Supplementary Material

Public Health Impact of the Adjuvanted RSVPreF3 Vaccine for Respiratory Syncytial Virus Prevention Among Older Adults in the United States

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Contents

Table S1. Description of Markov model health states and disease transition events

Health state / disease transition event[a]	Description
No RSV	At the start of the simulation, the entire population is in the "No RSV" health state. Individuals either remain in this health state (no symptomatic RSV-ARI case), die from other causes, or transition to the health state "Post-RSV" or "RSV-death" using age-dependent transition probabilities. Individuals who experience a symptomatic RSV-ARI case pass through the "Symptomatic RSV-ARI" disease transition event, as well as either the "RSV-URTD" or "RSV-LRTD" disease transition event (depending on how the symptomatic RSV-ARI case is classified) before reaching the "Post-RSV" or "RSV-Death" health state.
Symptomatic RSV-ARI	The "Symptomatic RSV-ARI" disease transition event keeps track of individuals experiencing a first symptomatic RSV-ARI case within the modeled time horizon. Due to the lack of long-term immunity after natural RSV infection, the model structure allows for individuals to become susceptible again after an initial case. Individuals experiencing subsequent symptomatic RSV-ARI case(s) within the modeled time horizon are tracked in a "Symptomatic RSV-ARI Reinfection" disease transition event. Rates of symptomatic RSV-ARI reinfection were assumed to be the same as for initial infection.
RSV-URTD	After the "Symptomatic RSV-ARI" disease transition event, symptomatic RSV-ARI cases are classified as being either RSV-URTD or RSV-LRTD, which impacts transition probabilities and health outcomes. The "RSV-URTD" disease transition event keeps track of individuals who develop a first RSV-URTD case within the modeled time horizon. RSV-URTD reinfection(s) are tracked in the "Reinfection with RSV-URTD" disease transition event (not shown in Figure 1).
RSV-LRTD	The "RSV-LRTD" disease transition event keeps track of individuals who develop a first RSV-LRTD case within the modeled time horizon. RSV-LRTD reinfection(s) are tracked in the "Reinfection with RSV- LRTD" disease transition event (not shown in Figure 1).
Post-RSV	The "Post-RSV" health state consists of individuals who recovered from at least one symptomatic RSV-ARI case. Individuals can transition out of this health state by dying from other causes or experiencing another symptomatic RSV-ARI case, based on age-dependent transition probabilities. Symptomatic RSV-ARI reinfections either pass again through disease transition events to the "Post-RSV" health state or the "RSV-Death" health state. Most individuals in the "Post-RSV" health state remain in this health state for the modeled time horizon.
RSV-Death and All-Cause-Death	These two absorbing health states keep track of RSV-related mortality and all-cause mortality, respectively. RSV-related mortality can only occur after hospitalization for RSV-LRTD. All-cause (i.e., non-RSV-specific) mortality is applied to two other health states (No RSV and Post-RSV).

[a] Instead of health states, the acute phase of a symptomatic RSV-ARI case is tracked using disease transition events (see Figure 1, in blue color), where individuals pass through when moving from one health state to another. The choice of using transition events is mainly driven by the model's 1-month cycle length and the RSV clinical representation that is typically shorter than 1 month but, in some cases, longer (e.g., due to complications).

Abbreviations: ARI, acute respiratory illness; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus; URTD, upper respiratory tract disease.

