

# Modeling Vaccination

# Interventions

- **Non-pharmaceutical interventions**
  - Sanitation
  - Social distancing
  - Masking
  - Education
- **Pharmaceutical interventions**
  - Therapeutics
    - Drugs, antivirals, antibody therapies
  - Prophylaxis
    - Vaccines, antibody therapies

# What do vaccines do?

- **Vaccine:** A preparation that is used to stimulate the body's immune response against pathogens.
- **Efficacy:** measured in a controlled clinical trial and is based on how many people who got vaccinated developed the 'outcome of interest' (usually disease) compared with how many people who got the placebo developed the same outcome.
- **Effectiveness:** a measure of how well vaccination works under real-world conditions to protect people against health outcomes such as infection, symptomatic illness, hospitalization, and death.

# What do vaccines do?

- **Prevent infection** – move you from S -> R
  - Measles, Oral polio vaccine
- **Prevent illness** – perhaps still transmission?
  - Inactivated polio vaccine, diphtheria
- **Prevent/reduce transmission** → reduce Beta
  - SARS-CoV-2, RTS,s
- **Accelerate clearance** → shorten L
  - SARS-CoV-2

How long does immunity last?  
For simplicity now, we'll  
assume that immunity is  
lifelong

# Herd Immunity

- Indirect protection to non-immune individuals due to the presence of immune individuals in the population

# Critical Herd Immunity Threshold

- When indirect protection is high enough, the risk to non-immune individuals falls to 0 because the endemic equilibrium is 0

# Critical Herd Immunity Threshold

$$R_0 = \frac{\beta S}{\gamma} = \beta S L$$

$$R_0 = \beta S L$$

$$1 = \frac{\beta S L}{R_0}$$

$$1 = \frac{1}{R_0} S \beta L$$

What fraction of Susceptibles  
need to be immune in order for  
 $\frac{1}{R_0} S$   
to remain?

# Critical Herd Immunity Threshold

$$R_0 = \frac{\beta S}{\gamma} = \beta S L$$

$$R_0 = \beta S L$$

$$1 = \frac{\beta S L}{R_0}$$

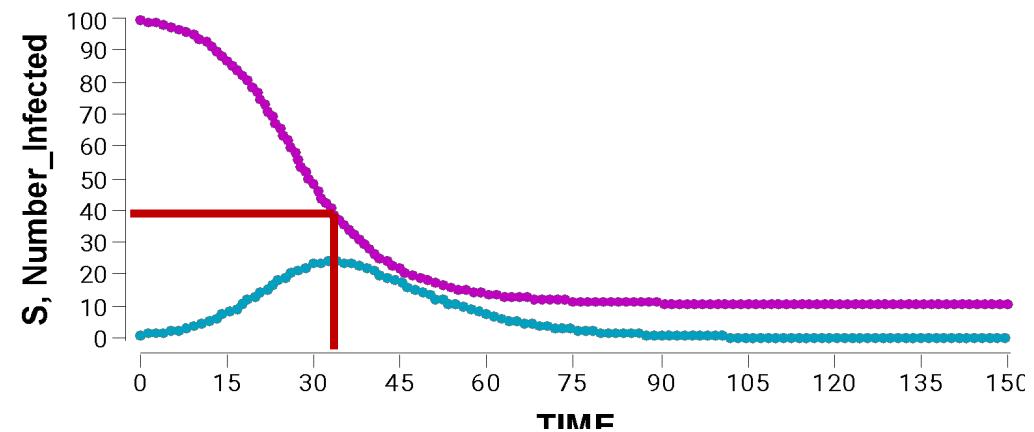
$$1 = \frac{1}{R_0} S \beta L$$

What fraction of Susceptibles  
need to be immune in order for  
 $\frac{1}{R_0} S$   
to remain?

$$T_c = 1 - \frac{1}{R_0}$$

# Critical Herd Immunity Threshold

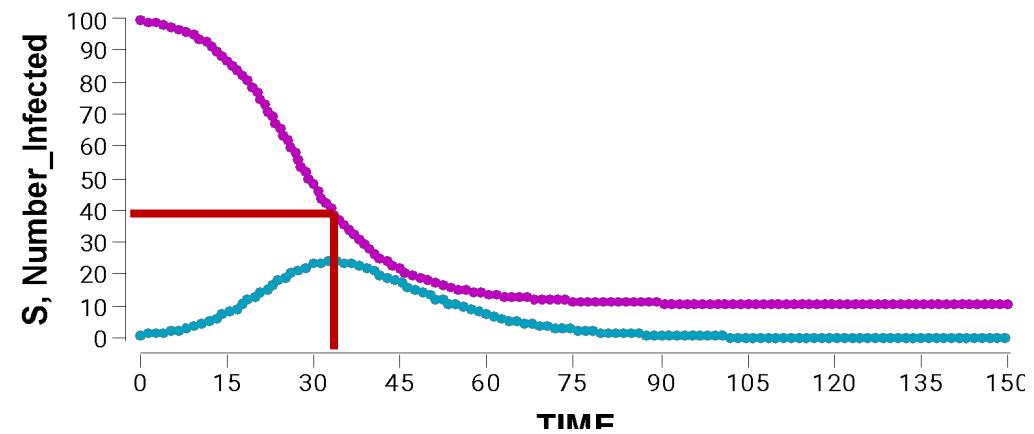
If  $T_c = 1 - \frac{1}{R_0}$  are immune  
**before** an outbreak then it  
won't be able to grow (on  
average)



If an outbreak takes off it **WILL**  
**NOT** stop when  $T_c = 1 - \frac{1}{R_0}$   
are immune

# Critical Herd Immunity Threshold

If  $T_c = 1 - \frac{1}{R_0}$  are immune  
**before** an outbreak then it  
won't be able to grow (on  
average)



If an outbreak takes off it **WILL**  
**NOT** stop when  $T_c = 1 - \frac{1}{R_0}$   
are immune  
Why not?

# Final Size Calculation

- $R_\infty = 1 - e^{-R_0 R_\infty}$

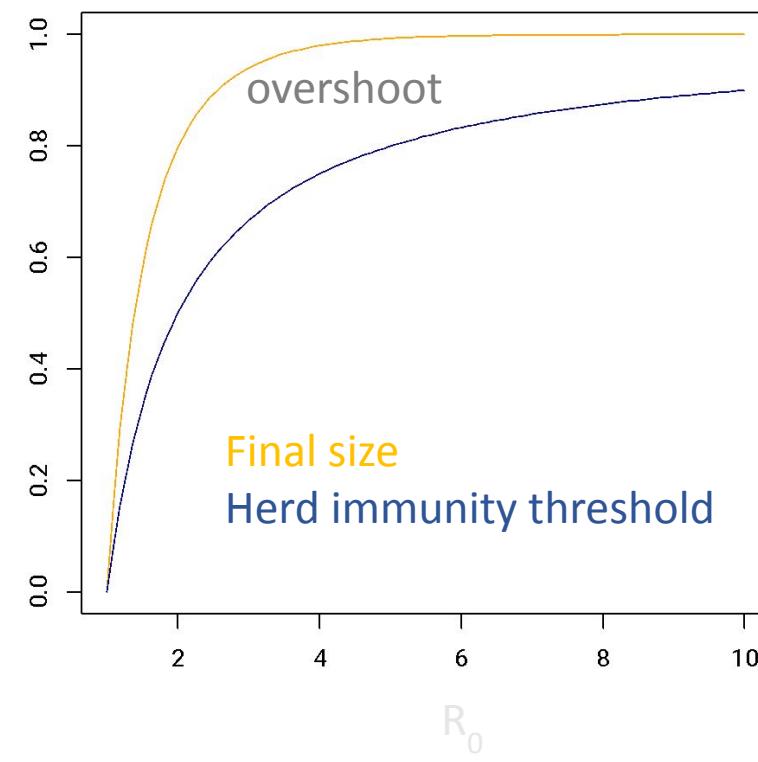
Where  $R_\infty$  is the proportion of the population infected at the end of the epidemic (the proportion in the R class at the end)

Citation:<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3506030/>

# Comparing $T_c$ and Final Size

Many more individuals will become infected in an epidemic (on average) than need to be immunized **BEFORE** an epidemic

Herd Immunity is a relevant concept throughout an epidemic (and helps stop them), the Herd Immunity Threshold is only relevant for preventing, not stopping outbreaks.



# Imperfect Vaccine Effectiveness

$$T_c = 1 - \frac{1}{R_0}$$

$$T_c = P(\text{vaccinated}) * \text{effectiveness}$$

$$P(\text{vaccinated}) = \frac{1}{\text{effectiveness}} \left( 1 - \frac{1}{R_0} \right)$$

$T_c$  are those effectively immunized. We must account for vaccine failure

NEWS | ONLINE FIRST



PDF [85 KB]



Figures



Save



Share



Reprints



Request

## Omicron variant and booster COVID-19 vaccines

Talha Khan Burki

Published: December 17, 2021 • DOI: [https://doi.org/10.1016/S2213-2600\(21\)00559-2](https://doi.org/10.1016/S2213-2600(21)00559-2) •  Check for updates

 PlumX Metrics

The original strain of SARS-CoV-2 has an R<sub>0</sub> of 2·5, while the delta variant (B.1.617.2) has an R<sub>0</sub> of just under 7. Martin Hibberd, professor of emerging infectious diseases at London School of Hygiene & Tropical Medicine (London, UK), reckons omicron's R<sub>0</sub> could be as high as 10. In the UK, cases of omicron are doubling

# Imperfect Vaccine Effectiveness

$$T_C = 1 - \frac{1}{R_0}$$

$$T_C = P(\text{vaccinated}) * \text{effectiveness}$$

$$P(\text{vaccinated}) = \frac{1}{\text{effectiveness}} \left( 1 - \frac{1}{R_0} \right)$$

(ex) Assume R<sub>0</sub>:

OG SARS-CoV-2 is 2.5

Delta is 7

Omicron is 10

What fraction of the population needs to be vaccinated if we have a vaccine that is 100%, 90%, 70% or 50% effective in blocking transmission?

# Exercises

(ex) Assume  $R_0$ :

OG SARS-CoV-2  $R_0 = 2.5$ : 60%

Delta is  $R_0 = 7$ : 86%

Omicron is  $R_0 = 10$ : 90%

What fraction of the population needs to be vaccinated if we have a vaccine that is 100% effective in blocking transmission?

# Exercises

(ex) Assume  $R_0$ :

OG SARS-CoV-2  $R_0 = 2.5$ : 60%, 67%, 86%, 120%

Delta is  $R_0 = 7$ : 86%, 95%, 122%, 170%

Omicron is  $R_0 = 10$ : 90%, 100%, 129%, 180%

What fraction of the population needs to be vaccinated if we have a vaccine that is 100%, 90%, 70% or 50% effective in blocking transmission?

# Initiatives

Disease Elimination and Eradication Efforts:

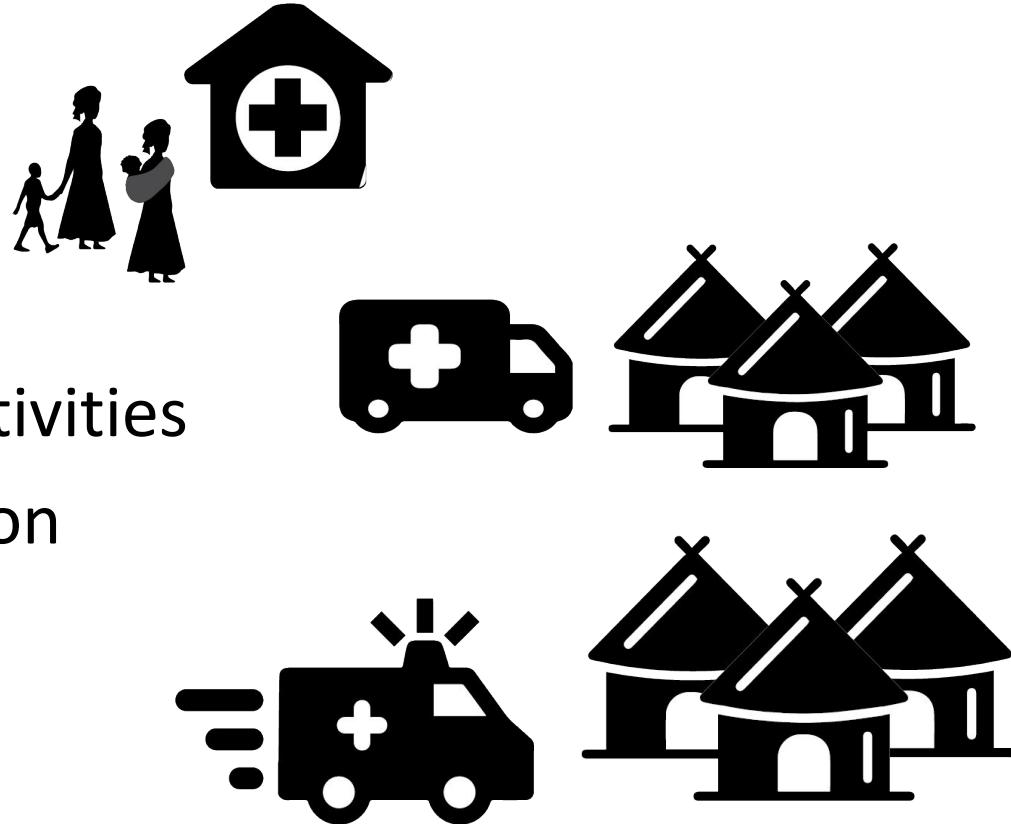
Malaria  
Rubella  
Rabies  
Measles

Which programs will be set back due to COVID-19 pandemic?



# How is vaccination delivered?

- Routine
  - 1<sup>st</sup> dose
  - 2<sup>nd</sup>, 3<sup>rd</sup>, etc dose ... opportunity
- Supplemental immunization activities
- Outbreak response immunization



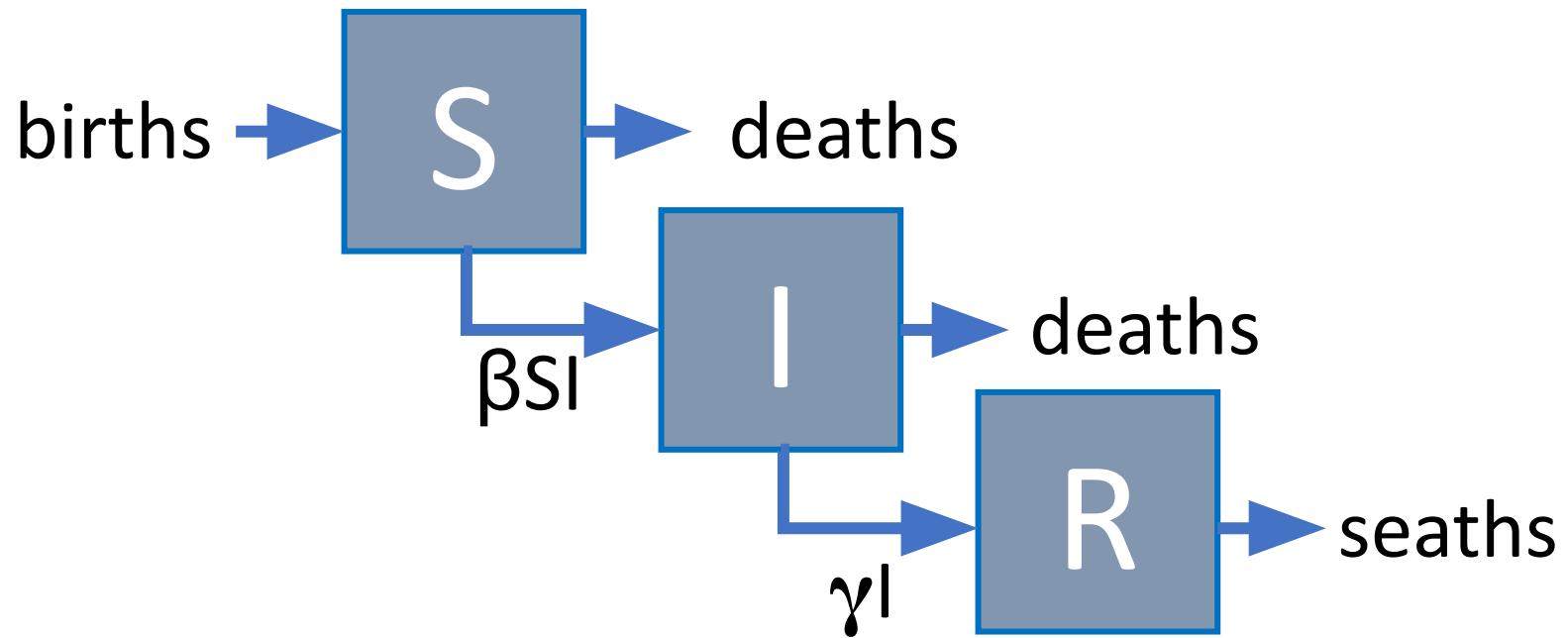
# How is vaccination delivered?

- Routine
  - 1<sup>st</sup> dose
  - 2<sup>nd</sup>, 3<sup>rd</sup>, etc dose ... opportunity
- Supplemental immunization activities
- Outbreak response immunization

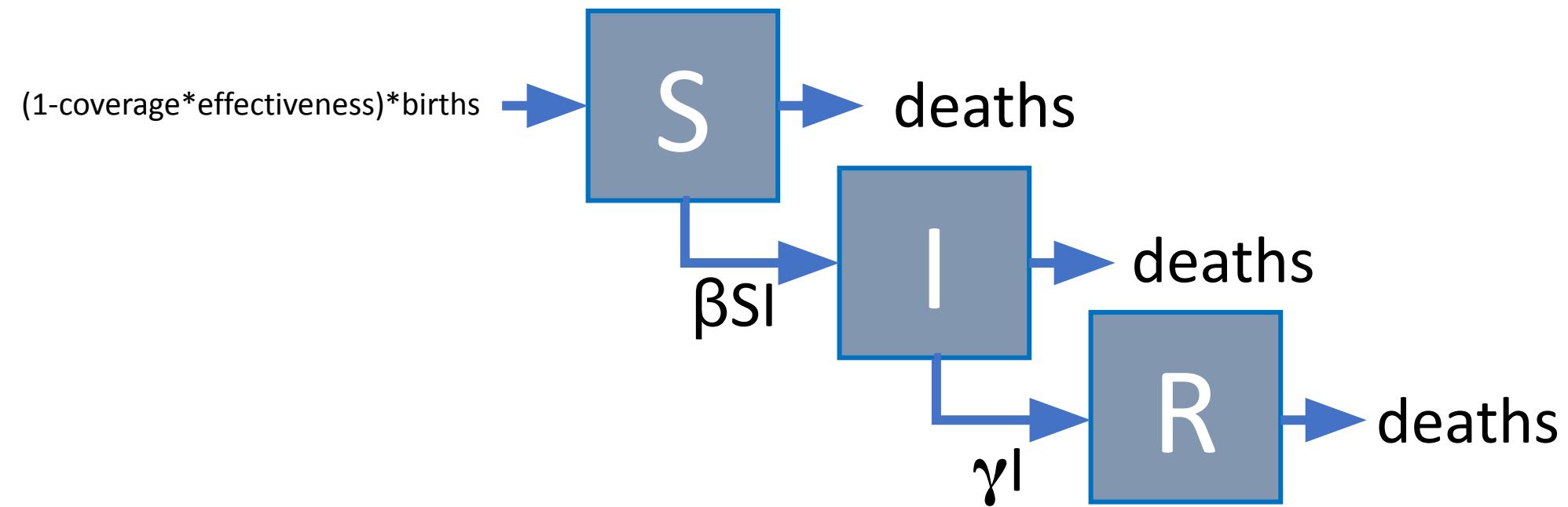


Vaccination with a single dose

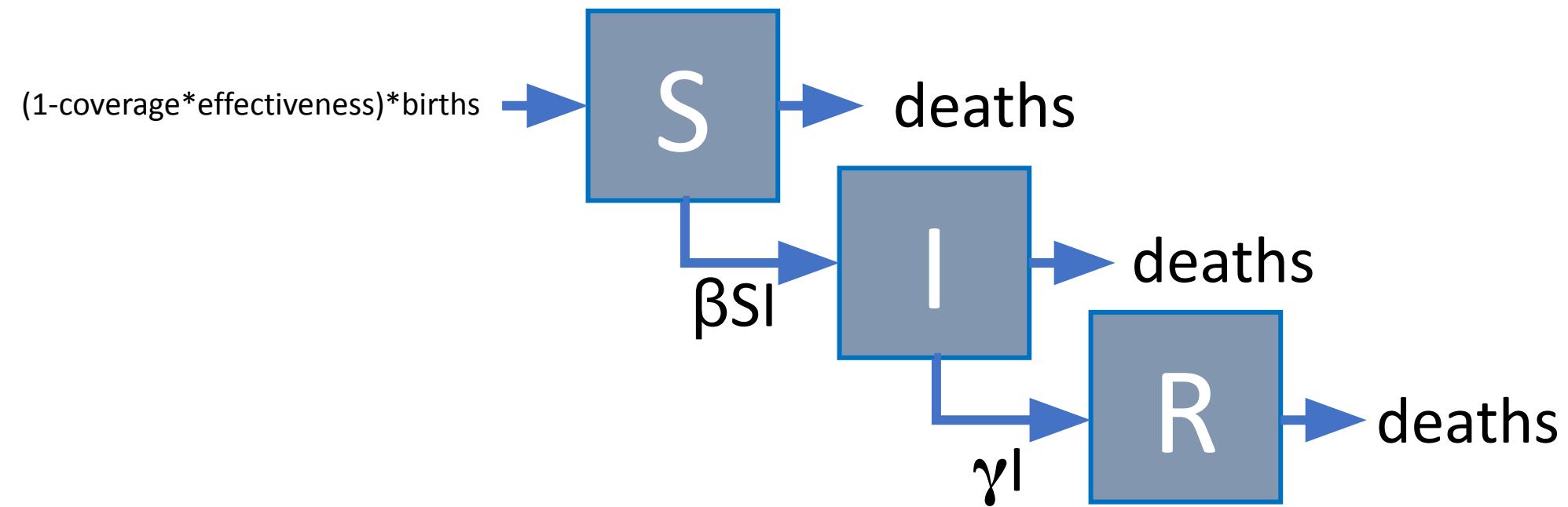
# How do we represent vaccination in models?



