2.0 Methods

2.1 Study Objective

We estimated the additional health and economic burden attributable to declines in childhood vaccination coverage across U.S. states. Using deterministic equilibrium transmission models with basic demography, we estimated incremental increases in cases, hospitalizations, and deaths, as well as parental workdays lost and costs (healthcare and productivity) relative to baseline vaccination coverage. Burden estimates assume that incidence is stable in a given year.

2.2 Key Question

What is the incremental impact on disease burden if vaccination coverage declines among infants, given current population immunity and state-specific demographics?

2.3 Model Overview

We developed state-level, disease-specific models for three vaccine-preventable diseases – rotavirus, pertussis, and invasive pneumococcal disease (IPD) - to estimate additional health and economic burden under vaccination coverage declines. Each disease and state was calculated independently using a deterministic endemic equilibrium framework with demographic turnover. This approach estimates the steady-state annual burden under stable transmission conditions for each pathogen across the 50 U.S. states and the District of Columbia. Model outputs are reported as equilibrium annual disease burden after either 1- or 5- years of lower coverage among infants, and assuming stable transmission and fixed scenario-specific vaccination coverage for equilibrium estimation.

2.4 Modeling Framework

2.4.1 Diseases and Age Groups Modeled

The modeling framework includes rotavirus, pertussis, and invasive pneumococcal disease (IPD) (Table 1).

Rotavirus was modeled among children aged 0-4 years using a Susceptible-Infectious-Recovered (SIR) structure, reflecting early-life concentration of disease burden.

Pertussis was modeled among children 0-14 years using a Susceptible-Infectious-Recovered-Susceptible (SIRS) structure to account for waning immunity and reinfection[1].

Pneumococcal disease was modeled with a focus on Invasive pneumococcal disease among children 0-4 years using an SIRS structure to represent waning protection against invasive disease risk in early childhood. [1] IPD was defined as bacteremia or meningitis, consistent with Active Bacterial Core Surveillance definitions[3]. Model outcomes therefore reflect IPD cases, hospitalizations, and deaths. Indirect effects are therefore estimated within the modeled age band and do not extend to older age groups.

These age bands reflect differences in disease epidemiology, vaccination schedules, and concentration of disease burden. All three pathogens generally exhibit endemic transmission patterns, making them suitable for this deterministic equilibrium solution.

Table 1: Diseases and age group modeled

Disease	Model	Age band	Rationale
Rotavirus	SIR	0-4	Burden concentrated in young children
Pertussis	SIRS	0-14 years	Waning immunity requires reinfection pathway
Pneumococcal	SIRS	0-4 years	Severe disease concentrated in young children

2.4.2 Equilibrium Incidence Framework

Annual per-capita incidence under varying vaccination coverage scenarios was estimated using deterministic equilibrium approximations of compartmental transmission models with demography. For each disease, state, and vaccine coverage decline *j* (0,0.20 in 0.01 increments), the models incorporated demographic turnover, disease-specific natural history parameters, state-specific age-band population sizes, and age-and state-specific vaccination coverage. The model was simulated for the age group as defined by disease and a state of residence, along with disease-specific parameters and age-band immunity status determined by age, state of residence, and vaccination coverage. Each disease and state was modeled independently with disease-specific parameters, state age-band population, and disease epidemiology profile (Table 2).

Key model inputs were the basic reproduction number R_0 for each disease and state-level age-band population, current vaccine coverage and demographic turnover.

2.4.3 Model Parameterization

Disease-specific parameters are described in Table 2. All natural history parameters were fixed at values informed by the literature.

Table 2: Descriptions, values, and references for model parameters.

Parameter description	Rotavirus	Pertussis	Pneumococcal
Model structure	SIR[2]	SIRS[2,4]	SIRS[5,6]
Modeled age band	0-4 years	0-14 years	0-4 years
Basic reproduction number (R_0)	4†	5†	5†
Vaccine effectiveness (VE*)	0.915[7]	0.850[8,9]	0.902[10]
Vaccination coverage	State-specific[11]	State-specific[12]	State-specific[11]
Waning immunity rate***	none	0.1[8]	0.1[13]
Demographic turnover rate (μ)	1/R**	1/R**	1/R**
Hospitalization rate	0.0143‡	0.05‡	0.83‡
Death rate	0.0000074‡	0.0005‡	0.0369‡
Average illness duration	5 days[14]	14 days[14]	8 days
Average hospitalization duration	5 days[14]	5.3 days[15]	4 days[16]
Average daily hospitalization cost	$1,748[17]	$1,665[18]	$4,758[19,16]

