

Late season interim estimates of influenza vaccine effectiveness reliably predict end of season estimates in Victoria, Australia, 2007 to 2012

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Twice each year the World Health Organization makes a recommendation for the composition of the influenza vaccine, based on circulating strains of influenza A(H3N2), A(H1N1) and B. Strain selection has always been based on immunogenicity studies with limited human data. Immunogenicity can be considered as a proxy for vaccine effectiveness (VE). However, only interim VE estimates for the target hemisphere can be considered in time for the strain selection meeting. Using surveillance data from Victoria, Australia, we retrospectively estimated and compared interim and final VE estimates for 2007 to 2012. In general, interim estimates were within five percentage points of final estimates. However, estimates made too early or in years of low influenza activity may be unreliable.

Introduction

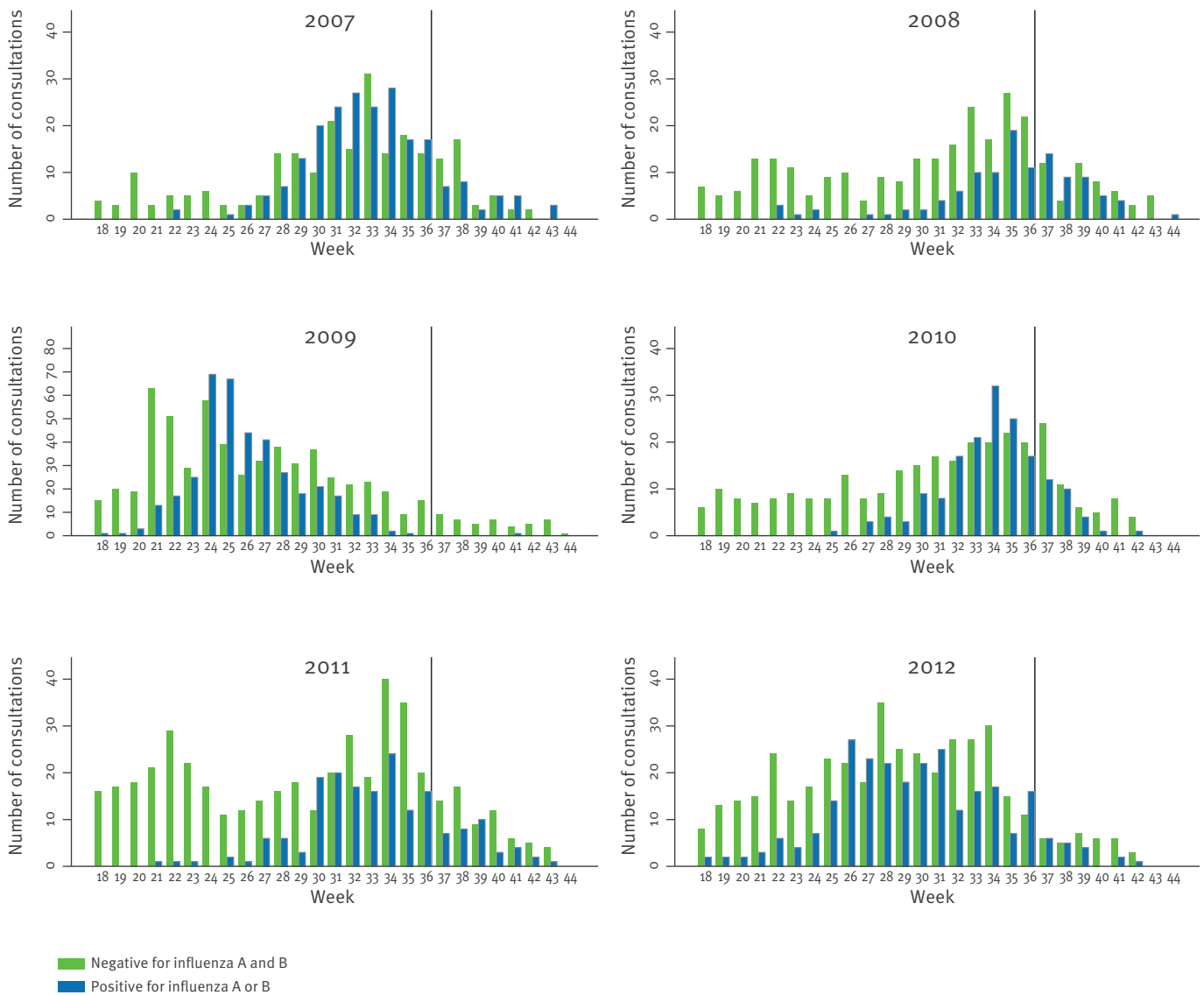
Twice every year, the World Health Organization (WHO) hosts an influenza vaccine strain selection meeting where data gathered by members of the Global Influenza Surveillance and Response System (GISRS) are reviewed and used to generate formal recommendations for the composition of seasonal influenza vaccines [1,2]. Recommendations for the northern hemisphere vaccine are made in February and for the southern hemisphere in September. Strain selection is based on serological data, with human data used to estimate immunogenicity, generally considered as a proxy for vaccine effectiveness (VE). At the February 2013 meeting, epidemiological data were submitted reporting interim VE estimates from surveillance systems in Canada, Europe and the United States (US). These estimates were published [3-8] and included for the first time with the package reviewed by GISRS meeting members. Final season estimates for the northern hemisphere were recently presented at the September 2013 meeting, as well as interim estimates for the southern hemisphere.

