SCHOOL OF PUBLIC HEALTH
EPIDEMIOLOGY
UNIVERSITY OF MICHIGAN

MDHHS

Investigating spatiotemporal disease patterns with mathematical modeling

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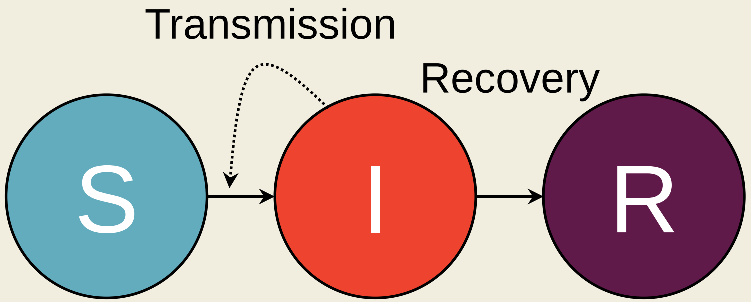
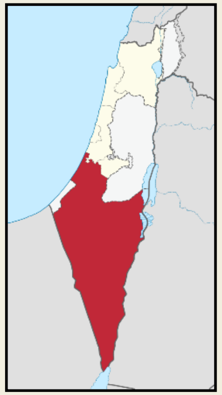
No conflicts of interest.

Outline



- What is mathematical modeling?
- Poliovirus outbreak in Israel



- Hepatitis A outbreak in Michigan

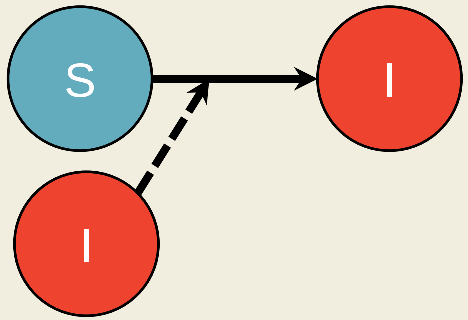
- In brief: COVID-19 epidemic in Michigan

Mathematical modeling can connect epidemiological theory to data.

Goal	Example question
Understand the disease processes	What's the incubation period of the coronavirus?
Make predictions	How many people will eventually be infected?
Examine counterfactuals	What would have happened if Wuhan hadn't been quarantined?
Select interventions	Should we close schools?

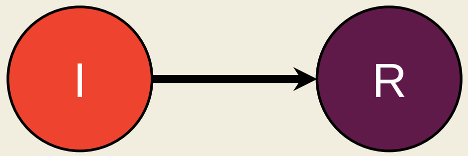
The fundamental disease processes are

Transmission



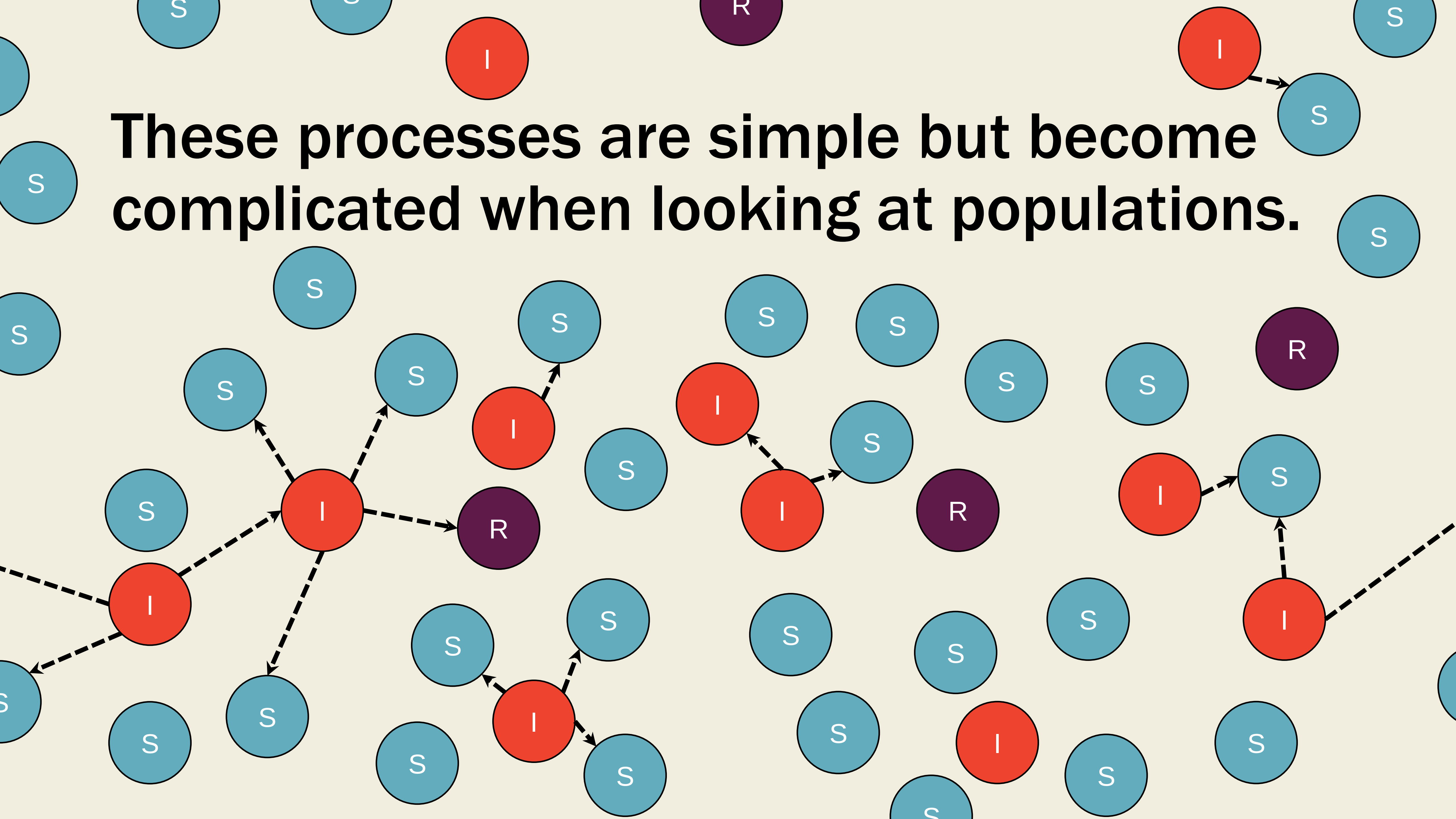
Susceptible people contact an infectious person and become infectious.

Recovery



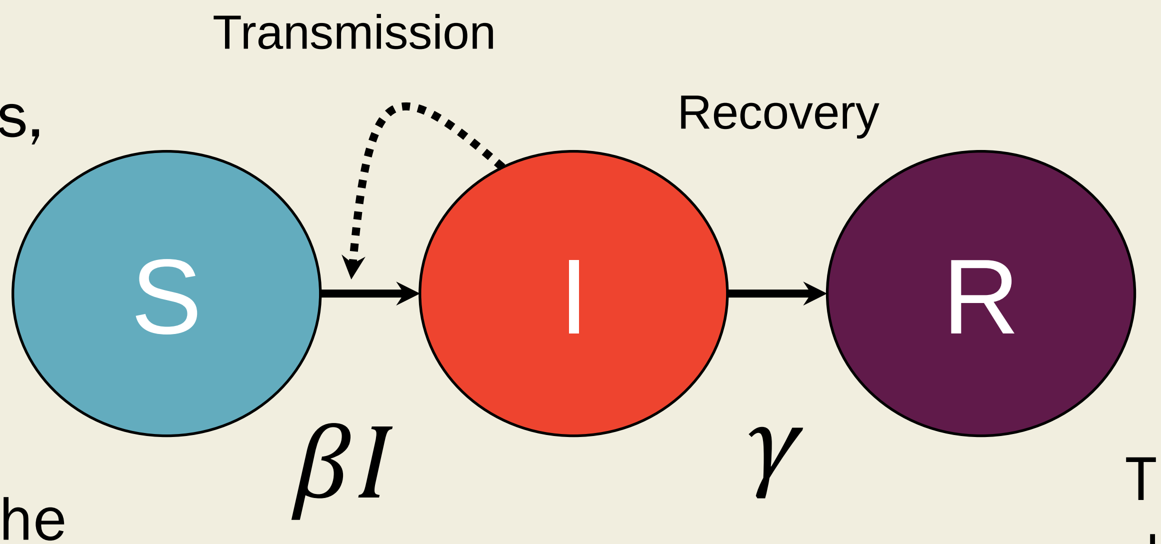
Infectious people eventually recover.

These processes are simple but become complicated when looking at populations.



We use simplifying assumptions to derive mathematical equations describing disease dynamics.

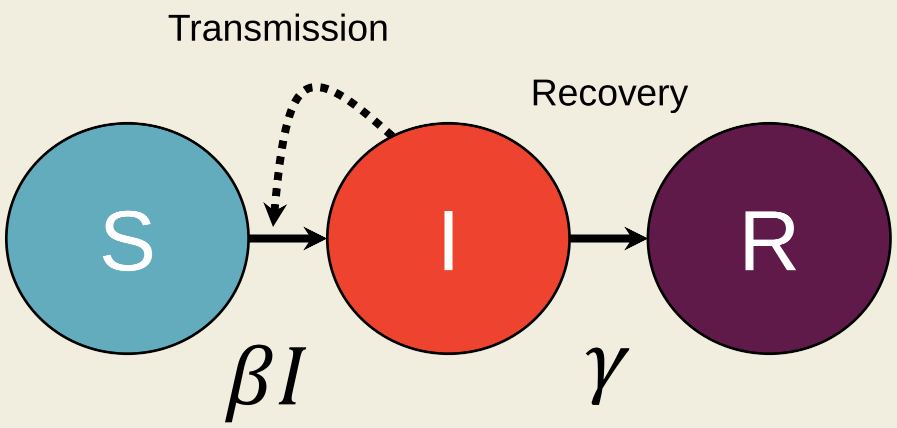
We track the fraction of people who are susceptible, infectious, or recovered.

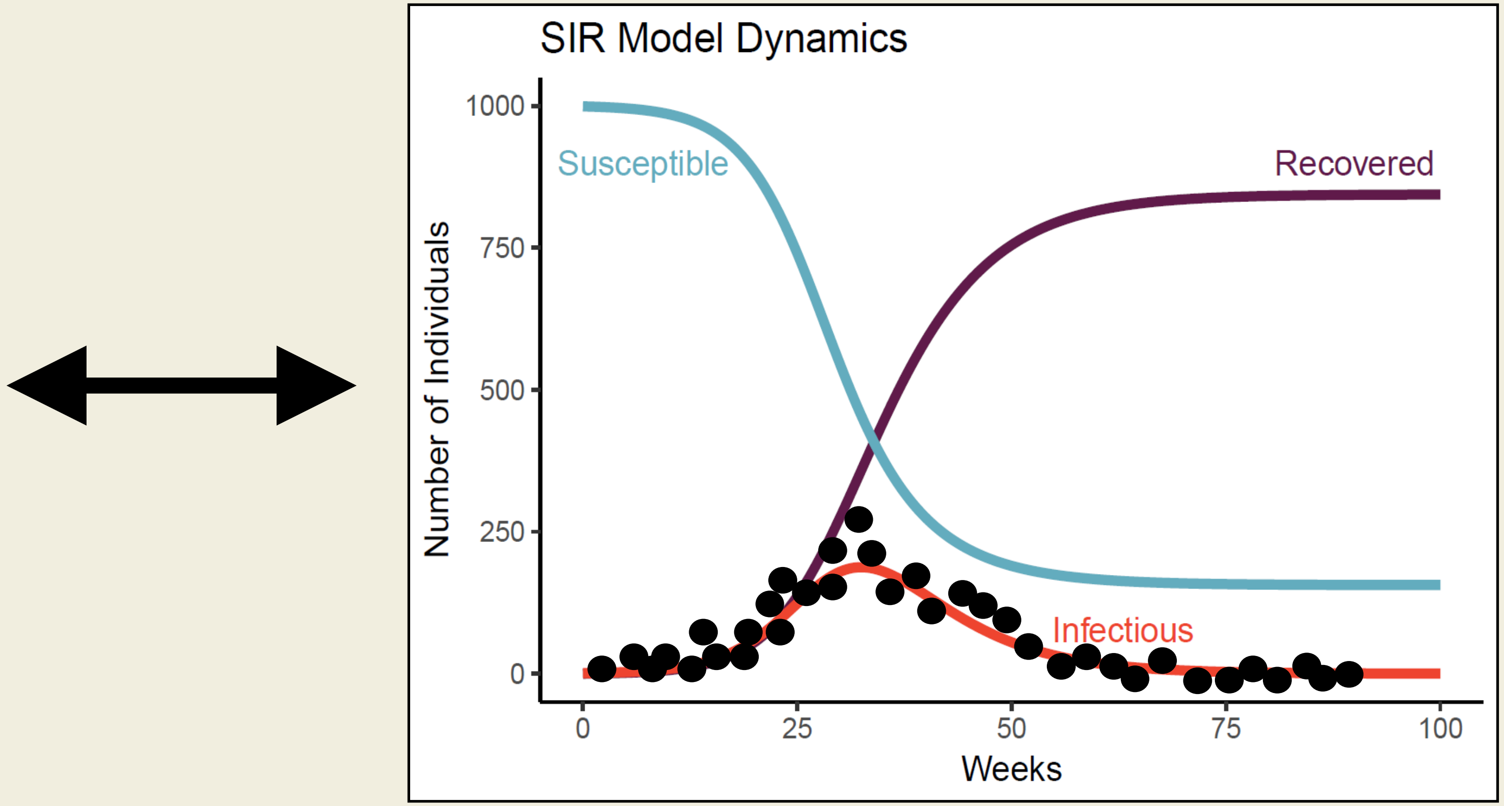


The rate of new cases depends on how fast the infection can spread (β) ***and*** on the fraction of people currently infectious.

The rate of recoveries depends on how fast the body clears the infection (γ).

We can see which disease properties best match up with available data.



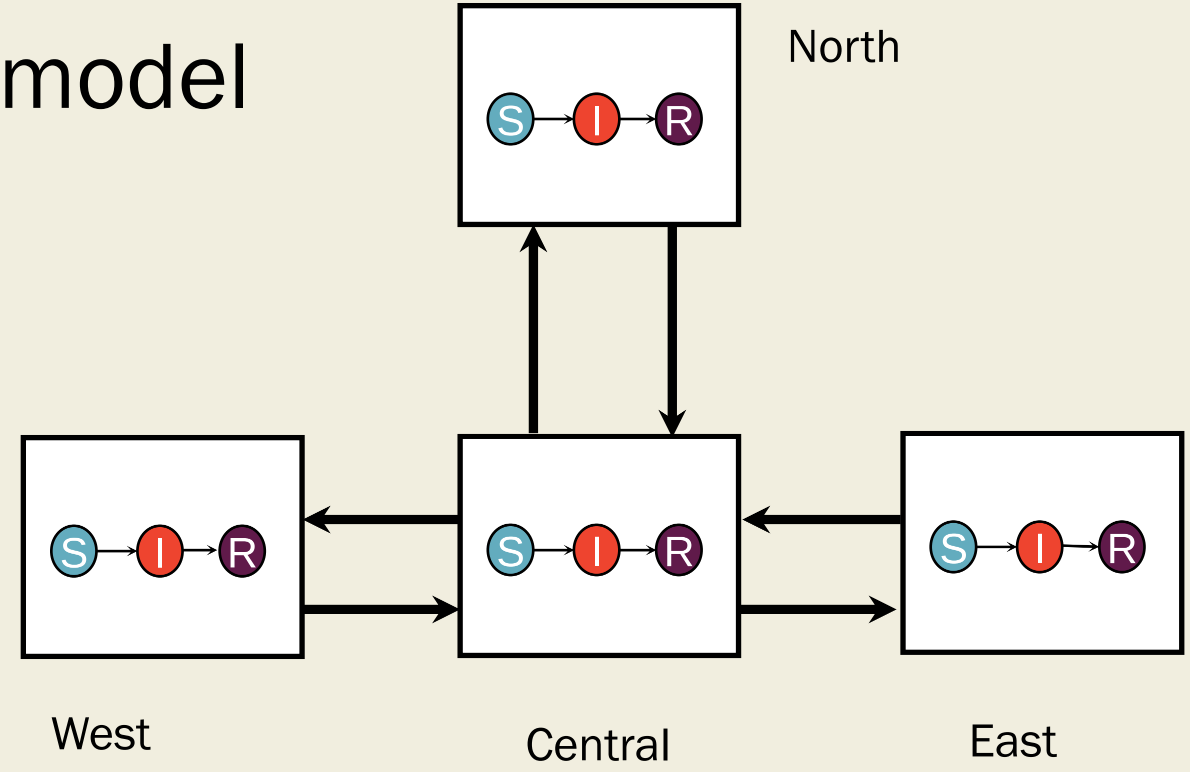


This general framework can be extended to include many other disease processes.

