large sample size to model VE by time since vaccination and currently, most of the seasonal observational studies lack the precision required to provide evidence for waning effectiveness.

In this study we pooled data across five post-pandemic seasons, namely 2010/11 to 2014/15, from the I-MOVE (influenza-monitoring vaccine effectiveness) multicentre case–control studies [2,4,13,14], to obtain a larger sample size to study the effects of time since vaccination on influenza type/subtype-specific VE. We measured influenza type/subtype-specific VE by time since vaccination for the overall season, but also in the early phase of the influenza season. Under the hypothesis that virological changes are fewer in the early season, waning of the vaccine effect should be present regardless of phase within the season.

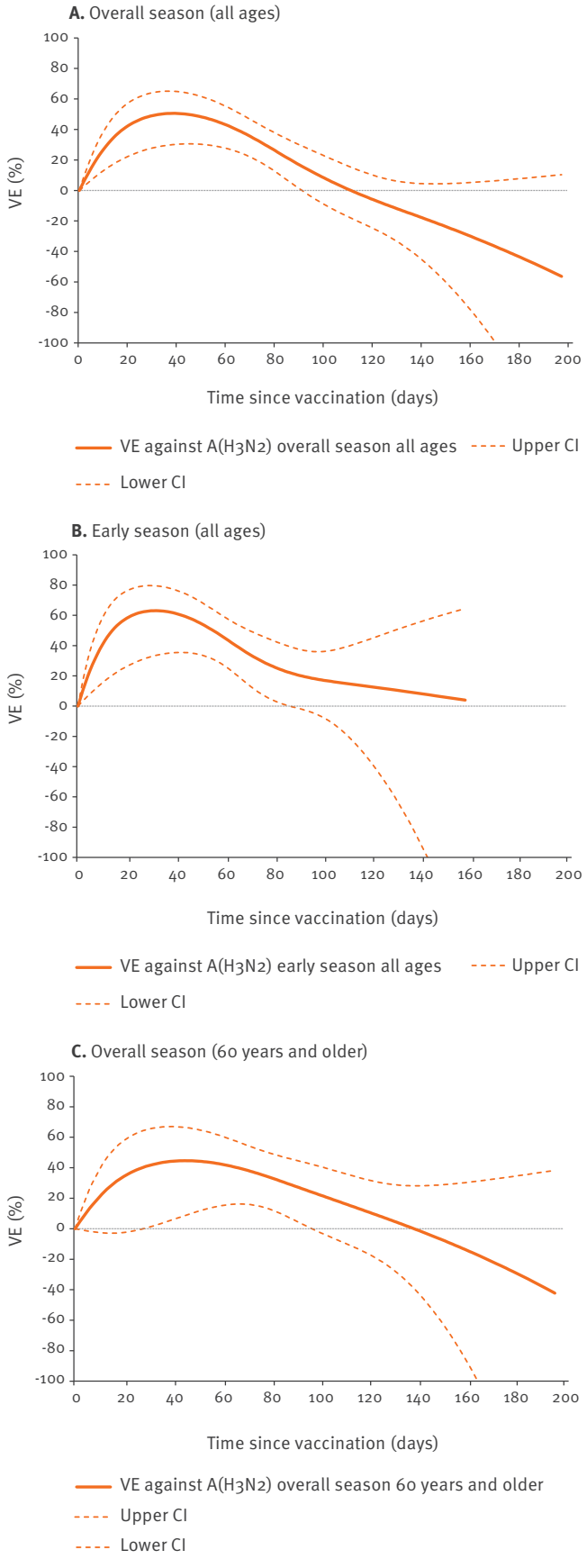
Methods

The I-MOVE multicentre case–control study methods are described in detail elsewhere [15,16], and are based on the European Centre for Disease Prevention and Control (ECDC) generic influenza VE case–control study protocol [17].

Briefly, several countries (between six and eight depending on the season, during the 2010/11 to 2014/15 study period) carried out a test-negative case–control study each season to measure influenza VE and sent their data to a central hub for pooled analysis. Participating practitioners interviewed and collected

Figure 2

Pooled-season adjusted vaccine effectiveness against influenza A(H3N2) by time since vaccination (days), I-MOVE multicentre case–control study, influenza seasons 2011/12–2014/15



CI: confidence intervals; VE: vaccine effectiveness.

naso-pharyngeal specimens from a systematic sample of or all patients, depending on age group, consulting for influenza like illness (ILI). Practitioners obtained clinical and epidemiological information, including vaccination status, date of vaccination and vaccine product. Cases were patients whose swabs tested positive for influenza virus using real-time reverse-transcription PCR (RT-PCR), controls were patients whose swabs tested negative for influenza virus using RT-PCR.

In the pooled analysis we included patients who consulted their practitioner more than 14 days after the start of national or regional seasonal influenza vaccination campaign, who met the criteria for the European Union ILI case definition [18], who were swabbed less than eight days after symptom onset and who did not receive antivirals before swabbing.

For each study site each influenza type/subtype- and season-specific study period began at the week of onset of the first influenza case and ended at the week of onset of the last influenza case after which there were at least two consecutive weeks with no further influenza-positive cases of that influenza type/subtype.

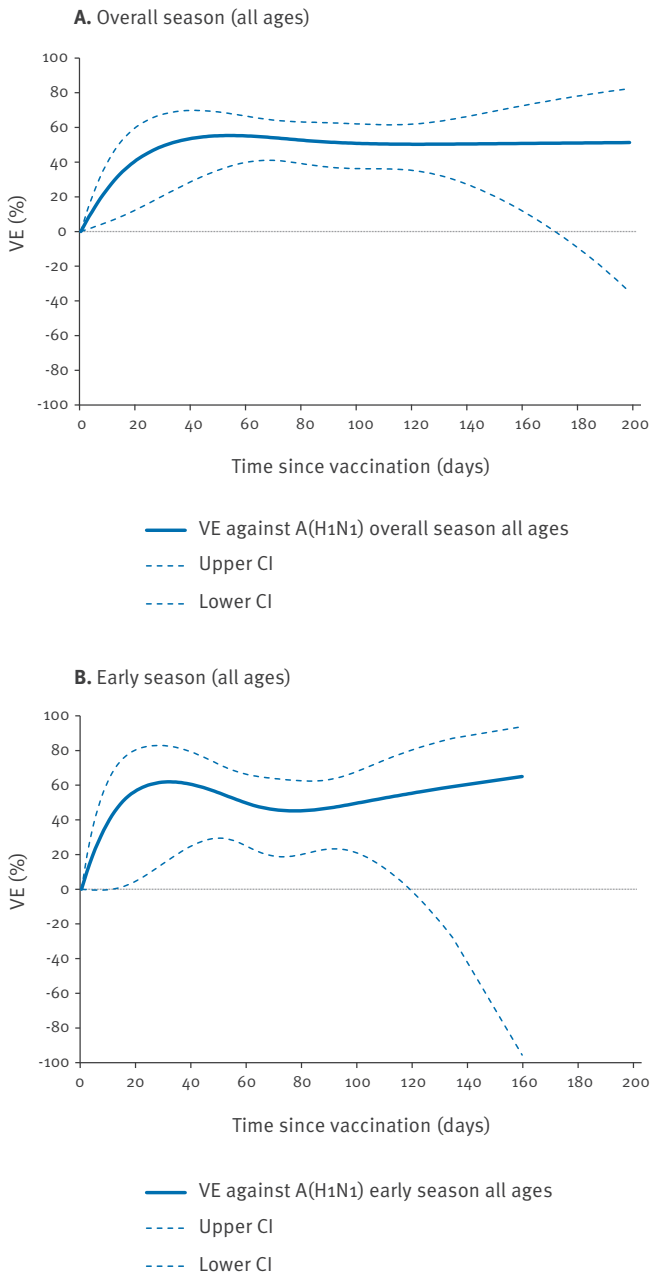
We defined patients as vaccinated if they had received at least one dose of influenza vaccine more than 14 days before symptom onset. Patients receiving a dose of vaccine < 15 days before symptom onset and receiving no dose of vaccine were defined as unvaccinated.

For each influenza season and for each influenza type/subtype-specific analysis we partitioned the influenza season into two and created an early and late influenza phase. This was based on a mid-season date with an equal number of type/subtype-specific cases by dates of onset on either side.

For each season, we used logistic regression to compute the odds ratio (OR) of being vaccinated in cases and controls. We estimated the type/subtype-adjusted influenza VE as (1 minus the OR)*100. Study site was modelled as a fixed effect and always included in the analysis model. We used Cochran's Q-test and the I^2 index to test for heterogeneity between seasons [19]. We pooled individual data across the seasons, always including study site and season as a fixed effect in the crude or adjusted analysis model. We measured VE where sample size was high enough (number of model parameters < 10–15% of number of cases) carrying out a complete analysis excluding patients with missing values for any of the variables in the model measuring VE. We included age, sex, presence of a risk factor for complications, including chronic conditions, pregnancy and obesity where available, and week of symptom onset as covariates in the models. Age was modelled using a restricted cubic spline, with four or three knots depending on sample size with knots specified according to Harrell [20].

Figure 3

Pooled season adjusted vaccine effectiveness against influenza A(H1N1)pdm09 by time since vaccination (days), I-MOVE multicentre case–control study, influenza seasons 2010/11 and 2012/13–2014/15



CI: confidence interval; VE: vaccine effectiveness.

We measured influenza type/subtype-specific VE for the whole influenza season, for the early and late influenza phase, and for all ages and among those aged 60 years and older.

We coded time since vaccination as date of onset of symptoms minus date of vaccination with persons not receiving the vaccine coded as '0 days' [21]. We modelled time since vaccination using a cubic spline, tail-restricted at the upper end, with four knots, two a priori at zero and 15 days and then at the 40th and 90th centile. Those vaccinated less than 15 days before symptom onset were modelled as well and were considered vaccinated for this time since vaccination analysis. We included season, study site and the same covariates as above in the analysis. We measured type/subtype-specific VE by time since vaccination for the whole influenza season and by early influenza phase among all ages. Among those aged 60 years and older we measured type/subtype-specific VE by time since vaccination for the whole influenza season. We did not attempt the modelling where the number of vaccinated cases was lower than 50.

In a sensitivity analysis we assessed the shape, the coefficients and the model fit using the Aikaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) of the model, with varying number and placement of knots. We further evaluated the inclusion of onset weeks in case of collinearity between the two time variables: time since vaccination and onset week. Where sample size was sufficiently large, we also modelled VE by time since vaccination for each individual season and for each influenza type/subtype.

Results

Among the five seasons studied (2010/11 to 2014/15), we included four seasons with influenza A(H3N2), four seasons with influenza A(H1N1)pdm09 and three seasons with influenza B in the analysis, as these were the seasons with sufficient circulation of these influenza types/subtypes to carry out our analyses. Influenza seasons varied in terms of start, intensity and duration by influenza type/subtype (Figure 1). Seventy-nine percent of vaccinations were carried out before the first influenza positive case in the study in each country. This varied by 40–100% by country.

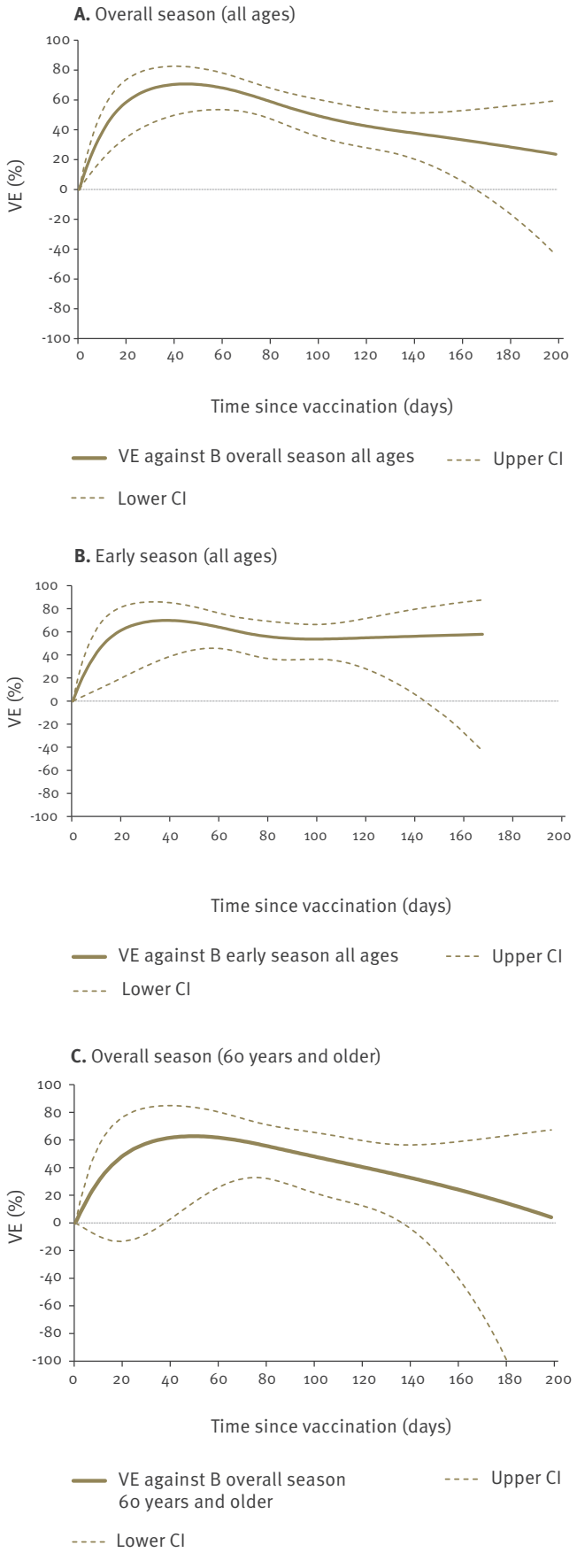
Among the 2,224 vaccinated patients (9.6%), the name of the vaccine product was available for 1,909 (85.8%). All vaccines were inactivated, with 52.4% (n=1,000) of patients vaccinated with egg-derived split virion, 24.8% (n=474) with egg-derived subunit, 21.1% (n=403) with adjuvanted and 1.7% (n=32) with cell-derived subunit vaccine. Patients vaccinated within 1.5 months (45 days) after begin of each season-specific vaccination campaign by country were more likely to be older than those vaccinated later: median age 64 (interquartile range (IQR) 46–73), compared with 53 (IQR 13–69), respectively. They were also more likely to have a chronic condition: 61.8% compared with 52.2%.

Influenza A(H3N2)

We included 13,738 ILI cases in the pooled-season complete case analysis for influenza A(H3N2), of which 4,759 (34.6%) were A(H3N2) influenza positive cases. Among those aged 60 and over we included 1,775 ILI cases, 672 (37.9%) of those were influenza A(H3N2) positive. The percentage of records dropped from the complete case analysis among all ages due to missing data was 5.5%.

Figure 4

Pooled season adjusted vaccine effectiveness against influenza B by time since vaccination (days), I-MOVE multicentre case–control study, influenza seasons 2010/11, 2012/13 and 2014/15



CI: confidence intervals; VE: vaccine effectiveness.

The VE by season against influenza A(H3N2) ranged between 5.9% and 42.2%. The pooled-season adjusted VE (psAVE) was 15.0%, with an I^2 index of 27.3%. Among those aged 60 years and older, the psAVE was 23.0% with an I^2 of 0.0% (Table 1).

Mid-season dates partitioning the early and late influenza phase varied by 13 days between seasons (30 January to 12 February). Among all ages the psAVE was 32.1% in the early phase and -2.8% in the late phase (Table 2). Among those aged 60 years and older the psAVE was 36.8% in the early phase and 9.2% in the late phase.

When modelling the psAVE by days since vaccination against influenza A(H3N2), we see an initial increase to a peak, followed by a steady decline. Among all ages the psAVE against A(H3N2) by days since vaccination initially increased to 50.6% at 38 days since vaccination (Figure 2). It then declined to 0% at 111 days since vaccination, continually declining thereafter.

In the early influenza phase, the psAVE showed a similar pattern to the overall phase, with a peak of 63.1% at day 32. The psAVE then declined to 4.0% at 159 days. No patient was vaccinated more than 159 days before symptom onset in the early phase.

Among those aged 60 years and older the psAVE increased initially to 44.6% at day 45. It then declined to 0% at day 140.

Influenza A(H1N1)pdm09

We included 11,385 ILI cases in the pooled-season complete case analysis against influenza A(H1N1)pdm09, of which 3,152 (27.7%) tested influenza A(H1N1)pdm09 positive. Among those aged 60 and over we included 1,228 ILI cases with 201 (16.4%) A(H1N1)pdm09-positive cases. Among all ages for the complete case analysis, we dropped 5.9% of records due to missing data.

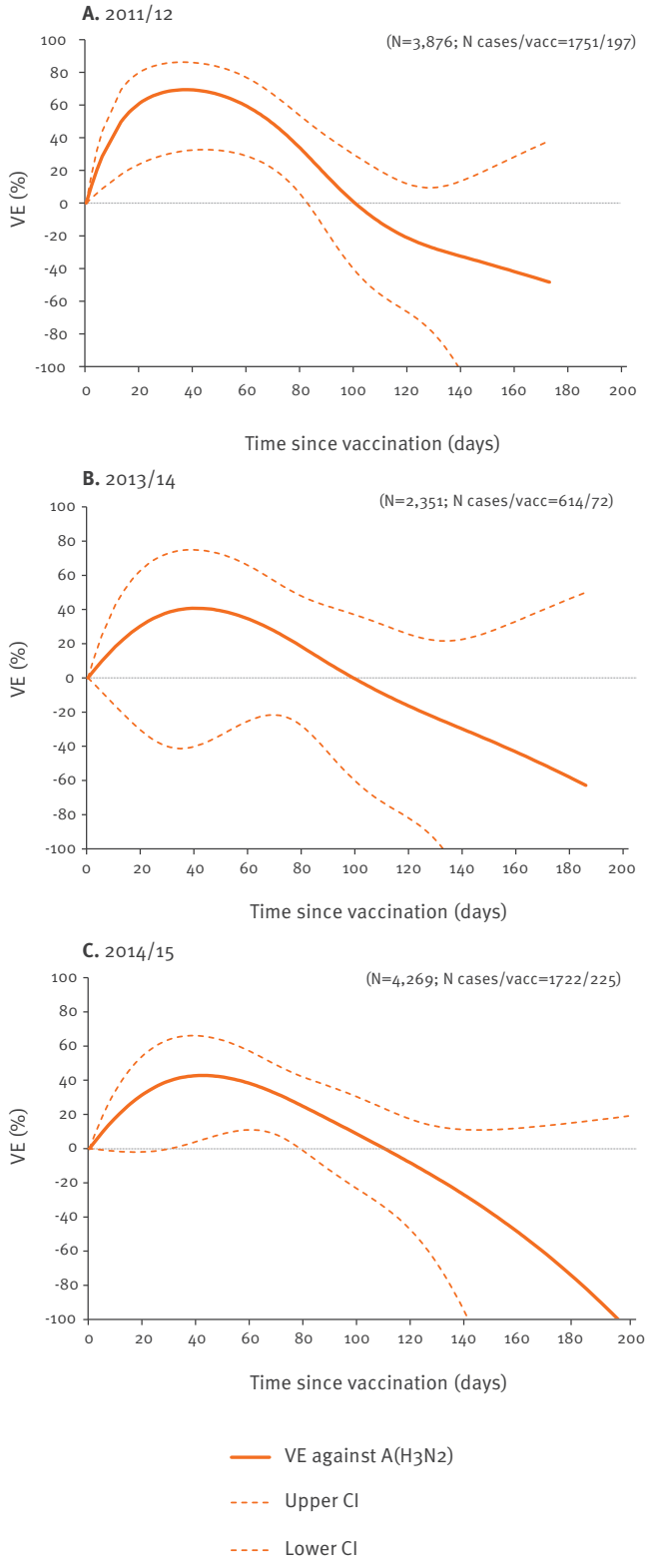
The VE estimates by season were between 47.5% and 53.8% against A(H1N1)pdm09 resulting in a psAVE of 52.2%. There was no statistical heterogeneity between season-specific VE estimates (I^2 index 0.0%). Among those aged 60 years and older, the psAVE was 54.0% with an I^2 of 39.4% (Table 1).

Mid-season dates partitioning the early and late influenza phase varied by 20 days (14 January to 3 February). The psAVE against influenza A(H1N1)pdm09 among all ages for the pooled early phase was 50.1% and 52.9% for the late phase (Table 2). Crude pooled-season VE against A(H1N1)pdm09 among those aged 60 and older in the pooled early phase was 44.7% and the AVE was 61.2% in the late phase, adjusted by month of onset of symptoms.

Modelling psAVE against influenza A(H1N1)pdm09 by days since vaccination did not suggest any decline in psAVE within the season. Among all ages the psAVE

Figure 5

Adjusted vaccine effectiveness against influenza A(H3N2), all ages, by season, I-MOVE influenza seasons (A) 2011/12, (B) 2013/14, (C) 2014/15



CI: confidence intervals; VE: vaccine effectiveness.

initially increased to 55.3% at day 54 (Figure 3). The psAVE then remained between 50.0% and 55.3% between 31 and 197 days since vaccination. No patients were vaccinated more than 197 days before symptom onset.

In the early influenza phase, the psAVE against influenza A(H1N1)pdm09 showed a similar pattern to the overall phase initially, reaching 61.9% at day 32. After that, the psAVE was variable, but never dipped below 45.2% (day 77). Sample size was too small to calculate the psAVE by time since vaccination among those aged 60 and older.

Influenza B

We included 10,900 ILI cases in the pooled-season complete case analysis, of which 3,617 (33.2%) were influenza B-positive. Among those aged 60 and over we included 1,274 ILI cases, among which 309 (24.3%) were influenza B-positive. For the complete case analysis among all ages, we dropped 5.3% of records due to missing data.

The season-specific VE against influenza B ranged from 47.6% to 55.0%, with a psAVE of 50.7%. There was no statistical heterogeneity between season-specific VE estimates for influenza B (I^2 index 0.0%). Among those aged 60 years and older, the psAVE was 45.7% against influenza B with an I^2 of 0.0% (Table 1).

Mid-season dates partitioning the early and late influenza phase varied by 19 days (31 January to 19 February) for influenza B. The psAVE against influenza B among all ages was 57.5% in the pooled early phase and 43.4% in the late phase (Table 2). The psAVE against influenza B among those aged 60 and older was 46.2% in the early phase and 44.5% in the late phase.

Modelling psAVE against influenza B in the overall season by days since vaccination showed an initial peak, followed by a decline. Among all ages, the psAVE against influenza B increased initially to 70.7% at day 44. It then declined to 21.4% at day 207 (Figure 4).

In the early influenza phase, the psAVE against influenza B peaked at 69.9% at day 39. It then dipped to 53.7% at day 99. The psAVE increased slightly after day 99 to 57.9% at day 169.

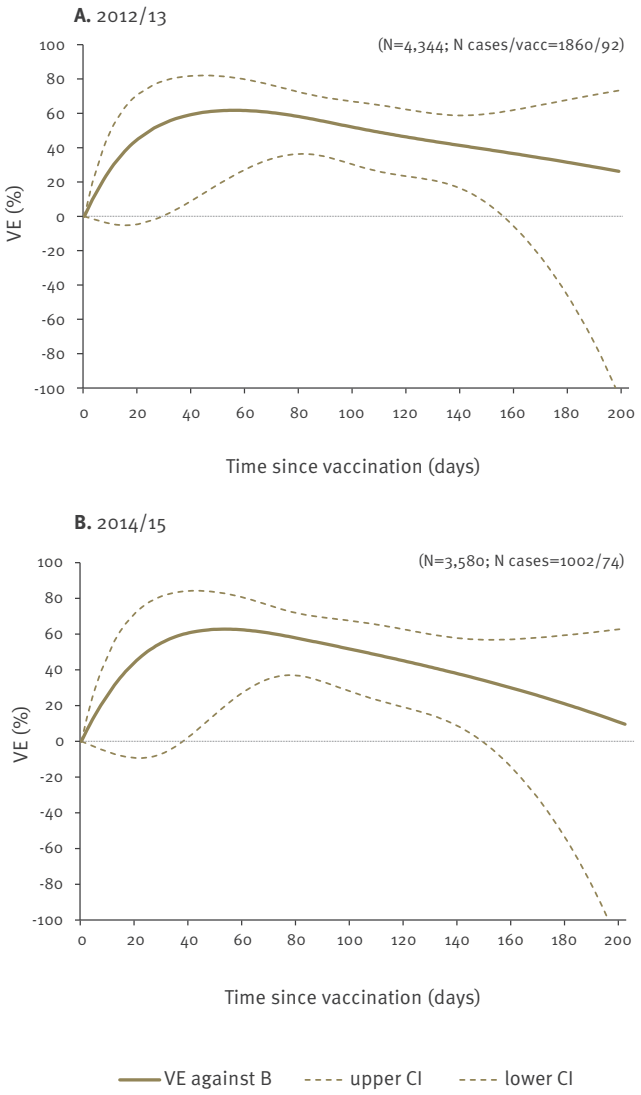
Among those aged 60 years and older the psAVE against influenza B increased initially to 62.7% at day 49. It then declined to 4.1% at day 197.

Sensitivity analyses

In the sensitivity analyses with varying location of knots there was almost no difference in model fit (as determined by the AIC/BIC) and the same aspect of graphs. Varying the number of knots resulted in little difference in model fit. Aspects of the graphs varied slightly with different number of knots, but maintained the general messages in terms of increase and decline.

Figure 6

Adjusted vaccine effectiveness against influenza B, all ages, by season, I-MOVE, influenza seasons (A) 2012/13, (B) 2014/15



CI: confidence intervals; VE: vaccine effectiveness.

We did not find collinearity, as measured by the variance inflation factor, between time since vaccination and onset weeks. The model fit based on both AIC and BIC were substantially better for models including onset weeks, compared with without, for all influenza type/subtypes.

Sample size permitted modelling VE by time since vaccination for some individual seasons: 2011/12, 2013/14 and 2014/15 against influenza A(H3N2) and 2012/13 and 2014/15 against influenza B. Similar patterns of decline in VE is seen for each individual season as for the pooled seasons (Figures 5–6).

Discussion

The pooling of our results across influenza seasons suggests a higher VE against influenza A(H3N2) in the early than in the late phase among all ages and among those aged 60 years and older. This was not observed for influenza A(H1N1)pdm09 and only a small decline in VE was observed against influenza B among all ages.

Modelling VE against influenza A(H3N2) by time since vaccination suggested an initial increase in VE up to 30 to 45 days since vaccination, which is in line with other studies [22]. But then the VE declined to less than 0% among all ages and in those 60 years and older in the overall season, although the upper CIs remained at about 0%. VE by time since vaccination against influenza B also declined after an initial peak among all ages and those aged over 60 years; however VE never declined to 0%. VE by time since vaccination against influenza A(H1N1)pdm09 among all ages remained stable. VE declined with time since vaccination in the early phase for influenza A(H3N2) but not for A(H1N1)pdm09 and B.

