Decline in seasonal influenza vaccine effectiveness with vaccination program maturation: A systematic review and meta-analysis

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Abstract

Objectives: Evidence suggests repeated influenza vaccination may reduce vaccine effectiveness (VE). Using influenza vaccination program maturation (number of years since program inception) [PM] as proxy for population-level repeated vaccination, we assessed the impact on pooled adjusted end-season VE estimates from outpatient test-negative design studies.

Methods: We systematically searched and selected full-text publications from January 2011 to February 2020 (PROSPERO: CRD42017064595). We obtained influenza vaccination program inception year for each country and calculated PM as the difference between the year of deployment and year of program inception. We categorized PM into halves (cut at the median), tertiles, and quartiles, and calculated pooled VE using an inverse variance, random effects model. The primary outcome was pooled VE against all influenza.

Results: We included 72 articles from 11,931 unique citations. Across the three categorizations of PM, a lower pooled VE against all influenza for all patients was observed with PM. Substantially higher reductions were observed in older adults (≥65 years). We observed similar results for A(H1N1)pdm09, A(H3N2) and influenza B.

Conclusions: The evidence suggests influenza VE declines with vaccination PM. This study forms the basis for further discussions and examinations of the potential impact of vaccination PM on seasonal VE.

Keywords: Seasonal Influenza; Systematic Review; Test-negative Design; Vaccine Effectiveness; Vaccination Program.
Introduction

Influenza is responsible for considerable morbidity and mortality every year worldwide. Following influenza vaccination, antibody titers to influenza antigens may persist for months. However, the changing nature of influenza viruses, particularly the influenza A type (antigenic drift), warrants reformulation of vaccine each influenza season in an attempt to match vaccine with the circulating virus strains. Vaccination is therefore recommended each season for better protection against circulating virus strains. However, vaccine seroresponse may be impaired with repeated vaccination.

Generally, seasonal influenza vaccination is recommended for individuals at least six months old, with emphasis on those at higher risk of developing complications such as the very young (<5), older adults (≥65), pregnant women and individuals with certain health conditions. Many countries have adopted annual influenza vaccination policy and have established annual vaccination programs. Many vaccination programs were not publicly funded (paid for from the public purse) at inception. Publicly funded vaccination in some countries is only available to some of the at-higher-risk population subgroups whereas some countries (or regions within some countries) offer universal vaccination (free for all). In addition, recommended influenza vaccines in each season may vary slightly across countries. However, publicly funded vaccination programs, even in some countries that have universal vaccination policy, was initially for a few at-higher-risk population subgroups, before gradually expanded to cover all eligible persons. Nevertheless, these programs have led to some increases in vaccination rates and, with the introduction of the test-negative design (TND) in influenza vaccine effectiveness (VE) estimations, have reignited interest in the potential impact of repeated influenza vaccination.

Studies in the late 20th century were either inconclusive or found no evidence of a negative impact of repeated influenza vaccination. In particular, a large randomized
controlled trial in the United States of America (USA) found some variations in infection rates between groups given one or more influenza vaccination but noted no consistent pattern of differences in relation to number of successive seasonal vaccinations. Recent studies have found reduced influenza VE in individuals who received prior repeated influenza vaccinations. A systematic review reported lower influenza VE against A(H3N2) and influenza B but not for A(H1N1) in individuals vaccinated in both current and previous seasons compared with those vaccinated only in current season.

While accumulating evidence suggests that repeated influenza vaccination may reduce VE at the individual-level, the impact on overall annual program effectiveness is still not clear. Understanding this impact may influence policy regarding population-wide annual influenza vaccination. We assessed the impact of repeated influenza vaccination on vaccine program effectiveness, using influenza vaccination program maturation (number of years since program inception) [PM] as proxy for population-level repeated vaccination.

**Methods**

We conducted a systematic review and meta-analysis following the Cochrane Handbook for Systematic Reviews of Interventions guidelines. Our findings are reported following the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42017064595). Details of our methods have been reported in a previous publication.

**Literature search strategy**

A methodologist designed a search strategy for the review in MEDLINE (Ovid). The search strategy was reviewed by a knowledge synthesis librarian using the PRESS checklist. The final search strategy (Appendix Table 1) was adapted for other bibliographic databases and
the following databases were searched for literature: MEDLINE (Ovid), Embase (Ovid), PubMed, Scopus (Elsevier) and Web of Science. Google Scholar and relevant websites were also searched for literature. Literature search was conducted in April 2017. Updated searches were carried out in July 2018 and February 2020.

**Literature selection**

All retrieved unique citations were imported into a specially designed Microsoft (MS) Access 2016 database (Microsoft Corporation, Redmond, WA, USA) for screening. We were only interested in TND studies of seasonal influenza VE conducted in outpatient settings after the 2009/10 influenza pandemic.

We considered for inclusion only country-specific studies published in a full-text manuscript, irrespective of language of publication. Influenza diagnosis/confirmation was by a reverse transcriptase-polymerase chain reaction (RT-PCR) assay or viral culture of a respiratory specimen. Study participants must have received seasonal influenza vaccine at least 14 days before onset of influenza-like symptoms. The symptoms must not have started more than 7 days before presentation for medical consultation. We included only multivariable adjusted end-season VE estimates against all influenza, influenza A subtypes: A(H1N1)pdm09 and A(H3N2), and influenza B. We excluded studies on hospitalized patients, and mixed hospitalized and outpatient data that could not be separated. We also excluded studies conducted in care homes, schools, military barracks, prisons, and within unique subgroups such as individuals with chronic diseases.

Two systematic reviewers independently screened the identified unique citations against the eligibility criteria using a two-stage sifting approach to screen titles/abstracts and full-text articles. All included studies were examined for overlap or duplication of data. Disagreements between the reviewers were resolved through discussion or involvement of a
third reviewer. The number of ineligible citations at the title/abstract screening stage, and both the number and reasons for ineligibility at the full-text article screening stage were documented and presented graphically as per PRISMA guidelines.

**Data extraction**

One reviewer extracted data from the included studies using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and a second reviewer independently checked the extracted data for errors. We extracted basic study details, participants’ characteristics (sample size; mean age; age range; sex distribution), and vaccine information (method of vaccination status confirmation). We also extracted respiratory specimen (type and swab time), influenza diagnostic/confirmatory test, adjusted covariates in VE analysis, and outcome/results (multivariable-adjusted VE against all influenza, influenza A subtypes: A(H1N1)pdm09 and A(H3N2), and influenza B; and their associated 95% confidence intervals [CI]). We determined vaccine antigenic similarity with circulating virus strains using reports from the World Health Organization (WHO), national influenza centers and region/country-specific centers for disease control.

