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Systematic review

Efficacy of influenza vaccines and its relationship with immunological surrogate endpoints: a systematic review and meta-analysis of randomized controlled trial

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ABSTRACT

Background: Vaccine efficacy may vary due to influenza strain types, their similarity, and vaccine type. The relationship between immunological surrogate endpoints and vaccine efficacy remains unclear, requiring further investigation to optimize vaccination strategies.
Objective: This systematic review aims to address two key issues. First, to evaluate the vaccine efficacy stratified by vaccine types and virus strains. Second, to explore the quantitative relationship between immunological surrogate endpoints and vaccine efficacy.
Data sources: We searched PubMed, Embase, and ClinicalTrials.gov databases.
Study eligibility criteria, patients, and interventions: We included randomized controlled trials (RCTs) published on 16 July 2024, that evaluated the efficacy of influenza vaccines against laboratory-confirmed influenza. Phase I/II clinical trials, abstracts, reviews, unregistered trials, duplicate studies, and studies lacking original data or efficacy results were excluded.
Methods: This systematic review evaluates influenza vaccine efficacy and immunogenicity, including RCTs with outcomes like geometric mean titre (GMT), seroprotection, and seroconversion rates. Data were extracted from multiple databases and assessed using Cochrane and Grading of Recommendations Assessment, Development and Evaluation (GRADE) frameworks.
Results: Twenty-six RCTs (104 931 participants) were included. Pooled vaccine efficacy against laboratory-confirmed influenza was 48.48% (95% CI, 41.9−54.29), with significant heterogeneity ($I^2 = 70.1\%$; $p < 0.0001$). Inactivated influenza vaccines had the highest vaccine efficacy (54.70%). Among different strains, the vaccine efficacy against H1N1 was the highest, reaching 59.38% (95% CI, 24.60 −78.12). We found a significant nonlinear relationship between standardized mean difference (SMD) in hemagglutination antibody titre (HAI) concentration and vaccine efficacy against symptomatic infections, but with low explanatory power, and seroconversion rates, seroprotection rates, and fold increase in GMT were strongly associated with viral attack rates with Medium explanatory power ($p < 0.05$ for all), with explanatory values of 0.5038, 0.464, and 0.286, respectively.
Discussion: This systematic review highlights that influenza vaccines provide moderate protection, whereas the inactivated influenza vaccine demonstrates higher efficacy. Seroconversion, seroprotection rates, and fold increase in GMT offer limited but valuable insights into vaccine performance. Annual vaccination is crucial for controlling both similar and dissimilar influenza strains. **Hong Cao, Clin Microbiol Infect 2026;32:30**

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Introduction

Influenza causes approximately 3 to 5 million cases of severe illness and about 500 000 deaths each year [1,2], placing a substantial burden on global public health systems [3],[4]. Vaccination is widely considered the most effective preventive measure against influenza [5,6]; however, its efficacy and effectiveness vary significantly [7–9]. This variation can be attributed to several factors, including the match between the vaccine strains and the circulating virus strains [10–12], differences in immune responses triggered by different vaccine types, and the ongoing evolution of the influenza virus [13,14]. In light of these complexities, it is essential to evaluate vaccine efficacy (VE) stratified by vaccine types and influenza virus strains and investigate the quantitative relationship between immunological surrogate endpoints and VE [15,16].

In this context, subgroup analysis from randomized controlled trials (RCTs) provides a valuable tool for assessing the efficacy of influenza vaccines. Specifically, meta-analysis of phase III and IV RCTs can overcome the limitations of individual studies [17–20], such as small sample sizes and limited generalizability, by aggregating results from multiple trials. This approach allows for a more accurate and broadly applicable assessment of VE, offering valuable insights for optimizing vaccination strategies. In this systematic review and meta-analysis, we concentrate on RCT-derived VE and its relationship to immunological surrogate endpoints. We acknowledge that real-world vaccine effectiveness may differ and that validating surrogates against observational effectiveness data warrants separate investigation.

However, conducting RCTs can be challenging due to ethical and practical constraints. In such cases, immunological surrogate endpoints have become widely accepted as an alternative method to evaluate VE [21–23]. Regulatory agencies such as the European Medicines Agency and the U.S. Food and Drug Administration introduced threshold-based approaches in 1997 and 2007 [24–27], respectively, to assess VE using surrogate endpoints, including seroconversion rates, seroprotection rates, and fold increase in geometric mean titre (GMT) [28–31]. Despite their widespread adoption, some studies have raised concerns about the validity and relevance of these surrogate endpoints in accurately reflecting VE [32]. This systematic review aims to address two key issues: first, evaluating the VE stratified by vaccine types and virus strains. Second, exploring the quantitative relationship between immunological surrogate endpoints and VE.

Materials and methods

Study objectives and outcomes of interest

This meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42024554628) and was conducted according to the 2020 Preferred Reporting Items for Systematic Review and Meta-Analyses [33] guideline, with literature retrieval up to 16 July 2024, aiming to evaluate the immunogenicity and efficacy of influenza vaccines. The primary objective was to examine how different vaccine types and influenza strains affect VE, whereas the secondary objective was to explore the role and validity of immunological surrogate endpoints in evaluating influenza vaccines.

Outcomes of interest include VE and immunogenicity assessed in randomized placebo-controlled trials. VE is calculated based on the risk of influenza infection confirmed by PCR, culture, or laboratory methods. Immunogenicity is assessed using three surrogate endpoints: the GMT of hemagglutination antibody titre (HAI), seroconversion rates, and seroprotection rates.

Inclusion and exclusion criteria

We included RCTs that assessed the efficacy of influenza vaccines. No language restrictions were applied during the search. Exclusion criteria included phase I and phase II trials, studies without efficacy data, conference abstracts, reviews, meta-analyses, letters, unregistered clinical trials, and studies with no original data. Among publications derived from the same study population, only the study with the longest follow-up was included.

Search and data extraction strategy

Data for the review were retrieved from PubMed, Web of Science, Ovid, Embase, The Lancet, and ClinicalTrials.gov, with a cutoff date of 16 July 2024. The search strategy combined keywords with database-specific terms, and the detailed search protocol is available in supplementary material. Two independent research teams (group 1: L.X. and group 2: L.J.X.) screened titles and abstracts and extracted data on study populations, control groups, vaccines used, efficacy, time from vaccination to immune response measurement, and immunogenicity endpoints. Any disagreements were resolved through discussion with a third reviewer (G.H.D.), and the extracted data were consolidated and visualized in an Excel spreadsheet.

Risk of bias assessment

The risk of bias in the included RCTs was assessed using the Cochrane Risk of Bias tool (Rob2). Each domain was rated for low, high, or unclear risk of bias. Additionally, the overall quality of evidence for each vaccine outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, considering bias risk, indirectness, imprecision, inconsistency, and publication bias. Risk of bias assessment was conducted independently by two researchers (G.H.D. and L. X.), and any disagreements were resolved through discussion, with unresolved issues adjudicated by a third reviewer (L.J.X.).

