Use of models in study design for dynamic systems: Ebola vaccine trial design

Steven Bellan, PhD, MPH
Dept. of Epidemiology & Biostatistics, College of Public Health
University of Georgia

DAIDD
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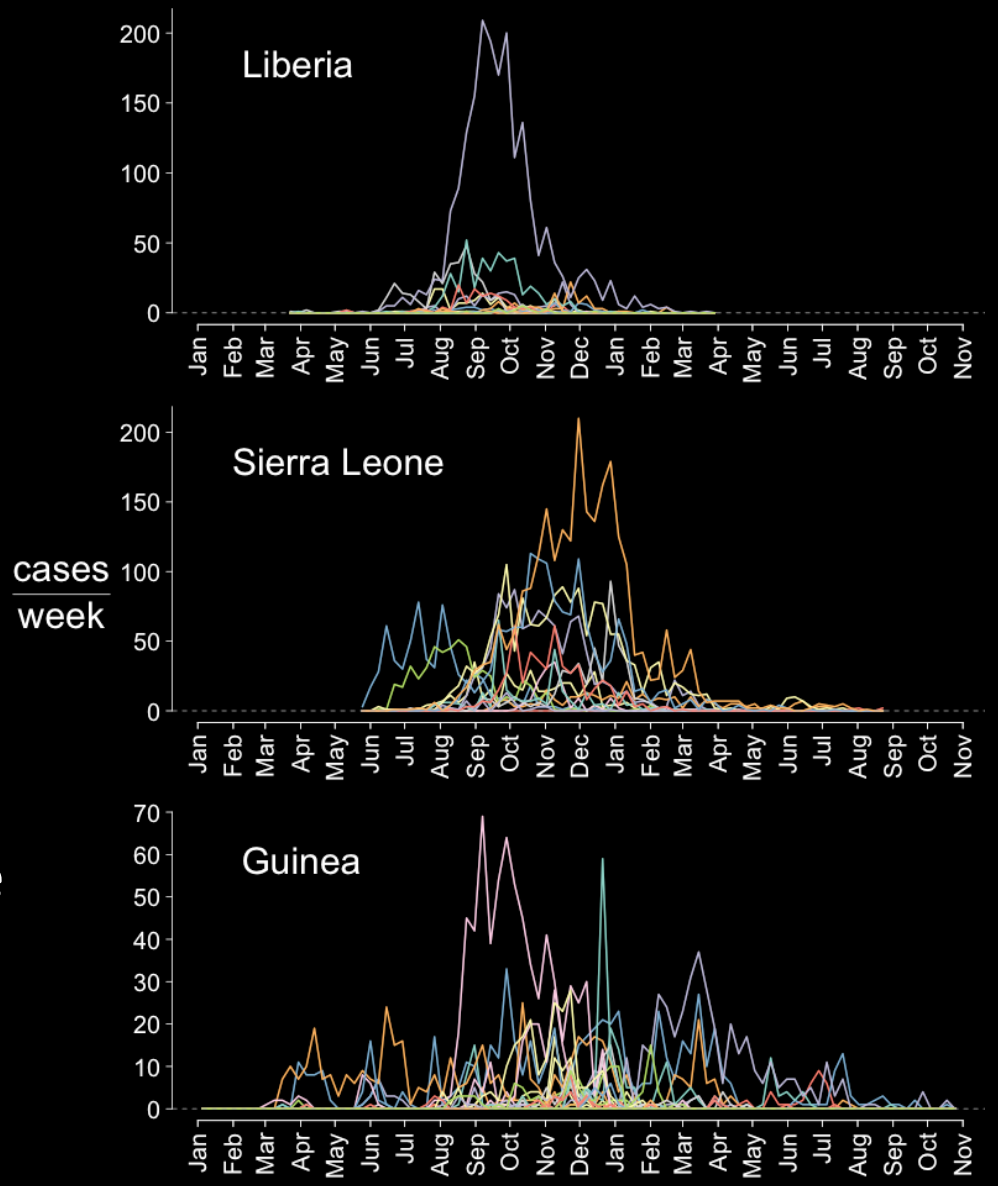
White Oak Conservation

The West African Ebola Epidemic

- What processes drive the epidemic?
- Who is at highest risk?
- When will it peak/end?
- Which interventions work?
- Optimal allocation of sparse resources?



Infectious Disease Research

Logistical, financial and ethical constraints limit quantity & quality of data

Perspectives from Two Disciplines

Classical Epidemiology	Mechanistic Epidemiology
Data-Centric	Process-Centric
(Public Health)	(Disease Ecology)
Risk Factors	Infectious Disease Dynamics
Biostatistics	Mathematical Modeling

Classical Epidemiology

- Does A cause B?

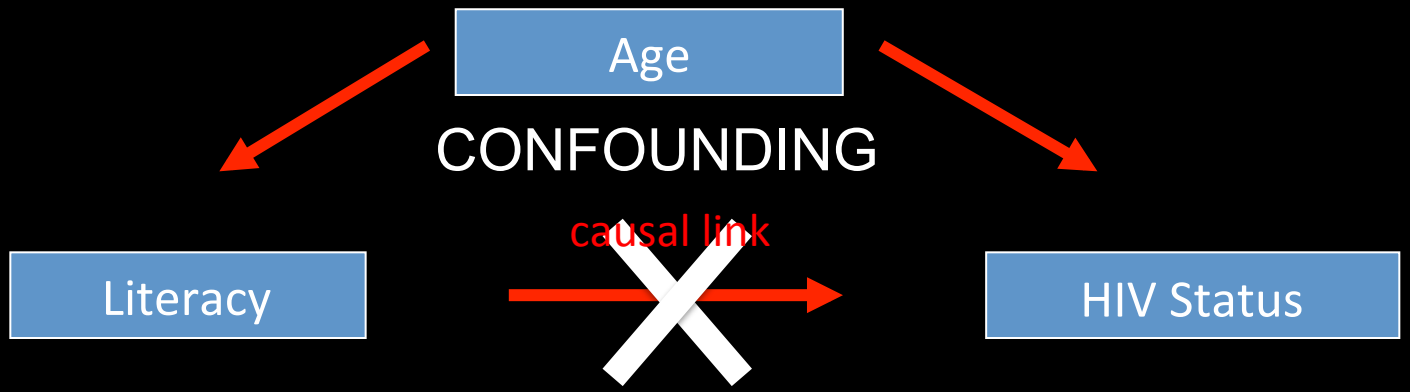
Classical Epidemiology

- Does literacy cause HIV?

Individual	Literate	HIV infected
1	0	0
2	0	0
3	0	0
4	0	1
5	1	1
6	1	0
7	1	1
8	1	1

HIV prevalence 3X greater amongst literate

- Find correlations that imply causality by accounting for
    1. random error: do we have enough data?
    2. bias: are design & analysis valid?



Classical Epidemiology

Infer causation via carefully identified correlations

Minimize bias via:

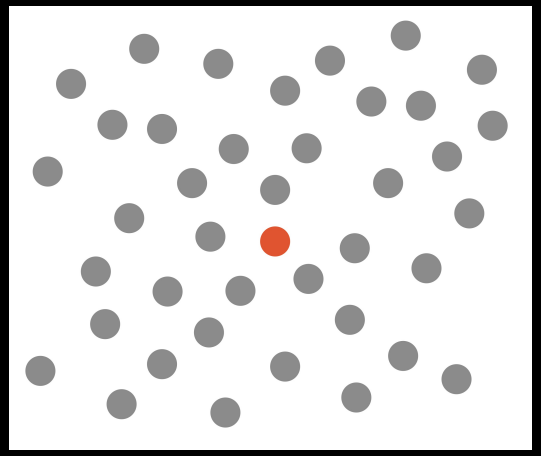
- study design: e.g. randomization, blinding
- analytical methods: e.g. causal inference modeling

What do *Introductory Epidemiology* courses teach?

- Measures of Disease
- Measures of Effect (of a risk factor)
- Study Designs for Measuring Effects
  - Dealing with random error
  - Dealing with confounding
  - Dealing with bias
- Biostatistical analyses for analyzing data

Mechanistic Epidemiology

- Scale up from individual processes to population patterns



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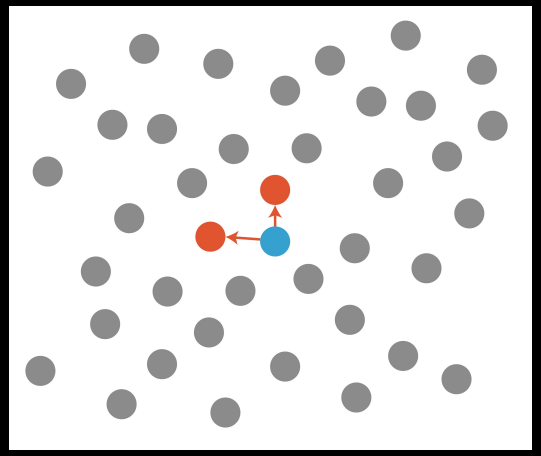

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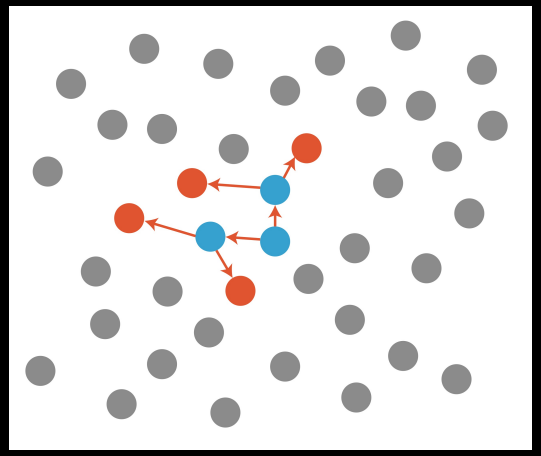

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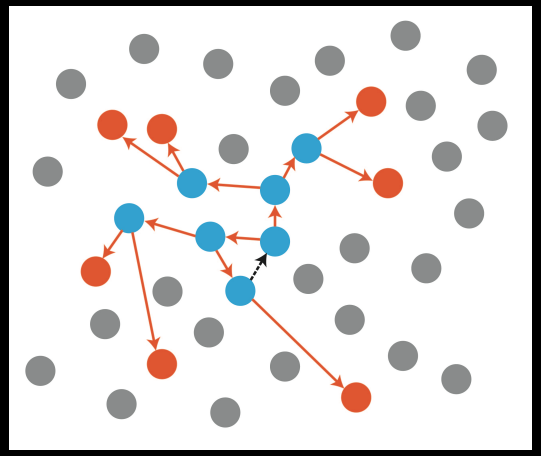

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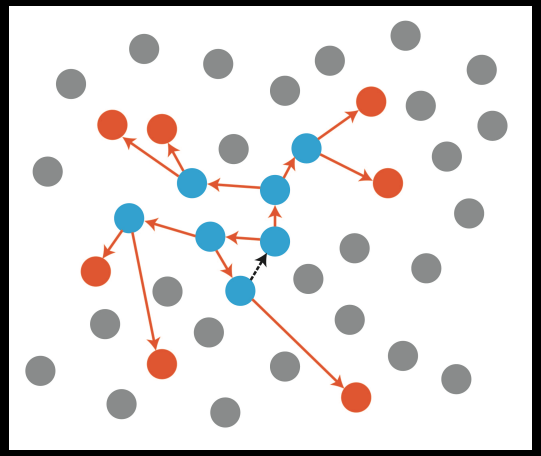
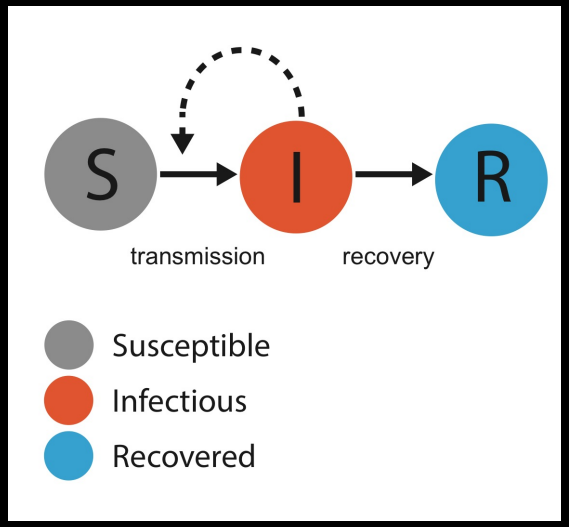


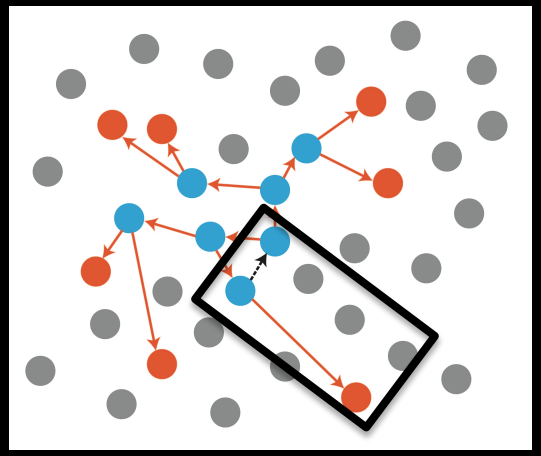
solid arrow = flow between disease states
dashed arrow = influence



How do contact processes cause epidemics?

Mechanistic Epidemiology

- Scale up from individual processes to population patterns



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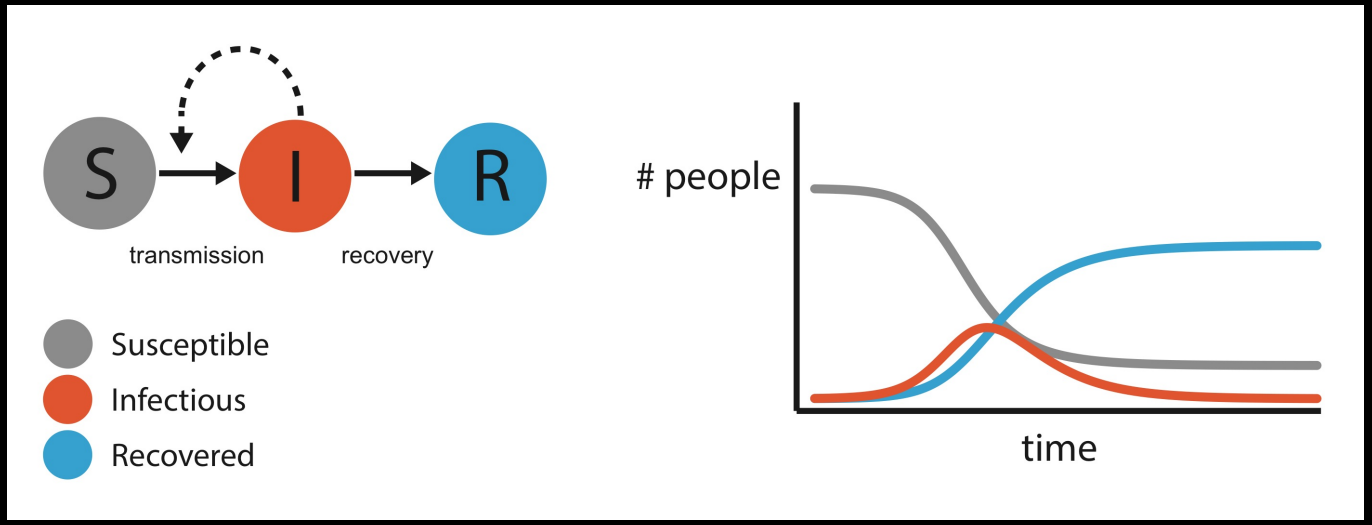

Mechanistic Epidemiology

- Scale up from individual processes to population patterns
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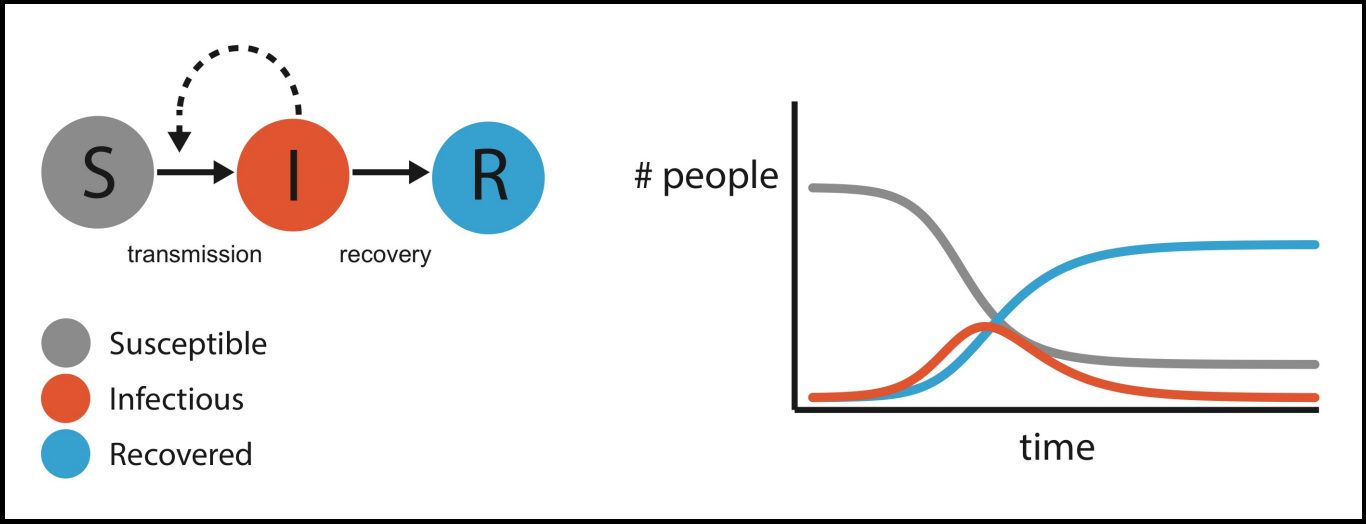

