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Importance of timely monitoring of seasonal influenza vaccine effectiveness

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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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Zika virus detection in cerebrospinal fluid from two patients with encephalopathy, Martinique, February 2016

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We report two cases of encephalopathy (one with seizures, one with electroencephalogram changes) in patients with Zika virus infection. The cases occurred on Martinique in February 2016, during the Zika virus outbreak. Awareness of the various neurological complications of Zika virus infection is needed for patients living in areas affected by Zika virus infections or for travellers to these areas.

We describe two cases of encephalopathy in patients with Zika virus infection detected on Martinique in February 2016. In both patients, Zika virus RNA was detected in their cerebrospinal fluid (CSF), plasma, and urine.

Description of the cases

Case 1

At the end of February 2016, two months after the detection of the first Zika virus-positive cases on Martinique, a previously healthy young adult was admitted to the University Hospital of Martinique, after having experienced an episode of convulsive seizures that occurred six hours after the onset of a dengue-like syndrome (fever, arthralgia, asthenia and headache). Upon initial clinical evaluation, the patient was febrile, with a low level of consciousness (Glasgow coma scale (GCS) 9) and no neurological focal signs. After direct intravenous injection of clonazepam (one milligram), the patient recovered to a normal level of consciousness (GCS 15). The patient was hospitalised for three days, then returned back home with symptomatic treatment of acetaminophen and codeine against headache and arthralgia. One week later, clinical assessment found no new neurological symptoms, but headache and arthralgia persisted for 45 days.

Brain magnetic resonance imaging (MRI) and video-electroencephalogram (EEG) performed on day 5 after onset of neurological symptoms, were normal.

Laboratory findings at onset of neurological symptoms showed normal blood count and a sterile CSF with no white blood cells (norm: ‹10/ml), and 0.20 g/L protein (norm: 0.15–0.40). The glycorachia/glycaemia ratio was normal (norm: ›0.5).

The patient was screened for the common aetiologies of viral encephalitis: test results for herpes simplex virus, varicella zoster virus and cytomegalovirus (CMV) by PCR were negative in CSF. Direct detection in CSF of enterovirus, dengue virus (DENV) and chikungunya virus by real-time RT-PCR were negative. Serological tests for HIV, CMV and venereal research disease laboratory (VDRL) were negative. Serology for toxoplasmosis was positive in IgG. Direct detection of *Leptospira* sp. in plasma by PCR was negative. *Cryptococcus* sp. antigenemia in serum was negative. Detection of Zika virus by real-time RT-PCR in plasma, cerebrospinal fluid and urine were positive (Table).

Case 2

In the last week of February 2016, a patient in their late 70s was brought to the University Hospital of Martinique by their family who reported symptoms including acute mental confusion, speech disorder,

Table

Clinical, neuroimaging, electroencephalography and microbiological findings in two cases of encephalopathy associated with Zika virus infection, Martinique, February 2016

Clinical features upon hospital admission		Case 1	Case 2
Body temperature		40 °C	37.2 °C
Headache		Yes	Yes
Conjunctivitis		No	Yes
Whole body maculopapular rash		No	No
Arthralgia		Yes	Yes
Myalgia		Yes	Yes
Altered mental status		Yes	Yes
Seizures		Yes	No
Focal neurologic findings		No	Yes
Additional tests			
CSF WBC count ≥ 5/mm³		No	No
Neuroimaging (magnetic resonance imaging)		Normal (day 5)	Leukoaraiosis (day 1)
Electroencephalography		Normal (day 5)	Focal activity (day 1)
Microorganism	**Detection**		
Mycoplasma spp.	Serology	IgM: 3,606.74 IU/mL (norm: <950 IU/mL) IgG: 2,412.94 IU/mL (norm: <1,200 IU/mL)	IgM: 193.58 IU/mL (norm: <950 IU/mL) IgG: 478.24 IU/mL (norm: <1,200 IU/mL)
Cryptococcus spp.	Antigen (serum)	Negative	Negative
Epstein–Barr virus	Serology	IgM anti-VCA: 0.11 IU/mL (norm: <0.9 IU/mL) IgG anti-VCA: 2.78 IU/mL (norm: <0.9 IU/mL) IgG anti-EBNA: 1.23 IU/mL (norm: <0.9 IU/mL)	IgM anti-VCA: 0.06 IU/mL (norm: <0.9 IU/mL) IgG anti-VCA: 2.82 IU/mL (norm: <0.9 IU/mL) IgG anti-EBNA: 3.09 IU/mL (norm: <0.9 IU/mL)
Human immunodeficiency virus	Serology	Ratio: 0.30 (norm: <0.9)	Ratio: 0.30 (norm: <0.9)
Herpes simplex virus	CSF (PCR)	Negative	Negative
Cytomegalovirus	Serology	Ratio IgM<0.7 (norm: <0.7) Ratio IgG<0.15 (norm: <0.5)	Ratio IgM: 0.20 (norm: <0.7) Ratio IgG: 0.163 (norm: <0.5)
	CSF (PCR)	Negative	Negative
Varicella zoster virus	CSF (PCR)	Negative	Negative
Enterovirus, including poliovirus	CSF (real-time RT-PCR)	Negative	Negative
Dengue virus	Serology	Ratio IgM: 4.37 (norm: <0.9) Ratio IgG: 5.65 (norm: <1.8)	Ratio IgM: 0.46 (norm: <0.9) Ratio IgG: 4.29 (norm: <1.8)
	Plasma (real-time RT-PCR)	Negative	Negative
	CSF (real-time RT-PCR)	Negative	Negative
Chikungunya virus	Serology	Ratio IgM: 0.239 (norm: <0.8) Ratio IgG: 5.403 (norm: <0.8)	Ratio IgM: 0.284 (norm: <0.8) Ratio IgG: 5.161 (norm: <0.8)
	Plasma (real-time RT-PCR)	Negative	Negative
	CSF (real-time RT-PCR)	Negative	Negative
Zika virus	Plasma (real-time RT-PCR)	Positive	Positive
	CSF (real-time RT-PCR)	Positive	Positive
	Urine (real-time RT-PCR)	Positive	Positive

CSF: cerebrospinal fluid; EBNA: Epstein–Barr nuclear antigen; IU: international unit; VCA: viral capsid antigen; WBC: white blood cell count.

and right facial palsy, which had started three hours before hospital admission. Upon initial clinical evaluation the patient was afebrile and aphasic; conjunctivitis, bilateral hands oedema, and peripheral arthritis were present. Facial palsy was not noticed upon clinical examination. Aphasia resolved spontaneously 45 minutes after the first clinical evaluation.

Upon initial clinical evaluation, brain MRI was only consistent with leukoaraiosis, and EEG revealed an unequivocal asymmetry with abnormal left frontotemporal slow waves. These waves were consistent with the presence of a pathological process, but had no specific pattern. The EEG performed one week later showed almost complete regression of the slow waves.

The analysis of CSF showed a protein count of 0.40 g/L and a white blood cell count of 2/mL. The glycorachia/glycaemia ratio was normal. PCR for common aetiologies of encephalitis was negative. Detection of Zika virus by real-time RT-PCR in plasma, CSF and urine gave a positive result (Table).

Discussion

Since December 2015, an outbreak of Zika virus infections has been ongoing on Martinique, a French West Indies island of 390,000 inhabitants. It spread rapidly, with more than 15,400 cases estimated as at 31 March 2016 [1]. Zika virus infection is usually benign, when symptomatic. The disease resembles uncomplicated dengue fever and lasts for four to seven days and is self-limiting. In Martinique, *Aedes aegypti* is assumed to be the unique vector of flaviviruses. Recent Zika virus epidemics in French Polynesia, Brazil, Central America and the French West Indies have been associated with neurological complications [2].

Over the past five years, there have been between one and three patients with encephalitis hospitalised monthly in the University Hospital of Martinique.

In this report, we present two cases of encephalopathy fulfilling the diagnostic criteria of the Consensus Statement of the International Encephalitis Consortium [3]. Based on the laboratory findings, we consider these cases as Zika virus-associated. In keeping with neurological findings in other arbovirus infections, the presentations were of non-specific nature; the spectrum of arboviral neurological disease may even lead to ischemic stroke [4]. Moreover, in arbovirus-related neurological disorders, imaging findings may be normal and different EEG abnormalities can be seen [5]. Zika virus is known as a neurotropic microorganism [6], however, both structural imaging and EEG can be normal in acute infection [5]. The mechanism of flavivirus infection of the central nervous system (CNS) is not clearly understood and pathology depends on the virus. Neurological involvement can be caused by direct damage of the nerve by the virus but also be immune mediated. For example, dengue virus can infect human astrocytes and brain microvascular endothelial cells, whereas West Nile virus infection could lead to a blood-brain barrier dysfunction [7].

Awareness of the wide spectrum of neurological symptoms of Zika virus infection is needed for patients living in, or travelling to areas affected by Zika virus infections. Knowledge of the pathophysiology of Zika virus infection and the reasons behind its predilection for the CNS is needed to design treatment strategies to mitigate significant morbidity.

Neuro-Zika Working Group

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Conflict of interest

None declared.

Authors' contributions

BR, KA, FN, SA, PH, AC wrote the manuscript.

BR, PH, AS, KA, YB, SG and the Neuro-Zika Working Group took part in the clinical management of the patients.

FN, RC collaborated in molecular biology techniques.

LF, RC, FN collaborated on the serological techniques.

All authors participated in the outbreak investigation.

All authors read and approved the final manuscript.

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High specificity of a novel Zika virus ELISA in European patients after exposure to different flaviviruses

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The current Zika virus (ZIKV) epidemic in the Americas caused an increase in diagnostic requests in European countries. Here we demonstrate high specificity of the Euroimmun anti-ZIKV IgG and IgM ELISA tests using putative cross-reacting sera of European patients with antibodies against tick-borne encephalitis virus, dengue virus, yellow fever virus and hepatitis C virus. This test may aid in counselling European travellers returning from regions where ZIKV is endemic.

Current interim guidelines in Europe for symptomatic patients and pregnant women returning from regions endemic for Zika virus (ZIKV) recommend serological testing from day 5 after onset of disease [1]. However, serological diagnosis remains challenging because of extensive cross-reactivity between antibodies against flaviviruses [2]. In Europe, tick-borne encephalitis virus (TBEV) is the most relevant flavivirus and might cause diagnostic problems in sera from European travellers returning from ZIKV endemic regions. Recently, an ELISA based on ZIKV NS1-antigen has been developed and shown to diagnose ZIKV infections [3]. Here, we evaluated the specificity of this novel ZIKV ELISA using sera from European patients with laboratory-confirmed and putative cross-reacting antibodies against different flaviviruses and other acute viral infections.

Human serum samples

Samples with a high potential of causing cross-reactions in serological flavivirus assays were chosen: acute TBEV infection, acute dengue virus infection, recently boostered tick-borne encephalitis (TBE) vaccination with high levels of TBEV IgG, recent yellow fever vaccination and viraemic hepatitis C virus (HCV) infection. TBEV, dengue and HCV sera contained laboratory-confirmed high levels of IgG antibodies against these viruses. All 26 dengue virus antibody-positive sera were from German travellers. Of these, 16 acute dengue sera were positive for anti-dengue virus IgM and for dengue virus NS1 antigen and were positive in dengue virus RT-PCR. Follow-up sera were available from 10 patients after laboratory-confirmed acute dengue infection and were anti-dengue virus IgG-positive only.

For evaluation of the ZIKV IgM ELISA, we used in addition sera from patients with polyclonal IgM stimulation (acute Eppstein-Barr virus (EBV) infection (n = 22), acute *Mycoplasma pneumoniae* infection (n = 8), primary cytomegalovirus (CMV) infection in pregnancy (n = 9), and primary human immunodeficiency virus (HIV) infection (n = 13)). All sera were submitted to the Institute of Virology, Freiburg, for routine diagnostics and were stored at −20 °C in an anonymised biobank before testing.

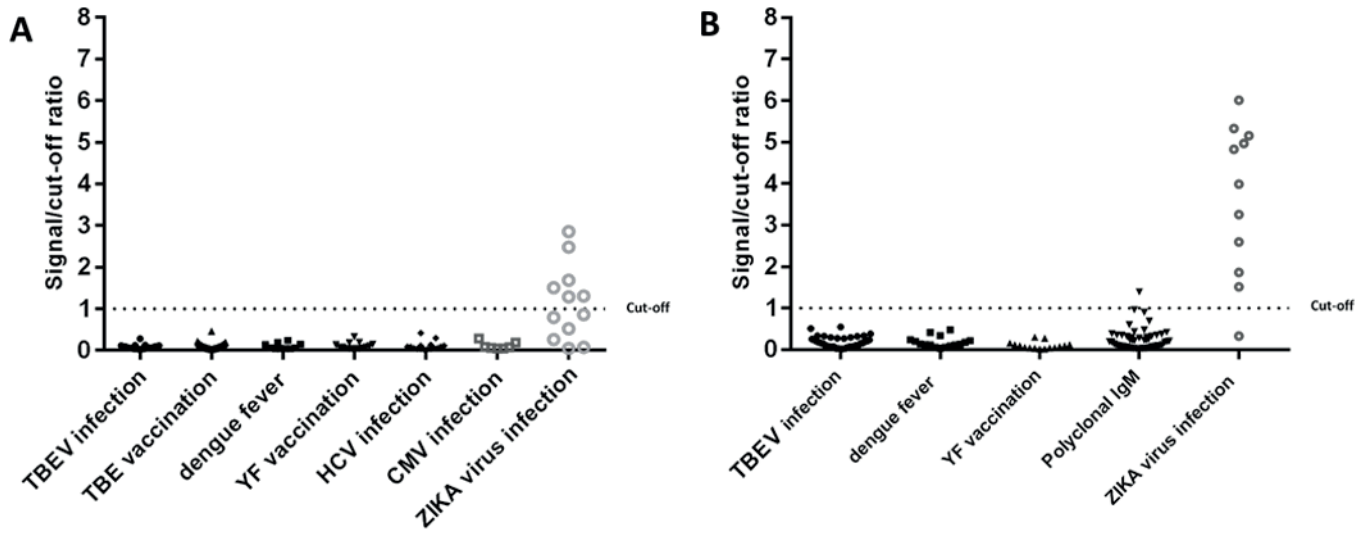
To confirm the capability of the ZIKV ELISA to detect ZIKV antibodies, we analysed 10 patient samples from Brazil with acute or recent ZIKV infection. For laboratory confirmation of ZIKV infection in these patients we used an indirect immunofluorescent assay (IIF) as described [4]. IIF titres for anti-ZIKV IgM ranged from 1:1,280 to 1:›20,480, and for anti-ZIKV IgG from 1:320 to 1:›20,480. All 10 Brazilian sera had previously tested negative at the Bernhard Nocht Institute for Tropical Medicine for IgM and IgG against dengue virus, and negative for dengue virus NS1 antigen. In addition, two serum samples from a German tourist returning from Brazil with ZIKV infection were available to us. The first sample had been taken on day 3 after symptom onset in 2015, a second sample one year later. The first serum sample tested ZIKV RT-PCR-negative, but a saliva sample from the same day (three days after symptom onset) tested RT-PCR-positive, confirming the diagnosis of acute ZIKV infection.