One limitation of this study is that we were unable to provide VE by time since vaccination against genetic clades of each influenza type/subtype. While there appears to be a waning of vaccine effect over time, we cannot disentangle to what extent this is due to virus change and subsequent non-matching of the vaccine or loss of vaccine-induced immunity within the individual. Information on genetic clade is available in I-MOVE since the 2013/14 season [14]. However, samples selected for sequencing were few and often not representative of the circulating viruses overall. In the 2015/16 season, I-MOVE will pilot a new method for selecting samples for genetic sequencing, using a systematic sampling approach.

Modelling time since vaccination against genetic clade would enable removal of much of the effects of virus change over time from the effects due to waning of vaccine-induced immunity. In this study, we modelled psAVE by time since vaccination restricting to the early phase of the influenza seasons, assuming that virological changes may be fewer in this phase, where we still see a decline in VE against influenza A(H3N2). The rates and timing of viral mutation during a season are unclear, however it has been suggested that significant amounts of antigenic drift can occur at any time of the season [23]. More information on distribution of genetic clades over time is needed.

We pooled data across seasons to increase sample size and therefore precision. While there was no statistical heterogeneity between season-specific VE estimates, there was some variation, particularly for A(H3N2). If there is a true decline in vaccine-induced immunity, then we expect the shape of the seasonal curve to be similar to the curve pooled across seasons, although point estimates along the curve may vary season on season. Single-season models of VE against influenza A(H3N2) and against influenza B by time since vaccination show similar curves to the pooled-season ones. Sample size did not permit modelling of VE against A(H1N1)pdm09 by season, nor modelling of

Table 1

Adjusted vaccine effectiveness against influenza A(H3N2), A(H1N1)pdm09 and B, among all ages and those aged 60 years and older, I-MOVE multicentre case–control study, influenza seasons 2010/11–2014/15

Influenza type / subtype for analysis	Study year	Study sites included[a]	Weeks included in the analysis	Mid-season date	All ages		60 years and older	
					Cases; vaccinated/ Controls; vaccinated[b]	Adjusted[b,c] VE (95% CI) all ages	Cases; vaccinated/ Controls; vaccinated[d]	Adjusted[d,e] VE (95% CI) all ages
A(H3N2)	2011/12	FR, ES, HU, IE, IT, PL, PT, RO	Wk 46, 2011–wk 17, 2012	12 Feb 2012	1,751;197 / 2,125;249	11.3 (-15.6–31.9)	251;134 / 268;131	14.9 (-33.4–45.8)
	2012/13	DE, ES, FR, IE, PL, PT, RO	Wk 43, 2012–wk 16, 2013	4 Feb 2013	672;46 / 2,340;212	42.2 (95%CI: 14.9–60.7)	72;22 / 190;83	52.8 (5.5–76.5)
	2013/14	DE, ES, HU, IE, PT, RO	Wk 47, 2013–wk 19, 2014	30 Jan 2014	614;72 / 1,737;208	5.9 (95%CI: -35.6–34.7)	78;38 / 183;94	40.7 (-18.0–70.2)
	2014/15	DE, ES, HU, IE, IT, PL, PT, RO	Wk 47, 2014–wk 16, 2015	1 Feb 2015	1,722;225 / 2,547;355	14.8 (-5.9–31.4)	270;114 / 438;199	15.2 (-20.4–40.3)
	Pooled	DE, ES, FR, HU, IE, IT, PL, PT, RO	All of the weeks mentioned above	NA	4,759;540 / 8,979;1040	15.0 (2.6–25.8) I^2: 27.3; p=0.248	672;308 / 1103;517	23.0 (3.2–38.7) I^2=0.0%; p=0.404
A(H1N1)pdm09	2010/11	FR, ES, HU, IE, IT, PL, PT, RO	Wk 48, 2010–wk 14, 2011	14 Jan 2011	1,139;39 / 2,116;227	53.8 (30.3–69.4)	50;12 / 284;147	73.1 [f] (44.7–86.9)
	2012/13	DE, ES, FR, IE, PL, PT, RO	Wk 47, 2012–wk 16, 2013	03 Feb-2013	978;44 / 2,218;214	50.3 (28.3–65.6)	50;11 / 204;90	59.1 [f] (14.3–80.5)
	2013/14	DE, ES, HU, IE, PT, RO	Wk 50, 2013–wk 17, 2014	23 Jan 2014	521;34 / 1,592;203	47.5 (16.4–67)	42;15 / 184;96	51.8 [f] (-0.5–76.9)
	2014/15	DE, ES, HU, IE, IT, PL, PT, RO	Wk 47, 2014–wk 16, 2015	31 Jan 2015	514;36 / 2,201;299	53.3 (29.6–69.0)	59;20 / 392;171	22.4 [f] (-44.4–58.4)
	Pooled	DE, ES, FR. HU, IE, IT, PL, PT, RO	All of the weeks mentioned above	NA	3,152;153 / 8,233;953	52.2 (41.6–60.9) I^2=0.0%; p=0.975	201;58 / 1,027;488	54.0 (38.5–64.0) I^2=39.4%; p=0.176
B	2010/11	FR, ES, HU, IE, IT, PL, PT, RO	Wk 45, 2010–wk 13, 2011	31 Jan 2011	754;32 / 2,131;233	55.0 (27.4–72.1)	49;18 / 284;144	42.7[f] (-12.2–70.7)
	2012/13	DE, ES, FR, IE, PL, PT, RO	Wk 47, 2012–wk 18, 2013	15 Feb 2013	1,860;92 / 2,484;236	49.3 (32.4–62)	131;38 / 225;98	39.9 (-3.4–65)
	2014/15	DE, ES, HU, IE, IT, PL, PT, RO	Wk 42, 2014–wk 19, 2015	19 Feb 2015	1,002;74 / 2578;354	47.6 (28.4–61.7)	129;33 / 441;195	53.2 (19.1–73)
	Pooled	DE, ES, FR, HU, IE, IT, PL, PT, RO	All of the weeks mentioned above	NA	3,617;198 / 7,283;830	50.7 (40.5–59.2) I^2=0.0%; p=0.872	309;89 / 965;445	45.7 (24.2–61.1) I^2=0.0%; p=0.801

CI: confidence intervals; NA: not applicable; VE: vaccine effectiveness; wk: week.

[a] DE: Germany, ES: Spain; FR: France; HU: Hungary; IE: Ireland; IT: Italy; PL: Poland; PT: Portugal; RO: Romania.

[b] Results from complete case analysis. In some analyses, onset weeks dropped from the model, due to only cases/controls in those weeks. Numbers of records therefore dropped: For A(H3N2) 2011/12: 11; 2012/13 45; 2013/14: 20; 2014/15: 222; pooled: 68 For A(H1N1)pdm09: 2012/13: 53; 2014/15: 205; pooled: 152. For B: 2010/11: 1; 2014/15: 152; pooled: 62.

[c] Adjusted by study site, age (as restricted cubic spline for all analyses except 2014/15 against A(H3N2) where age group is used), sex, presence of chronic disease and week of symptom onset. For the pooled-season results, VE is additionally adjusted by season. Results may vary to previously published estimates due to different models applied.

[d] Results from complete case analysis. In some analyses, onset weeks/months dropped from the model, due to only cases/controls in those weeks/months: Numbers of records therefore dropped: For A(H3N2) 2011/12: 23; 2012/13 15; 2013/14: 3; 2014/15: 33; pooled: 49. For A(H1N1)pdm09: 2012/13: 12; 2014/15: 10; pooled: 59. For B: 2012/13: 6; 2014/15: 31; pooled: 22.

[e] Adjusted by study site, age (as restricted cubic spline), sex, presence of chronic disease and week/month of symptom onset. For the pooled-season results, VE is additionally adjusted by season. Results may vary to previously published estimates due to different models applied.

[f] Crude VE. VE adjusted by study site only

VE against A(H3N2) or B for each season. Even when pooling across seasons, sample size remained limited and we were not able to estimate psAVE against influenza A(H1N1)pdm09 by time since vaccination among those aged 60 and older, nor psAVE by time since vaccination in the early season among those aged 60 and older against any influenza type/subtype. In addition, CIs were wide at the outer limits of time since vaccination, but precision was good between 60 and 120 days among all ages and for all influenza types/subtypes. This corresponds to 2 to 4 months after vaccination campaigns and is generally the period where the main epidemic occurs.

Different vaccines were used not only in the different seasons, but also by country and within regions within

Table 2

Pooled-season adjusted vaccine effectiveness against influenza A(H3N2), A(H1N1)pdm09 and B, among all ages and those aged 60 years and older, by early/late influenza phase, I-MOVE multicentre case–control study, influenza seasons 2010/11–2014/15

Influenza type/subtype	Age group	Season[a]	Cases;vacc/ Controls;vacc[b]	Adjusted VE (95%CI)[b,c]
A(H3N2)	All ages	Early pooled	2,395;207 / 4,552;490	32.1 (16.3–44.9)
		Late pooled	2,364;333 / 4,427;550	-2.8 (-23.5–14.4)
	60 years and older	Early pooled	286;109 / 5,17;235	36.8 (9.7–55.8)
		Late pooled	386;199 / 585;282	9.2 (-23.5–33.3)
A(H1N1)pdm09	All ages	Early pooled	1,573;69 / 3,243;346	50.1 (32.2–63.3)
		Late pooled	1,579;84 / 4,990;607	52.9 (38.5–64.0)
	60 years and older	Early pooled[d]	86;29 / 412;186	44.7 (7.5–67.0)
		Late pooled[e]	115;29 / 674;327	61.2 (37.7–75.8)
B	All ages	Early pooled	1,829;94 / 4,390;499	57.5 (43.8–67.8)
		Late pooled	1,788;104 / 2,893;331	43.4 (26.4–56.4)
	60 years and older	Early pooled[f]	166;50 / 584;273	46.2 (15.8–65.6)
		Late pooled[f]	143;39 / 399;177	44.5 (8.7–66.3)

CI: confidence intervals; VE: vaccine effectiveness.

[a] Distinction between early and late season was based on a mid-season date with an equal number of type/subtype-specific cases by dates of onset on either side.

[b] Results from complete case analysis. In some analyses, onset weeks/months dropped from the model, due to only cases/controls in those weeks. Numbers of records therefore dropped: For A(H3N2): all ages early season: 58; all ages late season: 10; 60 years and older early season: 38; 60 and older late season: 12. For A(H1N1)pdm09: all ages early season: 152. For B: all ages early season: 62; 60 years and older early season: 10; 60 years and older late season: 1.

[c] Adjusted by study site, age (as restricted cubic spline), sex, presence of chronic disease, week of symptom onset and season, unless otherwise specified.

[d] Crude VE. VE adjusted by study site and season only.

[e] Adjusted by study site, season and onset month only.

[f] Adjusted as in [b], but using onset month, rather than onset week.

countries. Some individuals were vaccinated with adjuvanted vaccine, which may elicit a different immune response, particularly in relation to duration of protection [24]. While 21% of vaccinated patients with known vaccination brand received an adjuvanted vaccine, 67% of these were vaccinated with a vaccine adjuvanted by aluminium gel phosphate, which has been reported to be inferior to emulsion adjuvants in other vaccines [25]. With an increase in sample size, estimates of psAVE by time since vaccination by group of vaccines (split virion, subunit, adjuvanted) could be carried out.

Immune response may differ by age group [26], which is why we estimated psAVE by time since vaccination among those aged 60 and over. PsAVE by time since vaccination was similar in this age group as in all ages. However, a greater sample size is needed to provide more precision, particularly when partitioning by early season. A larger sample size is also needed to provide estimates for other age groups.

In this study there was no change in VE against influenza A(H1N1)pdm09 by time since vaccination. This is in line with a study suggesting protection of monovalent A(H1N1) vaccination in children and adults that persisted across several seasons [27]. The vaccine component for A(H1N1)pdm09 was the same in all seasons of the study (A/California/7/2009 (H1N1)-like virus), indicating that the virus remained antigenically homogenous across these seasons [28].

VE against influenza B declined slightly with time since vaccination. The decline of VE by time since vaccination in the early influenza season stabilised around day 99 and the decline was less steep than in the overall season. This decline may be due to changes in circulating influenza B lineage towards the end of the season rather than a decline in vaccine-induced immunity. However single-season estimates from the 2014/15 season, where influenza B lineage circulation across the season is known, do not support this hypothesis. In the 2014/15 season, 71.6% (746/1038) of influenza B cases had lineage information available, among which 740 (99.2%) were B/Yamagata, yet we saw a small decline over time [29].

VE against influenza A(H3N2) declined considerably with time since vaccination. It is also known that this subtype undergoes rapid virological change. Our modelling suggests strong decline in AVE with time since vaccination in 2011/12, 2013/14 and 2014/15. During the 2011/12 and 2014/15 seasons, circulating influenza A(H3N2) viruses showed an imperfect match to the vaccine virus; however, during the 2013/14 season few characterised A(H3N2) viruses differed antigenically from the vaccine virus component [30-32]. If the decline in psAVE with time since vaccination is due at

least in part to waning of vaccine-induced immunity, further research is needed to understand why this is the case for influenza A(H3N2) in these seasons and B, but not for A(H1N1)pdm09.

Previous studies have suggested a within-season decline in VE by partitioning time within the season or time since vaccination into categories [5,6]. An Australian study reported a decline in VE, but it was sensitive to the cut-off chosen [33]. In this study we modelled time since vaccination as a spline, which provides added value to the categorical approach. It provides information on the change in AVE continuously for each day between vaccination and onset of symptoms. To our knowledge this type of modelling of AVE by time since vaccination has not been carried out in an influenza VE study before.

While more research is needed to address the effects of virological change over the season in the decrease in VE over time, this study suggests that there is some waning of immunity of the influenza A(H3N2) component of the vaccine and to a certain extent the B component of the vaccine. These findings underline the importance of carrying out influenza VE studies annually using standardised methodology and in numerous sites in order to continually increase our understanding of the variability of influenza VE.

Current season influenza VE has been suggested to vary by prior season influenza vaccine history [34-36]. Our study would benefit from having taken prior season influenza vaccination into account in the analysis, however, sample size for stratification by receipt of previous season vaccination is still small despite the five year pooling. In addition, it remains uncertain how many prior seasons' vaccination needs to be taken into account and cohort studies may be indicated.

A within-season waning of influenza vaccine effect has several important health and policy implications. A late influenza season may mean an increase in influenza burden, including increased hospitalisations and deaths among those vaccinated, within the season. Vaccination strategies would need to be reconsidered, and could include commencing vaccination campaigns later in the year, as is recommended for the 2015/16 influenza season in Spain [37], providing a booster dose of vaccine later in the influenza season or recommending antiviral treatment among vaccinated in an outbreak (for example in a care home) situation. Careful consideration of each strategy is needed, as for example later vaccination campaigns may result in missed opportunities to vaccinate, in case of an early season.

We urge other study teams to measure VE by time since vaccination, and if possible VE against clades – and to pool data to be able to provide results by age group and vaccine type/product. Serological studies are also needed to complement the VE results. More evidence is urgently needed to assess if the time and frequency of vaccination campaigns should be reviewed. Simultaneously resources should be invested in the development of an improved vaccine, to provide higher protection levels for all influenza types/subtypes overall and across each influenza season.

The I-MOVE multicentre case–control team

The I-MOVE multicentre case–control team, in addition to the 21 authors listed before (except Chris Robertson) consists of, in alphabetical order of countries:

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Acknowledgements

We are grateful to ECDC and WHO-EURO and all patients, practitioners and epidemiologists from the study sites who actively participated in the studies between 2010-11 and 2014-15. Germany: Michael Herzhoff, Unit for Data Management, Department for Infectious Disease Epidemiology, Robert Koch Institute; Spain: S de Mateo and C Delgado, National Centre of Epidemiology; I Casas and P Pérez Breña, National Centre of Microbiology; Manuel García Cenoz, Instituto de Salud Pública de Navarra, Navarra, CIBERESP; Jone M. Altzibar, Subdirección de Salud Pública de Guipuzkoa, País Vasco. CIBERESP; Inmaculada Aspirichaga Gamarra, Subdirección de Salud Pública y Adicciones de Bizkaia; Larraitz Etxebarriarteun Aranzabal, Subdirección de Salud Pública y Adicciones de Araba/Álava); Tomás Vega, Dirección General de Salud Pública e Investigación,

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Conflict of interest

None declared

Authors' contributions

EpiConcept: Esther Kissling undertook the statistical analysis on which the research article is based and led the writing of the article. Marta Valenciano coordinated the I-MOVE multicentre case–control study network. All authors provided contribution to the research article and approved the final version. Alain Moren contributed towards the analysis plan. Alain Moren and Marta Valenciano, were involved in the original methodological design of the I-MOVE multicentre case–control study. In general: Baltazar Nunes and Chris Robertson contributed significantly towards the analysis plan and validation of the modelling. Alain Moren, Marta Valenciano, Esther Kissling, Baltazar Nunes, Udo Buchholz, Amparo Larrauri, Jean Marie Cohen, Beatrix Oroszi, Caterina Rizzo, Ausenda Machado, Daniela Pitigoi, Lisa Domegan, Iwona Paradowska-Stankiewicz, Annicka Reuss, Isabelle Daviaud, Krisztina Horváth, Antonino Bella, Emilia Lupulescu and Joan O´Donnell, have all had a role in modification of this design over the years. All authors read, contributed and approved the manuscript final version. Germany: Annicka Reuss and Udo Buchholz were responsible for validation of data and interpretation of results in the German study site. Spain: Amparo Larrauri, Alin Gherasim and Silvia Jiménez-Jorge were responsible for the study design and coordination of the Spanish study site and the national database. Jesús Castilla, Fernando González Carril and Daniel Castrillejo were involved in the collection and collation of the data. Francisco Pozo undertook the genetic characterization of the influenza strains. All authors contributed to the interpretation of the results and final review of the paper. France: Jean Marie Cohen, Anne Mosnier and Isabelle Daviaud participated in the coordination of the French study site and management of the French database. Portugal: Baltazar Nunes and Ausenda Machado were responsible for the study design in Portugal study site. Ireland: Lisa Domegan and Joan O'Donnell were responsible for the study design and coordination of the Irish study site. Romania: Daniela Pitigoi coordinated epidemiological side of the Romanian study site. Daniela Pitigoi was responsible for the study design in Romanian study site. Daniela Pitigoi collected data and enrolled patients. Emilia Lupulescu coordinated the laboratory side of the study. Poland: Iwona Paradowska-Stankiewicz and Monika Korczyńska were responsible for the study design and coordination in the Polish study site.

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Research article

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

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Citation style for this article:
Pebody R, Warburton F, Ellis J, Andrews N, Potts A, Cottrell S, Johnston J, Reynolds A, Gunson R, Thompson C, Galiano M, Robertson C, Mullett D, Gallagher N, Sinnathamby M, Yonova I, Moore C, McMenamin J, de Lusignan S, Zambon M. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 mid-season results. Euro Surveill. 2016;21(13):pii=30179. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.13.30179

Article submitted on 26 February 2016 / accepted on 30 March 2016 / published on 31 March 2016

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

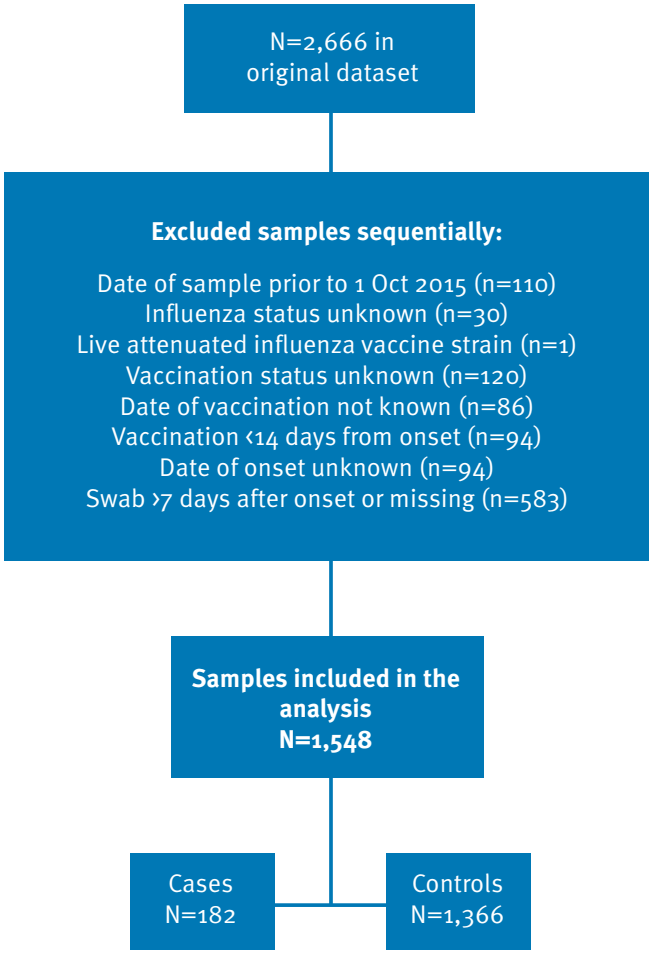
Study population and period

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

Figure 1

Specimen inclusion and exclusion criteria, interim 2015/16 influenza vaccine effectiveness evaluation, United Kingdom, 1 October 2015–22 January 2016 (n = 2,666)



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 (SIAT1) cells as previously described [7,8].

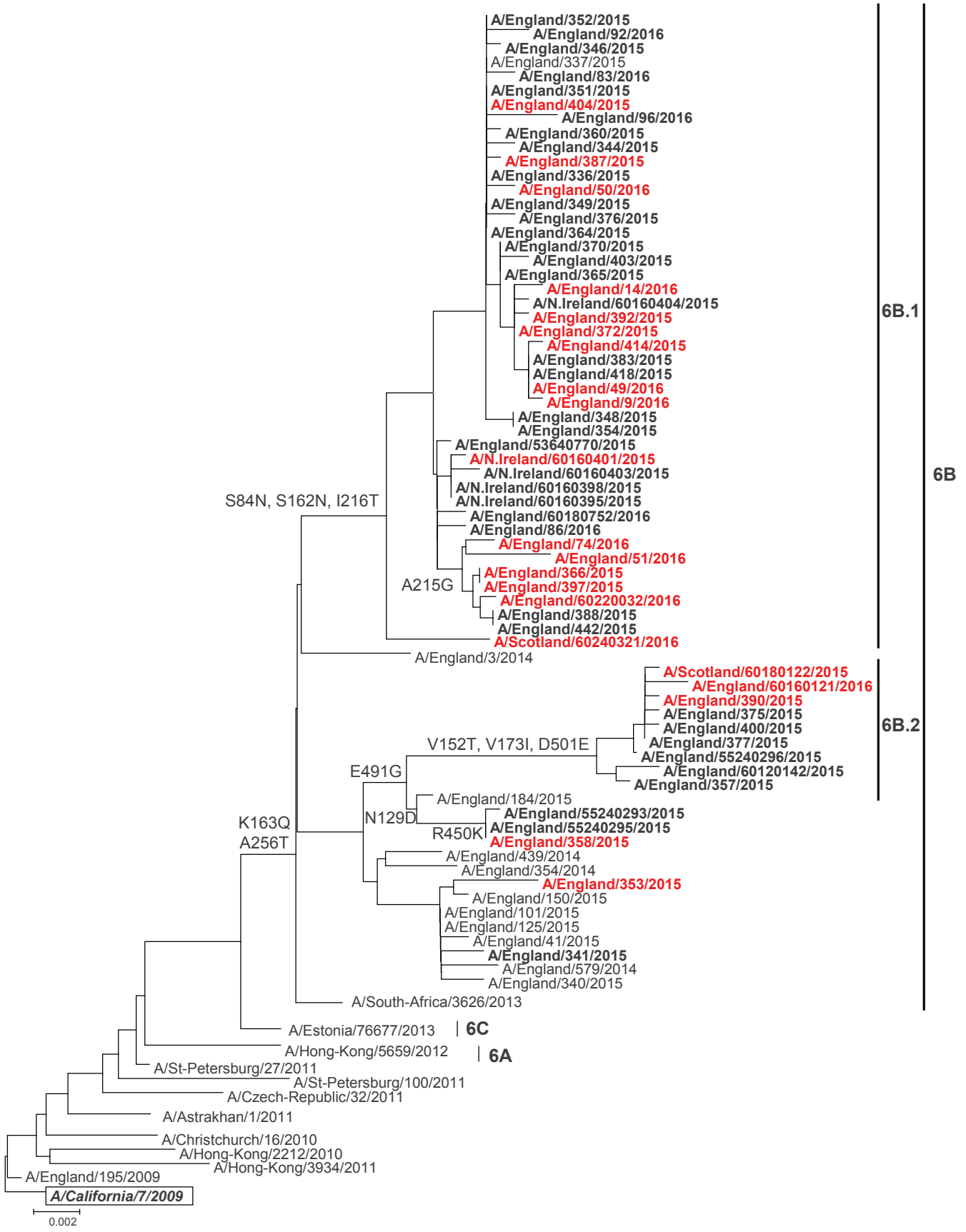
Influenza A(H1N1)pdm09 virus isolates with a haemagglutination titre ≥ 40 were characterised antigenically using post-infection ferret antisera in haemagglutination inhibition (HI) assays, with turkey red blood cells [9]. Reference virus strains used for HI assays included A/California/7/2009 (vaccine 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.

