JIMKI
JURNAL ILMIAH MAHASISWA
KEDOKTERAN INDONESIA

e-ISSN : 2721-1924 p-ISSN : 2302-6391

Tinjauan Pustaka

From Promise to Proof: Revealing the Comparative Performance of RSV Vaccines Through Network Meta-Analysis

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Abstract

Introduction: There is no consensus on the optimal vaccine platform for preventing respiratory syncytial virus (RSV) infection. Recent advances in RSV vaccine development aim to improve efficacy and safety across various platforms. This study aimed to compare the efficacy and safety of available RSV vaccines using a network meta-analytic approach to identify the most effective strategy for RSV prevention.
Methods: A systematic search of PubMed, ScienceDirect, Cochrane, and Scopus (up to November 2025) identified randomized controlled trials (RCTs) of RSV vaccines in healthy populations. Evaluated interventions included Ad26.RSV.preF–RSV preF, Ad26.RSV.preF, Bivalent RSVpreF, RSVPreF3OA, and placebo controls. Network meta-analyses were performed using the netmeta package in R. Risk of bias and certainty of evidence were appraised using RoB 2.0, CINeMA, and GRADE frameworks, respectively.
Result: Ten RCTs were analyzed. Ad26.RSV.preF–RSV preF Protein Vaccine possesses superior efficacy in reducing RSV-related respiratory illness compared to placebo (RR 0.25 [95% CI: 0.15-0.45]). Ranking analysis corroborated this finding, identifying it as the most effective intervention (P-score = 0.827). Safety profiles were comparable across all interventions; however, the precision of these estimates was limited by wide confidence intervals and substantial heterogeneity.
Conclusion: Ad26.RSV.preF–RSV preF demonstrated the highest efficacy for RSV prevention. However, their safety profile has not yet been clearly defined, and further research is needed to assess long-term effectiveness and monitor potential late adverse effects.

Kata Kunci: Efficacy, Respiratory Syncytial Virus, Respiratory Illness, Vaccines, Safety

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1. INTRODUCTION

Respiratory syncytial virus (RSV) is a highly transmissible RNA virus and a leading global cause of acute lower respiratory tract disease, producing substantial morbidity and mortality across vulnerable populations. In 2019, RSV was associated with an estimated 338,495 deaths and 14.9 million disability-adjusted life years worldwide, with the highest burden concentrated in low-SDI (Socio-Demographic Index) regions where constrained healthcare access and socioeconomic risk factors amplify disease severity.[1] Current epidemiologic estimates demonstrate that individuals aged 70 years and older now experience higher mortality rates than children under 5 years, underscoring the combined effects of population aging and increased susceptibility among adults with chronic cardiopulmonary comorbidities.[2] These trends indicate that RSV poses a substantial and growing threat to older adults, extending far beyond its historical characterization as a predominantly paediatric pathogen.

Immunization development for this pathogen has faced a long course with several obstacles to producing a safe and effective RSV vaccine. Early RSV vaccine development was hindered by the failure of the formalin-inactivated RSV vaccine, which produced weak antibodies, drove Th2-skewed responses, and caused enhanced respiratory disease in children. Progress was further limited by the lack of a defined correlate of protection, the virus's ability to cause frequent reinfections due to short-lived natural immunity, and repeated failures of subunit, attenuated, and vector-based candidates to generate sufficiently neutralizing responses. The difficulty of inducing strong immunity in older adults and the inability to stabilize the highly immunogenic prefusion F protein further delayed effective vaccine design.[3] All of these factors contributed to decades of unsuccessful attempts before modern preF-based vaccines became feasible. In Q1 2025, WHO announced its recommendation for RSV mitigation, endorsing Pfizer's RSVpreF, although the recommendation is presently restricted to use in pregnancy.[4] Considering RSV mitigation urgency, multiple ongoing trials are now racing their experiment in broad populations.