Table S2. Age-specific annual probability of all-cause mortality

Age	Annual probability of death	Age	Annual probability of death
60 years	0.010670	**81 years**	0.059479
61 years	0.011515	**82 years**	0.065797
62 years	0.012345	**83 years**	0.073678
63 years	0.013146	**84 years**	0.082232
64 years	0.013957	**85 years**	0.091981
65 years	0.014819	**86 years**	0.100813
66 years	0.015851	**87 years**	0.113298
67 years	0.016978	**88 years**	0.126982
68 years	0.018272	**89 years**	0.141894
69 years	0.019676	**90 years**	0.158045
70 years	0.021199	**91 years**	0.175420
71 years	0.022881	**92 years**	0.193977
72 years	0.024832	**93 years**	0.213643
73 years	0.026725	**94 years**	0.234314
74 years	0.030032	**95 years**	0.255856
75 years	0.032663	**96 years**	0.278104
76 years	0.036297	**97 years**	0.300870
77 years	0.039811	**98 years**	0.323946
78 years	0.044410	**99 years**	0.347113
79 years	0.048780	**≥100 years**	1.000000
80 years	0.053900		

The model accounted for all-cause mortality, which was derived from age-specific United States 2020 annualized values for probability of death [1], converted to monthly probabilities. To accommodate monthly model cycles, monthly mortality probabilities were calculated by dividing the annual mortality probability value by 12 using the formula Pm=1-(1-Pa)^(1/12), with Pm and Pa being the monthly and yearly probability, respectively.

Table S3. Seasonality adjustment factors for incidence of symptomatic RSV-ARI

Month	Seasonality adjustment factor[a]
January	275.4%
February	233.5%
March	174.4%
April	49.2%
May	16.2%
June	8.5%
July	6.0%
August	3.0%
September	10.3%
October	34.0%
November	102.7%
December	286.7%

[a] Seasonality multipliers were calculated based on the total number of PCR RSV detections each month from the National Respiratory and Enteric Virus Surveillance System (NREVSS) RSV data for 2018–2019 [2].

Abbreviations: ARI, acute respiratory illness; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.

Data analysis

Adjuvanted RSVPreF3 vaccine efficacy (VE) calculations

To estimate vaccine efficacy (VE) for use in the model, we obtained monthly data on the number of subjects (N) in each arm of the Adult Respiratory Syncytial Virus (AReSVi-006) phase 3 trial (placebo versus the adjuvanted RSVPreF3 vaccine), the number of respiratory syncytial virus acute respiratory illness (RSV-ARI) and lower respiratory tract disease (RSV-LRTD) cases (n), and the follow-up time in days (data on file).

We aggregated data timepoints where needed using a pre-determined threshold to have at least 8 RSV cases in the placebo arm. This threshold was used to improve the robustness of the VE estimates. The aggregation was performed by calculating the weighted average of the time points based on the number of cases in the placebo group. Next, we calculated VE for each of the timepoints by applying the following formula:

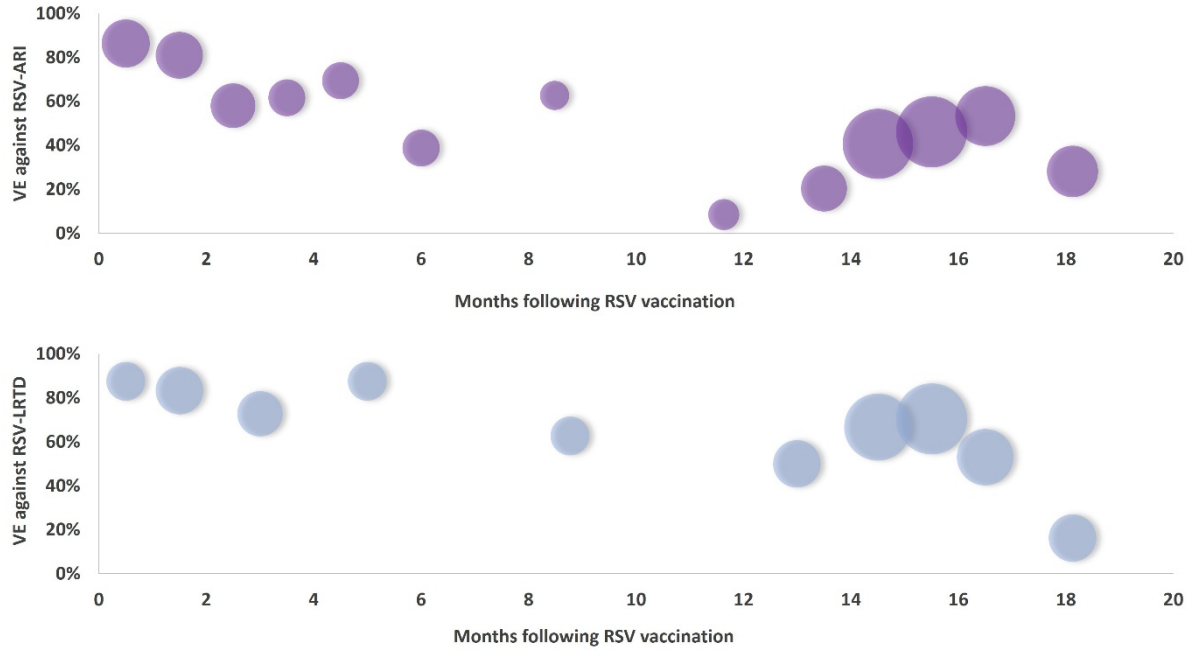
$$\mathrm{VE} = 1 - \left(\frac{Incidence\ in\ adjuvanted\ RSVPreF3\ arm}{Incidence\ in\ placebo\ arm}\right) \text{ with}$$

