Cost-Effectiveness of Maternal Vaccination to Prevent Respiratory Syncytial Virus Illness

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abstract

BACKGROUND AND OBJECTIVES: Respiratory syncytial virus (RSV) commonly causes hospitalization among US infants. A maternal vaccine preventing RSV in infants, RSV bivalent prefusion F maternal vaccine (RSVpreF), was approved by the US Food and Drug Administration and recommended by the Advisory Committee on Immunization Practices. Our objective was to evaluate the health benefits and cost-effectiveness of vaccinating pregnant persons in the United States using RSVpreF.

METHODS: We simulated RSV infection and disease with and without seasonal RSVpreF vaccination in half of the pregnant persons in the annual US birth cohort during weeks 32 through 36 of gestation. Model inputs came from peer-reviewed literature, Food and Drug Administration records, and epidemiological surveillance databases. The results are reported using a societal perspective in 2022 US dollars for a 1-year time frame, discounting future health outcomes and costs at 3%. Sensitivity and scenario analyses were performed.

RESULTS: Year-round maternal vaccination with RSVpreF would prevent 45 693 outpatient visits, 15 866 ED visits, and 7571 hospitalizations among infants each year. Vaccination had a societal incremental cost of $396 280 per quality-adjusted life-year (QALY) saved. Vaccination from September through January cost $163 513 per QALY saved. The most influential inputs were QALYs lost from RSV disease, the cost of the vaccine, and RSV-associated hospitalization costs; changes in these inputs yielded outcomes ranging from cost-saving to $800 000 per QALY saved.

CONCLUSIONS: Seasonal maternal RSV vaccination designed to prevent RSV lower respiratory tract infection in infants may be cost-effective, particularly if administered to pregnant persons immediately before or at the beginning of the RSV season.

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Dr Hutton conceptualized and designed the study, conducted the analyses, and drafted the initial manuscript; Drs Prosser, Ortega-Sanchez, Leidner, and Pike conceptualized and designed the study; Ms Rose and Ms Mercon collected data and drafted the initial manuscript; Drs McMorrow, Fleming-Dutra, Prill, and Jones conceptualized and designed the study and collected data; and all authors critically reviewed and revised the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

WHAT'S KNOWN ON THIS SUBJECT: RSV causes substantial hospitalization in US infants, and maternal vaccination has been shown to reduce lower respiratory illness from RSV in infants and children.

WHAT THIS STUDY ADDS: Maternal vaccination from September through January cost $163 513 per quality-adjusted life-year saved. Year-round vaccination cost $396 280 per quality-adjusted life-year saved. Results are sensitive to the timing of administration, quality-of-life lost from RSV, vaccine cost, and hospitalization costs.

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Respiratory syncytial virus (RSV) is an important cause of disease burden in infants in the United States, costing $472 million per year in the United States.[1] RSV is highly seasonal, with more infections in the winter and fewer infections in the summer.[2] Young infants are at the highest risk of severe disease from RSV infection,[3–5] so a maternal vaccine may help provide them with antibodies and protect them in those first months of life.[6,7] Pfizer's bivalent prefusion F maternal vaccine, RSV bivalent prefusion F maternal vaccine (RSVpreF), has been shown to have safety and efficacy in protecting infants from hospitalization and disease. However, with a price per dose of $295,[8] an unknown duration of protection beyond 6 months, and the potential for adverse events, the economic value of vaccination is of interest to policymakers. The results of this cost-effectiveness analysis were used by the Advisory Committee on Immunization Practices (ACIP) when deliberating whether to recommend the use of RSVpreF in pregnant people. In September 2023, the ACIP voted to recommend RSVpreF for pregnant people from 32 to 36 weeks' gestation, using seasonal administration to prevent RSV lower respiratory tract infection (LRTI) in infants.[9]

Our objective with this analysis was to evaluate the projected health benefits and cost-effectiveness of maternal RSVpreF vaccination for infants entering their first RSV season or born during RSV season compared with infants born to unvaccinated mothers. We also wanted to provide further transparency on the methods and results of our cost-effectiveness study used by ACIP as part of its discussions about whether to recommend RSVpreF use to pregnant people. A separate article analyzes nirsevimab.[10]

METHODS

To evaluate the projected impact of year-round and seasonal maternal vaccination with RSVpreF, we developed a decision analytical model of RSV disease simulating the short- and long-term impacts of RSV infection on infants in the following 2 scenarios: no vaccination and seasonal maternal vaccination over a 1-year time frame. For the base case scenario, we assumed a 50% uptake of RSVpreF in the US birth cohort administered between the beginning of week 32 and the end of week 36 of pregnancy (ie, 32 weeks and 0 days gestation to 36 weeks and 6 days gestation). We did not include the prevention of transmission, so the incremental cost-effectiveness ratios (ICERs) were invariant to uptake. RSV disease and economic outcomes were estimated by using the societal perspective, but we also explored a health system perspective.

Model Description

With a uniform distribution of US annual births, the model simulates the number of infants undergoing their first RSV season using monthly time steps. Infants face a seasonal risk of RSV infection, and the risk of medically attended RSV LRTI and RSV hospitalization differs on the basis of the specific month of birth and age of the child (Supplemental Fig 4 and Table 1). We included RSV-associated disease outcomes, along with resource utilization, such as outpatient visits, emergency department (ED) visits, hospitalizations, and premature deaths among infants (Fig 1). Likewise, we included potential vaccine-associated adverse events, such as injection site reactions, systemic reactions, and serious adverse events to the vaccinated pregnant individual along with potentially increased risk rates of premature delivery for the infant.[11] Each of the vaccine-associated adverse events, as well as the RSV disease outcomes, had associated costs and health-related quality of life losses.