Table 1

Influenza A(H1N1)pdm09 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/Astrakhan/1/2011	EPI319590	Russian Federation	2011-Feb-28	WHO National Influenza Centre, Saint Petersburg, Russian Federation	National Institute for Medical Research, London, UK
A/St. Petersburg/27/2011	EPI319527	Russian Federation	2011-Feb-14	WHO National Influenza Centre, Saint Petersburg, Russian Federation	National Institute for Medical Research, London, UK
A/England/3/2014	EPI503206	United Kingdom	2014-Jan-08	Microbiology Services Colindale, Public Health England, London, UK	National Institute for Medical Research, London, UK
A/Estonia/76677/2013	EPI466545	Estonia	2013-Mar-13	Health Protection Inspectorate, Tallin, Estonia	National Institute for Medical Research, London, UK
A/Hong Kong/5659/2012	EPI390473	Hong Kong (SAR)	2012-May–21	Government Virus Unit, Hong Kong (SAR)	National Institute for Medical Research, London, UK
A/Hong Kong/3934/2011	EPI326206	Hong Kong (SAR)	2011-Mar-29	Government Virus Unit, Hong Kong (SAR)	National Institute for Medical Research, London, UK
A/Hong Kong/2212/2010	EPI279895	Hong Kong (SAR)	2010-Jul-16	Government Virus Unit, Hong Kong (SAR)	National Institute for Medical Research, London, UK
A/Czech Republic/32/2011	EPI319447	Czech Republic	2011-Jan-18	National Institute of Public Health, Prague, Czech Republic	National Institute for Medical Research, London, UK
A/England/195/2009	EPI178507	United Kingdom	2009-Apr-28	Microbiology Services Colindale, Public Health England, London, UK	National Institute for Medical Research, London, UK
A/St. Petersburg/100/2011	EPI316435	Russian Federation	2011-Mar-14	Russian Academy of Medical Sciences, Saint Petersburg, Russian Federation	Centers for Disease Control and Prevention, Atlanta, US
A/South Africa/3626/2013	EPI577031	South Africa	2013-Jun-06	National Institute for Medical Research, London, UK	Centers for Disease Control and Prevention, Atlanta, US
A/Christchurch/16/2010	EPI280344	New Zealand	2010-Jul-12	WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia	Centers for Disease Control and Prevention, Atlanta, US
A/California/07/2009	EPI177294	United States	2009-Apr-09	Naval Health Research Center, San Diego, US	Centers for Disease Control and Prevention, Atlanta, US

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 <5 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): 3.0–64.7) 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

Table 2

Details for influenza A and B cases (n = 182) and controls (n = 1,366), United Kingdom, 1 October 2015–22 January 2016

	Control (n = 1,366)	Influenza B[a] (n = 20)	A(H1N1)[a] (n = 152)	A(H3N2) (n = 3)	A (unknown) (n = 9)	p value[b]
Age						
<5	163 (83.2%)	2 (1.0%)	33 (16.8%)	0 (0.0%)	0 (0.0%)	
5–17	193 (91.9%)	1 (0.5%)	16 (7.6%)	0 (0.0%)	0 (0.0%)	
18–44	502 (86.6%)	12 (2.1%)	63 (10.9%)	0 (0.0%)	3 (0.5%)	0.001
45–64	315 (88.0%)	4 (1.1%)	32 (8.9%)	2 (0.6%)	5 (1.4%)	
≥ 65	192 (95.0%)	1 (0.5%)	7 (3.5%)	1 (0.5%)	1 (0.5%)	
Missing	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	
Sex						
Female	840 (90.3%)	8 (0.9%)	73 (7.8%)	2 (0.2%)	7 (0.8%)	0.002
Male	522 (85.2%)	12 (2.0%)	78 (12.7%)	1 (0.2%)	2 (0.3%)	
Missing	4 (80.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	
Surveillance scheme						
Northern Ireland	33 (63.5%)	4 (7.7%)	9 (17.3%)	0 (0.0%)	6 (11.5%)	
RCGP	540 (87.8%)	4 (0.7%)	69 (11.2%)	2 (0.3%)	0 (0.0%)	<0.001
SMN	58 (75.3%)	1 (1.3%)	18 (23.4%)	0 (0.0%)	0 (0.0%)	
Scotland	701 (92.8%)	10 (1.3%)	42 (5.6%)	1 (0.1%)	3 (0.4%)	
Wales	34 (69.4%)	1 (2.0%)	14 (28.6%)	0 (0.0%)	0 (0.0%)	
Risk group						
No	908 (86.5%)	17 (1.6%)	119 (11.3%)	2 (0.2%)	6 (0.6%)	<0.001
Yes	414 (93.0%)	3 (0.7%)	25 (5.6%)	1 (0.2%)	2 (0.4%)	
Missing	44 (83.0%)	0 (0.0%)	8 (15.1%)	0 (0.0%)	1 (1.9%)	
Onset to swab						
0–1 days	145 (86.3%)	0 (0.0%)	21 (12.5%)	0 (0.0%)	2 (1.2%)	
2–4 days	713 (87.7%)	12 (1.5%)	84 (10.3%)	3 (0.4%)	3 (0.4%)	0.400
5–7 days	508 (89.6%)	8 (1.4%)	47 (8.3%)	0 (0.0%)	4 (0.7%)	
Vaccination status						
Unvaccinated	1,055 (87.0%)	16 (1.3%)	135 (11.1%)	2 (0.2%)	7 (0.6%)	
Vaccinated (14–91 days ago)	280 (92.7%)	3 (1.0%)	17 (5.6%)	1 (0.3%)	1 (0.3%)	0.013
Vaccinated(>91 days ago)	31 (93.9%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	
Primary school-age programme area						
No	594 (84.7%)	6 (0.9%)	99 (14.1%)	2 (0.3%)	0 (0.0%)	
Yes	768 (91.1%)	14 (1.7%)	53 (6.3%)	1 (0.1%)	9 (1.1%)	<0.001
Missing	4 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Month of event						
October	300 (98.7%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	
November	380 (96.4%)	5 (1.3%)	7 (1.8%)	2 (0.5%)	0 (0.0%)	<0.001
December	446 (85.9%)	5 (1.0%)	67 (12.9%)	0 (0.0%)	1 (0.2%)	
January	240 (72.5%)	9 (2.7%)	77 (23.3%)	0 (0.0%)	7 (2.1%)	

RCGP: Royal College of General Practitioners' Research and Surveillance Centre scheme; SMN: Public Health England Specialist Microbiology Network.

[a] Two people tested positive for both influenza B and A(H1N1)pdm09.

[b] Positive vs negative for influenza.

Numbers and row percentages (to indicate positivity rates) are shown.

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

Table 3

Samples positive (cases) and negative (controls) for influenza, by vaccination status and vaccine effectiveness estimate, United Kingdom, 1 October 2015–22 Jan 2016 (n = 1,548)

	Cases (vac/unvacc)	Controls (vac/unvacc)	Crude VE (95% CI)	Adjusted VE [a] (95% CI)
Influenza A and B	24/158	311/1,055	48.5% (19.4–67.1)	41.5% (3.0–64.7)
Influenza A(H1N1)pdm09	17/135	311/1,055	57.3% (28.1–74.6)	49.1% (9.3–71.5)
Influenza A	20/144	311/1,055	52.9% (23.5–71.0)	47.3% (9.0–69.5)

CI: confidence interval; VE: vaccine effectiveness.

[a] Adjusted for age group, sex, month, surveillance scheme and primary school-age programme area.

of circulating strains. Similar observations have been reported from other European countries [11]. The full picture of virological genetic variation requires further detailed analysis, which is not possible at this stage of the winter season.

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.

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Research article

Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case–Control Study, Europe 2014/15

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Citation style for this article:
Valenciano M, Kissling E, Reuss A, Rizzo C, Gherasim A, Horváth J, Domegan L, Pitigoi D, Machado A, Paradowska-Stankiewicz I, Bella A, Larrauri A, Ferenczi A, Joan O´Donell, Lazar M, Pechirra P, Korczyńska M, Pozo F, Moren A, on behalf of the I-MOVE multicentre case–control team. Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case–Control Study, Europe 2014/15. Euro Surveill. 2016;21(7):pii=30139. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.7.30139

Article submitted on 12 October 2015 / accepted on 25 November 2015 / published on 18 February 2016

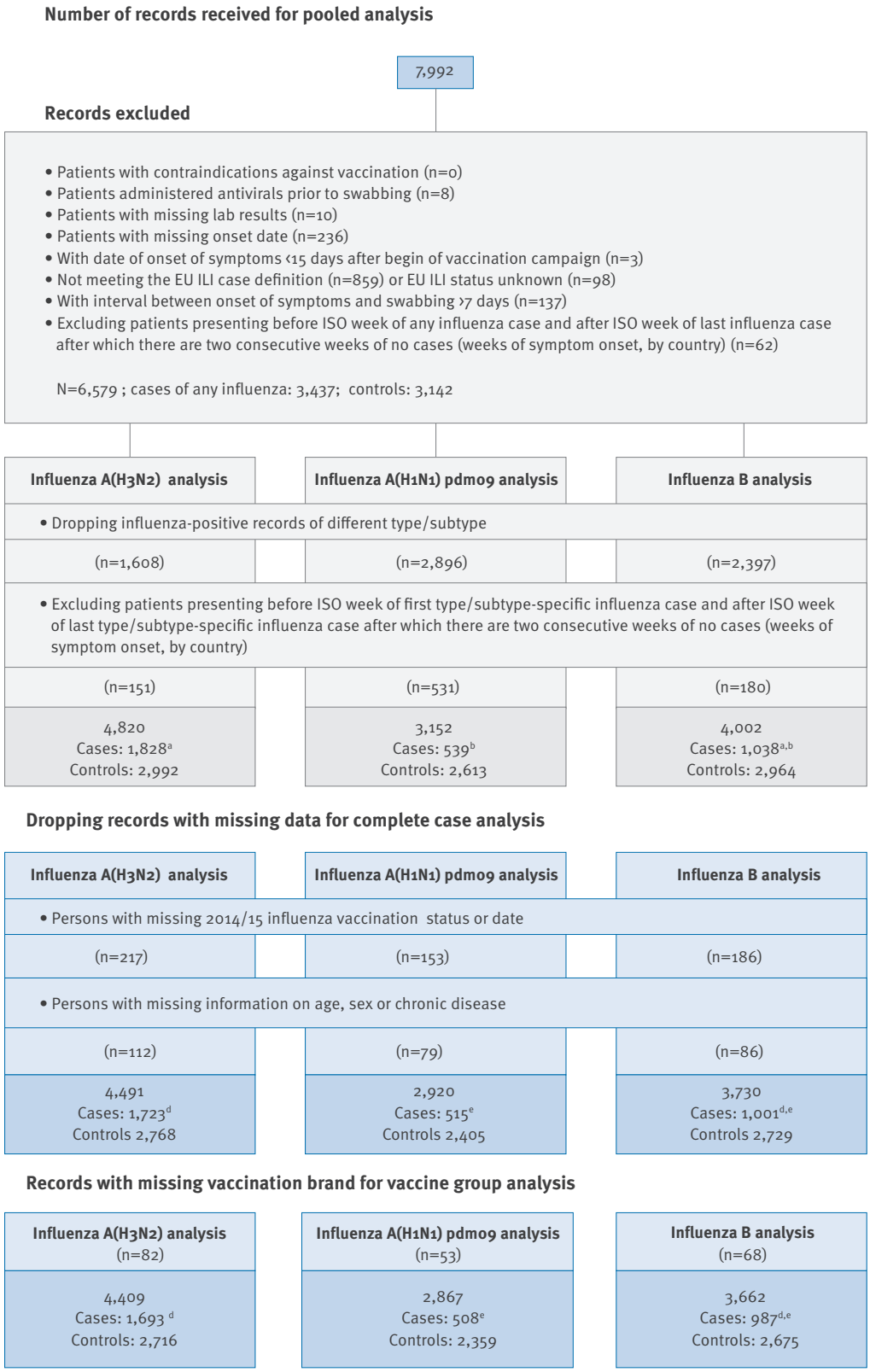
Influenza A(H3N2), A(H1N1)pdm09 and B viruses co-circulated in Europe in 2014/15. We undertook a multicentre case–control study in eight European countries to measure 2014/15 influenza vaccine effectiveness (VE) against medically-attended influenza-like illness (ILI) laboratory-confirmed as influenza. General practitioners swabbed all or a systematic sample of ILI patients. We compared the odds of vaccination of ILI influenza positive patients to negative patients. We calculated adjusted VE by influenza type/subtype, and age group. Among 6,579 ILI patients included, 1,828 were A(H3N2), 539 A(H1N1)pdm09 and 1,038 B. VE against A(H3N2) was 14.4% (95% confidence interval (CI): -6.3 to 31.0) overall, 20.7% (95%CI: -22.3 to 48.5), 10.9% (95%CI -30.8 to 39.3) and 15.8% (95% CI: -20.2 to 41.0) among those aged 0–14, 15–59 and ≥60 years, respectively. VE against A(H1N1) pdm09 was 54.2% (95%CI: 31.2 to 69.6) overall, 73.1% (95%CI: 39.6 to 88.1), 59.7% (95%CI: 10.9 to 81.8), and 22.4% (95%CI: -44.4 to 58.4) among those aged 0–14, 15–59 and ≥60 years respectively. VE against B was 48.0% (95%CI: 28.9 to 61.9) overall, 62.1% (95%CI: 14.9 to 83.1), 41.4% (95%CI: 6.2 to 63.4) and 50.4% (95%CI: 14.6 to 71.2) among those aged 0–14, 15–59 and ≥60 years respectively. VE against A(H1N1)pdm09 and B was moderate. The low VE against A(H3N2) is consistent with the reported mismatch between circulating and vaccine strains.

Introduction

In February 2014 each year, the World Health Organization (WHO) provides recommendations for the composition of the northern hemisphere vaccines, based on information from the WHO Global Influenza Surveillance and Response System. In 2014, the WHO vaccine strain selection committee recommended that the 2014/15 northern hemisphere influenza vaccine should include the same components as in 2013/14: an A/California/7/2009 (H1N1)pdm09-like

Figure 1

Flowchart of data exclusion for pooled analysis, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)



EU: European Union; ILI: influenza-like illness; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; ISO: International Organization for Standardization.

[a] Includes 15 influenza B + A(H3N2) co-infections.

[b] Includes 8 influenza B + A(H1N1)pdm09 co-infections.

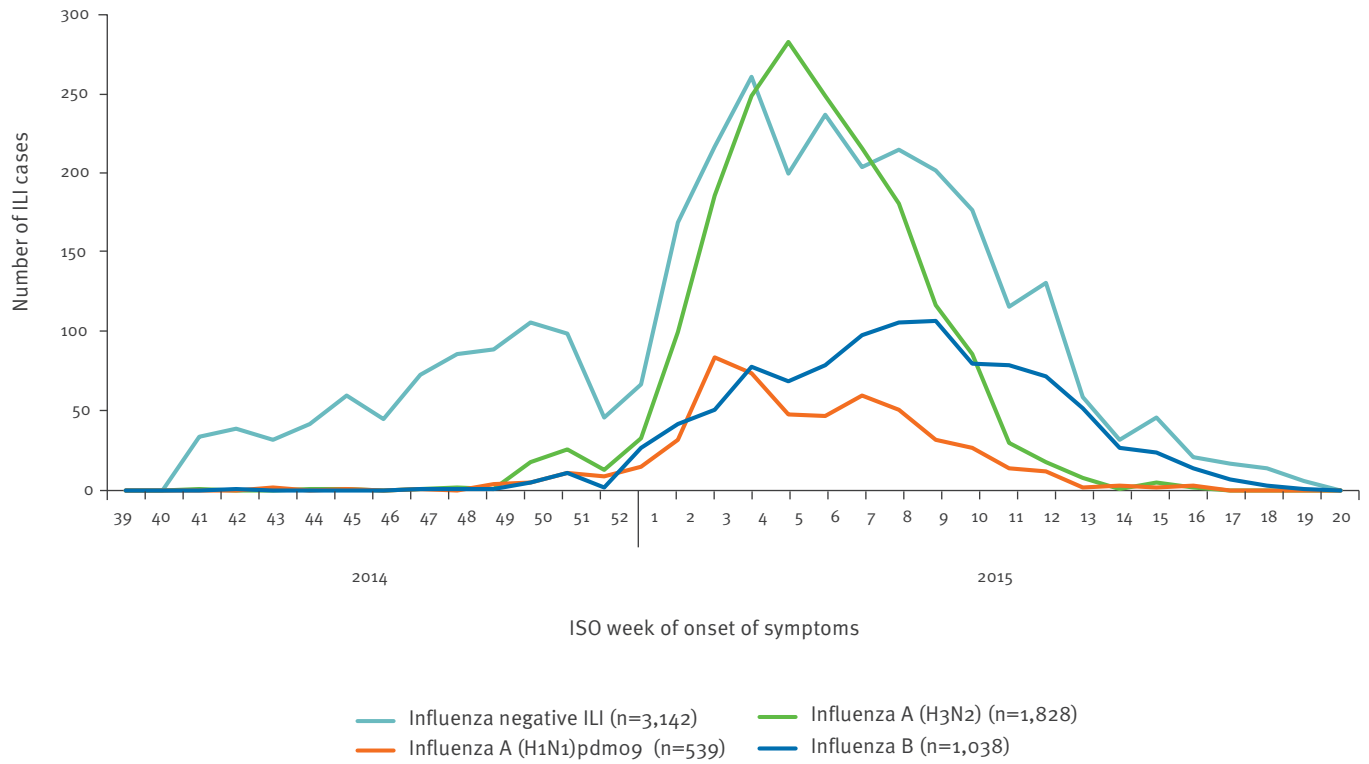
[c] Includes 3 influenza B + A(H3N2)pdm09, and 7 A(H1N1)pdm09 + A(H3N2) co-infections.

[d] Includes 14 influenza B + A(H3N2)pdm09 co-infections.

[e] Includes 7 influenza B + A(H1N1)pdm09 co-infections.

Figure 2

Number of influenza-like illness reports by case status and week of symptom onset, all influenza, target groups for vaccination, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015) (n=6,524[a])



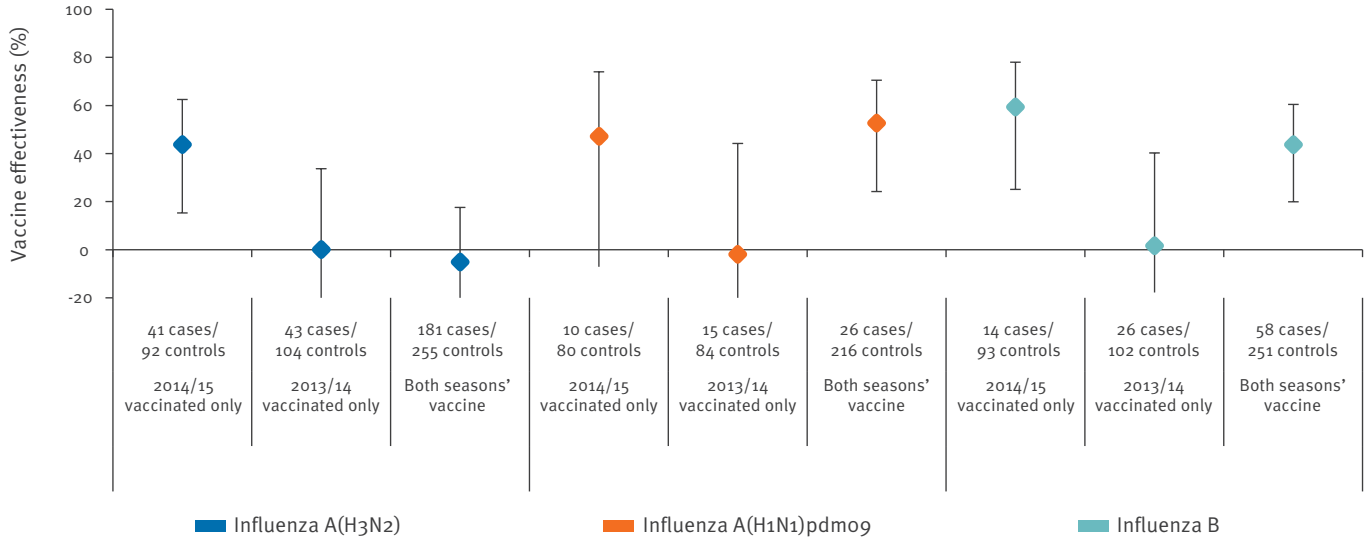
ILI: influenza-like illness; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe, ISO: International Organization for Standardization.

[a] This includes 15 influenza B+A(H3N2) co-infections and eight influenza B+A(H1N1)pdm09 co-infections. Note that numbers of cases come from influenza type/subtype specific databases. Some cases are excluded due to their restriction criteria. Any influenza A non-typed cases are dropped from analysis.

The proportion vaccinated with the 2014/15 influenza vaccine was 13.2% among controls, 13.0% among A(H3N2) cases, 6.9% among A(H1N1) pdm09 cases and 7.4% among B cases (Table 2).

Figure 3

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory confirmed influenza by influenza type/subtype, and by season of vaccination, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)



I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe.

virus, an A/Texas/50/2012 (H3N2)-like virus, and a B/Massachusetts/2/2012-like virus [1].

In September 2014, the WHO reported the emergence of two new influenza virus genetic clades for A(H3N2), clade 3C.2a and 3C.3a [1]. These clades had first circulated in Europe during the 2013/14 influenza season [2].

In December 2014, the United States (US) Centers for Disease Control and Prevention (CDC) issued a Health Alert reporting that 52% of the A(H3N2) viruses circulating were antigenically different from the A(H3N2) component of the northern hemisphere 2014/15 influenza vaccine. CDC recommended the use of antiviral medications where indicated for the treatment and prevention of influenza, as an adjunct to vaccination [3]. Concordant with the reports of the drifted A(H3N2) viruses, in January 2015, the US, Canada and the United Kingdom (UK) reported low influenza vaccine effectiveness (VE) against A(H3N2) [4-6]. Canadian results suggested that VE against influenza A(H3N2) among individuals who had been vaccinated in both 2013/14 and 2014/15 seasons was lower than among those who were only vaccinated in 2014/15 [5].

In Europe, the influenza season started later than in the US and Canada. Increased influenza activity in Europe was first reported in early January 2015, with a predominance of A(H3N2) but with influenza A(H1N1) pdm09 and B circulating as well [7].

For this seventh season of the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case–control study we aimed to measure the 2014/15 effectiveness of the seasonal influenza vaccine against the three co-circulating viruses by age group and by vaccine type. In addition, due to the potential implications for vaccination policy we explored the effect of previous vaccinations on the current season VE.

Methods

Eight study sites (Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania and Spain) participated in the test-negative 2014/15 multicentre case–control study. The methods have been described previously [7-9] and are based on the European Centre for Disease Prevention and Control (ECDC) generic case–control study protocol [10].Briefly, participating general practitioners (GPs) interviewed and collected naso-pharyngeal specimens from all (seven study sites) or a systematic sample (in Germany) of patients consulting for influenza- like illness (ILI) aged 60 (Germany, Poland, and three regions in Spain) or 65 years old (Hungary, Ireland, Italy, Portugal, Romania and three regions in Spain) and older and from a systematic sample of ILI patients in the other age groups. In Hungary, only patients aged 18 years or over were eligible for inclusion in the study. GPs collected clinical and epidemiological information as previously described [8]. We included patients in the study who presented to the GPs more than 14 days after the start of the national vaccination campaigns and who met the European Union (EU) ILI case definition [11], were swabbed within seven days of symptom onset, and who had not received antivirals before swabbing.

Cases were ILI patients who were swabbed and tested positive for influenza virus using real-time reverse-transcription PCR (RT-PCR). Controls were ILI patients who tested negative for any influenza virus using RT-PCR. Cases and controls were not included in the influenza type/subtype-specific analyses if fewer than five type/subtype-specific cases were reported by study site. Influenza A cases of unknown subtype were excluded from the analysis.

For each study site and for each influenza type/subtype, the study period started on the week of onset of the first influenza case recruited and ended on the week of onset of the last influenza case after which there were at least two consecutive weeks with no further influenza positive cases.

We defined a patient as vaccinated if they had received minimum one dose of 2014/15 influenza vaccine at least 15 days before ILI symptom onset. We considered all other patients unvaccinated. GPs ascertained vaccination based on vaccination records or patient's self-report.

For each study site, we compared the odds of vaccination in cases and controls calculating the odd ratio (OR). We conducted a complete case analysis excluding patients with missing values for any of the variables in the model measuring adjusted VE. We carried out a one-stage model with study site as a fixed effect. We used Cochran's Q-test and the I^2 index to test the heterogeneity between study sites [12].

We used a logistic regression model to calculate VE including potential confounding factors: age (modelled as a restricted cubic spline with four knots or age group as a categorical variable depending on the analysis), sex, presence of at least one underlying chronic condition (including pregnancy and obesity where available) and date of symptom onset (modelled as a restricted cubic spline with four knots where sample size allowed).

To study the effect of 2013/14 vaccination on the 2014/15 VE, we conducted a stratified analysis using four categories: individuals unvaccinated in both seasons (reference category), vaccinated in 2013/14 only, vaccinated in 2014/15 only, and those vaccinated in both seasons.