Statistical analyses

All analyses were performed in R (v4.2.1; R Core Team, Vienna, Austria) using the meta (v5.5-0; Guido Schwarzer), metafor (v3.4-0; Wolfgang Viechtbauer), dosresmeta (v3.0-0; Andrea Crippa), and ggplot2 (v3.4-0; Hadley Wickham) packages. Meta-analytic models: dichotomous outcomes (vaccine vs. control) were pooled as risk ratios (RRs) under a DerSimonian–Laird random-effects model; if I^2 <50%, a fixed-effect (Mantel–Haenszel) model was also reported for comparison. Between-study heterogeneity was quantified by Cochran's Q and I^2; τ^2 was estimated via the method of moments. We conducted mixed-effects meta-regression via metafor to investigate prespecified sources of heterogeneity. In univariate analyses, each of the following prespecified covariates was tested separately: vaccine type (inactivated influenza vaccine [IIV] vs. live attenuated influenza vaccine [LAIV] vs. recombinant hemagglutinin protein vaccine [RHPV]), influenza subtype (H1N1 vs. H3N2 vs. B), strain match (matched vs. mismatched), and age group (adult vs. paediatric). Given the relatively small number of studies available for each covariate, we adopted a pragmatic stepwise approach to reduce the risk of overfitting: only covariates showing a potential signal of association ($p < 0.10$) in univariate analysis were subsequently entered into the multivariable model. This multivariable analysis was performed as an exploratory assessment to examine whether observed univariate associations persisted after limited

adjustment. The univariate meta-regression results were considered the primary findings for interpretation. Forest plots were generated in metafor.

Immunogenicity endpoints were analysed in two stages: first, the association between standardized mean differences (SMDs) of log-transformed HAI titres and VE was assessed using conventional surrogate endpoint validation methods. Second, attack rate in the vaccinated (among vaccinated individuals [ARV] individuals) was modelled in relation to seroprotection rate, seroconversion rate, and GMT fold-rise using random-effects dose–response meta-analysis.

VE for each study was defined as $VE = (1-RR) \times 100\%$, where RR is the risk ratio of laboratory-confirmed influenza in vaccinated versus control groups. When VE was not directly reported in the original publication, RRs were calculated from raw event counts and converted to VE using this formula. Although summary of findings tables present pooled RRs, VE% is reported in the main text for ease of clinical interpretation; both measures are based on the same underlying effect estimates.

For correlation plots examining the relationship between immunological surrogate endpoints and VE or ARV, weighted analyses were used to account for differences in study precision. Each study's data point was weighted by the inverse of its variance, identical to the weighting scheme used in the meta-analyses, so that studies with larger sample sizes and narrower confidence intervals contributed more to the fitted relationships. Weighted Pearson correlation coefficients were computed, and fitted lines were generated using weighted least squares regression. These procedures ensured methodological consistency between the meta-analytic and correlation-based approaches.

Results

From the 5028 studies identified, this review included 26 eligible efficacy RCTs (Fig. 1; Table S4) [34–59]. A total of 63 100 participants were in the vaccinated groups and 41 831 participants in the placebo groups. The 26 RCTs evaluated the efficacy of full vaccination with inactivated vaccines, live attenuated vaccines, and recombinant protein vaccines. These studies also assessed vaccine performance against similar and dissimilar strains, as well as differential efficacy against H1N1, H3N2, and influenza B subtypes.

Overall efficacy and subgroup analysis of efficacy

Of the 5028 articles screened, 26 eligible efficacy RCTs [34–59] published across multiple studies were included in this review (Fig. 1). A total of 104 931 participants in vaccination groups and 41 831participants in placebo or control groups were analysed, with median follow-up durations ranging from 1 month to 6 months after the final vaccination in individual RCTs. These trials evaluated various influenza vaccines, IIV, RHPV, and LAIV. The pooled VE across all studies was 48.48% (95% CI, 41.94–54.29) under a random-effects model, indicating moderate protection against influenza. Significant heterogeneity was observed among studies ($I^2 = 70.1\%$; $\tau^2 = 0.0708$; $\chi^2 = 103.70$; $p < 0.0001$).

Individual study VE estimates varied widely. For example, the highest VE was reported for multivalent universal trivalent-adjuvanted group-targeted influenza preparation (MUTAGTIP) in Shabir (2011) [34] at 75.39% (95% CI, 13.84–92.97), whereas the lowest efficacy was observed for Nasovac-S in John (2016) [54], with

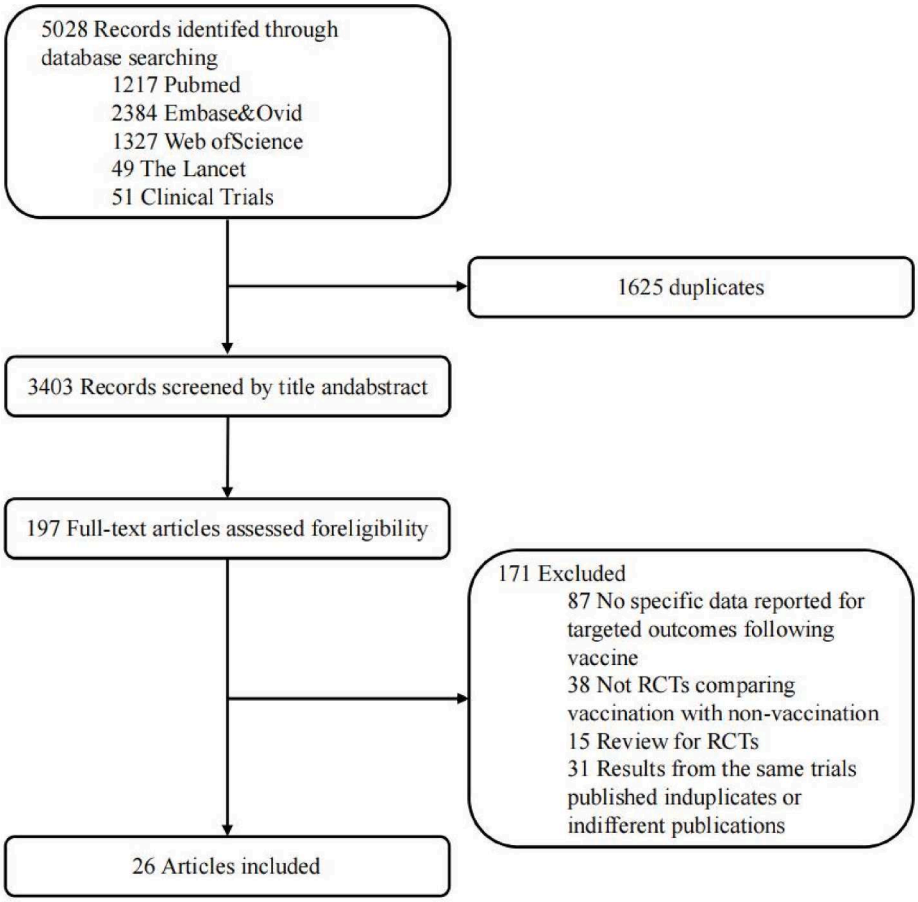

Fig. 1. Study selection. RCTs, randomized controlled trials.

