HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

From Testing to Distribution: Importance and Challenges of Estimating Protective Effects of COVID-19 Vaccines

Marc Lipsitch

NISS – Merck Meetup in Vaccine Development

September 16, 2020

Center *for* Communicable Disease Dynamics

MIDAS
Models of Infectious Disease Agent Study

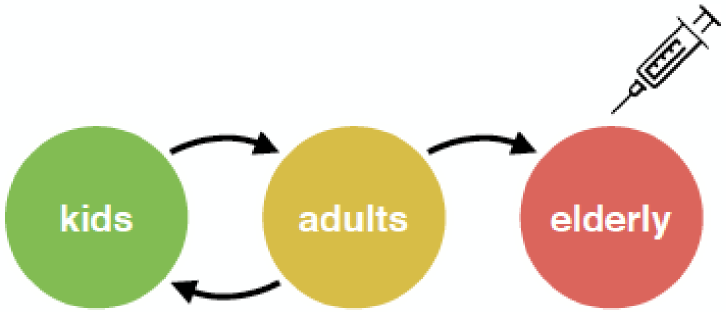
Funded by the National Institutes of Health

Disclosures

- Honoraria/consulting from Merck, Affinivax, Sanofi-Pasteur, Antigen Discovery
- Research funding (unrelated) from Pfizer
- Unpaid scientific advice to Janssen, Astra-Zeneca, Covaxx (United Biomedical)

Two ways to use vaccines

Direct Protection

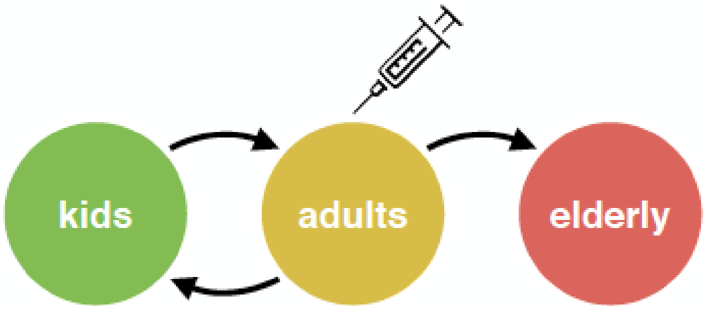


Protect the vulnerable

Requires that the vaccine is effective in these individuals (elderly, comorbid)

Unlikely we will know this at the first "successful" interim analysis because that will be declared when overall efficacy is found, underpowered for subgroups

Indirect Protection



Break the backbone of transmission

Requires that the vaccine reduces transmission by preventing infection and/or reducing infectiousness

Unlikely we will know this for most vaccines because the primary endpoint in all trials is symptomatic PCR+ disease and only some measure infection or infectiousness proxies

Commentary: M Lipsitch and NE Dean in review

Diagram: Dan Larremore

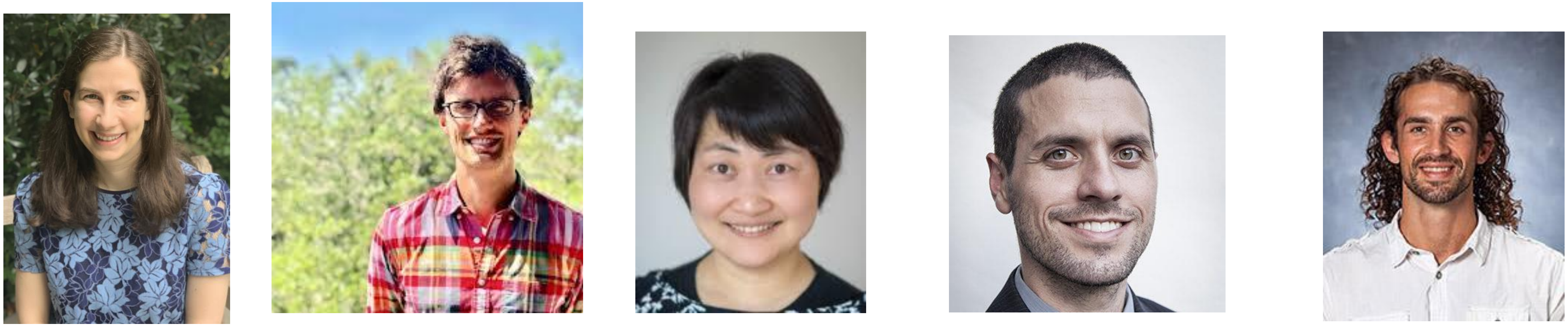
3 partial solutions

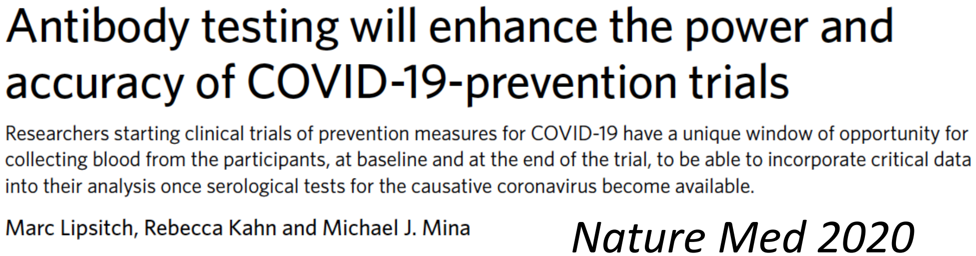
- Design trials to detect infection even when subclinical
- Estimate infectiousness in standard individually randomized vaccine trial using deep sequencing
- Check how much it matters for vaccine prioritization

Approach 1: Measure impact on infection using post-trial serology

- Need a marker of infection that is distinguishable from vaccine immunity (nonvaccine antibody, N protein)
- Need pre- (ideally) and post-study sera from a sample of (or all) participants
- Also has the advantage of correcting for bias in estimates of VE against infection

Approach 1: Measure impact on infection using post-trial serology





Antibody testing will enhance the power and accuracy of COVID-19-prevention trials

Researchers starting clinical trials of prevention measures for COVID-19 have a unique window of opportunity for collecting blood from the participants, at baseline and at the end of the trial, to be able to incorporate critical data into their analysis once serological tests for the causative coronavirus become available.

