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Decline in Seasonal Influenza Vaccine Effectiveness With Vaccination Program Maturation: A Systematic Review and Meta-analysis

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Background. Evidence suggests that repeated influenza vaccination may reduce vaccine effectiveness (VE). Using influenza vaccination program maturation (PM; number of years since program inception) as a 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 citations. Across the 3 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 that 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; vaccination program; vaccine effectiveness.

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) [1], warrants reformulation of vaccine each influenza season in an attempt to match vaccine with the circulating virus strains [2]. Vaccination is therefore recommended each season for better protection against circulating virus strains. However, vaccine seroresponse may be impaired with repeated vaccination [2].

Generally, seasonal influenza vaccination is recommended for individuals at least 6 months old, with an 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 [3, 4]. Many countries have adopted annual influenza vaccination policies and have established annual vaccination programs. Many vaccination programs are 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 policies, was initially for a few at-higher-risk population subgroups, before gradually being 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) [5, 6] 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 [7] or found no evidence of a negative impact of repeated influenza vaccination [8]. In particular, a large randomized controlled trial in the United States of America found some

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variations in infection rates between groups given 1 or more influenza vaccinations but noted no consistent pattern of differences in relation to number of successive seasonal vaccinations [9]. Recent studies have found reduced influenza VE in individuals who received prior repeated influenza vaccinations [10, 11]. 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 the current season [12].

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 (PM; number of years since program inception) as a 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 [13]. Our findings are reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [14]. 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 [15].

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 [16]. The final search strategy (Supplementary 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. The 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 2009/2010 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 2-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 are 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% CIs). 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 programs, and within-country regional differences in program inception (Supplementary Table 2). In countries with decentralized provincial/state health authorities where there was no single, countrywide inception year, we considered the earliest regional program inception year to be the 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 the 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, TX, 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 grouped vaccination PM into categories: 2 (Q2, cut at the median), 3 (Q3, tertiles), and 4 (Q4, quartiles). 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% CIs using an inverse-variance random-effects model. We assessed and quantified statistical heterogeneity between pooled VE using I^2 [18]. We utilized the χ^2 test to assess the statistical significance (P value) of the difference between pooled VE across categories of vaccination PM [19]. Where appropriate (≥10 studies), we assessed for publication bias statistically using Egger's regression test [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 citations, from which we included 72 full-text articles that met our inclusion criteria (Figure 1) [21–92]. Relevant study characteristics are summarized in Supplementary Table 3, and a geographic heat map and graphical representation of the included articles are presented in Supplementary Figure 1. Overall, there were 59 articles from

