Typhoid Fever in Santiago, Chile: Modern Insights Where Historical Data Meet Mathematical Modeling

Jillian Gauld, Dennis Chao, Hao Hu, Institute for Disease Modeling

Myron Levine, University of Maryland

April 4, 2017

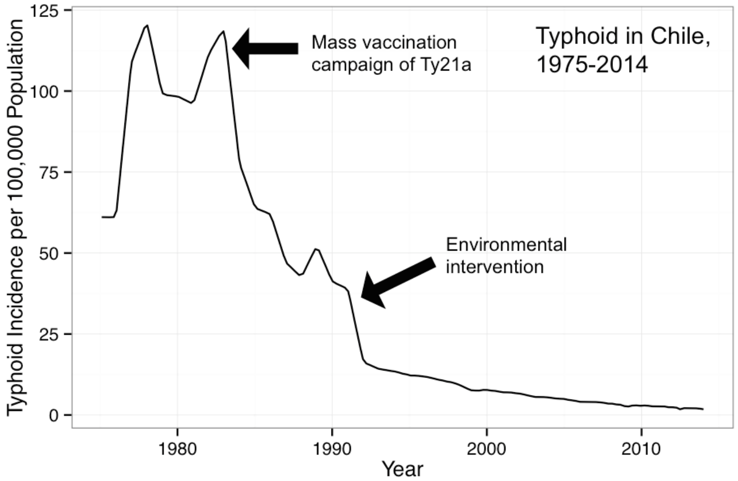
INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES

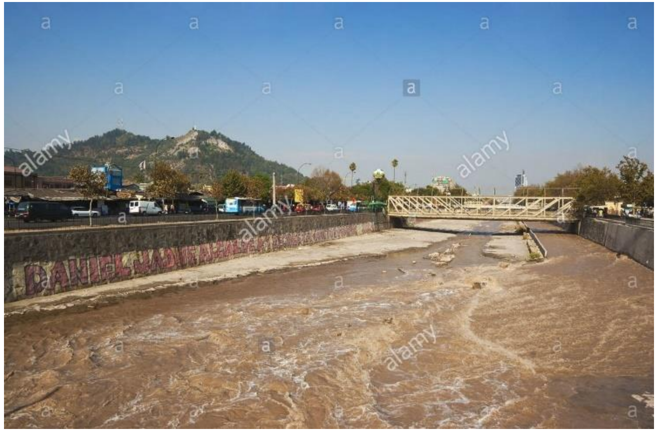
Outline

- Santiago overview
- Modeling project
- Model fitting
- Take-aways: site specific and new locations
- Understanding uncertainty in the face of vaccine projections

Santiago, Chile

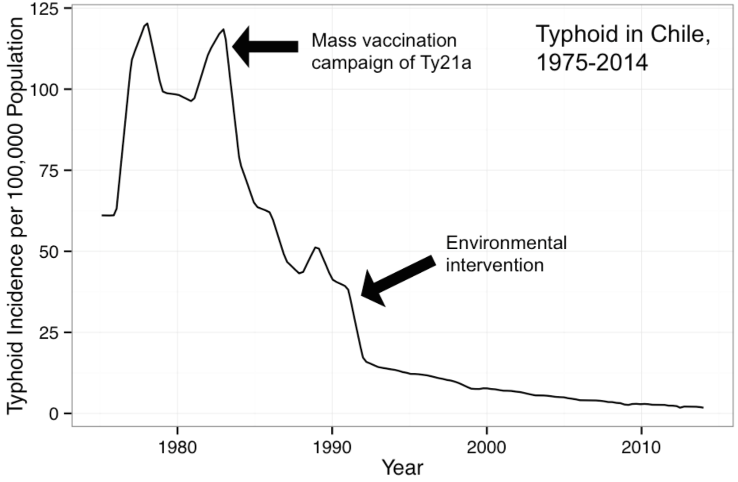
- Very low level typhoid incidence in modern day
- In the 1970-1980s: high endemic transmission despite >90% drinking water coverage and 80% connection to sewer system
- Decline in 1980s coincident with Ty21a vaccine trial, carrier finding and treatment
- 1991 ban of wastewater irrigation: sharp decline in cases





Santiago, Chile

- Very low level typhoid incidence in modern day
- In the 1970-1980s: high endemic transmission despite >90% drinking water coverage and 80% connection to sewer system
- Decline in 1980s coincident with Ty21a vaccine trial, carrier finding and treatment
- 1991 ban of wastewater irrigation: sharp decline in cases



Why model in Santiago?

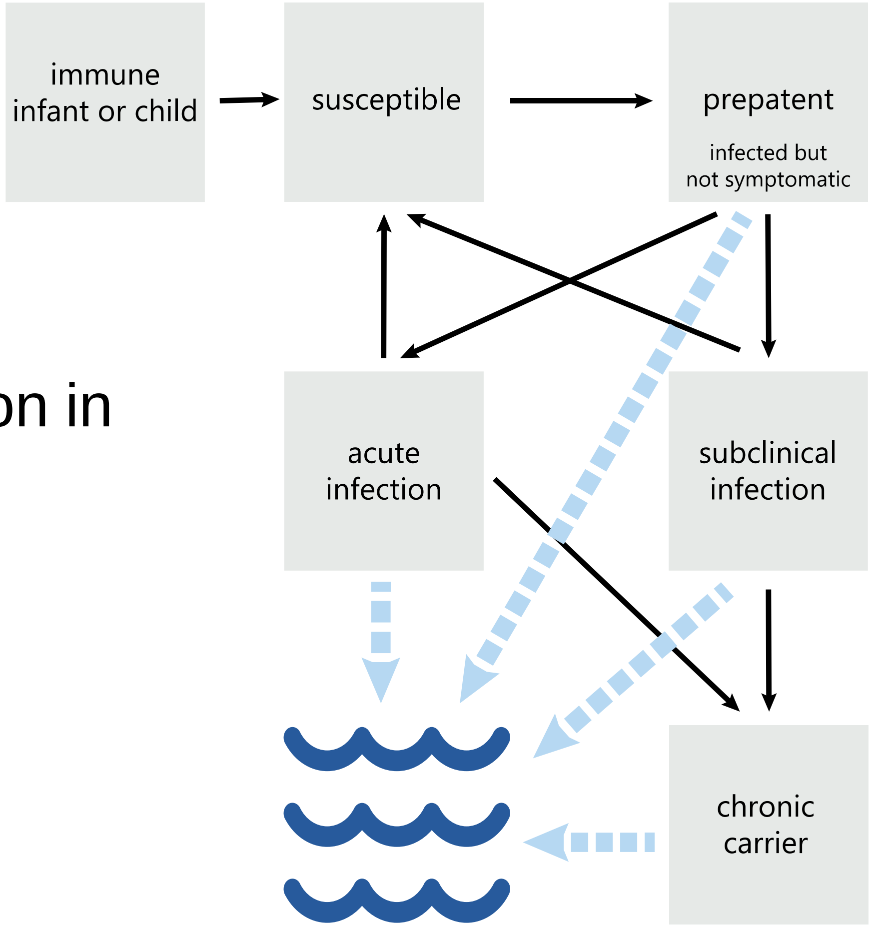
- Three different transmission periods in a single population/ demographic set
- Data that is not commonly available:
  - Age distribution, seasonality, *transmission route, carrier prevalence, short cycle-only transmission*
- Allows us to explore underlying mechanisms for observed dynamics and understand areas of uncertainty

INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES®

Modeling approach

Individual-based model:

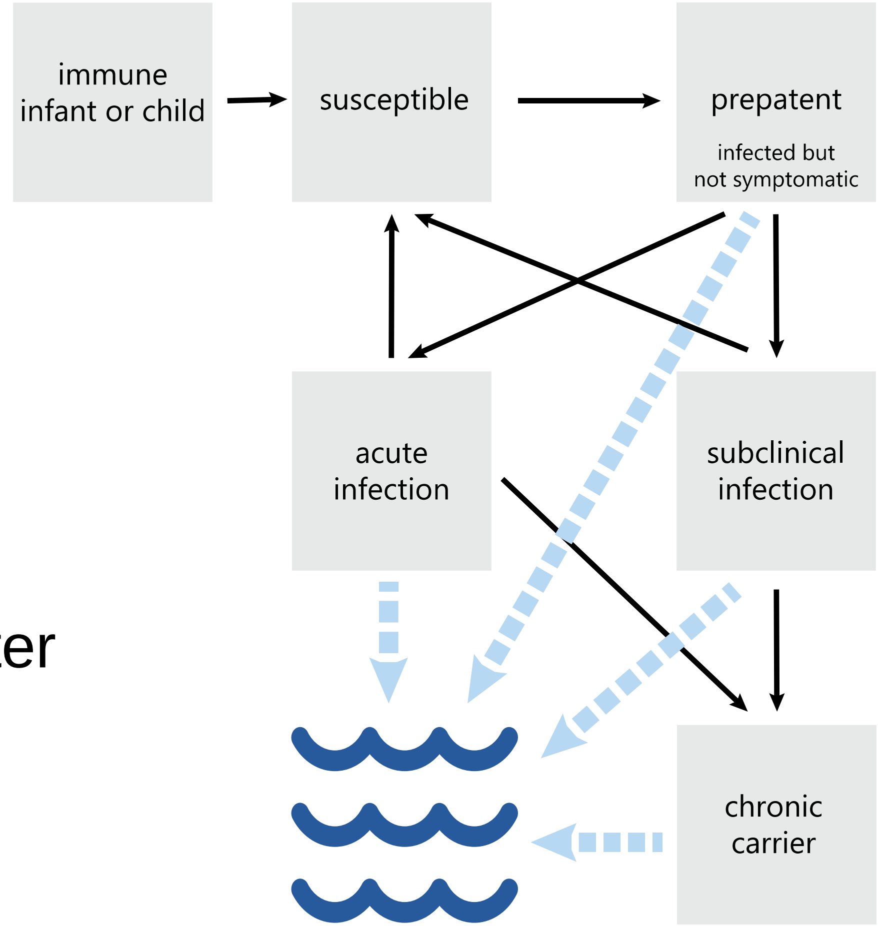
- Allows for *individual level* variation in parameters including immunity, shedding duration, and carrier probabilities



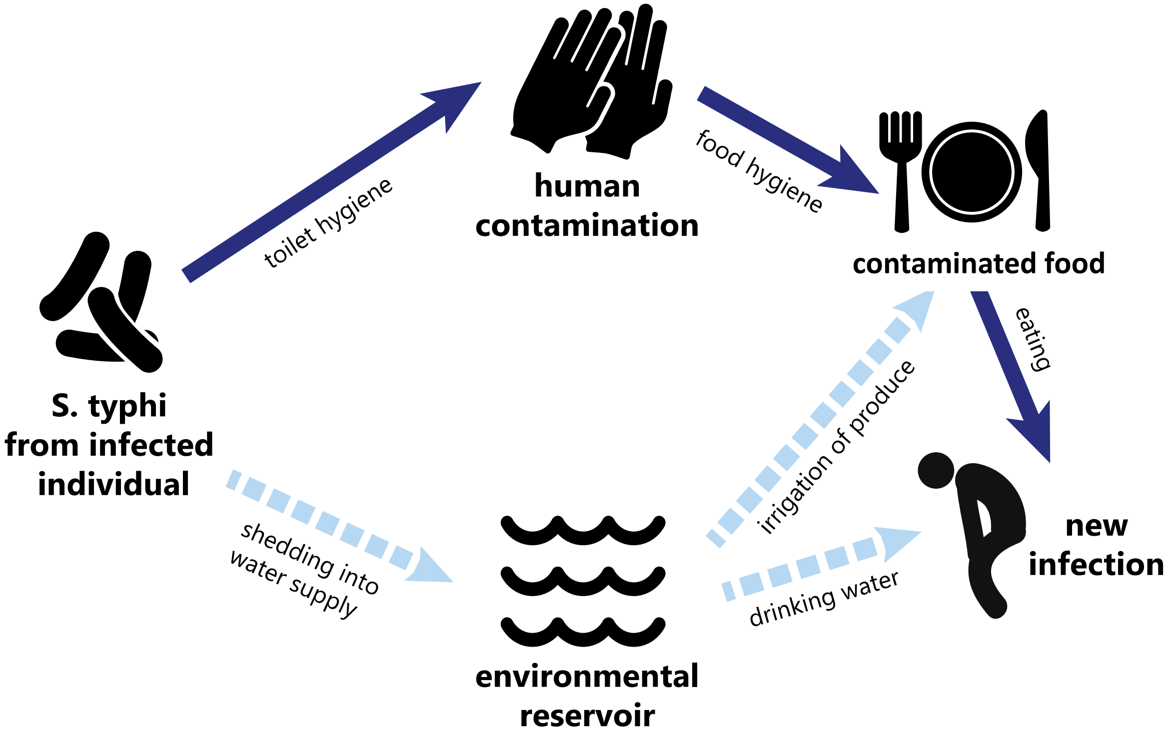
Modeling approach

Key components:

- Infections can be either *acute* or *subclinical*
- Permanent chronic carrier state
- Protection-per-infection parameter



Modeling transmission routes



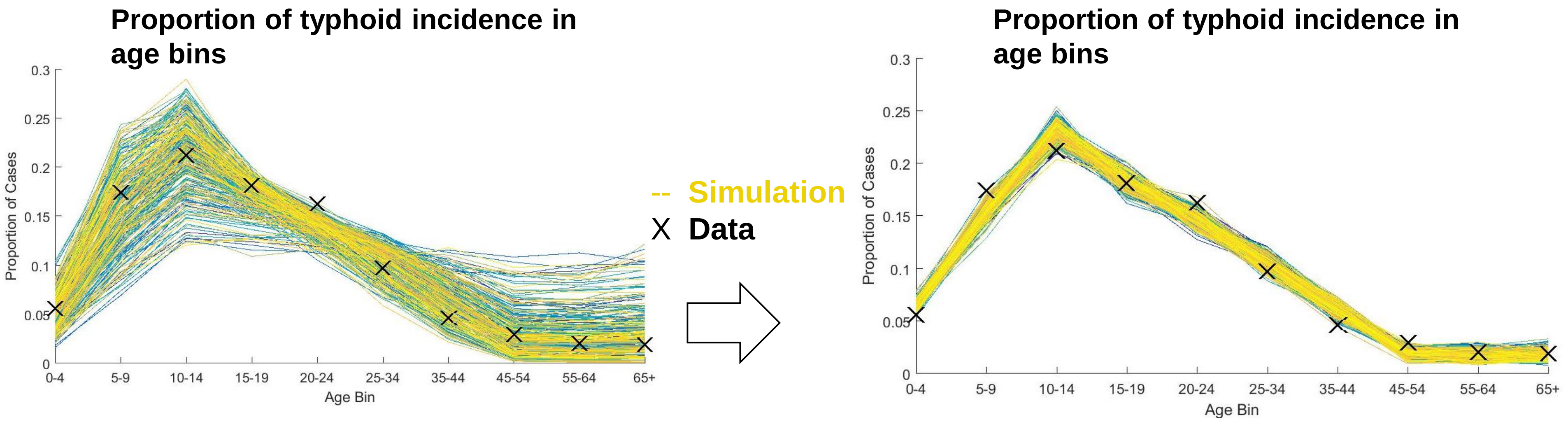
Distinct transmission routes in model:

Long cycle: Homogenous mixing, dose-response dynamics, decay in water/ environment

Short cycle: Non-seasonal, modeled as direct transmission

Model fitting process

- Optimization to maximize likelihoods informing model fit to age distribution, incidence, carrier prevalence, seasonality
- Provides point estimates for fitted parameters



Take-aways from model fitting

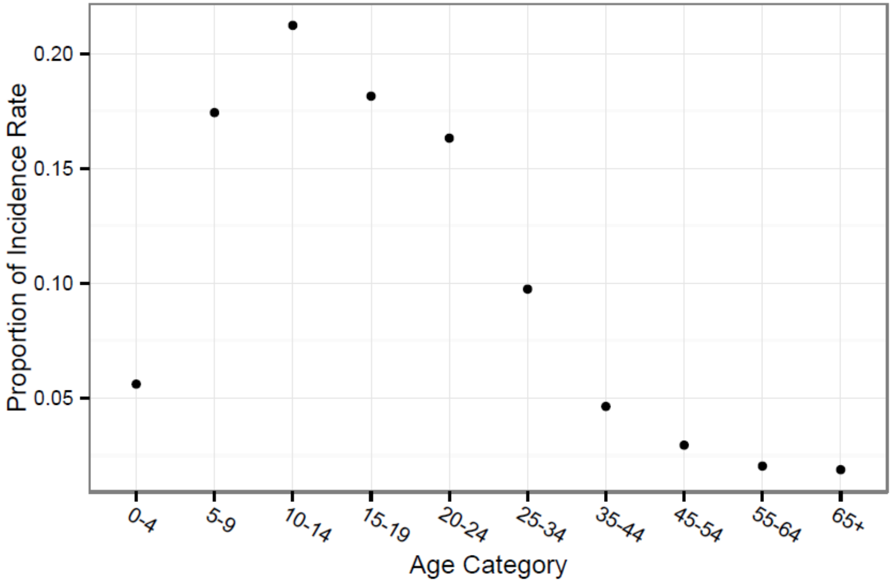
Immunity likely drives low incidence in adults

- Partial immunity after infection creates adult age distribution

We are likely catching a small fraction of total cases:

- <10% total cases (clinical/subclinical) reported in model

Pre-vaccine age distribution of typhoid incidence in Santiago, Chile



Take-aways from model fitting

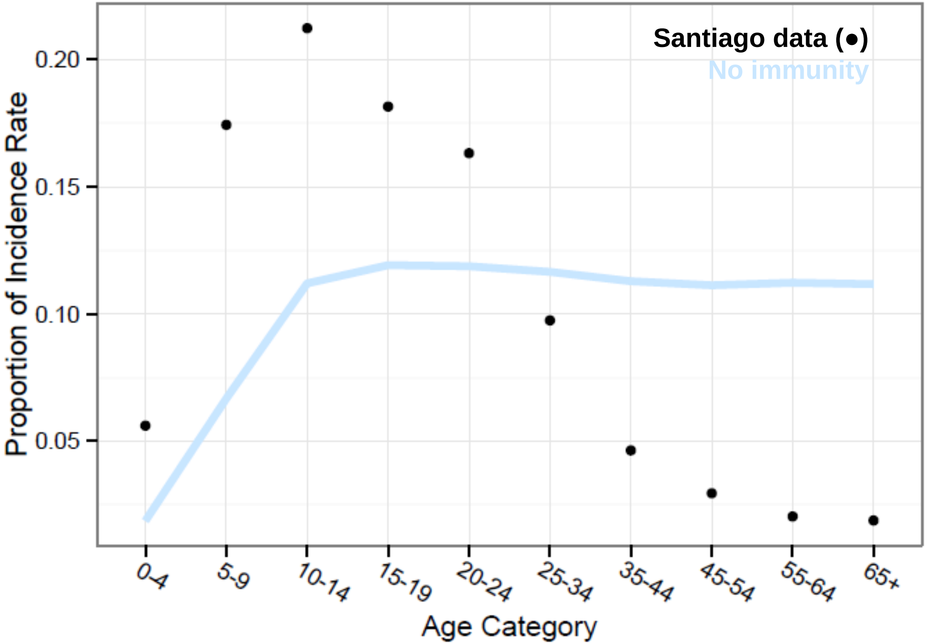
Immunity likely drives low incidence in adults

- Partial immunity after infection creates adult age distribution

We are likely catching a small fraction of total cases:

- <10% total cases (clinical/subclinical) reported in model

Pre-vaccine age distribution of typhoid incidence in Santiago, Chile



Take-aways from model fitting

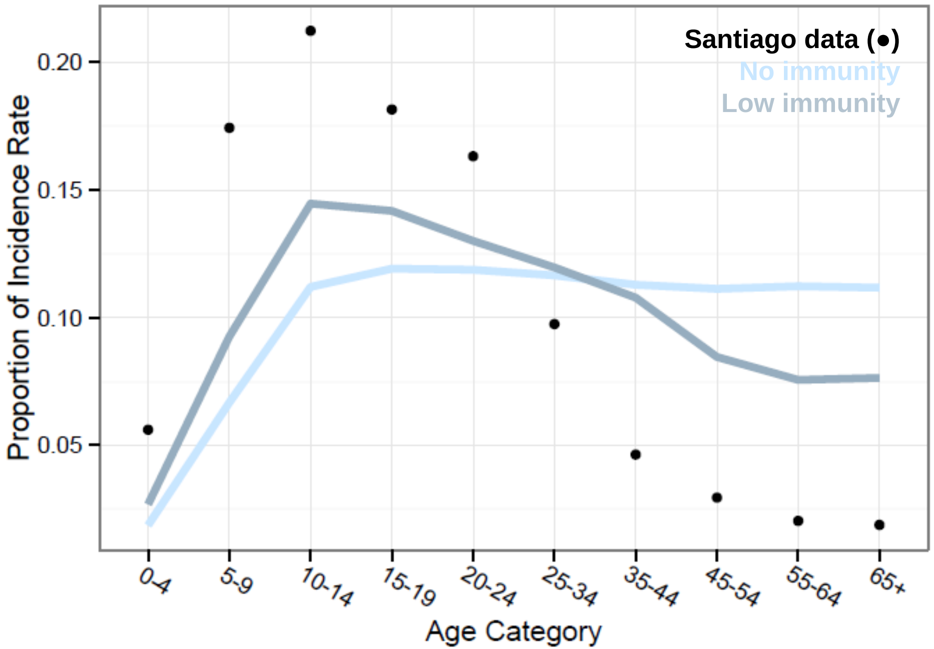
Immunity likely drives low incidence in adults

- Partial immunity after infection creates adult age distribution

We are likely catching a small fraction of total cases:

- <10% total cases (clinical/subclinical) reported in model

Pre-vaccine age distribution of typhoid incidence in Santiago, Chile



Take-aways from model fitting

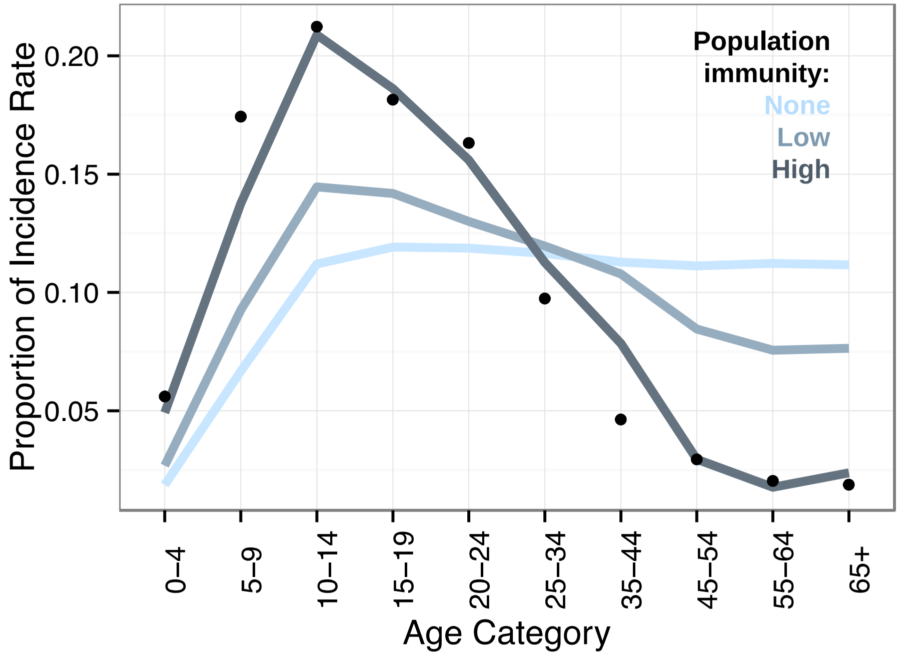
Immunity likely drives low incidence in adults

- Partial immunity after infection creates adult age distribution

We are likely catching a small fraction of total cases:

- <10% total cases (clinical/subclinical) reported in model

Pre-vaccine age distribution of typhoid incidence in Santiago, Chile

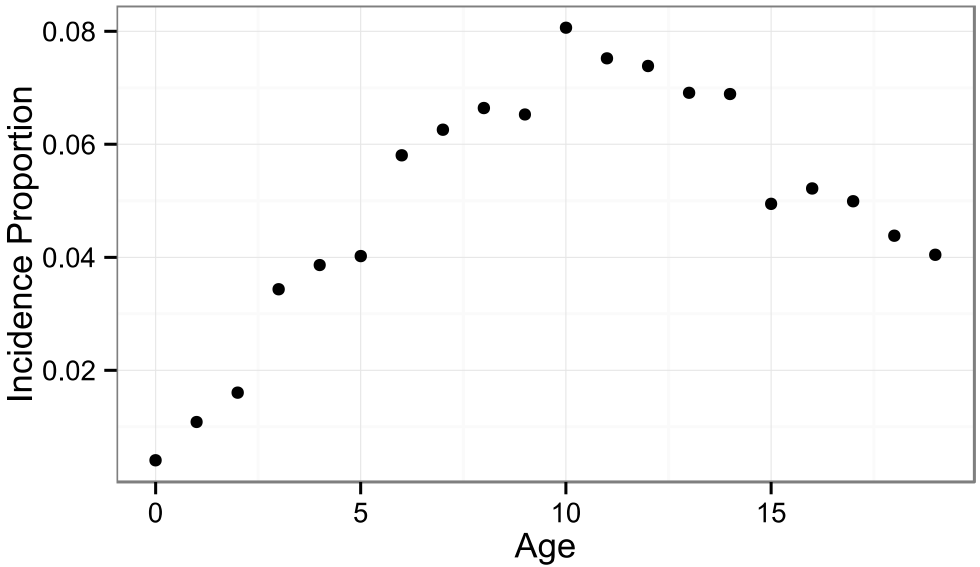


Take-aways from model fitting

Exposure likely drives childhood age distribution:

- Increases in incidence correlated with entry ages into preschool, elementary school system → potential exposure to new foods

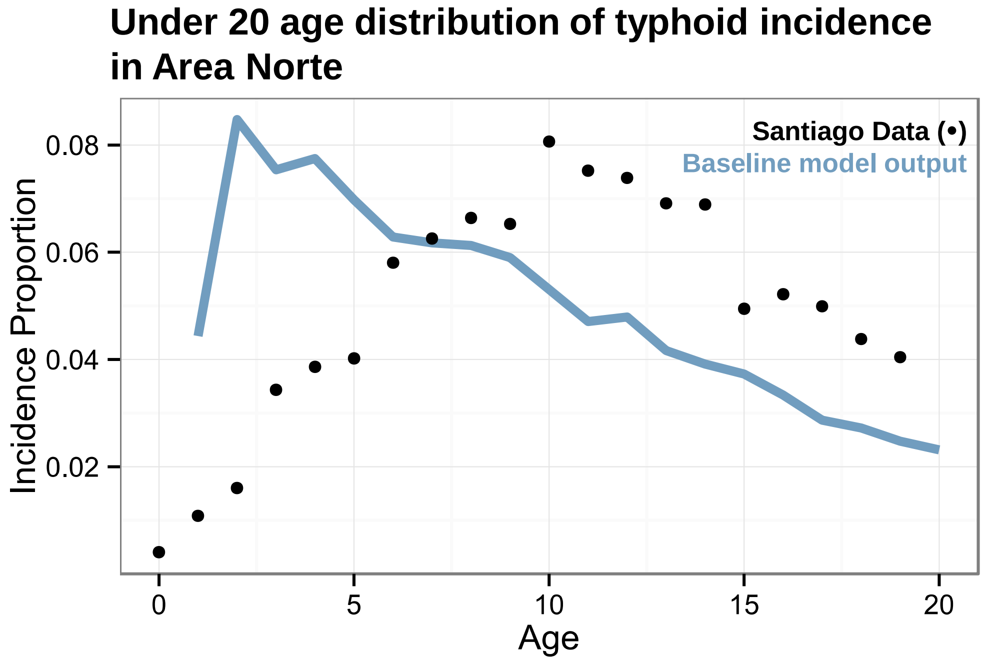
Under 20 age distribution of typhoid incidence in Area Norte, pre-vaccine era



Take-aways from model fitting

Exposure likely drives childhood age distribution:

- Increases in incidence correlated with entry ages into preschool, elementary school system → potential exposure to new foods

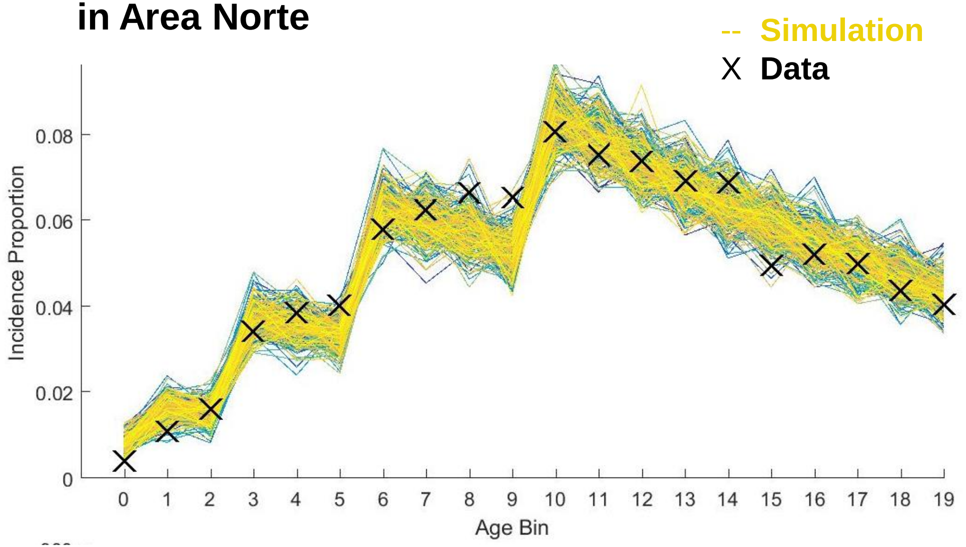


Take-aways from model fitting

Exposure likely drives childhood age distribution:

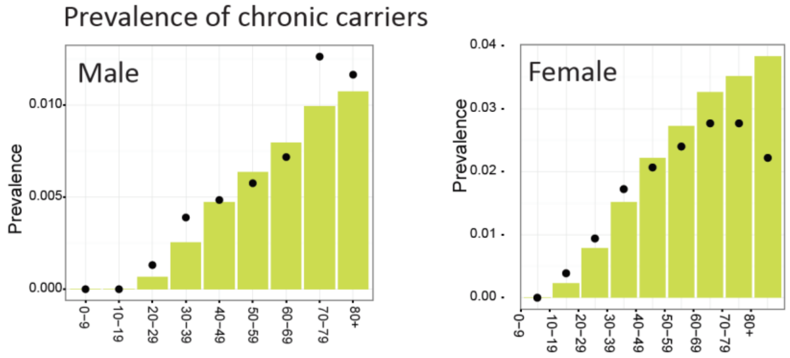
- Increases in incidence correlated with entry ages into preschool, elementary school system → potential exposure to new foods

Under 20 age distribution of typhoid incidence in Area Norte



We can estimate the probability of becoming a chronic carrier from infection

- Age/gender distribution determined by age distribution of gallstones
- Point estimates of probability of becoming a chronic carrier in range of estimates from Ames, 1943



Best-fit model estimates, cases resulting in carriers(%)

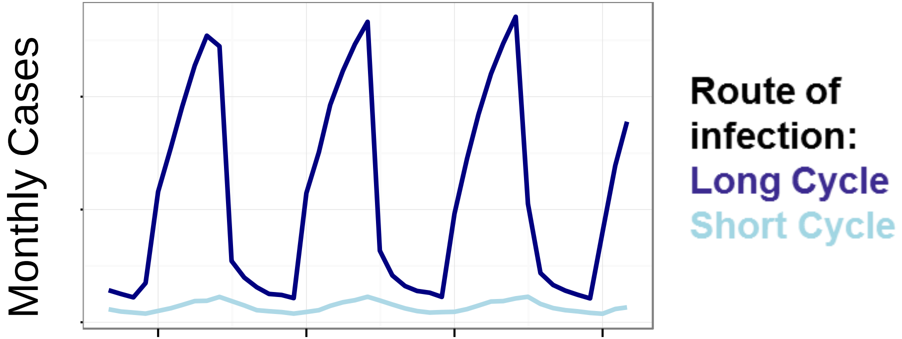
Age	Male	Female
10-19	0	1.4
20-29	0.68	3.3
30-39	2.0	6.0
40-49	2.5	7.2
50-59	3.0	8.4
60-69	3.7	9.7
70-79	6.5	9.7
80-90	6	7.8

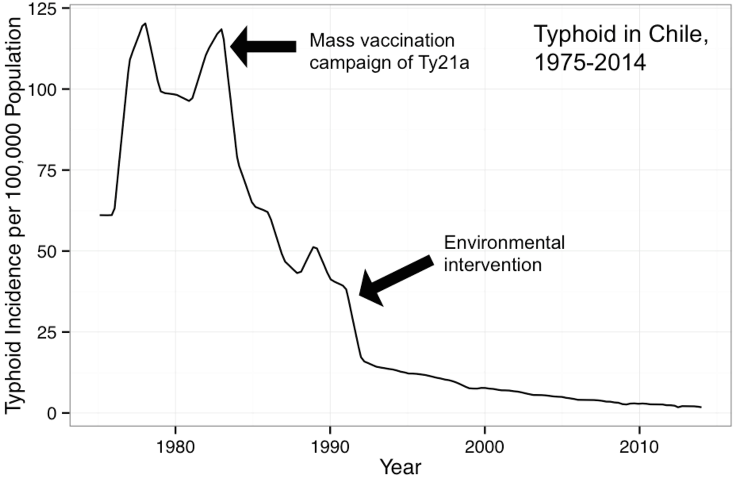
Age at Time of Typhoid	*Per cent Cases Resulting in Carriers*	
	Male	*Female*
Under 10	0.6	...
10–19	0.4	0.2
20–29	2.1	2.1
30–39	2.8	6.2
40–49	3.5	16.4
50–59	9.1	11.5
60 and over	6.2	9.4
	2.1	3.8
	2.9	

Ames, 1943

Impact of carriers in Santiago

- Acute transmission, chronic carriers both can trade-off to contribute to short cycle transmission in endemic period

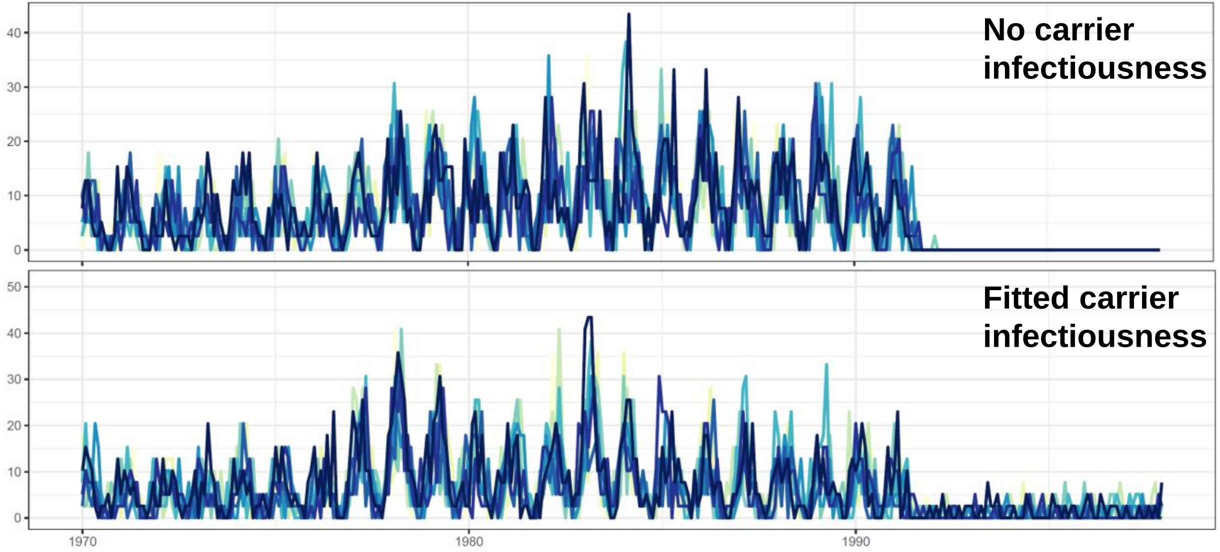




INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES

Impact of carriers in Santiago

- Acute transmission, chronic carriers both can trade-off to contribute to short cycle transmission in endemic period
- Extra data point: allows us to better estimate chronic carriage vs. acute transmission