We contacted the WHO, national Departments of Health/public health agencies, and national centers for disease control, for annual influenza vaccination program inception year for each country irrespective of program rollout plans, public funding of program, and within-country regional differences in program inception (Appendix Table 2). In countries with decentralized provincial/state health authorities where there may not be a single, countrywide inception year, we considered the earliest regional program inception year as program inception year for the country.
Study quality assessment

In the absence of a validated quality assessment tool for TND studies, we improvised quality assessment by examining relevant study characteristics that could introduce bias such as the methods of determination of vaccination status, participants’ enrollment and inclusion of age and/or medical condition, among other covariates in logistic regression model for VE analysis. We synthesized quality assessment in a tabular form for visualization.

Data synthesis and analysis

Relevant characteristics of the included studies were synthesized in a tabular form. Data management and analysis were implemented in STATA (version 13; StataCorp LP, Texas, USA). Our primary outcome was pooled influenza VE against all influenza across categories of vaccination PM. Our secondary outcome was pooled influenza VE against influenza A subtypes: A(H1N1)pdm09 and A(H3N2), and influenza B across categories of vaccination PM. We determined seasonal influenza vaccination PM by calculating the number of years from the year of program inception for each country to the beginning of each reported influenza season. We then categorized vaccination PM into two (Q2, cut at the median), three (Q3, tertiles) and four (Q4, quartiles) categories. We explored study variation (excess heterogeneity) using random effects meta-regression.¹⁷

We repeated the above PM categorization across levels of vaccine antigenic similarity with circulating virus strains, after identifying vaccine antigenic similarity as a potential source of heterogeneity across the studies. We pooled adjusted VE estimates and associated 95% CI using an inverse variance, random effects model. We assessed and quantified statistical heterogeneity between pooled VE using the I-squared statistic ($I^2$).¹⁸ We utilized the heterogeneity chi-squared statistic ($\chi^2$) in assessing the statistical significance ($p$-value) of the difference between pooled VE across categories of vaccination PM.¹⁹
appropriate (≥10 studies), we assessed for publication bias statistically, using Egger’s regression test.\textsuperscript{20} We conducted subgroup analysis using VE estimates reported specifically for older adults (>65 years), an important subgroup for influenza vaccination. We also conducted subgroup analysis by study country geographical region (hemisphere) for only the primary outcome.

**Results**

We identified 11,931 unique citations from which we included 72 full-text articles that met our inclusion criteria (Figure 1).\textsuperscript{21-92} Relevant study characteristics are summarized in Appendix Table 3 and a geographic heat map and graphical representation of the included articles are presented in Appendix Figure 1. Overall, there were 59 articles from the Northern hemisphere and 13 articles from the Southern hemisphere. PM ranged from one to 64 years. Study quality assessment is summarized in Appendix Table 4.

**Pooled VE against all influenza (all patients)**

Overall, we observed a lower pooled VE with PM across levels of Q2 and Q3 categories and across the first three levels of Q4; albeit with high heterogeneity (Table 1). Meta-regression revealed vaccine antigenic similarity with circulating virus strains as a possible explanation for the observed heterogeneity (p<0.001). Therefore, we conducted meta-analysis within levels of vaccine antigenic similarity for this and other assessed outcomes. Among studies with antigenically similar vaccine, we observed a lower pooled VE with PM across levels of Q2 category, from 54% (48–59%) for less than median to 46% (41–51%) for more than median, and the difference in VE was statistically significant (p=0.035) (Figure 2). We observed a lower pooled VE with PM across levels of Q3 category, from 55% (47–62%) for tertile 1 (youngest PM) to 50% (41–58%) for tertile 2 and to 45% (40–50%) tertile 3 (oldest
PM), although the difference in VE between tertiles 1 and 2, and between tertiles 2 and 3 were both non-significant (Figure 3). We also observed a lower pooled VE with PM across levels of Q4 category: from 57% (48–65%) for quartile 1 (youngest PM), to 52% (45–57%) quartile 2 and 46% (35–55%) and 46% (41–50%), quartiles 3 and 4, respectively. However, the difference in VE between quartiles 1 and 2, between quartiles 2 and 3, and between quartiles 3 and 4 were all non-significant (Figure 4). Largely similar observations were made among studies with antigenically dissimilar/partially similar vaccines (Appendix Figures 2–4), and when limited to the Northern and Southern hemispheres, particularly with high antigenic match (Appendix Figures 5–10).

**Pooled VE against all influenza (older adults)**

We made similar observations to the analyses with all patients across levels of Q2 and Q3 categories, and across three levels of Q4 category, but with significantly lower heterogeneity (Table 1). Among studies with antigenically similar vaccine, we observed a lower pooled VE with PM across levels of Q2 category, from 50% (34–62%) for less than median to a much lower 23% (10–35%) for more than median, and the difference in VE was statistically significant (p=0.005) (Appendix Figure 11). We observed a lower pooled VE with PM across levels of Q3 category, from 56% (36–69%) for tertile 1 (youngest PM) to a much lower 30% (10–46%) for tertile 2 and to 24% (9–37%) for tertile 3 (oldest PM). The difference in VE between tertiles 1 and 2 was statistically significant (p=0.037) but the difference in VE between tertiles 2 and 3 was non-significant (Appendix Figure 12). We also observed a lower pooled VE with PM across levels of Q4 category, from 54% (31–70%) for quartile 1 (youngest PM) to 46% (23–62%) for quartile 2 to 22% (-9% to 44%) and slightly higher 24% (9–37%) for quartiles 3 and 4, respectively, although the difference in VE between quartiles 1 and 2, and quartiles 2 and 3, were non-significant (Appendix Figure
There was a paucity of data to enable adequate assessment among studies with antigenically dissimilar/partially similar vaccines (Appendix Figures 14–16).

