

A Systematic Review and Meta-Analysis of Immunogenicity and Safety of the Influenza Vaccine in COPD Patients, and Its Relevance with Real-World Effectiveness

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Objective: A systematic review and meta-analysis was conducted to evaluate the immunogenicity and adverse events of influenza vaccines in patients with chronic obstructive pulmonary disease (COPD) and explored their relevance to real-world vaccine effectiveness (VE).

Methods: A systematic search of PubMed, Cochrane Library (Wiley), Google Scholar, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform using keywords of “influenza vaccine”, “immunogenicity”, “COPD”, and “Chronic Obstructive Pulmonary Disease” to identify relevant studies published up to April 24, 2024. These are randomized controlled trials and cross-sectional, prospective, and observational studies that included COPD patients, particularly those aged ≥ 50 years, which assessed the immunogenicity of inactivated trivalent and quadrivalent, split-virion influenza vaccines. The outcomes were geometric mean titer (GMT), seroprotection rate (SPR), seroconversion rate (SCR), and safety.

Results: Six studies involving 672 participants were retrieved. The pooled SCR in the intradermal subgroup was highest for A/H1N1 (68.6% [95% CI = 48.6–83.5%]) and A/H3N2 (65.8% [95% CI = 57.9–73.0%]). SPR was highest via subcutaneous route, reaching 96.0% for A/H3N2 however only one study was available, hence the findings should be interpreted with caution. The pooled mean difference in GMT was higher for intradermal than intramuscular vaccination, particularly for the A/H1N1 strain (8.38 vs 7.98) and A/H3N2 (7.97 vs 7.44). Local adverse events were more frequent with intradermal vaccination, particularly erythema (31.5%) and swelling (28.7%), while systemic events such as fever were rare ($<5\%$).

Conclusion: The GMT, SPR, and SCR of influenza vaccination in COPD patients were more robust in laboratory settings than in real-world VE, indicating a gap between antibody responses in real-world clinical practice and laboratory settings.

Keywords: immunogenicity, influenza vaccine, COPD, GMT, seroprotection, seroconversion

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality in the world and responsible for an estimated 3.5 million deaths in 2021, and this reflects about 5% of all deaths worldwide.¹ The global mortality burden by COPD increased by 14.1% from 2009 to 2019 and is projected to become a global burden with a 23% increase to near 600 million cases.^{2,3} Data from a tertiary care center in Southern India showed that patients hospitalized with influenza had an overall death rate of 12.3%, and COPD was found as the most prevalent comorbidity in 26.1% of these cases.⁴ Patients with COPD have recurrent acute worsening of the symptoms known as exacerbations, which requires additional treatment and often leads to a reduction in health status and increased risk of hospitalization, morbidity, and mortality.^{5,6}

The acute exacerbations of COPD (AECOPD) have diverse causes, pathophysiological mechanisms, underlying inflammation, symptoms, and severity.⁷ Viral infections are considered as a major causative factor in approximately 50% of all AECOPD, with influenza viruses found in up to 28% of the COPD patients who have exacerbations.⁸

Individuals with COPD are highly susceptible to influenza virus infection and its associated complications. This is due to the underlying respiratory problems associated with COPD, which may be further exacerbated by the impact of influenza.^{9,10} These exacerbations often lead to accelerated disease progression, increased risk of mortality, and a more rapid decline in pulmonary function.^{11,12} The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends annual influenza vaccination for individuals with COPD based on results from clinical trials that presented noteworthy reductions in the incidence of exacerbations per vaccinated subject compared to placebo-treated subjects.¹³ However, it remains unclear whether COPD patients produce adequate antibody responses to seasonal influenza vaccination. COPD is a chronic inflammatory disease resulting from recurrent exposure to lung irritants. Individuals with this disease are believed to have some level of immune dysfunction in comparison with healthy individuals.¹⁴ This relative immunodeficiency may reduce the immune response effectiveness of COPD patients to vaccination. T-cell exhaustion caused by chronic inflammation may lessen the ability to generate strong and effective T-cell responses to mRNA vaccines. This diminished cell-mediated immunity may affect the efficacy of mRNA vaccinations in people with pre-existing inflammatory diseases.¹⁵ Notably, the prevalence of COPD increases with age, peaking in the 65–74 year age bracket. Consequently, aging has been identified as a major factor involved in the pathogenesis of COPD, as it accompanies an immune system that is also undergoing an aging process known as immunosenescence.¹⁶ Immunosenescence, combined with the progressive enhancement of a proinflammatory condition characteristic of aging (inflammaging), which contributes to both increased vulnerability to severe infections and reduced vaccine responsiveness in the elderly.^{17–20}

Based on the issues raised above, patients with COPD are presumed to have a suboptimal antibody response to influenza vaccination, highlighting the importance of studying the immunogenicity of the vaccine in this population. The immunogenicity of influenza is commonly assessed using three primary indicators: geometric mean titer (GMT) of antibodies, seroprotection rate (SPR), and seroconversion rate (SCR). Immunogenicity, the ability of a vaccine to elicit an immune response after inoculation, also importantly contributes to vaccine effectiveness (VE).²¹ To our knowledge, only a limited number of studies have investigated the immunogenicity of influenza vaccines in patients with COPD. This study is the first meta-analysis that evaluated the immunogenicity of the influenza vaccine in patients with COPD, by synthesizing the published literature and compared GMT, SPR, and SCR, and their relevance to real-world VE.

Methods

Literature Search

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,²² and the protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42024616410).

A systematic literature search was conducted using electronic databases (PUBMED, Cochrane Library [Wiley], Google Scholar) to identify relevant studies published between June 1, 1977, and April 24, 2024. Manual searches were conducted on ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform to identify relevant ongoing or completed clinical trials. The search included the keywords of “influenza vaccine,” “immunogenicity,” “COPD,” and “Chronic Obstructive Pulmonary Disease”. These terms were searched as keywords (title or abstract words) and subject headings as appropriate.

Literature Selection

Abstracts identified through database searches were initially screened by a single reviewer (R.Y., F.N.A., or N.F.W.), and all studies that met the eligibility criteria at this stage were subjected to full-text review. The full-text articles were assessed by a single reviewer (R.Y., F.N.A., or N.F.W.). The calibration step was performed by a second reviewer (R.Y., F.N.A., or N.F.W.) prior to abstract screening and full-text review, until more than 70% agreement was reached.

Publications were included if they met all the following inclusion criteria: (i) randomized trials, cross-sectional studies, prospective studies, and observational studies investigating the immunogenicity of influenza vaccine in COPD patients; (ii) study participants were ≥ 50 years of age; (iii) studies assessed antibody response by the hemagglutinin inhibition (HAI) method; (iv) use of trivalent (TIV) or quadrivalent (QIV), inactivated, split-virion influenza vaccine; and (v) studies reporting results as the GMT, SPR, and SCR assessed at 4–6 weeks post-vaccination. Finally, if multiple doses, as well as a single dose, were evaluated in a study, we only included the results associated with single-dose administration. Non-English or Indonesian language studies, case reports, editorials, letters, review articles, animal studies, and studies evaluating whole-virus vaccines were excluded.

Data Extraction

The following information was extracted from each study: first author, publication year, study period, study location, study design, follow-up duration, participant age, influenza virus subtype, vaccine type, sample size, reported adverse events, inclusion and exclusion criteria, and immunogenicity outcomes. Immunogenicity was assessed based on three standard measures: GMT (defined as the antilog of the arithmetic mean of the log-transformed antibody titers), SCR (defined as the percentage of post-vaccination hemagglutination inhibition antibody titers $\geq 1:40$ in patients with pre-vaccination HAI titers $< 1:10$ or ≥ 4 -fold increase in the post-vaccination HAI titers in patients with pre-vaccination titers $\geq 1:10$) and SPR (defined as the percentage of participants achieving an HAI titer ≥ 40), in accordance to the European Medicines Agency (EMA) criteria for evaluating influenza vaccines.²³ Two reviewers (F.N.A. and N.F.W.) independently extracted all relevant outcomes using standardized extraction forms adapted from the Cochrane Collaboration. After the screening, the data extraction was finally approved by (R.Y.). Immunogenicity outcomes were extracted only for the HAI assays.

Quality Assessment

The Cochrane Handbook Risk of Bias Assessment Tool for Randomized Trials Version 2 (RoB 2) was used to assess the quality of randomised clinical trials. Each study was assessed across six domains: randomization process, timing of participants' identification or recruitment, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported results. Each domain was rated as having low risk, some concerns, or high risk of bias.²⁴

For observational studies, quality was assessed using the Newcastle–Ottawa Scale (NOS) scores, which evaluates studies based on three domains: selection (0–4), comparability (0–2), and outcome (0–3). The risk of bias was then categorized as low risk (7–9 points), moderate risk (4–6 points), or high risk (< 4 points).²⁵

Quality assessment was completed by two reviewers (F.N.A. and N.F.W.) independently. Disagreements between the two reviewers were settled by discussion, and a third reviewer (R.Y.) would arbitrate when the discussion did not resolve the disputed points. Studies were not excluded based on quality assessments.

