

Estimated Burden of Childhood Asthma Attributable to Infant RSV Lower Respiratory Tract Infection in the United States: A Modeling Study

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Title: Estimated Burden of Childhood Asthma Attributable to Infant RSV Lower Respiratory Tract Infection in the United States: A Modeling Study

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ABSTRACT

Background: Respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) is associated with subsequent childhood asthma. If causal, infant RSV LRTI would account for a substantial share of childhood asthma.

Methods: We developed a population-based model integrating national surveillance and epidemiologic data to estimate the fraction of asthma at age 6 attributable to medically attended infant RSV LRTI. The RSV LRTI-asthma odds ratio, 3.02 (95% CI 1.79–5.11), was derived from an asthma-restricted reanalysis of a published systematic review and meta-analysis. A secondary analysis estimated the RSV-attributable burden averted by a national nirsevimab program. The attributable fraction assumes the association is causal.

Results: In a modeled US birth cohort, we estimated 379,659 (95% uncertainty interval [UI] 204,518–544,801) medically attended RSV LRTI episodes during infancy. An estimated 46,663 (95% UI 17,104–83,969) cases of asthma at age 6, or 14.5% (95% UI 5.3–25.8) of the total, would be attributable to RSV LRTI. Using the published estimate of 2.45 (95% CI 1.23–4.88) from studies controlling for familial predisposition, the attributable fraction was 11.1% (95% UI 1.7–24.1). At 50% nirsevimab coverage, 12,804 (95% UI 4,648–24,050) cases, or 27.4% (95% UI 19.9–37.2) of the attributable burden, would be averted.

Discussion: Approximately 11–14% of childhood asthma at age 6 may be attributable to infant RSV LRTI, depending on the effect estimate used. Estimates of RSV impact that consider only acute outcomes may underestimate the benefits of prevention.

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INTRODUCTION

Infant respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) is a major cause of respiratory morbidity during infancy and has been associated with subsequent childhood asthma.^{1,2} Epidemiologic studies report a consistent association, including evidence of stronger effects following more severe early-life disease, and mechanistic studies support biological plausibility.³ Approximately 8.8% of US children aged 5–11 years have current asthma.⁴ Existing estimates of RSV-attributable asthma burden derive from individual cohorts and a systematic review,⁵⁻⁷ and the national burden in the United States has not been estimated. RSV immunization policy is informed by burden estimates that only count acute outcomes. If the association with asthma is causal, those estimates omit a large share of the total health burden that RSV prevention could avert.

We developed a population-based model to estimate the national burden of childhood asthma attributable to infant RSV LRTI in the United States.

METHODS

We developed a three-stage population-based model to estimate childhood asthma burden attributable to infant RSV LRTI in the United States. Detailed model structure, inputs, sources, and distributional assumptions are provided in the appendix (pp 2–7, 13).

Estimand and causal framework. Our estimand was the proportion of childhood asthma at age 6 attributable to medically attended RSV LRTI during the first year of life in a US annual birth cohort, reported as a population attributable fraction and as attributable cases. The attributable fraction compared burden in the absence of a national RSV prevention program (natural history scenario) with burden under a counterfactual scenario in which no infant experienced medically attended RSV LRTI. Children whose RSV infection was not medically attended or occurred after infancy were considered unexposed. We assumed no more than one

RSV LRTI episode during infancy per child. Interpreting this quantity as attributable burden requires that the association between infant RSV LRTI and subsequent asthma is causal. The counterfactual scenario defines the attributable fraction and is not an achievable level of prevention.

Stage 1: incidence of medically attended RSV LRTI. We parameterized medically attended RSV LRTI in infancy using a decision-analytic model previously developed in collaboration with the US Centers for Disease Control and Prevention (CDC).⁸ The model combines age- and care-setting-specific rates of RSV-associated medical encounters with national RSV seasonality, so modeled RSV risk varies with both age and calendar month. Hospitalization rates were derived from the CDC New Vaccine Surveillance Network (NVSN) using active prospective surveillance from 2016–20. Emergency department and outpatient rates were from NVSN surveillance conducted from 2000–09. The model classified all RSV-associated hospitalizations as LRTI and applied age-specific LRTI proportions to other encounters, based on a prior modeling study of RSV immunization strategies.⁹ Calendar-month seasonality was derived from monthly proportions of RSV detections reported to the CDC National Respiratory and Enteric Virus Surveillance System, 2015–19. We applied these rates to a national birth cohort of 3,664,292 infants and modeled monthly encounters during the first year of life, assuming a uniform monthly distribution of births and stable age-specific RSV incidence across the surveillance periods from which the rates were derived.