Laboratory investigation

We used the Euroimmun ZIKV ELISA (Euroimmun, Lübeck, Germany) according to the manufacturer's recommendation. In brief, sera were diluted 1:101 in

Figure 1

Anti-ZIKV signal/cut-off ratios in different cohorts, determined by the ZIKV ELISA for (A) IgG and (B) IgM



CMV: cytomegalovirus; ELISA: enzyme-linked immunosorbent assay; HCV: hepatitis C virus; TBE: tick-borne encephalitis; TBEV: tick-borne encephalitis virus; YF: yellow fever; ZIKV: Zika virus.

Table 1

Serological test results for different cohorts using the ZIKV IgG ELISA

Cohort	Number of samples	Origin of infection	Result ZIKV IgG ELISA		
			Negative	Borderline	Positive
TBEV infection[a]	21	Germany	21	0	0
TBE vaccination[a]	52	Germany	52	0	0
Dengue virus infection[b]	10	Endemic regions	10	0	0
Yellow fever vaccination[c]	15	Germany	15	0	0
HCV infection[d]	16	Germany	16	0	0
Acute ZIKV infection[e]	11	Brazil	5	1	5
Past ZIKV infection[e]	1	Brazil	0	0	1

ELISA: enzyme-linked immunosorbent assay; HCV: hepatitis C virus; IgG; immunoglobulin G; IgM: immunoglobulin M; TBE: tick-borne encephalitis; TBEV: tick-borne encephalitis virus; ZIKV: Zika virus.

[a] TBEV IgM and IgG detection was performed with Serion classic ELISA TBE IgM and IgG quant assay (Virion/Serion, Würzburg, Germany).

[b] Confirmed with SD dengue NS1+Ab Combo (MT Promedt Consulting, St. Ingbert, Germany).

[c] Documented yellow fever vaccination.

[d] Detection of HCV antibodies was done using the Architect Anti-HCV assay (Abbott, Wiesbaden, Germany).

[e] Detection of ZIKV antibodies was done using IIF as described in the text.

sample buffer and incubated at 37°C for 60 min in a microplate well. Before IgM detection, sera were pre-incubated with sample buffer containing rheumatoid factor absorbent as recommended. Further steps were done as described elsewhere, and the optical density (OD) was measured in a BEP III system (Siemens Healthcare, Munich, Germany). A signal-to-cut-off ratio was calculated, and values ‹0,8 were regarded as negative, ≥0,8 to ‹1,1 as borderline, and ≥ 1,1 as positive.

ZIKV IgG ELISA

The ZIKV IgG ELISA was positive or borderline in six of 10 samples from Brazilian patients with clinical and laboratory-confirmed acute ZIKV infection (Table 1). The first sample of a German tourist tested ZIKV IgG-negative, but was ZIKV IgG-positive one year after acute ZIKV infection (past ZIKV infection, Table 1). No IgG ELISA reactivity above the threshold for positivity was seen in any of the potentially cross-reacting samples (Figure).

Table 2

Serological test results for different cohorts using the ZIKV IgM ELISA

			Result ZIKV IgM ELISA		
Cohort	Number of samples	Origin of infection	Negative	Borderline	Positive
TBEV infection[a]	38	Germany	38	0	0
Dengue virus infection[b]	16	Endemic regions	16	0	0
Yellow fever vaccination[c]	15	Germany	15	0	0
Polyclonal IgM	52	Germany	49	2	1
ZIKV infection	11	Brazil	1[d]	0	10

ELISA: enzyme-linked immunosorbent assay; IgG; immunoglobulin G; IgM: immunoglobulin M; TBEV: tick-borne encephalitis virus; ZIKV: Zika virus.

[a] TBEV IgM and IgG detections were performed with Serion classic ELISA TBE IgM and IgG quant assay (Virion/Serion, Würzburg, Germany).

[b] SD dengue NS1+Ab Combo (MT Promedt Consulting, St. Ingbert, Germany), RT-PCR was done using the RealStar dengue RT-PCR kit (Altona Diagnostics, Hamburg, Germany).

[c] Documented yellow fever vaccination.

[d] German tourist day 3 after symptom onset.

Overall, specificity of the ZIKV IgG ELISA was 100% (95% confidence interval: 95.9–100.0).

ZIKV IgM ELISA

All 10 sera from the Brazilian patients tested positive using the ZIKV IgM ELISA (Table 2). One sample from a German patient with a polyclonal IgM (reactivity in TBE virus IgM and EBV IgM assay) was positive in the ZIKV IgM ELISA. Two samples from patients with acute EBV infection showed borderline results in the ZIKV IgM ELISA. None of the samples from patients with acute TBE virus infection, dengue fever, or recent yellow fever vaccination showed reactivity above the threshold for positivity, demonstrating the high specificity of the Euroimmun ZIKV IgM ELISA (Figure).

Discussion

There is now evidence of a causal relationship between ZIKV infection during pregnancy and severe birth defects [5,6]. In Europe, laboratory diagnosis should be performed in pregnant women returning from ZIKV endemic regions [7]. Follow-up ultrasound examinations and counselling are recommended for those with markers of recent ZIKV infection. In light of the possible severe consequences for pregnant women and their fetus, it is imperative that serological testing is highly specific.

The high degree of cross-reactivity of currently available serological flavivirus assays is a major issue of concern [8,9]. In Europe, TBEV is the most relevant flavivirus and TBE vaccination coverage ranges from 20% (southern Germany) to more than 80% (Austria) [10]. Of note, yellow fever vaccination is recommended for travellers to Brazil and other South American countries. In recent years, an estimated 300,000 to 350,000 travellers from Germany, Austria and Switzerland have visited Brazil and thus are currently at risk of having acquired ZIKV infection. Our results provide strong evidence that the Euroimmun ZIKV IgG ELISA is a specific tool and can be safely used to rule out ZIKV infection even on the background of pre-existing antibodies to different flaviviruses and other acute infections. Importantly, this also applies to dengue-positive sera as shown on a limited number of dengue virus antibody-containing sera from European travellers. However, more data is needed from regions where dengue is endemic, e.g. South America. Of note, IgM and IgG antibodies against ZIKV were unambiguously identified in positive patient sera. This ZIKV ELISA allows easy, specific and high-throughput testing of suspected cases. However, neutralising antibody detection assays remain the gold standard for diagnosis and evaluation of tests, although they are restricted to specialist laboratories and allow low to medium throughput only [11]. Clearly, further studies are needed to determine the sensitivity of the assay using a larger set of samples taken at different time points of the infection. Alternatively, a limited number of other commercial ZIKV serology tests are on the market or will be available in short time, but extensive validation data is pending to date.

The ZIKV ELISA may primarily aid gynaecologists and clinicians in travel medicine in the diagnosis of recent ZIKV infection and public health officials in developing guidelines on diagnostic algorithms for ZIKV infection. Interestingly, in the acute phase, testing of saliva samples using RT-PCR can increase the detection rate as seen in our German tourist and as reported elsewhere [12]. Of note, acute EBV can cause false positive IgM reactions in the ZIKV IgM ELISA, owing to a polyclonal stimulation of B cells, which makes it necessary to rule out acute EBV infection in ambiguous cases [13]. This was also seen in our results.

All sera with high antibody titres were retrieved from our local biobank. The availability of well-defined sera to validate novel assays is important for emerging pathogens [14]. Thus, collecting and sharing of sera by (national) laboratories should be promoted to strengthen preparedness for emerging diseases.

Conclusion

We provide evidence that the Euroimmun ELISA is highly specific and reliable when used for patients with previous flavivirus exposure or vaccination. This also applies to TBEV, which is of particular relevance for European patients. This diagnostic tool will aid in counselling patients, pregnant women and travellers after returning from ZIKV-endemic regions to Europe.

Conflict of interest

None declared.

Authors' contributions

DH, JSC, and MP wrote the manuscript. IH performed the laboratory investigation, JSC provided ZIKV patient sera. All authors participated in the investigation. All authors read and approved the final manuscript.

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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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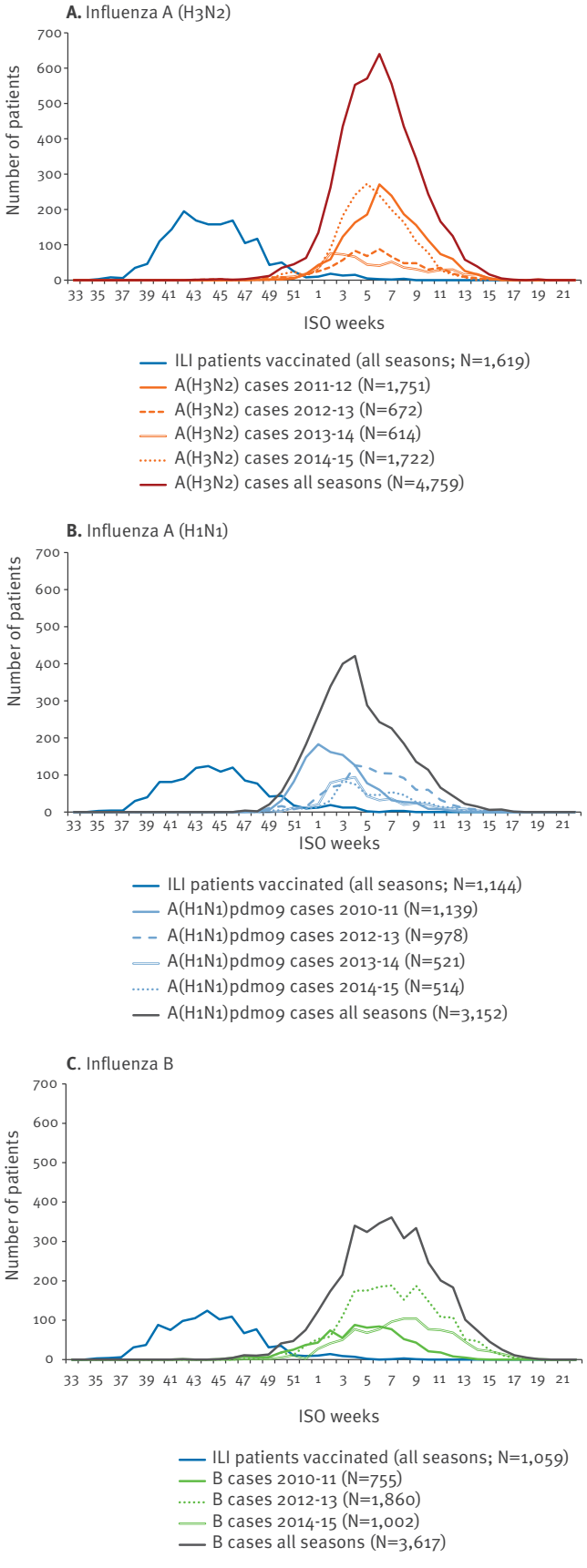
Since the 2008/9 influenza season, the I-MOVE multicentre case–control study measures influenza vaccine effectiveness (VE) against medically-attended influenza-like-illness (ILI) laboratory confirmed as influenza. In 2011/12, European studies reported a decline in VE against influenza A(H3N2) within 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.

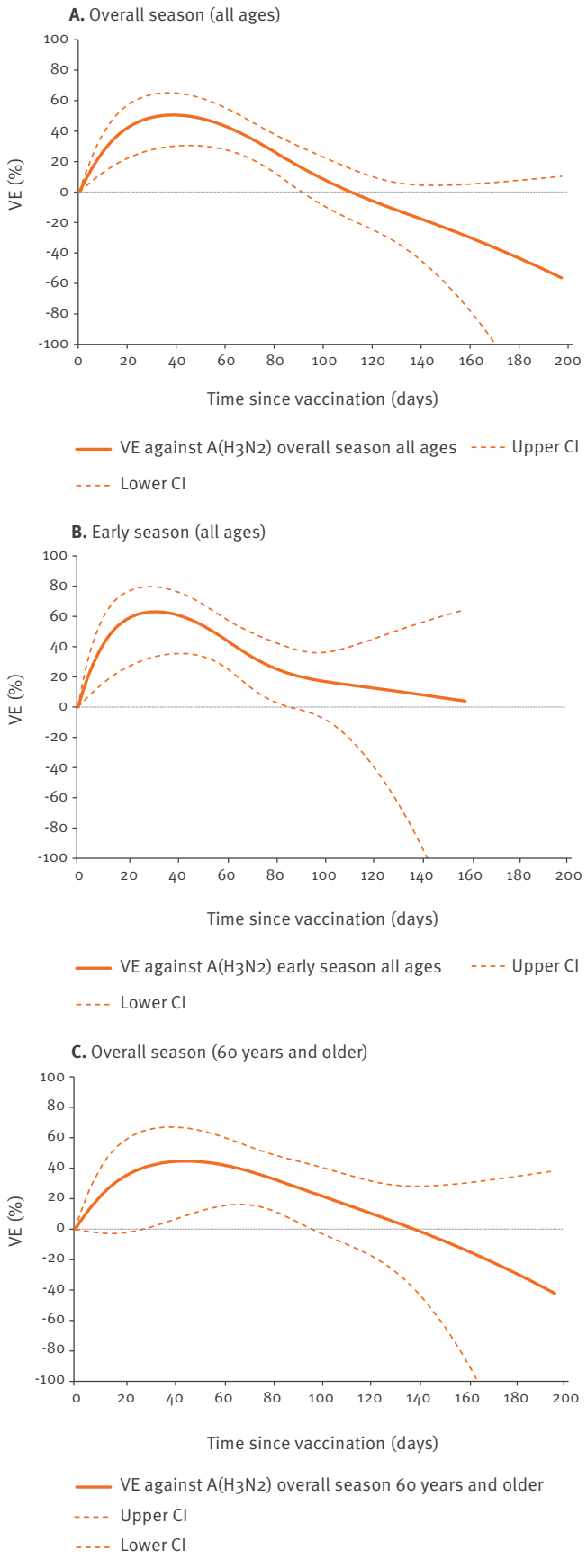
Methods

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.