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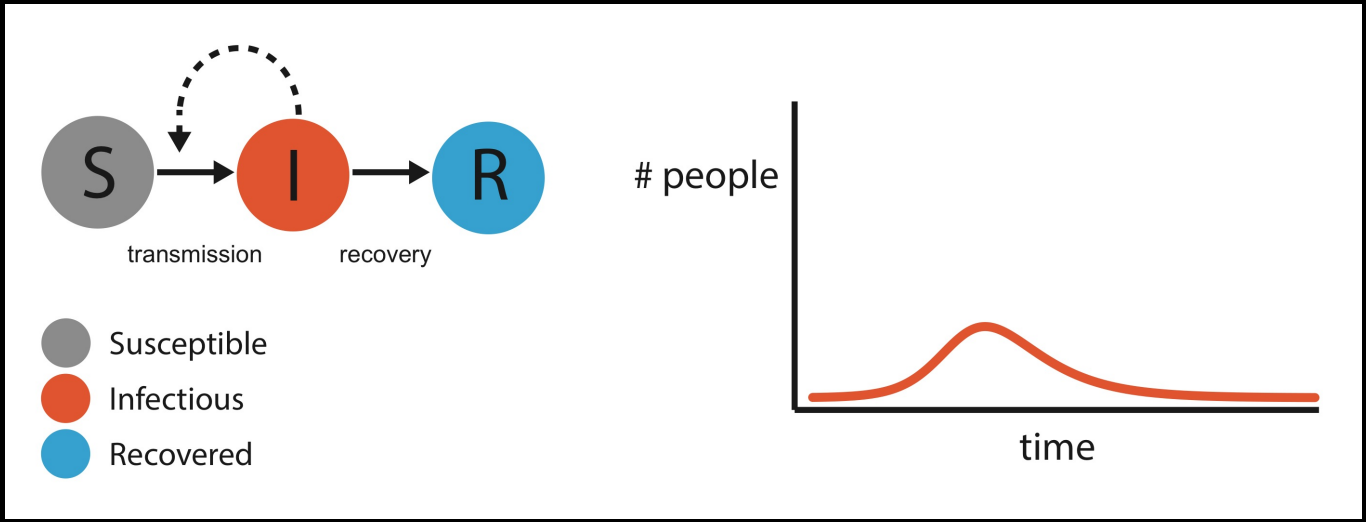

Mechanistic Epidemiology

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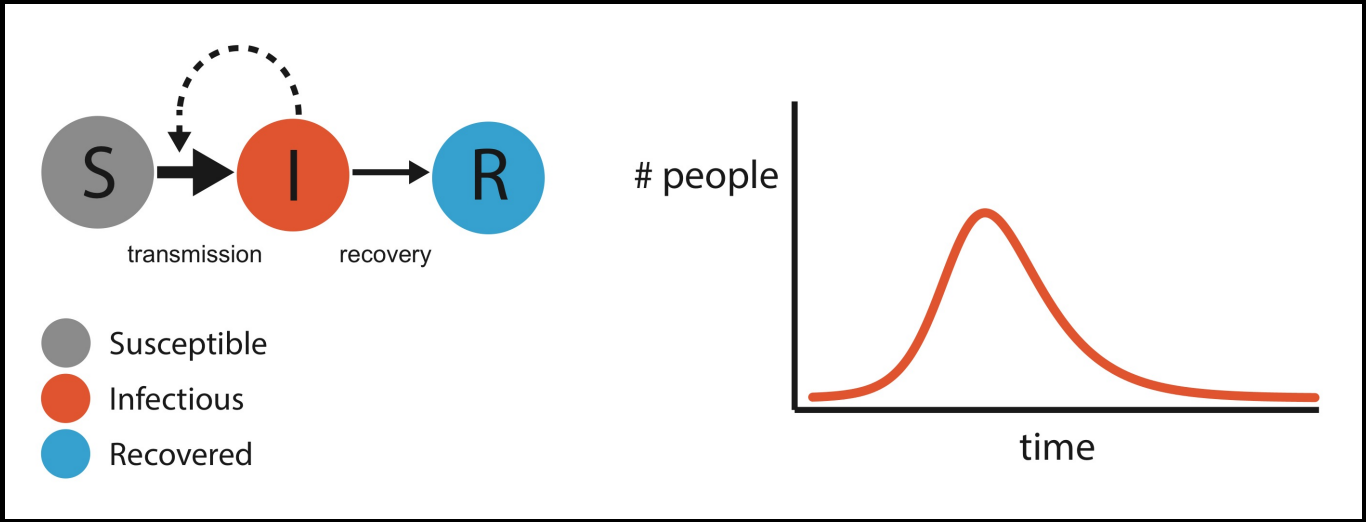
What if each person exposed 50% more people?



Mechanistic Epidemiology

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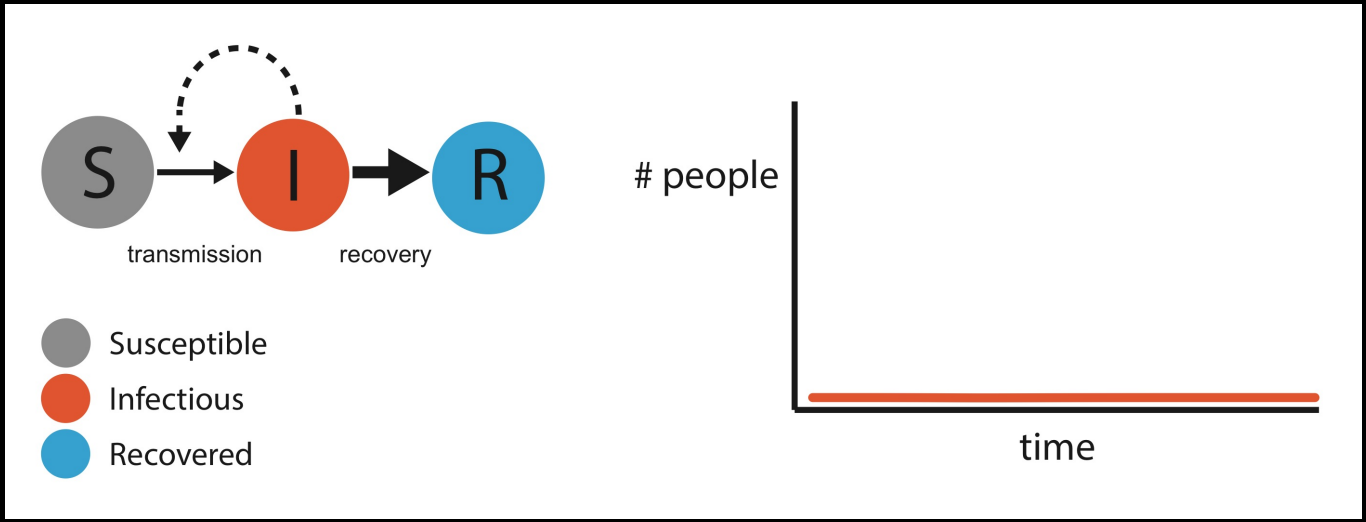
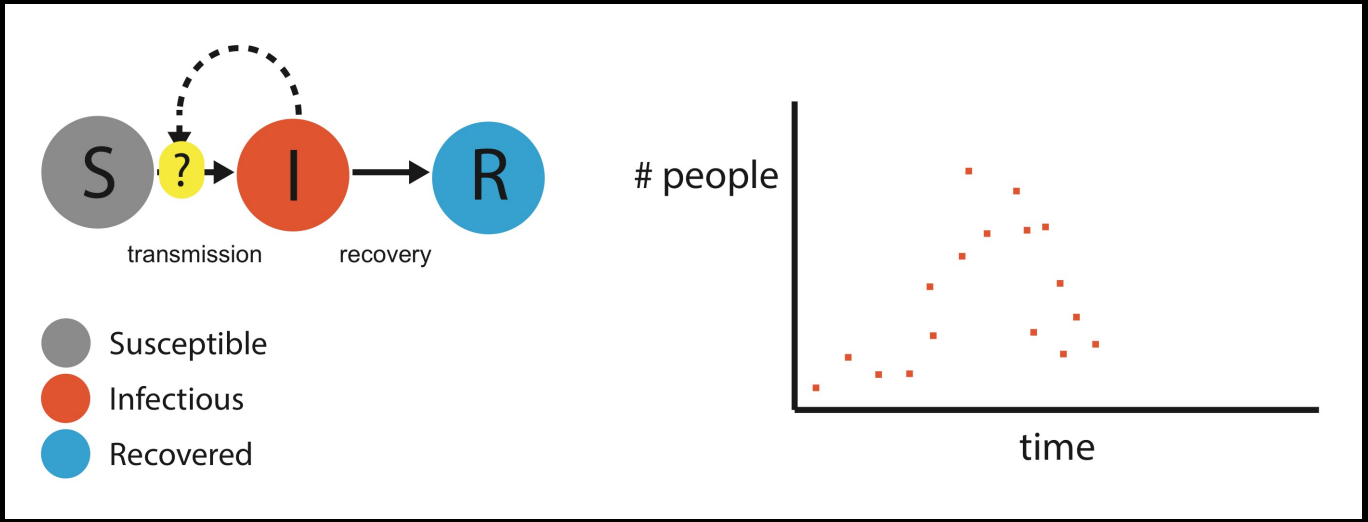
What if we treated people and doubled the rate of recovery?



Mechanistic Epidemiology

- Scale up from individual processes to population patterns
- “What if” scenarios not amenable to experimentation
- Estimating parameters by fitting available data



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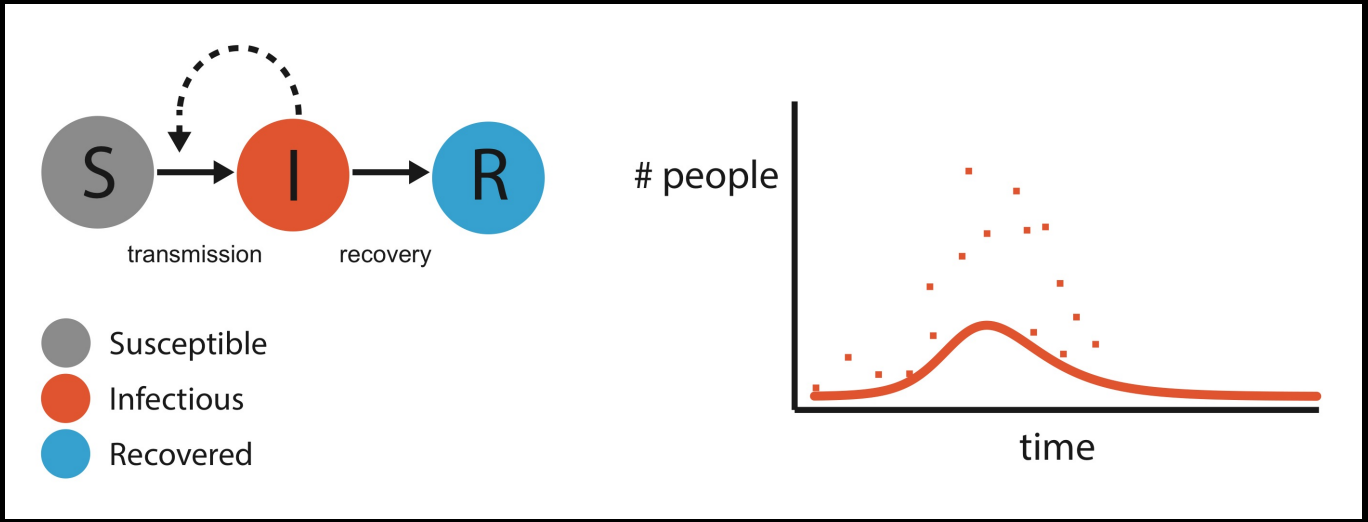

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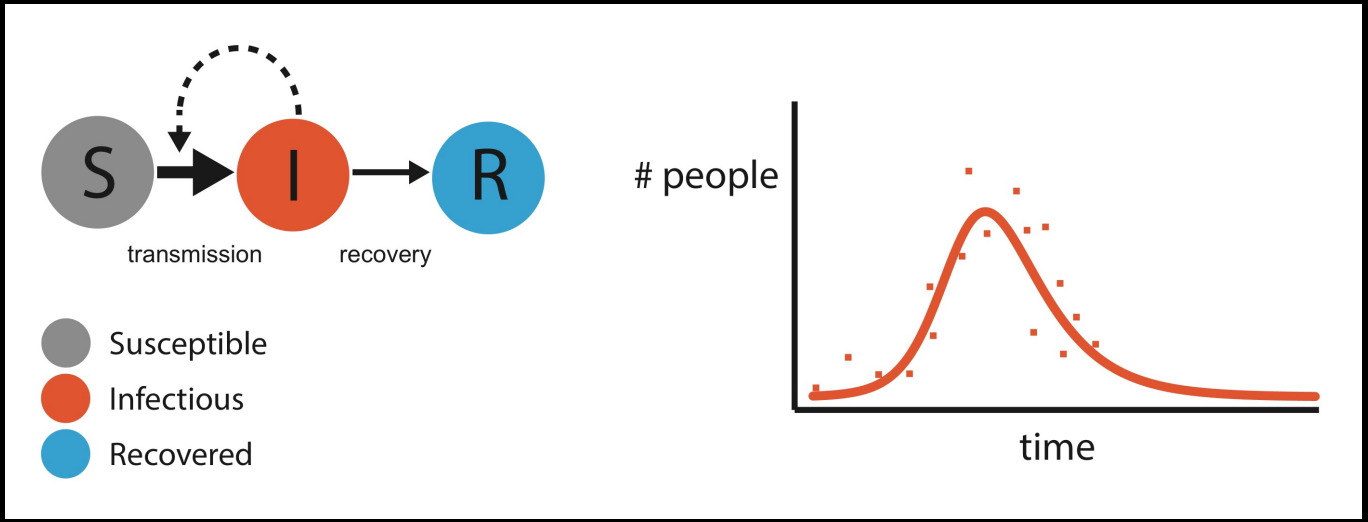
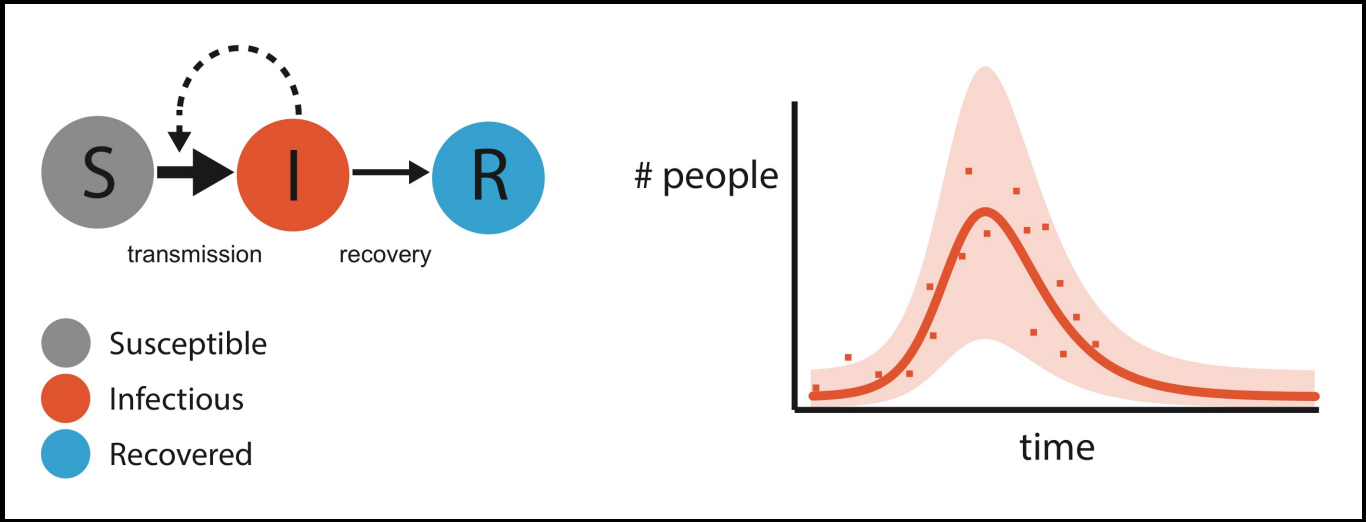