Interim estimates are vulnerable to change. First, as the season reaches its peak more data become available. For example, early US interim estimates released for the period from 3 December to 2 January 2013 [9] suggested a crude VE of 62% (95% confidence interval (CI): 51 to 71), while a second, lower interim estimate of 51% (95% CI: 43 to 58) was released later in February, with an adjusted estimate of 56% (95% CI: 47 to 63) [6]. The second interim estimate was made after the peak of influenza circulation had been reached, included more than double the sample size and had more complete information on covariates for adjustment and/or exclusion. Interim and final season estimates might also be expected to differ when the predominant type or subtype shifts within a season. For example, the early adjusted VE estimate from pooled European Influenza Monitoring Vaccine Effectiveness (I-MOVE) data in 2010/11 was 42% (95% CI: -7 to 69) [10] while the final estimate was 52% (95% CI: 30 to 67) [11]. In the interim analysis, 77% of viruses were influenza A(H1)pdm09 and 21% were influenza B, whereas the final analysis included 58% influenza A(H1)pdm09 and 38% influenza B viruses [10,11]. In the 2011/12 season final European estimates against influenza A(H3) were all revised down [12-14]. This was attributed to waning immunity against A(H3), a phenomenon that is being further investigated.

In the 2007/08 season, Belongia and colleagues compared interim and final estimates from US data, observing a difference of about seven percentage points (44%; 95% CI: 11 to 65 versus 37%; 95% CI: 22 to 49) [15]. They concluded that interim estimates were a useful indicator of VE mid-season. Systematic comparison of interim and final estimates has not been done since and has not been done for multiple seasons. To assess whether interim estimates reliably predicted final estimates, we compared retrospective interim and final VE estimates against influenza A and B for six influenza seasons, from 2007 to 2012, in Victoria, Australia.

FIGURE 1

Number of influenza-like-illness consultations per week by case status for the Victorian general practice sentinel surveillance network, Victoria, Australia, 2007–2012



Only patients from whom a swab was taken are included. The black vertical lines indicate the end of the interim period for the principle analysis (week 36). Note different y-axis scale used for 2009.

Methods

We used data collected as part of the Victorian General Practice Sentinel Surveillance network for the years 2007 to 2012 to calculate retrospective interim and final estimates. This network has been described in detail elsewhere [16]. Briefly, recruitment follows the case test-negative design [17–19]: a subset of patients seeing their general practitioner (GP) for influenza-like-illness (ILI; combination fever (measured or history of), cough and fatigue [20]) during the southern hemisphere influenza surveillance period are recruited at the GP's discretion, swabbed and tested for influenza by real-time reverse transcription-polymerase

chain reaction (RT-PCR). Those testing positive for influenza A or B are cases and those testing negative are non-cases. The GPs collect demographic data (age, sex), symptom onset date, vaccination status, vaccination date and, since 2011, the presence of conditions predisposing the patient to severe influenza (chronic heart disease, chronic respiratory disease, diabetes, impaired immunity, obesity, pregnancy). Surveillance generally begins in epidemiological week 18 in April/May and ends in week 44 in October/November.