Average daily wage	$ 200[20,21]	$ 200[20, 21]	$ 200[20,21]
Observed national cases	Derived	20,960[22]	Derived
Observed national hospitalizations	7,500[Δ]	1,027[Δ]	1,382[23,3]
Observed national deaths	5[§]	10[22]	51[23]

National case targets were derived from hospitalization targets using disease-specific hospitalization rates when direct cases estimates were unavailable. For pneumococcal disease, hospitalization and death rates are conditional on invasive pneumococcal infection (IPD). National hospitalization and death targets reflect observed annual IPD burden among children aged <5 years. Calibration was performed at the case level only; costs were derived from calibrated outcomes.

** Vaccine effectiveness (VE) is assumed to be against infection – for each pathogen, a proportion of infections become cases, and cases become hospitalized or die.*

*** R denotes age-band width (years), such that the demographic turnover (μ) = 1/R.*

****Waning immunity rate is expressed per year and assumes exponential loss of protection.*

[†]*Basic reproduction number*(R_0); initial values were informed by R_0 values *in the literature and subsequently calibrated to reproduce observed disease burden and vaccination impact in the modeled age bands in the U.S population.*

[‡]*Hospitalization and death rates are probabilities conditional on case.*

[Δ]*Observed national hospitalizations were used directly when available; otherwise, national case targets were inferred by back-calculating from hospitalization counts using disease-specific hospitalization probabilities.*

[§]*Observed national death represent annual national death targets.*

2.4.4 Model Structure and Equations

For each disease, state, and assumed coverage decline j (0.00, ….,0.20 in 0.01 steps), we computed the per capita annual incidence at endemic equilibrium. Table 3 summarizes model specifications and equations.

2.4.4.1 Parameter Estimation

Vaccine effectiveness was interpreted as protection against infection for the purposes of transmission dynamics and therefore entered the model through reduced susceptibility. Nonlinear indirect effects, including herd immunity, are captured by the equilibrium incidence equations. Disease-specific risk of hospitalization and death were applied conditional on infection. This approach isolates indirect and herd effects operating through reduced transmission while preserving empirically observed severity profiles among breakthrough infections.

Vaccination reduces susceptibility by an effective protection level of

$$v = VE \times v_{struct},$$

where v_{struct} is the structural age-band vaccination coverage and VE *is the direct protection against infection*, yielding an effective reproduction number defined[24] as:

$$R_{eff} = R_0(1 - v)$$

2.4.4.2 Equilibrium Incidence Definition

The per-capita incidence i at endemic equilibrium was defined as the product of the disease-specific equilibrium incidence scaling factor (prefactor) and the deficit from the herd immunity threshold[25]:

$$i = \underbrace{prefactor}_{per\ year}\ x\ \left(1 - \frac{1}{R_0(1-v)}\right)$$

For diseases modeled using an SIR structure (rotavirus), equilibrium incidence is governed by the demographic turnover, [2,25] and defined as:

$$i_{SIR} = \mu\left(1 - \frac{1}{R_0(1-v)}\right)$$

where $\mu = \frac{1}{R}$ represents the per-capita turnover rate for an age band of width R years.

For diseases modeled using an SIRS structure (pertussis and invasive pneumococcal disease) with waning at rate ω and recovery at rate Y, both in per-year units, the per-capita annual incidence[2,25] was defined as:

$$i_{SIRS} = \frac{(\gamma + \mu)(\mu + \omega)}{\gamma + \mu + \omega}\left(1 - \frac{1}{R_0(1-v)}\right)$$

Annual age-band case counts were computed as:

$$I_{annual} = i \times N_{age-band},$$

where $N_{age-band}$ is the relevant state-specific population in the modeled age group. Incidence is truncated at zero when $R_0(1-v) \leq 1$.

2.4.4.3 Structural Vaccination Coverage

The structural age-band vaccination coverage entering transmission was defined as:

$$v_{struct} = X - wj,$$

Where X is the baseline coverage, j is the proportional reduction in newborn coverage, R is the width of the modeled age band in years, A accrual window length, and

$$w = \min\left(1, \frac{A}{R}\right)$$

represents the fraction of the age band replaced over an accrual period. For a one-year accrual window (A = 1), this simplifies to $v_{struct} = X - j/R$

Table 3: Summary of model components and equations.