# How do we represent vaccination in models?



# How do we represent vaccination in models?



All models are approximations

Does this approximation seem reasonable?

**Table 1** Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2025

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2).

Vaccine and other immunizing agents	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
Respiratory syncytial virus (RSV-mAb [Nirsevimab])						1 dose depending on maternal RSV vaccination status (See Notes)				1 dose (8 through 19 months), See Notes							
Hepatitis B (HepB)		1st dose	← 2nd dose →				← 3rd dose →										
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)			1st dose	2nd dose	3rd dose			← 4th dose →			5th dose						
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		← 3rd or 4th dose (See Notes) →										
Pneumococcal conjugate (PCV15, PCV20)			1st dose	2nd dose	3rd dose		← 4th dose →										
Inactivated poliovirus (IPV)			1st dose	2nd dose		← 3rd dose →					4th dose						See Notes
COVID-19 (1vCOV-mRNA, 1vCOV-aPS)																	
Influenza (IIV3, cIIV3)	or									1 or 2 doses annually						1 dose annually	
Influenza (LAIV3)																	1 dose annually
Measles, mumps, rubella (MMR)					See Notes		← 1st dose →				2nd dose						
Varicella (VAR)							← 1st dose →				2nd dose						
Hepatitis A (HepA)					See Notes		2-dose series (See Notes)										
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)												1 dose					
Human papillomavirus (HPV)												See Notes					
Meningococcal (MenACWY-CRM ≥2 mos, MenACWY-TT ≥2 years)							See Notes				1st dose		2nd dose				
Meningococcal B (MenB-4C, MenB-FHbp)														See Notes			
Respiratory syncytial virus vaccine (RSV [Abrysvo])														Seasonal administration during pregnancy (See Notes)			
Dengue (DEN4CYD: 9–16 yrs)												Seropositive in endemic dengue areas (See Notes)					
Mpox																	

Range of recommended ages for all children

Range of recommended ages for catch-up vaccination

Range of recommended ages for certain high-risk groups or populations

Recommended vaccination can begin in this age group

Vaccination is based on shared clinical decision-making

No Guidance/Not Applicable

**Table 1** Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2025

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2).

Maybe

Vaccine and other immunizing agents	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
Respiratory syncytial virus (RSV-mAb [Nirsevimab])						1 dose depending on maternal RSV vaccination status (See Notes)				1 dose (8 through 19 months), See Notes							
Hepatitis B (HepB)		1st dose	← 2nd dose →				← 3rd dose →										
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)			1st dose	2nd dose	3rd dose			← 4th dose →			5th dose						
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		← 3rd or 4th dose (See Notes) →										
Pneumococcal conjugate (PCV15, PCV20)			1st dose	2nd dose	3rd dose		← 4th dose →										
Inactivated poliovirus (IPV)			1st dose	2nd dose		← 3rd dose →					4th dose					See Notes	
COVID-19 (1vCOV-mRNA, 1vCOV-aPS)											See Notes						
Influenza (IIV3, cIIV3)							1 or 2 doses annually						1 dose annually				
Influenza (LAIV3)	or											1 or 2 doses annually	or			1 dose annually	
Measles, mumps, rubella (MMR)					See Notes		← 1st dose →				2nd dose						
Varicella (VAR)							← 1st dose →				2nd dose						
Hepatitis A (HepA)					See Notes		2-dose series (See Notes)										
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)												1 dose					
Human papillomavirus (HPV)												See Notes					
Meningococcal (MenACWY-CRM ≥2 mos, MenACWY-TT ≥2 years)						See Notes					1st dose		2nd dose				
Meningococcal B (MenB-4C, MenB-FHbp)														See Notes			
Respiratory syncytial virus vaccine (RSV [Abrysvo])														Seasonal administration during pregnancy (See Notes)			
Dengue (DEN4CYD: 9–16 yrs)												Seropositive in endemic dengue areas (See Notes)					
Mpox																	

Range of recommended ages for all children

Range of recommended ages for catch-up vaccination

Range of recommended ages for certain high-risk groups or populations

Recommended vaccination can begin in this age group

Vaccination is based on shared clinical decision-making

No Guidance/Not Applicable

**Table 1** Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2025

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2).

Maybe

Vaccine and other immunizing agents	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
Respiratory syncytial virus (RSV-mAb [Nirsevimab])						1 dose depending on maternal RSV vaccination status (See Notes)				1 dose (8 through 19 months), See Notes							
Hepatitis B (HepB)		1st dose	← 2nd dose →				← 3rd dose →										
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)			1st dose	2nd dose	3rd dose			← 4th dose →			5th dose						
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		← 3rd or 4th dose (See Notes) →										
Pneumococcal conjugate (PCV15, PCV20)			1st dose	2nd dose	3rd dose		← 4th dose →										
Inactivated poliovirus (IPV)			1st dose	2nd dose		← 3rd dose →					4th dose					See Notes	
COVID-19 (1vCOV-mRNA, 1vCOV-aPS)																	
Influenza (IIV3, cIIV3)																	
Influenza (LAIV3)																	
Measles, mumps, rubella (MMR)						See Notes	← 1st dose →				2nd dose						
Varicella (VAR)							← 1st dose →				2nd dose						
Hepatitis A (HepA)						See Notes		2-dose series (See Notes)									
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)														1 dose			
Human papillomavirus (HPV)														See Notes			
Meningococcal (MenACWY-CRM ≥2 mos, MenACWY-TT ≥2 years)														1st dose	2nd dose		
Meningococcal B (MenB-4C, MenB-FHbp)																	
Respiratory syncytial virus vaccine (RSV [Abrysvo])																	
Dengue (DEN4CYD: 9–16 yrs)																	
Mpox																	

What does it mean that these vaccines are received later?

Range of recommended ages for all children

Range of recommended ages for catch-up vaccination

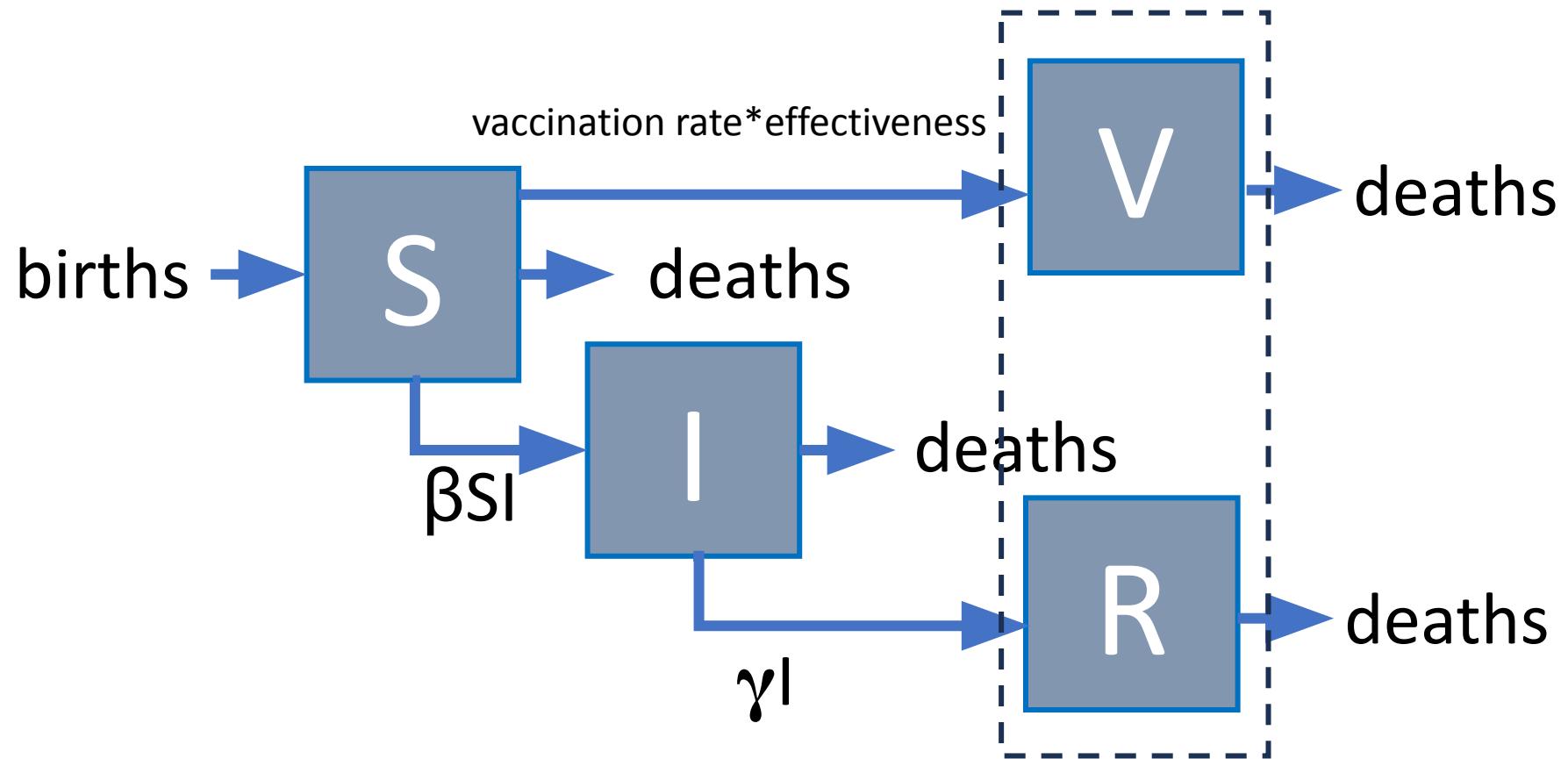
Range of recommended ages for certain high-risk groups or populations

Recommended vaccination can begin in this age group

Vaccination is based on shared clinical decision-making

No Guidance/Not Applicable

# How do we represent vaccination in models?

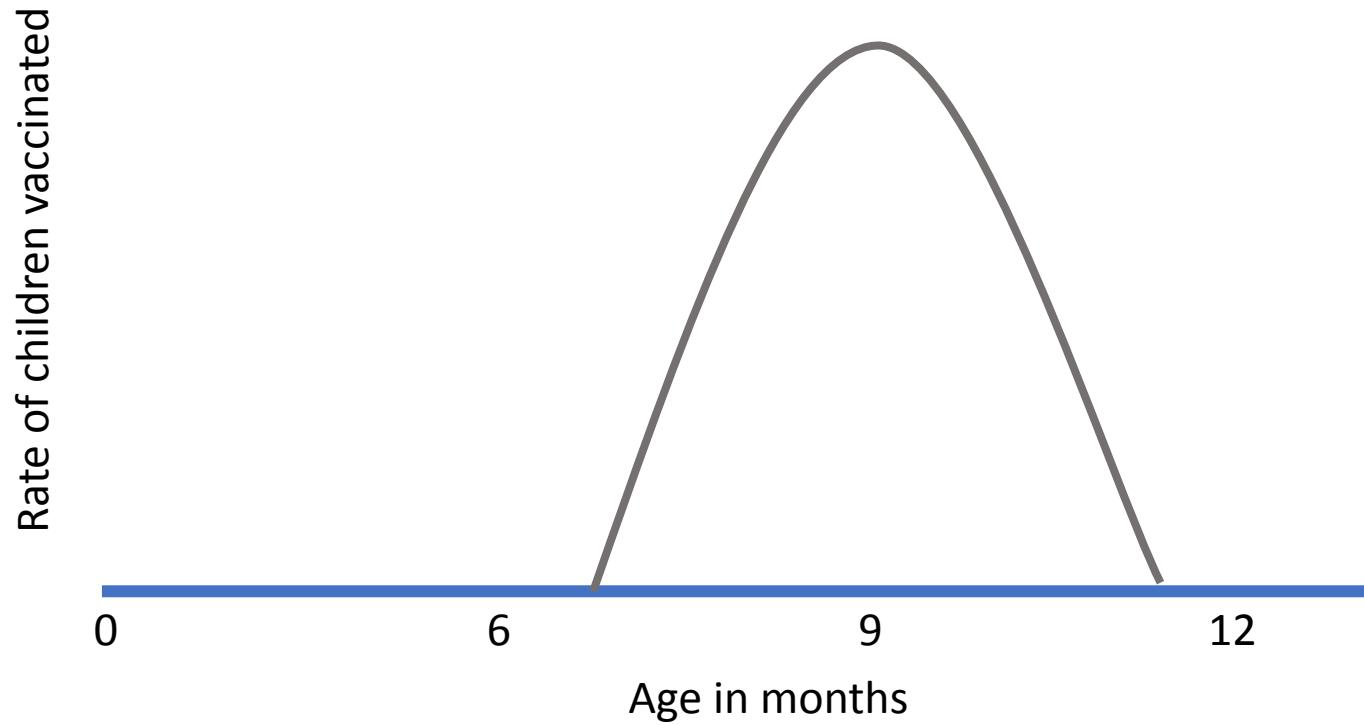


# Interactive Session: simulating vaccination

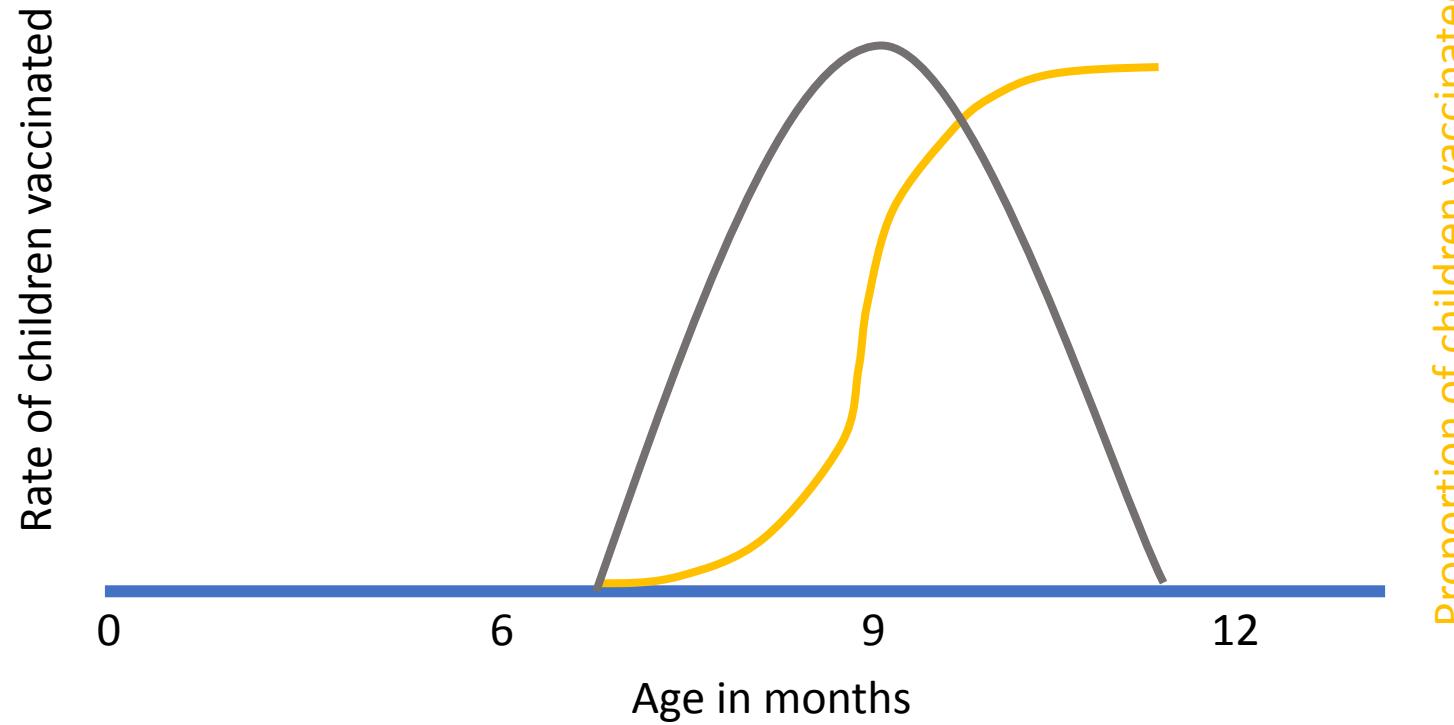
R-file: SIRModel 2birthsdeaths\_seasonality\_vaccination.r

# Vaccination at Age

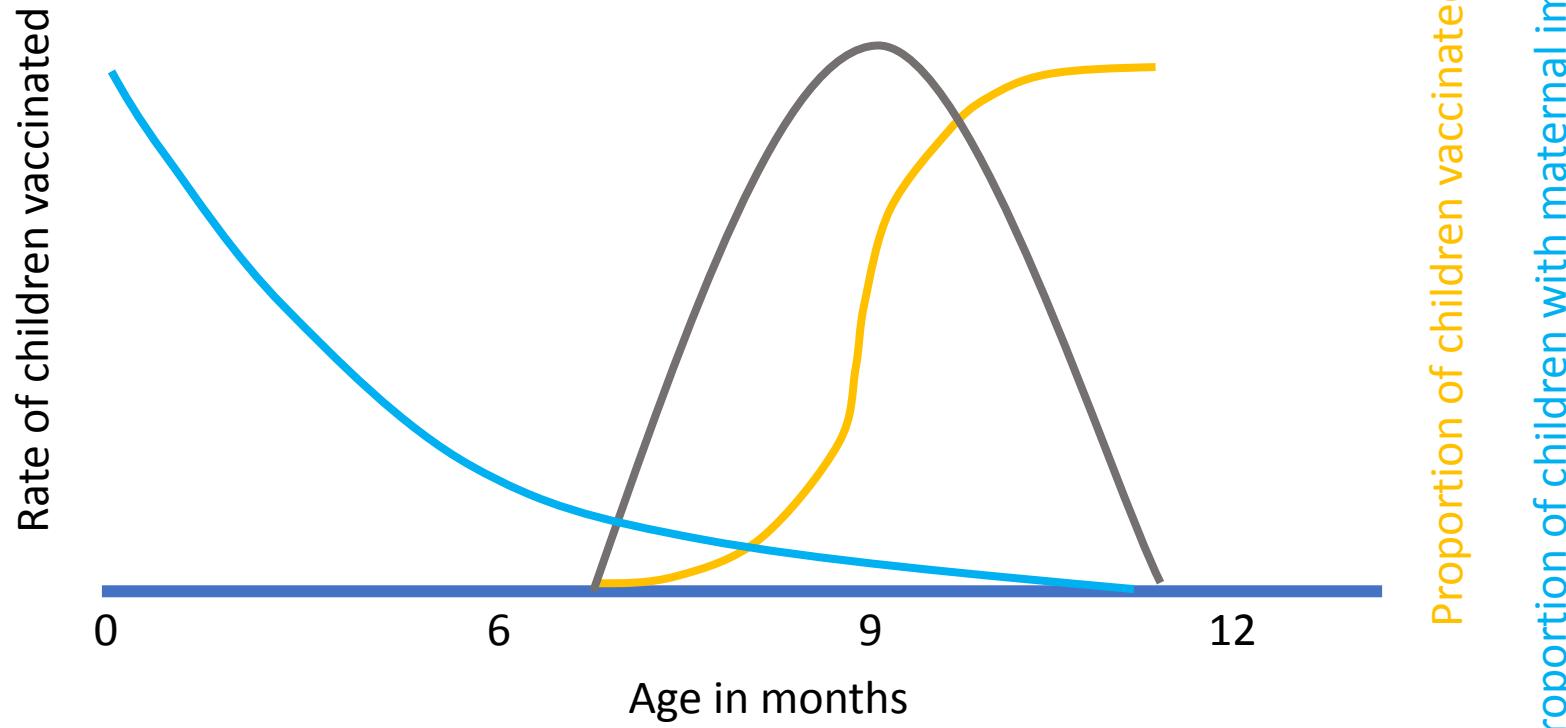
# Vaccination at specific ages



# Vaccination at specific ages



# Vaccination at specific ages



# Maternal Immunity

- Antibodies from immune mothers are passively transferred to infant
- Infant cannot produce new antibodies. Transferred antibodies (and immunity) degrades approximately exponentially.

**Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis**

Laura M Nic Lochlainn, Brechje de Gier, Nicoline van der Maas, Peter M Strebel, Tracey Goodman, Rob S van Binnendijk, Hester E de Melker, Susan J M Hahné

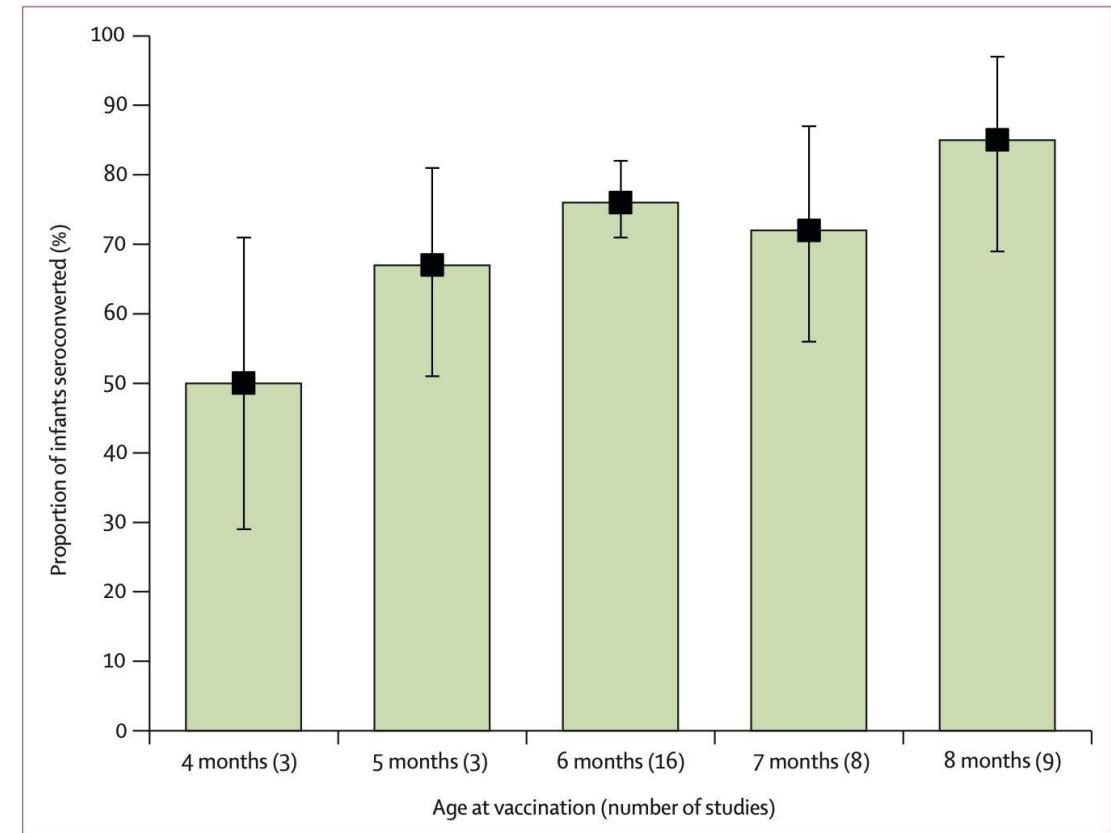
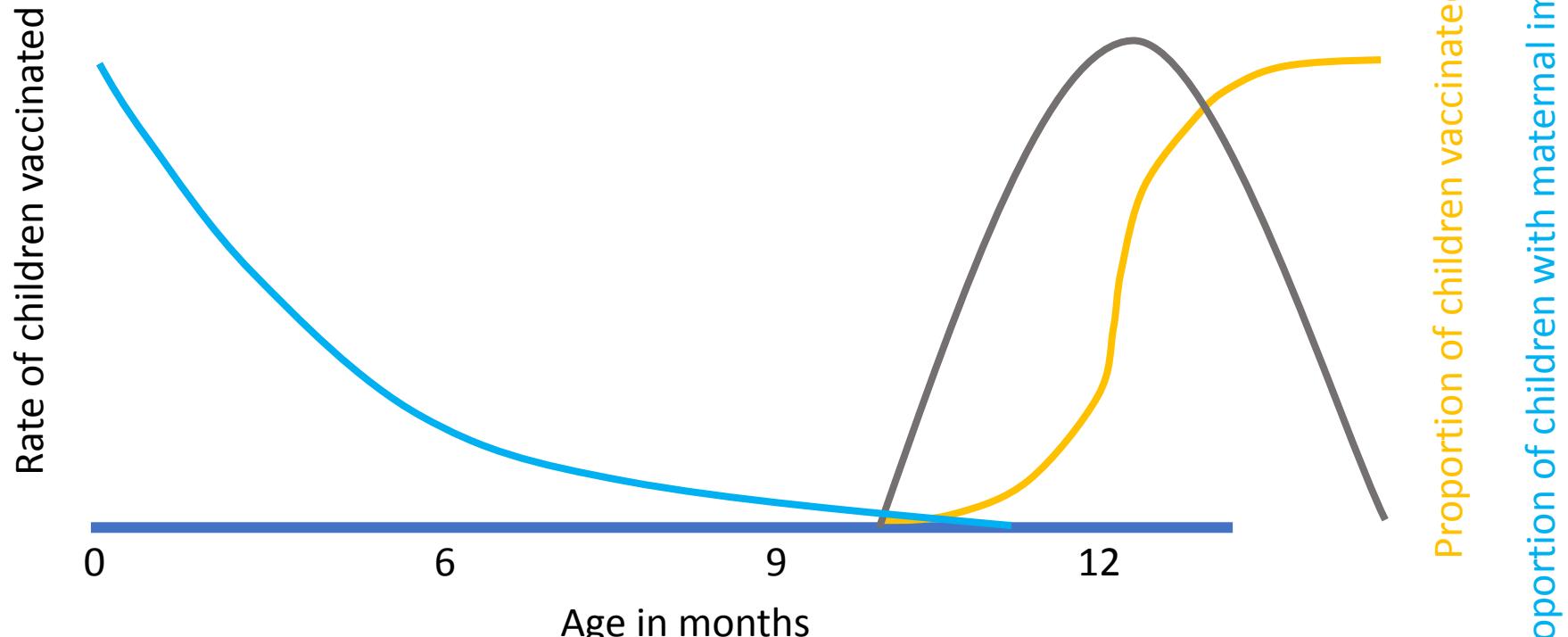
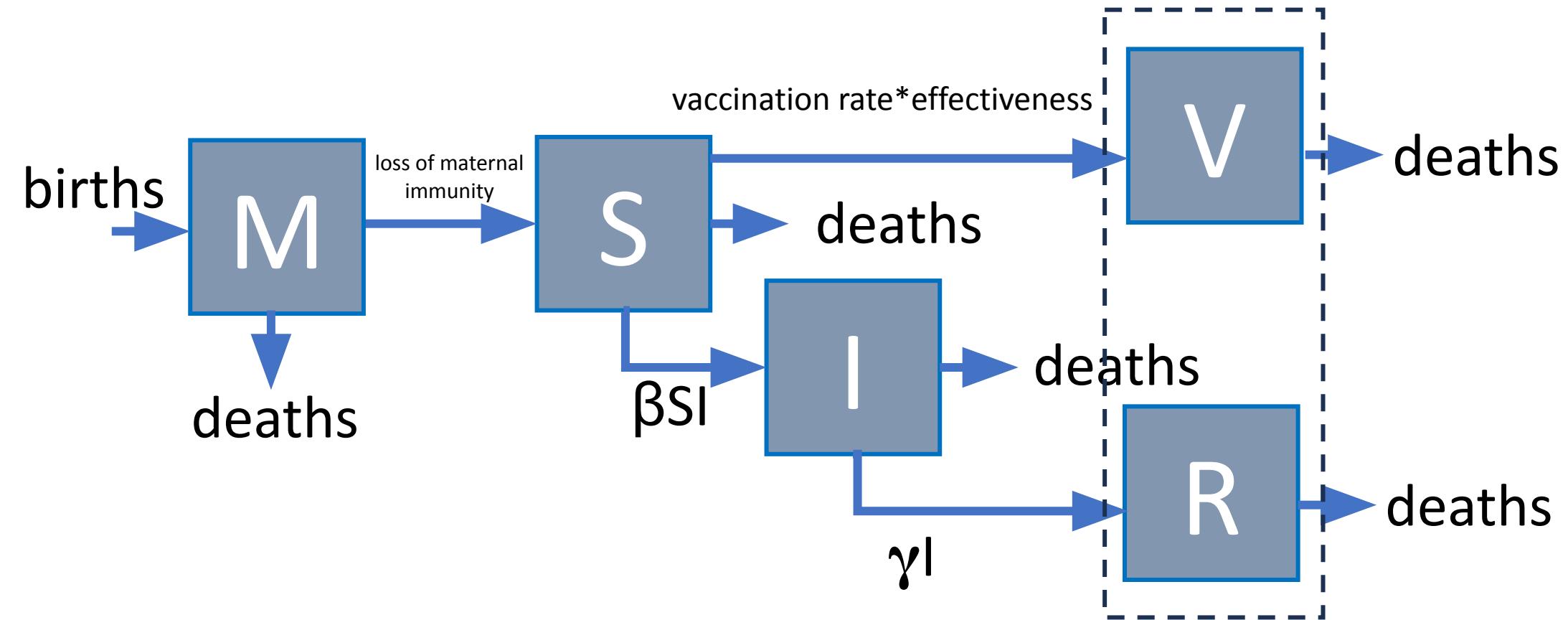


Figure 2: Pooled estimates of proportion of infants seroconverted, by age of MCV1 (4-8 months) with 95% CIs  
MCV1=first dose of measles-containing vaccine.

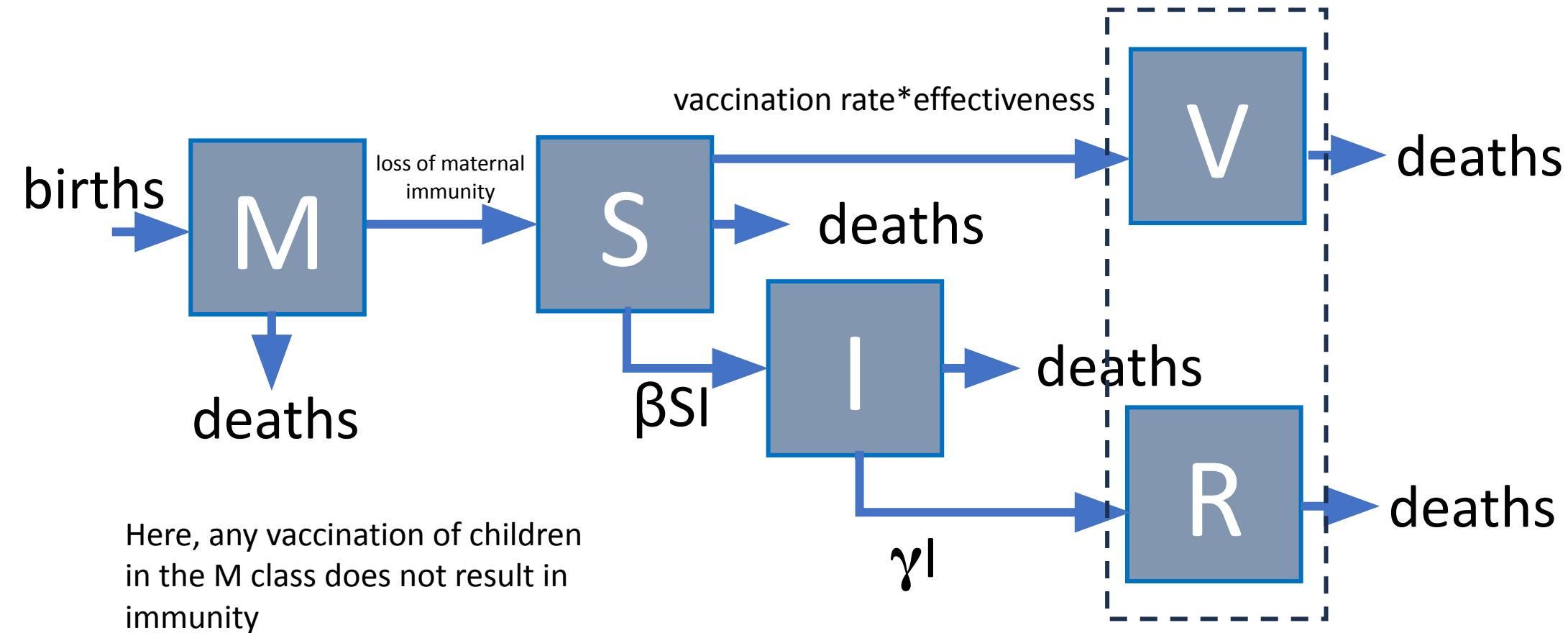
# Vaccination at specific ages



# Adding a Maternal Immunity Class

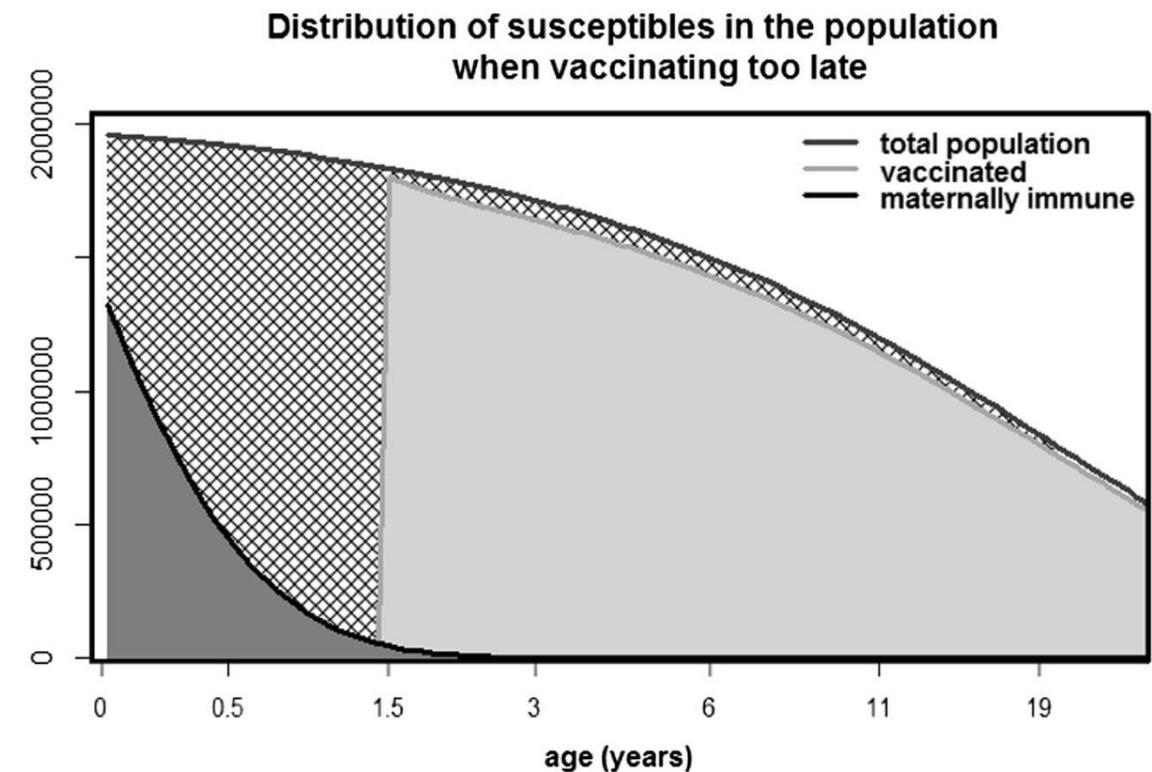
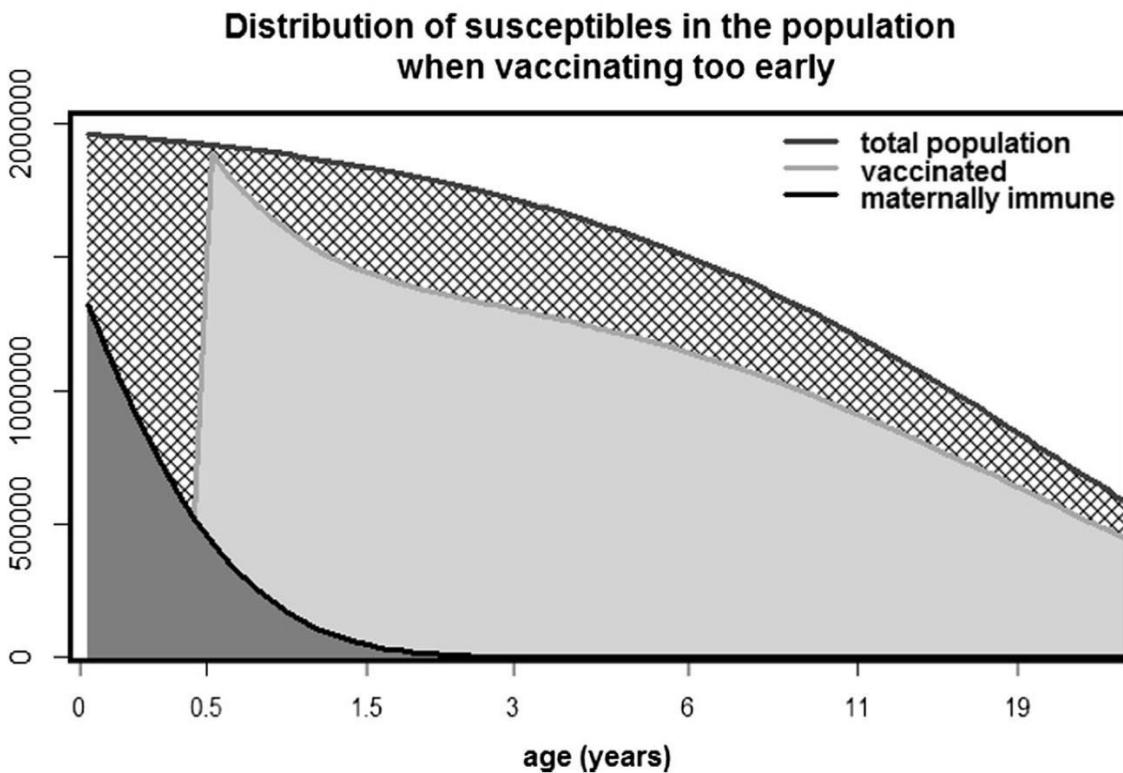


# Adding a Maternal Immunity Class



# Timing of the First Dose

Label y axis



# Second Doses

# Second Doses

- Routine Immunization
- Supplemental Immunization
- Outbreak Response Immunization

# Second Doses

- Routine Immunization (Measles as an example)
  - Delivered through “well-child” visits at targeted ages
  - 1<sup>st</sup> dose recommended at 9-12 months, timing dependent on prevalence
  - 2<sup>nd</sup> dose recommended at 24 months or higher, varies by country. Goal is immunize those who failed to seroconvert with first dose
  - Formally, 2<sup>nd</sup> dose coverage is recorded as the fraction of children with 1<sup>st</sup> dose that receive a 2<sup>nd</sup> dose. However, this convention is not universal.
- Supplemental Immunization
- Outbreak Response Immunization

# Second Doses

- Routine Immunization
- Supplemental Immunization (SIA)
  - Periodic, large-scale vaccination of all children (regardless of prior vaccination) within a target age group.
  - Modeled after PAHO strategy of “catch up”, “keep up”, “follow up”
  - Models have been useful in determining the frequency and age targets for these campaigns
  - Implementation in models as a single time point move from S to R, resulting in a large reduction in S class in the target age groups.
- Outbreak Response Immunization

# Second Doses

- Routine Immunization
- Supplemental Immunization (SIA)
- Outbreak Response Immunization
  - Vaccination activities that are triggered by the occurrence of an outbreak
  - Indiscriminate targeting of all children within an age window (e.g. 6-59m)
  - Triggers (e.g. number of cases), speed, scale, and coverage of response varies by country and the organization conducting the ORI
  - Modelling has been useful in identifying age targets and evaluating the potential trade-offs between speed and coverage. As outbreak progresses there is less indirect (herd) benefit of each dose.

