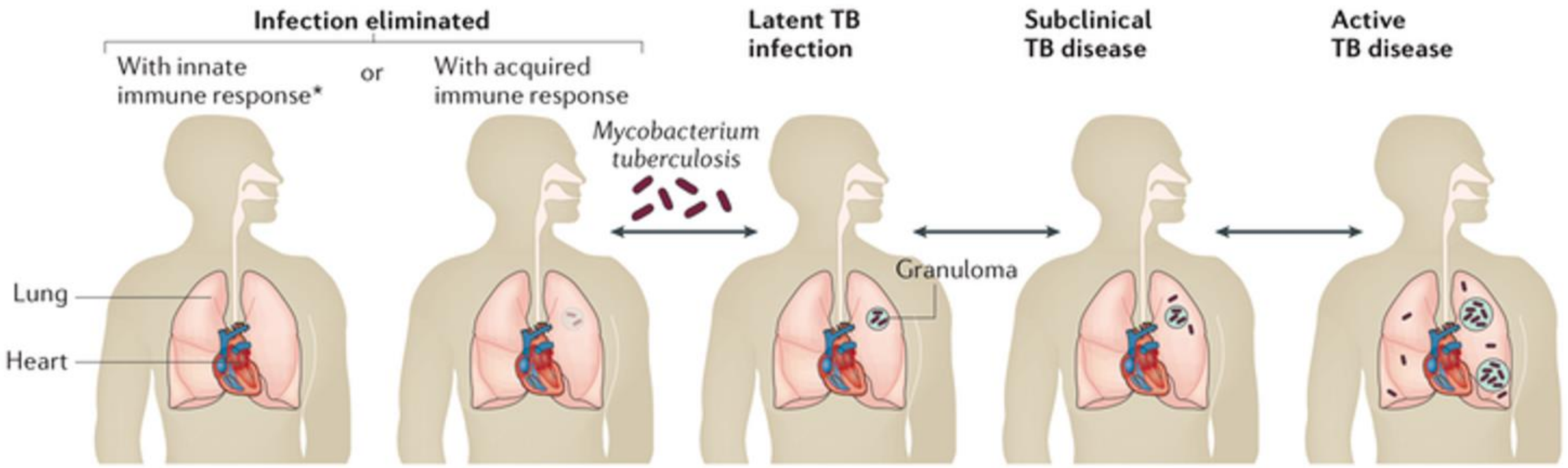
Natural History of TB, RSV, and Rotavirus

TB

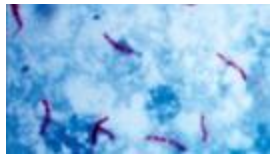
A 'spectrum' of infection and disease



Pai et al. Nature Rev. 2016

Tuberculosis transmission and natural history of infection

Mycobacterium tuberculosis



Wang et al. Science 2021

Infection -> disease

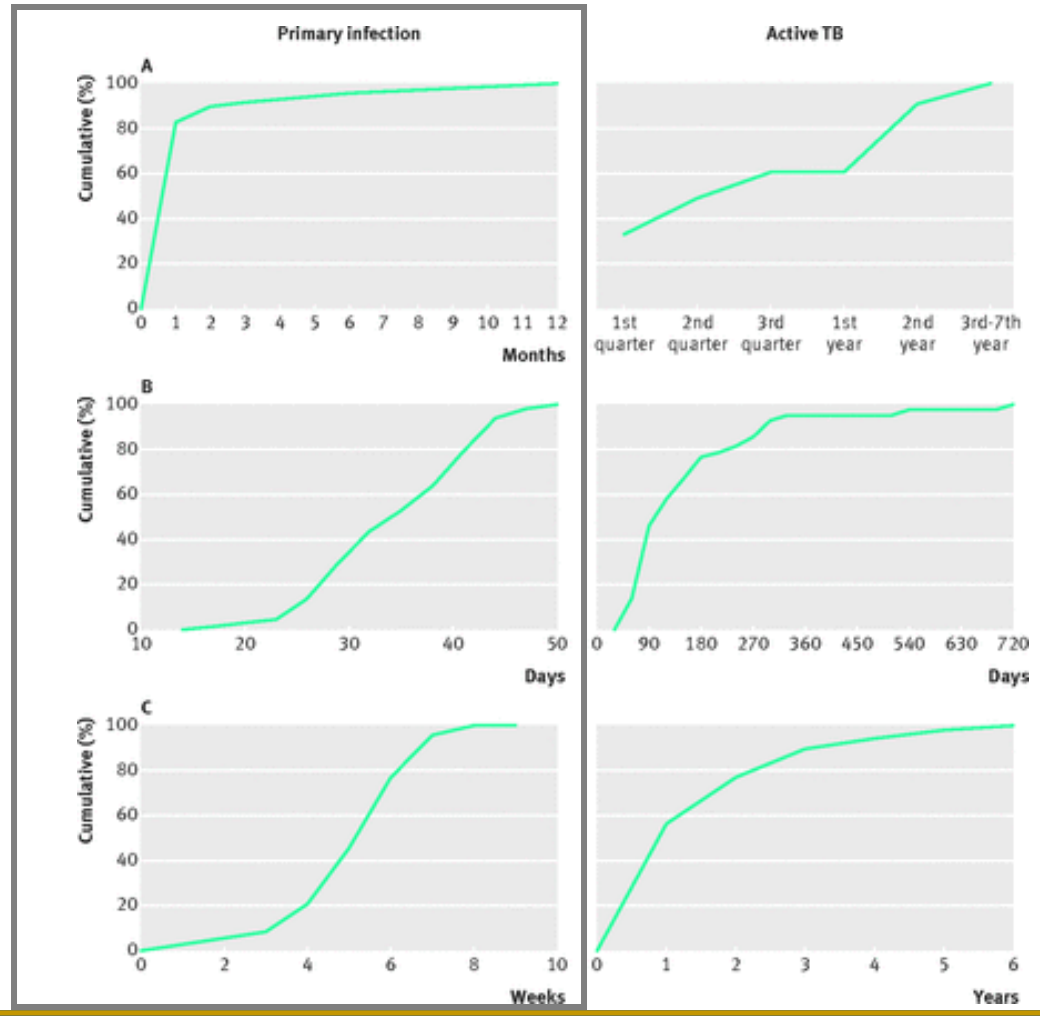
- The 'rule of thumb': 10% progress from infection to disease
  - 5% in first five years, 5% thereafter
- Depends on age, sex, genetic predisposition, comorbidity status (HIV, other immunosuppresive conditions)
  - HIV: >20x increased risk of progression (WHO)
- Previous infection is protective
  - 0.8x decreased risk of progression (Andrews *et al* 2012)
- Self-cure (disease), self-clearance (infection)?
- 'Asymptomatic' but infectious TB?

Incubation and latent periods (pre-antibiotic era)

Faroe islands, 1939-47

Stockholm, 1940s

Norway, 1930s



Incubation: most < 6 wks

(exposure to positive test for infection)

Latent: 3-9 mo

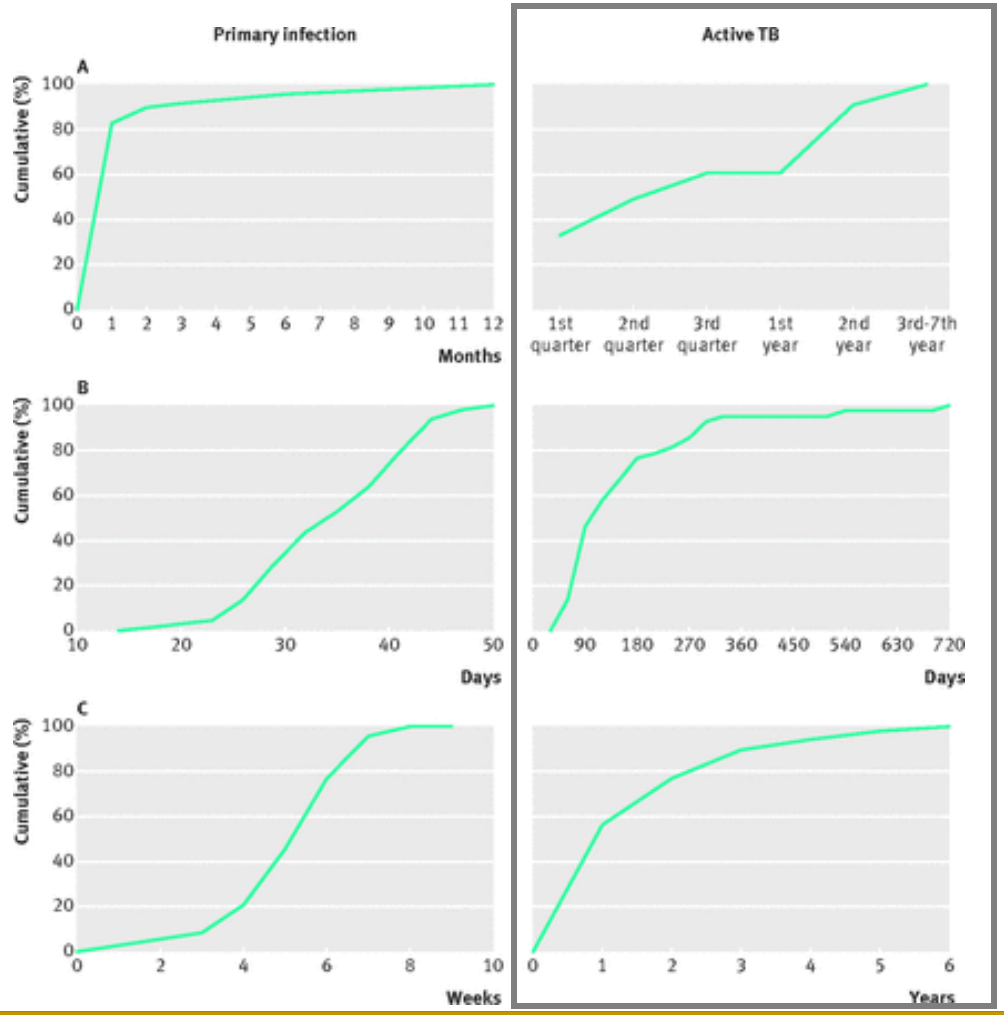
(positive test for infection to clinical symptoms)

Incubation and latent periods (pre-antibiotic era)