0.43% (95% CI, −23.11 to 19.46). Vaccines such as Fluarix and Vaxigrip consistently demonstrated protective effects, with VE estimates exceeding 50% across multiple studies. In contrast, vaccines like Nasovac-S showed lower and less consistent efficacy, as their confidence intervals frequently overlapped zero, indicating non-significant effects.

The observed heterogeneity may be due to differences in vaccine types, study populations, and the alignment between vaccine strains and circulating strains of influenza. Larger studies with higher sample sizes generally provided more precise estimates, as evidenced by narrower confidence intervals (Fig. 2).

Different vaccines subgroup analysis of efficacy

The meta-analysis evaluated the efficacy of three types of influenza vaccines—IIV, LAIV, and RHPV—based on pooled data from 26 studies [34–59]. For IIV, the random-effects model analysis included 1245 cases in the intervention group ($n = 49\,319$) and 2074 cases in the control group ($n = 32\,057$), yielding a VE of 54.70% (95% CI, 47.34–61.03). Significant heterogeneity was observed ($I^2 = 64.8\%$; $\tau^2 = 0.0621$; $\chi^2 = 51.07$; $p < 0.0001$), indicating variability among study populations, vaccine formulations, and circulating influenza strains. In contrast, LAIV demonstrated a pooled VE of 35.88% (95% CI, 25.55–44.78) based on 1063 cases in the intervention group ($n = 11\,137$) and 1113 cases in the control group ($n = 7572$). The heterogeneity was substantial ($I^2 = 62.5\%$; $\tau^2 = 0.0316$; $\chi^2 = 26.66$; p 0.0029), with efficacy varying significantly across studies, likely due to differences in age groups, geographic settings, and vaccine compositions.

For RHPV, the analysis included 69 cases in the intervention group ($n = 2644$) and 122 cases in the control group ($n = 2455$), with a VE of 46.93% (95% CI, 29.07–60.29). No significant heterogeneity was observed ($I^2 = 0\%$; $\tau^2 = 0$; p 0.3341), indicating consistency in results across the limited number of studies available. When all vaccine types were analysed collectively, the random-effects model produced an overall VE of 48.48% (95% CI, 41.94–54.29), based on 2347cases in the intervention group ($n = 63\,100$) and 2614cases in the control group ($n = 41\,831$). The heterogeneity across all studies was significant ($I^2 = 70.1\%$; $\tau^2 = 0.0708$; $\chi^2 = 103.70$; $p < 0.0001$), reflecting the diverse efficacy profiles of the different vaccine platforms. A test for subgroup differences confirmed statistically significant variations in VE among the three types ($\chi^2 = 10.32$; df = 2; p 0.0057), emphasizing the need to consider specific vaccine characteristics and target populations in future influenza immunization strategies (Fig. 3).

Different influenza strain subgroup analysis of efficacy

The meta-analysis assessed VE against different influenza subtypes (H1N1, H3N2, and B) across 11 studies [38,39,42,46,47,49,51,55,57–59]. For H1N1, the random-effects model demonstrated an overall VE of 59.38% (95% CI, 24.60–78.12), based on data from 318 cases in the intervention group ($n = 24\,318$) and 349 cases in the control group ($n = 16\,847$). Heterogeneity was significant ($I^2 = 88.7\%$; $\tau^2 = 0.6981$; $\chi^2 = 71.01$; $p < 0.0001$), suggesting variations in study populations, vaccine types, and circulating strains. For H3N2, the pooled VE was lower at 41.84% (95% CI, 26.45–54.01), derived from 606 cases in the intervention group ($n = 28\,644$) and 721 cases in the control group ($n = 21\,169$), with substantial heterogeneity ($I^2 = 75.7\%$; $\tau^2 = 0.0990$; $\chi^2 = 45.31$; $p < 0.0001$). This reduced efficacy aligns with challenges posed by antigenic drift in H3N2 strains.

For influenza B, the pooled VE was 19.21% (95% CI, −20.10 to 45.66), based on 677 cases in the intervention group ($n = 32\,451$) and 549 cases in the control group ($n = 22\,465$). Heterogeneity remained high ($I^2 = 87.7\%$; $\tau^2 = 0.3219$; $\chi^2 = 73.18$; $p < 0.0001$), highlighting differences across studies and geographic regions. The overall random-effects model integrating all subtypes yielded a VE of 41.39% (95% CI: 25.53–53.87), with significant heterogeneity ($I^2 = 85.7\%$; $\chi^2 = 209.69$; $p < 0.0001$). A test for subgroup differences indicated statistically significant variability in efficacy among the three influenza subtypes ($\chi^2 = 3.74$; df = 2;