# Interactive session: SIAs

R-file: SIRModel 2birthsdeaths\_seasonality\_vaccination\_SIA.r

# SIR MODELS & HERD IMMUNITY

MICAELO E. MARTINEZ

EMORY UNIVERSITY DEPT. OF BIOLOGY

# Susceptible-Infected-Recovered Models

(1) Population size

$$N = S + I + R$$

(2) Change in susceptible over time

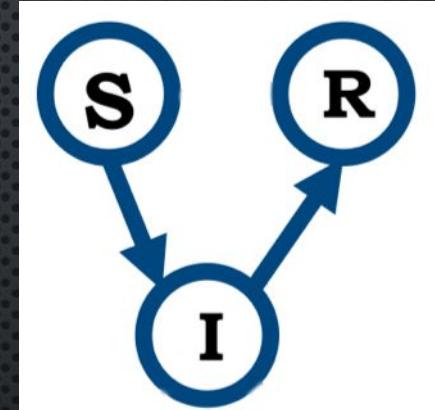
$$\frac{dS}{dt} = \mu N - \beta IS - \delta S$$

(3) Change in infected over time

$$\frac{dI}{dt} = \beta IS - \gamma I - \alpha I - \delta I$$

(4) Change in recovered over time

$$\frac{dR}{dt} = \gamma I - \delta R$$



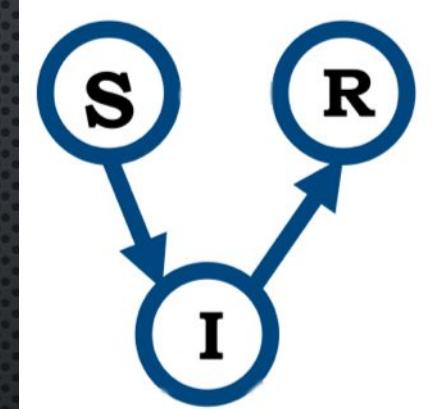
# Susceptible-Infected-Recovered Models

- + individuals added to the class
- individuals leaving the class

(2) Change in susceptible over time

$$\frac{dS}{dt} = \mu N - \beta IS - \delta S$$

New infections  
New births  
Natural death



# Susceptible-Infected-Recovered Models

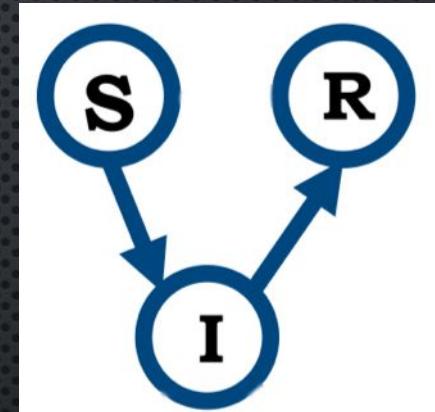
- + individuals added to the class
- individuals leaving the class

(3)

Change in infected over time

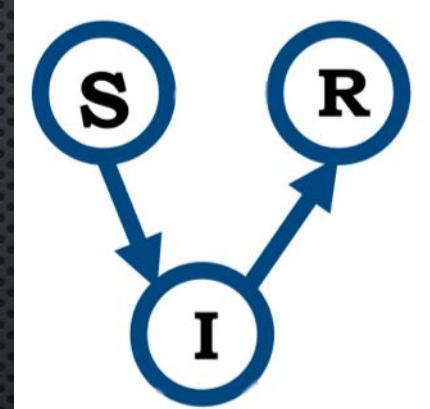
$$\frac{dI}{dt} = \beta I S - \gamma I - \alpha I - \delta I$$

New infections  
recovery      Infection-induced mortality  
Natural death



# Susceptible-Infected-Recovered Models

- + individuals added to the class
- individuals leaving the class



(4)

Change in recovered over time

$$\frac{dR}{dt} = \gamma I - \delta R$$

Natural  
death  
recovery

# Growth of the Infected Class

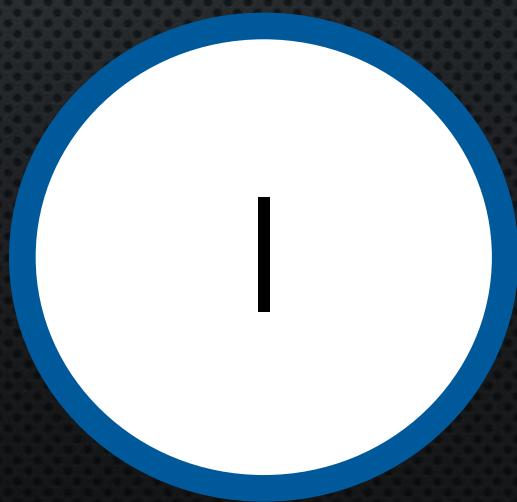
$$\frac{dI}{dt} = \beta IS - \gamma I - \alpha I - \delta I$$

$$\frac{dI}{dt} = \underbrace{\beta SI}_{\text{Rate in}} - \underbrace{(\gamma + \alpha + \delta)I}_{\text{Rate out}}$$

Rate  
in

Rate  
out

Rate  
in



Rate  
out

# Change in Infected Class

$$\beta S = (\gamma + \alpha + \delta)$$

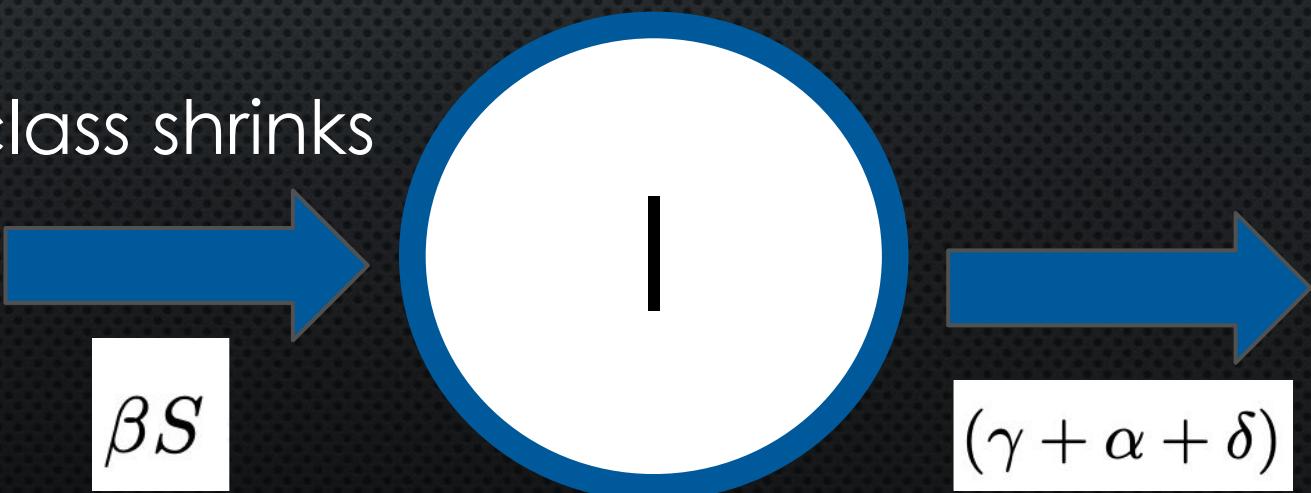
Size of infected class remains constant

$$\beta S > (\gamma + \alpha + \delta)$$

Infected class grows (rate in > rate out)

$$\beta S < (\gamma + \alpha + \delta)$$

Infected class shrinks

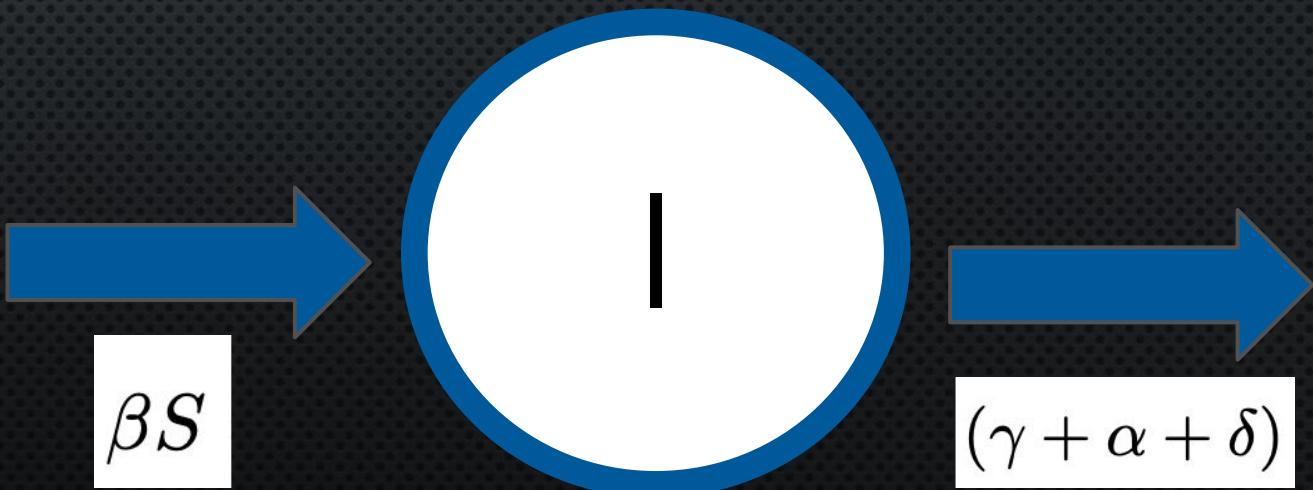


# Calculating the Reproductive Ratio

$$\frac{\beta S}{(\gamma + \alpha + \delta)}$$

Called the reproductive ratio because it tells us how many new infections “reproduced” by each infected individual before they leave the infected class

If greater than 1, the infectious agent is successfully spreading and the infected class grows in size



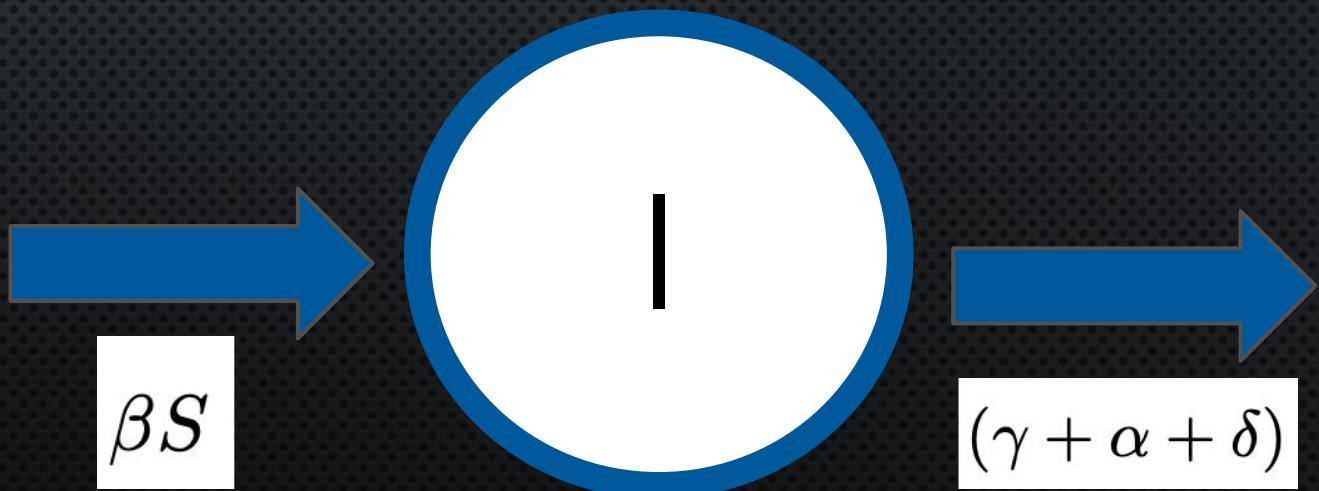
# Calculating the Reproductive Ratio

- **basic reproduction number,  $R_0$ :** average number of infections caused by a typical infected individual in a population consisting only of susceptibles; if  $R_0 > 1$ , the infectious agent can start to spread.

$$\frac{\beta S}{(\gamma + \alpha + \delta)}$$

For  $R_0$  assume  $S = N$

$S$ ,  $I$ , and  $R$  are fractions of the population in each class, so  $N = 1$



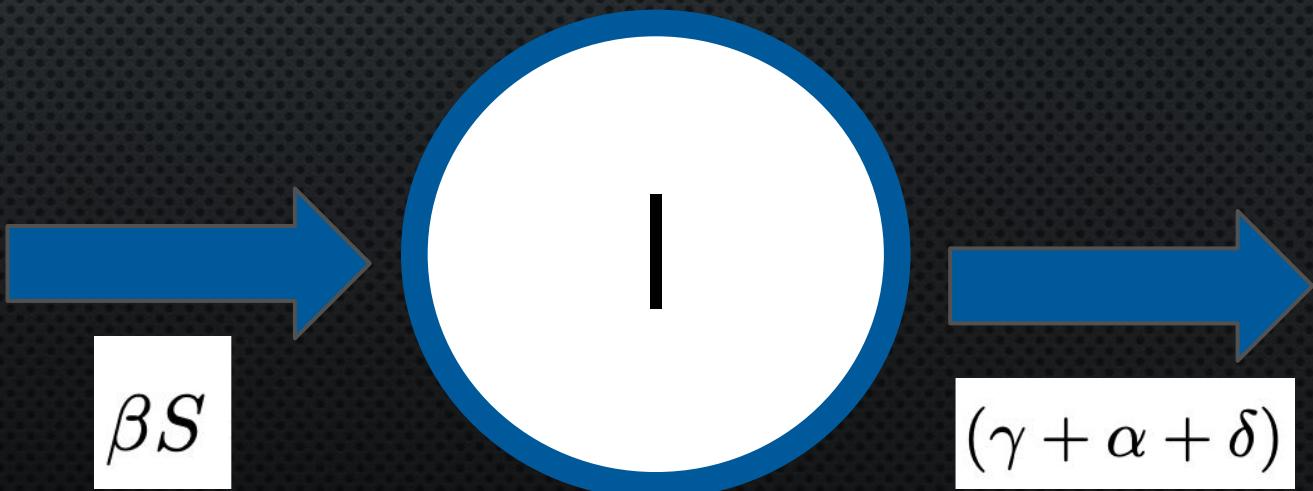
# Calculating the Reproductive Ratio

- **basic reproduction number,  $R_0$ :** average number of infections caused by a typical infected individual in a population consisting only of susceptibles; if  $R_0 > 1$ , the infectious agent can start to spread.

$$R_0 = \frac{\beta}{\gamma + \alpha + \delta}$$

For  $R_0$  assume  $S = N$

$S$ ,  $I$ , and  $R$  are fractions of the population in each class, so  $N = 1$

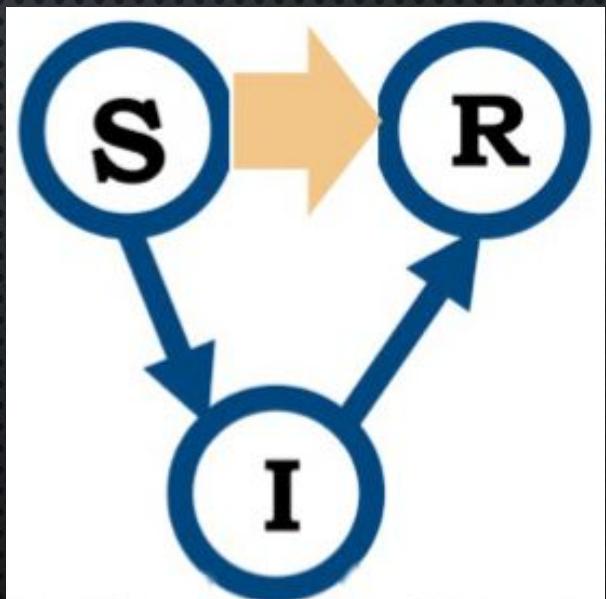


- Anthrax
- Cervical Cancer (Human Papillomavirus)
- Diphtheria
- Hepatitis A
- Hepatitis B
- *Haemophilus influenzae type b* (Hib)
- Human Papillomavirus (HPV)
- Influenza (Flu)
- Japanese encephalitis (JE)
- Measles
- Meningococcal
- Mumps
- Pertussis
- Pneumococcal
- Polio
- Rabies
- Rotavirus
- Rubella
- Shingles (Herpes Zoster)
- Smallpox
- Tetanus
- Typhoid
- Tuberculosis (TB)
- Varicella (Chickenpox)
- Yellow Fever

# Vaccination

To keep the infected class from growing,  $S$  can be reduced via vaccination

$$\frac{\beta S}{(\gamma + \alpha + \delta)}$$

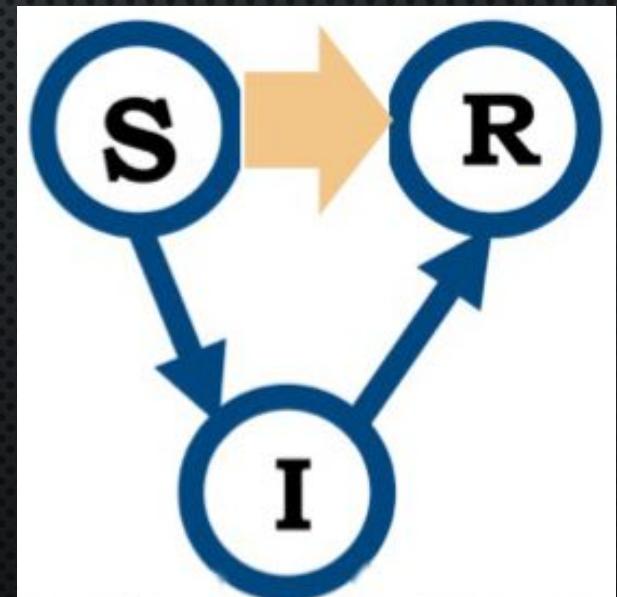


# Herd Immunity

$$\frac{\beta S}{(\gamma + \alpha + \delta)} < 1$$

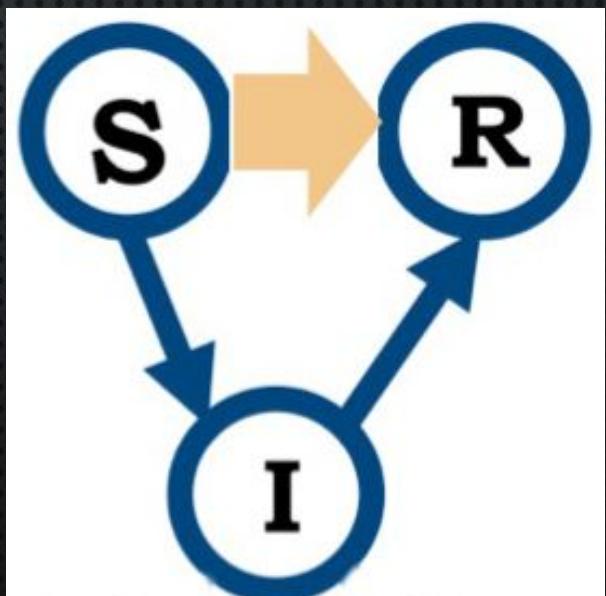
Vaccinate enough such that infected class shrinks

To keep the infected class from growing (prevent epidemics), not everyone needs to be vaccinated

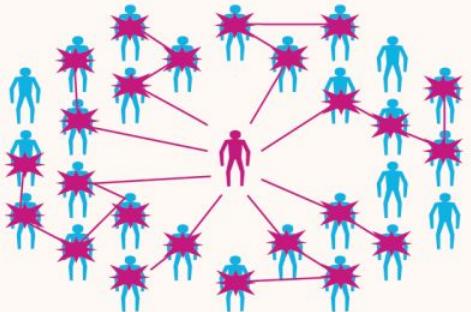


# Herd Immunity

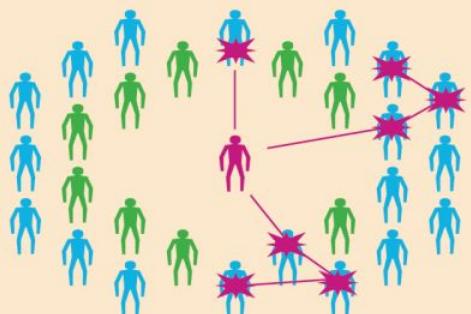
A sufficient proportion of a population is immune (via vaccination and/or prior infection) to make transmission unlikely. Even individuals not vaccinated (such as newborns and those with chronic illnesses) are offered some protection because the disease has little opportunity to spread within the population.



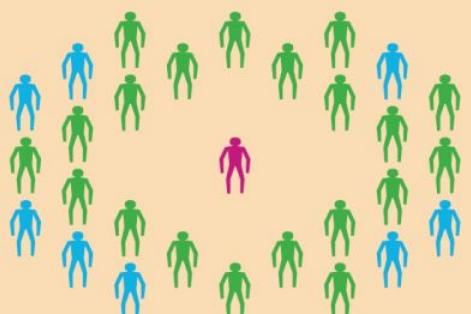
## HOW HERD IMMUNITY WORKS



When no one has immunity, contagion has many opportunities to spread quickly.



The more immunity we have in the system, the less often contagion comes into contact with the susceptible.



Spread of contagious disease is contained.

# Herd Immunity

Credit: UC Davis

# Disease Eradication

Disease eradication: driving the infectious agent to extinction  
(local vs. global)

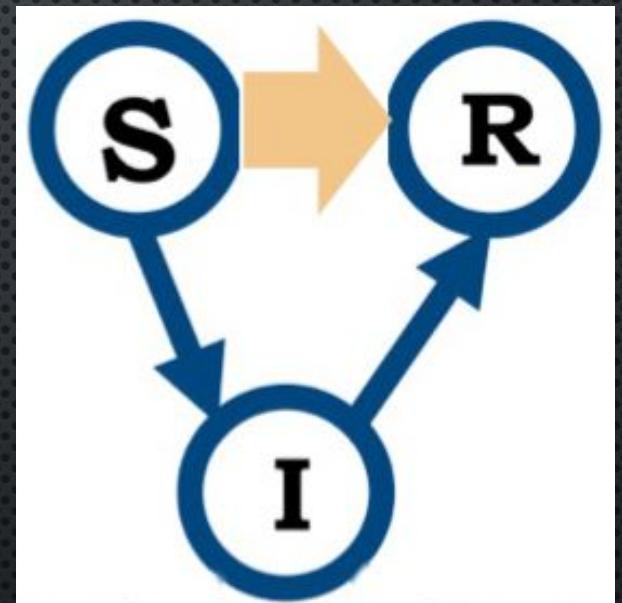
$$\frac{\beta S}{(\gamma + \alpha + \delta)} < 1$$

Local eradication happens if  $S$  is small-enough that the number of infected individuals declines to zero

# Eradication Criterion

Calculating the critical vaccination fraction

$$\frac{\beta S}{(\gamma + \alpha + \delta)} < 1$$



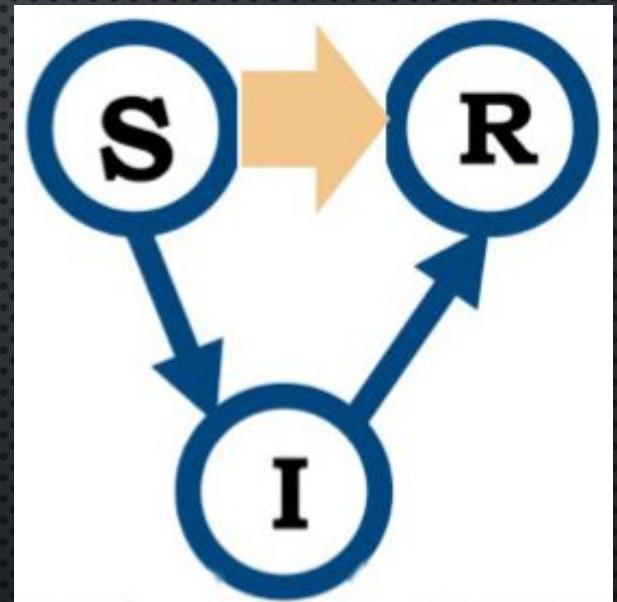
# Eradication Criterion

Calculating the critical vaccination fraction

$$S < \frac{\gamma + \alpha + \delta}{\beta}$$

$$S_{\text{critical}} = \frac{\gamma + \alpha + \delta}{\beta} = \frac{1}{R_0}$$

$$V_{\text{critical}} = 1 - \frac{1}{R_0}$$



# R<sub>0</sub> and Eradication

infection	Geographic location	R <sub>0</sub>	V <sub>critical (%)</sub>
measles	England & Wales	16-18	94%
measles	Kansas, USA	5-6	83%
pertussis	Maryland, USA	16-17	94%
chicken pox	New Jersey, USA	7-8	88%
mumps	Netherlands	11-14	93%
rubella	West Germany	6-7	86%
polio	USA	5-6	83%

