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Influenza vaccine effectiveness by test-negative design – Comparison of inpatient and outpatient settings

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Abstract

Background—Observational studies of influenza vaccine effectiveness (VE) are increasingly using the test-negative design. Studies are typically based in outpatient or inpatient settings, but these two approaches are rarely compared directly. The aim of our study was to assess whether influenza VE estimates differ between inpatient and outpatient settings.

Methods—We searched the literature from Medline, PubMed and Web of Science using a combination of keywords to identify published studies of influenza VE using the test-negative design. Studies assessing any type of influenza vaccine among any population in any setting were considered, while interim studies or re-analyses were excluded. Retrieved articles were reviewed, screened and categorized based on study setting, location and influenza season. We searched for parallel studies in inpatient and outpatient settings that were done in the same influenza season, in the same location, and in the same or similar age groups. For each of the pairs identified, we estimated the difference in VE estimates between settings, and we tested whether the average difference was significant using a paired *t*-test.

Results—In total 25 pairs of estimates were identified that permitted comparisons between VE estimates in inpatient and outpatient study settings. Within pairs, the prevalence of influenza was generally higher among patients enrolled in the outpatient studies, while influenza vaccination coverage among the test-negative control groups was generally higher in the inpatient studies. There was no heterogeneity in the paired differences in VE, and the pooled difference in VE between inpatient and outpatient studies was −2% (95% confidence interval: −12%, 10%).

Conclusions—We found no differences in VE estimates between inpatient and outpatient settings by studies using the test-negative design. Further research involving direct comparisons of VE estimates from the two settings in the same populations and years would be valuable.

Keywords

Influenza; Vaccination; Vaccine effectiveness; Public health; Case control study

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1. Introduction

Influenza viruses are associated with a substantial disease burden of both medically attended ambulatory care and hospitalizations [1,2]. Vaccination is the best means of preventing influenza virus infections, but influenza vaccine effectiveness (VE) may differ from year to year and among different populations. Recently, there have been increasing numbers of studies estimating influenza VE using the test-negative design [3]. In this study design, patients are enrolled in outpatient clinics and/or hospitals based on a clinical case definition such as acute respiratory illness (ARI) or other syndromes consistent with influenza virus infections. Patients are then tested for influenza virus, and VE is estimated from the odds ratio comparing the odds of vaccination among patients testing positive for influenza versus those testing negative, adjusting for potential confounding factors. This study design is believed to be valid under a range of scenarios [4,5]. Importantly, this design is easy to implement in both inpatient and outpatient settings.

Estimates obtained from inpatient and outpatient settings in the same population may be expected to differ for several reasons. First, patients presenting to hospitals may present later in infection, may be older and may be more likely to be co-infected with another respiratory virus. There may therefore be a greater number of false negatives due to reduced viral shedding with time and age [6]. Such reduced sensitivity in case ascertainment can result in attenuation of the odds ratio [3]. In addition, patients at the highest risk of hospitalization, if infected, may be less protected by the vaccine because of poorer VE in people of older age [7] or immunosuppression as a result of chronic underlying conditions [8]. Furthermore, VE estimates between settings may also differ according to vaccine type or brand used. However, few previous studies have directly compared estimates in hospital-based studies with those from outpatient-based studies [9,10].

The aim of this study was to compare directly the VE estimates obtained from studies based in hospitalized patients with studies that recruited patients in an outpatient setting, using the test-negative design. Because VE can vary from location to location and from year to year, and by age, we intended to focus on comparisons of VE estimates from the same location and influenza season and in the same or similar age groups.

2. Methods

2.1. Study search and selection

We previously conducted a review of test-negative studies of influenza VE [3]. All papers identified as meeting the search criteria in that study were also included in the present analysis. The first online searches were updated on 22 July 2015. A second search was done on 28 December 2015. Papers were searched on Medline, PubMed and Web of Science for the following key words:

1. “Influenza” OR “flu”.
2. “Vaccine effectiveness” OR “VE”.
3. “Test-negative” OR “test negative” OR “case-control” OR “case control”.

4. 1, 2 and 3.