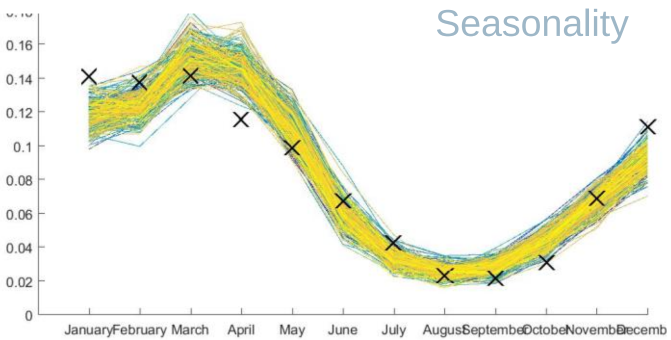


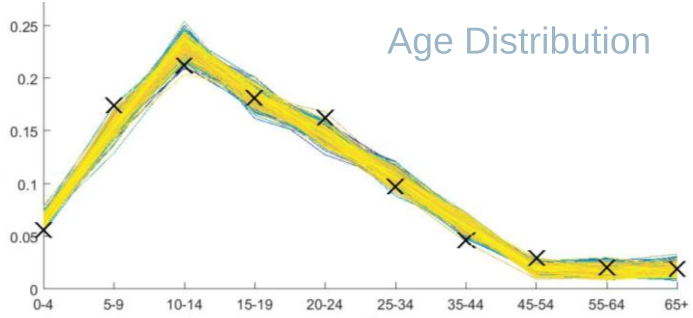
INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES

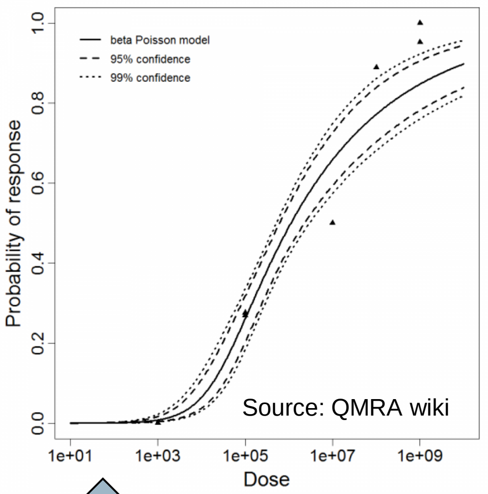
Multiple fits to Santiago data are possible within parameter uncertainty

Daily exposure rate: 0.5

Approximately 50% of population exposed daily







-- **Simulation**

X **Data**

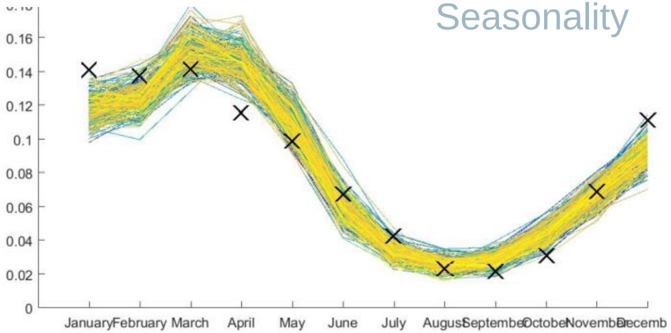
Daily exposure rate: 0.005

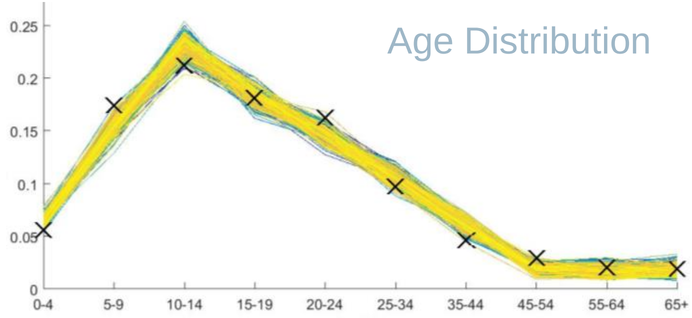
Approximately 0.5% of population exposed daily

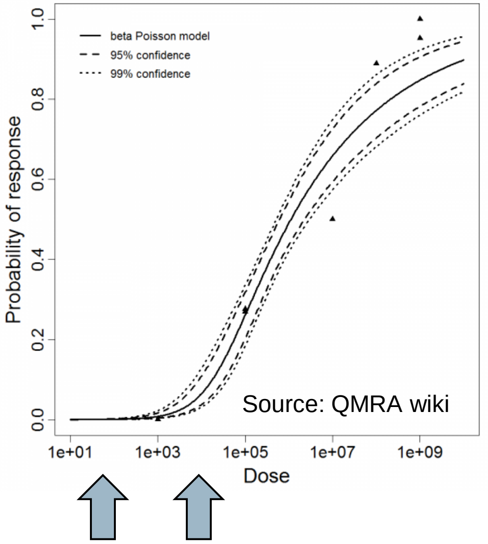
Multiple fits to Santiago data are possible within parameter uncertainty

