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Establishing Immune Correlates of Protection Against Respiratory Syncytial Virus Infection to Accelerate Vaccine Development: A Model-Based Meta-Analysis

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ABSTRACT

The objectives of this study were to quantify the relationship between vaccine-induced immunogenicity responses and the protection against respiratory syncytial virus (RSV) infection-related clinical outcomes, and to evaluate immunogenicity as a surrogate marker for vaccine efficacy (VE) to accelerate RSV vaccine development. Serum neutralizing activity (SNA) and cell-mediated immunity (CMI) may serve as surrogate markers for the protection against RSV infection and are evaluated as immunogenicity endpoints in clinical trials of RSV vaccine candidates. Two meta-analytical approaches were applied to data from seven randomized placebo-controlled clinical trials that investigated RSV vaccines in older adults. The primary analysis examined the relationship between SNA and VE across three different clinical severity levels: (1) acute respiratory infection, (2) RSV lower respiratory tract disease (LRTD) with ≥2 clinical symptoms, and (3) RSV LRTD with ≥3 clinical symptoms (LRTD 3+). Furthermore, the additional contribution of CMI to VE, after accounting for the effect of SNA, was explored in a secondary analysis. The results demonstrated a positive correlation between SNA and VE across three clinical severity levels. Higher CMI was associated with higher VE specifically for RSV LRTD 3+, the most severe clinical level, suggesting that CMI may be correlated with additional clinical benefits in mitigating the severity of RSV infection. These findings provided preliminary evidence for immune correlates of protection against RSV infection and may aid in accelerating the development of new RSV vaccines.

1 | Introduction

Vaccine development, particularly in the late stages, is time-consuming and expensive. The probability of success that a vaccine would progress from phase 2 studies to licensure within 10 years was 10.0%, with an average timeline of 4.4 years from phase 2 studies to approval [1]. In general, a phase 3 field study to evaluate clinical efficacy responses requires a huge amount of time and cost given that a phase 3 field study of respiratory syncytial virus (RSV) vaccines requires tens of thousands of participants, which may disincentivize vaccine development from pharmaceutical industries [2–4]. Recently, the utilization of immune Correlates of Protection (CoP) has been discussed to efficiently accelerate vaccine clinical development [5]. A CoP is broadly defined as an immune marker that predicts vaccine-induced efficacy against specific clinical disease endpoints [5]. Establishing a CoP may facilitate an immunobridging strategy, allowing for indication expansion or new approval based on immunogenicity data without necessitating a large-scale phase 3 field study. Immunobridging strategies have been employed to demonstrate vaccine-induced efficacy using immune markers for conditions not investigated

Study Highlights

- What is the current knowledge on the topic?
  - Although immune correlates of protection (CoP) against respiratory syncytial virus (RSV) infection have not been well established, immunogenicity markers, including serum neutralizing activity (SNA) and cell-mediated immunity (CMI), have been associated with decreased infection rates and/or decreased disease severity of RSV infection.
- What question did this study address?
  - This study aimed to quantify the relationships between immunogenicity responses induced by RSV vaccines and the protection against RSV infection-related clinical outcomes, based on a meta-analytical approach.
- What does this study add to our knowledge?
  - Our findings indicated that SNA induced by various vaccines correlated with vaccine efficacy across three different clinical severity levels, suggesting CoP against RSV infection. CMI may be correlated with additional clinical benefit in mitigating the severity of RSV infection.
- How might this change drug discovery, development, and/or therapeutics?
  - The application of the meta-analytical approach can enhance the understanding of CoP and accelerate the development of future vaccines.

in phase 3 field studies, such as different demographic groups [6, 7]. Notably, an immunobridging strategy that utilized neutralizing antibody titers as the primary endpoint was implemented for the approval of new vaccines against SARS-CoV-2 [8, 9]. The background to this is that meta-analyses have revealed that neutralizing antibody titers following SARS-CoV-2 vaccination correlate with the effectiveness of preventing COVID-19 infection, which primarily affects the respiratory system, similar to RSV infection [10, 11].

RSV is a common contagious virus that causes infections of the respiratory tract and can cause more severe disease such as pneumonia in infants and young children as well as older adults [12, 13]. Since the initial failure of a formalin-inactivated RSV vaccine in the 1960s, there have been various research initiatives aimed at developing RSV vaccines, including protein-based, live-attenuated or chimeric, recombinant vector-based, and nucleic acid-based vaccines [14, 15]. Advancements in understanding of the RSV fusion protein have facilitated rapid progress in the development of RSV vaccines. In 2023–2024, the Food and Drug Administration (FDA) approved two subunit vaccines, Arexvy (RSVPreF3) and Abrysvo (RSVpreF), as well as an mRNA vaccine, Mresvia (mRNA-1345) [16–18]. A recent review indicated that there are currently 24 vaccines in the clinical stage of development, including the licensed vaccines [19]. Some evidence suggests that both humoral and cell-mediated immunity (CMI), such as serum neutralizing activity (SNA), interferon-gamma (IFN-γ), and cluster of differentiation 4 glycoprotein $(CD4)^+$ T cells, have been associated with decreased infection rate (IR) and/or decreased disease severity, and may serve as surrogate markers for the protection of RSV infection [20–22]. These immunogenicity markers are evaluated as immunogenicity endpoints in clinical trials of RSV vaccine candidates. A quantitative understanding of the relationship between immunogenicity and vaccine efficacy (VE) has the potential to mitigate the risks associated with running a phase 3 study [2–4]. While an RSV vaccine candidate, VN-0200, was in development and undergoing a phase 2 dose finding study, a model-based meta-analysis (MBMA) was designed to elucidate the relationship between immunogenicity and vaccine efficacy (VE) and to leverage this knowledge in the immunobridging strategy for VN-0200. This phase 2 study investigated the dose–response relationship for immunogenicity of different dose combinations of VAGA-9001a as the antigen and an MABH-9002b adjuvant in elderly subjects [23].