Marc Lipsitch, Rebecca Kahn and Michael J. Mina

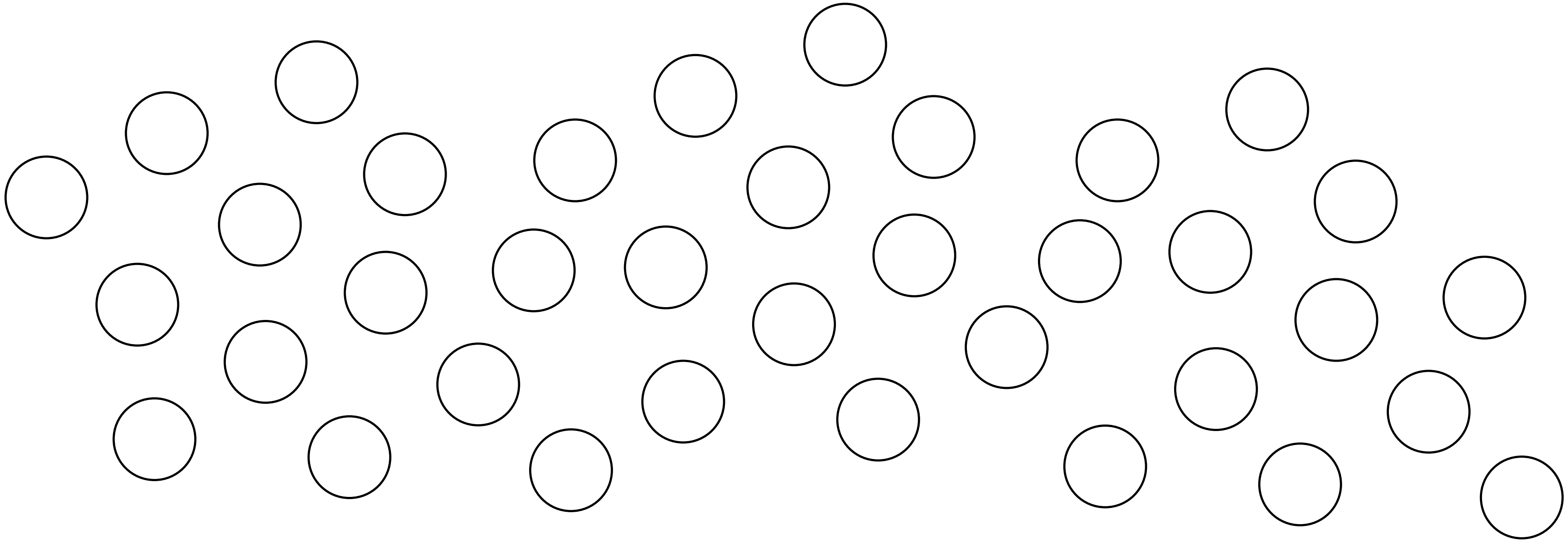
Nature Med 2020

Analyzing Vaccine Trials in Epidemics With Mild and Asymptomatic Infection

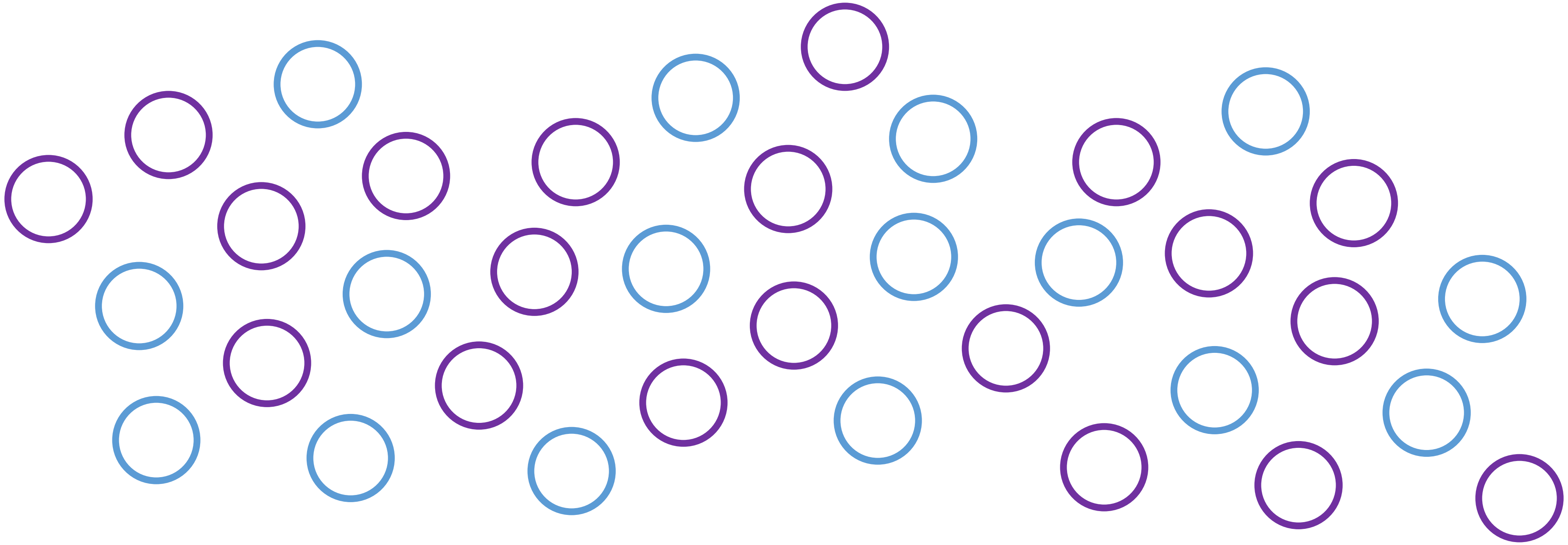
AJ Epidemiology 2019

Rebecca Kahn*, Matt Hitchings, Rui Wang, Steven E. Bellan, and Marc Lipsitch

Bias in VE estimation when consider only symptomatic infections

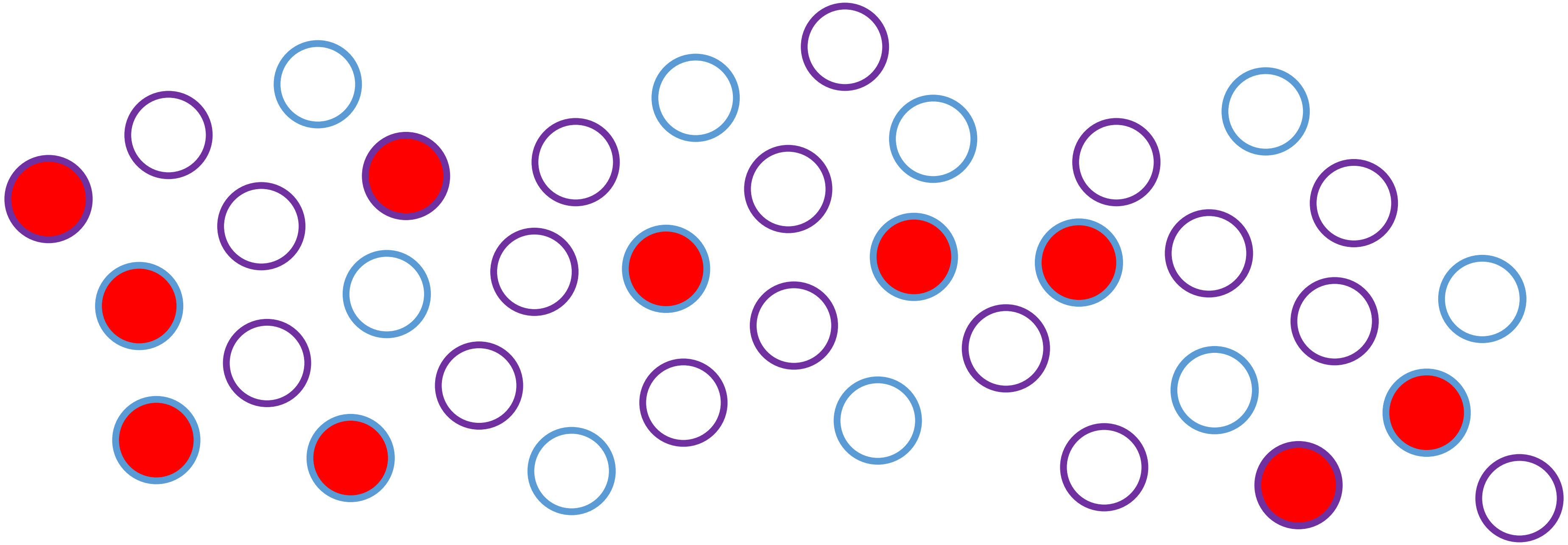


Bias in VE estimation when consider only symptomatic infections



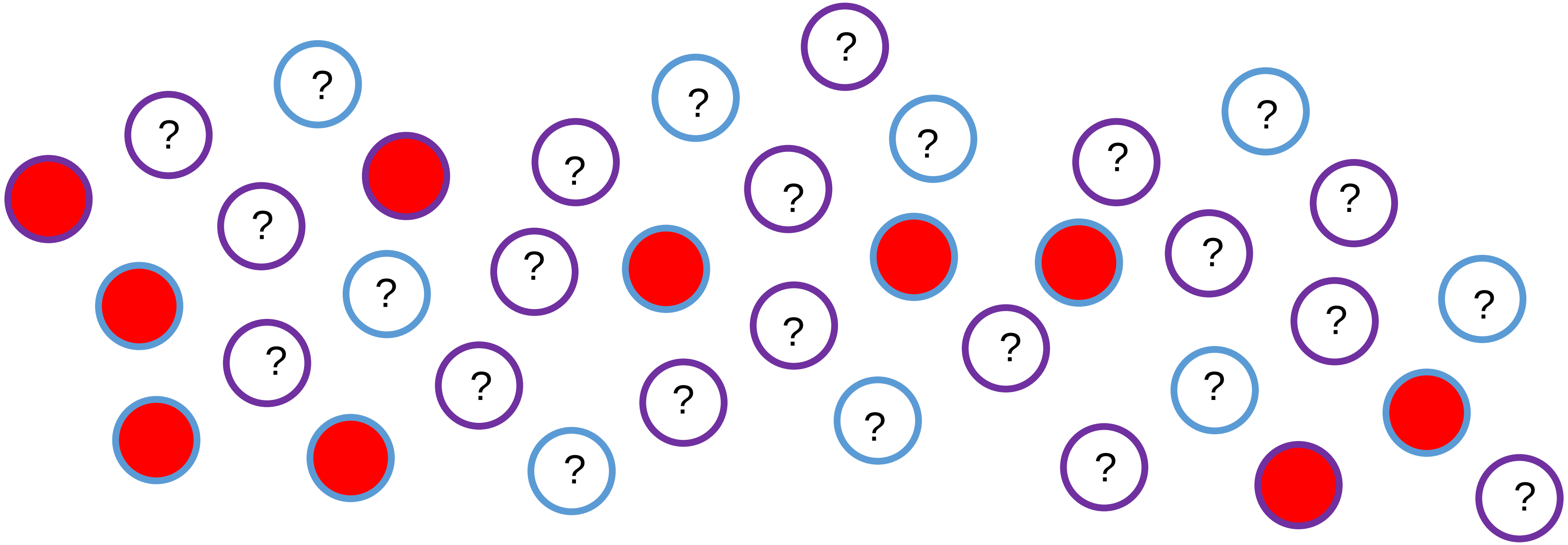
