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Clinical and economic outcomes associated with respiratory syncytial virus vaccination in older adults in the United States

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ABSTRACT

Background: Respiratory syncytial virus (RSV) is an important cause of lower respiratory infections and hospitalizations among older adults. We aimed to estimate the potential clinical benefits and economic value of RSV vaccination of older adults in the United States (US).

Methods: We developed an economic model using a decision-tree framework to capture outcomes associated with RSV infections in US adults aged ≥ 60 years occurring during one RSV season for a hypothetical vaccine versus no vaccine. Two co–base-case epidemiology sources were selected from a targeted review of the US literature: a landmark study capturing all RSV infections and a contemporary study reporting medically attended RSV that also distinguishes mild from moderate-to-severe disease. Both base-case analyses used recent data on mortality risk in the year after RSV hospitalizations. Direct medical costs and quality-adjusted life-years (QALYs) lost per case were obtained from the literature and publicly available sources. Model outcomes included the population-level clinical and economic RSV disease burden among older adults, potential vaccine-avoidable disease burden, and the potential value-based price of a vaccine from a third-party payer perspective.

Results: Our two base-case analyses estimated that a vaccine with 50% efficacy and coverage matching that of influenza vaccination would prevent 43,700–81,500 RSV hospitalizations and 8,000–14,900 RSV-attributable deaths per RSV season, resulting in 1,800–3,900 fewer QALYs lost and avoiding $557-$1,024 million. Value-based prices for the co–base-case analyses were $152-$299 per vaccination at a willingness to pay of $100,000/QALY gained. Sensitivity analyses found that the economic value of vaccination was most sensitive to RSV incidence and increased posthospitalization mortality risks.

Conclusions: Despite variability and gaps in the epidemiology literature, this study highlights the potential value of RSV vaccination for older adults in the US. Our analysis provides contemporary estimates of the population-level RSV disease burden and insights into the economic value drivers for RSV vaccination.

1. Introduction

Respiratory syncytial virus (RSV) is an important cause of lower respiratory infections and hospitalizations in older adults, with a pattern of seasonal incidence in the United States (US) typically spanning from late autumn to early spring [1-3]. After initial observation during outbreaks among older populations in long-term care facilities [4,5], landmark studies also have established RSV as a cause of severe illness in healthy, community-dwelling, older adults [6,7]. Despite evidence suggesting that severe RSV infection may result in greater morbidity and mortality in older adults than severe influenza [8,9], RSV remains underrecognized in routine clinical practice in this population [2,10].

There are currently no pharmacological interventions approved for the prevention or treatment of RSV infection in older adults [11]. This, along with limitations on the availability and accuracy of point-of-care RSV diagnostic testing [12], has contributed to the underrecognition of RSV in this population. However, a number of vaccines are in development for the prevention of RSV in older adults [13], spurring initiatives in the US and globally to advance understanding of the epidemiology and burden of RSV disease and develop the evidence required to evaluate the impact of these new technologies [14,15]. In particular, public health decision makers and budget holders will need to understand the potential clinical and economic impacts of RSV vaccination when developing recommendations and making funding decisions [16].

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In contrast with the extensive cost-effectiveness literature for RSV prevention strategies in infants [17,18], the literature on the potential economic value of RSV vaccination in older adults is limited [19-21]. Notably, the only economic analysis of RSV vaccination for older adults in the US of which we are aware [19] was conducted prior to the publication of landmark, community-based epidemiological studies [6,7]. While there have been advances in population-level modeling of RSV transmission [21,22], there remains a need for a contemporary analysis of the potential economic value of RSV vaccination in older adults in the US.

The primary objectives of this study were to estimate the magnitude of the clinical and economic burden attributable to RSV disease among older adults in the US and to estimate the potential value-based price (VBP) from a cost-effectiveness perspective of an RSV vaccine for this population. Additionally, this study also aimed to provide insights on the impact of emerging research on RSV disease severity and associated long-term outcomes [8,23] on the potential economic value of vaccinating older adults against RSV.

2. Methods

2.1. Modeling approach

We developed a decision-tree model to capture outcomes associated with RSV infections in older adults in the US occurring during one RSV season for a hypothetical RSV vaccine compared with no vaccine (Fig. 1). The model structure reflects the hierarchy of RSV endpoints and severity definitions in US benchmark studies [11,24]. The target population was defined as US adults aged 60 years or older in alignment with the target population for many vaccines in development [25]. The time horizon of one RSV season was selected in alignment with efficacy endpoints for RSV vaccines in late-stage development [13] and because evidence suggests that infection with RSV does not confer immunity at levels that would be protective in subsequent RSV seasons [1,26]. The model was designed to conduct analyses from the perspective of a third-party payer in the US. Our approach expands on the structures used in previous economic analyses of RSV vaccination in older adults [19,20] by categorizing RSV infections according to symptom-based severity levels [23] and by capturing mortality during 30-day and 12-month time periods after RSV hospitalizations [8].

Specifically, our model structure categorizes all laboratory-confirmed RSV infections as either moderate-to-severe lower respiratory tract disease (msLRTD) or mild acute respiratory infection (mARI) based on the number of observed symptoms (see Fig. 1 note). By explicitly incorporating RSV severity, the model can account for differences in resource utilization (e.g., hospitalization) and costs between severity levels [23] and evaluate scenarios where vaccination attenuates the severity of breakthrough infections in those vaccinated, as observed with other respiratory vaccines [27]. We categorize cases within each severity level according to the intensity of resource utilization: hospitalization; outpatient, emergency department (ED) visit; outpatient, no ED visit; or no health care provider (HCP) visit. Cases requiring multiple categories of resource use are categorized by the maximum level of care received, leading to a distribution across mutually exclusive resource utilization categories that may differ between msLRTD and mARI. While cases not requiring an HCP visit are not always captured in observational epidemiology studies, we included them in the model to allow for cases that affect quality of life without rising to the level of an HCP visit. This category includes asymptomatic cases, as observed in some prospective surveillance studies [6].