The objectives of this meta-analysis were to quantify the relationship between immunogenicity responses and the protection against RSV infection-related clinical outcomes using publicly available aggregate-level data and to evaluate immunogenicity as a surrogate marker for VE to accelerate RSV vaccine development.

2 | Methods

2.1 | Literature Search and Data Selection

A systematic literature search was conducted to develop a clinical outcomes database of clinical trials that investigated the immunogenicity or systemic protection of currently approved or in development vaccines against RSV. Relevant sources were identified with studies from PubMed and the ClinicalTrials.gov registry for which results were published, as well as the FDA or the European Medicines Agency briefing document and company briefing documents and press releases. An analysis dataset was constructed from a subset of the clinical outcomes database. Selected studies included large scale randomized placebo-controlled trials of phase 2b and later in older adults (≥ 60 years). Early-phase clinical trials were excluded due to small sample size and the lack of reported VE. VE was defined as the relative risk of IR in vaccinated and unvaccinated groups: $VE = (1 - IR_{vaccinated}/IR_{unvaccinated}) \times 100$. IR was reported by clinical severity level, and VE was categorized as overall virus positive, RSV acute respiratory infection (ARI), RSV lower respiratory tract disease (LRTD), RSV-LRTD with ≥ 2 clinical symptoms (LRTD 2+) and RSV-LRTD with ≥ 3 clinical symptoms (LRTD 3+). Immunogenicity endpoints, including SNA and CMI (IFN-γ and $CD4^+$ T cells), were captured when reported. For studies that did not report both SNA and CMI, these data were imputed by "cross-matching" with the studies that were conducted under the same sponsor with similar design, similar study population, and the same intervention. This cross-matching expanded the analysis dataset for the estimation of the relationships between immunogenicity response and clinical efficacy. Immunogenicity responses assessed approximately 28 days after the single dose were used for the analysis, as this time point is commonly employed for evaluating immunogenicity following vaccination. In case where different RSV subtypes were reported, "RSV subtype A (RSV-A) and/or RSV subtype B (RSV-B)" was selected for

efficacy (VE) endpoints. Both RSV-A and RSV-B SNA were considered for immunogenicity responses. A detailed explanation of literature search and data selection were provided in the Supporting Information.

2.2 | Analysis Methodology

Two types of analyses were performed: (1) the primary analysis to characterize the relationship between SNA and VE, and (2) a secondary exploratory analysis to investigate the additional contribution of CMI to VE, after accounting for the effect of SNA.

2.2.1 | Primary Analysis

The primary analysis describing the relationship between SNA and VE was conducted using a multivariate linear mixed-effects model weighted by the standard error (SE) of VE, implemented in the nlme R package. The VE values were transformed into a negative effect size, which was expressed as the sum of the transformed intercept and slope of SNA, as shown in the following equations.

$$-\log\left(1-\frac{\mathrm{VE}_{ik}}{100\,\%}\right)=\mathrm{Intercept}_k+\mathrm{Slope}_k\times\mathrm{SNA}_i+\eta_i+\varepsilon_{ik} \tag{1}$$

$$\mathrm{SNA}_i=\log_2\left(\mathrm{SNA}_{\mathrm{vaccine},i}\right)-\log_2\left(\mathrm{SNA}_{\mathrm{placebo},i}\right) \tag{2}$$

VE_{ik} is the vaccine efficacy expressed in percent of study i and clinical severity level k. $\mathrm{Intercept}_k$ is the typical VE at clinical severity level k at equal SNA titer in the active and placebo arms. Slope_k is the relationship between the transformed VE and SNA_i at clinical severity level k, where the placebo-corrected SNA, SNA_i, is the difference in SNA on a log2 scale between the vaccine and placebo arm in study i. In the primary analysis, RSV-A SNA values were utilized. η_i is between-trial variability in study i estimated with an additive normal distribution. ε_{ik} is residual variability at clinical severity level k in study i estimated with an additive normal distribution. Residual error was weighted by the SE of VE at clinical severity level k in the active arm j of study i. The SE was translated using the Delta method for the linear model. The VE values were back-transformed to the original scale using the following formula: VE = 100 × (1 − exp[−(Intercept + Slope × SNA)]). Two sensitivity analyses were performed. A leave-one-out analysis was performed to assess the stability of the results by sequential omitting each included studies. Additionally, RSV-B SNA values were used instead of RSV-A to assess the impact of different RSV subtype. Parameter estimates, SE, and 95% confidence intervals (CI) were reported, with statistical significance defined as $p < 0.05$.

2.2.2 | Secondary Analysis

The additional contribution of CMI to VE, after accounting for the effect of SNA was investigated in an exploratory manner. Previous studies have indicated that CMI is associated with decreased severity of RSV infection, which served as the hypothesis for our analysis [21, 22]. In this context, the previously described linear mixed-effects model was extended by incorporating the slope of CMI, as shown in the following equations. Due to the limited number of $CD4^+$ T cell data available, only IFN-γ data was used in the analysis.

$$\begin{aligned}-\log\left(1-\frac{\mathrm{VE}_{ik}}{100\%}\right)&=\mathrm{Intercept}_k\\&+\mathrm{Slope}_k\times\mathrm{SNA}_i+\mathrm{Slope}_{ifn,k}\times\mathrm{CMI}_i+\eta_i+\varepsilon_{ik}\end{aligned} \tag{3}$$

$$\mathrm{CMI}_i=\ln\left(\text{IFN-}\gamma_{\mathrm{vaccine},i}\right)-\ln\left(\text{IFN-}\gamma_{\mathrm{placebo},i}\right) \tag{4}$$

$\mathrm{Slope}_{\mathrm{IFN},k}$ is the relationship between the transformed VE and CMI_i at clinical severity level k, where the placebo-corrected CMI, CMI_i, is the difference in IFN-γ response on a natural logarithm scale between the vaccine and placebo arm in study i.