$$Incidence = \frac{\mathrm{n}}{\mathrm{Fup}}$$

Where adjuvanted RSVPreF3 = intervention arm, n = number of RSV-ARI or RSV-LRTD cases, and Fup= follow-up time.

This approach resulted in VE estimates at 13 timepoints for VE against RSV-ARI and 10 timepoints for VE against RSV-LRTD, as can be seen in Supplementary Figure 1 below. The size of the bubbles indicates the relative incidence in the placebo arm at each timepoint.

Supplementary Figure 1. Adjuvanted RSVPreF3 vaccine efficacy estimates for different timepoints



Note: The size of each data point in the figure represents the relative weight based on the number of RSV cases observed in the placebo arm of the phase 3 clinical trial.

Abbreviations: ARI, acute respiratory illness; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus; VE, vaccine efficacy.

We then performed a weighted least squares (WLS) regression on both VE endpoints. The weights were determined by the number of cases in the placebo group (size of the bubbles in Supplementary Figure 1 above). This approach ensured that data points where there were more cases in the placebo arm (and thus where we had more robust VE estimates) were considered more influential to the model fit. Given the seasonality of RSV (i.e., with more RSV cases typically observed between October through April), we had more robust estimates of VE during the RSV season.

The intercepts of the WLS regression models provided the base-case inputs for peak VE against RSV-ARI and peak VE against RSV-LRTD; the slopes of the WLS regression models provided the base-case inputs for monthly waning of VE.

The intercept represents peak VE at 15 days post vaccination, which is why only 50% of peak VE was applied in the first cycle of the model (month 1). VE waning was then applied beginning in month 2 of the model (i.e., VE in month 2 was estimated as $VEpeak - 1 * waning$). The monthly VE waning estimate (i.e., slope parameter) was applied as a percentage point decrease in VE in each subsequent month of the modeled time horizon as well.

In order to estimate uncertainty around the WLS regression coefficients, we performed a bootstrap procedure. We used SAS® Release 9.4 (SAS Institute Inc., Cary, NC) statistical software to assign probabilities to cases occurring at each of the aggregated time points, for both endpoints (RSV-ARI and RSV-LRTD), and for both intervention and placebo arms. Base probabilities were calculated from the AReSVi-006 phase 3 clinical trial's midpoint aggregated data on the number of subjects (N), number of events (n), and the follow-up time (Fup). Applying these base probabilities, samples were drawn from a uniform distribution to simulate events at each timepoint, in each arm and for both endpoints. The SAS script then performed a WLS regression as described for the base-case estimates. The WLS coefficients needed to satisfy two criteria in order to be retained:

- Intercept ≤1 (i.e., ensuring efficacy ≤100%) AND
- Slope ≤0 (i.e., ensuring efficacy does not increase over time)

If these criteria were not met, a new sample was drawn (up to a maximum of 1,000 estimates retained). For these 1,000 slopes and intercepts, we calculated the lower bound (2.5th percentile), the upper bound (97.5th percentile), and the standard error. Peak VE and waning against RSV-ARI and RSV-LRTD are presented in Table S4 below.