We limited analyses to medically attended RSV LRTI during the first year of life because this exposure has the strongest and most consistently reported association with subsequent asthma and the claims data used to identify unique episodes covered only the first RSV season.^{3,7,10,11} Medically attended RSV LRTI incidence declines after infancy, steeply for hospitalization and modestly in ambulatory settings.^{12,13}

Stage 2: derivation of unique RSV LRTI episodes. We summed encounters across settings and adjusted for multiple encounters associated with the same illness episode. The relationship between encounters and episodes was derived from a retrospective study of healthcare utilization during acute RSV LRTI among US infants during their first RSV season, which applied two ICD-10-CM case definitions.¹⁴ We used the broad definition, which retains all RSV-coded events and adds events coded as unspecified bronchiolitis. This definition better matched our incidence inputs because surveillance used broad acute respiratory illness criteria, RSV testing is not routine in non-hospitalized infants, and infant bronchiolitis during the RSV season is predominantly caused by RSV.^{15,16} We weighted ratios of episodes to encounters from commercial and Medicaid claims by national estimates of insurance coverage among US children, yielding a correction factor of 65.3% (95% UI 65.1–65.5) so that 100 encounters correspond to approximately 65 unique episodes. Under the narrow definition, the correction factor was 59.7% (95% UI 59.5–60.0).

Stage 3: effect estimate, prevalence anchor, and attributable burden. We drew the effect estimate from a WHO-commissioned systematic review and meta-analysis of laboratory-confirmed RSV LRTI and subsequent wheezing illness.² To align with our exposure and outcome definitions, the lead author of that review (SMB) conducted a post hoc reanalysis of the published dataset, restricted to estimates in which the outcome was described as asthma and ascertained at age 6 or later, and modeled so that the estimate also reflects exposure confined to the first year of life. The reanalysis yielded an adjusted odds ratio of 3.02 (95% CI 1.79–5.11), which we used as the primary effect estimate. The conditional intercept was selected to match our estimand: asthma at age 6 following medically attended RSV LRTI confined to the first year of life, among studies limiting genetic confounding. Details of the model specification and alternative estimates are given in the appendix (pp 7–9). The published estimate of 2.45, which retains adjustment for familial predisposition but includes a broader spectrum of wheezing

illness and RSV LRTI exposure outside the first year of life, is reported as a sensitivity analysis. The source review did not stratify by care setting, so a single effect estimate was applied to outpatient, emergency department, and hospitalized episodes.

Baseline asthma prevalence came from CDC national asthma surveillance. Current asthma was defined by parent or guardian report that a healthcare provider had ever diagnosed the child with asthma and that the child still had asthma. We used the estimate for children aged 5 to 11 years, 8.8% (95% CI 8.1–9.6), the narrowest age band containing age 6.⁴ We modeled asthma at age 6 because preschool wheezing is common and largely transient, and most of it has resolved by school age.¹⁷

Asthma prevalence among children without (P0) and with (P1) prior RSV LRTI was derived by solving the odds ratio jointly with national asthma prevalence expressed as the exposure-weighted average of P0 and P1. The corresponding relative risk was calculated directly as P1/P0. P0, P1, and the relative risk were calculated within each simulation trial from that trial's sampled values. Combining an adjusted odds ratio with an unadjusted prevalence introduces noncollapsibility bias. At this baseline risk, the bias is small and would slightly overstate the attributable fraction.¹⁸ The attributable fraction was the proportional reduction in all-cause asthma prevalence between the natural history scenario and the counterfactual scenario. A step-by-step derivation is in the appendix (p 14).

Uncertainty. We evaluated uncertainty using Monte Carlo simulation with 10,000 trials.

Lognormal distributions were used for incidence parameters, the prevalence anchor, and the effect estimate. Beta distributions were used for proportions, including the LRTI proportion of events from surveillance, the encounter-to-episode correction factor, and nirsevimab effectiveness. The correction factor interval reflects sampling variability in the mean number of encounters per episode. Population size, birth cohort size, and insurance coverage proportions were held fixed. Parameters were sampled independently, except that incidence in adjacent

months of age was correlated at 0.75. Correlation between different parameters drawn from overlapping data sources was not modeled. Point estimates reflect base-case parameter values, and 95% uncertainty intervals (UIs) are the 0.025 and 0.975 quantiles of simulated values.