2.2.3 | Imputation Approaches

For the analyses using RSV-B SNA and IFN-γ data, complete case analysis (CCA) and multiple imputation (MI) were conducted to treat missing data. Multiple imputation by chained equations was performed using the mice R package. The missing data imputation using cross-matching, as described above, was performed prior to the MI procedure. Therefore, the data obtained through cross-matching were treated as observed data. In the imputation model, RSV-A SNA, RSV-B SNA, IFN-γ, and the three severity levels of VE were included as predictors. $CD4^+$ T cell was excluded due to the limited number of available data. Imputed values for outcome variables in the analysis model (i.e., VE values) were excluded post imputation under "multiple imputation then deletion" approach [24]. We generated 50 imputed datasets to ensure stable estimates. For the imputation model, we preferred Bayesian linear regression based on method = "norm" over method = "norm.nob" because it accounts for both parameter uncertainty and residual error, which is advantageous especially in small samples [25]. Predictive mean matching based on method = "pmm" was considered less suitable as it was difficult to find good matches in small samples [26]. The model parameters were estimated in each imputed dataset and pooled using Rubin's rules, with 95% CI calculated using the t-distribution and degrees of freedom as defined by Rubin [27].

3 | Results

3.1 | Overview of Analysis Dataset

A total of seven vaccine efficacy studies were included in the analysis dataset [2–4, 28–31]. An overview of the analysis dataset is provided in Tables 1 and 2. The reported VE values were categorized based on the endpoint definition in each study. Since viral positive and RSV-LRTD outcomes were reported in only 1 and 2 studies, respectively, these endpoints were excluded from the analysis. The meta-analysis focused on three VE severity levels: RSV-ARI, RSV-LRTD 2+, and RSV-LRTD 3+. All studies were conducted with a single dose of the tested vaccine or placebo and covered a single RSV season (from fall

TABLE 1 | Summary of included studies.

Vaccines	Study	Population	Control	Participants	Clinical outcomes	Immunogenicity outcomes
RSVpreF3 120 μg with AS01E adjuvant	ARreSVi-006 [2] (NCT04886596)	Older adults (≥60)	Placebo	24,966	RSV-ARI[a] RSV-LRTI RSV-LRTD 2+ RSV-LRTD 3+[b]	SNA (RSV-A, RSV-B) $CD4^+$ T cells [32]
mRNA-1345 50 μg	ConquerRSV [3] (NCT05127434)	Older adults (≥60)	Placebo	35,541	RSV-ARI RSV-LRTD 2+ RSV-LRTD 3+	SNA (RSV-A, RSV-B) [33]
Ad26 RSV preF 1×10^{11} viral particles with RSV preF 150 μg	CYPRESS [28] (NCT03982199)	Older adults (≥65)	Placebo	5782	RSV-ARI[c] RSV-LRTD 2+ RSV-LRTD 3+	SNA (RSV-A, RSV-B) IFN-γ
MEDI-7510 120 μg with glucopyranosyl lipid adjuvant	D4420C00005 [29] (NCT02508194)	Older adults (≥60)	Placebo	1900	Virus positive RSV-ARI RSV-LRTI RSV-LRTD 2+	SNA (RSV-A) [34] IFN-γ [34]
RSVpreF 120 μg	RENOIR [4] (NCT05035212)	Older adults (≥60)	Placebo	34,284	RSV-ARI RSV-LRTD 2+ RSV-LRTD 3+	SNA (RSV-A, RSV-B) [35] IFN-γ[e] [36], $CD4^+$ T cells[e] [36]
RSV F 135 μg	Resolve [30] (NCT02608502)	Older adults (≥60)	Placebo	11,856	RSV-ARI RSV-LRTD 3+[d]	SNA (RSV-A, RSV-B)[f] [37]
MVA-BN-RSV 3×10^8 infectious units	VANIR [31] (NCT05238025)	Older adults (≥60)	Placebo	18,348	RSV-ARI RSV-LRTD 2+ RSV-LRTD 3+	SNA (RSV-A, RSV-B) IFN-γ[g] [38]

Abbreviations: ARI, acute respiratory infection; CD4, cluster of differentiation 4; IFN-γ, interferon-gamma; LRTD, lower respiratory tract disease; LRTD 2+, LRTD with ≥2 clinical symptoms; LRTD 3+, LRTD with ≥3 clinical symptoms; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; RSV-A, RSV subtype A; RSV-B, RSV subtype B; SNA, serum neutralizing activity.

[a]RSV-ARI ≥2 symptoms in AReSVi-006 study was lumped as RSV-ARI.

[b]RSV-severe LRTI in AReSVi-006 study defined as at least two lower respiratory signs or accessed as assessed as severe by the investigator was lumped as RSV-LRTD 3+.

[c]Case definition 3 in CYPRESS study defined as either two or more symptoms of LRTI or one or more symptoms of LRTI plus at least one systemic symptom. Case definition 3 captured all RT-PCR–confirmed RSV-mediated ARI in this trial, so it was lumped as RSV-ARI.

[d]RSV-moderate–severe LRTI in Resolve study was considered as part of RSV-LRTD 3+.

[e]IFN-γ and $CD4^+$ response of 120 μg without adjuvant arm in RENOIR study was cross-matched from 120 μg arm with adjuvant in Phase 1/2 study, which mentioned that no difference in T-cell response between dose levels or with and without CpG/$Al(OH)_3$ in phase 1/2 results.