Consistent with our previous study, only studies using the test-negative design on any type of influenza vaccination were considered. Articles that did not use a test-negative design, were a reanalysis of previously published data, or reported only interim estimates were excluded. Articles were restricted to English. Two reviewers (SF and SGS) independently retrieved and identified articles fitting the inclusion criteria. All studies meeting the inclusion criteria were reviewed for study setting (inpatient, outpatient or both), influenza season, and geographic location. Studies which pooled results for inpatients and outpatients and did not provide any breakdown were not considered further. The remaining articles were then grouped according to the season and location. Within these groups, studies were further scrutinized to identify pairs or triplets of papers from the same location and influenza season that reported VE estimates for the same influenza type/subtype and the same or similar age groups.

Study design features were abstracted using a standardized form. We extracted information on study location, setting, season, surveillance system, circulating influenza type/subtype, type of influenza vaccine, population age or age group, interval since onset to presentation, definitions of comorbidities, number of influenza positive and negative included in primary analysis, number of vaccinated among each group, and the statistical model used. Adjusted VE estimates were abstracted for influenza overall or the type/subtype common to both studies in each pair and, where possible, for specific age groups. To minimize discrepancies associated with different cut-points for age groupings in study pairs, we contacted authors and requested re-estimation of VE for consistent age groups within each pair.

2.2. Study comparison

To examine whether there were any significant differences in VE point estimates against influenza overall or by type/subtype within study pairs, we used a paired student *t*-test comparing the differences between the VE estimates of inpatient settings with those of outpatient settings for all pairs. For each study pair, the difference in VE estimates (ΔVE) was calculated as

$$\Delta\mathrm{VE}=\mathrm{VE}_{\mathrm{ip}}-\mathrm{VE}_{\mathrm{op}}$$

where $\mathrm{VE}_{\mathrm{ip}}$ was the VE estimated in the inpatient study and $\mathrm{VE}_{\mathrm{op}}$ was the VE estimated in the outpatient study. 95% confidence intervals for ΔVE were calculated by bootstrapping, using 1000 resamples [11]. Pooled ΔVE estimates against influenza A or B were calculated after removing estimates on duplicated age groups, assuming a fixed effects model, and heterogeneity was examined by I^2 and Cochran's Q test. Considering heterogeneity on severity and VE may differ between influenza type/subtype, pooled ΔVE estimates against influenza by type/subtype were also calculated. To examine if variation exists between countries, we estimated country-stratified pooled ΔVE if more than one pair was available. Differences in study design features were compared by whether the ΔVE was positive or negative. All analyses were conducted using R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 85 full-text articles were retrieved from the previous systematic review [3], to which a further 35 articles were added from the updated search to give a total of 120 published test-negative studies. Grouping studies by location, season, age group and VE estimates by type/subtype, we identified 8 study pairs/triplet from a total of 14 publications [9,10,12–23] (Table 1, Fig. 1). These 8 pairs/triplet included VE estimates from five countries: Australia (n = 2), Canada (n = 1), USA (n = 1), Spain (n = 2), and New Zealand (n = 2) (Fig. 1). Of the Australian triplet, one inpatient study was paired with two different outpatient studies, and VE estimates against all influenza and H1N1 virus were compared, respectively (Table 1) [12,13,20]. One study in Spain and two studies in New Zealand reported estimates from both inpatient and outpatient settings and were thus self-paired (Table 1) [9,10,23]. In summary 14 studies were included which contributed 7 pairs and 1 triplet, providing 25 pairs of VE estimates available for further analysis (Fig. 1, Table 2).

The 14 studies reported VE estimates in five influenza seasons from 2010 to 2014 (Table 1). In some cases, the geographic locations from which patients were recruited were not exactly the same. For example, of the study triplet from Australia, inpatient estimates at a national level were compared with outpatient estimates at a regional level [12,13,20]. The periods during which patients were recruited were closely aligned. With the exception of the three self-paired studies, all study pairs used a different clinical case definition, included different variables in their statistical model, and specified their variables differently (Table 1) [9,10,23]. Intervals from illness onset to presentation varied between settings, with most outpatient studies restricted to 7 days since onset, while four among eight inpatient studies did not have a restriction [14,16,21,24].