Mechanistic Epidemiology

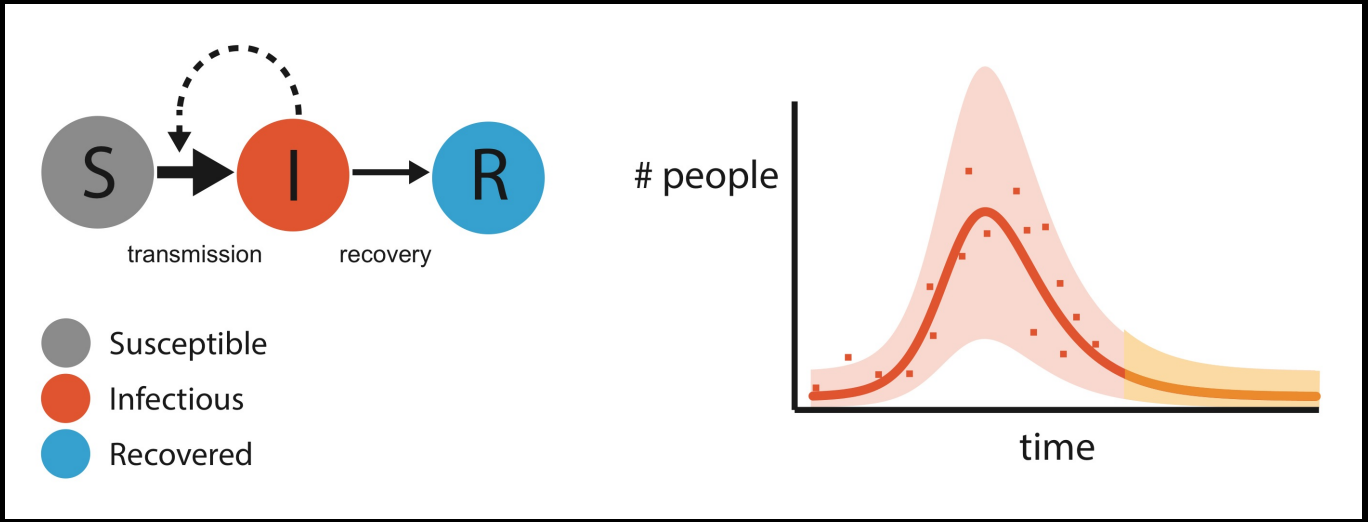
- Scale up from individual processes to population patterns
- "What if" scenarios not amenable to experimentation
- Estimating parameters by fitting available data

Estimate transmission rate or other model parameters
(with confidence intervals)



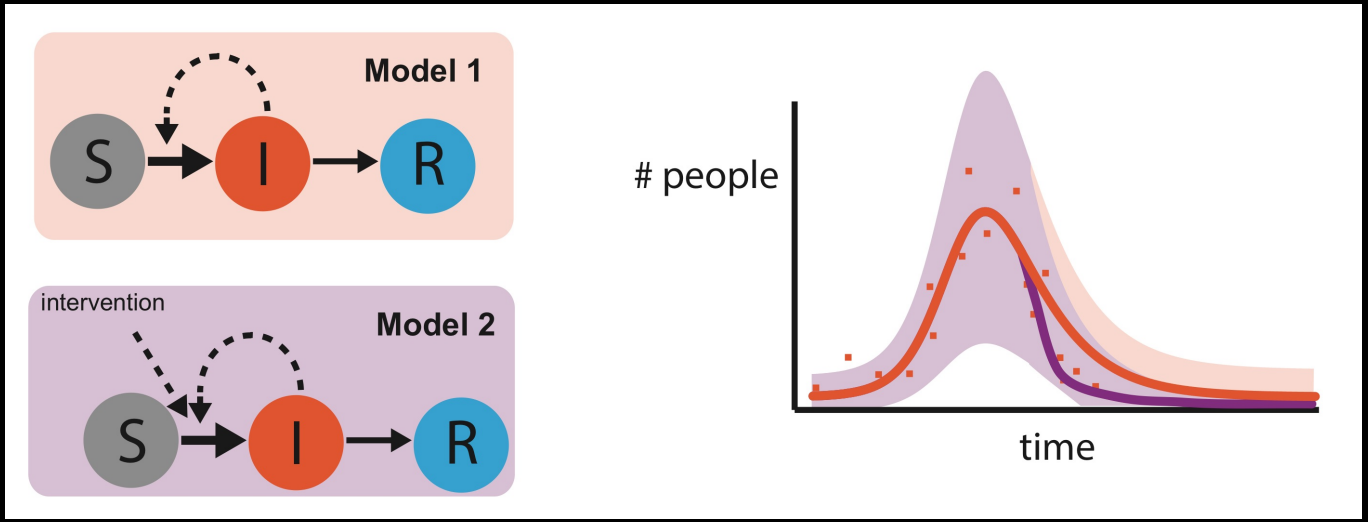
Mechanistic Epidemiology

- Scale up from individual processes to population patterns
- “What if” scenarios not amenable to experimentation
- Estimating parameters by fitting available data
- Prediction



Mechanistic Epidemiology

- Scale up from individual processes to population patterns
- “What if” scenarios not amenable to experimentation
- Estimating parameters by fitting available data
- Prediction
- Model selection (choosing between alternative hypotheses)



Mechanistic Epidemiology

- Scale up from individual processes to population patterns
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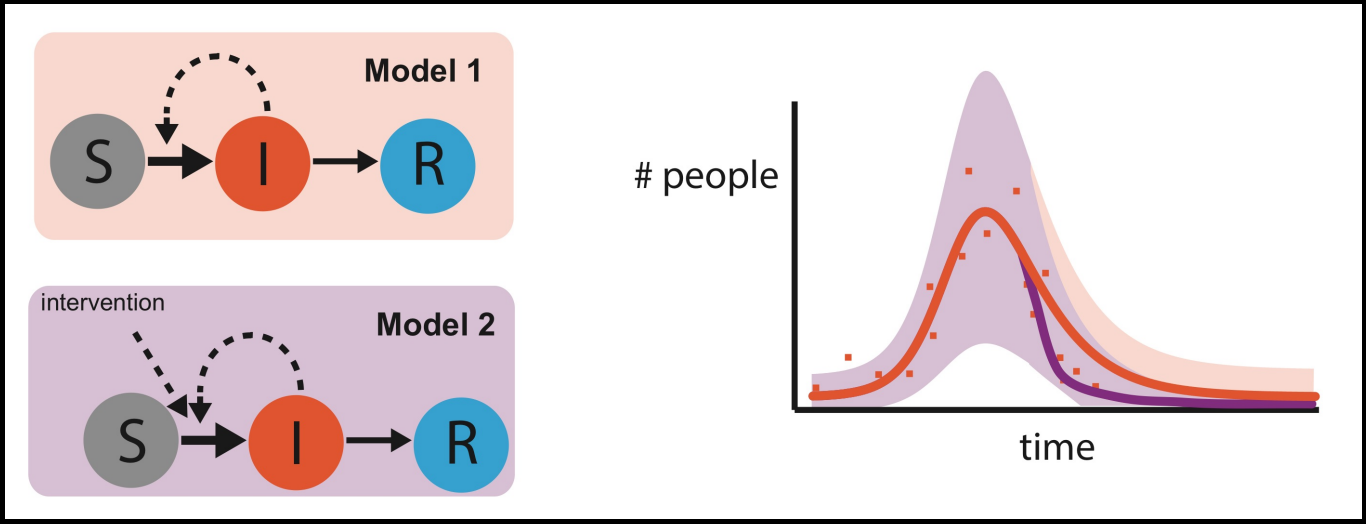
- Estimating parameters by fitting available data
- Prediction
- Model selection

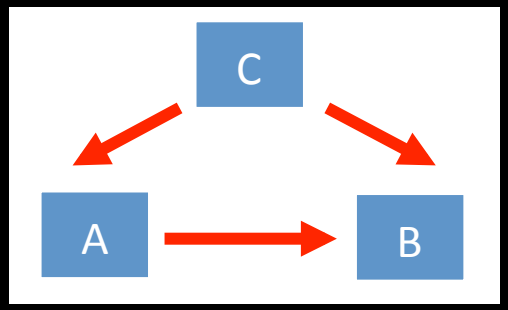
data focus emerged in last 10 years



Classical Epidemiology

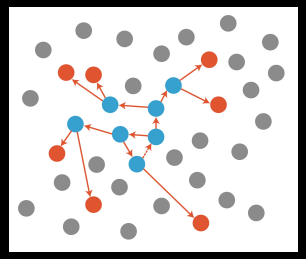
Data-Centric

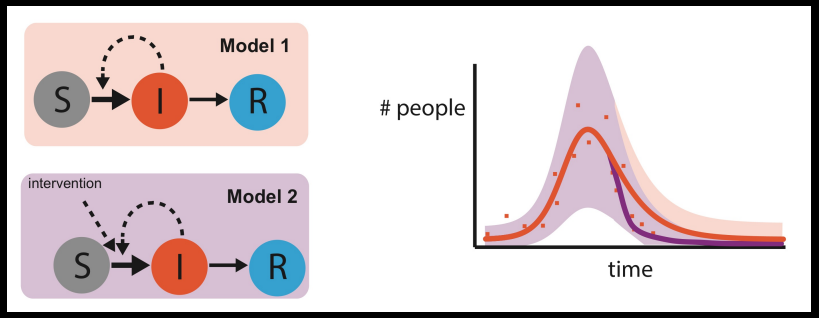
Individual	Literate	HIV infected	Age	SES
1	0	0	5	high
2	0	0	8	high
3	0	0	7	low
4	0	1	16	low
5	1	1	35	low
6	1	0	28	high
7	1	1	18	low
8	1	1	45	high



Mechanistic Epidemiology

Process-Centric





An Integrative Approach

Mechanistically model both observation processes & underlying epidemiological processes

Vaccine Efficacy Trials

- Compare disease risk between
  vaccinated & *unvaccinated* participants.

- If high risk people choose to be vaccinated, confounding

- Confounding avoided by randomization

- Randomized double-blinded placebo-controlled trials

Is randomization ethical?

- You are a HCW in Sierra Leone,
  many colleagues have died of Ebola.
- A vaccine appears safe and promising.
- Would you want to be randomized to placebo?

Equipoise

Uncertainty regarding whether
a participant is better off
receiving intervention or placebo.

Stepped Wedge Cluster Trial

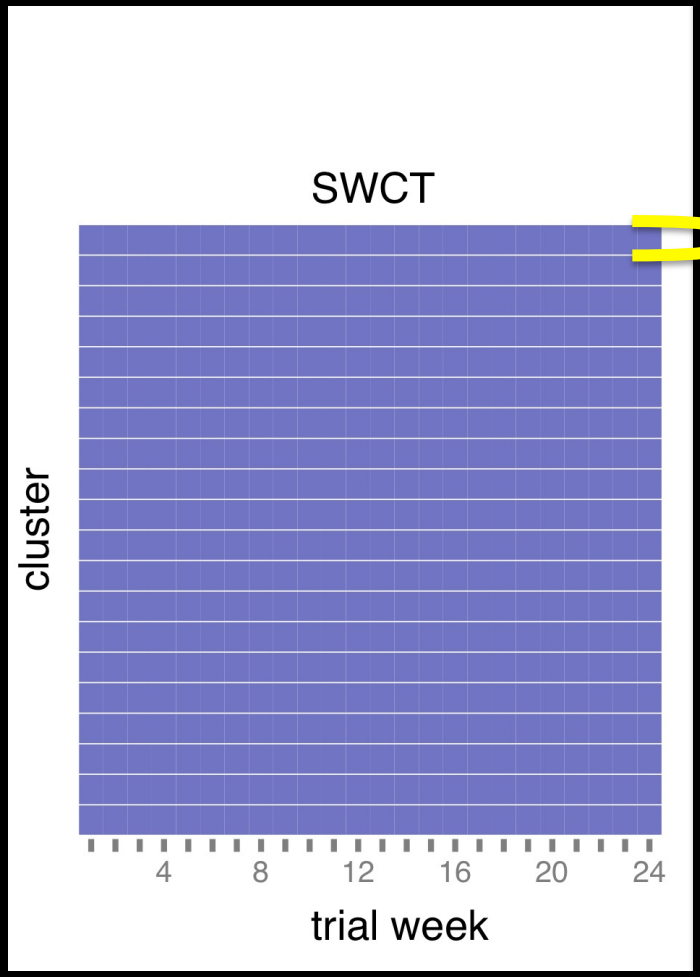
- Evaluate vaccine when ethically problematic to withhold intervention

- Vaccinate everyone *as fast as possible*, by groups, in random group-order

- Compare infection risk between
  vaccinated & *not-yet-vaccinated* individuals

- Randomized group-order avoids confounding

Stepped Wedge Cluster Trial

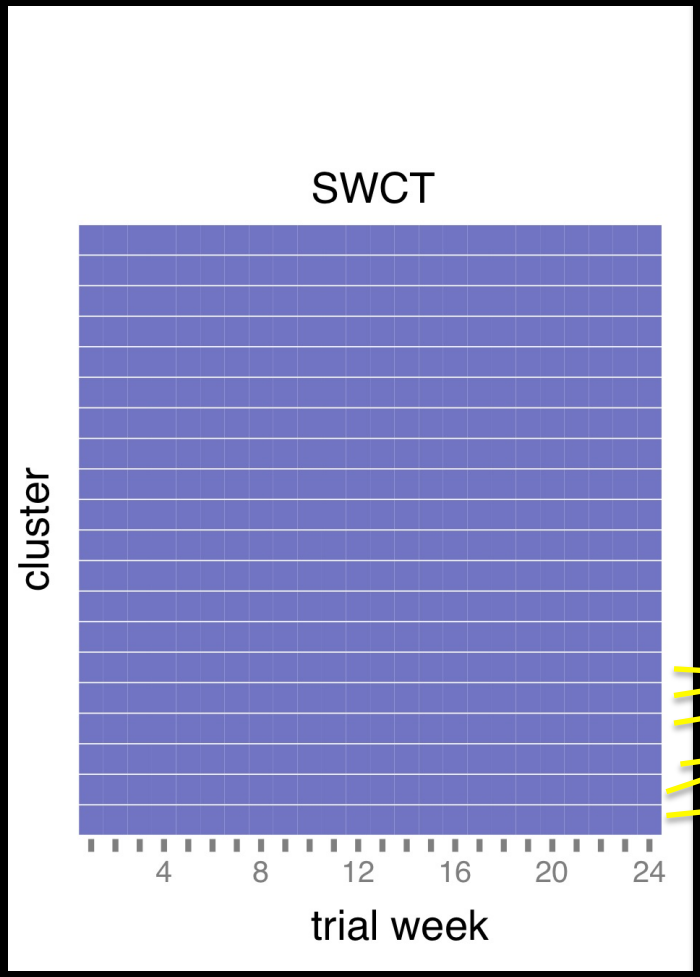


Cluster of 300 frontline caregivers (HCW+)

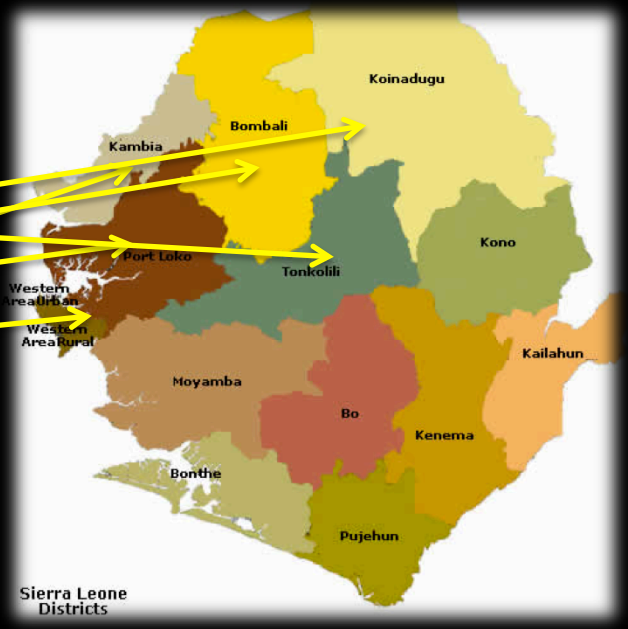
x20

Observed for 24 weeks (6 months)