There are several vaccine platforms in use for example a vector only constructs, two-protein formulations, vector-plus-protein combinations, and protein-based products formulated with an adjuvant. Ad26.RSVpreF is a

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vector-only construct that produces strong cellular immunity and a favorable safety profile in adults. Trial data showed that antibody titers required further augmentation, which led to a subsequent trial incorporating a purified recombinant RSV preF protein as a booster. RSVPreF3 is a protein-based vaccine using AS01E as an adjuvant for their older adults population. Adjuvant utilization was deemed necessary by investigators due to immunosenescence. Lastly, Bivalent RSVpreF is two separate prefusion F proteins using RSV-A and RSV-B, providing the broadest antigenic coverage among these platforms.[3]

Although previous systematic reviews have confirmed that RSV prefusion-F vaccines are efficacious and safe, they evaluated each vaccine platform in isolation and did not establish how these platforms compare against each other.[5] No prior synthesis has quantified the relative efficacy, safety hierarchy, or probability of superiority between subunit, adenovirus-based, mixed vector-protein, and bivalent vaccine formulations. Consequently, comparative effectiveness across platforms remains unclear, leaving clinicians without evidence-based guidance on which RSV vaccine strategy offers the greatest clinical benefit. This study aimed to evaluate and compare existing and emerging RSV vaccines through network meta-analysis, providing robust evidence to identify the most effective immunization strategies for broad-scale RSV prevention.

2. METHODS

Study Design and Search Strategy

This systematic review and network meta-analysis were performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Network Meta-Analysis Checklist Item[6] and Cochrane Handbook for Systematic Review of Intervention.[7]

We conducted data search of the relevant studies on Cochrane Library, PubMed, Science Direct, and Scopus up to November 11, 2025 with these relevant keywords: ("Respiratory Syncytial Virus" OR “RSV”) AND (“vaccine” OR “vaccines” OR "Ad26.RSV.preF–RSV preF protein vaccine" OR "RSVPreF3 OA" OR “Ad26.RSV.preF" OR “RSVpreF”). Afterwards, we added Medical Subject Headings (MeSH) terms with several free terms to construct the database-specific search item.

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Study Selection and Eligibility Criteria

Search results for each database were gathered and managed using Rayyan.ai.[10] After that, we deleted the duplication we found and screened the remaining articles based on title, abstract, and full-paper to meet our patient, intervention, comparison, and study design (PICO(s)) framework outlined in **Table 1**.[7] Each article is reviewed by all reviewers to minimize potential bias. Any conflicts that arise will be resolved through discussion.

Table 1. PICO(s) Framework

Population	Medically Stable Patient
Intervention	Ad26.RSV.preF–RSV preF protein vaccine, RSVPreF3 OA, Ad26.RSV.preF, Bivalent RSVpreF
Comparison	Placeboo
Outcome	Relative Risk (RR) considering number of patients who experience RSV-related respiratory distress episodes
Study	Randomized Controlled Trial Study

The inclusion criteria include: Peer-reviewed articles, and containing binary RSV-related Respiratory distress events data. Additionally, the exclusion criteria were: irretrievable full-text articles; population with pregnant women.

Data Extraction

Two investigators (HAH and MIM) extracted data from each included study using Google Sheets. After that, BNA checked the collected data within the included studies. The included data is extracted by inserting it into tubular sheet consisting of 1) Author and year of publication; 2) Study Location; 3) Study Design; 4) Total Study participant; 5) Population characteristic; 6) Intervention type; 7) Age; 8) Total RSV-related respiratory distress Event each Intervention; 9) Total sample each intervention; 10) Adverse event.

Assessed Outcome

The primary outcome of this study was efficacy, assessed using the risk ratio based on the number of patients who experienced RSV-related respiratory distress episodes, analyzed as dichotomous outcomes. RSV-related respiratory distress was defined as clinically significant lower respiratory symptoms attributable to respiratory syncytial virus infection, typically characterized by increased work of breathing, tachypnea, wheezing, hypoxia, or any episode requiring medical

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evaluation or intervention due to impaired respiratory function.[8]

The secondary outcome in this study was adverse events, assessed using risk ratios based on Grade 3 adverse events reported as dichotomous outcomes. Grade 3 adverse events are defined as severe, medically significant events that are not immediately life-threatening but may require hospitalization or prolongation of hospitalization, and can be disabling or limit the patient's ability to perform self-care activities of daily living.[9]

