Statistical power and validity of Ebola vaccine trials in Sierra Leone

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with

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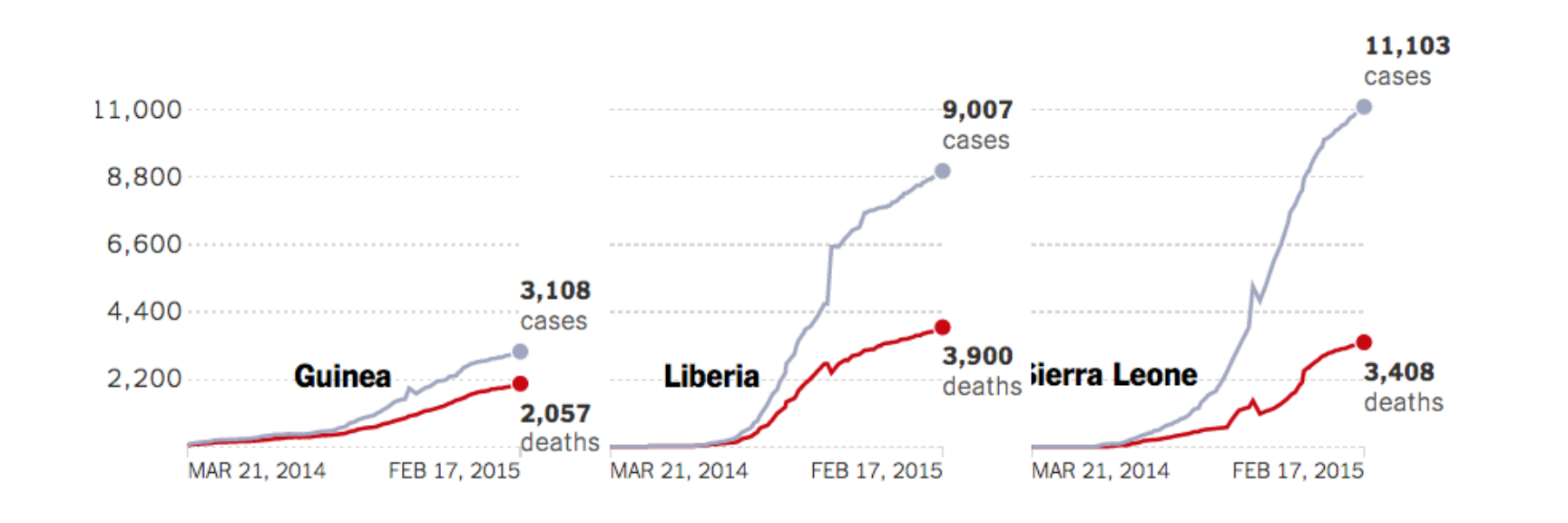
Presented by JRC Pulliam, DAIDD clinic

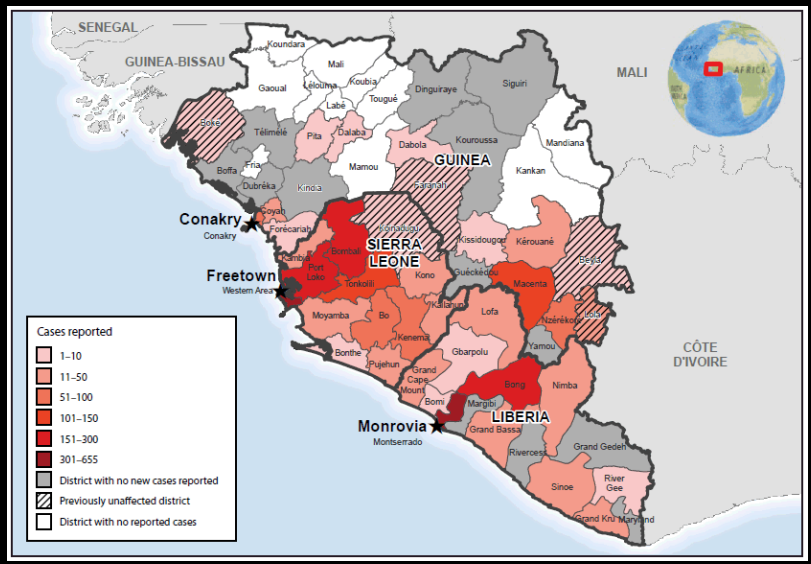
December 16, 2015

Ebola in West Africa



26,000 reported cases
11,000 reported deaths

1.5-3X underreporting?