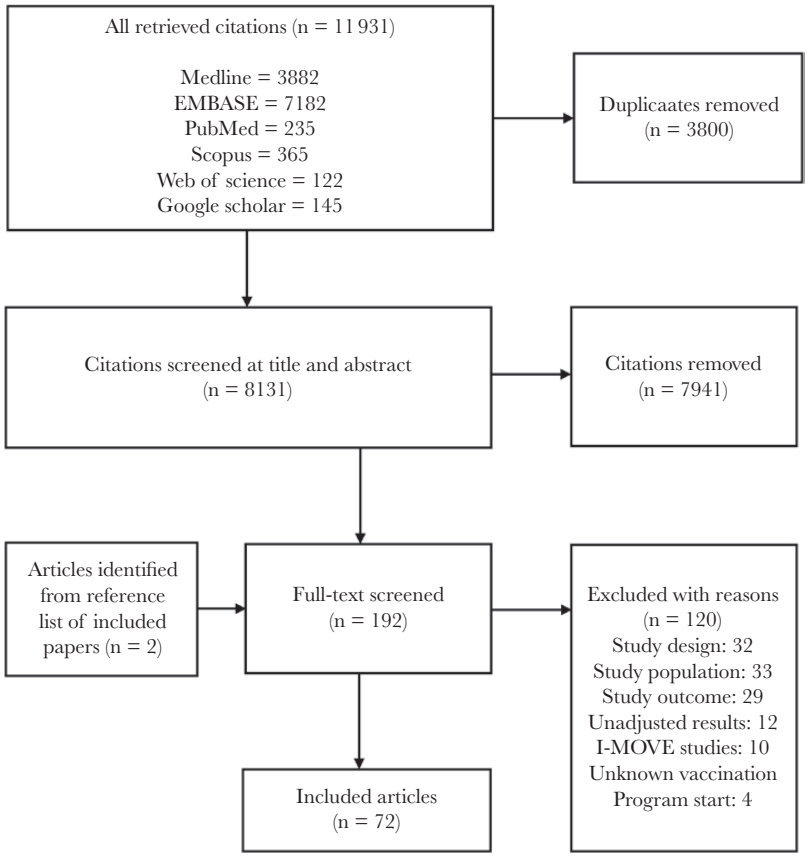

Figure 1. Modified Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart (study selection process).

the Northern hemisphere and 13 articles from the Southern hemisphere. PM ranged from 1 to 64 years. Study quality assessment is summarized in Supplementary 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 3 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 ($P < .001$). Therefore, we conducted meta-analysis within levels of vaccine antigenic similarity for this and other assessed outcomes. Among studies with antigenically similar vaccines, 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 ($P = .035$) (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 differences in VE between tertiles 1 and 2 and between tertiles 2 and 3 were both nonsignificant (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%) for quartile 2, and 46% (35%–55%) and 46% (41%–50%) for quartiles 3 and 4, respectively. However, the differences in VE between quartiles 1 and 2, between quartiles 2 and 3, and between quartiles 3 and 4 were all nonsignificant (Figure 4). Largely similar observations were made among studies with antigenically dissimilar/partially similar vaccines (Supplementary Figures 2–4), and when limited to the Northern and Southern hemispheres, particularly with high antigenic match (Supplementary 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 3 levels of Q4 category, but with significantly lower heterogeneity (Table 1). Among studies with antigenically similar vaccines, 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 ($P = .005$) (Supplementary 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 ($P = .037$), but the difference in VE between tertiles 2 and 3 was nonsignificant (Supplementary 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 a slightly higher 24% (9%–37%) for quartiles 3 and 4, respectively, although the differences in VE between quartiles 1 and 2 and between quartiles 2 and 3 were nonsignificant (Supplementary Figure 13). There was a paucity of data to enable adequate assessment among studies with antigenically dissimilar/partially similar vaccines (Supplementary Figures 14–16).

Pooled VE Against Influenza A Subtypes and Influenza B (All Patients)

When limited to studies with antigenically similar vaccines, we observed a lower pooled VE against A(H1N1)pdm09 with PM across levels of Q2 category ($P = .023$), Q3 category (mainly between tertile 1 [youngest PM] and tertile 2; $P = .065$), and, to some extent, Q4 category. Q4 category did not show a consistent reduction across the 4 levels, mostly due to quartile 4 (oldest PM) being driven by studies from the United States (80%) (Supplementary Table 5). This was also the case for A(H3N2): Q2 ($P = .12$) and Q3 (mainly between tertile 1 [youngest PM] and tertile 2; $P = .15$; with tertile 3 [oldest PM] driven by studies from the United States [86%]); and influenza B: Q2 ($P = .38$) and Q3 (mainly tertile 1 [youngest PM] and tertile 2; $P = .33$; with tertile 3 [oldest PM] driven by studies from the United States [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 United States (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 vaccines. We observed a lower pooled VE against A(H3N2) and influenza B with PM across levels of Q2 category and Q4 category among studies with antigenically dissimilar/partially similar vaccines. The opposite observation was, however, made across levels of Q3 category with regard to influenza B (Supplementary Table 5).

Pooled VE Against Influenza A Subtypes and Influenza B (Older Adults)

Among studies with antigenically similar vaccines, we observed a lower pooled VE against A(H1N1)pdm09 with PM across only levels of Q2 category (Supplementary Table 6). There was not enough data to enable adequate assessment of A(H3N2). However, among studies with antigenically dissimilar/partially similar vaccines, 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 (Supplementary 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 vaccines (Supplementary Table 6). There was not enough data to enable assessment among studies with antigenically dissimilar/partially similar vaccines. None of the differences between VE across levels of the categories were statistically significant.