# Eradication vs. Elimination

Global Eradication:  
driving the infectious  
agent to **extinction**  
**globally**

Disease Elimination:  
interruption of endemic  
transmission or  
maintaining the disease  
below a defined  
threshold

# What have we eradicated or eliminated?

## Eradicated:

Smallpox

Rinderpest (veterinary)

## Eliminated:

Leprosy

Measles (regions)

Rubella (Americas)

## Eradication Attempts:

Yellow fever

Yaws

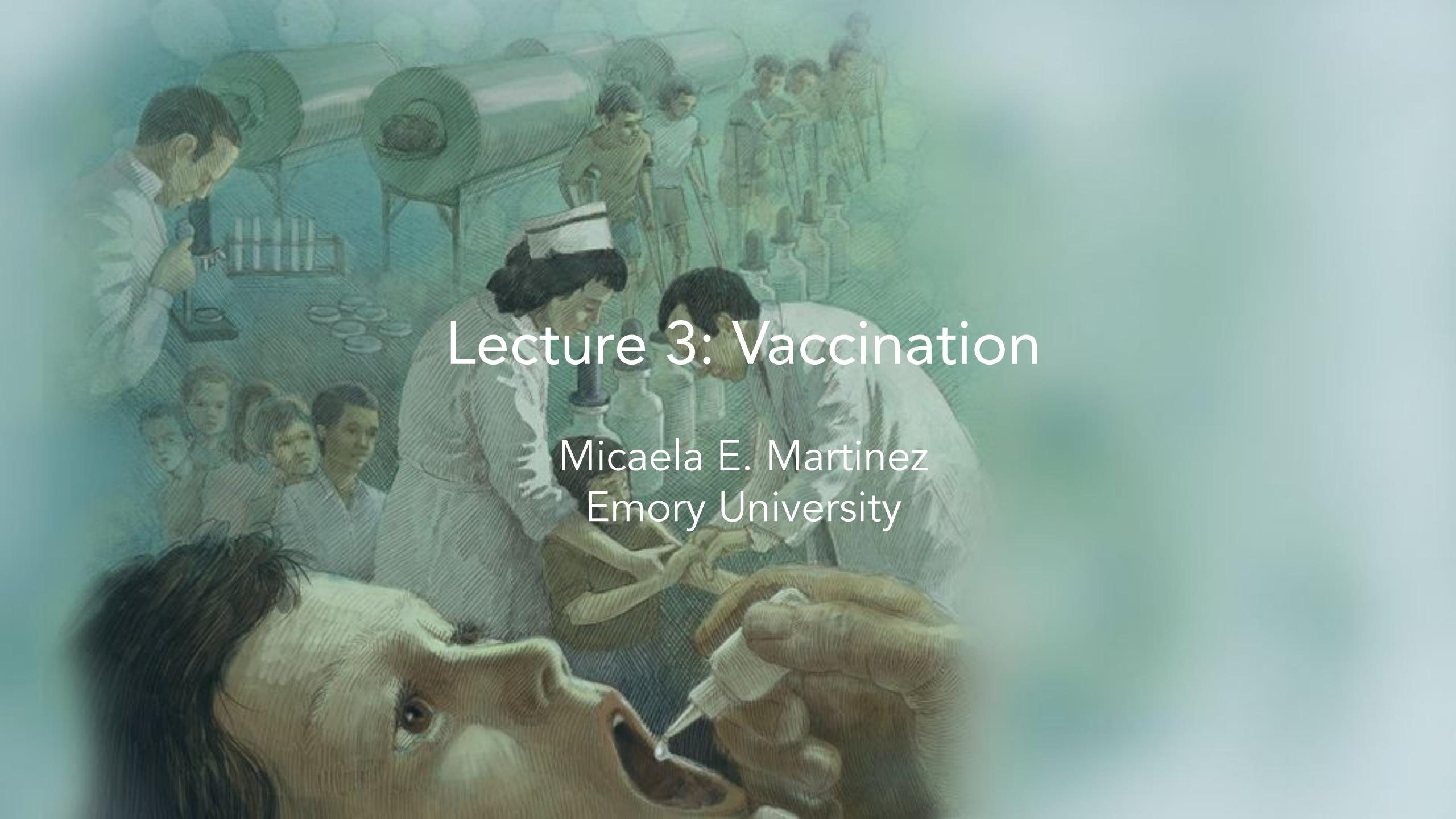
Malaria

## Eradication “in progress”:

Polio

Guinea Worm

break



# Lecture 3: Vaccination

Micaela E. Martinez  
Emory University

# Vaccine Modes of Action

Vaccines have several modes of action, i.e., the way(s) by which they confer protection.

These can include any of the following alone or in combination:

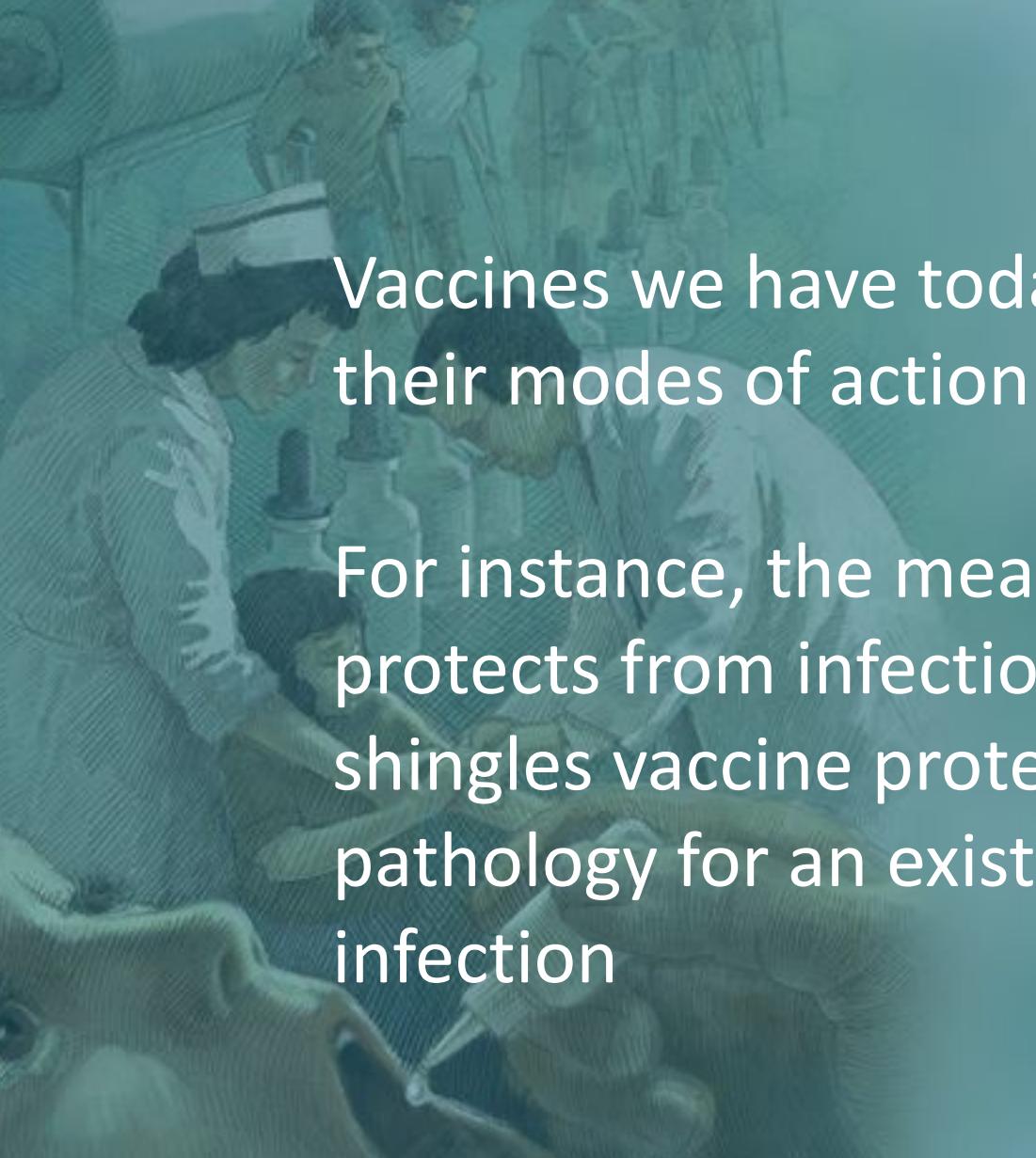
- protection from infection
- reduction of shedding
- protection from disease/pathology

# Vaccine Modes of Action

- Vaccines that protect from infection are considered “transmission blocking”
- Vaccines that reduce shedding by vaccinated individuals who become infected are transmission reducing vaccines
- Vaccines that protect from pathology/disease but don't reduce susceptibility to infection or shedding are not transmission reducing vaccines

- Anthrax
- Cervical Cancer (Human Papillomavirus)
- Diphtheria
- Hepatitis A
- Hepatitis B
- *Haemophilus influenzae* type b (Hib)
- Human Papillomavirus (HPV)
- Influenza (Flu)
- Japanese encephalitis (JE)
- Measles
- Meningococcal
- Mumps
- Pertussis
- Pneumococcal
- Polio
- Rabies
- Rotavirus
- Rubella
- Shingles (Herpes Zoster)
- Smallpox
- Tetanus
- Typhoid
- Tuberculosis (TB)
- Varicella (Chickenpox)
- Yellow Fever

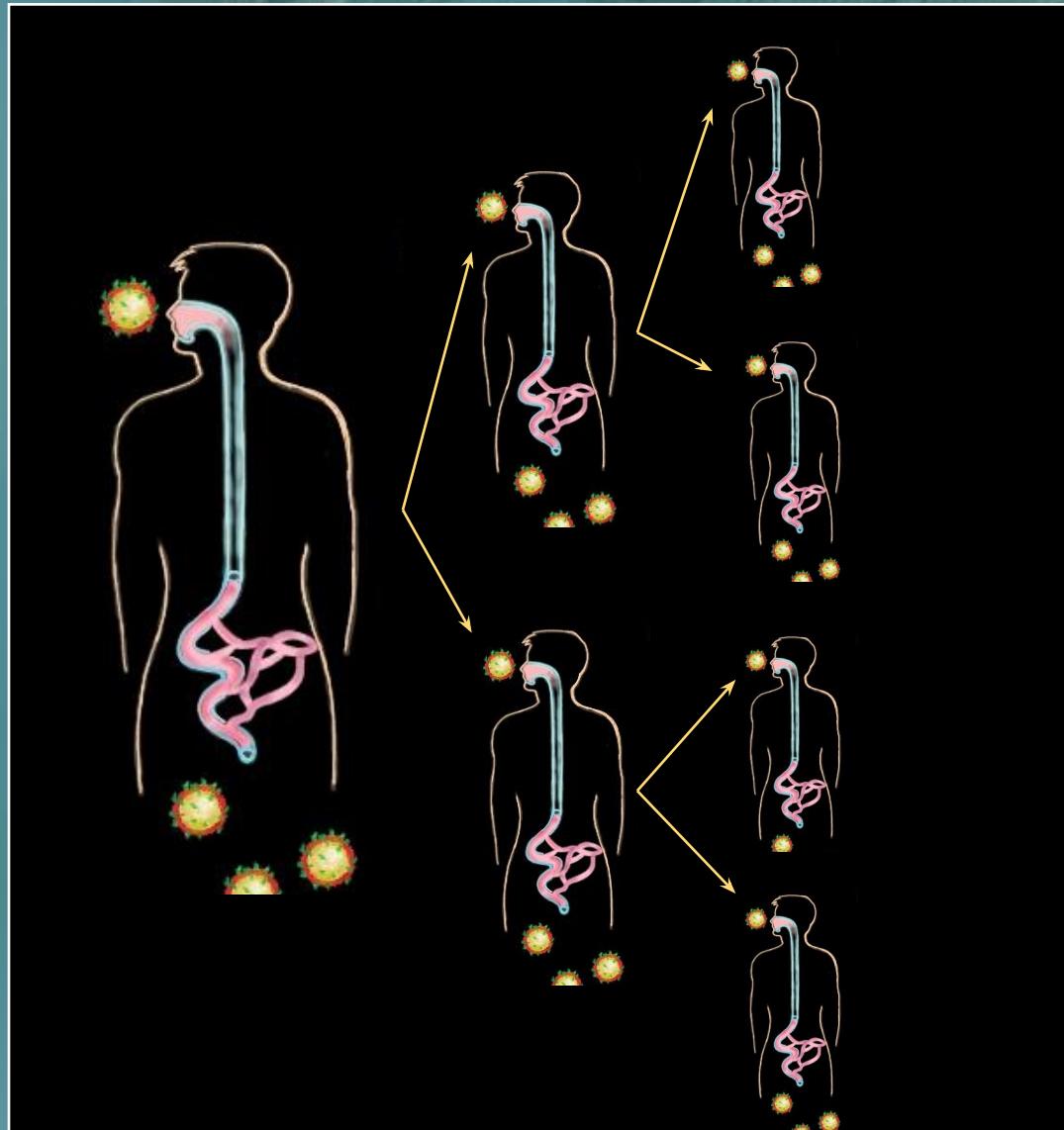
# Vaccine Modes of Action



Vaccines we have today differ in their modes of action

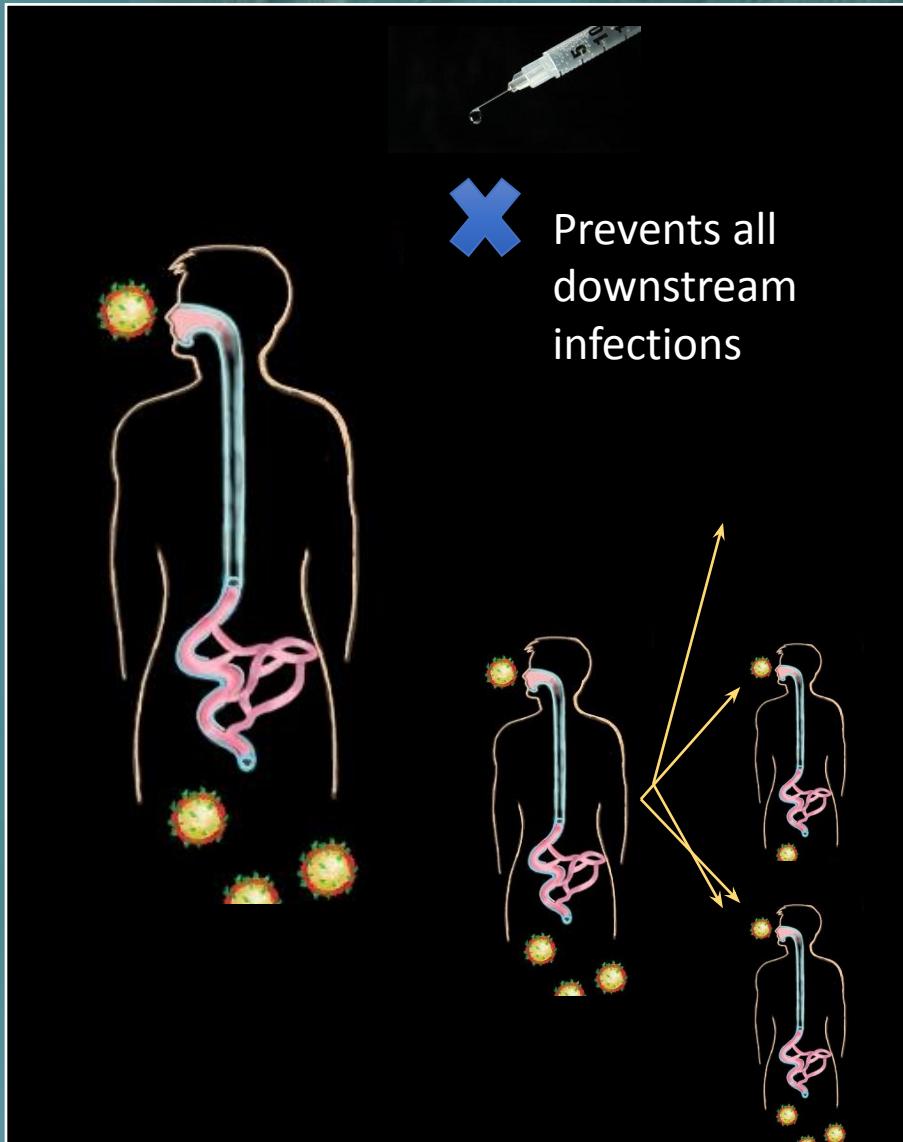
For instance, the measles vaccine protects from infection, while the shingles vaccine protects from pathology for an existing latent infection

# How do vaccines work? [Mode of action]



Consider a fecal-oral transmission enteric pathogen where each infected individual infects 2 others

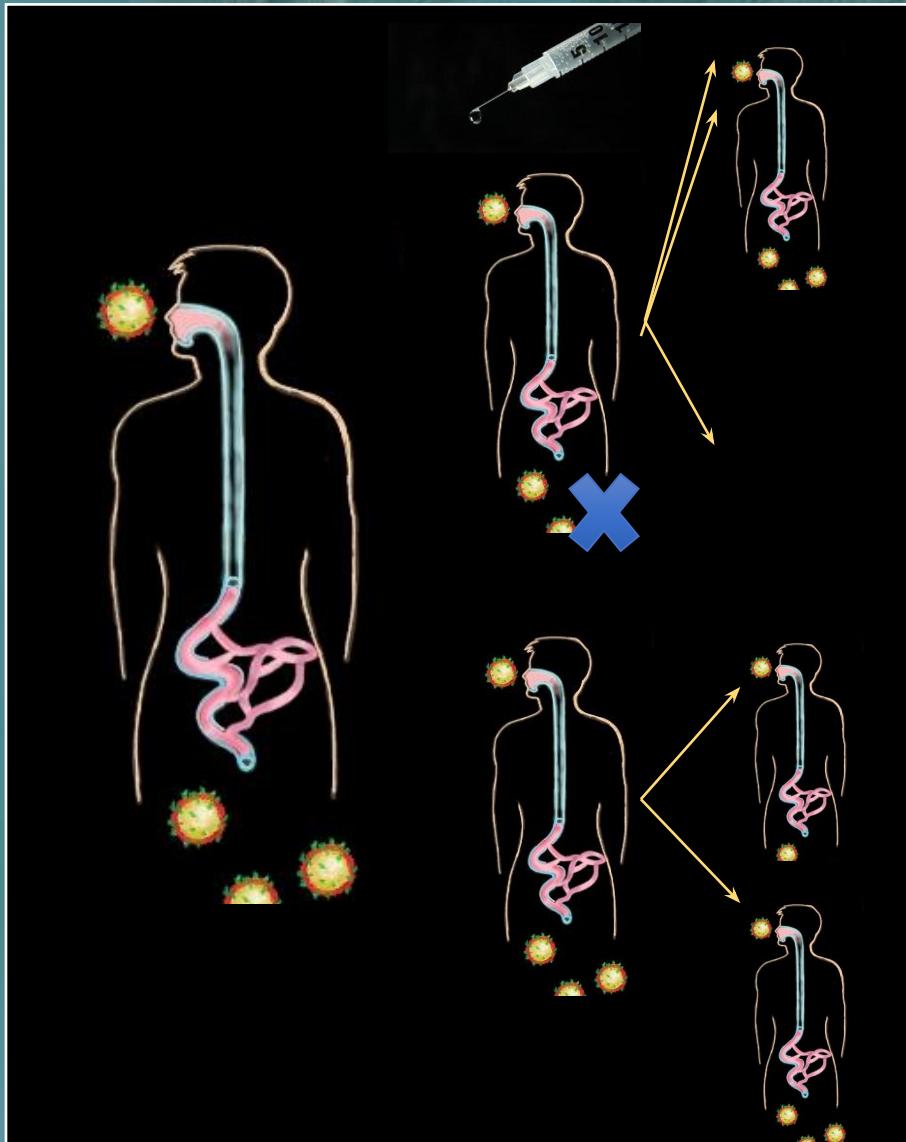
# How do vaccines work? [Mode of action]