Stepped Wedge Cluster Trial



Clusters from geographically distinct areas



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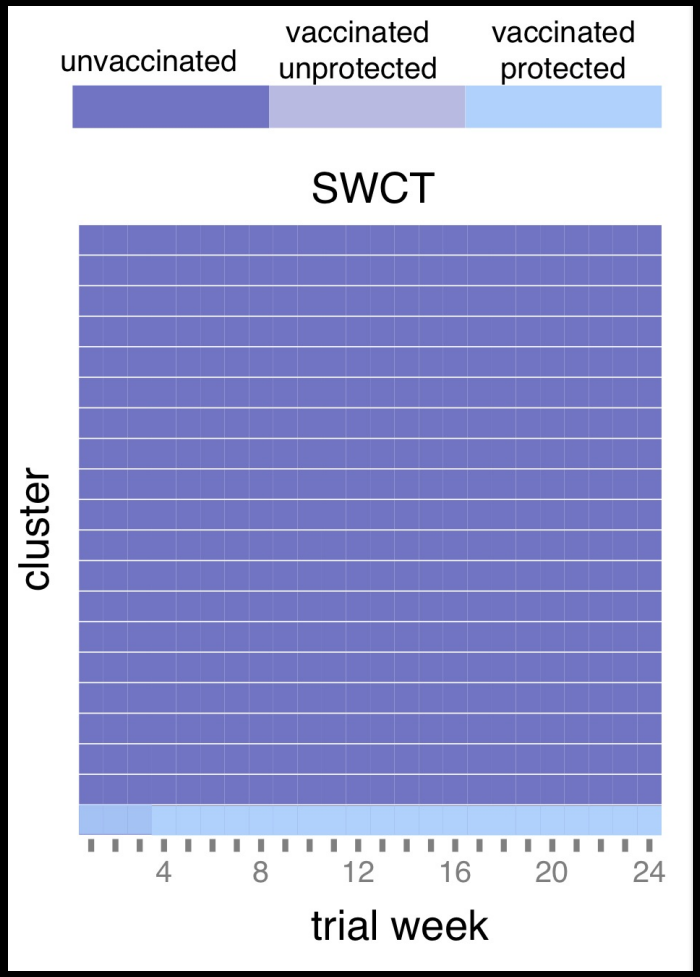
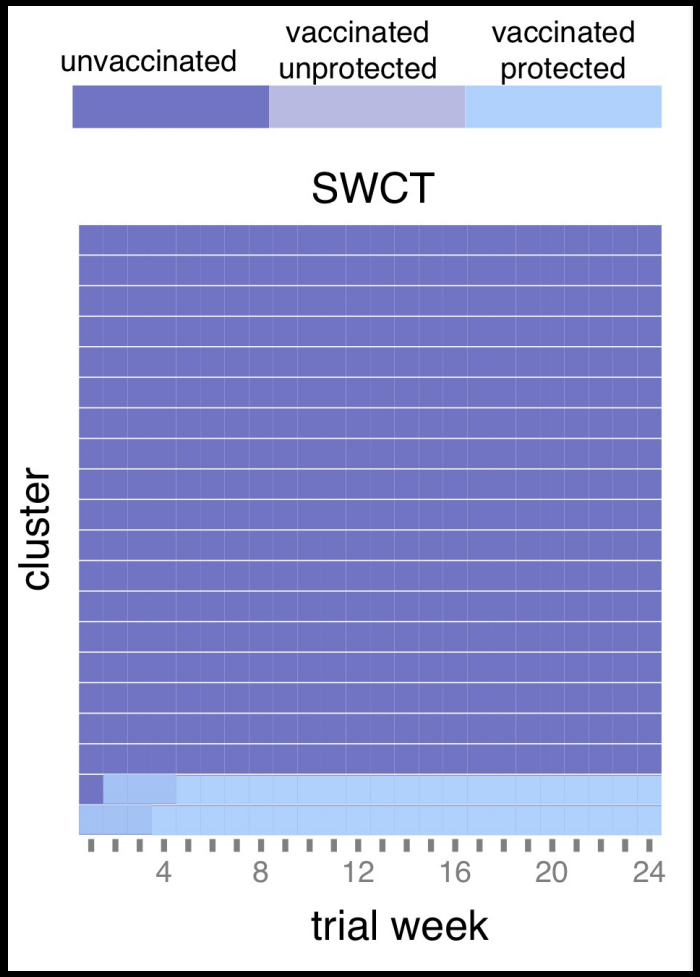


Vaccinate one cluster each week

Stepped Wedge Cluster Trial



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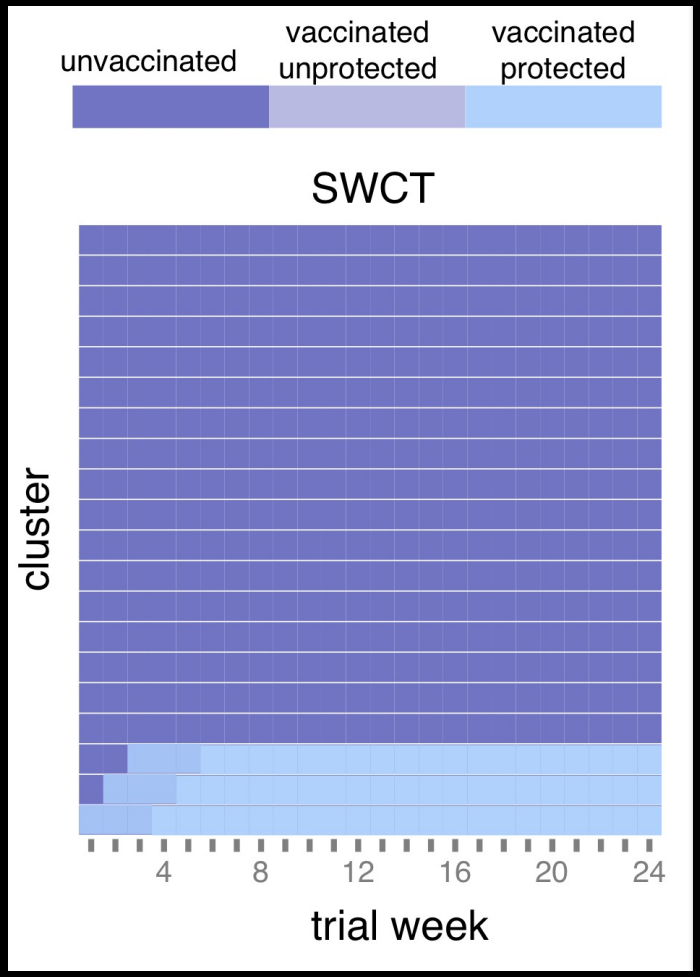

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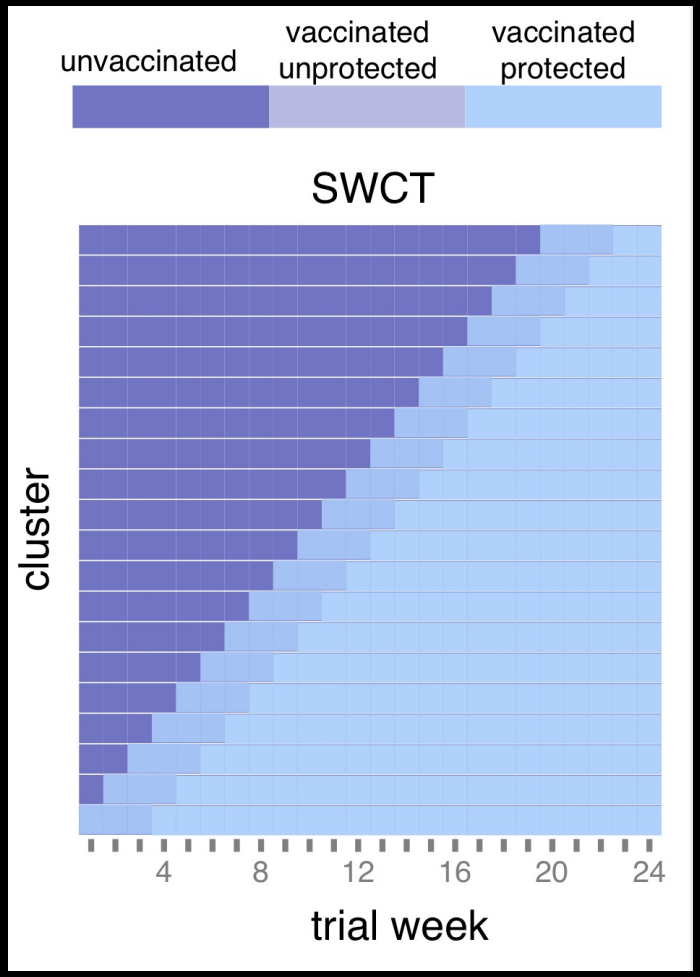
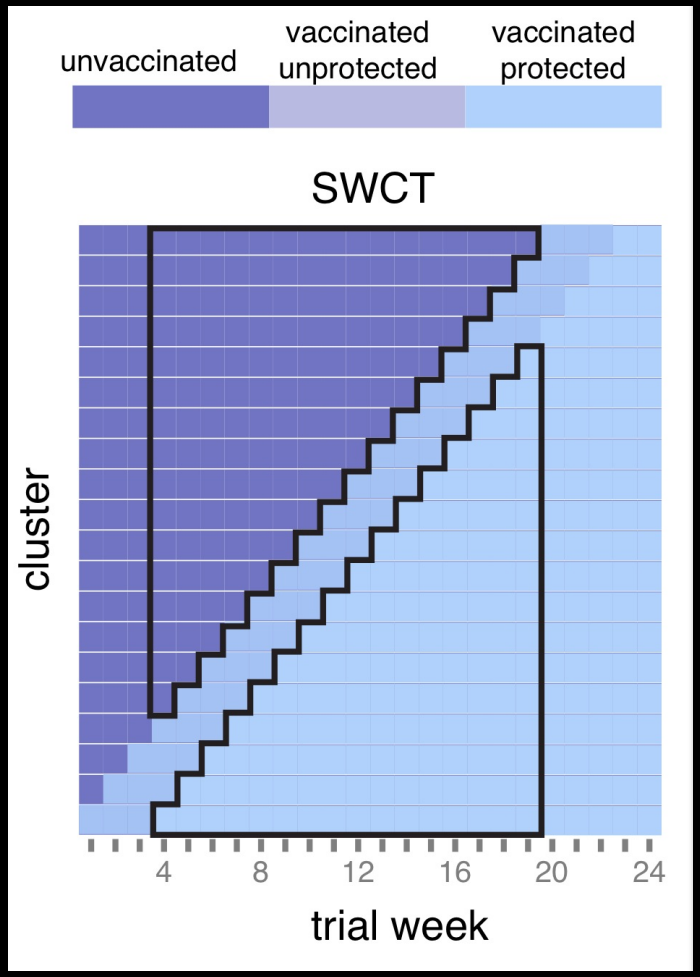


Vaccinate one cluster each week

Everyone vaccinated to avoid equipoise dilemma

Stepped Wedge Cluster Trial

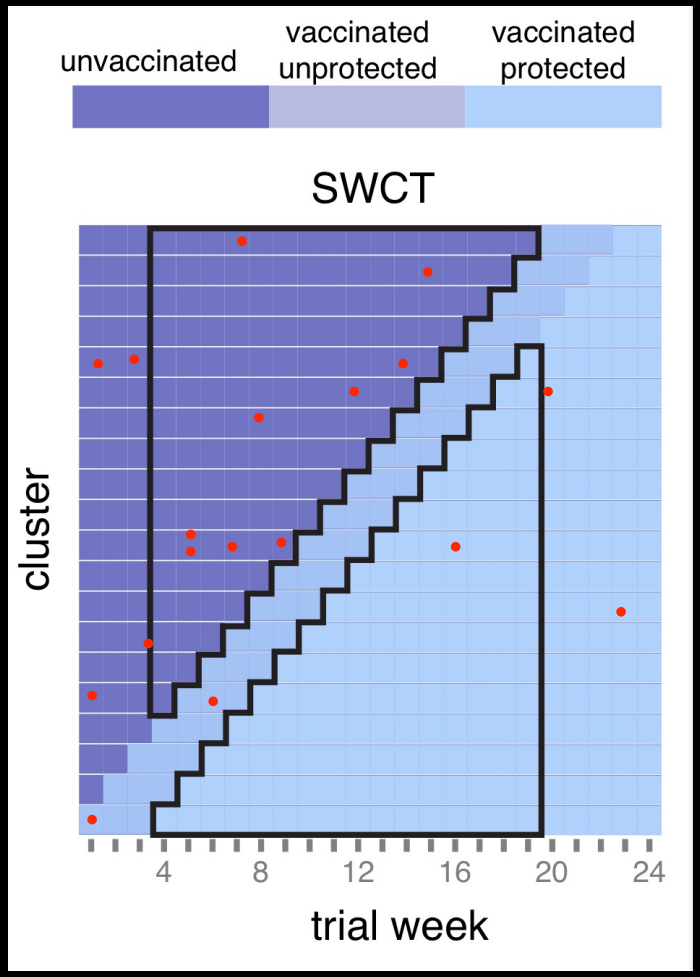


Vaccinate one cluster each week

Everyone vaccinated (no equipoise issues)

Compare # infections between vaccinated & not-yet-vaccinated

Stepped Wedge Cluster Trial



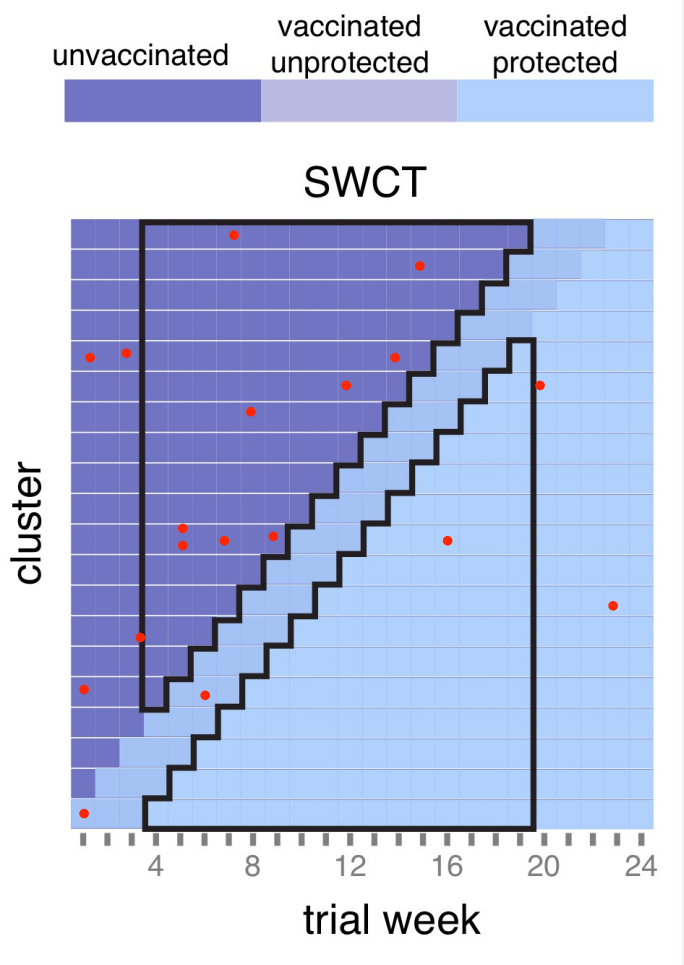
Vaccinate one cluster each week

Everyone vaccinated (no equipoise issues)

Compare # infections between vaccinated & not-yet-vaccinated

- infected participant

Stepped Wedge Cluster Trial

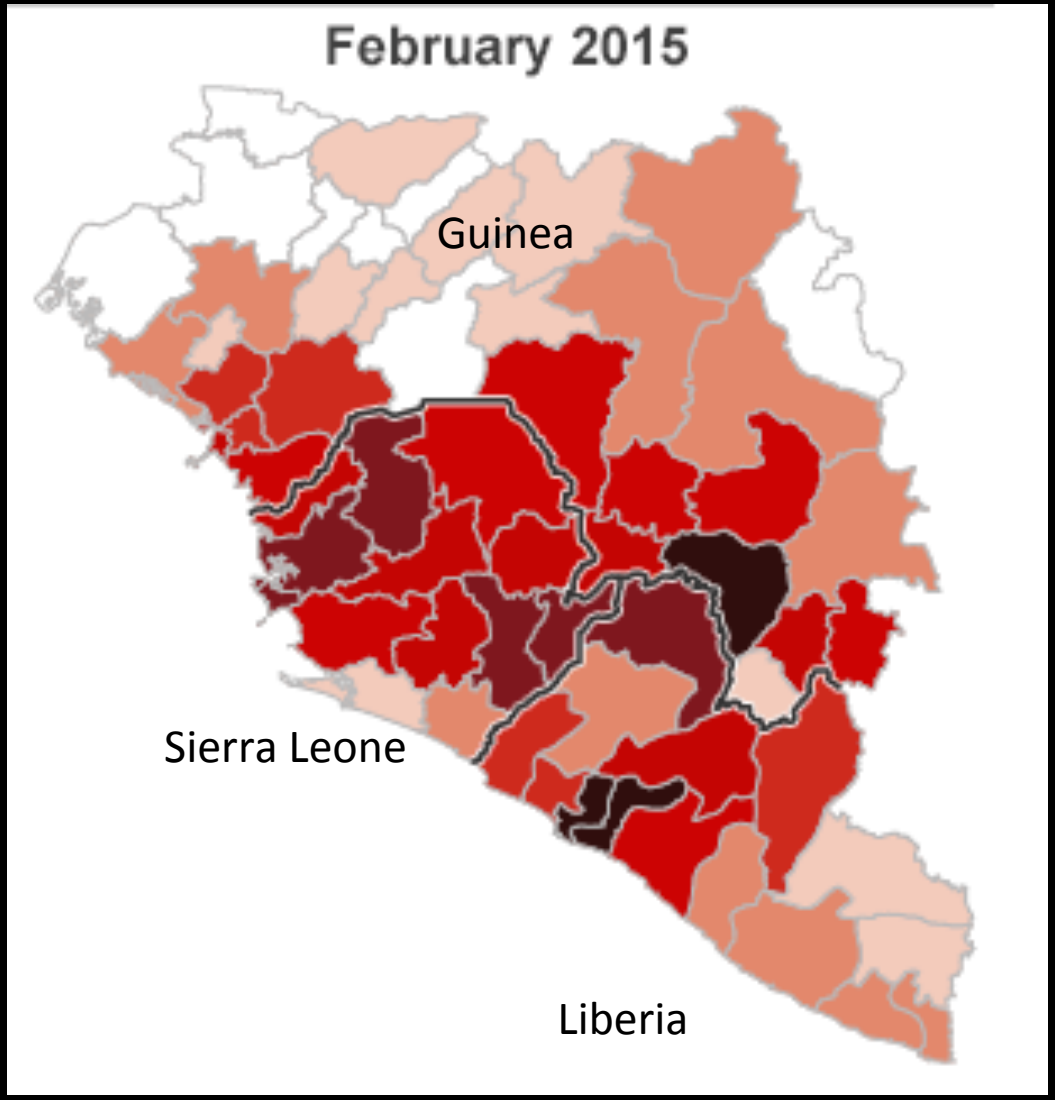


Nov 2014: To avoid equipoise dilemma CDC proposed this design.