**Pooled VE against influenza A subtypes and influenza B (all patients)**

When limited to studies with antigenically similar vaccine, we observed a lower pooled VE against A(H1N1)pdm09 with PM across levels of Q2 category (p=0.023), Q3 category (mainly between tertile 1 (youngest PM) and tertile 2 [p=0.065]) and, to some extent, Q4 category. Q4 category did not show a consistent reduction across the four levels mostly due to quartile 4 (oldest PM) being driven by studies from the USA (80%) (Appendix Table 5). This was also the case for A(H3N2): Q2 (p=0.12), Q3 (mainly between tertile 1 (youngest PM) and tertile 2 [p=0.15], with tertile 3 (oldest PM) driven by studies from the USA [86%]) and influenza B: Q2 (p=0.38), Q3 (mainly tertile 1 (youngest PM) and tertile 2 [p=0.33], with tertile 3 (oldest PM) driven by studies from the USA [87%]). No clear pattern was observed across the levels of Q4 category for both, mostly due to quartile 4 (oldest PM) being driven by studies from the USA (100% and 75% for A(H3N2) and influenza B, respectively). Similar observations were made with regard to A(H1N1)pdm09 among studies with antigenically dissimilar/partially similar vaccine. We observed a lower pooled VE against A(H3N2) and influenza B with PM across levels of Q2 and Q4 categories among studies with antigenically dissimilar/partially similar vaccine. The opposite observation was however, made across levels of Q3 category with regard to influenza B (Appendix Table 5).

**Pooled VE against influenza A subtypes and influenza B (older adult patients)**

Among studies with antigenically similar vaccine, we observed a lower pooled VE against A(H1N1)pdm09 with PM across only levels of Q2 category (Appendix Table 6). There was not enough data to enable adequate assessment of A(H3N2). However, among studies with
antigenically dissimilar/partially similar vaccine, we observed considerably lower pooled VE against A(H3N2) with PM across levels of Q2 category, Q3 category (mainly between tertiles 1 (youngest PM) and 2) and, to some extent, across levels of Q4 category (Appendix Table 6). We also observed a lower pooled VE against influenza B with PM across levels of Q2 category, Q3 category (mainly between tertiles 1 (youngest PM) and 2), and levels of Q4 category among studies with antigenically similar vaccine (Appendix Table 6). There was not enough data to enable assessment among studies with antigenically dissimilar/partially similar vaccine. None of the differences between VE across levels of the categories was statistically significant.

Discussion

We assessed the association between seasonal influenza vaccination PM and influenza VE, utilizing evidence from TND studies in outpatient settings after the 2009/10 influenza pandemic. Irrespective of our categorization of PM, we observed a largely consistent trend. Among studies with antigenically similar vaccine, VE against all influenza declined with PM, with higher decline observed in older adults. Similar observations were made when limited to the Northern and Southern hemispheres. Overall, the difference in VE between the levels of PM categories was mostly statistically significant for the two-level PM category (Q2). Considerably similar observations were made among studies with antigenically dissimilar/partially similar vaccines and with regard to VE against A(H1N1)pdm09, A(H3N2) and influenza B, except for a few inconsistencies (overall downward trend appears reversed) mainly due to higher VE in tertile 3 (oldest PM) compared with tertile 2 in some of the Q3, and in Q4 categories. The inconsistencies were mainly driven by studies from the USA, which contributed 75% to 100% of the studies within these levels. Being from a more affluent country, this could reflect early adoption of quadrivalent, high-dose, adjuvanted and
recombinant vaccines in the USA, which have been shown to offer improved efficacy,\textsuperscript{93,94} and may therefore have reversed or arrested any downward trends in VE. Examination of influenza VE over time in a large population of healthy people for whom vaccination is mandatory and vaccination and health care data are electronically available (for e.g., military and healthcare personnel) may help validate our findings.

There are currently no similar published studies to compare our findings against. However, our findings could be compared against what is currently known regarding repeat vaccination. Influenza vaccine remains the only vaccine regularly reformulated and administered every year due to influenza virus antigenic evolution. Whereas some studies have reported that repeated influenza vaccination may increase the risk of influenza infection, especially the A(H3N2),\textsuperscript{80,95,96} others have reported no evidence of loss of protection including against A(H3N2) even when the circulating virus strains are antigenically dissimilar from the vaccine component.\textsuperscript{97} A recent publication demonstrated that repeat seasonal influenza vaccination reduced antibody-affinity maturation to hemagglutinin 1 (HA1) domain of all three influenza virus strains irrespective of the vaccine platform.\textsuperscript{98} The study highlighted an important influence of repeat vaccination on antibody-affinity maturation which may contribute to lower influenza VE as we observed. A recent systematic review and meta-analysis of 20 studies (including TND, cohort and case-control) observed lower influenza VE against A(H3N2) and influenza B, but not against A(H1N1), in individuals vaccinated in both current and previous seasons compared with those vaccinated only in current season.\textsuperscript{12} These findings are similar to our findings except for A(H1N1). However, it is not clear if data from hospitalized patients were included among the analyzed studies. Such inclusion may explain the observed no difference found with regard to A(H1N1). A study investigated the impact of repeated vaccination on VE against A(H3N2) and influenza B in the USA.\textsuperscript{11} Utilizing five years of vaccination data, the authors found that
current season VE against A(H3N2) was significantly higher among vaccinated individuals with no prior vaccination history compared with those with a frequent vaccination history (p=0.01). A similar observation was made with respect to influenza B (p=0.05). These findings align largely with our findings in both all patients and older adults and particularly within our Q2 category, although we observed an opposite trend within the Q3 category when data were limited to studies with antigenically dissimilar/partially similar vaccine for all patients. An explanation for such a trend may be differences in study characteristics; particularly, patients’ age and comorbidity status. Another explanation could be the increasing use of quadrivalent influenza vaccines over the trivalent vaccines in the older programs, which are in the more affluent countries. Over the past years, seasonal influenza vaccines increasingly contain both influenza B strains (two distinct lineages) in addition to the influenza A subtypes (quadrivalent vaccine) instead of just having a single component for influenza B in addition to two influenza A subtypes (trivalent vaccine) as was previously the case. This may have concealed the trend towards a reduced VE with repeated vaccinations, particularly for influenza B.

It has been suggested that the protection conferred by influenza vaccine in a season could prevent the natural immunity from exposure to circulating influenza viruses, and may therefore increase the risk of infection and impact VE in subsequent season(s). The “antigenic distance” phenomenon has also been proposed; suggesting that negative interference from previous seasonal influenza vaccine on the current season’s VE may occur when previous and current season’s vaccines are antigenically closely related, but the previous season and the current circulating influenza virus strains are largely antigenically apart. Furthermore, evidence from studies on animals suggest that repeated vaccination could affect the development of cross-reactive immunity against influenza subtypes, suggestively facilitated by a decreased virus-specific CD8+ T-cell response.
seasonal vaccination has also been shown to affect development of virus-specific CD8+ T-cell immunity in children. These suggest repeated influenza vaccination may adversely affect VE and could be plausible biological explanations of our review findings. However, the issue of reduced influenza VE with repeated vaccination is multifaceted.