(1) Reduces susceptibility to infection

*Protects vaccinated individual & others in the population (ripple effect)*

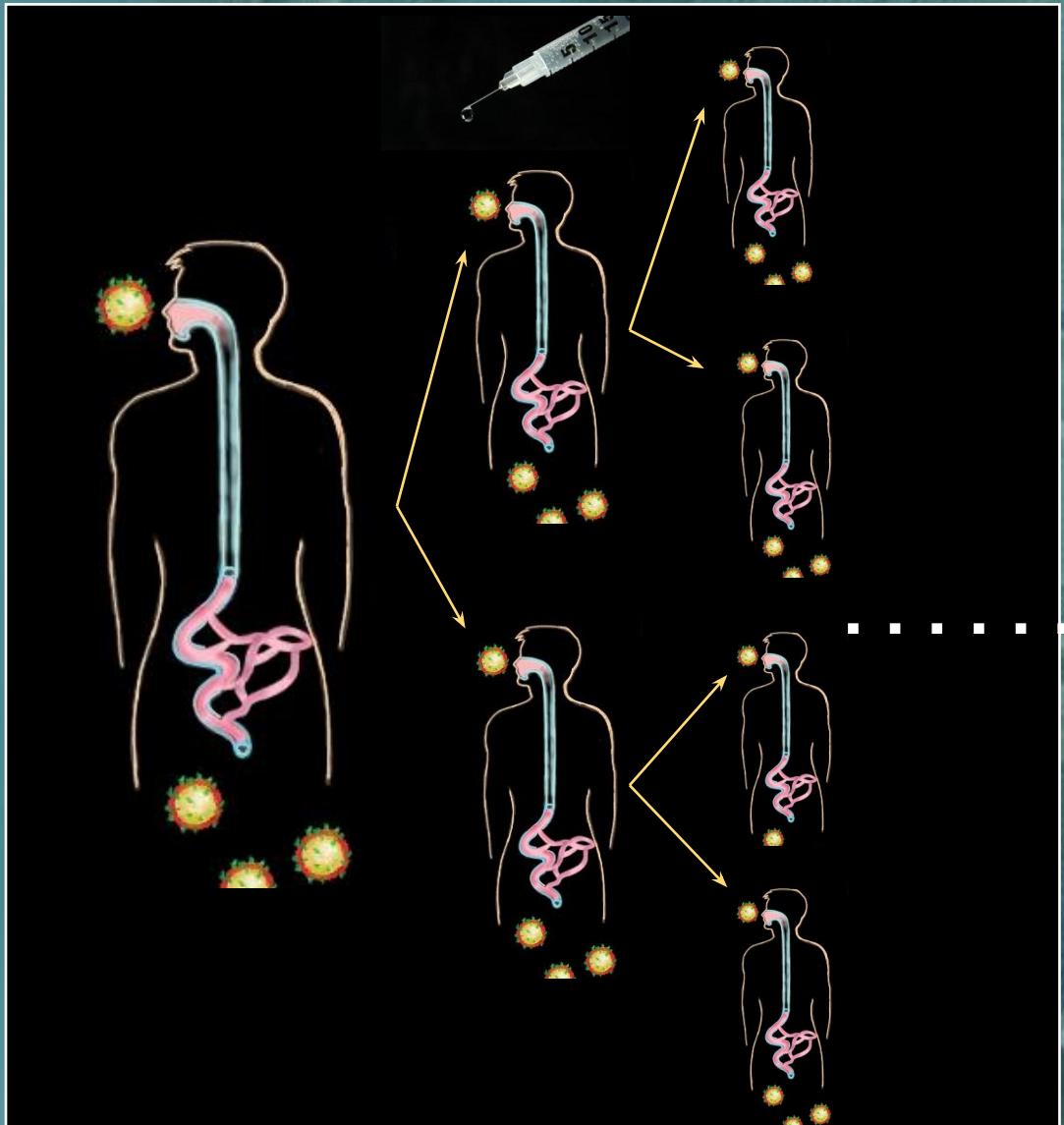
# How do vaccines work? [Mode of action]



(2) Reduces infectiousness

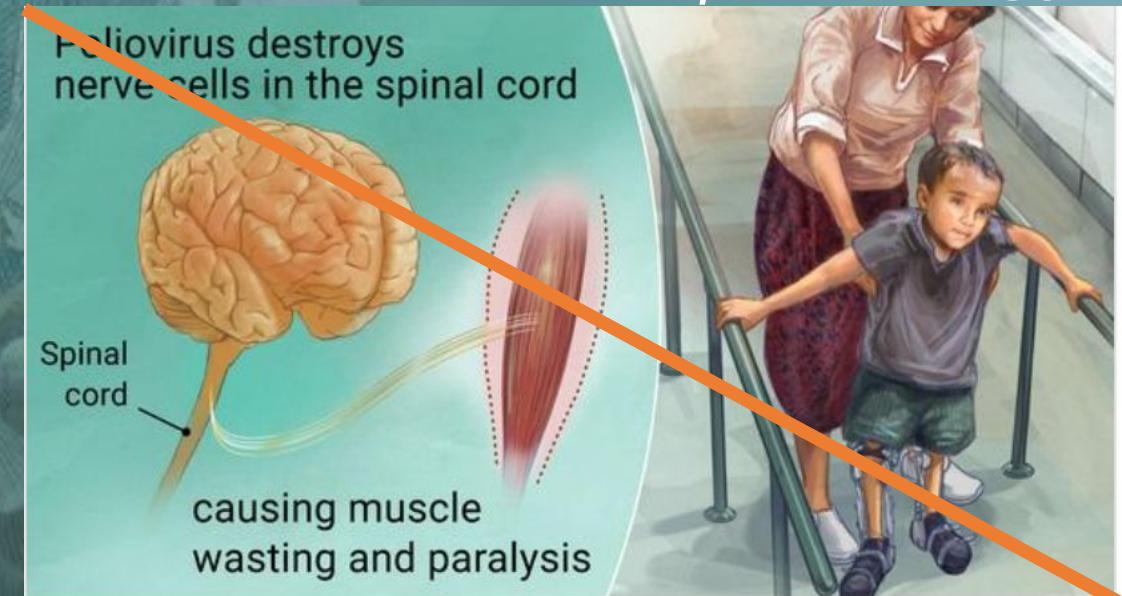
*Protects others in the population  
(downstream effect)*

# How are the vaccines working?

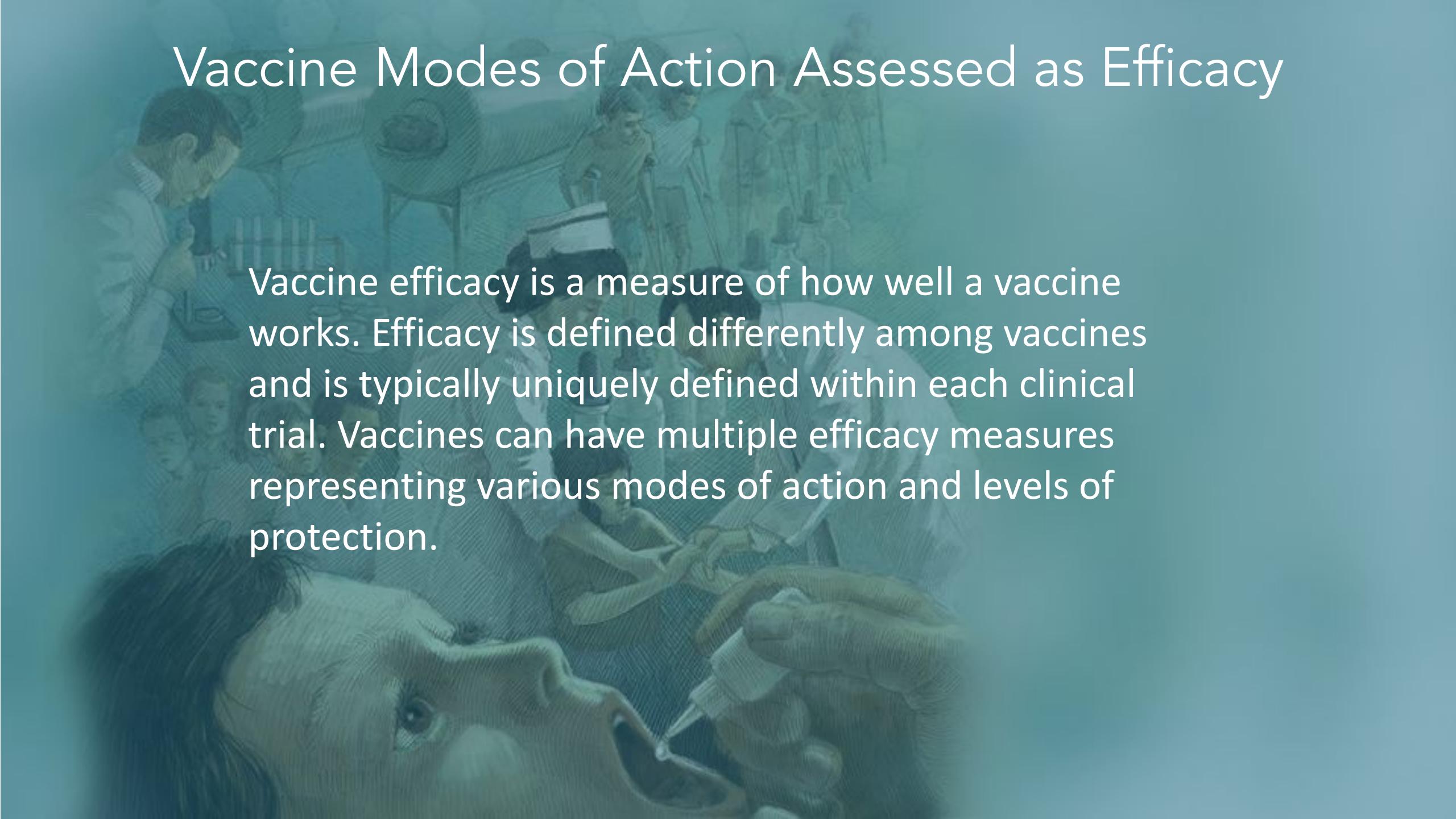


## (3) Reduces symptoms

*Protects vaccinated individuals from pathology*



# Vaccine Modes of Action Assessed as Efficacy



Vaccine efficacy is a measure of how well a vaccine works. Efficacy is defined differently among vaccines and is typically uniquely defined within each clinical trial. Vaccines can have multiple efficacy measures representing various modes of action and levels of protection.

# Exploring Efficacy with the COVID-19 Vaccines in the US

Pfizer-BioNTech  
COVID-19 Vaccine

**Vaccines and Related Biological Products Advisory Committee Meeting**  
**December 10, 2020**

**FDA Briefing Document**

**Pfizer-BioNTech COVID-19 Vaccine**

# Pfizer-BioNTech COVID-19 Vaccine

## Primary Efficacy Analyses

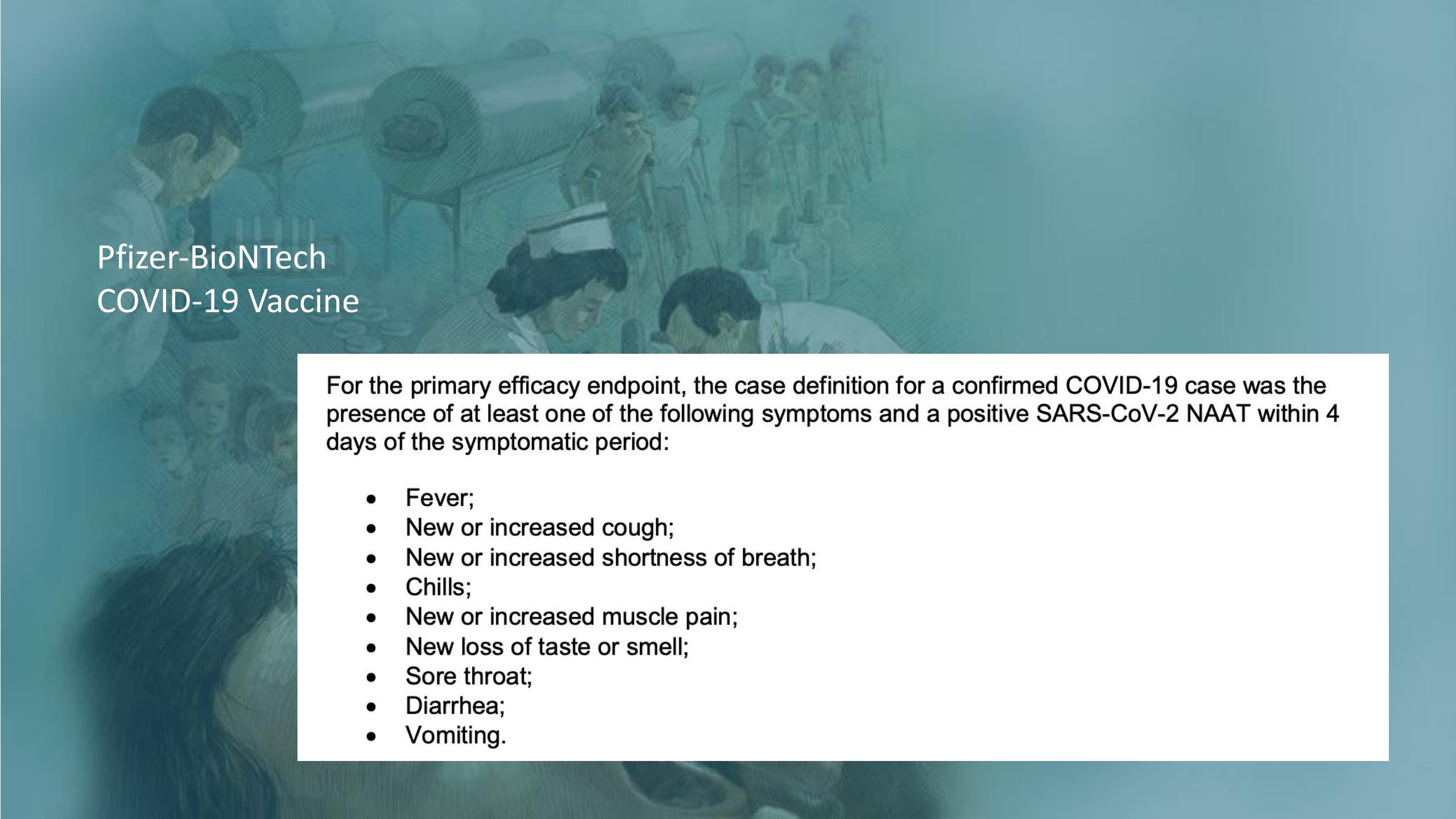
### Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group ([Table 6](#)). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

**Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population**

Pre-specified Age Group	BNT162b2 N <sup>a</sup> = 18198 Cases n1 <sup>b</sup> Surveillance Time <sup>c</sup> (n2 <sup>d</sup> )	Placebo N <sup>a</sup> = 18325 Cases n1 <sup>b</sup> Surveillance Time <sup>c</sup> (n2 <sup>d</sup> )	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6) <sup>e</sup>	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6) <sup>f</sup>	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8) <sup>f</sup>	NA



## Pfizer-BioNTech COVID-19 Vaccine

For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was the presence of at least one of the following symptoms and a positive SARS-CoV-2 NAAT within 4 days of the symptomatic period:

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

# Exploring Efficacy with the COVID-19 Vaccines in the US

Primary Efficacy for Pfizer COVID-19 vaccine:

Individuals get 2 doses and have no evidence of SARS-CoV-2 infection prior to 7 days after dose 2 (i.e., they are given enough time for both doses to work)

Cases counted starting 7 days after dose 2

Cases of COVID-19 defined as one or more symptoms and positive PCR test within 4d of symptoms



# Pfizer-BioNTech COVID-19 Vaccine used six efficacy metrics

## Primary Efficacy Endpoints

Study C4591001 has two primary endpoints:

**First primary endpoint:** COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed  $\geq 7$  days after Dose 2

**Second primary endpoint:** COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed  $\geq 7$  days after Dose 2

## Secondary Efficacy Endpoints

Study C4591001 has secondary endpoints based on different approaches to COVID-19 case evaluation criteria as follows:

13

Pfizer-BioNTech COVID-19 Vaccine  
VRBPAC Briefing Document

**COVID-19 confirmed at least 14 days after Dose 2:** COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed  $\geq 14$  days after Dose 2

**Severe COVID-19:** incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1)  $\geq 7$  days after Dose 2 or (2)  $\geq 14$  days after Dose 2

**CDC-defined COVID-19:** incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1)  $\geq 7$  days after Dose 2 or (2)  $\geq 14$  days after Dose 2.

# Exploring Efficacy with the COVID-19 Vaccines in the US

**Vaccines and Related Biological Products Advisory Committee Meeting**  
**December 17, 2020**

**FDA Briefing Document**

**Moderna COVID-19 Vaccine**

# Exploring Efficacy with the COVID-19 Vaccines in the US

Other essential workers were also represented. The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS CoV-2 at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (Viracor; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

Moderna  
vaccine

For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was defined as:

- At least TWO of the following systemic symptoms: Fever ( $\geq 38^{\circ}\text{C}$ ), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), or
- At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; and
- NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

# Exploring Efficacy with the COVID-19 Vaccines in the US

**Table 9. Interim Analysis<sup>a</sup> for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set**

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934	Placebo Group N=13883	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
	Cases n (%) (Incidence rate per 1,000 person- years)	Cases n (%) (Incidence rate per 1,000 person- years)		
All participants	5 (<0.1) 1.840	90 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%	NA

Moderna  
vaccine

# Exploring Efficacy with the COVID-19 Vaccines in the US

- The primary vaccine efficacy endpoints for the Pfizer and Moderna Emergency Use Authorization in the US were measures of protection from symptomatic infection
- Both trials used different definitions of efficacy, but still arrived at similar efficacy measures for their mRNA vaccines
- The take away is that efficacy may be uniquely defined by each trial, and for each vaccine, but each efficacy measure can be biologically interpreted by considering which mode(s) of action the efficacy measure addresses

# Exploring Efficacy with the COVID-19 Vaccines in the US

2/22/2021

Can COVID vaccines stop transmission? Scientists race to find answers

**nature**

Content ▾ Journal Info ▾ Publish ▾

---

nature > news > article

**NEWS** · 19 FEBRUARY 2021

## Can COVID vaccines stop transmission? Scientists race to find answers

Controlling the pandemic will require shots that prevent viral spread, but that feature is difficult to measure.

Smriti Mallapaty

# Exploring Efficacy with the COVID-19 Vaccines in the US

## Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data

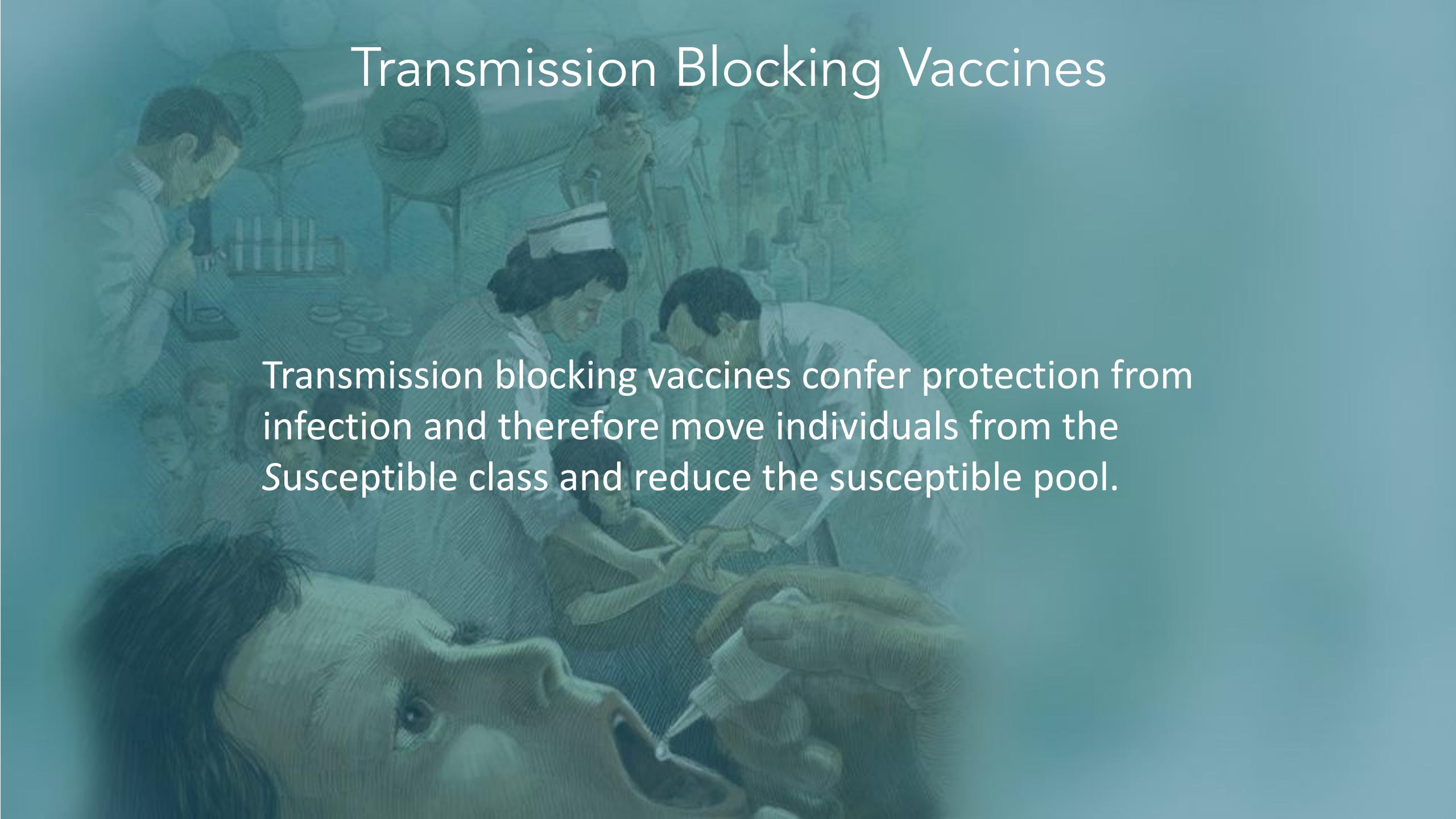


Eric J Haas, Frederick J Angulo, John M McLaughlin, Emilia Anis, Shepherd R Singer, Farid Khan, Nati Brooks, Meir Smaja, Gabriel Mircus, Kaijie Pan, Jo Southern, David L Swerdlow, Luis Jodar, Yeheskel Levy, Sharon Alroy-Preis

Published May 15, 2021

**Findings** During the analysis period (Jan 24 to April 3, 2021), there were 232 268 SARS-CoV-2 infections, 7694 COVID-19 hospitalisations, 4481 severe or critical COVID-19 hospitalisations, and 1113 COVID-19 deaths in people aged 16 years or older. By April 3, 2021, 4714 932 (72·1%) of 6 538 911 people aged 16 years and older were fully vaccinated with two doses of BNT162b2. Adjusted estimates of vaccine effectiveness at 7 days or longer after the second dose were 95·3% (95% CI 94·9–95·7; incidence rate 91·5 per 100 000 person-days in unvaccinated vs 3·1 per 100 000 person-days in fully vaccinated individuals) against SARS-CoV-2 infection, 91·5% (90·7–92·2; 40·9 vs 1·8 per 100 000 person-days) against asymptomatic SARS-CoV-2 infection, 97·0% (96·7–97·2; 32·5 vs 0·8 per 100 000 person-days) against symptomatic COVID-19, 97·2% (96·8–97·5; 4·6 vs 0·3 per 100 000 person-days) against COVID-19-related hospitalisation, 97·5% (97·1–97·8; 2·7 vs 0·2 per 100 000 person-days) against severe or critical COVID-19-related hospitalisation, and 96·7% (96·0–97·3; 0·6 vs 0·1 per 100 000 person-days) against COVID-19-related death. In all age groups, as vaccine coverage increased, the incidence of SARS-CoV-2 outcomes declined. 8006 of 8472 samples tested showed a spike gene target failure, giving an estimated prevalence of the B.1.1.7 variant of 94·5% among SARS-CoV-2 infections.