For RSV hospitalizations, the model considers deaths occurring within 30 days of admission (while hospitalized or after discharge) and deaths occurring between 30 days and 12 months of admission. While not routinely reported in previous epidemiology studies or economic analyses, recently published data on deaths during the immediate postdischarge period in the US [8] are consistent with data observed outside the US [28]. Including deaths between 30 days and 12 months of an RSV hospitalization in an economic model for RSV represents a step toward more comprehensively capturing long-term RSV-associated outcomes that are specific to

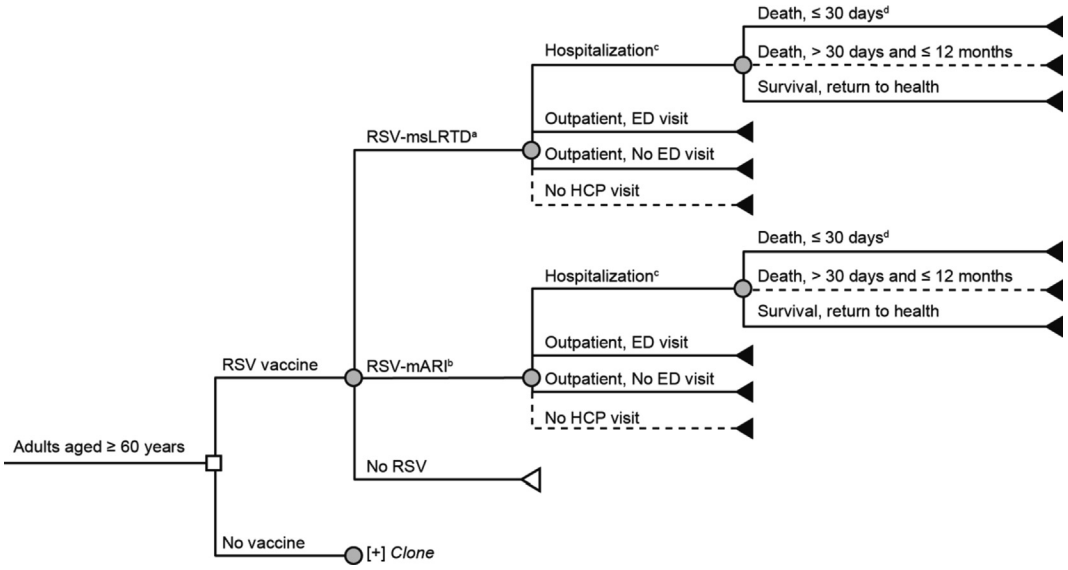

Fig. 1. Model Structure. ED = emergency department; HCP = health care provider; mARI = mild acute respiratory infection; msLRTD = moderate-to-severe lower respiratory tract disease; RSV = respiratory syncytial virus. Note: The same model structure is used for both base-case epidemiology scenarios. Outcomes presented with dashed lines (– – –) are optional depending on the selected source for epidemiology data. [a] RSV-msLRTD is defined as laboratory-confirmed RSV infection with at least 3 of cough, wheezing, sputum production, shortness of breath, or observed tachypnea. [b] RSV-mARI is defined as laboratory-confirmed RSV infection not meeting the definition of RSV-msLRTD, including asymptomatic infections. [c] Location of care is determined by the highest level of care received during the RSV infection, and the distribution of care locations may differ between RSV-mARI and RSV-msLRTD. [d] Timing of death is measured from hospital admission.

older adults (e.g., frailty, nursing home placement [14]). However, these data must be considered carefully in light of the underlying risk of mortality for older adults who may have other comorbidities.

For hypothetical RSV vaccination in the older adult population, our model considers vaccine coverage and vaccine efficacy against RSV infections with the flexibility to consider differing efficacy against mARI and msLRTD cases. The model does not consider indirect protection of those not vaccinated (i.e., herd immunity). While the exclusion of herd immunity may underestimate the clinical benefit of RSV vaccination, a recent dynamic model for RSV transmission suggested minimal indirect protection for older adult vaccination strategies [22].

2.2. Model parameters

The data to parameterize the model were identified from the published literature and other publicly available sources. We conducted a targeted review of the literature on the epidemiology of RSV disease in older adults in the US to identify the epidemiology parameters for the model (see the Supplementary Materials for additional details). Other required parameters for the model included the direct costs and quality-adjusted life-years (QALYs) lost per RSV case and the QALYs lost per RSV death. The RSV vaccine attributes required for the model included coverage, efficacy, and administration costs.

2.3. Epidemiology

On the basis of the results of the targeted literature review, we used two co–base-case sets of epidemiology parameters (Table 1). The first set of epidemiology parameters was based on the landmark study by Falsey and colleagues [6], which used community-based RSV surveillance to estimate the incidence of all RSV infections. The second set of epidemiology parameters was based on a more recent study by Belongia and colleagues [23], which relied on retrospective medical record abstraction to estimate the incidence of medically attended RSV cases. For both base-case epidemiology selections, the size of the population aged 60 years or older was obtained from national US population statistics [29].

For the co–base-case epidemiology parameters from Falsey and colleagues [6], the overall average seasonal incidence of any RSV infection was 5% (the midpoint of the observed range of 3%-7% in healthy older adults) [6]. We derived an estimate for the percentage of all RSV infections hospitalized (6.7%) by weighting the reported hospitalization rates among healthy and high-risk cohorts according to the proportion of older adults with two or more comorbidities in a large influenza vaccine trial [30]. Because the study by Falsey and colleagues [6] did not report symptom-based severity levels, it was assumed that 20% of all RSV infections met the msLRTD criteria based on the proportion of influenza-like illnesses in a separate community-based, prospective study that met similar severity criteria [31]. The percentage of msLRTD cases hospitalized (11.2%) was taken from the hospitalization rate among moderate-to-severe influenza-like illnesses in the same study, which then allowed the proportion of mARI cases hospitalized (5.6%) to be calculated. Additional details on other levels of resource utilization and the associated derivations for this co–base-case epidemiology selection are presented in Table 1 and Supplementary Table S-1.