Data Synthesis and Statistical Analysis

The primary outcome of this meta-analysis was immunogenicity assessed using GMT, SCR, and SPR. For dichotomous outcomes (SPR and SCR), pooled event rates were calculated with corresponding 95% confidence intervals (CIs) using a random-effects model. For the continuous outcome (GMT), mean GMT values and standard deviations (SDs) were extracted from each study. The mean difference (MD) between pre- and post-vaccination GMTs was calculated and reported as pooled MD with a 95% CI.²⁶ The secondary outcome was safety, including systemic and local adverse events (AEs). Stratified analyses by strain (H1N1, H3N2, and B strains) were performed for GMT, SPR, and SCR.

Statistical heterogeneity among the included studies was assessed using Cochran's Q-test and quantified using the I^2 statistic, with a value $\geq 50\%$ considered to represent substantial heterogeneity. Data analyses were conducted using Comprehensive Meta-Analysis (CMA) version 4.

Sensitivity analysis was conducted using the leave-one-out method in CMA version 4. This approach involved systematically removing one study at a time and recalculating the overall effect size to assess the influence of each study on the pooled result. If the exclusion of a single study causes a substantial change in the overall estimate, it may indicate

that the study disproportionately affects the findings. By contrast, the minimal variation in the pooled effect across iterations suggests a stable and reliable summary estimate.

Results

Quality Assessment, Literature Search and Characteristics of the Eligible Studies

The flow diagram for the selection of studies and quality of the included studies are summarized in Figures 1 and 2. The literature search yielded 63 citations, of which 17 were excluded because the title or abstract was duplicated, not presented in English or Indonesian, the study was stopped early, or the results were not posted yet. Full articles of the remaining 46 studies were retrieved for further evaluation, from which a further 37 studies were excluded because the title or abstract was not related or the study was a review article. The remaining nine studies were sought for retrieval, however one study was excluded because the seroconversion data in their study were mixed between patients with and without vaccinations. Furthermore, one study was excluded because evaluated whole-virus vaccine, resulting in the inclusion of seven studies in the review. Additionally, one study was also excluded because it provided HAI assay results as a geometric mean titer with 95% CI in the form of a figure. We contacted the author to request the numeric data, but did not receive any responses.

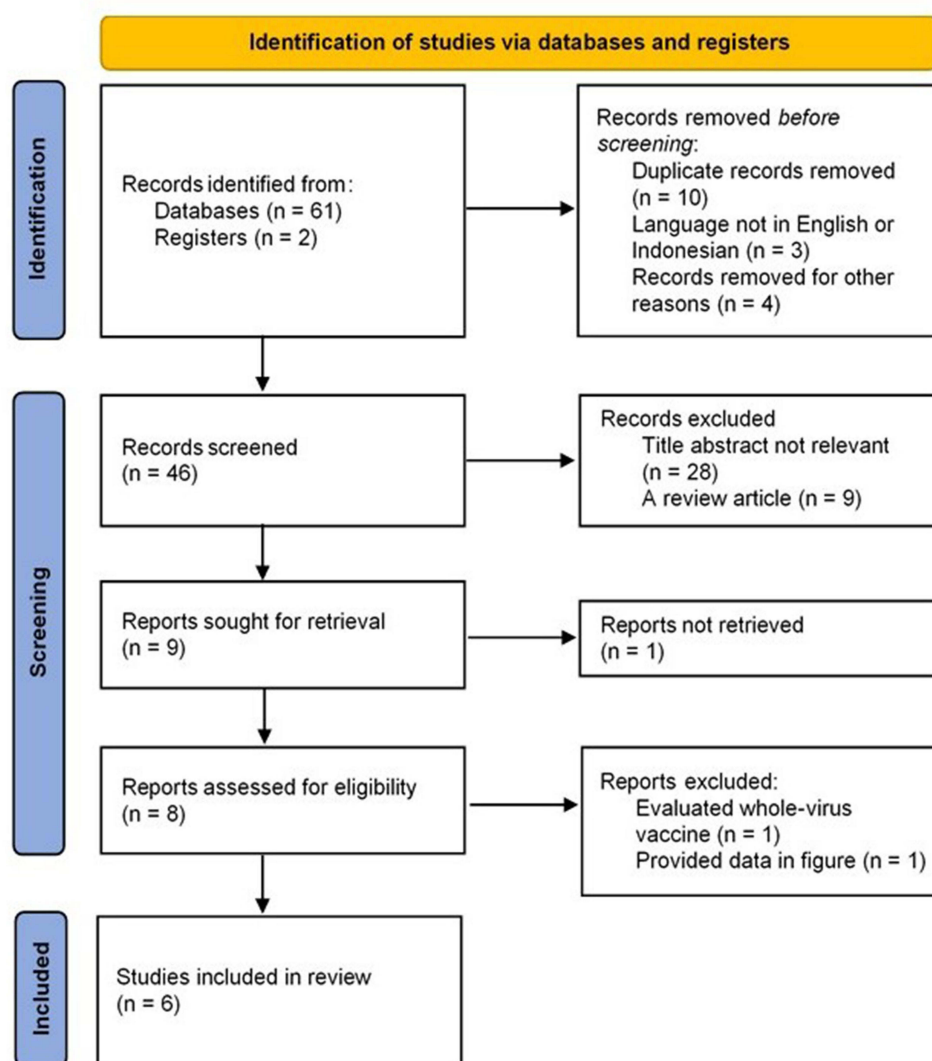


Figure 1 PRISMA flow diagram-studies on the immunogenicity of influenza vaccines given to COPD patients.

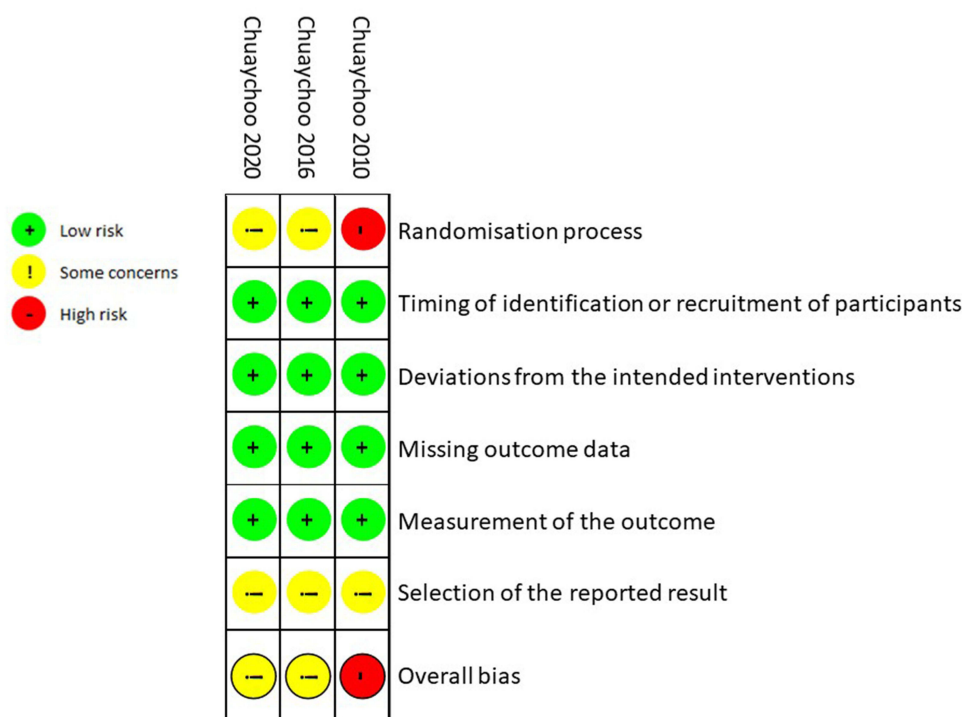


Figure 2 The risk of bias summary for each randomized controlled-study included.