Faroe islands, 1939-47

Stockholm, 1940s

Norway, 1930s



Incubation: most < 6 wks

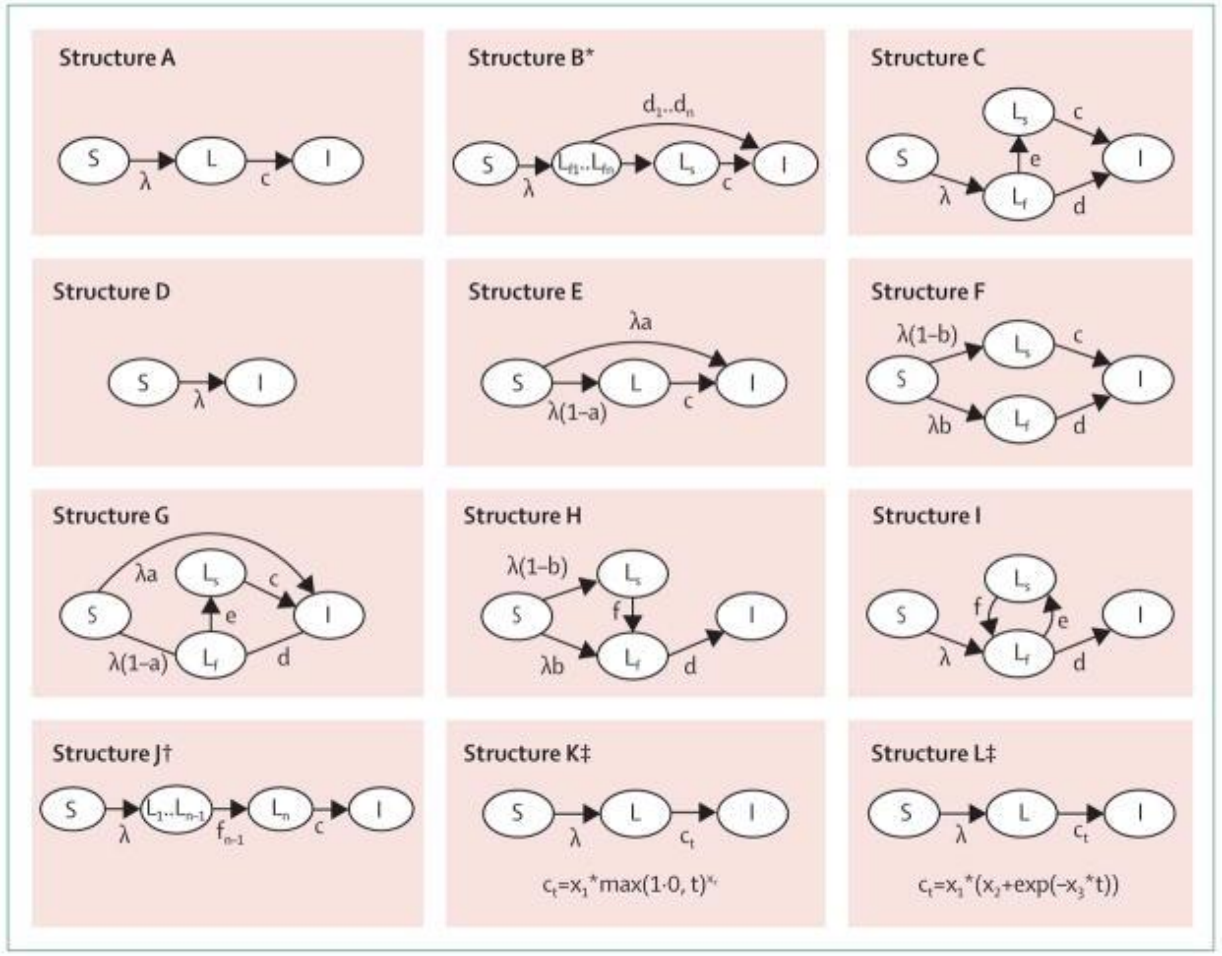
(exposure to positive test for infection)

Latent: 3-9 months

(positive test for infection to clinical symptoms)

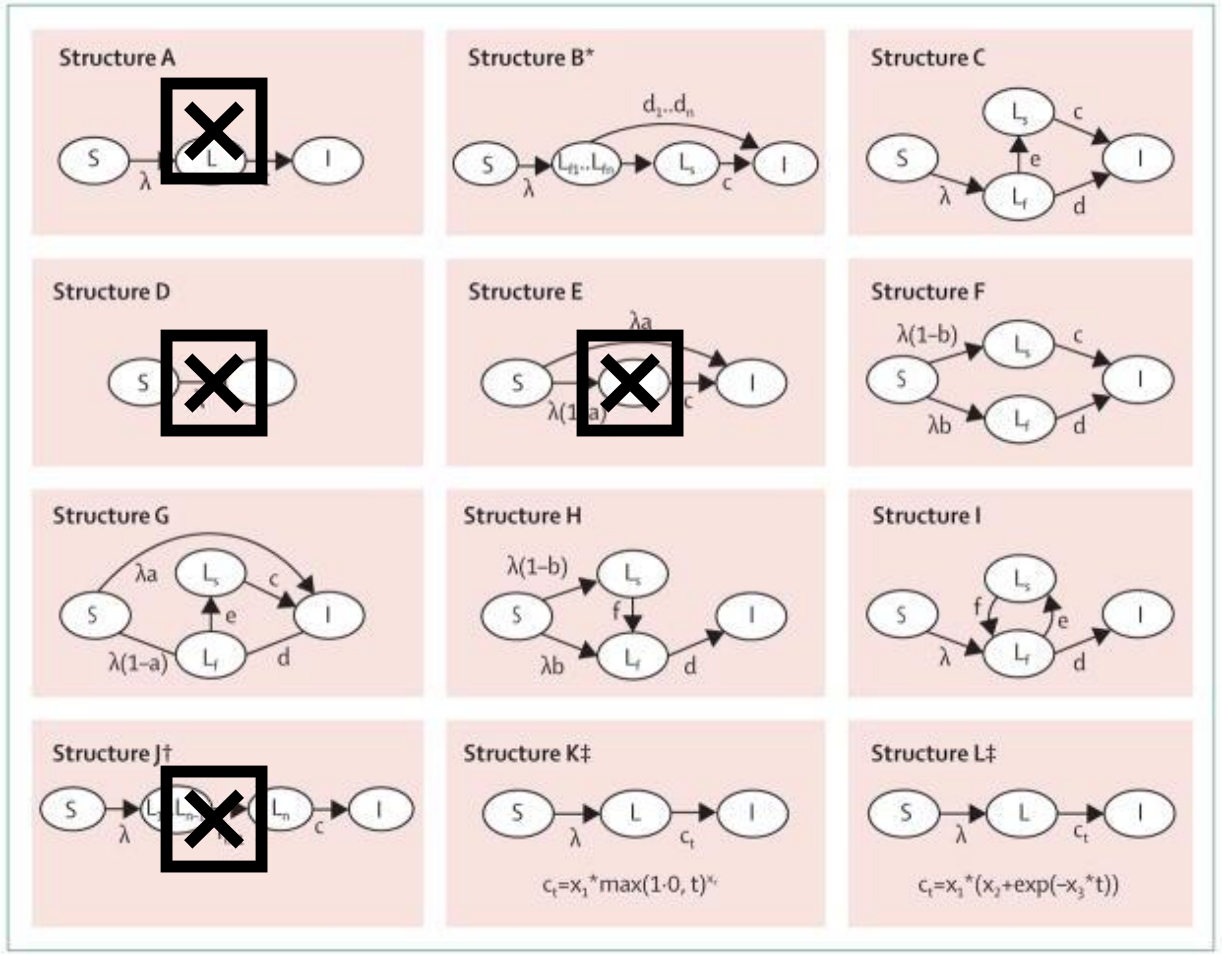
Behr et al. BMJ 2018

Modeling progression to TB disease



Menzies et al. Lancet ID 2018

Modeling progression to TB disease



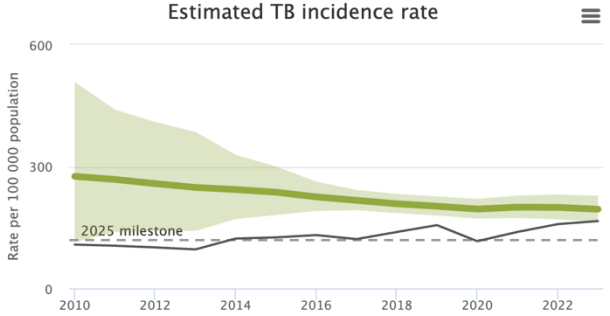
- **Requires 2 'E' (or latent, L) compartments**
- **'Fast' and 'slow' progression routes**
- **Model we'll use tomorrow is closest to Structure C**

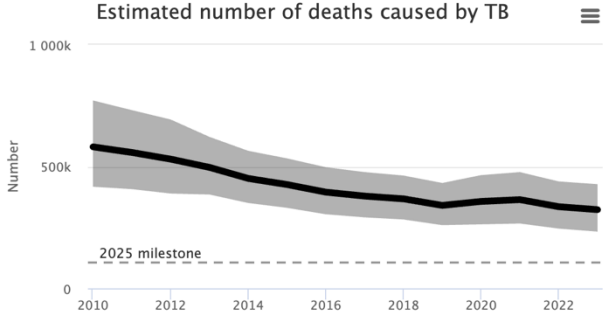
Data sources: WHO Global TB Report

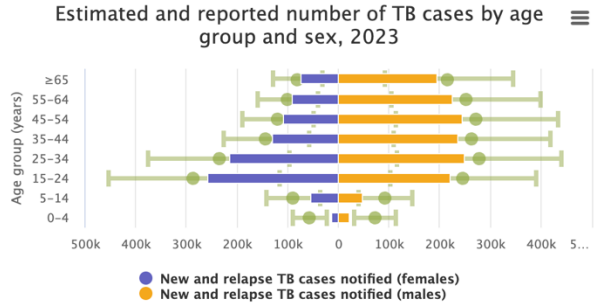
Tuberculosis profile: India

Data last updated: 2024-10-08

CHARTS | DATA TABLES







Treatment success rate and cohort size

	Success	Cohort
People with a new or relapse case of TB started on treatment for TB 2022	89%	2 194 723
People with a previously treated case of TB (but not a relapse case) started on treatment for TB 2022	85%	146 377
People with a new or relapse case of TB who are living with HIV started on treatment for TB 2022	79%	35 179
People started on treatment for TB that is resistant to rifampicin (MDR/RR-TB) 2021	73%	31 506
People started on treatment for TB that is resistant to both rifampicin and fluoroquinolones (pre-XDR-TB/XDR-TB) 2021	69%	7 029

TB case notifications

People diagnosed with a new or relapse case of TB, 2023	2 382 714
– % tested with rapid diagnostics at time of diagnosis	32%
– % with known HIV status	96%
– % pulmonary	75%
– % of pulmonary cases that are bacteriologically confirmed	62%
– % women aged ≥15 years	37%
– % men aged ≥15 years	58%
– % people aged 0-14 years	5%
Total cases notified, 2023	2 517 810

Estimates of TB burden

Estimates of TB burden are produced by WHO in consultation with countries. Ranges represent uncertainty intervals.