Even though we observed a trend that may suggest VE declines with PM, cautious interpretation of our findings is necessary because of limitations of our review and potential confounding that we could not explore. The studies reviewed differed by methods of participant enrollment, determination of influenza vaccination status and respiratory specimen type. Sample size varied across studies and statistical models differed significantly. However, in all of the studies, vaccination was at least 14 days before symptom onset, respiratory specimen swab collected within 7 days of symptom onset, and influenza diagnosis made by the gold standards (RT-PCR or viral culture), satisfying major conditions for TND study of influenza VE. A significant weakness of our review is the nature of the ecological data and the impact that differences in important characteristics such as age, sex, comorbidity status, prior history of influenza vaccination, and “healthy vaccinee” effect (bias because of more healthier individuals vaccinated over time) across studies might have had on our findings. It was also not possible to assess the impact of differences in vaccination rates across studies. A lack of data resulted in a few data points for some outcomes, limited statistical power for some of the analyses and precluded analysis in some cases. Nevertheless, findings from this review contribute significantly to the evidence base and provide population-level insights that may be of use to public health decision-making.

A major strength of this systematic review is its uniqueness. To the best of our knowledge, it is the first review to assess the impact of seasonal influenza vaccination PM on influenza VE. The evidence considered in this review was based on influenza VE estimates from TND study type, widely credited with reducing biases due to differential healthcare-
seeking behaviour between vaccinated and unvaccinated persons, differential misclassification of infection status, and easy access to study controls that are more representative of the case source population. Our analysis was particularly in-depth, covering three different categorizations of PM with a good spread of the data across levels of each category. We explored differences that may exist between influenza types/subtypes and compared the overall analyses with those for older adults, considering that this unique subpopulation is possibly the most adherent to influenza vaccination and, therefore, would likely present good insights with respect to the potential impact of PM on VE.

**Conclusions**

The evidence suggests influenza VE declines with vaccination PM, with potentially higher reduction among older adults when compared with all patients. Our findings form the basis for further discussions and examinations of the potential impact of influenza PM on seasonal VE but do not justify the curtailment or cessation of national annual vaccination programs which continue to offer substantial net public health benefit.
**Author contributions:** Conception (J.S.N-V-T); Design (G.N.O, S.M.M & J.S.N-V-T); Data collection (G.N.O, F.R, T.A, S.K.H & L.L); Data analysis/interpretation (G.N.O, C.H.R, S.M.M & J.S.N-V-T); Draft manuscript (G.N.O); Domain expert guidance (S.M.M & J.S.N-V-T); Manuscript revisions (G.N.O, F.R, T.A, S.K.H, L.L, C.H.R, S.M.M & J.S.N-V-T); Approval for submission (G.N.O, F.R, T.A, S.K.H, L.L, C.H.R, S.M.M & J.S.N-V-T).

**Funding:** No external funding was obtained for this study. G.N.O is a recipient of the Manitoba Training Program Fellowship Award, the Centre on Aging Betty Havens Memorial Graduate Fellowship Award, and the Evelyn Shapiro Award, all for health services research.

**Conflict of interest statement:** J.S.N-V-T was an employee of SmithKline Beecham plc. (now GlaxoSmithKline), and Aventis-Pasteur MSD (now Sanofi-Pasteur MSD) prior to 2005, both of whom manufacture influenza vaccines; he divested or relinquished all shareholdings, share options or accrued pension rights in both companies in 2005. He is seconded to the Department of Health and Social Care, England (DHSC). The views in this manuscript are those of the authors and do not necessarily represent those of DHSC. S.M.M is supported, in part, by funding from the Canada Research Chairs Program. S.M.M has received unrestricted research grants from GlaxoSmithKline, Merck, Sanofi Pasteur, Pfizer and Roche-Assurex for unrelated studies, and fees as an advisory board member for Sanofi Pasteur. C.H.R. has received an unrestricted research grant from Pfizer for an unrelated study. The other authors declare that they have no conflicts of interest.

**Patient Consent Statement:** This study does not include factors necessitating patient consent.
Acknowledgements: We thank Drs. Iwona Paradowska-Stankiewicz, Romana Tandara Haček, Daniel Levy-Bruhl, Sabine Reiter, Josefa Masa Calles, Suzanne Cotter, AnnaSara Carnahan, Aurora Limia, Franz Allerberger, Martin Sprenger, Aharon Glatman-Freedman, Gerald Haidinger, and Nesrin Cilingiroglu for responding kindly to our request for information.
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### Tables