Among 25 pairs of VE estimates, 14 estimates were against all influenza while the other 11 were for particular influenza types/subtypes (Figs. 1 and 2). All pairs were matched based on having the same age range of patients except for one pair in Canada (Table 2) [14,15]. Fourteen pairs provided VE estimates for patients of all ages [9,10,21–23], two pairs on children eligible for influenza vaccine [9,23], six pairs focused on adults [9,12,13,16–20,23], and four pairs were restricted to elderly adults aged ≥50 or ≥65 years old (Fig. 1, Table 2) [9,14,15,18,19,23]. Although most (n = 24) age ranges were the same, the mean/median age included in each study was rarely reported, so we could not ascertain whether there was a substantial difference in the age distributions. The proportions of patients with high risk conditions were always higher among inpatient settings when comparisons were possible. In one case, in the pair of studies conducted in Spain in the 2011–2012 season, only patients in a target group for vaccination were recruited for the outpatient study [14,15]. Among 14 pairs comparing influenza overall, the proportion of patients testing positive for any influenza virus ranged from 9.5% to 33.3% in inpatient settings, and from 14.0% to 60.7% in outpatient settings. The proportion of any influenza positive cases was higher in outpatient settings in most pairs (n = 12; Table 2), while one pair from Australia reported significantly lower influenza positivity among outpatients [12,13]. In contrast, vaccination coverage obtained from either influenza-positive cases or influenza-negative controls was generally higher among inpatients. Among influenza-negative controls (n = 14), vaccination

coverage in the inpatient control group was more than 20 percentage points higher in 6 pairs than among the corresponding outpatient control group [9,12–17,21–23].

VE estimates in both settings demonstrated a modest to high effectiveness of influenza vaccine (Table 2, Fig. 2). Using a paired student t-test to compare 25 pairs of VE estimates, we found that there was no significant difference in VE estimates between inpatient and outpatient setting ($p = 0.840$) and no significant difference in VE against influenza A or B ($p = 0.755$). Within each pair, confidence intervals overlapped with ΔVE across zero except one pair from New Zealand estimating VE for children aged 6 months to 17 years (Fig. 2). Point estimates of ΔVE against any influenza virus ranged from −110% to 119%, and ranged from −29% to 31% against influenza by type/subtype. In meta-regression, we removed estimates by age group when overall estimates available, restricted to VE estimates against any influenza virus, and I^2 and Cochran's Q test implied no heterogeneity. Pooled ΔVE from seven pairs was −2% (−12%, 10%), consistent with no substantial differences between VE estimates in hospital-based studies or outpatient studies (Fig. 2). The number of pairs was not enough to conduct a meta-regression to identify whether certain study design features were associated with positive or negative ΔVE. However, univariate analyses suggested there were no clear patterns. For example, studies which used differing age ranges, different statistical models, different variable specification, different restriction criteria or a different study period were balanced by ΔVE (Table 2). Pooled ΔVE was −5% (95% CI: −28%, 18%) against H1N1, −21% (95% CI: −45%, 4%) against H3N2, and 16% (95% CI: −7%, 39%) against influenza B, with three pairs pooled from each type/subtype. When stratified by country, we were able to estimate pooled ΔVE from Australia, Spain and New Zealand. For each country, the confidence interval of the pooled ΔVE crossed zero (Australia: 7% (95% CI: −12%, 30%); Spain: −18% (95% CI: −44%, 13%); New Zealand: −8% (95% CI: −27%, 10%)). No country-specific patterns were observed, but the number of pairs was small.

4. Discussion

From 120 articles assessing influenza VE using the test-negative design, we identified 14 publications with suitable information for paired comparison of VE estimates between inpatient and outpatient settings. Based on 25 pairs of VE estimates for 5 countries from 2010 to 2013, despite some absolute differences within many pairs, we found no evidence of substantial statistical difference in the VE estimates in the inpatient study and the outpatient study, with pooled ΔVE = −2% (95%CI: −12%, 10%).

Studies included varied in clinical case definitions, statistical models, variable specification and exclusion criteria. Nevertheless, the tendency for ΔVE to be positive or negative was not clearly associated with any differences in design features among studies. In outpatient settings, patients with medically attended influenzalike illness (ILI) or ARI were recruited, while in inpatient settings, patients could be hospitalized with severe acute respiratory illness (SARI) or any condition potentially related to influenza, with or without ARI/ILI and with varying time frames since symptoms onset. These variations in clinical case definition in inpatient populations may mean that among the hospitalization studies included, the patient populations were quite different and may have different distributions of confounding factors between test-positive and test-negative patients. It would be interesting to continue

this comparison within strata using standardized clinical case definitions for inpatients. Such studies should also account for relevant confounding factors, which were not always done in the studies included here.