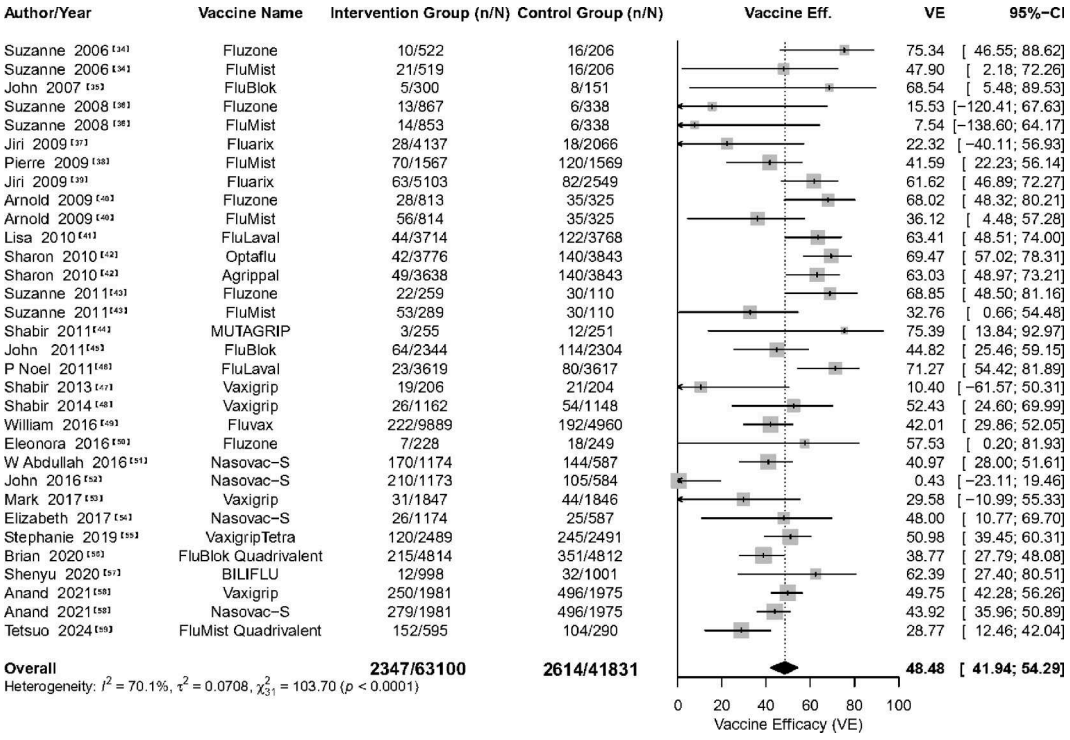

Fig. 2. Forest plot for efficacy of influenza vaccine on preventing infections across all studies. VE, vaccine efficacy.

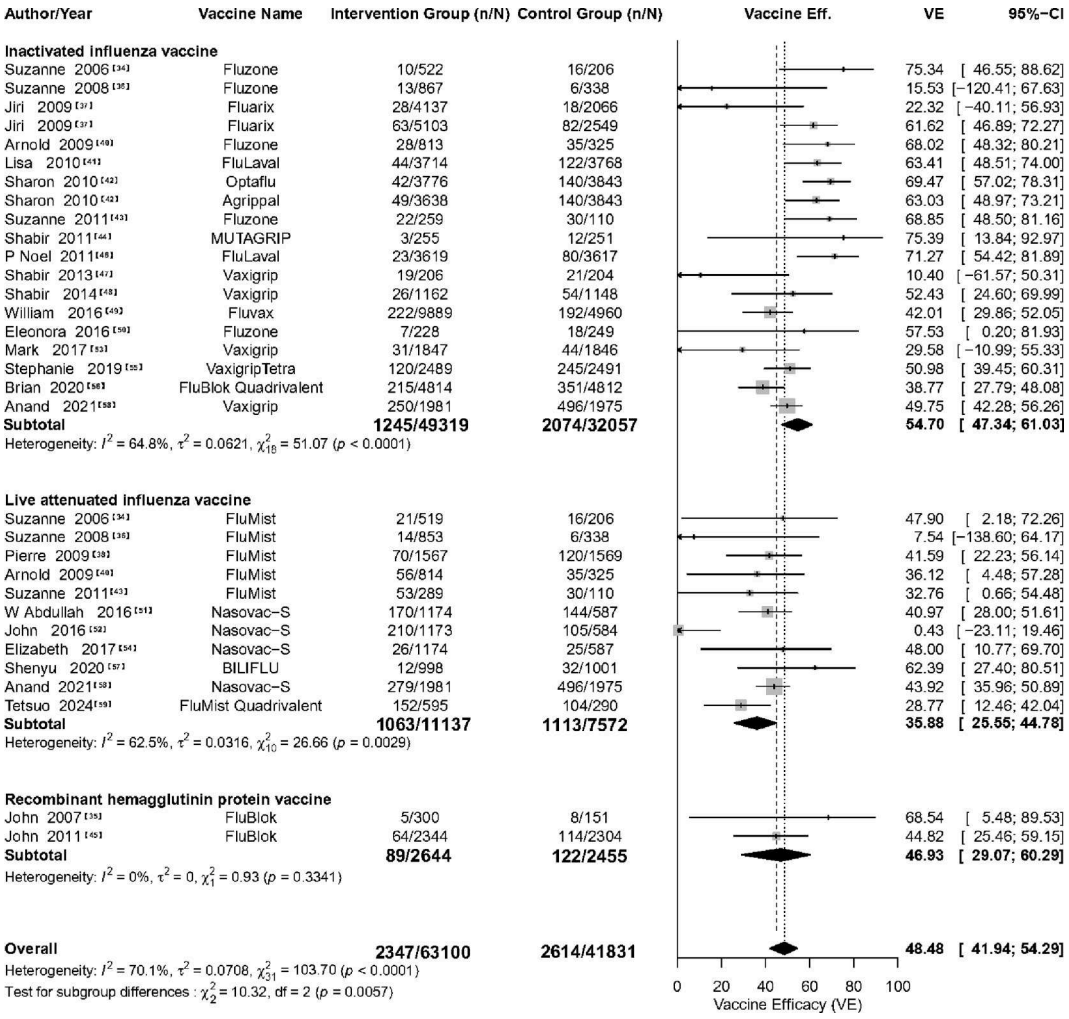

Fig. 3. Forest plot for the efficacy of different types of influenza vaccines in preventing infections. VE, vaccine efficacy.

p 0.1538). These results emphasize the differential effectiveness of influenza vaccines across subtypes and underline the need for subtype-specific strategies in vaccine development and deployment (Fig. 4).

Dissimilar and similar influenza strain subgroup analysis of efficacy

The meta-analysis examined seven RCTs [38,39,41,42,46,56,57] to evaluate VE against influenza strains, categorized as either similar or dissimilar to the vaccine strain. For dissimilar influenza strains, the common-effects model yielded a pooled VE of 50.09% (95% CI, 42.96–56.32), based on 321 cases in the intervention group (n = 28 720) and 552 cases in the control group (n = 22 649). The heterogeneity was low (I^2 = 44.8%; τ^2 = 0.0417; χ^2 = 12.67; p 0.0806), indicating consistent findings across studies. This suggests moderate protection even when the vaccine and circulating strains are antigenically mismatched.

For similar influenza strains, the random-effects model demonstrated a higher pooled VE of 64.30% (95% CI, 50.61–74.19), based on 263 cases in the intervention group (n = 28 720) and 536 cases in the control group (n = 22 649). Substantial heterogeneity was observed (I^2 = 74.2%; τ^2 = 0.1554; χ^2 = 27.09; p 0.0003), reflecting variability in vaccine formulations and population demographics. The overall pooled VE across all strain categories was 58.48% (95% CI, 49.57–65.81), with moderate heterogeneity (I^2 = 64.5%; τ^2 = 0.0917; χ^2 = 42.21; p 0.0002). The test for subgroup differences between dissimilar and similar strains was not statistically significant (χ^2 = 2.06; df = 1; p 01510), suggesting comparable protection levels across strain categories (Fig. 5).

Dose–response relationship of HAI

We observed a nonlinear dose–response relationship between log-transformed SMDs of HAI titres and VE against symptomatic infections after accounting for outliers. However, this association showed substantial unexplained variability, and the results should be interpreted with caution, given that the nonlinearity may not generalize to untransformed SMDs or other immunogenicity measures.