[f]135 μg arm in Resolve study was matched from 90 μg arm in phase 1 study, and dose dependent response was not observed in phase 1 study.

[g]3×10^8 infectious units/0.5 mL was matched from 5×10^8 infectious units/0.5 mL in phase 1 study as most close dose.

to the end of spring). Immunogenicity endpoints were derived from vaccine efficacy studies or cross-matched from earlier-phase studies with similar study populations and interventions [32–38]. RSV-A SNA data was available for all studies, whereas RSV-B SNA data was missing in one study and IFN-γ response was missing in three studies. Only two studies reported or could be cross matched for $CD4^+$ T cells data.

3.2 | Relationship Between SNA and VE

A total of 19 VE values across seven studies were included in the analysis. The results of the analysis describing the relationship between RSV-A SNA and VE are presented in Figure 1. This analysis demonstrated that higher RSV-A SNA levels were associated with increased VE across three different clinical severity levels. The final parameter estimates and goodness-of-fit plots are provided in Table 3 and Figure S11, respectively. The final model included three clinical severity-specific slopes and intercepts. The SNA slopes were statistically significant. Intercepts represented the VE when SNA levels were equal between vaccinated and placebo groups. In this case, similar infection rates in both groups would result in theoretical VE close to zero, which explains the lack of statistical significance of the intercept parameters. As shown in Figure 1, the overlaid observed VE and the final model predictions indicated that the model adequately described the data for RSV-ARI and RSV-LRTD 3+, although some underprediction was observed for RSV-LRTD 2+. Subsequently, RSV-B SNA values were

TABLE 2 | Summary of analysis dataset.

VE Study	RSV-ARI (%)[a]	RSV-LRTD2+ (%)[a]	RSV-LRTD3+ (%)[a]	RSV-A SNA[b]	RSV-B SNA[b]	IFN-γ[b]	$CD4^+$ T cells[b]
AReSVi-006	71.7 [56.2, 82.3]	82.6 [57.9, 94.1]	94.1 [62.4, 99.9]	10.7	8.1	—	8.3
ConquerRSV	68.4 [50.9, 79.7]	83.7 [66.1, 92.2]	82.4 [34.8, 95.3]	7.7	9.8	—	—
CYPRESS	69.8 [43.7, 84.7]	75.0 [50.1, 88.5]	80.0 [52.2, 92.9]	13.0	10.3	12.8	—
D4420C00005	−7.1 [−106.9, 44.3]	−36.9 [−188.2, 33.5]	—	2.5	—	9.0	—
RENOIR	62.1 [37.1, 77.9]	66.7 [28.8, 85.8]	85.7 [32.0, 98.7]	13.9	12.8	20.6	2.5
Resolve	12.6 [−14.0, 33.0]	—	−7.9 [−84.0, 37.0]	1.6	1.4	—	—
VANIR	48.8 [25.8, 64.7]	59.0 [34.7, 74.3]	42.9 [−16.1, 71.9]	1.6	1.5	3.5	—

Abbreviations: ARI, acute respiratory infection; CD4, cluster of differentiation 4; IFN-γ, interferon-gamma; LRTD, lower respiratory tract disease; LRTD 2+, LRTD with ≥2 clinical symptoms; LRTD 3+, LRTD with ≥3 clinical symptoms; RSV, respiratory syncytial virus; RSV-A, RSV subtype A; RSV-B, RSV subtype B; SNA, serum neutralizing activity, VE, vaccine efficacy.
[a]VE values were presented as the original scale and its 95% confidence interval.
[b]Immunogenicity values were presented as the ratio to placebo on the original scale.