How do you test a new vaccine/drug?

- Animal trials

- Human Trials by Phase

  I. Safety

  II. Safety, immunogenicity, dosage

  III. Efficacy (does it work)

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?

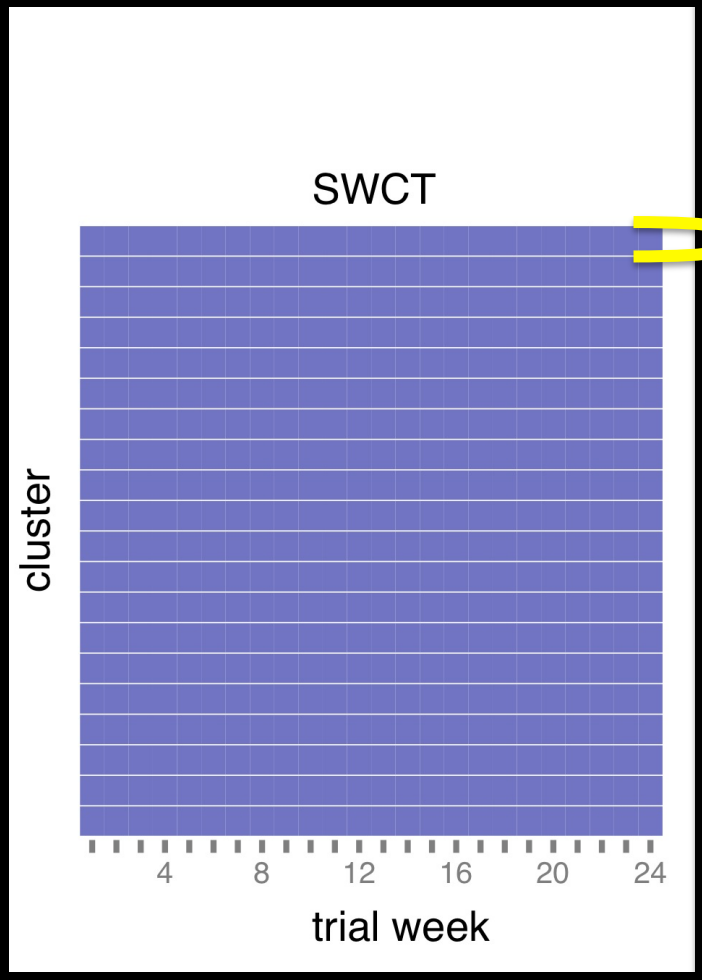
Equipoise

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

Stepped Wedge Cluster Trial

- Evaluate vaccine when there is *no equipoise*
- Vaccinate everyone *as fast as possible*, by groups
- Randomize group-order of vaccination
- Compare infection risk between
  vaccinated & *not-yet-vaccinated* individuals
- Randomized group-order avoids confounding