Model Inputs

Epidemiology

Model inputs for the annual incidence of RSV were based on several recent epidemiological studies of inpatient, ED, and outpatient disease burden associated with RSV (Table 1).[2–4,12] Because these sources did not distinguish between upper and LRTIs, we relied on previous estimates that 100% of RSV-associated hospitalizations are due to LRTI, and 50% to 65% of ED and 30% to 65% of outpatient visits associated with RSV are due to LRTI (Table 1).[13] For our model, we assumed that RSV-associated deaths happen only among those infants hospitalized, and estimates are based on RSV mortality rates for children aged 0 to 23 months hospitalized with RSV.[14–16] We did not include the long-term sequelae associated with RSV infection (eg, asthma). Seasonality by month came from prepandemic data (2015–2019) on the proportion of RSV cases per month across the whole United States from the National Respiratory and Enteric Virus Surveillance System (Supplemental Fig 4).[17] Although the RSV season can differ by geographic region, national averages were used in this analysis. We did not distinguish between RSV subtypes.

Vaccine Effects

RSVpreF efficacy data were from the reported phase 3 clinical trial (Table 1).[11] We assumed that efficacy follows a sigmoid decay from months 0 to 5.9 after birth and is equal to 0% at month 6 (Supplemental Fig 5A). The assumptions of reduced maternal vaccine efficacy over time and no efficacy after 6 months were based on the trial showing no significant efficacy after 6 months and efficacy for infants aged 0 to 180 days compared with infants aged 0 to 90 days; additionally, waning effectiveness data of other vaccines administered during pregnancy has been shown after 3 months of age.[11,18,19] For the base case scenario, the average efficacy in the first 180 days after birth matched the reported efficacy

TABLE 1 Model Parameters for Cost-Effectiveness Analysis of Maternal RSV Vaccination				
Model Input Parameter	**Base Case**	**Range**	**Distribution**	**Source**
Epidemiological				
Category of RSV incidence per 100 000 infants				
Inpatient				
Age 0 mo	1760	1560–1970	Lognormal	CDC NVSN[2],a
Age 1 mo	3110	2850–3390	Lognormal	
Age 2 mo	2230	2030–2450	Lognormal	
Age 3 mo	1560	1390–1740	Lognormal	
Age 4 mo	1360	1200–1520	Lognormal	
Age 5 mo	1090	960–1250	Lognormal	
Age 6 mo	960	810–1120	Lognormal	
Age 7 mo	800	640–960	Lognormal	
Age 8 mo	730	600–880	Lognormal	
Age 9 mo	840	680–990	Lognormal	
Age 10 mo	600	480–730	Lognormal	
Age 11 mo	600	490–730	Lognormal	
Age 12 mo	630	500–750	Lognormal	
Age 13 mo	500	380–620	Lognormal	
Age 14 mo	580	470–700	Lognormal	
Age 15 mo	540	430–660	Lognormal	
Age 16 mo	400	290–510	Lognormal	
Age 17 mo	370	270–460	Lognormal	
Age 18 mo	370	260–480	Lognormal	
Age 19 mo	340	250–450	Lognormal	
Age 20 mo	280	190–370	Lognormal	
Age 21 mo	210	140–290	Lognormal	
Age 22 mo	180	120–260	Lognormal	
Age 23 mo	290	200–380	Lognormal	
Proportion with LRTI				
Age 0–5 mo	1	0.5–1.0	—	Assumption based on Rainisch 2020[13]
Age 6–23 mo	1	0.5–1.0	—	Assumption based on Rainisch 2020[13]
ED				
Age 0–5 mo	7500	5500–7500	Lognormal	Lively 2019 (base case and range),[4] Hall 2009 (range)[3]
Age 6–11 mo	5800	5700–5800	Lognormal	Lively 2019 (base case and range),[4] Hall 2009 (range)[3]
Age 12–23 mo	3200	3200–5300	Lognormal	Hall 2009 (base case and range),[3] Lively 2019 (range)[4]
Proportion with LRTI				
Age 0–5 mo	0.65	0.25–1.0	β	Assumption based on Rainisch 2020[13]
Age 6–23 mo	0.5	0.25–1.0	β	Assumption based on Rainisch 2020[13]
Medically attended outpatient				
Age 0–5 mo	21 600	13 200–21 600	Lognormal	Lively 2019 (base case and range),[4] Hall 2009 (range)[3]
Age 6–11 mo	24 600	17 700–24 600	Lognormal	
Age 12–23 mo	18 440	6600–29 620	Lognormal	Lively 2019 (base case and range)[4], Jackson 2021 (range),[12] Hall 2009 (range)[3]
Proportion with LRTI				
Age 0–5 mo	0.65	0.25–1.0	β	Assumption based on Rainisch 2020[13]
Age 6–23 mo	0.3	0.1–1.0	β	Assumption based on Rainisch 2020[13]
RSV mortality per hospitalization				
Age 0–5 mo	0.0010	0.0004–0.0020	β	Doucette 2016,[14] Hansen 2022[16]
Age 6–11 mo	0.0010	0.0004–0.0020	β	
Age 12–23 mo	0.003	0.0028–0.0034	β	Gupta 2016[15]