We calculated the risk ratio based on the number of patients and samples for each intervention using Rstudio.[10] The random effect sizes were used to allow for inevitable heterogeneity. The rating of heterogeneity was assessed based on CINeMA by comparing the 95% confidence interval (CI) with the 95% prediction interval and the clinically meaningful threshold. We also assessed statistical heterogeneity in each pairwise and network meta-analysis comparison using Q-values and I2 statistics. P-scores were calculated to rank each treatment in the network based on its efficiency. In network meta-analyses, efficiency is determined by the treatment effect (TE) and the standard error of the treatment effect (seTE). A treatment is considered highly efficient if it has a high TE and a low seTE. On the other hand, low efficiency is defined by a low TE and a high seTE.[11] P-scores range from 0 to 1 and indicate the likelihood of a treatment being one of the best options in the network. We present the p-score results using a heat plot for more straightforward interpretation.[12]

Quality Assessment for Individual Studies

We assessed the potential bias in the final study results using the Risk of Bias Tool for randomized trials (RoB 2.0).[13] This tool encompasses five domains and includes 28 signaling questions focused on areas like randomization, interventions, outcome data, and reported results. Two independent reviewers (MIM and BNA) conducted the quality assessments for the randomized trials. Furthermore, another independent reviewer (HAH) re-evaluated and oversaw the biased judgment outcomes. An independent reviewer (MIM) conducted the visual analysis using RoBVIS[14].

Statistical Analysis

Network Meta-Analysis

We estimated the risk ratio (RR) using R studio. We used the

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following three consecutive R packages: "netmeta", "meta", and "readxl".[11,15,16] We used the "netgraph" function to show a network graph of all interventions we compared. We also used Restricted Maximum Likelihood (REML) to measure the outcome and used random effects to measure the heterogeneity.[17] Heterogeneity criteria divisions of 0%, 24%, 50%, and 75% represent insignificant, low, medium, high, and very high heterogeneity criteria respectively with the less than 5% p-values appearing statistically significant.[18] We assessed the p-score with "rankogram" and presented it as a heat plot with "plot" function. Publication bias was evaluated with the funnel plot and Egger regression through symmetrical evaluation.

Bias Across Intervention and Reported Outcome, and GRADE Assessment

We evaluated the potential for within-study bias and outcome reporting bias using the RoB-ME tool, which consists of eleven questions organized into four distinct steps. To assess the credibility of each comparison in the network meta-analysis, we integrated the findings into the Confidence in Network Meta-Analysis (CINeMA) application,[19,20] an adaptation of the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation).[19, ,20, 21, 22]

3. RESULT AND DISCUSSION

In the PRISMA flowchart (**Figure 1.**), a total of 15,988 records were identified through four databases named Cochrane Library, PubMed, Scopus, and ScienceDirect. A total of 4,800 duplicate records were removed before screening, leaving 11,188 unique records for title and abstract assessment. After this screening stage, 11,107 records were excluded.

Subsequently, 81 full-text articles were sought for retrieval, of which 18 articles could not be retrieved due to inaccessible full texts or unavailable documents. The remaining 63 articles were assessed for eligibility. Following a detailed full-text evaluation, 28 articles were excluded for involving the wrong population, 18 were excluded because they were non-RCT designs, and 7 were excluded due to insufficient or incomplete data.

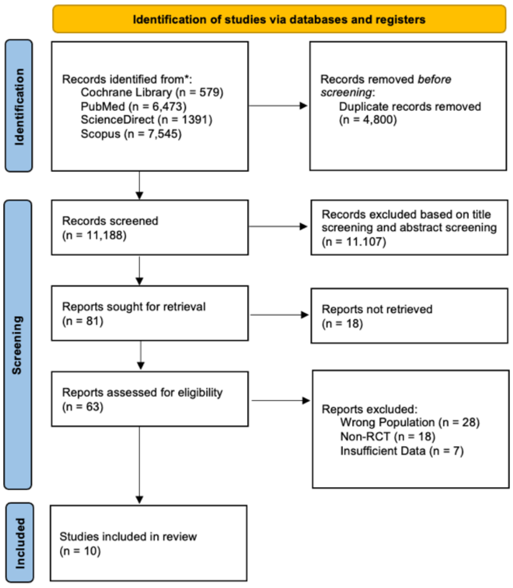


Figure 1. Prisma Flowchart

Ten RCTs with a total of 114,799 samples were included for quantitative and qualitative analysis.[23-32] The largest sample size was contributed by Walsh et al. (2023)[32] with 32,614 participants, while the smallest was from Stuart et al. (2022)[30] with 26 participants. Across all age groups (children [<18 years old], adults [18-60 years old], and older adults [>60 years old]), the pooled weighted mean age of participants was approximately 69 years. These trials were conducted across diverse global regions, including countries in Africa, Asia, Europe, North America, South America, and Oceania. Interventions evaluated included: Ad26.RSV.preF–RSV preF Vaccine, Ad26.RSV.preF Vaccine, BivalentRSVpreF Vaccine, RSVPreF3 OA Vaccine. Details of individual study designs, sample sizes, vaccine doses, and regimens are provided in **Appendix 1.**