The analysis of the relationship between SMD and VE showed that excluding negative VE values enhanced model robustness and interpretability, as these anomalies often arise from small sample sizes. The estimated parameter (β = 0.46649; SE = 0.10343) was highly significant (t = 4.51; p 0.00089), indicating a strong relationship between SMD in HAI and VE. A series of sensitivity analysis confirmed the robustness of the main findings, despite the limited data available (Fig. 6; Table S3, Figs. S9–S11).

Linear regression of attack rate on the seroprotection rate

When the seroprotection rate in the intervention group was ≥70%, 73.3% of the VE estimates were ≥50%. We observed a linear

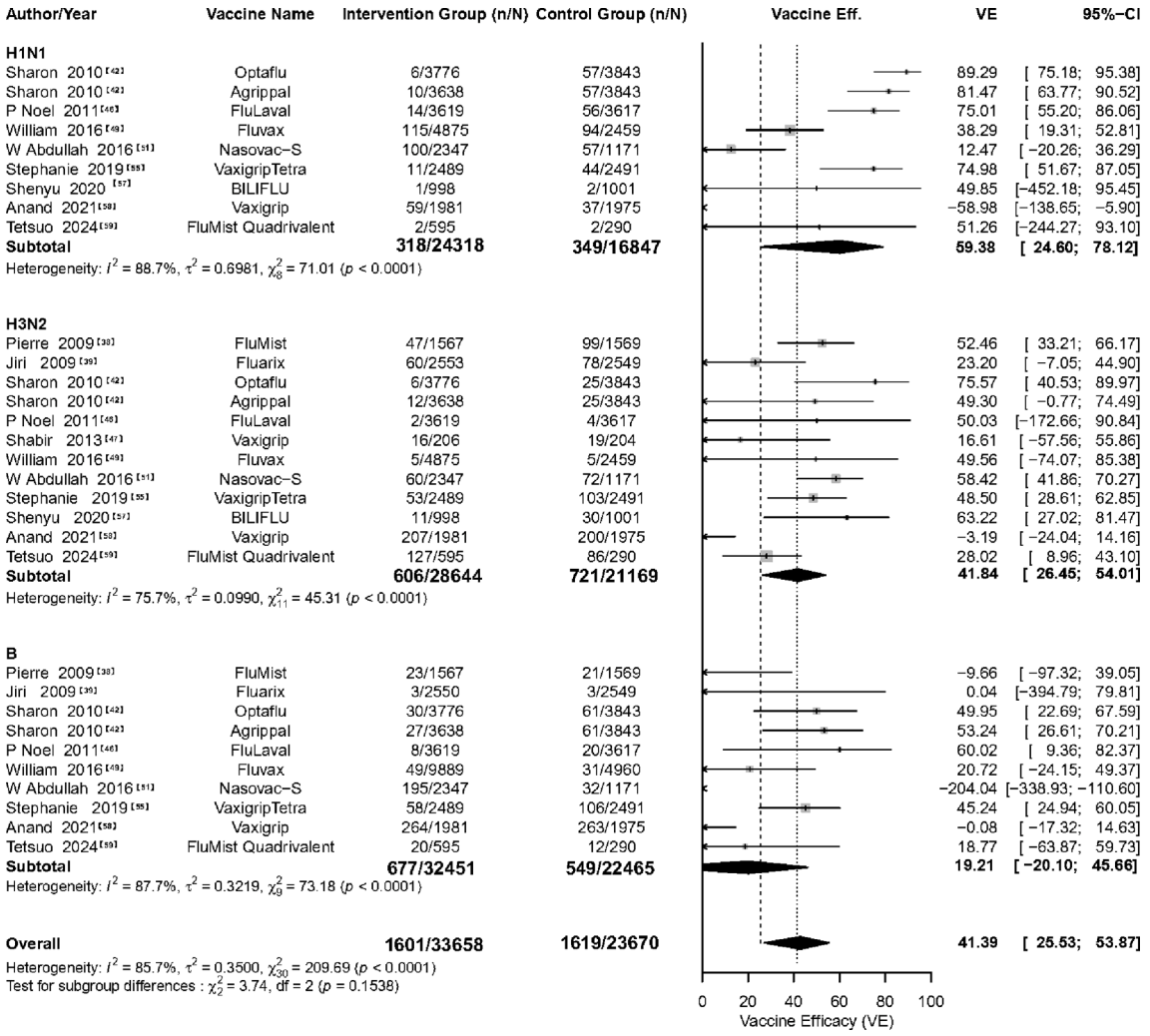

Fig. 4. Forest plot for the efficacy of influenza vaccines in preventing different influenza. VE, vaccine efficacy.

relationship between the seroprotection rate and the attack rate for symptomatic infections. This relationship remained significant after adjusting for outliers, although some unexplained variation in the regression persisted.

Linear regression showed that seroprotection rates explained 50.38% of the variation in viral attack rates ($R^2 = 0.3354$; adjusted $R^2 = 0.3052$). A 1% increase in seroprotection among the population reduced the viral attack rate by 0.0135 units ($\beta_1 = -0.0135$; p 0.003020), with the intercept ($\beta_0 = 1.691$; $p < 0.001$) indicating an estimated viral attack rate of 1.691 at zero seroprotection. The model was significant ($F = 11.10$; p 0.00302044) with a residual standard error of 0.3926 and no autocorrelation (Durbin–Watson = 2.1176). A series of sensitivity analyses showed similar results to the main findings (Fig. 7; Table S3, Figs. S12–S14).

Linear regression of attack rate on the seroconversion rate

When the seroconversion rate in the intervention group was ≥70%, 73.3% of the VE estimates were ≥50%. We observed a linear relationship between the seroconversion rate and the attack rate for symptomatic infections. This relationship remained significant after adjusting for outliers, although some unexplained variation in the regression persisted.

Study evaluated the relationship between seroconversion rates among the population and viral attack rates using a linear regression model. Seroconversion rates were significant predictors, showing a negative correlation with viral attack rates. The model explained 46.4% of the variance ($R^2 = 0.3974$; adjusted $R^2 = 0.3673$), suggesting moderate explanatory power. The intercept ($\beta_0 = 3.2711$; $p < 0.001$) indicated an estimated viral attack rate of 3.2711 when the seroconversion rate is zero. The regression coefficient ($\beta_1 = -0.038479$; p 0.001662) revealed that each 1% increase in seroconversion reduces the viral attack rate by 0.038.

The model was significant ($F = 13.19$; p 0.00166155). A series of sensitivity analyses showed similar results to the main findings (Fig. 8; Table S3, Figs. S15–S17).