Of the six included studies, three were randomized clinical trials with a total of 385 participants,^{27–29} one was an intervention-cohort study of 88 participants,¹⁴ one was an observational study with a total of 147 participants (75 COPD patients vs 72 healthy subjects),³⁰ and one was a prospective cohort study of 52 participants (27 COPD patients vs 25 lung cancer patients)³¹ (Table 1). Two studies were multi-center;^{14,30} and four studies were single-center.^{27–29,31} Four studies^{28–31} involved only participants aged ≥ 50 years. One trial²⁷ included participants aged ≥ 18 years, and one study¹⁴ included subjects aged < 80 years. Those one trial²⁷ included both young adult and elderly participants performed separate analyses for all age populations and elderly populations only, and those one study¹⁴ performed in subjects aged < 80 years provided a separate analysis for participants aged ≥ 65 years and > 60 years. One study³⁰ divided the data by strain for H1N1 (H1N1_A/CALIFORNIA/07/2009-like and H1N1_A/MICHIGAN/45/2015-like), H3N2 (H3N2_A/SWITZERLAND/ 9715293/2013-like and H3N2_A/HONG KONG/4801/2014-like), and B strain (B/PHUKET/3073/2013-like and B/BRISBANE/60/2008-like). One trial²⁷ was at high risk, and two trials^{28,29} had some concerns (Figure 2). Two studies^{30,31} had an NOS score of 9 and one study¹⁴ had a score of 6 (Supplementary Table S1).

Meta-Analysis of Immunogenicity Seroconversion

The summarized pooled event rates of SCR of influenza vaccines in three strains and all subgroups of the administration route are presented in Figure 3. Three studies^{27–29} reported SCR via intradermal (ID) route. The pooled SCR was 26.8% (95% CI = 9.2–56.9%, $I^2 = 91.9\%$, $p = 0.000$) for the influenza B strain; 68.6% (95% CI = 48.6–83.5%, $I^2 = 84.6\%$, $p = 0.002$) for the influenza A/H1N1 strain; and 65.8% (95% CI = 57.9–73.0%, $I^2 = 17.5\%$, $p = 0.297$) for the influenza A/H3N2 strain (Figure 3A). Five studies^{14,27–30} reported the SCR of the influenza vaccine via intramuscular (IM) route, with one study³⁰ divided by strain. In this subgroup, the pooled SCR was 38.3% (95% CI = 23.2–56.0%, $I^2 = 89.6\%$, $p = 0.000$) for the influenza B strain; 53.7% (95% CI = 28.9–76.8%, $I^2 = 94.4\%$, $p = 0.000$) for the influenza A/H1N1 strain; and 54.9% (95% CI = 27.2–79.8%, $I^2 = 95.0\%$, $p = 0.000$) for the influenza A/H3N2 strain (Figure 3B). Meanwhile, the SCR of the influenza vaccine via subcutaneous (SC) route was only reported by one study,³¹ involving 26 COPD

Table I Summary of Study Characteristics

Study (Year), Ref. [Publication Dates]	Type of Study	Country	Vaccine Strains	Dose Used in Study	Total Number of Patients	Age	Outcomes	Max. Follow-Up Duration
Chuaychoo et al, 2010 ²⁷	Randomized, controlled, open-label study	Thailand	TIV: A/New Caledonia/20/99 (H1N1) A/California/7/2004 (H3N2) B/Malaysia/2506/2004	ID 6 µg IM 15 µg	81 (m 75, f 6) 75 (m 68, f 7)	≥18	AEs, GMT, SCR, SPR	12 months
Chuaychoo et al, 2016 ²⁸	Prospective randomized, open-label study	Thailand	TIV: A/California/7/2009 (H1N1)-like virus A/Perth/16/2009 (H3N2)-like virus B/Brisbane/60/2008-like virus	ID 9 µg IM 15 µg	75 (m 68, f 7) 74 (m 68, f 6)	≥60	AEs, GMT, SCR, SPR, Influenza-related acute respiratory illness	4 weeks
Nakashima et al, 2017 ³¹	Prospective	Japan	TIV: A/California/7/2009 (H1N1) pdm09 A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012 (B/Yamagata lineage)	SC 15 µg	COPD 27 (m 23, f 3) vs lung cancer 25 (m 18, f 17)	Mean 70.7 ± 7.4 vs 68.0 ± 6.3	GMT, SCR, SPR	6 weeks
Chuaychoo et al, 2020 ²⁹	Prospective, randomized, open-label study	Thailand	TIV: A/California/7/2009 (H1N1)-like virus A/Perth/16/2009 (H3N2)-like virus B/Brisbane/60/2008-like virus	ID 9 µg IM 15 µg	41 (m 36, f 5) 39 (m 38, f 1)	≥60	AEs, GMT, SCR, SPR	12 months
Li et al, 2021 ¹⁴	Multicenter-intervention cohort study	China	TIV: A/Brisbane/02/2018 (H1N1) A/Kansas/14/2017 (H3N2) B/Maryland/15/2016	IM 15 µg	88 (m 65, f 23)	<80	AEs, GMT, SCR, SPR	5 weeks
Snape et al, 2022 ³⁰	Multicenter non-randomised, unblinded, observational study	Australia	TIV or QIV: H1N1_A/CALIFORNIA/07/2009-like H1N1_A/MICHIGAN/45/2015-like H3N2_A/SWITZERLAND/ 9715293/2013-like H3N2_A/HONG KONG/4801/2014-like B/PHUKET/3073/2013-like B/BRISBANE/60/2008-like	IM 15 µg	COPD 75 (m 52, f 23) vs healthy 72 (m 35, f 37)	≥50	SCR, SPR, GMT	28 days

Abbreviations: AEs, adverse events; f, female; m, male; SCR, seroconversion rate; SPR, seroprotection rate; TIV, trivalent; QIV, quadrivalent.

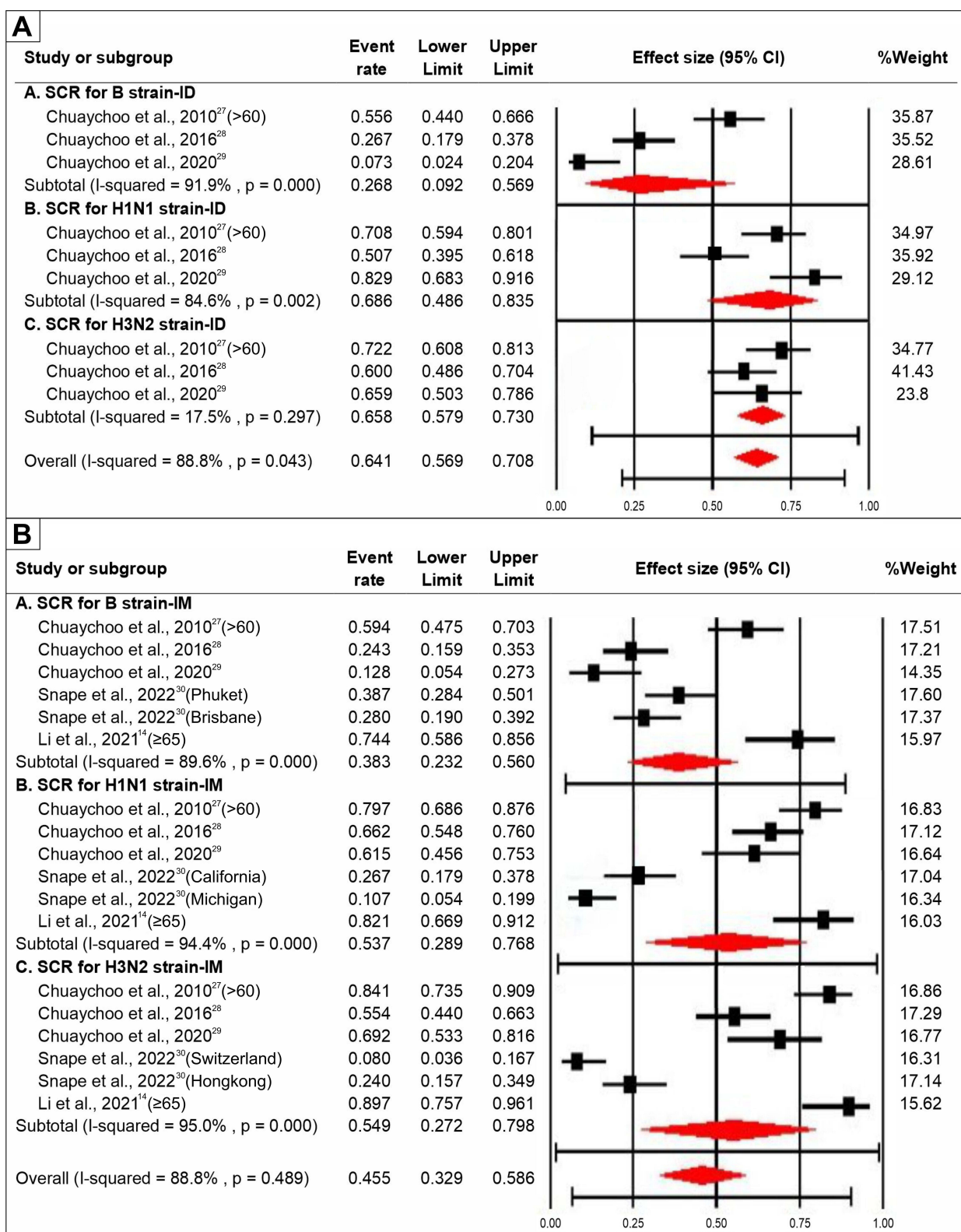


Figure 3 Forest plots of seroconversion rate (SCR) of each strain of influenza vaccine in (A) intradermal and (B) intramuscular sub-group. Each square shows the point estimate of the SCR (event rate) for each individual study, with the size of the square indicating the relative weight that the study contributes to the meta-analysis. The horizontal black lines indicate 95% CIs for each study. Red diamonds represent the pooled effect estimates for each influenza strain and the overall analysis. The width of each diamond represents the 95% CI for the pooled estimate. The vertical line indicates the reference (no effect). I^2 and p-values are reported as indicators of between-study heterogeneity.

patients. Because only one study was available, no statistical pooling or meta-analysis was performed. Instead, the results are presented descriptively.