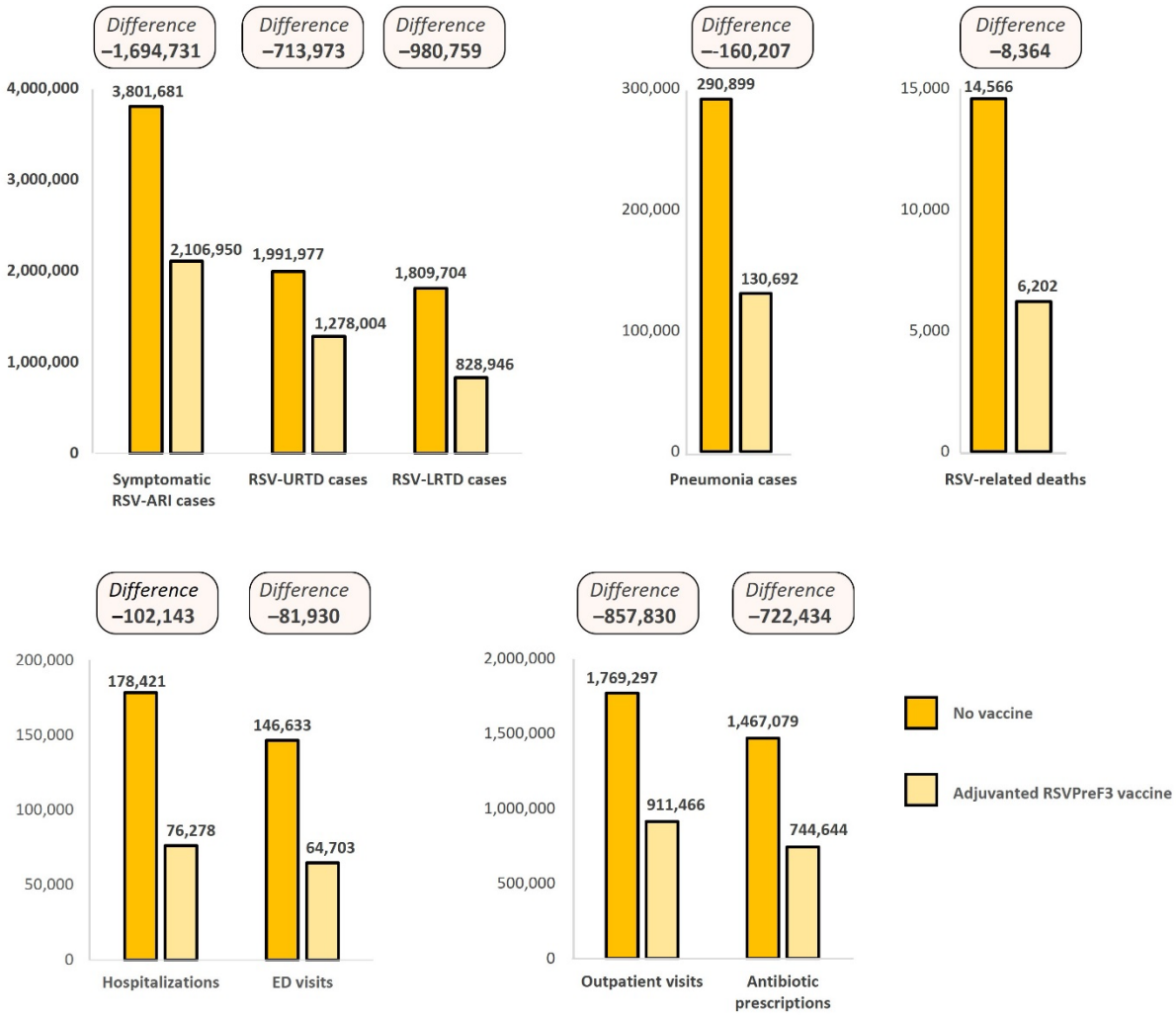
Table S4. Vaccine efficacy-specific model inputs