TABLE 1 Continued

Model Input Parameter	Base Case	Range	Distribution	Source
Intervention efficacy				
Initial efficacy (0—5 mo) against medically attended outpatient or ED RSV-associated LRTI	51.3%	29.4%—66.8%	β	Kampmann 2023[11]
Initial efficacy (0—5 mo) against hospitalized RSV-associated LRTI	56.8%	10.1%—80.7%	β	Kampmann 2023[11]
Efficacy 6—12 mo	0	—	—	
Adverse events				
RSVpreF				
Probabilities of maternal adverse events				
Systemic reaction	0	—	—	Kampmann 2023[11]
Injection site reaction	0.41	0.38—0.44	β	Kampmann 2023[11]
Probability of outpatient visit given Injection site reaction	0.02	0.015—0.025	β	Curran, 2019[34]
Hypothetical serious adverse event	0.000001	0—0.0002	β	(Guillain-Barre) Prosser 2006[35],a
Excess risk of prematurity from vaccination	0	0—0.02		Assumption, Kampmann 2023[11]
Maternal QALYs lost because of adverse events				
Injection site reaction	0	—	—	Assumption
Systemic reaction	0	—	—	Assumption
Serious adverse event	0.141	0.092—0.199	Lognormal	Prosser 2006[35]
Infant QALYs lost				
Late prematurity	0.03	0—1.2	Lognormal	Werner 2015,[36] Petrini 2008,[37] Hironen 2014,[38] Crump 2021,[39] Darcy-Mahoney 2016,[40] Carroll 2009,[41] Payakachat 2014[42]
Costs due to adverse events				
Cost of outpatient visit for systemic reaction (non-high-risk)	$313	$27–$1337	Lognormal	Marketscan unpublished, Deluca 2023[23]
Cost of outpatient visit for injection site reaction	$367.76	$23.15—$1758	Lognormal	Marketscan unpublished, Deluca 2023[23]
Recipient time for office visit (h)	2	1–3	Normal	Ray 2015[43]
Serious adverse event	$36 163.76	$10 372.31–$122 145.60	Lognormal	Prosser 2006[35]
Lifetime cost of late prematurity				
Medical	$23,241	$11 621–$46 482	Lognormal	Waitzman, Jalali, Grosse 2021[44]
Productivity	$11 447	$5724–$22 894	Lognormal	Waitzman, Jalali, Grosse 2021[44]
Maternal daily productivity	190	169.41—211.03	Lognormal	Grosse 2019[24],b
Cost inputs				
RSV-specific inpatient costs (per inpatient case)				
Age 0—11 mo	$11 487	4804—86 646	Lognormal	Bowser 2022[1],a
Age 12—23 mo	$11 469	4804—86 646	Lognormal	Bowser 2022[1],a
Days lost productivity	7.4	0–14	Lognormal	Fragaszy 2018,[25] Petrie 2016,[26] Van Wormer 2017[27]
RSV-specific ED costs (per ED visit)				
Age 0—11 mo	$563	544–581	Lognormal	Bowser 2022[1],a
Age 12—23 mo	$563	544–581	Lognormal	Bowser 2022[1],a
Days lost productivity	2.5	0–5	Lognormal	Fragaszy 2018,[25] Petrie 2016,[26] Van Wormer 2017[27]
RSV-specific outpatient costs (outpatient visit)				
Age 0—11 mo	$82	46–118	Lognormal	Bowser 2022[1],a
Age 12—23 mo	$82	46—118	Lognormal	Bowser 2022[1],a

TABLE 1 Continued

Model Input Parameter	Base Case	Range	Distribution	Source
Days lost productivity	2.5	0–5	Lognormal	Fragaszy 2018,[25] Petrie 2016,[26] Van Wormer 2017[27]
Lifetime productivity for those <1 y old	$1 795 936	1 346 951—2 244 919	Lognormal	Grosse 2019[24],c
Palivizumab costs (for both strategies)				
Fraction of children that are high-risk	1.6%	0%	1.6%	Sanofi[45]
Fraction of children at high-risk receiving palivizumab	75%	0%	100%	Sobi 2021[46]
Palivizumab cost per dose	$1228	—	—	Shahabi 2018[47]
Doses per patient	4.167[d]	—	—	Assumption
Maternal vaccination related costs				
RSVpreF per dose	$295[e]	50–500	—	Manufacturer, CDC[8]
RSVpreF administration	$16.96	15–22	Lognormal	Physician fee schedule,[48] HCPCS 90460
Maternal daily productivity	$190	169.41—211.03	Lognormal	Grosse 2019[24]
Discount rate	0.03	0.0—0.07	—	—
Quality of life lost because of RSV				
Quality-adjusted life-days[f] lost from acute RSV				
Outpatient				Glaser[28] (base case), Regnier[29] (lower bound), JIVE COVID/RSV Utilities (unpublished, upper bound)
Child	3.1	1.8—16.6	Lognormal	
Caregiver	1.5	0—9.1	Lognormal	
ED				
Child	4.9	2.9—16.6[g]	Lognormal	
Caregiver	2.5	0—9.1	Lognormal	
Hospitalized				
Child	6.2	3.7—26.5	Lognormal	
Caregiver	2.4	0—13.6	Lognormal	
Discounted QALYs lost from death				
First year of life	28.40	—	—	Calculated from year 2020 life tables[49]
Second year of life	28.38	—	—	

CDC, Centers for Disease Control and Prevention; JIVE/COVID RSV Utilities, Joint Initiative in Vaccine Economics unpublished study of RSV utilities; NVSN, New Vaccine Surveillance Network. —, ranges and distributions are not varied in sensitivity analyses.

Efficacy is assumed to be effective against LRTI only in the base case (0% efficacy against non-LRTI outcomes). Distribution is used for the probabilistic sensitivity analysis. The mean is the same as the base case value with a SD of one-quarter of the range.

[a] This is based on the CDC New Vaccine Surveillance Network (NVSN) hospitalization rates from December 2016 to September 2020 for children under 2 years of age.