VE estimates from the sentinel network have been reported for all years from 2007 to 2012 [21–24]. The

present analysis compared interim with end-of-surveillance period estimates, where the interim period ended to coincide with the WHO vaccine strain selection meeting in September. This meeting usually falls around week 38, so the interim period was restricted to weeks 18 to 36, to hypothetically allow two weeks to generate estimates and submit the report to the WHO. Final estimates were calculated using the entire surveillance period (weeks 18–44). For simplicity, we used all available data for weeks 18 to 36 or weeks 18 to 44, without considering other markers for influenza activity (such as ILI or laboratory indicators), which we have previously shown can influence VE estimates in seasons when the VE estimates are not robust [25].

VE was estimated as $(1 - OR)$ using logistic regression. Patients were considered vaccinated if they had received the vaccine ≥ 14 days prior to the onset of symptoms and excluded if vaccination took place < 14 days. Patients were considered influenza-positive if they tested positive to any of influenza A(H1), A(H3) or influenza B viruses by real-time RT-PCR, but no separate analyses were conducted for type or subtype. Models were adjusted for age group (< 18 , 18–64, ≥ 65 years) and week of presentation. The sensitivity of the estimates was tested in four ways: (i) the end of the interim period was brought forward by one and two weeks; (ii) final estimates excluded patients presenting more than eight days after symptom onset to reduce the possibility of false negative results, an exclusion which may not be possible in an interim analysis; (iii) estimates were restricted to people in a target group for vaccination (people with predisposing conditions or aged ≥ 65 years); and (iv) different variables for adjustment were used in the interim and final models. The fourth sensitivity analysis was based on the likely scenario where some information would be missing for the interim analysis, such as complete data on the presence of a condition predisposing to severe influenza and the date of onset, and where a decision was made to change the age groups used to increase comparability with other studies. Thus, the model for the final VE estimate included a variable representing the presence of at least one comorbid condition and a variable indicating the time between onset and consultation, an additional age group was added (< 18 , 18–44, 45–64, ≥ 65 years) and month was used instead of week to denote calendar time. The third and fourth sensitivity analyses were restricted to the years 2011 and 2012 because data on predisposing conditions were only available for these two years.

Results

The data available for each year are shown in Figure 1 with lines indicating the end of the interim period. For all years, the peak of the season preceded the end of the interim period. The characteristics of participants were not different for interim and final estimates (Table).

Interim and final estimates were determined using the same model adjusting only for age group and week. There were no statistical differences between estimates, with point estimates varying by up to five percentage points (Figure 2). For 2007, 2008, 2010 and 2011 interim point estimates were lower than final estimates, while for other years interim estimates were higher. In the first sensitivity analysis, when the interim period was shortened by one week, there continued to be little difference in estimates for all years except 2008, where estimates differed by more than 10 percentage points. Shortened by a further week, estimates for 2008 continued to show great variability, and the direction of effect was reversed.

The second sensitivity analysis excluded people presenting more than eight days since symptoms onset (or for whom the onset date was not recorded), resulting in the exclusion of 437 people from the analysis (Table). VE estimates with this exclusion criterion were 61% (95% CI: 30 to 79) for 2007, -7% (95% CI: -123 to 49) for 2008, -2% (95% CI: -49 to 30) for 2009, 69% (95% CI: 41 to 84) for 2010, 48% (95% CI: -2 to 74) for 2011, and 44% (95% CI: 12 to 64) for 2012. VE estimates were within four percentage points of those made without the exclusion criterion, with the exception of 2009; The 2009 estimates differed by nine percentage points and this year had the most exclusions ($n=197$).

The third and fourth sensitivity analyses were restricted to 2011 and 2012, the only two years for which data on comorbidity were collected. When interim and final estimates were compared for only those people in a target group for vaccination, the interim estimate was 61% (95% CI: -149 to 94) for 2011, while the final estimate was 48% (95% CI: -110 to 87). For 2012, the interim estimate was 30% (95% CI: -60 to 69), while the final estimate was 32% (95% CI: -52 to 70). Interim and final estimates were also compared when using different models for the estimates. The interim model adjusted for age group (< 18 , 18–64, ≥ 65 years) and week, while the final model included presence of a predisposing condition, days between symptom onset and consultation, an additional age group (< 18 , 18–44, 45–64, ≥ 65 years) and month. The interim and final estimates for 2011 were 44% (95% CI: -26 to 75) and 43% (95% CI: -20 to 73) respectively, and for 2012 were 49% (95% CI: 21 to 68) and 44% (95% CI: 13 to 69).