VE input	Base-case value	Range		Source
		Lower bound	Upper bound	
Peak VE against RSV-ARI	74.17%	56.39%	94.01%	AReSVi-006 phase 3 clinical study [3, 4] (and data on file)
Monthly waning rate for VE against RSV-ARI[a]	2.26%	0.30%	4.32%	
Peak VE against RSV-LRTD	88.02%	65.80%	99.20%	
Monthly waning rate for VE against RSV-LRTD[a]	2.10%	0.14%	4.30%	

[a] Monthly waning rate is applied as an absolute percentage point decrease starting in month 2 of the modeled time horizon.

Abbreviations: ARI, acute respiratory illness; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus.

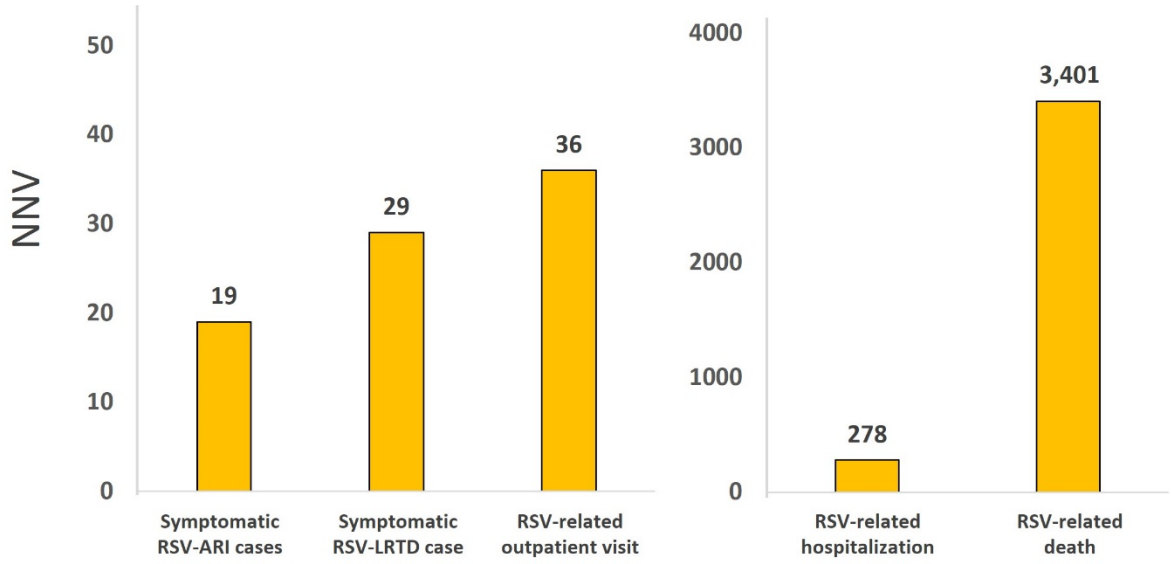
Supplementary Figure 2. RSV-related health outcomes and healthcare resource use among US adults aged ≥60 years in year 1.



Note: On an annual basis (i.e., in the first year of the modeled time horizon), the burden of RSV among older adults in the absence of vaccination includes over 3.8 million symptomatic RSV-ARI cases (approximately 2.0 million RSV-URTD and 1.8 million RSV-LRTD cases). The model further estimates 178,421 RSV-related hospitalizations, 146,633 ED visits, 1,769,297 outpatient visits, 1,467,079 antibiotic prescriptions, 290,899 x-ray confirmed pneumonia cases, and 14,566 RSV-related deaths annually among adults aged ≥60 years without vaccination.