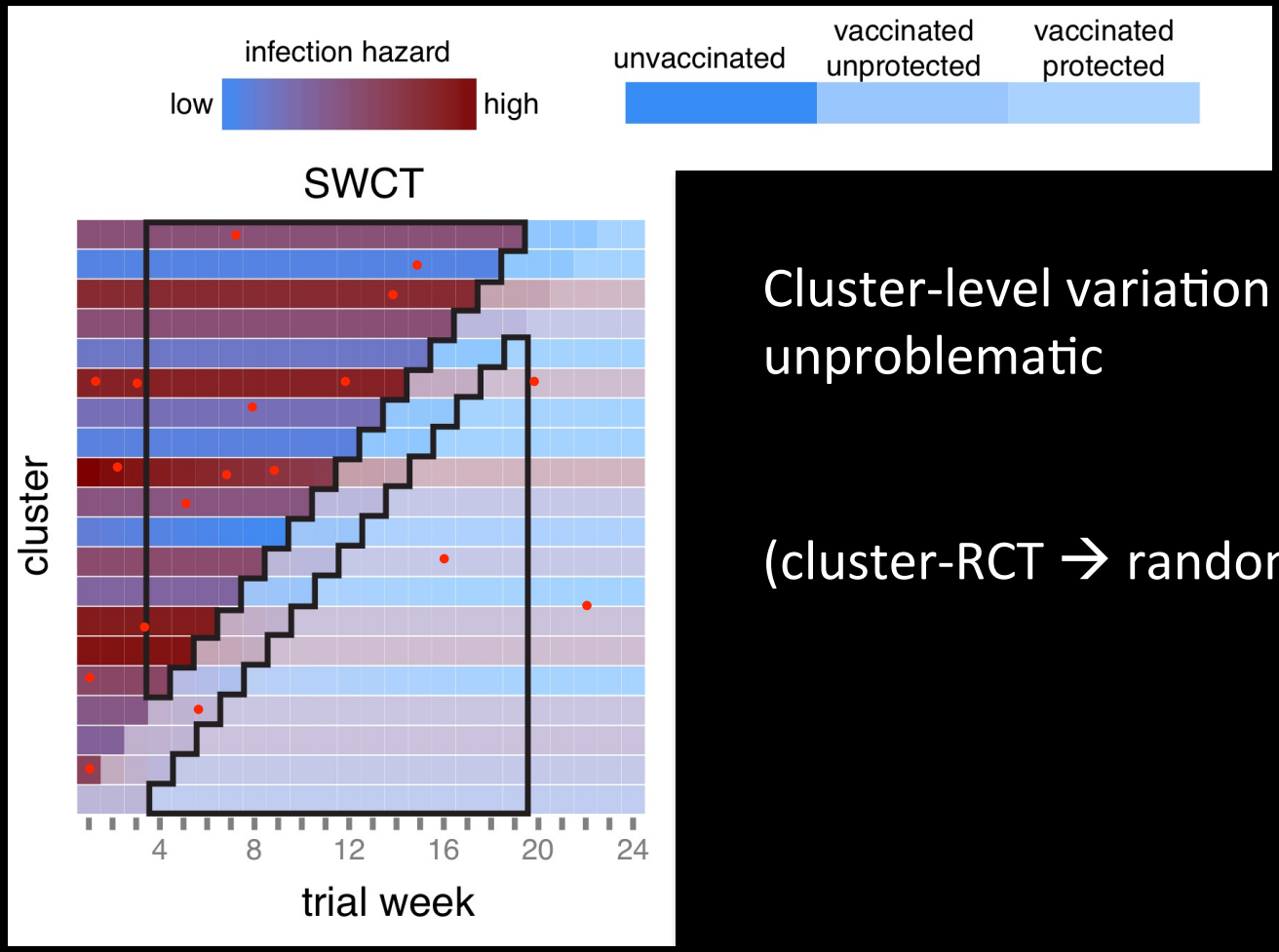
Jan 2014: Uncertain about SWCT given declining incidence.

Offered quantitative assessment.

Regional Variation in Ebola Cases



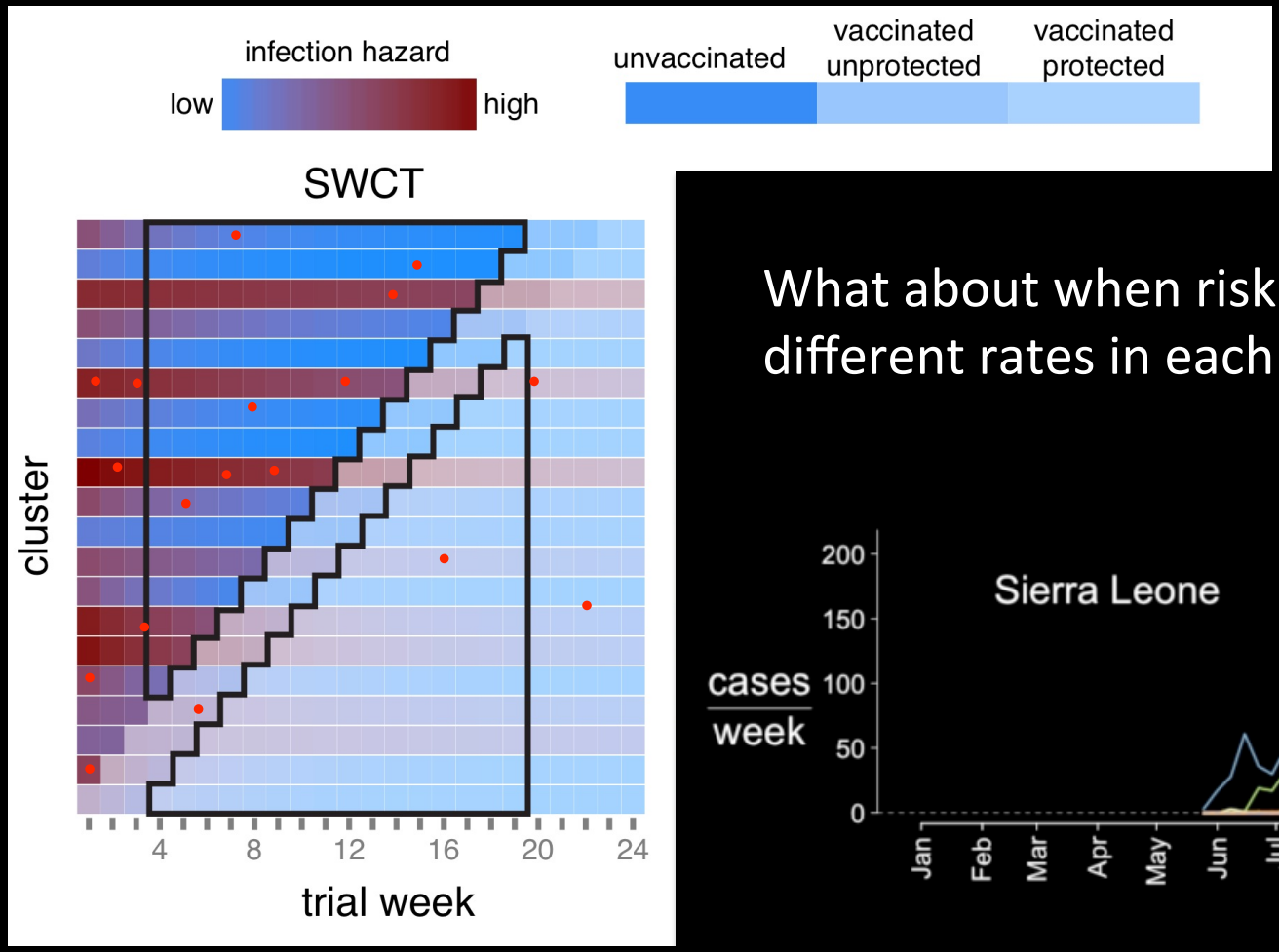
Stepped Wedge Cluster Trial



Cluster-level variation unproblematic

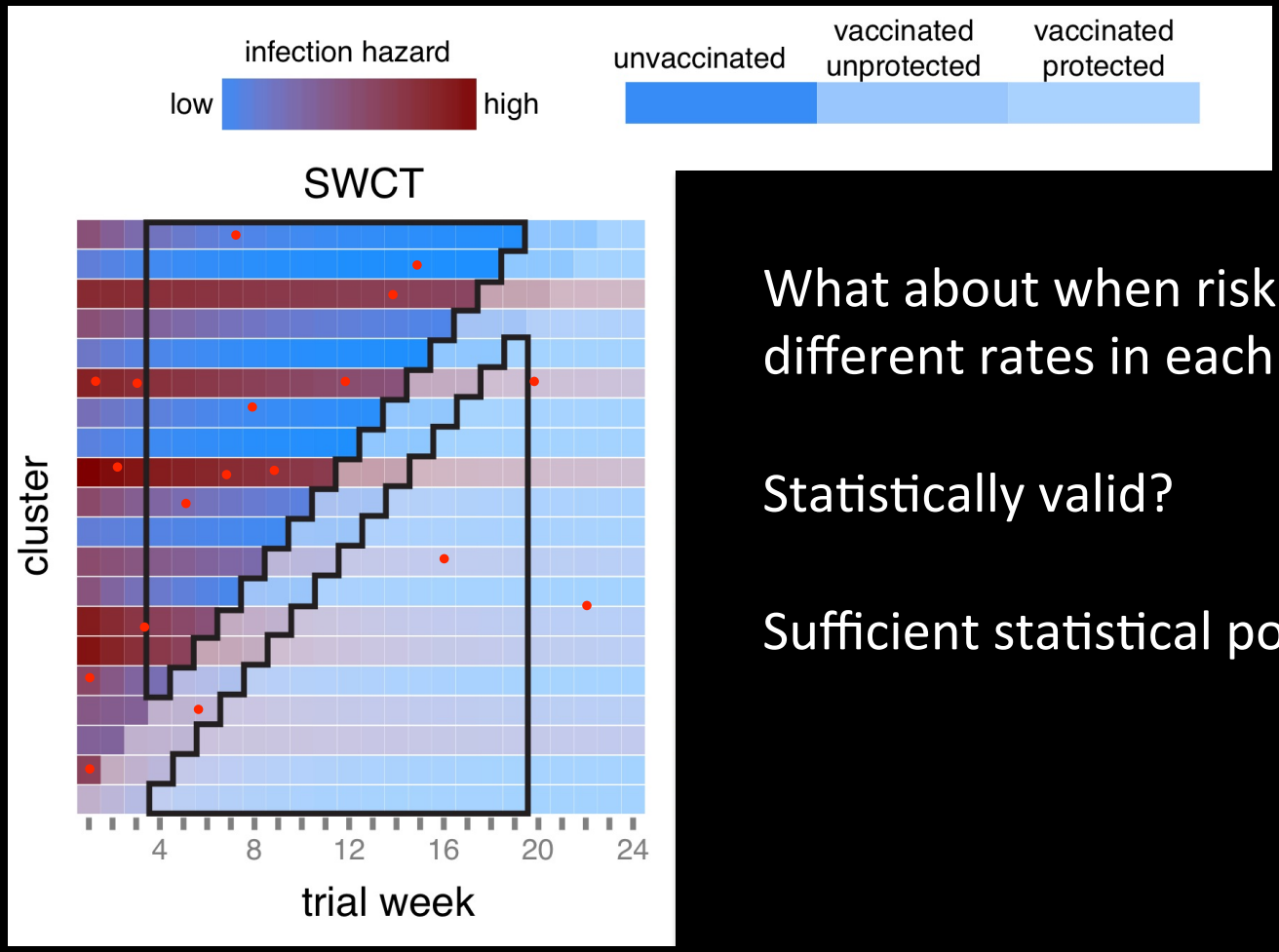
(cluster-RCT → random effects)

Stepped Wedge Cluster Trial



What about when risk is declining at different rates in each district?

Stepped Wedge Cluster Trial



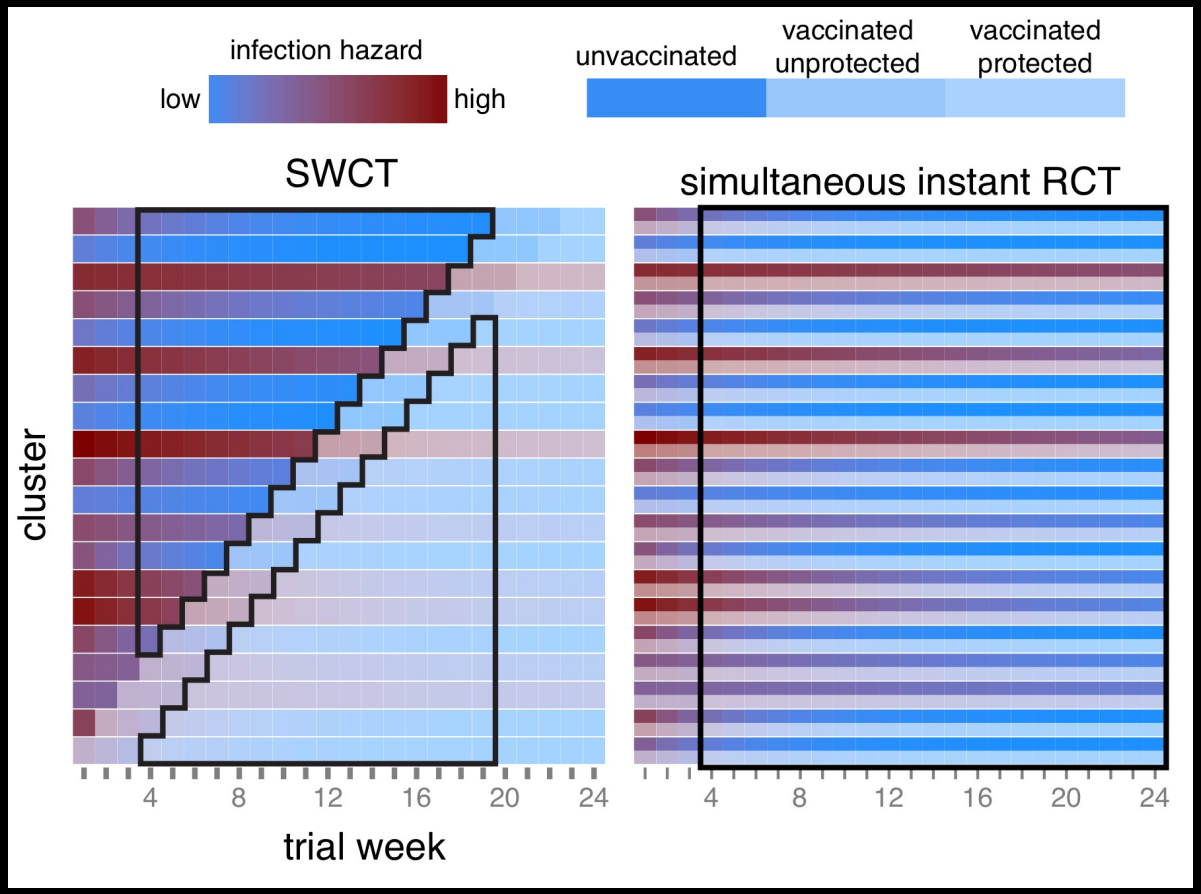
What about when risk is declining at different rates in each district?

Statistically valid?