[b] The daily productivity rate is calculated by dividing mean annual total productivity (both market and nonmarket) for ages 15 to 99 by 365 days and inflated from the 2016 to the 2022 value using the Federal Reserve gross domestic product implicit price deflator.

[c] Lifetime productivity is taken from Table 2 of Grosse[24] for age 0 lifetime total productivity (both market and nonmarket) assuming 1% annual productivity growth and a 3% discount rate and inflated from 2016 to 2022 dollars using the Federal Reserve gross domestic product implicit price deflator.

[d] Based on an assumption, 66% receive 5 doses and 8.3% each receive 4, 3, 2, and 1 doses.

[e] The price list price was not published until after the ACIP recommendation was made.

[f] A quality-adjusted life-day is 1/365 of a QALY.

[g] The upper bound for sensitivity analysis utilities was not directly measured for the ED in the JIVE/COVID RSV Utilities study, but outpatient values were used.

in the trial. We also explored other functional forms for waning efficacy for alternative scenarios. One was a constant rate for efficacy during the first 180 days (Supplemental Fig 5B). The authors of another analysis used more optimistic assumptions that the efficacy against RSV-associated hospitalization was equivalent to the reported efficacy against severe medically attended RSV LRTI for full-term infants, and efficacy declined moderately during the first 6 months and then declined to zero efficacy at 10 months (Supplemental Fig 5C).[20] The Supplemental Information includes more detail on the precise definitions of efficacy scenarios and how they comport with trial data.

Maternal vaccine adverse event rates for injection site and systemic reactions came from the phase 3 clinical trial reports[11] (Table 1). The trial did not observe differential rates of systemic reactions in the vaccine and placebo groups, but we included a rate of 1 in 1 million of a hypothetical serious adverse event. We also included a 41% chance of injection site reaction. The Supplemental

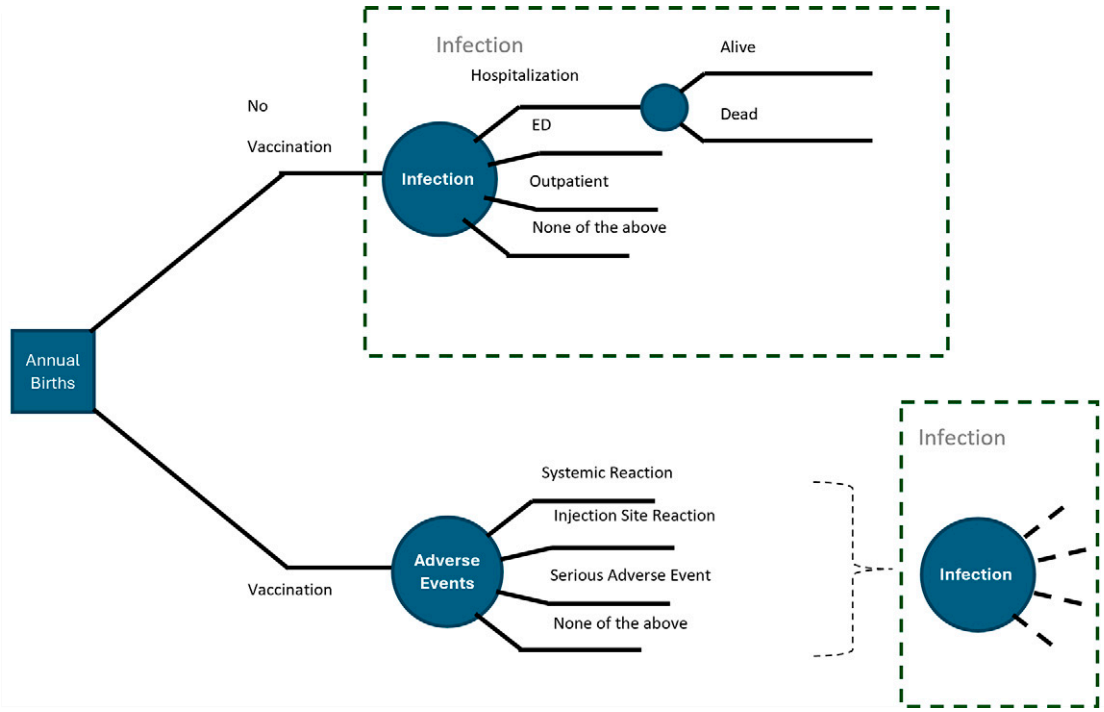

FIGURE 1
Decision tree model diagram.

Information includes the logic behind the serious adverse event and preterm birth assumptions.

In our model of the RSVpreF policy, we assumed that 50% of pregnant persons intend to vaccinate between the beginning of week 32 and the end of week 36 (the weeks recommended for vaccination).[21] Although the fraction of pregnant persons vaccinated affects the overall population-wide outcomes, it does not affect the ICERs. We assumed births occurring within 2 weeks of vaccination received no protection against RSV illness (Supplemental Fig 6).[22] For those born premature, if they were born >2 weeks after vaccination, we assumed full protection.

Because the trial results did not reveal efficacy against upper respiratory tract infection (URTI), we assumed that RSVpreF vaccination had zero efficacy against RSV URTI.