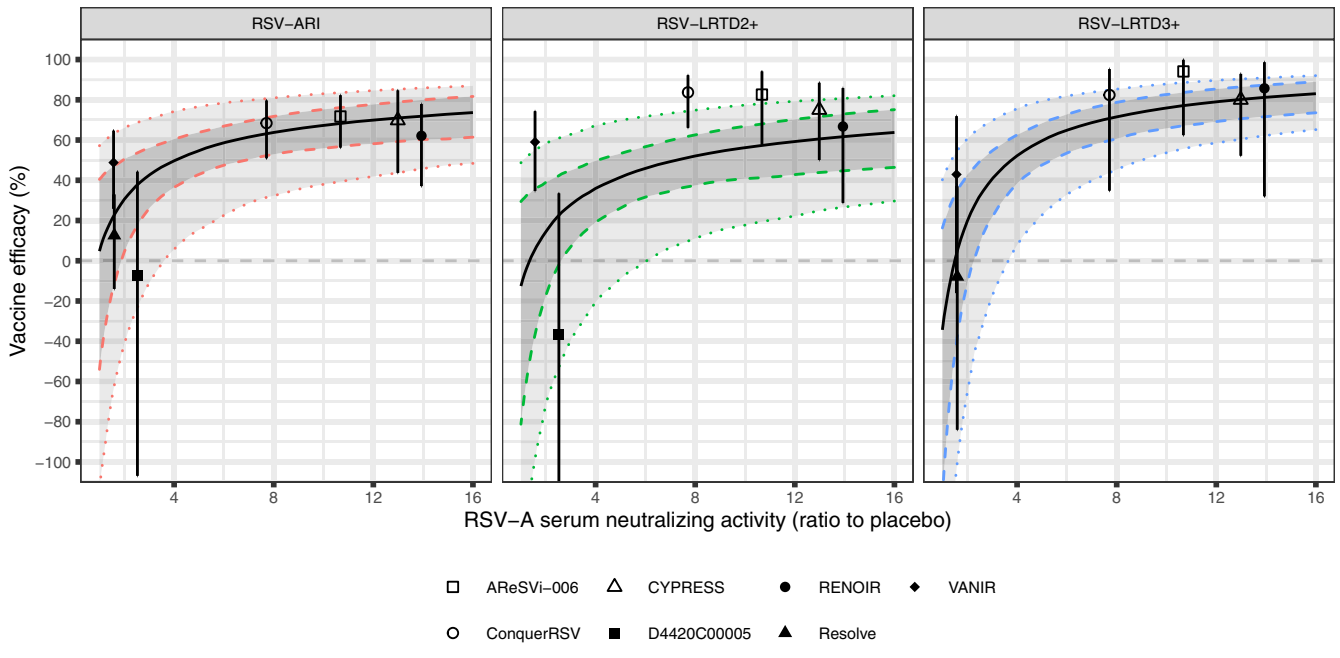

FIGURE 1 | Relationship between RSV-A serum neutralizing activity and vaccine efficacy across three different clinical severity levels based on complete case analysis. The solid, dashed, and dotted lines represent typical value, 95% confidence interval and 95% prediction interval for vaccine efficacy (VE) calculated based on the variance–covariance matrix and between-trial variability, respectively. The plots and error bars represent observed VE values and 95% confidence intervals, respectively. ARI, acute respiratory infection; LRTD, lower respiratory tract disease; LRTD 2+, LRTD with ≥2 clinical symptoms; LRTD 3+, LRTD with ≥3 clinical symptoms; RSV, respiratory syncytial virus; RSV-A, RSV subtype A.

TABLE 3 | Parameter estimates.

SNA-VE model						
RSV subtype for SNA	**RSV-A SNA**			**RSV-B SNA**		
Analysis type	**Primary analysis based on CCA approach**			**Sensitivity analysis based on MI approach**		
Parameter description	**Estimate**	**SE**	**95% CI**	**Estimate**	**SE**	**95% CI**
RSV-ARI intercept	0.047	0.296	[−0.531, 0.626]	0.108	0.280	[−0.517, 0.732]
RSV-LRTD2+ intercept	−0.121	0.296	[−0.700, 0.458]	0.115	0.343	[−0.710, 0.939]
RSV-LRTD3+ intercept	−0.293	0.297	[−0.874, 0.287]	−0.210	0.278	[−0.830, 0.409]
SNA slope on RSV-ARI	0.323	0.110	[0.109, 0.537]	0.304	0.107	[0.064, 0.544]
SNA slope on RSV-LRTD2+	0.285	0.110	[0.070, 0.501]	0.226	0.170	[−0.258, 0.710]
SNA slope on RSV-LRTD3+	0.517	0.117	[0.289, 0.745]	0.527	0.109	[0.286, 0.768]
Between-trial variability (SD)	0.315	—	—	0.339	—	—
SNA + CMI-VE model						
RSV subtype	**RSV-A SNA**			**RSV-A SNA**		
Analysis type	**CCA approach**			**MI approach**		
Parameter description	**Estimate**	**SE**	**95% CI**	**Estimate**	**SE**	**95% CI**
RSV-ARI intercept	0.150	0.509	[−0.893, 1.193]	0.051	0.247	[−0.490, 0.591]
RSV-LRTD2+ intercept	−0.069	0.509	[−1.112, 0.974]	−0.168	0.247	[−0.709, 0.373]
RSV-LRTD3+ intercept	−0.573	0.528	[−1.655, 0.509]	−0.298	0.309	[−1.02, 0.425]
SNA slope	0.256	0.185	[−0.179, 0.690]	0.321	0.091	[0.120, 0.521]
IFN-γ slope on RSV-LRTD3+	0.418	0.112	[0.189, 0.648]	0.111	0.138	[−2.00, 2.23]
Between-trial variability (SD)	0.382	—	—	0.318	—	—

Abbreviations: ARI, acute respiratory infection; CCA, complete case analysis; CI, confidence interval; CMI, cell-mediated immunity; IFN-γ, interferon-gamma; LRTD, lower respiratory tract disease; LRTD 2+, LRTD with ≥2 clinical symptoms; LRTD 3+, LRTD with ≥3 clinical symptoms; MI, multiple imputation; RSV, respiratory syncytial virus; SD, standard deviation; SE, standard error; SNA, serum neutralizing activity; VE, vaccine efficacy.

used instead of RSV-A to assess the impact of different RSV subtypes. A correlation between RSV-B SNA and VE across the three clinical severity levels was also identified, as depicted in Figure 2. The parameter estimates derived from RSV-B SNA based on the MI approach were comparable to those obtained from RSV-A SNA data (Table 3). These results aligned with the high correlation observed between RSV-A and RSV-B SNA (Figure S3). The results of the leave-one-out analysis to assess the stability of the results by sequential omission of included studies were shown in Figure S13. The exclusion of the VANIR study had a relatively significant impact on the estimated slopes for RSV-LRTD 2+. However, the estimated slopes for RSV-ARI and RSV-LRTD 3+ remained significant even when any study was omitted. Collectively, these results suggested that SNA may serve as a useful surrogate marker for VE against RSV infection. For instance, a ratio of RSV-A SNA titer to placebo of eight would correspond to an approximately 70% VE for RSV-LRTD 3+ based on the typical predictions.