Discussion

We found that interim VE estimates over six influenza seasons closely approximated final estimates when the interim period was limited to week 36. When the interim period was shortened, estimates for 2008 were different by more than ten percentage points. Estimates for 2008 showed the greatest instability, which may be explained by that year's smaller sample size and the timing of the season, the peak of which fell later than in other years in week 35 (Figure 1). Only one interim estimate has previously been reported for this surveillance network, for the 2009 pandemic [26], a season

TABLE

Characteristics of patients with influenza-like-illness, Victoria, Australia, 2007–2012

	2007			2008			2009			2010			2011			2012		
	Interim n (%)	Final n (%)	p-value ^a	Interim n (%)	Final n (%)	p-value ^a	Interim n (%)	Final n (%)	p-value ^a	Interim n (%)	Final n (%)	p-value ^a	Interim n (%)	Final n (%)	p-value ^a	Interim n (%)	Final n (%)	p-value ^a
Total swabbed	392	466	ND	310	404	ND	1,010	1,060	ND	391	478	ND	551	665	ND	653	710	ND
Total included ^b	386	458	ND	304	396	ND	955	1,003	ND	378	464	ND	530	632	ND	627	678	ND
Sex ^c																		
Female	182 (47)	217 (47)	0.9	151 (50)	192 (48)	0.8	452 (48)	474 (48)	1	169 (49)	208 (50)	0.8	266 (50)	317 (50)	1	326 (52)	356 (53)	0.9
Male	204 (53)	241 (53)		153 (50)	204 (52)		493 (52)	519 (52)		179 (51)	212 (50)		263 (50)	313 (50)		301 (48)	322 (47)	
Age group																		
<18 years	64 (17)	73 (16)		44 (14)	62 (16)		264 (28)	273 (27)		77 (20)	98 (21)		172 (32)	200 (32)		162 (26)	172 (25)	
18–64 years	298 (77)	357 (78)	1	235 (77)	306 (77)	0.8	653 (68)	691 (69)	1	289 (76)	353 (76)	0.9	337 (64)	409 (65)	0.9	415 (66)	455 (67)	0.9
≥65 years	24 (6)	28 (6)		25 (8)	28 (7)		38 (4)	39 (4)		12 (3)	13 (3)		21 (4)	23 (4)		50 (8)	51 (8)	
Vaccination status																		
Unvaccinated	316 (82)	370 (81)	0.7	244 (80)	326 (82)	0.5	760 (80)	798 (80)	1	300 (79)	372 (80)	0.8	467 (88)	548 (87)	0.5	475 (76)	516 (76)	0.9
Vaccinated	70 (18)	88 (19)		60 (20)	70 (18)		195 (20)	205 (20)		78 (21)	92 (20)		63 (12)	84 (13)		152 (24)	162 (24)	
Influenza A or B																		
Negative	198 (51)	240 (52)	0.7	232 (76)	282 (71)	0.1	570 (60)	617 (62)	0.4	238 (63)	296 (64)	0.8	385 (73)	452 (72)	0.7	382 (61)	415 (61)	0.9
Positive	188 (49)	218 (48)		72 (24)	114 (29)		385 (40)	386 (38)		140 (37)	168 (36)		145 (27)	180 (28)		245 (39)	263 (39)	
Influenza type/subtype																		
A(H1)	46 (24)	48 (22)		4 (6)	4 (4)		343 (89)	343 (89)		121 (86)	146 (87)		26 (18)	27 (15)		23 (9)	23 (9)	
A(H3)	115 (61)	127 (58)		22 (31)	41 (36)		7 (2)	7 (2)		7 (5)	7 (4)		46 (32)	64 (36)		198 (80)	205 (78)	
A(mixed)	1 (1)	1 (0)	0.5	0(0)	0(0)	0.4	0(0)	0(0)	1	0(0)	0(0)	1	0(0)	0(0)	0.6	0(0)	0(0)	0.5
A(NS)	7 (4)	7 (3)		1 (1)	6 (5)		35 (9)	36 (9)		8 (6)	11 (7)		4 (3)	9 (5)		0(0)	0(0)	
B	19 (10)	35 (16)		45 (63)	63 (55)		0(0)	0(0)		4 (3)	4 (2)		69 (48)	80 (44)		24 (10)	35 (14)	
Presentation after time of symptoms onset (exclusion of > 8 days or date of symptom unknown made for final estimates only in sensitivity analysis 2) ^d																		
≤8 days	NA	412 (90)	NA	NA	359 (91)	NA	806 (80)	NA	425 (92)	NA	425 (92)	NA	NA	588 (93)	NA	NA	604 (89)	NA
>8 days or onset date unknown	NA	46 (10)	NA	NA	37 (9)	NA	197 (20)	NA	39 (8)	NA	39 (8)	NA	NA	44 (7)	NA	NA	74 (11)	NA
In a target group for vaccination (for sensitivity analysis 3) ^e																		
No	ND	ND	NA	ND	ND	NA	ND	ND	NA	ND	ND	NA	ND	ND	NA	462 (87)	550 (87)	0.9
Yes	ND	ND	NA	ND	ND	NA	ND	ND	NA	ND	ND	NA	68 (13)	82 (13)	0.9	129 (21)	136 (20)	0.8
Has a condition predisposing to severe influenza (for sensitivity analysis 3 and 4) ^f																		
No	ND	ND	NA	ND	ND	NA	ND	ND	NA	ND	ND	NA	411 (88)	483 (88)	0.9	473 (82)	512 (82)	0.9
Yes	ND	ND	NA	ND	ND	NA	ND	ND	NA	ND	ND	NA	55 (12)	67 (12)	0.9	103 (18)	109 (18)	0.9