Secondary analysis. We estimated how much of the RSV-attributable burden would be averted by a national nirsevimab program at 50% coverage. Through the 2025–26 US RSV season, reported infant RSV monoclonal antibody coverage ranged from 40– 60%.¹⁹ Nirsevimab performance (efficacy, duration of protection, and waning) was derived from trial data and expert opinion in a model developed in collaboration with CDC collaborators and vetted by the Advisory Committee on Immunization Practices (ACIP) RSV Work Group.⁸ Efficacy against medically attended RSV LRTI was parameterized as 79.0% during months 1 to 5, declining to 25% thereafter and then to 0% by month 10, with the transition modeled using a sigmoid function. Reported coverage is not disaggregated by product, and we modeled nirsevimab alone. This analysis does not estimate the impact of prevention as currently delivered. Optimization across products or coverage scenarios was outside the scope of this study.

Sensitivity analyses. Post hoc sensitivity analyses examined how the attributable fraction and averted burden depended on the incidence of RSV LRTI episodes, effect estimate, case definition, and prevention assumptions. For the attributable fraction, one-way sensitivity analysis varied each input across its uncertainty interval while holding the others at their point estimates to show which inputs most influenced the estimate. We then repeated the primary analysis under two alternative specifications: the published odds ratio of 2.45 in place of the asthma-restricted estimate, and the encounter-to-episode correction factor derived under the narrow case definition. For averted burden, we repeated the secondary analysis at 90% nirsevimab coverage with base-case efficacy, and at 50% coverage with effectiveness and waning derived from post-licensure studies.

Statistical software. Analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Research ethics. Because this study used publicly available aggregate data without direct human participant involvement, institutional review board approval was not required.

Role of the funding source. This research was supported by the University of Maryland, Baltimore through a Targeted Pivoting Programmatic Research Grant. The funder had no role in study design, data collection, analysis, interpretation, or the decision to submit for publication.

RESULTS

RSV LRTI burden during the first year of life. In a US birth cohort of 3,664,292 infants, the model estimated 581,346 (95% UI 313,569–833,450) medically attended RSV LRTI encounters during infancy across outpatient, emergency department, and hospital settings (Table 1). Encounters exceed episodes because a single illness can involve more than one care setting. After adjustment, this corresponded to 379,659 (95% UI 204,518–544,801) unique RSV LRTI episodes, an incidence of 10.4% (95% UI 5.6–14.9) of the modeled cohort.

Asthma burden at age 6 attributable to infant RSV LRTI. With the adjusted odds ratio of 3.02 calibrated to a national asthma prevalence of 8.8%, asthma prevalence at age 6 was 7.5% (95% UI 6.4–8.6) among children without prior medically attended RSV LRTI and 19.8% (95% UI 13.7–27.9) among those with it, corresponding to a relative risk of 2.63 (95% UI 1.68–4.07) (Table 1).

An estimated 322,458 (95% UI 295,513–349,389) children in the modeled cohort would have had asthma at age 6, corresponding to an asthma prevalence of 8,800 (95% UI 8,065–9,535) per 100,000 children. Under the counterfactual scenario, in which no infants have RSV LRTI, 275,795 (95% UI 234,061–316,212) children would have had asthma at age 6 (Figure 1).

If the association is causal, the difference corresponds to 46,663 (95% UI 17,104–83,969) cases of asthma at age 6 attributable to medically attended RSV LRTI during infancy, or 14.5% (95% UI 5.3–25.8) of the total burden.

Sensitivity analyses of the attributable fraction. Varying the adjusted odds ratio across its 95% UI changed the attributable fraction from 6.6% to 24.2%, varying modeled RSV LRTI incidence changed it from 8.2% to 19.8% (Figure 2). The asthma prevalence anchor and encounter-to-episode correction had little influence, with attributable fractions of 14.2% to 14.7% and 14.4% to 14.5%, respectively.

With the published estimate of 2.45, the attributable fraction was 11.1% (95% UI 1.7–24.1). With the narrower encounter-to-episode case definition, the attributable fraction was 13.4% (95% UI 4.9–24.0).