3.3 | Contribution of CMI to VE

In the exploratory analysis of the additional contribution of CMI to VE, a parsimonious model based on AIC and the identifiability of parameters was considered to avoid overparameterization. A significant challenge encountered during model development was the high proportion of missing values in the IFN-γ data. Initially, the model development process was started using complete case data for both RSV-A SNA and IFN-γ. A total of 11 VE values across four studies were included in the CCA. In order to account for the possible source of bias represented by the exclusion of studies with incomplete data, the analysis was extended to all available data using MI without altering the model structure. The final model included the three clinical severity-specific intercepts, a common SNA effect to three severity levels, and the IFN-γ effect on RSV-LRTD 3+. Differences in parameter estimates were observed between MI and CCA (Table 3). The common SNA effect in MI (0.321, SE = 0.091) was comparable to the SNA effect on RSV-ARI (0.323, SE = 0.110) and RSV-LRTD2+ (0.285, SE = 0.110) in the primary SNA-VE analysis but smaller than the SNA effect on RSV-LRTD3+ (0.517, SE = 0.117) estimated in the primary analysis. The smaller effect could be explained by part of the contribution to VE for RSV-LRTD3+ being accounted for by the IFN-γ effect. The clinical severity-specific intercept and between-trial variability estimated in MI were comparable to those in the primary analysis. The simulated

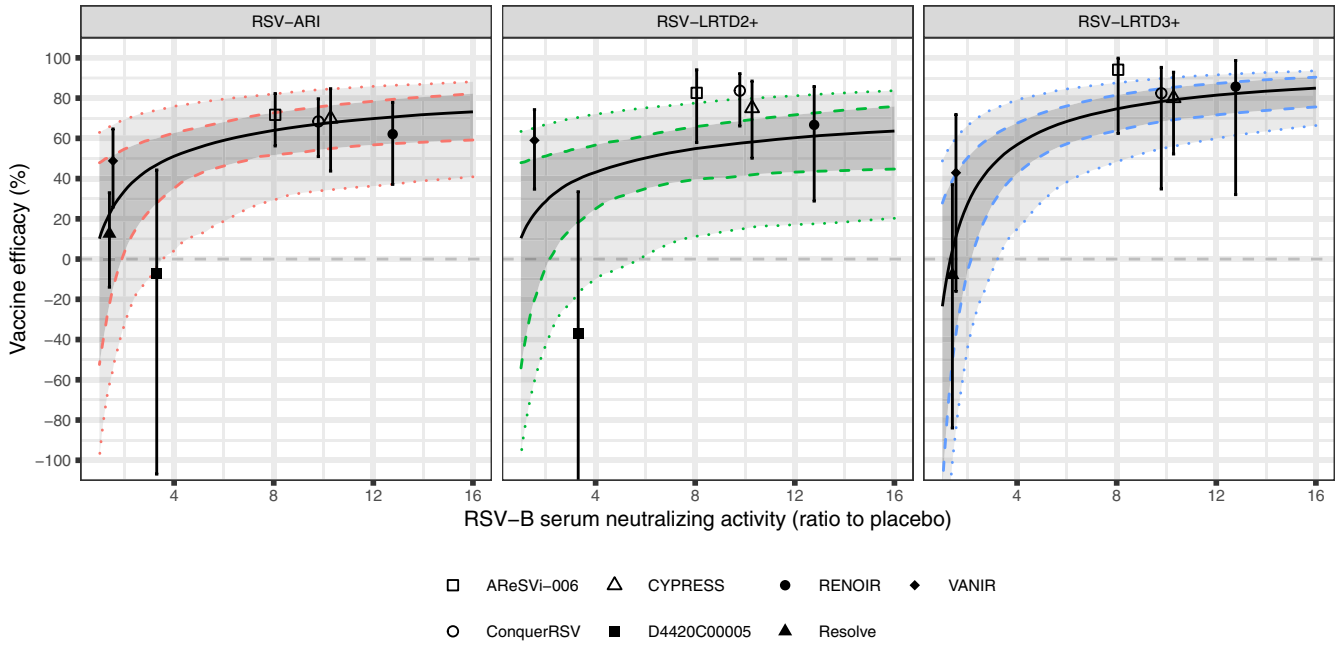

FIGURE 2 | Relationship between RSV-B serum neutralizing activity and vaccine efficacy across three different clinical severity levels based on a multiple imputation approach. The solid, dashed, and dotted lines represent typical value, 95% confidence interval and 95% prediction interval for vaccine efficacy (VE) calculated based on the variance–covariance matrix and between-trial variability, respectively. The plots and error bars represent observed VE values and 95% confidence intervals, respectively. Multiple imputation was applied to treat missing data. The median of imputed RSV-B values in D4420C00005 was plotted. ARI, acute respiratory infection; LRTD, lower respiratory tract disease; LRTD 2+, LRTD with ≥ 2 clinical symptoms; LRTD 3+, LRTD with ≥ 3 clinical symptoms; RSV, respiratory syncytial virus; RSV-B, RSV subtype B.

VE based on the MI model using RSV-A and IFN-γ was shown in Figure 3, suggesting that CMI may be correlated with additional clinical benefits in mitigating the severity of RSV infection. The simulated VE based on the CCA model is provided in the Supporting Information (Figure S9).

4 | Discussion

In this study, the relationship between immunogenicity responses induced by RSV vaccines and VE was evaluated using a meta-analytical approach. To the best of our knowledge, this study represents the first MBMA aimed at quantifying the relationship between SNA and VE in RSV while also investigating the additional contribution of CMI to VE.

