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# The impact of repeated vaccination on influenza vaccine effectiveness: a systematic review and meta-analysis

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## Abstract

**Background:** Conflicting results regarding the impact of repeated vaccination on influenza vaccine effectiveness (VE) may cause confusion regarding the benefits of receiving the current season's vaccine.

**Methods:** We systematically searched MEDLINE, Embase, PubMed, and Cumulative Index to Nursing and Allied Health Literature from database inception to August 17, 2016, for observational studies published in English that reported VE against laboratory-confirmed influenza for four vaccination groups, namely current season only, prior season only, both seasons, and neither season. We pooled differences in VE (ΔVE) between vaccination groups by influenza season and type/subtype using a random effects model. The study protocol is registered with PROSPERO (registration number: CRD42016037241).

**Results:** We identified 3435 unique articles, reviewed the full text of 634, and included 20 for meta-analysis. Compared to prior season vaccination only, vaccination in both seasons was associated with greater protection against influenza H1N1 (ΔVE = 26%; 95% CI, 15% to 36%) and B (ΔVE = 24%; 95% CI, 7% to 42%), but not H3N2 (ΔVE = 10%; 95% CI, −6% to 25%). Compared to no vaccination for either season, individuals who received the current season's vaccine had greater protection against H1N1 (ΔVE = 61%; 95% CI, 50% to 70%), H3N2 (ΔVE = 41%; 95% CI, 33% to 48%), and B (ΔVE = 62%; 95% CI, 54% to 68%). We observed no differences in VE between vaccination in both seasons and the current season only for H1N1 (ΔVE = 4%; 95% CI, −7% to 15%), H3N2 (ΔVE = −12%; 95% CI, −27% to 4%), or B (ΔVE = −8%; 95% CI, −17% to 1%).

**Conclusions:** From the patient perspective, our results support current season vaccination regardless of prior season vaccination. We found no overall evidence that prior season vaccination negatively impacts current season VE. It is important that future VE studies include vaccination history over multiple seasons in order to evaluate repeated vaccination in more detail.

**Keywords:** Influenza, Vaccine effectiveness, Repeated vaccination

## Background

Seasonal influenza vaccination is the predominant strategy for preventing influenza-related morbidity and mortality. Annual vaccination is recommended because of waning immunity and because influenza strains undergo antigenic drift, necessitating reviewing and, in most seasons, changing of the vaccine to better match the upcoming season's strains [1]. Because of the frequently changing vaccine, influenza vaccine effectiveness (VE) is assessed annually.

With increasing numbers of people being immunized against influenza annually, the impact of repeated vaccination has gained significant interest. Of particular concern are older adults (65 years and above), who tend to have more comorbidities as they age, as both age and co-morbidities increase their risk of influenza-associated complications [2]. If repeated vaccination negatively

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impacts current VE, then having been repeatedly vaccinated in earlier years may be detrimental to the protection of older adults when they need it most. Studies from the 1970s and 1980s found inconsistent results regarding the impact of repeated vaccination [3, 4]. In 1999, a systematic review and meta-analysis of field studies, trials, and serologic studies found no evidence of negative impacts of repeated vaccination [5]. More recently, some studies have found VE to be reduced in those who received repeated prior influenza vaccinations [6–8].

Since most VE studies now report estimates taking into account vaccination status for both current and prior seasons, we sought to evaluate the impact of repeated vaccination on VE through a systematic review and meta-analysis. We aimed to assess the impact of repeated vaccination to provide evidence to support patient and clinician decision-making about receiving the current season's influenza vaccine. We considered two patient-relevant scenarios, (1) for those who received last season's vaccine, should they also receive this season's vaccine? (vaccination in both seasons versus prior season only) and (2) for those who did not receive last season's vaccine, should they receive this season's vaccine? (vaccination in current season only versus neither season). We also considered a policy-relevant scenario, comparing VE for vaccination in both seasons versus the current season only. This latter scenario is not relevant to patients because they cannot alter their vaccination history; however, the findings may influence policy decisions regarding whether or not to offer annual vaccination to the entire population if there was evidence suggesting that repeated vaccination could negatively impact future VE.

## Methods

### Search strategy and selection criteria

We searched MEDLINE, Embase, PubMed, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases from inception to August 17, 2016. We developed a unique search strategy for each database with the assistance of a scientific librarian; across all databases, the search terms included "influenza", "immunization", "vaccine", and "effectiveness", and articles were restricted to those published in English (Additional file 1). Two reviewers (SB, LR) independently screened titles and abstracts, and hand-searched the references of the included articles.

Eligible studies used observational study designs (e.g., prospective cohort, test-negative case-control) and reported VE against medically attended, laboratory-confirmed influenza for four mutually exclusive vaccination groups, namely current season only, prior season only, both current and prior seasons, and neither season (reference group). Prior season vaccination referred primarily to vaccination status in the year immediately prior to the season being examined. Studies with other definitions of prior season (e.g., any dose in the prior two seasons) were excluded from the meta-analysis, but were described in a qualitative synthesis. We excluded interim VE reports that were superseded by end-of-season reports, and conference abstracts and proceedings. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting results [9].

### Risk of bias assessment

We used the Newcastle–Ottawa scale (NOS) to assess the risk of bias of included case-control and cohort studies [10]. Two reviewers (SB, LR) independently evaluated the quality of each study based on the domains of selection, comparability, and either exposure (for case-control studies) or outcome (for cohort studies). For studies using the test-negative design, we determined whether calendar time had been included in the adjusted analyses [11]. Studies were categorized as being at low, moderate, or high risk of bias if they were missing one or less items, two to three items, or more than three items on the NOS, respectively [12]. Any disagreements between the two reviewers were resolved by consensus.

### Data analysis

Two reviewers (SB, LR) abstracted the data using a structured electronic data extraction form, extracting study characteristics (e.g., study design, recruitment setting, case definition) and VE estimates for the four vaccination groups, with discrepancies adjudicated by consensus. Whenever possible, we extracted VE reports by influenza type/subtype and age group and only included the most specific results reported (e.g., by age group or influenza type/subtype) in the meta-analysis. Because specific lineage information for influenza B was often unavailable, we used overall estimates for influenza B.

For each study included in the meta-analysis, VE estimates for current season only, prior season only, and both current and prior seasons were assessed against the reference group who were not vaccinated in either season. In the present study, VE estimates from each study were compared for those vaccinated in both the current and prior seasons to those vaccinated in the prior season only and to those vaccinated in the current season only by subtracting the VE estimates. The absolute differences in VE (ΔVE) were stratified by influenza type/subtype and season and calculated as (1) vaccinated in both seasons compared to the prior season only ($\Delta VE = VE_{both} - VE_{prior\ only}$), and (2) vaccinated in both seasons compared to the current season only ($\Delta VE = VE_{both} - VE_{current\ only}$). In both of the

above scenarios, a ΔVE greater than zero implies a higher VE estimate when vaccinated in both seasons than in either the current or the prior season only. We also assessed the VE of those vaccinated in the current season only compared to those vaccinated in neither season (pooled $VE_{current\ only}$).

We calculated confidence intervals for ΔVE by bootstrapping using 1000 samples [13]. Similar to previous work [14], we took 1000 samples from $VE_{current\ only}$, $VE_{prior\ only}$, and $VE_{both}$. We then estimated 1000 measures of ΔVE for both $\Delta VE = VE_{both} - VE_{current\ only}$ and $\Delta VE = VE_{both} - VE_{prior\ only}$; the 2.5% and 97.5% percentiles for ΔVE were computed as the confidence intervals. We used a random effects model to pool ΔVE estimates to compare the overall difference between vaccination in both seasons with vaccination in either the prior season only or the current season only. To compare VE for those vaccinated in the current season versus those vaccinated in neither season, we used a random effects model to pool the log odds ratio of the current season only VE estimates and converted the final pooled estimate back to a measure of VE. Statistical heterogeneity was assessed using the $I^2$ statistic and Cochran's Q test. Meta-analyses were performed in MetaXL (Version 2.2, EpiGear International Ltd., Queensland, Australia) with bootstrapping procedures and figures produced in R (Version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria).

