Systematic Review

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.

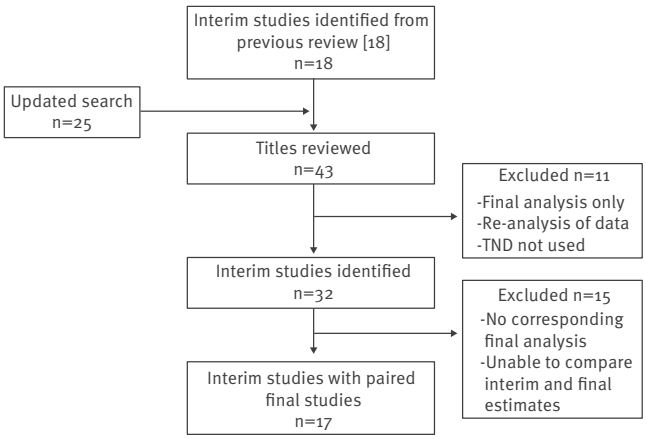
Once all interim papers were identified, their corresponding end-of-season report was located. This was a specific search using the author names, location and season of the interim paper to identify the paper reporting final estimates.

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 the epidemic curve provided in final analyses), any other exclusions (e.g. patients with missing information, children younger than a certain age), variables included in the model to estimate VE and their specification, and reported interim and final VE estimates. If the methods referred to a previous paper, the methods in the previous paper were recorded. If the specification of a variable was not mentioned, it was assumed that it had not been taken into consideration in the analysis. In some instances where information was not available, the authors were contacted to provide this information.

Figure 1

PRISMA flow diagram showing search strategy



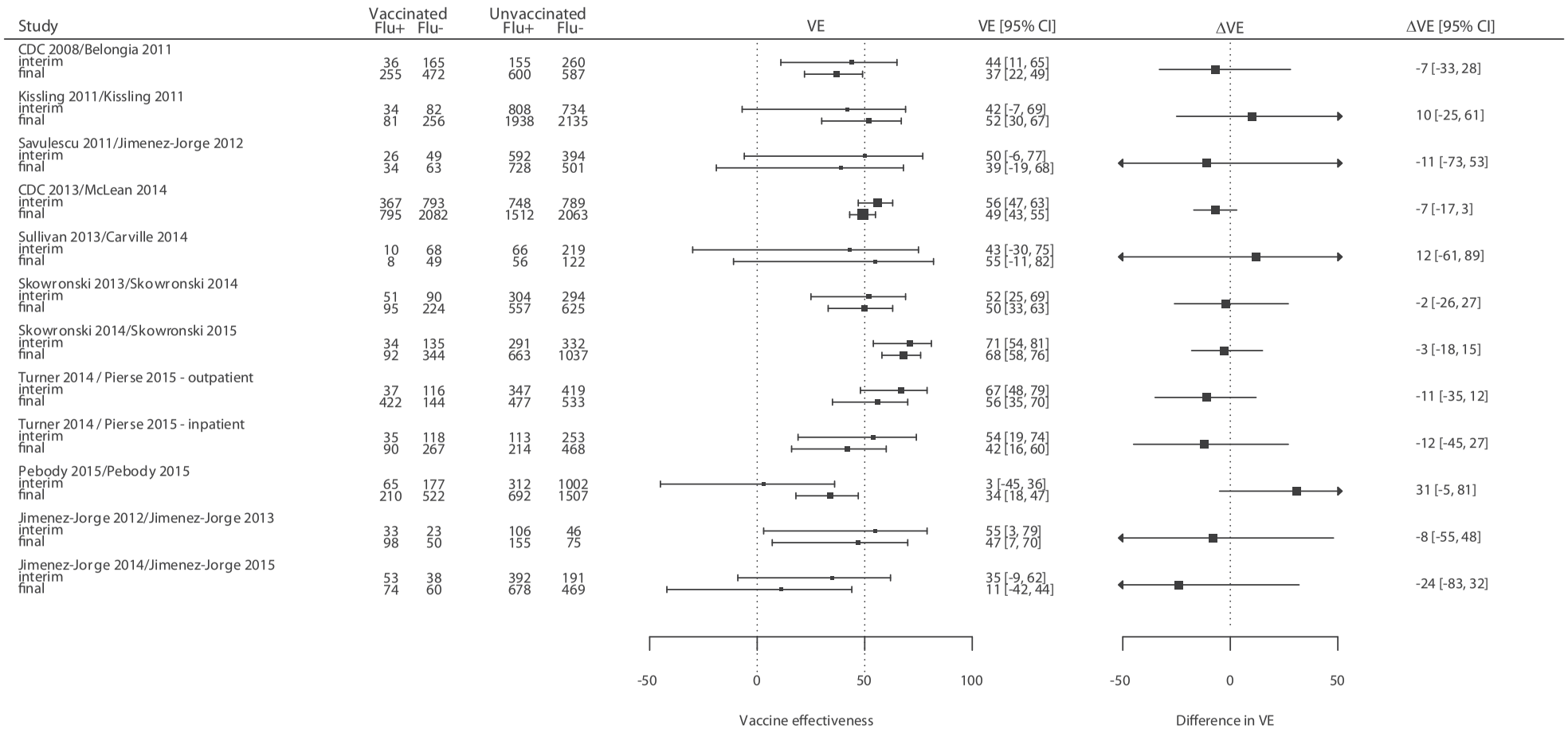
PRISMA: preferred reporting items for systematic reviews and meta-analyses; TND: test-negative design.