We measured VE by age group (0–14, 15–59 and ≥60 years) and by type of vaccine (adjuvanted, egg-derived inactivated subunit, cell-derived inactivated subunit, egg-derived inactivated split virion). We excluded

Figure 4

Phylogenetic tree I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

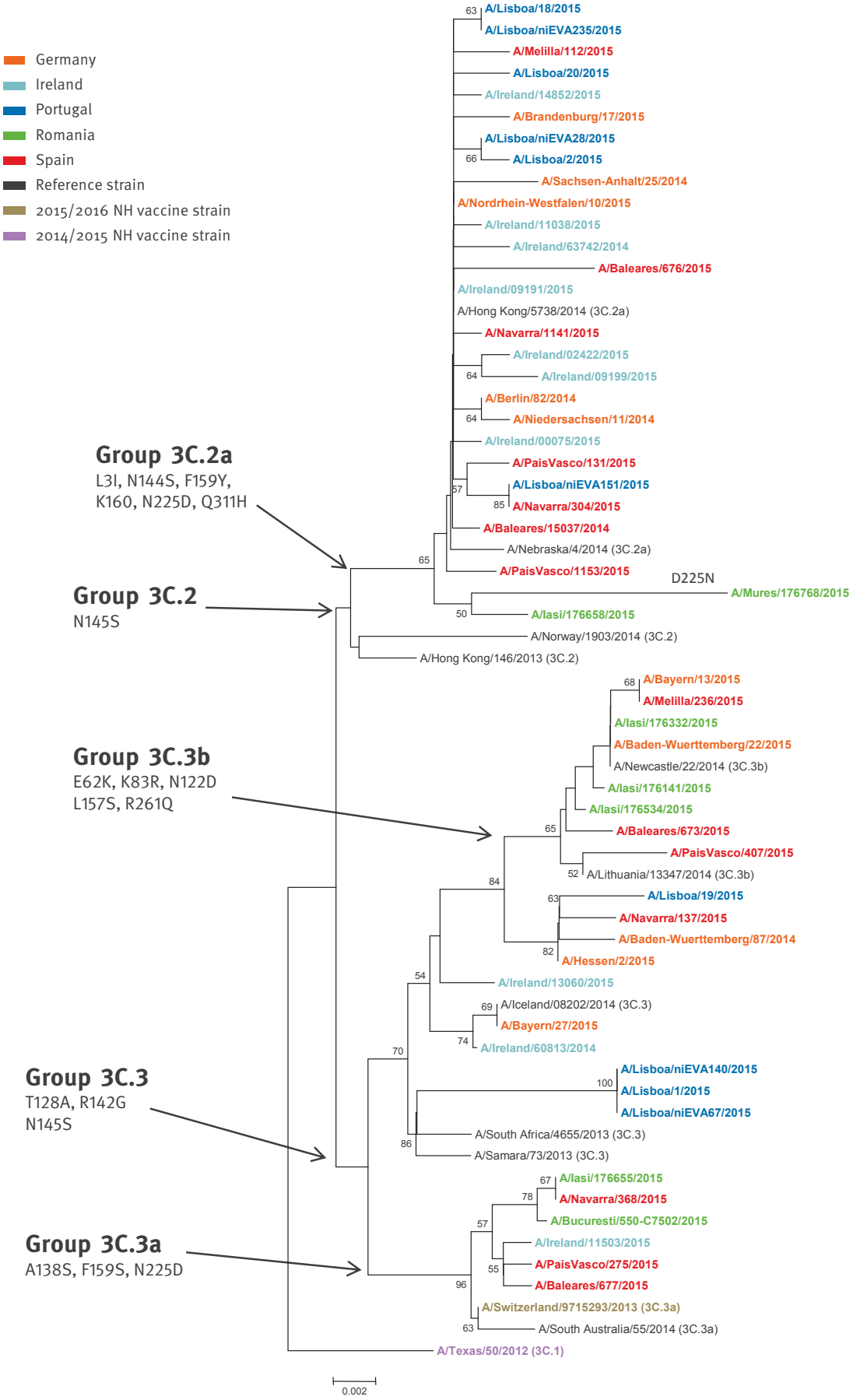


Table 1 a

Details of influenza haemagglutinin sequences obtained from GISAID used in the phylogenetic analysis, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

Segment ID	Segment	Country	Collection date	Isolate name	Originating Laboratory	Submitting Laboratory	Authors
I-MOVE sequences							
EPI568197	HA	Germany	2 Feb 2015	A/Bayern/27/2015	NA	Robert Koch Institute	Wedde, M; Schweiger, S
EPI568195	HA		28 Jan 2015	A/Brandenburg/17/2015			
EPI566844	HA		19 Jan 2015	A/Bayern/13/2015			
EPI566843	HA		26 Jan 2015	A/Baden-Wuerttemberg/22/2015			
EPI566664	HA		9 Jan 2015	A/Nordrhein-Westfalen/10/2015			
EPI566662	HA		20 Jan 2015	A/Hessen/2/2015			
EPI566657	HA		22 Dec 2014	A/Sachsen-Anhalt/25/2014			
EPI562792	HA		22 Dec 2014	A/Baden-Wuerttemberg/87/2014			
EPI562791	HA		18 Dec 2014	A/Berlin/82/2014			
EPI562793	HA		24 Dec 2014	A/Niedersachsen/11/2014			
EPI599601	HA	Ireland	2 Mar 2015	A/Ireland/14852/2015	National Virus Reference Laboratory	National Virus Reference Laboratory	Dunford, L
EPI599599	HA		17 Feb 2015	A/Ireland/13060/2015			
EPI599597	HA		13 Feb 2015	A/Ireland/11503/2015			
EPI599594	HA		9 Feb 2015	A/Ireland/09191/2015			
EPI599593	HA		13 Jan 2015	A/Ireland/02422/2015			
EPI582398	HA		13 Feb 2015	A/Ireland/11038/2015			
EPI582390	HA		9 Feb 2015	A/Ireland/09199/2015			
EPI582379	HA		25 Nov 2014	A/Ireland/60813/2014			
EPI555113	HA		12 Dec 2014	A/Ireland/63742/2014			
EPI582380	HA		22 Dec 2014	A/Ireland/00075/2015			
EPI583766	HA	Portugal	3 Mar 2015	A/Lisboa/20/2015	Instituto Nacional de Saude	INSA National Institute of Health Portugal	Guiomar, R;Pechirra, P; Cristóvão, P; Costa, I
EPI583765	HA		20 Feb 2015	A/Lisboa/19/2015			
EPI583762	HA		16 Feb 2015	A/Lisboa/niEVA235/2015			
EPI583761	HA		6 Feb 20150	A/Lisboa/18/2015			
EPI583759	HA		22 Jan 2015	A/Lisboa/niEVA151/2015			
EPI583741	HA		29 Jan 2015	A/Lisboa/2/2015			
EPI583740	HA		27 Jan 2015	A/Lisboa/1/2015			
EPI565347	HA		16 Jan 2015	A/Lisboa/niEVA140/2015			
EPI558632	HA		2 Jan 2015	A/Lisboa/niEVA67/2015			
EPI558621	HA		30 Dec 2014	A/Lisboa/niEVA28/2015			
EPI599624	HA	Romania	11 Feb 2015	A/Bucuresti/550-C7502/2015	Cantacuzino Institute	Cantacuzino Institute	NA
EPI599678	HA		19 Jan 2015	A/Iasi/176332/2015			
EPI599698	HA		22 Jan 2015	A/Iasi/176534/2015			
EPI600298	HA		23 Jan 2015	A/Iasi/176655/2015			
EPI599769	HA		26 Jan 2015	A/Iasi/176658/2015			
EPI599770	HA		26 Jan 2015	A/Mures/176768/2015			
EPI599771	HA		13 Jan 2015	A/Iasi/176141/2015			
EPI566948	HA	Spain	3 Feb 2015	A/Baleares/676/2015	Servicio de Microbiología Hospital Universitario Son Espases	Instituto de Salud Carlos III	Pozo,F Calderon,A; Gonzalez -Esguevillas,M; Molinero,M; Casas,I
EPI616537	HA		10 Mar 2015	A/Navarra/1141/2015			
EPI616553	HA		10 Mar 2015	A/PaisVasco/1153/2015			
EPI559629	HA		17 Jan 2015	A/Melilla/236/2015			
EPI557585	HA		12 Jan 2015	A/Melilla/112/2015			
EPI616494	HA		3 Feb 2015	A/Baleares/677/2015			
EPI616493	HA		3 Feb 2015	A/Baleares/673/2015			
EPI557566	HA		13 Dec 2014	A/Baleares/15037/2014			
EPI566285	HA		21 Jan 2015	A/Navarra/368/2015	Servicio de Microbiología Complejo Hospitalario de Navarra		
EPI559633	HA		12 Jan 2015	A/Navarra/137/2015			
EPI567981	HA		23 Jan 2015	A/PaisVasco/407/2015			
EPI566296	HA		15 Jan 2015	A/PaisVasco/275/2015			
EPI566975	HA		12 Jan 2015	A/PaisVasco/131/2015			
EPI566282	HA		19 Jan 2015	A/Navarra/304/2015			

GISAID: Global Initiative on Sharing Avian Influenza Data.

Table 1 b

Details of influenza haemagglutinin sequences obtained from GISAID used in the phylogenetic analysis, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

Segment ID	Segment	Country	Collection date	Isolate name	Originating Laboratory	Submitting Laboratory	Authors
I-MOVE sequences							
Reference sequences							
EPI398417	HA	United States	15 Apr 2012	A/Texas/50/2012	Texas Department of State Health Services-Laboratory Services	Centers for Disease Control and Prevention	NA
EPI460558	HA	Russian Federation	12 Mar 2013	A/Samara/73/2013	WHO National Influenza Centre Russian Federation	National Institute for Medical Research	
EPI696965	HA		29 Jan 2015	A/South Australia/55/2014 (14/226)	NA	National Institute for Biological Standards and Control (NIBSC)	Nicolson, C
EPI466802	HA	South Africa	25 Jun 2013	A/South Africa/4655/2013	Sandringham, National Institute for Communicable D	National Institute for Medical Research	NA
EPI536340	HA	Iceland	10 Jun 2014	A/Iceland/08202/2014	Landspitali - University Hospital		
EPI539598	HA	Lithuania	8 May 2014	A/Lithuania/13347/2014	Lithuanian AIDS Center Laboratory		
EPI541459	HA	Australia	16 Jun 2014	A/Newcastle/22/2014	WHO Collaborating Centre for Reference and Research on Influenza		
EPI426061	HA	Hong Kong (SAR)	11 Jan 2013	A/Hong Kong/146/2013	Government Virus Unit		
EPI539806	HA	Hong Kong (SAR)	30 Apr 2014	A/Hong Kong/5738/2014			
EPI539619	HA	United States	11 Mar 2014	A/Nebraska/4/2014	Centers for Disease Control and Prevention		
EPI530687	HA	Switzerland	6 Dec 20130	A/Switzerland/9715293/2013	Hopital Cantonal Universitaire de Geneve		

GISAID: Global Initiative on Sharing Avian Influenza Data.

study sites from the vaccine type analysis, where the given type of vaccine was not available.

We conducted four sensitivity analyses (i) restricting the study to patients swabbed less than 4 days after symptom onset, (ii) restricting to the population targeted for vaccination as defined in each country [23] (iii) excluding patients vaccinated < 15 days after symptom onset, (iv) calculating adjusted VE using a two-stage model using random effects.

The respective country's National Influenza Reference Laboratories tested swab specimens for influenza by real-time RT-PCR assays. In Spain, other laboratories participating in the National Influenza Sentinel Surveillance System tested specimens. In each study site, a non-random selection of positive specimens or isolated viruses from positive specimens were subsequently sent to the corresponding National Influenza Centre, where influenza diagnosis was confirmed and viruses characterised either by sequencing the HA1 coding portion of the haemagglutinin gene (genetic characterisation) or by haemagglutination inhibition (antigenic characterisation). The criteria to select the specimens for genetic and antigenic characterisation varied by study site.

For the I-MOVE pooled analysis, the Spanish and Portuguese National Influenza Centres analysed the nt and amino acid sequences of the HA1 coding portion of the haemagglutinin gene and used the neighbour-joining method and the Kimura 2-parameter nt substitution model for phylogenetic analysis. A phylogenetic tree was constructed with a bootstrap analysis of 500 replicates (values above 50 are shown) using MEGA software version 6 (Tamura, Stecher, Peterson, Filipski,

and Kumar 2013). 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).

Results

Within the I-MOVE multicentre case–control study, the start of country-specific study periods ranged from week 41, 2014 (Germany) to week 3, 2015 (Poland), and the end from week 13, 2015 (Portugal) to week 19, 2015 (Germany). Study period duration ranged from 14 (Poland) to 31 (Germany) weeks.

Among the 7,992 ILI patients recruited, 6,579 ILI patients met the eligibility criteria including 3,142 testing negative for all influenza viruses. For the influenza type/subtype-specific analysis datasets, we included 1,828 influenza A(H3N2), 1,038 influenza B, 539 influenza A(H1N1)pdm09 (Figure 1).

The median onset date was 1 February for A(H1N1) pdm09, 1 February for A(H3N2), and 20 February for B cases (Figure 2). Forty-one percent of A(H3N2) cases were recruited in Germany, 44% of A(H1N1)pdm09 in Italy and 30% of B cases in Spain.

The median age was higher in influenza B cases (39 years) compared with influenza A(H3N2) and A(H1N1) cases (28 and 30 years respectively) and controls (31 years).

The proportion of patients swabbed more than three days after ILI onset was 15.9% among controls, and 10.3%, 13.5% and 15.9% among A(H3N2), A(H1N1) pdm09 and B cases respectively.

The proportion of patients belonging to the target group for vaccination, or with at least one chronic condition or with at least one hospitalisation in the previous 12 months was similar between influenza A(H3N2), A(H1N1)pdm09, B cases and controls.

Nine percent of controls, and 11%, 5% and 6% of A(H3N2), A(H1N1)pdm09 and B cases had received both the 2013/14 and the 2014/15 vaccines.

Of the 735 vaccinated individuals, 620 (84%) had information on the vaccine type received; they were vaccinated with ten different brands. By vaccine type, 40% had received egg-derived inactivated subunit (used in all sites except in Hungary and Italy), 33% egg-derived inactivated split virion (used in all sites except in Ireland and Romania), 21% adjuvanted (used in Germany, Hungary, Italy and Spain) and 5% cell-derived inactivated subunit vaccines (used in Germany and Spain).

After excluding patients with missing information (n=833; 7%), we included 4,491, 2,920 and 3,730 patients in the complete case analysis of VE against influenza A(H3N2), A(H1N1)pdm09 and B respectively (Figure 1).

The I^2 was<50% (p >0.05) when assessing crude type/subtype specific VE by study site and age group. Sample size among the 0–14 year-olds for the A(H1N1) pdm09 analysis was too small to carry out tests for heterogeneity. When assessing crude VE against A(H3N2) by study site among the target group for vaccination, the I^2 was 61.5% (p=0.016).

Influenza A(H3N2)

The overall adjusted VE against influenza A(H3N2) was 14.4% (95% CI: -6.3 to 31.0) (Table 3).

Adjusted VE was 20.7% (95% CI: -22.3 to 48.5) among the 0–14 year olds, 10.9% (95% CI: -30.8 to 39.3) among the 15–59 year olds and 15.8% (95% CI: -20.2 to 41.0) among those ≥60 years. By vaccine type, the adjusted VE point estimates were lower for cell-derived inactivated subunit vaccines (-9.3%) compared with egg-derived inactivated subunit, egg-derived inactivated split virion, and adjuvanted vaccines (10.9%, 18.6% and 14.0% respectively) (Table 4).

The adjusted VE was 43.7% (95% CI: 15.3 to 62.5) among those vaccinated in 2014/15 only, 0.0% (95%CI: -50.7 to 33.7) among those vaccinated in 2013/14 only, and -5.2% (95%CI: -34.3 to 17.6) among those vaccinated in both seasons (Table 4, Figure 3).

The overall adjusted VE point estimate was similar to the adjusted VE among those swabbed less than 4 days of symptom onset (17.4%) and to the adjusted VE excluding individuals vaccinated less than 15 days after symptom onset (13.7%). The adjusted VE point estimate was higher when restricting the analysis to the target population (26.2%) (Table 2). The adjusted VE estimates using a two-stage random effects model were similar (within 6 % points) to the one-stage pooled analysis VE for all population and restricted to the target group for vaccination (Table 2). The two-stage VE point estimate in the ≥60 year- olds was 10% higher than the one-stage VE but three study sites were excluded from the two-stage analysis due to their limited sample size.

One hundred and fourteen (6%) of the 1,828 A(H3N2) viruses included in the analysis were genetically or antigenically characterised. Seventy-five viruses of the 114 (66%) were antigenically distinct from the vaccine virus A/Texas/50/2012: 58 belonged to clade 3C.2a, represented by A/HongKong/5738/2014, and 17 belonged to clade 3C.3a represented by A/Switzerland/9715293/2013 (Table 5).

Of the 114 characterised A(H3N2) viruses, 107 (94%) were sequenced. Compared with A/Texas/50/2012, 17 viruses had the T128A, R142G and N145S mutations that define the group 3.C represented by A/Samara/73/2013. Eight viruses had in addition the

Table 2

Details for influenza, A(H3N2), A(H1N1)pdm09 and influenza B cases and controls, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015) (n=6,524[a])

Variables	Number of test-negative controls /total n(%) (n=3,142) [b]	Number of influenza A(H3N2) cases /total n(%) (n=1,828)[c]	Number of influenza A(H1N1) pdm09 /total n(%) (n=1,038)[d]	Number of influenza B cases /total n(%) (n=539) [c,d]
Median age (years)	31.0	28.0	30.0	39.0
Missing	5	1	1	0
Age groups				
0–4 years	620/3,137 (19.8)	212/1,827 (11.6)	136/538 (25.3)	62/1,038 (6)
5–14 years	459/3,137 (14.6)	451/1,827 (24.7)	85/538 (15.8)	219/1,038 (21.1)
15–59 years	1,539/3,137 (49.1)	885/1,827 (48.4)	256/538 (47.6)	619/1,038 (59.6)
≥60 years	519/3,137 (16.5)	279/1,827 (15.3)	61/538 (11.3)	138/1,038 (13.3)
Missing	5	1	1	0
Sex				
Female	1,610/3,132 (51.4)	945/1,825 (51.8)	283/539 (52.5)	556/1,037 (53.6)
Missing	10	3	0	1
Days between onset of symptoms and swabbing				
0	254/3,142 (8.1)	128/1,828 (7)	55/539 (10.2)	32/1,038 (3.1)
1	1,076/3,142 (34.2)	662/1,828 (36.2)	206/539 (38.2)	286/1,038 (27.6)
2	816/3,142 (26)	574/1,828 (31.4)	128/539 (23.7)	317/1,038 (30.5)
3	497/3,142 (15.8)	275/1,828 (15)	77/539 (14.3)	238/1,038 (22.9)
4–7	499/3,142 (15.9)	189/1,828 (10.3)	73/539 (13.5)	165/1,038 (15.9)
Seasonal vaccination, 2014/15e	392/2,978 (13.2)	228/1,759 (13.0)	36/522 (6.9)	75/1,010 (7.4)
Missing	164	69	17	28
Previous season influenza vaccination				
Not vaccinated or vaccinated<15 days before onset	2,432/2,918 (83.3)	1,461/1,733 (84.3)	464/515 (90.1)	901/1,001 (90)
Current season vaccination only	98/2,918 (3.4)	41/1,733 (2.4)	10/515 (1.9)	14/1,001 (1.4)
Previous season vaccination only	113/2,918 (3.9)	47/1,733 (2.7)	15/515 (2.9)	27/1,001 (2.7)
Current and previous season vaccination	275/2,918 (9.4)	1,84/1,733 (10.6)	26/515 (5.0)	59/1,001 (5.9)
Missing	224	95	24	37
2014/15 vaccine type				
Not vaccinated or vaccinated<15 days before onset	2,586/2,978 (82.3)	1,531/1,759 (83.8)	486/522 (90.2)	935/1,010 (90.1)
Egg-derived inactivated subunit	124/2,978 (3.9)	89/1,759 (4.9)	10/522 (1.9)	27/1,010 (2.6)
Egg-derived inactivated split virion	115/2,978 (3.7)	56/1,759 (3.1)	16/522 (3)	19/1,010 (1.8)
Adjuvanted	81/2,978 (2.6)	38/1,759 (2.1)	3/522 (0.6)	8/1,010 (0.8)
Cell- derived inactivated subunit	10/2,978 (0.3)	13/1,759 (0.7)	0/522 (0)	7/1,010 (0.7)
Unknown vaccine type	62/2,978 (2)	32/1,759 (1.8)	7/522 (1.3)	14/1,010 (1.3)
Missing vaccination status or date	164	69	17	28
At least one chronic condition	661/3,024 (21.9)	384/1,776 (21.6)	110/525 (21.0)	216/1,023 (21.1)
Missing	118	52	14	15
At least one hospitalisation in the previous 12 months for chronic conditions	56/3,100 (1.8)	25/1,806 (1.4)	7/534 (1.3)	23/1,033 (2.2)
Missing	42	22	5	5
Belongs to target group for vaccination	902/3,069 (29.4)	511/1,801 (28.4)	141/530 (26.6)	301/1,029 (29.3)
Missing	73	27	9	9
Study sites				
Germany	1,472/3,142 (46.8)	741/1,828 (40.5)	185/539 (34.3)	268/1,038 (25.8)
Ireland	109/3,142 (3.5)	102/1,828 (5.6)	11/539 (2)	57/1,038 (5.5)
Hungary	379/3,142 (12.1)	232/1,828 (12.7)	32/539 (5.9)	42/1,038 (4)
Portugal	102/3,142 (3.2)	45/1,828 (2.5)	0/539 (0)	98/1,038 (9.4)
Italy	594/3,142 (18.9)	229/1,828 (12.5)	237/539 (44)	123/1,038 (11.8)
Poland	77/3,142 (2.5)	18/1,828 (1)	21/539 (3.9)	70/1,038 (6.7)
Romania	76/3,142 (2.4)	80/1,828 (4.4)	43/539 (8)	73/1,038 (7)
Spain	333/3,142 (10.6)	381/1,828 (20.8)	10/539 (1.9)	307/1,038 (29.6)

I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe.

[a] This includes 15 influenza B+A(H3N2) co-infections and 8 influenza B+A(H1N1)pdm09 co-infections. Note that numbers of cases come from influenza type/subtype specific databases. Some cases are excluded due to their restriction criteria. Any influenza A non-typed cases are dropped from analysis.

[b] Controls from 'any influenza' analysis used.

[c] Includes 15 influenza B+A(H3N2) co-infections.

[d] Includes 8 influenza B+A(H1N1)pdm09 co-infections.

[e] Vaccination more than 14 days before onset of influenza like illness symptoms.

Table 3

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza by influenza type/subtype, overall and by age groups, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

Type/subtype	Analysis scenario		N[a,b]	Cases;vaccinated/Controls; vaccinated[a,b]	Crude VE[a,c]	95% CI	Adjusted VE	95% CI
A(H3N2)	1-stage pooled analysis[d]	All ages	4,491	1,723;225/2,768;365	-1.9	-22.2 to 15.1	14.4	-6.3 to 31.0
		0–14 years	1,505	607;54/898;64	-38.4	-103.5 to 5.9	20.7	-22.3 to 48.5
		15–59 years	2,245	846;57/1,399;91	-2.2	-45.3 to 28.1	10.9	-30.8 to 39.3
		≥60 years	741	270;114/471;210	7.3	-26.9 to 32.2	15.8	-20.2 to 41.0
		Target group for vaccination	1,287	483;155 / 804;276	10.9	-14.5 to 30.6	26.2	1.6 to 44.7
		Vaccinated <15 days excluded	4,475	1,718;225/2,757;365	-1.8	-22.2 to 15.1	13.7	-7.2 to 30.5
		Restricted delay onset and swabbing<4 days	3,869	1,543;196/2,326;280	-10.1	-34.4 to 9.8	17.4	-4.6 to 34.8
	2-stage pooled analysis	All ages	4,503	1,724;225/2,779;366	-0.6	-31.2 to 22.8	9.0	-28.2 to 35.4
		0–14[e] years	1,418	564;54/853;63	-42.2	-109.2 to 3.3	22.9	-20.7 to 50.8
		15–59[f] years	2,192	853;57/1,357;88	-6.6	-53.2 to 25.8	12.3	-31.6 to 41.5
		≥60[g] years	678	254;108/424;187	11.3	-24.9 to 37.1	25.5	-24.5 to 55.4
		Target group for vaccination[h]	1,240	473;153/767;274	6.4	-43.2 to 38.9	20.7	-32.5 to 52.5
A(H1N1)pdm09	1-stage pooled analysis[i]	All ages	2,920	515;36/2,405;314	53.7	33.1 to 68.0	54.2	31.2 to 69.6
		0–14 years	1,023	211;8/812;63	59.9	13.4 to 81.5	73.1	39.6 to 88.1
		15–59 years	1,436	245;8/1191;75	47.5	-13.1 to 75.6	59.7	10.9 to 81.8
		≥60 years	451	59;20/392;171	22.4	-44.4 to 58.4	22.4	-44.4 to 58.4
		Target group for vaccination	832	138;26/694;232	53.8	26.0 to 71.2	53.6	22.1 to 72.3
		Vaccinated<15 days excluded	2,914	515;36/2,399;314	53.9	33.3 to 68.1	54.5	31.6 to 69.7
		Restricted delay onset and swabbing<4 days	2,471	443;26/2,028;242	57.8	35.3 to 72.5	61.0	37.7 to 75.6
	2-stage pooled analysis	All ages[j]	2,650	494;34/2,156;285	53.6	20.6 to 72.9	53.5	27.8 to 70.1
		0–14[k] years	916	196;7/720;59	59.5	-79.6 to 90.9	71.6	20.5 to 89.9
		15–59[l] years	941	195;7/746;52	35.4	-51.3 to 72.4	51.8	-15.9 to 79.9
		≥60[m] years	290	41;18/249;120	15.8	-65.3 to 57.1	NA	NA
		Target group for vaccination[n]	536	105;22/431;160	53.8	22.3 to 72.5	58.4	10.7 to 80.6
Influenza B	1-stage pooled analysis	All ages	3,730	1,001;74 / 2,729;362	47.9	31.3 to 60.4	48.0	28.9 to 61.9
		0–14 years	1,143	269;11 / 874;62	37.8	-23.2 to 68.6	62.1	14.9 to 83.1
		15–59 years	1,986	602;29 / 1,384;94	29.6	-10.3 to 55.0	41.4	6.2 to 63.4
		≥60years	601	130;34 / 471;206	54.4	25.8 to 72.0	50.4	14.6 to 71.2
		Target group for vaccination	1,083	290;56 / 793;273	54.6	35.2 to 68.2	49.8	26.2 to 65.9
		Vaccinated <15 days excluded	3,719	998;74/2,721;362	47.8	31.3 to 60.4	47.8	28.6 to 61.8
		Restricted delay onset and swabbing <4 days	3,132	841;63/2,291;278	41.8	21.3 to 57.0	44.4	21.8 to 60.5
	2-stage pooled analysis	All ages	3,734	1,003;74/2,731;363	48.9	25.3 to 65.0	51.5	26.8 to 61.8
		0–14[p] years	1,057	230;12/827;61	29.5	-41.3 to 64.8	47.5	-15 to 76.0
		15–59 years	1,995	603;29/1,392;96	28.1	-17.1 to 55.9	43.2	5.2 to 66.0
		≥60[q] years	611	132;34/479;208	53.5	24.1 to 71.5	54.1	22.4 to 72.8
		Target group for vaccination[r]	1,057	293;56/764;266	54.9	27.2 to 72.0	56.0	26.2 to 73.8

CI: confidence interval; DE: Germany; ES: Spain; HU: Hungary; IE: Ireland; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; IT: Italy; PL: Poland; PT: Portugal; RO: Romania; VE: vaccine effectiveness.

[a] Based on the complete case analysis: records with missing age, sex, chronic condition, vaccination status are dropped.

[b] Totals may differ between one-stage and two-stage models, as adjustment at study site-level may vary to the one-stage pooled model adjustment, resulting in different missing data dropped depending on included covariates. In addition different numbers of study sites may be included in each analysis due to sample size issues.

[c] Crude VE adjusted by study site.

[d] Data adjusted for age (restricted cubic spline), onset date (restricted cubic spline), sex, chronic condition and study site. Exceptions are A(H3N2) all ages, where age groups (0–4, 5–14, 15–59 and ≥60 years) are used instead of restricted cubic splines.

[e] Study sites include DE, ES, IT. HU not included in the 0–14 year old analysis, as no patients included aged <18 years. Sample size too low for IE, PT and RO.

[f] Study sites include DE, ES, HU, IE, IT, PT, RO. Sample size too low for PL. Crude VE for RO used in adjusted estimate, due to low sample size.

[g] Study sites include DE, ES, HU, IT, RO. IE, PL and PT not included due to low sample size. Crude VE for RO used in adjusted estimate, due to low sample size.

[h] Study sites include DE, ES, IE, IT, PL, PT, RO. HU not included in the 0–14 year old analysis, as no patients included aged <18 years.

[i] Data adjusted for age (restricted cubic spline), onset date (restricted cubic spline), sex, chronic condition and study site. Exceptions the A(H1N1)pdm09 analysis among the elderly, where data are adjusted for age (restricted cubic spline), onset date (restricted cubic spline), and study site only.

[j] Study sites include DE, HU, IE, IT, RO, PL. ES and IE dropped from analysis due to small sample size.

[k] Study sites include DE, IT. ES, IE, PL, RO not included as sample size too low. HU not included in the 0–14 year old analysis, as no patients included aged<18 years.

[l] Study sites include DE, IT, RO. ES, HU, IE and PL not included as sample size too small. Crude VE for RO used in adjusted estimate, due to low sample size.

[m] Study sites include DE, IT. ES, HU, IE, PL and RO not included as sample size too small. Only crude VE available, due to low sample size.

[n] Study sites include DE, IT, RO. ES, HU, IE and PL not included as sample size too small. Crude VE for RO used in adjusted estimate, due to low sample size.

[o] Data adjusted for age (restricted cubic spline), onset date (restricted cubic spline), sex, chronic condition and study site. Exceptions the B analysis among the elderly, where data are adjusted for age (restricted cubic spline), onset date (restricted cubic spline), and study site only.

[p] Study sites include DE, ES, IT. IE, PL, PT and RO not included as sample size too low. HU not included in the 0–14 year old analysis, as no patients included aged<18 years.

[q] Study sites include DE, ES, HU, IE, IT, PL, PT, RO. Crude VE for DE, HU, IE, PL and RO due to low sample size.