In this study, the SCR were reported as 46.0% for the influenza B strain; 42.0% for the influenza A/H1N1 strain; and 50.0% for the influenza A/H3N2 strain. These values suggest a generally strong immune response following SC administration; however, given the small sample size and lack of replication in other studies, the findings should be interpreted with caution and cannot be generalized.

Overall, vaccination via ID showed higher SCR than via IM and SC for the A/H1N1 and A/H3N2 strains, whereas the B strain was superior via SC route. Both ID and IM groups showed significant heterogeneity ($p < 0.05$) between studies, particularly for the A/H1N1 and B strains, indicating variability in outcomes across studies.

Seroprotection

The SPR of pre-vaccination via ID route were reported by three studies.^{27–29} The pooled SPR was 14.8% (95% CI = 8.0–25.9%, $I^2 = 48.5\%$, $p = 0.143$) for influenza B strain; 38.3% (95% CI = 22.9–56.5%, $I^2 = 82.5\%$, $p = 0.003$) for influenza A/H1N1 strain; and 40.8% (95% CI = 25.1–58.7%, $I^2 = 82.1\%$, $p = 0.004$) for influenza A/H3N2 strain (Figure 4A). Four studies^{27–30} reported SPR before vaccination via IM route, with one study divided by strain.³⁰ The pooled SPR was 30.0% (95% CI = 9.9–62.6%, $I^2 = 95.6\%$, $p = 0.000$) for the influenza B strain; 32.4% (95% CI = 24.6–41.3%, $I^2 = 62.1\%$, $p = 0.032$) for the influenza A/H1N1 strain; and 24.7% (95% CI = 14.7–38.3%, $I^2 = 82.4\%$, $p = 0.000$) for the influenza A/H3N2 strain (Figure 4B). Meanwhile, study conducting the SC route did not report the SPR prior to vaccination.

The SPR after vaccination via ID route were reported by three studies.^{27–29} The pooled SPR was 36.7% (95% CI = 13.9–67.7%, $I^2 = 92.7\%$, $p = 0.000$) for the influenza B strain; 88.6% (95% CI = 56.3–97.6%, $I^2 = 91.2\%$, $p = 0.000$) for the influenza A/H1N1 strain; and 86.9% (95% CI = 78.8–92.2%, $I^2 = 39.3\%$, $p = 0.192$) for the influenza A/H3N2 strain (Figure 5A). The SPR after vaccination via IM were reported by five studies,^{14,27–30} with one study³⁰ divided by the strain. The pooled SPR was 69.3% (95% CI = 40.8–88.0%, $I^2 = 94.0\%$, $p = 0.000$) for the influenza B strain; 81.4% (95% CI = 57.0–93.5%, $I^2 = 93.9\%$, $p = 0.000$) for the influenza A/H1N1 strain; and 70.8% (95% CI = 39.2–90.1%, $I^2 = 95.4\%$, $p = 0.000$) for the influenza A/H3N2 strain (Figure 5B). Meanwhile, the SPR post-vaccination via SC was reported only in one study.³¹ No statistical pooling or meta-analysis was performed, instead, the results are presented descriptively. In this study, the SPR were reported as 92.0% for the influenza B strain; 81.0% for the influenza A/H1N1 strain; and 96.0% for the influenza A/H3N2 strain. These values reflect the results of that individual study rather than pooled estimates. Overall, the SPR for A/H1N1 and A/H3N2 strains via the ID route were higher compared to IM route. Conversely, IM vaccination resulted in greater SPR for the B strain than in ID route. Notably, based on a single study, the SC route had the highest SPR across all three strains. However, given limited SC data, these findings should be interpreted with caution.

Geometric Mean Titer

Differences in GMT before and after vaccination were analyzed across three influenza strains: B, A/H1N1, and A/H3N2. Three studies^{27–29} were included in the analysis of GMT in the ID subgroup. Using a random-effects model, the pooled mean difference was 5.83 (95% CI = 3.68–7.99; $I^2 = 95.4\%$, $p < 0.001$) for the influenza B strain; 8.38 (95% CI = 7.31–9.46; $I^2 = 63.5\%$, $p = 0.064$) for the influenza A/H1N1 strain, and 7.97 (95% CI = 6.81–9.13; $I^2 = 72.1\%$, $p = 0.028$) for the influenza A/H3N2 strain. These results indicate a significant increase in GMTs after vaccination, particularly for A strains. Overall, the pooled GMT difference across all strains was 7.91 (95% CI = 7.17–8.65), with high heterogeneity ($I^2 = 93.3\%$, $p < 0.001$) (Figure 6A).

GMT via the IM route was also analyzed across four studies.^{14,27–29} Using a random-effects model, the pooled mean difference was 6.02 (95% CI = 3.10–8.93; $I^2 = 98.1\%$, $p = 0.000$) for the influenza B strain; 7.98 (95% CI = 6.74–9.22; $I^2 = 79.7\%$, $p = 0.002$) for the influenza A/H1N1 strain; and 7.44 (95% CI = 5.78–9.10; $I^2 = 90.1\%$, $p < 0.001$) for the influenza A/H3N2 strain. These results indicate a consistent and significant increase in GMTs following vaccination across all strains, with the highest responses observed for the A strains. Overall, the pooled GMT difference across all strains was 7.60 (95% CI = 6.66–8.54), accompanied by high heterogeneity ($I^2 = 96.8\%$, $p < 0.001$) (Figure 6B). In