## Results

We identified 3435 unique articles from the database searches (Fig. 1). After screening titles and abstracts, we selected 634 articles for full-text review. Of these, 27 studies met the inclusion criteria for the qualitative synthesis, and 20 were included in the meta-analysis [6–8, 15–38]. We observed excellent agreement between

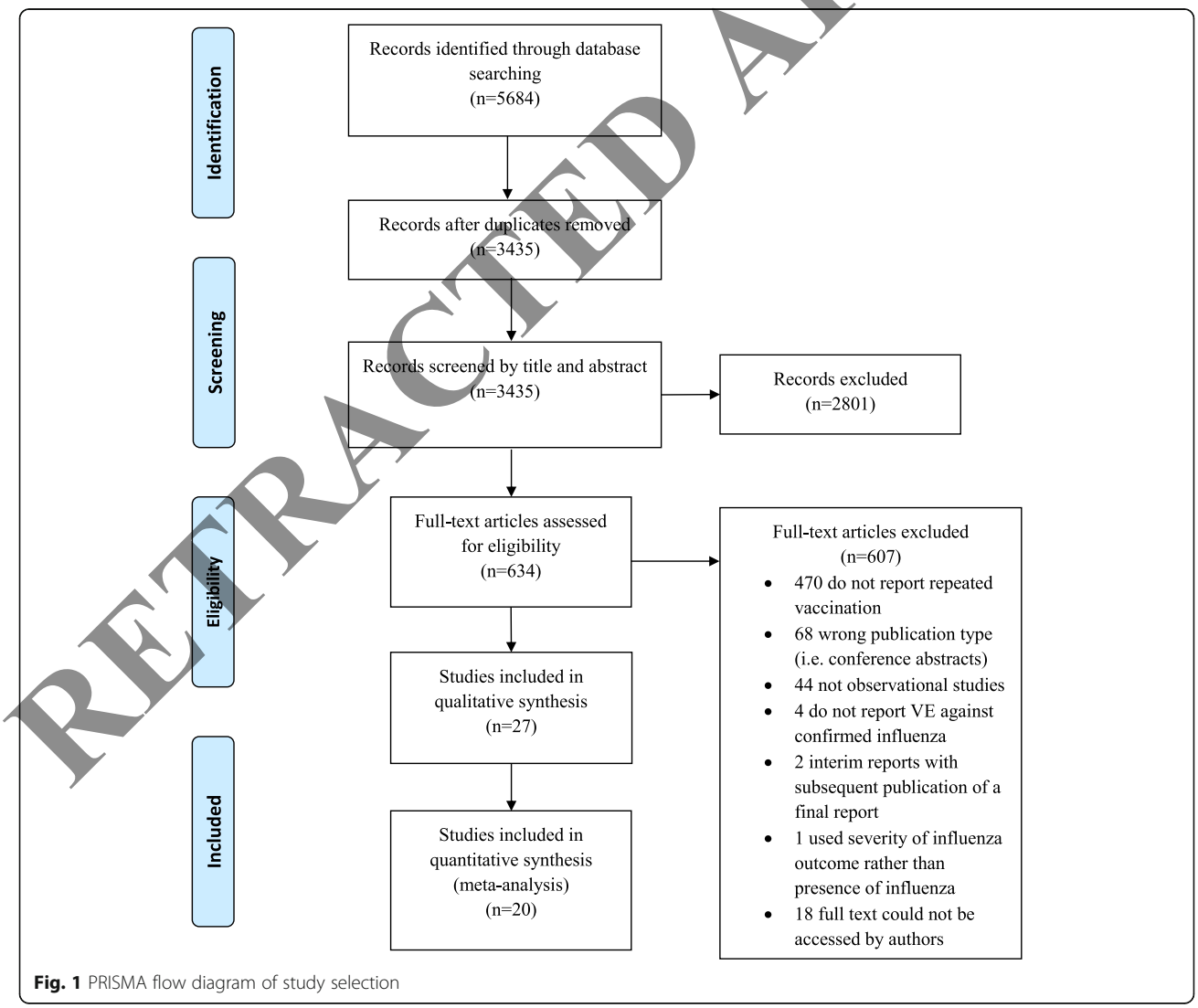


**Fig. 1** PRISMA flow diagram of study selection

reviewers for the title and abstract screen (kappa, κ = 0.94) and for the full-text review (κ = 0.98). No additional studies were identified from hand-searching references. One study was excluded from the qualitative synthesis and meta-analysis because, while it included persons with laboratory-confirmed influenza in the vaccination groups of interest, the study provided VE estimates only for severe or fatal influenza outcomes rather than for any laboratory-confirmed influenza [39]. We excluded seven studies from the meta-analysis but included them in the qualitative synthesis – four studies because they only provided VE estimates for any influenza rather than by influenza type/subtype [15, 23, 32, 33], one because 'prior season vaccination' was not restricted to the immediate year prior to the study season [18], and two for both reasons [16, 27].

The 27 included studies captured influenza seasons between 2004–2005 and 2014–2015, with most reporting estimates for the 2010–2011 to 2014–2015 seasons (Table 1). One study was from the southern hemisphere [33], one was restricted to pregnant women [36], and two were in pediatric populations [17, 35]. Most studies featured outpatient data, but two used inpatient data only [25, 38] and two used data from both settings [15, 16]. All studies used reverse-transcriptase polymerase chain reaction testing to confirm influenza infection.

For 25 of the 27 studies, we extracted the variables included in the multivariable regression models used to obtain VE estimates (Additional file 2: Table S1); the remaining two studies did not clearly report these variables. All 25 studies with available information adjusted for age, and the majority adjusted for presence of high-risk conditions or comorbidities ($n = 17$; 68%) and calendar time ($n = 16$; 64%). Many studies also adjusted for time between illness onset and sample collection ($n = 12$; 48%) and sex ($n = 10$; 40%).

All except one [26] of our included test-negative design studies were deemed to be at low risk of bias, and all included calendar time in their adjusted models [6–8, 15, 16, 18–21, 24, 25, 27–31, 33, 35, 37, 38]. The remaining case-control studies were also categorized as being at low risk of bias [17, 36], as were all the included cohort studies [22, 23, 32, 34]. Details of the evaluation of the included studies are provided in Additional file 3: Figure S1.

Among the 20 articles included in the meta-analysis, there were 16 analyses for influenza H1N1, 17 for H3N2, and 14 for B that compared VE among those vaccinated in both seasons to those vaccinated in the prior season only. When compared to vaccination in the prior season only, VE was higher for vaccination in both seasons for influenza H1N1 (ΔVE = 26%; 95% CI, 15% to 36%; $I^2 = 0\%$) and B (ΔVE = 24%; 95% CI, 7% to 42%; $I^2 = 44\%$), but not H3N2 (ΔVE = 10%; 95% CI, −6% to 25%; $I^2 = 33\%$) (Table 2, Figs. 2, 3, and 4). When stratified by influenza season, the results for all seasons were consistent with the overall results (Additional file 2: Table S2).

Sixteen analyses for influenza H1N1, 17 for H3N2, and 15 for B compared VE among those vaccinated in the current season only to those vaccinated in neither season. VE was higher for vaccination in the current season compared to neither season for influenza H1N1 (ΔVE = 61%; 95% CI, 50% to 70%; $I^2 = 28\%$), H3N2 (ΔVE = 41%; 95% CI, 33% to 48%; $I^2 = 0\%$), and B (ΔVE = 62%; 95% CI, 54% to 68%; $I^2 = 0\%$) (Table 2, Figs. 5, 6, and 7). The results for individual seasons were consistent with the overall results (Additional file 2: Table S2).

Overall, among the 20 included articles, 16 analyses for influenza H1N1, 17 for H3N2, and 15 for B compared VE in those vaccinated in both seasons to those vaccinated in the current season only. We observed no statistically significant VE differences between vaccination in both seasons and vaccination in the current season only for influenza H1N1 (ΔVE = 4%; 95% CI, −7% to 15%; $I^2 = 0\%$), H3N2 (ΔVE = −12%; 95% CI, −27% to 4%; $I^2 = 52\%$), or B (ΔVE = −8%; 95% CI, −17% to 1%; $I^2 = 0\%$) (Table 2, Figs. 8, 9, and 10). The results for individual seasons were consistent with the overall result except for the 2014–2015 season. For that season alone, VE was lower in those vaccinated in both the current and prior seasons compared to those vaccinated only in the current (2014–2015) season (three studies, ΔVE = −54%; 95% CI, −88% to −20%) (Additional file 2: Table S2).