**Table 1**: Results of pooled vaccine effectiveness (VE) against all influenza

| Influenza type, analyzed subgroups/PM categories | No. of studies | Pooled VE (95% CI) | I-squared statistic (%) | Publication bias (Egger’s test p-value) |
|-------------------------------------------------|----------------|--------------------|--------------------------|----------------------------------------|
| **All influenza**                                |                |                    |                          |                                        |
| Overall                                         |                |                    |                          |                                        |
| Q2                                              |                |                    |                          |                                        |
| Less than median                                | 36             | 50 (42 – 57)       | 74.7                     | 0.067                                  |
| More than median                                | 36             | 35 (29 – 40)       | 78.8                     | 0.239                                  |
| Q3                                              |                |                    |                          |                                        |
| Tertile 1 (youngest)                            | 26             | 50 (37 – 60)       | 74.7                     | <0.001                                 |
| Tertile 2                                       | 22             | 41 (30 – 50)       | 78.6                     | 0.742                                  |
| Tertile 3 (oldest)                              | 24             | 38 (32 – 43)       | 80.0                     | 0.571                                  |
| Q4                                              |                |                    |                          |                                        |
| Quartile 1 (youngest)                           | 21             | 52 (39 – 62)       | 67.3                     | 0.029                                  |
| Quartile 2                                      | 15             | 49 (36 – 59)       | 81.8                     | 0.315                                  |
| Quartile 3                                      | 18             | 23 (10 – 34)       | 66.7                     | 0.678                                  |
| Quartile 4 (oldest)                             | 18             | 41 (36 – 47)       | 81.3                     | 0.432                                  |
| **Antigenically similar vaccine**               |                |                    |                          |                                        |
| Q2                                              |                |                    |                          |                                        |
| Less than median                                | 22             | 54 (48 – 59)       | 25.6                     | 0.071                                  |
| More than median                                | 21             | 46 (41 – 51)       | 71.9                     | 0.564                                  |
| Q3                                              |                |                    |                          |                                        |
| Tertile 1 (youngest)                            | 17             | 55 (47 – 62)       | 34.5                     | 0.042                                  |
| Tertile 2                                       | 13             | 50 (41 – 58)       | 62.9                     | 0.654                                  |
| Tertile 3 (oldest)                              | 13             | 45 (40 – 50)       | 71.2                     | 0.561                                  |
| Q4                                              |                |                    |                          |                                        |
| Quartile 1 (youngest)                           | 14             | 57 (48 – 65)       | 30.2                     | 0.163                                  |
| Quartile 2                                      | 8              | 52 (45 – 57)       | 18.7                     | –                                      |
| Quartile 3                                      | 13             | 46 (35 – 55)       | 78.7                     | 0.918                                  |
| Quartile 4 (oldest)                             | 8              | 46 (41 – 50)       | 52.2                     | –                                      |
| **Antigenically dissimilar/partially similar vaccine** |      |                    |                          |                                        |
| Q2                                              |                |                    |                          |                                        |
| Less than median                                | 15             | 30 (12 – 44)       | 67.5                     | 0.006                                  |
| Group                     | No. | Pooled VE (95% CI) | I-squared statistic (%) | Publication bias (Egger’s test p-value) |
|---------------------------|-----|--------------------|-------------------------|----------------------------------------|
| More than median          | 14  | 20 (11 – 28)       | 52.1                    | 0.059                                  |
| Q3                        |     |                    |                         |                                        |
| Tertile 1 (youngest)      | 12  | 37 (12 – 55)       | 73.5                    | 0.004                                  |
| Tertile 2                 | 9   | 13 (~4 to 27)      | 57.8                    | –                                      |
| Tertile 3 (oldest)        | 8   | 25 (18 – 31)       | 19.2                    | –                                      |
| Q4                        |     |                    |                         |                                        |
| Quartile 1 (youngest)     | 12  | 37 (12 – 55)       | 73.5                    | 0.004                                  |
| Quartile 2                | 3   | 17 (3 – 29)        | 0                       | –                                      |
| Quartile 3                | 7   | 10 (~18 to 31)     | 66.2                    | –                                      |
| Quartile 4 (oldest)       | 7   | 24 (17 – 31)       | 30.5                    | –                                      |
| All patients: Northern hemisphere | | | | |
| **Influenza type, analyzed subgroups/PM categories** | **No. of studies** | **Pooled VE (95% CI)** | **I-squared statistic (%)** | **Publication bias (Egger’s test p-value)** |
| **All influenza**         |     |                    |                         |                                        |
| Overall                   |     |                    |                         |                                        |
| Q2                        |     |                    |                         |                                        |
| Less than median          | 30  | 38 (26 – 48)       | 81.1                    | 0.280                                  |
| More than median          | 24  | 38 (32 – 43)       | 80.0                    | 0.571                                  |
| Q3                        |     |                    |                         |                                        |
| Tertile 1 (youngest)      | 18  | 44 (28 – 57)       | 84.2                    | 0.309                                  |
| Tertile 2                 | 18  | 23 (10 – 34)       | 66.7                    | 0.678                                  |
| Tertile 3 (oldest)        | 18  | 41 (36 – 47)       | 81.5                    | 0.432                                  |
| Q4                        |     |                    |                         |                                        |
| Quartile 1 (youngest)     | 15  | 39 (20 – 54)       | 80.4                    | 0.096                                  |
| Quartile 2                | 15  | 36 (20 – 49)       | 82.1                    | 0.810                                  |
| Quartile 3                | 12  | 32 (20 – 43)       | 79.4                    | 0.025                                  |
| Quartile 4 (oldest)       | 12  | 41 (35 – 47)       | 82.0                    | 0.451                                  |
| **Antigenically similar vaccine** | | | | |
| Q2                        |     |                    |                         |                                        |
| Less than median          | 17  | 50 (41 – 58)       | 61.2                    | 0.979                                  |
| More than median          | 13  | 45 (40 – 50)       | 71.2                    | 0.561                                  |
| Q3                        |     |                    |                         |                                        |
| Tertile 1 (youngest)      | 10  | 55 (45 – 63)       | 54.9                    | 0.940                                  |
| Tertile 2                 | 12  | 43 (32 – 52)       | 73.7                    | 0.813                                  |
| Tertile 3 (oldest)        | 8   | 46 (41 – 50)       | 52.2                    | –                                      |
| Q4                        |     |                    |                         |                                        |
### Antigenically dissimilar/partially similar vaccine

| Quartile | No. of studies | Pooled VE (95% CI) | I-squared statistic (%) |
|----------|----------------|-------------------|------------------------|
| Q2       |                |                   |                        |
| Less than median | 12 | 12 (-9 to 29) | 66.0 | 0.163 |
| More than median | 12 | 25 (17 – 31) | 32.4 | 0.230 |
| Q3       |                |                   |                        |
| Tertile 1 (youngest) | 8 | 23 (-8 to 45) | 74.5 | – |
| Tertile 2 | 8 | 11 (-10 to 27) | 62.3 | – |
| Tertile 3 (oldest) | 8 | 25 (18 – 31) | 19.2 | – |
| Q4       |                |                   |                        |
| Quartile 1 (youngest) | 7 | 24 (-14 to 50) | 75.0 | – |
| Quartile 2 | 5 | 8 (-13 to 25) | 44.1 | – |
| Quartile 3 | 6 | 18 (-4 to 35) | 52.8 | – |
| Quartile 4 (oldest) | 6 | 26 (20 – 31) | 11.4 | – |

### All patients: Southern hemisphere

| Influenza type, analyzed subgroups/PM categories | No. of studies | Pooled VE (95% CI) | I-squared statistic (%) |
|-------------------------------------------------|----------------|-------------------|------------------------|
| **All influenza**                                |                |                   |                        |
| Overall                                         |                |                   |                        |
| Q2                                              |                |                   |                        |
| Less than median                                | 9 | 62 (50 – 71) | 12.1 |
| More than median                                | 9 | 52 (46 – 57) | 0 |
| Q3                                              |                |                   |                        |
| Tertile 1 (youngest)                            | 7 | 65 (51 – 75) | 20.1 |
| Tertile 2                                       | 5 | 49 (37 – 59) | 0 |
| Tertile 3 (oldest)                              | 7 | 53 (46 – 59) | 0 |
| Q4                                              |                |                   |                        |
| Quartile 1 (youngest)                           | 5 | 62 (38 – 77) | 39.4 |
| Quartile 2                                      | 4 | 62 (46 – 73) | 0 |
| Quartile 3                                      | 5 | 51 (39 – 60) | 0 |
| Quartile 4 (oldest)                             | 4 | 52 (44 – 59) | 4.3 |
| **Antigenically similar vaccine**                |                |                   |                        |
| Q2                                              |                |                   |                        |
| Less than median                                | 9 | 58 (47 – 67) | 28.5 |
| More than median                                | 4 | 52 (44 – 59) | 4.3 |
| Q3                                              |                |                   |                        |
| Tertile 1 (youngest)                            | 5 | 69 (54 – 79) | 26.8 |
| Tertile 2                                       | 4 | 49 (36 – 59) | 0 |
| Tertile 3 (oldest)                              | 4 | 52 (44 – 59) | 4.3 |
| Q4                                              |                |                   |                        |
| Quartile 1 (youngest)                           | 5 | 69 (54 – 79) | 26.8 |
### Older adults