	Number	Rate per 100 000 population
Total TB incidence, 2023	2 800 000 (2 360 000–3 280 000)	195 (164–228)
TB incidence in people living with HIV, 2023	42 000 (36 000–50 000)	2.9 (2.5–3.5)
Multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) incidence, 2023	110 000 (82 000–130 000)	7.4 (5.7–9.1)
TB deaths in HIV-negative people, 2023	315 000 (233 000–428 000)	22 (16–30)
TB deaths in people with HIV, 2023	8 200 (5 900–11 000)	0.57 (0.41–0.76)

https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&tab=%22tables%22&lan=%22EN%22&iso2=%22IN%22&entity_type=%22country%22

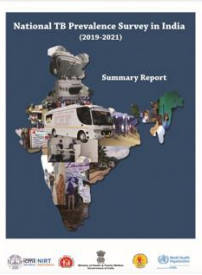
Data sources: TB prevalence surveys

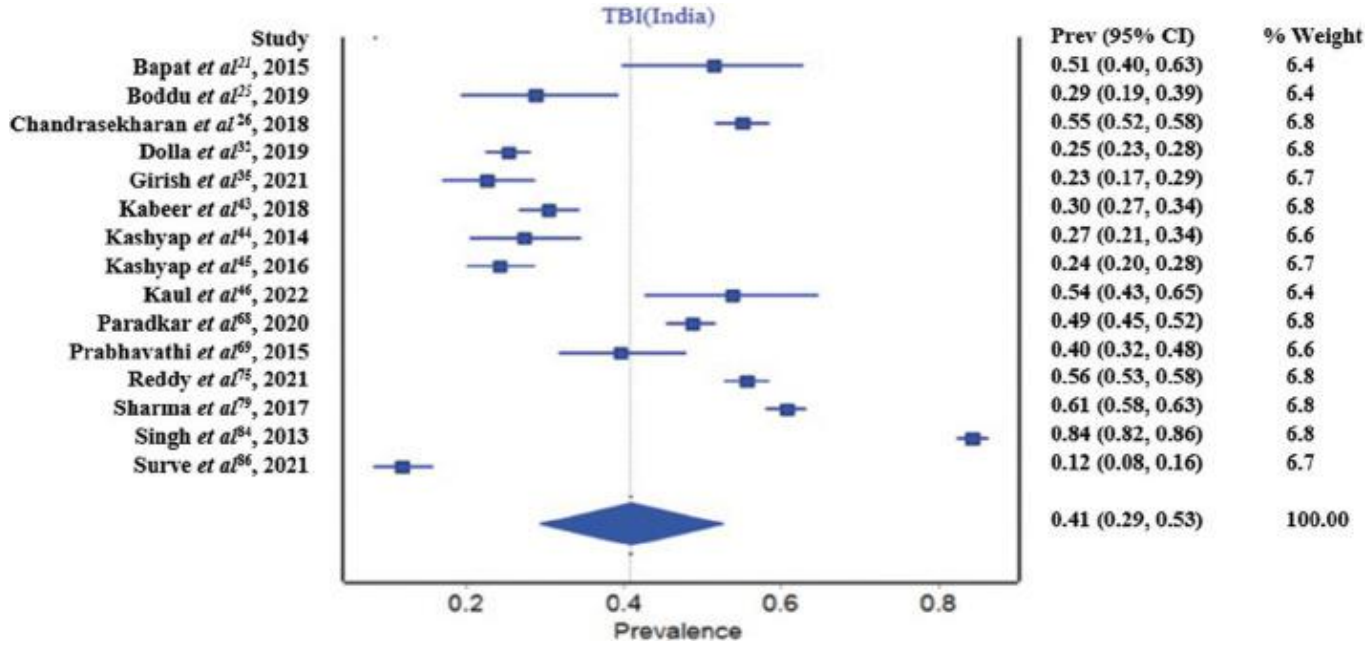
Most recent TB prevalence survey: 2019-2021

Country-level and by state

Prevalence, microbiologically confirmed PTB in ≥ 15 years age: **316 per lakh population**

The prevalence of TB infection among population ≥ 15 years age: **31.4%**





Chauhan *et al*. IJMR 2023

RSV

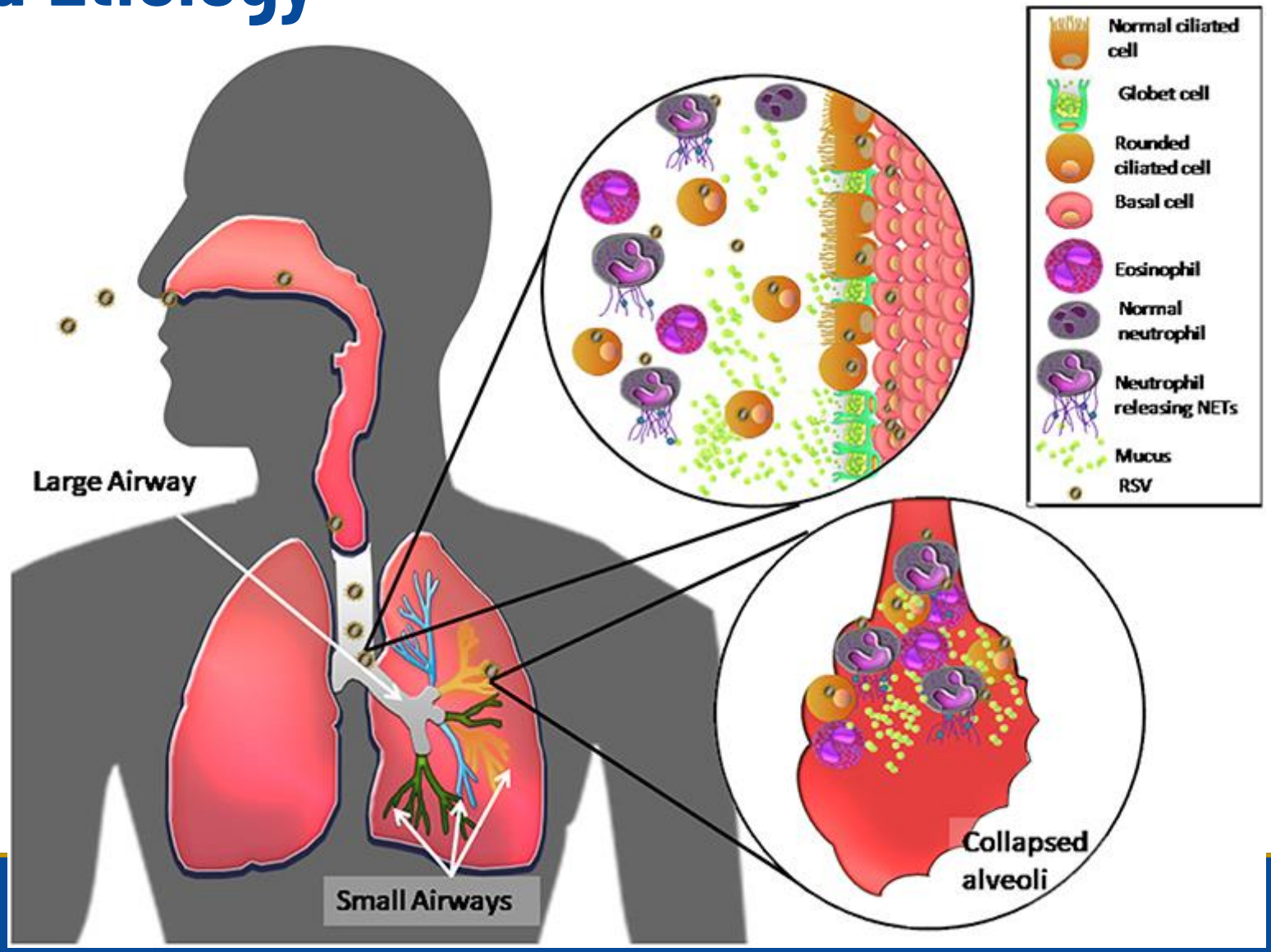
Introduction to RSV

- RSV is a negative-sense, single-stranded RNA virus.
    - Enveloped virus with surface proteins F and G
- Identified in 1956 in chimpanzees and later in children in 1957
- Major cause of respiratory infections in all age groups.

RSV Transmission and Etiology

Spread through respiratory droplets, direct contact, & fomites

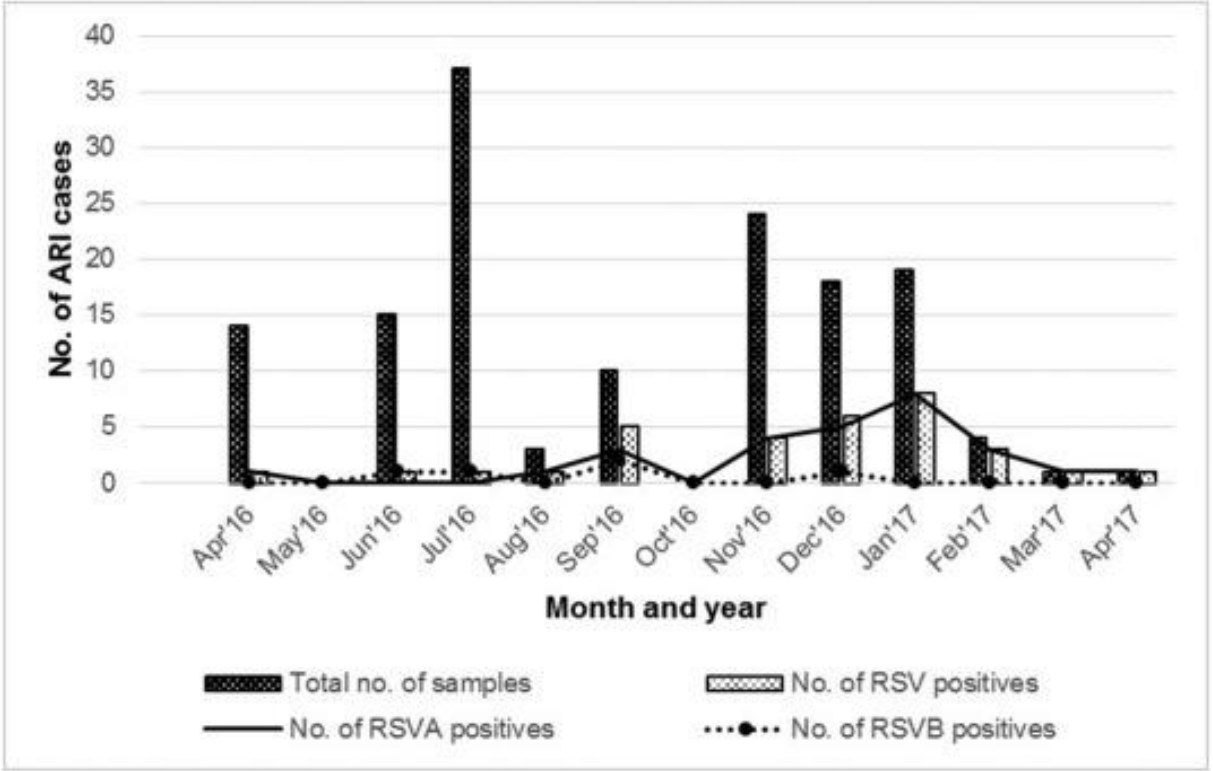
Virus infects epithelial cells in respiratory tract



https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2019.02152/full

RSV Epidemiology

The total number of RSV positives correlated with mean monthly maximum temperature, mean monthly minimum temperature, and average relative humidity in Chennai, India 2016-2017.