A(NS): influenza A (not subtype); NA: not applicable; ND: not determined.

^a p-values are for the chi-squared test comparing characteristics of patients used in the interim versus final estimates.

^b Patients were excluded if missing vaccination status or age.

^c Figures may not sum to 'Total included' due to missing data. Complete information on sex was not a criterion for inclusion in the analysis.

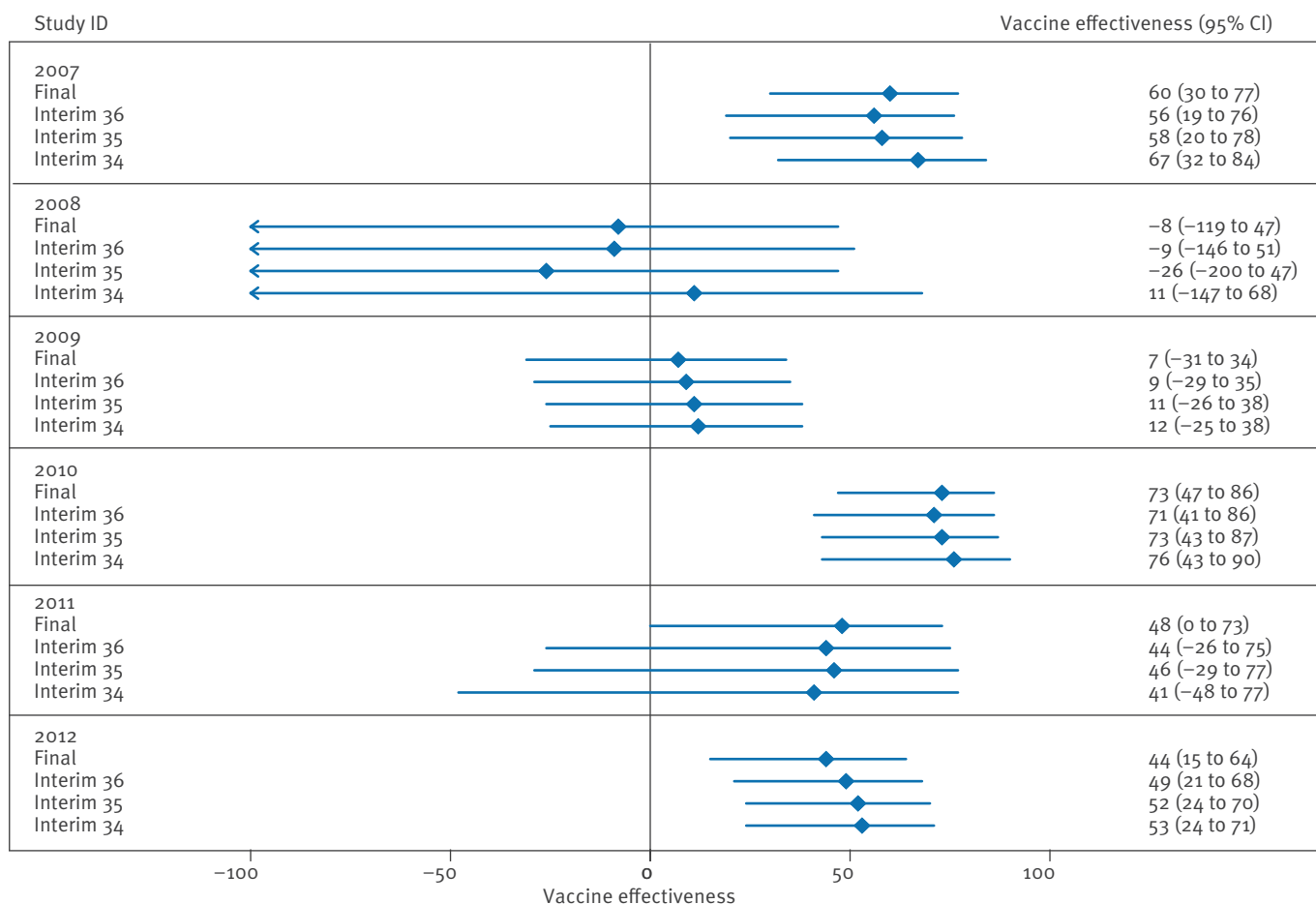
^d Data not provided for interim columns because this exclusion was only made for final estimates in sensitivity analysis 2.