Costs

The cost of RSVpreF was set to $295 on the basis of its private sector cost per dose.[8] We assumed it would be provided at a routine obstetrics visit, so we did not include direct and indirect costs associated with an extra health care visit, but we did include the cost to administer the vaccine (Table 1). We included costs of palivizumab for high-risk infants (Table 1). We assumed RSVpreF immunization did not affect palivizumab utilization. Medical costs of adverse events were derived from a MarketScan analysis on adverse events associated with influenza vaccination.[23] We also included productivity losses from RSV disease and adverse events (Table 1).[24] RSV health care utilization costs were from a systematic literature review of RSV disease costs in infants (Table 1).[1] We also included caregiver productivity losses from infant infections, and infant productivity losses from RSV-related deaths (Table 1).[25–27] Because we take a societal perspective, we also included overall general health care costs including those not related to RSV (Supplemental Table 5).

Quality Adjustments

We included both quality-adjusted life-years (QALYs) lost by the child and QALYs lost by caregivers during the child's illness. A systematic review of the literature on the impact of RSV on child and caregiver quality of life[28] was used for our base case QALYs lost from RSV-related hospitalizations, ED visits and outpatient visits. We based the lower bound on a study by Regnier[29] and the upper bound was based on an unpublished preference survey of parents of children who had experienced RSV illness (Table 1). We also included QALYs lost from deaths on the basis of lost quality-adjusted life expectancy (Table 1).

Analysis

Health and Economic Outcomes

The model simulated RSV LRTI-associated outpatient visits, ED visits, hospitalizations, and deaths to calculate total medical and indirect costs, QALYs lost and an ICER in

terms of dollars per QALYs gained when comparing RSVpreF vaccination with no vaccination. We also reported number needed to vaccinate to prevent an undesirable RSV disease outcome (eg, number of pregnant persons needed to vaccinate to prevent an infant RSV-associated hospitalization or death) as well as the cost per RSV disease outcome averted (eg, cost per hospitalization or death averted). Costs are reported in 2022 US dollars, for a 1-year policy time frame, and costs and outcomes are discounted at 3%. We used Microsoft Excel 365 to calculate the results.

Sensitivity and Scenario Analyses

We conducted a variety of 1-way, two-way, and probabilistic sensitivity analyses (Supplemental Table 6). We conducted several scenario analyses with varying efficacy assumptions. We also evaluated a combination of assumptions on efficacy, hospitalization costs, and mortality risks. Because RSV is seasonal, we also examined several scenarios assuming RSVpreF would be administered at different times of the year. Probabilistic sensitivity analysis assigned distributions to all input parameters (see Table 1) and conducted 1000 Monte Carlo simulation iterations to calculate 95% credible intervals and to calculate uncertainty in overall results using cost-effectiveness acceptability curves.

Finally, we explored an additional scenario in which we assume the infant will also be receiving nirsevimab (regardless of infant risk; Supplemental Table 7).[10] This is comparing a combined strategy of RSVpreF administration and nirsevimab with a strategy of nirsevimab administration alone (the base case analysis involves the assumption that nirsevimab is not administered). No studies are available that have directly compared antibody levels or effectiveness among those infants who received nirsevimab with infants born to people who received an RSV vaccine during pregnancy. Because we lack clinical evidence of combined RSVpreF and nirsevimab efficacy, we assumed the efficacy of combined RSVpreF and nirsevimab protection to be the higher efficacy of either RSVpreF or nirsevimab at a particular age of the infant at a particular time (Table 1 and Supplemental Fig 7).

RESULTS

Health and Economic Impact of Vaccination

Our model projects that vaccinating approximately half of pregnant persons with the RSVpreF vaccine during weeks 32 through 36 of gestation (Supplemental Fig 6) would avert 7571 (16%) hospitalizations each year (Table 2) while causing 725 501 pregnant persons to experience injection site reactions and 1.8 serious adverse events. To prevent 1 RSV LRTI hospitalization among infants would require 234 pregnant persons to be vaccinated during pregnancy with RSVpreF.

Although an additional $666 million would be spent on RSVpreF and its administration, $100 million in medical costs would be saved and $53 million in productivity costs would be saved, leading to an annual societal net investment of $513 million (Table 3).

The model projects a net gain of 1294 QALYs, 943 from the children and 351 from their caregivers because

TABLE 2 Cost-Effectiveness Outcomes for Maternal RSV Vaccine

Intervention Strategy	RSV Outcomes						
	Lower Respiratory or Total	No. Outpatient Visits (95% Credible Interval)	No. ED Visits (95% Credible Interval)	No. Inpatient Visits (95% Credible Interval)	No. Deaths (95% Credible Interval)	Costs in Millions (95% Credible Interval)	QALYs Lost (95% Credible Interval)
No vaccination	LRTI	392 446 (142 364 to 643 076)	142 449 (72 535 to 198 938)	47 758 (41 846 to 53 990)	48 (18 to 95)		
	Total	846 451 (567 354 to 880 777)	243 675 (205 251 to 250 016)	47 758 (41 846 to 53 990)	48 (18 to 95)	1651 (855 to 3896)	18 151 (6827 to 43 251)
RSVPreF maternal vaccination*	LRTI	346 753 (120 119 to 588 093)	126 584 (64 976 to 178 190)	40 187 (33 685 to 47 924)	40 (0 to 0)		
	Total	800 759 (547 649 to 842 140)	227 810 (194 459 to 238 883)	40 187 (0 to 42 879)	40 (15 to 81)	2164 (1431 to 4055)	16 857 (6255 to 40 499)
Difference	LRTI	−45 693 (−74 816 to −14 386)	−15 866 (−26 188 to −5154)	−7571 (−53 856 to −5819)	−8 (−17 to −2)		
	Total	−45 693 (−74 816 to −14 386)	−15 866 (−26 188 to −5154)	−7571 (−53 856 to −5801)	−8 (−17 to −2)	513 (126 to 665)	−1,294 (−2891 to −469)
Cost per outcome averted	Total	11 224 (2770 to 39 413)	32 324 (7792 to 108 076)	67 735 (2723 to 97 263)	67 735 135 (12 125 466 to 315 160 690)	N/A	396 280 (75 565 to 1 253 765)

Negative numbers in the "difference" row indicate "gains" or events "saved" with the RSVpreF arm compared with no vaccination. Positive numbers indicate "worse" outcomes like increased costs.