Secondary analysis: asthma burden averted under modeled nirsevimab coverage. With modeled 50% nirsevimab coverage, RSV LRTI episodes fell to 275,482 (95% UI 142,313–406,782). An estimated 12,804 (95% UI 4,648–24,050) attributable asthma cases were averted, 27.4% (95% UI 19.9–37.2) of the attributable burden and 4.0% (95% UI 1.5–7.4) of all asthma at age 6, leaving 33,858 (95% UI 11,998–61,615) residual attributable cases. All-cause asthma prevalence at age 6 under modeled nirsevimab coverage was 8,451 (95% UI 7,701–9,225) per 100,000 children (Table 2).

Sensitivity analyses of asthma burden averted under modeled nirsevimab coverage.

Compared with 27.4% averted in the base case, increasing coverage to 90% under the original effectiveness profile averted 23,047 asthma cases (95% UI 8,410–42,941), 49.4% (35.7–67.3) of the attributable burden and 7.1% (2.6–13.3) of all-cause asthma. At 50% coverage, applying the post-licensure effectiveness profile averted 10,718 cases (95% UI 3,943–18,622), 23.0%

(95% UI 19.7–26.3) of the attributable burden and 3.3% (95% UI 1.2–5.8) of all-cause asthma. Neither assumption altered the attributable fraction.

DISCUSSION

We estimate that 14.5% of asthma cases at age 6 in the United States may be attributable to RSV LRTI during infancy, corresponding to approximately 47,000 attributable cases among children born in a single year. Using the previously published odds ratio of 2.45 instead of the asthma-restricted estimate of 3.02, the attributable fraction was 11.1%. The restricted estimate better matches this analysis because it reflects asthma measured at age 6 or older following RSV LRTI confined to the first year of life. Current estimates of RSV burden and prevention impact count only acute outcomes.⁸ If early-life RSV LRTI contributes causally to subsequent asthma, those estimates omit a substantial long-term respiratory consequence. Decisions on RSV immunization policy, implementation, and product development rely on those estimates. Independent prospective cohorts report similar attributable fractions. In two large US cohorts, 10–13% of childhood asthma cases were attributable to infant bronchiolitis occurring during the RSV season.⁵ The INSPIRE cohort estimated 15.0% (95% CI 2.2–26.8) of childhood asthma attributable to RSV infection during infancy, with a risk ratio of 1.33 (95% CI 1.05–1.69).⁷ A multicountry study estimated that 14.1% (95% CI 8.7–19.4) of cumulative reported wheeze between ages 2 and under 6 years was attributable to RSV LRTI of any severity during the first two years of life.⁶ These cohorts measured broader exposures than ours. INSPIRE counted any RSV infection, which occurred in more than half of infants, and the multicountry study counted RSV LRTI of any severity through the second year of life. They also enrolled different populations. INSPIRE was restricted to healthy, term infants of normal birthweight, born so that all were 6 months of age or younger at the start of their first RSV season. The attributable fractions are similar, but these differences meant we could not substitute their effect estimates into our model (appendix pp 11–12).

Although the mechanisms linking early-life RSV LRTI to subsequent asthma are not fully understood, epidemiologic, mechanistic, and prevention evidence is consistent with a causal relationship.^{3,7,10,20-22} Prospective cohort studies show that RSV LRTI precedes subsequent asthma, and more severe illness is associated with greater subsequent risk, a severity-dependent gradient.^{3,7,22} Mechanistic studies suggest that RSV may alter airway and immune development during infancy.^{3,7} In the Drakenstein Child Health Study, early-life LRTI was associated with impaired lung function trajectories independent of baseline lung function,²³ arguing against pre-existing airway differences as the explanation, and a later analysis found that RSV LRTI, compared with non-RSV LRTI, was associated with a lower expiratory flow ratio consistent with airflow obstruction.¹¹ A 2020 systematic review of RSV prevention studies found no significant association between prophylaxis and subsequent asthma risk overall, though the association was significant among studies of higher quality.²¹ An expert review convened by the World Health Organization (WHO) found the observational evidence consistent with a causal relationship but did not conclude that causation was established, because the available trials were underpowered for asthma and had not shown prevention.¹⁰

A central challenge in interpreting this evidence is the possibility of shared susceptibility to both severe RSV illness and later asthma. Genetic predisposition is often considered the most important potential confounder of this association. Twin analyses drawing on the same Danish registry have examined this.²⁴⁻²⁶ The design that most directly separates genetic susceptibility reported a within-pair odds ratio of 1.21 (95% CI 0.36–4.00) among 37 monozygotic pairs discordant for RSV hospitalization.²⁶ The interval is uninformative, spanning substantial protection to a large effect. Cohabiting twins almost certainly infect one another, so a discordant pair contrasts severity of response, not presence of infection. In the studies contributing to our effect estimate, control for genetic predisposition was indirect. Most relied on proxies such as family history of asthma or atopy, so residual heritable confounding cannot be excluded.