- Latent period
- Stage progression
- Birth & death
- Death from infection
- Subpopulations
- Environmental transmission
- Vector transmission
- Multiple disease strains
- Seasonality
- Behavior
- Interventions
  - Vaccination
  - Prophylaxis
  - Treatment
  - Quarantine

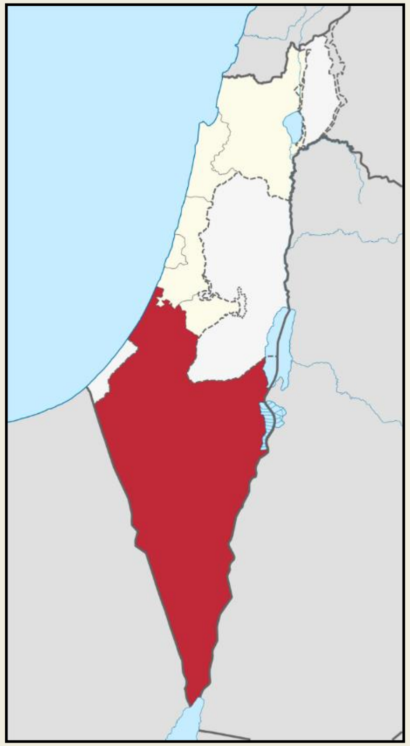
One way to model spatial dynamics is through interconnected populations

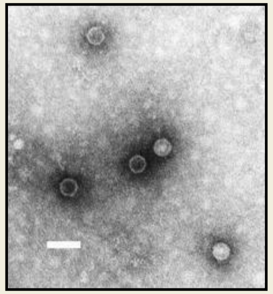
"Metapopulation" model



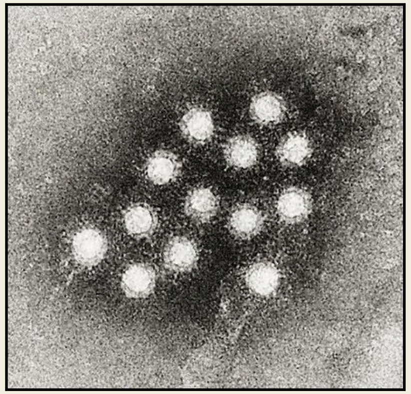
We’ll look at two examples of model exploring spatiotemporal patterns of disease.

Poliovirus in Israel





Hepatitis A in Michigan



Environmental pathogen surveillance of wastewater

Time-varying viral shedding intensity in the 2013 silent polio outbreak in Israel

Acknowledgements

Collaborators

- Joe Eisenberg, Michigan
- Marisa Eisenberg, Michigan
- Jim Koopman, Michigan
- Connor Pomeroy, Michigan
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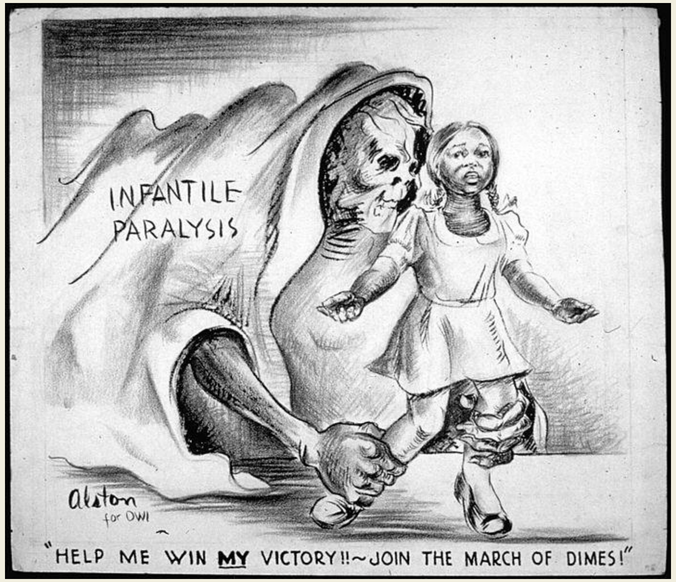
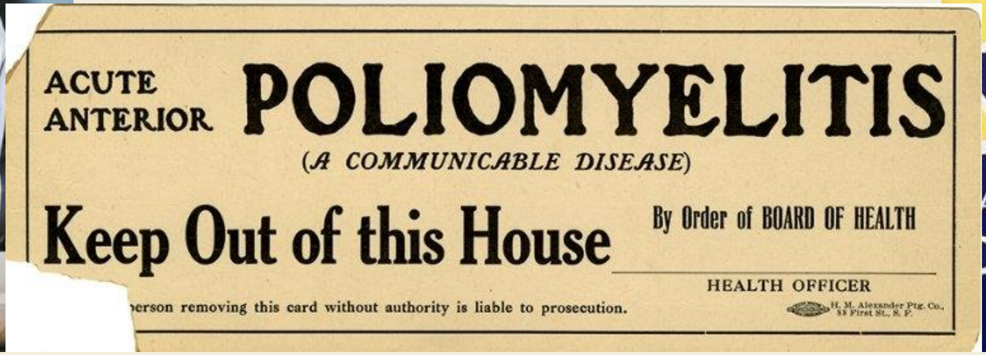
- Musa Hindiyeh, Central Virology Lab, Israel
- Yossi Manor, Central Virology Lab, Israel
- Itamar Grotto, Ministry of Health, Israel

Funded by

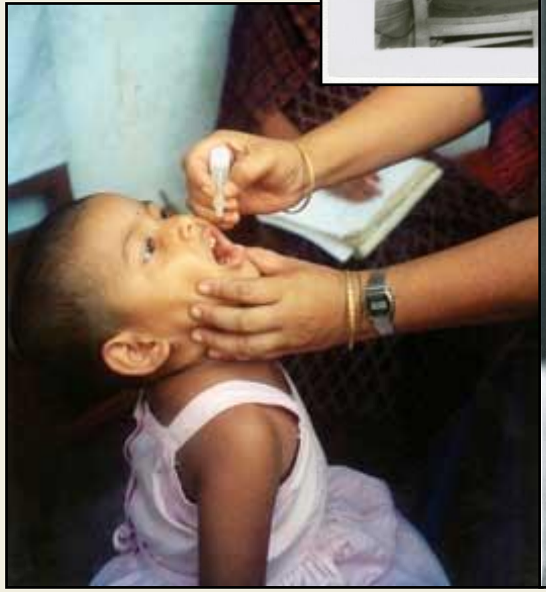
Polio was once a major childhood disease.

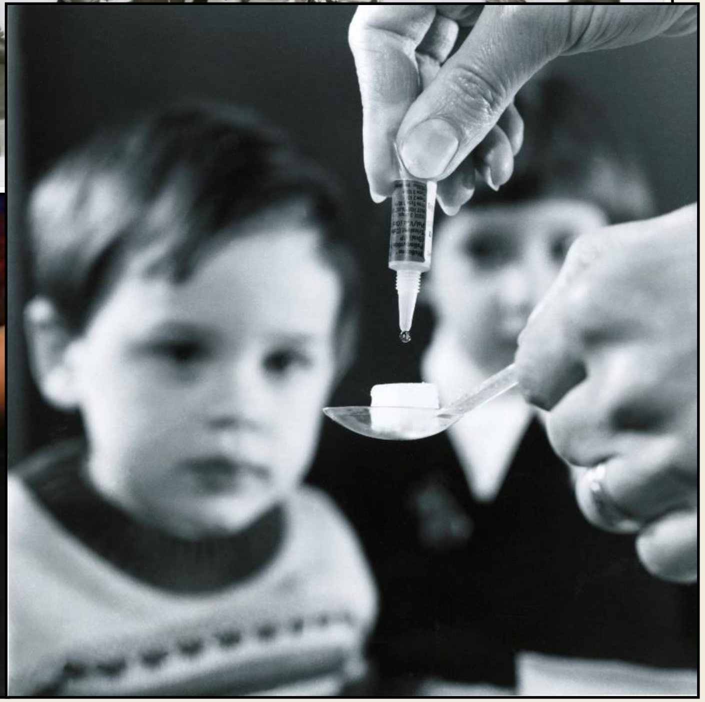




Polio has been targeted for global eradication.

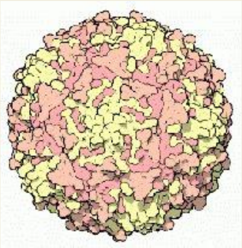
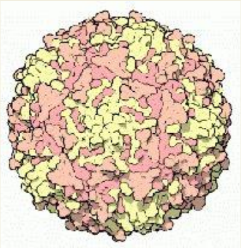
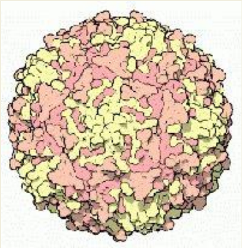
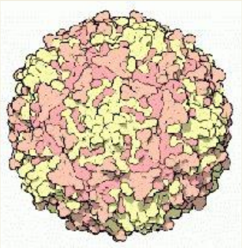
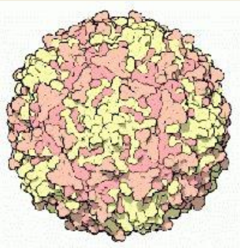
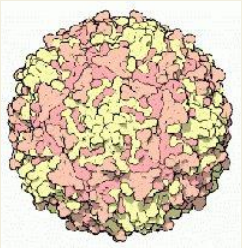
- Two vaccines
  - Inactivated polio vaccine (IPV) prevents paralysis (humoral immunity) but not infection
  - Oral polio vaccine (OPV) creates gut immunity and is transmissible, with the potential to regain virulence
- Wild poliovirus has nearly been eliminated
  - Endemic in Afghanistan, Pakistan



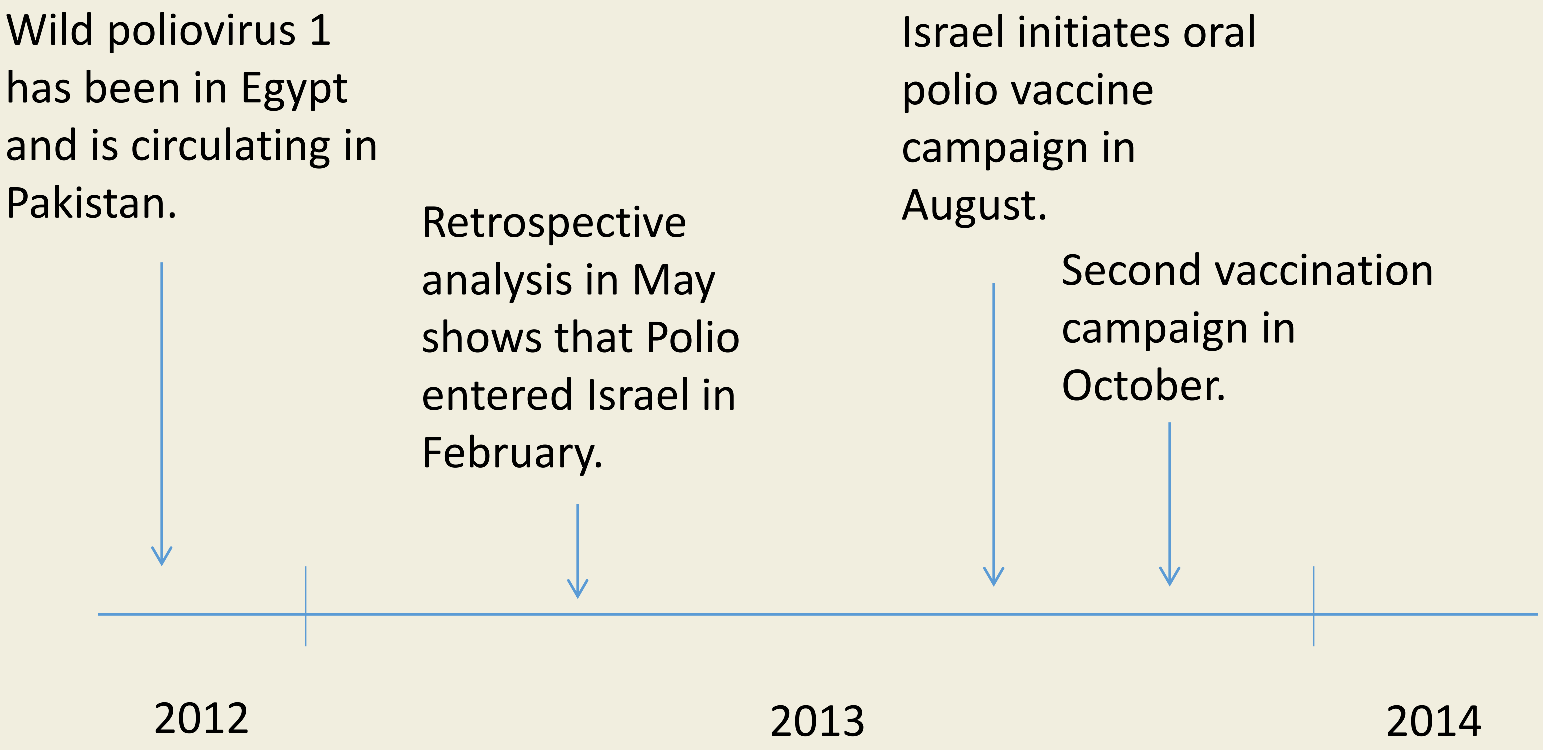


But, polio has been difficult to completely eradicate.

- Fecal-oral transmission route
- Symptoms (paralysis) are rare, allowing for silent circulation
- Vaccine-strains have mutated to regain virulence and cause outbreaks
- Waning immunity may extend periods of risk beyond what was previously thought

In 2013, Israel experienced an unexpected outbreak of polio.



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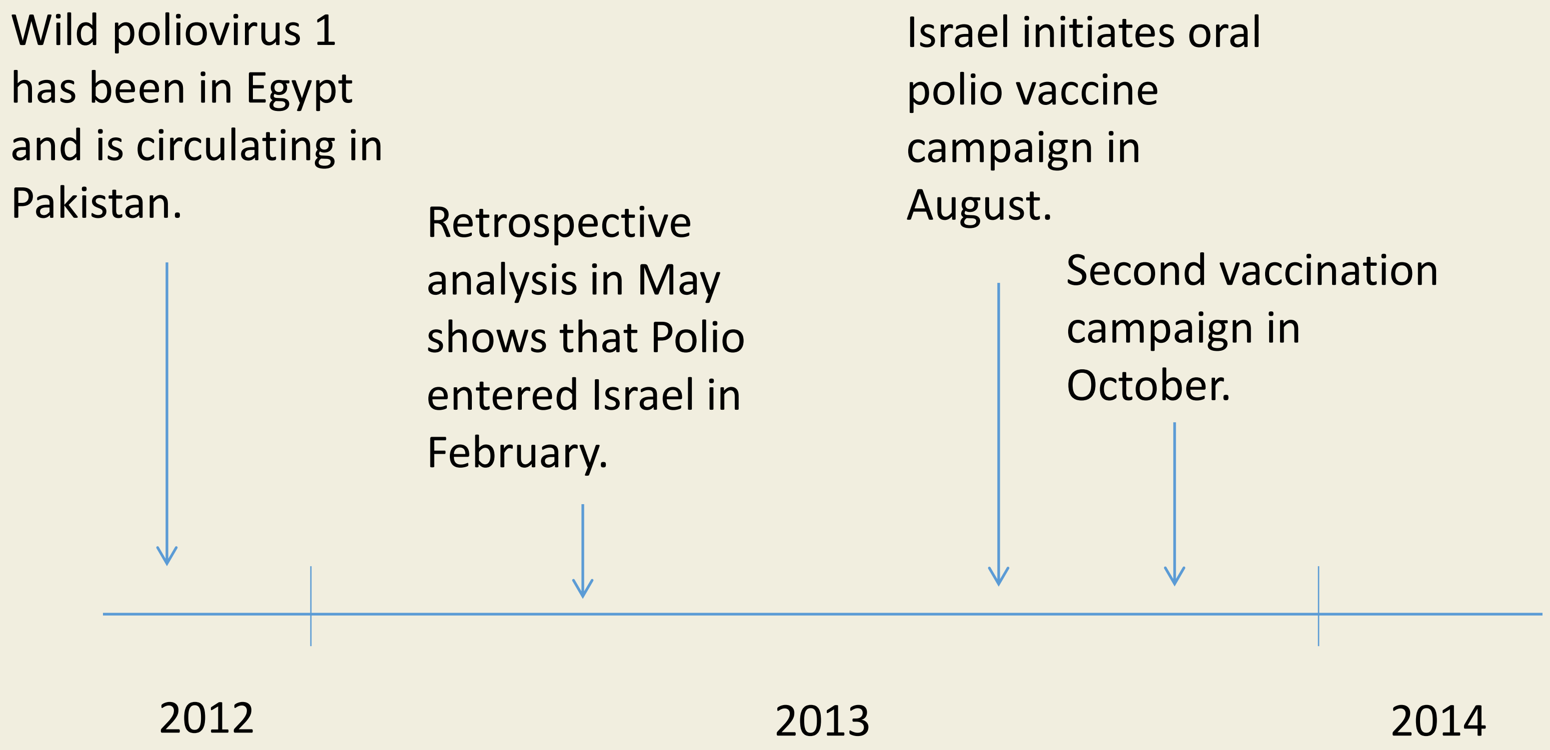
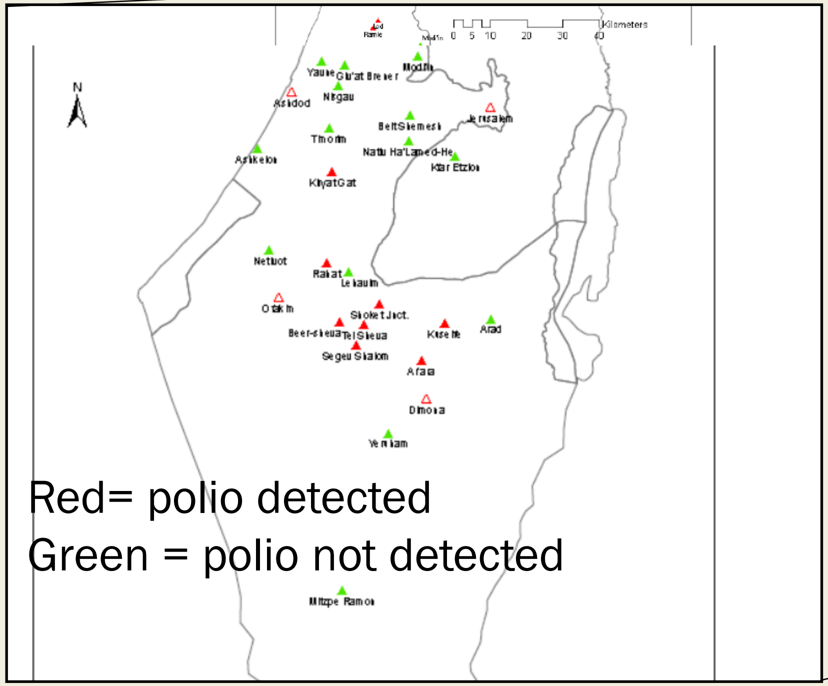
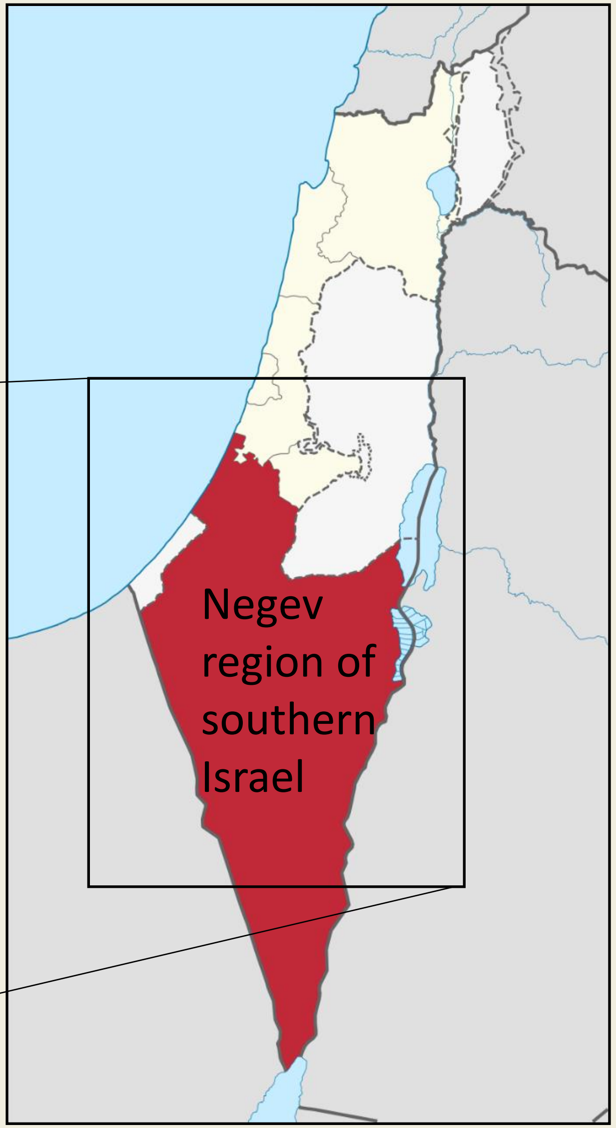