Linear regression of attack rate on the fold increase in GMT

When the GMT fold increase was ≥2.5, 69.2% of the VE estimates were ≥50%. We observed a linear relationship between the GMT fold increase and the attack rate for symptomatic infections. This relationship remained significant after adjusting for outliers, although some unexplained variation in the regression persisted.

The study assessed the relationship between GMT fold increases among the population and viral attack rates using a linear regression model. GMT fold increases were significant predictors, demonstrating a negative correlation with viral attack rates. The model explained 28.6% of the variance ($R^2 = 0.3651$; adjusted $R^2 = 0.3397$), indicating modest explanatory power. The intercept

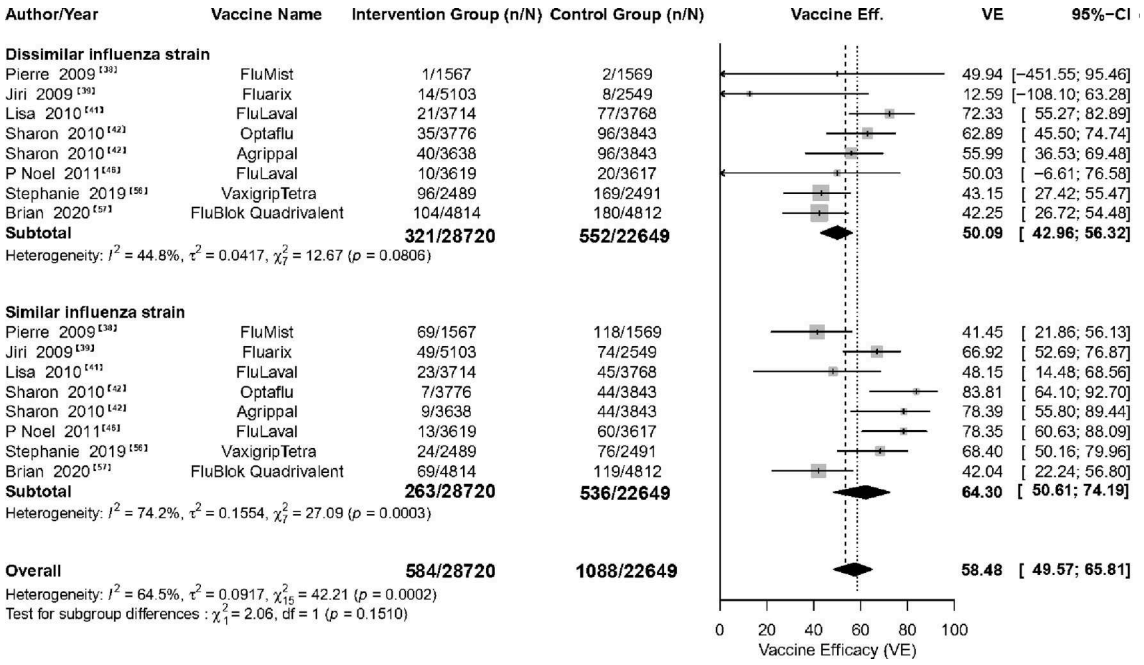

Fig. 5. Forest plot for the efficacy of the vaccine against different or the same strains of influenza. VE, vaccine efficacy.

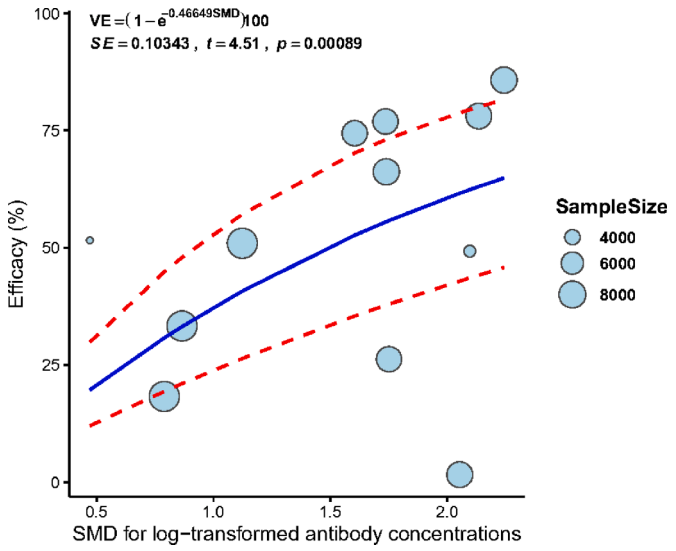

Fig. 6. Relationship between vaccine efficacy and standardized mean difference (SMD) for log-transformed antibody concentrations. The blue line represents the fitted nonlinear dose–response relationship between SMD of log-transformed HAI titres and vaccine efficacy (VE). The red dashed lines indicate the 95% bootstrap percentile confidence intervals, reflecting the uncertainty in the modelled association.

($\beta_0 = 1.121$; $p < 0.001$) suggested an estimated viral attack rate of 1.121 when GMT fold increases are zero. The regression coefficient ($\beta_1 = -0.067$; p 0.000845) showed that each unit increase in GMT fold reduces the viral attack rate by 0.067.

The model was statistically significant ($F = 14.38$; p 0.000845). Sensitivity analysis conducted after excluding outliers confirmed the robustness of the results (Fig. 9; Table S3, Figs. S18–S20).

Meta-regression analyses

The univariate meta-regression results (Table S4) are presented as the primary findings, as they are less affected by model complexity, given the limited number of studies per covariate. Vaccine type significantly reduced τ^2 from 0.12 to 0.098 ($R^2 = 18\%$; p 0.023), whereas influenza subtype reduced τ^2 to 0.102 ($R^2 = 15\%$; p 0.041). Strain match explained 9% of heterogeneity ($\tau^2 = 0.109$; p 0.068), and age group showed no statistically significant association (p 0.21).

As an exploratory step, we constructed a multivariable model including only covariates with $p < 0.10$ in univariate analyses (vaccine type and subtype). In this model, τ^2 decreased to 0.087 ($R^2 = 27\%$). Vaccine type remained significant ($\beta = -0.14$; SE = 0.06; p 0.012) as did subtype ($\beta = -0.11$; SE = 0.05; p 0.029), whereas strain match was no longer significant after adjustment (p 0.11).