Shared susceptibility also has non-genetic sources. Prematurity, low birth weight, maternal comorbidity, and socioeconomic disadvantage each increase the risk of RSV LRTI and of asthma, so failure to control for them would be expected to bias our estimate away from the null. We could not adjust for them directly because adjustment occurs within the contributing studies, which addressed these factors inconsistently. Antibiotics, bronchodilators, and corticosteroids given for the index illness different: they are downstream of RSV LRTI, not confounders, and adjusting for them would block part of the pathway from RSV LRTI to later asthma.

Definitive randomized evidence may be difficult to obtain. A 2018 sample size analysis found that among plausible scenarios, the required enrollment ranged from 6,196 to 4.7 million mother-infant pairs per arm, with 75% requiring more than 31,060 and 47% requiring more than 100,000.²⁷ Randomizing infants to no prevention is also no longer straightforward now that immunoprophylaxis is recommended.¹ Randomized evidence may remain limited to underpowered follow-up of trial participants, leaving observational studies as the main evidence available.

Asthma in children is a clinical diagnosis.^{10,28} In children younger than 5 years, spirometry with bronchodilator response cannot reliably be obtained. From about age 5, objective testing can support the diagnosis, although there is no single diagnostic reference standard. Ascertainment at age 6 reduces the contribution of transient early-childhood wheezing phenotypes that have resolved by school age.¹⁷ Under nondifferential outcome misclassification, imperfect specificity would generally attenuate the exposed-unexposed contrast and bias the attributable fraction toward the null.²⁹ Differential ascertainment could bias the estimate in either direction. Children with documented RSV LRTI have more healthcare encounters, which could increase both true detection and false diagnosis of asthma in that group.

In the modeled 50% nirsevimab prevention scenario, RSV-attributable asthma burden fell by 27.4%, leaving 33,858 attributable cases. Nirsevimab provides strong protection during early

infancy, but protection wanes during the first year and is incomplete even during the covered period. RSV LRTI in the second year was outside our exposure window, and second-season immunoprophylaxis is recommended only for a small group of high-risk children.¹ At 90% coverage, the reduction would be 49.4%, and protection extending beyond early infancy would reduce the remainder further.

Our analysis has several strengths. Restricting the effect estimate to asthma at age 6 or later following first-year exposure corrected a mismatch with the broader wheezing outcome in the published analysis.² The restricted and published effect estimates nevertheless produced relatively similar attributable burdens. The analysis focused on medically attended RSV LRTI, the severity range most consistently associated with subsequent asthma. The probabilistic analysis incorporated uncertainty from every input for which a distribution was specified, and sensitivity analyses tested several additional assumptions. The attributable fraction uncertainty interval was wide, but even the lower bound corresponds to approximately 17,000 attributable cases in a birth cohort. Narrowing this interval will depend primarily on better measurement of the RSV-asthma association and secondarily on better incidence data.

Our study is subject to limitations. Inputs were national aggregates, so the estimates are national averages and do not describe burden by sex, race, or ethnicity. Each effect estimate involved a trade-off: the restricted estimate better matched our estimand but came from a smaller subset, and the published estimate was drawn from the broader analysis but was less closely aligned with our outcome definition. Asthma definitions varied across contributing studies, all of which were conducted in high-income countries. Combining the adjusted odds ratio with the unadjusted prevalence anchor introduces a small noncollapsibility bias that would slightly overstate the attributable fraction. The encounter-to-episode relationship was derived from insured populations and may not reflect uninsured children. Non-medically attended RSV infection and RSV LRTI occurring during the second year of life were treated as unexposed in

our model, which could understate total burden. In the secondary analysis, preventing an RSV LRTI episode is assumed to remove its associated asthma risk in full. A structured assessment of these and other potential sources of bias, with their likely direction of effect, is given in the appendix (pp 16–17).