We found that influenza positivity was generally lower among hospitalized patients. One potential reason is that inpatient studies may include proportionately more false test-negatives due to longer delays between illness onset and admission. As reported by a meta-analysis, the average duration of viral shedding was about 5 days since illness onset [6], while only three of eight inpatient studies restricted interval since symptoms onset to 7 days. This also may be partly affected by the age mix of patients within each matched pair. Although estimates were matched based on the same or a similar age group, the age distribution within each study was unclear. Thus, there may have been heterogeneity in viral load and shedding, and proportion influenza-positive [6,25].

In contrast, vaccination coverage among influenza-positive cases and influenza-negative controls was generally higher among inpatients. This is likely indicative of high risk status because hospitalized patients have severe disease and may therefore be more likely to be in a group indicated for vaccination. In the countries from which the included studies were derived, vaccination was provided free-of-charge to the elderly, and in most of these countries was also provided to people with high-risk conditions.

Except for one pair of VE estimates for children from New Zealand, we did not find any evidence of heterogeneity between VE estimates for all types/subtypes or in analyses stratified by type/subtype against hospitalization or outpatient consultations among each of the pairs. In the New Zealand study, the difference might be associated with residual confounding, and the authors of that article could not explain the observation [23]. Our findings are consistent with previous studies examining a broad range of assumptions of test-negative studies by modeling methods [5], and indicate that the test-negative design provides similar estimates of influenza VE in inpatient settings compared to the estimates that can be obtained from test-negative studies in outpatient settings (Fig. 2). Nevertheless, the tests used to detect heterogeneity may not have had high sensitivity with so few studies [26].

Inactivated influenza vaccines were the most frequently used types of vaccine in the studies reported here. Our findings are consistent with the view that inactivated influenza vaccines provide moderate protection against infection but do not provide any additional protection against severe disease requiring hospitalization if breakthrough infection (vaccine failure) occurs [27,28].

This study was limited by the few studies available that could be paired. While test-negative studies have been done in many other locations in outpatient setting, few studies have been reported in inpatient settings. A further barrier to effective matching was the use of slightly different age ranges for estimates. Where possible inpatient and outpatient VE estimates should be reported using comparable age groups. A further limitation arose from the use of inexact matching on geographical areas. In small countries, strain circulation may not differ very much among regions. However, for large countries like Australia and Canada, the

influenza seasons may differ somewhat across the country. Thus, matching a state or province estimate with a country-wide estimate may not be appropriate.

In conclusion, we did not observe substantial statistical heterogeneity between VE estimates in inpatient settings and outpatient settings based on 25 pairs of VE estimates against all influenza or by type/subtype from 14 published test-negative studies. After matching by season, geographic region and age group, VE estimates obtained from inpatient settings were not consistently higher than those from outpatient settings. Our study indicates that the application of the test-negative design in hospital settings tends to give similar estimates of VE compared to test-negative studies in outpatient settings (to within 10 percentage points). Further research involving direct comparisons of VE estimates from the two designs in the same populations and years would be valuable.

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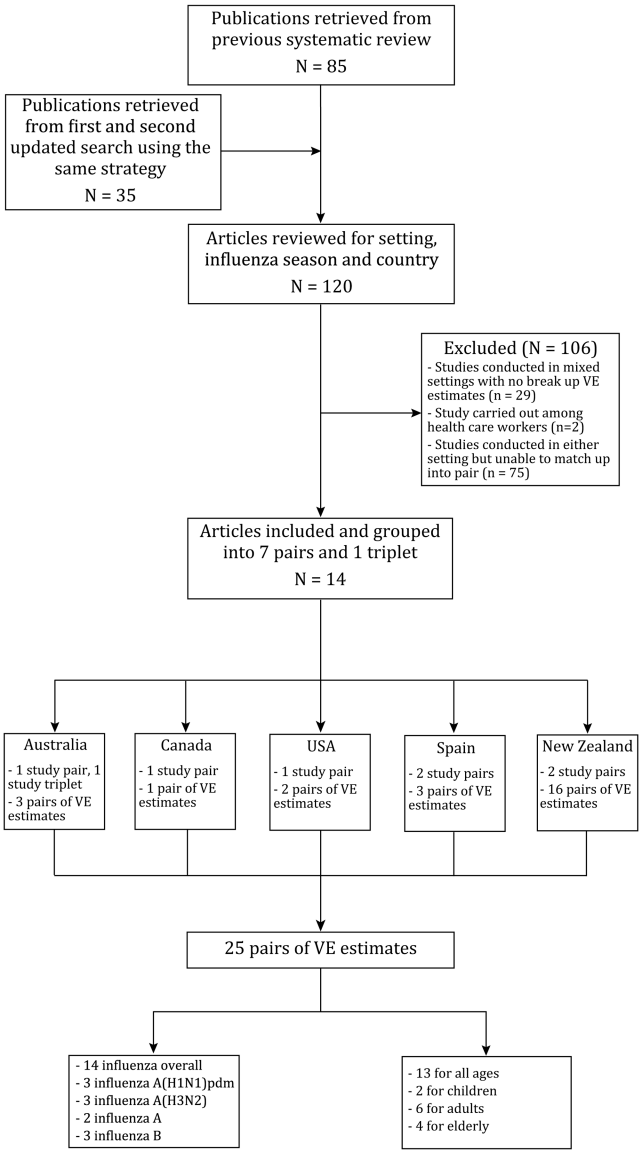