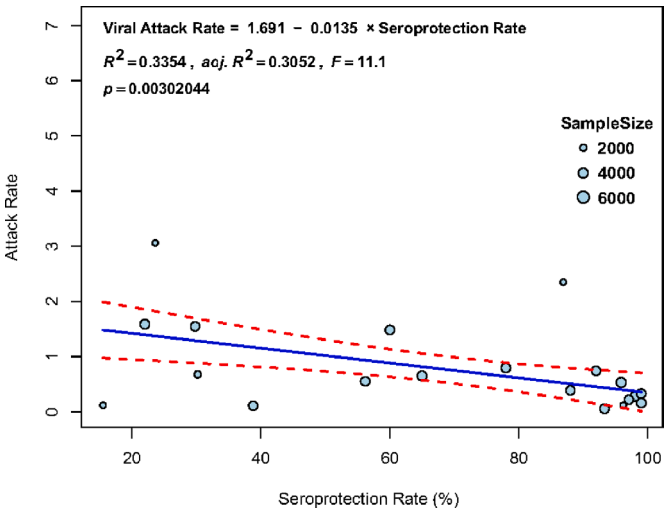

Fig. 7. Linear regression of attack rate vs. seroprotection rate. The blue line represents the fitted nonlinear dose–response relationship between standardized mean difference (SMD) of log-transformed HAI titres and vaccine efficacy (VE). The red dashed lines indicate the 95% bootstrap percentile confidence intervals, reflecting the uncertainty in the modelled association.

Begg's test and Egger's test

Begg's test and Egger's test showed no clear evidence of publication bias (Tables S1 and S2, Figs. S1–S3).

ROB2 assessment

The ROB2 assessment indicates varied bias levels across studies. Most of the included studies were judged to have low risk of bias in the domain of random sequence generation, indicating appropriate methods for randomization. For allocation concealment, several studies were assessed as having unclear risk of bias, primarily due to insufficient reporting of concealment methods. Blinding of participants and personnel was a high risk in some trials, especially in open-label studies where blinding was not feasible or reported. Outcome assessment blinding was generally adequate, although a few studies had unclear risk due to a lack of description. Incomplete outcome data were managed appropriately in most studies, with low risk of attrition bias. Selective reporting was found to be low risk in most cases, although one or two studies showed unclear risk due to the absence of a preregistered protocol. Other sources of bias, such as baseline imbalances or early stopping of trials, were low or unclear risk depending on the study (Figs. S4 and S5).

GRADE assessment

The GRADE assessment of LAIV revealed moderate to low-quality evidence for preventing influenza, with the most reliable results from culture and RT-PCR confirmation. Evidence based on serology or general laboratory methods showed greater inconsistency. IIV reduced influenza risk by 40% to 60% in culture, RT-PCR, and lab-confirmed cases, with moderate-quality evidence. However, combined confirmation methods lowered evidence quality. The RHPV showed promising efficacy, with relative risk reductions from 0.31 to 0.61, but a wide confidence interval (0.10–0.95) for RT-PCR-confirmed cases suggests uncertainty. Overall, the evidence quality for this vaccine was low to very low, indicating the need for further high-quality research (Figs. S6–S8).

Discussion

This systematic review and meta-analysis show that influenza vaccines provide moderate protection against laboratory-confirmed infections, with an overall VE of 48.48%. Among the vaccine types analysed, IIV had the highest efficacy at 54.70%, underscoring its reliability as a preventive measure. LAIV and RHPV, although less effective overall, remain useful in specific situations due to their unique immune mechanisms and production advantages [13]. However, there is a notable lack of phase III and IV RCT data for DNA and mRNA vaccines [60,61]. These newer vaccine platforms show promise in early studies due to their ability to quickly adapt to viral mutations, induce strong immune responses, and avoid the use of live viruses, making them strong candidates for future vaccine development [62–64].

The study also highlights differences in VE among influenza subtypes (H1N1, H3N2, and B) and between antigen-matched and mismatched strains [15,16]. Although antigen matching remains a key goal, matched strains had an efficacy of 64.30%, compared with 50.09% for mismatched strains. This suggests that current vaccines may offer broader protection than previously thought. Cross-protection may arise from conserved regions in hemagglutinin (HA) or neuraminidase (NA) proteins and cross-reactive T-cell immunity [65,15]. However, the lower efficacy against H3N2 emphasizes the need for improved surveillance and the adoption

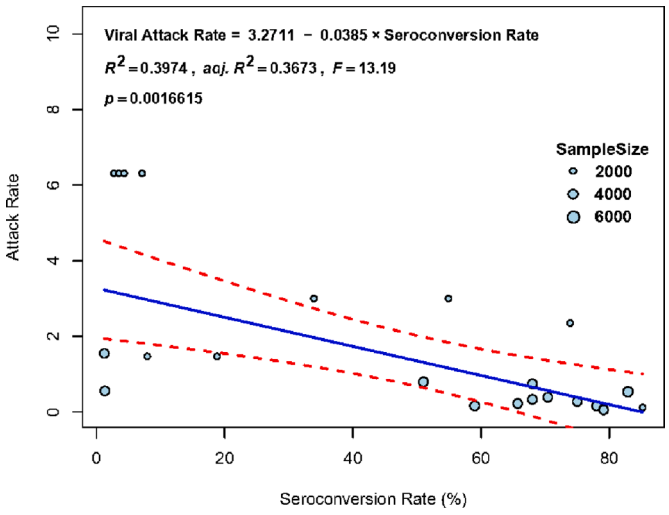

Fig. 8. Linear regression of attack rate vs. seroconversion rate. The blue line represents the fitted nonlinear dose–response relationship between standardized mean difference (SMD) of log-transformed HAI titres and vaccine efficacy (VE). The red dashed lines indicate the 95% bootstrap percentile confidence intervals, reflecting the uncertainty in the modelled association.

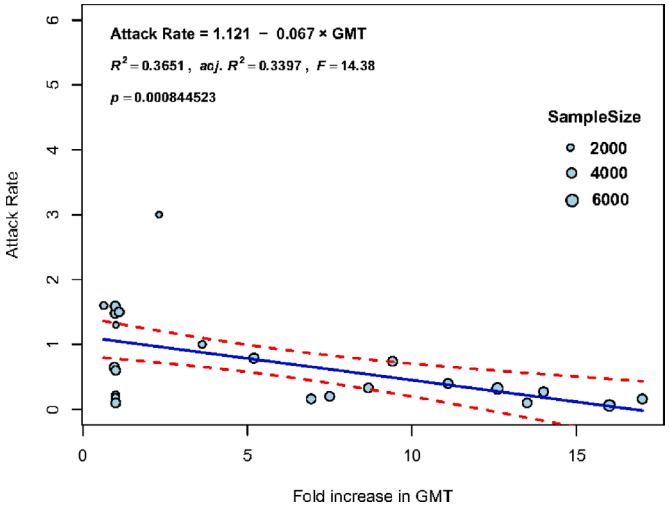

Fig. 9. Linear regression of attack rate on the fold increase in geometric mean titre. The blue line represents the fitted nonlinear dose–response relationship between standardized mean difference (SMD) of log-transformed HAI titres and vaccine efficacy (VE). The red dashed lines indicate the 95% bootstrap percentile confidence intervals, reflecting the uncertainty in the modelled association.

of new technologies like mRNA vaccines to address its high mutation rate [63,64].