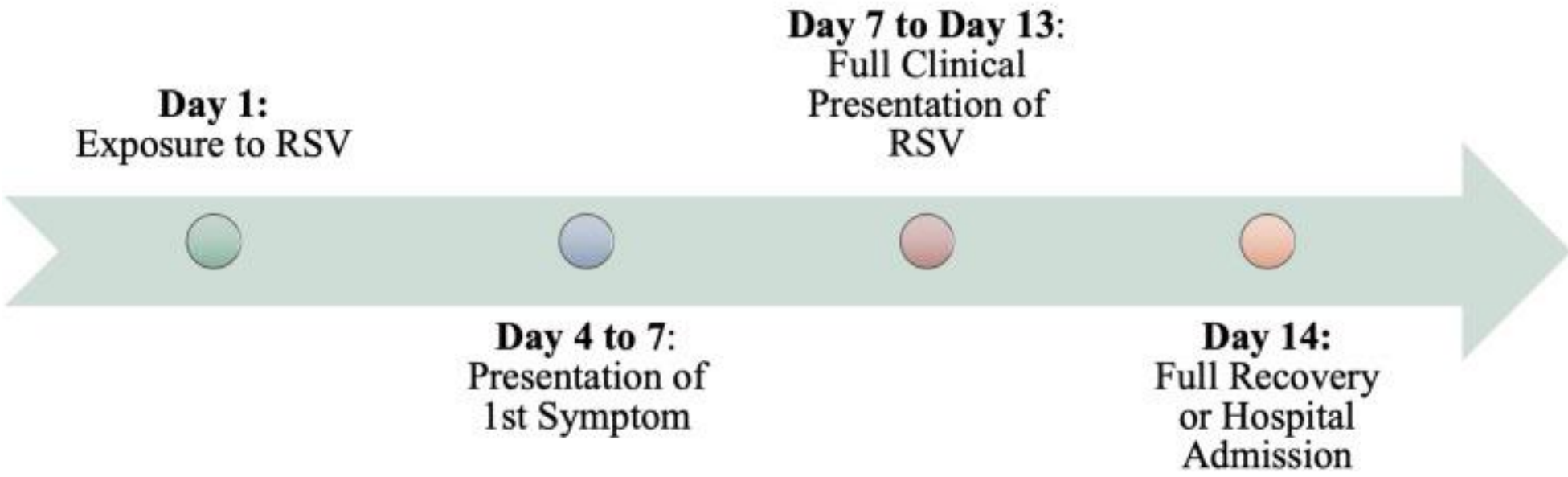


https://www.sciencedirect.com/science/article/pii/S2213398418300769

Clinical Manifestations

- Infants, elderly, and immunocompromised individuals/those with underlying conditions are most at risk for severe disease
- Ranges from mild cold-like symptoms to severe bronchiolitis and pneumonia
- In **Infants**: Bronchiolitis, pneumonia, and severe respiratory distress.
- In **Adults**: Common cold symptoms but can be severe in the elderly and immunocompromised.