But, fortunately, no one was paralyzed. How did we know the outbreak was happening?

Environmental surveillance (ES) detected the the 2013 Israel outbreak

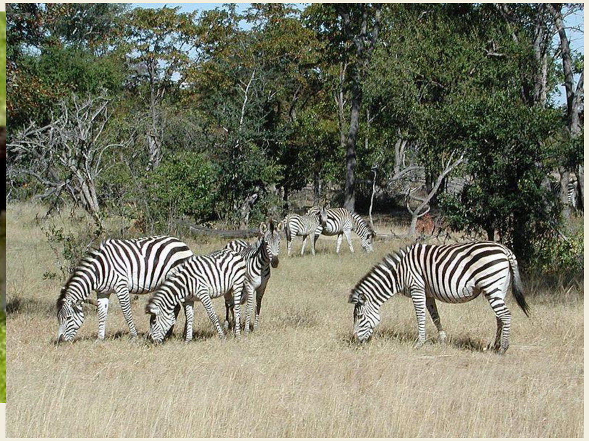
- Robust ES network in place since 1989
- Quantitative, direct, real-time PCR (665 samples)
- We analyze ES from 7 sewage plants or trunk lines





Environmental surveillance (ES) can enhance disease surveillance and control.

Wastewater



Wildlife feces

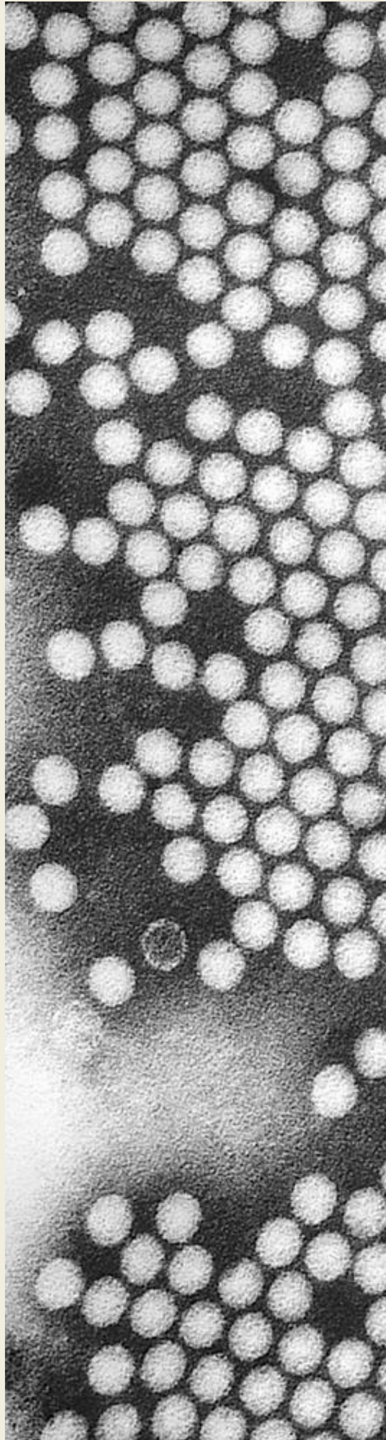
Aerosols

ES is aiding in global polio eradication.

- Acute flaccid paralysis (AFP) surveillance is standard for detecting circulating polio
- But transmission can be silent, especially in regions with high IPV coverage
- ES can detect circulation much earlier

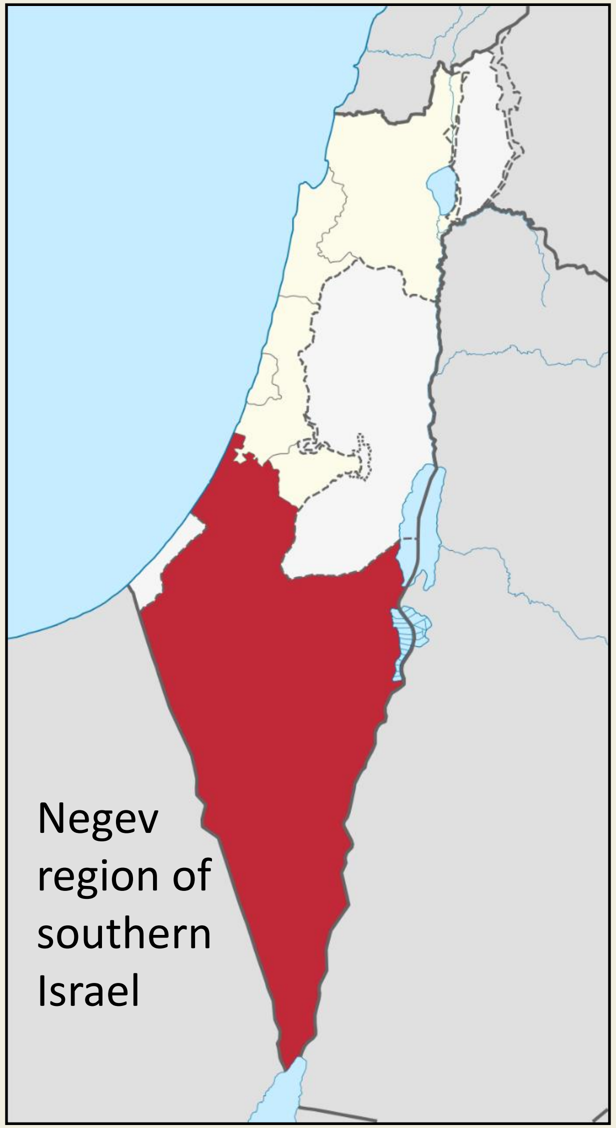



Source: WHO



The Israel outbreak was primarily in Bedouin children under 10.

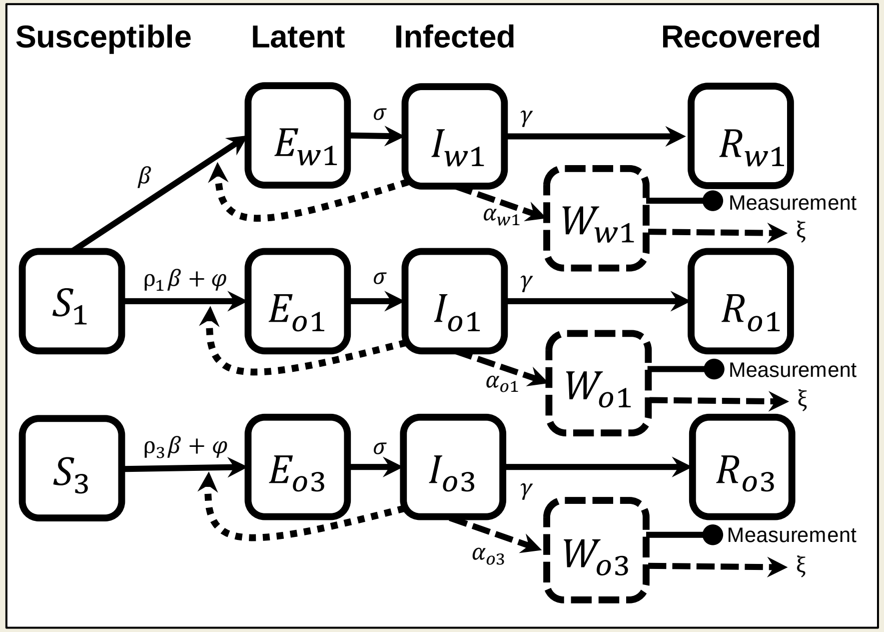
- Bedouins people live in cities, recognized communities, and unrecognized communities in Southern Israel.
- Sanitation conditions vary dramatically in these communities.



Credit: Mohamad Torokman/ REUTERS

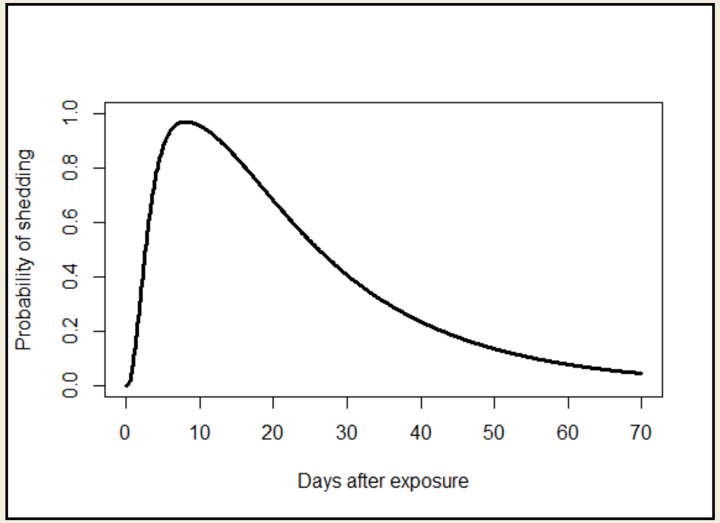
We don’t know how many people were infected, just the concentration of polio in sewage.

- Infected people shed polio into sewage.
- Poliovirus at each site is diluted by a different volume of sewage.
- There are three strains of polio circulating
  - Wild type virus (strain 1)
  - Vaccine type virus (strain 1)
  - Vaccine type virus (strain 3)



But, how do we know how much virus people are shedding? Doesn't it change over the infectious period?

Probability of shedding as a function of time since exposure



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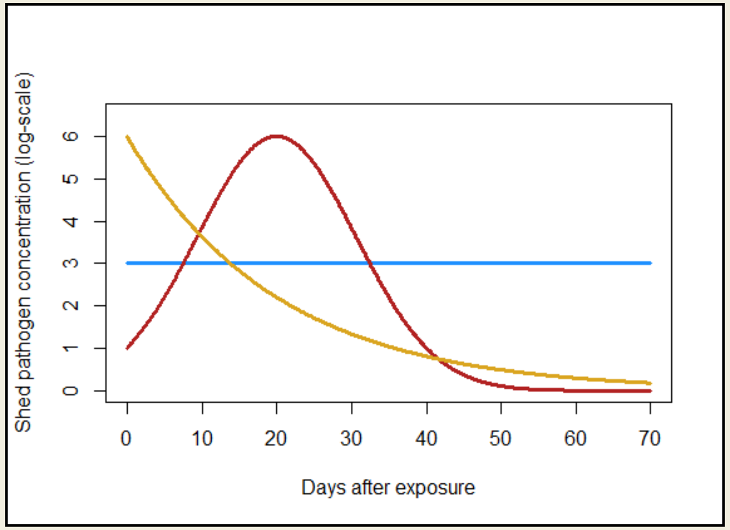
Concentration of pathogens shed if shedding, as a function of time since exposure



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Total pathogen load observed in ES

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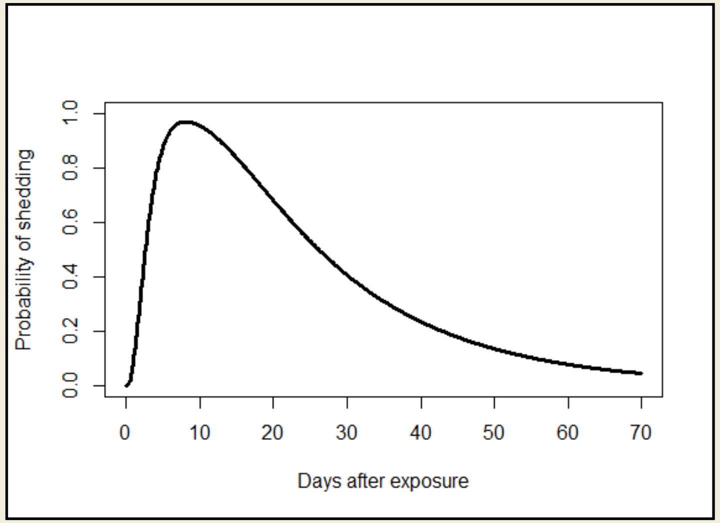

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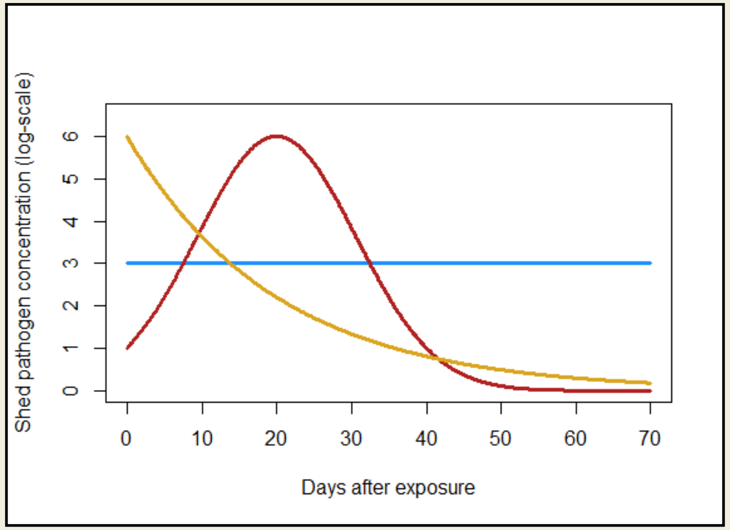

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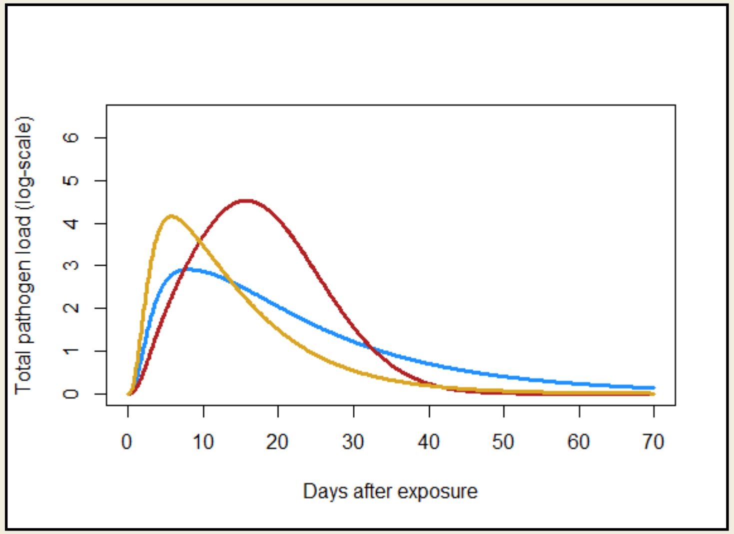