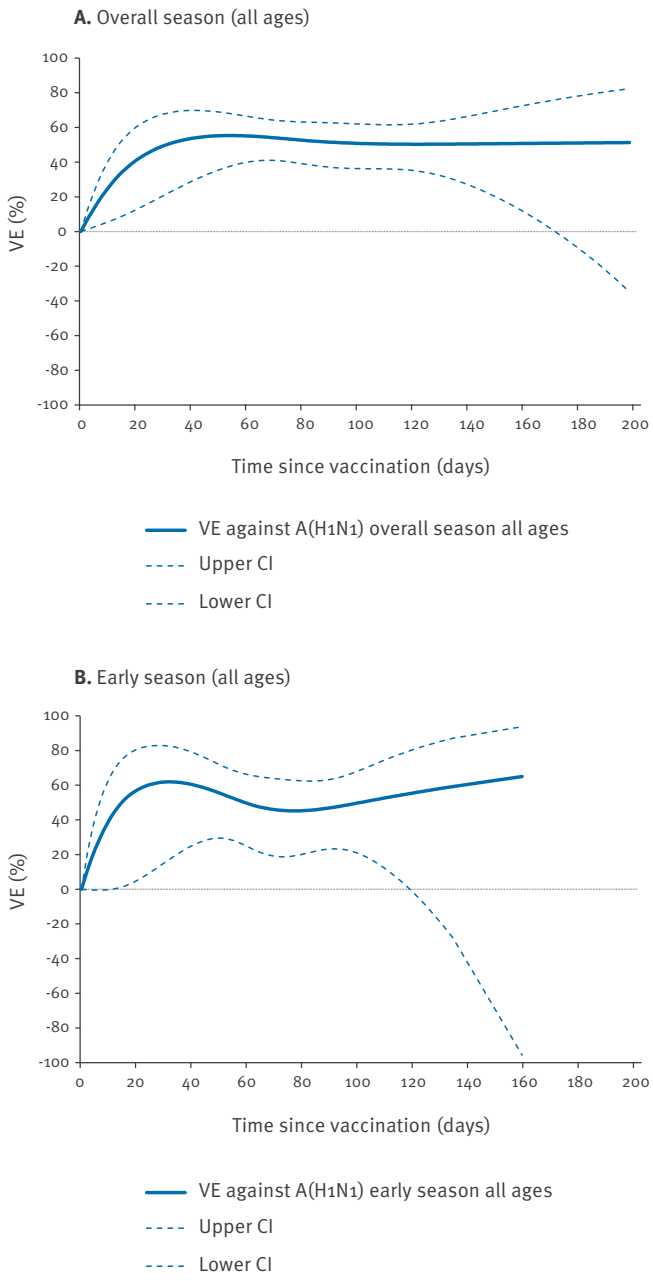
We defined patients as vaccinated if they had received at least one dose of influenza vaccine more than 14 days before symptom onset. Patients receiving a dose of vaccine < 15 days before symptom onset and receiving no dose of vaccine were defined as unvaccinated.

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.

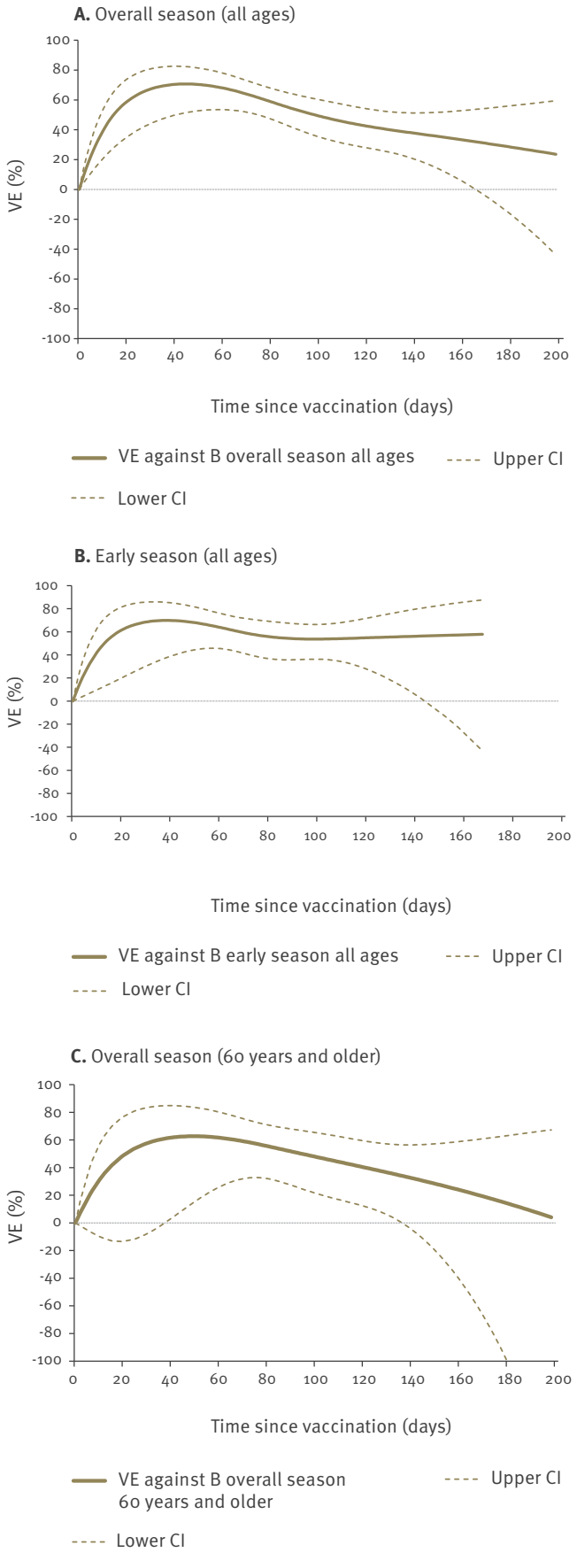
Among the 2,224 vaccinated patients (9.6%), the name of the vaccine product was available for 1,909 (85.8%). All vaccines were inactivated, with 52.4% (n=1,000) of patients vaccinated with egg-derived split virion, 24.8% (n=474) with egg-derived subunit, 21.1% (n=403) with adjuvanted and 1.7% (n=32) 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.

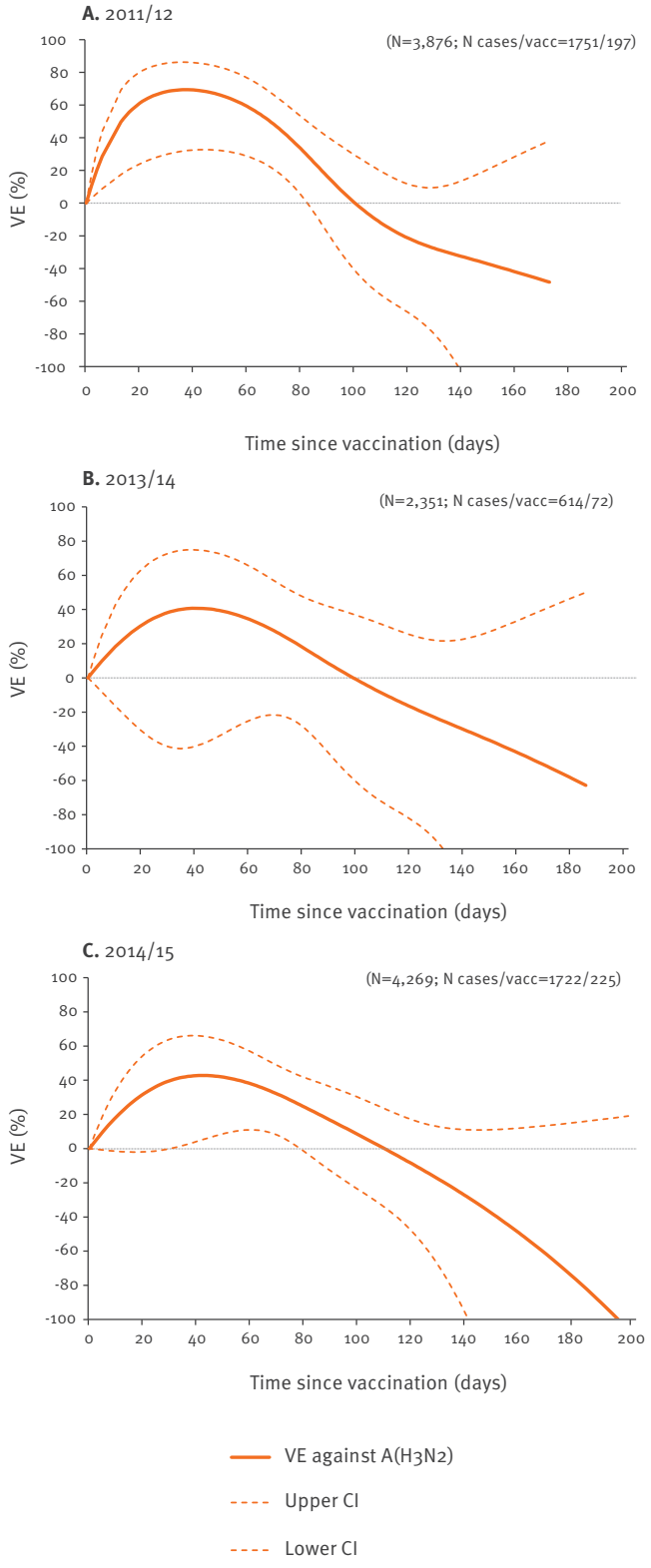
The VE estimates by season were between 47.5% and 53.8% against A(H1N1)pdm09 resulting in a psAVE of 52.2%. There was no statistical heterogeneity between season-specific VE estimates (I^2 index 0.0%). Among those aged 60 years and older, the psAVE was 54.0% with an I^2 of 39.4% (Table 1).

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.

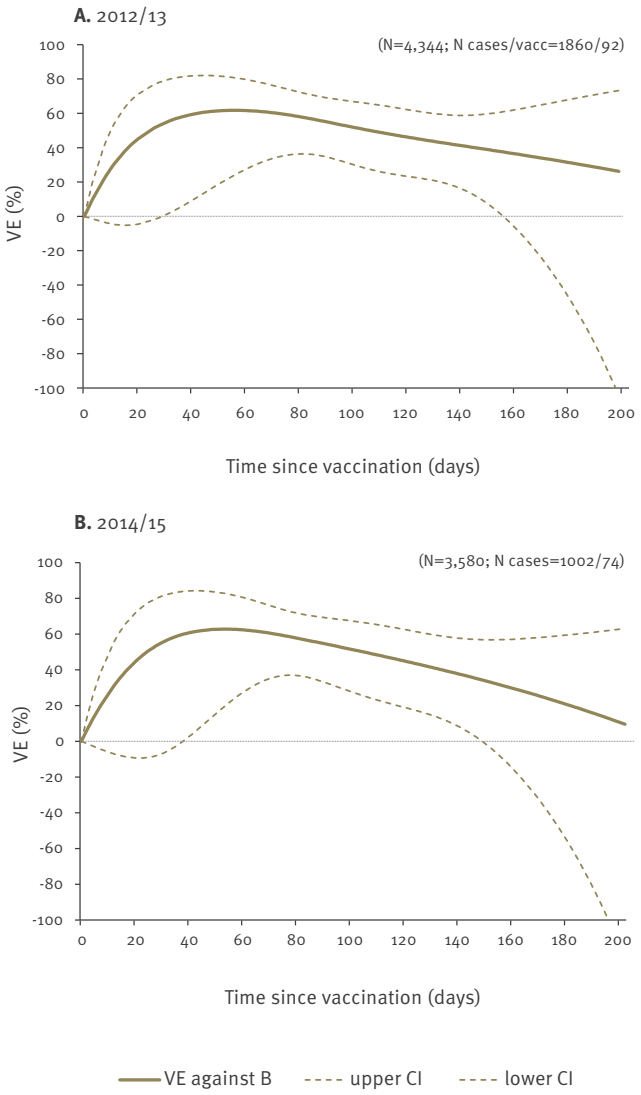
Among those aged 60 years and older the psAVE against influenza B increased initially to 62.7% at day 49. It then declined to 4.1% at day 197.

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 VE against A(H3N2) or B

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

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 countries. Some individuals were vaccinated

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.

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.

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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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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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Pandemic vaccination strategies and influenza severe outcomes during the influenza A(H1N1)pdm09 pandemic and the post-pandemic influenza season: the Nordic experience

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During the 2009/10 influenza A(H1N1)pdm09 pandemic, the five Nordic countries adopted different approaches to pandemic vaccination. We compared pandemic vaccination strategies and severe influenza outcomes, in seasons 2009/10 and 2010/11 in these countries with similar influenza surveillance systems. We calculated the cumulative pandemic vaccination coverage in 2009/10 and cumulative incidence rates of laboratory confirmed A(H1N1)pdm09 infections, intensive care unit (ICU) admissions and deaths in 2009/10 and 2010/11. We estimated incidence risk ratios (IRR) in a Poisson regression model to compare those indicators between Denmark and the other countries. The vaccination coverage was lower in Denmark (6.1%) compared with Finland (48.2%), Iceland (44.1%), Norway (41.3%) and Sweden (60.0%). In 2009/10 Denmark had a similar cumulative incidence of A(H1N1)pdm09 ICU admissions and deaths compared with the other countries. In 2010/11 Denmark had a significantly higher cumulative incidence of A(H1N1)pdm09 ICU admissions (IRR: 2.4; 95% confidence interval (CI): 1.9–3.0) and deaths (IRR: 8.3; 95% CI: 5.1–13.5). Compared with Denmark, the other countries had higher pandemic vaccination coverage and experienced less A(H1N1)pdm09-related severe outcomes in 2010/11. Pandemic vaccination may have had an impact on severe influenza outcomes in the post-pandemic season. Surveillance of severe outcomes may be used to compare the impact of influenza between seasons and support different vaccination strategies.

Background

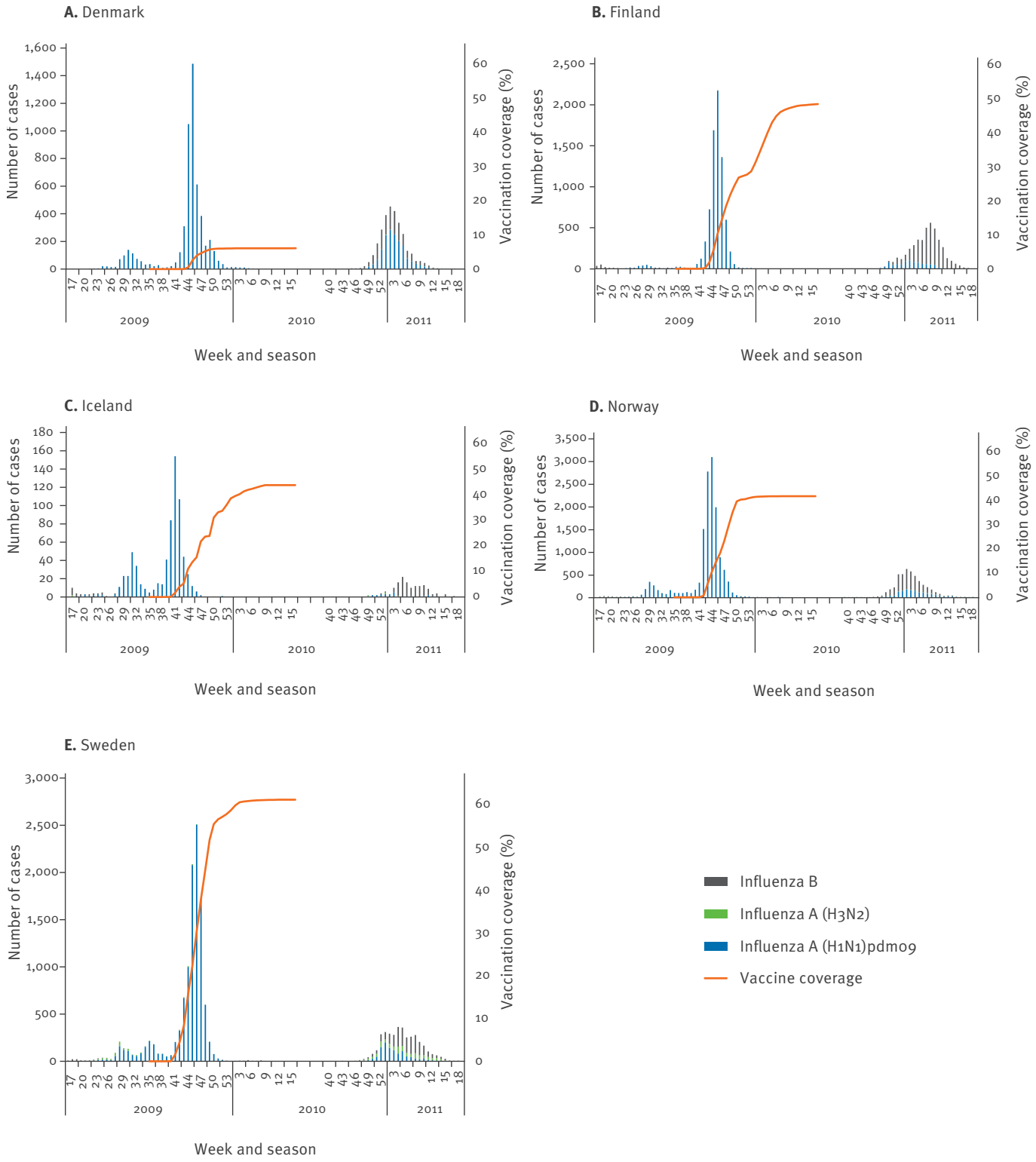
In 2009, the World Health Organization recommended adjuvanted vaccines in response to the A(H1N1)pdm09 pandemic [1]. The five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) all used the monovalent AS03-adjuvanted pandemic influenza vaccine Pandemrix [2].