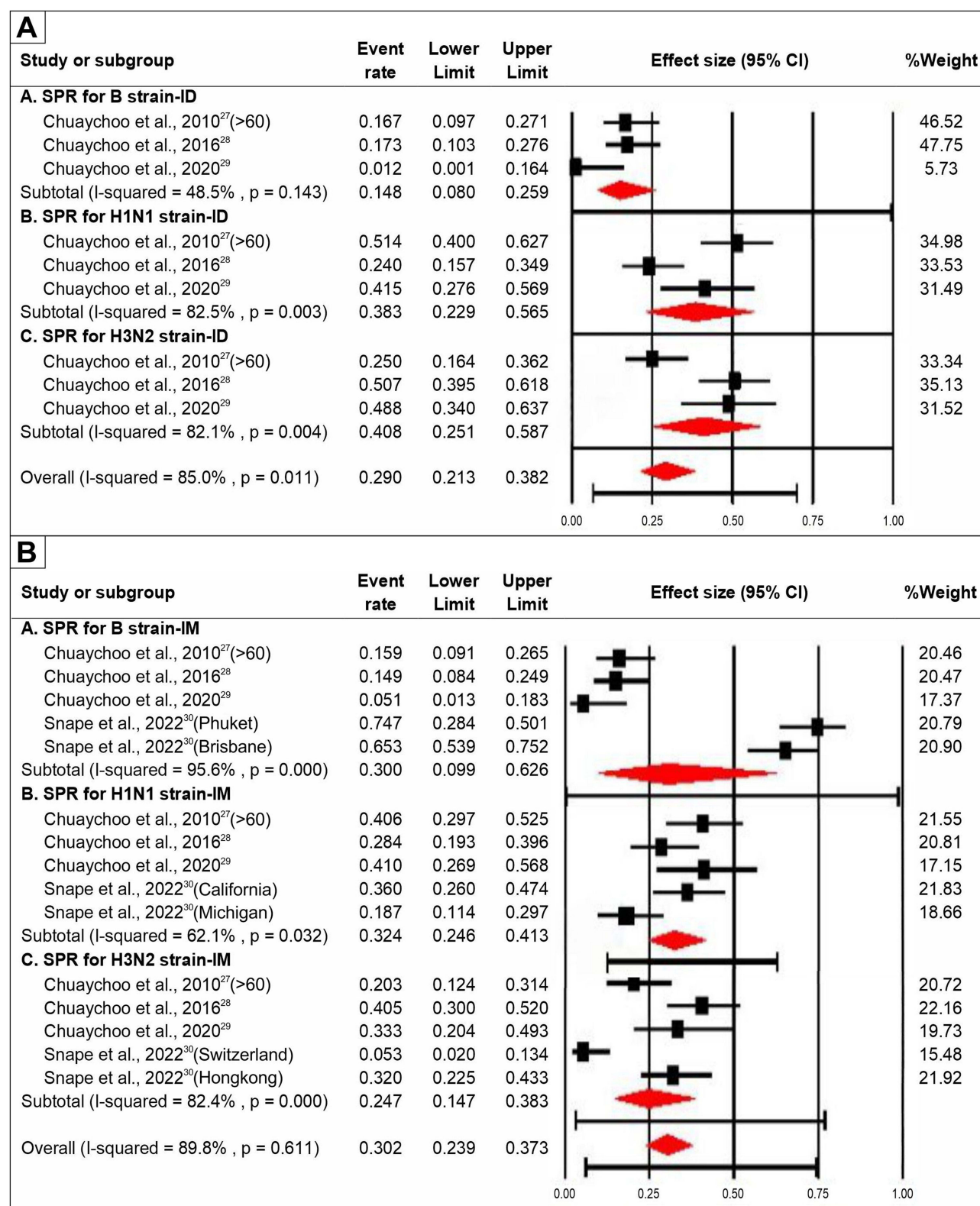


Figure 4 Forest plots of seroprotection rate (SPR) pre-vaccination in (A) intradermal, and (B) intramuscular sub-group. Each black square shows the point estimate of the SPR (event rate) for each individual study, and the size of the square is proportional to the relative weight of the study in the meta-analysis. The horizontal black lines represent the 95% CIs. The red diamond represents the pooled effect estimate for each influenza strain and the overall analysis; the width of the diamond corresponds to the width of the respective 95% CI. The vertical line indicates the reference (no effect). I^2 and p-values are reported as indicators of between-study heterogeneity.

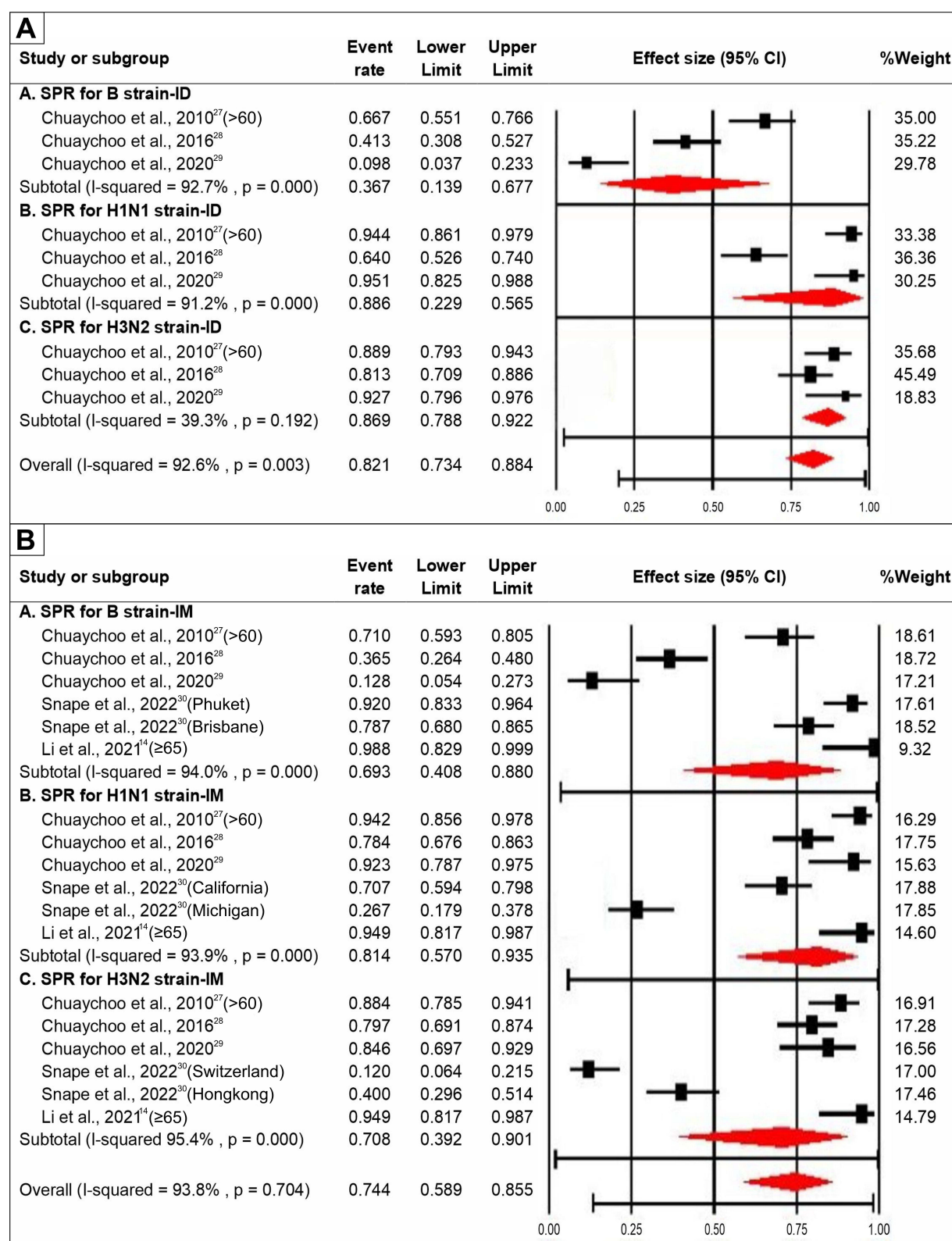


Figure 5 Forest plots of seroprotection rate (SPR) post-vaccination in (A) intradermal and (B) intramuscular sub-group. Each black square shows the point estimate of the SPR (event rate) for each individual study, and the size of the square is proportional to the relative weight of the study in the meta-analysis. The horizontal black lines represent the 95% CIs. The red diamond represents the pooled effect estimate for each influenza strain and the overall analysis; the width of the diamond corresponds to the width of the respective 95% CI. The vertical line indicates the reference (no effect). I^2 and p-values are reported as indicators of between-study heterogeneity.