We found that SNA induced by various vaccines was correlated with VE across three different clinical severity levels, thereby suggesting the presence of immune CoP against RSV infection. Numerous studies have demonstrated the relationship between RSV SNA and protection against RSV infection at the individual level [39, 40], including three recently approved RSV vaccines that were studied in older adults and exhibited promising immunogenicity responses, particularly in terms of high RSV-neutralizing antibody responses [2–4, 32]. Additionally, a previously published MBMA showed that higher RSV SNA was associated with lower RSV incidence rates across different clinical severity levels [41]. One of the advantages of MBMA lies in its ability to incorporate differences between studies, such as patient characteristics and study design, as covariates within the model structure. This enhances the comparability of results and increases the number of available studies compared to traditional meta-analyses; indeed, they developed the MBMA model using 53 studies identified through a comprehensive literature search to describe the relationship between SNA and IR for vaccines and RSV neutralizing monoclonal antibodies across a diverse range of populations. Our analysis focused on phase 2b and later randomized, placebo-controlled studies in older adults for the purpose of utilizing the immunobridging strategy for VN-0200. We used a simple meta-regression-based approach with SNA approximately 1 month after vaccination as the explanatory variable and VE, the primary efficacy endpoint, as the outcome variable. Consequently, while only seven studies were included in our MBMA, the fit-for-purpose modeling approach enhanced the transparency of the analysis and the ease of interpretation. This facilitates stakeholder understanding and makes it easier to use in decision-making. It is considered desirable for VE against confirmed severe RSV disease to exceed 70% in pediatric populations [42], and sample size for certain phase 3 field studies in older adults has been calculated under the assumption that the true VE was 70% [2, 4]. In our model predictions, VE exceeding 70% against RSV-LRTD3+ would correspond to RSV-A SNA ratio above 8. For RSV-LRTD2+, the model underpredicted VE and cannot estimate a 70% threshold within the observed SNA range, though observed VE tended to exceed 70% when the ratio was above 8. This suggests the current model may not adequately capture a steeper relationship between SNA and RSV-LRTD2+. The steeper relationships could hypothetically be described by the sigmoid Emax model; however, the limited data, especially lacking a moderate SNA ratio of 3 to 7, made applying it challenging.

The contribution of CMI to VE was investigated in an exploratory manner using a linear mixed-effects model that

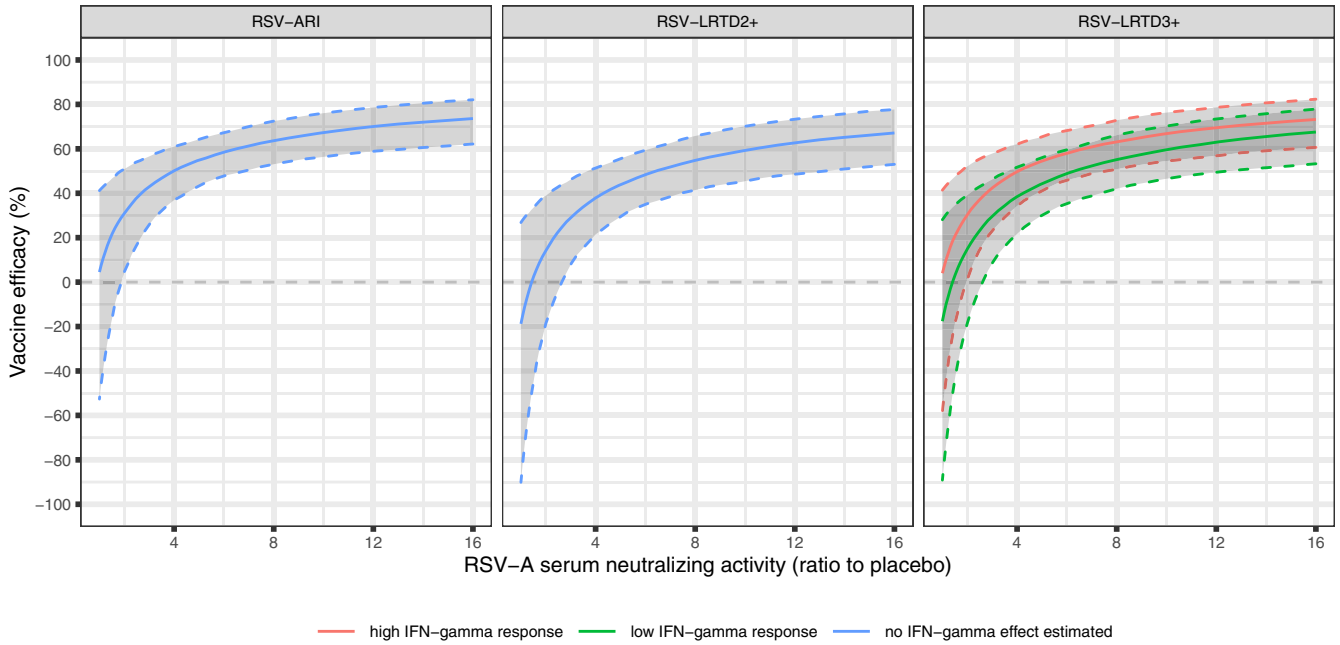

FIGURE 3 | Contribution of cell-mediated immunity to vaccine efficacy. The solid and dashed lines represent typical value and 95% confidence interval for vaccine efficacy (VE) calculated based on the variance–covariance matrix, respectively. For RSV-ARI and RSV-LRTD2+, no IFN-γ effect on VE was estimated; therefore, the simulated VE is based solely on RSV-A SNA and shown in blue shaded regions. For RSV-LRTD3+, IFN-γ effect on VE was included; therefore, VEs were simulated when the IFN-γ response (ratio to placebo) are equal to 3.5 and 20.6 (corresponding to the observed range), and are shown in green and red regions, respectively. Multiple imputation was applied to treat missing data. ARI, acute respiratory infection; LRTD, lower respiratory tract disease; LRTD 2+, LRTD with ≥2 clinical symptoms; LRTD 3+, LRTD with ≥3 clinical symptoms; RSV, respiratory syncytial virus; RSV-A, RSV subtype A.