Fig. 1.

Flow chart of identification of eligible studies for comparing VE estimates between inpatient and outpatient settings using the test-negative design.

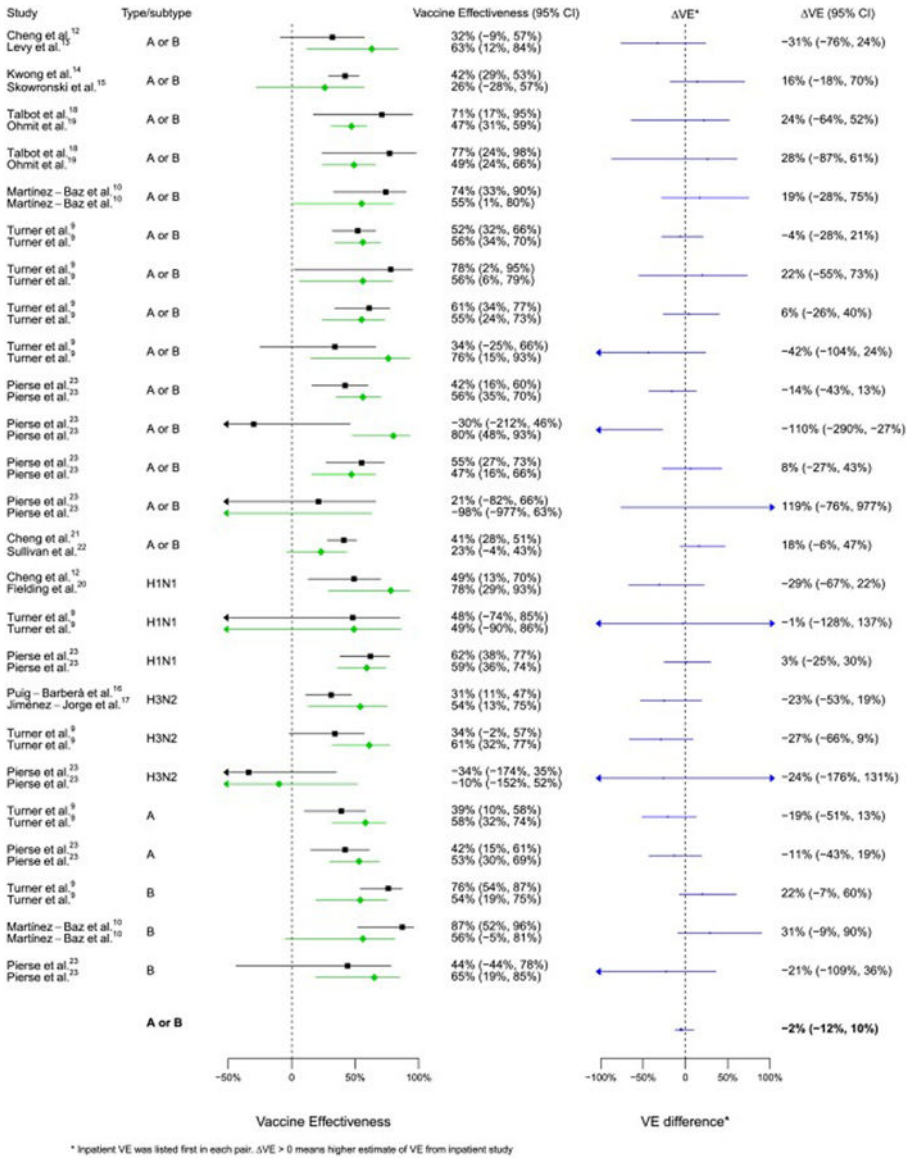

Fig. 2.