Stepped Wedge Cluster Trial

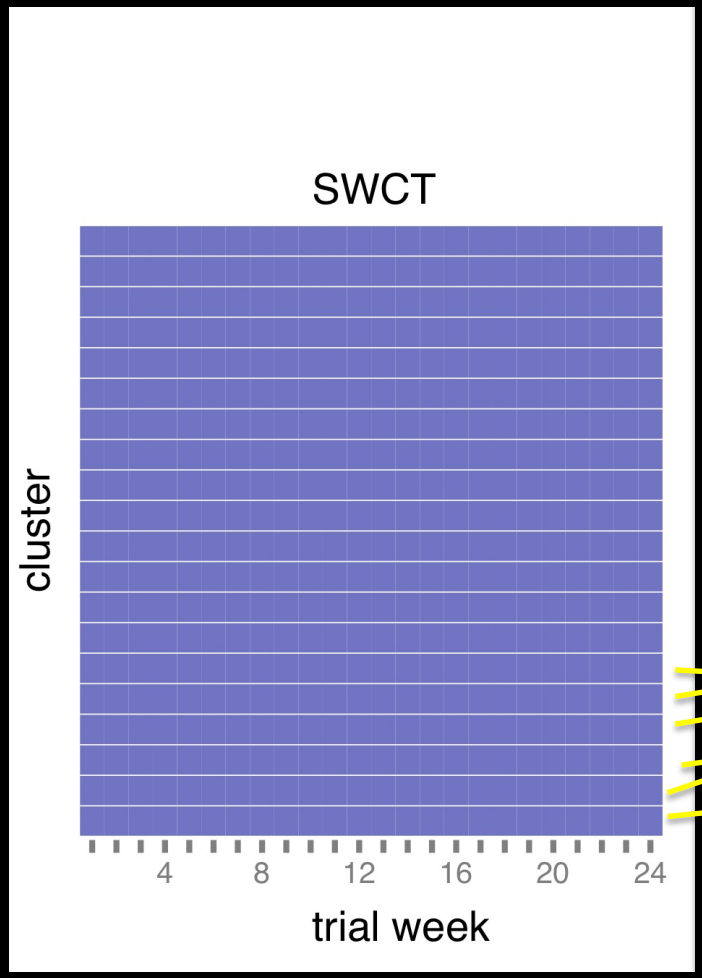


Cluster of 300 frontline caregivers (HCW+)

x20

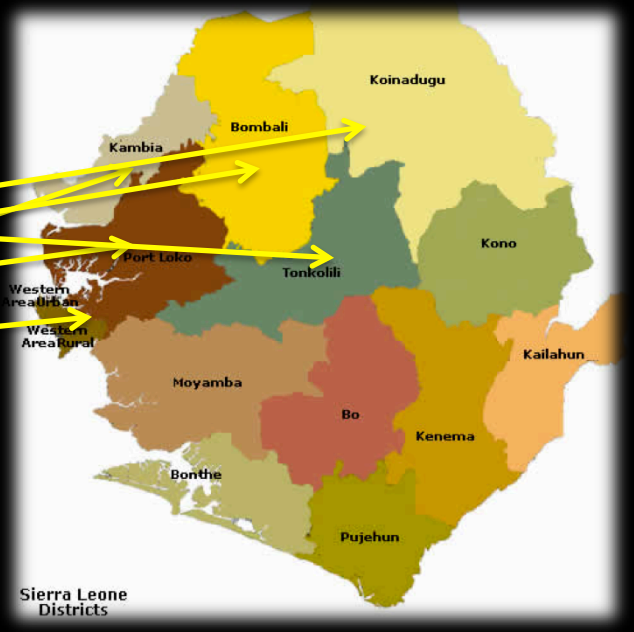
Observed for 24 weeks (6 months)