Vaccine
Control

Bias in VE estimation when consider only symptomatic infections



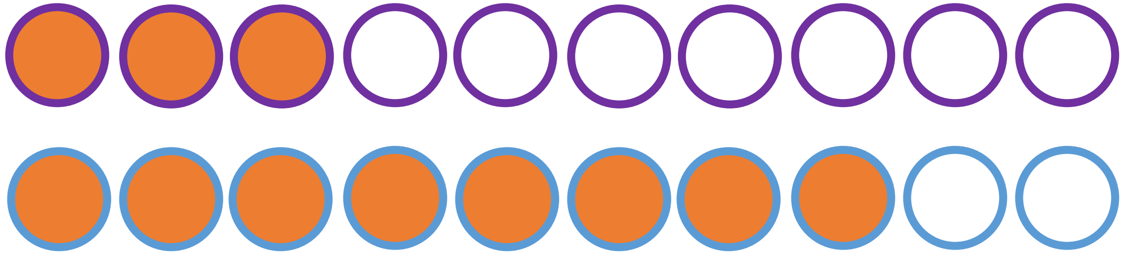
Vaccine
Control
Symptoms

Bias in VE estimation when consider only symptomatic infections



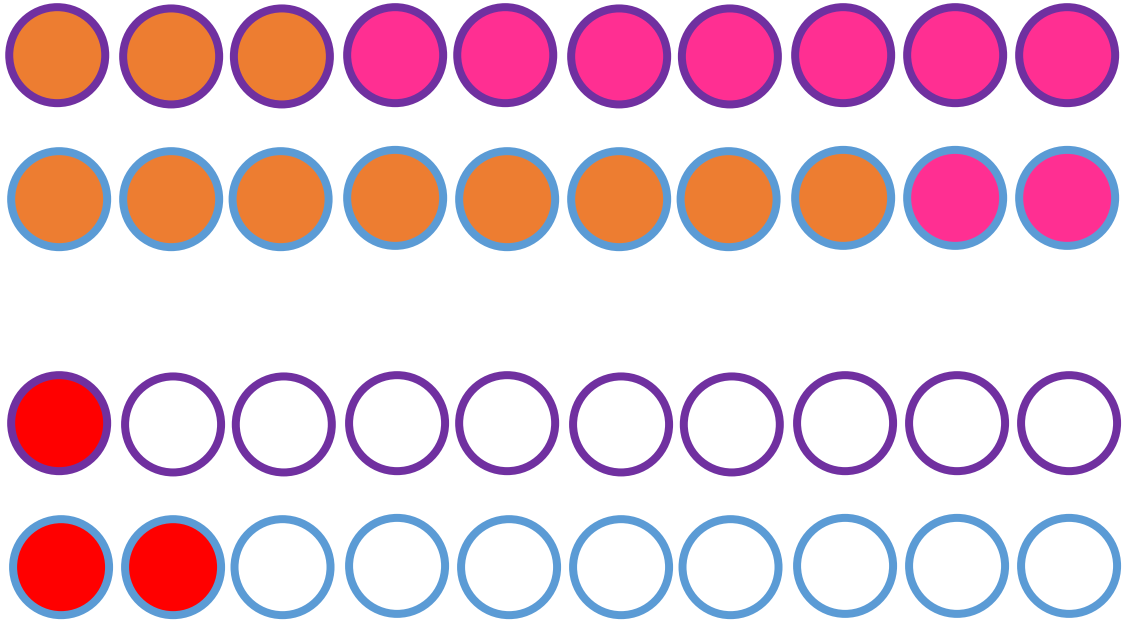
Vaccine
Control
Symptoms

Bias arises due to differential misclassification of at risk person-time

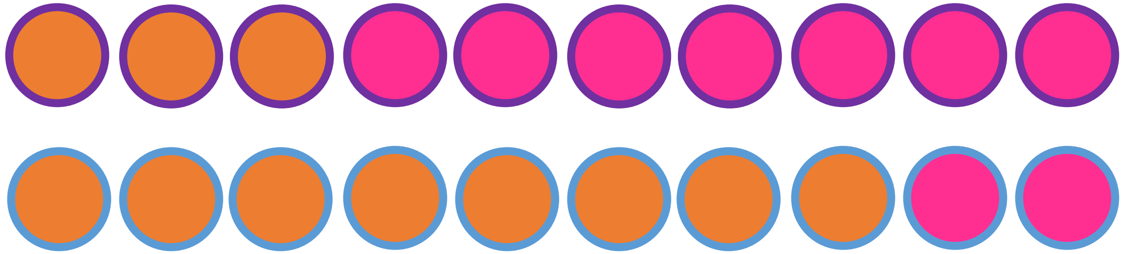


Vaccine
Control
Infected

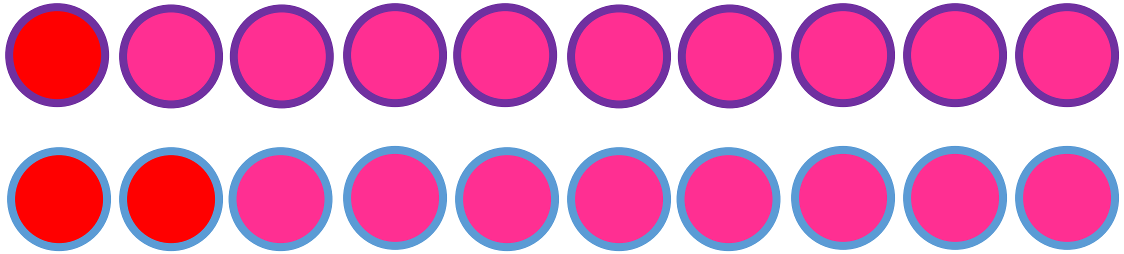
Bias arises due to differential misclassification of at risk person-time