Several studies have estimated the effectiveness of the pandemic vaccine in preventing A(H1N1)pdm09 during the pandemic [3-7]. In addition, others have shown an effect against influenza A(H1N1)pdm09 in the post-pandemic season as well as persistence of antibodies in children at sub-national or national level [8-10]. It is therefore possible that a high pandemic vaccination coverage in a population would affect the distribution of circulating influenza subtypes and disease severity for a longer period after a pandemic. We are not aware of any studies that assessed how different pandemic vaccination strategies may have affected the influenza type/subtype distribution and the epidemiology of severe influenza in the post-pandemic season.

The five Nordic countries are comparable with regards to demography [11], universal and equal access to the healthcare system [12], and healthcare practices [13]. They also had similar surveillance systems during the pandemic [14-18]. Furthermore, all Nordic countries established or strengthened their surveillance of severe influenza cases through reporting of influenza

Figure 1

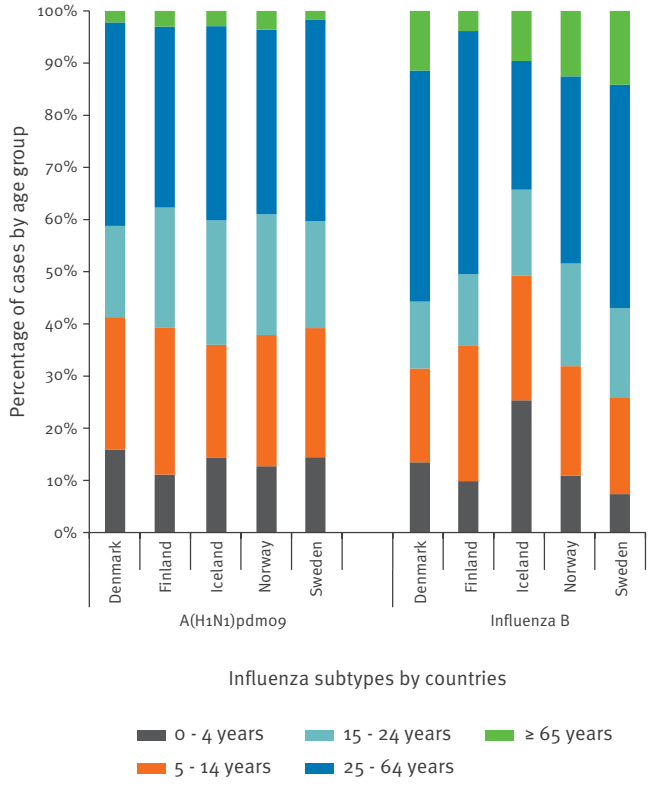
Cumulative pandemic vaccination coverage and laboratory-confirmed influenza A(H1N1)pdm09, influenza B and A(H3N2) cases by week, influenza seasons 2009/10 and 2010/11, Denmark, Finland, Iceland, Norway and Sweden



Finland data refers to A(H1N1)pdm09 (in blue), not subtyped influenza A (in green) and influenza B (grey)

Figure 2

Influenza A(H1N1)pdm09 and influenza B distribution by age group and country, Denmark, Finland, Iceland, Norway and Sweden, influenza seasons 2009/10 and 2010/11



Distribution of influenza A(H3N2) not shown due to small number of cases.

A(H1N1)pdm09-related intensive care unit (ICU) admissions and deaths in the 2009/10 and 2010/11 influenza seasons [14-19].

The objective of this study was to compare the five Nordic countries in terms of circulating influenza types/subtypes and severe outcomes of influenza in the seasons 2009/10 and 2010/11 in relation to the pandemic vaccination coverage and the timing of vaccination.

Methods

Study design and period

We conducted an ecological study where we retrospectively compared aggregated data from two consecutive influenza seasons: the pandemic season 2009/10 (week 17 2009 – week 17 2010) and the post-pandemic season 2010/11 (week 40 2010 – week 20 2011) in the five Nordic countries.

Data collection

The national public health institutes of the five countries provided information about the recommendations for (i) pandemic vaccination such as target groups, beginning of vaccination campaigns and number of doses indicated, and (ii) virological sampling of patients with suspected influenza i.e. target groups and sampling protocols.

Each of the countries uses national unique personal identification numbers which enables the linkage of different national health registers but only aggregated data were provided for the current study. The public health institutes provided data on laboratory-confirmed influenza cases by type/subtype, influenza A(H1N1)pdm09-related ICU admissions, influenza-related deaths, and the percentage of samples that tested positive for influenza from laboratories as well as the number of persons vaccinated. These numerator data were stratified by week of the influenza season. We obtained population denominators from Eurostat [11].

Definitions

The weekly and cumulative pandemic vaccination coverages were calculated based on the individual registration of vaccinated individuals from each country by dividing the number of vaccinated individuals by the country population.

Notification of confirmed influenza A(H1N1)pdm09 cases was mandatory in Finland, Iceland, Norway and Sweden [15,16,20]. In Denmark, notification was only mandatory in the 2009/10 season [17]. In season 2010/11, information on laboratory-confirmed cases was obtained from a newly established national database comprising all influenza test results [21]. Therefore, all laboratories in each of the Nordic countries were included in the reporting. The weekly and cumulative incidences of laboratory-confirmed influenza A(H1N1)pdm09, A(H3N2) and influenza B cases were calculated by dividing the number of cases by 100,000 country population for each season.

We defined severe outcomes of influenza A(H1N1)pdm09 as influenza-related ICU admissions and deaths. During the pandemic, the surveillance of the A(H1N1)pdm09 cases included all ICUs in each of the five Nordic countries. The testing recommendations at hospital level were to swab all patients hospitalised with influenza-like illness symptoms or lower airway infections during the pandemic [22-24]. The A(H1N1)pdm09 testing recommendations did not change during the 2010/11 season [25,26]. The cumulative incidences of influenza-related ICU admissions were calculated by dividing the number of patients admitted to the ICUs and diagnosed with influenza A(H1N1)pdm09 by 100,000 country population for each season.

The number of influenza-related deaths was identified by obtaining information from the civil registry on date of death among the A(H1N1)pdm09 confirmed cases in Denmark, Finland and Sweden. Deaths that occurred within 30 days after the last influenza positive sample were considered. Each case was then reviewed and validated by national medical officers. In Iceland and

Table 1

Timing of recommendations of pandemic vaccination to target groups in Denmark, Finland, Iceland, Norway and Sweden, during the 2009/10 influenza A(H1N1)pdm09 pandemic

Country	Target groups recommended by week			
	Underlying conditions[a]	Healthcare workers and key community professions[b]	Pregnant women	Healthy population ≥ 6 months of age
Denmark	Week 43: < 65 years of age Week 49: ≥ 65 years of age	Week 43	Week 45: 2nd and 3rd trimester	Not recommended
Finland	Week 45	Week 43	Week 44	Week 46: 6–35 months Week 47: 3–24 years
Iceland	Week 45	Week 42–43	Week 45	Week 48
Norway	Week 38	Week 38	Week 38	Week 43
Sweden	Week 42	Week 42	Week 42	Week 44–46[c]

[a] The countries included one or more of the following: pulmonary diseases, cardiovascular diseases, haemoglobinopathies, diabetes type 1 or 2, congenital or acquired immune deficiencies, neuromuscular conditions, chronic liver or renal failure, other diagnoses which pose a serious health risk in conjunction with influenza.

[b] The countries included one or more of the following: police, firemen, firefighters, etc.

[c] According to regional planning.

Norway, a case-based reporting of all deaths associated with A(H1N1)pdm09 was in place from hospitals and healthcare facilities. The influenza-related mortality was calculated by dividing the number of influenza confirmed deaths by 100,000 country population for each season.

Data analysis

The pandemic vaccination coverage during the pandemic season was compared between the five countries.

In each influenza season, we compared the country incidence of laboratory-confirmed influenza by type/subtype, A(H1N1)pdm09-related ICU-admissions and the A(H1N1)pdm09-related mortality. These indicators were also compared by age groups.

A Poisson regression model was used to compare the indicators between the Nordic countries for each influenza season. We estimated the incidence risk ratio (IRR) and corresponding 95% confidence intervals (CI) for Denmark vs the other four countries, using the other countries as a reference. The statistical analysis was carried out using Stata 12 software.

Ethical considerations

The study only included aggregated surveillance data without personal identifiers. Therefore, no ethical approval was needed according to each country's national regulations.

Results

Vaccination recommendations and coverage during the pandemic

In 2009, all countries recommended pandemic vaccination for healthcare workers, pregnant women and individuals aged six months or more with one or more chronic medical condition which increased the risk for influenza-related complications, from week 38 to 45 (Table 1). In addition, Finland, Iceland, Norway and Sweden but not Denmark, recommended vaccination to the whole population aged six months of age or more from week 43 to 48.

Finland, Iceland and Norway recommended one vaccine dose for individuals aged 10 years or more. Sweden and Denmark started by recommending two doses and changed to one dose in week 46 and 49 of 2009, respectively, for individuals aged above 10 years old with a functioning immune system. Denmark, Iceland, Norway and Sweden recommended two doses for children below 10 years of age, while Finland recommended only one dose in this age group. Norway changed the recommendation to one dose in the same age group in week 51.

The Nordic countries started to administer the vaccine in September in Finland and in October 2009 in Denmark, Iceland, Norway and Sweden. The cumulative coverage of administered vaccines by the end of the pandemic was significantly lower in Denmark, 6.1%, compared with Finland, 48.2%, Iceland 44.1%, Norway 41.3% and Sweden 60.0%. The percentage of vaccinated children below five years of age in Denmark was 0.3%, in Finland 73%, in Iceland 43% and in Norway 47%; data for Sweden was not available. The percentage of vaccinated population above 65 years of age in Denmark was 18%, compared with 49% in Finland, 59% in Iceland and 53% in Norway. In the 2010/11 season, the trivalent seasonal influenza vaccine (TIV) included A(H1N1)pdm09 as one of the three viruses, and this vaccine type was used in all five countries; Pandemrix was not in use during this season.

Table 2

Rates of laboratory-confirmed influenza A(H1N1)pdm09 and ICU admissions and deaths related to influenza A(H1N1)pdm09, influenza seasons 2009/10 and 2010/11, Denmark, Finland, Iceland, Norway and Sweden

Country	Laboratory-confirmed A(H1N1)pdm09				A(H1N1)pdm09-related ICU admissions				A(H1N1)pdm09-related deaths			
	Season 2009/10		Season 2010/11		Season 2009/10		Season 2010/11		Season 2009/10		Season 2010/11	
	n	Incidence n/100,000 (95%CI)	n	Incidence n/100,000 (95% CI)	n	Incidence n/100,000 (95%CI)	n	Incidence n/100,000 (95%CI)	n	Incidence n/100,000 (95%CI)	n	Incidence n/100,000 (95%CI)
Denmark	5,497	99.3 (96.7–101.9)	1,671	30.2 (28.7–31.6)	93	1.6 (1.3–2.0)	106	1.9 (1.5–2.3)	30	0.5 (0.3–0.7)	53	0.9 (0.7–1.2)
Finland	7,666	143.2 (140.0–146.4)	877	16.3 (15.3–17.5)	133	2.4 (2.0–2.9)	52	0.9 (0.7–1.2)	44	0.8 (0.6–0.1)	13	0.2 (0.1–0.4)
Iceland	696	219.1 (203.4–236.0)	24	7.5 (5.0–11.3)	17	5.3 (3.3–8.6)	1	0.3 (0.04–2.2)	2	0.6 (0.1–2.5)	0	0
Norway	13,707	282.1 (277.4–286.9)	1,365	28.0 (26.6–29.6)	147	3.0 (2.5–3.5)	43	0.8 (0.6–1.1)	32	0.6 (0.4–0.9)	1	0.02 (0.00–0.1)
Sweden	11,002	117.7 (115.6–120.0)	1,125	12.0 (11.3–12.7)	116	1.2 (1.0–1.4)	64	0.6 (0.5–0.8)	36	0.3 (0.2–0.5)	9	0.09 (0.05–0.2)
	p value<0.001		p value<0.001		p value<0.001		p value<0.001		p value<0.05		p value<0.001	

n: number; CI: confidence interval; ICU: intensive care unit.
p values were calculated through Poisson regression.

Incidence of laboratory-confirmed influenza and recommendations for testing

The weekly incidence of reported laboratory confirmed A(H1N1)pdm09 cases peaked in week 42 of 2009 in Iceland, week 45 in Norway, week 46 in Denmark and Finland and week 47 in Sweden. At the peak in each country, the cumulative pandemic vaccine coverage was below 10% for all countries except Sweden, where it was 30% (Figure 1).

During the pandemic, the influenza A(H1N1)pdm09 virus was predominant among laboratory-confirmed influenza cases compared with influenza B and A(H3N2) viruses in the five Nordic countries. In Finland there was only information on A(H1N1)pdm09, but not on other subtypes of influenza A (Figure 1). In the 2010/11 season, influenza B was predominant in Finland, Iceland, Norway and Sweden, contrary to Denmark where A(H1N1)pdm09 was predominant (Figure 1).