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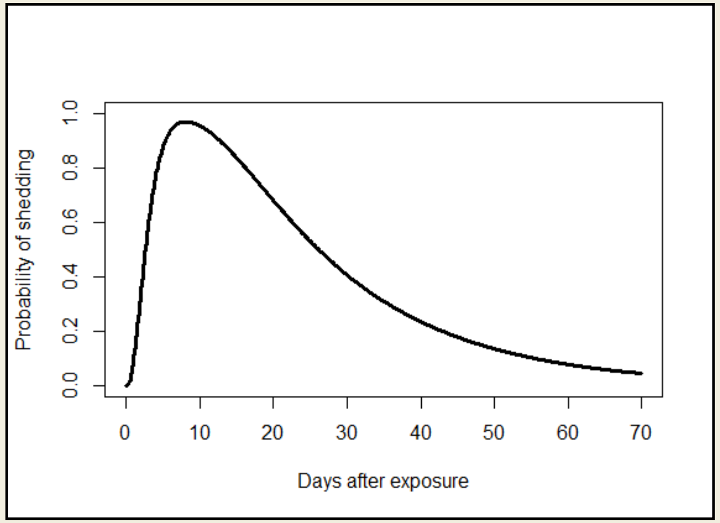

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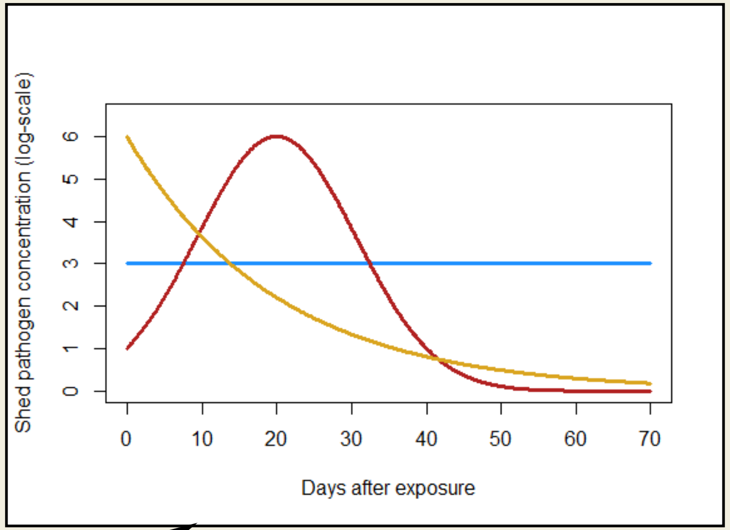

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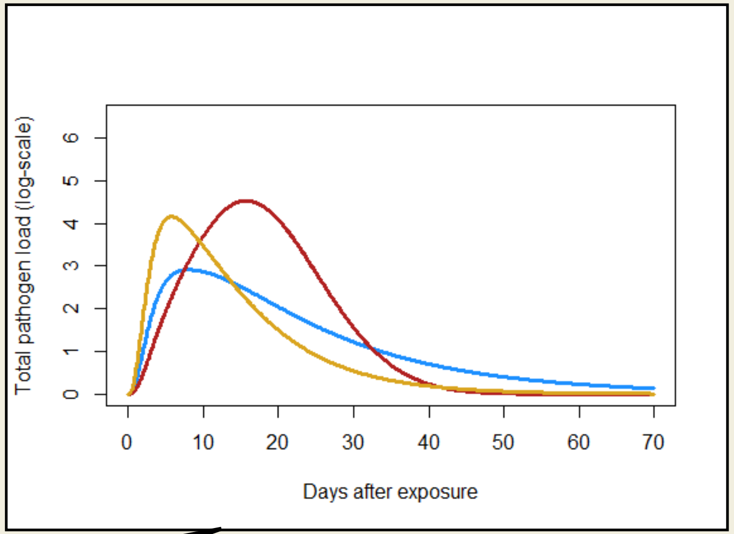
Total pathogen load observed in ES



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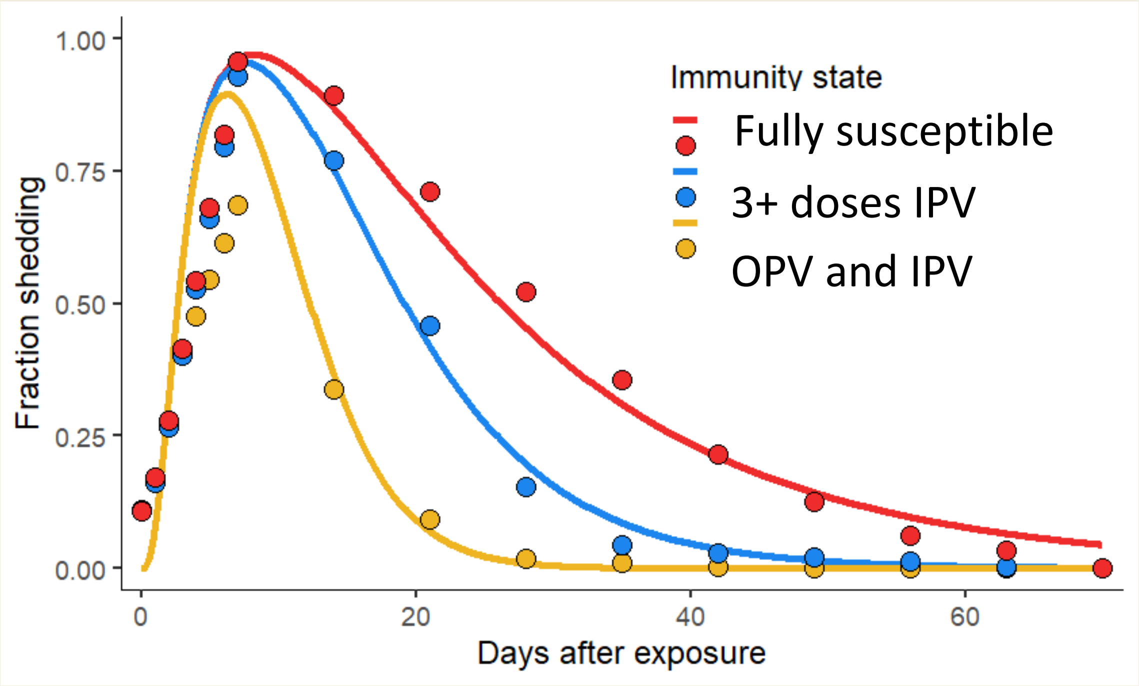
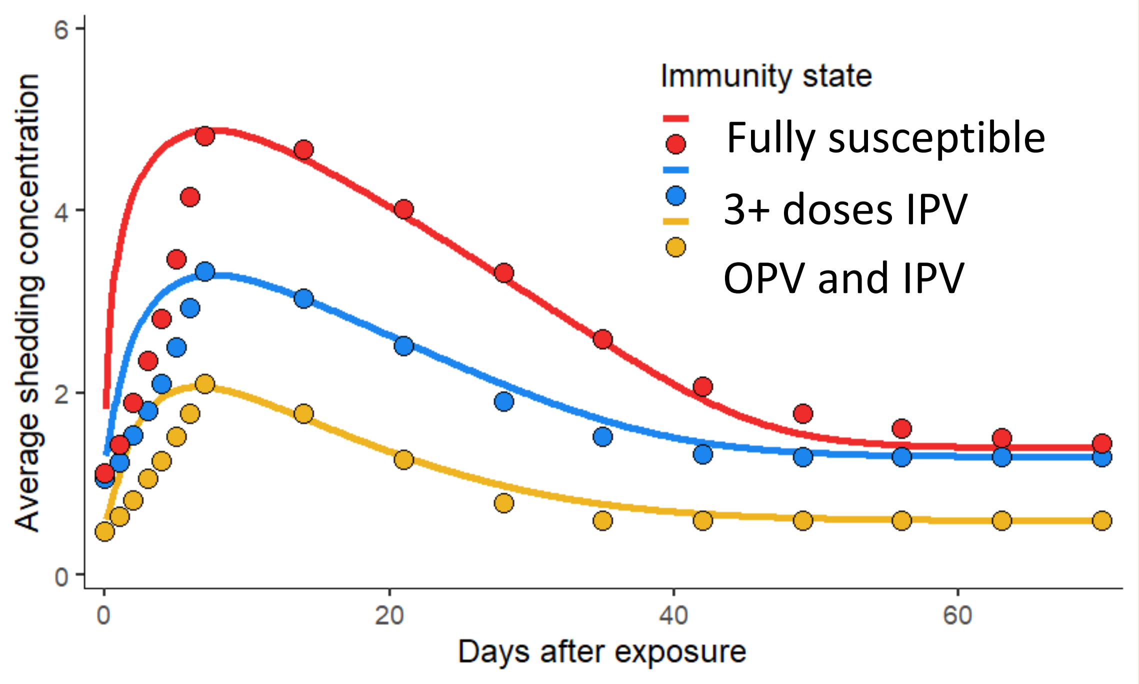
We create a flexible model framework for shedding for different immunity states based on previous expert elicitation.

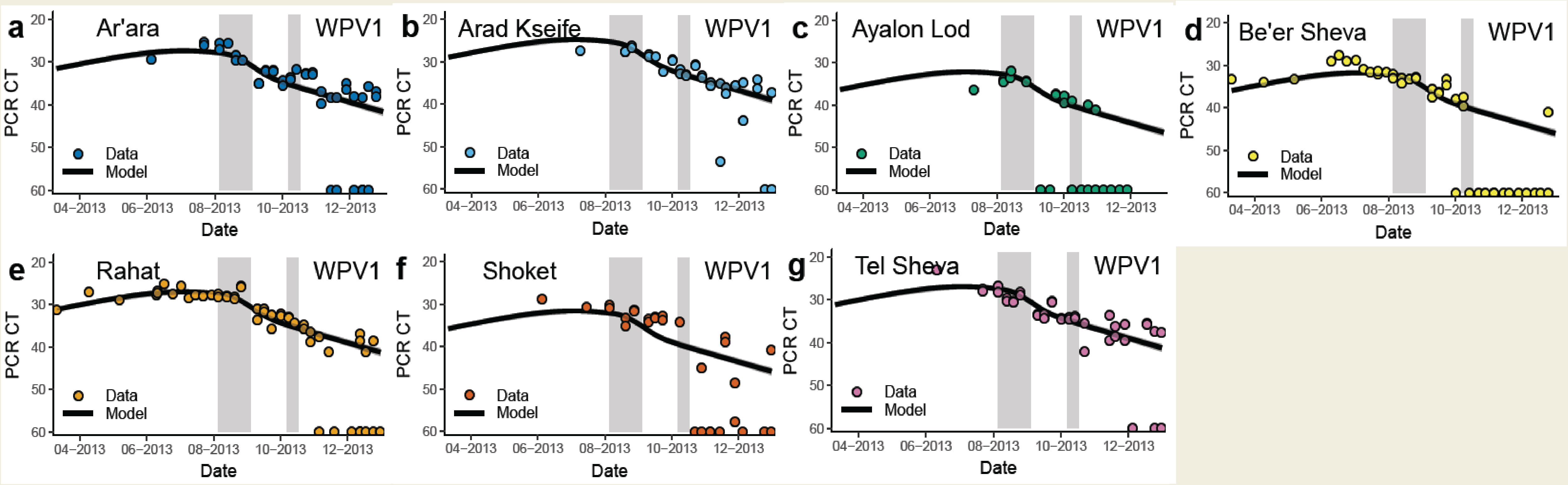
Fraction of population shedding



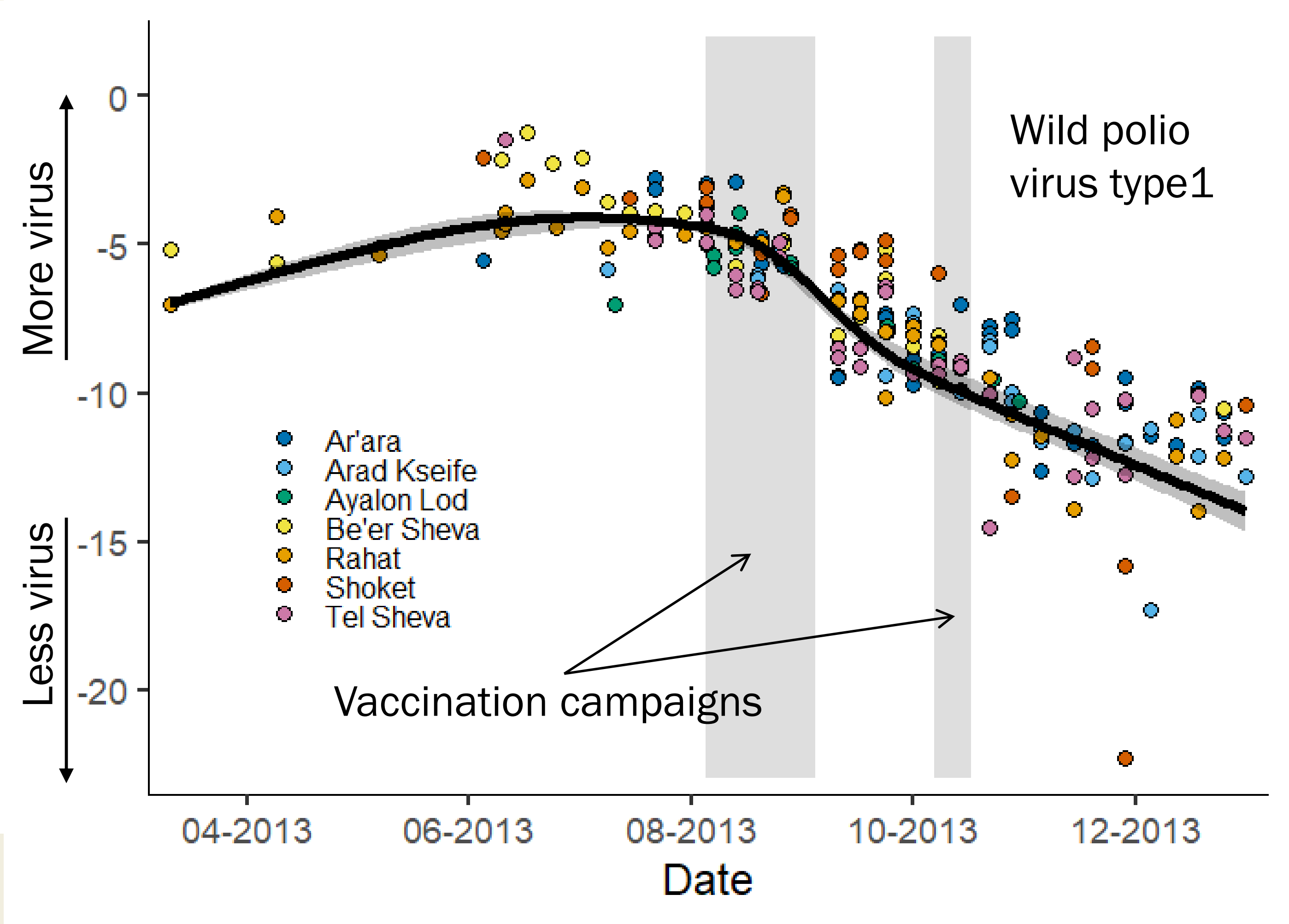
Average shedding concentration

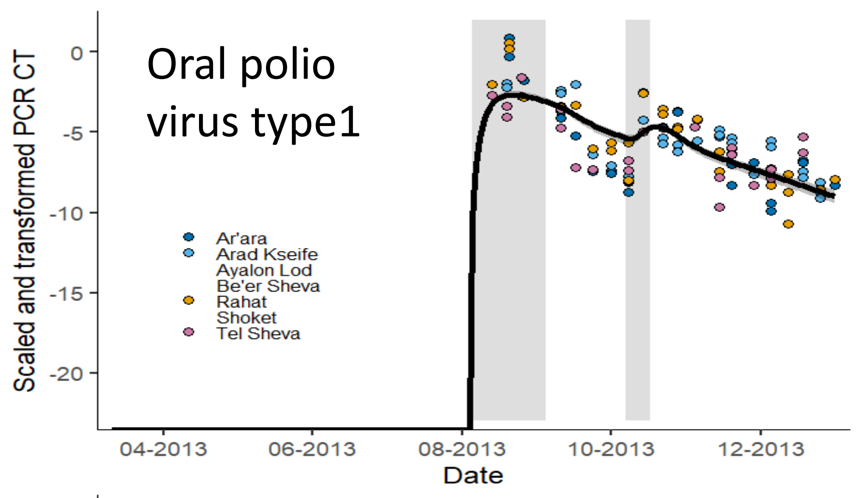


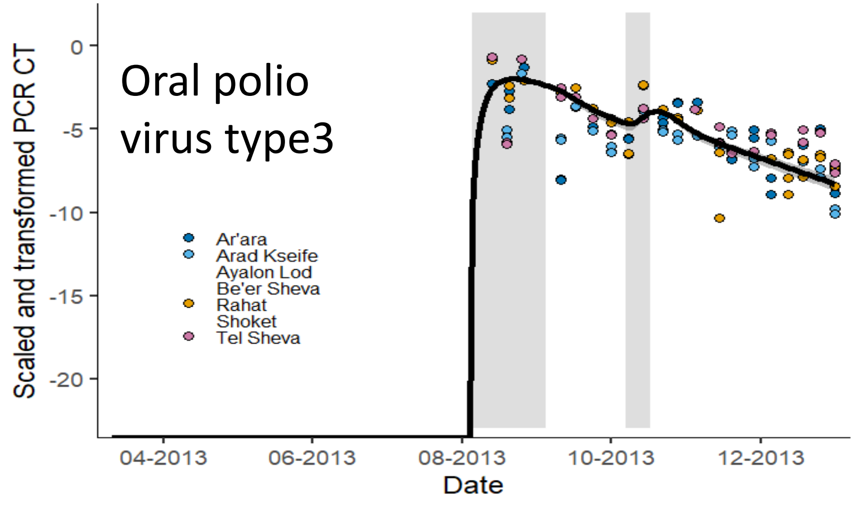
We use this model fit the data at each of 7 sites in Southern Israel.