For the co–base-case epidemiology parameters from Belongia and colleagues [23], the overall incidence of medically attended RSV cases was 1.39% per season [23], among which 24.3% met the msLRTD criteria. The corresponding rates of hospitalization for this scenario were 11.9% of medically attended cases overall, 28.8% of medically attended msLRTD cases, and 6.5% of medically attended mARI cases. Estimates for other levels of resource utilization for this co–base-case epidemiology selection are presented in Table 1.

For both base-case analyses, the proportion of RSV hospitalizations resulting in death within 30 days of admission was 8.7% (5.6% in the hospital and 3.1% after discharge) [8] (Table 1). This estimate

Table 1
Epidemiology and Clinical Model Parameters.

Model Parameter	Co–Base-Case Analysis Using Falsey and Colleagues [6]		Co–Base-Case Analysis Using Belongia and Colleagues [23]	
	Default (range), %	Sources	Default (range), %	Sources
RSV incidence				
RSV overall, % per season	5.0 (3.0–7.0)	Falsey et al. [6]	1.4 (0.8–2.1)	Belongia et al. [23]
RSV-msLRTD, % of cases	20.0 (10.0–30.0)	Falsey et al. [31]	24.3 (19.1–29.9)	
Location of care (% of cases)[a]				
RSV overall (for reference)				
Hospitalization	6.7 (5.2–8.3)	Falsey et al. [6], DiazGranados et al. [30]	11.9 (8.2–16.3)	Belongia et al. [23]
ED visit	3.7		5.3	
Physician visit	22.0		82.7	
No HCP visit	67.6		—	
RSV-msLRTD				
Hospitalization	11.2 (8.7–14.0)	Falsey et al. [31]; Assumptions	28.8 (18.1–40.9)	Belongia et al. [23]
Outpatient, ED visit	6.2		6.8	
Outpatient, no ED visit	37.0		64.4	
No HCP visit	45.6		—	
RSV-mARI				
Hospitalization	5.6 (4.4–7.0)	Derived	6.5 (3.4–10.5)	Belongia et al. [23]
Outpatient, ED visit	3.1		4.9	
Outpatient, no ED visit	18.3		88.6	
No HCP visit	73.0		—	
RSV-attributable deaths (% of hospitalizations)[b]				
Within 30 days of admission (including in hospital)	8.7 (6.6–11.0)	Ackerson et al. [8]		
Between 30 days and 12 months after admission	9.6 (0.0–13.0)	Ackerson et al. [8], Carey et al. [33], Arias et al. [32]		

ED = emergency department; HCP = health care provider; mARI = mild acute respiratory infection; msLRTD = moderate-to-severe lower respiratory tract disease; RSV = respiratory syncytial virus.

[a] Additional derivation details are provided in Supplementary Table S-1.

[b] Additional derivation details are provided in Supplementary Table S-2.

was not adjusted for the underlying risk of mortality in these patients due to the short duration of time involved. However, the proportion of RSV hospitalizations resulting in death between 30 days and 12 months of admission reported in the literature (16.9%) [8] was adjusted for underlying mortality risk. Specifically, the average age and Charlson Comorbidity Index score for the patients hospitalized in the study were combined with age- and comorbidity-specific mortality risks [32,33] to estimate an underlying mortality risk of 7.3% (see Supplementary Table S-2 for additional details). The resulting adjusted mortality estimate (i.e., the RSV-attributable excess mortality risk) used in the model for the period between 30 days and 12 months after RSV hospitalization (9.6%) reflects the difference between the observed proportion of RSV hospitalizations resulting in deaths and the estimated underlying mortality risk during the same period.

2.4. Direct medical costs per RSV case

We obtained estimates of the direct costs per RSV case from the literature and other publicly available costing sources according to the level of resource utilization required (Table 2). Costs obtained from the literature were inflated to 2019 US$ using the US Consumer Price Index for Health Care [34]. Because the literature on RSV-specific costs for older adults in the US is limited [35,36], we instead used recent cost estimates for respiratory illnesses more broadly [37,38]. The available cost estimates did not differentiate between symptom-based severity levels, so the same set of values was used for the msLRTD and mARI severity levels.

The cost per RSV hospitalization was obtained from the average cost of inpatient stays for respiratory conditions among individuals aged 65 years and older from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample [37] (HCUP does not report costs specific to those aged 60 years and older). This estimate includes medications, intensive care unit stays, and mechanical ventilation required during the inpatient stay. Based on a study finding that 25% of RSV hospitalizations were admitted through the ED [39], the cost per hospitalization used in the model reflected the average cost from HCUP plus 25% of the cost of an ED visit. The cost of an RSV-associated ED visit was derived from a published estimate for the cost of upper respiratory tract infections in the ED [38]. The cost for an outpatient visit not involving the ED was set to the cost of a general practitioner visit from standard national costing estimates [40]. For all nonhospitalized RSV cases, including those not requiring a HCP visit, we included the costs of prescription medications (antibiotics, bronchodilators, and oral steroids) on the basis of the reported utilization [6] and unit costs [41] for each medication. Additional details on the derivation of the direct costs per RSV case are presented in Supplementary Table S-3.

2.5. QALYs lost per RSV case

Our literature review did not identify any studies reporting utility values specific to RSV disease in older adults. As a result, we used the utility weights for hospitalizations and outpatient visits from the previous economic analysis of RSV disease in older adults in the US [19]. These utility weights were specific to respiratory illness in older adults and were comparable to values used in the recent economic analysis for RSV disease in the Netherlands [20]. The available utility weights did not differentiate between symptom-based severity levels, so the same set of values was used for the msLRTD and mARI severity levels.