* RSVpreF maternal vaccination intended for 50% of the US birth cohort administered in weeks 32 through 36 of gestation.

TABLE 3 Resulting Costs (in Millions of 2022 US Dollars) Lost From Pediatric RSV

Intervention Strategy	Medical						Productivity					Total
	Intervention (95% Credible Interval)	Outpatient (95% Credible Interval)	ED (95% Credible Interval)	Inpatient (95% Credible Interval)	Total RSV Medical (95% Credible Interval)	Total Health System (95% Credible Interval)	Outpatient (95% Credible Interval)	ED (95% Credible Interval)	Inpatient (95% Credible Interval)	Deaths (95% Credible Interval)	Total Productivity (95% Credible Interval)	(95% Credible Interval)
No vaccination	225 (103 to 398)	69 (38 to 101)	137 (116 to 142)	549 (25 to 2744)	755 (216 to 2960)	980 (387 to 3193)	402 (121 to 871)	116 (39 to 260)	67 (24 to 147)	86 (31 to 175)	671 (338 to 1161)	1651 (855 to 3896)
RSVPreF maternal vaccination*	891 (710 to 1148)	66 (36 to 96)	128 (109 to 136)	462 (21 to 2353)	656 (200 to 2529)	1547 (989 to 3457)	380 (114 to 823)	108 (36 to 242)	57 (20 to 124)	72 (26 to 149)	617 (308 to 1078)	2164 (1431 to 4055)
Difference	666 (606 to 750)	−4 (−7 to −1)	−9 (−15 to −3)	−87 (−470 to −3)	−100 (−481 to −13)	566 (185 to 708)	−22 (−54 to −4)	−8 (−19 to −2)	−11 (−26 to −3)	−14 (−32 to −3)	−53 (−95 to −23)	513 (126 to 665)

Negative numbers in the "difference" row indicate savings with the RSVpreF arm compared with no vaccination.

* RSVpreF maternal vaccination intended for 50% of the US birth cohort administered in weeks 32 through 36 of gestation.

of lower RSV burden (Table 4). The societal cost of RSVpreF vaccination for pregnant persons is $396 280 per QALY gained and $67 735 per RSV LRTI-associated hospitalization averted (Table 2). From a health system perspective, the cost is $437 607 per QALY gained (Supplemental Table 8).

Sensitivity and Scenario Analyses

We conducted many sensitivity and scenario analyses (Supplemental Table 6). The results are sensitive to a wide number of inputs and assumptions (Fig 2). Specifically, for the first 1 percentage point increase in the risk of prematurity from the vaccine (ie, from 0% to 1%), the societal ICER increased almost 4 times (up to >$1.4 million per QALY saved) mostly because of the dramatic losses in QALYs (Supplemental Fig 8). If quality of life losses from RSV were measured by using the highest QALY loss values for children and their caregivers for all types of RSV LRTI events, then the ICER dropped to $95 313 per QALY gained. However, when RSV QALY losses were measured by using their lowest values for children and when caregivers did not experience any QALY losses, the societal cost increased up to $794 009 per QALY gained. Other influential factors in order of the magnitude of their effect on cost-effectiveness (Fig 2) were the RSVpreF vaccine cost per dose (Fig 3), inpatient medical costs, the potential effect of RSV on URTI, and RSV mortality.

The alternative assumption of constant 6-month vaccine efficacy (Supplemental Fig 5B) did not have a considerable impact on the ICER, as it reduced the societal cost to $361 679 per QALY gained, ∼8.8% reduction (Supplemental Table 9). However, the alternative assumption of more optimistic efficacy (Supplemental Fig 5C) did have a bigger impact on the ICER, dropping the cost to $282 287 per QALY gained, ∼28% reduction (Supplemental Table 9).

Supplemental Figure 9 shows a scenario analysis varying vaccine efficacy, hospitalization cost, and RSV mortality. If RSV hospitalizations are more expensive or associated with higher mortality, maternal RSVpreF vaccination becomes more cost-effective. In special circumstances, combining high vaccine efficacy with high hospitalized mortality (1%), and high cost per hospitalization ($45 000), RSVpreF vaccination could potentially be cost-saving (ie, cost per QALY saved <0).

In the probabilistic sensitivity analysis, we found 3% of simulations had a societal cost <$100 000 per QALY saved, 8% of simulations had a societal cost <$200 000 per QALY saved, and 53% had a cost <$500 000 per QALY saved (Supplemental Fig 10).

We also evaluated scenarios related to the timing of RSVpreF administration (Supplemental Fig 11). The ICER of RSVpreF varied widely on the basis of the month of administration (Supplemental Fig 11A). Specifically, the ratios of cost per QALY saved when RSVpreF is administered