We estimate that approximately 11–14% of childhood asthma at age 6 in the United States may be attributable to infant RSV LRTI, depending on the effect estimate used. If the association is causal, RSV represents a preventable contributor to childhood asthma.

CONTRIBUTORS: IMG, DWH, AJD, MCF, and JRO contributed to study design. IMG and MCF built and ran the attributable burden model. DWH developed and ran the RSV incidence model. SMB conducted the restricted meta-analytic reanalysis that produced the effect estimate. IMG, DWH, and MCF contributed to data collection and data analysis and interpretation. IMG, MCF, and JRO drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version to be published. IMG, DWH, MCF, and JRO accessed and verified the underlying data. All authors had full access to all the data in the study and accepted responsibility for the decision to submit for publication.

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DATA AVAILABILITY STATEMENT: This study used published aggregate data and collected no individual participant data. Model input parameters, assumptions, and other data needed to reproduce the analyses are provided in the appendix (pp 2–11, 13–15). Code for the attributable burden model (<https://github.com/MCFitz/RSV-asthma-US>), data and code for the systematic review and meta-analysis (<https://brunwasser.github.io/whorsv.github.io/>) and for the restricted reanalysis (<https://brunwasser.github.io/rsv.asthma.burden/>), and simulation outputs from the RSV incidence model (<https://doi.org/10.5281/zenodo.22797654>) are publicly available without restriction.

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Table 1. Estimated childhood asthma burden attributable to medically attended infant RSV lower respiratory tract infection, United States

Study results	Value (95% UI)
RSV LRTI during infancy	
Healthcare encounters, outpatient, n	392,446 (144,352–641,906)
Healthcare encounters, emergency department, n	142,449 (70,672–198,642)
Healthcare encounters, hospitalization, n	46,451 (40,698–52,667)
Healthcare encounters, all settings, n	581,346 (313,569–833,450)
Unique illness episodes, n	379,659 (204,518–544,801)
RSV LRTI incidence, % of birth cohort	10.4 (5.6–14.9)
Derived risk parameters	
Asthma prevalence, no RSV LRTI (P0), %	7.5 (6.4–8.6)
Asthma prevalence, RSV LRTI (P1), %	19.8 (13.7–27.9)
Relative risk of asthma given RSV LRTI	2.63 (1.68–4.07)
Asthma at age 6	
All-cause cases, n (natural history scenario)	322,458 (295,513–349,389)
All-cause cases, no RSV LRTI, n (counterfactual scenario)	275,795 (234,061–316,212)
RSV-attributable cases, n	46,663 (17,104–83,969)
RSV-attributable prevalence per 100,000 children in the birth cohort	1,273 (467–2,292)
Population attributable fraction of asthma, %	14.5 (5.3–25.8)

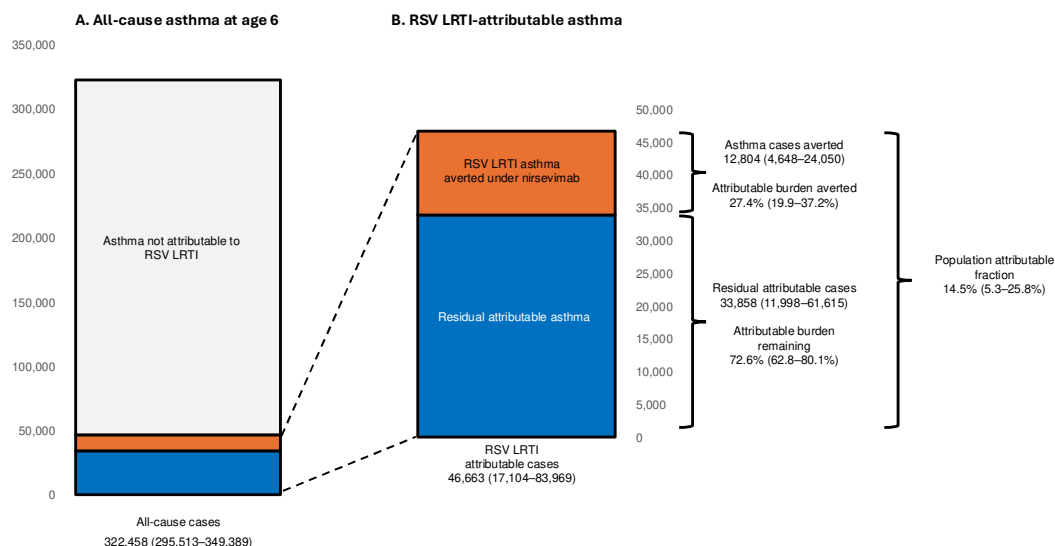
All values are modeled estimates for a US birth cohort. Healthcare encounters were estimated from age-specific RSV incidence inputs. Unique illness episodes were derived from encounters using national insurance claims. We assumed no more than one RSV LRTI episode per child. All-cause cases are estimated under the natural history scenario, the absence of a national RSV prevention program. All-cause cases, no RSV LRTI, are estimated under the counterfactual scenario, in which no infant experiences medically attended RSV LRTI. All-cause asthma prevalence is current asthma among US children aged 5–11 years from the National Health Interview Survey, 2016–18. P0 and P1 are asthma prevalences without and with medically attended infant RSV LRTI, derived jointly from the adjusted odds ratio and all-cause prevalence. The population attributable fraction assumes a causal association. Parentheses indicate 95% uncertainty intervals (UI), defined by the 0.025 and 0.975 quantiles of 10,000 Monte Carlo iterations. Point estimates are base-case values. RSV=respiratory syncytial virus. LRTI=lower respiratory tract infection. UI=uncertainty interval.