Table 1. Results of Pooled Vaccine Effectiveness Against All Influenza

All Patients				
Influenza Type, Analyzed Subgroups/PM Categories	No. of Studies	Pooled VE (95% CI)	I^2, %	Publication Bias, Egger's Test *P* Value
All influenza				
Overall				
Q2				
Less than median	36	50 (42–57)	74.7	.067
More than median	36	35 (29–40)	78.8	.239
Q3				
Tertile 1 (youngest)	26	50 (37–60)	74.7	<.001
Tertile 2	22	41 (30–50)	78.6	.742
Tertile 3 (oldest)	24	38 (32–43)	80.0	.571
Q4				
Quartile 1 (youngest)	21	52 (39–62)	67.3	.029
Quartile 2	15	49 (36–59)	81.8	.315
Quartile 3	18	23 (10–34)	66.7	.678
Quartile 4 (oldest)	18	41 (36–47)	81.3	.432
Antigenically similar vaccine				
Q2				
Less than median	22	54 (48–59)	25.6	.071
More than median	21	46 (41–51)	71.9	.564
Q3				
Tertile 1 (youngest)	17	55 (47–62)	34.5	.042
Tertile 2	13	50 (41–58)	62.9	.654
Tertile 3 (oldest)	13	45 (40–50)	71.2	.561
Q4				
Quartile 1 (youngest)	14	57 (48–65)	30.2	.163
Quartile 2	8	52 (45–57)	18.7	–
Quartile 3	13	46 (35–55)	78.7	.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	.006
More than median	14	20 (11–28)	52.1	.059
Q3				
Tertile 1 (youngest)	12	37 (12–55)	73.5	.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	.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^2, %	Publication Bias, Egger's Test *P* Value
All influenza				
Overall				
Q2				
Less than median	30	38 (26–48)	81.1	.280
More than median	24	38 (32–43)	80.0	.571
Q3				
Tertile 1 (youngest)	18	44 (28–57)	84.2	.309
Tertile 2	18	23 (10–34)	66.7	.678
Tertile 3 (oldest)	18	41 (36–47)	81.5	.432
Q4				
Quartile 1 (youngest)	15	39 (20–54)	80.4	.096
Quartile 2	15	36 (20–49)	82.1	.810
Quartile 3	12	32 (20–43)	79.4	.025
Quartile 4 (oldest)	12	41 (35–47)	82.0	.451

Table 1. Continued

All Patients: Northern Hemisphere				
Influenza Type, Analyzed Subgroups/PM Categories	No. of Studies	Pooled VE (95% CI)	I^2, %	Publication Bias, Egger's Test *P* Value
Antigenically similar vaccine				
Q2				
Less than median	17	50 (41–58)	61.2	.979
More than median	13	45 (40–50)	71.2	.561
Q3				
Tertile 1 (youngest)	10	55 (45–63)	54.9	.940
Tertile 2	12	43 (32–52)	73.7	.813
Tertile 3 (oldest)	8	46 (41–50)	52.2	–
Q4				
Quartile 1 (youngest)	9	52 (43–61)	38.7	–
Quartile 2	8	48 (30–61)	75.0	–
Quartile 3	8	45 (36–53)	75.9	–
Quartile 4 (oldest)	5	45 (40–50)	67.3	–
Antigenically dissimilar/partially similar vaccine				
Q2				
Less than median	12	12 (–9 to 29)	66.0	.163
More than median	12	25 (17–31)	32.4	.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^2, %
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
Quartile 2	4	49 (36–59)		0
Quartile 3	2	58 (45–68)		0
Quartile 4 (oldest)	2	49 (34–60)		45.6

Table 1. Continued

Older Adults				
Influenza Type, Analyzed Subgroups/PM Categories	No. of Studies	Pooled VE (95% CI)	I^2, %	Publication Bias, Egger's Test *P* Value
All influenza				
Overall				
Q2				
Less than median	12	43 (22–58)	30.2	.696
More than median	12	23 (12–33)	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 (–9 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	–

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.
Abbreviations: PM, program maturation; VE, vaccine effectiveness.