How did the virus spread across the south? Essentially, the outbreaks happened in parallel.







What does the model tell us?

- The data are consistent with shedding intensity changing over time.
- Estimated recovery time is longer than expert opinion would have predicted for the likely immune status of the population.
  - Are we wrong about the effect of vaccination on recovery time?
- There were differences in dynamics in the cities with different ethnic make-up.
  - May indicate comparatively little contact between Jewish and Bedouin under-10-year-olds.

Conclusions

- Environmental surveillance has a lot of potential to inform public health
- ES signal is a jumble of who is shedding when and how much
- We’re limited in our understanding of time-varying shedding and how to model it
- More basic science on both shedding and environmental persistence will help increase ES usefulness

The impact of vaccination in controlling the hepatis A outbreak

Spatiotemporal patterns of the Michigan outbreak, 2016–18

This project has been a collaboration between UM and MDHSS.

- UM co-authors
  - Joseph Eisenberg
  - Jonathon Zelner
  - Marisa Eisenberg
- MDHSS co-authors
  - Lynsey Kimmins
  - Macey Ladisky
  - Jim Collins

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  - Jeremy Kuo
  - Robert Swanson
  - Jevon McFadden
  - Sarah Davis
  - Cole Burkholder
  - Monique Foster

- Funded by

MIDAS

Funded by the National Institutes of Health

Michigan experienced an outbreak of hepatitis A over the last several years.

Hep A cases soar to 10 times normal in region

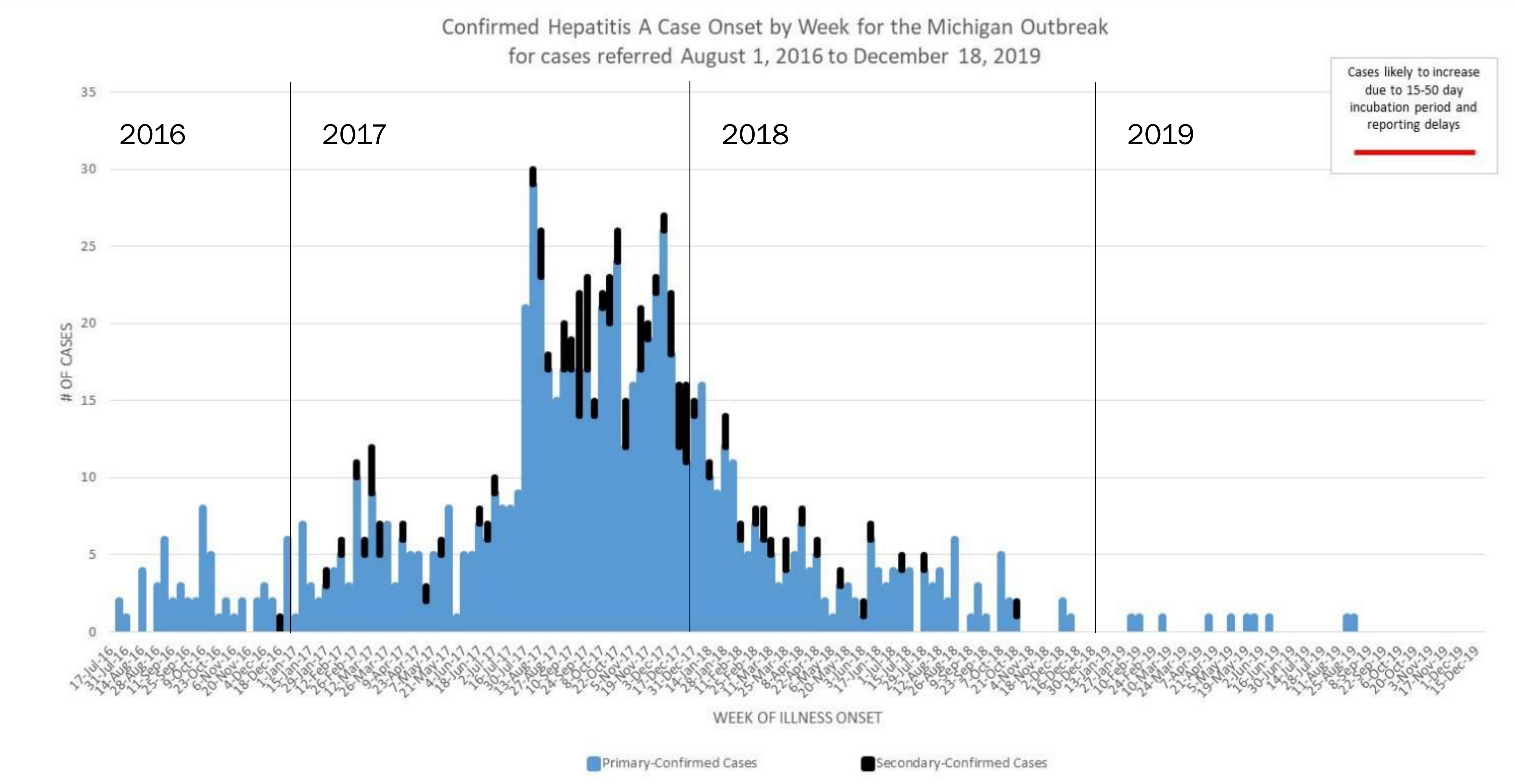
Sarah Rahal, The Detroit News   Published 12:10 a.m. ET Dec. 11, 2017 | Updated 11:36 a.m. ET Dec. 11, 2017

30 Dead, 920 Sickened In Michigan Hepatitis A Outbreak, According To Health Dpt.

WWJ NEWS
SEPTEMBER 20, 2019 - 2:38 PM

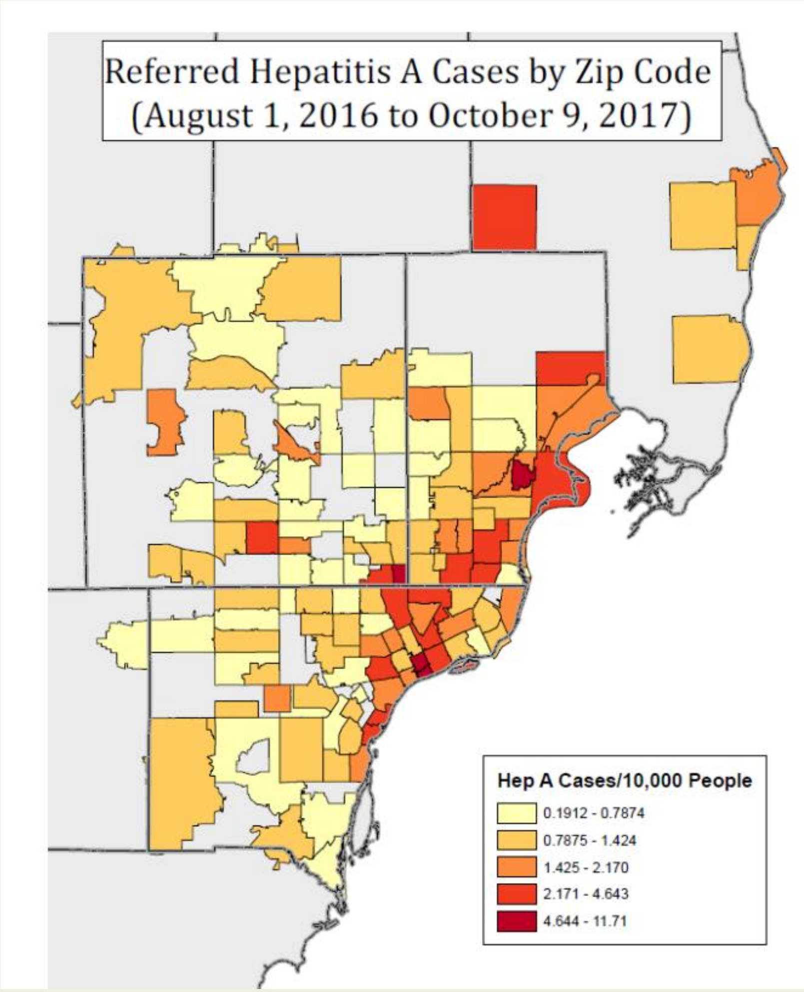
As Michigan deals with hepatitis A outbreak, vaccine supplies run low

By SARAH CWIEK • NOV 23, 2017



Source: MDHHS

The outbreak spread outward from Southeast Michigan.



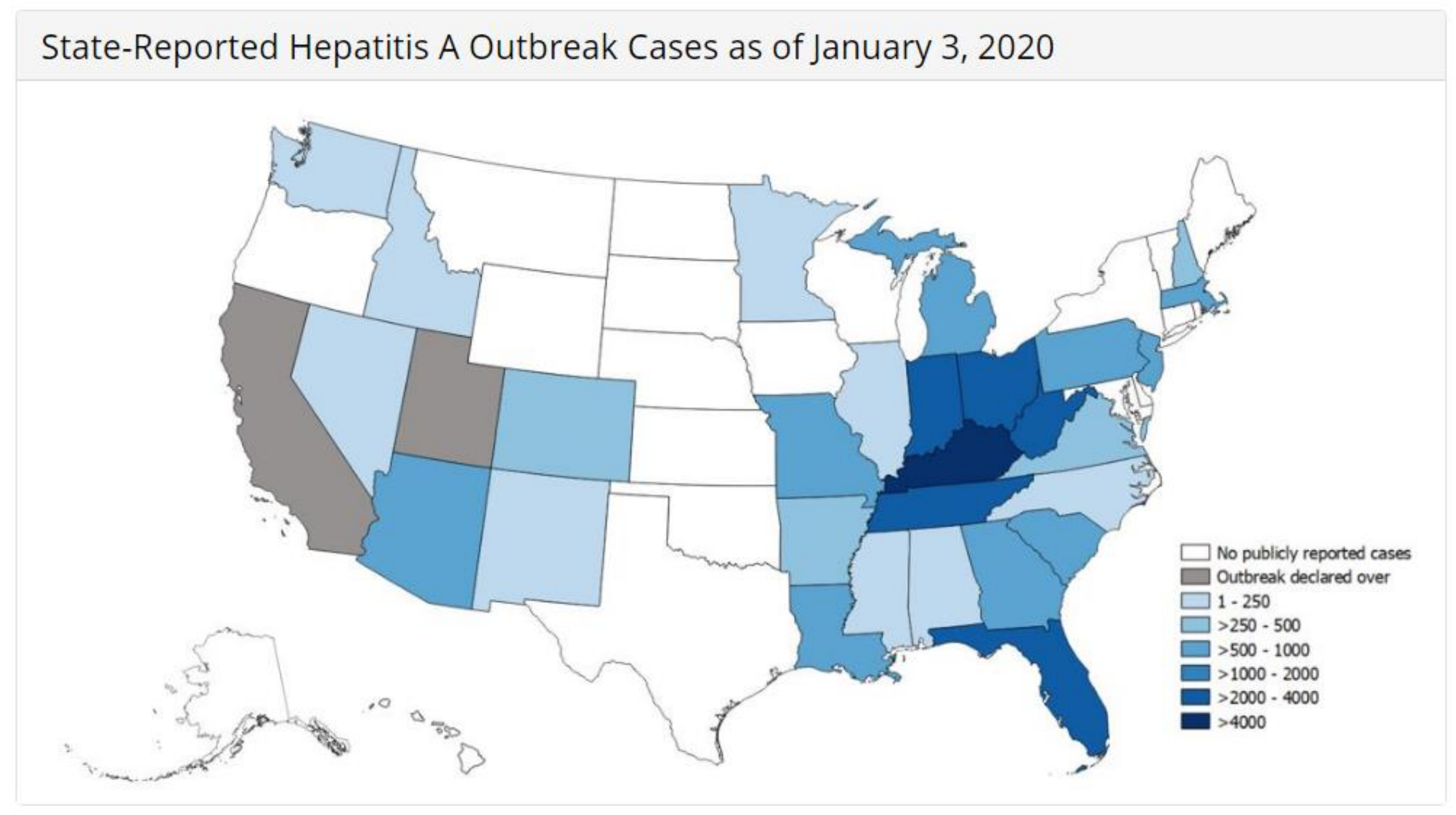
Source: Detroit Health Department

Source: US Census

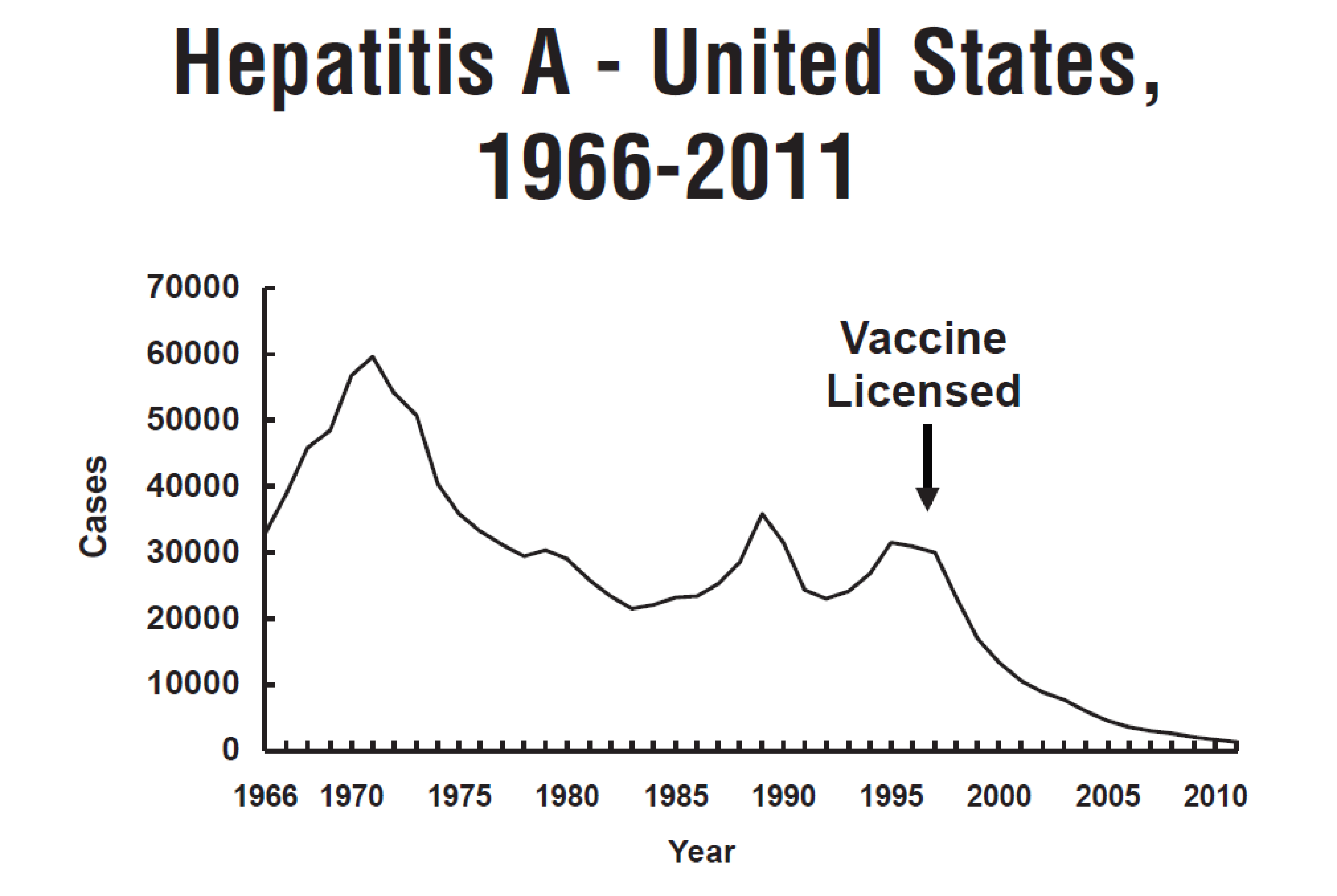
The Michigan outbreak is one of 30 states in the US with a recent or ongoing outbreak.

As of January 3, 2020:

Cases: 29,804
Hospitalizations: 18,143 (61%)
Deaths: 302 (1.0%)



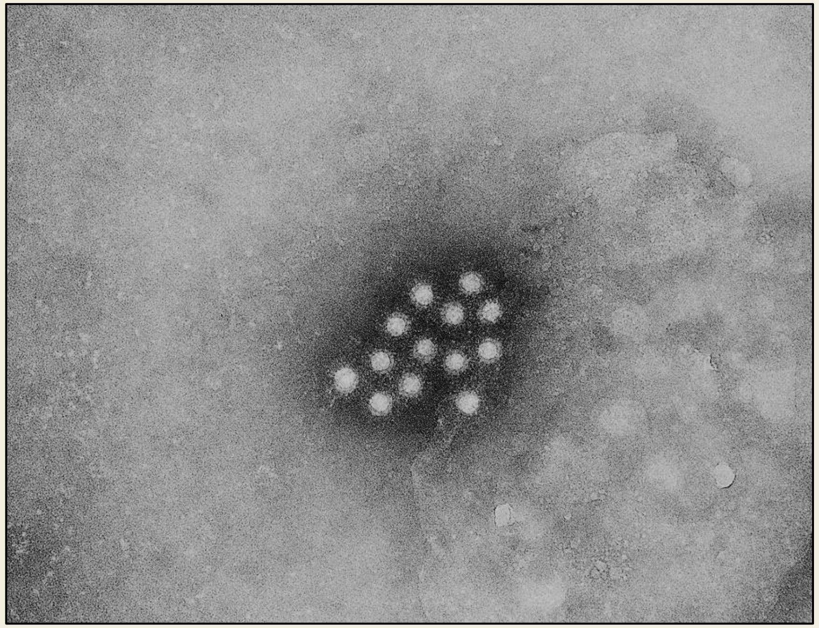
Incidence of hepatitis A reached historic lows after vaccines were introduced in 1996.