Table 2. Estimated RSV lower respiratory tract infection during infancy and associated asthma outcomes at age 6, by prevention scenario

	No RSV prevention program (natural history scenario)	Nirsevimab prevention scenario	Decrease, % (95% UI)
Unique illness episodes, n	379,659 (204,518–544,801)	275,482 (142,313–406,782)	27.4 (19.9–37.2)
All-cause asthma cases, n	322,458 (295,513–349,389)	309,654 (282,002–337,472)	4.0 (1.5–7.4)
RSV-attributable asthma cases, n	46,663 (17,104–83,969)	33,858 (11,998–61,615)	27.4 (19.9–37.2)
Asthma cases averted, n	--	12,804 (4,648–24,050)	--

All values are modeled estimates for a US birth cohort. We assumed no more than one RSV LRTI episode per child. The natural history scenario assumes no national RSV prevention program. The nirsevimab scenario assumes 50% coverage, approximating reported 2025–26 US infant RSV monoclonal antibody coverage.¹⁹ Nirsevimab performance (efficacy, duration of protection, and waning) was derived from trial data and expert opinion in a model developed in collaboration with CDC collaborators and vetted by the Advisory Committee on Immunization Practices (ACIP) RSV Work Group.^{8,30} Reported coverage includes all RSV preventive products, whereas the modeled efficacy and waning profile is nirsevimab-specific. The scenario does not estimate the impact of prevention as currently delivered. The percentage decrease in RSV-attributable asthma equals the percentage decrease in RSV LRTI episodes because the risk difference is held constant. Parentheses indicate 95% uncertainty intervals (UI), defined by the 0.025 and 0.975 quantiles of 10,000 Monte Carlo iterations. Point estimates are base-case values. RSV=respiratory syncytial virus. LRTI=lower respiratory tract infection. UI=uncertainty interval.