^e Target group for vaccination includes people aged >65 years or with a condition predisposing them to severe influenza (not collected in 2007–2010).

^f Data on predisposing conditions not collected in 2007–2010.

FIGURE 2

Interim and final vaccine effectiveness estimates against influenza A and B for six influenza seasons, Victoria, Australia, 2007–2012



CI: confidence interval; ID: identity.

All models adjusted for age group (<18, 18–64, ≥65 years) and week of presentation. Oldest age group dropped from all models in 2010 due to perfect prediction (no unvaccinated cases). Final refers to the period defined by weeks 18–44; interim 36 is weeks 18–36; interim 35 is weeks 18–35; interim 34 is weeks 18–34.

which started and peaked earlier than in other years. The final estimate for that year used a more complete model with data collected over a much longer period but the VE point estimate was the same, and differed by only four percentage points when the analysis was restricted to the weeks of maximum influenza activity [22]. Thus, interim estimates may be their most reliable when made after the peak, which is more likely in seasons which start early. For weeks 18 to 36 of the 2013 season, our interim estimate at the time of writing was 43% (95% CI: -30 to 75). However, like 2008, the 2013 season has been characterised by a late start and relatively low activity. In addition the VE estimate was unusually sensitive to the model used. Consequently, we expect the interim estimate for 2013 to be less reliable than in other years.

We expected interim estimates would be their least reliable when made for specific, smaller groups, such

as people in a target group for vaccination. Moreover in the presence of waning VE within a season, it would be expected that the distribution of vaccinated cases would be skewed towards the end of the season, resulting in a lower final VE estimate. For example, in the 2011/12 European season, pooled estimates against A(H3) for people in a target group for vaccination were 43% (95% CI: -0.4 to 68) in the interim [27] and 25% (95% CI: -6 to 46) at the end of the season [12]. Similarly, our final estimates for people in a target group for vaccination in 2011 declined 13 percentage points, from 61% to 48%. Conversely, estimates increased two percentage points in 2012 but the sample size was larger in 2012 and the season peaked earlier. Meaningful differences between interim and final estimates might also be expected when making estimates separately for each type/subtype, as the distribution of cases may be skewed or the number of exposed cases may be small.

Estimates varied little when the model used for final estimates was altered, as was done in the second and fourth sensitivity analyses. The restriction of patients to include only those presenting within eight days was done to reduce the possibility of false negatives. However, this modification to the model may not be expected to alter estimates, as imperfect, nondifferential sensitivity in the presence of perfect specificity will not usually bias estimates [19, 28]. In contrast, modifying the covariates in the model might be expected to have a greater impact on both point estimates (by removing or introducing bias) and precision. By comparison with the principle analysis, we observed modest changes using a larger model, suggesting the more parsimonious model would have sufficed for these data. However, this may not always be the case. In some circumstances, larger models can reduce the effective sample size used due to complete or quasi-complete separation (also known as perfect prediction), which can inflate estimates and reduce precision [29]. For the data reported here, perfect prediction led to the loss of the oldest age group in the 2010 analyses. This problem has also been reported by the I-MOVE investigators when including calendar time (week) as a categorical variable, due to perfect prediction within a week or weeks [11]. In such cases, it may be preferable to employ methods such as exact logistic regression or penalised likelihood estimation to avoid generating biased estimates [29].