Why are these outbreaks happening?

Hepatitis A

- Viral infection of the liver
- Symptoms, including jaundice, occur in about 75% of adults
- Clinical illness usually lasts less than 2 months
- Fecal-oral transmission route



Hepatitis A virus. Source: CDC

Jaundice from hepatitis A infection. Source: CDC

Previous outbreaks were largely foodborne. These new outbreaks are driven by person-to-person contact.

- Highest risk groups
  - People who use drugs (injection or non-injection)
  - People experiencing unstable/transient housing or homelessness
  - Men who have sex with men (MSM)
  - People who are or recently were incarcerated
  - People with chronic liver disease (cirrhosis, hepatitis B, or hepatitis C)

In Michigan, many cases were substance users.

High-risk indicators	% (N)
None reported (includes loss to follow-up)	34.2% (311)
Substance use	46.9% (427)
Non-IV only	18.9% (172)
IV only	7.8% (71)
Both	17.4% (159)
Unknown	2.7% (25)
History of hepatitis B/C	25.6% (233)
Homelessness/transient housing	12.5% (114)
Institutionalized	10.9% (100)
Men who have sex with men	8.7% (79)

Includes 18% lost to follow-up

25.2% injection drug use

Much lower than in outbreaks in California and other states

Vaccination, including at public clinics, increased in 2017–18.

Detroit targets hepatitis A outreach: "What we're trying to do is reach people where they are"

By SARAH CWIEK • DEC 19, 2017

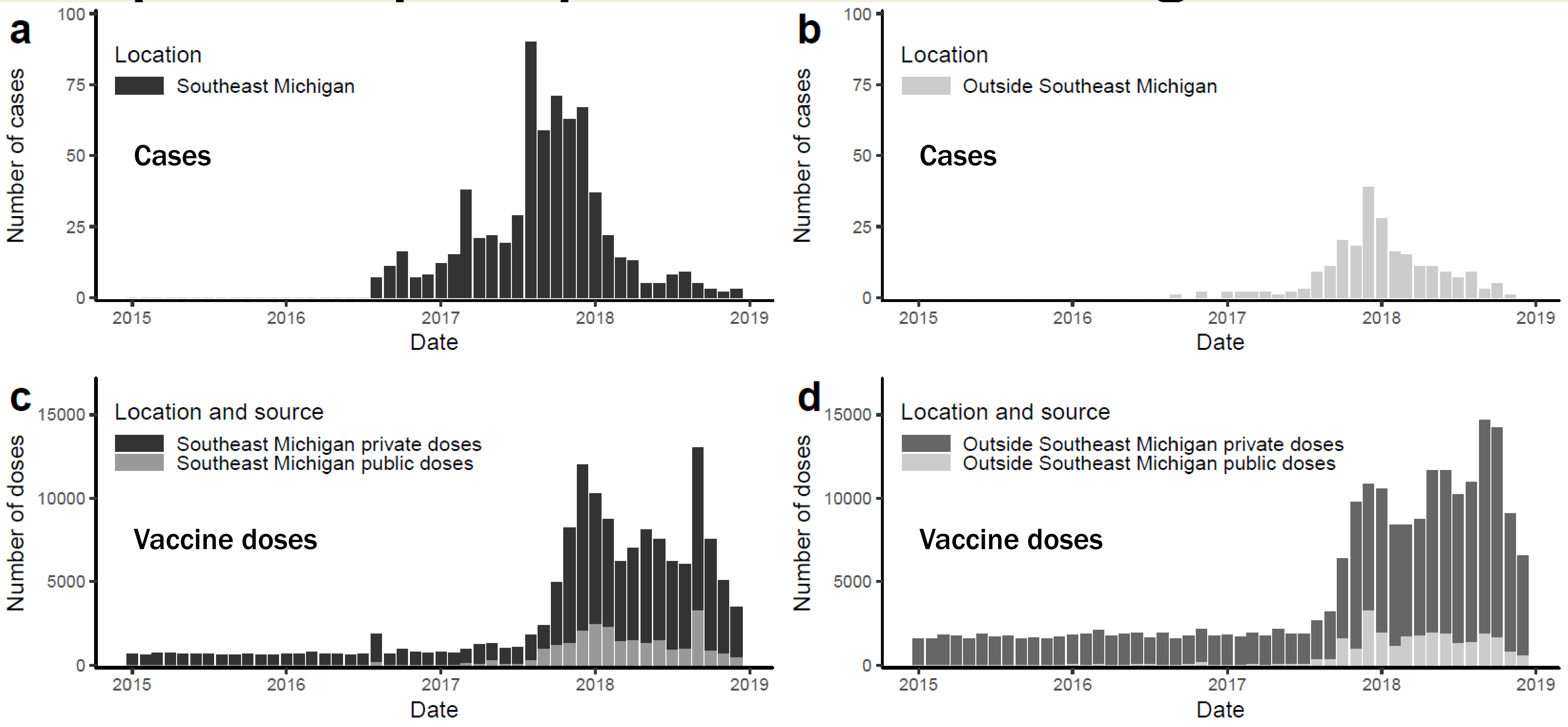
Mobile hepatitis A vaccination clinics making stops at venues popular with high-risk populations to combat outbreak

FOR IMMEDIATE RELEASE: March 5, 2018

25 counties receive $20K from MDHHS to combat hepatitis A outbreak

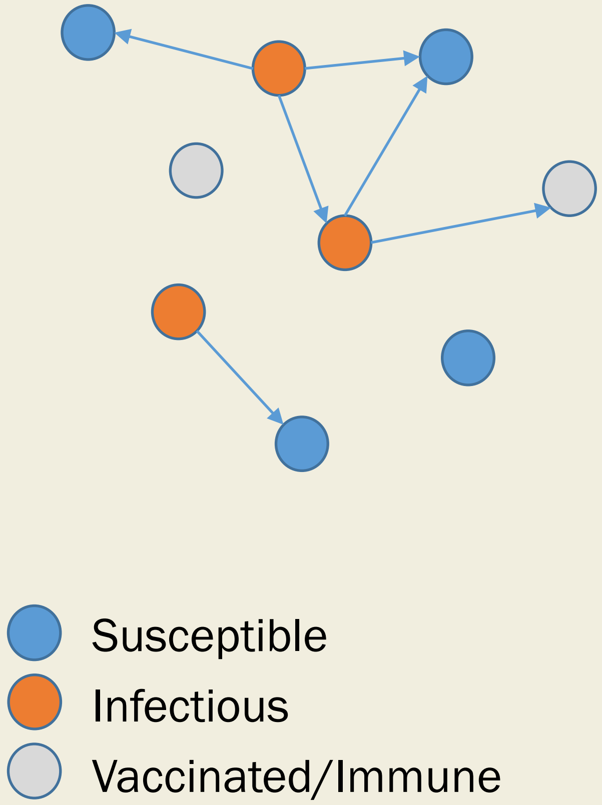
By LARA MOEHLMAN • MAR 26, 2018

How did vaccination efforts impact the spatiotemporal patterns of the Michigan?

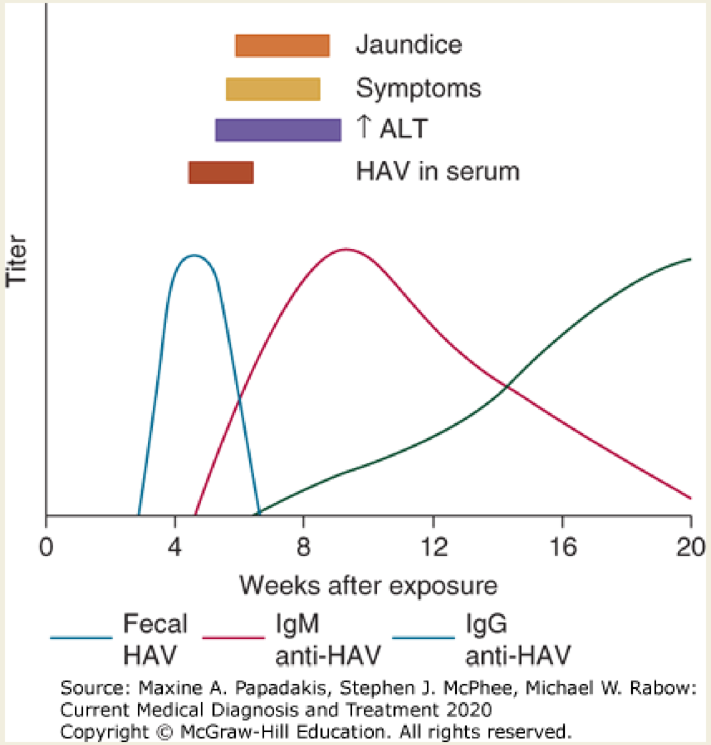


Again, we use mathematical modeling to connect epidemiological theory to data.

Person-to-person transmission

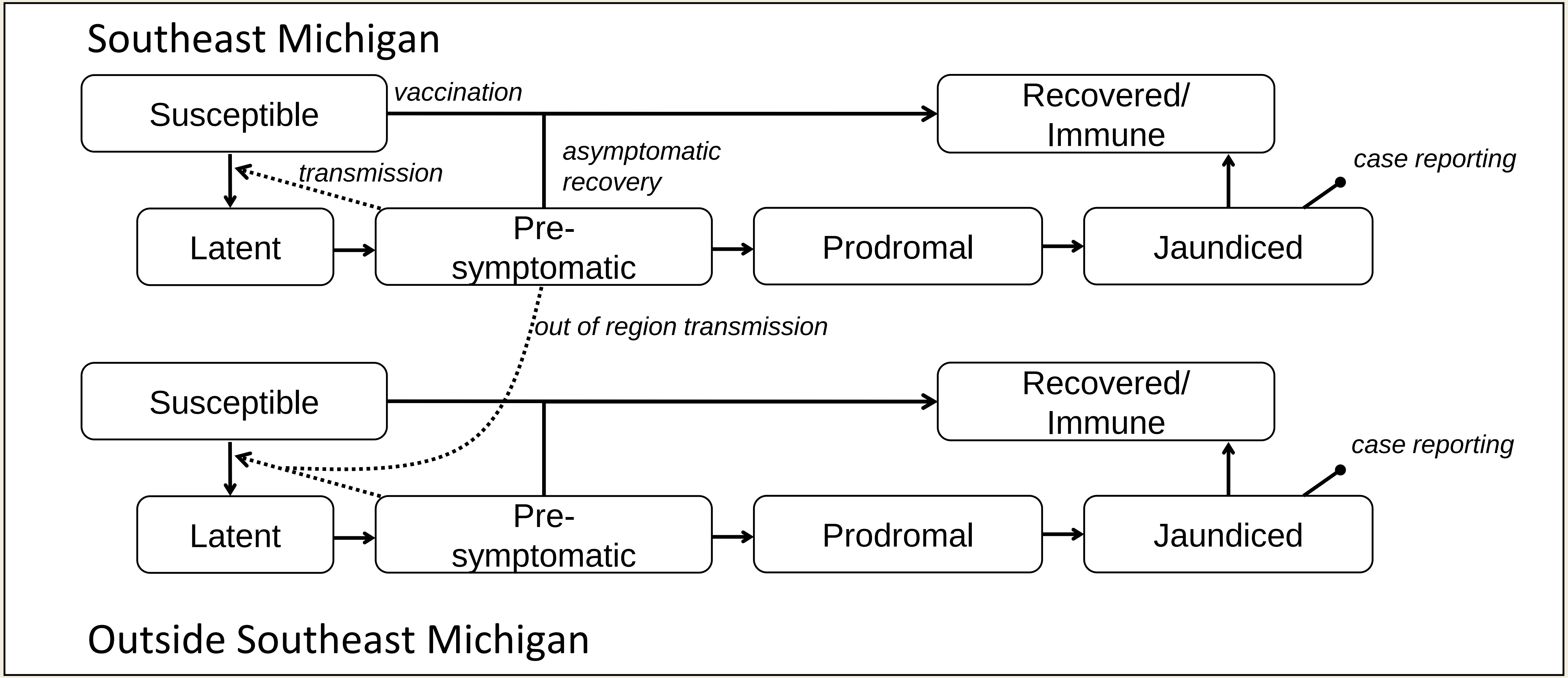


Disease progresses through different stages



Force of infection from southeast outward

We model the population moving through different stages but only observe the case reporting.



Assumptions and unknowns

- We only model the “at-risk” population. We do not know exactly who these people are or even how big this population is.
- The at-risk population in Southeast Michigan was distinct from the at-risk population in the rest of the state.
- Only a fraction of the given doses of hepatitis A vaccine were given to people who were actually at risk. We don’t know what this fraction is ahead of time.
- Only a fraction of people who are jaundiced seek medical care and are counted as cases. We don’t know what this fraction is ahead of time.
- Transmission may be seasonal.

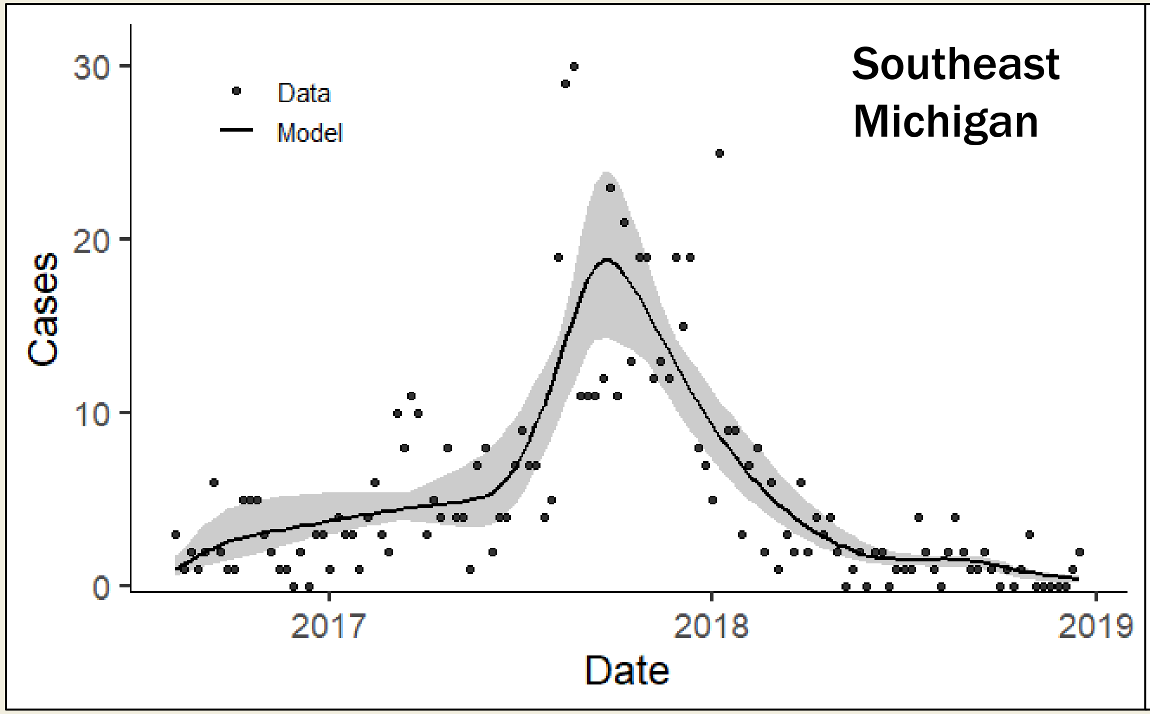
We use data provided by MDHHS.

- Michigan Disease Surveillance System (MDSS)
  - cases of hepatitis A that are confirmed by lab testing
  - 910 cases in 2016 to 2018
- Michigan Care Improvement Registry (MCIR)
  - doses of hepatitis A vaccine that are voluntarily reported for adults ages 19+ (first dose only)

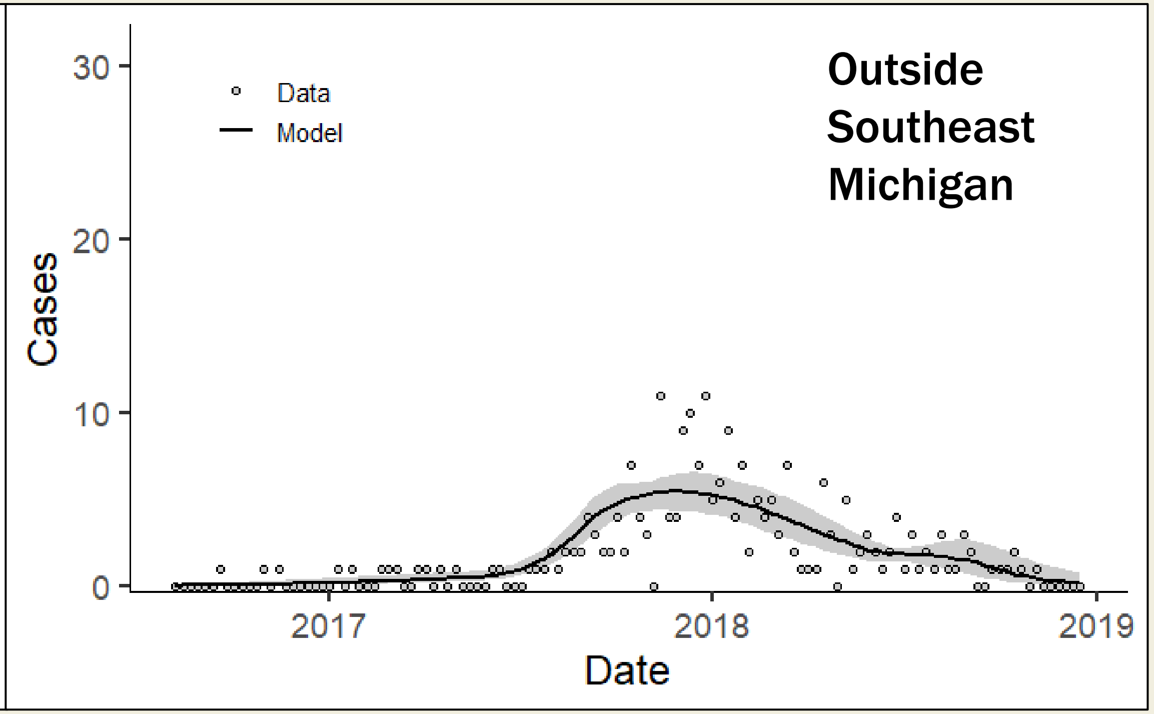
We use the model to estimate key parameters.