Bias arises due to differential misclassification of at risk person-time



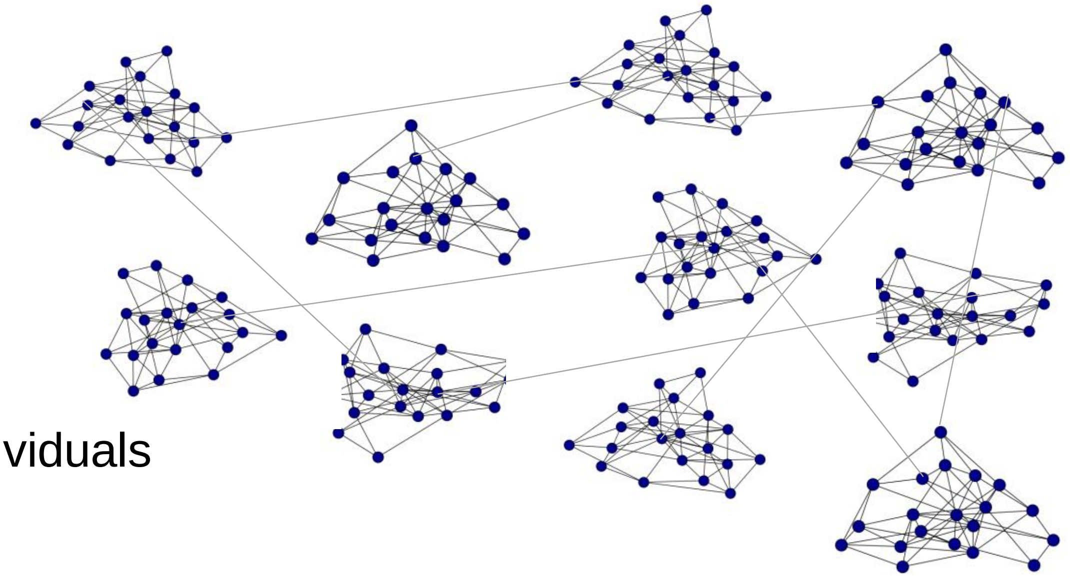
Vaccine
Control
Infected
At risk



Vaccine
Control
Symptoms
Perceived at risk

- Susceptibles are removed faster than we observe - more so for controls
- Apparent incidence in controls is underestimated more than in vaccine group → bias towards the null

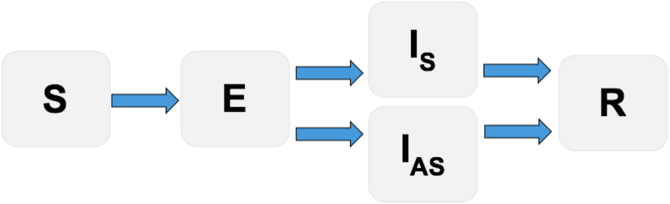
Methods



- Generate a network of individuals grouped into communities

- All individuals are also connected to a larger main population

- Simulate an epidemic



S

E

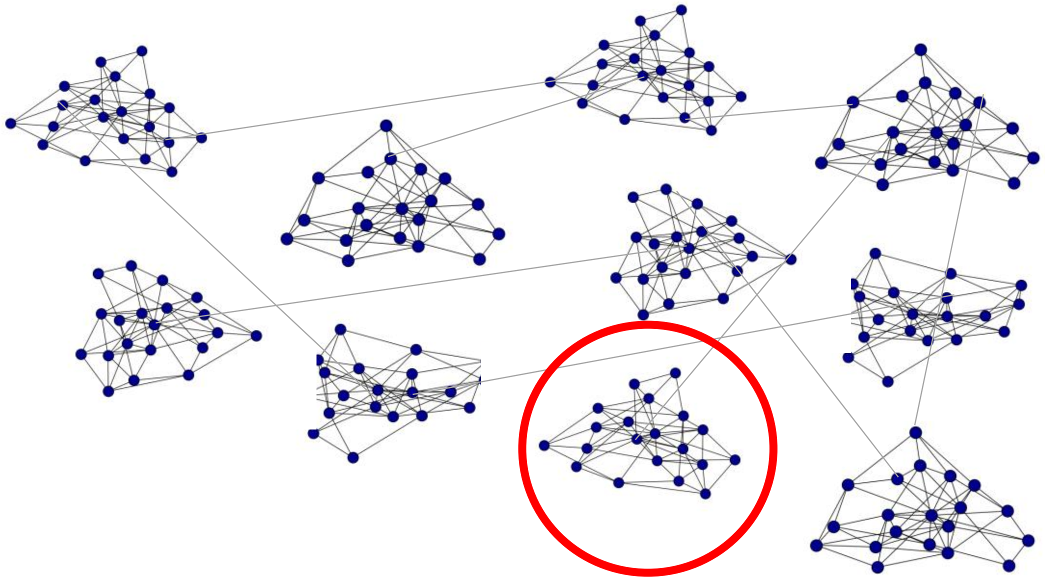
I_S

I_{AS}

R

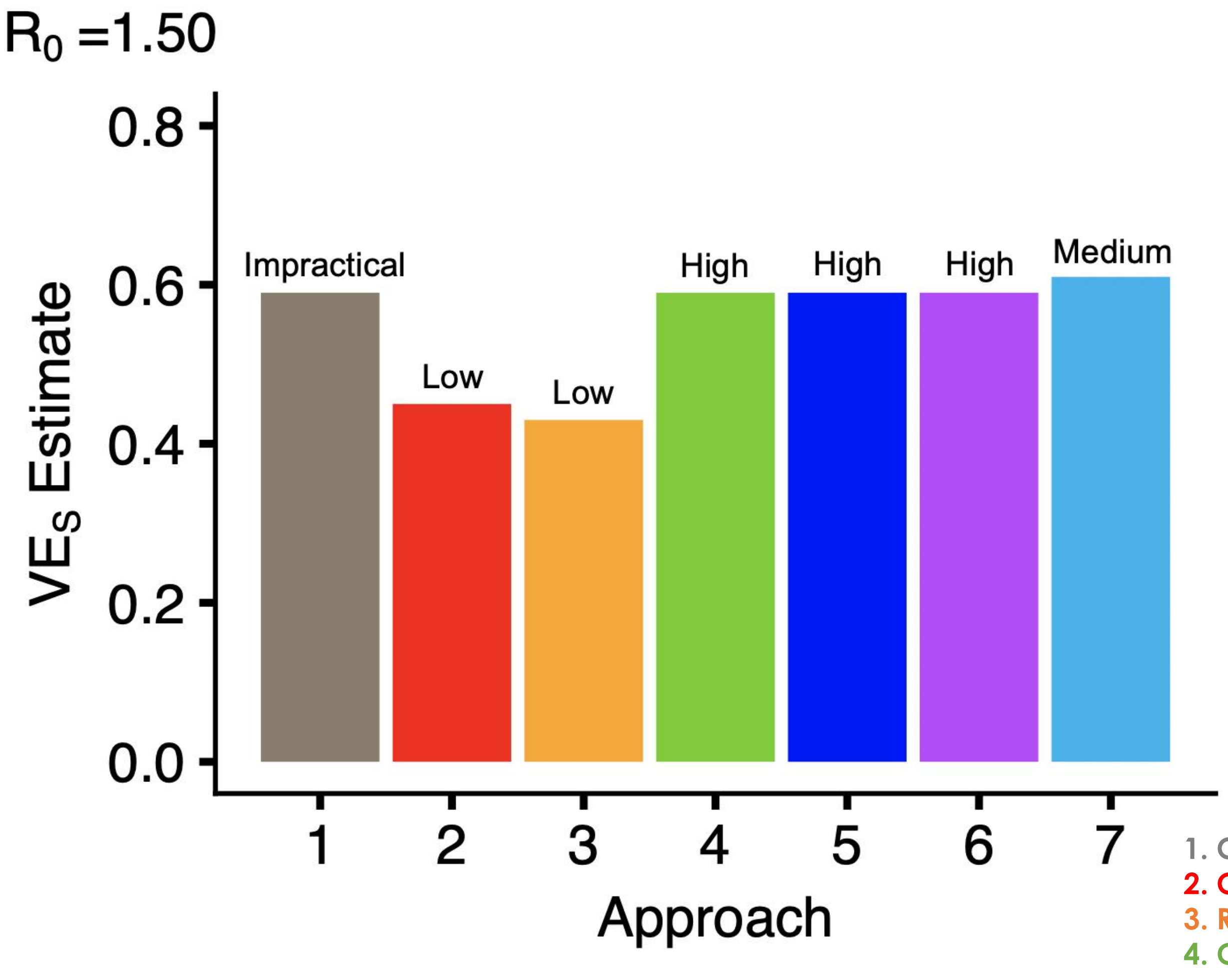
- A connection between two people represents a daily contact between them, meaning all susceptible individuals have a daily probability of infection from each of their infectious neighbors of $1\text{-}e^{-\beta}$,where β is the force of infection.