The selected utility weights were paired with age-specific general population utility weights for the US [42] to estimate utility decrements, which were then multiplied by a duration of impact specific to each level of resource utilization to yield the QALYs lost per case (Table 2). Because quality-of-life impacts may persist after interaction with HCPs, we set the duration of disutility for hospitalizations to 14 days, which is equal to the length of stay in older studies [6,19] but longer than the length of stay in more recent studies [39,43,44]. The duration of utility impact for outpatient visits was set to 7 days [19]. Data were not identified to distinguish utility weights between outpatient visits involving an ED visit and those not involving an ED visit. Symptomatic cases not requiring an HCP visit were assumed to experience the same utility decrement as outpatient cases for half the duration. Additional details on the derivation of the QALYs lost per RSV case are presented in Supplementary Table S-4.

We estimated the QALYs lost per RSV death using a life table approach [32] accounting for age-specific utility weights for the general population [42] and discounting [45] (Table 2). For the purposes of estimating QALYs lost, deaths occurring between 30 days and 12 months after RSV hospitalization were assumed to occur midyear, resulting in slightly fewer QALYs lost than deaths occurring within 30 days of an RSV hospitalization.

2.6. Vaccine attributes

The plausible attributes for a hypothetical RSV vaccine for older adults selected for the analysis are presented in Table 3. The size and age of the eligible population were based on US population

Table 2
Costs and Quality-Adjusted Life-Years Lost due to RSV Cases and Deaths.

Model Parameter	Direct Medical Costs (2019 US$)		QALYs Lost	
	Default (range)	Sources	Default (range)	Sources
Acute RSV cases[a]				
Hospitalization (range)	$11,684 ($6,804-$15,876)	HCUPnet [37], Widmer et al. [39], Caldwell et al. [38], Falsey et al. [6],	0.0200 (0.0100–0.0300)	Gessner [19], Janssen and Szende [42]; Assumptions
Outpatient, ED visit	$761	RedBookOnline [41],	0.0037	
Outpatient, no ED visit	$126	Essential RBRVS [40]	0.0037	
No HCP visit	$4		0.0016	
RSV-related deaths				
Within 30 days of admission	—	—	9.1 (7.2–11.0)[b]	Arias et al. [32], Janssen and Szende [42],
Between 30 days and 12 months after admission	—		8.7 (6.9–10.6)[b]	Institute for Clinical and Economic Review [45]

ED = emergency department; HCP = health care provider; mARI = mild acute respiratory infection; msLRTD = moderate-to-severe lower respiratory tract disease; QALY = quality-adjusted life-year; RSV = respiratory syncytial virus; US = United States.

[a] Outcomes per acute RSV case were assumed not to differ between RSV-mARI and RSV-msLRTD cases. Additional derivation details are provided in Supplementary Table S-3 (direct costs) and Supplementary Table S-4 (QALYs lost).

[b] QALYs lost per RSV-related death were estimated using a life table approach, with a mean age of 71 years (sensitivity range = 66–76 years) [32], age-based EQ-5D utilities for the general US population [42], and an annual discounting rate of 3% [45].

Table 3
Attributes of a Hypothetical Vaccine for RSV in Older Adults.

Vaccine Attribute	Value (range)	Sources
Eligible population (aged ≥ 60 years)		
Size	71,070,304	US Census Bureau [29]
Mean age (years)	71	
Coverage and costs		
Coverage	65.3%	US Centers for Disease Control and Prevention [46]
Administration cost per vaccination[a]	$16.94 ($0-$25)	Essential RBRVS [40]
Efficacy, %		
Reduction in RSV overall	50.0 (40.0–60.0)	Assumptions
Reduction in RSV-msLRTD[b]	65.0 (52.0–78.0)	

mARI = mild acute respiratory infection; msLRTD = moderate-to-severe lower respiratory tract disease; RSV = respiratory syncytial virus.
[a] Current Procedural Terminology code 90471 was used for the vaccine administration cost [40].
[b] Reduction in RSV-mARI cases is derived from the reductions in RSV overall and in RSV-msLRTD.

estimates [29]. Predicted coverage for an RSV vaccine was assumed to equal current coverage levels for seasonal influenza vaccination among US adults aged 65 years or older [46]. The vaccine administration cost was set to the cost of routine immunization administration in an office setting from standard national costing estimates [40].

Vaccine efficacy against RSV disease overall (without differentiating by severity) was assumed to equal 50%. Higher vaccine efficacy of 65% was assumed for msLRTD, reflecting the phenomenon observed for other respiratory vaccines where vaccination attenuates the severity of breakthrough infections [27]. The vaccine was not assumed to have any additional impact on the outcomes per RSV case (percentages of cases hospitalized, percentage of hospitalizations resulting in death) beyond the indirect impact of shifting the distribution between msLRTD and mARI.

2.7. Model outcomes and analysis

We developed the model to estimate population-level outcomes and outcomes per individual for a hypothetical RSV vaccine compared with no vaccination. All analyses were conducted for both co–base-case sets of epidemiology parameters. For the analysis of the clinical and economic burden of RSV, the population-level outcomes reported are the absolute and incremental numbers of individuals vaccinated, RSV cases by severity, direct costs associated with RSV disease, and QALYs lost due to RSV disease. For the value-based pricing analysis, the incremental QALYs gained (i.e., QALY losses avoided) and incremental direct medical costs are reported on a per-individual basis along with the VBP (the vaccine price at which the incremental cost per QALY gained equals society's willingness to pay [WTP] for improvements in health) for the hypothetical RSV vaccine. Reflecting the time horizon of one RSV season, cost and health outcomes were not discounted, with the exception of QALYs lost due to RSV deaths, which were discounted at a rate of 3% per year [45]. Value-based price estimates assumed WTP thresholds of $50,000 and $100,000 per QALY gained [45].