TABLE 4 QALYs Lost From Pediatric RSV to Infants and Their Caregivers

Intervention Strategy	Adverse Events (95% Credible Interval)	Outpatient		ED		Inpatient		Deaths	Total		Grand Total (95% Credible Interval)
		Child (95% Credible Interval)	Caregiver (95% Credible Interval)	Child (95% Credible Interval)	Caregiver (95% Credible Interval)	Child (95% Credible Interval)	Caregiver (95% Credible Interval)	Child (95% Credible Interval)	Child (95% Credible Interval)	Caregiver (95% Credible Interval)	
No vaccination	0 (0 to 0)	7153 (635 to 27 034)	3580 (211 to 17 460)	3290 (748 to 9186)	1645 (240 to 5543)	807 (127 to 2884)	320 (24 to 1360)	1356 (506 to 2703)	12 606 (4156 to 33 120)	5545 (1051 to 19 742)	18 151 (6827 to 43 251)
RSVPreF maternal vaccination*	0 (0 to 2)	6766 (601 to 25 695)	3387 (201 to 16 340)	3075 (700 to 8520)	1538 (225 to 5169)	679 (106 to 2421)	269 (20 to 1146)	1141 (420 to 2302)	11 663 (3753 to 31 078)	5194 (975 to 18 666)	16 857 (6255 to 40 499)
QALYs gained	0 (0 to 2)	386 (−1542 to −25)	193 (−958 to −9)	214 (−638 to −32)	107 (−386 to −11)	128 (−472 to −15)	51 (−230 to −3)	215 (−494 to −52)	943 (−2243 to −320)	351 (−1212 to −66)	1294 (−2891 to −469)

Negative numbers in the "QALYs gained" row indicate losses with the RSVpreF arm compared with no vaccination.
* RSVpreF maternal vaccination intended for 50% of the US birth cohort administered in weeks 32 through 36 of gestation.

to pregnant persons right before or at the start of the RSV season were much lower. With the complex interaction of seasonality, decreasing hospitalization risk with age, and decreasing vaccine efficacy after birth, the most cost-effective month to administer RSVpreF is anticipated to be in November, right at the start of the expected RSV season, with a societal cost of $107 544 per QALY gained (Supplemental Fig 11A). Administration of RSVpreF during the range of months from September through January would cost $163 513 per QALY gained (Supplemental Fig 11B).

Lastly, we simulated a scenario with RSVpreF vaccination added in an environment in which nirsevimab was expected to be administered (ie, comparing RSVpreF vaccination and nirsevimab administration to the infant with only nirsevimab administration). In this scenario, the ICER increases dramatically, because RSVpreF offers marginal additional protection beyond what might be expected from nirsevimab alone. In that case, the best month to vaccinate pregnant persons would be in April (because this model involves the assumption that nirsevimab will be administered in October for children born in April, and RSVpreF would result in protection during the tail end of the RSV season during April); however, the ICER was still high at $2.4 million per QALY saved (Supplemental Fig 12). The ICERs of RSVpreF administration during other months are even higher in this scenario.

DISCUSSION

Our model reveals that year-round maternal vaccination of half of the pregnant persons with RSVpreF during 32 through 36 weeks' gestation will decrease RSV LRTI medical events (ie, outpatient and ED patient visits, hospitalizations, and deaths) but will also increase societal costs, resulting in $396 280 per QALY saved. RSVpreF has the potential to be cost-effective under certain conditions and in specific situations. The magnitude of QALYs lost because of RSV illness can raise or reduce the ICER. The vaccine cost per dose and mortality associated with RSV illness also can impact the ICER. In addition, the month in which RSVpreF is administered has a significant impact on the ICER. The ACIP recommendation was limited to seasonal administration (ie, September to January for most of the United States), in part to maximize cost-effectiveness and benefits.[9] Administration in September through January had an ICER of $163 513 per QALY saved. Finally, if vaccination increases the risk of prematurity, the societal costs per QALY saved with RSVpreF vaccination will substantially increase.

To our knowledge, there are no published cost-effectiveness studies on maternal vaccination to prevent RSV disease in US infants. There has been, however, another unpublished manufacture-sponsored cost-effectiveness analysis that was also discussed and summarized for ACIP consideration and decision-making.[20] Although there were

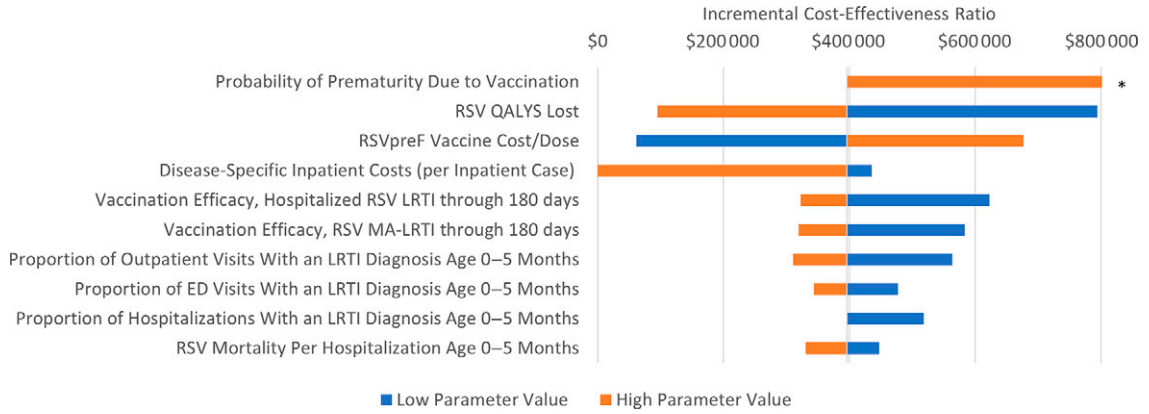

FIGURE 2

One-way sensitivity analyses. MA, medically attended. The ICER measures the cost per QALY saved of RSVpreF use in pregnant persons at weeks 32 through 36 of gestation. The colored bars reveal how the ICER can change as the parameter assumptions change. In this figure, parameters are ranked by their influence on the base case ICER. For example, if the RSVpreF cost per dose is low (blue bar), then the ICER drops to $61 281 per QALY gained. If the cost per dose is high (orange bar), then the ICER rises to $676 586 per QALY gained. * If the excess probability of prematurity due to vaccination increases to 2%, the ICER increases to >$7.4 million per QALY gained.

considerable similarities in the modeling approach and sources of inputs, the authors of this other analysis reported substantially lower ICERs (ie, ~$85 000 per QALY saved). The main reason for the difference in ICER with our model is the selection of inputs and the adoption of critical assumptions. Among the most influential assumptions, the manufacturer's analysis adopts (1) a relatively higher initial efficacy, (2) a longer assumption for the duration of protection, with a linear decay in efficacy finally reaching 0% at 9 months, and (3) higher medical costs for hospitalization and ED and outpatient visits.