In 2009/10, the incidence of laboratory-confirmed A(H1N1)pdm09 influenza was significantly lower in Denmark compared with the other four Nordic countries (IRR: 0.6; 95% CI: 0.6–0.6; p value<0.001) (Table 2, 3). In 2010/11, the cumulative incidence of A(H1N1)pdm09 influenza was lower in all countries compared with 2009/10 (Table 2). In contrast to the previous season, it was significantly higher in Denmark than in the other four Nordic countries (IRR: 1.8; 95% CI: 1.7–1.9; p value<0.001) (Table 2, 3).

Recommended target groups for testing were similar in the five countries. The swabbing of cases and their contacts started in week 17 in Sweden, week 18 in Denmark, Finland and Norway and week 21 in Iceland. The swabbing recommendations changed to only risk group patients or close contacts of confirmed cases in all countries from week 29 in Denmark and Sweden, week 30 in Norway, week 31 in Finland and week 33 in Iceland (Table 4).

The number of positive A(H1N1)pdm09 cases among the total tested was available in Iceland (19.6%), Norway (21.4%) and Sweden (23.6%) in the 2009/10 season. In season 2010/11, the percentage of positives decreased in the three countries and was 3.5% in Iceland, 6.4% in Norway and 6.2% in Sweden.

Influenza A(H1N1)pdm09-related ICU admissions and mortality

During the pandemic season, the incidence of A(H1N1)pdm09-related ICU admissions was statistically significantly lower in Denmark and Sweden than in Finland, Iceland and Norway (Table 2). In the 2010/11 season, the incidence was lower than during the pandemic in all countries except for Denmark. In 2010/11, Denmark had a higher incidence of A(H1N1)pdm09-related ICU admissions (IRR: 2.4; 95% CI: 1.9–3.0; p value<0.001) compared with the other Nordic countries (Table 2,3).

In the 2009/10 season, there were no statistically significant differences between the influenza A(H1N1)pdm09-related mortality in the five countries (Table 2,3). In 2010/11, the influenza A(H1N1)pdm09-related mortality was significantly higher in Denmark compared

Table 3

Rates of laboratory-confirmed influenza A(H1N1)pdm09 and influenza B cases, ICU admissions and mortality due to influenza A(H1N1)pdm09 in Denmark compared with the other countries (Finland, Iceland, Norway and Sweden), influenza seasons 2009/10 and 2010/11

Rates of laboratory-confirmed influenza A(H1N1)pdm09 and influenza B cases, A(H1N1)pdm09 ICU admissions and mortality	Season 2009/10						Season 2010/11					
	Denmark				Other countries[a]		Denmark				Other countries[a]	
	Incidence n/100,000	95% CI	IRR[b] (95% CI)	p value	Incidence n/100,000	95% CI	Incidence /100,000	95% CI	IRR[b]	p value	Incidence /100,000	95% CI
A(H1N1)pdm09	99.3	96.7–102.0	0.6 (0.6–0.6)	p<0.001	166.4	164.7–168.2	30.2	28.8–31.7	1.8 (1.7–1.9)	p<0.001	16.9	16.4–17.5
Influenza B	NA	NA	NA	NA	NA	NA	23.4	22.1–24.7	0.5 (0.5–0.5)	NA	43.7	42.8–44.6
A(H1N1)pdm09-related ICU admissions	1.7	1.4–2.0	0.8 (0.6–1.0)	p=0.064	2.1	1.9–2.3	1.9	1.6–2.3	2.4 (1.9–3.0)	p<0.001	0.8	0.7–0.9
A(H1N1)pdm09-related mortality	0.5	0.4–0.8	0.9 (0.6–1.4)	p=0.781	0.6	0.5–0.7	0.9	0.7–1.2	8.3 (5.1–13.5)	p<0.001	0.1	0.1–0.2

CI: confidence interval; ICU: intensive care unit; IRR: incidence risk ratio; NA: not available.

[a] Other countries: Finland, Iceland, Norway and Sweden.

[b] Reference group: Other countries.

with the other countries (IRR: 8.3; 95% CI: 5.1–13.5; p value<0.001).

Discussion

There was a wide variation in pandemic vaccination strategies during the pandemic in Europe, and the influenza A(H1N1)pdm09 pandemic vaccination coverage previously reported for the entire population ranged from 0.5% to 59% across European countries [27]. We evaluated how the pandemic and the post-pandemic influenza seasons progressed in the Nordic countries and present the results in light of the different vaccination strategies used. A similar approach would have been difficult at the European level due to the heterogeneous populations, different healthcare and different influenza surveillance systems. The Nordic countries are comparable regarding these factors which gave us a unique opportunity to study differences in severe outcomes of influenza A(H1N1)pdm09 in the pandemic and post-pandemic seasons in relation to the vaccination coverage during the pandemic.

The pandemic vaccination coverage was 6% in Denmark where vaccination was only recommended for at-risk groups, compared with 41 to 60% in the other four Nordic countries where vaccination was recommended for the whole population. The timeliness of vaccination varied by a few weeks with Sweden having the highest proportion of the population vaccinated before the epidemic peak.

All Nordic countries reported that the most frequent influenza type during the pandemic was A(H1N1) pdm09, with Denmark and Sweden having the lowest rates of laboratory-confirmed A(H1N1)pdm09 cases overall and cases admitted to ICU. However, in the following influenza season, 2010/11, A(H1N1)pdm09 dominated in Denmark, whereas influenza type B was the predominant virus in the other four Nordic countries. Furthermore, in the 2010/11 season, Denmark experienced a higher incidence of A(H1N1)pdm09-related ICU admissions and deaths than the other Nordic countries.

The higher incidence of laboratory-confirmed influenza A(H1N1)pdm09 cases and related ICU admissions and deaths in Denmark in the 2010/11 season could be due to less natural or vaccine-induced immunity in the population in the post-pandemic season compared with the other countries. Studies on the burden of the pandemic influenza in Denmark have estimated a clinical attack rate of 5% [28] which is indeed lower than the clinical attack rate of 30% estimated in Norway [29]. However, the latter number was obtained by using a different method [29]. Clinical attack rates were not available for the other Nordic countries.

Other European countries have reported findings similar to those observed in Denmark. In 2010/11, the United Kingdom (UK) reported a higher level of daily number of confirmed and suspected influenza cases in critical care and a higher number of deaths compared with the 2009/10 pandemic season [30,31]. Pandemic vaccination coverage was estimated to be 15% for the general population in Scotland [32]. The coverage was 35% for the risk groups in the UK where it provided some protection against laboratory-confirmed influenza A(H1N1)

Table 4

Timing of recommendations of influenza testing, Denmark, Finland, Iceland, Norway and Sweden, 2009/10 influenza A(H1N1)pdm09 pandemic

Country	Groups recommended for testing and week	
	Cases[a] and their contacts	Cases at risk of severe disease and their contacts
Denmark	Week 18	Week 29
Finland	Week 18	Week 31
Iceland	Week 21	Week 33
Norway	Week 18	Week 30
Sweden	Week 17	Week 29

[a] Individuals fulfilling the national case definition for suspected case of influenza A(H1N1)pdm09.

pdm09 in the 2010/11 season according to a vaccine effectiveness study [10]. In Greece, where a 3% population pandemic vaccination coverage was reported, higher ICU admission rates and higher overall population mortality due to influenza A(H1N1)pdm09 was also reported in 2010/11 compared with the previous season [33]. In Ireland, 23% of the population eligible for vaccination was vaccinated during the pandemic and the number of influenza A(H1N1)pdm09-related ICU admissions and deaths increased from the 2009/10 to the 2010/11 influenza season [34].

Adjuvanted vaccines have shown to provide longer lasting immunity in children, adults and populations with chronic conditions compared with non-adjuvanted vaccines [8,9,35]. They induce antibodies that show higher levels of haemagglutination inhibition and influenza-neutralising activity than non-adjuvanted vaccines [36-38]. In addition, the 2009 pandemic vaccine strain closely matched the influenza A(H1N1)pdm09 virus strain that circulated during the season 2010/11. Thus, in 2010/11 the population of the Nordic countries could have been protected to some extent by the pandemic vaccine administered more than one year earlier.

Several national and sub-national studies have reported the prevailing effectiveness of the pandemic vaccine in 2009/10 in preventing influenza A(H1N1)pdm09 during season 2010/11. In Sweden, the pandemic vaccine effectiveness (VE) was 72% against hospitalisation in 2010/11 [8]. In Finland, the VE against A(H1N1)pdm09 influenza was 81% if vaccinated with pandemic vaccine and 88% if vaccinated with either pandemic vaccine or TIV in 2010/11 [39]. In UK, the VE against A(H1N1) pdm09 in 2010/11 was 34% if vaccinated with pandemic vaccine; 46% if vaccinated with TIV in 2010/11 and 63% if vaccinated with both [10]. These results are in line with our findings of a lower incidence of severe influenza outcomes in 2010/11 in the four countries with higher pandemic vaccination coverage compared with Denmark.

Limitations

Although the five Nordic countries have similar healthcare systems, they may have had different testing practices for influenza confirmation and subtyping, and thus ascertainment of the diagnosis. This would have affected the comparability of the data between countries and between the two seasons. This limitation is however minimised due to three facts. Firstly, testing recommendations were similar in the five countries from the beginning of the pandemic and changed to only risk group patients or close contacts of laboratory-confirmed cases in all countries from week 29 to 32. Furthermore, testing bias probably did not affect the ICU admission rates, as the testing recommendations at hospital level (including ICU units) in all countries were to swab all patients hospitalised with influenza symptoms or lower airway infection [22-26]. Secondly, the proportion of specimens positive for influenza was similar among the three countries with available information which may additionally indicate that the case ascertainment was comparable throughout this period. The percentage of positive samples reflects the influenza transmission if systematically sampled e.g. in sentinel systems. But different criteria for diagnostic swabbing of symptomatic patients (e.g. more severely ill patients with higher likelihood of being influenza positive) could also have accounted for differences in the percentage between countries. Thirdly, the age distribution of laboratory-confirmed influenza A(H1N1) pdm09 and influenza B was similar (Figure 2) between the countries in the two seasons which also points towards a comparable case ascertainment. In addition, the testing practices may have changed due to different disease awareness during the pandemic and the following year. However, there is no evidence that changes in disease awareness between the two seasons would have differed markedly between the countries concerned.

Data on the TIV coverage in the five countries in 2009/10 and 2010/11 seasons was not included in the analysis, as it was not available for all countries. This could have influenced the morbidity and mortality due to influenza in both seasons, as in Canada, where studies have shown an increased risk of influenza A(H1N1) pdm09 in 2009/10 among TIV recipients in 2008/09 [40]. Therefore, the TIV in 2009/10 and 2010/11 could have influenced the morbidity and mortality due to influenza in both seasons. However, in the Nordic countries the TIV was only offered to the risk groups and not to the general population, and it is therefore likely to have had a minor impact on the overall incidence of disease. In addition, the coverage in 2010/11 would only have had an impact on the results if there were differences in the risk groups or coverages in the other Nordic countries compared with Denmark. This is not the case since the seasonal vaccination recommendations were similar in the Nordic countries and included the same risk groups, except for the recommendation of vaccinating healthy children in Finland [41]. Moreover, vaccination coverages in the season

2010/11 were similar in three of the Nordic countries in the elderly population: 50% in Denmark, 47% in Norway among elderly and risk groups, and 54% in Sweden [42].

The optimal design to address a prolonged effect of the pandemic vaccine would have been a multi-country register-based study with individual level information on pandemic and seasonal vaccinations and influenza A(H1N1)pdm09 outcomes. If this data had been available it would have been possible to conduct pandemic VE analysis with stratification on previous TIV vaccination in the two seasons.

Finally, it is a limitation that we only included information on vaccination coverage as a predictor of severe outcomes of influenza, when influenza transmission is known to be influenced by a range of factors other than vaccination such as population density, social factors, weather conditions and latitude which were not taken into account in this study.

Conclusions and recommendations

Our observational study allowed a comprehensive description of timing and coverage of the pandemic vaccinations and severe outcomes of influenza A(H1N1) pdm09 during the pandemic and following season in the five Nordic countries.

In response to the A(H1N1)pdm09 pandemic, Finland, Iceland, Norway and Sweden recommended vaccination to the whole population at a certain time of the pandemic and reached coverages of 41 to 60%, whereas Denmark throughout the pandemic only recommended to vaccinate risk groups , leading to a coverage of 6% of the population. This difference does not seem to have influenced the timing of the epidemic nor the disease burden in the 2009/10 pandemic season, probably because the vaccines were distributed too late relative to the epidemic peak. However, in the following influenza season 2010/11, the four countries with higher pandemic vaccination coverage experienced a season dominated by influenza B and had less influenza A(H1N1)pdm09-related severe outcomes compared with Denmark. Our results indicate that the adjuvanted pandemic vaccination may have had an impact on influenza type/subtype distribution and influenza-related severe outcomes in the season following the pandemic, although other factors may have also played a role.

We did not aim to answer the question about the most appropriate vaccination strategy during a pandemic. However, the study indicates that different vaccination strategies may have had consequences for the influenza season following the pandemic season and this should be part of an overall assessment of a pandemic response. In such an assessment the risk of severe and unexpected rare adverse events also needs to be taken into consideration when evaluating the risk/benefit of a pandemic vaccination campaign.

In order to support the assessment of vaccination strategies, we recommend the use of comprehensive influenza surveillance systems that, in addition to surveillance of influenza intensity and circulating subtypes, also include severe influenza-related outcomes to monitor changes in the impact of influenza between seasons across countries. We also recommend to keep the same surveillance systems in place in the seasons following the pandemic, in order to enable full evaluation of the impact of pandemic vaccination campaigns.

The Nordic influenza comparison group

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Conflict of interest

None declared

Authors' contributions

Julita Gil Cuesta wrote the study protocol, coordinated the data collection, analysed the data and wrote the manuscript. Kåre Mølbak and Annika Linde conceived the study. Tyra Grove Krause conceived the study, contributed with the data from her respective country and wrote the manuscript. Preben Aavitsland, Hélène Englund, Ólafur Gudlaugsson, Siri Helene Hauge, Outi Lyytikäinen, Guðrún Sigmundsdóttir, Anders Tegnell, and Mikko Virtanen contributed to the study design, contributed with the data from their respective countries and wrote the manuscript. The Nordic influenza comparison group contributed to the study design and critical review of the manuscript. All authors reviewed and approved the final version of the manuscript.

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

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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.

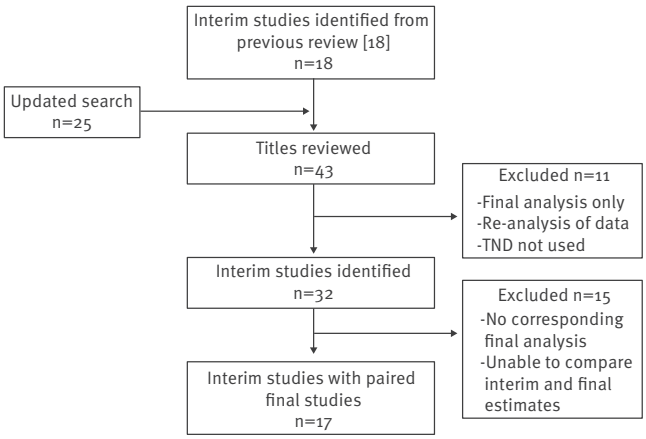
Once all interim papers were identified, their corresponding end-of-season report was located. This was a specific search using the author names, location and season of the interim paper to identify the paper reporting final estimates.