Methods



- Enroll people into a trial and individually randomize them to vaccine or control
    - The vaccine is **leaky** meaning it reduces the probability of infection upon each exposure
- Use a variety of statistical methods to estimate vaccine efficacy with the goal of identifying the most accurate and efficient
- Determine if one community is representative of the entire trial

Can get accurate VE_S estimate without monitoring time of infection for everyone



1. Cox “Perfect Knowledge”
2. Cox: Symptomatic Only
3. Relative Risk Estimate
4. Corrected Relative Risk Estimate
5. Interval Censored (3 intervals)
6. Interval Censored Cox Model (1 interval)
7. Imputation

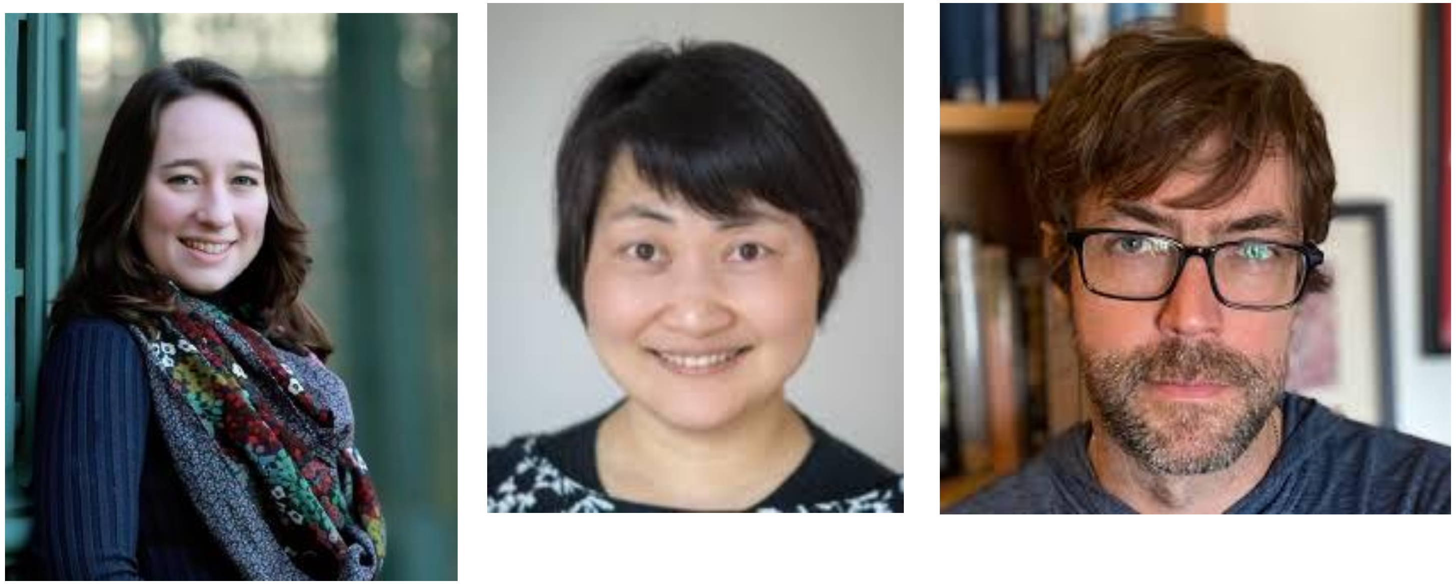
Approach 1 key points

- Unobserved infections bias RCT and observational VE estimates of impact on infection toward the null
- Worse as time passes -> “waning”
- For trial, can solve the problem with serologic testing of a random sample once at end of study + imputation of infection times
- An unbiased estimate of impact on infection would provide evidence about the potential of a vaccine for herd immunity

Approach 2: Measure infectiousness in an individually randomized vaccine trial

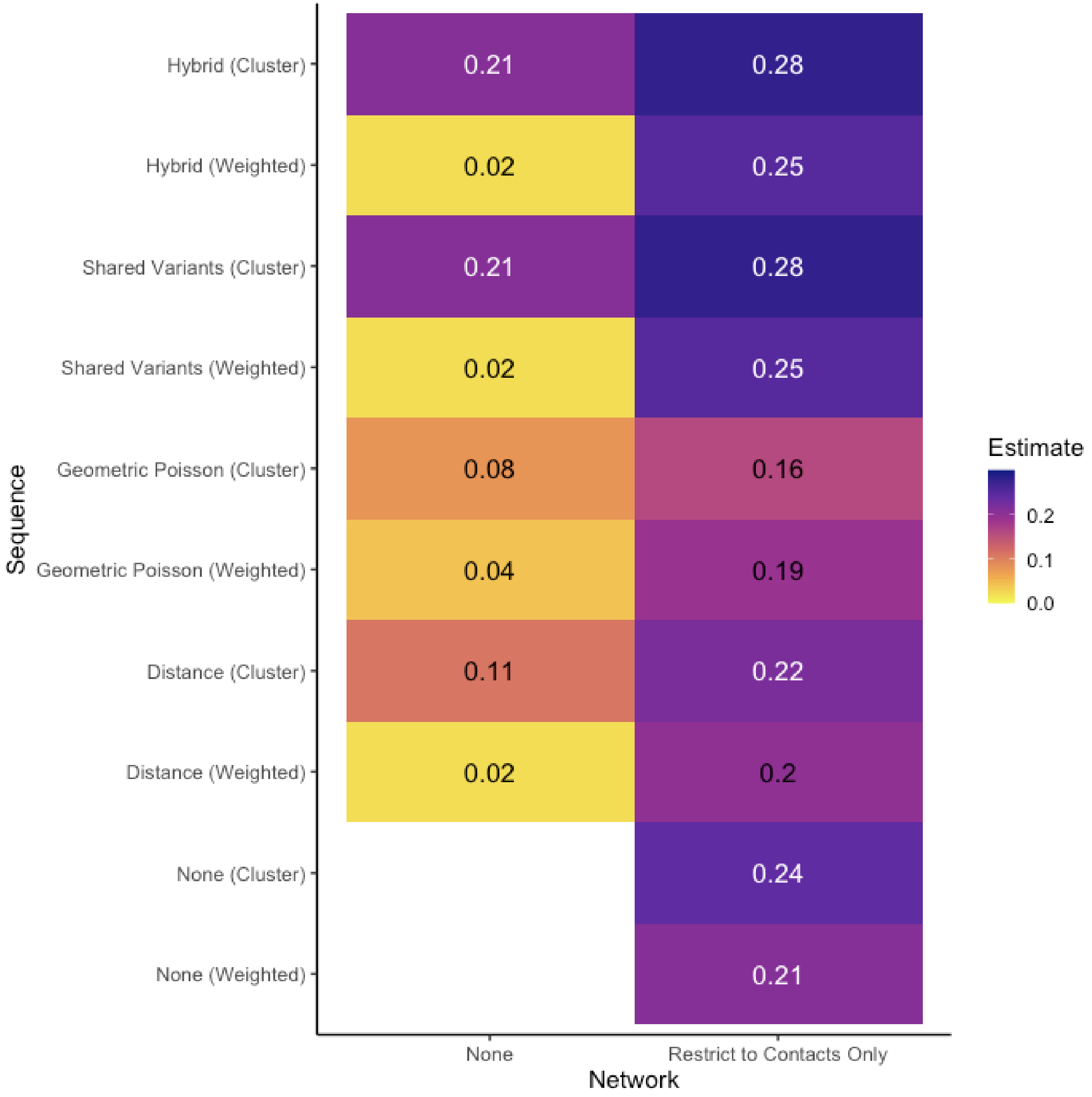
Leveraging pathogen sequence and contact tracing data to enhance vaccine trials in emerging epidemics
Rebecca Kahn, Rui Wang, Sarah Leavitt, William P. Hanage, Marc Lipsitch