- **Transmission rates**: within SE Michigan, outside SE Michigan, and the transmission from SE outside
- **Vaccine coverage parameters**: transform number of doses into vaccination rates
- **Reporting parameters**: connect reported cases to modeled fraction of people infected

We use the model to approximate epidemic trajectories.



Cumulative incidence: **44%** (95% CI: 38–54%)



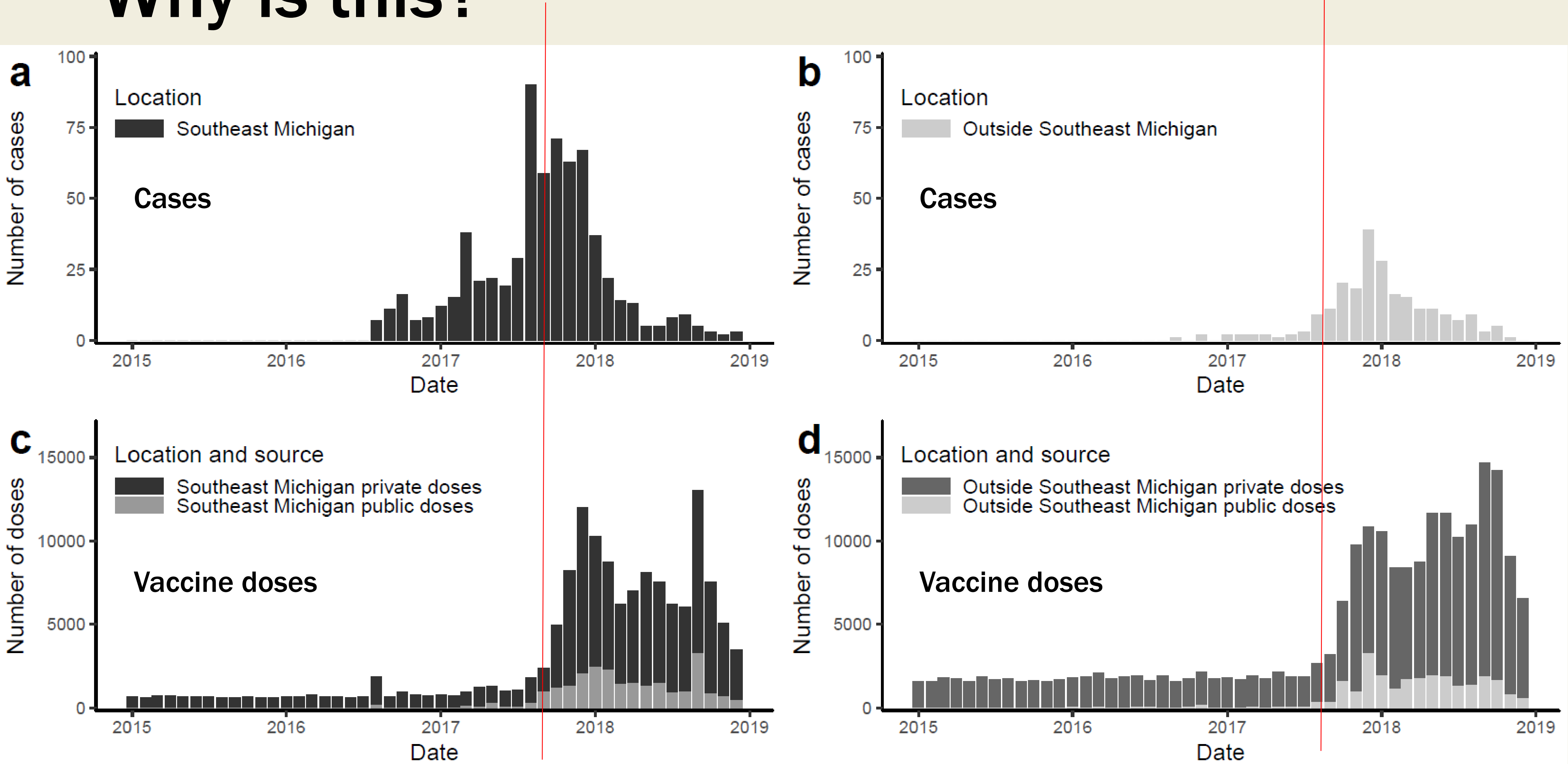
Cumulative incidence: **5%** (95% CI: 0.3–20%)

Vaccination probably did not make much difference in SE Michigan. But it made a big difference in the rest of the state.

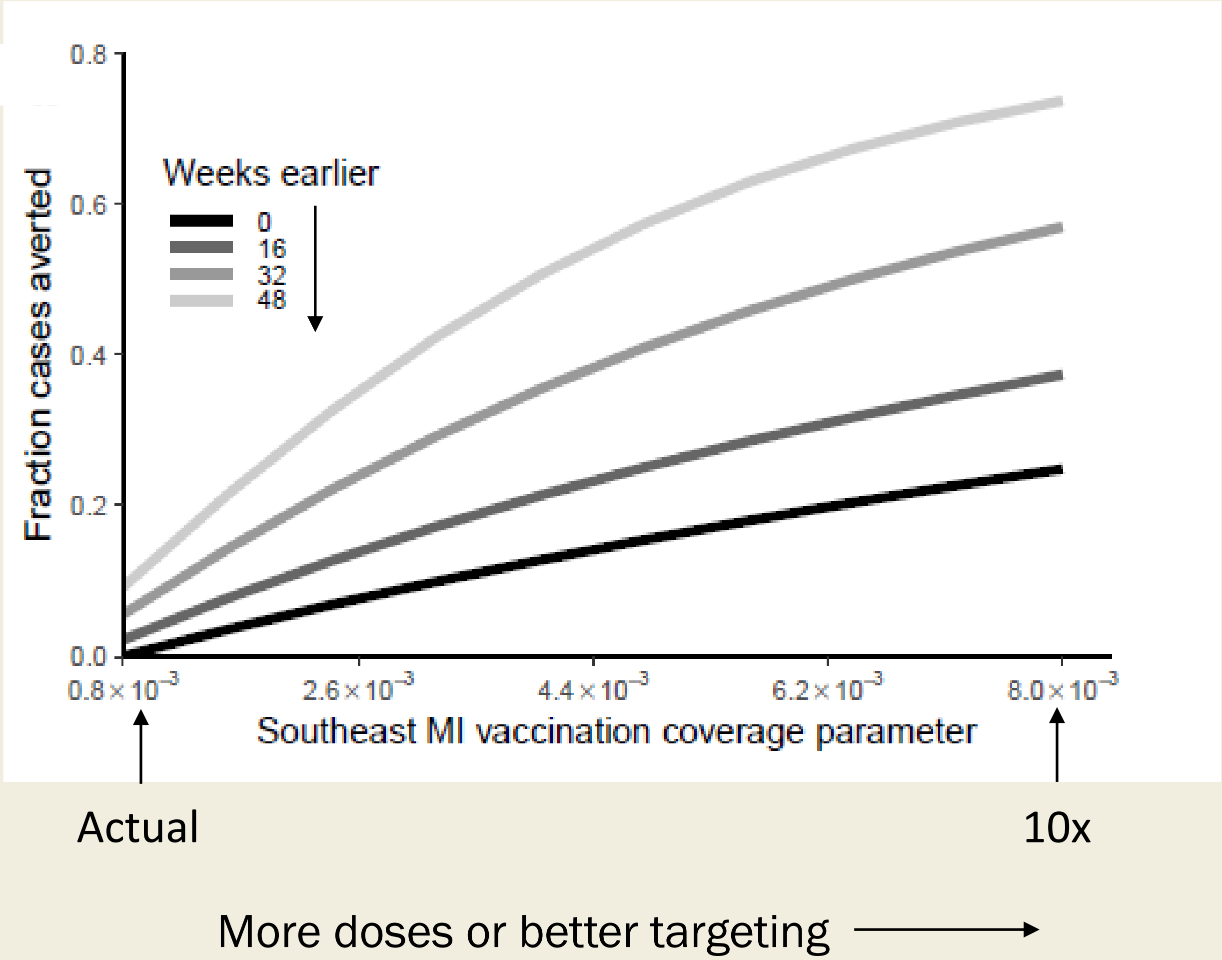
- Southeast Michigan
  - 3% (95% CI: 1–8%) of cases were averted (about 20 cases)

- Outside southeast Michigan
  - 91% (95% CI: 85–97%) of cases were averted (about 2300 cases)
  - Outbreak could have lasted another 3 years

Why is this?


a
Location
Southeast Michigan
Cases
Number of cases
Date
b
Location
Outside Southeast Michigan
Cases
Number of cases
Date
c
Location and source
Southeast Michigan private doses
Southeast Michigan public doses
Vaccine doses
Number of doses
Date
d
Location and source
Outside Southeast Michigan private doses
Outside Southeast Michigan public doses
Vaccine doses
Number of doses
Date

It takes time to intervene in outbreaks. How much faster would we have to be?



- Better targeting or more doses would have minimal impact without also earlier implementation, and vice versa.
- Both of these things are hard!
  - Need epidemiological surveillance to establish risk
  - High-risk people are hard to reach

What’s the big picture?

- Little impact of vaccination in Southeast Michigan, large impact in the rest of the state.
- Bright side: vaccination is effective, so even if the campaign did not stop this outbreak, it will help prevent the next one.
- Reactive control strategies will always be less effective than proactive control strategies.
  - Recommend: continuous vaccination of high-risk groups, especially in urban centers (hubs)
    - Herd immunity likely needs 65-80% vaccine coverage
    - Not always possible when resources are limited
  - Hepatitis A outbreaks are continuing to emerge; can smart resource allocation prevent outbreaks in other large cities?

What’s the big picture?

- We don’t know who was “at-risk” in this outbreak.
  - We know some high-risk indicators, but we don’t know the relative risk for people with those indicators
  - Can make it hard to target vaccine clinics to those who need them.
  - This is one of the largest sources of uncertainty in this analysis.
- The Michigan outbreak differed from other outbreaks
  - More substance users and fewer people with transient housing
    - Affects the relative importance of public sanitation campaigns
  - Higher hospitalization (80% vs 60%) and death (3.3% vs. 1.0%) rates than nationally.
    - More vulnerable population, or more effective system?

What’s the big picture?

- The modes of transmission remain unclear
  - Is hepatitis A actually spread by substance use, or is substance use a confounder?
    - Hep A can be bloodborne, but we don’t know if that’s an epidemiologically relevant pathway
    - Increased interest in syringe-service/needle-exchange programs
  - Contact or molecular tracing might help make pathways more clear

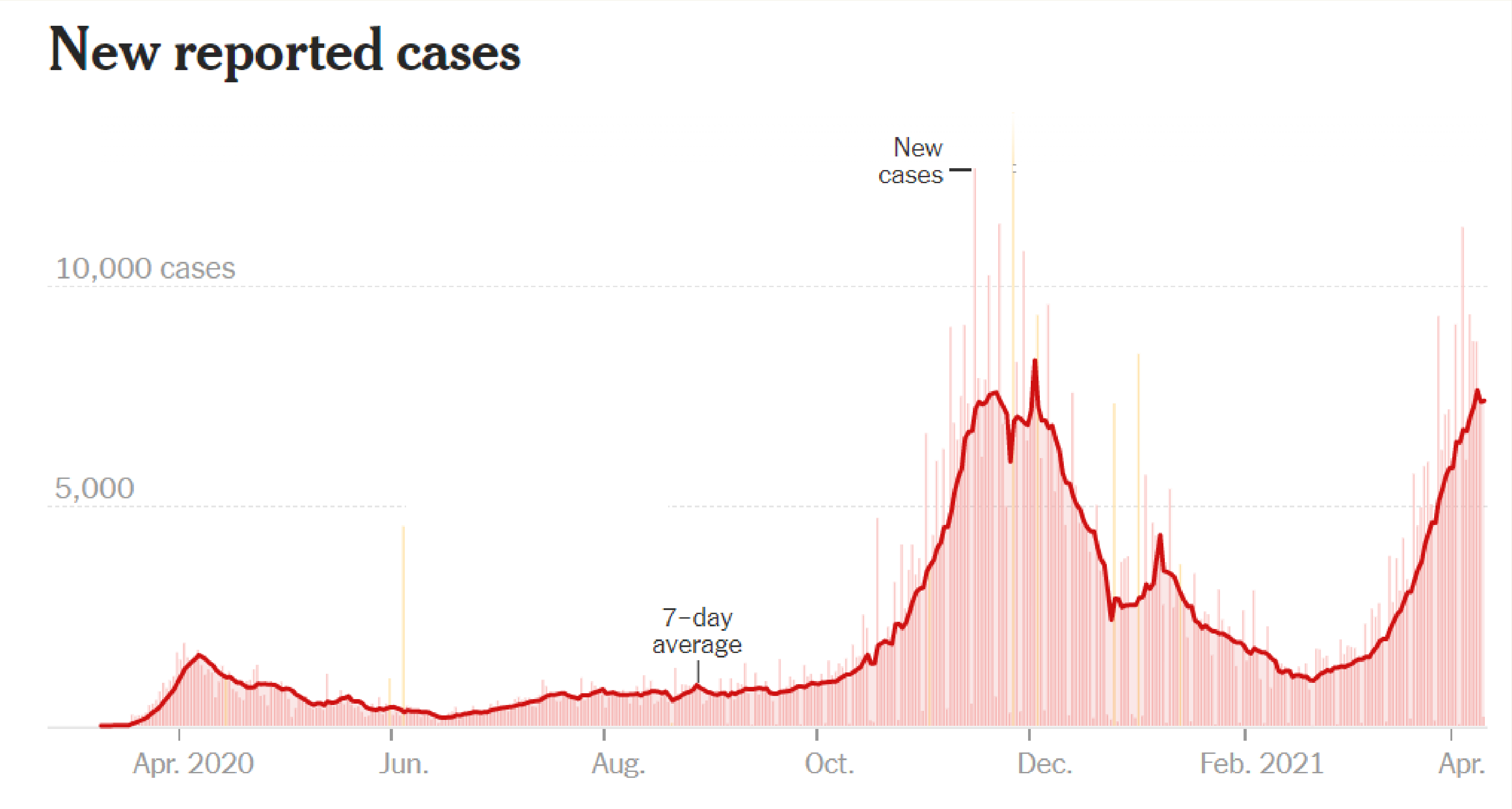
Modeling to guide COVID-19 policy: forecasts, scenarios, and counterfactuals

SARS-CoV-2 epidemic in Michigan, 2020–21

This work has been a collaboration between UM and MDHHS.

- UM co-authors
  - Marisa Eisenberg
  - Joshua Petrie
  - Emily Martin
  - Sandro Cinti
  - Peter DeJonge
  - Jeremy D'Silva
- Also thanks to
  - Sarah Lyon-Callo & MDHHS team
  - Paul Hurtado
  - Many others!

We have all been living through the global COVID-19 pandemic for the past year.