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

Figure 1

PRISMA flow diagram showing search strategy



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

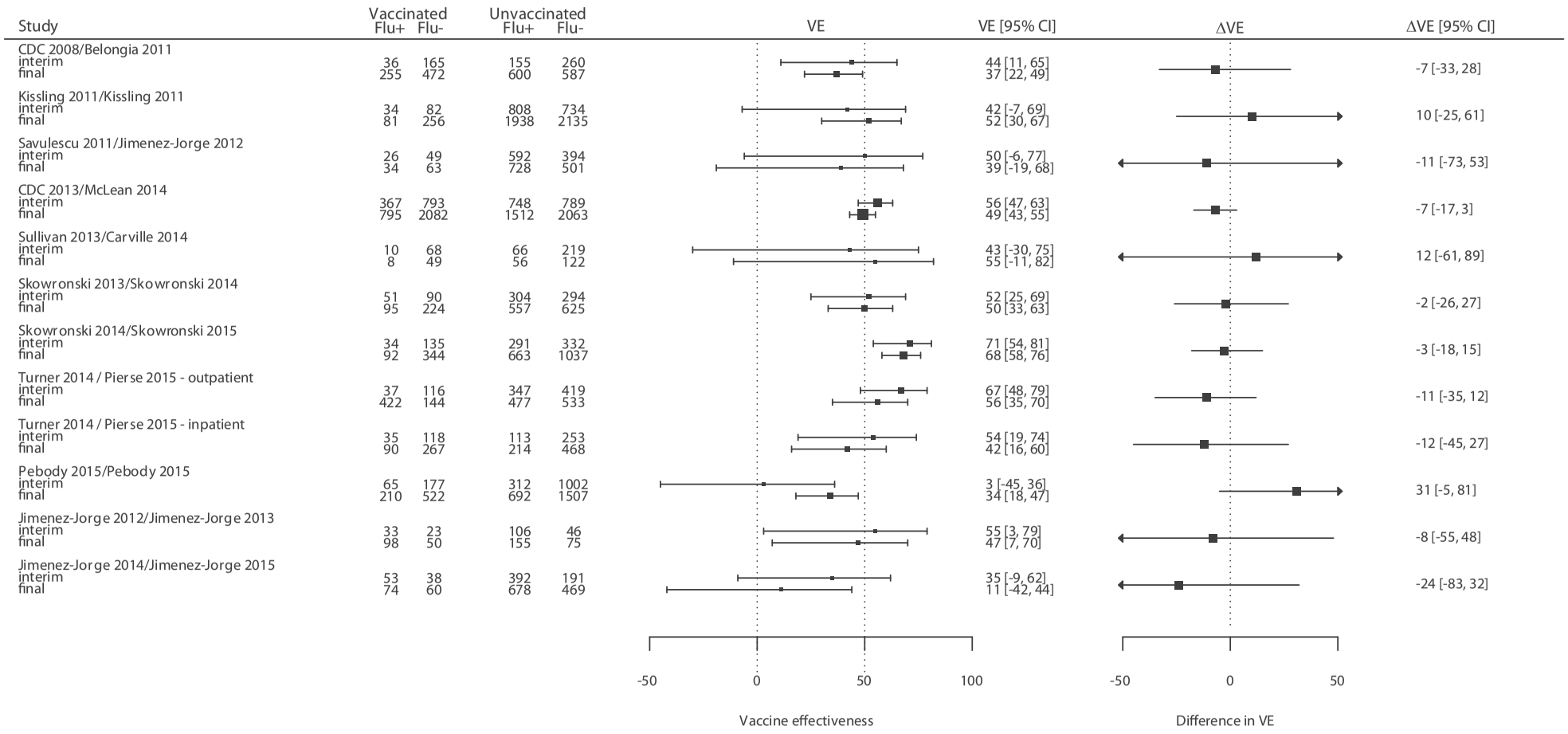
the epidemic curve provided in final analyses), any other exclusions (e.g. patients with missing information, children younger than a certain age), variables included in the model to estimate VE and their specification, and reported interim and final VE estimates. If the methods referred to a previous 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.

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

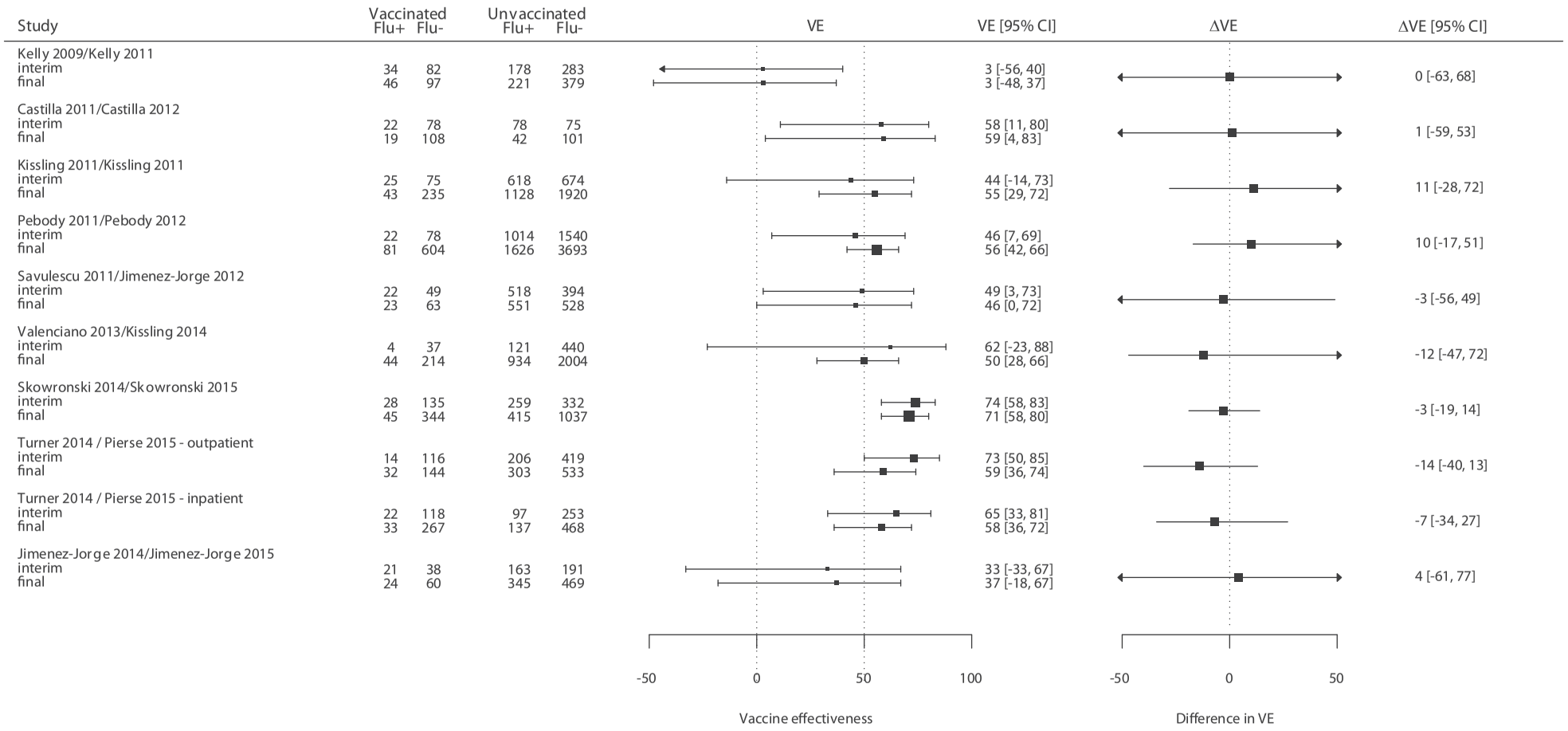


CI: confidence interval; Flu+: influenza-positive; Flu–: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

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

Figure 3

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

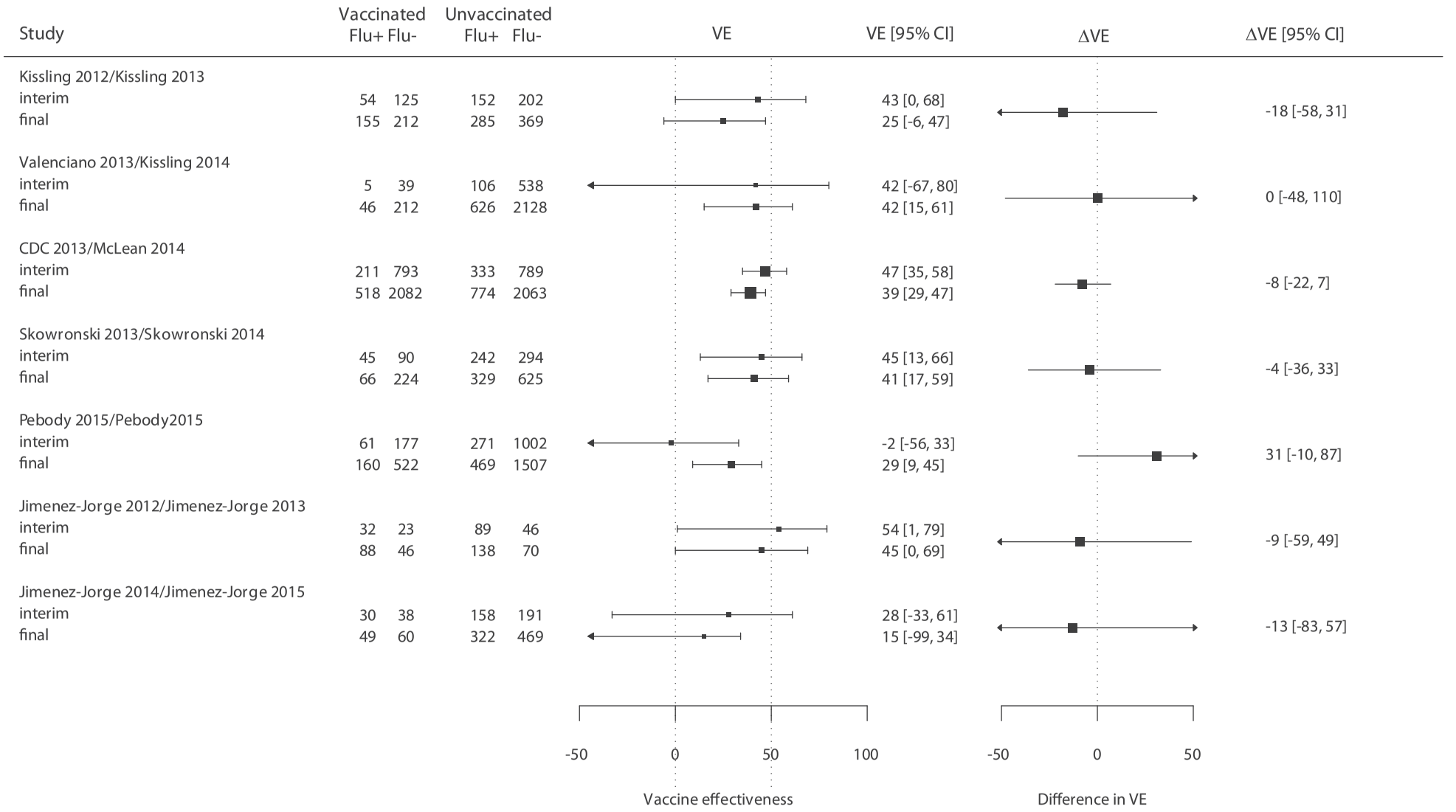


CI: confidence interval; Flu+: influenza-positive; Flu–: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

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

Figure 4

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

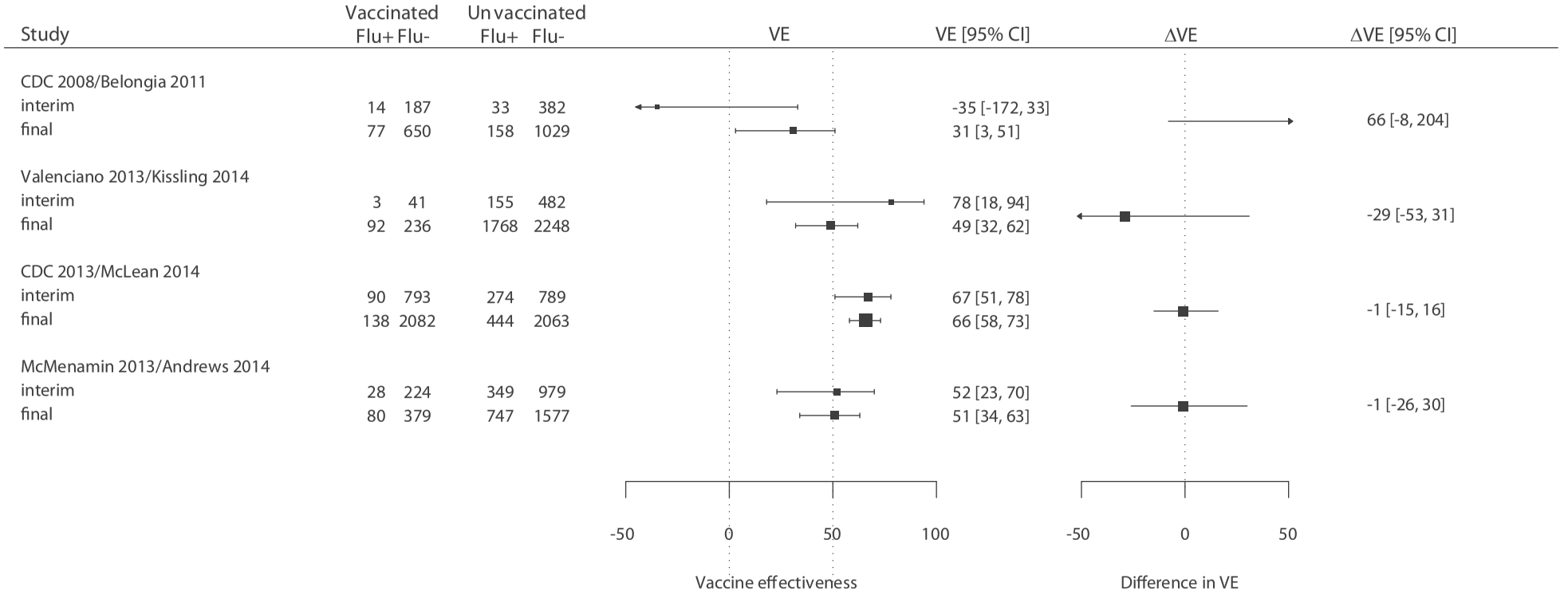


CI: confidence interval; Flu+: influenza-positive; Flu−: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

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.