Risk of Bias

In the assessment of RoB 2.0 (**Figure 2.**), all included studies demonstrated a low risk of bias across all domains, reflecting strong consistent methodological quality. This consistent low-risk outcome strengthens confidence in the findings and supports their inclusion in the overall analysis.

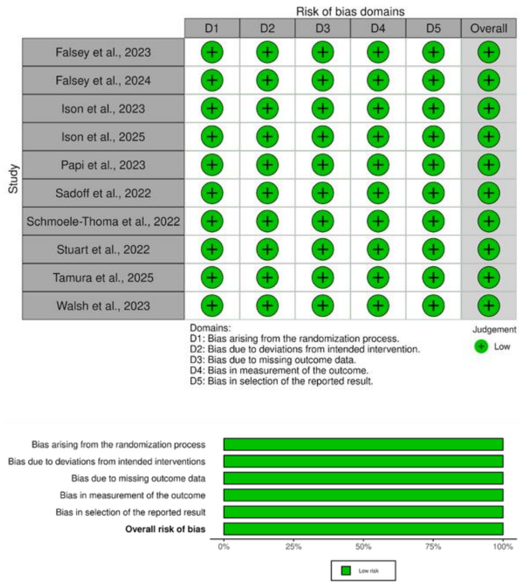
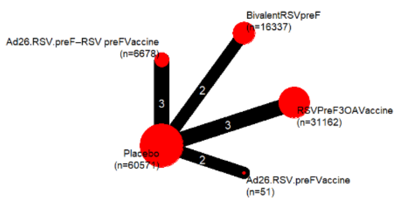


Figure 2. RoB 2.0 Traffic Light and Summary Plot

Vaccine Efficacy



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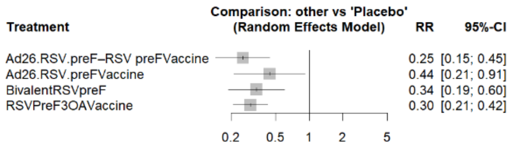


Figure 3. Netgraph and forest efficacy vaccine

The netgraph (**Figure 3.**) demonstrated the structural relationship among the intervention, where circle size represents the participants number and line thickness depicted studies number comparing related intervention. The absence of closed loops in this geometry precludes the assessment of inconsistency between direct and indirect evidence between direct and indirect evidence. Consequently, relative treatment effects between each vaccine are estimated exclusively through indirect comparisons.

Ad26.RSV.preF–RSV preF Protein Vaccine is most efficacious in reducing respiratory distress related RSV with a RR of 0.25 (95% CI: 0.15-0.45). This data corresponds to a 75% reduction in the risk of RSV-related respiratory distress. Another vaccine also showed strong protective efficacy for reducing respiratory distress related RSV with a RR of 0.26 (95% CI: 0.21-0.42) for RSVPreF3OA; RR 0.34 (95% CI: 0.19–0.60) for Bivalent RSVpreF; 0.44 (95% CI: 0.21-0.91) for Ad26.RSV.preF. All those interventions provided statistically significant protection compared to placebo. The overall comparison is shown in **Figure 3.** Furthermore, the analysis revealed a medium heterogeneity across the entire analysis (I^2 = 41.4%). Consequently, publication bias was conducted through funnel plot visual inspection and egger regression. Visual inspection implies asymmetry. At variance with that, egger regression bias estimation suggests insignificant publication bias ER -0.39; p-value: 0.622, demonstrating that publication bias could not be substantiated.