[r] Study sites include DE, ES, HU, IE, IT, PL, PT, RO. Crude VE for HU, IE and RO due to low sample size.

mutations G5E and N31S. Twenty viruses belonged to the group 3C.3b represented by A/Newcastle/22/2014 and characterised by T128A, R142G, N145S, E62K, K83R, N122D, L157S and R261Q mutations. Seven of these presented an additional amino acid change Q197H at the antigenic site B (Figure 4).

Twelve viruses belonged to the group 3C.3a that harbours the T128A, R142G, A138S, N145S, F159S and N225D mutations. Nine of them had an extra mutation K276N at the antigenic site C. Fifty-eight viruses belonged to group 3C.2a and the only mutations identified were L3I, N144S, N145S, F159Y, K160T, N225D and Q311H - amino acid mutations that define the group.

Influenza A(H1N1)pdm09

The overall adjusted VE against influenza A(H1N1) pdm09 was 54.2% (95% CI: 31.2 to 69.6) (Table 3).The adjusted VE was 73.1% (95% CI: 39.6 to 88.1) among the 0–14 year olds, 59.7% (95% CI: 10.9 to 81.8) among the 15–59 year olds and 22.4% (95% CI: -44.4 to 58.4) among those ≥60 years of age.

By vaccine type, the adjusted VE point estimate was higher for the adjuvanted vaccine (79.8%) than for the egg-derived inactivated subunit and the inactivated split virion vaccines (53.0% and 51.5% respectively). We could not compute the VE for the cell-derived inactivated subunit due to small numbers (7 controls vaccinated and no cases vaccinated) (Table 4).

The adjusted VE point estimate was lower (-1.9%) among those vaccinated in 2013/14 only compared with those vaccinated in 2014/15 only (47.2%) and to those vaccinated in both seasons (52.7%) (Table 4).

The overall adjusted VE point estimate did not vary when restricting the analysis to the target group for vaccination (53.6%), when excluding those vaccinated<15 days (54.5%) before symptom onset and when using a two-stage pooled model (53.5%). It was 61.0% when restricted to those swabbed less than 4 days of symptom onset (Table 3).

Of the 539 A(H1N1)pdm09 viruses, 24 (4%) were genetically characterised and all belonged to the group 6B defined by the amino acid substitutions D97N, K163Q, S185T, S203T, A256T and K283E compared with A/California/07/2009.

Influenza B

The overall adjusted VE against influenza B was 48.0% (95% CI: 28.9 to 61.9). The adjusted VE was 62.1% (95% CI: 14.9 to 83.1) among the 0–14 year olds, 41.4% (95% CI: 6.2 to 63.4) among the 15–59 year olds and 50.4% (95% CI: 14.6 to 71.2) among those ≥60 years old (Table 3).

By vaccine type, the adjusted VE point estimates were lower for cell-derived inactivated subunit vaccines (16.0%) than for egg-derived subunit, split virion and adjuvanted vaccines (52.4%, 60.1%, 51.9% respectively) (Table 4).

The adjusted VE point estimate was lower among those vaccinated only in 2013/14 (1.7%) than among those vaccinated only in 2014/15 (59.4%) or among those vaccinated in both seasons (43.8%) (Table 4).

There was less than 9% absolute difference between the overall adjusted VE point estimates and the VE in all sensitivity analyses (Table 3). The two-stage VE point estimate in the 0–14 years old was 15% lower than the one-stage VE point estimate but five study sites were excluded from the two-stage analysis due to their limited sample size.

Among 746 cases for which the lineage was available, 740 (99.2%) were Yamagata and six Victoria.

One hundred and fifty-three (15%) of the 1,038 B viruses were characterised: 151 B Yamagata and two B Victoria viruses. Of the 151 B Yamagata lineage viruses genetically characterised, 148 (98%) belonged to B/Phuket/3073/2013, clade 3 and three to B/Massachusetts/02/2012. The two B Victoria viruses genetically characterised belonged to B/Brisbane/60/2008 (1A).

Discussion

The results of the I-MOVE multicentre case–control study suggest a low 2014/15 influenza VE against medically attended ILI due to A(H3N2) and a moderate VE against medically attended ILI due to A(H1N1)pdm09 or B.

The sample size of the I-MOVE multicentre case–control study for the 2014/15 season was one of the largest since 2008/09. We could estimate VE against the three circulating viruses. However, with the low influenza vaccination coverage in the participating sites, we still have limited statistical power for some subgroup analyses that provide important information for public health action like VE by previous vaccination or VE by type of vaccine. The current sample size is still too small to measure VE by vaccine product.

Measuring VE by study sites was not among the objectives of our multicentre study. In addition, as in previous seasons, study sites, sample size pending, are publishing their own results. However, even if not statistically significant, VE may differ between study sites. Differences in site-specific adjusted VE may be explained, among other factors, by variability due to the limited number of samples, unknown residual confounding, or different vaccines used. In future seasons we are confident that, with more resources, sample sizes should increase allowing for better adjustment and stratification including by vaccine brand.

Integrating virological and epidemiological information is essential to interpret VE estimates [5]. For the

Table 4

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory- confirmed influenza by influenza type/subtype, by vaccine type and by influenza vaccination status in 2013/14, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

Influenza type/subtype		Vaccine type	N	Cases/controls	Crude VE[a,b]	95% CI	Adjusted VE[c]	95% CI
A(H3N2)	By vaccine type	Unvaccinated	3,901	1,498/2,403	Ref	NA	Ref	NA
		Egg-derived inactivated subunit	205	88/117	-5.7	-41.7 to 21.2	10.9	-24.3 to –36.1
		Egg-derived inactivated split virion	164	56/108	-0.4	-41.2 to 28.6	18.6	-17.4 to 43.5
		Adjuvanted	116	38/78	11.8	-32.7 to 41.4	14.0	-34.1 to 44.9
		Cell-Derived inactivated subunit	23	13/10	-15.3	-167.0 to 50.2	-9.3	-159.1 to 53.9
		Unknown	82	30/52	-12.0	-77.1 to 29.2	21.3	-29.7 to 52.3
	By previous vaccination	Unvaccinated in both seasons	3,697	1,434/2,263	Ref	NA	Ref	NA
		Vaccinated in 2014/15 only	133	41/92	29.8	-2.7 to 52.0	43.7	15.3 to 62.5
		Vaccinated in 2013/14 only	147	43/104	28.2	-3.4 to 50.2	0.0	-50.7 to 33.7
		Vaccinated in both seasons	436	181/255	-16.4	-43.1 to 5.3	-5.2	-34.3 to 17.6
A(H1N1)pdm09	By vaccine type	Unvaccinated	2,570	479/2,091	Ref	NA	Ref	NA
		Egg-derived inactivated subunit	113	10/103	47.1	-4.5 to 73.2	53.0	4.1 to 76.9
		Egg-derived inactivated split virion	104	16/88	47.5	8.1 to 70.0	51.5	13.4 to 72.8
		Adjuvanted	73	3/70	84.4	49.3.to.95.2	79.8	31.0.to.94.1
		Cell-derived inactivated subunit	7	0/7	NA	NA	NA	NA
		Unknown	53	7/46	24.8	-70.7 to 66.8	35.3	-48.5 to 71.8
	By previous vaccination	Unvaccinated in both seasons	2,438	459/1,979	Ref	NA	Ref	NA
		Vaccinated in 2014/15 only	90	10/80	46.6	-5.8 to 73.0	47.2	-7.1 to 74.0
		Vaccinated in 2013/14 only	99	15/84	11.8	-56.8 to 50.4	-1.9	-86.2 to 44.2
		Vaccinated in both seasons	242	26/216	53.8	28.9 to 69.9	52.7	24.2 to 70.5
B	By vaccine type	Unvaccinated	3,294	927/2,367	Ref	NA	Ref	NA
		Egg-derived inactivated subunit	146	27/119	49.3	20.7 to 67.6	52.4	22.9 to 70.6
		Egg-derived Inactivated split virion	119	18/101	59.5	30.8 to 76.3	60.1	30.1 to 77.3
		Adjuvanted	86	8/78	51.3	-4.1 to 77.2	51.9	-6.2 to 78.2
		Cell-derived Inactivated subunit	17	7/10	22.5	-108.0 to 71.1	16.0	-129.9 to 69.3
		Unknown	68	14/54	25.0	-40.7 to 60.0	27.3	-40.2 to 62.3
	By previous vaccination	Unvaccinated in both seasons	3,127	894/2,233	Ref	NA	Ref	NA
		Vaccinated in 2014/15 only	107	14/93	61.1	29.8 to 78.4	59.4	25.1 to –78.0
		Vaccinated in 2013/14 only	128	26/102	20.3	-26.6 to 49.8	1.7	-61.8 to 40.3
		Vaccinated in both seasons	309	58/251	43.3	22.5 to 58.6	43.8	20.0 to 60.5

CI: confidence interval; Ref: reference; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; NA: not applicable; VE: vaccine effectiveness.

[a] Based on the complete case analysis: records with missing age, sex, chronic condition, vaccination status are dropped).

[b] Crude VE adjusted by study site.

[c] Data adjusted for age (restricted cubic spline or age group), onset date (restricted cubic spline), sex, chronic condition and study site.

Note: Egg-derived inactivated subunit vaccines used in DE, IE, PO, PT, RO, ES.

Egg-derived inactivated Split virion vaccines used in DE, HU, IT, PO, PT, ES.

Adjuvanted vaccines used in DE, HU, IT, ES.

Cell-derived inactivated subunit vaccines used in Germany, ES.

Table 5

Influenza A(H3N2), A(H1N1)pdm09, B Yamagata, B Victoria viruses characterised by clade and study site, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015) (n=291)

Characterised viruses	Clade	Germany N	Hungary N	Ireland N	Portugal N	Romania N	Spain N	Total (%)
A(H3N2) (n=114)								
A/HongKong/5738/2014	3C.2a	12	NA	11	14	2	19	58 (51)
A/Switzerland/9715293/2013	3C.3a	NA	NA	1	NA	11	5	17 (15)
A/Samara/73/2013	3C.3	5	NA	3	4	3	4	19 (17)
A/Newcastle/22/2014	3C.3b	5	2	1	NA	3	9	20 (17)
Total A(H3N2)	NA	22	2	16	18	19	37	114 (100)
A(H1N1)pdm09 (n=24)								
A/SouthAfrica/3626/2013	6B	12	NA	5	2	5	NA	24 (100)
B Yamagata (n=151)								
B/Phuket/3073/2013	Clade 3	31	NA	5	56	28	28	148 (98)
B/Massachusetts/02/2012	Clade 2	NA	NA	NA	1	2	NA	3 (2)
Total B Yamagata	NA	31	NA	5	57	30	28	151 (100)
B Victoria (n=2)								
B/Brisbane/60/2008	NA	NA	NA	2	NA	NA	NA	2 (100)

NA: not applicable.

last two seasons, the I-MOVE multicentre case–control teams have made an effort to include genetic and antigenic results from a sample of the cases included in the study. However, the proportion of strains genetically and antigenically characterised (8.5%) is still low, and varied by site. Two study sites (Italy, Poland) could not provide results and some sites with a low number of cases characterised a higher proportion of viruses than sites with high number of cases. For instance, 11 of the 17 clade 3C.3a viruses characterised were from Romania, a site that contributed to only 4.4% of the A(H3N2) cases. In addition, the viruses characterised were selected according to virological surveillance objectives (e.g. selection of viruses from more severe cases, from vaccinated cases, etc.). Due to the non-random selection and the different proportion of viruses characterised we cannot exclude that the viruses characterised may not be representative of the viruses from cases included in the study. For the 2015/16 season, the I-MOVE multicentre case–control study will pilot a selection procedure aiming to provide a representative sample of viruses characterised. If resources are available, the number of viruses characterised should increase.

The VE against influenza A(H3N2) was low overall, by age group and among the target group for vaccination. Four different genetic clades of A(H3N2) viruses (3C.2a, 3C.3a, 3C.3 and 3C.3b) circulated in the eight countries participating in I-MOVE. The low VE are in concordance with the high proportion (66%) of 3C.2a and 3C.3a drifted viruses identified among those genetically characterised. Additional mutations were detected in the 3C.3 and 3C.3b influenza A(H3N2) viruses characterised but those are considered antigenically similar to the vaccine virus [13]. This season, estimates are similar to the VE against A(H3N2) we observed in 2011/12 and 2013/14 [8,9]. They are lower than the final 2014/15 VE against A(H3N2) reported in the UK even if the proportion of drifted virus among those genetically characterised are higher in UK than in our study [14]. VE against A(H3N2) was below 20% for all vaccine types with a lower point estimate for the cell-derived subunit vaccine. The effectiveness was lower in those vaccinated in both 2013/14 and 2014/15 than in those vaccinated only in the 2014/15 season. These observations are in line with the results of the 2014/15 early A(H3N2) VE estimates in Canada [5] and with those observed in previous studies [15-17]. They are congruent with the hypothesis that prior immunisation may decrease the effectiveness of the vaccine and that this negative interference is more important when the antigenic distance is small between successive vaccine components but large between vaccine and circulating strain [18]. These conditions were present in 2014/15 with an unchanged A(H3N2) vaccine component compared with the 2013/14 vaccine and with a mismatch between the vaccine and a high proportion of circulating strains. However, those results may be due to chance, or to bias. We need a much larger sample size to have higher precision in the estimates and to study the effect of prior vaccinations by age group. In our study, individuals vaccinated in both seasons are older than those vaccinated only in one season (median age 63 years and 50 years respectively). Unmeasured differences between individuals vaccinated in two consecutive seasons and those vaccinated only in one season may have affected the results. Previous vaccination was documented through GP records or patient self-reports and may be subject to error. Since neither the ILI patient nor the GPs knew if the patient was an influenza case we are confident that differential recall

did not bias the results. If the results were not due to bias or to chance, concurrent immunological studies will be essential to better understand the biological mechanism behind, and the role of natural vs vaccine-acquired immunity.

The VE estimates against influenza A(H1N1)pdm09 are similar to our results in previous seasons [7-9]. The laboratory results indicate that the strains isolated from study participants were similar to the A(H1N1) pdm09 component of the 2014/15 influenza vaccine. As in 2013/14, we observed a lower VE among the elderly and higher among those aged 0–14 years old, however sample sizes were small in the age group analyses. The VE point estimates of the adjuvanted vaccines were higher but the small sample size in the analysis does not allow a comparison of effectiveness between vaccine types.

The VE against influenza B ranged from 41% to 62% in the overall population and was 56% in the target group for vaccination. Our estimates are similar to those reported by the UK [14]. Nearly all viruses (99%) for which lineage was available were B/Yamagata and 98% of those characterised belonged to clade 3 that is antigenically similar to the vaccine virus. VE was similar by vaccine type with lower point estimate for cell-derived inactivated subunit vaccines but the sample size is too low to interpret this observed difference. The results suggested no effect of the 2013/14 vaccine and a slightly lower VE among those vaccinated in both seasons.

This is the third season we provide VE by vaccine type. A high proportion of vaccinated study participants (84%) had vaccine product documented. Even with one of the largest sample size since 2008/09, the numbers are still too low to measure adjusted VE by vaccine type and age group. The European Medicines Agency (EMA) requests that vaccine producers provide product-specific vaccine effectiveness [19]. Taking into account the high number of vaccine products and the low vaccination coverage in countries participating in the study [20] the sample size to measure VE by vaccine product with high precision has to be much larger and substantial additional resources are needed. In a survey among I-MOVE partners to assess the feasibility of conducting product-specific VE in Europe (data not shown) most experts considered that in terms of resources allocation, providing precise estimates early in the season, by age group, by previous vaccination were of higher priority than measuring VE by product.

In summary, the 2014/15 results suggest a moderate effectiveness against influenza A(H1N1)pdm09 and B. The low effectiveness of the influenza vaccines against A(H3N2) observed again this season underlines the need to improve the A(H3N2) component of the vaccine especially among the target group for vaccination. This would be even more important if the observed negative effect of previous vaccination was confirmed. Since A(H3N2) virus is generally associated with more severe disease in the elderly and high-risk groups [21,22] and the vaccine is less effective against this influenza subtype, in seasons of A(H3N2) circulation early antiviral treatment should be recommended in these groups [3,6].

The effect of previous vaccinations is one of the questions that I-MOVE and other influenza VE teams in the US, Canada and Australia started to raise some years ago [17,24-27]. This is an important issue that may impact vaccination policy in Europe. They need to be addressed through international collaboration, a multidisciplinary approach and with long-term scientific independent studies. The I-MOVE multicentre case–control study should continue to increase the sample size and to strengthen the virological component of the study to contribute to answer these questions.

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Acknowledgements

We acknowledge the authors, originating and submitting laboratories of the sequences from GISAID's EpiFlu Database on which this research is based. The list of sequences used is detailed in Table 1 in the text. All submitters of data may be contacted directly via the GISAID website www.gisaid.org.

WHO-EURO contributed to the funding of the study site in Romania; ECDC contributed to the funding of the study coordination and three study sites.

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WHO-EURO funded part of the study.

Rodica Popescu and Odette Popovici, National Centre of Surveillance and Control of communicable Diseases, Bucharest.

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Conflict of interest

None declared.

Authors' contributions

All authors provided contribution to the research article and approved the final version.

Marta Valenciano, coordinated the I-MOVE multicentre case control study network, supervised the statistical analysis and interpretation of the results, led the writing of the research article.

Esther Kissling was responsible for the data management of the multicentre study, undertook the statistical analysis on which the research article is based, contributed to the writing of the research article

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Concordance of interim and final estimates of influenza vaccine effectiveness: a systematic review

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Citation style for this article:
Leung VK, Cowling BJ, Feng S, Sullivan SG. Concordance of interim and final estimates of influenza vaccine effectiveness: a systematic review. Euro Surveill. 2016;21(16):pii=30202. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.16.30202

Article submitted on 10 September 2015 / accepted on 25 January 2016 / published on 21 April 2016

The World Health Organization's Global Influenza Surveillance and Response System meets twice a year to generate a recommendation for the composition of the seasonal influenza vaccine. Interim vaccine effectiveness (VE) estimates provide a preliminary indication of influenza vaccine performance during the season and may be useful for decision making. We reviewed 17 pairs of studies reporting 33 pairs of interim and final estimates using the test-negative design to evaluate whether interim estimates can reliably predict final estimates. We examined features of the study design that may be correlated with interim estimates being substantially different from their final estimates and identified differences related to change in study period and concomitant changes in sample size, proportion vaccinated and proportion of cases. An absolute difference of no more than 10% between interim and final estimates was found for 18 of 33 reported pairs of estimates, including six of 12 pairs reporting VE against any influenza, six of 10 for influenza A(H1N1)pdm09, four of seven for influenza A(H3N2) and two of four for influenza B. While we identified inconsistencies in the methods, the similarities between interim and final estimates support the utility of generating and disseminating preliminary estimates of VE while virus circulation is ongoing.

Introduction

Influenza vaccination is currently the main strategy for reducing the burden of influenza morbidity and mortality. Influenza viruses continuously evolve by undergoing antigenic drift and the composition of influenza vaccines therefore varies each year to account for antigenic changes in circulating viruses. The inability to use randomised trials to measure the efficacy of the influenza vaccine each year has resulted in the use of observational studies to determine annual vaccine effectiveness. However, observational studies such as cohort or case control studies can be subject to a number of biases.

The test-negative design (TND) is increasingly being used to measure influenza vaccine effectiveness (VE). The theory and methodology behind the TND has been discussed in detail previously [1-3]. Briefly, patients presenting for medical attention with a respiratory infection are swabbed and tested for influenza. Those testing positive are the cases and those testing negative are the comparison group [3]. Laboratory end points such as PCR-confirmed influenza are preferred in the TND, rather than low-specificity endpoints which could lead to underestimation of the effect of vaccination [4].

This design is favoured for the reporting of mid-season estimates, which provide a preliminary indication of vaccine performance during the season [5-21]. Early VE estimates may be useful to public health authorities in the event of a pandemic or in a season where VE appears to be low, to guide resource allocation or initiate additional preventive measures. Belongia et al. have shown that interim estimates can be reliable to within 10 percentage points of the final estimate [22], while Sullivan et al. demonstrated that estimates made in seasons with an early start showed greatest reliability to within 10 percentage points [19]. Jimenez-Jorge et al. also found agreement between mid- and end-of-season estimates in their comparison over four seasons in Spain [23], supporting the use of interim estimates. However, studies of interim influenza VE estimates might be expected to ignore desired exclusion criteria due to small sample sizes and incomplete data. The objective of this review is to examine differences in reported interim and final influenza vaccine effectiveness estimates derived by the test-negative design, with particular reference to changes in the

analytical approach used between interim and final estimation.

Methods

Search strategy

Studies reporting influenza VE estimates were initially retrieved from PubMed on 8 November 2013 as part of a review of test-negative studies which focused solely on final estimates, excluding interim estimates [24]. At that time, articles were searched using combinations of the following terms: (i) 'influenza' OR 'flu', (ii) 'vaccine effectiveness OR 'VE', (iii) 'test-negative' OR 'test negative' OR 'case-control' OR 'case control'.

We used the list of excluded papers to identify interim estimates for this review. In addition, a further search of PubMed, Medline, Web of Science and Embase was conducted on 19 December 2014 and updated on 5 December 2015 using the above search terms as well as the following: (iv) 'interim' OR 'mid-season' OR 'mid season' OR 'early estimates'.

Complementary to the online search, the reference lists of retrieved articles were reviewed to identify additional studies. Articles were also identified, between May 2012 and December 2015, from influenza email alerts from the Centre for Infectious Disease Research and Policy (CIDRAP, http://www.cidrap.umn.edu/). We excluded articles which did not use the test-negative design or were a re-analysis of data, end of season analyses without corresponding interim analyses and interim analyses without corresponding final analyses. Searches were limited to articles in English only.

The titles of all papers identified were independently screened by two authors (VKL and SGS). Abstracts of potentially relevant papers were reviewed for eligibility, and the full text of eligible articles was reviewed. Studies reporting interim effectiveness estimates for any type of influenza vaccine (trivalent inactivated, live-attenuated, monovalent, adjuvanted/non-adjuvanted or unspecified) were considered.

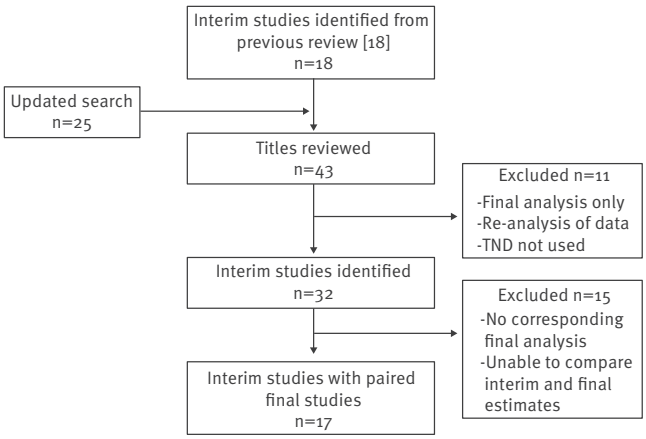
Once all interim papers were identified, their corresponding end-of-season report was located. This was a specific search using the author names, location and season of the interim paper to identify the paper reporting final estimates.

Data retrieval

Study design and analysis features were reviewed for each article using a standardised data collection form. Specific features reviewed included the study setting, source population, case definition (including whether acute respiratory illness or influenza-like illness was used and any restrictions on time since symptom onset) exposure definition (including any restrictions on the period between vaccination and symptoms onset), study period or season, timing of interim estimates in relation to the peak (determined by reviewing the epidemic curve provided in final analyses), any other exclusions (e.g. patients with missing information, children younger than a certain age), variables included in the model to estimate VE and their specification, and reported interim and final VE estimates. If the methods referred to a previous paper, the methods in the previous paper were recorded. If the specification of a variable was not mentioned, it was assumed that it had not been taken into consideration in the analysis. In some instances where information was not available, the authors were contacted to provide this information.

Figure 1

PRISMA flow diagram showing search strategy



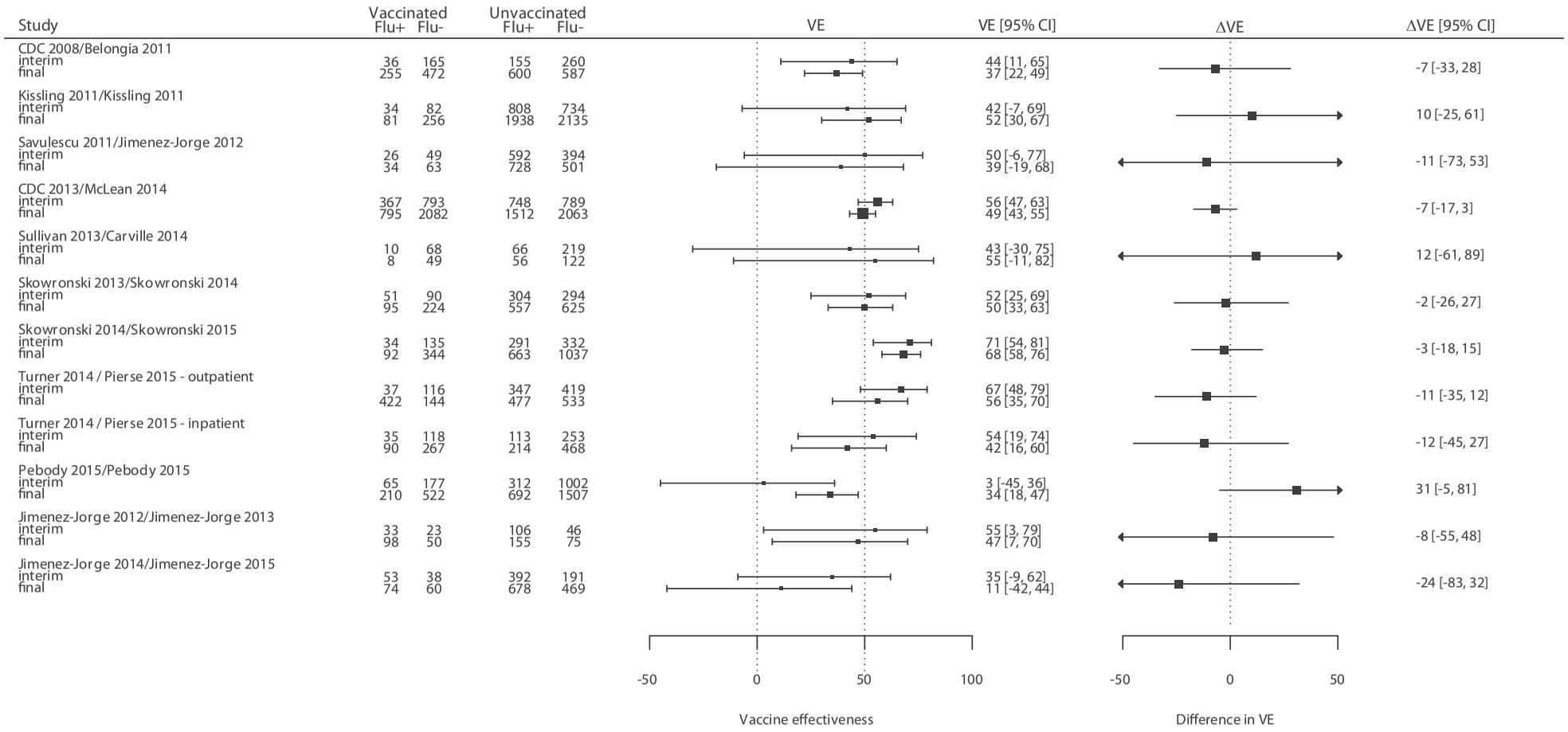
PRISMA: preferred reporting items for systematic reviews and meta-analyses; TND: test-negative design.