In our base case analysis, we focused on comparing RSVpreF with no vaccination. This baseline scenario does not consider the use of nirsevimab. In our analysis of nirsevimab compared with no immunization, we found a lower ICER of $153 517 per QALY saved, suggesting that it would be more cost-effective compared with RSVpreF alone.[10] Caution is urged in directly comparing the results of these models because the model inputs are based on efficacy trials with different definitions of outcomes, and the duration of the protection of both products remains unknown. In an environment in which nirsevimab is expected to be used, adding RSVpreF vaccination in addition to nirsevimab administration dramatically increases costs, with only marginal improvements in health. However, this analysis relies on speculative assumptions because there

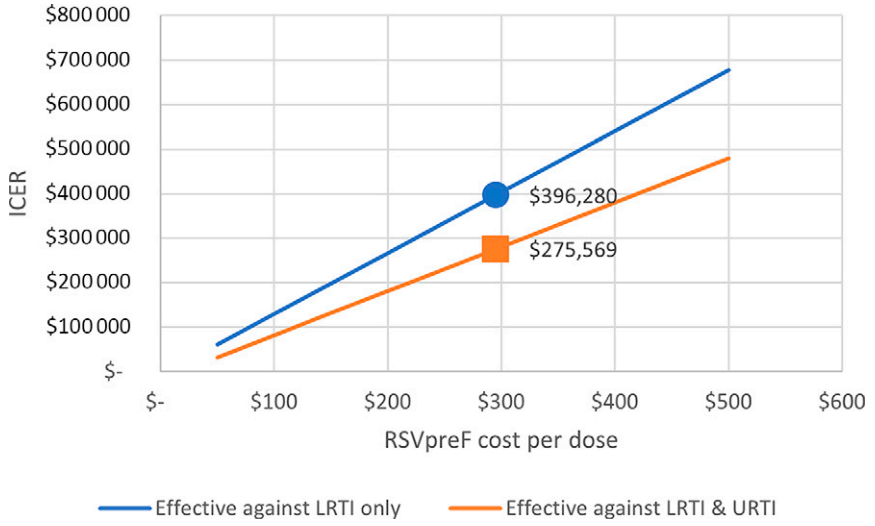

FIGURE 3

The effect of varying cost per dose of RSVpreF on the ICER for preventing RSV LRTI (base case) or when assuming equal efficacy also preventing RSV URTI (Scenario). The dot represents the base case cost of RSVpreF of $295 per dose.

are no trials that have measured the combined efficacy of administering nirsevimab to an infant born to a person who had been vaccinated with RSVpreF. The Centers for Disease Control and Prevention recommends the use of either RSVpreF in pregnant people or nirsevimab in infants, but administration of both products is not needed for most infants.[9]

Our analysis is subject to several limitations. As a model-based analysis, the results are subject to model structure and input choices. No data on RSV outcomes in pregnant persons from the clinical trials data are available, and the model involves the assumption that the RSV vaccine does not prevent the transmission of RSV. Because the RSVpreF vaccine reduces RSV disease in individuals other than infants, the cost-effectiveness of RSVpreF vaccination would improve. However, those of childbearing age are generally at low risk of RSV, and pregnancy is not known to be a risk factor for severe outcomes with RSV.[30,31] The model also does not include specific explicit clinical risk groups that stratify infants at increased risk for severe RSV illness because the vaccine was designed to be administered to a general population. With that said, our model inputs are designed to represent the general population of infants. Our analysis also does not include any impact of RSVpreF vaccination on disease transmission dynamics. Although a 2016 model-based analysis of a theoretical RSV vaccine reveals that the protection of children may reduce RSV infections in other unvaccinated populations,[32] there is no evidence the RSVpreF vaccine reduces transmission. If maternal RSVpreF vaccination were to reduce population RSV transmission, then our ICER would be expected to decrease. Additionally, infant RSV antibody levels could be reduced if the mother had a poor immune response to the vaccine (eg, immunocompromising conditions) or had a condition associated with reduced transplacental antibody transfer (eg, HIV).[33] We were also uncertain of a variety of inputs, particularly related to vaccine effectiveness, QALYs lost from RSV, and prematurity. These and other assumptions can dramatically change the cost-effectiveness of RSVpreF. Additional research on these assumptions may be valuable.

CONCLUSIONS

A seasonal maternal vaccination program with RSVpreF aimed at preventing RSV LRTI in infants is likely to decrease the disease burden of RSV LRTI but at a sizable societal cost. RSVpreF has the potential to be cost-effective in specific circumstances, particularly when administered at the ideal gestational and seasonal time.

ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
ED: emergency department
ICER: incremental cost-effectiveness ratio
LRTI: lower respiratory tract infection
QALY: quality-adjusted life-year
RSV: respiratory syncytial virus
RSVpreF: respiratory syncytial virus bivalent prefusion F maternal vaccine
URTI: upper respiratory tract infections

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