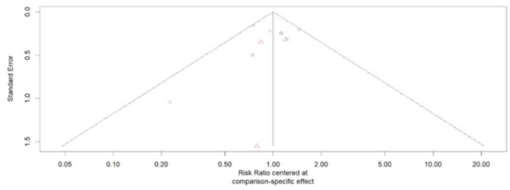


Figure 4. Funnel Plot

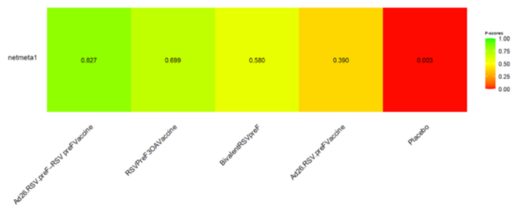


Figure 5. P-score Efficacy

Ranking analysis identified the Ad26.RSV.preF–RSV preF Protein Vaccine as the optimal intervention (P-score: 0.827), reflecting the highest probability of superior effectiveness. RSVPreF3 OA Vaccine secured the second rank (P-score: 0.699), distinctly outperforming both the standalone Bivalent RSVpreF Vaccine (P-score: 0.58) and the Ad26.RSV.preF (P-score: 0.39), while Placebo placed at the lowest tier (P-score: 0.003). The substantial margin between the Ad26.RSV.preF–RSV preF Protein Vaccine and RSVPreF3 OA Vaccine suggests a clinically meaningful distinction, reinforcing the Ad26.RSV.preF–RSV preF Protein Vaccine as the most effective strategy in this network.

Safety Profile

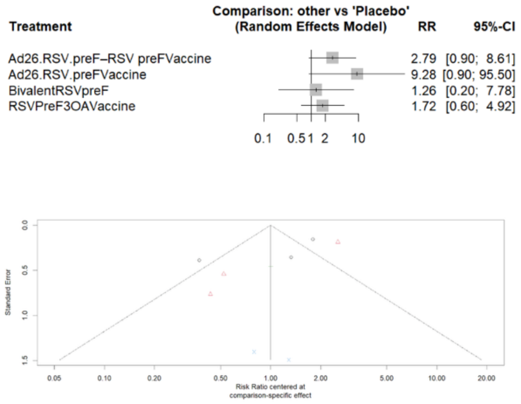
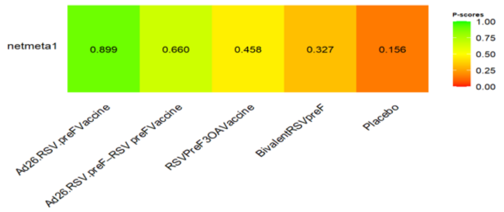


Figure 6. Forest AE and Funnel Plot

For the safety profile, we conducted a grade 3 adverse event for the outcome. The analysis indicated that no intervention reached statistical significance regarding the induction of Grade 3 adverse events. The Ad26.RSV.preF exhibited the highest risk estimate (RR: 9.28; 95% CI: 0.9–95.5), representing the most unfavorable safety profile within the network. That data indicate that Ad26.RSV.preF is more likely to have a 9,28-fold increased risk of developing grade 3 adverse events compared to the placebo group. The Ad26.RSV.preF–RSV preF Protein Vaccine ranked second in risk magnitude RR: 2.79 (95% CI: 0.90–8.61), followed by the RSVPreF3 OA RR: 1.72 (95% CI: 0.60–4.92). Conversely, Bivalent RSVpreF Vaccine demonstrated the most favorable safety profile RR: 1.26 (95% CI: 0.20–7.78). Comprehensive comparisons are delineated in **Figure 6**. Notably, substantial heterogeneity (I^2 = 80.9%) was observed globally. Due to limited network connectivity, the specific origins of this inconsistency remain indeterminate. regarding publication bias, while funnel plot inspection suggested asymmetry, Egger's regression did not reach statistical significance (ER: -2.003; p= 0.0629), indicating insufficient evidence to confirm publication bias.



Forest 7. P-scores SAE

Ranking analysis established the Ad26.RSV.preF as the superior intervention (P-score: 0.899). The Ad26.RSV.preF–RSV preF Protein Vaccine occupied the second tier (P-score: 0.660), followed by the RSVPreF3 OA (P-score: 0.458) and the Bivalent RSVpreF Vaccine (P-score: 0.327); Placebo demonstrated the least favorable outcome (P-score: 0.156). The marked disparity between Ad26.RSV.preF and the Ad26.RSV.preF–RSV preF Protein Vaccine P-score suggest a substantial clinical implication, emphasizing Ad26.RSV.preF as the most effective vaccine in terms of protecting from grade 3 adverse event in this network meta-analysis.