Among the studies included in the qualitative synthesis but not the meta-analysis, three presented results using a definition of 'prior season vaccination' that included multiple prior seasons and therefore did not meet the inclusion criteria for the meta-analysis [16, 18, 27]. One of these studies considered vaccination history over two consecutive seasons using data from nine influenza seasons (2000–2001 to 2008–2009); those vaccinated in the current season only had the highest VE [27]. A study of VE against influenza H1N1 during 2013–2014 assessed the impact of any prior vaccination since 2009, and the results varied by age group, tending to slightly favor either those vaccinated in the current season only or those vaccinated in both seasons [18]. Finally, a study from Spain that assessed vaccination over the current and two prior seasons showed a range of results [16]. Residual VE without current vaccination was noted if vaccinated in both the prior two seasons. For both influenza H3N2 and B, vaccination in the current season and one prior season resulted in considerably lower VE, whereas vaccination in the current and both prior seasons resulted in higher VE. VE against influenza B was highest among those vaccinated in the current season only compared to the other vaccination groups, whereas this group had the lowest VE against H3N2 [16].

**Table 1** Study characteristics of articles included in the meta-analysis and/or qualitative synthesis

| Author, year, reference | Country | Study design | Current season | Prior season | Influenza type | Age group |
|---|---|---|---|---|---|---|
| Jimenez-Jorge et al., 2012 [19] | Spain | Test-negative case-control | 2010–2011 | 2009–2010 | H1N1 | All ages |
| Martinez-Baz et al., 2013 [20] | Spain | Test-negative case-control | 2010–2011 | 2009–2010 | H1N1 | All ages |
| Savulescu et al., 2011 [26] | Spain | Test-negative case-control | 2010–2011 | 2009–2010 | H1N1 | All ages |
| Skowronski et al., 2012 [29] | Canada | Test-negative case-control | 2010–2011 | 2009–2010 | H1N1 | All ages |
| Syrjanen et al., 2014 [34] | Finland | Cohort | 2010–2011 | 2009–2010 | H1N1 | 18–75 years |
| Fu et al., 2015 [17] | China | Case-control | 2012–2013 | 2011–2012 | H1N1 | a) 20–35 months, 1 current dose; b) 20–35 months, 2 current doses; c) 3–6 years |
| Gaglani et al., 2016[a] [18] | United States | Test-negative case-control | 2013–2014 | 2009–2010 to 2012–2013 | H1N1 | ≥9 years |
| Ohmit et al., 2016 [22] | United States | Prospective cohort study | 2013–2014 | 2012–2013 | H1N1 | a) 9 and older; b) under 9 years |
| Thompson et al., 2014[b] [36] | United States | Case-control | 2010–2011 and 2012–2013 | 2009–2010 and 2010–2011 | H1N1, H3N2, B | Mean age 30 years |
| Skowronski et al., 2014 [30] | Canada | Test-negative case-control | 2011–2012 | 2010–2011 | H1N1, H3N2, B | ≥2 years |
| Rondy et al., 2015 [25] | France, Italy, Lithuania, Spain | Test-negative case-control | 2012–2013 | 2011–2012 | H1N1, H3N2, B | ≥18 years |
| Skowronski et al., 2014 [28] | Canada | Test-negative case-control | 2012–2013 | 2011–2012 | H1N1, H3N2, B | ≥2 years |
| Valenciano et al., 2016 [37] | Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain | Test-negative case-control | 2014–2015 | 2013–2014 | H1N1, H3N2, B | All ages |
| Pebody et al., 2013 [24] | United Kingdom | Test-negative case-control | 2010–2011 | 2009–2010 | H1N1, B | All ages |
| Skowronski et al., 2015 [31] | Canada | Test-negative case-control | 2013–2014 | 2012–2013 | H1N1, B | ≥2 years |
| McLean et al., 2014 [6] | United States | Test-negative case-control | 2004–2005 to 2012–2013 | Variable | H3N2, B | a) 9–49; b) 50 and older |
| McLean et al., 2015 [21] | United States | Test-negative case-control | 2012–2013 | 2011–2012 | H3N2, B | a) 9–17; b) 18–49; c) 50–64; d) 65 and older |
| Thompson et al., 2016 [35] | United States | Test-negative case-control | 2012–2013 | 2011–2012 | H3N2, B | a) 2–8 years, 1 dose prior season; b) 2–8 years, 2 doses prior season |
| Skowronski et al., 2016 [7] | Canada | Test-negative case-control | 2014–2015 | 2013–2014 | H3N2, B | ≥2 years |
| Simpson et al., 2015[a] [27] | Scotland | Test-negative case-control | 2008–2009 | 9 prior seasons | All influenza | All ages |
| Castilla et al., 2011[a] [15] | Spain | Nested test-negative case- control | 2010–2011 | 2009–2010 | All influenza | All ages |
| Ohmit et al., 2014 [8] | United States | Test-negative case-control | 2011–2012 | 2010–2011 | H3N2 | ≥9 years |

**Table 1** Study characteristics of articles included in the meta-analysis and/or qualitative synthesis *(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| Ohmit et al., 2015[a] [23] | United States | Prospective cohort study | 2012–2013 | 2011–2012 | All influenza | All ages |
| Smithgall et al., 2016[a] [32] | United States | Surveillance | 2013–2014 | 2012–2013 | All influenza | All ages |
| Castilla et al., 2016[a] [16] | Spain | Test-negative case-control | 2014–2015 | 2013–2014 and 2012–2013 | All influenza | All ages |
| Sullivan & Kelly, 2013[a] [33] | Australia | Re-analysis | a) Southern hemisphere 2011; b) Southern hemisphere 2012 | Southern hemisphere 2010 and 2011 | All influenza | All ages |
| Petrie et al., 2016 [38] | United States | Test-negative case-control | 2014–2015 | 2013–2014 | H3N2 | ≥18 years |

[a]Study not included in meta-analysis
[b]Study population included pregnant women only

Six studies [15, 16, 23, 27, 32, 33] presented results for any influenza rather than by influenza type/subtype, two of which were summarized above because they also used multiple prior seasons [16, 27]. There were five estimates from the four remaining studies not summarized above. Of these, three favored vaccination in the current season only, and two favored vaccination in both seasons. None of the estimates favored vaccination in the prior season only. In the one study that presented two VE estimates, seasonal differences were apparent. In the southern hemisphere 2011 season, the highest VE was observed among those who had been vaccinated in both current and prior seasons, but in the southern hemisphere 2010 season, the highest VE was observed among those who had received the current season vaccine only [33].

## Discussion

We found that, irrespective of a patient's vaccination status for the prior season, current season vaccination is associated with greater protection against laboratory-confirmed infection by influenza H1N1 and B. This was evident comparing vaccination in both seasons to vaccination in the prior season only. Furthermore, compared to no vaccination for either season, individuals who received the current season's vaccine had greater protection against all three influenza types/subtypes. Therefore, vaccination in the current season is generally the best option for the patient. Recent studies have raised questions about the impact of repeated vaccination [6–8], which is of concern to policymakers with regard to annual influenza vaccination recommendations. Of relevance to the policymaker (but not the patient, who cannot alter their vaccination history), we observed no differences in VE between vaccination in both seasons and vaccination in the current season only for any influenza type/subtype, providing no overall evidence of harm from repeated vaccination. The 2014–2015 influenza season was an exception, where pooled VE across three studies was lower for those vaccinated in both the current and prior season compared to those vaccinated in the current season alone. Based on the NOS, we assessed that the studies included in this review had a low risk of bias. However, the theoretical underpinnings of the test-negative design are still in the process of explication [40–42], and there has not yet been a theoretical assessment of the potential biases in evaluation of repeated vaccine effects using the test-negative design.