Comparison of interim and final estimates

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

Figure 2

Comparison of overall interim and final influenza vaccine effectiveness estimates

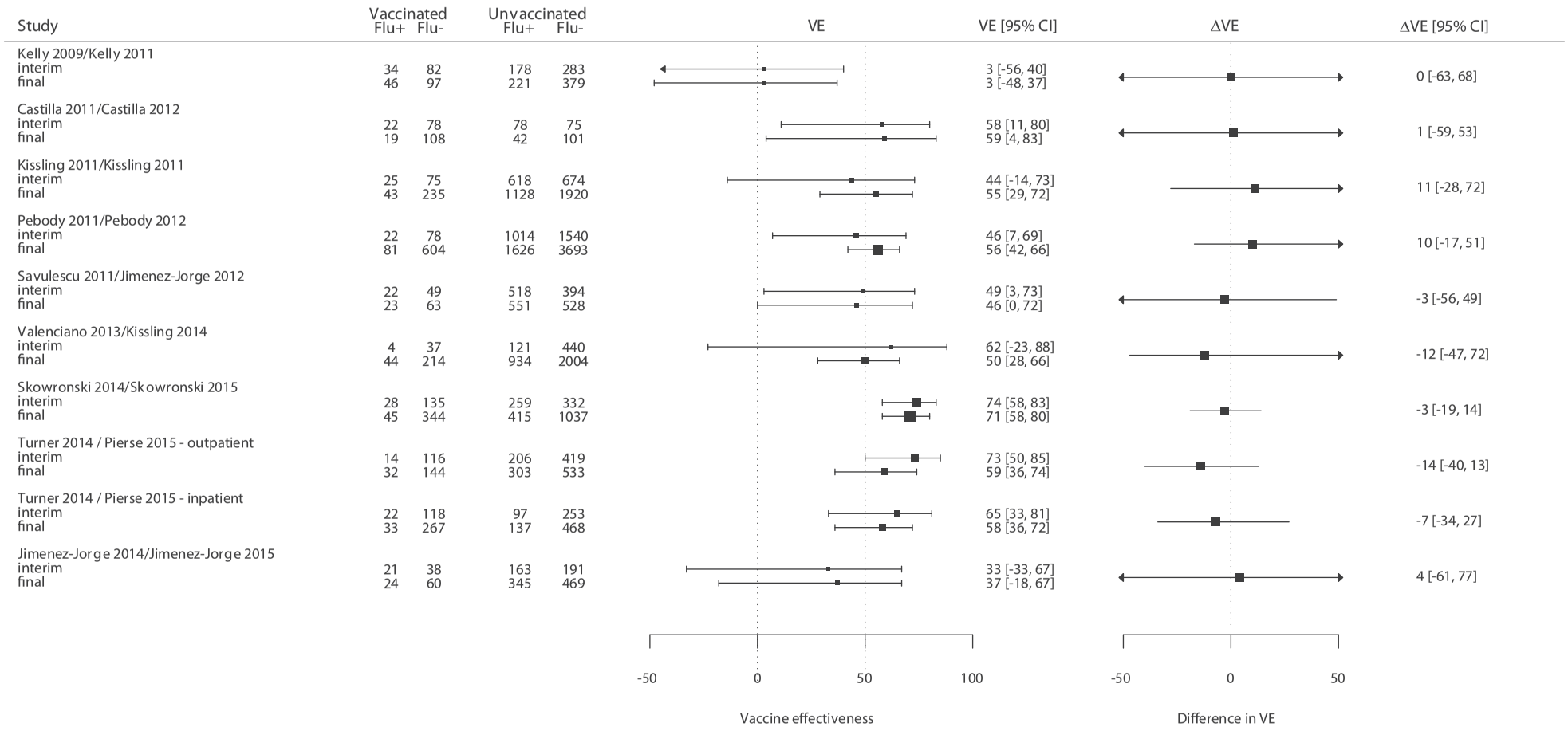


CI: confidence interval; Flu+: influenza-positive; Flu–: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