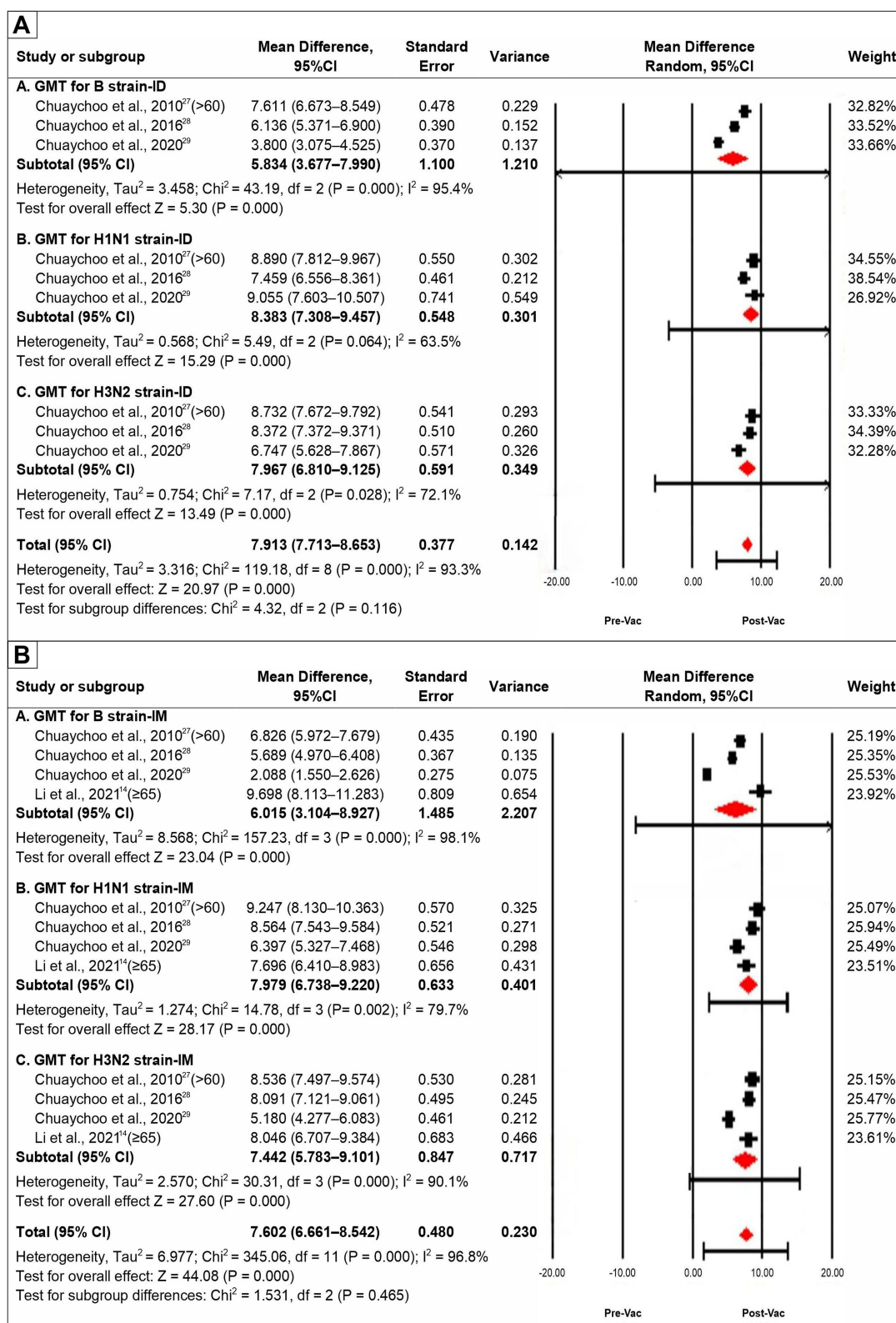


Figure 6 Forest plots of geometric mean titer (GMT) of each strain of influenza vaccine in (A) intradermal, and (B) intramuscular sub-group. Each black square represents the mean difference (MD) for each individual study, with the size of the square proportional to the study's weight in the meta-analysis. The horizontal black lines define the 95% CIs for each study. Red diamonds represent the pooled effect estimates, where the width of the diamond corresponds to the 95% CI for each influenza strain (B, H1N1, and H3N2) and the overall summary effect. The vertical line at zero indicates no difference between pre- and post-vaccination titers. I^2 and p-values are reported as indicators of heterogeneity between studies analyzed under a random-effects model.

general, both ID and IM routes are effective in increasing GMT post-vaccination. The ID route showed a slightly higher GMT increase, particularly for A/H1N1 and A/H3N2 strains.

One study³¹ utilizing the SC route reported post-vaccination GMT values for all three influenza strains. The GMT for each strain was 91 for influenza B strain, 123 for influenza A/H1N1 strain, and 173 for influenza A/H3N2 strain, with a sample size of 26. The study did not provide baseline (pre-vaccination) GMT values, nor did it include measures of variability such as confidence intervals or standard deviations. Due to the lack of these key parameters, the data from this study could not be included in the quantitative synthesis of GMT.

Safety

The AEs for ID subgroup, including erythema, itching, swelling, ecchymosis, fever, myalgia, and headache were reported by three studies.^{27–29} In this sub-group, local AEs were highly prevalent, particularly erythema (97.3%) and swelling (98.6%), both with no observed heterogeneity ($I^2 = 0\%$) (Figure 7). Itching (31.8%) and ecchymosis (33.0%) showed moderate to high heterogeneity. Systemic AEs were less common, including fever (7.3%), myalgia (13.2%), and headache (11.8%), with high variability across studies ($I^2 > 60\%$) (Figure 7). Overall, vaccination via ID has been shown to cause frequent mild local reactions and low rates of systemic AEs.

The AEs in the IM subgroup, including erythema, itching, swelling, ecchymosis, myalgia, and headache were reported by three studies^{27–29} and by four studies^{14,27–29} for fever. In this subgroup, local AEs were less frequent than those in the ID route were. The pooled event rates were 29.9% for erythema, 7.3% for itching, 21.5% for swelling, and 10.8% for ecchymosis, with moderate to high heterogeneity (I^2 ranging from 50.8% to 92.2%) (Figure 8). Systemic AEs occurred at lower rates, including fever (7.4%), myalgia (17.8%), and headaches (15.2%), all of which showed moderate heterogeneity ($I^2 > 60\%$) (Figure 8). Overall, vaccination via IM was shown to have lower rates of both local and systemic AEs than vaccination via ID.

The Association Between Antibody Responses and Real-World Vaccine Effectiveness

Real-world VE data were reviewed to assess the clinical relevance of pooled immunogenicity outcomes observed in this meta-analysis. The ID route showed high post-vaccination SPR for the A/H1N1 (88.6%) and A/H3N2 (86.9%) strains, whereas the IM route yielded slightly lower but still strong responses (81.4% for A/H1N1 and 70.8% for A/H3N2). These immunogenicity outcomes suggest that patients with COPD remain immunologically responsive, particularly to influenza A strains.

When compared with real-world effectiveness data, the magnitude of these antibody responses was generally inconsistent and even higher with observed clinical protection. A test-negative study in Ontario, Canada reported an adjusted VE of 43% (95% CI = 33–52%) against influenza-associated hospitalizations among older adults with COPD across six influenza seasons.³²

Sensitivity Analysis

A sensitivity analysis was performed using CMA V4 with one study removed method to assess the influence of each individual study. No individual study significantly influenced the overall effect sizes of GMT, SCR, and SPR. The pooled estimates remained consistent across all outcomes, indicating that the results were not driven by any single study. However, significant heterogeneity ($I^2 > 85\%$) between studies and wide prediction intervals were observed in several outcomes, suggesting variability in effect estimates across populations and settings (Supplementary Figures S1–S8).

Regarding AEs, ID vaccination consistently showed higher rates of local reactions, particularly erythema (0.973) and swelling (0.986), both with $I^2 = 0\%$. In contrast, IM vaccination showed lower rates of erythema (0.299; $I^2 = 92.2\%$) and swelling (0.215; $I^2 = 50.8\%$). Itching and ecchymosis were more frequently reported with ID (0.318 and 0.330, respectively) than with IM (0.073 and 0.108, respectively), although both outcomes exhibited moderate to high heterogeneity. Systemic AEs such as fever, myalgia, and headache occurred at low to moderate rates between routes, with ID slightly lower to IM. However, the wide prediction intervals and high heterogeneity in both groups suggest notable variability (Supplementary Figures S9–S18).