**Table 2** Comparison of vaccine effectiveness (VE) by vaccination group and influenza type/subtype

| VE comparison | Relevance of results | H1N1 | H3N2 | B |
|---|---|---|---|---|
| Vaccinated both seasons versus vaccinated prior season only<br>$\Delta VE^a$ (95% CI)<br>$\Delta VE = VE_{both} - VE_{prior\ only}$ | Patient and policy perspectives | **26% (15% to 36%)** | 10% (–6% to 25%) | **24% (7% to 42%)** |
| Vaccinated current season only versus vaccinated neither season (reference group)<br>Pooled $VE_{current\ only}$ | Patient and policy perspectives | **61% (50% to 70%)** | **41% (33% to 48%)** | **62% (54% to 68%)** |
| Vaccinated both seasons versus vaccinated current season only<br>$\Delta VE^a$ (95% CI)<br>$\Delta VE = VE_{both} - VE_{current\ only}$ | Policy perspective | 4% (–7% to 15%) | –12% (–27% to 4%) | –8% (–17% to 1%) |

Bold type-face indicates significant results
[a]$\Delta VE > 0$ implies higher vaccine effectiveness estimate when vaccinated in both seasons

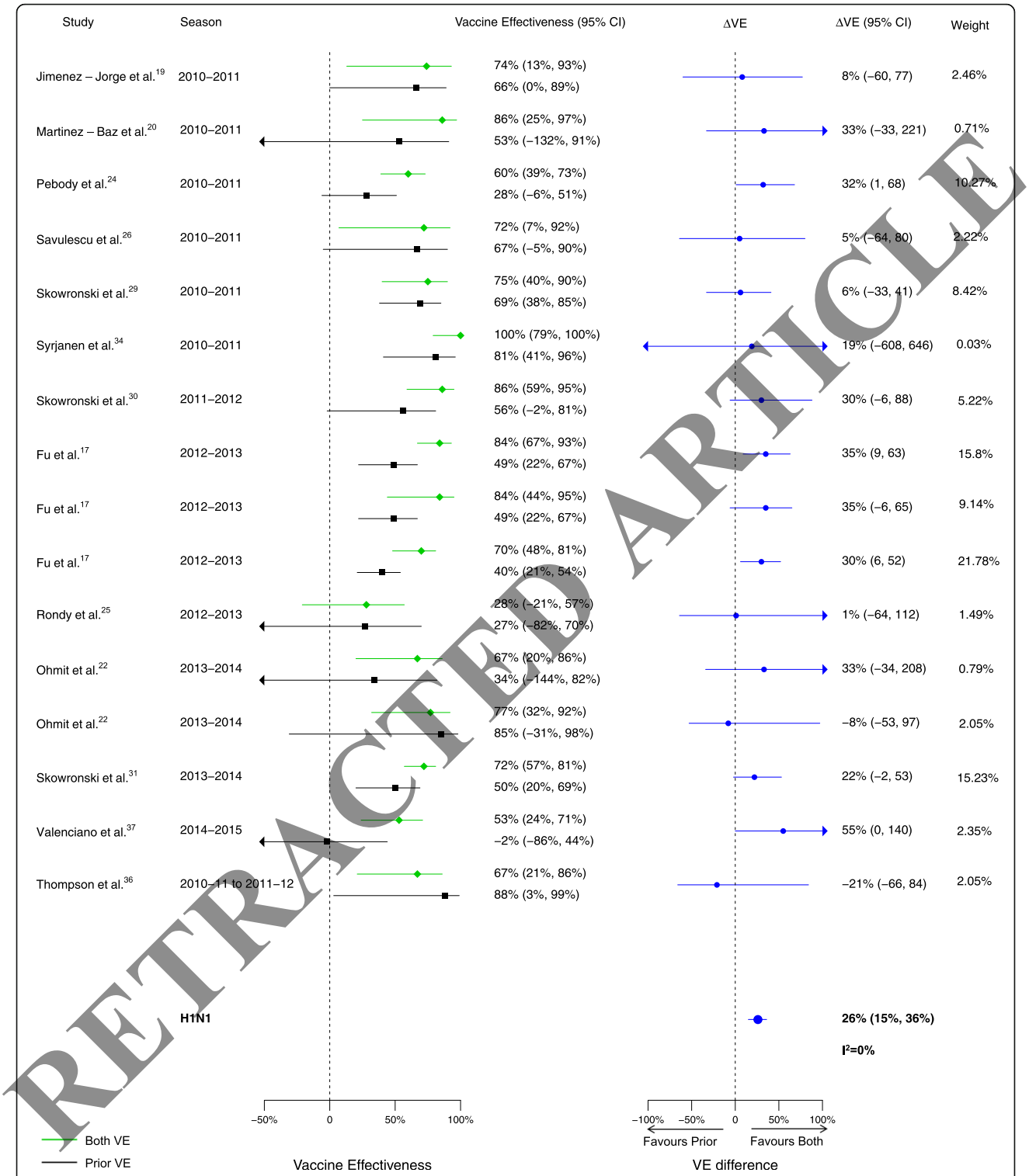


**Fig. 2** Comparison of vaccine effectiveness (VE) estimates against influenza H1N1 in those vaccinated in both seasons versus those vaccinated in the prior season only



The results of this review are similar to those found by Beyer et al. in 1999 [5]; their meta-analysis of seven field studies and 12 serologic studies found no significant difference between the single and multiple vaccination groups. However, our study represents an advance by including studies that feature contemporary laboratory

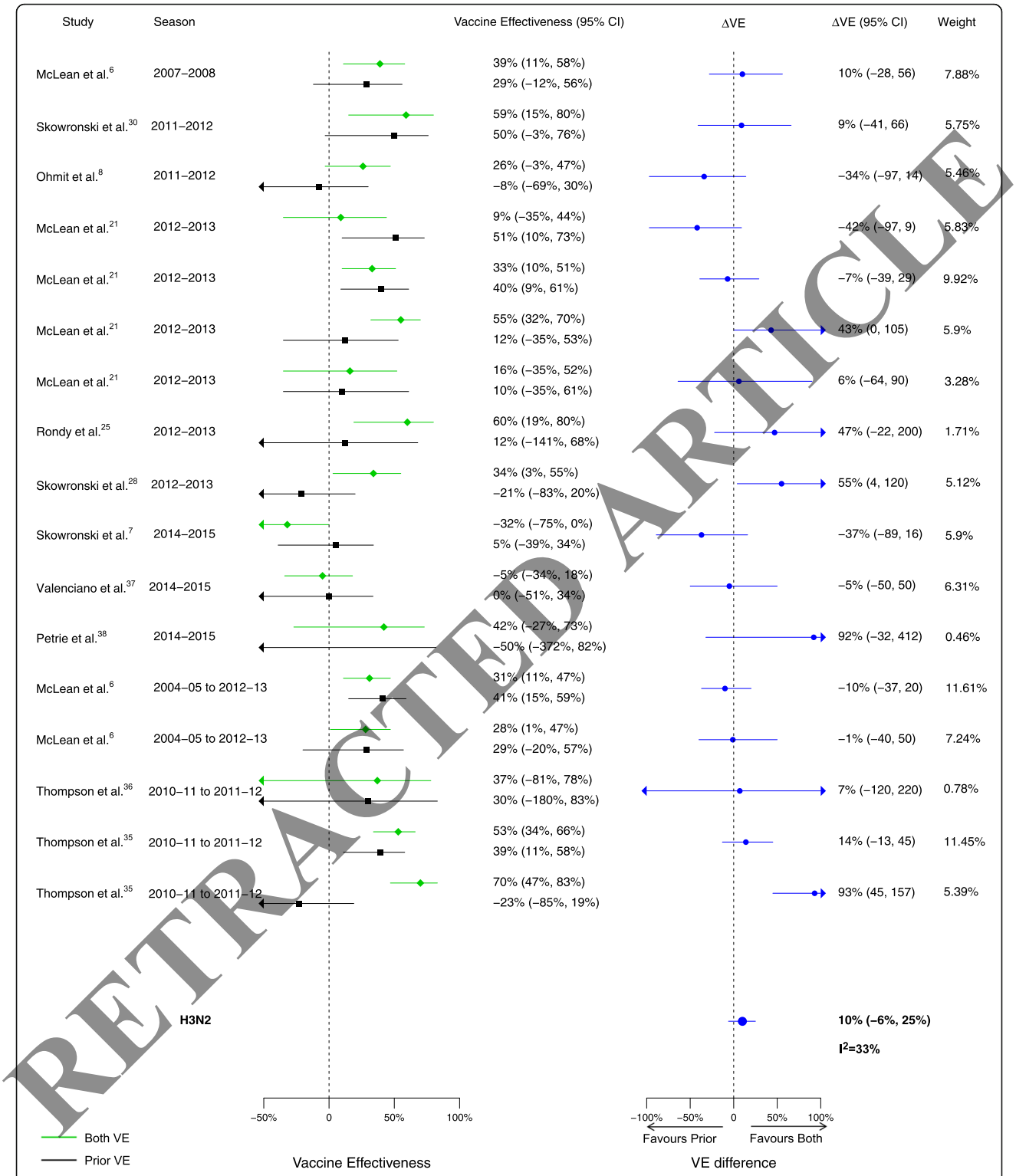


**Fig. 3** Comparison of vaccine effectiveness (VE) estimates against influenza H3N2 in those vaccinated in both seasons versus those vaccinated in the prior season only



testing methods and study designs with consistent vaccination comparison groups. A recently published meta-analysis reported pooled VE estimates for the same vaccination status groups as our study (prior only, current only, both seasons) [43]. Similar to the present results, that study found VE to be consistently lowest