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

Figure 3

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

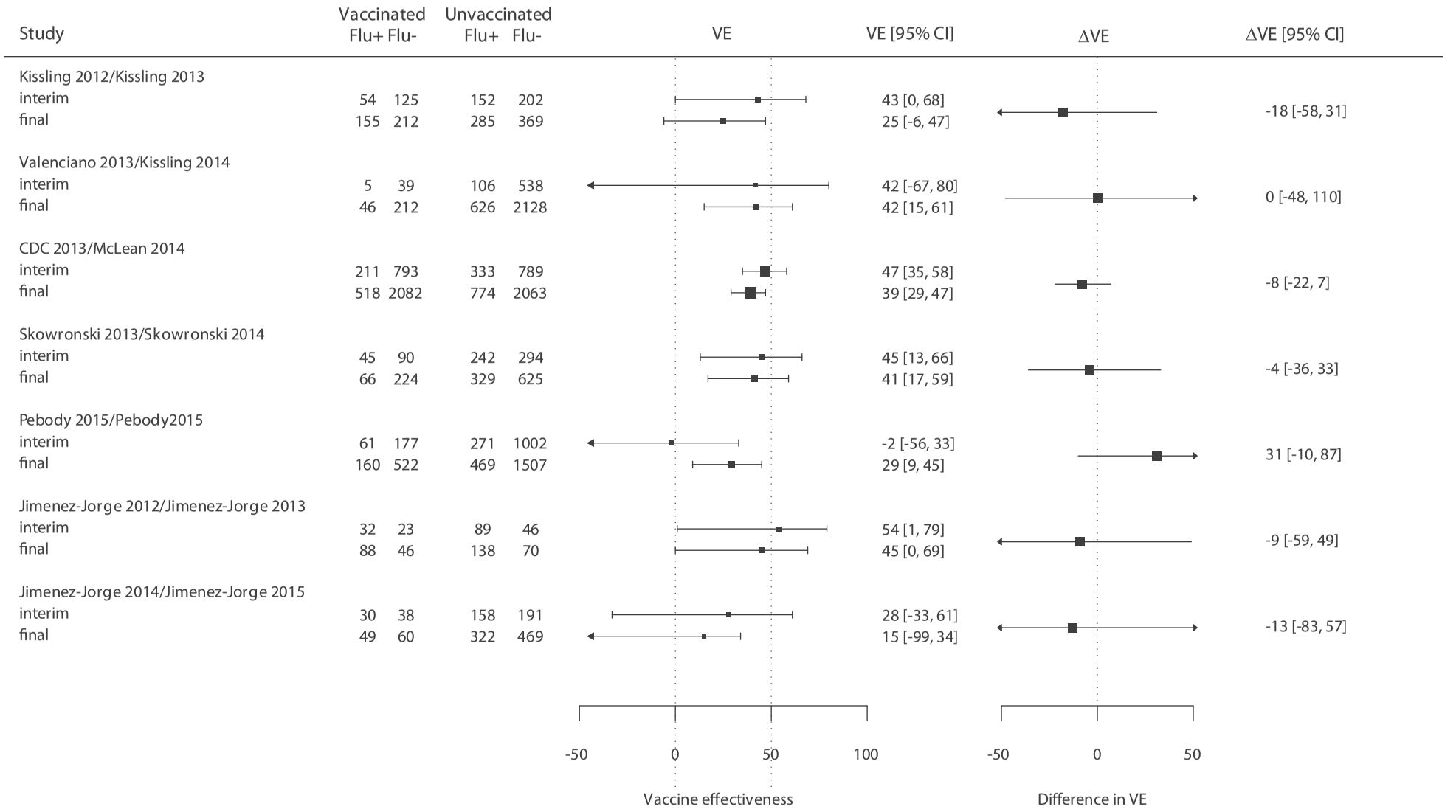


CI: confidence interval; Flu+: influenza-positive; Flu–: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