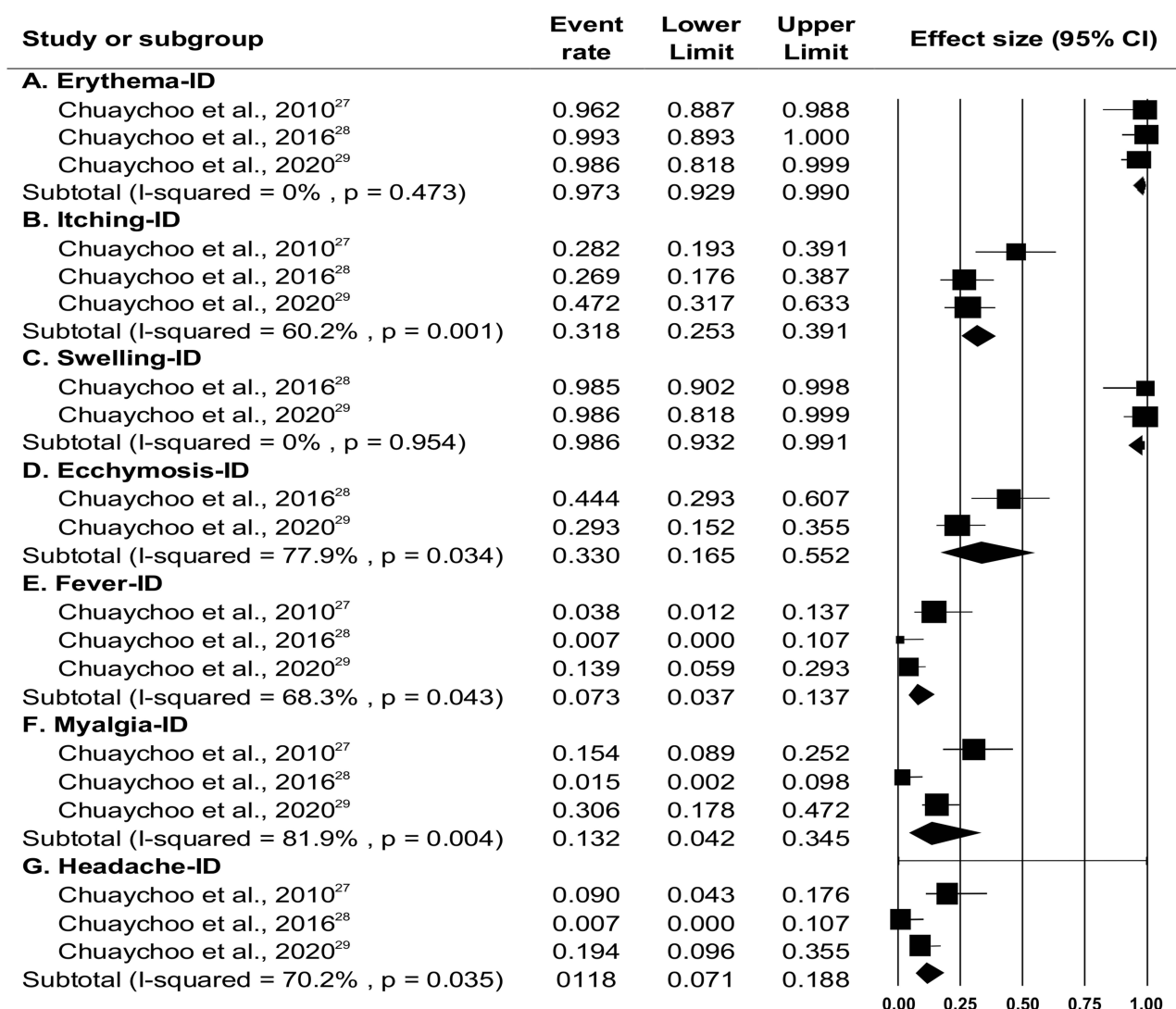


Figure 7 Forest plots of local and systemic adverse events (AEs) following intradermal (ID) influenza vaccination in patients with COPD. Each black square is an event rate reported in individual study, and the size of each black square is proportional to the study weight in the meta-analysis. The horizontal black line is a 95% confidence interval (CIs) and the diamonds are the pooled estimates of the effect for each adverse event. The vertical line is the reference (event rate = 0). All analyses were a random-effects model.

Sensitivity analysis was conducted only for each indicator, with more than two studies reporting them. Hence, indicators such as GMT, SCR, and SPR in the SC administration route were not analyzed, as only one study has reported it. Adverse events, including swelling and ecchymosis, in both ID and IM studies were also not analyzed because only two studies reported them.

Discussion

This systematic review and meta-analysis synthesized evidence from randomized controlled trials, cross-sectional studies, prospective studies, and observational studies that evaluated the immunogenicity and safety of seasonal influenza vaccination in individuals with COPD. Despite exhaustive literature searches, only six studies met our inclusion criteria. Nonetheless, this meta-analysis provides comprehensive evidence that seasonal influenza vaccination retains substantial immunogenicity in COPD patients.

Across three immunogenicity endpoints: SCR, SPR, and GMT, the findings consistently demonstrated that COPD patients are capable of mounting robust antibody responses, particularly against the A/H1N1 and A/H3N2 strains,

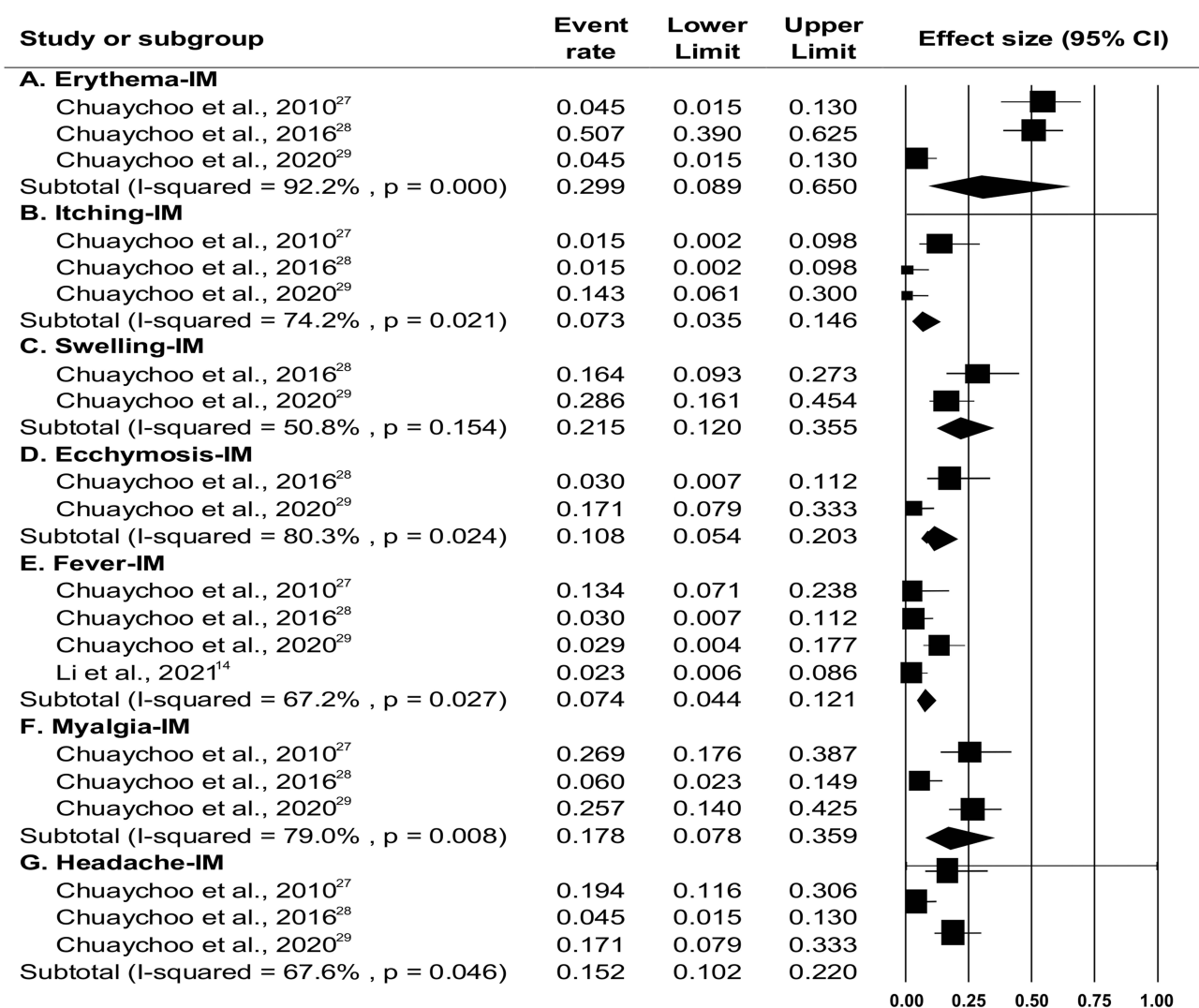


Figure 8 Forest plots of local and systemic adverse events (AEs) following intramuscular (IM) influenza vaccination in patients with COPD. Each black square is an event rate reported in individual study, and the size of each black square is proportional to the study weight in the meta-analysis. The horizontal black line is a 95% confidence interval (CIs) and the diamonds are the pooled estimates of the effect for each adverse event. The vertical line is the reference (event rate = 0). All analyses were a random-effects model.

regardless of the route of administration. This observation is noteworthy given that the pathogenesis of COPD is widely known to be caused by accelerated lung aging. The incidence of COPD is strongly related to age and remains uncommon in individuals aged ≤ 40 years but increases markedly to $> 10\%$ at the age of ≥ 40 years. This age-associated progressive decline in immune function is known as immunosenescence.^{16,33} Therefore, in this study, we focused on subjects aged ≥ 50 years to observe the immunogenicity of influenza vaccination in this high-risk population. Despite the well-established impact of immunosenescence, chronic inflammation, and the use of immunosuppressive therapies such as corticosteroids in COPD, which are typically associated with impaired vaccine responses,^{34,35} our results show that both ID and IM vaccination can elicit high post-vaccination SPRs ($> 80\%$) and substantial GMT increases in influenza A strains. The predominance of robust responses to influenza A strains may partially be explained by epidemiological and immunological factors. Influenza A viruses are the only influenza viruses responsible for major pandemics known to cause flu pandemics, particularly subtypes H1N1 and H3N2, which are the primary contributors to seasonal influenza outbreaks and global pandemics, such as the 2009 H1N1 and 1968 H3N2 pandemics.^{36–38} Moreover, mounting evidence indicates that cellular immunity, especially CD4⁺ and CD8⁺ T cell responses, to influenza A are highly robust and cross-

reactive across subtypes. For instance, memory CD8⁺ T cells primed by seasonal H1N1 can produce IFN- γ and cross-react with H3N2 and even with heterologous strains such as H5N1.^{39–41}

However, the interpretation of these pooled estimates must be approached with caution. The number of available studies for each analysis was small, and substantial between-study heterogeneity was detected (I^2 values frequently >90%). This heterogeneity likely arises from variations in study design, vaccine formulations, participant characteristics (eg, age, disease severity), and laboratory assay methods used to determine antibody titers. The random-effects model was applied to account for such variability, and prediction intervals were reported to reflect the potential range of true effects across future studies. Nevertheless, the wide confidence intervals and high I^2 indicate that the true effect sizes may differ substantially across settings.