Sufficient statistical power?

Bellan et al. 2015. *Lancet Inf Dis*.

Other Options

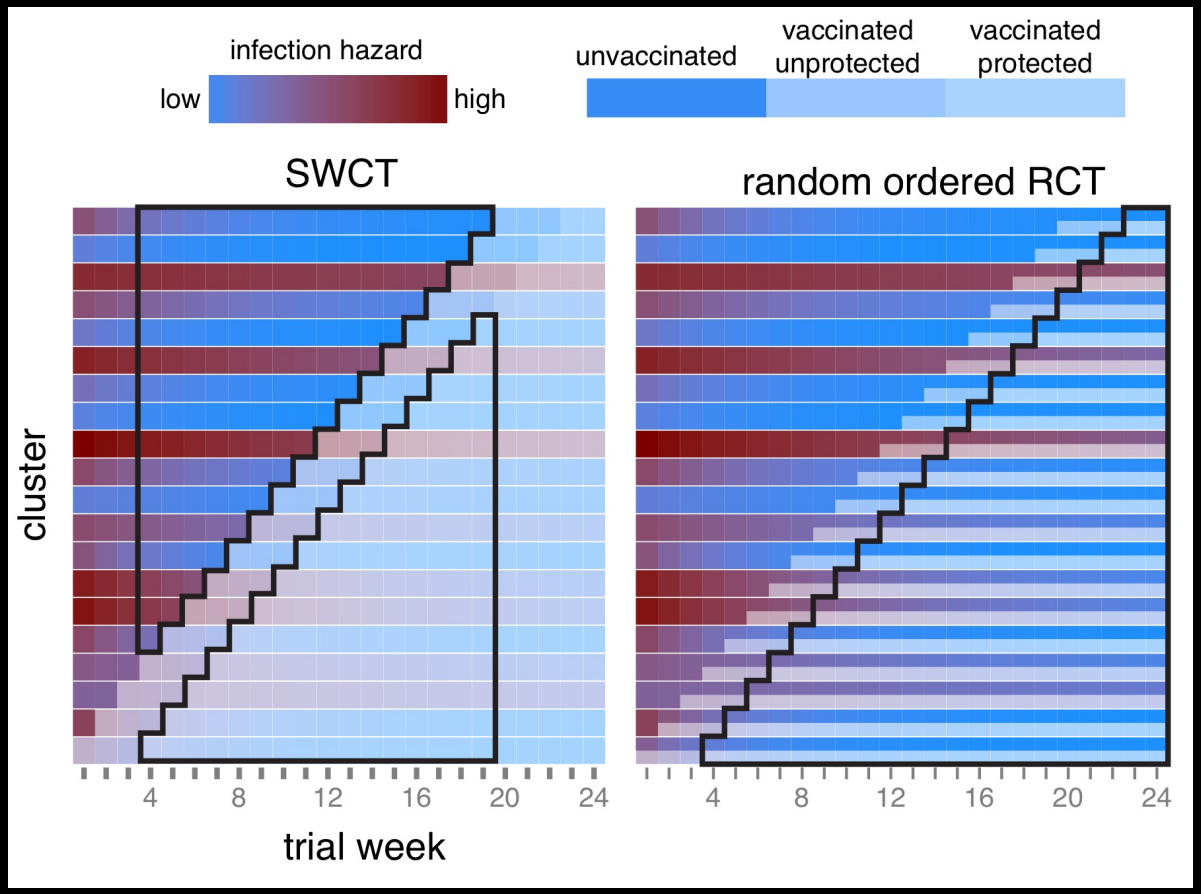


Vaccinate half of each cluster immediately.

Compare arms in same clusters.

Not logistically feasible.

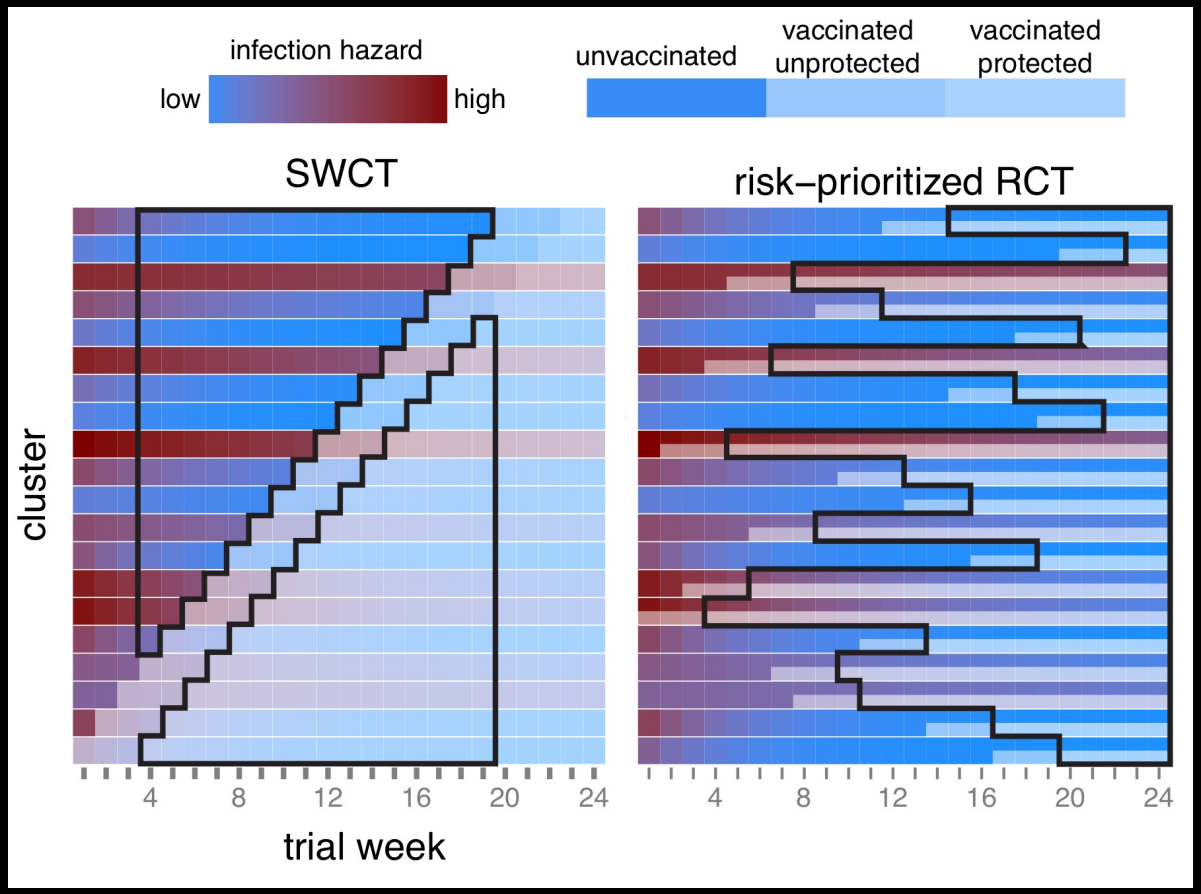
Other Options



Vaccinate half of each cluster 1 week at a time.

Compare arms in same clusters.

Other Options

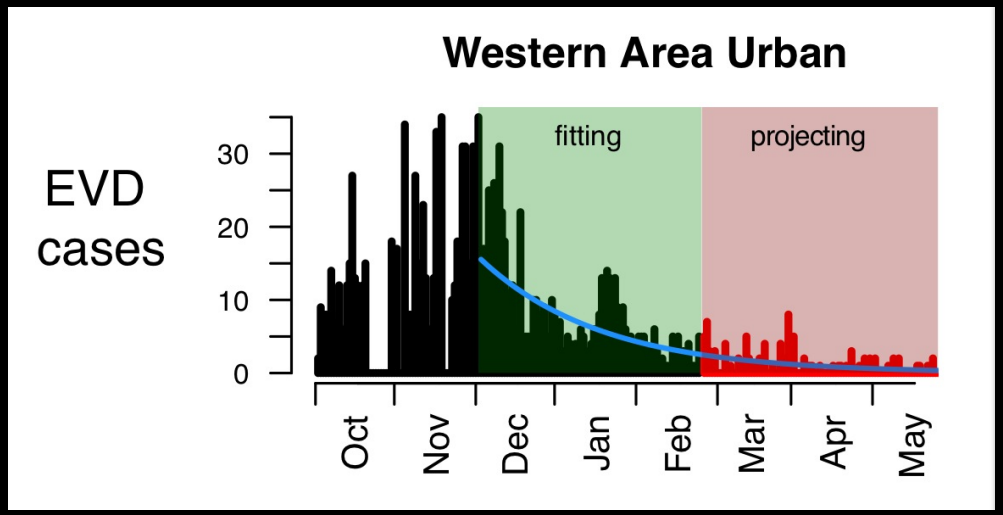


Vaccinate half of each cluster 1 week at a time.

Compare arms in same clusters.

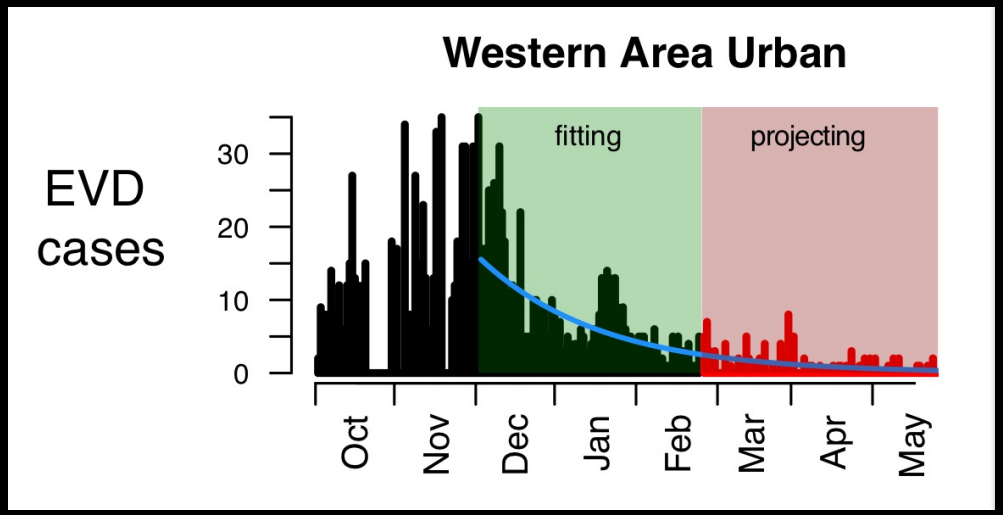
Prioritize high risk clusters.

Project Declining Epidemics



Exponential decay models fit to district-level incidence

Project Declining Epidemics



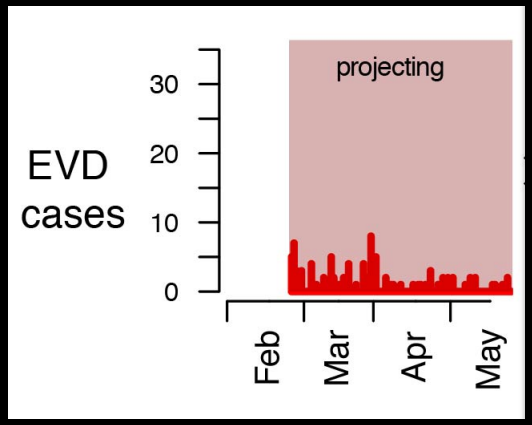
Exponential decay models fit to district-level incidence

Stochastic models simulate random fluctuations in cases

Project Declining Epidemics

Then, assume 5% of all cases occur in health care workers.

Faye et al. 2015. *Lancet Inf Dis*.



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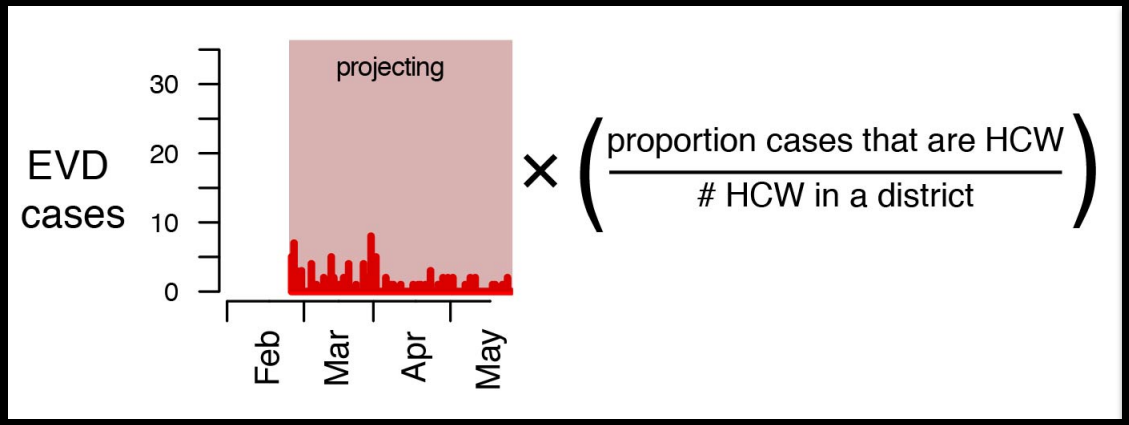

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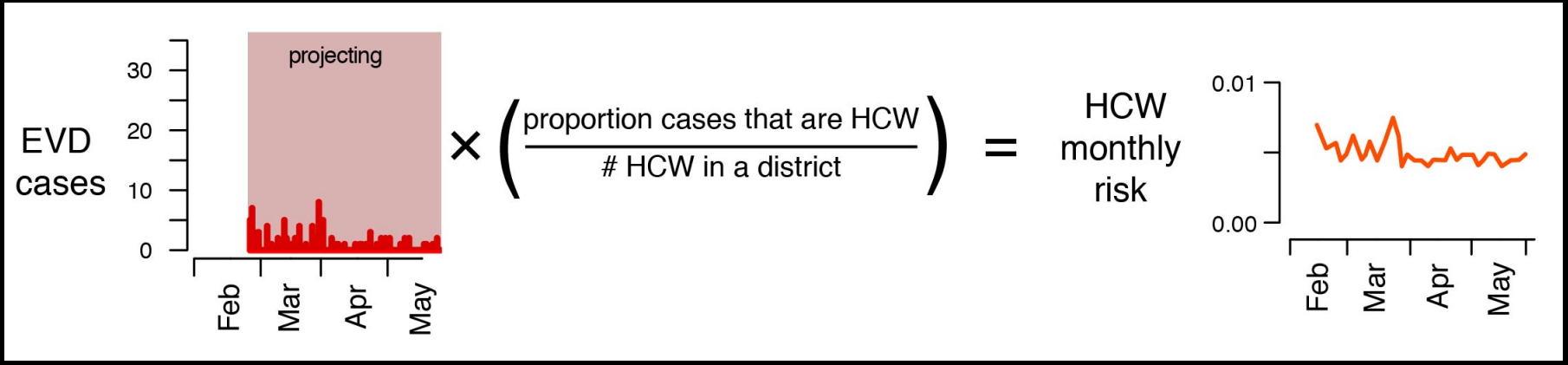


Example

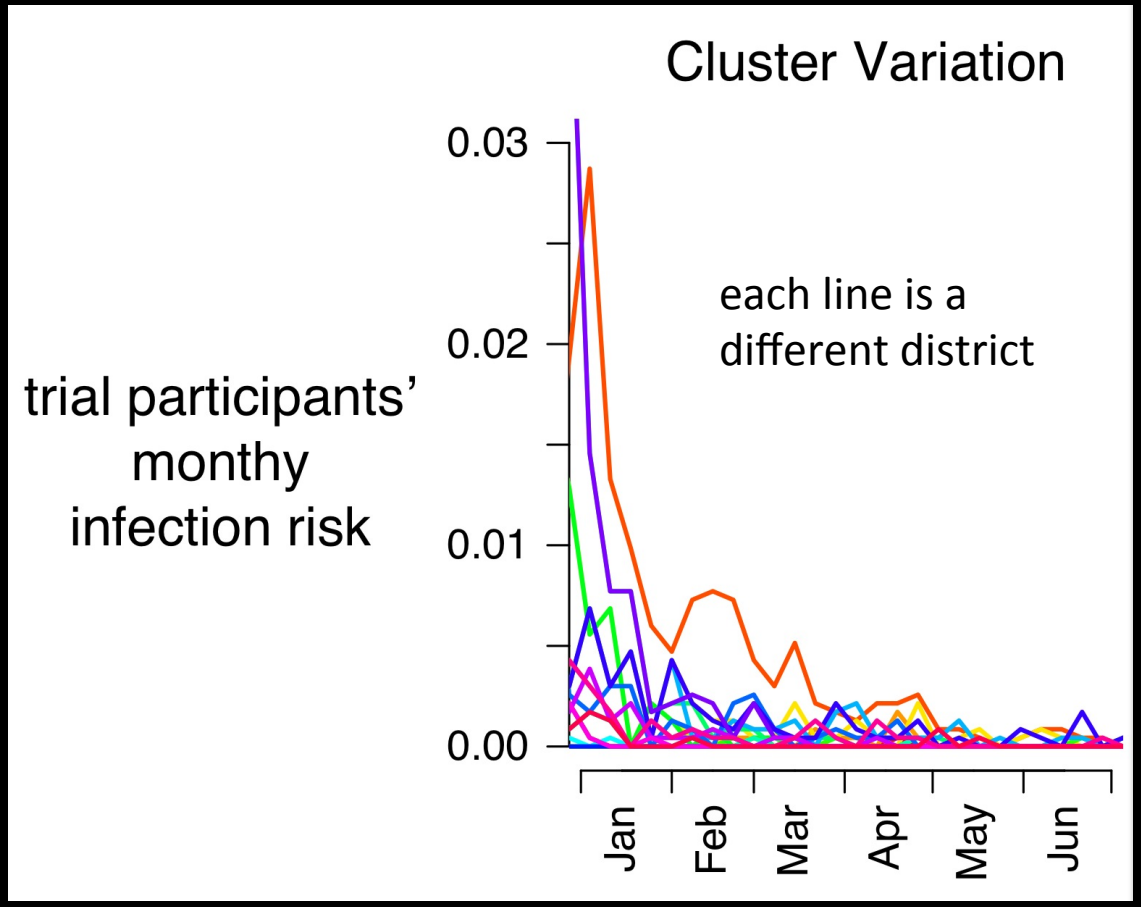
100 cases in a district in March ➔ 5 cases in HCW