Submitted to Medrxiv and a journal



Deep sequence plus contact info in an individually-randomized trial can provide a nearly unbiased estimate of vaccine effect on infectiousness (VE_I)

builds on prior work led by Colin Worby (AJEpid 2017) on use of deep + consensus sequence to



Other approaches

Infectiousness/herd effects

- Follow trial participants for subclinical infection (Oxford AZ trial)
- Add households, other contacts to vaccine trials
- Cluster-randomized trials
- Best done during period of early scarcity when randomization is clearly ethical

VE in subgroups

- Combine data from multiple trials
- Continue trials beyond EUA
- Correlates of protection
- Observational studies (test-negative for example)

NE Dean and M Lipsitch submitted

Approach 3: See if there are robust approaches to prioritization that don't depend too much on vaccine characteristics

Model-informed COVID-19 vaccine prioritization strategies by age and serostatus

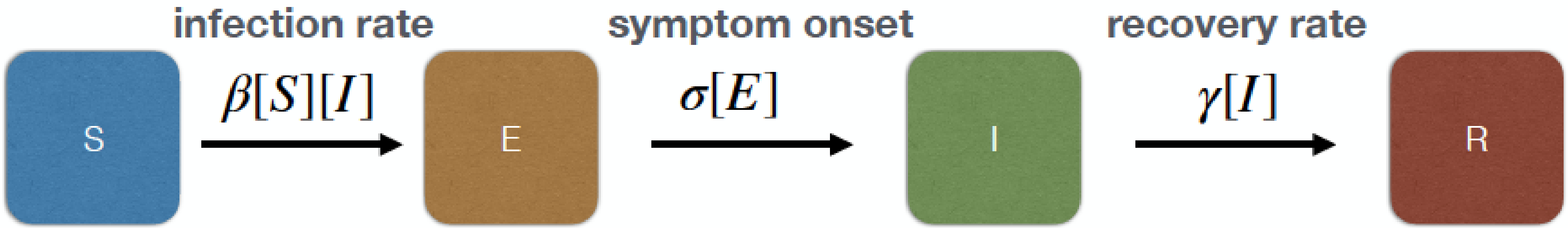
Kate M. Bubar,[1,2*] Stephen M. Kissler,[3] Marc Lipsitch[3,4], Sarah Cobey[5], Yonatan H. Grad[3], Daniel B. Larremore[6,7*]

SLIDES FOR THIS PART BY DAN LARREMORE (AN IMPROVEMENT)

The model for SARS-CoV-2:

People move between the compartments of this “compartmental model”:

Susceptible **E**xposed **I**nfected **R**ecovered



But in this kind of model, everyone is the same. We need more structure!

Stratified compartmental models

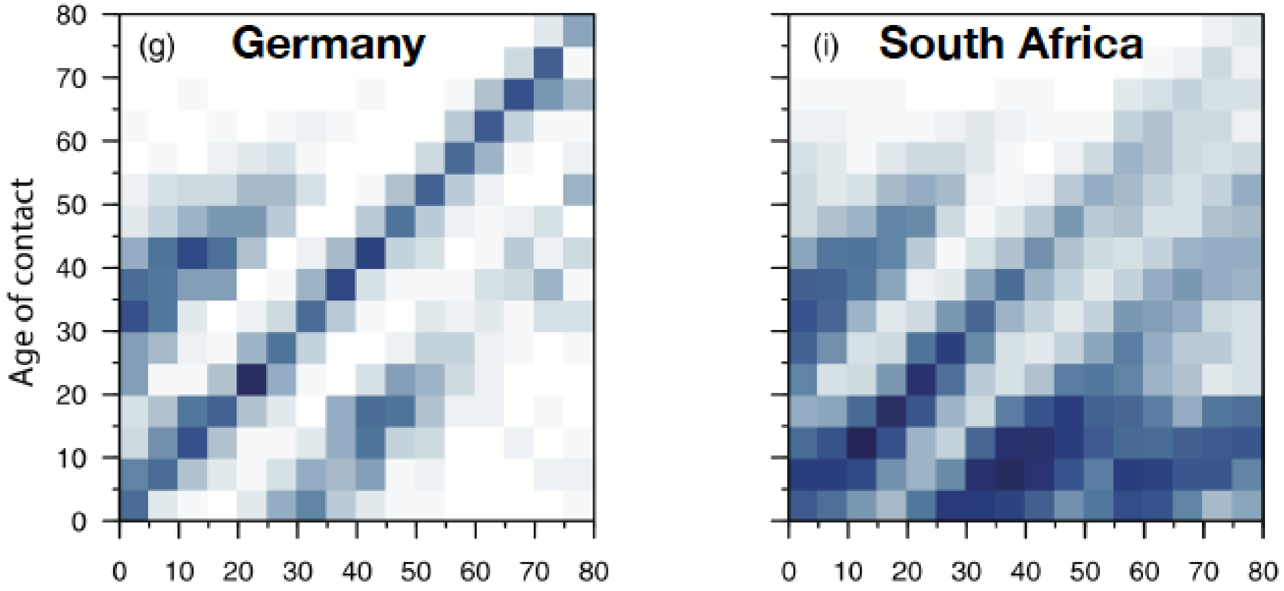
e.g. POLYMOD-type age-structured SEIR models


OPEN ACCESS Freely available online PLoS MEDICINE

Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases

Joël Mossong[1,2*], Niel Hens[3], Mark Jit[4], Philippe Beutels[5], Kari Auranen[6], Rafael Mikolajczyk[7], Marco Massari[8], Stefania Salmaso[8], Gianpaolo Scalia Tomba[9], Jacco Wallinga[10], Janneke Heijne[10], Malgorzata Sadkowska-Todys[11], Magdalena Rosinska[11], W. John Edmunds[4]

The POLYMOD study and others like it have mapped age-contact structure.