#### Influenza type, analyzed subgroups/PM categories

| Influenza type, analyzed subgroups/PM categories | No. of studies | Pooled VE (95% CI) | I-squared statistic (%) | Publication bias (Egger’s test p-value) |
|-------------------------------------------------|----------------|-------------------|-------------------------|---------------------------------------|
| All influenza                                    |                |                   |                         |                                       |
| **Overall**                                     |                |                   |                         |                                       |
| Q2                                              |                |                   |                         |                                       |
| Less than median                                | 12             | 43 (22 – 58)      | 30.2                    | 0.696                                 |
| More than median                                | 12             | 23 (12 – 33)      | 0                       | 0.536                                 |
| Q3                                              |                |                   |                         |                                       |
| Tertile 1 (youngest)                            | 8              | 56 (37 – 69)      | 0                       | –                                     |
| Tertile 2                                       | 8              | 17 (–6 to 35)     | 9.9                     | –                                     |
| Tertile 3 (oldest)                              | 8              | 26 (14 – 36)      | 0                       | –                                     |
| Q4                                              |                |                   |                         |                                       |
| Quartile 1 (youngest)                           | 7              | 54 (32 – 69)      | 0                       | –                                     |
| Quartile 2                                      | 5              | 35 (3 to 59)      | 53.2                    | –                                     |
| Quartile 3                                      | 6              | 21 (–4 to 39)     | 0                       | –                                     |
| Quartile 4 (oldest)                             | 6              | 24 (11 – 35)      | 0                       | –                                     |
| **Antigenically similar vaccine**               |                |                   |                         |                                       |
| Q2                                              |                |                   |                         |                                       |
| Less than median                                | 9              | 50 (34 – 62)      | 0                       | –                                     |
| More than median                                | 8              | 23 (10 – 35)      | 0                       | –                                     |
| Q3                                              |                |                   |                         |                                       |
| Tertile 1 (youngest)                            | 6              | 56 (36 – 69)      | 0                       | –                                     |
| Tertile 2                                       | 7              | 30 (10 – 46)      | 4.4                     | –                                     |
| Tertile 3 (oldest)                              | 4              | 24 (9 – 37)       | 0                       | –                                     |
| Q4                                              |                |                   |                         |                                       |
| Quartile 1 (youngest)                           | 5              | 54 (31 – 70)      | 0                       | –                                     |
| Quartile 2                                      | 4              | 46 (23 – 62)      | 0                       | –                                     |
| Quartile 3                                      | 4              | 22 (–8 to 44)     | 3.8                     | –                                     |
| Quartile 4 (oldest)                             | 4              | 24 (9 – 37)       | 0                       | –                                     |
| **Antigenically dissimilar/partially similar vaccine** |            |                   |                         |                                       |
| Q2                                              |                |                   |                         |                                       |
| Less than median                                | 4              | 5 (–46 to 38)     | 0                       | –                                     |
| More than median                                | 3              | 21 (–1 to 39)     | 0                       | –                                     |
| Q3                                              |                |                   |                         |                                       |
| Tertile 1 (youngest) | 3 | 26 (-31 to 58) | 0 | – |
|----------------------|---|----------------|---|---|
| Tertile 2            | 2 | -16 (-87 to 28) | 0 | – |
| Tertile 3 (oldest)   | 2 | 24 (0 – 42)     | 0 | – |

PM = program maturation; Q2, Q3 and Q4 = categories of seasonal influenza vaccination program maturation; Less than median = lower half of the sorted data; More than median = higher half of the sorted data; CI = confidence interval.
Figures

Figure 1: Modified PRISMA flowchart (study selection process)

Figure 2: Forest plot of vaccine effectiveness (VE) against all influenza across Q2 category (all patients: studies with antigenically similar vaccine)

Less than median = lower half of the sorted data; More than median = higher half of the sorted data; CI = confidence interval

Figure 3: Forest plot of vaccine effectiveness (VE) against all influenza across Q3 category (all patients: studies with antigenically similar vaccine)

CI = confidence interval

Figure 4: Forest plot of vaccine effectiveness (VE) against all influenza across Q4 category (all patients: studies with antigenically similar vaccine)

CI = confidence interval
Figure 1

All retrieved citations (n = 11,931)
- Medline = 3,882
- EMBASE = 7,182
- PubMed = 235
- Scopus = 365
- Web of Science = 122
- Google Scholar = 145

Duplicates removed (n = 3,800)

Citations screened at title and abstract (n = 8,131)

Citations removed (n = 7,941)

Articles identified from reference lists of included papers (n = 2)

Full-text screened (n = 192)

Excluded with reasons (n = 120)
- Study design: 32
- Study population: 33
- Study outcome: 29
- Unadjusted results: 12
- I-MOVE studies: 10
- Unknown vaccination program start: 4