Abbreviations: ARI, acute respiratory illness; ED, emergency department; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus; URTD, upper respiratory tract disease; US, United States.

Supplementary Figure 3. Numbers needed to vaccinate (NNV) to avoid outcomes over 3-year time horizon



Note: NNV were calculated by dividing the number of older adults who were vaccinated by the incremental number of each outcome avoided as a result of vaccination.

Abbreviations: ARI, acute respiratory illness; LRTD, lower respiratory tract disease; NNV, number needed to vaccinate; RSV, respiratory syncytial virus.

Comparison of modeled RSV burden with previous studies

Results from the current model provide important insights into the burden of RSV among older adults and can be compared to previous estimates from the published literature. In the absence of RSV vaccination, the model estimated a substantial burden of RSV among US older adults, including over 3.8 million cases of symptomatic RSV-ARI annually (**Supplementary Figure 2**). Rates of symptomatic RSV-ARI were based on the landmark prospective surveillance study by Falsey et al. [5], without adjustment for potential underdetection. We did not adjust symptomatic RSV-ARI incidence for underdetection because Falsey et al. used multiple methods for RSV case detection. However, recent data evaluating the burden of RSV-associated hospitalization suggest that previously reported data may underestimate the true burden, and that adjustment may still be required even when multiple testing methodologies are used [6].

Several model inputs related to medically-attended RSV were obtained from the literature review and meta-analysis by McLaughlin et al. [7], after adjustment for under-ascertainment. For the full population aged ≥60 years, our model estimates a medically-attended RSV incidence rate of 2,135 per 100,000 in the absence of vaccination. In comparison, Belongia et al. [8] reported an average seasonal incidence of 1,390 medically-attended RSV cases per 100,000 over 12 seasons in Marshfield, Wisconsin, where RSV cases were detected via reverse transcription polymerase chain reaction (RT-PCR) alone, without adjustment for potential under-ascertainment. In the present model, the rates of medically-attended RSV are more closely aligned with those from the study by Jackson et al., which reported mean annual incidence rates based on data over 5 seasons (2011–2012 through 2015–2016) in Washington State [9]. That study reported mean rates of medically-attended

RSV cases of 14.5 per 1,000 population for adults aged 50–64 years and 23.2 for adults aged ≥65 years [9] (vs. rates of approximately 17.2 and 22.8 per 1,000 population, respectively in the present model). Our model's estimated 1.8 million medically-attended RSV cases each year among adults aged ≥60 years in the absence of vaccination is higher than estimates from the previous analyses by Herring et al. (1.0–1.2 million medically-attended cases) [10]. These comparisons highlight the importance of adjusting medically-attended RSV disease burden estimates to account for RSV under-ascertainment in order to appropriately capture the full burden of disease.

Without RSV vaccination, the model estimates 178,421 RSV-related hospitalizations among older adults annually. These results closely align with estimates from the study by Falsey et al. (177,525 annual RSV-related hospitalizations among adults aged ≥65 years) [5] and the previous analysis by Herring et al. (117,895–237,627 annual RSV-related hospitalizations among adults aged ≥60 years) [10]. The current model's hospitalization rates are also in line with those from Branche et al. (33.5–63.0 per 100,000 for 50–64-year-olds and 136.9–255.6 per 100,000 for those aged ≥65 years) [11] and an earlier study by Widmer et al. (82 per 100,000 for 50–64-year-olds and 254 per 100,000 for those aged ≥65 years) [12], particularly since these studies relied on RT-PCR testing and did not adjust for under-ascertainment. Another recent modeling analysis by Van Effelterre et al. used a dynamic transmission model to estimate that as many as 4.27 million symptomatic RSV-ARI cases occur in US adults aged ≥60 years annually in the absence of vaccination, including 1.44 million medically-attended cases, 172,108 RSV-related hospitalizations, and 14,943 RSV-related deaths [13].

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