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Subgroup Analysis

Table 2. Subgroup Analysis

Subgroup	Intervention	RR (95% CI)	p-value	Heterogeneity (I^2)
Older Adults	Ad26.RSV.preF–RSV preF Vaccine	0.25 [0.14; 0.44]	< 0.0001	44.80%
	Bivalent RSV preF	0.37 [0.19; 0.73]	0.0039	
	RSVPreF3 OA Vaccine	0.29 [0.21; 0.41]	< 0.0001	
Adults	Ad26.RSV.preF Vaccine	0.31 [0.06; 1.47]	0.1409	58.90%
	Bivalent RSV preF	0.25 [0.03; 1.93]	0.184	

Subgroup analysis stratified by study population was performed to address heterogeneity. Among older adults, Ad26.RSV.preF conferred the strongest protection (RR 0.25; 95% CI: 0.14–0.45), outperforming RSVPreF3 OA (RR 0.29 [0.21; 0.41]) and Bivalent RSV preF (RR 0.37 [0.19; 0.73]) amidst moderate heterogeneity (I^2 = 44.8%). In contrast, the adult subgroup (I^2 = 58.9%) showed no statistically significant efficacy for either Ad26.RSV.preF (RR 0.31 [0.06; 1.47]) or Bivalent RSV preF (RR 0.25 [0.03; 1.93]). Although a reduction in heterogeneity was not observed, this subgroup analysis was performed to enhance the generalizability of the findings across diverse populations.

GRADE Assessment

Given the presence of closed loops, the absence of wide mean differences in serious adverse events (SAEs), and the moderate heterogeneity observed in both efficacy and SAE outcomes, we conducted a GRADE assessment to systematically evaluate the certainty of the evidence. The certainty of evidence regarding efficacy outcomes ranged from very low to high, with ratings downgraded due to three primary limitations.

First, incoherence and imprecision were identified, as the Risk Ratio confidence intervals were sufficiently wide to span the line of no effect. Second, heterogeneity confounded the Ad26.RSV.preF Vaccine versus Placebo comparison, driven by demographic disparities between the Sadoff et al. (2022) and Stuart et al. (2022) cohorts. Third, reporting bias compromised Ad26.RSV.preF–RSV preF Protein Vaccine comparisons (Tamura et al., 2025; Falsey et al., 2024), as data for RSV-related respiratory distress were presented exclusively as percentages rather than absolute event counts. High certainty of evidence found in Ad26.RSV.preF–RSV preF Protein Vaccine:Placebo and

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BivalentRSVpreF:Placebo comparison.

Moderate certainty of evidence found in Ad26.RSV.preF–RSV preFVaccine:Placebo comparison. All remaining comparison was valued at low or very low certainty of evidence. A comprehensive overview of these assessments is available in **Supplementary Files 1**. All comparisons of AE outcome was evaluated as very low certainty of evidence. The certainty of evidence for all AE outcomes was assessed as very low. Specifically, the rating for Grade 3 adverse events was downgraded due to serious imprecision and inconsistency in the effect estimates.

In our study, Ad26.RSV.preF-RSVpreF protein vaccine demonstrated the strongest efficacy signal for reducing RSV-associated respiratory distress. The vector and double protein regimen yielded a pooled risk ratio of 0.25, with statistically significant precision (95% CI 0.15–0.45), indicating a substantial reduction in respiratory-distress events compared with placebo. Following this, the RSVPref3 OA vaccine exhibited a comparable effect, with a Risk Ratio of 0.26 (95% CI: 0.21-0.42), likewise indicating a statistically significant reduction in respiratory-distress outcomes. These results introduce new evidence to previous meta analyses, which is the vaccine comparative ranking.