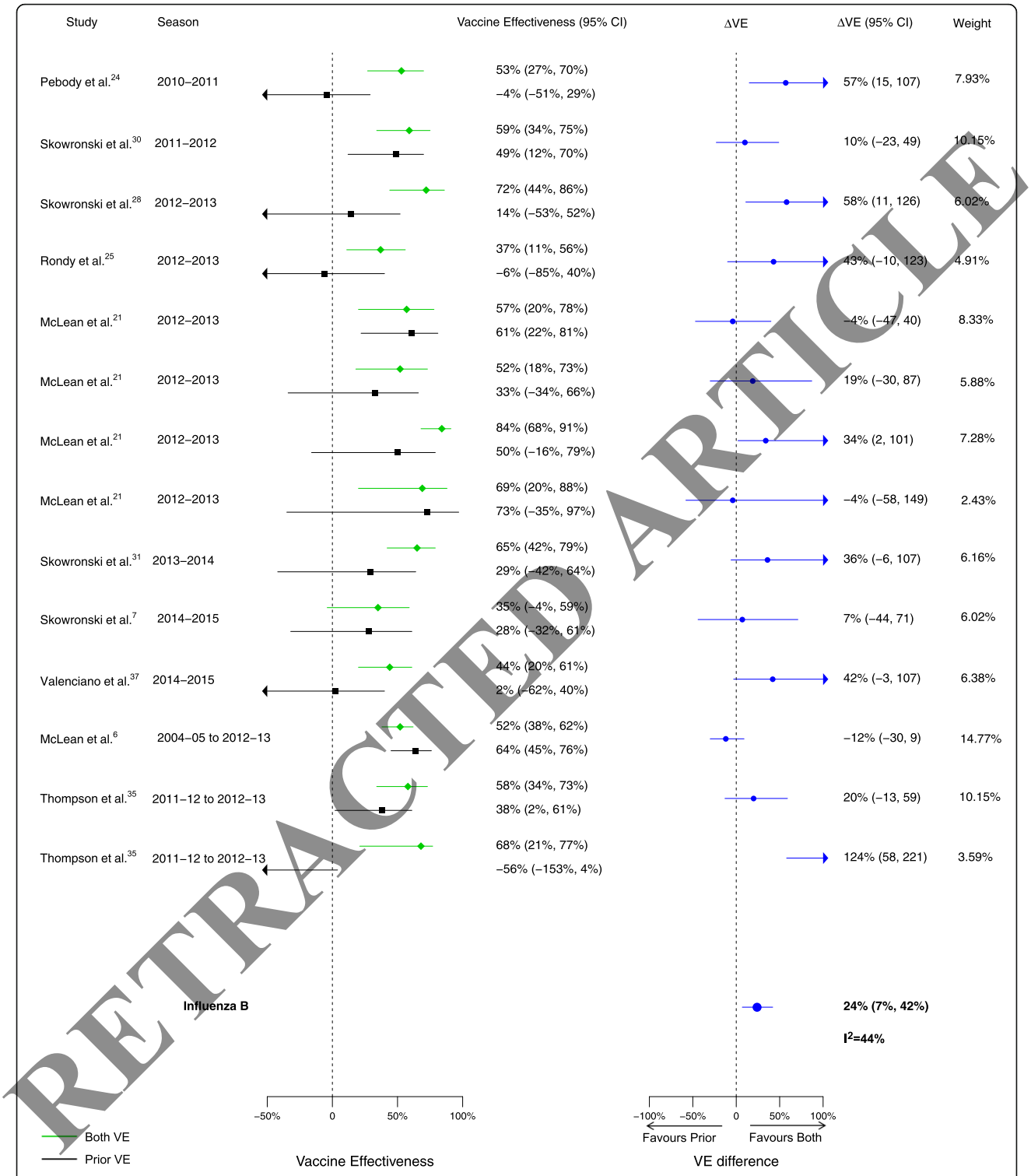


**Fig. 4** Comparison of vaccine effectiveness (VE) estimates against influenza B in those vaccinated in both seasons versus those vaccinated in the prior season only

among those vaccinated during the prior season only. Additionally, for the 2014–2015 season, VE against H3N2 was found to be higher for those vaccinated in the current season only compared to those vaccinated during both seasons. However, that study did not examine the differences in VE as presented in this study.

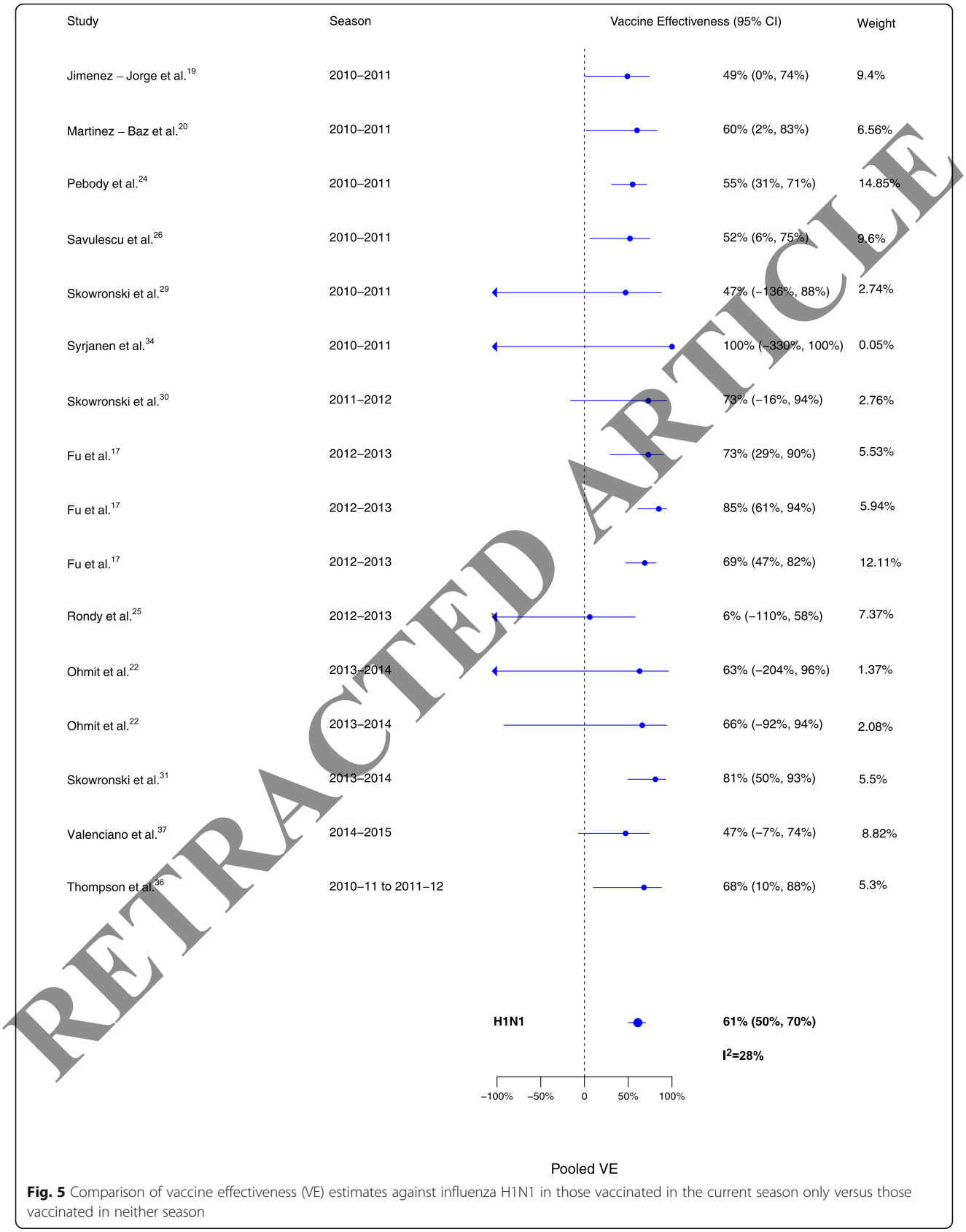


**Fig. 5** Comparison of vaccine effectiveness (VE) estimates against influenza H1N1 in those vaccinated in the current season only versus those vaccinated in neither season