# Transmission Blocking Vaccines

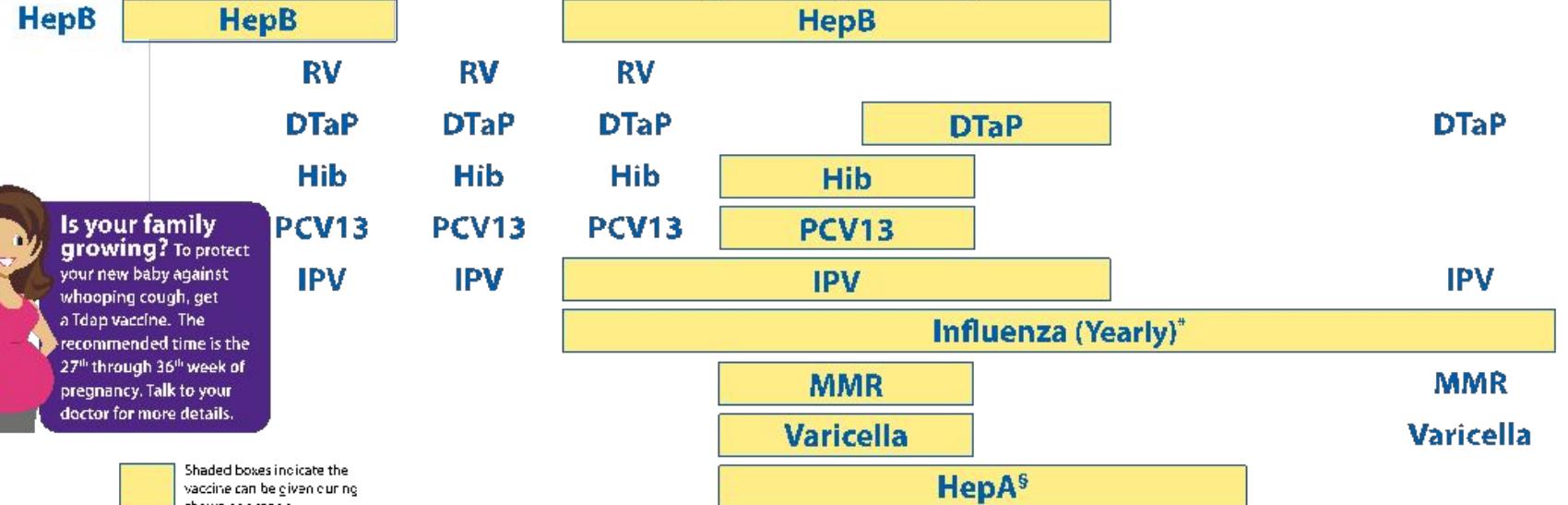


Transmission blocking vaccines confer protection from infection and therefore move individuals from the Susceptible class and reduce the susceptible pool.

# Types of Vaccine Administration

- Routine immunization
- Pulsed vaccination/vaccination campaigns
- Catch-up campaigns
- Initial roll-out of new vaccine, often phased by risk and/or age group

## 2020 Recommended Immunizations for Children from Birth Through 6 Years Old



**NOTE:**  
If your child misses a shot,  
you don't need to start over. Just go  
back to your child's  
doctor for the next shot.  
Talk with your child's doctor  
if you have questions  
about vaccines.

**FOOTNOTES:**

- \* Two doses given at least four weeks apart are recommended for children age 6 months through 8 years of age who are getting an influenza (flu) vaccine for the first time and for some other children in this age group.
- † Two doses of HepA vaccine are needed for lasting protection. The first dose of HepA vaccine should be given between 12 months and 23 months of age. The second dose should be given 6 months after the first dose. All children and adolescents over 24 months of age who have not been vaccinated should also receive 2 doses of HepA vaccine.
- If your child has any medical conditions that put him at risk for infection or is traveling outside the United States, talk to your child's doctor about additional vaccines that he or she may need.

See back page for  
more information on  
vaccine-preventable  
diseases and the  
vaccines that  
prevent them.

Infant  
vaccination is  
the most  
common routine  
immunization

For more information, call toll free  
**1-800-CDC-INFO** (1-800-232-4636)  
or visit  
[www.cdc.gov/vaccines/parents](http://www.cdc.gov/vaccines/parents)



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention



American Academy  
of Pediatrics  
DEDICATED TO THE HEALTH OF ALL CHILDREN



# Indirect Protection via Cocooning

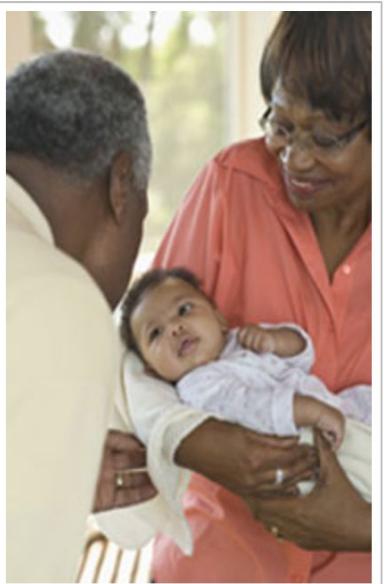
## Surround Babies with Protection



[Español \(Spanish\)](#)

You can provide indirect protection to your baby by making sure everyone who is around him is up to date with their whooping cough vaccine. When your baby's family members and caregivers get a whooping cough vaccine they are not only protecting their own health, but also helping form a "cocoon" of disease protection around the baby during the first few months of life. Anyone who is around babies should be up-to-date with their whooping cough vaccine.

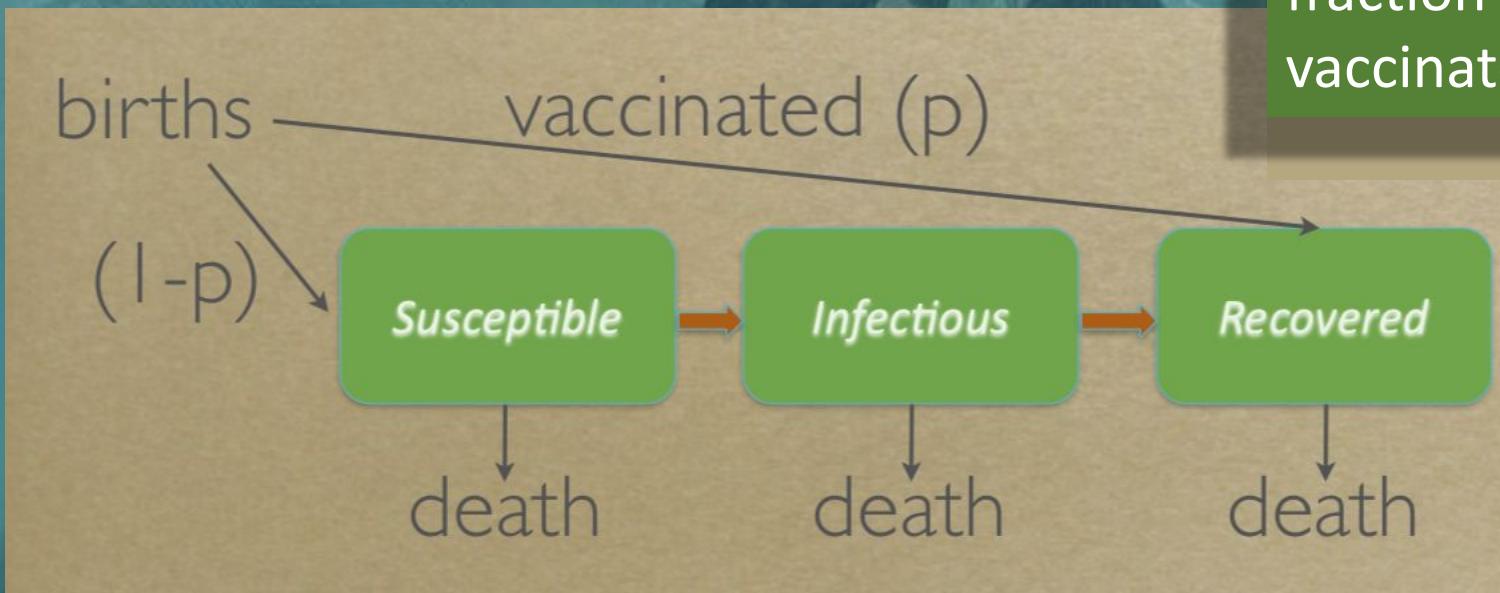
**Your baby is most likely to catch whooping cough from someone at home**



Infants too young to be vaccinated may be cocooned by vaccinated caretakers. This is one way in which vaccinated individuals may confer indirect protection to unvaccinated individuals



# Infant Immunization – Routine Vaccination



Infant immunization generally treated in SIR models as a fraction ( $p$ ) of newborns vaccinated

# Infant Immunization – Routine Vaccination

$$\frac{dS}{dt} = \mu(1 - p) - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI - (\mu + \gamma)I$$

$$\frac{dR}{dt} = \mu p + \gamma I - \mu R$$

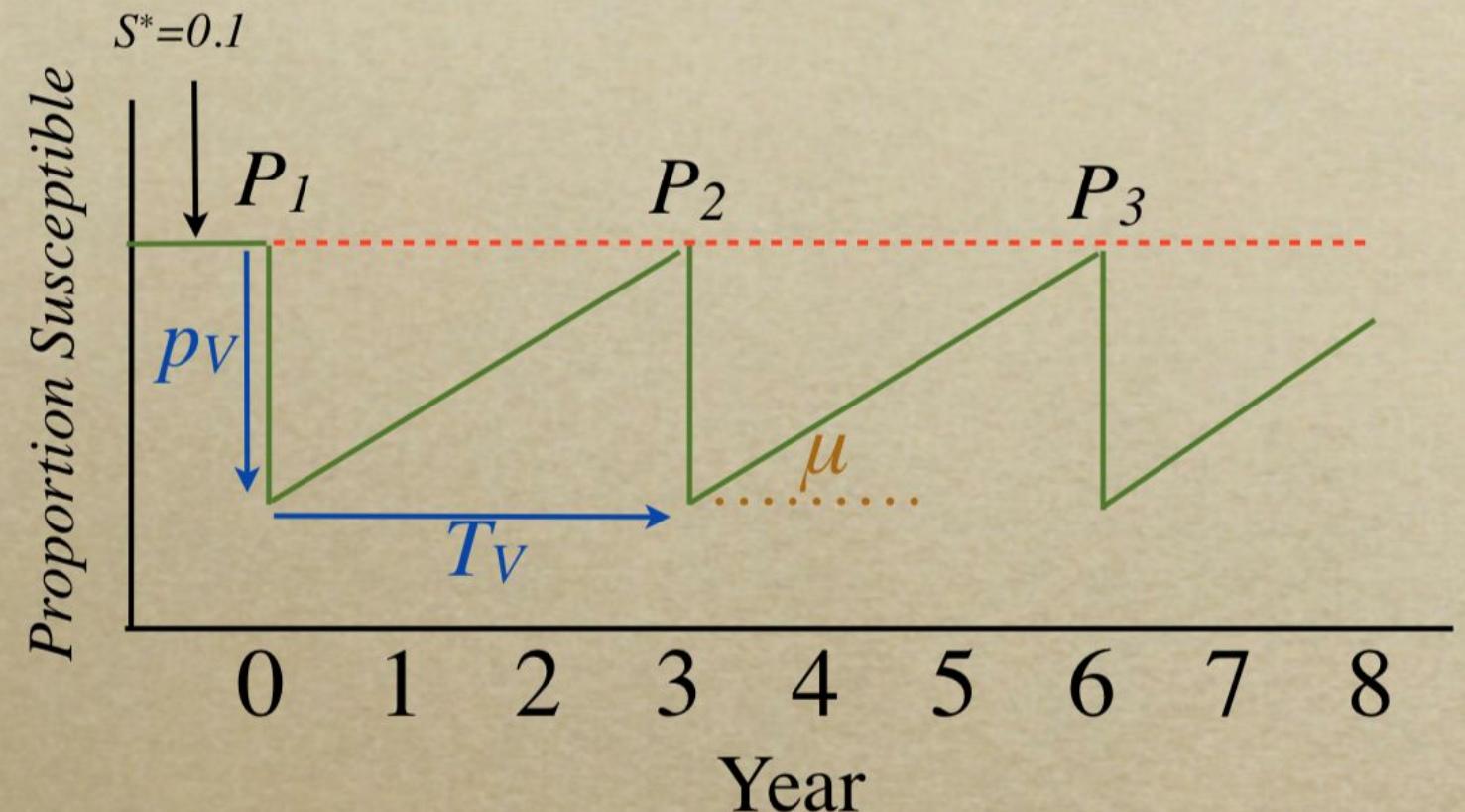
If  $p$  is the critical vaccination threshold;  
 $p = 1 - (1/R_0)$

Vaccinate new birth cohorts at the critical vaccination level.

Catch-up campaigns can also be used to fill immunity gaps in older age groups

# Pulsed Vaccination & Vaccination Campaigns

- pulse vaccinate to drop the susceptibility pool far below the critical threshold
- new births will build up the susceptible pool
- pulse again before the susceptible pool grows too much



# Polio Vaccination

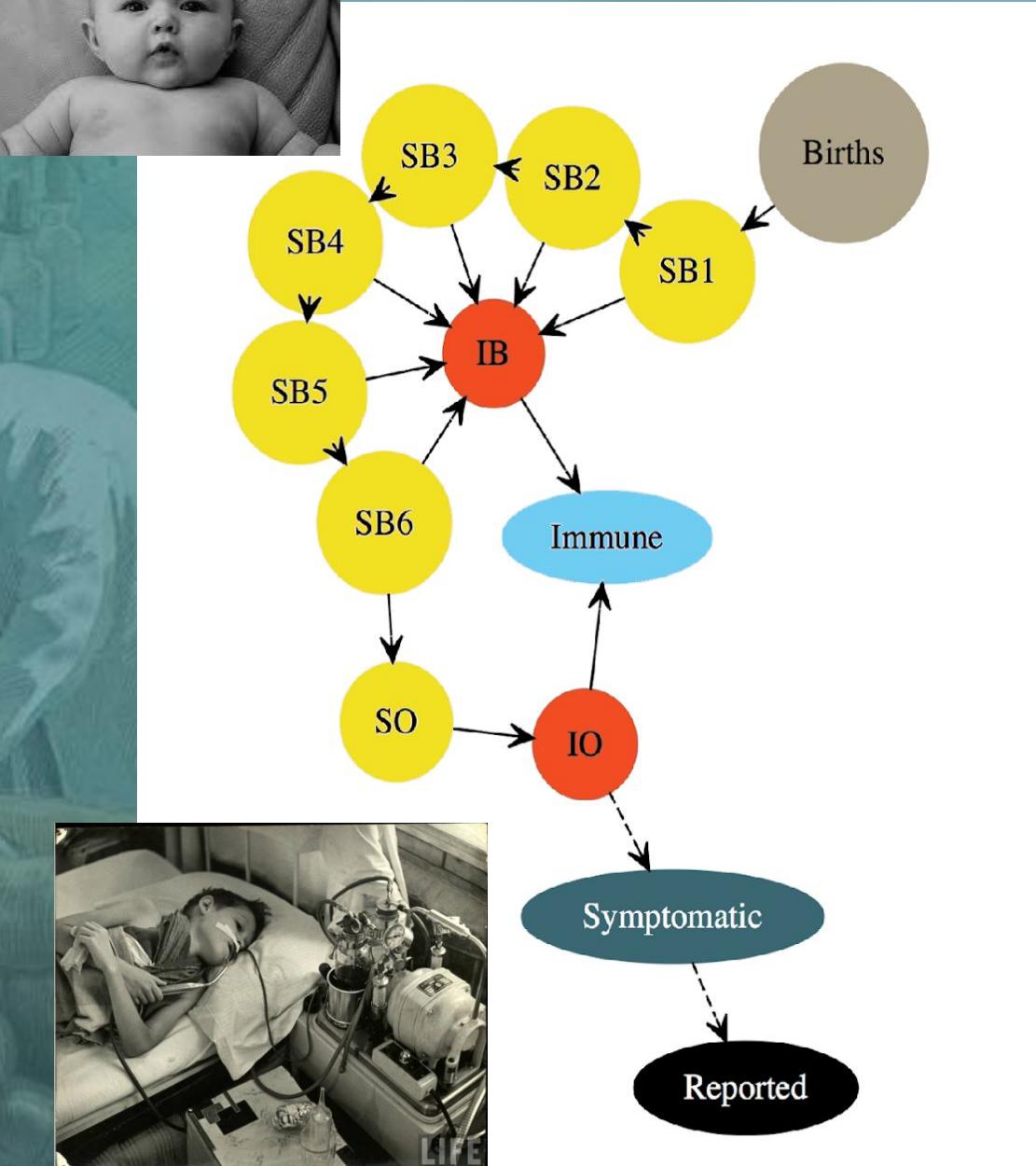


IPV was initially studied and rolled-out in 2nd and 3rd graders before expanding across age groups and eventually becoming an infant vaccine

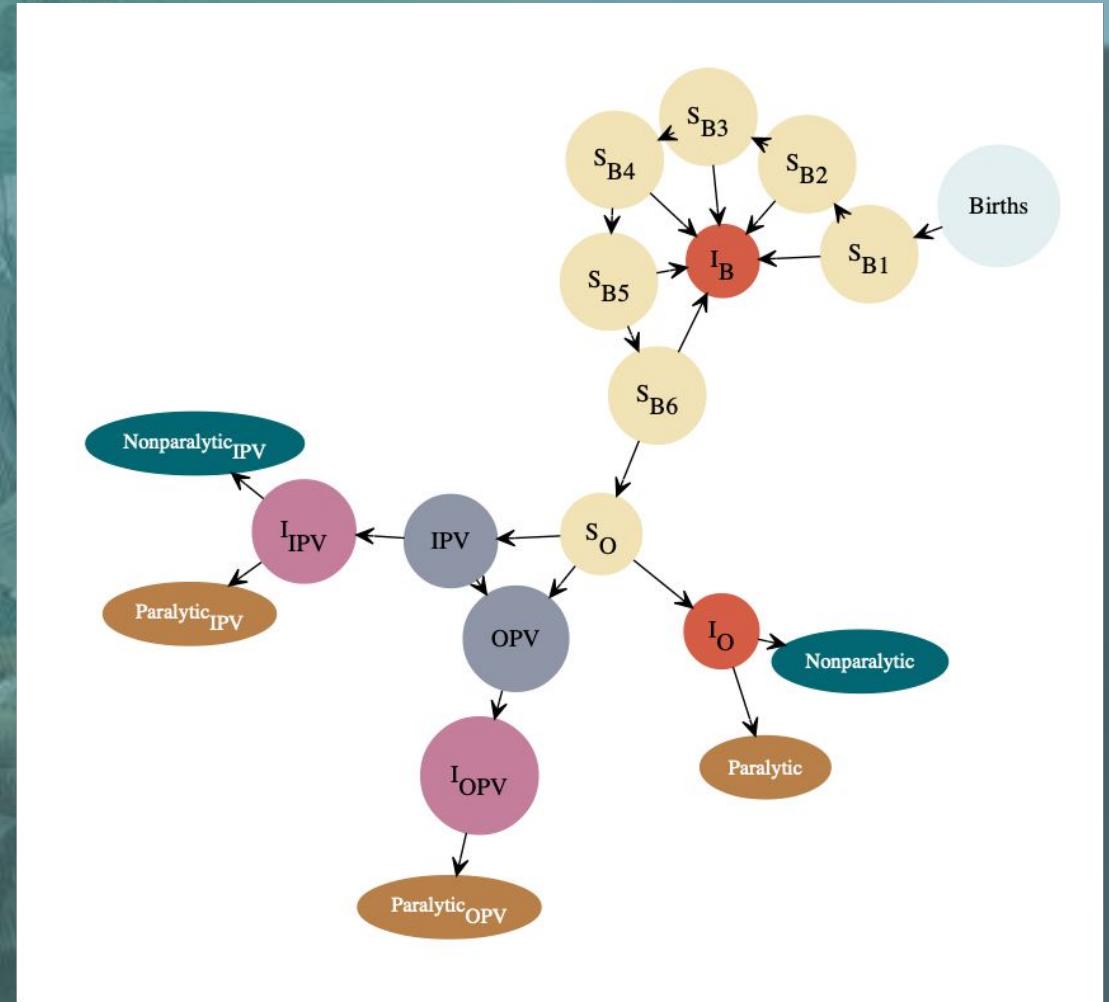
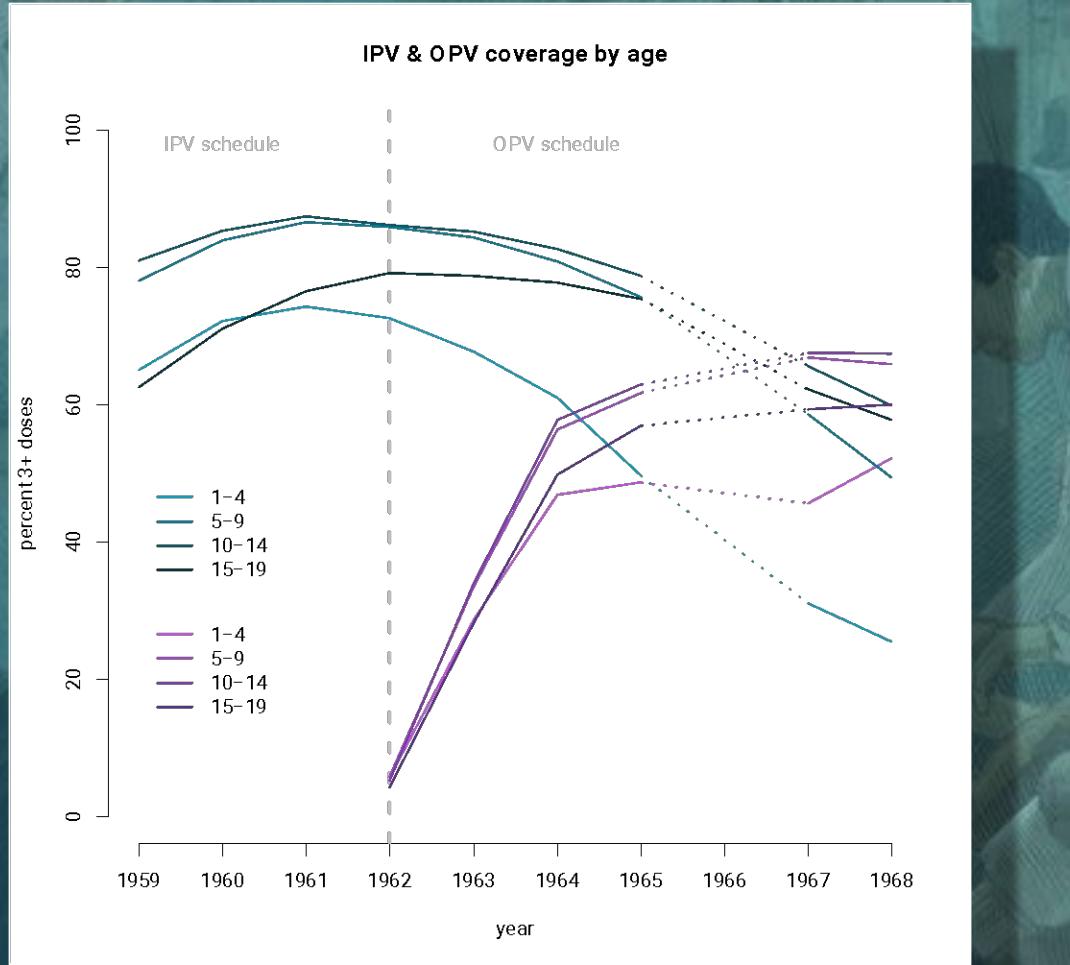
# Modeling Pre-Vaccine Transmission Dynamics