Component	Definition	Formula
Model type	Compartmental model models	SIR (rotavirus), SIRS (pertussis, Pneumococcal disease)
Basic reproduction number	Expected secondary cases in fully susceptible population	R_0
Effective reproduction number	Reproduction number under vaccination	$R_{eff} = R_0(1-v)$

Structural age-band coverage	Average across modeled age band	$v_{struct} = X - wj$
Effective protection	Vaccine-induced reduction in susceptibility to infection in modeled age band.	$v = VE \times v_{struct}$
Demographic turnover	Demographic inflow and outflow	$\mu = \frac{1}{R}$
General per-capita incident	Incidence at equilibrium	$i = \underbrace{prefactor}_{per\ year} \times \left(1 - \frac{1}{R_0(1-v)}\right)$
SIR Incidence (i_{SIR})	Rotavirus equilibrium incidence	$i_{SIR} = \mu\left(1 - \frac{1}{R_0(1-v)}\right)$
SIRS Incidence ()	Pertussis equilibrium incidence	$i_{SIRS} = \frac{(\gamma + \mu)(\mu + \omega)}{\gamma + \mu + \omega}\left(1 - \frac{1}{R_0(1-v)}\right)$
Annual incident cases	Age-specific annual cases	$I_{annual} = i * N$
Additional burden	Difference vs baseline	$\Delta = Outcome_{decline} - Outcome_{baseline}$

VE *is the direct protection against infection. Nonlinear effects (like herd immunity) are captured by the incidence equation*

2.5 Vaccination Coverage Declines Assumptions

Birth-only Coverage Decline

Coverage declines were applied exclusively to newborn cohorts and average across the age band, so the effective coverage (structural age-band coverage) entering transmission through the structural age-band vaccination coverage as defined in section 2.4.4

Under this framework, a 20% newborn coverage decline corresponds to a 4 percentage-point reduction in structural coverage for children aged 0-4 years for rotavirus and IPD and a 1.33 percentage-point reduction for children aged 0-14 years for pertussis. So, the effective protection entering transmission was $v = VE \times v_{struct(j)}$.

2.6 Population and Demographic Inputs

State-level population estimates (total and age-specific) were obtained from the U.S. Census Bureau American Community Survey (ACS) 2023[26], five-year estimates, accessed through the tidycensus R package. For each U.S. state s, we extracted the total population (all ages), $N_{s,\ all\ ages}$, and the age-specific populations for 0-4 years and 0-14 years[26]. Age- and state-specific vaccination coverage was extracted from the CDC's SchoolVaxView[12] and ChildVaxView[11] among kindergartners and young children aged 0-35 months, respectively.

Demographic turnover within each modeled age band was approximated using a constant inflow/outflow rate based on the width of the age band. For an age band spanning R years, the turnover rate was defined as μ = 1/R per year (where R is the age band width), reflecting uniform aging into and out of the modeled age group under stable population approximation.

2.7 Outcome definitions

The transmission model produces the annual number of infections at endemic equilibrium. For outcome estimation and calibration, infections were mapped to cases based on pathogen-specific clinical definitions.

For rotavirus, cases correspond to symptomatic rotavirus gastroenteritis, recognizing a spectrum of disease severity.

Pertussis, is a notifiable disease, so the model represents symptomatic clinical pertussis, a fraction of which result in hospitalization and death.

For pneumococcal disease, modeled cases correspond specifically to invasive pneumococcal disease episodes (e.g., bacteremia or meningitis), consistent with Active Bacterial Core Surveillance definitions, a fraction of which result in hospitalization and death.

For each state, disease, and coverage decline scenario, outcomes were estimated using equilibrium incidence and over 1-year and 5-year periods of declining vaccine coverage, representing the total burden expected over those periods under endemic equilibrium conditions. Outcomes included annual incident cases, hospitalizations, deaths, parental workdays lost and direct medical and productivity costs.

Annual outcome counts are defined as

$$count = i * N_{(s,\ age-band),}$$

where i is the equilibrium per-capita incidence and $N_{(s,\ age-band)}$ is the state-age-band population. Outcomes were reported as absolute counts and rates per 100,000 age-band population.