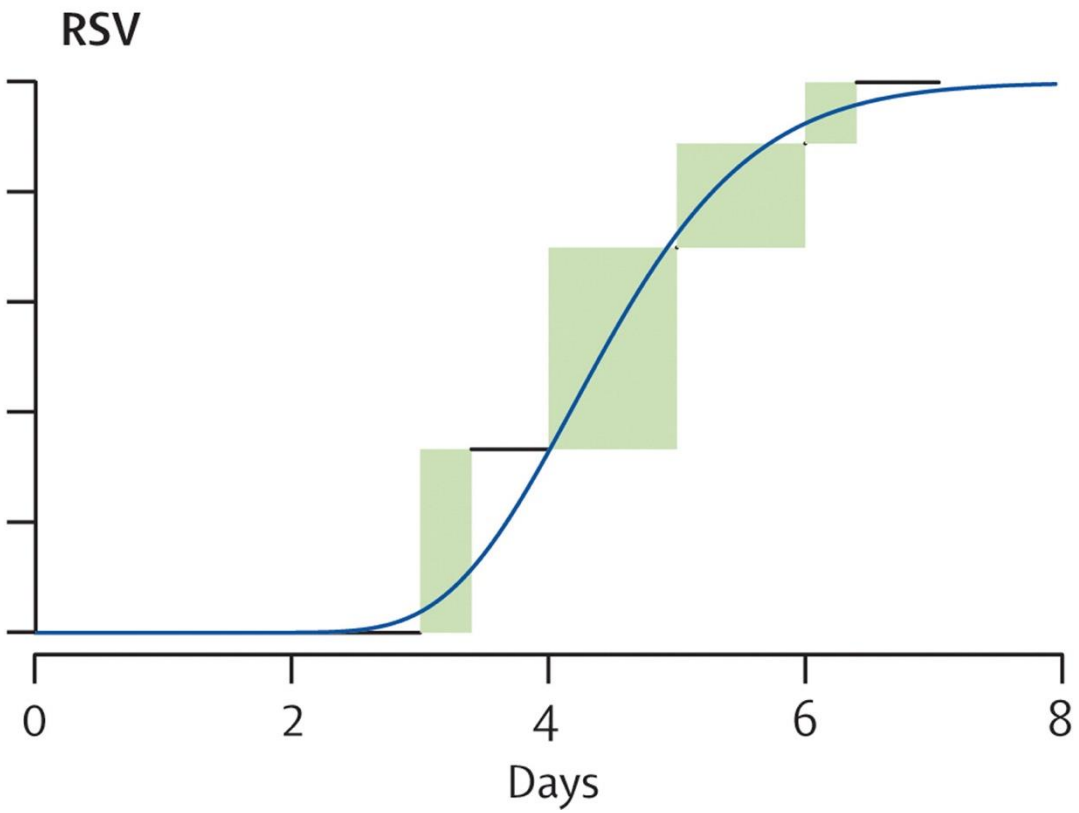
Timeline of RSV Infection



https://pmc.ncbi.nlm.nih.gov/articles/PMC10111061/

Incubation Period

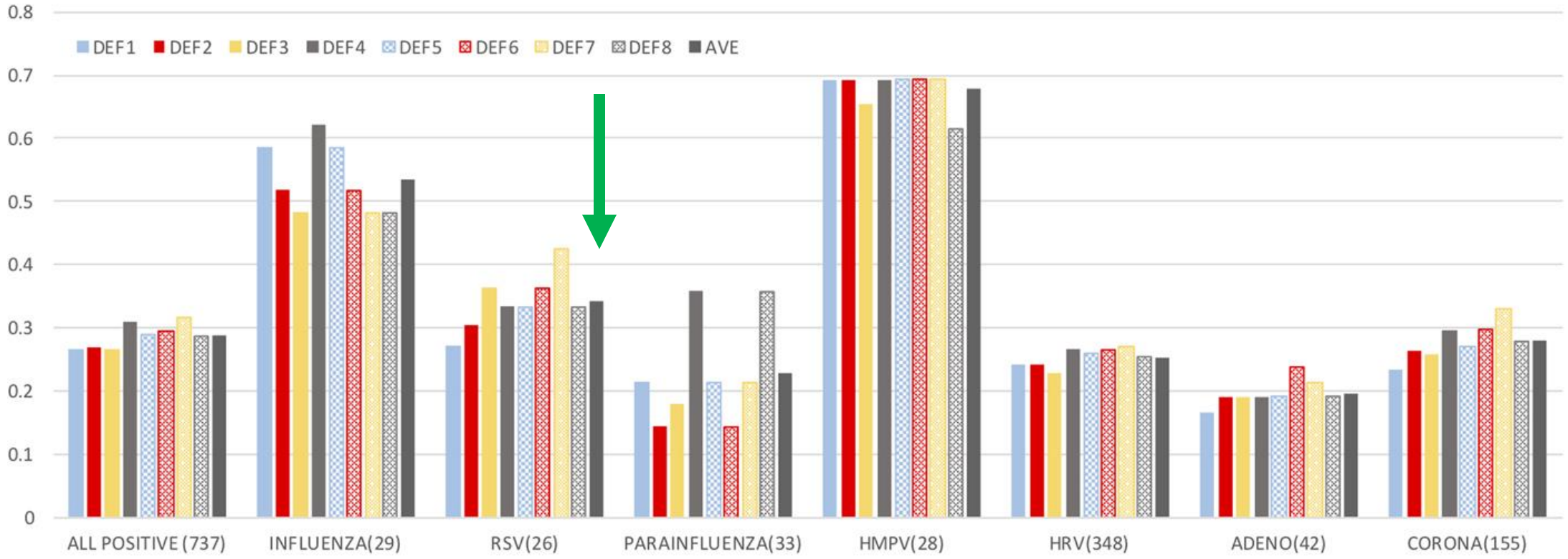
3-7 days



https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(09)70069-6/fulltext

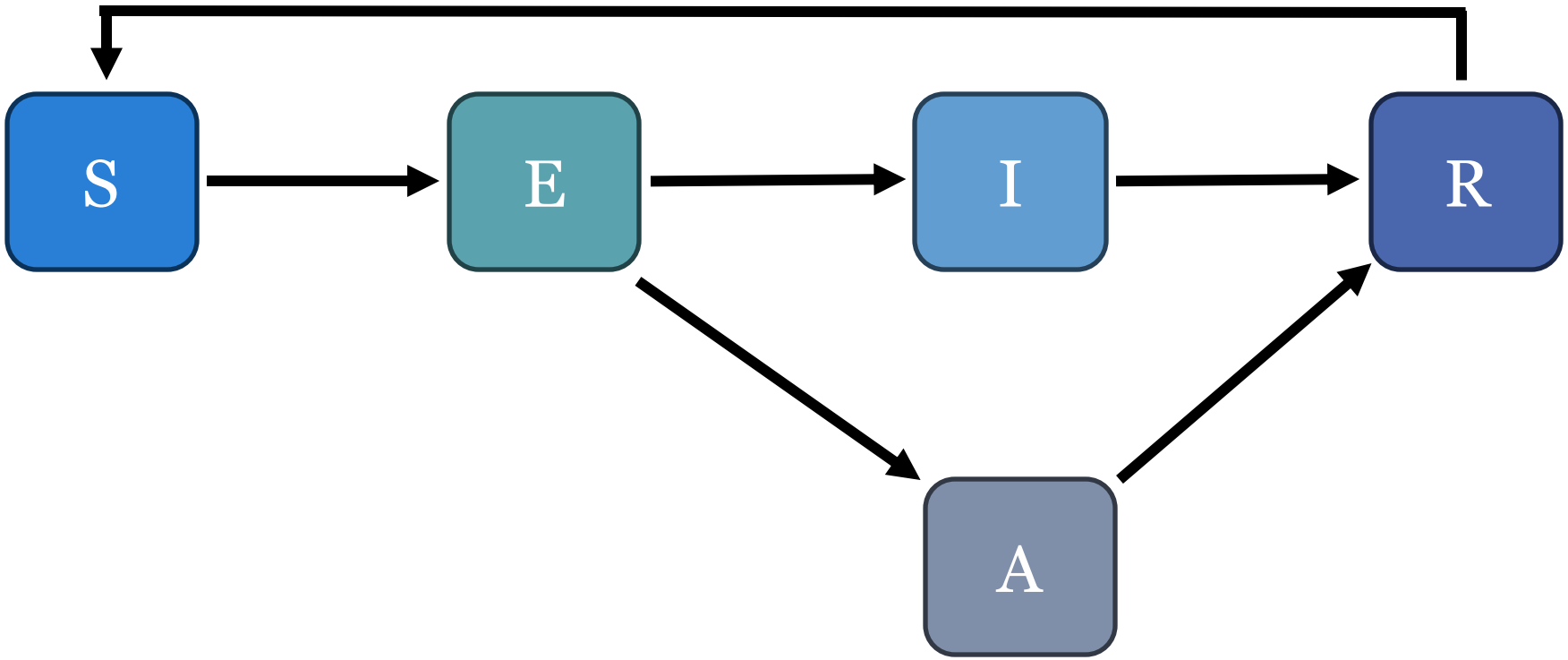
Symptomatic Ratio

Only about 35% of RSV infections are symptomatic



https://www.cambridge.org/core/journals/epidemiology-and-infection/article/rates-of-asymptomatic-respiratory-virus-infection-across-age-groups/D8E75BDC5B16AEC88DB57CD9B291BB37

RSV Diagram



Rotavirus

Natural Immunity to rotavirus

The New England Journal of Medicine

ROTAVIRUS INFECTION IN INFANTS AS PROTECTION AGAINST SUBSEQUENT INFECTIONS

F. Raúl Velázquez, M.D., David O. Matson, M.D., Ph.D., Juan J. Calva, M.D., M. Lourdes Guerrero, M.D., Ardythe L. Morrow, Ph.D., Shelly Carter-Campbell, Ph.D., Roger I. Glass, M.D., Ph.D., Mary K. Estes, Ph.D., Larry K. Pickering, M.D., and Guillermo M. Ruiz-Palacios, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Protective Effect of Natural Rotavirus Infection in an Indian Birth Cohort

Beryl P. Gladstone, Ph.D., Sasirekha Ramani, Ph.D., Indrani Mukhopadhya, Ph.D., Jayaprakash Muliyil, M.D., Dr.P.H., Rajiv Sarkar, M.Sc., Andrea M. Rehman, Ph.D., Shabbar Jaffar, Ph.D., Miren Iturriza Gomara, F.R.C.Path., James J. Gray, F.R.C.Path., David W.G. Brown, F.R.C.Path., Ulrich Desselberger, F.R.C.Path., Sue E. Crawford, B.S., Jacob John, M.D., Sudhir Babji, M.D., Mary K. Estes, Ph.D., and Gagandeep Kang, M.D., Ph.D.

Velazquez, NEJM, 1996

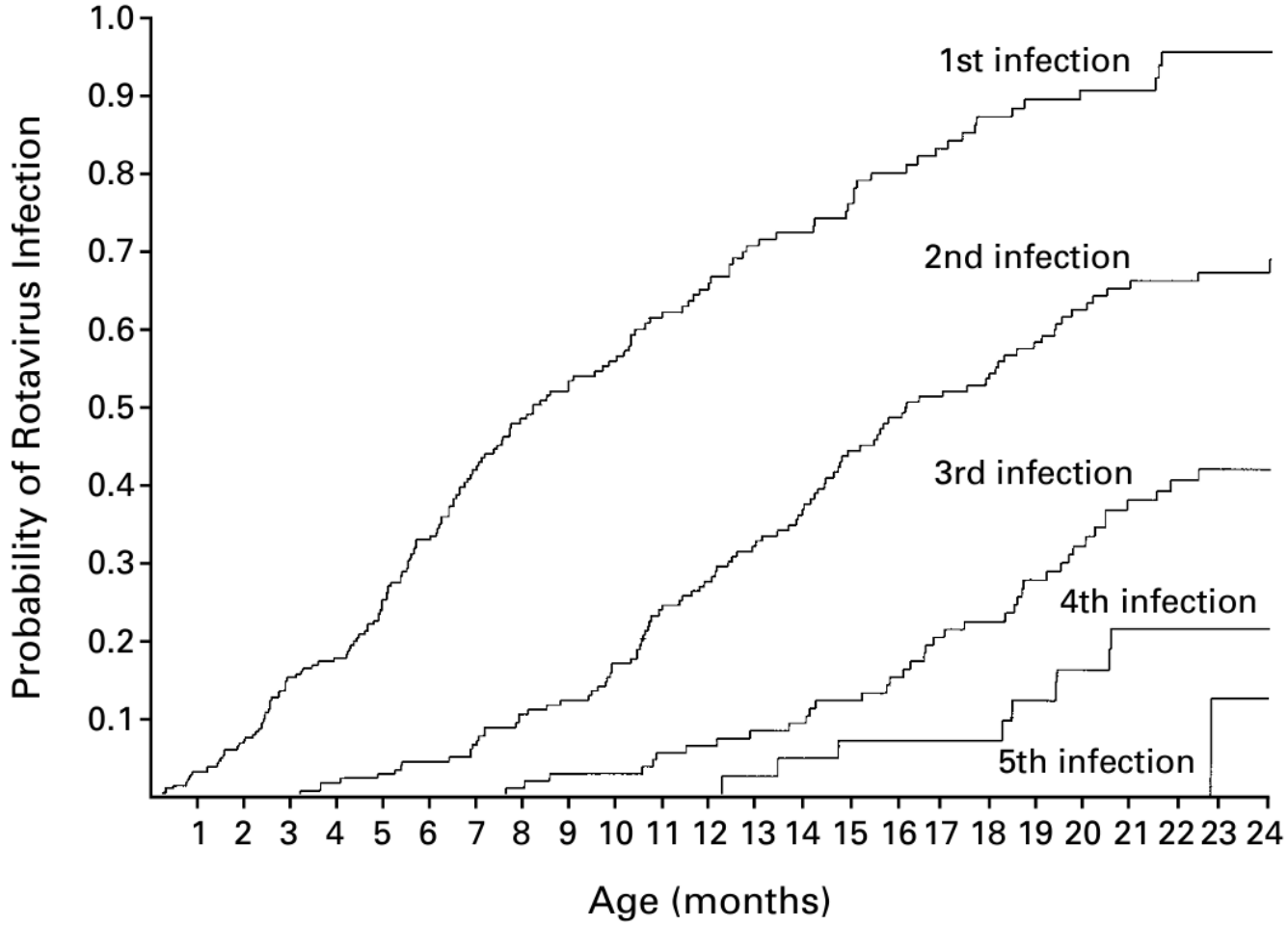


Figure 1. Cumulative Probability of First and Subsequent Natural Rotavirus Infections during the First Two Years of Life.

Velazquez, NEJM, 1996

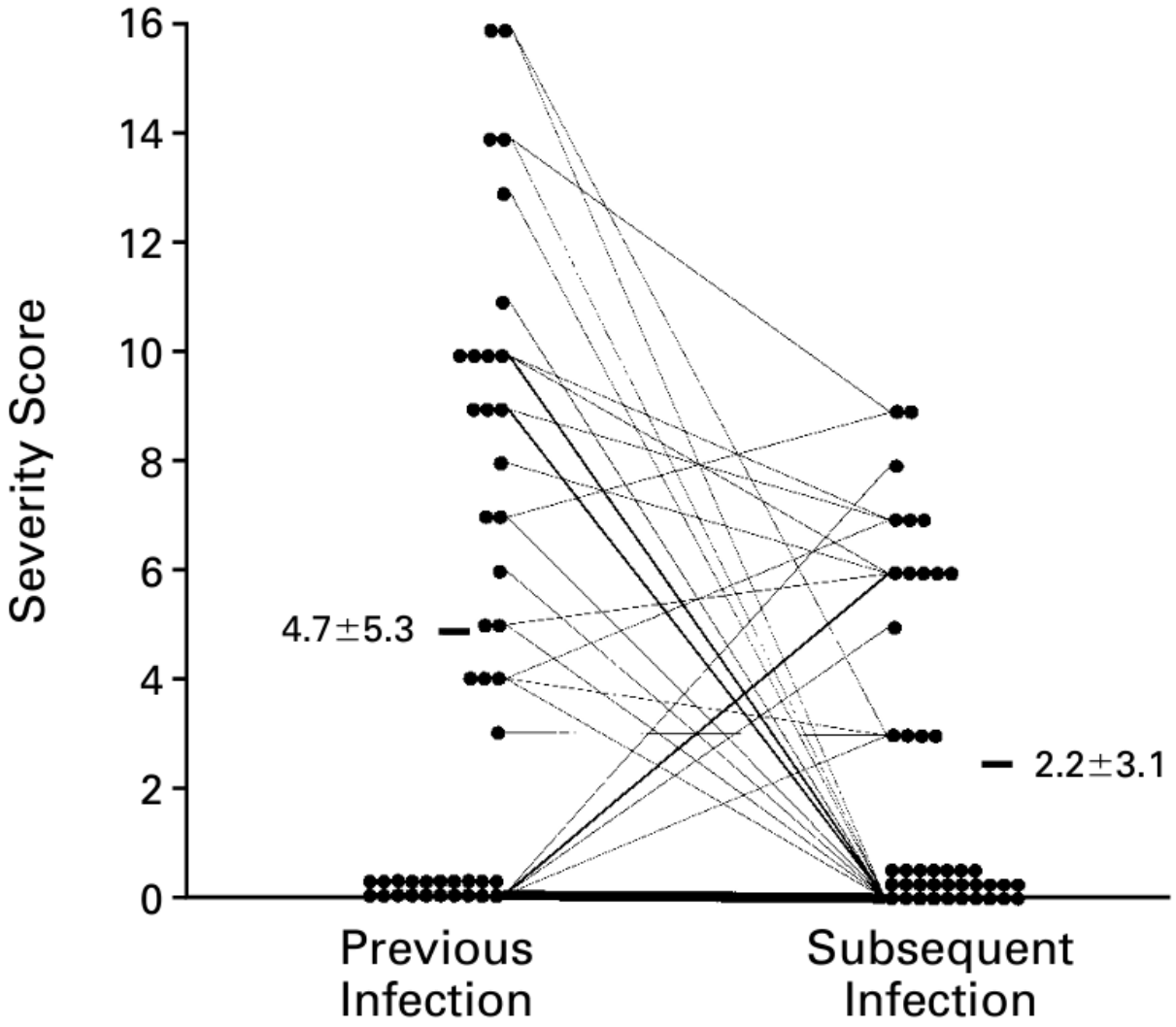


Figure 2. Severity of 43 Rotavirus Infections as Compared with the 43 That Followed Them.