If there are

5 HCW cases/500 HCW = 0.01 risk per month

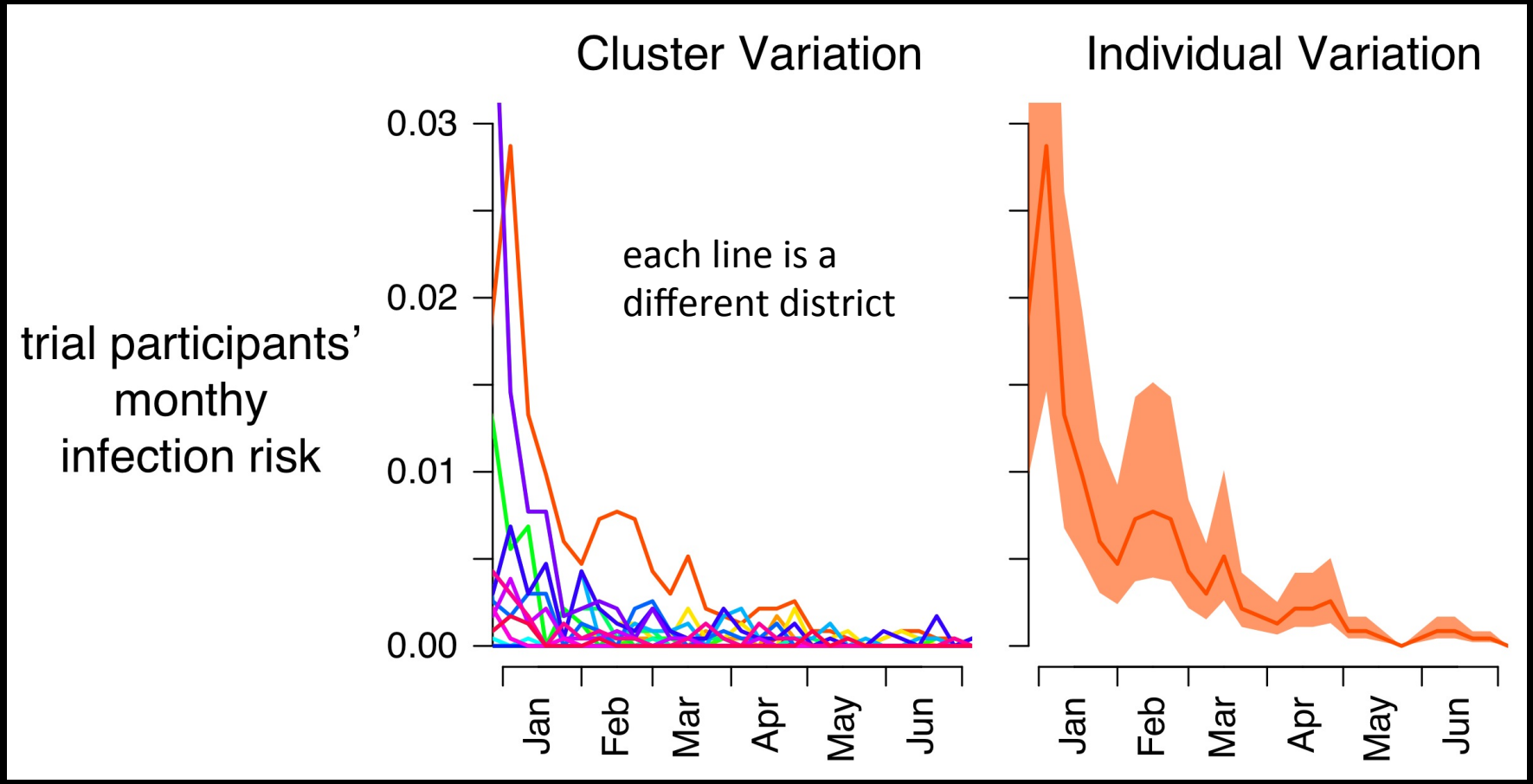
Modeling Ebola Risk

HCW risk varies by district



Modeling Ebola Risk

HCW risk varies by district and individually



Evaluating Trial Designs

1. Fit epidemic declines with decay model.

2. Simulate stochastic epidemic projections
3. Simulate trial population with risk determined by projections.
4. Simulate vaccine trial design.
5. Analyze data.

× 2000 for each scenario

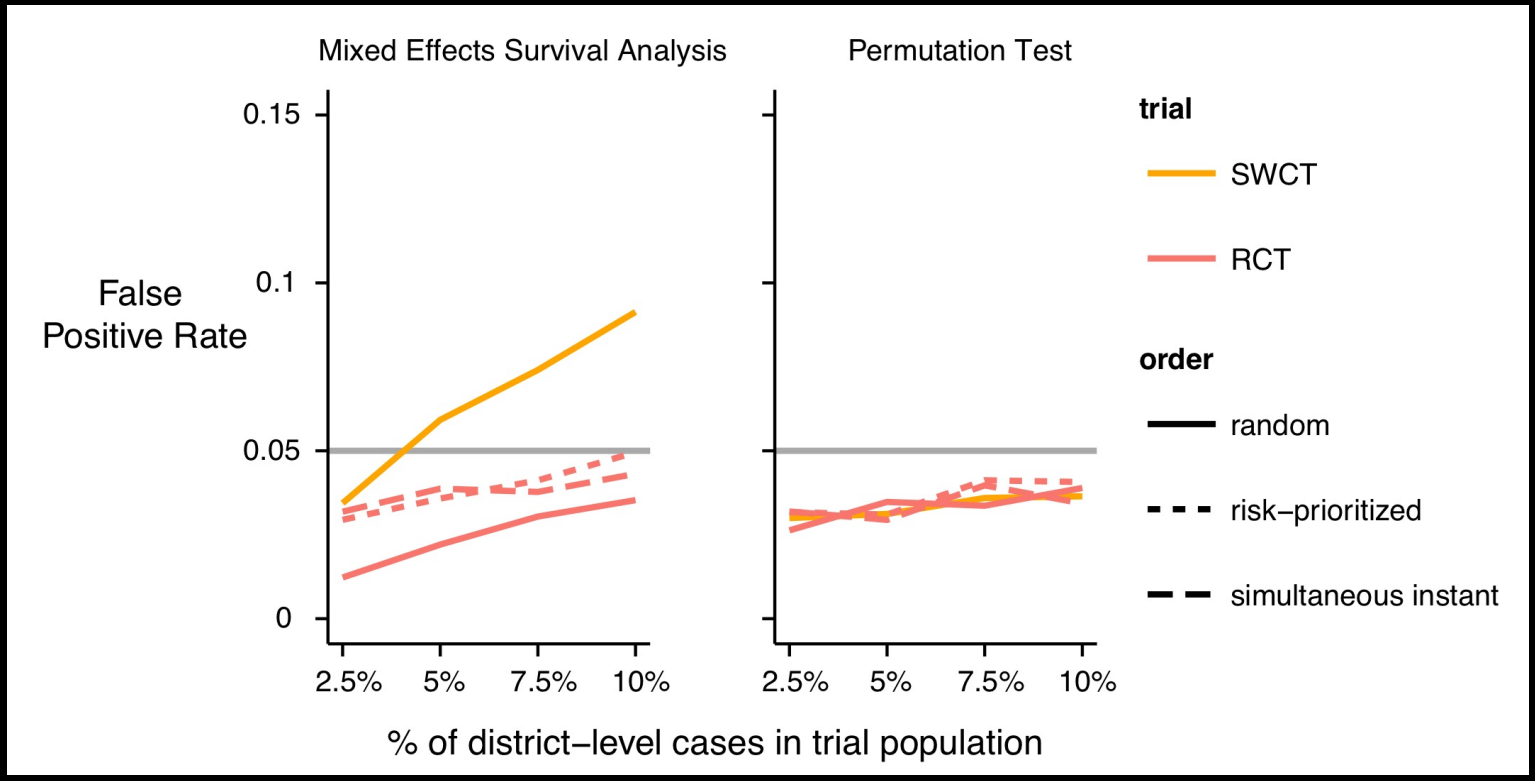
False Positive Rate

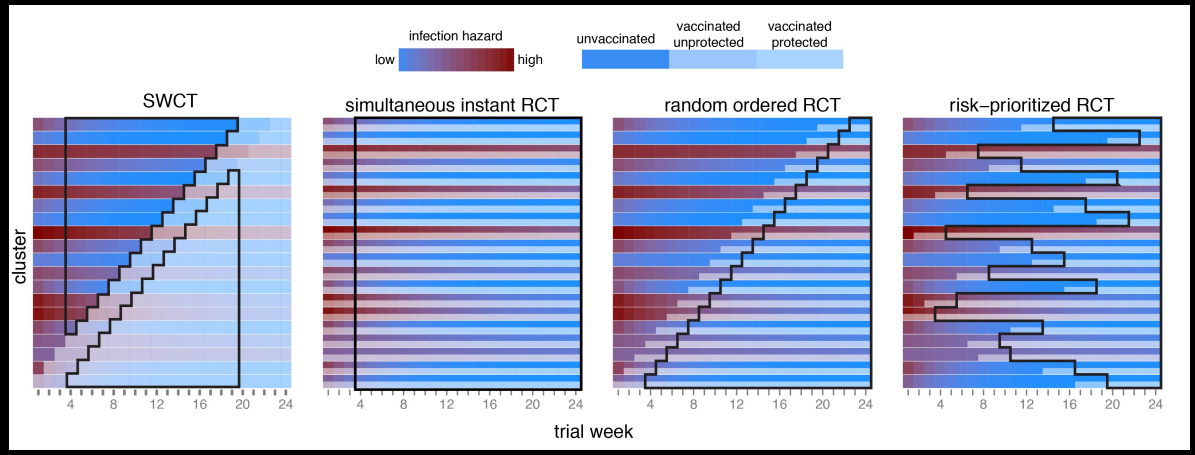
If vaccine is *not* efficacious, % times we conclude it is efficacious

Statistical Power

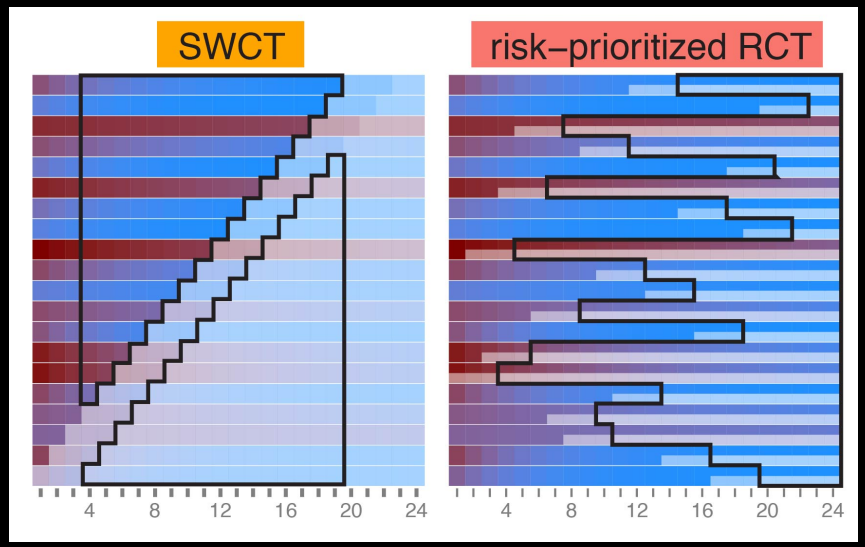
If vaccine is efficacious, % times we conclude it is efficacious

False Positive Rates

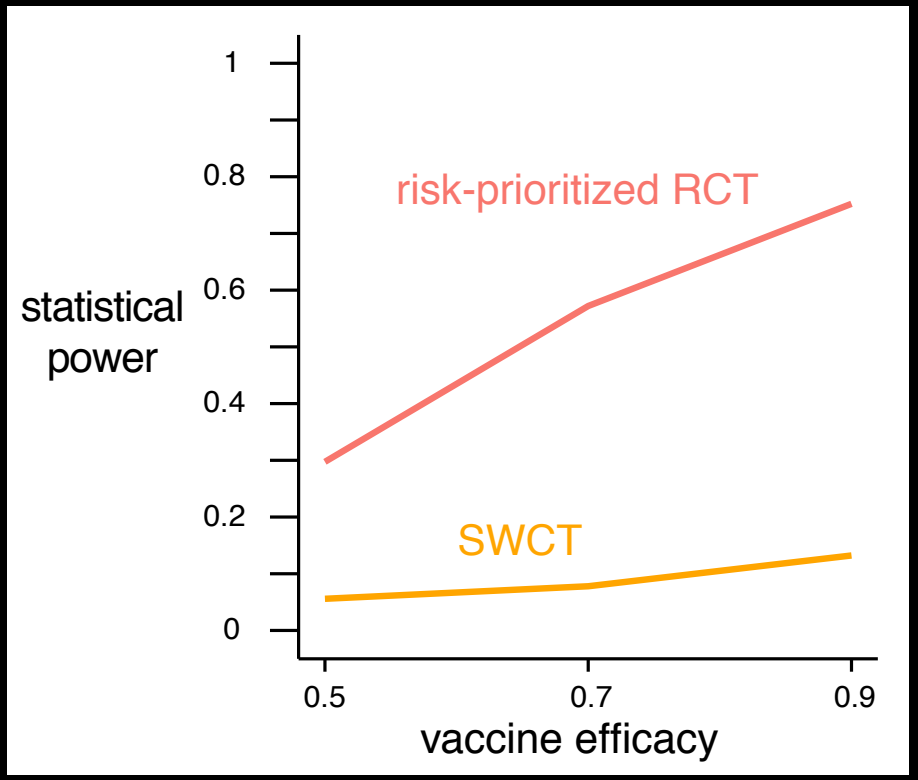




Statistical Power



Risk-prioritized RCT far more statistically powerful in this context.