Comparison of VE estimates against influenza overall or by type/subtype between 25 matched pairs.

Table 1

Comparison of study design between inpatient and outpatient settings from 14 publications.

Study	Country	Season	Setting	Case definition	Interval since onset	Dominant type/subtype[b]	Vaccine match[c]	Time in model	Comorbid in model	% with high-risk condition
Cheng et al. [12]	Australia	2010	Inpatient	Admission	Unrestricted	H1pdm	Yes	Fortnight	Yes	79%
Levy et al. [13]	Western Australia		Outpatient	ILI	≤4d			Week	No	NA
Fielding et al. [20]	Victoria, Australia		Outpatient	ILI	≤4d			Month	No	
Kwong et al. [14]	Ontario, Canada	2010–2011	Inpatient	Admission	Unrestricted	H3	Yes	Month	Yes	≥72.8%[d]
Skowronski et al. [15]	Canada		Outpatient	ILI	≤7d			Week	Yes	34.9%
Puig-Barberàet al.[a] [16]	Valencia, Spain	2011–2012	Inpatient	ILI	Not specified	H3	No	Week	No	88%
Jimenez-Jorge et al.[a] [17]	Spain		Outpatient	ILI	≤7d			Week (cat)	No	62.9%
Talbot et al. [18]	Tennessee, USA	2011–2012	Inpatient	ARI	≤10d	H3	No	Onset to admission	Yes	86%
Ohmit et al. [19]	USA		Outpatient	ARI	≤7d			Fortnight	Yes	25.4%
Cheng et al. [21]	Australia	2012	Inpatient	Admission	Not specified	H3	No	Not specified	Yes	83.2%
Sullivan et al. [22]	Australia		Outpatient	ILI	Not specified			Month	No	NA
Martinez-Baz et al. [10]	Narrava, Spain	2012–2013	Inpatient	ILI	≤7d	B	Yes	Month	Yes	NA
Martinez-Baz et al. [10]	Narrava, Spain		Outpatient	ILI	≤7d			Month	Yes	NA
Turner et al. [9]	Auckland, New Zealand	2013	Inpatient	SARI	≤7d	H3	Yes	Week	Yes	64.5%
Turner et al. [9]	Auckland, New Zealand		Outpatient	ILI	≤7d			Week	Yes	NA
Pierse et al. [23]	Auckland, New Zealand	2014	Inpatient	SARI	≤7d	H1pdm	Yes	Timing of the intervention to peak of season	Yes	51%
Pierse et al. [23]	Auckland, New Zealand		Outpatient	ILI	≤7d			Timing of the intervention to peak of season	Yes	26%

[a] Enrolled patients targeted for influenza vaccination. Cases were positive for influenza A(H3N2) virus.

[b] Information retrieved either from studies or the WHO website.

[c] Information retrieved either from studies or the WHO website.

[d] 72.8% was the percentage of subjects with chronic cardiovascular disease.

Table 2

Comparison of study laboratory results, vaccination coverage and vaccine effectiveness between inpatient and outpatient settings from 25 pairs of estimates.[a]