The relatively recent adoption of the test-negative study design [17-19] has permitted rapid dissemination of VE estimates on a yearly and interim basis, and consideration of these estimates in vaccine strain selection meetings has been suggested for some time [30]. However at this early stage, VE estimates are unlikely to influence strain selection; VE studies are less developed than the immunogenicity studies that have been used for decades to guide strain selection and should not yet be expected to provide reliable estimates of VE by type, sub-type, age-group and target group. However, our results illustrate the likely range of protection afforded by trivalent influenza vaccines (the only vaccines licensed in Australia) and support the use of late interim estimates as a proxy for final estimates. As VE studies evolve, their usefulness for strain selection should improve. The results presented here are hypothetical comparisons using cleaned data. It would be instructive to see a similar retrospective comparison for countries in the northern hemisphere.

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Conflict of interest

None declared.

Authors' contributions

SGS conceptualised the study, undertook analysis and interpretation of the data, and participated in writing the manuscript. HK conceptualised the study, undertook interpretation of the data and participated in writing the manuscript.

References

1. Barr IG, McCauley J, Cox N, Daniels R, Engelhardt OG, Fukuda K, et al. Epidemiological, antigenic and genetic characteristics of seasonal influenza A(H1N1), A(H3N2) and B influenza viruses: basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009-2010 Northern Hemisphere season. *Vaccine*. 2009;28(5):1156-67. <http://dx.doi.org/10.1016/j.vaccine.2009.11.043>. PMID:20004635.
2. World Health Organization (WHO). WHO recommendations on the composition of influenza virus vaccines. Geneva: WHO. [Accessed 23 Sep 2013]; Available from: <http://www.who.int/influenza/vaccines/virus/recommendations/en/>
3. Valenciano M, Kissling E, I-MOVE case-control study team. Early estimates of seasonal influenza vaccine effectiveness in Europe: results from the I-MOVE multicentre case-control study, 2012/13. *Euro Surveill*. 2013;18(7):pii=20400. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20400>
4. Skowronski DM, Janjua NZ, De Serres G, Dickinson JA, Winter A, Mahmud SM, et al. Interim estimates of influenza vaccine effectiveness in 2012/13 from Canada's sentinel surveillance network, January 2013. *Euro Surveill*. 2013;18(5):pii=20394. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20394>
5. McMenamin J, Andrews N, Robertson C, Fleming DM, Durnall H, von Wissmann B, et al. Effectiveness of seasonal 2012/13 vaccine in preventing laboratory-confirmed influenza infection in primary care in the United Kingdom: mid-season analysis 2012/13. *Euro Surveill*. 2013;18(5):pii=20393. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20393>
6. Centers for Disease Control and Prevention (CDC). Interim adjusted estimates of seasonal influenza vaccine effectiveness - United States, February 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62(7):119-23. PMID:23425960.
7. Castilla J, Martínez-Baz I, Martínez-Artola V, Fernandez-Alonso M, Reina G, Guevara M, et al. Early estimates of influenza vaccine effectiveness in Navarre, Spain: 2012/13 mid-season analysis. *Euro Surveill*. 2013;18(7):pii=20404. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20404>
8. Bragstad K, Emborg HD, Fischer TK, Voldstedlund M, Gubbels S, Andersen B, et al. Low vaccine effectiveness against influenza A(H3N2) virus among elderly people in Denmark in 2012/13 - a rapid epidemiological and virological assessment. *Euro Surveill*. 2013;18(6):pii=20397. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20397>
9. Centers for Disease Control and Prevention (CDC). Early estimates of seasonal influenza vaccine effectiveness--United States, January 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62(2):32-5. PMID:23325354.
10. Kissling E, Valenciano M, I-MOVE case-control studies team. Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010/11: I-MOVE, a multicentre case-control study. *Euro Surveill*. 2011;16(11):pii=19818. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19818>. PMID:21435329.
11. Kissling E, Valenciano M, Cohen JM, Oroszi B, Barret AS, Rizzo C, et al. I-MOVE multi-centre case control study 2010-11: overall and stratified estimates of influenza vaccine effectiveness in Europe. *PLoS One*. 2011;6(11):e27622. <http://dx.doi.org/10.1371/journal.pone.0027622>. PMID:22110695. PMCid:PMC3216983.
12. Kissling E, Valenciano M, Larrauri A, Oroszi B, Cohen JM, Nunes B, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case-control study. *Euro Surveill*. 2013;18(5):pii=20390. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20390>