Key immunological endpoints were identified as predictors of VE, including the SMD in antibody concentration, seroprotection rate, seroconversion rate, and GMT fold increase [66,67]. Nonlinear regression analysis revealed a significant correlation between SMD in HAI and VE ($\beta = 0.46649$; p 0.00089), although the model had limited explanatory power due to substantial unexplained variation.

It should be noted that our definition of "substantial unexplained variation" relates to the wide confidence bands observed in the dose–response model, rather than low R^2 values. Despite high R^2 values, the small sample size ($n = 12$) introduces uncertainty.

Seroprotection rate was the strongest predictor, with a 1% increase in seroprotection rate reducing the attack rate by 0.0135

units (p 0.003020), explaining 50.38% of the variation. This highlights the importance of achieving adequate seroprotection at the population level to reduce disease transmission. Cross-validation and sensitivity analyses confirmed the robustness of this model.

Similarly, the seroconversion rate showed a significant correlation with attack rates. A 1% increase in seroconversion rate reduced the attack rate by 0.038479 units (p 0.001662), explaining 46.4% of the variation ($R^2 = 0.3974$). This indicates that the seroconversion rate reflects both individual immune responses and population level protection. Validation analysis further confirmed the model's stability. GMT fold increases were also negatively associated with attack rates, although the explanatory power was lower. Each unit increase in GMT fold reduced the attack rate by 0.067 units (p 0.000845), explaining 28.6% of the variation ($R^2 = 0.3651$). Despite its modest predictive power compared with seroprotection and seroconversion rates, sensitivity analysis confirmed the reliability of this finding. These results emphasize the importance of seroprotection rate, seroconversion rate, and GMT fold increase as critical indicators for evaluating and optimizing VE.

We chose to use the ARV group rather than VE or relative risk (RR) as the outcome in our modelling of immunogenicity endpoints, based on the rationale that VE is a derived measure that combines outcomes from both vaccinated and placebo groups. Since our immunological markers (e.g. seroprotection rate) are typically only available for vaccinated individuals, ARV offers a more direct and observable link between immunogenicity and clinical outcomes. Nevertheless, we acknowledge that this approach does not fully address the predictive capacity of these markers across both trial arms, which is a necessary criterion for a surrogate endpoint. Therefore, our results should be interpreted as demonstrating a partial surrogate relationship—specifically within the vaccinated population—rather than full validation of these markers as substitutes for VE.

Additionally, since our analysis was based on aggregated data from multiple studies, rather than individual participant data (IPD), unmeasured heterogeneity—such as differences in follow-up duration, age distributions, comorbidities, and laboratory methods for measuring immunological endpoints—may have contributed to residual variation in the observed associations. Future IPD meta-analyses are warranted to more precisely account for these factors and validate whether these immunogenicity markers can serve as consistent surrogate endpoints across different populations and trial settings.

Using immunological markers as surrogate endpoints for VE presents both opportunities and challenges. VE is a ratio-based measure derived from attack rates in both vaccinated and unvaccinated groups and is subject to instability when control group attack rates are low or vary across studies. By contrast, using attack rate ARV allows for more stable modelling of associations with immunological endpoints. This strategy improves interpretability while acknowledging that ARV is a proxy, not a replacement, for VE. Our study demonstrates how surrogate markers can be used to approximate clinical protection when direct VE data are limited or difficult to compare.

Our meta-regression analysis was designed with univariate models as the primary focus, given the relatively small number of studies contributing to each covariate. This approach minimizes overfitting and preserves interpretability. The multivariable model, constructed using only covariates with $p < 0.10$ in univariate analysis, was intended as an exploratory assessment to examine whether observed associations persisted after limited adjustment.

This study has several limitations. Significant heterogeneity in study design, vaccine types, and population characteristics may have introduced bias. The applicability of SMD, seroprotection rate, seroconversion rate, and fold increase in GMT in older adults and immunocompromised populations remains uncertain and requires further research. The underrepresentation of certain subgroups, such as immunocompromised individuals, limits the generalizability of the findings. Additionally, the wide confidence intervals for recombinant vaccines highlight the need for more high-quality RCTs. Finally, the limited sample size for immunological endpoints may not fully represent diverse populations.

Few RCTs provided efficacy estimates stratified into paediatric (<18 years), adult (18–64 years), and elderly (≥65 years) groups, preventing robust subgroup meta-analysis by age. Future clinical trials should report age-specific outcomes to enable more precise assessment of vaccine performance in these key populations.

Future research should explore the standardization of immunogenicity measurements, their predictive validity across populations, and how best to integrate them into vaccine evaluation frameworks. As regulatory agencies increasingly consider immune correlates in accelerated approval pathways [68], studies like ours contribute to establishing quantitative thresholds and modelling strategies for evaluating vaccine protection without relying solely on traditional VE estimates [69,70].

Conclusion

This systematic review highlights that influenza vaccines provide moderate protection against laboratory-confirmed influenza, with a pooled VE estimated at 47.88%. Our analysis found significant correlations between VE and various immunological surrogates, with moderate-to-strong correlation coefficients. Specifically, the correlation between VE and HAI titre was $r = 0.75$ (95% CI, 0.65–0.84), indicating a strong positive relationship. Similarly, VE showed a moderate positive correlation with the seroprotection rate ($r = 0.55$; 95% CI, 0.45–0.64). These findings suggest that higher immune responses, as measured by HAI titres and seroprotection rates, are associated with higher VE, supporting their potential use as surrogates for predicting vaccine performance.

CRediT authorship contribution statement

Hong Cao and Handa Ge: Title and abstract screening. Handa Ge and Yong Gan: Accessing articles for inclusion. Handa Ge or Xiao Li: Resolving discrepancies through discussion. Jiaxin Lv, Xiao Li, Lilong Xiao, and Handa Ge: Data extraction, Synthesize, Data visualization using Excel spreadsheets. Handa Ge and Jiaxin Lv: Accessing the risk of bias in the included randomized controlled trials using the Cochrane Risk of Bias tool (RoB2). Handa Ge: Resolving disagreements through discussion, Adjudicating persistent discrepancies. Jiaxin Lv: Evaluating the overall quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Da Feng: Leading thesis design, Conducting research. Da Feng, Hong Cao, Handa Ge, Xiao Li, and Jiaxin Lv: Writing- original draft. Da Feng, Handa Ge, Hong Cao, Andrew Lee, Jian Zou, Mingwang Shen, and Minghuan Jiang: Review. All authors reviewed and approved the final version of the manuscript.

Transparency declaration

Potential conflict of interest

The authors declare that they have no competing interests.

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Data availability

Extracted data are available almost entirely in the review (including supplementary information). Remaining data regarding the immunological surrogate endpoints are available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.09.005.

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