DISCUSSION

We assessed the association between seasonal influenza vaccination PM and influenza VE utilizing evidence from TND studies in outpatient settings after the 2009/2010 influenza pandemic. Irrespective of our categorization of PM, we observed a largely consistent trend. Among studies with antigenically similar vaccines, 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 2-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 Q4 categories. The inconsistencies were mainly driven by studies from the United States, 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 United States, which have been shown to offer improved efficacy [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, eg, military and health care personnel) may help validate our findings.

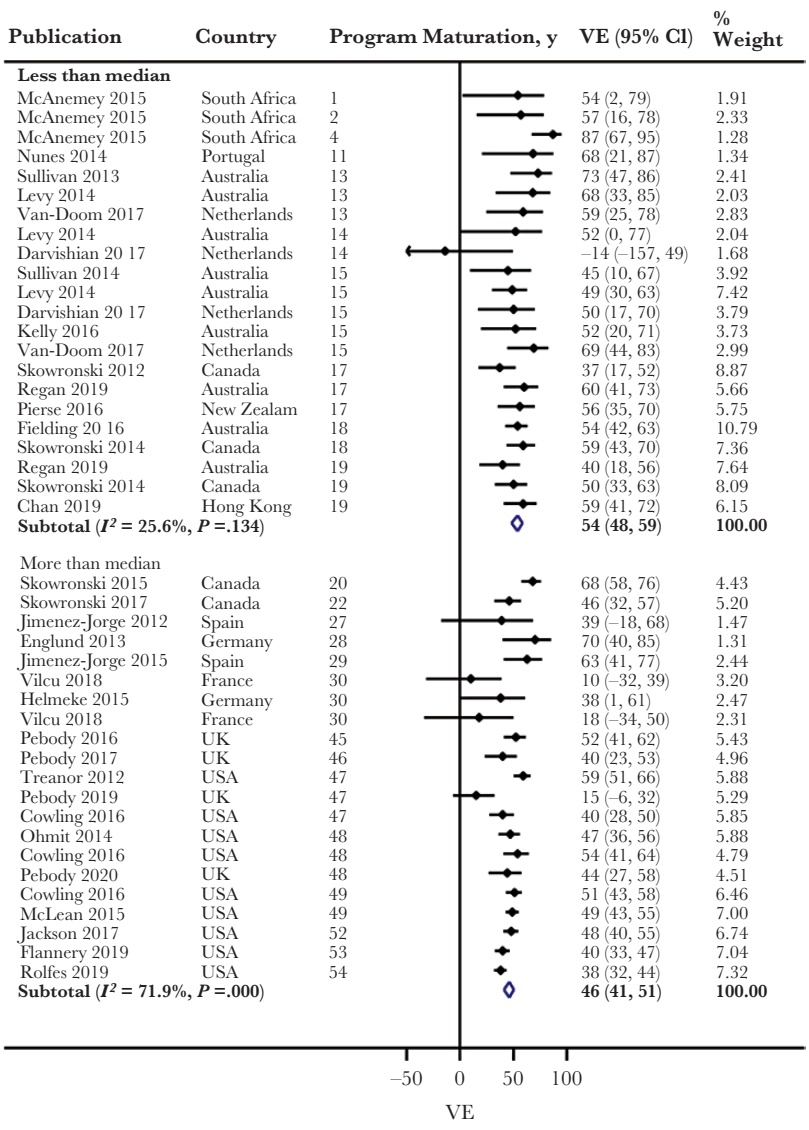

Figure 2. Forest plot of vaccine effectiveness (VE) against all influenza across Q2 category (all patients: studies with antigenically similar vaccine). Less than median = lower half of the sorted data; more than median = higher half of the sorted data.