While comparative risk ratios describe clinical protection, immunogenicity must be interpreted through the underlying structural drivers of response, including antigen format, delivery platform, and adjuvant design, each of which determines the magnitude, phenotype, and durability of the vaccine-induced immune profile. Both vaccines, Ad26.RSV.preF–RSV preF and RSVPreF3 OA, generate rapid and high neutralizing-antibody responses that remain elevated through the first season. Their durability differs in a meaningful way. Revaccination with RSVPreF3 OA in the following year does not improve clinical protection, while a single dose of Ad26.RSV.preF–RSV preF maintains efficacy across three seasons, consistent with more durable Th1-dominant CD4 and CD8 memory.[28,30]

Both platforms avoid the Th2-skewed responses associated with historical vaccine failures. The Ad26 vector drives a strong IFN-γ and IL-2 profile, and AS01E provides comparable Th1-directing effects for the protein-based regimen. In older adults, Ad26.RSV.preF–RSV preF preserves antibody and cellular responses even in individuals over 75 years of age.[23] RSVPreF3 OA relies heavily on AS01E to offset immunosenescence, and although boosting restores titers, clinical protection still declines across seasons. Taken together, the protein–adjuvant platform demonstrates strong initial immunogenicity but limited durability, whereas the vector-based regimen establishes more sustained cellular memory and longer-lasting protection.[24-27,28,30]

Grade 3 adverse events were uncommon across all included trials, yet their occurrence remains analytically relevant because even infrequent severe events inform the safety margin and comparative tolerability of all regimens. Safety profile analysis indicated that Ad26.RSV.preF is more likely to have a 9,28-fold increased risk of developing grade 3 adverse events compared to the placebo group (RR: 9.28; 95% CI: 0.9–95.5). However, current analyses were proven to be statistically insignificant and need to be interpreted cautiously. Evidence synthesis narrates the adverse events as typical vaccine reactogenicity, not a unique safety signal.

Regardless, our article has some limitations that need to be addressed. This network meta-analysis is constrained by the absence of direct head-to-head comparisons between vaccine platforms, which limits inference to indirect estimates. Heterogeneity across study populations, including differences in age structure, comorbidity burden, and regional RSV circulation, further reduces the interpretability of pooled effects.

The analysis integrates data from large, multicenter randomized trials conducted across multiple global regions, yielding a substantial combined sample size. Methodologic rigor is supported by compliance with PRISMA-NMA standards and by the study's high-certainty ratings under the GRADE framework and low risk of bias by RoB 2.0.

4. CONCLUSION

Among available RSV vaccine platforms, Ad26.RSV.preF–RSV preF Protein Vaccine demonstrates the highest efficacy and effectivity profile, although a comprehensive understanding of comparative safety remains limited by sparse Grade 3 adverse-event data. Direct comparative trials between platforms are still required to validate these findings and establish definitive clinical guidance.

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Appendix 1. Study Characteristic

Author, Year	Research Center	Study Design	Population (Mean ± SD)	Intervention	Control	Duration & Frequencies	Highlighted Findings
Sadoff et al., 2022	United Kingdom	RCT	Healthy adult aged 18–50 years (30.52 ± 6.28)	Ad26.RSV.preF (n=27)	Placebo (n= 26)	Single Dose	Ad26.RSV.preF drove viral replication down to nearly undetectable levels, generated a rapid and pronounced rise in antibody titers within 28 days, and leveraged the prefusion-F antigen together with the Ad26 vector to elicit a highly robust neutralizing immune response.
Schmoele-Thoma et al., 2022	United Kingdom	RCT	Healthy adult aged 18–50 years (29.5 ± 7.25)	Bivalent RSVpreF (n=31)	Placebo (n=31)	Single Dose	RSVpreF reduced viral replication to undetectable levels in culture, and by day 28 it produced approximately 20-fold increases in neutralizing antibody titers compared with placebo.
Stuart et al., 2022	United States, Finland, United Kingdom	RCT	Healthy adult aged 18–50 years (36.75 ± 5) Children aged 12–24 months (17.75 ± 2.5)	Ad26.RSV.preF (n=24)	Placebo (n=12)	Single Dose	Ad26.RSV.preF drives a safe, antiviral Th1-dominant T-cell response and avoids the dangerous Th2 response that caused past RSV vaccine failures.
Falsey et al., 2023	United States	RCT	Adults ≥ 65 years in good or stable health (76.3 ± 8.3)	Ad26.RSV.preF–RSV preF protein (n=2801)	Placebo (n=2791)	Single Dose	Ad26.RSV.preF–RSV preF protein vaccine generated robust humoral and cellular immune responses, with significant increases in neutralizing antibodies, serum preF IgG, and RSV-F–specific T-cell responses that remained above baseline for at least six months. Importantly, the cellular responses may be especially protective in older adults, who typically have age-related declines in T-cell immunity.