Protection against subsequent infection and disease: Mexico

	Middle income-Mexico
Relative risk of **infection** following	
First infection	0.62
Second infection	0.37
Third infection	0.37
Proportion of infections with **diarrhea**	
First infection	0.39
Second infection	0.16
Third infection	0.20
Fourth infection	0.12
Proportion of diarrhea with **severe GE**	
First infection	0.28
Second infection	0.15
Third infection	0
Fourth infection	0

Velazquez, NEJM, 199
Gladstone, NEJM, 201

Protection against subsequent infection and disease: Mexico and India

	Middle income-Mexico	Low income India
Relative risk of **infection** following		
First infection	0.62	0.62
Second infection	0.37	0.48
Third infection	0.37	0.33
Proportion of infections with **diarrhea**		
First infection	0.39	0.32
Second infection	0.16	0.28
Third infection	0.20	0.18
Fourth infection	0.12	0.18
Proportion of diarrhea with **severe GE**		
First infection	0.28	0.15
Second infection	0.15	0.22
Third infection	0	0.23
Fourth infection	0	0.24

Similar protection against infection and disease

Velazquez, NEJM, 199
Gladstone, NEJM, 201

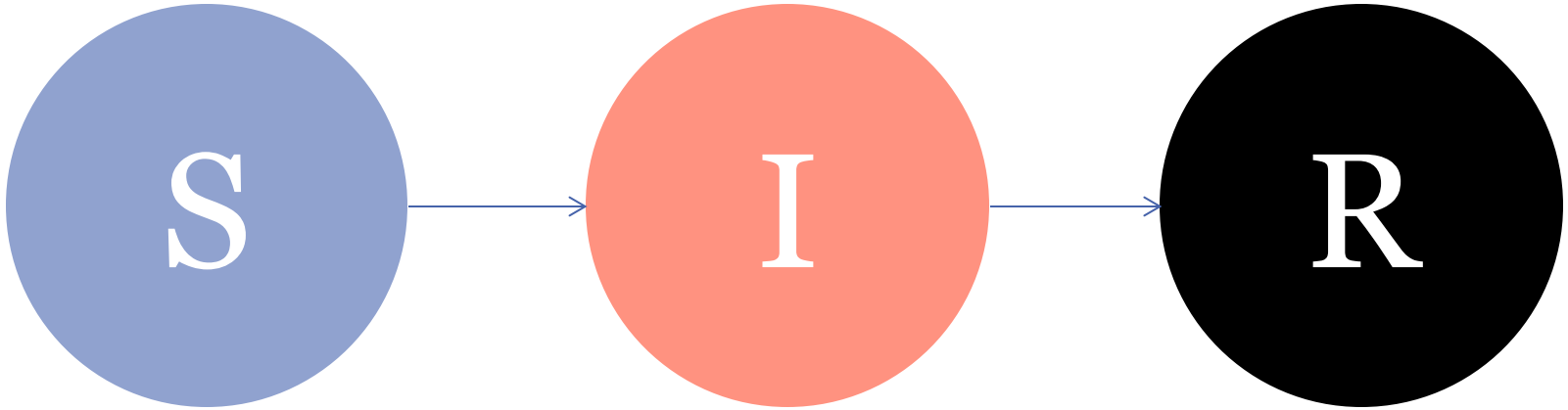
Protection against subsequent infection and disease: Mexico and India

	Middle income-Mexico	Low income India
Relative risk of **infection** following		
First infection	0.62	0.62
Second infection	0.37	0.48
Third infection	0.37	0.33
Proportion of infections with **diarrhea**		
First infection	0.39	0.32
Second infection	0.16	0.28
Third infection	0.20	0.18
Fourth infection	0.12	0.18
Proportion of diarrhea with **severe GE**		
First infection	0.28	0.15
Second infection	0.15	0.22
Third infection	0	0.23
Fourth infection	0	0.24

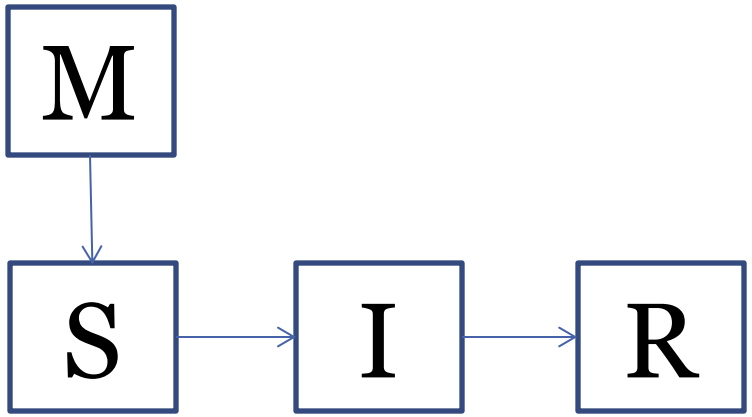
Severe outcome continue in Indian kids

Velazquez, NEJM, 199
Gladstone, NEJM, 201

How would you expand the SIR model to capture the natural history of rotavirus?