To align modeled outputs with observed national disease burden, disease-specific calibration factors were applied to annual modeled case counts, such that baseline case estimates matched empirical observed national case targets. When direct national case targets were not available, national hospitalization targets were used to infer corresponding case targets by back-calculating cases from hospitalization counts using disease-specific hospitalization rates. Modeled cases were then calibrated to these inferred case targets. Hospitalizations and deaths were subsequently derived from the calibrated cases using fixed disease-specific rates. Calibration was applied only at the case level; costs and productivity losses were not independently calibrated but instead derived from calibrated outcome counts multiplied by fixed unit cost inputs.

2.8 Additional Burden

The primary outcomes of interest were additional (incremental) burdens attributable to coverage declines, defined as differences relative to baseline coverage:

$$\Delta_{Outcome} = Outcome_{decline} - Outcome_{baseline}$$

Some states and scenarios may return estimated additional cases if zero. This occur when baseline vaccination coverage maintains the effective reproduction number below the epidemic threshold ($R_{eff} \leq 1$), such that small coverage declines do not produce sustained transmission under equilibrium assumptions. As coverage declines further and R_{eff} exceeds 1, cases emerge. Zero additional cases therefore reflect threshold behavior in equilibrium transmission models rather than absence of disease risk.

2.9 Cost estimation

Direct medical and productivity costs were estimated using disease-specific inputs for hospitalization rates and duration, cost per hospital day, days of illness, and daily wage loss. Productivity costs were estimated using a fixed national daily average derived from the U.S. Bureau of Labor Statistics (BLS) data on average weekly earnings for private sector employees[21].

The expected total cost per infection was defined as:

$$Cost_{per\ infection} = (Hosp\ rate\ x\ Days\ hosp\ x\ \ Cost\ per\ hopsital\ day) + \ (Days\ ill\ x\ Daily\ wage)$$

Total and incremental costs were calculated by multiplying the per-infection costs by the corresponding calibrated case counts accrued over the specified accrual period.

2.10 Software and Reproducibility

All analysis was conducted in R using reproducible project structure. Package versions were managed using renv. All parameters were externalized in configuration files to enable transparency and replication.

2.11 Assumptions

Consistent with prior equilibrium transmission analyses, we assumed:

- Vaccination coverage declines affect infants only
- Risk is homogeneous within a state and the modeled age band (e.g. same risk for <5-year-olds for rotavirus and the same risk for <15-year-olds for pertussis).
- No transmission coupling between states
- Pathogen characteristics, vaccine performance, hospitalization/death risks and per-unit economic impacts do not vary by state
- Endemic equilibrium represents long-run average annual burden
- Impact estimates are for the year following 1- or 5- years of lower vaccine coverage under stable endemic equilibrium
- Demographic turnover is approximated by uniform aging through the modeled age band (μ = 1/R)

References

1. Keeling MJ. *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press; 2008.

2. Hethcote HW. *The Mathematics of Infectious Diseases* *. Vol 42. 2000:599-653. http://www.siam.org/journals/sirev/42-4/37190.html

3. CDC. ABCs Bact Facts Interactive Data Dashboard. Active Bacterial Core surveillance (ABCs). August 21, 2025. Accessed January 27, 2026. https://www.cdc.gov/abcs/bact-facts/data-dashboard.html

4. Roddam AW. Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation: O Diekmann and JAP Heesterbeek, 2000, Chichester: John Wiley pp. 303, £39.95. ISBN 0-471-49241-8. *Int J Epidemiol*. 2001;30(1):186-186. doi:10.1093/IJE/30.1.186

5. Malik TM, Mohammed-Awel J, Gumel AB, Elbasha EH. Mathematical assessment of the impact of cohort vaccination on pneumococcal carriage and serotype replacement. *J Biol Dyn*. 2021;15(S1):S214-S247. doi:10.1080/17513758.2021.1884760

6. Løchen A, Anderson RM. Corrigendum to “Dynamic transmission models and economic evaluations of pneumococcal conjugate vaccines: a quality appraisal and limitations” [Clin Microbiol and Infect 26 (1) (2020) 60–70]. *Clin Microbiol Infect*. 2021;27(10):1545-1545. doi:10.1016/j.cmi.2021.07.001

7. Martinón-Torres F, Bouzón Alejandro M, Redondo Collazo L, et al. Effectiveness of rotavirus vaccination in Spain. *Hum Vaccin*. 2011;7(7):757-761. doi:10.4161/hv.7.7.15576

8. Domenech De Cellès M, Rohani P, King AA. Duration of Immunity and Effectiveness of Diphtheria-Tetanus-Acellular Pertussis Vaccines in Children. *JAMA Pediatr*. 2019;173(6):588-594. doi:10.1001/jamapediatrics.2019.0711

9. Redfield RR, Kent CK, Leahy MA, et al. *Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Morbidity and Mortality Weekly Report Recommendations and Reports Centers for Disease Control and Prevention MMWR Editorial and Production Staff (Serials) MMWR Editorial Board*. Vol 67. 2018. https://www.cdc.gov/vaccines/acip.