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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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Lessons learnt to keep Europe polio-free: a review of outbreaks in the European Union, European Economic Area, and candidate countries, 1973 to 2013

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Between 1973 and 2013, 12 outbreaks of paralytic poliomyelitis with a cumulative total of 660 cases were reported in the European Union, European Economic Area and candidate countries. Outbreaks lasted seven to 90 weeks (median: 24 weeks) and were identified through the diagnosis of cases of acute flaccid paralysis, for which infection with wild poliovirus was subsequently identified. In two countries, environmental surveillance was in place before the outbreaks, but did not detect any wild strain before the occurrence of clinical cases. This surveillance nonetheless provided useful information to monitor the outbreaks and their geographical spread. Outbreaks were predominantly caused by poliovirus type 1 and typically involved unvaccinated or inadequately vaccinated groups within highly immunised communities. Oral polio vaccine was primarily used to respond to the outbreaks with catch-up campaigns implemented either nationwide or in restricted geographical areas or age groups. The introduction of supplementary immunisation contained the outbreaks. In 2002, the European region of the World Health Organization was declared polio-free and it has maintained this status since. However, as long as there are non-vaccinated or under-vaccinated groups in European countries and poliomyelitis is not eradicated, countries remain continuously at risk of reintroduction and establishment of the virus. Continued efforts to reach these groups are needed in order to ensure a uniform and high vaccination coverage.

Introduction

In 1995, the Global Commission for the Certification of the Eradication of Poliomyelitis (GCC) was established to oversee polio eradication certification activities on a global level. The commission defined essential monitoring systems on which the certification of eradication should be based – the surveillance for acute flaccid paralysis (AFP) and for wild poliovirus. These technical requirements reflected the basic principles of the World Health Organisation (WHO) for the eradication of wild poliovirus (WPV), which were to (i) achieve and maintain high routine immunisation coverage; (ii) improve surveillance systems (including AFP surveillance) and (iii) conduct supplementary immunisation activities (SIAs), including national immunisation days (NIDs) in all endemic areas and mopping-up immunisation in high risk areas in low incidence countries [1]. Substantial progress has been made to reach worldwide eradication. However, specific areas continue to cause concern. At the beginning of 2015, Afghanistan and Pakistan continued to have circulation of WPV type 1 (WPV1) [2].

In 1998, the last case of poliomyelitis caused by endemic WPV in the WHO European Region occurred in eastern Turkey, in an unvaccinated two-year-old. In 2001, this Region experienced its last outbreak of WPV with cases in Bulgaria. In 2002, the European Region of WHO was declared polio free and has since maintained this status [3]. However, this is repeatedly challenged. In 2010, WPV1 imported from Pakistan caused a large outbreak in Tajikistan that spilled over into neighbouring countries [4]. From February 2013 to March 2014, Israel detected WPV1 in sewage samples [5]. However, no clinical cases of polio were notified in Israel, the West Bank or the Gaza Strip. Since late 2013, some incidents related to polio have also been reported from countries boarding the WHO European Region. In October of that year, Syria confirmed WPV circulation [5]. In March 2014, Iraq reported its first case of paralytic poliomyelitis since 2000 [6]. In September 2014, a factory in Belgium accidentally released WPV into a river that flows through areas populated with communities with suboptimal coverage against poliomyelitis in the Netherlands [7]. These events reminded countries in Europe that poliovirus could be reintroduced as long as it has not been eradicated. Given the presumed population flow to and from countries where WPV is

still circulating and the social and geographical clustering of population groups with low vaccine uptake in Europe [8], WPV could be imported and re-established.

In the 1960s, mass vaccination against poliomyelitis started in the European Union (EU)/European Economic Area (EEA) [9], increasing coverage in the general population. Until 1973 there were significant variations in vaccination coverage, leaving large immunity gaps in the population and outbreaks of poliomyelitis continued to occur [9]. After 1973, when coverage was higher, outbreaks were less common. A better understanding of these post 1973 outbreaks could support our assessment of the current risk for WPV reintroduction in Europe and inform preparedness for responding to any such reintroduction. We systematically reviewed published reports of outbreaks of poliomyelitis affecting the EU/EEA and its candidate countries during the period from January 1973 to December 2013 to characterise populations affected, describe response measures and understand the role of environmental surveillance.

Methods

Search strategy

We conducted a systematic literature search to identify original articles in PubMed and Embase bibliographic databases as of 5 March 2014. The search strategies submitted were combining controlled vocabulary (MeSH and Emtree terms) and natural vocabulary for representing the concepts of 'poliomyelitis', 'outbreak', and 'case/case report'. We defined the period of interest as a forty year period from 1973 to 2013. Geographical terms were included in the search strings in order to retrieve more accurate results. The geographical terms included all EEA countries and EU Member States (MS), as well as candidate and potential candidate countries for the EU (as of 24 November 2014, these countries were: Albania, Bosnia and Herzegovina, Iceland, Kosovo under UN Security Council Resolution 1244, Montenegro, Serbia, the former Yugoslav Republic of Macedonia, and Turkey) [10]. The search was not restricted by date or language. Outbreaks outside the area of interest were included in the review but informed the discussion.

Data abstraction

We initially screened articles retrieved through the search based on the title and abstract to identify papers that fulfilled at least two of the following inclusion criteria:

(i) The paper reported or described a single case or clustering of cases of WPV in a country or area;

(ii) The paper provided concrete data on one or more EU/EEA countries and candidate countries or areas affected within;

(iii) The paper reported on response measures to an outbreak.

Reports were included in the full text analysis if they were in Dutch, English, French, Italian, Polish or Spanish. Reports were excluded if they only referred to areas outside of the EU/EEA and candidate countries, or if they described long-term trends in poliomyelitis epidemiology. Missing abstracts or abstracts that did not provide sufficient information to be definitely excluded from the study were also included in the full text analysis.

We abstracted data from articles according to a predefined template to recover information on (i) date of onset of cases, detection, response and the date of the final case; (ii) type of vaccine used in the SIAs; (iii) use of environmental surveillance to detect or manage the outbreak and (iv) socio-demographic characteristics of the affected population.

Data analysis

An outbreak was defined as a single case or a clustering of cases of WPV in a country or area in excess of what normally would be expected, where routine vaccination was already in place and for which response measures had to be implemented. We analysed the data abstracted to estimate the number of cases and the case fatality ratio and to describe geographical spread, type of poliovirus involved, and characteristics of the population affected (e.g. age groups, general population vs specific subgroup). We categorised outbreaks as to whether they were associated with poor access to vaccination, poor availability of the vaccine or lack of acceptance of the vaccination. We calculated the duration of the outbreak as well as the time taken to respond. If there were no exact dates reported, we used information available to estimate the duration of the outbreak.

Results

Results of the search

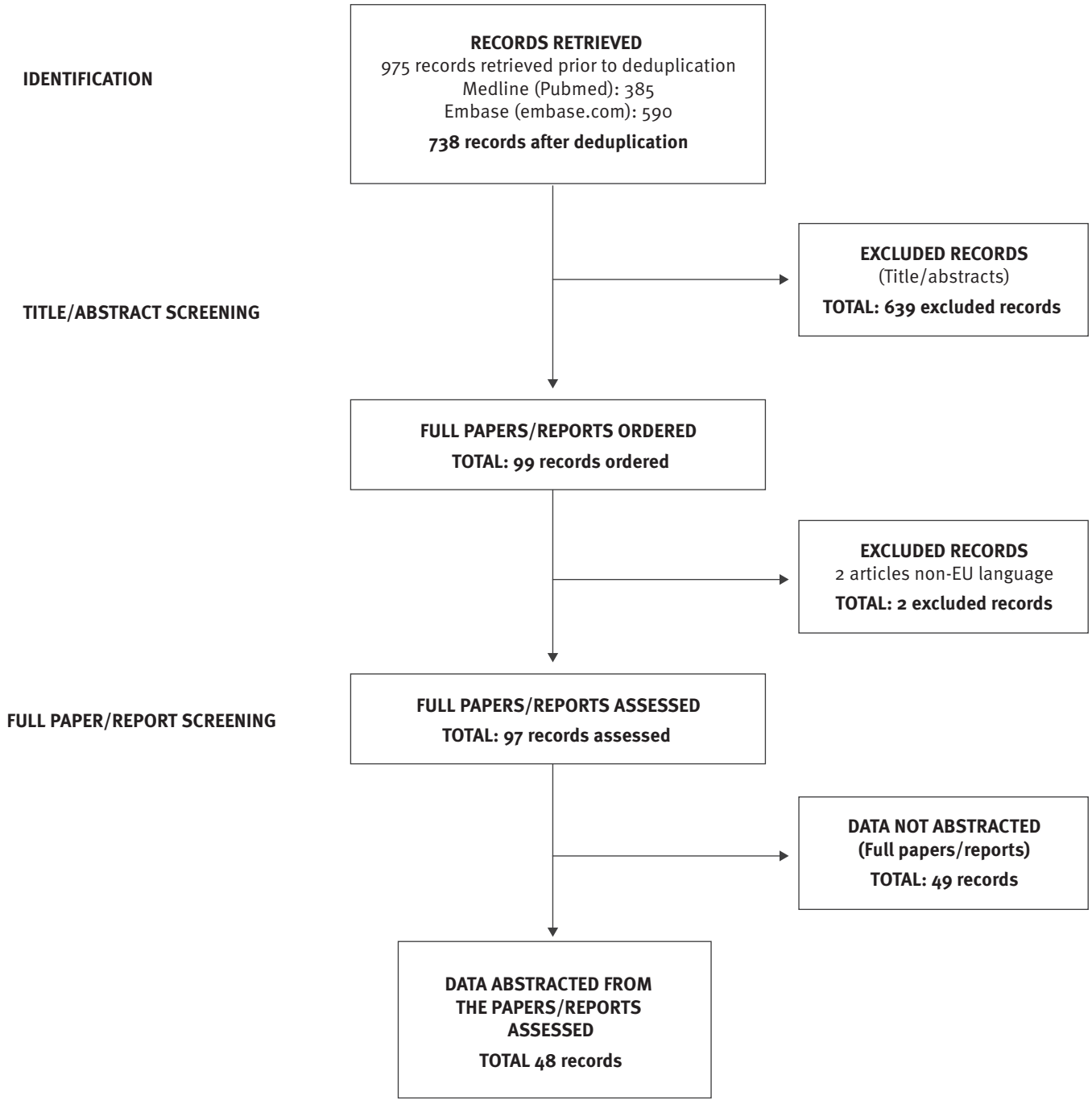
The literature search retrieved 738 records and articles after deduplication, of which 97 fulfilled the inclusion criteria. The full text evaluation identified 45 of these articles as relevant for this study from which data would be abstracted and a further three which could offer complementary data on already retrieved outbreaks (Figure).

Outbreaks identified

Twelve outbreaks were reported across eight countries of interest in the period from 1975 to 2001 (Table). Six of 12 outbreaks included more than three areas, where clinical cases were reported in a country and were thus classified as national outbreaks. On four occasions epidemiological and microbiological investigations identified cases and established chains of transmission in other countries, from the Netherlands to Canada in 1978 and 1992 [11,12], from Albania to Greece and

Figure 1

Flow diagram for the selection of studies on polio in the European Union /European Economic Area and candidate countries[a], published 1973–2013 (n=738)



[a] As of 24 November 2014, these countries were: Albania, Bosnia and Herzegovina, Iceland, Kosovo under UN Security Council Resolution 1244, Montenegro, Serbia, the former Yugoslav Republic of Macedonia, and Turkey.

Kosovo under UN Security Council Resolution 1244 in 1996 [13], and from Bulgaria to eight countries in 1991 [14].

The number of clinical cases reported within the outbreaks ranged from one to 161, with the largest outbreaks in Romania in 1980 (161 cases), Albania in 1996 (143 cases) and the Netherlands in 1978 (110 cases).

Age distribution

In five outbreaks (1977 in Sweden, 1978 in Albania, 1980–1982 and 1990–1992 in Romania and 2001 in Bulgaria) the age of the affected population ranged from six months to three years with a median age of less than two years (Table). An additional outbreak in Bulgaria from 1990 to 1991 mainly concerned the same age group, whereby the median age was reported to be less than a year, and except for one adult case, all cases were less than 18 months-old. In two outbreaks (1975 in Germany and 1978 in the Netherlands), the median ages were respectively of 6.5 and 10.5 years with a range of <1–20 years. In three outbreaks (1984–1985 in Finland, 1992–1993 in the Netherlands and 1996 in Albania) the median age was between 18 and 28 years-old with the total age range from <1 to 61 years. Only in one outbreak (1976 in Greece) was the age of the affected population not specified.

Case fatality

Whether deaths occurred or not within an outbreak was reported in seven of the 12 outbreaks. Among these seven, two outbreaks had no fatalities. For the outbreaks where deaths were reported, there were in total 21 deaths for 351 cases corresponding to an overall case fatality ratio of 6%. Of the 21 deaths reported, 16 occurred during the 1996 outbreak in Albania that had the highest case fatality ratio (16/145: 11%) [15]. The distribution of deaths across age groups was as follows: three deaths in those under 10 years of age with one death among an infant under one year-old; six deaths among 11 to 18 year-olds, seven deaths among 19 to 25 year-olds and five deaths (23%) in cases older than 26 years.

Social characteristics of the affected population and vaccine efficacy

Five of the 12 outbreaks occurred in vulnerable groups for which access to healthcare, including vaccination presented difficulties. Of these five outbreaks, four were specifically among the Roma population (Greece in 1976, Romania from 1990–1992, and in Bulgaria in 1990–1991 and in 2001) and one among families from low income groups (Germany in 1975). Three of the 12 outbreaks affected specific geographically clustered communities refusing vaccination on religious grounds while no clinical cases were reported in the general population (two in the Netherlands in 1978 and 1992–1993 and one in Sweden in 1977) [16-20]. Three of the 12 outbreaks occurred among the general population (Romania 1980–1982, Finland 1984–1985 and Albania 1996). Only one outbreak in Albania (1978) did not specify the social characteristics of the affected population.

Four of the 12 outbreaks occurred due to problems within programmes, or problems with the regular vaccine, its supply and/or distribution. Programmatic errors lead to disruptions in the regular polio vaccination programmes or resulted in the use of a vaccine with suboptimal efficacy. Prior to the 1978 outbreak in Albania, there was an interruption in supply of vaccine imported from China, which led to decreased coverage. In 1984 in Finland, the polio vaccine used in routine vaccination programmes was of lower potency against one of the polio strains (polio type 3) which, in combination with decreasing vaccination coverage among the general population, may have contributed to the occurrence of clinical cases [21]. In 1980 in Romania, a monovalent type 1 oral polio vaccine (OPV), given as a single dose at six weeks of age, resulted in cases among cohorts that were inadequately vaccinated [22]. In 1996 in Albania, a concurrence of different circumstances and events contributed to reduced vaccination coverage. First, OPV was stored for several years at room temperature, which affected its potency. Second, population movement from endemic countries and the unstable regional political environment lead to WPV importation. WPV then circulated among unprotected segments of the population [15,23,24].