Comparison of interim and final estimates

The VE estimates reported by each interim/final study pair were plotted using forest plots and compared visually. Changes between interim and final estimates of 10 or more percentage points were considered meaningful differences [19,22]. The difference in VE estimates (ΔVE) between final and interim analyses was calculated. Confidence intervals were estimated using bootstrapping and were based on each study's standard error estimated from reported confidence intervals. We attempted to evaluate whether any design features were associated with ΔVE. This was done in two ways: (i) univariate linear regression, modelling each design feature explored on the absolute value of ΔVE, and (ii) logistic regression, where the outcome was a change in ΔVE of 10 or more percentage points. Multivariate models were explored using stepwise regression to identify which variables were most influential on the value of ΔVE or a change in ΔVE of 10 or more percentage points. We used stepwise regression to limit the size of the final model; given the small number of data points, a full model would have been overparameterised. Akaike information criterion (AIC) were used to choose variables for the final model using the stepAIC package in R. Design features were specified as the absolute difference between interim and final estimate

Figure 2

Comparison of overall interim and final influenza vaccine effectiveness estimates

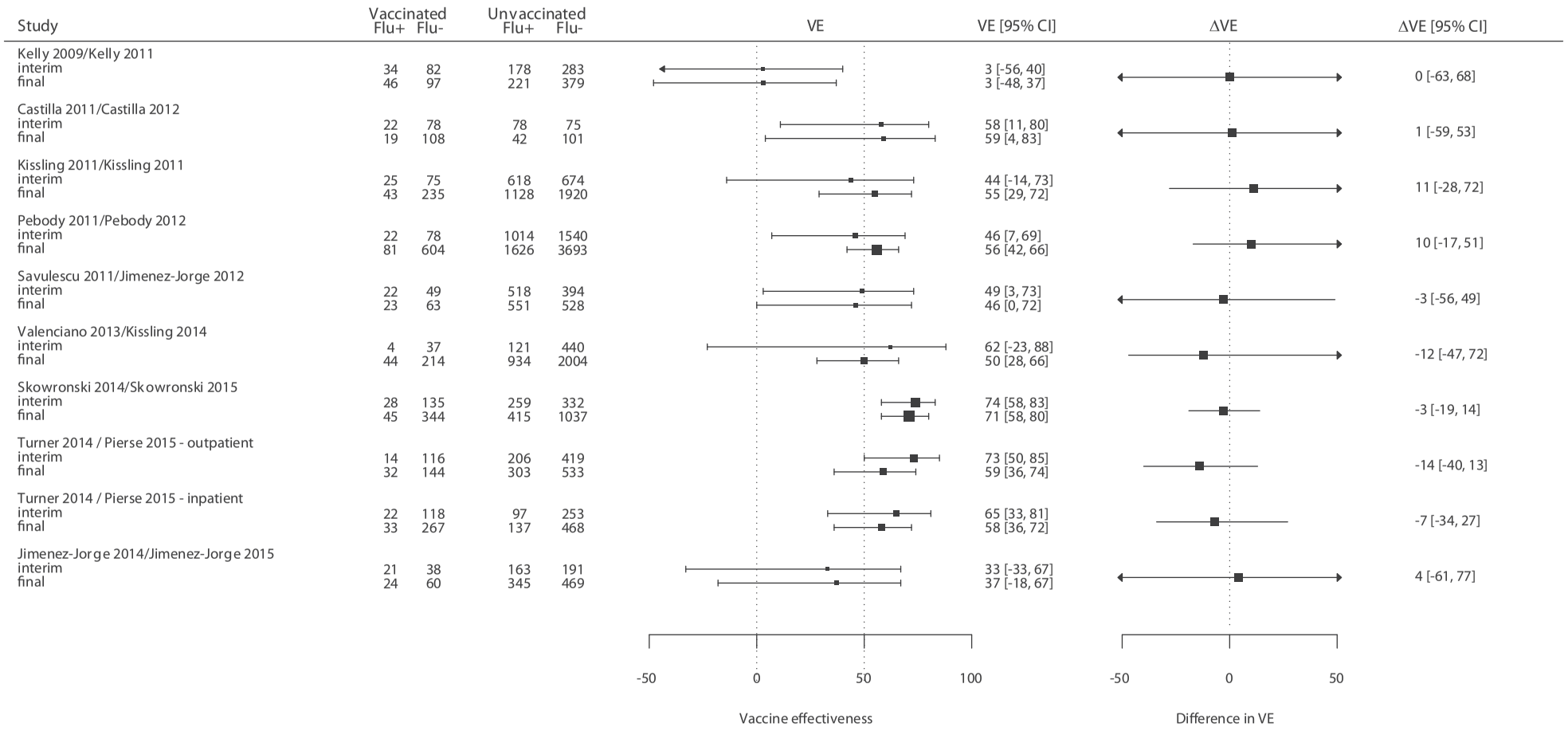


CI: confidence interval; Flu+: influenza-positive; Flu–: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

VE estimated based on $(1 - OR_{adj}) \times 100\%$.

Figure 3

Comparison of interim and final vaccine effectiveness estimates for influenza A(H1N1)pdm09

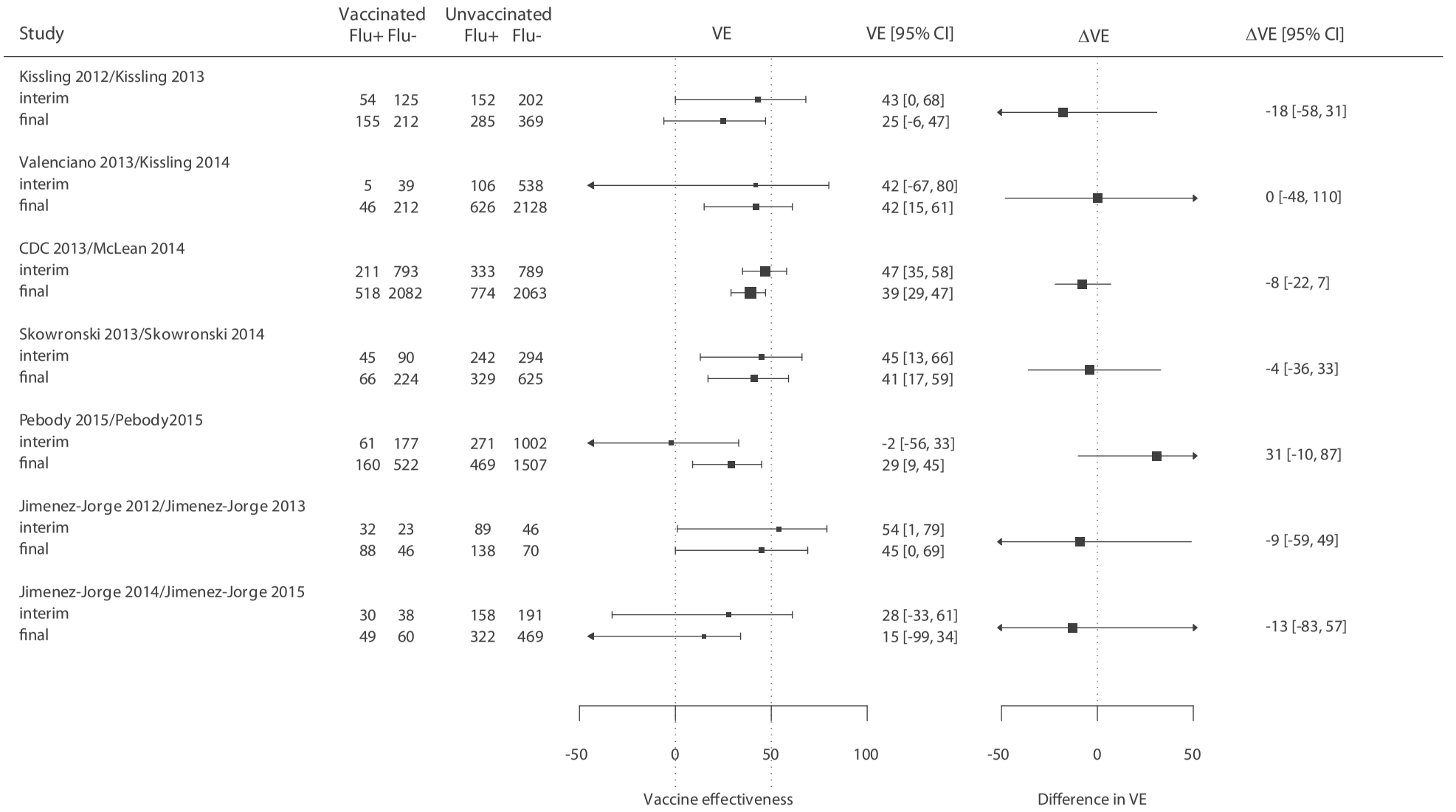


CI: confidence interval; Flu+: influenza-positive; Flu–: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

VE estimated based on $(1 - OR_{adj}) \times 100\%$.

Figure 4

Comparison of interim and final vaccine effectiveness estimates for influenza A(H3N2)

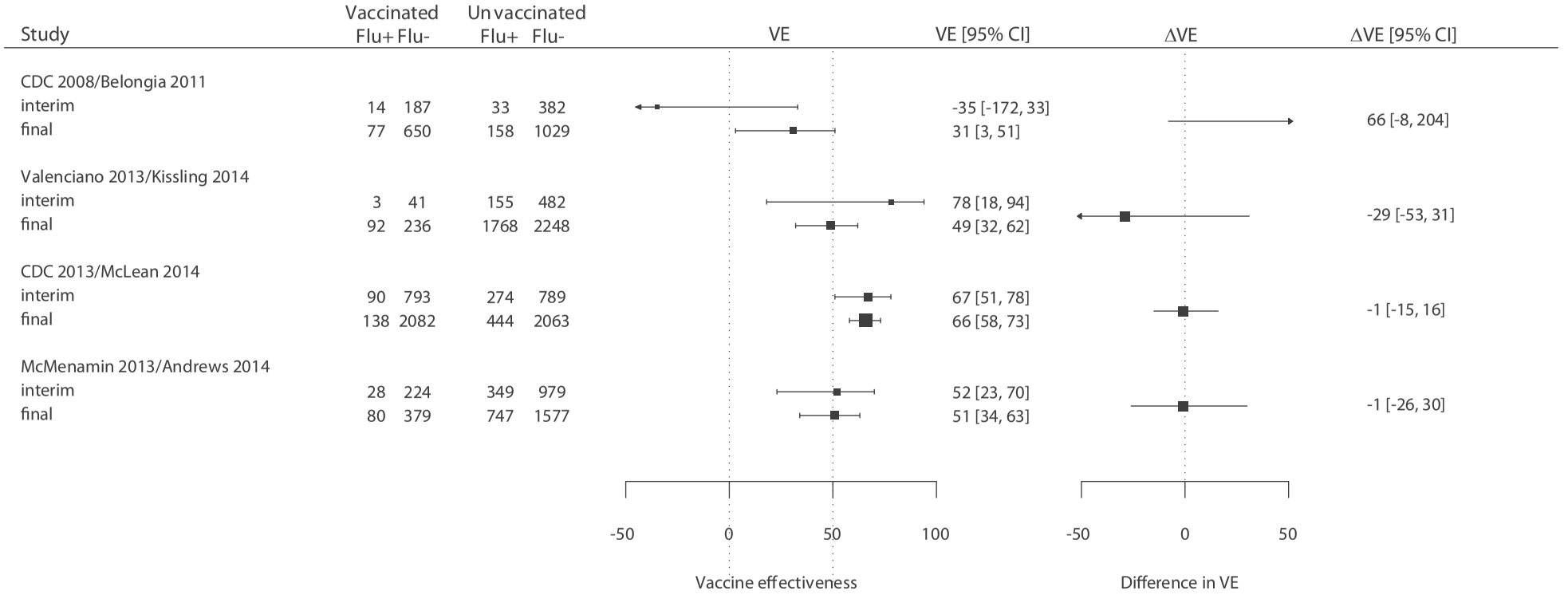


CI: confidence interval; Flu+: influenza-positive; Flu−: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

VE estimated based on $(1 - OR_{adj}) \times 100\%$.

Figure 5

Comparison of interim and final vaccine effectiveness estimates for influenza B



CI: confidence interval; Flu+: influenza-positive; Flu−: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

VE estimated based on $(1 - OR_{adj}) \times 100\%$.

for sample size, proportion positive, proportion of vaccinated non-cases, number of weeks studied and number of covariates in the model. For other design features, the change in variable specification was used as a predictor; this included a change in specification of calendar time, vaccination definition, exclusion criteria related to time since onset, and statistical model. We also examined whether there was a change in the dominant strain during the season and whether the interim estimate was made before or after the peak. All analyses were performed using R version 3.1.3.

Results

Of the 43 interim studies reviewed (Figure 1), we located a corresponding final VE estimate for 17 [5-23,25-40].

The characteristics of the paired interim and final analyses are summarised in Table 1. Studies were reported from North America, Europe and Australasia, with a total of 17 countries represented. The 2013/14 final published estimate for Spain was included as part of analyses comparing interim and final estimates over a number of seasons [23]. Two interim reports published for the 2012/13 northern hemisphere season in the United States (US) were published one month apart. The first interim estimate [41] was excluded from the comparison as the number of cases was substantially smaller than those used in the second interim estimate for the season [7]. Three interim studies reported age-specific estimates. No studies reported sex-specific estimates and only one interim study reported VE by risk group [16]. Eight northern hemisphere interim studies [5,6,13-15,17,18,21] and one southern hemisphere study [10] were published before or during the World Health Organization's (WHO) vaccine strain selection meeting.

Comparison of interim vs final vaccine effectiveness analyses

Interim and final study pairs were reviewed to identify differences within and between pairs in the methods used to make estimates. A summary of these changes is shown in Table 2.

Setting and source population

In none of the study pairs were there changes to the study setting between interim and final estimates. One pair of studies from New Zealand reported estimates for both community and hospital settings [20,37]. The source population differed in the final analyses of three studies where data were pooled from multiple surveillance networks or sites [31,33,36]. Pooled final estimates commonly included data from additional surveillance sites which may not have had any cases at the time the interim estimate was made. For example, during the European 2011/12 season some countries were unable to provide data for the interim estimate [12]. In general, sample sizes in final analyses of VE increased compared with the interim analyses. One interim study reported a larger sample size (n = 285 [19]) than the corresponding final estimate study (n = 262 [26]), which was associated with the application of stricter criteria for the definition of the study period used and subsequent exclusion of many non-cases.

Influenza-like illness definition

The clinical case definition used to identify patients was generally termed influenza-like illness (ILI); however in the US studies, acute respiratory illness (ARI) was used as the clinical case definition. The list of symptoms included in each definition remained the same between the interim study and final study in all but one pair [27]. The interim analysis for the 2010/11 season in Spain based the ILI definition on the International classification of primary care (ICPC) code for fever, whereas the final analysis provided a more specific definition for ILI. This did not appear to alter the point estimates for influenza A(H1N1)pdm09 (interim VE: 58%, 95% confidence interval (CI): 11–80; final VE: 59%, 95% CI: 29–72) [5,27]. All studies included fever in the case definition for ILI, while only one study specified a temperature-based definition [13].

Influenza case definition

Cases of influenza were defined differently in two pairs of interim and final analyses. The case definition used in the interim analysis for the 2010/11 season in the United Kingdom (UK) [14] included individuals with ILI who were swab-positive for any influenza, regardless of type or subtype. The definition used in the final analysis [36] only included individuals who were swab-positive for influenza A(H1N1)pdm09 or influenza B. Conversely, Kissling et al. [12] included only patients who were positive for influenza A(H3N2) in their interim analysis, while the case definition for the final analysis included all patients who were swab-positive for any influenza [33]. However, the final analysis was later restricted to influenza A(H3N2) as this was the predominant circulating subtype during the season. Their end-of-season point estimate for influenza A(H3N2) decreased by 18 percentage points from the interim estimate (interim VE: 43%, 95% CI: 0–68; final VE: 25%, 95% CI: −6 to 47).

Exposure

The classification of patients as vaccinated generally did not differ within study pairs. The definition for vaccination was not reported in the interim analysis for the Australian 2009 season [10]. In the final analysis [30], the vaccinated population was restricted to those presenting 14 days or more after vaccination.

Study periods

The criteria used to define the start of the study period for interim analyses varied among studies. Two studies started with the commencement of surveillance [10,19], six started when there was evidence of circulation based on laboratory-confirmed cases [5-8,16,20]. Five studies used only the weeks with cases, a certain period after the vaccination campaign [11,12,17,18,21,42], while four studies did not clearly define their study period [9,13-15].

Table 1

Studies reporting interim and corresponding final influenza vaccine effectiveness estimates (n = 34)

Reference	Study	Interim/ final	Influenza season	Country	Types of patients	Target groups	Vaccine
[6]	CDC 2008	Interim	2007/08	United States	Inpatients and outpatients	All ages	TIV
[22]	Belongia et al. 2011	Final	2007/08	United States	Inpatients and outpatients	All ages	TIV
[10]	Kelly et al. 2009	Interim	2009	Australia	Outpatients	All ages	TIV
[30]	Kelly et al. 2011	Final	2009	Australia	Outpatients	All ages	TIV
[5]	Castilla et al. 2011	Interim	2010/11	Spain	Inpatients and outpatients	Target group for vaccination	TIV, MIV
[27]	Castilla et al. 2012	Final	2010/11	Spain	Inpatients and outpatients	Target group for vaccination	TIV, MIV
[42]	Kissling et al. 2011	Interim	2010/11	Europe	Outpatients	All ages	TIV
[32]	Kissling et al. 2011	Final	2010/11	Europe	Outpatients	Target group for vaccination	TIV, adjuvanted vaccine
[14]	Pebody et al. 2011	Interim	2010/11	United Kingdom	Outpatients	All ages	TIV, MIV
[36]	Pebody et al. 2013	Final	2010/11	United Kingdom	Outpatients	All ages	TIV, MIV
[16]	Savulescu et al. 2011	Interim	2010/11	Spain	Outpatients	Target group for vaccination	TIV, AMIV
[29]	Jimenez-Jorge et al. 2012	Final	2010/11	Spain	Outpatients	Target group for vaccination	TIV, MIV
[12]	Kissling et al. 2012	Interim	2011/12	Europe	Outpatients	Target group for vaccination	TIV
[33]	Kissling et al. 2013	Final	2011/12	Europe	Outpatients	Target group for vaccination	TIV
[21]	Valenciano et al. 2013	Interim	2012/13	Europe	Outpatients	Target group for vaccination	TIV
[31]	Kissling et al. 2014	Final	2012/13	Europe	Outpatients	Target group for vaccination	TIV
[7]	CDC 2013	Interim	2012/13	United States	Outpatients	All ages	TIV
[34]	McLean et al. 2014	Final	2012/13	United States	Outpatients	All ages	TIV
[13]	McMenamin et al. 2013	Interim	2012/13	United Kingdom	Outpatients	Target group for vaccination	TIV
[25]	Andrews et al. 2014	Final	2012/13	United Kingdom	Outpatients	All ages	TIV
[19]	Sullivan et al. 2013	Interim	2013	Australia	Outpatients	All ages	TIV
[26]	Carville et al. 2015	Final	2013	Australia	Outpatients	All ages	TIV
[18]	Skowronski et al. 2013	Interim	2012/13	Canada	Outpatients	All ages	TIV
[39]	Skowronski et al. 2014	Final	2012/13	Canada	Outpatients	All ages	TIV
[43]	Skowronski et al. 2014	Interim	2013/14	Canada	Outpatients	All ages	TIV
[38]	Skowronski et al. 2015	Final	2013/14	Canada	Outpatients	All ages	TIV, LAIV, adjuvanted TIV
[15]	Pebody et al. 2015	Interim	2014/15	United Kingdom	Outpatients	All ages	TIV
[35]	Pebody et al. 2015	Final	2014/15	United Kingdom	Outpatients	All ages	TIV, LAIV
[8]	Jimenez-Jorge et al. 2012	Interim	2011/12	Spain	Outpatients	All ages, target group for vaccination	TIV
[28]	Jimenez-Jorge et al. 2013	Final	2011/12	Spain	Outpatients	All ages, target group for vaccination	TIV
[9]	Jimenez-Jorge et al. 2014	Interim	2013/14	Spain	Outpatients	All ages	TIV
[23]	Jimenez-Jorge et al. 2015	Final	2013/14	Spain	Outpatients	All ages	TIV
[20]	Turner et al. 2014	Interim	2014	New Zealand	Inpatients and outpatients	All ages	TIV
[37]	Pierse et al. 2015	Final	2014	New Zealand	Inpatients and outpatients	All ages	TIV

AMIV: adjuvanted monovalent influenza vaccine; CDC: Centers for Disease Control and Prevention; LAIV: live-attenuated influenza vaccine; MIV: monovalent influenza vaccine; TIV: trivalent influenza vaccine.

Table 2a

Changes in vaccine effectiveness estimates by type/subtype and differences between interim and final studies in model specification (n = 34)

Reference	Study	Interim/ final	ΔVE (95% CI)	Sample size	% cases	ILI restriction criteria	Dominant strain[a]	% vaccinated non-cases	Vaccination definition[b]	Calendar time in model	Reported start date[c]	Interim estimate made pre/ post peak	Number of weeks in model	Number of covariates in model	Model change
All influenza															
[6]	CDC 2008	Interim	−7 (−33 to 28)	616	31	<8 d	A/H3	39	≥14 d	Week	21/01/2008	Pre	3	3	No
[22]	Belongia et al. 2011	Final		1,914	45	<8 d	A/H3	45	≥14 d	Week	21/01/2008		10	3	
[42]	Kissling et al. 2011	Interim	10 (−25 to 61)	1,658	51	<8 d	A/H1	10	≥14 d	Week	7/11/2010	Post	12	9	Yes
[32]	Kissling et al. 2011	Final		4,410	46	<8 d	A/H1	11	≥14 d	Week	7/11/2010		23	9	
[16]	Savulescu et al. 2011	Interim	−11 (−73 to 53)	1,061	58	<8 d	A/H1	11	≥14 d	Week	12/12/2010	Post	9	3	No
[29]	Jimenez-Jorge et al. 2012	Final		1,326	57	<4 d	A/H1	11	≥14 d	Week	12/12/2010		15	3	
[7]	CDC 2013	Interim	−7 (−17 to 3)	2,697	41	<7 d	A/H3	50	≥14 d	Not adjusted	3/12/2012	Post	7	5	Yes
[34]	McLean et al. 2014	Final		6,452	36	<7 d	A/H3	50	≥14 d	Fortnight	3/12/2012		60	4	
[19]	Sullivan et al. 2013	Interim	12 (−61 to 89)	363	21	<8 d	B	24	≥14 d	Week	29/04/2013	Post	19	2	Yes
[26]	Carville et al. 2015	Final		235	27	<8 d	B	29	≥14 d	Time from peak	29/04/2013		18	3	
[18]	Skowronski et al. 2013	Interim	−2 (−26 to 27)	739	48	<7 d	A/H3	23	≥14 d	Week	1/11/2012	Post	12	5	Yes
[39]	Skowronski et al. 2014	Final		1,501	43	<7 d	A/H3	26	≥14 d	Week	1/11/2012		26	5	
[43]	Skowronski et al. 2014	Interim	−3 (−18 to 15)	792	41	<7 d	A/H1 and B	29	≥15 d	Week	1/11/2013	Pre	12	5	Yes
[38]	Skowronski et al. 2015	Final		2,136	35	<7 d	A/H1	25	≥15 d	Week	1/11/2013		26	5	
[8]	Pebody et al. 2015	Interim	31 (−5 to 81)	1,556	24	<7 d	A/H3	15	≥14 d	Month	1/10/2014	Post	15	6	No
[28]	Pebody et al. 2015	Final		2,931	31	<7 d	A/H3	26	≥14 d	Month	1/10/2014		28	6	
[8]	Jimenez-Jorge et al. 2012	Interim	−8 (−55 to 48)	208	67	<8 d	A/H3	33	≥14 d	Week	25/12/2011	Post	8	3	No
[28]	Jimenez-Jorge et al. 2013	Final		378	67	<8 d	A/H3	40	≥14 d	Week	25/12/2011		19	3	
[9]	Jimenez-Jorge et al. 2014	Interim	−24 (−83 to 32)	674	66	<8 d	A/H3 and A/H1	17	≥14 d	Week	9/12/2013	Post	7	9	No
[23]	Jimenez-Jorge et al. 2015	Final		1,281	59	<8 d	A/H3 and A/H1	11	≥14d	Week	9/12/2013		19	2	
[20]	Turner et al. 2014 (outpatient)	Interim	−11 (−35 to 12)	919	42	<7 d	A/H1	22	≥15 d	Week	2/06/2014	Post	13	2	Yes
[37]	Pierse et al. 2014 (outpatient)	Final		1,576	57	<7 d	A/H1	21	≥15 d	Time to peak	2/06/2014		27	9	
[20]	Turner et al. 2014 (inpatient)	Interim	−12 (−45 to 27)	519	29	<7 d	A/H1	32	≥15 d	Week	2/06/2014	Post	13	2	Yes
[37]	Pierse et al. 2014 (inpatient)	Final		1,039	29	<7 d	A/H1	36	≥15 d	Time to peak	2/06/2014		27	9	

CI: confidence interval; ILI: influenza-like illness.

[a] A/H1 refers to A(H1N1)pdm09.

[b] Vaccination definition: threshold used to classify a patient as vaccinated; figures refer to the number of days since vaccination.

[c] Reported start date is either the date reported in the paper or was inferred if only the week was reported. Note that it refers to the date surveillance started; VE estimates may have been made for a different period.