Study	Age group	Influenza type/subtype	No. of positive/negative	Difference of test-positive proportion (95% CI)	No. of vac/pos	Vaccine coverage (among test-positive)	No. of vac/neg	Vaccine coverage (among test-negative)	Difference of vaccination coverage (95% CI)[b]	Adjusted VE (95% CI)	ΔVE (95% CI)
Cheng et al. [12]	≥18y	A or B	199/398	10% (4%, 16%)	57/199	29%	213/398	54%	30% (23%, 37%)	32%(−9%, 57%)	−31% (−76%, 24%)
Levy et al.[a] [13]			88/296		7/88	8%	70/296	24%	21% (13%, 29%)	63% (12%, 84%)	
Kwonget al. [14]	65+y	A or B	569/1661	−9%(−14%, −4%)	238/569	42%	934/1661	56%	21% (14%, 28%)	42% (29%, 53%)	16% (−18%, 70%)
Skowronski et al. [15]	50+y		116/222		37/116	32%	78/222	35%	10% (1%, 19%)	26% (−28%, 57%)	
Talbot et al. [18]	≥18y	A or B	17/152	−4% (−14%, 4%)	6/17	35%	97/152	64%	17% (9%, 25%)	71%(17%, 95%)	24% (−64%, 52%)
Ohmit et al. [19]			380/2235		122/380	32%	1055/2235	47%	3% (−20%, 26%)	47% (31%, 59%)	
Talbot et al. [18]	≥50y	A or B	13/124	−5%(−1%, 0%)	5/13	39%	89/124	72%	10%(1%, 19%)	77% (24%, 98%)	28% (−87%, 61%)
Ohmit et al. [19]			149/917		64/149	43%	563/917	61%	−4% (−32%, 24%)	49% (24%, 66%)	
Martinez-Baz et al. [10]	All ages	A or B	53/133	−32%(−40%, −24%)	11/53	21%	55/133	41%	3% (−8%, 14%)	74% (33%, 90%)	19% (−28%, 75%)
Martinez-Baz et al. [10]			317/205		14/317	4%	78/205	38%	16% (5%, 27%)	55% (1%, 80%)	
Turner et al. [9]	All ages	A or B	224/818	−11%(−14%, −8%)	82/224	37%	372/818	46%	28% (24%, 32%)	52% (32%, 66%)	−4% (−28%, 21%)
Turner et al. [9]			482/1013		44/482	9%	177/1013	18%	28% (21%, 35%)	56% (34%, 70%)	
Turner et al. [9]	6m-17y	A or B	51/306	−17%(−22%, −12%)	2/51	4%	40/306	13%	5% (1%, 9%)	78% (2%, 95%)	22% (−55%, 73%)
Turner et al. [9]			215/476		10/215	5%	37/215	8%	−1%(−7%, 5%)	56% (6%, 79%)	
Turner et al. [9]	18-64y	A or B	102/285	−7%(−13%, −1%)	26/102	26%	145/285	51%	30% (23%, 37%)	61% (34%, 77%)	6% (−26%, 40%)
Turner et al. [9]			248/489		24/248	10%	101/489	21%	16% (7%, 25%)	55% (24%, 73%)	
Turner et al. [9]	≥65y	A or B	71/227	−5%(−17%, 7%)	54/71	76%	187/227	82%	1% (−11%, 13%)	34% (−25%, 66%)	−42% (−104%, 24%)
Turner et al. [9]			19/48		10/19	53%	39/48	81%	24% (−1%, 49%)	76% (15% 93%)	
Pierse et al. [23]	All ages	A or B	304/735	−12%(−16%, −8%)	90/304	30%	267/735	36%	15% (10%, 20%)	42% (16%, 60%)	−14% (−43%, 13%)
Pierse et al. [23]			477/677		55/477	12%	144/677	21%	18% (12%, 24%)	56% (35%, 70%)	
Pierse et al. [23]	6m-17y	A or B	84/347	−18%(−24%, −12%)	9/84	11%	31/347	9%	−3% (−8%, 2%)	−30%(−212%, 46%)	−110% (−290%, −27%)
Pierse et al. [23]			174/284		5/174	3%	35/284	12%	8%(1%, 15%)	80% (48%, 93%)	
Pierse et al. [23]	18-64y	A or B	169/214	−1%(−7%, 5%)	41/169	24%	95/214	44%	23%(15%, 31%)	55% (27%, 73%)	8% (−27%, 43%)
Pierse et al. [23]			285/349		35/285	12%	74/349	21%	12% (4%, 20%)	47% (16%, 66%)	
Pierse et al. [23]	≥65y	A or B	51/174	−6%(−19%, 7%)	40/51	78%	141/174	81%	2% (−11%, 15%)	21% (−82%, 66%)	119%(−76%, 977%)
Pierse et al. [23]			18/44		15/18	83%	35/44	80%	−5% (−26%, 16%)	−98% (−977%, 63%)	
Cheng et al. [21]	All ages	A or B	963/1216	2%(−1%, 5%)	437/963	45%	689/1216	57%	30% (26%, 34%)	41%(28%, 51%)	18% (−6%, 47%)
Sullivan et al. [22]			593/821		116/593	20%	218/821	27%	26% (22%, 30%)	23% (−4%, 43%)	
Cheng et al. [24]	≥18y	H1N1	163/398	−2% (−9%, 5%)	40/163	25%	213/398	54%	39%(31%, 47%)	49% (13%, 70%)	−29% (−67%, 22%)
Fielding et al. [20]			91/123		4/91	5%	21/123	13%	20% (12%, 28%)	78% (29%, 93%)	
Turner et al. [9]	All ages	H1N1	13/818	−1%(−2%, 0%)	5/13	39%	372/818	46%	28% (24%, 32%)	48% (−74%, 85%)	− 1% (−128%, 136%)
Turner et al. [9]			30/1013		3/30	10%	177/1013	18%	29% (0%, 58%)	49% (−90%, 86%)	
Pierse et al. [23]	All ages	H1N1	170/735	−14%(−18%, −1%)	33/170	19%	267/735	36%	15% (10%, 20%)	62% (38%, 77%)	3% (−25%, 30%)
Pierse et al. [23]			324/677		32/324	10%	144/677	21%	10% (3%, 17%)	59% (36%, 74%)	