Daily exposure rate: 0.5

Approximately 50% of population exposed daily





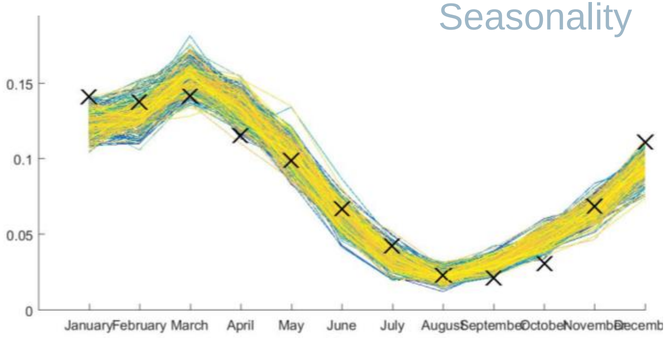


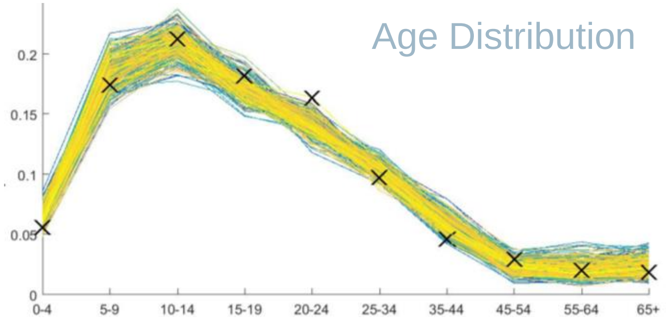
-- **Simulation**

X **Data**

Daily exposure rate: 0.005

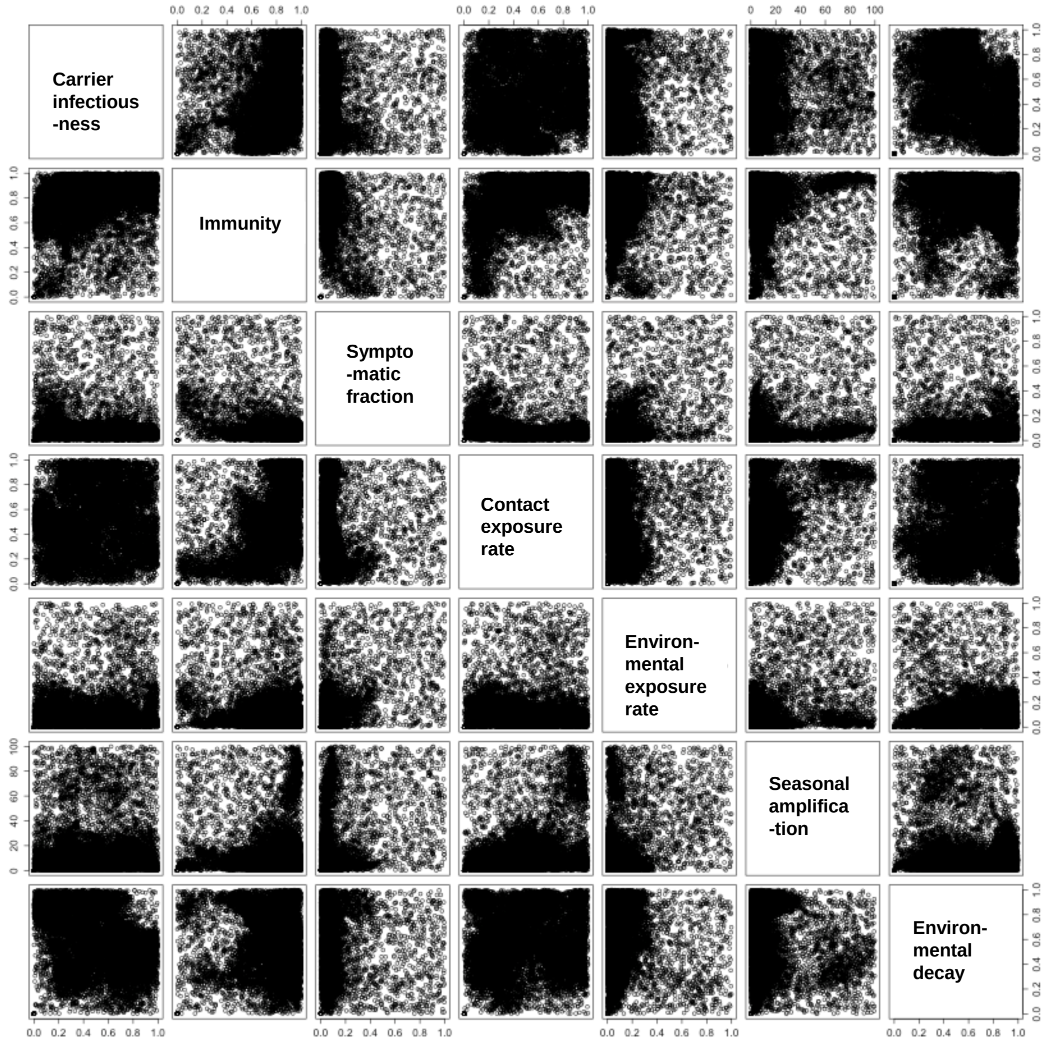
Approximately 0.5% of population exposed daily





History matching for unknown parameters

- Many parameter combinations can be fitted to data
- Automated methods to find best fit points across range of parameter unknowns
- Estimate error bounds due to parameter uncertainty for WASH/ vaccine intervention projections



Perspectives from modeling historical data

- Many model mechanisms for Santiago can be used in modern locations
- Age specific exposure, seasonality, need to be understood from site to site: data available?
- Even with many variables that are typically unknown in most settings (transmission route, chronic carriers burden and impact), we still have parameter unknowns that would affect uncertainty estimates for vaccination
- New tools will provide built-in error-bound estimates for vaccine impact due to parameter uncertainty

Thank you!

Santiago data sharing:

- Catterina Ferreccio
- Rosanna Lagos

UNIVERSITY OF MARYLAND

jgauld@intven.com

INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES®

Salmonella Typhi & *S.* Paratyphi isolates from pediatric enteric fever cases, Area Norte, Santiago, 2006-2015

	Casos <15 years		Annual mean population, age <15 yrs	Annual mean Typhi incidence, age <15 yrs/10^5	Annual mean Paratyphi B incidence, age <15 yrs/10^5
1982	***56****		27,305	227.1	
2006-10	***12***	***6***	185,930	0.64	0.32
2011-15	***5***	***0***	194,873	0.25	0

* This group included children from 6-17 years of age who received placebo enrolled in a field trial in Area Norte

The 18 cases of enteric fever in years 2006-2010 was higher than the 5 cases in years 2011-2015 (p=0.0089, corrected Chi square)