10. Andrejko KL, Gierke R, Rowlands JV, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease among children in the United States between 2010 and 2019: An indirect cohort study. *Vaccine*. 2024;42(16):3555-3563. doi:10.1016/j.vaccine.2024.04.061

11. Vaccination Coverage among Young Children (0 – 35 Months) | ChildVaxView | CDC. https://www.cdc.gov/childvaxview/about/interactive-reports.html

12. Vaccination Coverage and Exemptions among Kindergartners | SchoolVaxView | CDC. https://www.cdc.gov/schoolvaxview/data/index.html#cdc_data_surveillance_section_1-schoolvaxview-interactive

13. Nurhonen M, Cheng AC, Auranen K. Pneumococcal Transmission and Disease In Silico: A Microsimulation Model of the Indirect Effects of Vaccination. *PLoS ONE*. 2013;8(2). doi:10.1371/journal.pone.0056079

14. Table of Contents | Pink Book | CDC. https://www.cdc.gov/pinkbook/hcp/table-of-contents/index.html

15. Lopez MA, Cruz AT, Kowalkowski MA, Raphael JL. Trends in hospitalizations and resource utilization for pediatric pertussis. *Hosp Pediatr*. 2014;4(5):269-275. doi:10.1542/hpeds.2013-0093

16. Mohanty S, Cossrow N, White M, et al. Burden of invasive pneumococcal disease, non-invasive all-cause pneumonia, and acute otitis media in hospitalized US children: a retrospective multi-center study from 2015 to 2020. *BMC Health Serv Res*. 2024;24(1). doi:10.1186/s12913-024-11898-w

17. Widdowson MA, Meltzer MI, Zhang X, Bresee JS, Parashar UD, Glass RI. Cost-effectiveness and potential impact of rotavirus vaccination in the United States. *Pediatrics*. 2007;119(4):684-697. doi:10.1542/peds.2006-2876

18. Masseria C, Martin CK, Krishnarajah G, Becker LK, Buikema A, Tan TQ. Incidence and burden of pertussis among infants less than 1 year of age. *Pediatr Infect Dis J*. 2017;36(3):e54-e61. doi:10.1097/INF.0000000000001440

19. Averin A, Weycker D, Lapidot R, et al. Cost of invasive pneumococcal disease, all-cause pneumonia, and all-cause otitis media among commercial-insured US children. *J Med Econ*. 2025;28(1):517-523. doi:10.1080/13696998.2025.2484919

20. *USUAL WEEKLY EARNINGS OF WAGE AND SALARY WORKERS FIRST QUARTER 2025*. www.bls.gov/cps

21. Total private average hourly earnings and weekly hours and earnings by state. https://www.bls.gov/charts/state-employment-and-unemployment/average-hourly-earnings-and-weekly-hours-and-earnings-by-state.htm

22. CDC, Ncird. *2024 Provisional Pertussis Surveillance Report - January 2025*. 2024. https://wonder.cdc.gov/nndss/static/2024/52/2024-52-table990.html

23. Wasserman M, Chapman R, Lapidot R, et al. Twenty-year public health impact of 7- And 13-valent pneumococcal conjugate vaccines in US children. *Emerg Infect Dis*. 2021;27(6):1627-1636. doi:10.3201/eid2706.204238

24. Diekmann O., Heesterbeek JAP. *Mathematical Epidemiology of Infectious Diseases : Model Building, Analysis, and Interpretation*. John Wiley; 2000:303.

25. Clancy D. Generality of endemic prevalence formulae. *Math Biosci*. 2015;269:30-36. doi:10.1016/j.mbs.2015.08.011

26. Bureau UC. State Population Totals and Components of Change: 2020-2025. Census.gov. Accessed January 27, 2026. https://www.census.gov/data/tables/time-series/demo/popest/2020s-state-total.html