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) [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 [97]. A recent publication demonstrated that repeat seasonal influenza vaccination reduced antibody-affinity maturation to hemagglutinin 1 (HA1) domain of all 3 influenza virus strains irrespective of the vaccine platform [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 the current season [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 lack of 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 United States [11]. Utilizing 5 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

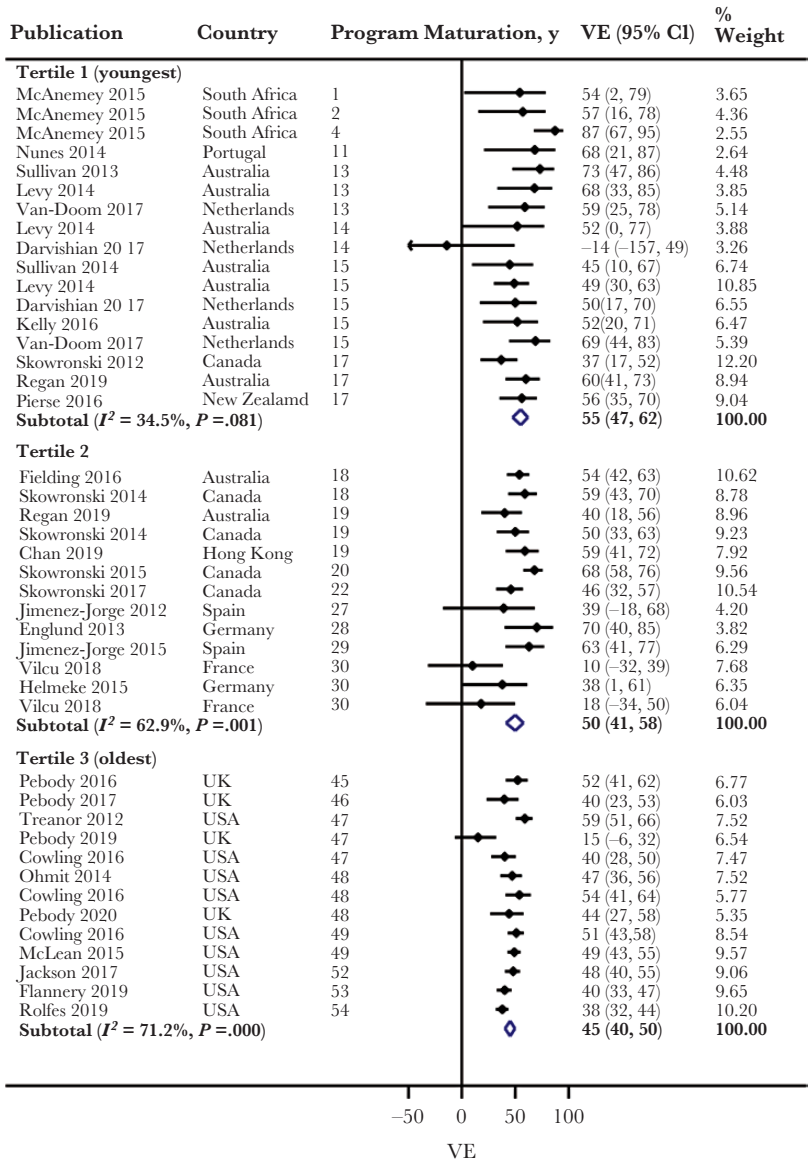

Figure 3. Forest plot of vaccine effectiveness (VE) against all influenza across Q3 category (all patients: studies with antigenically similar vaccine).

vaccination history (P = .01). A similar observation was made with respect to influenza B (P = .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 vaccines for all patients. An explanation for such a trend may be differences in study characteristics, particularly patient age and comorbidity status. Another explanation could be the increasing use of quadrivalent influenza vaccines over trivalent vaccines in the older programs, which are in the more affluent countries. In recent years, seasonal influenza vaccines increasingly contain both influenza B strains (2 distinct lineages) in addition to the influenza A subtypes (quadrivalent vaccine) instead of just having a single component for influenza B in addition to 2 influenza A subtypes (trivalent vaccine), as was previously the case. This may have concealed the trend toward 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 seasons [7]. The "antigenic distance" phenomenon has also been proposed, suggesting that negative interference from the previous seasonal influenza vaccine on the current season's VE may occur when the previous and current season's vaccines are antigenically closely related, but the previous season and the current circulating influenza virus strains are largely antigenically distinct [99]. Furthermore, evidence from studies on animals suggests that repeated vaccination could affect the