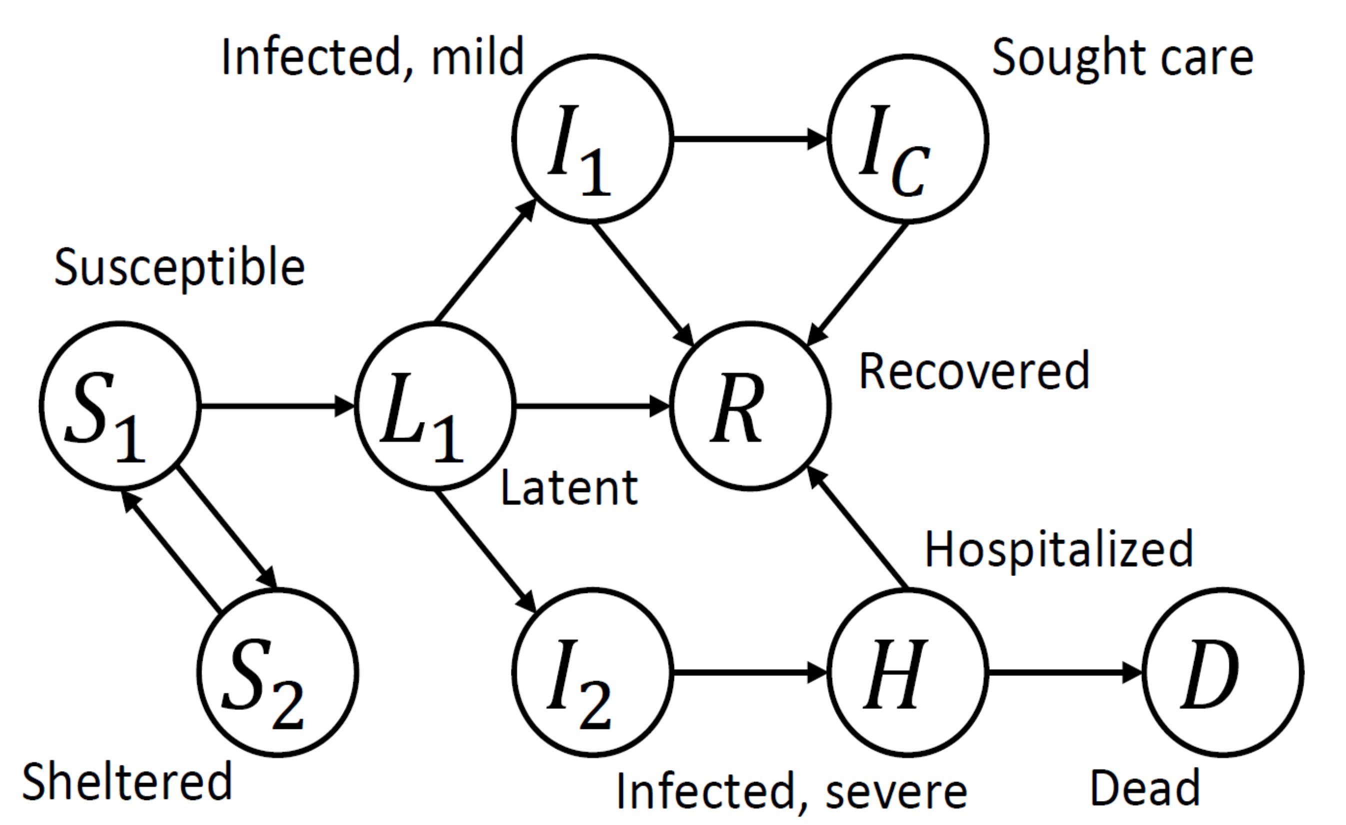


Confirmed and probable COVID-19 cases in Michigan

Early in the epidemic, there were many unknowns, but action was needed.

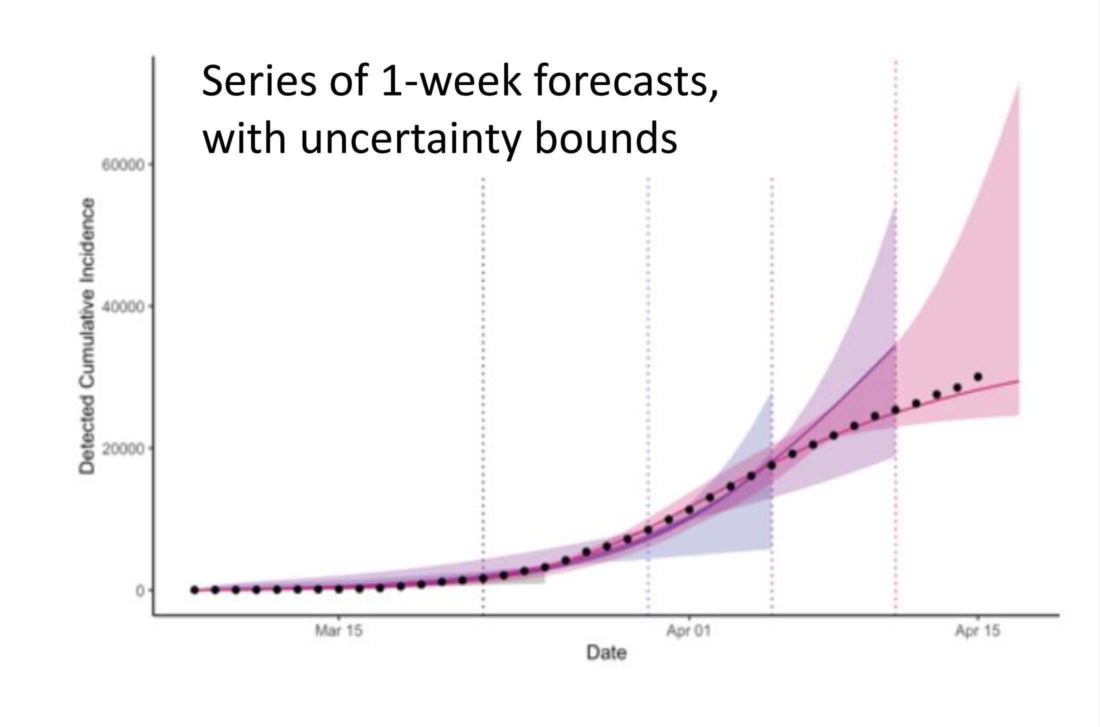
- To support MDHHS and the Governor of Michigan we sought to provide:
  - Short-term forecasts
  - Long-term scenarios
  - Estimates of what-would-have-happened-if scenarios

We developed a model of COVID-19 disease transmission, testing, hospitalization and death.

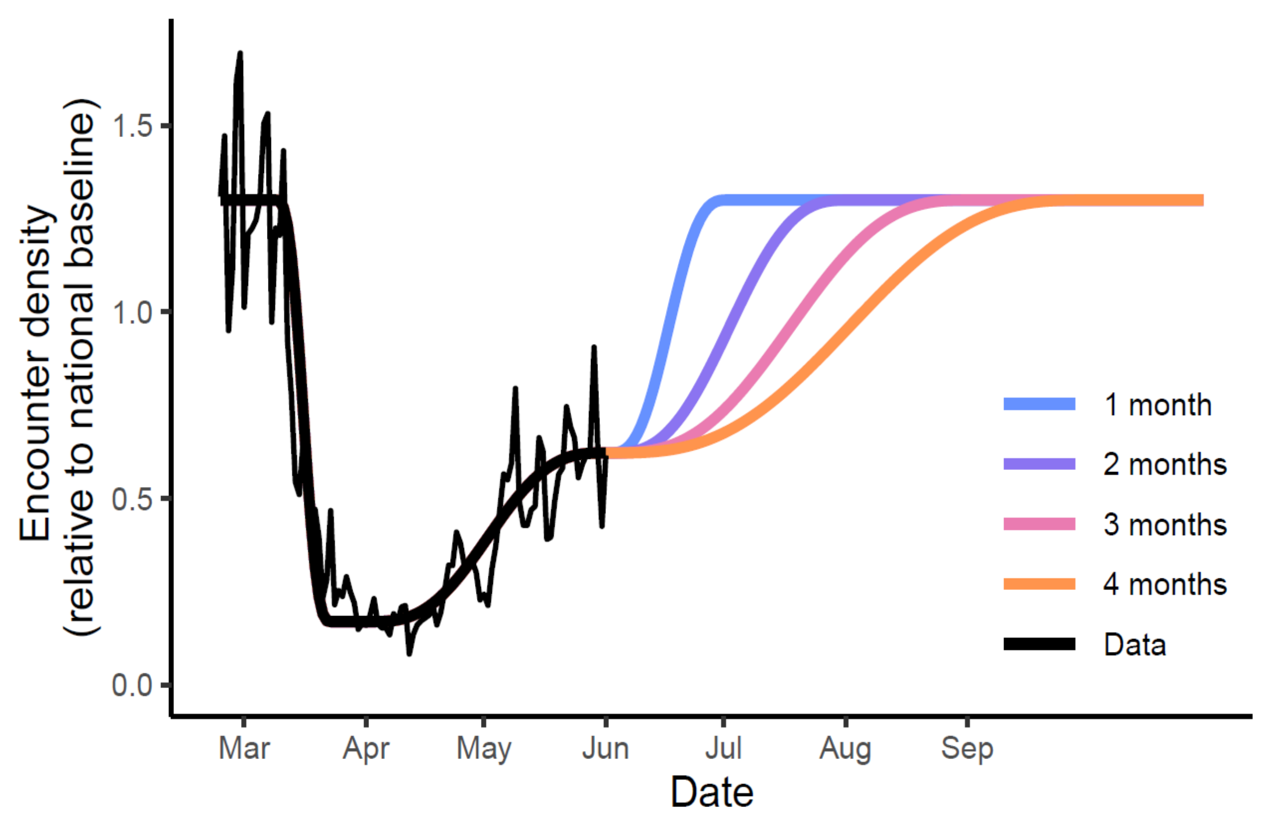


Forecasting outbreaks long into the future is not possible, but short-term predictions can be accurate.

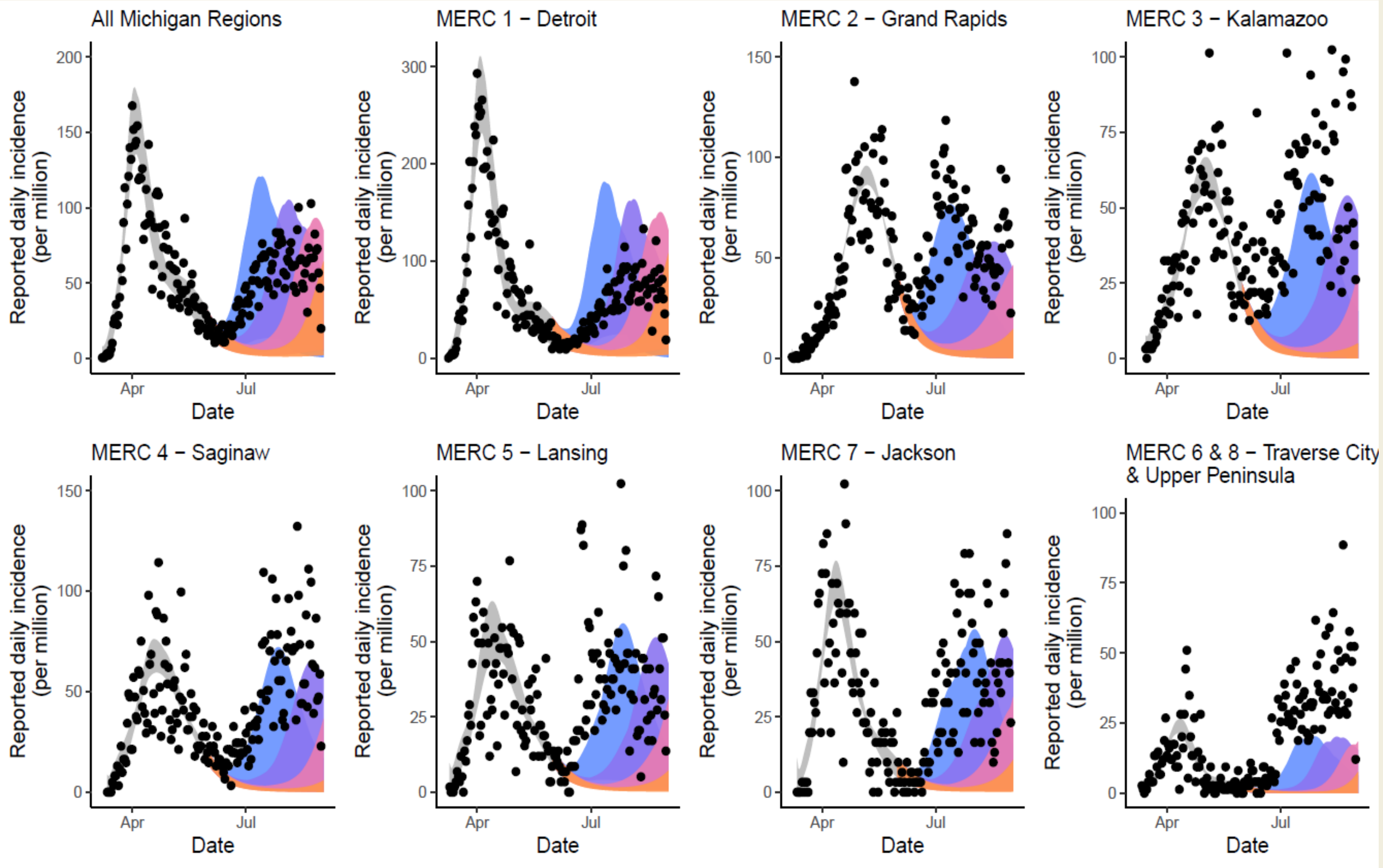
- Disease parameters were highly uncertain, so we simulated 1000 different trajectories based on reasonable ranges of values.



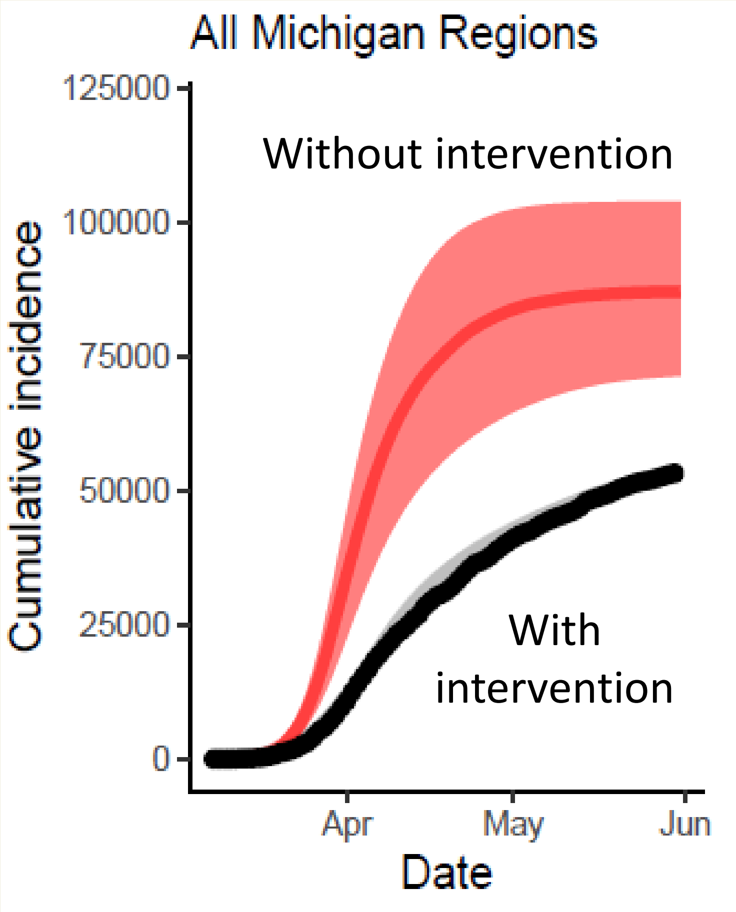
As we moved into the summer, we wanted to understand how cases might return if when social distancing waned.



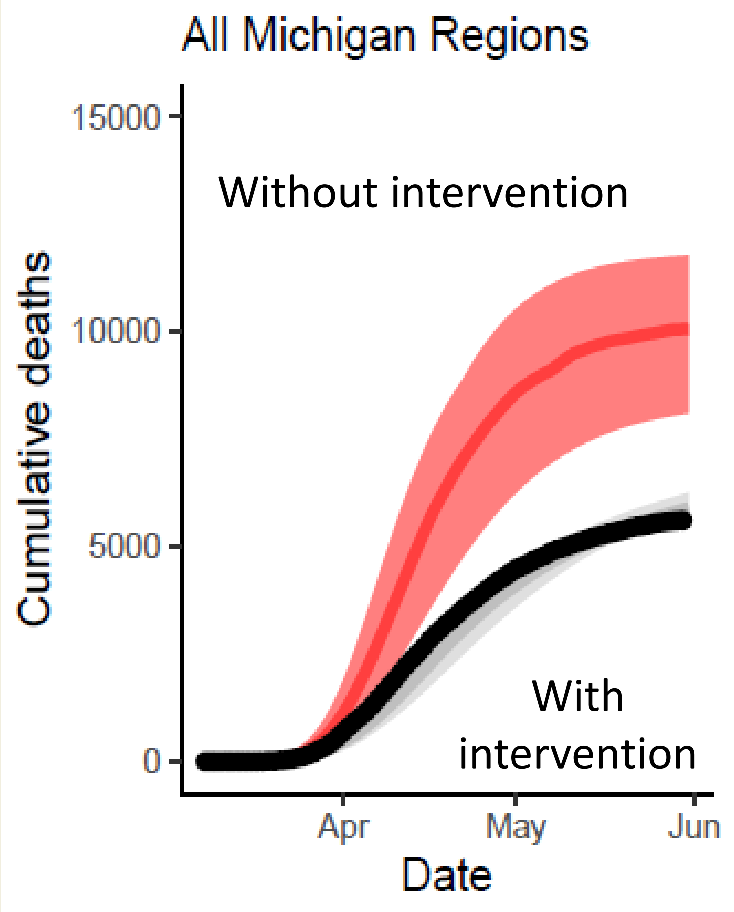
The Summer 2020 peaks were largely consistent with our scenarios.



We also wanted to know what would have happened without the Stay Home, Stay Safe order.



33,000 cases averted



4,200 deaths averted

Conclusions

- The COVID-19 pandemic has placed unprecedented demands on modelers.
- Policy makers have evolving needs; modelers need flexibility and capacity.
- Even relatively short-term projections can be subject to large uncertainty.
- This outbreak has underscored the importance of strong connections between academic and government public health and the need for modeling literacy.

Some final thoughts

- Infectious disease modeling is a tool used to systematically explore the larger public health implications of what we know about a disease and how it is spread.
- We can better understand both what *did* happen and what *might have* happened.
- We need robust, high-quality data collection to pair with modeling.
- The answers you derive from a model depend on your assumptions, so you need to make sure the assumptions are reasonable.

Questions?

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