Study	Age group	Influenza type/subtype	No. of positive/negative	Difference of test-positive proportion (95% CI)	No. of vac/pos	Vaccine coverage (among test-positive)	No. of vac/neg	Vaccine coverage (among test-negative)	Difference of vaccination coverage (95% CI)[b]	Adjusted VE (95% CI)	ΔVE (95% CI)
Puig-Barberà et al. [16]	≥18y	H3N2	544/1370	−38%(−44%, −32%)	314/544	58%	855/1370	62%	20% (10%, 30%)	31% (11%, 47%)	−23% (−53%, 19%)
Jimenez-Jorge et al. [17]			204/103		84/204	41%	44/103	43%	16% (8%, 24%)	54% (13%, 75%)	
Turner et al. [9]	All ages	H3N2	119/818	2%(−1%, 5%)	51/119	43%	372/818	46%	28% (24%, 32%)	34%(−2%, 57%)	−27% (−66%, 9%)
Turner et al. [9]			116/1013		20/116	17%	177/1013	18%	26%(15%, 37%)	61% (32%, 77%)	
Pierse et al. [23]	All ages	H3N2	53/735	−1%(−4%, 2%)	27/53	51%	267/735	36%	15% (10%, 20%)	−34%(−174%, 35%)	−24% (−176%, 131%)
Pierse et al. [23]			53/677		12/53	23%	144/677	21%	28% (10%, 46%)	− 10%(−152%, 52%)	
Turner et al. [9]	All ages	A	163/818	−6% (−9%, −3%)	68/163	42%	372/818	46%	28% (24%, 32%)	39% (10%, 58%)	−19% (−51%, 13%)
Turner et al. [9]			290/1013		28/290	10%	177/1013	18%	32% (24%, 40%)	58% (32%, 74%)	
Pierse et al. [23]	All ages	A	275/735	− 10% (−14%, −6%)	78/275	28%	267/735	36%	15% (10%, 20%)	42%(15%, 61%)	−11% (−43%, 19%)
Pierse et al. [23]			396/677		47/396	12%	144/677	21%	16% (10%, 22%)	53% (30%, 69%)	
Turner et al. [9]	All ages	B	62/818	−9%(−12%, −6%)	14/62	23%	372/818	46%	28% (24%, 32%)	76% (54%, 87%)	22% (−7%, 60%)
Turner et al. [9]			196/1013		18/196	8%	177/1013	18%	14% (3%, 25%)	54% (19%, 75%)	
Martinez-Baz et al. [10]	All ages	B	32/114	−33%(−41%, −25%)	5/32	16%	48/114	42%	32%(22%, 42%)	87% (52%, 96%)	31% (−9%, 90%)
Martinez-Baz et al. [10]			231/194		11/231	5%	20/194	10%	11% (−2%, 24%)	56%(−5%, 81%)	
Pierse et al. [23]	All ages	B	29/735	−7%(−10, −4%)	12/29	41%	267/735	36%	15% (10%, 20%)	44% (−44%, 78%)	−21%(−109%, 36%)
Perse et al. [23]			81/677		8/81	10%	144/677	21%	31% (12%, 50%)	65%(19%, 85%)	

[a] Inpatient results were listed first in each pair.

[b] Difference of vaccination coverage among test-negative were listed first, and among test-positive were listed second in each pair.