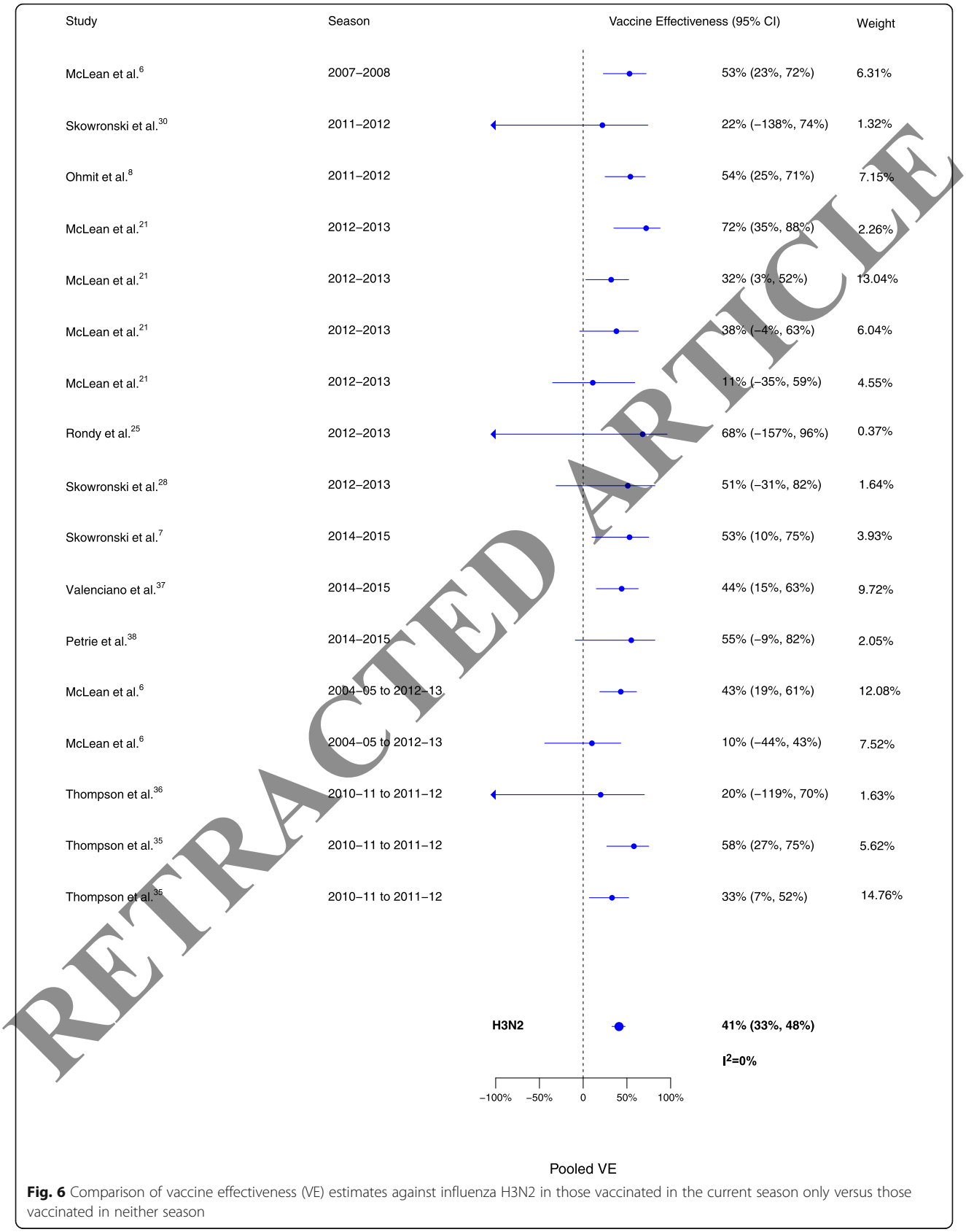


**Fig. 6** Comparison of vaccine effectiveness (VE) estimates against influenza H3N2 in those vaccinated in the current season only versus those vaccinated in neither season

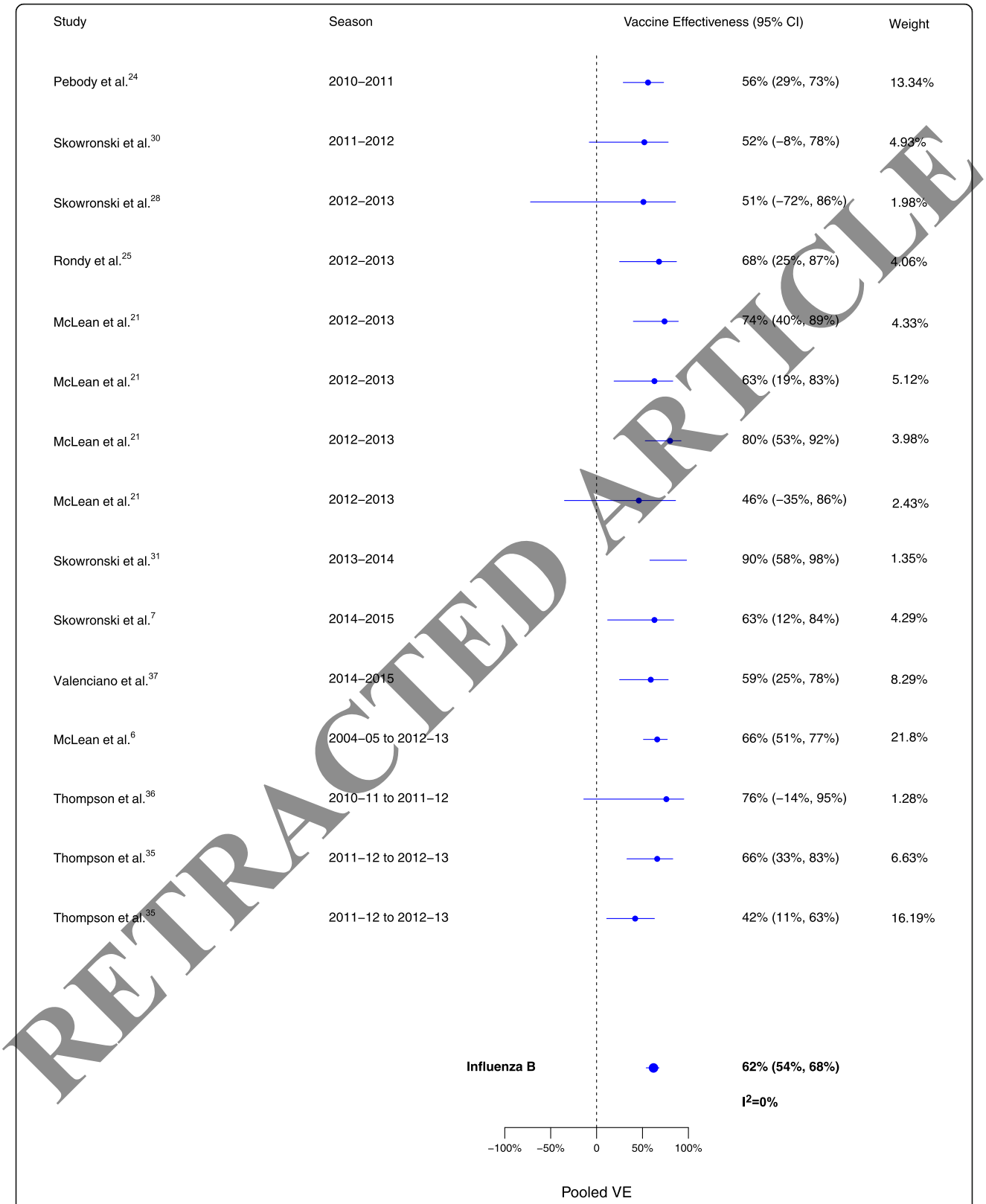




**Fig. 7** Comparison of vaccine effectiveness (VE) estimates against influenza B in those vaccinated in the current season only versus those vaccinated in neither season