Included articles (n = 72)
| Publication       | Country  | Program maturation (in years) | VE (95% CI) | % Weight |
|------------------|----------|-------------------------------|-------------|----------|
| **Less than median** |          |                               |             |          |
| McAneney 2015    | South Africa | 1                             | 54 (2, 79)  | 1.91     |
| McAneney 2015    | South Africa | 2                             | 57 (16, 78) | 2.33     |
| McAneney 2015    | South Africa | 4                             | 87 (67, 95) | 1.28     |
| Nunes 2014       | Portugal  | 11                            | 68 (21, 87) | 1.34     |
| Sullivan 2013    | Australia | 13                            | 73 (47, 86) | 2.41     |
| Levy 2014        | Australia | 13                            | 68 (33, 85) | 2.03     |
| van-Doom 2017    | Netherlands | 13                           | 59 (25, 78) | 2.83     |
| Levy 2014        | Australia | 14                            | 52 (0, 77)  | 2.04     |
| Darvishian 2017  | Netherlands | 14                           | -1.14 (-157, 49) | 1.68 |
| Sullivan 2014    | Australia | 15                            | 45 (10, 67) | 3.92     |
| Levy 2014        | Australia | 15                            | 49 (30, 63) | 7.42     |
| Darvishian 2017  | Netherlands | 15                           | 50 (17, 70) | 3.79     |
| Kelly 2016       | Australia | 15                            | 52 (20, 71) | 3.73     |
| van-Doom 2017    | Netherlands | 15                           | 69 (44, 83) | 2.99     |
| Skowronski 2012  | Canada    | 17                            | 37 (17, 52) | 8.87     |
| Regan 2019       | Australia | 17                            | 60 (41, 73) | 5.66     |
| Pierse 2016      | New Zealand | 17                           | 56 (35, 70) | 5.75     |
| Fielding 2016    | Australia | 18                            | 54 (42, 63) | 10.79    |
| Skowronski 2014  | Canada    | 18                            | 59 (43, 70) | 7.36     |
| Regan 2019       | Australia | 19                            | 40 (18, 56) | 7.64     |
| Skowronski 2014  | Canada    | 19                            | 50 (33, 63) | 8.09     |
| Chan 2019        | Hong Kong | 19                            | 59 (41, 72) | 6.15     |
| **Subtotal (I-squared=25.6%, p=0.134)** | | | **54 (48, 59)** | **100.00** |
| **More than median** |          |                               |             |          |
| Skowronski 2015  | Canada    | 20                            | 68 (58, 76) | 4.43     |
| Skowronski 2017  | Canada    | 22                            | 46 (32, 57) | 5.20     |
| Jimenez-Jorge 2012 | Spain | 27                           | 39 (-18, 68) | 1.47 |
| Englund 2013     | Germany   | 28                            | 70 (40, 85) | 1.31     |
| Jimenez-Jorge 2015 | Spain | 29                           | 63 (41, 77) | 2.44     |
| Vilcu 2018       | France    | 30                            | 10 (-32, 39) | 3.20 |
| Helmeke 2015     | Germany   | 30                            | 38 (1, 61)  | 2.47     |
| Vilcu 2018       | France    | 30                            | 18 (-34, 50) | 2.31 |
| Pebody 2016      | UK        | 45                            | 52 (41, 62) | 5.43     |
| Pebody 2017      | UK        | 46                            | 55 (23, 53) | 4.96     |
| Treanor 2012     | USA       | 47                            | 59 (31, 66) | 5.88     |
| Pebody 2019      | UK        | 47                            | 15 (-6, 32)  | 5.29 |
| Cowling 2016     | USA       | 47                            | 40 (28, 50) | 5.85     |
| Ohmit 2014       | USA       | 48                            | 47 (36, 56) | 5.88     |
| Cowling 2016     | USA       | 48                            | 54 (41, 64) | 4.79     |
| Pebody 2020      | UK        | 48                            | 44 (27, 58) | 4.51     |
| Cowling 2016     | USA       | 49                            | 51 (43, 58) | 6.46     |
| McLean 2015      | USA       | 49                            | 49 (43, 55) | 7.00     |
| Jackson 2017     | USA       | 52                            | 48 (40, 55) | 6.74     |
| Flannery 2019    | USA       | 53                            | 40 (33, 47) | 7.04     |
| Rolfe 2019       | USA       | 54                            | 38 (32, 44) | 7.32     |
| **Subtotal (I-squared=71.9%, p=0.000)** | | | **46 (41, 51)** | **100.00** |

**Figure 2**
Figure 3

| Publication          | Country    | Program maturation (in years) | VE (95% CI) | % Weight |
|----------------------|------------|--------------------------------|-------------|----------|
| **Tertile 1 (youngest)** |            |                                |             |          |
| McAneney 2015        | South Africa | 1                              | 54 (2, 79)  | 3.65     |
| McAneney 2015        | South Africa | 2                              | 57 (16, 78) | 4.36     |
| McAneney 2015        | South Africa | 4                              | 87 (67, 95) | 2.55     |
| Nunes 2014           | Portugal    | 11                             | 68 (21, 87) | 2.64     |
| Sullivan 2013        | Australia   | 13                             | 73 (47, 86) | 4.48     |
| Levy 2014            | Australia   | 13                             | 68 (33, 85) | 3.85     |
| van-Doorn 2017       | Netherlands | 13                             | 59 (25, 78) | 5.14     |
| Levy 2014            | Australia   | 14                             | 52 (0, 77)  | 3.88     |
| Darwishian 2017      | Netherlands | 14                             | -14 (-157, 49) | 3.26 |
| Sullivan 2014        | Australia   | 15                             | 45 (10, 67) | 6.74     |
| Levy 2014            | Australia   | 15                             | 49 (30, 63) | 10.85    |
| Darwishian 2017      | Netherlands | 15                             | 50 (17, 70) | 6.55     |
| Kelly 2016           | Australia   | 15                             | 52 (20, 71) | 6.47     |
| van-Doorn 2017       | Netherlands | 15                             | 69 (44, 83) | 5.39     |
| Skowronske 2012      | Canada      | 17                             | 37 (17, 52) | 12.20    |
| Regan 2019           | Australia   | 17                             | 60 (41, 73) | 8.94     |
| Pierse 2016          | New Zealand | 17                             | 56 (35, 70) | 9.04     |
| **Subtotal (I-squared=34.5%, p=0.081)** |            |                                | 55 (47, 62) | 100.00  |

**Tertile 2**

| Publication          | Country    | Program maturation (in years) | VE (95% CI) | % Weight |
|----------------------|------------|--------------------------------|-------------|----------|
| Fielding 2016        | Australia  | 18                             | 54 (42, 63) | 10.62    |
| Skowronske 2014      | Canada     | 18                             | 59 (43, 70) | 8.78     |
| Regan 2019           | Australia  | 19                             | 40 (18, 56) | 8.96     |
| Skowronske 2014      | Canada     | 19                             | 50 (33, 63) | 9.23     |
| Chan 2019            | Hong Kong  | 19                             | 59 (41, 72) | 7.92     |
| Skowronske 2015      | Canada     | 20                             | 68 (58, 76) | 9.56     |
| Skowronske 2017      | Canada     | 22                             | 46 (32, 57) | 10.54    |
| Jimenez-Jorge 2012   | Spain      | 27                             | 39 (-18, 68) | 4.20 |
| England 2013         | Germany    | 28                             | 70 (40, 85) | 3.82     |
| Jimenez-Jorge 2015   | Spain      | 29                             | 63 (41, 77) | 6.29     |
| Vilcu 2018           | France     | 30                             | 10 (-32, 39) | 7.68 |
| Helmeke 2015         | Germany    | 30                             | 38 (1, 61)  | 6.35     |
| Vilcu 2018           | France     | 30                             | 18 (-34, 50) | 6.04 |
| **Subtotal (I-squared=62.9%, p=0.001)** |            |                                | 50 (41, 58) | 100.00  |