13. Pebody RG, Andrews N, McMenamin J, Durnall H, Ellis J, Thompson CI, et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection. *Euro Surveill.* 2013;18(5):pii=20389. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20389>
14. Castilla J, Martínez-Baz I, Martínez-Artola V, Reina G, Pozo F, García Cenoz M, et al. Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12. *Euro Surveill.* 2013;18(5):pii=20388. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20388>
15. Belongia EA, Kieke BA, Donahue JG, Coleman LA, Irving SA, Meece JK, et al. Influenza vaccine effectiveness in Wisconsin during the 2007-08 season: comparison of interim and final results. *Vaccine.* 2011;29(38):6558-63. <http://dx.doi.org/10.1016/j.vaccine.2011.07.002>. PMID:21767593.
16. Kelly H, Carville K, Grant K, Jacoby P, Tran T, Barr I. Estimation of influenza vaccine effectiveness from routine surveillance data. *PLoS One.* 2009;4(3):e5079. <http://dx.doi.org/10.1371/journal.pone.0005079>. PMID:19333374. PMCid:PMC2658741.
17. Foppa IM, Haber M, Ferdinands JM, Shay DK. The case test-negative design for studies of the effectiveness of influenza vaccine. *Vaccine.* 2013;31(30):3104-9. <http://dx.doi.org/10.1016/j.vaccine.2013.04.026>. PMID:23624093.
18. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine.* 2013;31(17):2165-8. <http://dx.doi.org/10.1016/j.vaccine.2013.02.053>. PMID:23499601.
19. Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *Int J Epidemiol.* 2007;36(3):623-31. <http://dx.doi.org/10.1093/ije/dym021>. PMID:17403908.
20. Thursky K, Cordova SP, Smith D, Kelly H. Working towards a simple case definition for influenza surveillance. *J Clin Virol.* 2003;27(2):170-9. [http://dx.doi.org/10.1016/S1386-6532\(02\)00172-5](http://dx.doi.org/10.1016/S1386-6532(02)00172-5). PMID: 12829039.
21. Fielding JE, Grant KA, Tran T, Kelly HA. Moderate influenza vaccine effectiveness in Victoria, Australia, 2011. *Euro Surveill.* 2012;17(11):pii=20115. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20115>. PMID:22449867.
22. Fielding JE, Grant KA, Garcia K, Kelly HA. Effectiveness of seasonal influenza vaccine against pandemic (H1N1) 2009 virus, Australia, 2010. *Emerg Infect Dis.* 2011;17(7):1181-7. <http://dx.doi.org/10.3201/eid1707.101959>. PMID:21762570. PMCid:PMC3381383.
23. Fielding JE, Grant KA, Papadakis G, Kelly HA. Estimation of type- and subtype-specific influenza vaccine effectiveness in Victoria, Australia using a test negative case control method, 2007-2008. *BMC Infect Dis.* 2011;11:170. <http://dx.doi.org/10.1186/1471-2334-11-170>. PMID:21669006. PMCid:PMC3131256.
24. Kelly HA, Grant KA, Fielding JE, Carville KS, Looker CO, Tran T, et al. Pandemic influenza H1N1 2009 infection in Victoria, Australia: No evidence for harm or benefit following receipt of seasonal influenza vaccine in 2009. *Vaccine.* 2011;29(37):6419-26. <http://dx.doi.org/10.1016/j.vaccine.2011.03.055>. PMID:21473950.
25. Sullivan SG, Tay EL, Kelly H. Variable definitions of the influenza season and their impact on vaccine effectiveness estimates. *Vaccine.* 2013;31(40):4280-3. <http://dx.doi.org/10.1016/j.vaccine.2013.06.103>. PMID:23850417.
26. Kelly H, Grant K. Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. *Euro Surveill.* 2009;14(31):pii=19288. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19288>
27. Kissling E, Valenciano M, I-MOVE case-control studies team. Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicentre case-control study, 2011/12. *Euro Surveill.* 2012;17(15):pii=20146. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20146>. PMID:22516046.
28. Greenland S, Lash TL. Bias Analysis. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins, 2008:345-80.
29. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. *Stat Med.* 2002;21(16):2409-19. <http://dx.doi.org/10.1002/sim.1047>. PMID:12210625.
30. Skowronski DM, De Serres G, Dickinson J, Petric M, Mak A, Fonseca K, et al. Component-specific effectiveness of trivalent influenza vaccine as monitored through a sentinel surveillance network in Canada, 2006-2007. *J Infect Dis.* 2009;199(2):168-79. <http://dx.doi.org/10.1086/595862>. PMID:19086914.