Table 2b

Changes in vaccine effectiveness estimates by type/subtype and differences between interim and final studies in model specification (n = 34)

Reference	Study	Interim/ final	ΔVE (95% CI)	Sample size	% cases	ILI restriction criteria	Dominant strain[a]	% vaccinated non-cases	Vaccination definition[b]	Calendar time in model	Reported start date[c]	Interim estimate made pre/ post peak	Number of weeks in model	Number of covariates in model	Model change
Influenza A(H1N1)pdm09															
[10]	Kelly et al. 2009	Interim	0 (−63 to 68)	577	37	≤4 d	A/H1	22	Not stated	Not adjusted	27/04/2009	Post	12	1	Yes
[30]	Kelly et al. 2011	Final		743	36	≤4 d	A/H1	20	≥14 d	Period	27/04/2009		34	2	
[5]	Castilla et al. 2011	Interim	1 (−59 to 53)	253	40	Not stated	A/H1	51	≥14 d	Period	24/10/2010	Post	13	6	Yes
[27]	Castilla et al. 2012	Final		270	23	Not stated	A/H1	52	≥14 d	Period	12/12/2010		16	9	
[42]	Kissling et al. 2011	Interim	11 (−28 to 72)	1,392	46	<8 d	A/H1	10	≥14 d	Week	7/11/2010	Post	12	9	Yes
[32]	Kissling et al. 2011	Final		3,326	35	<8 d	A/H1	11	≥14 d	Week	7/11/2010		23	9	
[14]	Pebody et al. 2011	Interim	10 (−17 to 51)	2,654	39	<29 d	A/H1	5	≥14 d	Month	1/09/2010	Post	19	3	Yes
[36]	Pebody et al. 2012	Final		6,004	28	<29 d	A/H1	14	≥14 d	Month	1/09/2010		28	4	
[16]	Savulescu et al. 2011	Interim	−3 (-56 to 49)	983	55	<8 d	A/H1	11	≥14 d	Week	12/12/2010	Post	9	3	No
[29]	Jimenez-Jorge et al. 2012	Final		1,165	49	<4 d	A/H1	11	≥14 d	Week	12/12/2010		15	3	
[21]	Valenciano et al. 2013	Interim	−12 (−47 to 72)	602	21	<8 d	A/H3	8	>15 d	Month	21/10/2012	Post	13	4	Yes
[31]	Kissling et al. 2014	Final		3,196	31	<8 d	A/H3	10	>15 d	Week	21/10/2012		28	4	
[43]	Skowronski et al. 2014	Interim	−3 (−19 to 14)	754	38	<7 d	A/H1 and B	29	≥15 d	Week	1/11/2013	Pre	12	5	Yes
[38]	Skowronski et al. 2015	Final		1,841	25	<7 d	A/H1	25	≥15 d	Week	1/11/2013		26	5	
[9]	Jimenez-Jorge et al. 2014	Interim	4 (−61 to 77)	413	45	<8 d	A/H3 and A/H1	17	≥14 d	Week	9/12/2013	Post	7	9	No
[23]	Jimenez-Jorge et al. 2015	Final		898	41	<8 d	A/H3 and A/H1	11	≥14 d	Week	9/12/2013		19	2	
[20]	Turner et al. 2014 (outpatient)	Interim	−14 (−40 to 13)	755	29	<7 d	A/H1	22	≥15 d	Week	2/06/2014	Post	13	2	Yes
[37]	Pierse et al. 2014 (outpatient)	Final		1,001	33	<7 d	A/H1	21	≥15 d	Time to peak	2/06/2014		27	9	
[20]	Turner et al. 2014 (inpatient)	Interim	−7 (−34 to 27)	490	24	<7 d	A/H1	32	≥15 d	Week	2/06/2014	Post	13	2	Yes
[37]	Pierse et al. 2014 (inpatient)	Final		905	19	<7 d	A/H1	36	≥15 d	Time to peak	2/06/2014		27	9	
Influenza A(H3N2)															
[12]	Kissling et al. 2012	Interim	−18 (−58 to 31)	533	39	<8 d	A/H3	38	≥14 d	Week	27/11/2011	Post	12	6	Yes
[33]	Kissling et al. 2013	Final		1,021	43	<8 d	A/H3	36	≥14 d	Month	2/10/2011		33	6	
[21]	Valenciano et al. 2013	Interim	0 (−48 to 110)	688	16	<8 d	A/H3	7	≥15 d	Month	21/10/2012	Post	13	4	Yes
[31]	Kissling et al. 2014	Final		3,012	22	<8 d	A/H3	9	≥15 d	Week	21/10/2012		28	4	

CI: confidence interval; ILI: influenza-like illness.

[a] A/H1 refers to A(H1N1)pdm09.

[b] Vaccination definition: threshold used to classify a patient as vaccinated; figures refer to the number of days since vaccination.

[c] Reported start date is either the date reported in the paper or was inferred if only the week was reported. Note that it refers to the date surveillance started; VE estimates may have been made for a different period.

Table 2c

Changes in vaccine effectiveness estimates by type/subtype and differences between interim and final studies in model specification (n = 34)

Reference	Study	Interim/ final	ΔVE (95% CI)	Sample size	% cases	ILI restriction criteria	Dominant strain[a]	% vaccinated non-cases	Vaccination definition[b]	Calendar time in model	Reported start date[c]	Interim estimate made pre/ post peak	Number of weeks in model	Number of covariates in model	Model change
Influenza A(H3N2)															
[7]	CDC 2013	Interim	−8 (−22 to 7)	2,126	26	<7 d	A/H3	50	≥ 14 d	Not adjusted	3/12/2012	Post	7	5	Yes
[34]	McLean et al. 2014	Final		5,437	24	<7 d	A/H3	50	≥ 14 d	Fortnight	3/12/2012		60	4	
[18]	Skowronski et al. 2013	Interim	−4 (−36 to 33)	671	43	<7 d	A/H3	23	≥ 14 d	Week	1/11/2012	Post	12	5	Yes
[39]	Skowronski et al. 2014	Final		1,244	32	<7 d	A/H3	26	≥ 14 d	Week	1/11/2012		26	5	
[15]	Pebody et al. 2015	Interim	31 (−10 to 87)	1,511	22	<7 d	A/H3	15	≥ 14 d	Month	1/10/2014	Post	15	6	No
[35]	Pebody et al. 2015	Final		2,658	24	<7 d	A/H3	26	≥14 d	Month	1/10/2014		28	6	
[8]	Jimenez-Jorge et al. 2012	Interim	−9 (−59 to 49)	190	64	<8 d	A/H3	33	≥ 14 d	Week	25/12/2011	Post	8	3	No
[28]	Jimenez-Jorge et al. 2013	Final		342	66	<8 d	A/H3	40	≥14 d	Week	25/12/2011		19	3	
[9]	Jimenez-Jorge et al. 2014	Interim	−13 (−83 to 57)	417	45	<8 d	A/H3 and A/H1	17	≥14 d	Week	9/12/2013	Post	7	9	No
[23]	Jimenez-Jorge et al. 2015	Final		900	41	<8 d	A/H3 and A/H1	11	≥14 d	Week	9/12/2013		19	2	
Influenza B															
[6]	CDC 2008	Interim	66 (−8 to 204)	616	8	<8 d	A/H3	33	≥14 d	Week	21/01/2008	Pre	3	3	No
[22]	Belongia et al. 2011	Final		1,914	12	<8 d	A/H3	39	≥14 d	Week	21/01/2008		10	3	
[21]	Valenciano et al. 2013	Interim	−29 (−53 to 31)	681	23	<8 d	A/H3	8	≥15 d	Month	21/10/2012	Pre	13	4	Yes
[31]	Kissling et al. 2014	Final		4,344	43	<8 d	A/H3	10	≥15 d	Week	21/10/2012		28	4	
[7]	CDC 2013	Interim	−1 (−15 to 16)	1,946	19	<7 d	A/H3	50	≥14 d	Not adjusted	3/12/2012	Post	7	5	Yes
[34]	McLean et al. 2014	Final		4,727	12	<7 d	A/H3	50	≥14 d	Fortnight	3/12/2012		60	4	
[13]	McMenamin et al. 2013	Interim	−1 (−26 to 30)	1,580	24	<29 d	B	19	≥14 d	Month	1/10/2012	Pre	14	4	Yes
[25]	Andrews et al. 2014	Final		2,783	30	<7 d	B	19	≥14 d	Month	1/10/2012		29	5	

CI: confidence interval; ILI: influenza-like illness.

[a] A/H1 refers to A(H1N1)pdm09.

[b] Vaccination definition: threshold used to classify a patient as vaccinated; figures refer to the number of days since vaccination.

[c] Reported start date is either the date reported in the paper or was inferred if only the week was reported. Note that it refers to the date surveillance started; VE estimates may have been made for a different period.

In general, the study period was defined in the same manner for final estimates, and the majority (n = 15) of studies commenced their study period on the same date for both interim and final analyses. In Spain in 2010/11, the interim analysis commenced in October, while the final analysis used data only from early December; the interim and final VE estimates made for influenza A(H1N1)pdm09 against trivalent influenza vaccines (TIV) and monovalent influenza vaccines (MIV) were within 10 percentage points of each other [5,27]. Conversely, the study period reported for the European 2011/12 final analysis commenced earlier than the study period of the interim analysis, and larger variation between the estimates for influenza A(H3N2) was observed (VE: 43%, 95% CI: 0–68% [12] vs VE: 25%, 95%CI: –6 to 47% [33], respectively). In Australia in 2013, while the interim and final studies listed the same commencement date, the interim estimate was based on all available data for the surveillance period, while the final estimate was based on the weeks with cases and non-cases; thus the effective start date differed. The final estimate for all influenza (55%, 95% CI: –11 to 82) in that study pair [26] increased by 12 percentage points compared with the interim estimate (43%, 95% CI: –30 to 75) [19].

Outcome

Among interim studies, patients were restricted to those presenting within four [10], seven [6,7,15,17-20], eight [8,9,11,12,16,21] or 29 days [13,14], while in one study, no such restrictions were mentioned [5]. These same restrictions applied in the final analyses in all but two studies. The interim estimate for the 2010/11 season in Spain restricted analyses to patients swabbed within eight days of symptom onset [16], whereas the final analyses was further restricted to within four days of symptom onset [8]. Similarly the 2012/13 season in the UK applied a restriction of less than 29 days for their interim analysis [13] and altered the cut-off to less than seven days for the final analysis [25]. In both the Spanish and UK studies, final VE estimates were decreased compared with the interim estimates.

Variables included in the model to estimate vaccine effectiveness

Interim and final estimates for all influenza (n = 12 studies) and for influenza A(H1N1)pdm09 (n = 10 studies) were most commonly reported, while seven studies reported estimates for influenza A(H3N2) and four studies reported estimates for influenza B. All studies used logistic regression to estimate VE. Compared with interim analyses (which used between one and nine variables), end-of-season VE models used between two and 10 variables. Differences in the variables included in regression models were noted in 12 of the paired studies.

All estimates were adjusted for age, specified as a categorical variable. The specification of age changed between interim and final analysis for six study pairs, either by the use of different categories [22,26,27], re-specification as 10-year bands [32] or using cubic splines [31,34].

Calendar time was included in the model for 15 interim and corresponding final analyses. This variable was described in final analyses as a phase or period [27,30,34], week of swabbing, enrolment or symptom onset [22,23,28,29,31-33,38,39], month of sample collection or symptom onset [25,35,36], or time relative to peak [26,37]. It was not included for two interim studies [7,10] but subsequently included in the model to estimate end-of-season VE [30,34]. The definition of calendar time varied in three pairs of interim and final analyses. In the model used to estimate interim VE for the 2012/13 European season, month of symptom onset was included as the calendar time variable [21], while week of symptom onset was used in the final model instead [31]. In both the Australian 2013 and New Zealand 2014 studies, week of presentation was used in interim analyses [19,20], while time relative to peak was used in the final analyses [26,37].

Seven study pairs included some adjustment for the presence of chronic medical conditions in both interim and final analyses, while five included this adjustment only in the final analysis [25-27,34,37].

Hospitalisation in the previous year, outpatient visits in the previous year and previous receipt of pneumococcal vaccine were included in the model to estimate end-of-season VE of one study, but were not included for adjustment in the interim analysis [5]. Another study adjusted for days from illness onset to enrolment, self-rated health and race/ethnicity [7] in the interim analysis, but did not adjust for these variables in their final analyses. Other variables included in both interim and final analyses included location or study site [5,7,11,13-15,17,18,25,27,32,34-36,38,39], history of smoking [8,11,28,32], receipt of previous influenza vaccine [11,16,29,32] and children in the household [5,27].

Comparison of interim and final vaccine effectiveness estimates

Interim and final VE estimates by type and subtype are shown in Figure 2–5.

In general, mid-season estimates were higher than end-of-season estimates. An absolute difference of less than 10 percentage points between interim and final estimates was found for 18 of 33 reported pairs of estimates, including five of 12 pairs reporting VE against any influenza, six of 10 for influenza A(H1N1)pdm09, four of seven for influenza A(H3N2) and two of four for influenza B. The largest difference between interim and final estimates was observed in the 2008/09 season in the US (interim VE: –35%, 95% CI:-172 to 33 [6]; final VE: 31%, 95% CI: 3–51 [22]). In contrast, there were no changes to the point estimates for influenza A(H1N1) pdm09 in the 2009 Australian season [10,30] and for influenza A(H3N2) in the 2012/13 European season

Table 3

Summary of changes in study characteristics that influenced differences in vaccine effectiveness estimates

Characteristic	Linear model of ΔVE				Logistic model of ΔVE>10%			
	Univariate		Multivariable		Univariate		Multivariable	
	β (se)	p[a]	β (se)	p[a]	OR (95% CI)	p[b]	OR (95%CI)	p[b]
Intercept	NA	NA	−0.2046 (3.42)	0.95	NA	NA	4.55 (0.9–63.24)	NR
Sample size	0.0003 (0.0027)	0.9	NR	NR	1 (1–1)	0.7	1.001 (1.0001–1.002)	0.07
Proportion of cases	−0.17 (0.37)	0.7	NR	NR	1.09 (1–1.21)	0.1	1.13 (1–1.34)	0.07
Proportion of non-cases vaccinated	1.85 (0.61)	0.005	1.68 (0.56)	0.006	1.07 (0.92–1.27)	0.4	NA	NR
Number of additional weeks in final estimate	−0.19 (0.24)	0.4	NR	NR	0.92 (0.78–1)	0.2	0.85 (0.67–0.95)	0.04
Number of covariates	−0.08 (0.94)	0.9	NR	NR	1.04 (0.84–1.31)	0.7	NA	NR
Change in calendar time specification (yes/no)	−12.03 (5.95)	0.05	−13.97 (5.51)	0.02	1.43 (0.35–5.98)	0.6	NA	NR
Change to vaccination definition (yes/no)	36.13 (11.21)	0.4	NR	NR	1.07 (0.04–28.62)	0.6	NA	NR
Change to restriction on duration of illness (yes/no)	−4.47 (10.72)	0.7	NR	NR	0.5 (0.02–5.77)	0.6	NA	NR
Estimate made pre-peak (pre/post)	5.83 (7.94)	0.5	13.03 (7.48)	0.09	0.46 (0.06–2.8)	0.4	0.04 (0–0.67)	0.06
Change to predominant strain (yes/no)	−2.19 (12.95)	0.9	NR	NR	Inest	Inest	NA	NR
Any change to model specification (yes/no)	−9.18 (6.54)	0.2	NR	NR	0.69 (0.16–2.98)	0.6	NA	NR

β: regression coefficient; CI: confidence interval; ΔVE: difference in vaccine effectiveness estimates; inest: inestimable; NA: not applicable; NR: not retained; OR: odds ratio; se: standard error for the coefficient.

[a] In linear models, p was measured by *t*-test.

[b] In logistic models, p was measures by chi-square test.

[21,31]. However, all interim and final estimates compared displayed overlapping confidence intervals.

Univariate linear regression models suggested that only the proportion of vaccinated non-cases had a significant effect on the value of ΔVE (Table 3). The multivariate model identified that the proportion of vaccinated non-cases, change in how calendar time was specified and whether the interim estimate was made before the peak were the most influential variables; these were retained in the stepwise model. Using logistic regression, no design feature was identified as being statistically associated with a change in ΔVE of at least 10 percentage points in the univariate models. The stepwise model identified sample size, the proportion positive, the number of weeks studied, the proportion of vaccinated non-cases and whether the interim estimate was made before the peak as the most influential factors.

Discussion

We reviewed 17 pairs of published interim and final influenza VE studies that used the test-negative design to evaluate whether interim estimates can reliably predict final estimates. In general, interim estimates closely approximated final estimates, with 18 of 33 final estimates for all types and subtypes reported within 10 percentage points of their corresponding interim estimate. We attempted to explain discordance between pairs by examining their methodological differences and identified some inconsistencies between interim and final estimation. Within many of the study pairs, definitions for ILI, fever, study population, vaccination status, and the cut-off applied to the duration between patient presentation and symptom onset remained the same. The major differences were related to the change in study period and the concomitant changes in sample size, proportion vaccinated and proportion positive. In the two stepwise models we attempted, the variables identified as important predictors differed, with the exception of whether the interim estimate was

made before or after the peak of the season. A previous study comparing interim and final estimates in Victoria, Australia, suggested that interim estimates may be most reliable when made after the peak of the influenza season, which was attributed to the gain in sample size when estimates are made later in the season. However, such a clear trend was not identified in a similar analysis performed in Spain [23].

Differences between interim and final estimates were most noticeable for estimates made against any influenza and influenza B. That concordance was better within subtypes possibly reflects how the summary estimate is influenced by individual specific type/subtype estimates as their prevalence changes throughout the season. Although we did not find a change in dominant strain to be an important predictor of ΔVE, we were unable to capture the more subtle influence of changes in the proportionate mix of types/subtypes as the seasons progressed. We also noted that final estimates were generally lower than interim estimates, which raises questions about waning vaccine effectiveness as the season progresses.

The largest methodological differences within study pairs were in the specification of the statistical model. When we examined whether a change to the regression model was associated with a change in the VE estimate, we found no statistical difference. This is consistent with findings from Victoria, Australia, where it was noted that estimates varied only slightly when the model used for final estimates was modified [19], and raises the question of whether it is necessary to adjust for additional variables just because they are available. In studies of VE, we are trying to estimate a causal effect [24]. Thus, it could be argued that in principle, the model used for calculating VE should be decided a priori and should not change between interim and final estimation. We acknowledge that important information on known confounders may be incomplete when calculating interim estimates. In such cases, one must be mindful of statistical biases, such as biases associated with complete-case analysis, where missing data may not be missing at random, or sparse data, both of which can result in a loss of precision and inflated estimates. However, the use of identical methods provides an assurance that heterogeneity between interim and final estimates is not due to methodological differences and permits focus on other possible causes, such as the change in virus circulation and waning VE. As a minimum, reports should include in their sensitivity analyses a comparison of interim and final estimates using an identical analytical approach.

The results of our regression should be interpreted with caution. Firstly, the number of pairs available was probably insufficient to detect important associations, and certainly a multivariate model containing all predictors would have been overparameterised. With only 33 observations in the model, a change in value of any one predictor could substantially change the size and importance of the association estimated. We were also unable to explore any interactions and it is likely that the effect of any of predictors explored would vary across levels of other predictors. Secondly, although a study may have reported a certain study period, this did not necessarily correspond to the date range of the observations used in the VE estimation. This was noted in the 2013 studies in Australia, but could also happen as a consequence of covariate specification. For example, specification of week as a categorical variable can lead to perfect prediction [43] and loss of observations from weeks without both a case and a non-case. Truncation of the data by the regression programme will result in the loss of observations and reported sample sizes may therefore be misleading. Thus, it is possible that some of the predictors specified in our regression models were incorrectly calculated. Finally, we calculated ΔVE based on each study's point estimate only. Although ΔVE was calculated with a confidence interval, our regression models focussed on the median only. We did not exclude studies with large confidence intervals because their width is tied to sample size, which was one of the factors we were interested in exploring.

Interim estimates provide an early snapshot of the influenza vaccine's effectiveness during a season, but their validity and reliability needs to be assured. End-of-season estimates have advantages over interim estimates in terms of gains in sample size and the longer time available to undertake the analysis. However, they typically take more than six months to publish, which is well beyond their usefulness for policy. Interim estimates are also more useful than final estimates for decision making around vaccine composition. The WHO's Global Influenza Surveillance and Response System meets twice a year to generate a recommendation for the composition of the seasonal vaccine. Since February 2013, interim and final VE estimates generated from surveillance data have been presented at this meeting [44]. The utility of VE estimates in strain composition is limited to scenarios where the virological and serological data are inconclusive, there are suitable, alternative candidates vaccine viruses, and VE suggests poor performance of the current component. However, because of their timeliness, it is the interim, not the final, VE estimates that are informative in such a scenario.

Given the potential utility of interim VE estimates and the variability between methods used to estimate interim and final VE, it would be worthwhile implementing the use of a standard model for estimating interim VE. Such a model might include a minimum set of known confounders in the statistical model, use of standardised inclusion criteria, and minimum sample size and/or standard error requirements. In conducting this review, we identified inconsistencies in the way data are reported, particularly case and vaccination status, highlighting the need for a standardised reporting template. The similarities observed between

interim and final estimates support the feasibility of generating and disseminating preliminary estimates of VE while virus circulation is ongoing.

Acknowledgements

Financial support: The WHO Collaborating Centre for Reference and Research on Influenza is funded by the Australian Government Department of Health. This work has received financial support from the Area of Excellence Scheme of the Hong Kong University Grants Committee (grant no. AoE/M-12/06) and the Harvard Center for Communicable Disease Dynamics from the National Institute of General Medical Sciences (grant no. U54 GM088558). The funding bodies were not involved in the collection, analysis, and interpretation of data, the writing of the article, or the decision to submit it for publication.

Conflict of interest

BJC has received research funding from MedImmune Inc. and Sanofi Pasteur for influenza vaccine efficacy and effectiveness studies, and has consulted for Crucell NV on pharmaceutical options for influenza control. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Authors' contributions

VKYL undertook data collection and analysis, interpretation of the data and participated in manuscript development and editing. BJC conceptualised the study, undertook interpretation of the data and participated in manuscript development and editing. SF participated in data collection, data analysis and interpretation; SGS conceptualised the study, undertook data collection and analysis, interpretation of the data and participated in manuscript development and editing.

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Systematic Review

Herd effect from influenza vaccination in non-healthcare settings: a systematic review of randomised controlled trials and observational studies

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Citation style for this article:
Mertz D, Fadel SA, Lam P, Tran D, Srigley JA, Asner SA, Science M, Kuster SP, Nemeth J, Johnstone J, Ortiz JR, Loeb M. Herd effect from influenza vaccination in non-healthcare settings: a systematic review of randomised controlled trials and observational studies. Euro Surveill. 2016;21(42):pii=30378. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.42.30378

Article submitted on 21 October 2015 / accepted on 23 April 2016 / published on 20 October 2016

Influenza vaccination programmes are assumed to have a herd effect and protect contacts of vaccinated persons from influenza virus infection. We searched MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Global Health and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to March 2014 for studies assessing the protective effect of influenza vaccination vs no vaccination on influenza virus infections in contacts. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using a random-effects model. Of 43,082 screened articles, nine randomised controlled trials (RCTs) and four observational studies were eligible. Among the RCTs, no statistically significant herd effect on the occurrence of influenza in contacts could be found (OR: 0.62; 95% CI: 0.34–1.12). The one RCT conducted in a community setting, however, showed a significant effect (OR: 0.39; 95% CI: 0.26–0.57), as did the observational studies (OR: 0.57; 95% CI: 0.43–0.77). We found only a few studies that quantified the herd effect of vaccination, all studies except one were conducted in children, and the overall evidence was graded as low. The evidence is too limited to conclude in what setting(s) a herd effect may or may not be achieved.

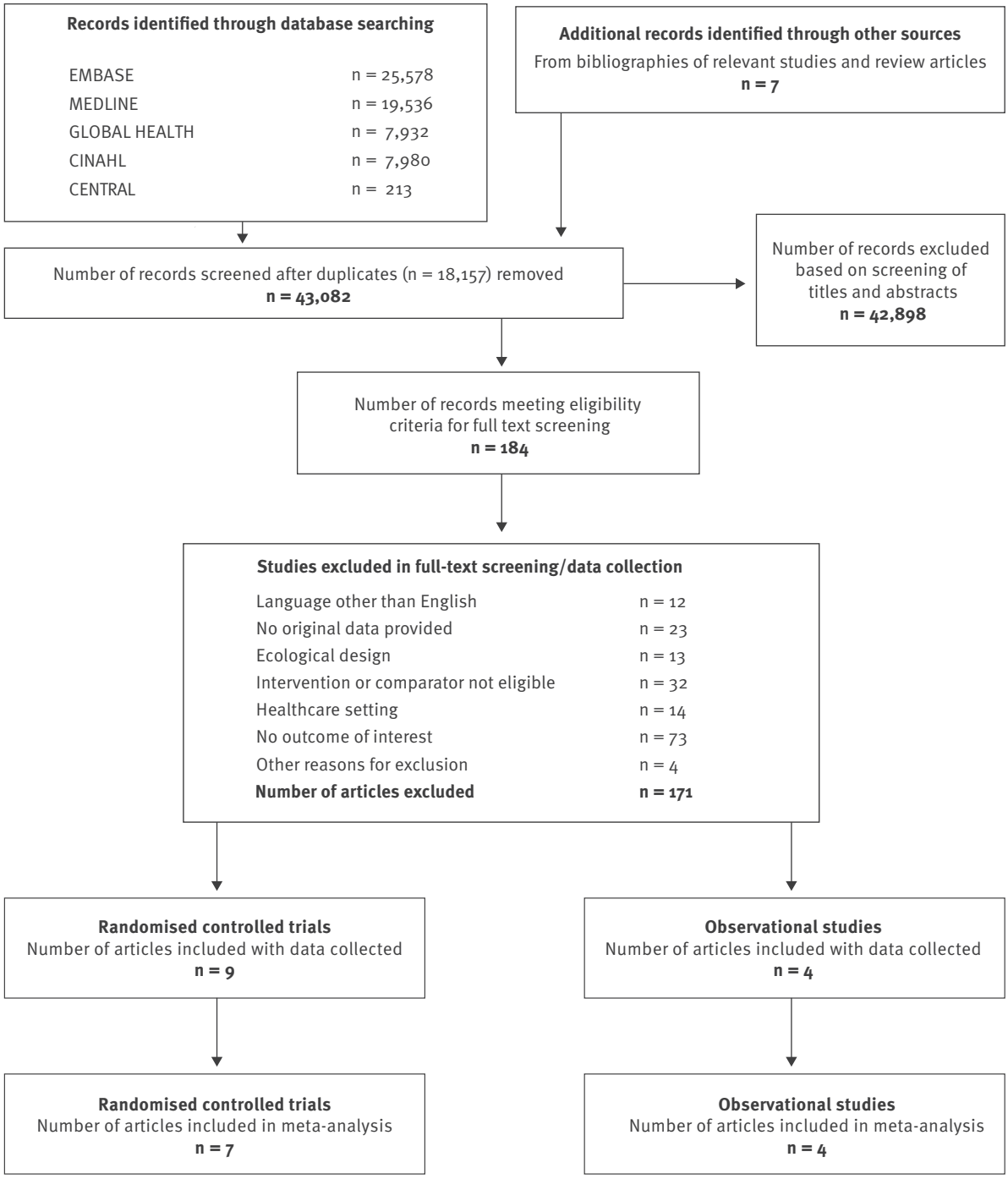
Introduction

Influenza is a major cause of morbidity and mortality worldwide [1-3]. Many countries recommend vaccination against influenza to prevent influenza infections, in particular for groups at high risk for complications [4-7]. Some high risk groups, such as young children and elderly persons (commonly defined as those above 65 years of age), experience decreased influenza vaccine effectiveness compared with healthy adults [8,9], complicating influenza prevention strategies. Moreover, because such groups represent a minority of the population at large, the population-wide impact of vaccination of risk groups may be limited [7,10].