2.8. Analysis of uncertainty

We assessed the impact of uncertainty on the results of our analysis by reporting results using two different sets of epidemiology data sources and by conducting one-way sensitivity analyses and joint scenario analyses on RSV incidence and vaccine efficacy. The co–base-case analyses reflect the variability in the US epidemiology literature stemming, at least in part, from differences in study design (population-based surveillance vs. retrospective medical record abstraction) and the definition of RSV incidence (all infections vs. medically attended cases). Additionally, uncertainty ranges around the co–base-case RSV incidence estimates were defined using the seasonal variability reported in the two sources. For other parameters, ranges around the base-case values were identified from published second-order uncertainty estimates (e.g., standard errors) or by varying key assumptions. The parameter ranges used for all uncertainty analyses are presented with the base-case values (Tables 1-3).

3. Results

3.1. Population-level disease burden

For the co–base-case analysis using the epidemiology parameters derived from Falsey and colleagues [6], the model predicted over 3.5 million RSV infections annually in the US population aged 60 years or older without RSV vaccination (Table 4). These infections resulted in approximately 1.15 million medically attended RSV cases, 237,600 RSV hospitalizations, and 43,400 RSV-attributable deaths. For this analysis, the model predicted the loss of nearly 400,000 QALYs annually, primarily due to RSV-attributable deaths, and estimated annual direct RSV-related medical costs approaching $3 billion.

The co–base-case analysis using the epidemiology parameters from Belongia and colleagues [23] predicted approximately 987,900 medically attended cases resulting in roughly 117,900 RSV hospitalizations and 21,500 RSV-attributable deaths in the older adult population without RSV vaccination (Table 4). In this analysis, the model predicted the loss of approximately 196,000 QALYs, with annual direct RSV-related medical costs in excess of $1.5 billion.

For a vaccine against RSV with the default attribute assumptions (65.3% coverage, 50% efficacy against RSV disease overall, 65% efficacy against RSV-msLRTD), the two base-case analyses predicted that vaccination would prevent 322,500 to 395,500 cases of medically attended RSV, 43,700 to 81,500 RSV hospitalizations, and 8,000 to 14,900 RSV-attributable deaths per year (Table 4). Avoiding these clinical outcomes would translate to 72,800 to 136,300 fewer QALYs lost per year and a reduction of $557 million to $1.02 billion in direct costs due to RSV disease each year. Based on these outcomes, the number needed to vaccinate to prevent one medically attended RSV case, RSV hospitalization, and RSV-attributable death ranged from 117 to 144, 569 to 1,061, and 3,113 to 5,804, respectively.

3.2. Value-based pricing analysis

To estimate the potential VBP of an RSV vaccine from a third-party payer perspective, the population-level health and cost outcomes (Table 4) were translated to incremental outcomes per vaccine-eligible individual and per vaccinated individual (Table 5)

Table 4
Expected Population-Level Health and Cost Outcomes.

Outcome	Co–Base-Case Analysis Using Falsey and Colleagues [6]			Co–Base-Case Analysis Using Belongia and Colleagues [23]		
	No Vaccination	Vaccination	Incremental	No Vaccination	Vaccination	Incremental
Number of selected outcomes						
Individuals vaccinated	—	46,408,909	46,408,909	—	46,408,909	46,408,909
RSV infections overall	3,553,515	2,393,292	−1,160,223	—	—	—
Medically attended RSV cases	1,152,951	757,410	−395,541	987,877	665,335	−322,542
RSV hospitalizations	237,627	156,105	−81,522	117,895	74,165	−43,730
RSV-attributable deaths	43,449	28,543	−14,906	21,556	13,561	−7,996
QALYs lost						
Due to acute RSV cases	11,674	7,766	−3,908	5,366	3,538	−1,828
Due to RSV-attributable deaths	385,855	253,481	−132,375	191,436	120,428	−71,008
Direct medical costs ($ millions)						
Due to acute RSV cases	$2,986.0	$1,961.9	-$1,024.2	$1,520.7	$963.4	-$557.3
Number needed to vaccinate						
Per RSV infection avoided			40.0			—
Per medically attended RSV case avoided			117			144
Per RSV hospitalization avoided			569			1,061
Per RSV-attributable death avoided			3,113			5,804

QALY = quality-adjusted life-year; RSV = respiratory syncytial virus.

Table 5
Value-Based Pricing Results.

Expected Outcome	Co–Base-Case Analysis Using Falsey and Colleagues [6]		Co–Base-Case Analysis Using Belongia and Colleagues [23]	
	Per Eligible Individual	Per Vaccinated Individual	Per Eligible Individual	Per Vaccinated Individual
Incremental QALYs lost per individual				
Due to acute RSV cases	−0.00005	−0.00008	−0.00003	−0.00004
Due to RSV-attributable deaths	−0.00186	−0.00285	−0.00100	−0.00153
Total incremental QALYs lost	−0.00192	−0.00294	−0.00102	−0.00157
Incremental direct medical costs per individual				
Vaccine administration costs	$11.06	$16.94	$11.06	$16.94
Due to acute RSV cases	−$14.41	−$22.07	−$7.84	−$12.01
Total incremental costs excluding vaccine acquisition	−$3.35	−$5.13	$3.22	$4.93
Value-based price[a] per vaccination				
WTP = $50,000 per QALY gained	$151.96		$73.54	
WTP = $100,000 per QALY gained	$298.79		$152.01	

QALY = quality-adjusted life-year; RSV = respiratory syncytial virus; WTP = willingness to pay.
[a] For the VBP analysis, QALYs gained are equivalent to QALY losses avoided.

(noting that cost-effectiveness ratios and thus VBPs are not influenced by vaccine coverage in the absence of indirect protection). We estimated the VBP per vaccination for a given WTP threshold by combining vaccine administration costs with the direct RSV costs avoided and the incremental QALYs gained per individual. For the co–base-case analysis using the epidemiology parameters derived from Falsey and colleagues [6], the VBP per vaccination estimates were $151.96 and $298.79 for WTP thresholds of $50,000 and $100,000 per QALY gained, respectively. For the co–base-case analysis using the epidemiology parameters from Belongia and colleagues [23], the corresponding VBP estimates were $73.54 and $152.01 per vaccination (Table 5).