In particular, the ID route demonstrated slightly superior immunogenicity compared with the IM route, with consistently high GMT and SCR values. This aligns with a previous study showing that low-dose vaccines administered intradermally via microneedles elicit equivalent immune responses compared to full-dose IM administration.⁴² Enhanced immune responses following intradermal administration of influenza vaccines have also been reported in multiple studies.^{43–45} This is likely due to the efficient activation of skin-resident dendritic cells (DCs), which facilitate more effective antigen presentation. DCs play a pivotal role in orchestrating adaptive immune responses, not only by initiating immunity against pathogens but also by maintaining tolerance to non-threatening antigens.^{46,47} Although the pooled analysis showed numerically higher GMTs for the ID route compared to the IM route, particularly for the A/H1N1 strain (8.38 vs 7.98), these differences should not be interpreted as clinically significant. The differences in the means were small and based on log-transformed values, and 0.4 difference would unlikely reflect a meaningful biological difference. The SC route, although promising based on one study, lacks sufficient data for firm conclusions. Results for this route should be interpreted as observational rather than inferential, representing data from a single small cohort and not a pooled effect. Further studies with larger sample sizes and direct comparisons between the different administration routes are warranted to validate the immunogenicity of the SC route in COPD patients.

It is essential when considering the safety findings to be aware of the differences in study methodologies. Collection of adverse events was performed using active and passive surveillance systems and likely accounts for the wide range of reported rates. The pooled incidence of local reactions such as erythema in the ID group (97.3%) may appear high, but these events were uniformly mild, short-lived, and expected due to the dermal administration route. Overall, both the ID and IM vaccinations were well tolerated. This finding is consistent with previous studies, which reported that local reactions occur significantly more often with intradermal vaccination, yet are typically mild and transient.^{42,48,49} Systemic reactions such as headache and myalgia were infrequent (~15%) and comparable to baseline rates seen in older chronic disease populations that are susceptible to exacerbations when exposed to systemic inflammatory stress.^{16,33,50} Importantly, most included studies did not include a placebo or unvaccinated comparator group, which limited the assessment of vaccine-attributable risk. Therefore, the safety results should be interpreted as descriptive summaries rather than precise comparative estimates.

In this meta-analysis, COPD patients exhibited strong immunogenicity as shown by higher seroprotection and seroconversion compared to real-world VE.³² Using a test-negative design, a study estimated the influenza VE for preventing influenza-related hospitalizations in COPD patients between 2011 and 2015.⁵¹ The study demonstrated that the VE was 43–49% during the first 3 years, but declined to 6% only in the last year because of an antigenic mismatch between vaccine and circulating influenza virus strain. Similarly, another study revealed low VE in COPD patients in overall ages by only 11.9%, and 49.1% in patients aged ≥ 65 years old.⁵² These findings suggested that the antibody response in real-world settings is not as robust as in laboratory conditions for COPD patients. However, vaccination could reduce the risk of respiratory failure by 38%⁵¹ in influenza-related hospitalizations in vaccinated COPD patients vs unvaccinated patients, and by a 13% reduction⁸ in the risk of respiratory failure (adjusted odds ratio [aOR] = 0.87; 95% CI = 0.79–0.96). This highlights the fact that the influenza vaccine remains essential for patients with COPD. The moderate VE in patients with COPD may be attributable to low immunogenicity and/or high susceptibility to hospitalization due to respiratory illness in general.³²

Although this meta-analysis reported high SPR and SCR among COPD patients, influenza VE in COPD populations is frequently considered lower in real-world settings. This disparity can be explained by several

factors. First, hemagglutination inhibition titers, serving as a surrogate marker of immunity, reflect mostly humoral antibody responses and do not include mucosal or cellular immunity, such as T-cell memory, which plays a critical role in long-term protection, especially in older adults.³⁴ Second, clinical trial populations frequently include COPD patients who are healthier and more closely monitored than real-world populations that are generally older, frailer, and more comorbid.^{53,54} Third, VE may be reduced by antigenic mismatch between the vaccine strain and the circulating strain, however the level of immunogenicity does not lower because HAI assays are usually performed against vaccine strains rather than the actual circulating viruses.⁵⁵ Therefore, high immunogenicity observed under controlled conditions does not always translate into optimal clinical effectiveness in real-world settings.⁵⁶

However, the immunogenicity endpoints analyzed (SPR, SCR, and GMT) are surrogate markers and do not directly measure real-world protection, which also acts as a limitation of this meta-analysis. Nevertheless, high SPR and GMT values are associated with reduced influenza-related exacerbations and hospitalizations, outcomes highly relevant to COPD care.⁵¹ Future studies may need to link these immunogenicity endpoints with clinical outcomes, particularly in severe COPD populations and during seasons with high vaccine-strain mismatch. Second, methodological variability across studies, including differences in assay techniques, antigenic components, and timing of outcome assessment, may have contributed to substantial heterogeneity.

The majority of pooled analyses showed significant heterogeneity, which was most likely due to differences in study design, vaccine formulations, demographic characteristics, and outcome measurement. Subgroup analyses were conducted by vaccine administration route (ID, IM, and SC) to identify potential sources of heterogeneity. Results showed modest decreases in I^2 among subgroups. The reported heterogeneity should be interpreted as true clinical and methodological diversity across the studies rather than a measure of random error.

Notably, these findings have several limitations. First, the small number of eligible studies limits the precision and robustness of the pooled estimates. Second, substantial heterogeneity present across studies (I^2 often >90%), suggesting that the included populations, vaccine formulations, and laboratory techniques were not fully comparable. Third, while sensitivity analysis indicated that no single study significantly influenced the pooled results, the total number of studies was small. As a result, the apparent stability found should be interpreted as the stability of a small and heterogeneous dataset rather than evidence of strong robustness. The wide prediction intervals, especially for adverse events, further emphasize the heterogeneity based on study design, surveillance intensity, and reporting standards. The strength of evidence in this meta-analysis should also be interpreted cautiously. Among the included randomized controlled trials, one was evaluated as having a high risk of bias and two as having some concerns, while one of the observational studies showed score of six based on NOS scores. These limitations most likely increased uncertainty into the pooled estimates. Despite those limitations, the direction of effect was consistent across studies toward preserved immunogenicity in COPD patients, which confirms the biological validity of the findings and their clinical relevance.

Conclusion

Influenza vaccination remains safe and immunogenic in older COPD patients who are susceptible to immunosenescence and chronic inflammation. Both intradermal and intramuscular routes excellent seroprotection and seroconversion, notably against the A/H1N1 and A/H3N2 strains, with generally mild adverse events. However, the small number of studies, wide confidence intervals, and substantial heterogeneity across analyses reduce the overall certainty of evidence. Consequently, the conclusions derived from this meta-analysis should be considered preliminary and hypothesis-generating rather than definitive. Nevertheless, the consistent direction of effect supports the biological plausibility of influenza vaccination benefit. These findings highlight the importance of maintaining high influenza vaccine coverage in reducing exacerbations and hospitalizations among COPD patients, reinforcing its position as a critical public health intervention.

Abbreviations

AECOPD, acute exacerbations of COPD; AEs, adverse events; aOR, adjusted odds ratio; CIs, confidence intervals; COPD, chronic obstructive pulmonary disease; DCs, dendritic cells; GMT, geometric mean titer; HAI, hemagglutination inhibition; ID, intradermal; IM, intramuscular; MD, mean difference; NOS, Newcastle–Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QIV, quadrivalent; SC, subcutaneous; SCR, seroconversion rate; SDs, standard deviations; SPR, seroprotection rate; TIV, trivalent; VE, vaccine effectiveness.

Data Sharing Statement

All data underlying the results are available as part of the article/supplementary material and no additional source data are required. The data included in this meta-analysis were obtained from previously published studies and datasets, which have been cited in the references. The analysis results of this study have been reported in this article and can be obtained from the corresponding author upon reasonable request.

Ethics Approval

This study was an observational study. The Research Ethics Committee confirmed that ethical approval was not required.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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