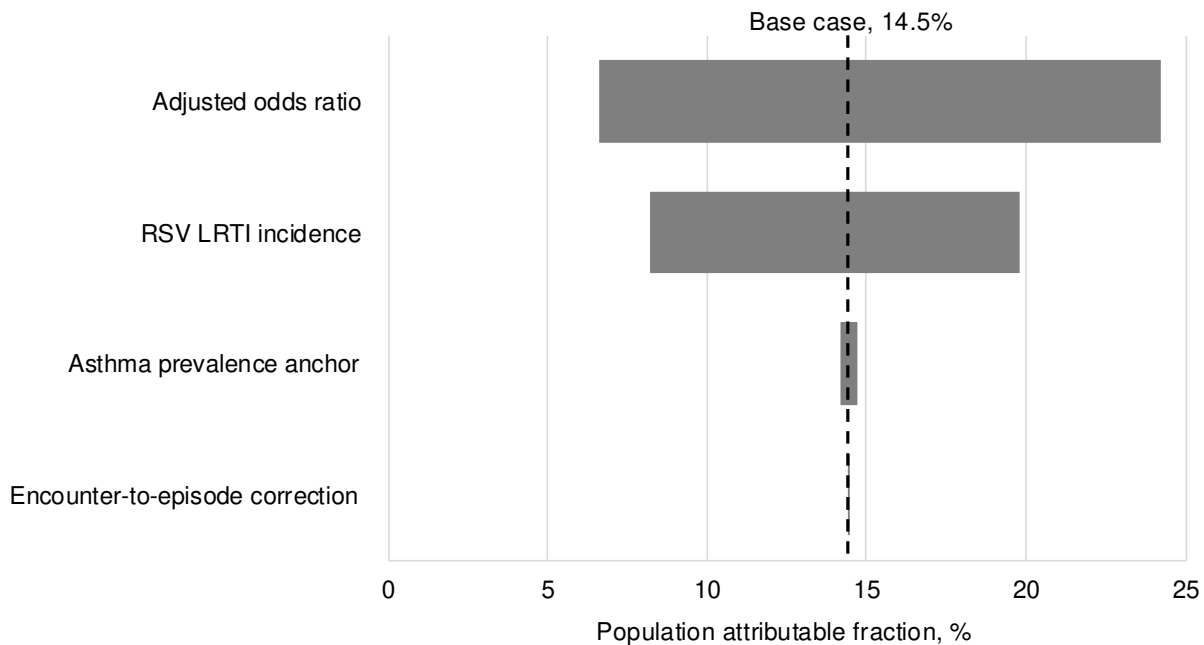
Figure 1. Estimated asthma burden at age 6 attributable to medically attended infant RSV lower respiratory tract infection, United States



Values are modeled estimates for a US birth cohort. Panel A shows all-cause asthma cases at age 6, 322,458, divided into cases not attributable to RSV LRTI and cases attributable to RSV LRTI, 46,663. Panel B expands the attributable portion, showing 33,858 residual attributable cases remaining under modeled 50% nirsevimab coverage and 12,804 cases averted, representing 27.4% of the attributable burden. The y-axis scale differs between panels to facilitate visualization of the smaller RSV-attributable burden in Panel B. Parentheses indicate 95% uncertainty intervals (UI), defined by the 0.025 and 0.975 quantiles of 10,000 Monte Carlo iterations. RSV=respiratory syncytial virus. LRTI=lower respiratory tract infection. UI=uncertainty interval.

Alt text: Stacked bar chart with two panels showing childhood asthma burden attributable to infant RSV lower respiratory tract infection in a US birth cohort. Panel A shows all-cause asthma cases at age 6, 322,458, divided into cases not attributable to RSV LRTI and cases attributable to RSV LRTI, 46,663. Panel B expands the attributable portion, showing 33,858 residual attributable cases remaining under modeled 50% nirsevimab coverage and 12,804 cases averted, representing 27.4% of the attributable burden. A bracket indicates the population attributable fraction of asthma, 14.5%.

Figure 2. One-way sensitivity analysis of the population attributable fraction of childhood asthma



One-way sensitivity analysis showing the effect of varying individual model inputs on the estimated population attributable fraction of asthma at age 6 attributable to medically attended RSV lower respiratory tract infection (LRTI) during infancy. Each evaluated input was varied to the extremes of its 95% uncertainty interval (UI) while all other inputs were held at their base-case values. The vertical reference line indicates the base-case population attributable fraction of 14.5%. The estimate was most sensitive to the adjusted odds ratio for asthma following RSV LRTI and to modeled RSV LRTI incidence, with little influence from the asthma prevalence anchor or the encounter-to-episode correction. RSV=respiratory syncytial virus. LRTI=lower respiratory tract infection. UI=uncertainty interval.

Alt text: Horizontal bar chart showing four model inputs ranked by their effect on the population attributable fraction of childhood asthma attributable to infant RSV LRTI. A dashed vertical line marks the base-case population attributable fraction of 14.5%. The adjusted odds ratio shows the widest range, from 6.6% to 24.2%. Modeled RSV LRTI incidence shows the next widest range, from 8.2% to 19.8%. The baseline asthma prevalence anchor shows a narrow range, from 14.2% to 14.7%. The encounter-to-episode correction shows the narrowest range, from 14.4% to 14.5%.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [RSVAsthmasupplement20260629tosubmittoresearchsquare.pdf](#)
- [RSVLRTIOutcomeConfidenceIntervalsCurated20260628.xlsx](#)