3.3. Sensitivity analysis

One-way sensitivity analyses were conducted around both co-base cases to better understand the impact of uncertainty and variability in key parameters on the potential economic value of RSV vaccination. For both co–base-case analyses, the parameter with the greatest influence on economic value (as measured by the VBP at a WTP of $100,000 per QALY gained) was the seasonal incidence of RSV disease among unvaccinated older adults (Fig. 2a-b). Other parameters with a significant impact on VBP estimates were the mortality risk between 30 days and 12 months of an RSV hospitalization and the QALYs lost per RSV-associated death, both of which affected the VBP by 20% or more in either direction. Of note, excluding the risk of mortality beyond 30 days after an RSV hospitalization reduced the VBPs by approximately 50% for each epidemiology scenario, emphasizing the added economic value demonstrated by more fully capturing the posthospitalization outcomes reported in recent studies [8]. Vaccine efficacy levels had a greater impact on VBP estimates for the co–base-case analysis using the Falsey and colleagues epidemiology parameters [6] (Fig. 2a) than for the co–base-case analysis using the Belongia and colleagues epidemiology parameters [23] (Fig. 2b), likely owing to the lower number of hospitalizations and deaths predicted for the latter analysis.

Finally, the joint impact of variations in seasonal incidence and vaccine efficacy on VBP estimates was explored (Fig. 3a-b). When using epidemiology parameters derived from Falsey and colleagues [6] (Fig. 3a), joint consideration of lower incidence (3% annually) and lower efficacy (40% overall; 52% against msLRTD) resulted in a VBP of $134.61, while joint consideration of higher incidence (7% annually) and higher efficacy (60% overall; 78% against

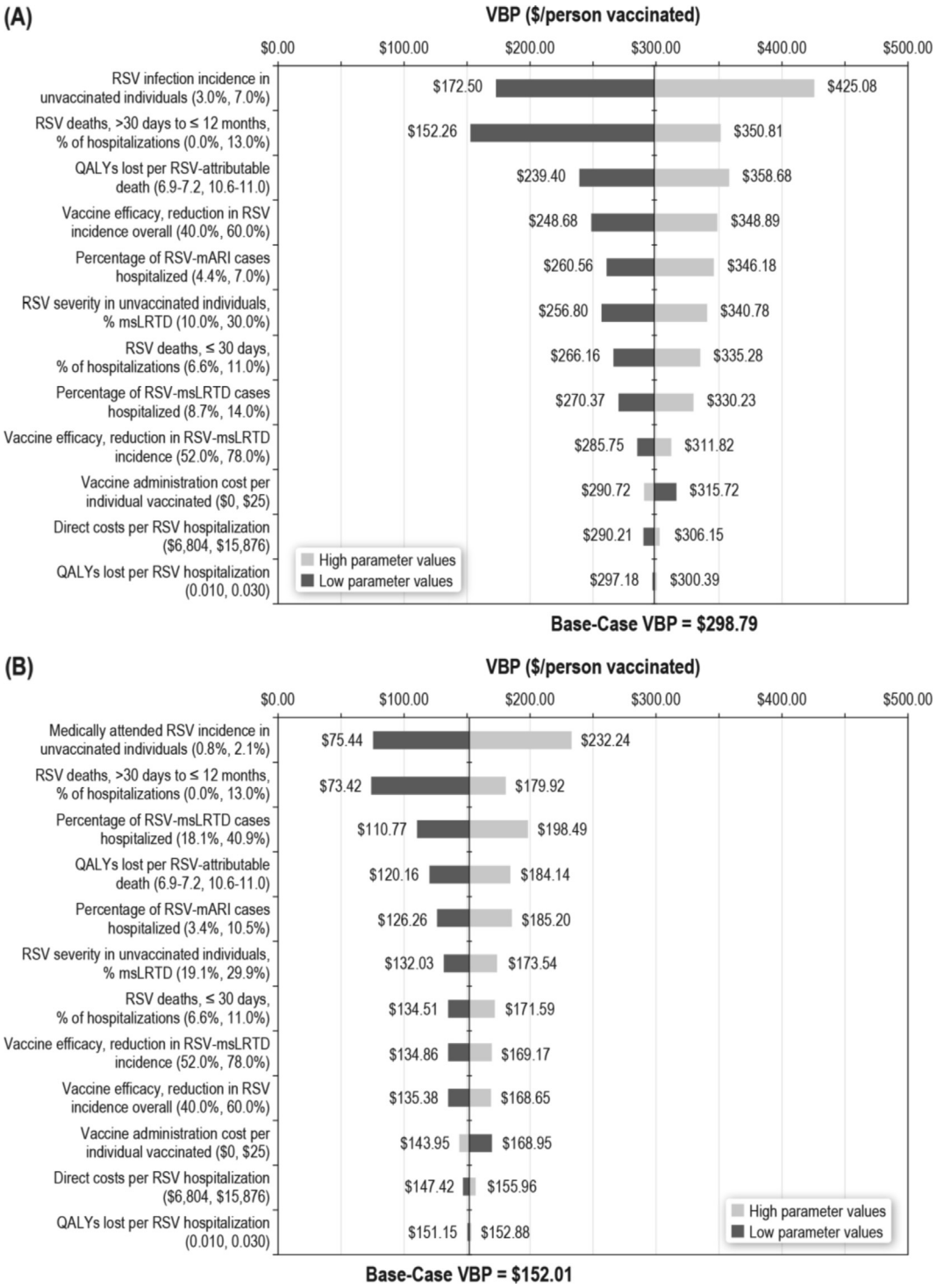

Fig. 2. One-Way Sensitivity Analysis Results for the Co–Base-Case Analyses. mARI = mild acute respiratory infection; msLRTD = moderate-to-severe lower respiratory tract disease; QALY = quality-adjusted life-year; RSV = respiratory syncytial virus; VBP = value-based price. Note: VBPs were estimated using a willingness-to-pay threshold of $100,000 per QALY gained. Panel (A) results are for the co–base-case analysis using the epidemiology parameters from Falsey and colleagues [6]. Panel (B) results are for the co–base-case analysis using the epidemiology parameters from Belongia and colleagues [23].

msLRTD) resulted in a VBP of $513.48. When using epidemiology parameters from Belongia and colleagues [23] (Fig. 3b), lower incidence (0.76% annually) paired with lower efficacy (40% overall; 52% against msLRTD) resulted in a VBP of $56.96, while higher incidence (2.05% annually) paired with higher efficacy (60% overall; 78% against msLRTD) resulted in a VBP of $282.07.