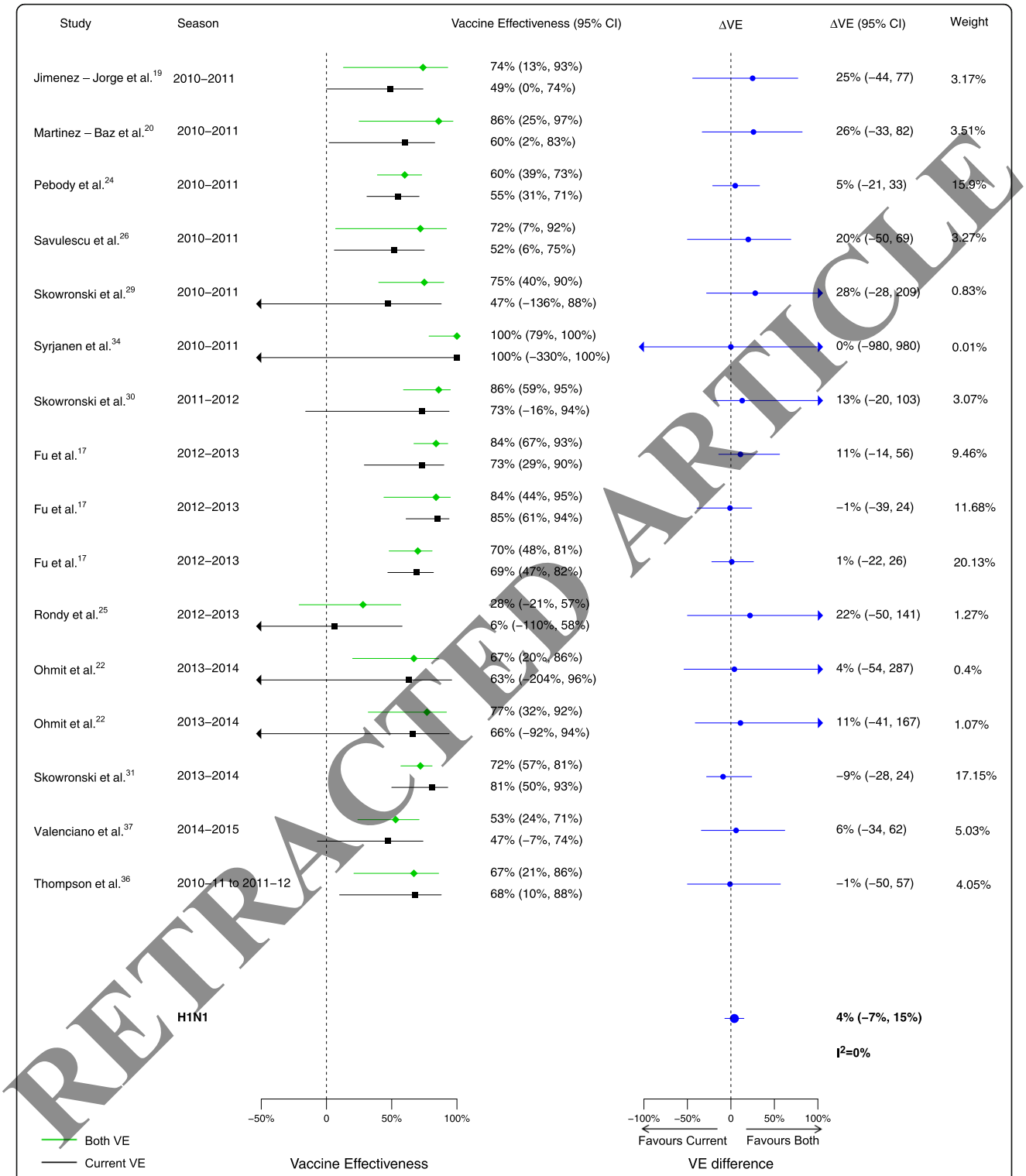


**Fig. 8** Comparison of vaccine effectiveness (VE) estimates against influenza H1N1 in those vaccinated in both seasons versus those vaccinated in the current season only



In our review, the comparison groups used in the meta-analysis provided a more refined calculation of VE that accounted for recent vaccination history. Standard VE calculations (those that do not account for prior vaccination history of the vaccinated group) compare those vaccinated in the study season (a mixture of subjects

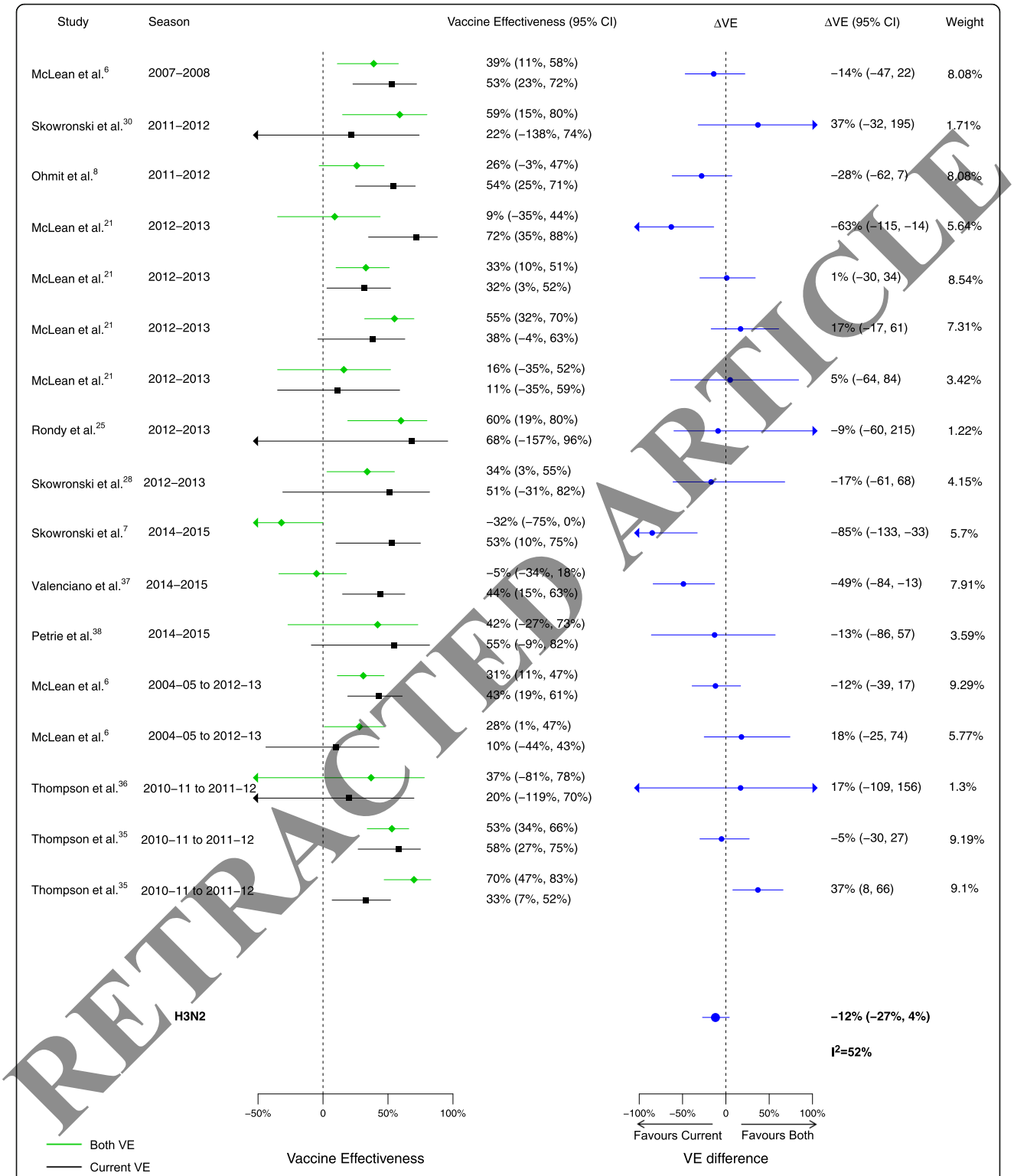


**Fig. 9** Comparison of vaccine effectiveness (VE) estimates against influenza H3N2 in those vaccinated in both seasons versus those vaccinated in the current season only