Age-stratified SEIR models allow us to ask more targeted questions!

knowns:

1. The vaccine will initially be scarce.

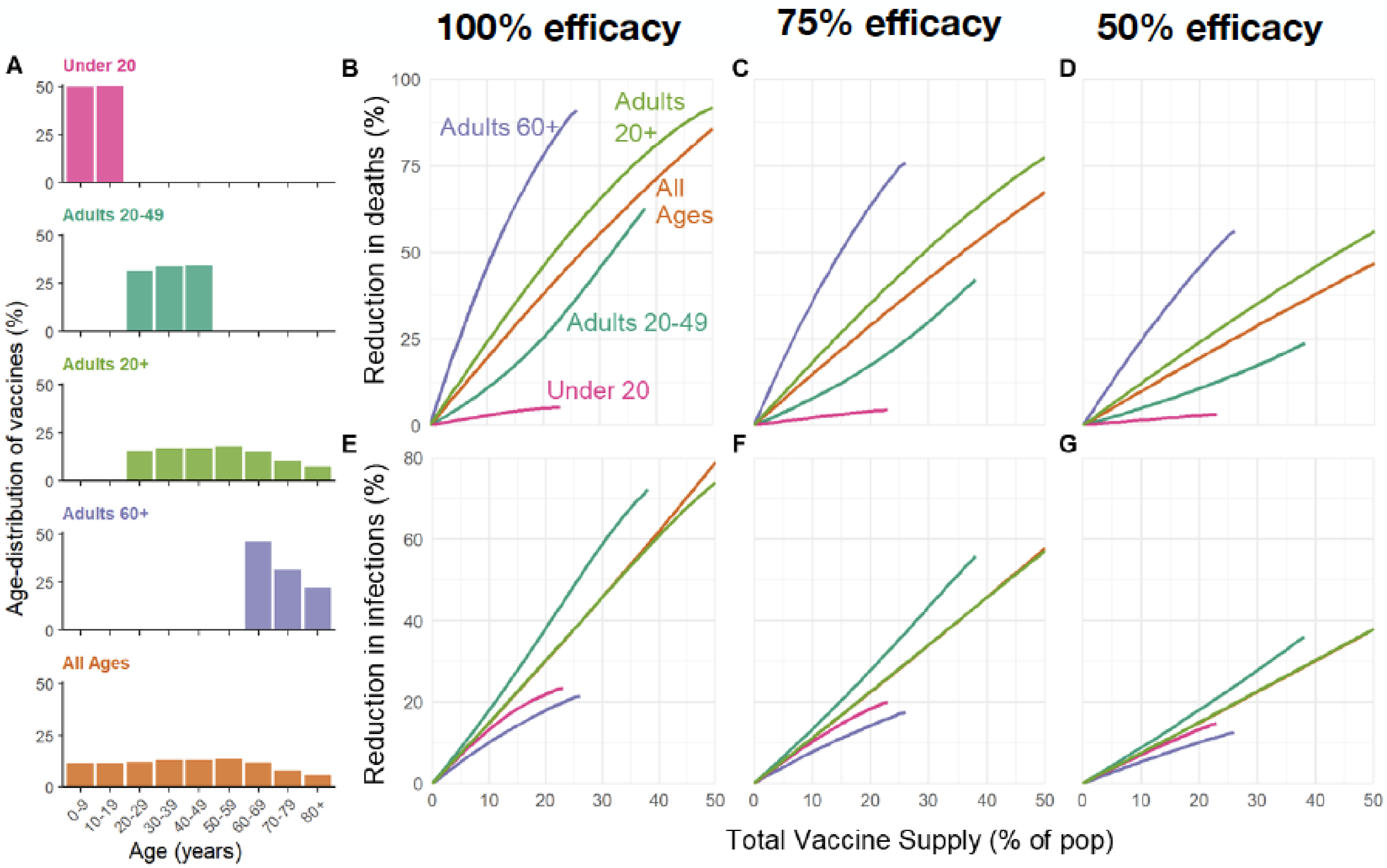
unknowns:

1. **Safety:** who is the vaccine approved for?
2. **Efficacy:** how protective is the vaccine?
3. **Age-related effects:** is the vaccine equally effective across ages?
4. **Vax properties:** transmission blocking?

variables:

1. **Demographics:** what's the age distribution in the population?
2. **Age-contact structure:** are families multihousehold? Do people of all ages work? Strict retirement age?
3. **Seroprevalence:** what fraction of the population has antibodies already? And, do they correlate with protection?

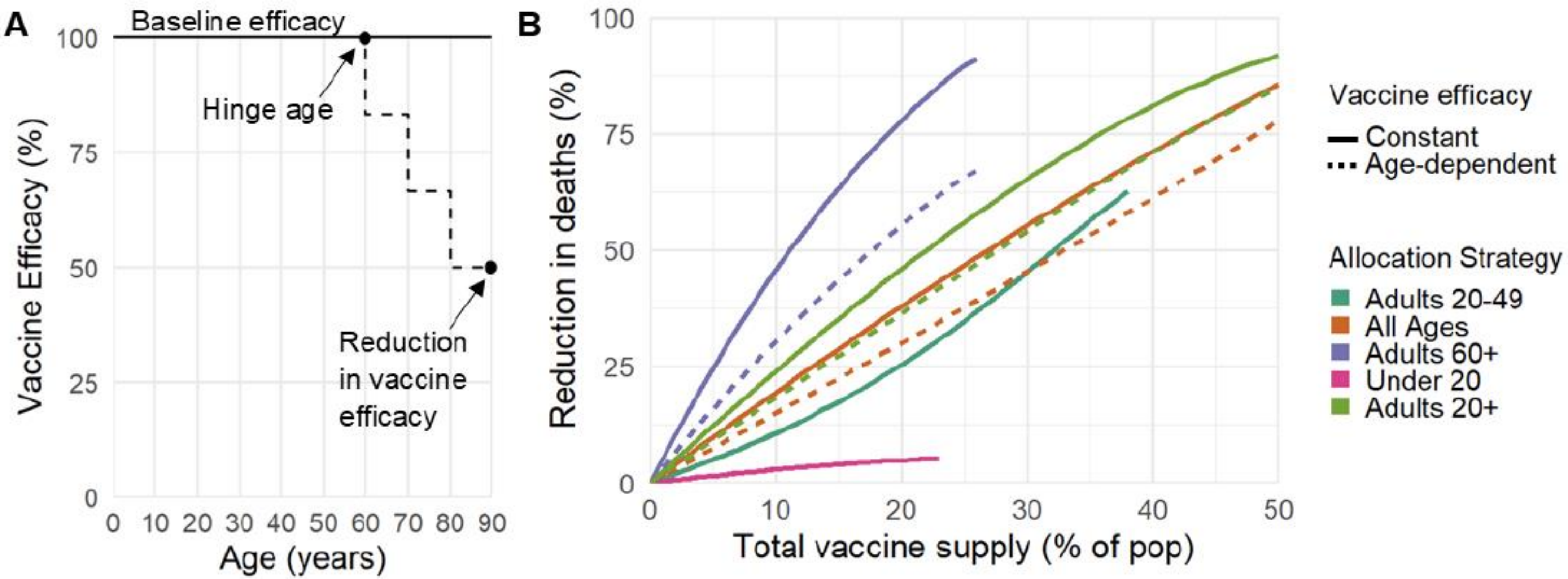
How do different prioritizations play out?