incorporated the transformed SNA and IFN-γ data. Previous studies have indicated that CMI is associated with reduced severity of RSV infection, which served as the hypothesis for our analysis [21, 22]. In general, the protective efficacy of vaccines is mediated by inducing humoral immunity, such as neutralizing antibodies, and CMI. Neutralizing antibodies serve as a great deal of the protection against RSV infection by inhibiting the attachment and entry of the virus into host cells, suppressing viral replication and proliferation [39]. In contrast, CMI participates in clearing virus-infected cells. Specific T-cell response, a type of CMI, promotes viral elimination, supports humoral immunity, and plays a key role in reducing the severity of RSV infection [43]. Both vaccine-induced humoral immunity and CMI may jointly contribute to protection against RSV infection, and CMI may be correlated with additional clinical benefits in reducing the severity of RSV infection. For the vaccines exhibiting high IFN-γ responses, VE for RSV-LRTD3+ was found to be higher than VE for RSV-ARI and RSV-LRTD2+, which supports our analysis [4, 28]. Further clinical studies that investigate vaccines with high and low CMI response, such as a comparison of VE between adjuvanted and non-adjuvanted vaccine with the same antigen and dosage, would be helpful in validating our model.

We used MI to handle the high proportion of missing IFN-γ data. MI, which assumes data are missing at random (MAR), can reduce bias compared to CCA, which requires the stronger missing completely at random assumption [44]. It accounts for dependencies between variables by estimating the missing data using the other variables. To make the MAR assumption more plausible, the imputation model in MI included all explanatory and outcome variables. We acknowledge important limitations related to the small sample size and dataset heterogeneity that challenge the validity of MAR assumptions. The small number of observed IFN-γ data points ($n=4$) limited characterization of its distribution, challenging the MAR assumption. While D4420C0005 and Resolve showed negative VE values and differed markedly from other studies, this can be partly explained by their low SNA levels. Nonetheless, this heterogeneity raises questions about the MAR assumption, and it should be noted that the range of imputed values is comparable to or wider than the range of observed cases (Figure S7). Given these considerations, MI results should be interpreted with caution. To our knowledge, the application of MI in MBMA remains limited, and further studies would be useful [45, 46].

Beyond the limitations related to the MI approach discussed above, the most notable is the small sample size. Our analysis included 19 VE values from seven studies, a relatively small number but representing a specific and relatively robust dataset. Restricting the analysis to older adults, focusing on large-scale randomized placebo-controlled trials, and using the comparative endpoint VE may have helped reduce data heterogeneity and enabled parameter estimation despite limited data. Expanding the dataset by adding underpowered small studies would likely increase noise rather than provide useful information. Turner et al. noted that in meta-analyses, underpowered studies add little when at least two adequately powered studies exist [47]. Nonetheless, the limited sample size remains an important limitation that may affect the generalizability of our findings. Additionally, there were several challenges and limitations associated with the application of a meta-analytical approach to public data on RSV vaccines. First, while ideally immunogenicity

data come from vaccine efficacy studies, some studies lacked such data. To address this, we cross-matched data from studies with the same sponsor and similar design, populations, and interventions, following previous meta-regression methods [10, 11]. The cross-matching was done prior to MI, and the matched data was subsequently treated as observed. Although this expanded the dataset, bias may have been introduced due to single imputation from imperfectly matched data. Second, inconsistency in study design, including variations in study duration, geographic regions, and the collection time and measurement assay for immunogenicity, may have introduced bias into the analysis. To minimize such bias, immunogenicity endpoints for SNA and CMI were placebo corrected. The effects of study duration and the collection time for SNA were evaluated in the exploratory covariate analysis but were not statistically significant. Third, the endpoint for VE used reported values that did not account for differences between RSV subtypes (i.e., RSV-A and/or RSV-B), whereas the endpoint for SNA employed either RSV-A or RSV-B. The two major RSV subtypes, RSV-A and RSV-B, generally co-circulate within a season, with their prevalence varying across seasons and regions [48]. The similarities in disease severity between RSV-A and RSV-B indicate the necessity of targeting both subtypes for effective prevention, which provided the rationale for the definition of VE in our analysis [49]. Furthermore, due to the high correlation between RSV-A and RSV-B SNA (Spearman correlation coefficient of 0.89), we opted to use only one subtype in the analysis to avoid issues of multicollinearity. As illustrated in Figures 1 and 2, the quantitative relationship between SNA and VE was consistent regardless of whether RSV-A or RSV-B SNA was employed in the analysis.

In conclusion, this study quantified the relationship between immunogenicity responses and protection against RSV infection-related clinical outcomes using a meta-analytical approach. The findings provide preliminary evidence that SNA might serve as a surrogate marker for VE against RSV infection, but further research with expanded datasets and individual-level data is needed to confirm this. Although no definitive conclusions can be drawn regarding the contribution of CMI to VE, it is suggested that CMI may be correlated with additional clinical benefits in mitigating the severity of RSV infection. CoP play a critical role in accelerating vaccine development by enabling immunobridging strategies. We recognize that this analysis for the immunobridging evidence falls within the high model impact area outlined in the ongoing ICH M15 on model-informed drug development and therefore believe that the results of this analysis should be carefully considered in interactions with regulatory authorities [50]. We hope that this study will contribute valuable insights supporting the development of future RSV vaccines and lead to the accumulation of further evidence.

Author Contributions

Y.K. wrote the manuscript; Y.K., L.Q., S.S., P.M.D., and K.Y. designed the research; Y.K., L.Q., S.S., P.M.D., M.K., and K.Y. performed the research; Y.K. and L.Q. analyzed the data.

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Conflicts of Interest

Yushi Kashihara, Shinji Shimizu, Masakatsu Kotsuma, and Kazutaka Yoshihara are employees of Daiichi Sankyo Co. Ltd. Li Qin and Paul Matthias Diderichsen are employees of Certara Netherlands, bv.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** psp470133-sup-0001-DataS1.docx.