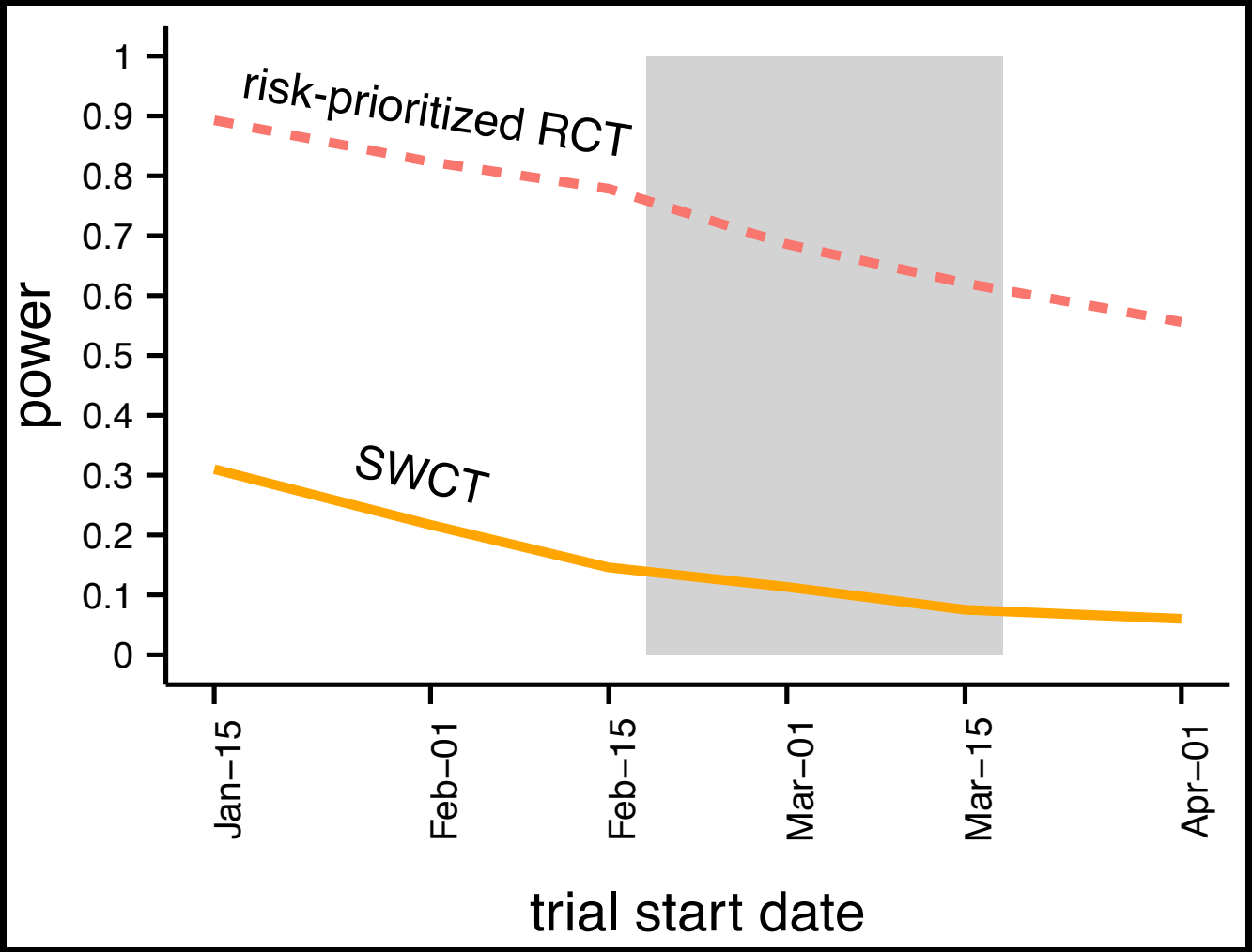


SWCT has < 15% power of detecting an efficacious vaccine.

Very inefficient for spatiotemporally variable settings

Bellan et al. 2015. *Lancet ID*.

Speed is a Priority!



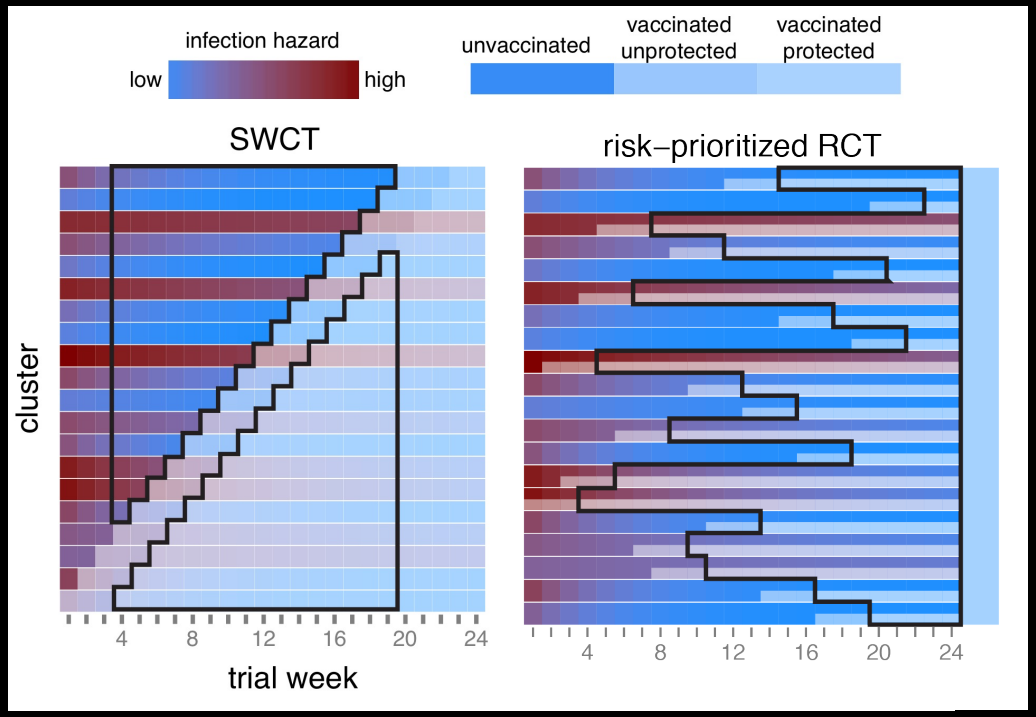
Bellan et al. 2015. *Lancet ID*.

What about ethics?

Avoids Equipoise Concern

1. No control groups
2. Vaccinate everyone *as fast as possible*

   (no prioritization of information over outcomes)



But high risk people should be vaccinated first…

Bellan et al. 2015. *Lancet ID*.

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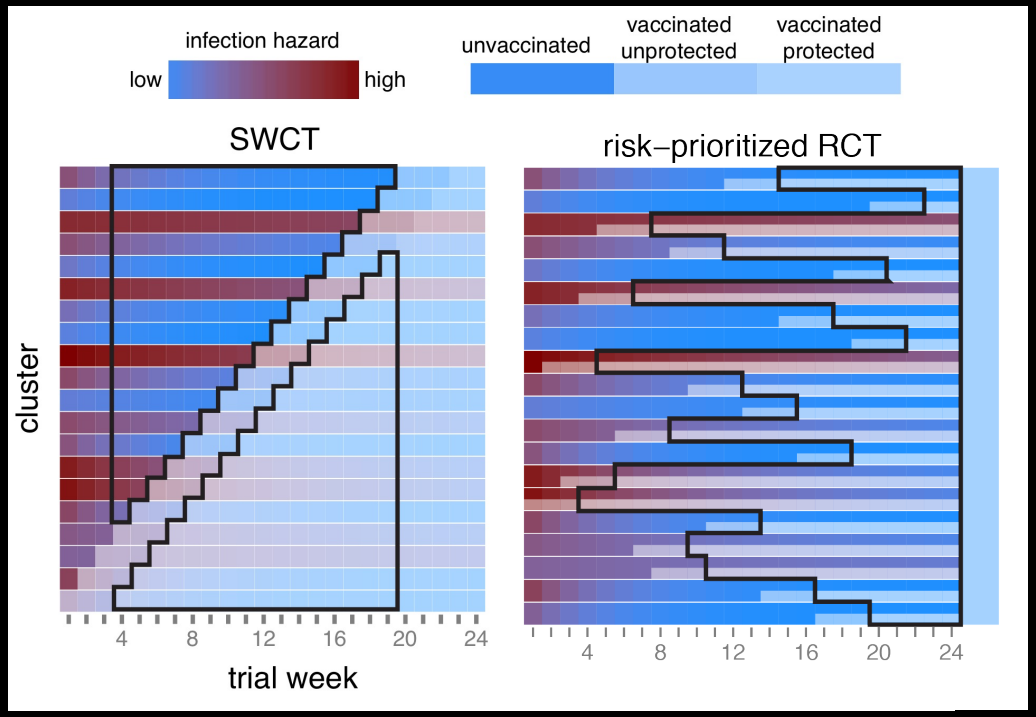

But high risk people should be vaccinated first…

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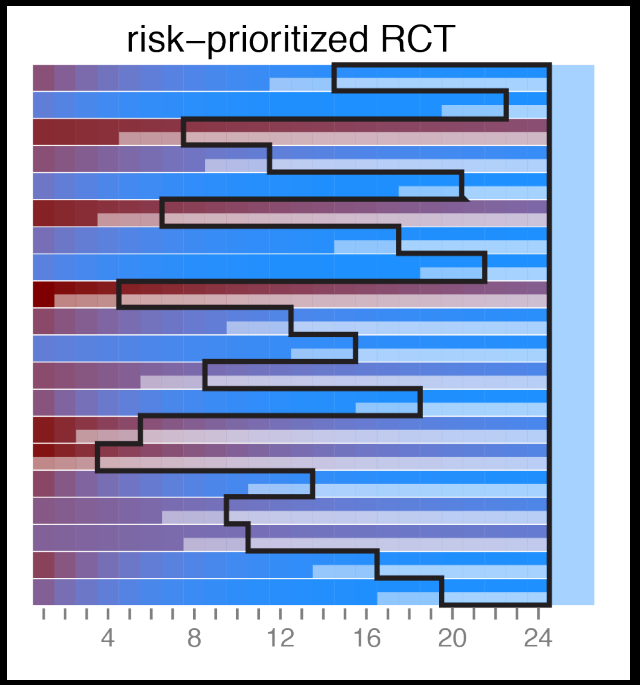
CDC

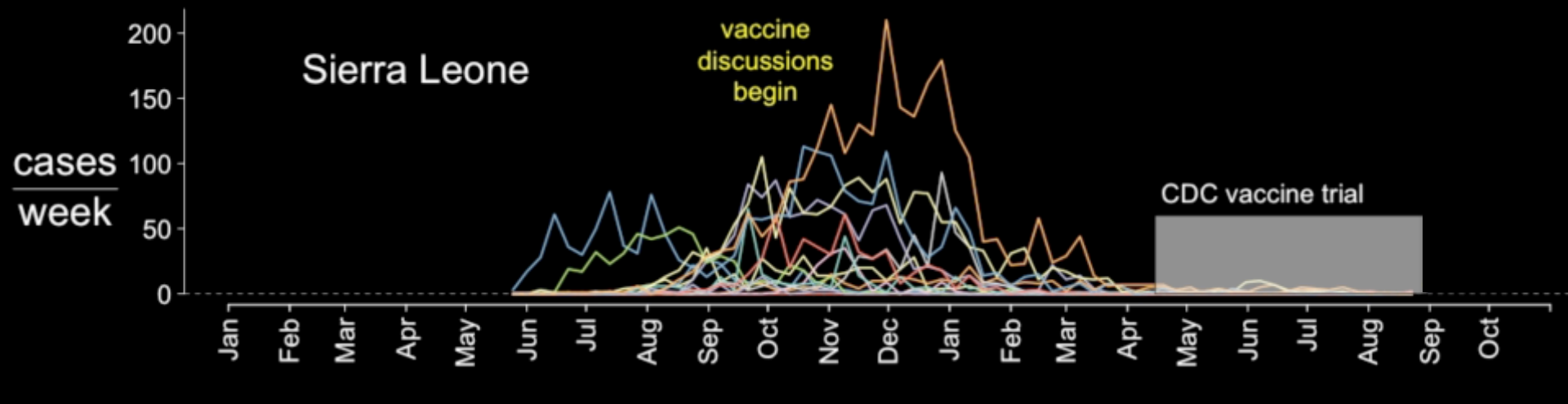
STRIVE

Sierra Leone Trial to Introduce a Vaccine against Ebola



Informed by our analysis,
CDC did a risk-prioritized RCT.

Vaccinated everyone at the end.



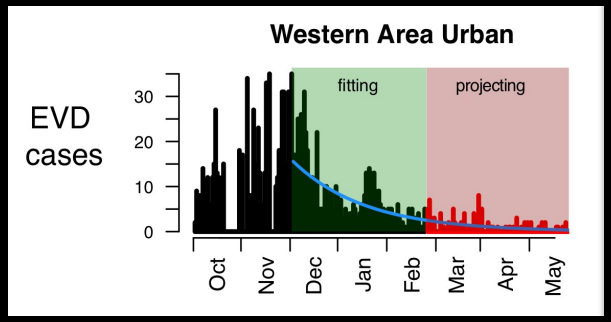
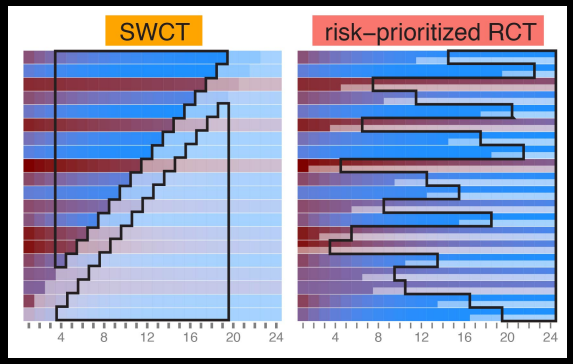
Computational Resources

- 600,000 simulated trials (2K for 300 scenarios)
- 480 million statistical models fit
- 2 days on TX Advanced Computing Cluster
- Total analysis done in 3 weeks

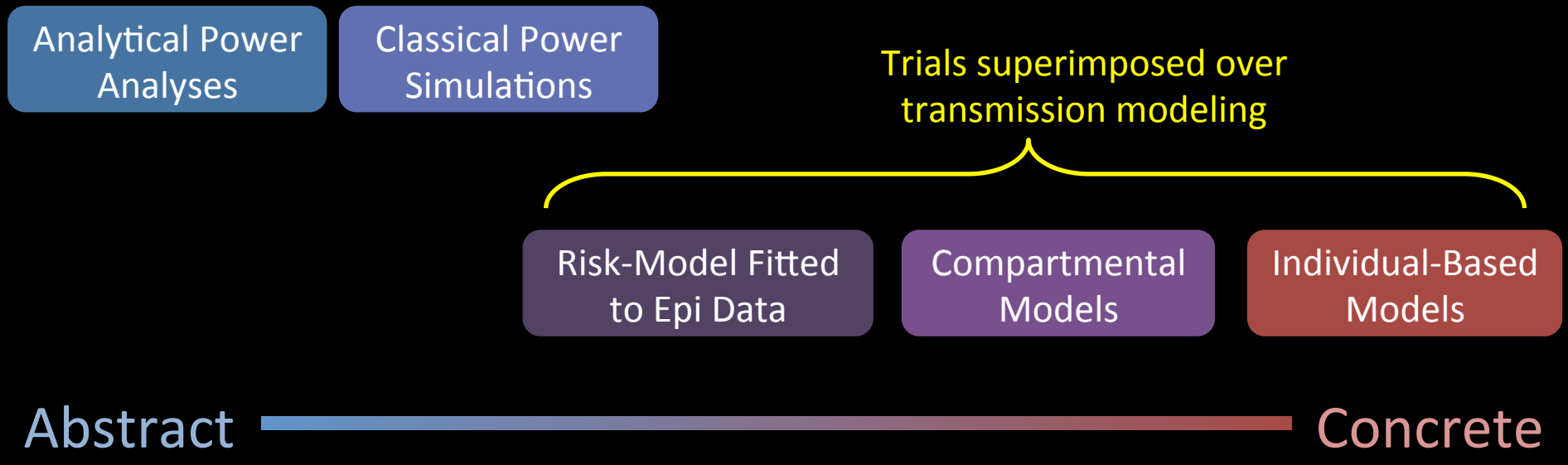
Interactions with CDC

- Dialogue/collaboration with CDC Modelers (Lopman, Gambhir)
- Results discussed in CDC Vaccine Team Meetings
- CDC already leaning towards phased-RCT due to adaptability in declining epidemic context
- Results were influential in helping CDC think through new design
- Ongoing CDC STRIVE began April 14th

Integrative Approach

	process-centric	data-centric
Ebola vaccine (study planning)		

Philosophy of Modeling & Trial Design



Rigorous insight into designs

Fast

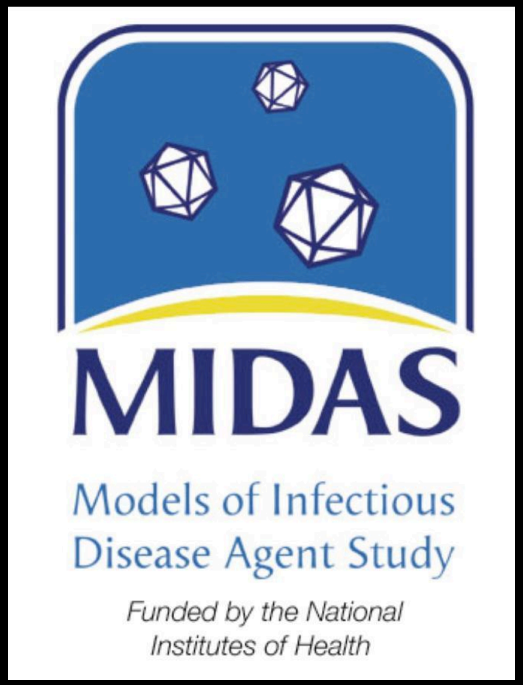
Idealized, not applicable to real world scenarios

Complexity aimed at capturing realism

Challenging to understand how assumptions influence results

Acknowledgements

- Lauren Ancel Meyers, Jonathan Dushoff, Juliet Pulliam, Carl Pearson, Alison Galvani, Manoj Gambhir, Ben Lopman, Travis Porco, David Champredon, Spencer Fox, Laura Skrip
- International Clinics on Infectious Disease Dynamics and Data (ICI3D)
- GA Tech Conference: Modeling the Spread & Control of Ebola in W Africa



Title: Use of models in study design for dynamic systems: Ebola vaccine trial design
Attribution: Steve Bellan, Clinic on Dynamical Approaches to Infectious Disease Data
For further information please contact Steve Bellan (steve.bellan@uga.edu).