Stepped Wedge Cluster Trial



24 weeks of observation

20 clusters (each row), 300 people each



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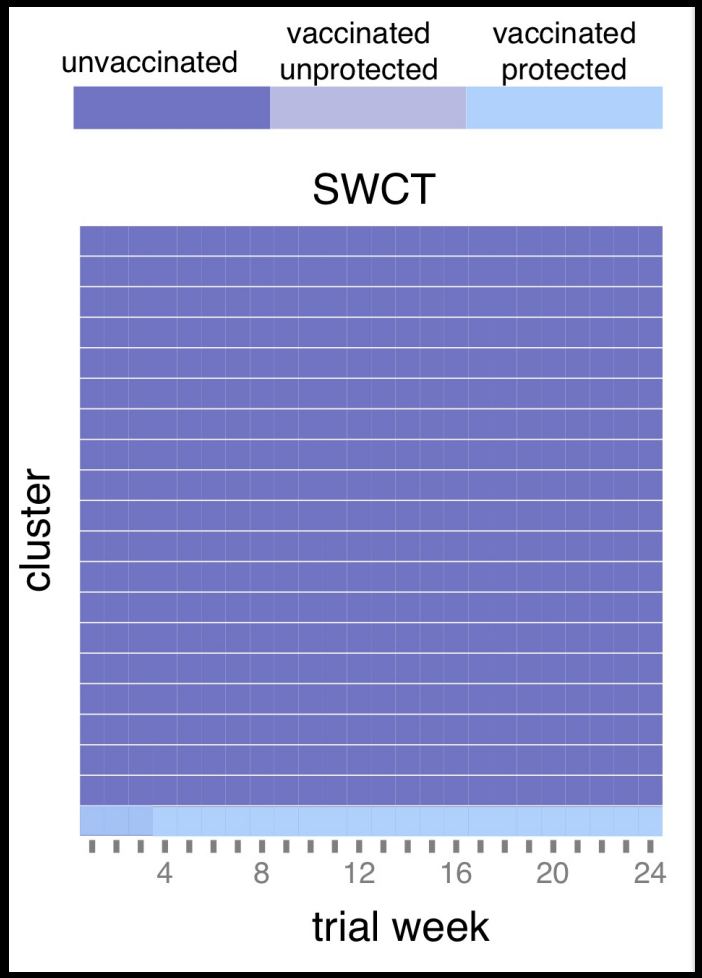

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Vaccinate one cluster (district) each week

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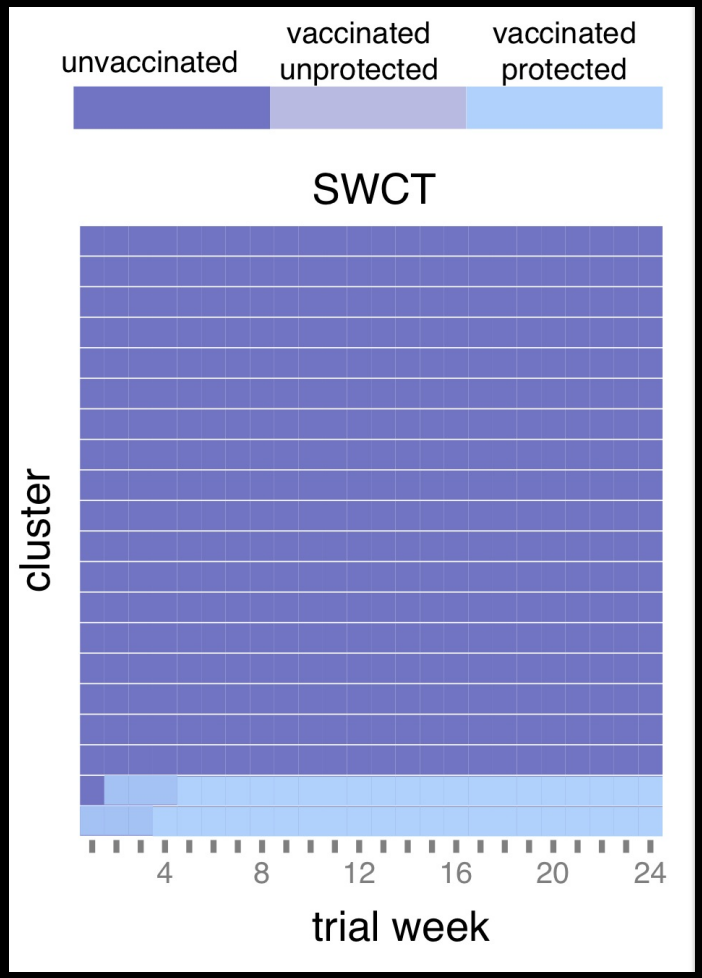