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

Figure 4

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

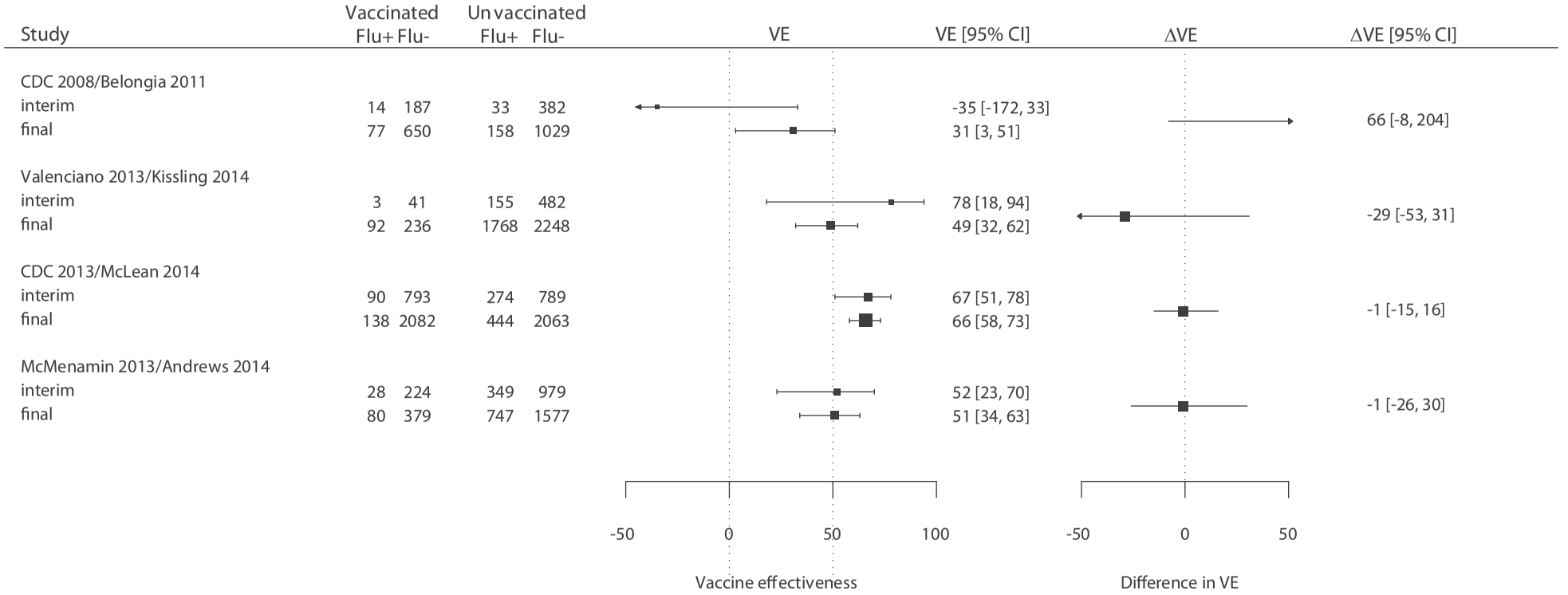


CI: confidence interval; Flu+: influenza-positive; Flu−: influenza-negative; OR_{adj}: adjusted odds ratio; VE: vaccine effectiveness.

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

Figure 5

Comparison of interim and final vaccine effectiveness estimates for influenza B



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

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

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

Results

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

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

Comparison of interim vs final vaccine effectiveness analyses

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

Setting and source population

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

Influenza-like illness definition

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

Influenza case definition

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

Exposure

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

Study periods

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

Table 1

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

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

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

Table 2a

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

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

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

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

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

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

Table 2b

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

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

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

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

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

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

Table 2c

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

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

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

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

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

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

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

Outcome

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

Variables included in the model to estimate vaccine effectiveness

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

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

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

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

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

Comparison of interim and final vaccine effectiveness estimates

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

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

Table 3

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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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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