**Tertile 3 (oldest)**

| Publication          | Country    | Program maturation (in years) | VE (95% CI) | % Weight |
|----------------------|------------|--------------------------------|-------------|----------|
| Pebody 2016          | UK         | 45                             | 52 (41, 62) | 6.77     |
| Pebody 2017          | UK         | 46                             | 40 (23, 53) | 6.03     |
| Treanor 2012         | USA        | 47                             | 59 (51, 66) | 7.52     |
| Pebody 2019          | UK         | 47                             | 15 (-6, 32) | 6.54     |
| Cowling 2016         | USA        | 47                             | 40 (28, 50) | 7.47     |
| Ohmit 2014           | USA        | 48                             | 47 (36, 56) | 7.52     |
| Cowling 2016         | USA        | 48                             | 54 (41, 64) | 5.77     |
| Pebody 2020          | UK         | 48                             | 44 (27, 58) | 5.35     |
| Cowling 2016         | USA        | 49                             | 51 (43, 58) | 8.54     |
| McLean 2015          | USA        | 49                             | 49 (43, 55) | 9.37     |
| Jackson 2017         | USA        | 52                             | 48 (40, 55) | 9.06     |
| Flannery 2019        | USA        | 53                             | 40 (33, 47) | 9.65     |
| Rolfs 2019           | USA        | 54                             | 38 (32, 44) | 10.20    |
| **Subtotal (I-squared=71.2%, p=0.000)** |            |                                | 45 (40, 50) | 100.00  |

**VE**

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### Figure 4

| Publication        | Country     | Program maturation (in years) | VE (95% CI) | % Weight |
|--------------------|-------------|------------------------------|-------------|----------|
| **Quartile 1 (youngest)** |             |                              |             |          |
| McAneney 2015      | South Africa| 1                            | 54 (2, 79)  | 5.29     |
| McAneney 2015      | South Africa| 2                            | 57 (16, 78) | 6.30     |
| McAneney 2015      | South Africa| 4                            | 87 (67, 95) | 3.72     |
| Nunes 2014         | Portugal    | 11                           | 68 (21, 87) | 3.86     |
| Sullivan 2013      | Australia   | 13                           | 73 (47, 86) | 6.47     |
| Levy 2014          | Australia   | 13                           | 68 (33, 85) | 5.58     |
| van-Doorn 2017     | Netherlands | 13                           | 59 (25, 78) | 7.40     |
| Levy 2014          | Australia   | 14                           | 52 (0, 77)  | 5.62     |
| Darvishian 2017    | Netherlands | 14                           | 74 (43, 87) | 7.64     |
| Sullivan 2014      | Australia   | 15                           | 45 (10, 67) | 9.61     |
| Levy 2014          | Australia   | 15                           | 49 (30, 63) | 15.09    |
| Darvishian 2017    | Netherlands | 15                           | 50 (17, 70) | 9.35     |
| Kelly 2016         | Australia   | 15                           | 52 (20, 71) | 9.24     |
| van-Doorn 2017     | Netherlands | 15                           | 69 (44, 83) | 7.74     |
| **Subtotal (I-squared=30.2%, p=0.135)** |             |                              | 57 (48, 65) | 100.00   |
| **Quartile 2**     |             |                              |             |          |
| Skowronski 2012    | Canada      | 17                           | 37 (17, 52) | 5.28     |
| Skowronski 2012    | Australia   | 17                           | 60 (41, 73) | 8.48     |
| Regan 2019         | New Zealand | 17                           | 56 (35, 70) | 8.64     |
| Fielding 2016      | Australia   | 18                           | 54 (42, 63) | 20.43    |
| Skowronski 2014    | Canada      | 18                           | 59 (43, 70) | 11.85    |
| Regan 2019         | Australia   | 19                           | 40 (18, 56) | 12.46    |
| Skowronski 2014    | Canada      | 19                           | 50 (33, 63) | 13.45    |
| Chan 2019          | Hong Kong   | 19                           | 59 (41, 72) | 9.40     |
| **Subtotal (I-squared=18.7%, p=0.282)** |             |                              | 52 (45, 57) | 100.00   |
| **Quartile 3**     |             |                              |             |          |
| Skowronski 2015    | Canada      | 20                           | 68 (58, 76) | 8.67     |
| Skowronski 2017    | Canada      | 22                           | 46 (32, 57) | 9.31     |
| Jimenez-Jorge 2012 | Spain       | 27                           | 39 (-18, 68) | 4.44    |
| England 2013       | Germany     | 28                           | 70 (40, 85) | 4.08     |
| Jimenez-Jorge 2015 | Spain       | 29                           | 63 (41, 77) | 6.25     |
| Vilcu 2018         | France      | 30                           | 10 (-32, 39) | 7.33    |
| Helmeke 2015       | Germany     | 30                           | 38 (1, 61)  | 6.29     |
| Vilcu 2018         | France      | 30                           | 18 (-34, 50) | 6.04    |
| Pebody 2016        | UK          | 45                           | 52 (41, 62) | 9.49     |
| Pebody 2017        | UK          | 46                           | 40 (23, 53) | 9.13     |
| Treanor 2012       | USA         | 47                           | 59 (51, 66) | 9.81     |
| Pebody 2019        | UK          | 47                           | 15 (-6, 32) | 9.38     |
| Cowling 2016       | USA         | 47                           | 40 (28, 50) | 9.79     |
| **Subtotal (I-squared=78.7%, p=0.000)** |             |                              | 46 (35, 55) | 100.00   |
| **Quartile 4 (oldest)** |             |                              |             |          |
| Omhit 2014         | USA         | 48                           | 47 (36, 56) | 10.07    |
| Cowling 2016       | USA         | 48                           | 54 (41, 64) | 6.61     |
| Pebody 2020        | UK          | 48                           | 44 (27, 58) | 5.93     |
| Cowling 2016       | USA         | 49                           | 51 (43, 58) | 12.67    |
| McLean 2015        | USA         | 49                           | 49 (43, 55) | 15.92    |
| Jackson 2017       | USA         | 52                           | 48 (40, 55) | 14.21    |
| Flannery 2019      | USA         | 53                           | 40 (33, 47) | 16.23    |
| Rolles 2019        | USA         | 54                           | 38 (32, 44) | 18.37    |
| **Subtotal (I-squared=52.2%, p=0.041)** |             |                              | 46 (41, 50) | 100.00   |