Influenza vaccine modelling and ecological studies identifying benefits of herd effect have informed seasonal and pandemic influenza vaccine policies [10,11], herd effect being usually defined as the indirect protection of individuals susceptible to infection when a sufficient proportion of the population is immune to the pathogen. Vaccinating persons most likely to respond to the influenza vaccine and relying on herd effect to reduce the chance of exposure to influenza may protect unvaccinated or high-risk individuals. Herd effect may therefore mitigate the consequences of impaired vaccine response in some high-risk groups [12-14].

Figure 1

Flowchart of included and excluded randomised control trials and observational studies identified in a systematic review of herd effect from influenza vaccination in non-healthcare settings



[a] Two randomised control trials did not report all numerator and denominator data and therefore could not be included in the meta-analysis.

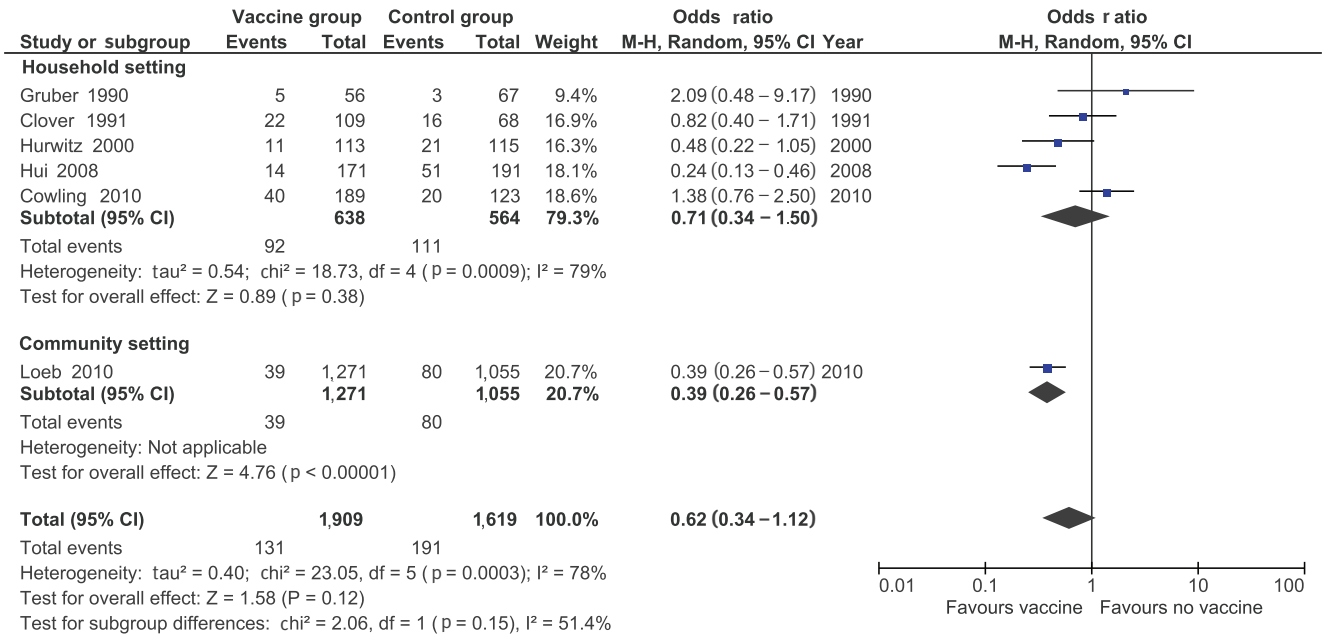
The purpose of this systematic review was to summarise the evidence on herd effect from influenza vaccination outside healthcare settings. These data may help to inform public health on influenza vaccine research and policy development.

Methods

All decisions regarding eligibility criteria, search strategy, study selection, assessment of risk for bias, explanation for heterogeneity, data collection and analysis were established before data collection. The protocol was registered with the international prospective register of systematic reviews (PROSPERO) [15]

Figure 2

Meta-analysis of seven included randomised controlled trials reporting on influenza infections in contacts of influenza vaccinated vs unvaccinated individuals in non-healthcare settings



CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel.

(CRD42014009401) and was reported in accordance with the PRISMA statement [16].

Eligibility criteria and outcomes assessed

Studies assessing the protective effect of influenza vaccination vs no influenza vaccination (either no vaccination, placebo or alternative vaccine) on contacts of any age group in a non-healthcare setting were eligible. The definition of contacts was broad and included anyone in the same community, school or household. Study designs included randomised controlled trials (RCTs) and observational studies with a non-influenza vaccine comparator group. For the latter study type, quasi-experimental (before–after) studies, cohort studies, case–control studies and cross-sectional studies were eligible. Ecological studies and modelling studies were excluded. We also excluded studies conducted within healthcare institutions, such as nursing homes and hospitals, and studies in languages other than English.

The primary outcome was influenza in non-vaccinated contacts exposed to persons vaccinated against influenza vs those not vaccinated. Influenza included both laboratory-confirmed influenza (defined by one or more of the following: nucleic acid amplification testing, viral culture, antigen detection, pre-/post-season or acute/convalescent serology) or non-laboratory-defined evidence. Non-laboratory-defined evidence required the presence of influenza-like illness (ILI, as per the study definition) within a period of time when laboratory-confirmed influenza was circulating in the study area. Secondary outcomes included hospitalisation, pneumonia and death.

Search strategy, study selection and data extraction

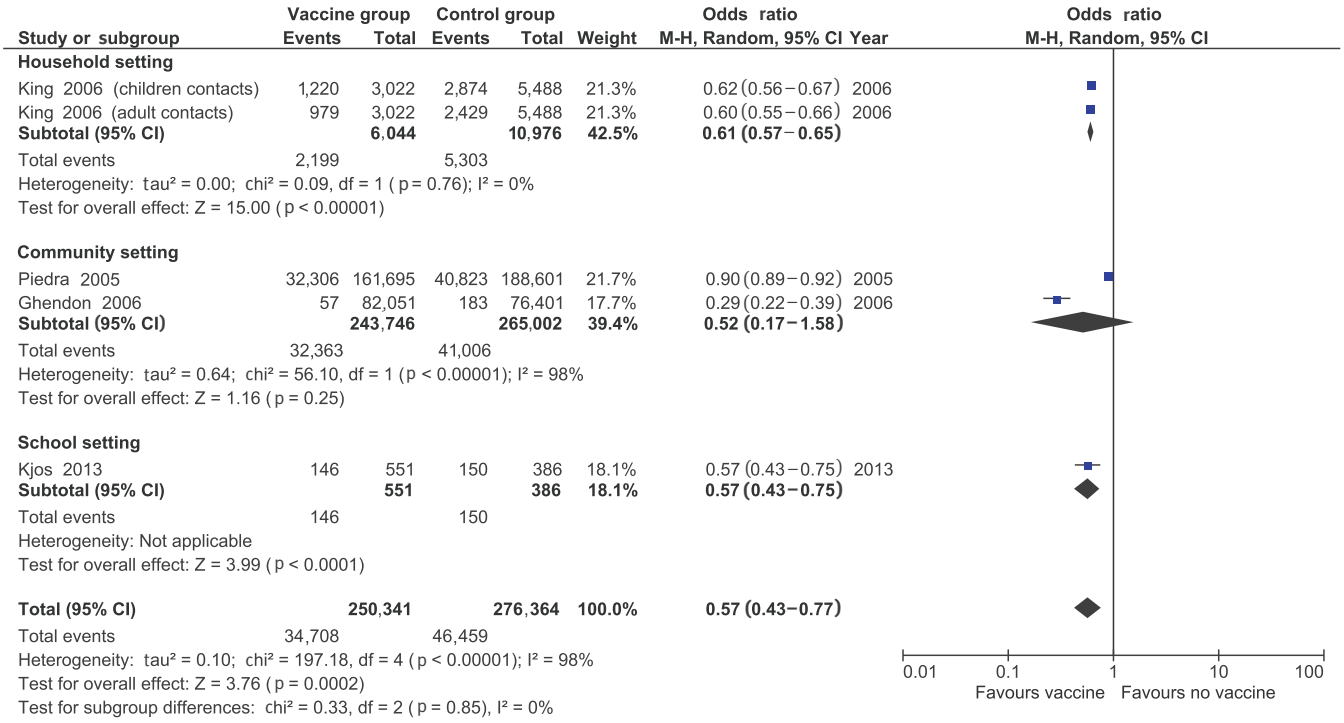
We searched MEDLINE (since 1950), EMBASE (since 1980), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (since 1982), Global Health (since 1973) and the Cochrane Central Register of Controlled Trials (CENTRAL) up to 7 March 2014. We also searched reference lists of identified articles and those of review articles for eligible studies.

Multiple teams of two reviewers independently screened titles and abstracts and, for studies identified by at least one reviewer to be of potential interest, full-text articles were screened. Data from eligible studies were extracted independently by two reviewers using a database. Any disagreement between the reviewers was resolved by consensus or arbitration by a third reviewer. We attempted to contact the first and corresponding author of the original article whenever potentially important information was missing.

Assessment of the risk of bias and of the overall quality of evidence was also conducted by two reviewers independently. We used the Cochrane Review Collaboration's tool [17] to assess the risk of bias for RCTs, and the Newcastle-Ottawa scale (NOS) [18] to assess the quality of observational studies. The overall quality of evidence was assessed using the grading of recommendations assessment, development and

Figure 3

Meta-analysis of four included observational studies reporting on influenza infections in contacts of influenza vaccinated vs unvaccinated patients in non-healthcare settings



CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel.

evaluation (GRADE) criteria [19]. Given the small number of studies, no formal assessment of the risk of publication bias could be conducted [20].

Data analysis

We performed meta-analyses of RCTs and observational studies separately. We calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) as summary estimates using random-effects modelling (using RevMan 5.3 [21]).

We planned a priori to conduct two subgroup analyses. First, we examined herd effect by study setting, comparing the effect in household studies, school-based studies (where the impact on non-vaccinated schoolchildren was measured) and community studies. For community studies, those comparing geographically defined areas with different vaccination strategies were considered. We hypothesised that the closer the contact was to vaccinated persons, the stronger the effect would be. Second, we assessed whether the herd effect of the vaccination in young children (up to 5 years of age) was different from that in older children and teenagers (5–18 years), and in adults.

Heterogeneity was evaluated using x2 and I2 statistics [22]. We considered a x2 of‹0.10 or an I2 statistic of›50% to reflect significant heterogeneity. If significant heterogeneity was found, we planned to perform additional subgroup analyses. Our a priori hypotheses to explain heterogeneity beyond the planned subgroup analyses were: laboratory-confirmed vs non-laboratory-confirmed influenza cases, and cases confirmed by nucleic acid amplification testing and viral culture vs cases confirmed by other laboratory methods. We also analysed the predominant circulating type/subtype (influenza A(H3N2) orA(H1N1), and influenza B).

Results

After removing 18,157 duplicates, we screened a total of 43,082 titles and abstracts, reviewed 184 full-text articles and included nine RCTs and four observational studies in our systematic review (Figure 1). Of the 13 RCTs and observational studies, seven were conducted in North America, and two each in Italy and Russia, and one in Malaysia and Hong Kong Special Administrative Region, respectively (Table 1).

Findings from randomised controlled trials

Of the nine RCTs included, seven were conducted in a household setting, one in a school and one in a community setting (Table 1). The intervention group consisted of children in all but one study. The total sample

Table 1

Study characteristics of studies included in a systematic review of herd effect arising from influenza vaccination in non-healthcare settings

First author [source]	Study location	Study period	Predominant influenza virus type or subtype	Intervention group	Setting	Number of vaccinees	Number of contactsa	Laboratory confirmation of influenza
Randomised control trials								
Gruber [29]	United States	1985/86	B	Children aged 3–18 years	Household	133	123	Yes
Clover [33]	United States	1986/87	A(H1N1)	Children aged 3–19 years	Household	194	177	Yes
Rudenko[b] [23]	Russia	1989–91	A(H3N2)	Children aged 7–14 years	School	11,071	Not available	No
Hurwitz [13]	United States	1996/97	Influenza B	Children aged 2–5 years	Household	127	228	No
Esposito [34]	Italy	2000/01	H1N1	Children aged 0.5–9 years	Household	127	349	No
Principi[b] [24]	Italy	2001/02	Influenza B	Children aged 0.5–5 years	Household	303	1,098	No
Hui [31]	Malaysia	2005	Not reported	Adults aged 18–64 years	Household	346	362	No
Cowling [30]	Hong Kong SAR	2008/09	A(H3N2)	Children aged 6–15 years	Household	119	312	Yes
Loeb [12]	Canada	2009	A(H3N2)	Children aged 1.5–15 years	Community	947	2,326	Yes
Observational studies (all cohort studies)								
Piedra [26]	United States	1998–2001	A(H3N2)	Children aged 1.5–18 years	Community	ca 40,000	350,296	No
Ghendon [25]	Russia	2001–03	A(H3N2)	Children aged 3–17 years	Community	87,221	158,451	No
King [14]	United States	2004/05	A(H3N2)	Children aged 5–14 years	Household	2,717	3,022[c]	No
Kjos [27]	United States	2010/11	A(H3N2)	Children, age unavailable	Elementary school (5–10 year-olds)	1,012	937	No

SAR: Special Administrative Region.

[a] The definition of contacts was broad and included anyone in the same community, school or household.

[b] The randomised control trial did not report all numerator and denominator data and therefore could not be included in the meta-analysis.

[c] In this study, the number of contacts was not reported. The number shown is the number of households (3,022) included in the analysis in intervention schools; there were 5,488 households in control schools).

size of contacts was 4,975, with one study –the largest– not reporting the total number of contacts [23].

A total of six RCTs provided data for the primary analysis comparing influenza-like illness in contacts of vaccinated vs unvaccinated persons (Figure 2). Overall, no statistically significant herd effect was found (OR: 0.62; 95% CI: 0.34–1.12), with significant statistical heterogeneity ($I^2 = 78\%$). Only one study, by Loeb et al., assessed contacts for influenza virus infection at community level: vaccination of children reduced the influenza infection rate for the community (OR: 0.39; 95% CI: 0.26–0.57) [12]. In contrast, there was no statistically significant effect in the subgroup of RCTs assessing household contacts (OR: 0.71; 95% CI: 0.34–1.50). No other differences between subgroups were found (p = 0.15 for subgroup differences). There was an 86% reduction in the odds of 5–17 year-old contacts of vaccinated individuals becoming infected as compared with contacts of unvaccinated individuals (OR: 0.14; 95% CI: 0.03–0.70), while no statistically significant differences were found when contacts were less than five years-old or adults. This difference across age groups was not statistically significant (p = 0.26).

Given the significant amount of statistical heterogeneity in the primary analyses, we conducted additional subgroup analyses. Subgrouping by whether or not influenza was laboratory confirmed did not significantly reduce statistical heterogeneity (p for subgroup differences was 0.06; $I^2 = 70{\cdot}8\%$), with a significant effect on influenza infections in contacts in RCTs with no laboratory confirmation (OR: 0.33; 95% CI: 0.17–0.64; $I^2 = 43\%$; n = 2) and no effect in RCTs using laboratory confirmation (OR: 0.87; 95% CI: 0.40–1.89; $I^2 = 81\%$; n = 4). Subgrouping by type of laboratory confirmation or by influenza virus type/subtype could not further explain the statistical heterogeneity.

Two RCTs provided data on hospitalisation of contacts, with no statistically significant difference seen (OR 0.83; 95% CI: 0.17–4.1). Only the RCT by Loeb et al. [12] reported on mortality and pneumonia in contacts, with no effect of the vaccine on either of these outcomes in

Table 2

Risk of bias in nine included randomised controlled trials reporting on influenza infections in contacts of influenza vaccinated vs unvaccinated individuals in non-healthcare settings

First author [source]	Risk of bias						
	Sequence generation	Allocation concealment	Blinding of patients	Blinding of healthcare provider	Blinding of outcome adjudicators	Incomplete data addressed	Selective reporting
Gruber [29]	NK	NK	Low	Low	Low	Low	Low
Clover [33]	NK	NK	Low	NK	Low	Low	Low
Rudenko [23]	NK	NK	Low	NK	Low	Low	Low
Hurwitz [13]	NK	NK	Low	NK	NK	NK	Low
Esposito [34]	Low	NK	Low	Low	Low	Low	Low
Principi [24]	NK	NK	High	High	NK	Low	Low
Hui [31]	NK	NK	High	High	Low	Low	Low
Cowling [30]	Low	NK	Low	Low	Low	Low	Low
Loeb [12]	Low	Low	Low	Low	Low	Low	Low
Percentage low risk of bias[a]	33	11	22	33	78	89	100

NK: not known, as either unclear or not reported.

[a] The percentage low risk of bias for each domain was calculated by dividing the number of randomised controlled trials (RCTs) at low risk of bias by the total number of RCTs (n = 9).

community contacts. Because of the limited number of studies reporting these outcomes, no subgroup analyses could be performed.

Two other RCTs demonstrated a herd effect of influenza vaccination, but the data provided in the publications did not report the numerators and denominators needed for our meta-analysis, and we were unable to obtain further data or information from the authors. Principi et al. concluded that influenza vaccination significantly reduced the direct and indirect influenza-related costs in healthy children and their unvaccinated family members [24]. Rudenko et al. found that the use of a live attenuated influenza vaccine was associated with a lower rate of influenza-like illness in school staff and non-vaccinated children when comparing schools that had vs schools that did not have an institutional influenza vaccination programme [23].

Findings from observational studies

A total of four observational studies were identified (Table 1). The intervention groups consisted of children in all the studies. Two studies were conducted in a community setting, and one each in the household and school setting. The total sample size of contacts was more than 500,000. The level of analysis was the household, and not the individual person, in one of the studies [14].

Meta-analysis showed a significant reduction of influenza illness in contacts of vaccinated patients (OR 0.57; 95% CI: 0.43–0.77) (Figure 3). Heterogeneity was very high ($I^2 = 98\%$); however, the direction of the effect was identical in all studies, only the amount of the effect size varied across studies. No age-specific data were available. When comparing the three study settings, no significant subgroup effect was found (p = 0.85 for subgroup differences). Given that all studies were lacking laboratory confirmation, and all were conducted during influenza A(H3N2)-predominant influenza seasons, no further subgroup analyses could be performed.

Only Ghendon et al. [25] reported on pneumonia, and found a significant reduction in contacts of influenza vaccinated patients (OR: 0.38; 95% CI: 0.30–0.50). Hospital admission was only reported in one study [14]; showing higher hospital admission rates in contacts of vaccinated persons (OR: 1.92; 95% CI: 1.17–3.14). There were no studies reporting on mortality endpoints.

Risk of bias and grading of evidence

The most common potential risks of bias in the included RCTs were lack of appropriate generation of the randomisation sequence, lack of allocation concealment and lack of blinding of patients and healthcare providers (Table 2). The RCTs scored a mean of 4.3 (range: 2–7) when assessed against seven domains.

The observational studies were awarded a mean of 6.25 points of a maximum of nine on the Newcastle-Ottawa scale, i.e. they were in a middle range of risk of bias (7 for Piedra et al. [26] and Ghendon et al. [25], 6 for Kjos [27] and 5 for King et al. [14]).

Applying GRADE criteria, we decreased the level of evidence for the primary outcome because of serious limitations in the quality of the studies (i.e. risk of bias in RCTs and observational design in non-RCTs) and inconsistency with significant statistical heterogeneity. Therefore, the overall level of evidence supporting a herd effect of influenza vaccines in preventing

influenza virus infection in contacts in non-healthcare settings was considered to be low.

Discussion

We found an overall low level of evidence supporting an indirect or herd effect of influenza vaccination in preventing influenza virus infection in vaccinated persons' contacts. In all but one study we identified, children were vaccinated. While observational studies showed a significant effect, the summary estimates from RCTs did not show a statistically significant effect. Few data were available on herd effect of influenza vaccination preventing hospital admission, pneumonia and death.

Point estimates of four of the six RCTs that reported on the prevention of influenza virus infection in contacts of vaccinated persons pointed towards a potential benefit of vaccination, but no significant effect was found overall. In an RCT by Loeb et al. involving Hutterite communities [12], vaccination of children in an enclosed community significantly reduced influenza infections in contacts. The uptake of influenza vaccination in that RCT, which had a low risk of bias in all domains assessed, was ca 83%. The RCT confirmed the findings from an observational study by Monto et al. that found a similar effect at the population level by vaccinating schoolchildren in one community in Michigan, United States [28]. However, no strong evidence was found in a household setting [29,30]. A possible explanation is that vaccinating only one child per household, as done in the study by Cowling et al., may have been insufficient to have a measurable effect [30]. In the study by Gruber et al., in contrast, all children three years of age and older received the vaccine, but again there was no effect on household contacts. However, the study was limited by the low attack rate and was therefore likely underpowered [29]. Furthermore, the authors argued that the non-vaccinated contacts were likely to be immune to the predominant influenza B strain that circulated in previous years. It is therefore unclear what key factors are needed to achieve a herd effect in the household, particularly given the importance of the broader community as a potential source of infection of the non-vaccinated. Notably, the only study that investigated herd effect of influenza vaccination of adults did find a statistically significant effect [31]. However, this study had significant methodological limitations, including lack of blinding. It should be acknowledged that two studies that both reported a significant herd effect of influenza vaccination could not be included in the meta-analysis because of the lack of detail reported in the published article, and no additional information could be obtained from the authors [23,24].

In contrast to our findings from RCTs, we found evidence of herd effect following influenza vaccination in observational studies, which was corroborated by a recent observational study by Pannaraj et al., who found that unvaccinated children may be protected in schools with vaccination rates approaching 50% [32].

Our extensive screening of over 40,000 studies found very few studies that were designed to measure herd effects of influenza vaccination. One reason for this may be the cost of community influenza surveillance as well as the cost of clinical trials. While modelling studies demonstrate that herd immunity can be achieved by vaccinating young children [10], we are surprised by how few studies with laboratory-confirmed influenza as an outcome support the modelling literature. Moreover, there are very limited data available to estimate herd effect of influenza vaccination programmes. As indirect benefits would increase the cost-effectiveness of these programmes, such data would be highly valuable for vaccine advisory bodies and decision makers evaluating whether to initiate or expand influenza vaccine programmes.

Our review highlights the need for more rigorous studies using laboratory-confirmed influenza virus infections as an outcome. Data on a herd effect on outcomes other than influenza virus infection were sparse, due either to outcomes not being measured or to inadequate power to detect a difference. Although the effect of influenza vaccination on mortality has been demonstrated through modelling [10], high-quality studies would better support the ability of influenza vaccination to prevent hospital admissions, pneumonia or death in contacts through herd effect.

Strengths of this systematic review include a systematic, protocol-driven and comprehensive review with extensive literature search strategy including RCTs and observational studies. In addition, rigorous assessment of eligibility ensured high reliability of the results. All subgroup analyses were defined a priori. A rigorous use of the GRADE approach ensured a transparent and comprehensive approach to evaluate overall quality of the studies. An important limitation, however, was the presence of statistically significant heterogeneity that could not be explained by a priori defined subgroup analyses. We assume that differences in study designs and clinical heterogeneity in terms of study population, outcome assessment and health service resources may have resulted in differences in outcomes that could not be explained by the intervention per se. Furthermore, differences in vaccine effectiveness in case of mismatch and existing immunity if the circulating strain had been dominant for several seasons may have introduced heterogeneity across the included studies. Another major limitation was the potential risk of bias in the majority of studies, which further decreased the level of evidence. Finally, all but one study vaccinated children, thus, no generalisation to vaccination programmes in adults can be made, and the evidence is too limited to conclude in what setting(s) a significant herd effect may or may not be achieved.

In summary, herd effects are assumed with influenza vaccine programmes, but there are few studies that quantify the herd effect of vaccination. We found low-level evidence supporting a herd effect of vaccination

on influenza virus infection in contacts of vaccinated persons. Further rigorous studies are needed in order to better understand under which circumstances vaccination may prevent influenza and its complications in contacts.

Acknowledgements

This work was funded by a grant from the World Health Organization. JRO is a staff member of the World Health Organization. The author alone is responsible for the views expressed in this publication, which do not necessarily represent the decisions, policy or views of the World Health Organization.

DM is a recipient of a Research Early Career Award from Hamilton Health Sciences Foundation (Jack Hirsh Fellowship). The authors would like to acknowledge the contributions of the United States Centers for Disease Control and Prevention (CDC), which provides financial support to the World Health Organization Initiative for Vaccine Research (U50 CK000431).

Conflict of interest

SPK received travel grants from Pfizer and Novartis. DT received grant funding from GSK Canada. SAF, PL, JS, SAA, MS, JN, JJ, JRO, DM, ML: none declared.

Authors' contributions

Conception and design (DM, JRO, ML), data acquisition (SAF, PL, DT, JS, SAA, MS, SPK, JN, JJ), interpretation of data (DM, JRO, ML), drafting the manuscript (DM, ML), revising manuscript for important intellectual content (SAF, PL, DT, JS, SAA, MS, SPK, JN, JJ, JRO). All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Early influenza vaccine effectiveness results 2015-16: I-MOVE multicentre case-control study

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Citation style for this article:
Kissling E, Valenciano M. Early influenza vaccine effectiveness results 2015-16: I-MOVE multicentre case-control study. Euro Surveill. 2016;21(6):pii=30134. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.6.30134

Article published on 11 February 2016

On 11 February 2016, the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) published the 2015–16 interim vaccine effectiveness (VE) estimates against influenza from a multi-centre case control study in 10 study sites: Germany, France, Hungary, Ireland, Italy, Poland, Portugal, Spain, Sweden and the Netherlands, on their website [1].

Adjusted VE interim results against any influenza among all ages were at 46.3% (95% confidence interval (CI): 4.9–69.7%) and 45.2% (95% CI: -12.5–73.3%) among the 18–64 year olds. Among those aged 65 years and older, there were only 14 influenza cases in the study. The adjusted VE against influenza A(H1N1) pdm09 was at 44.2% (95% CI: -3.1–69.8%) among all ages and thus lower compared with end of season estimates published in previous years (55.5% in 2010–11, 50.4% in 2012–13; 47.5% in 2013–14, 54.2% in 2014–15).

Early season influenza VE was measured against medically-attended laboratory-confirmed influenza from week 41/2015 to week 3/2016 using a test-negative design as described in the I-MOVE generic protocol [2] and in the I-MOVE multicentre case–control publications [3]. Some 1,933 influenza-like illness patients among whom 348 were positive to influenza were included: four cases of influenza A not subtyped, 246 A(H1N1)pdm09, 21 A(H3N2), and 77 influenza B cases. Among the 37 influenza B cases where lineage was available, 36 (97.3%) were of the Victoria lineage, a lineage not included in the trivalent vaccine.

For this interim analysis, there was no information on genetic characterisation of the viruses. The recently published European Centre for Disease Prevention and Control risk assessment [4] reported that all A(H1N1) pdm09 viruses characterised in the European Union up to week three belonged to the 6B subgroup.

The interim estimates should be interpreted with caution. The 2015–16 season started late in the participating countries and the sample size for these interim estimates is low, resulting in low precision. The final estimates will be available at the end of the influenza season.

Read more here.

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TQ-AD-16-004-EN-C

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ISSN 1025 496X