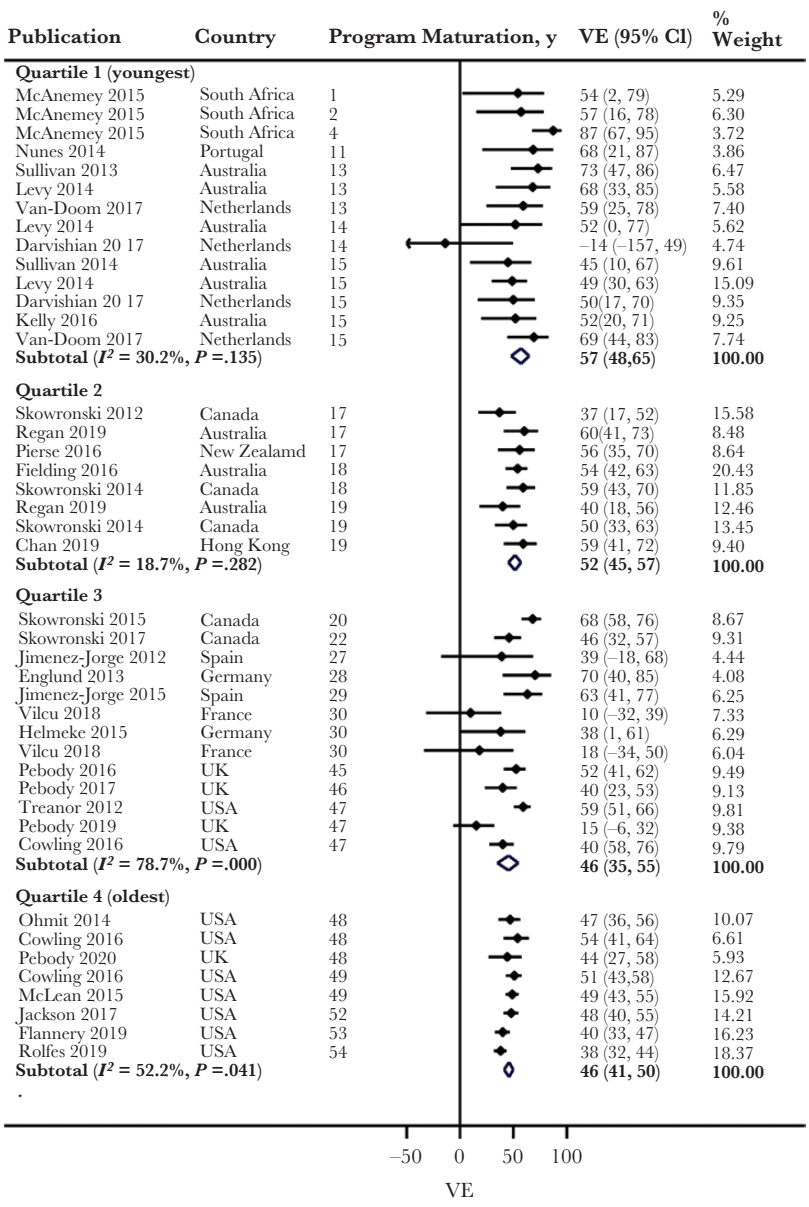

Figure 4. Forest plot of vaccine effectiveness (VE) against all influenza across Q4 category (all patients: studies with antigenically similar vaccine).

development of cross-reactive immunity against influenza subtypes, suggestively facilitated by a decreased virus-specific CD8+ T-cell response [100]. Repeated seasonal vaccination has also been shown to affect development of virus-specific CD8+ T-cell immunity in children [101]. These studies suggest that repeated influenza vaccination may adversely affect VE, which could be a plausible biological explanation 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 that VE declines with PM, cautious interpretation of our findings is necessary because of the 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, the respiratory specimen swab was collected within 7 days of symptom onset, and influenza diagnosis was made using 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 health care–seeking behavior between vaccinated and unvaccinated persons, differential misclassification of infection status, and easy access to study controls who are more representative of the case source population [5]. Our analysis was particularly in-depth, covering 3 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 that 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.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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