Types of data that can be used:

- Monthly, weekly, daily cases, hospitalizations, or deaths
- Monthly or annual births
- Annual population size



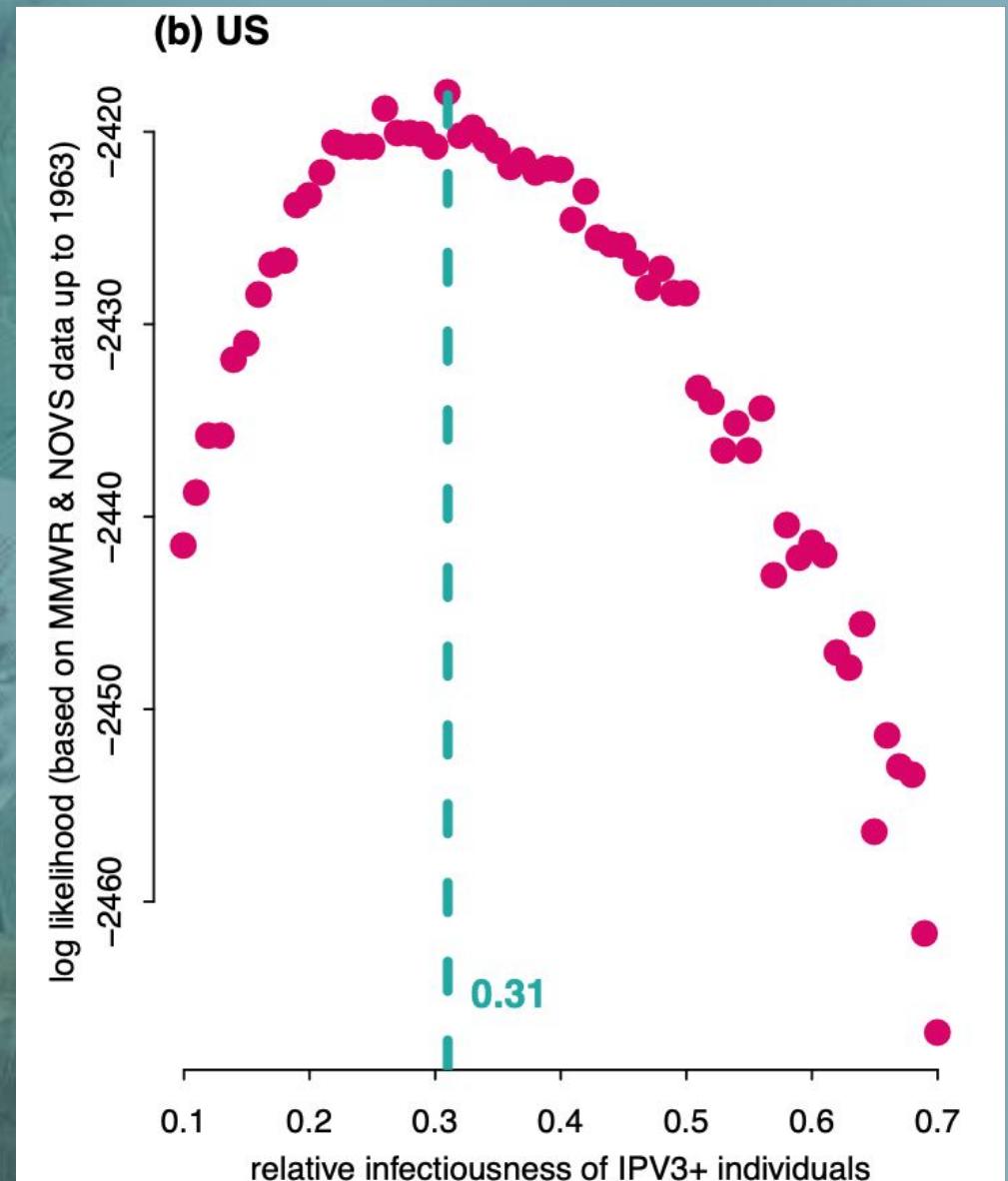
# Modeling Vaccine-Era Transmission Dynamics



# Salk Vaccine Efficacy

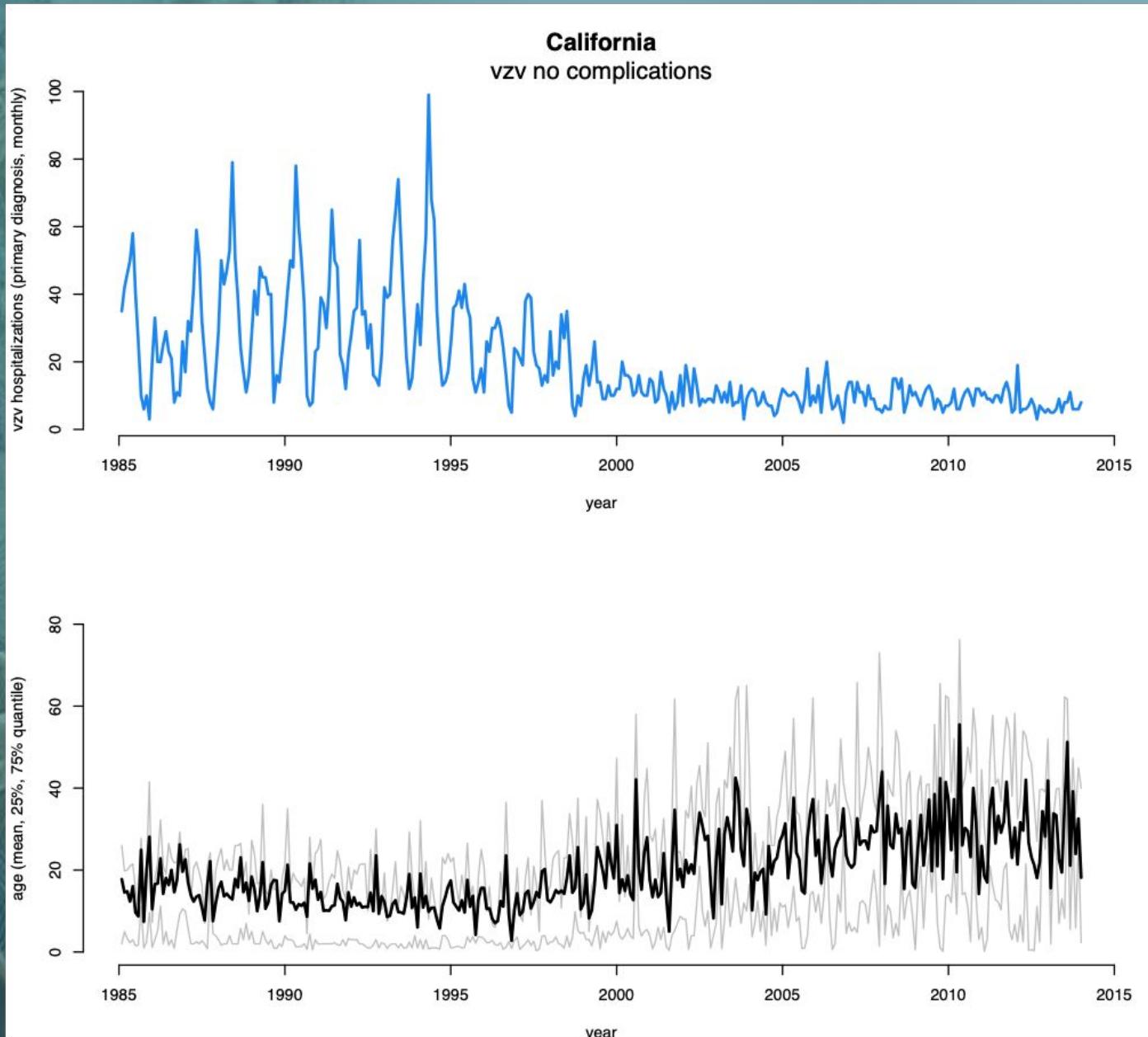


- Relative rates, compared to unvaccinated individuals
- Identifiability is an issue
- Integrate clinical trial data



# Considerations for New Vaccine Roll-Out

When transmission-reducing vaccines are rolled out, for childhood infectious diseases, there is often an increase in the mean age of infection as shown here by chickenpox hospitalizations in California



# Measles Status

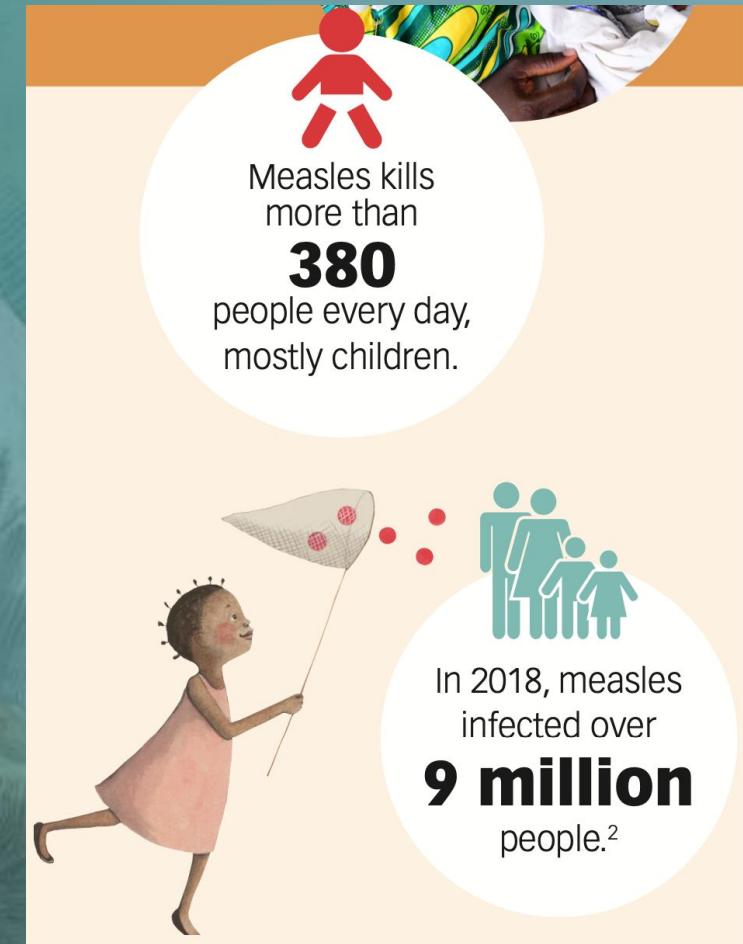
[Health Topics ▾](#)[Countries ▾](#)[Newsroom ▾](#)[Emergencies ▾](#)

[Home](#) / [News](#) / UNICEF and WHO warn of perfect storm of conditions for measles outbreaks, affecting children

## UNICEF and WHO warn of perfect storm of conditions for measles outbreaks, affecting children

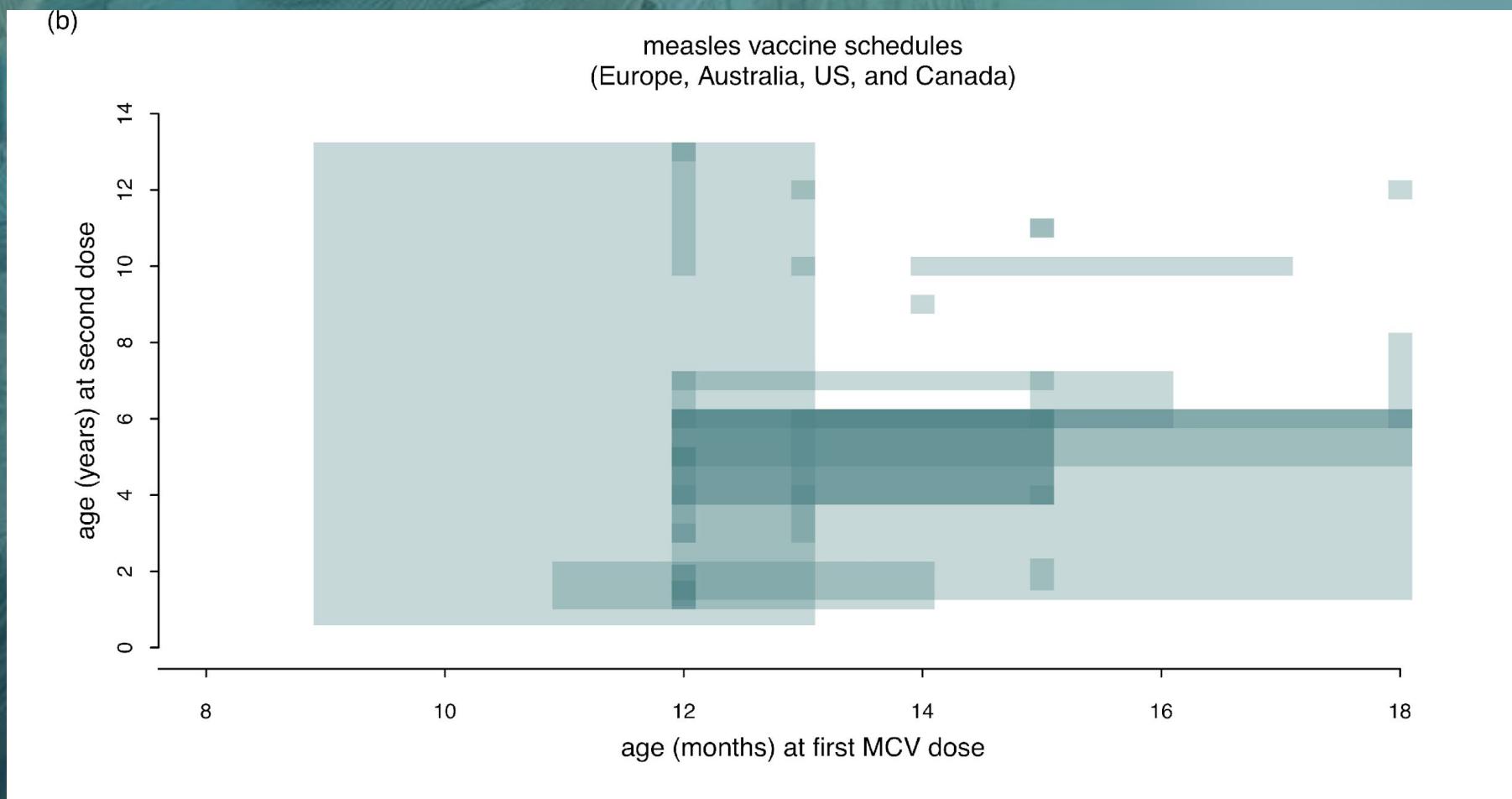
Reported worldwide measles cases increased by 79% in the first 2 months of 2022, compared to the same period in 2021, as WHO and UNICEF warn conditions ripe for serious outbreaks of vaccine-preventable illnesses

27 April 2022 | Joint News Release | New York/Geneva | Reading time: 4 min (1136 words)

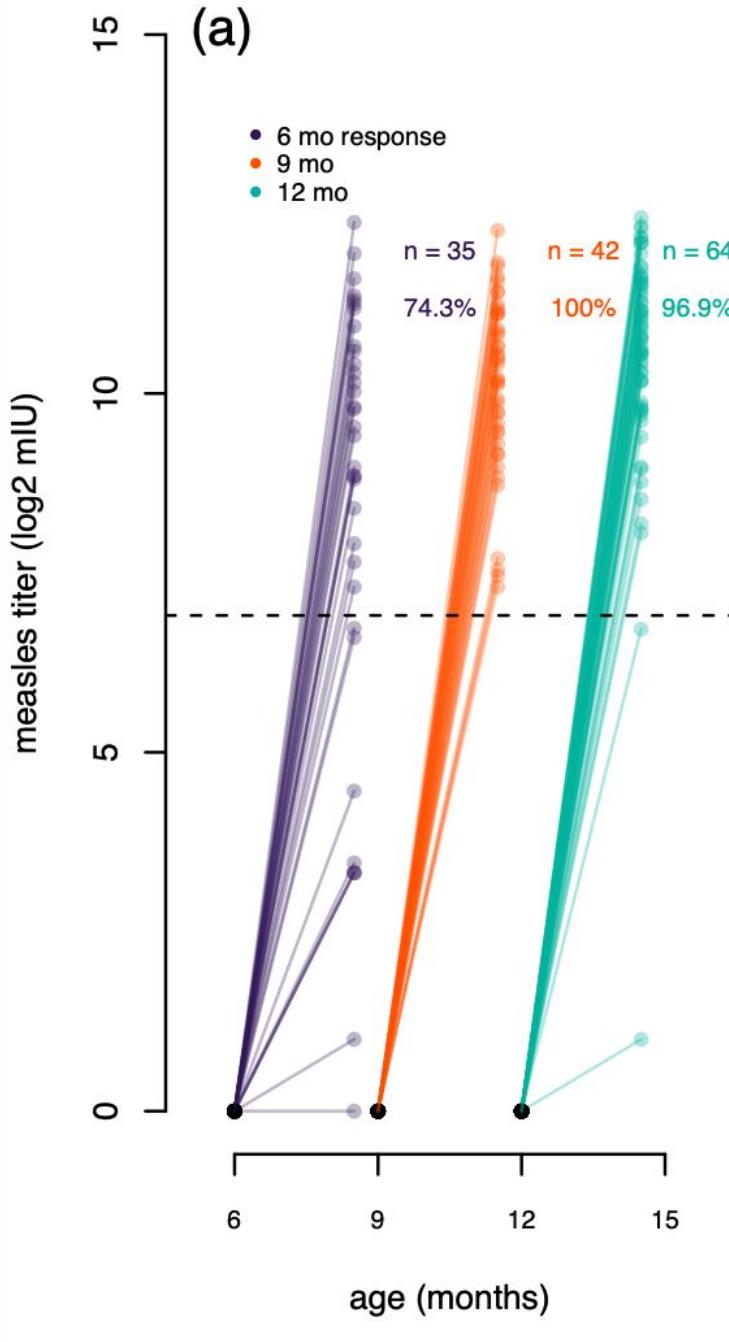


Stats from Measles & Rubella Initiative 2020 fact sheet.

# Measles Routine Vaccination Schedule Differs Among Countries



# Variation in Vaccine Response



Young infants are less likely to have a robust antibody response to their first dose of measles vaccine

Martinez, Wallinga, Gans, et al (in prep)

# Childhood Diseases as a Global Problem

5.3M under-5 deaths in 2018

50% from sepsis, tetanus, pneumonia, diarrhea, malaria, AIDS, measles, and meningitis

70-80% are infant deaths

# Childhood Diseases as a Global Problem

5.3M under-5 deaths in 2018

50% from sepsis, tetanus,  
pneumonia,  
AIDS, measles

70-80% are i