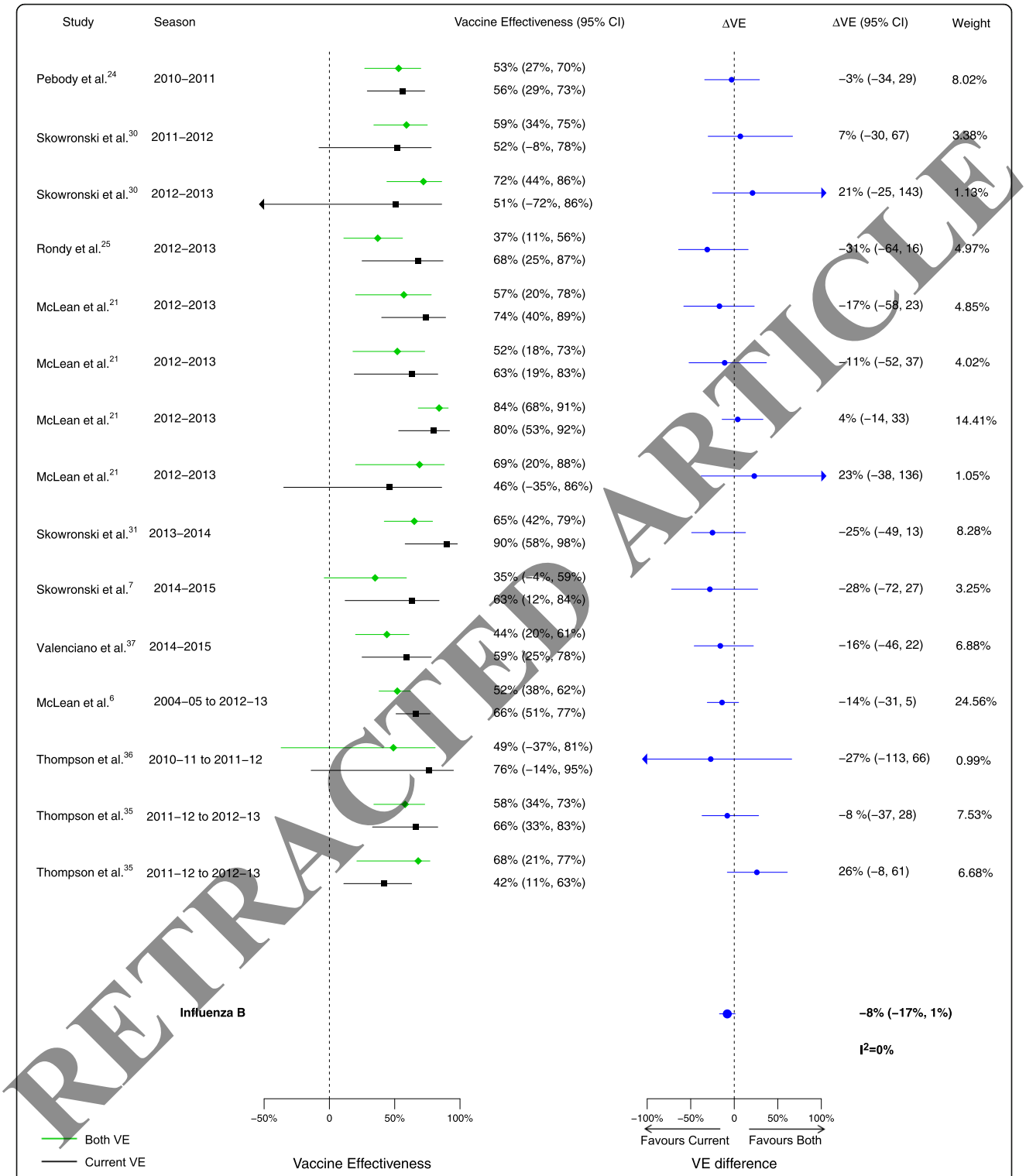


**Fig. 10** Comparison of vaccine effectiveness (VE) estimates against influenza B in those vaccinated in both seasons versus those vaccinated in the current season only



vaccinated in the current season only and those with current and prior vaccination) to a reference group of those not vaccinated in the study season (which includes both those vaccinated in neither season and those vaccinated in the prior season only). Our study allowed for these vaccination groups to be analyzed separately to

understand the impact of prior season vaccination on current season VE.

Our study was further strengthened by aligning the VE comparisons with patient and policy perspectives in order to aid decision-making by patients, practitioners, and policymakers. Additionally, by calculating the differences in VE between the various vaccination groups within each study, we controlled for any methodological biases unique to a particular study, since these biases would apply equally to each vaccination group. Thus, rather than first pooling the VE estimates from each vaccination group across studies and subsequently taking the difference, we pooled the differences obtained from VE estimates within each study. Finally, because VE can vary by age group and influenza type/subtype, this study was strengthened by the detailed stratification of results by type/subtype, as well as by using VE estimates for the most specific patient groups (e.g., age-stratified groups rather than 'all ages').

This study also has some limitations. First, the analysis accounts only for vaccination status in one prior season. Results might differ when considering a patient's vaccination history over a greater number of seasons, which is particularly significant when considering the importance of influenza VE in older adults who have potentially received many years of consecutive vaccinations. McLean et al. [6] found no difference when exploring VE over two consecutive seasons, but when they used a reference group with no vaccination over six seasons, those vaccinated in the current season only and not in the previous five seasons had the highest VE against influenza H3N2 and B, with progressively lower VE with increasing vaccines received over the previous five seasons. Few studies reported on vaccination history beyond prior and current seasons, and they did not group history consistently; therefore, further analysis incorporating the effects of serial vaccination from these studies was not possible, but is an important analysis to conduct in the future when more data are available. Second, our study did not account for past influenza infection, which may have provided some protective effect against laboratory-confirmed influenza in subsequent seasons [44]. A patient's first exposure to influenza vaccination or infection can impact subsequent responses to vaccination or infection (referred to as original antigenic sin or back-boosting), which was not accounted for in this study [45]. Third, this study did not differentiate between the types of influenza vaccines used (e.g., live attenuated or inactivated; quadrivalent or trivalent; adjuvanted or unadjuvanted; high dose or standard dose). Given the differing types of immune response induced by these various products, different impacts of prior vaccination on current season VE may ensue. Fourth, we evaluated the absolute difference in VE instead of assessing a ratio; the latter could be considered more appropriate given the scale on which VE is calculated. However, the reporting of ratios introduces other challenges such as accommodating negative values and estimating confidence intervals. Since deriving practical conclusions for annual vaccine decision-making was the goal, we reported more intuitive differences in VE, as others have done previously [14, 46]. Finally, based on the limited available information in each study, we could not adjust for the match between the current season's vaccine and the circulating strains, the prior season's vaccine and the current season's circulating strains, nor changes in vaccine strains from one season to another, all of which may affect VE from one year to the next, as noted by Smith et al.'s [47] antigenic distance hypothesis. Skowronski et al. [48] recently examined VE for influenza H3N2 in Canada using this framework, and concluded that the effects of repeated vaccination were consistent with the antigenic distance hypothesis. We attempted to assess VE based on antigenic distance in the included articles by considering the vaccine strain and circulating strain match where possible, but not all studies provided detailed strain information. In the articles with sufficient information, the variation of vaccine and circulating strain matches were too few and were grouped by season, and as seasonal analysis was already included in our meta-analysis, no further information was gained. However, consistent with Skowronski et al.'s findings [48], we observed a significant negative interference in the 2014–2015 influenza season, supporting the antigenic distance hypothesis which predicts that this would occur when vaccine strains are homologous from one year to the next but the prior season's vaccine does not match the current circulating strain. Future VE studies should continue to incorporate vaccination status in prior seasons and provide as much detail as possible to allow assessment of the match between vaccine and circulating strains and the changes in vaccine strains over time. Future studies should also assess the impact of vaccination over multiple past seasons.

## Conclusions

In conclusion, from the patient's perspective, vaccination in the current season is generally the best option regardless of prior season vaccination. From a policy perspective, our study found no overall evidence that repeated vaccination over two seasons has a negative impact on current season VE.

## Additional files

**Additional file 1:** Database search strategy. (DOCX 18 kb)

**Additional file 2: Table S1.** Study characteristics of articles included in the meta-analysis and/or qualitative synthesis. **Table S2.** Meta-analysis pooled results by influenza season and influenza type/subtype. (DOCX 40 kb)

**Additional file 3: Figure S1.** Results of the risk of bias assessment by category using the Newcastle–Ottawa Scale. (PDF 54 kb)

**Abbreviations**
NOS: Newcastle–Ottawa Scale; VE: vaccine effectiveness; ΔVE: absolute difference in vaccine effectiveness

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**Availability of data and materials**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**
BFW had the idea for the review, and SAB and LCR managed the literature search and data extraction. BFW, JCK, RGS, SAB, and LCR developed the analysis plan. SAB and SF conducted the analysis and developed the figures. LCR wrote the original draft of the manuscript. BFW, JCK, SF, BJC, RGS, SAB, and LCR determined the study approach, interpreted the results, and critically reviewed the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**
Not applicable.

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Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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