Our model of rotavirus



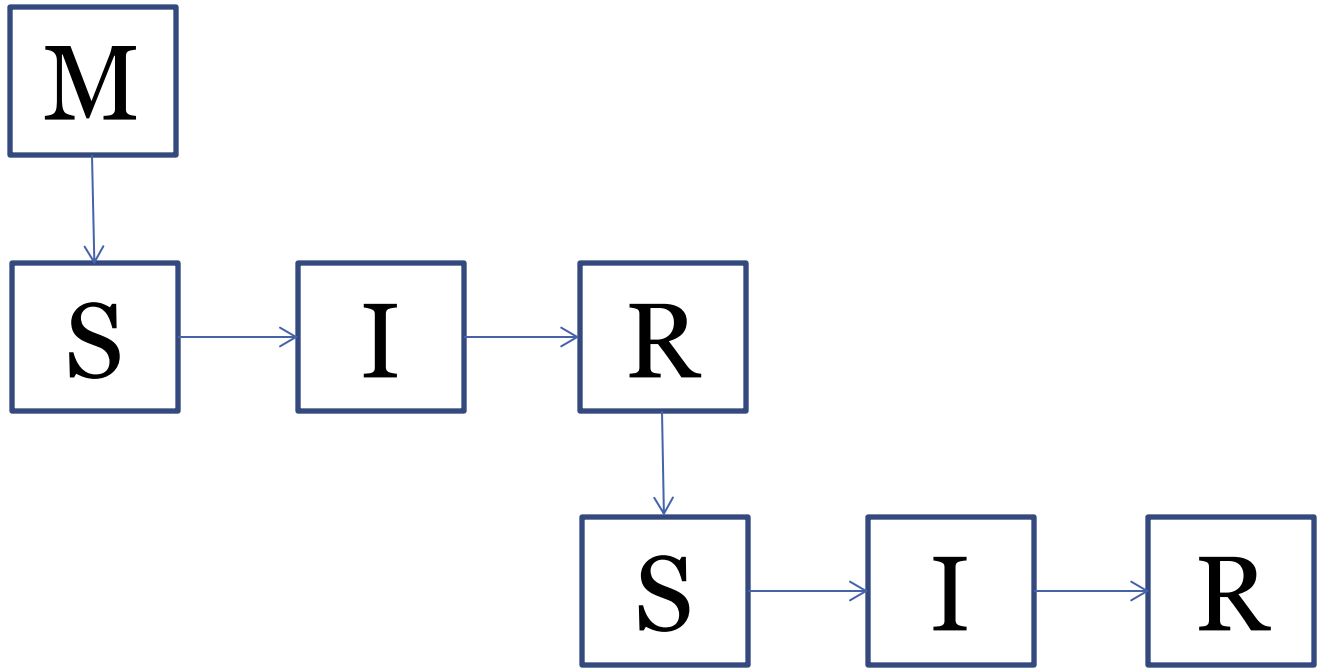
Maternal immunity

Primary infection

Pitzer et al, Science 2009

Atchison et al, Vaccine 2010

Lopman et al, PLoS One 2012



Maternal immunity

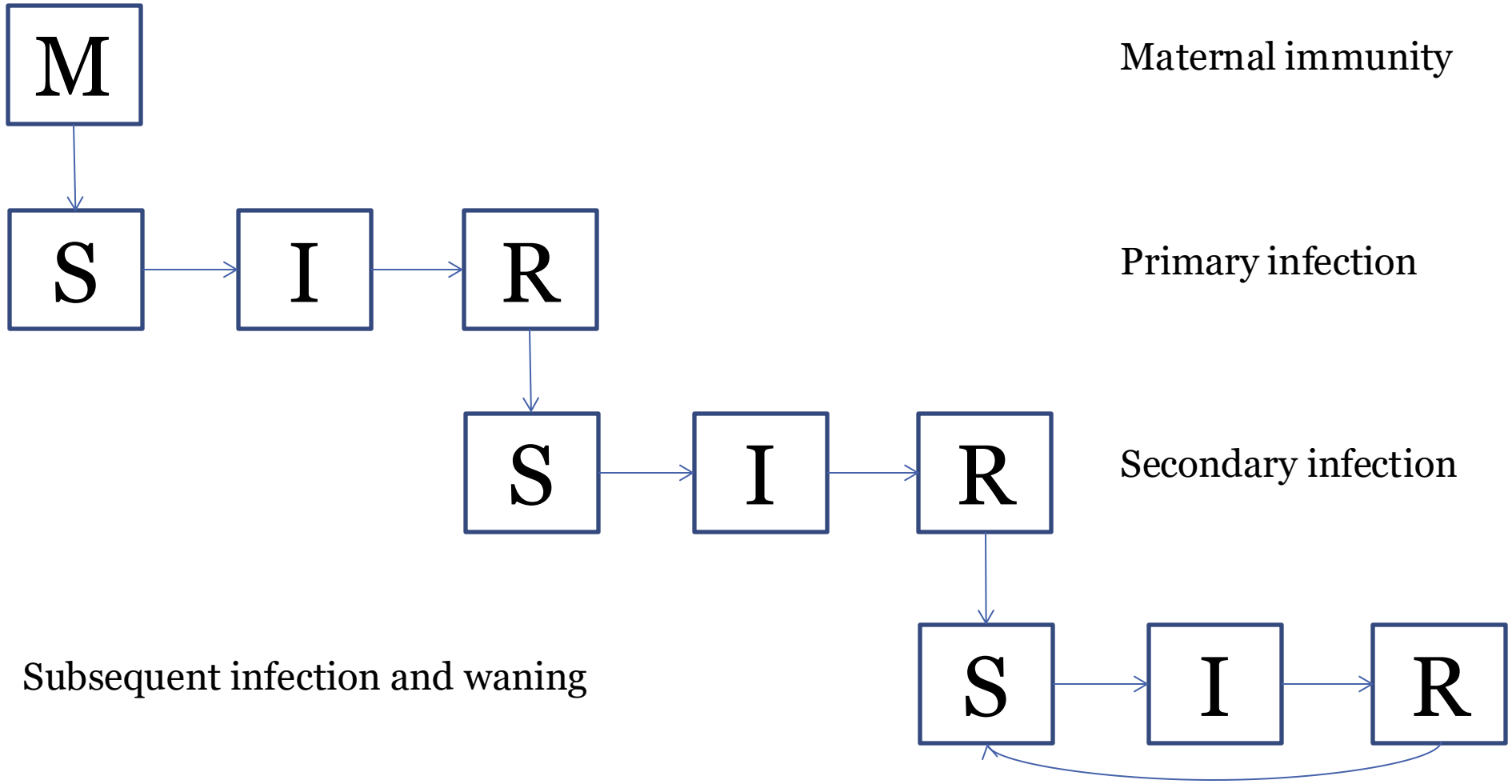
Primary infection

Secondary infection

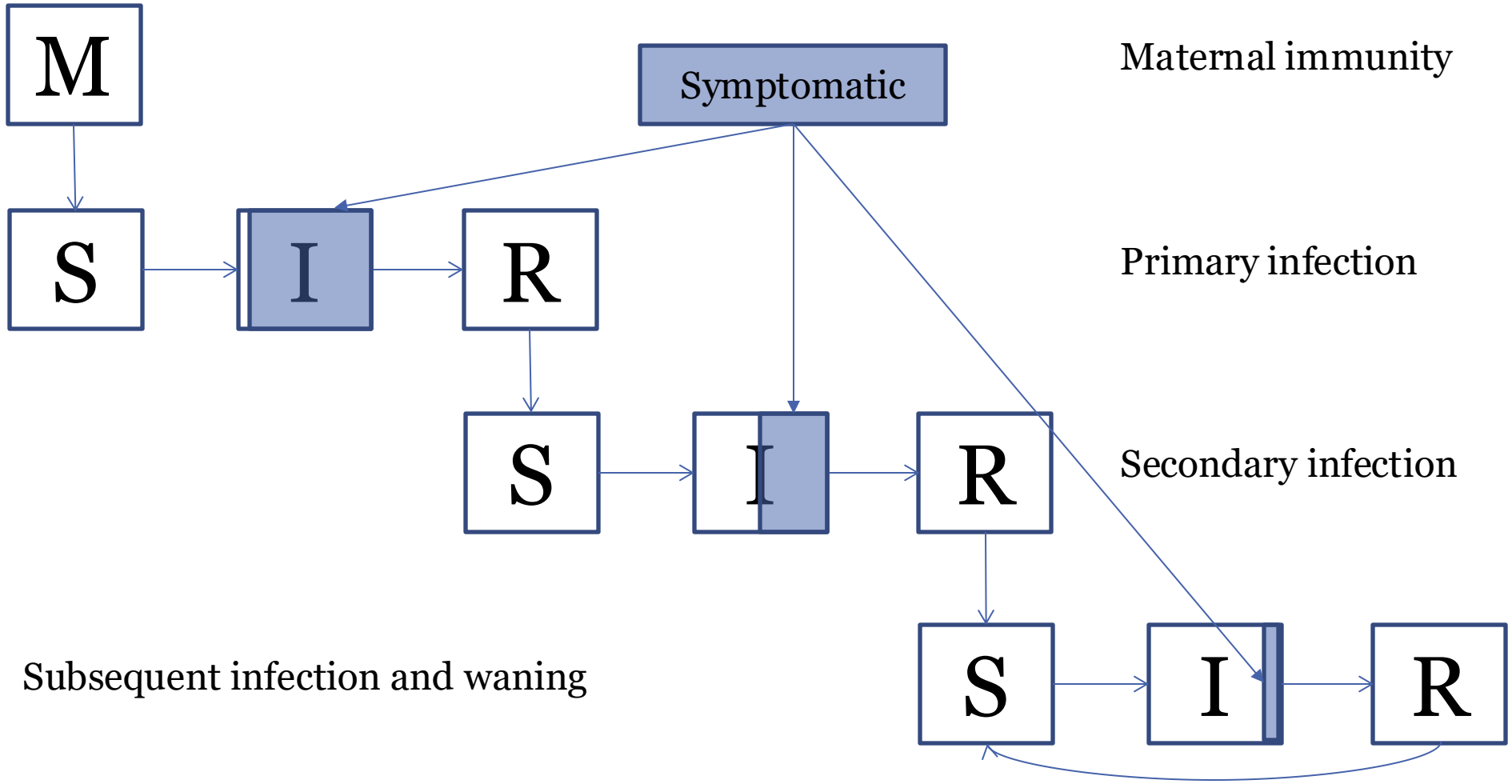
Pitzer et al, Science 2009

Atchison et al, Vaccine 2010

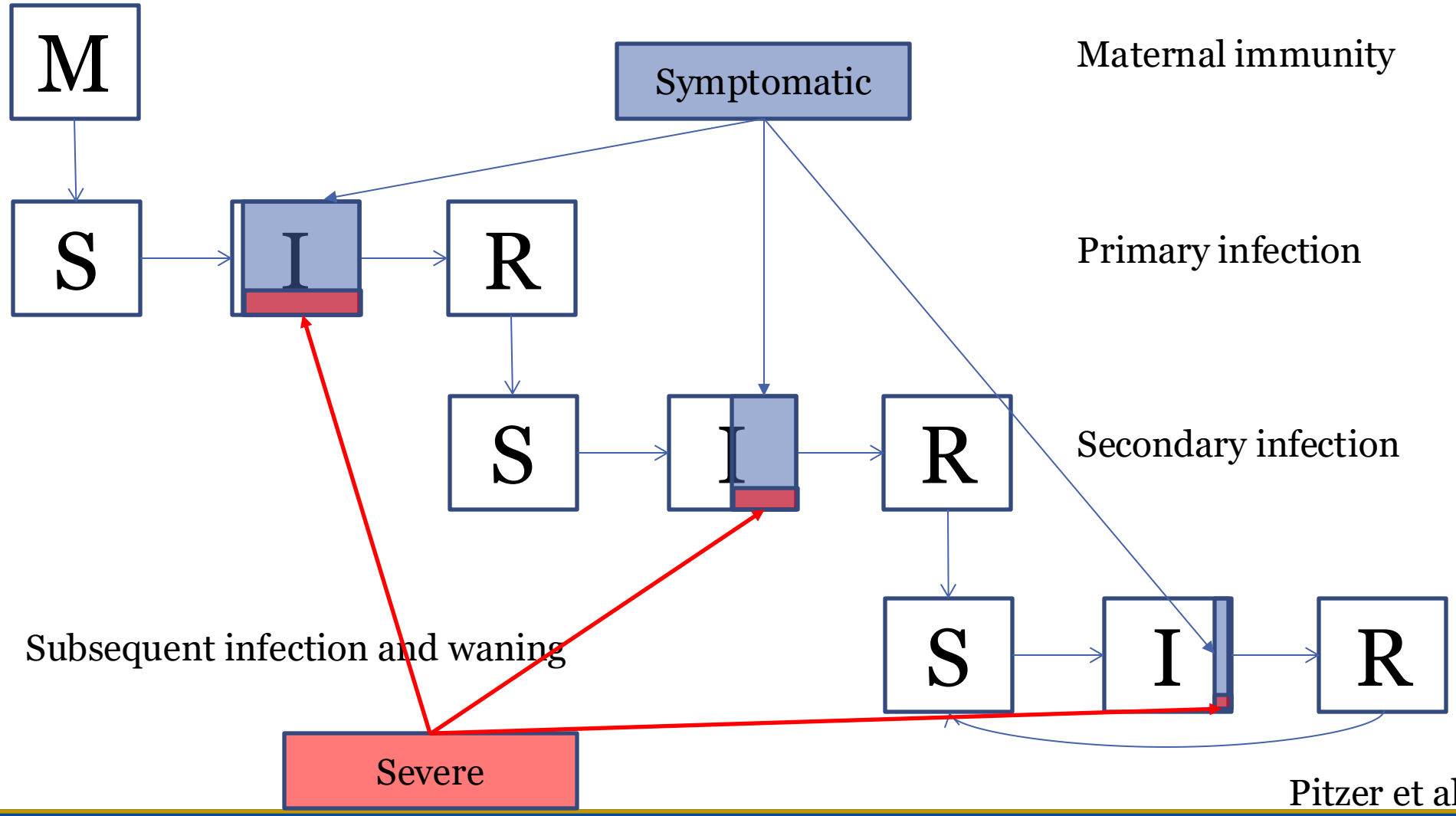
Lopman et al, PLoS One 2012



Pitzer et al, Science 2009
Atchison et al, Vaccine 2010
Lopman et al, PLoS One 2012



Pitzer et al, Science 2009
Atchison et al, Vaccine 2010
Lopman et al, PLoS One 2012