Ison et al., 2023	19 countries across Africa, Asia, Australia, Europe, and North America.	RCT	Adults ≥ 60 years (69.6 ± 6.5)	RSVPreF3 OA (n=6228)	Placebo (n=12503)	Single Dose with Revaccination 1 year later	The RSVPreF3 OA vaccine showed 67.2% efficacy in preventing RSV-LRTD with a single dose over two seasons, and 78.8% efficacy against severe RSV-LRTD. Revaccination a year later did not significantly increase efficacy, showing similar results (67.1% against RSV-LRTD). The vaccine was well tolerated, with a safety profile similar to the first dose
Papi et al., 2023	17 countries in Africa, Asia, Australia, Europe, and North America.	RCT	Adults ≥ 60 years (69.6 ± 6.5)	RSVPreF3 OA (n=12466)	Placebo (n=12494)	Single Dose	The RSVPreF3 OA vaccine showed 67.2% efficacy in preventing RSV-LRTD with a single dose over two seasons, and 78.8% efficacy against severe RSV-LRTD. Revaccination a year later did not significantly increase efficacy, showing similar results (67.1% against RSV-LRTD). The vaccine was well tolerated, with a safety profile similar to the first dose
Walsh et al., 2023	7 countries across Africa, Asia, Europe, North America, and South America.	RCT	Healthy Adults ≥ 60 years with stable chronic conditions (68.3 ± 6.16)	Bivalent RSVpreF (n=16306)	Placebo (n=16308)	Single Dose	RSVpreF generated a rapid and pronounced rise in neutralizing antibodies after just one dose, with older adults showing substantial boosts in both RSV-A and RSV-B titers. This demonstrates that the prefusion-F antigen retains strong immunogenicity even in individuals aged ≥60 years, a group typically affected by age-related declines in immune responsiveness.
Falsey et al., 2024	United States	RCT	Adults ≥ 65 years in good or stable health (71.0 ± 8.3)	Ad26.RSV.preF–RSV preF protein (n=2891)	Placebo (n=2891)	Single Dose	The study demonstrates that T-cell responses induced by the Ad26.RSV.preF–RSV preF protein vaccine remain elevated for up to 1.5 years after vaccination, supporting its

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							long-lasting protective effect against RSV. Evidence indicates that CD4+, CD8+, and Th1 memory T-cells are essential for effective RSV immunity, and the vaccine successfully stimulated these responses—CD4+ T-cell responses in 63.6% of participants and CD8+ responses in 27.3% at day 169. Importantly, the immune profile showed a Th1-dominant signature, which is associated with antiviral defense and avoids the harmful Th2-biased responses previously linked to enhanced respiratory disease in older RSV vaccine attempts. This sustained, Th1-oriented cellular immunity provides strong mechanistic support for the vaccine's durable protection across multiple RSV seasons.
Ison et al., 2025	18 countries across Africa, Asia, Australia, Europe, and North America.	RCT	Healthy Adults ≥ 60 years with medically stable (69.5 ± 6.5)	RSVPreF3 OA (n=12468)	Placebo (n=12468)	Single Dose	RSVPreF3 OA vaccine demonstrated its efficacy over three RSV seasons in older adults (aged 60 and above). A single dose of the vaccine provided a cumulative efficacy of 62.9% against RSV-related lower respiratory tract disease (RSV-LRTD) over the three seasons, with efficacy observed against both RSV A (69.8%) and RSV B (58.6%). A second dose administered one year after the first did not significantly improve efficacy, which remained within the same range (67.8%) as a single dose. The vaccine showed consistent protection across subgroups, including participants with pre-existing medical conditions and those considered pre-frail. Although efficacy

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							decreased over time, with the lowest efficacy seen in the third season (48.0%), it remained higher compared to the placebo group. The vaccine had an acceptable safety profile, with serious adverse events and fatalities equally distributed between the vaccine and placebo group
Tamura et al., 2025	Japan	RCT	Adults aged ≥60 years who may have medically treated underlying conditions (70 ± 5.2) Adults aged 20–59 years with a chronic heart or lung disease (70 ± 5.2)	Ad26.RSV.preF–RSV preF protein (n=996)	Placebo (n=1007)	Single Dose	Immunogenicity followed the expected viral-vector pattern: younger adults generated the highest peak antibody levels, but older adults still produced strong neutralizing responses, demonstrating that the vaccine remains effective even in the context of age-related immune decline.