4. Discussion

In this study we developed an economic model bridging the gap between landmark epidemiology studies for RSV disease in older adults [6] and more recent studies [8,23] to provide stakeholders in the US with contemporary estimates of the potential clinical

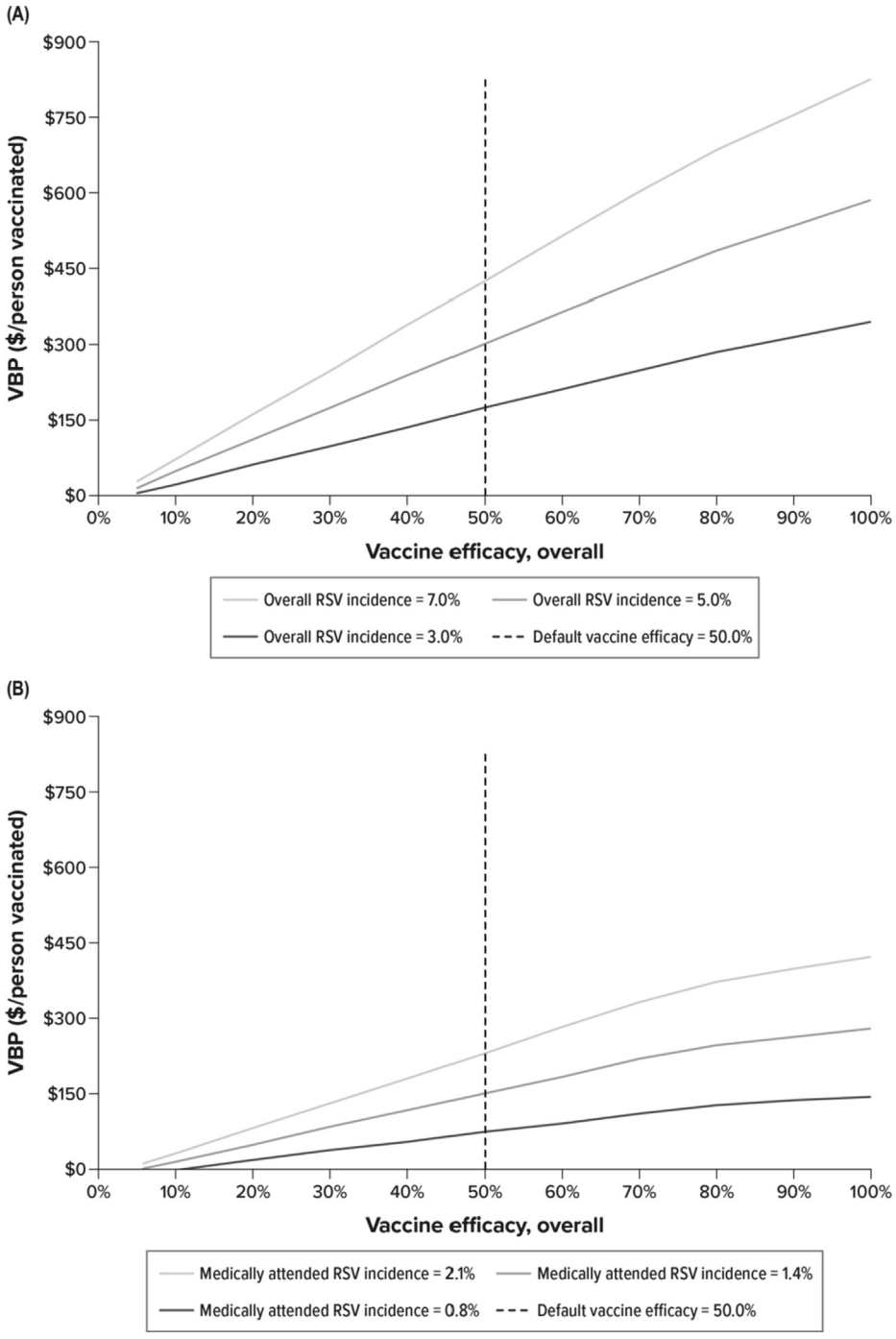

Fig. 3. Joint Impact of Incidence and Efficacy on Vaccine Value-Based Prices. mARI = mild acute respiratory infection; msLRTD = moderate-to-severe lower respiratory tract disease; QALY = quality-adjusted life-year; RSV = respiratory syncytial virus; VBP = value-based price. Note: Value-based prices were estimated using a willingness-to-pay threshold of $100,000 per QALY gained. Panel (A) results are for the co–base-case analysis using the epidemiology parameters from Falsey and colleagues [6]. Panel (B) results are for the co–base-case analysis using the epidemiology parameters from Belongia and colleagues [23].

and economic impact of RSV vaccination in this population. For the two base-case analyses, reflecting different sets of epidemiology parameters from the US literature, the model predicted 117,900 to 237,600 RSV hospitalizations and 21,600 to 43,400 RSV-attributable deaths per year in the older adult population without RSV vaccination, resulting in 191,400 to 385,900 QALYs lost and $1.52 to $2.99 billion in direct medical costs per year. A vaccine against RSV with coverage matching influenza vaccination levels and 50% efficacy overall that also attenuates the severity of breakthrough cases in vaccinated individuals was predicted to avoid 43,700 to 81,500 hospitalizations and 8,000 to 14,900 deaths per year, resulting in 1,800 to 3,900 fewer QALYs lost and avoiding $557 to $1,024 million in direct medical costs annually. The VBP analyses indicated that a vaccine against RSV in older adults is likely to be cost-effective at prices ranging from $73.54 to $298.79 per vaccination, depending on the epidemiology data used and the WTP threshold considered.