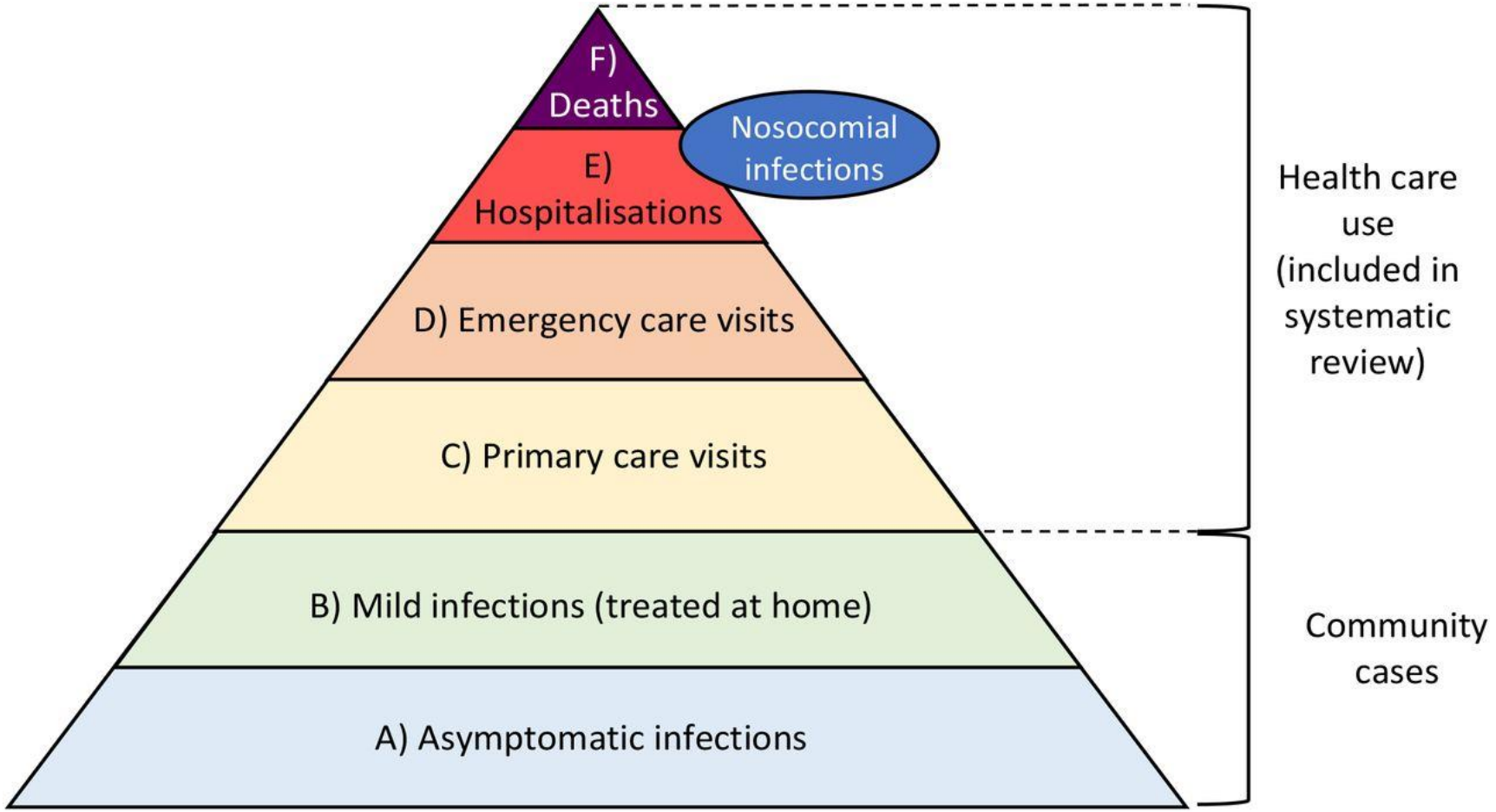
Pitzer et al, Science 2009
Atchison et al, Vaccine 2010
Lopman et al, PLoS One 2012

Surveillance data sources for rotavirus

Purpose of rotavirus surveillance

1. monitor the impact of vaccination in reducing morbidity and mortality from rotavirus disease over time
2. evaluate vaccine effectiveness in field use and identify and determine the causes of possible vaccine failure
3. monitor the possible emergence of rotavirus strains that might escape vaccination
4. identify population groups that might not be adequately covered by vaccination
5. continue to monitor the safety of rotavirus vaccines.

Surveillance pyramid for rotavirus



Ardura-Garcia, Vaccine 2021

Only a tiny fraction of rotavirus infections are detected by surveillance

We have natural history parameters to parameterize:

- proportion(symptomatic | infection)
- proportion(severe | symptomatic)

We almost never know:

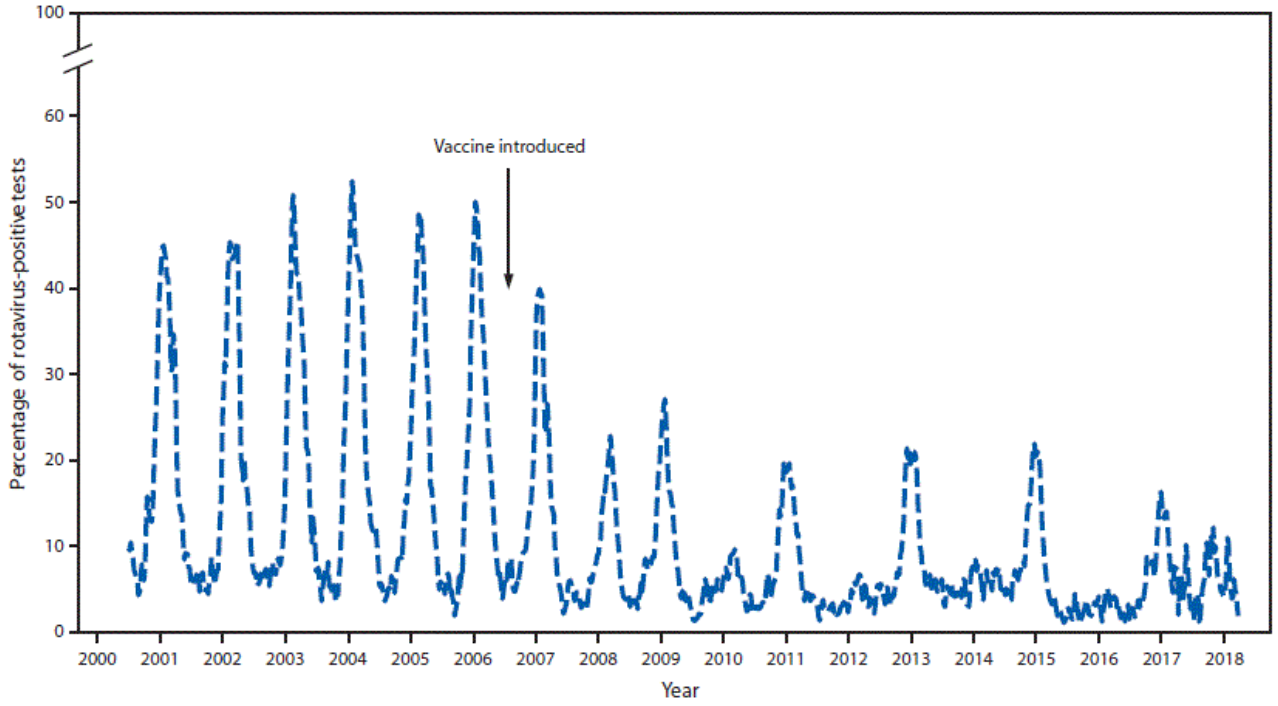
- probability (seeking care | severe) or
- probability (captured by surveillance | severe)

Therefore, we estimate this probability in model-fitting, e.g.:

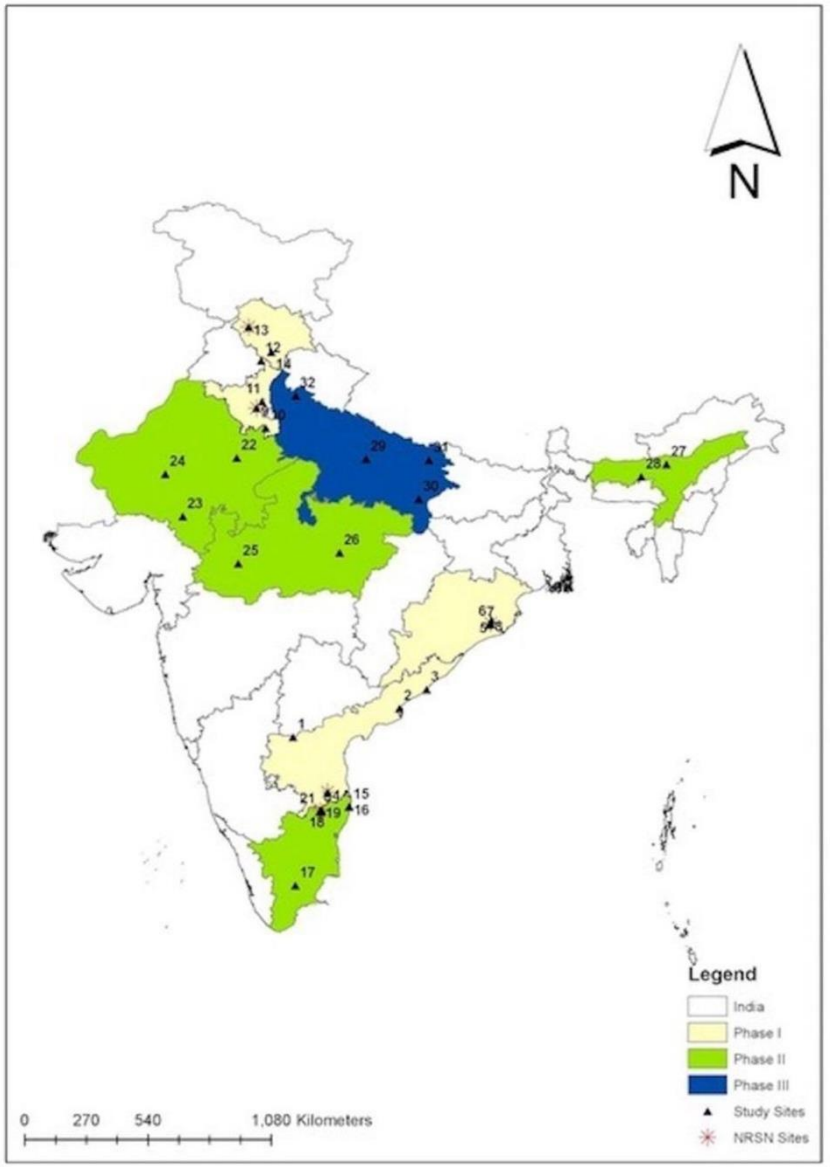
- Ghana: 0.01 to 0.1 (Asare, Vaccine 2020)
- Malawi: 0.017 (Pitzer, NPJ Vaccines 2024)

Rotavirus vaccine impact in the United States

Hallowell 2019, *MMWR*



Location of surveillance sites in states introducing ROTAVAC



Bhat et al, Vaccine 2025

EMORY

ROLLINS
SCHOOL OF
PUBLIC
HEALTH