mortality

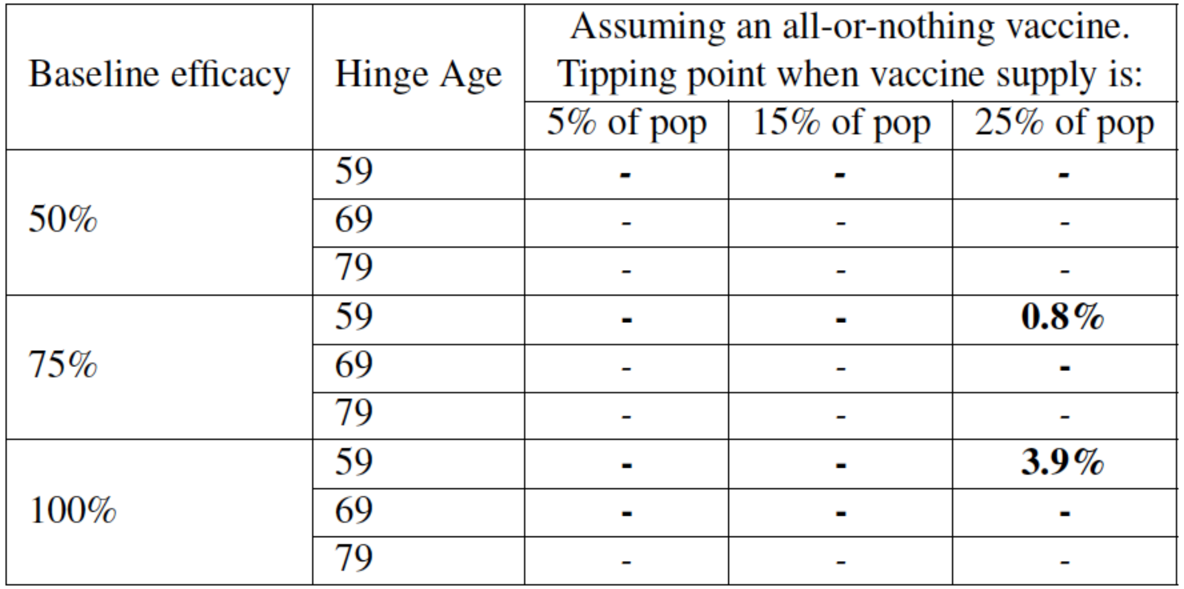
infections

What about variation in efficacy by age?



Prioritizing the elderly (similarly, comorbid) to reduce deaths is robust to:

Variations in efficacy by age

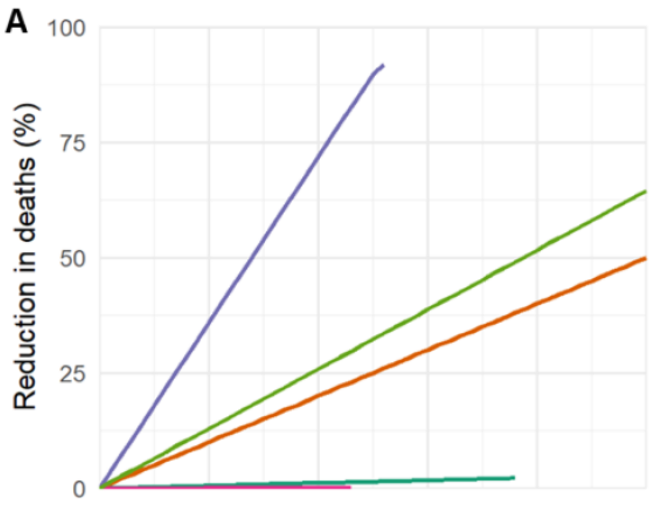


Baseline efficacy	Hinge Age	Assuming an all-or-nothing vaccine. Tipping point when vaccine supply is:		
		5% of pop	15% of pop	25% of pop
50%	59	**-**	**-**	**-**
	69	-	-	-
	79	-	-	-
75%	59	**-**	**-**	**0.8%**
	69	-	-	**-**
	79	-	-	-
100%	59	**-**	**-**	**3.9%**
	69	**-**	**-**	**-**
	79	-	-	-

Vaccine that protects only against symptoms/death: no effect on infections

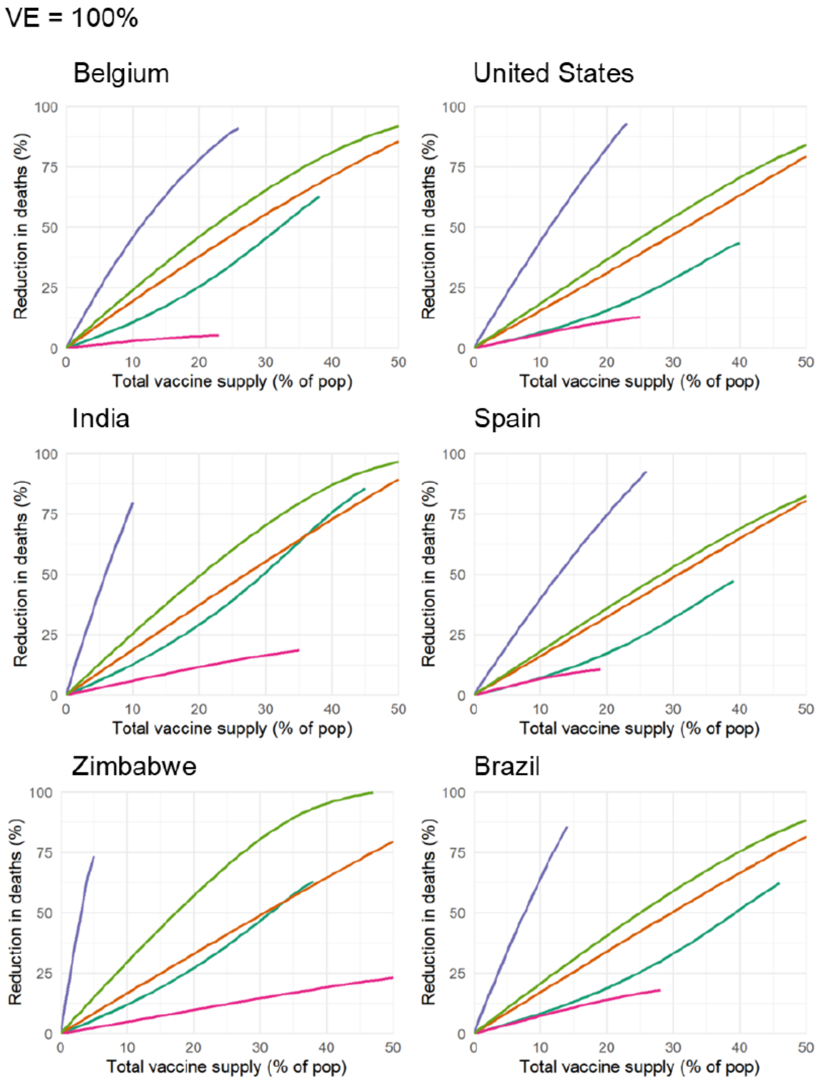
$VE_S = 0$, $VE_I = 0$, $VE_P = 1$

($\alpha = 1$, $\omega = 1$)



Prioritizing the elderly (similarly, comorbid) to reduce deaths is robust to:

Demography



Also to leaky or all-or-nothing vaccine

Summary

- When we have to roll out a vaccine, we will have imperfect information about efficacy in high-impact subgroups (elderly, comorbid) and impact on infection/transmission
- Post-trial serology and regular viral testing of all participants can help estimate impact on transmission
- Virus sequencing during trial can provide nearly unbiased estimate of infectiousness impact
- Basic principle to prioritize elderly, comorbid is robust to many different vaccine variants
- Have not considered prioritizing essential or HC workers.
- Still need to know these properties of vaccines: to know how many doses needed, how well transmission-blocking strategies can work, etc.