Our population-level estimates of disease burden from the two base-case analyses bracket the infection and hospitalization benchmarks most commonly cited for the US (2.6 million infec-

tions and 177,000 hospitalizations annually [6,24]), while suggesting a much larger number of RSV-attributable deaths per year (benchmarked at 11,000–14,000 annually [6,24,47]). The difference between our model predictions for infections and hospitalizations based on Falsey and colleagues [6] and the benchmark estimates attributed to this same study stems from our inclusion of 60–64 year olds and our use of more recent population size estimates. The annual incidence of medically attended RSV is comparable between our two base-case analyses (1.4%-1.6%), indicating that the difference between the two base-case analyses for predicted RSV hospitalizations stems from the lower rate of hospitalization observed in the study by Belongia and colleagues (11.9% of medically attended cases) [23] compared with the previous landmark study by Falsey and colleagues (20.6% of medically attended cases) [6]. The higher predicted number of RSV-associated deaths in our model for both base-case analyses compared with benchmark estimates is driven by the inclusion of increased mortality risk over the 12 months after RSV-related hospitalization [8].

Among the strengths of our study are the advancement of a new model structure and the updated consideration of US epidemiology data. By accounting explicitly for RSV disease severity, differences in resource utilization between severity levels, and long-term outcomes, the model structure represents a step forward from previously published economic analyses [19,20] and provides a framework for future economic evaluations of RSV vaccination in the US and other markets. Because of the wide uncertainty in the literature and the seasonal variability of RSV disease incidence, we chose to report population-level outcomes as a range reflecting two sets of US epidemiology data. This approach provides up-to-date evidence-based ranges for the clinical and economic burden of RSV disease in older adults without RSV vaccination and provides reference points for the potential health gains and cost offsets achievable with a vaccine. The VBP analysis and accompanying sensitivity analyses highlight the central importance of seasonal RSV disease incidence levels, RSV hospitalization rates, and posthospitalization mortality risks, in addition to the obvious role of vaccine efficacy, in determining the economic value of RSV vaccination in a population of older adults.

Among these influential parameters, the uncertainty around the average seasonal incidence of RSV disease in older adults merits further discussion. The widely cited range of 2%-10% per season [2] relies primarily on the lone, community-based RSV surveillance study in the literature [6] and emphasizes the seasonal variability of RSV disease incidence. Furthermore, the studies used to obtain average seasonal RSV disease incidence estimates for the two base-case analyses [6,31] were conducted in geographically restricted regions that may not be representative of the entire US population. Additional community-based, surveillance studies spanning a greater number of years and a diversity of geographical regions would be required to obtain more precise estimates of the average seasonal RSV incidence among the overall population of older adults in the US. Such studies also would reduce the uncertainty around the economic value of RSV vaccination in this population.

A number of other limitations should be noted when considering the implications of this analysis. As with all economic models, the reliability of the results depends on the quality of the input data used to populate the model. This limitation is particularly relevant for the current analysis because of the difference in predictions from the two base-case sources on the epidemiology of RSV disease. Some estimates derived from Falsey and colleagues [6] were taken from comparable studies in influenza, which benefits from a more extensive literature (especially in older adults) and an established national surveillance program in the US. Additionally, estimates of direct medical costs and utility weights specific to RSV disease were not available, leading to reliance on estimates from respiratory conditions overall. The extent to which RSV-associated outcomes per case differ from other respiratory conditions in older adults will influence the population-level clinical and economic outcomes and the VBP estimates. While the consideration of RSV-attributable excess mortality risk after hospitalizations represents an important step forward, the current analysis does not account for frailty and other quality-of-life impacts experienced by older adults during recovery from acute respiratory illnesses [48]. Finally, the current analysis did not include several population-level factors that may influence RSV-associated outcomes and the economic value of RSV vaccination in older adults, including the role of cardiopulmonary comorbidities, the impact of herd immunity, the potential for vaccine efficacy lasting more than 1 year, and the societal costs (e.g., lost productivity, caregiver burden) associated with RSV infections.

This study provides further evidence of the significant burden of RSV disease among older adults in the US. This burden is substantial relative to other vaccine-preventable diseases in older adults [49,50], with only influenza and pneumococcal disease exceeding the RSV disease economic burden ranging from $1.5 billion to $3.0 billion estimated in this analysis. This study also sheds light on the potential health benefits and economic value of RSV vaccines currently in development. The variability observed in the epidemiology literature, especially between newer community-based observational studies and previous landmark studies, was reflected in the model predictions for key outcomes such as RSV hospitalizations and death, underscoring the importance of ongoing RSV surveillance initiatives. Also, the modeling approach represents a general framework for future research addressing key remaining data gaps, notably RSV-specific costs and utilities and a more complete understanding of the long-term complications of RSV hospitalization in elderly populations. Despite the variability observed in the epidemiology literature and these key data gaps, the VBP analysis suggested that RSV vaccination in older adults is likely to be cost-effective at a price comparable to other vaccines for older populations in the US. As progress toward an effective RSV vaccine continues, this analysis provides public health decision makers, researchers, and other stakeholders with contemporary estimates of the population-level burden of RSV disease and fundamental insights into the factors that drive the potential economic value of RSV vaccination.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The financial support for this study was provided by Novavax, Inc. RTI Health Solutions received funding under a research contract with Novavax, Inc. to conduct this study and to provide editorial support in the form of manuscript writing, styling, and submission. William Herring and Sandra Talbird are employees of RTI Health Solutions, an independent nonprofit research organization, which received funding pursuant to a contract from Novavax, Inc. Yuanhui Zhang was an employee of RTI Health Solutions at the time this research was conducted. Vivek Shinde and Brian Rosen are employees and shareholders of Novavax, Inc. Jeffrey Stoddard was an employee of Novavax, Inc. at the time this research was conducted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.12.002.

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