Identification of outbreaks

The duration of the outbreaks varied between seven to 90 weeks for nine outbreaks where data was available. In all outbreaks, identification of the outbreak was due to diagnosis of cases of AFP, following which poliovirus was identified through a laboratory investigation. In 1991 in Bulgaria, the onset of paralysis in the first suspected case was in late December 1990 and the polio diagnosis was in late January 1991 [14]. In the Netherlands in 1978, polio was suspected four weeks after paralysis [17]. These patients had presented with AFP to a medical facility but the diagnosis was initially not suspected and diagnosis was delayed [17].

Timeliness of response

The exact start date of the SIA was only available in four (Finland in 1984; Bulgaria in 1991; the Netherlands 1992 and Albania in 1996) of the outbreaks. In three outbreaks the number of weeks had to be estimated because only a month but not a day was specified. For those where exact dates were specified, the response time ranged between one and 24 weeks. The quickest response was in the Netherlands in 1992 (first case: 17 September, beginning of the SIAs: 22 September, five days later).

Vaccine used in supplementary immunisation activities

In seven of the 12 outbreaks, OPV was used exclusively in SIAs. In five of these, tOPV was used and in two outbreaks the exact type of OPV was unspecified. In two outbreaks, OPV was used in combination

Table

Overview of polio outbreaks, European Union /European Economic Area and candidate countries, 1973–2013

Year	Country	N or L spread[a]	Poliovirus type(s)	Cases N		Deaths N	Age in years of affected population Median (range)	Affected population	Duration of outbreak in weeks	Weeks between 1st case and SIA	Acceptance of SIA vaccine		SIA vaccine		AFP surveillance		Environmental surveillance (at time of outbreak)	Ref.
				All	Paralytic						Before outbreak	After outbreak	OPV	IPV	At time of outbreak	Implemented (year)		
1975	Germany	L	1	5	NS	NS	6.5 (<1 – 12)	Lower socio –economic income group	7	NS	No	Yes	OPV (unspecified)	No	No	1998	NS	[42]
1976	Greece	L	1	7	NS	NS	NS (NS)	Roma	NS	NS	NS	NS	NS	NS	No	1998	NS	[43]
1977	Sweden	L	2	1	NS	0	2 (2)	Group refusing vaccination	NS	NS	No	Yes	NS	NS	No	–[b]	Yes	[29]
1978	Albania	N	NS	71	NS	NS	NS (0.5 – <2)	NS	NS	NS	NS	NS	NS	NS	No	1993	NS	[23]
1978	Netherlands	N	1	110	80	1	10.5 (<1 –20)	Group refusing vaccination	30.5	2	No	No	mOPV1	DT–Polio	No	1992	Yes	[11,17,20]
1980 –1982	Romania	N	1	161	NS	NS	NS (<1 – 3)	General population	90	NS	Yes	Yes	tOPV	No	No	1992	No	[22,44]
			2	15	NS	NS	NS (<1 – 3)											
1984 –1985	Finland	N	3	10	9	1	28 (6 – 48)	General population	24	16	Yes	Yes	tOPV[c]	IPV	No	2000	No	[21,25,26,45-47]
1990 –1992	Romania	L	1	13	NS	1	2 (<1 –3)	Roma	76	2 –4	Yes	Yes	tOPV	No	No	1992	No	[22,27,44]
1990 –1991	Bulgaria	L	1	43	NS	NS	<1 (NS)[d]	88% cases were Roma	20	4	Yes	Yes	OPV (unspecified)	No	No	1993	No	[14]
1992 –1993	Netherlands	N	3	71	NS	2	18 (<1 – 61)	Groups refusing vaccination	20	<1	No	No	tOPV	No	Yes	1992	Yes	[12,16,18,19, 28,48,49]
1996	Albania	N	1	143	NS	16	21 (<1 –52)	General population	28	24	Yes	Yes	tOPV	No	Yes	1993	NS	[13,15,24,50,51]
2001	Bulgaria	L	1	3	NS	0	NS (<1)	Roma	8	3	Yes	Yes	tOPV	No	Yes	1993	No	[52-54]

AFP: acute flaccid paralysis; DT: diphtheria, tetanus; L: local; mOPV1: monovalent oral polio vaccine type 1; N: national; NS: not specified; OPV: oral polio vaccine; IPV: inactivated polio vaccine; Ref: references; SIA: supplementary immunisation activities; tOPV: trivalent oral polio vaccine.

[a] National spread was defined as cases in more than three areas in one country.

[b] No AFP surveillance, but mandatory notification of viral meningoencephalitis since 2004.

[c] Only used in the nationwide campaign between February and mid-March 1985.

[d] 42 of the 43 cases in the outbreak were less than 18 months, one case was an adult of unspecified age.

with inactivated polio vaccine (IPV). In 1978 in the Netherlands, diphtheria tetanus (DT)-polio was used in combination with mOPV1 [17]. In 1984 to 1985 in Finland, IPV was used in addition to tOPV, although the tOPV was only used in the nationwide campaign [25]. In three outbreaks the vaccine used for response was not specified.

Supplementary immunisation activities' strategies

Catch-up campaigns were implemented either nationwide or restricted in terms of geographical areas or age groups. In 1978 and 1992 in the Netherlands, catch-up vaccinations with OPV were offered to those with direct contact with cases or to those who had been incompletely vaccinated through the regular vaccination programme with IPV. In 1984, Finland initially intensified the national vaccination programme of preschool aged children with IPV from November 1984 (first case diagnosed in October 1984) and in total 1.5 million doses of IPV were administered. Vaccination was then extended for all adults when cases were reported in this age group [21,26]. In 1990 in Romania, SIAs were conducted in four districts where cases had been reported. Immunisation occurred on a house-to-house basis with 102,000 children vaccinated with OPV (96%‹3 years) [27]. In 1991 in Bulgaria, mass vaccination was conducted for all Roma children‹7 years of age. In addition, all other children among the general population‹1.5 years of age were vaccinated [14]. In 2001 in Bulgaria, SIAs were conducted for children‹8 years of age in the area affected by the outbreak as well as three neighbouring districts.

Environmental surveillance

In Sweden (1977) and the Netherlands (1978), environmental surveillance was in place and routinely used before the outbreaks of poliomyelitis. However, in both outbreaks WPV was not detected in sewage or recreational water before the onset of the first clinical case [28,29]. In 1977 in Sweden, after the outbreak had been detected, WPV type 2 was isolated from sewage systems that served the affected area as well as other parts where no people known to shed the virus lived. The virus was also isolated from sewage plants in Stockholm. Faecal specimens from close contacts, other contacts and individuals with no known contact to cases suggested circulation only in close contacts (25 schoolchildren and families from the same group refusing vaccination, all unvaccinated) [29]. In 1978 in the Netherlands, environmental surveillance indicated that circulation of the virus did not affect the population immunised with IPV or unvaccinated people living within well-vaccinated communities [20]. Wild poliovirus circulated only within sections of the populations that had, on the whole, refused vaccination.

In 1982, Finland had discontinued its nationwide systematic environmental surveillance but with the diagnosis of first case in August 1984 collection and testing of environmental was resumed. Sewage specimens yielded results positive for WPV until February 1985 and indicated a geographical spread of the outbreak strain in the vaccinated population. Vaccine-type virus was subsequently isolated in sewage specimens 14 weeks after the vaccination campaign and 100,000 people were estimated to be shedding WPV 3. The last specimen with documented poliovirus content was collected in Helsinki late June 1985, more than eight weeks after the OPV vaccination campaign [25].

In 1992 in the Netherlands, environmental surveillance did not detect circulation of the virus before the first case but it did retrospectively confirm that WPV type 3 had circulated three weeks before the first clinical cases ten kilometres from where this case was reported [28]. It confirmed the precise location of the infection and suggested the possibility that people living in villages downstream from the initial case might be exposed. In doing so, it allowed for the targeted intervention of SIAs. Environmental investigations identified WPV in 23 of 269 samples from sewage pipelines in 120 locations, only in the risk area.

Discussion

In our review, those most affected by poliomyelitis outbreaks were communities within the general population who were not vaccinated or under vaccinated. These can be split into two groups. The first group comprises populations that are hard to reach (e.g. the Roma community) or people living in poor socio-economic environments. They are not inherently opposed to vaccination but they may have poor access to vaccination or lack awareness of the importance of vaccination against polio. The second group includes those who refused vaccination, such as the anthroposophic and religious communities. This included communities in the Netherlands, where vaccine acceptance is influenced by factors such as how convenient it is to get vaccinated, complacency regarding not being vaccinated and confidence in the vaccine [30]. People who refuse vaccination may also do so either because they are hesitant about whether or not to get vaccinated, or alternatively because they are opposed to vaccination.

In 2015, the WHO's Strategic Advisory Group of Experts on Immunization (SAGE) examined the causes of vaccine hesitancy in order to identify approaches to increase global vaccination acceptance [31]. Vaccine hesitancy is addressed in guidelines from public health organisations in Europe, which aim to provide methods and tools to assist national immunisation programmes to design targeted strategies that increase vaccination uptake [32,33].

Groups opposing vaccination are not unique to Europe. In Nigeria, India and Pakistan, groups refusing vaccination against polio and limiting vaccination efforts almost brought the elimination of polio to a standstill [34]. India and Nigeria have engaged with the groups opposing vaccination and the results have shown that such interventions have a positive impact on vaccination

uptake. To increase vaccination uptake among groups refusing vaccination the WHO, regional and local policymakers and non-governmental organisations (NGOs) set up programmes specifically targeting these groups. These outreach programmes focused on interpersonal communication and social mobilisation as a route to changing social norms around vaccination by engaging local opinion leaders and organisations with influence in their communities [35].

The outbreaks affecting initially unvaccinated communities reviewed in this study did not spread to the general population or to subgroups of the general population with suboptimal vaccination coverage that lived within well-vaccinated communities. Outbreaks within the general population occurred only when there was a disruption in the normal vaccine distribution and storage. The age groups affected were best explained by poliomyelitis susceptibility gaps, highlighting the role of routine childhood immunisation and catch-up programmes to protect the whole population.

In all outbreaks, cases were detected when presenting with AFP and confirmed with laboratory tests. Not all countries had implemented AFP surveillance at the time of the outbreaks (Table). In our review, prompt introduction of SIA and catch-up vaccinations contributed to a marked decline of cases. Rapid response in the affected community is crucial to bringing an outbreak under control. Evidence on early containment also stemmed from the experience of outbreaks that were not included in our literature review. In April 2010, Tajikistan faced a large outbreak of poliomyelitis that spread to four neighbouring countries (Kazakhstan, Russia, Turkmenistan and Uzbekistan) [36]. The rapid, large scale SIA response targeting affected areas and age groups quickly brought the outbreak under control. In July to October 2011, China experienced a polio outbreak in southern Xinjiang. Four weeks after confirmation of the outbreak, China launched SIAs and the outbreak was stopped within six weeks of the laboratory confirmation of the index case. Aggressive action, including widespread vaccination of susceptible hosts, interrupted the outbreak quickly [37]. The WHO has issued poliomyelitis outbreak response guidelines, which suggests that after laboratory confirmation, SIAs need to start as soon as possible [38].

The European Regional Certification Commission for Poliomyelitis RCC and the WHO have included environmental surveillance in their eradication strategic plans to supplement AFP surveillance [39]. Regular environmental surveillance is already in place in Croatia, Estonia, Finland, Italy, Latvia and Lithuania and as of March 2015, the European Office of the WHO was in the final stage of the production of guidelines on environmental surveillance for detection of poliovirus [39]. In 2013 in Israel, environmental surveillance served as an early warning tool and allowed the public health authorities to take immediate preventive measures [5]. In the two countries in this review where environmental surveillance was in place, the surveillance did not detect WPV circulation before the detection of clinical cases. However, as the outbreaks in Sweden, the Netherlands and Finland suggested, environmental surveillance provided an understanding as to when transmission started, delineated the geographical spread of transmission, including possible locations where there might have been a risk of exposure, and allowed for targeted SIAs.

This review has some limitations. First, we lacked the information to identify which vaccine was most suitable to respond to an outbreak. The response at the time depended on the availability of the vaccine. Further analysis on the impact of SIAs would be useful in evaluating the effectiveness of response measures, in order to improve these measures as well as the timeliness of the response, for which information was only available in four of the outbreaks. Second, the review did not address outbreaks caused by vaccine derived polio viruses (VDPV). This was outside the scope of the review although we acknowledge that in the post-elimination phase VDPV may circulate in settings with low coverage and OPV use. On 28 August 2015, two cases of paralytic poliomyelitis caused by circulating vaccine-derived poliovirus type 1 (cVDPV1) were confirmed in Ukraine. According to an initial assessment, the risk of importation to the EU is considered as low but it served as another reminder to countries that polio remains a threat and to conduct a rapid review of national polio outbreak response plans [2]. Third, the review did not allow for the identification of the environmental surveillance schemes that would best detect WPV before clinical cases, including which geographical areas need to be sampled to monitor areas close to at risk-populations. As such, our findings do not provide a robust evidence base for decisions relating to the use of, and the sampling strategy for, environmental surveillance, particularly in the absence of an outbreak.

Our review leads us to a number of conclusions. First, the key element for Europe to remain polio free is to ensure uniform, high vaccination coverage. As long as there are non-vaccinated or under-vaccinated groups in European countries and poliomyelitis is not eradicated, these groups are continuously at risk. Second, there is an ongoing need to address the problem of groups who refuse vaccination and have low confidence in vaccination programmes. They represent a potential reservoir for WPV and the setting for clinical cases. Third, when outbreaks occur, quick intervention through SIAs is important to allow rapid containment. Fourth, while environmental surveillance may not detect wild strains before the occurrence of clinical cases, it may provide useful information for monitoring and controlling outbreaks, such as their geographical extent.

To protect Europe from reintroduction of polio, we first need to identify ways to increase the vaccination coverage in the pockets of under-immunised populations.

To do so, it is important to ensure that all communities have facilitated access to vaccination and are informed of its benefits. Confidence in vaccination programmes must be improved in groups that refuse vaccination, maybe through targeted interpersonal outreach and communication through mediators from these communities. A trustworthy dialogue should be started with the parental groups refusing vaccination, moreover their meeting and interaction with healthcare professionals should be improved [40]. If reintroduction occurs, SIAs must be conducted with the vaccine readily available so as not to delay the intervention and according to the WHO guidelines for outbreak response [41]. Lastly, lessons learnt from past outbreaks on the failure of environmental surveillance schemes to detect WPV circulation before the identification of clinical cases should be taken into account in developing guidance on conducting environmental surveillance near vulnerable populations. However, the recent example of the detection of silent transmission of WPV1 through environmental surveillance in Israel has shown the potential of this method to serve as a useful early warning system to mitigate the risk of reintroduction of WPV [5].

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Conflict of interest

None declared.

Authors' contributions

Tarik Derrough and Alexandra Salekeen both contributed equally to this paper and were responsible for data abstraction, summarisation and drafting of the manuscript. All authors revised and approved the final version of the manuscript.

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