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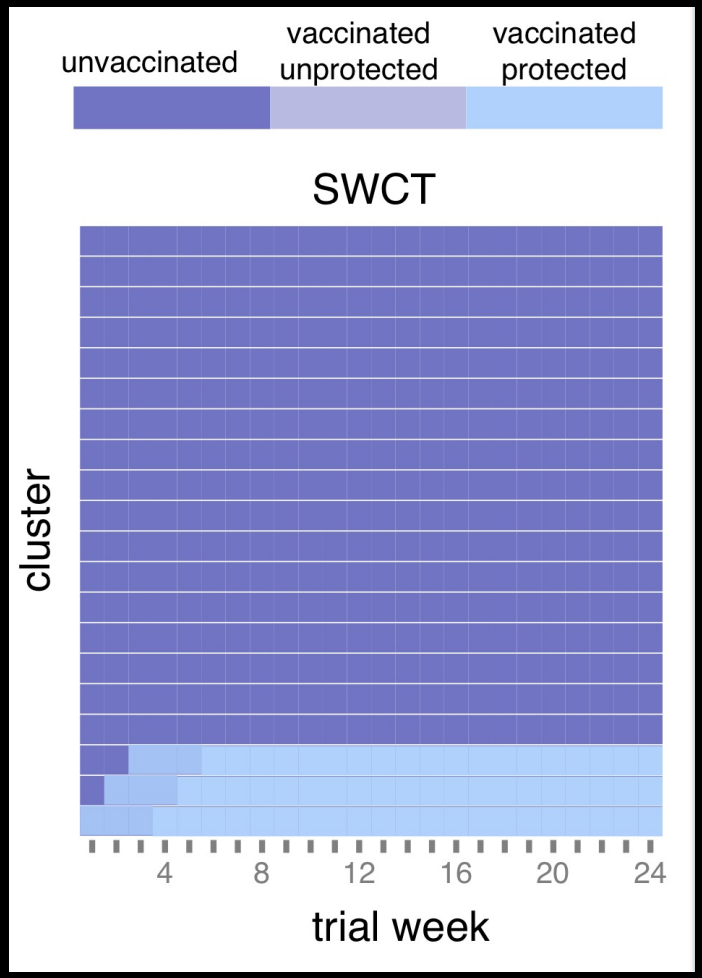

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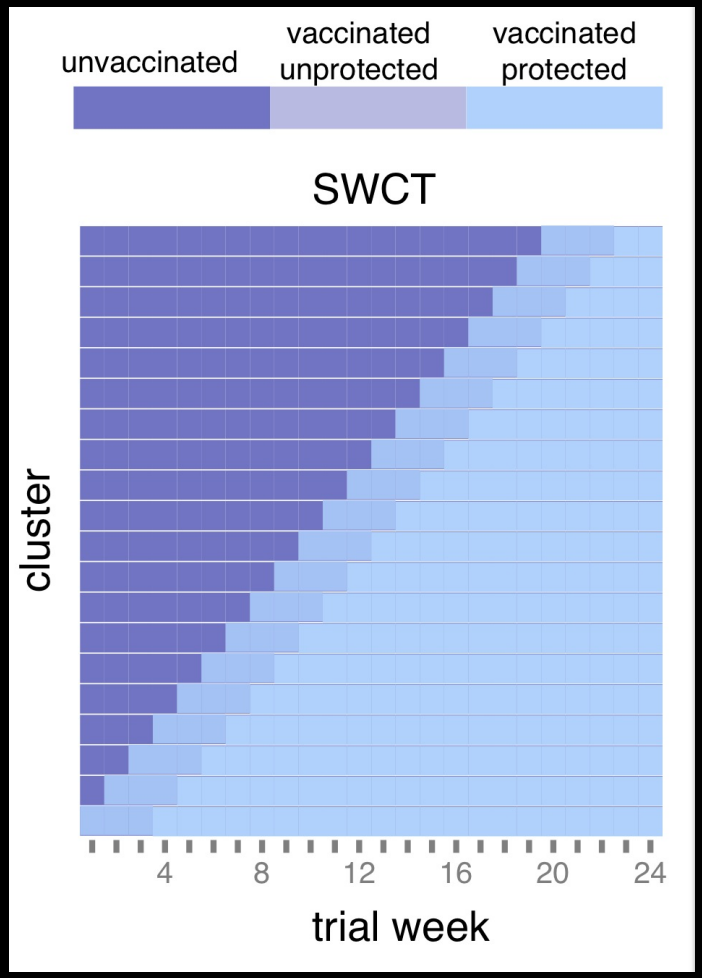

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Everyone is vaccinated (avoid equipoise dilemma)

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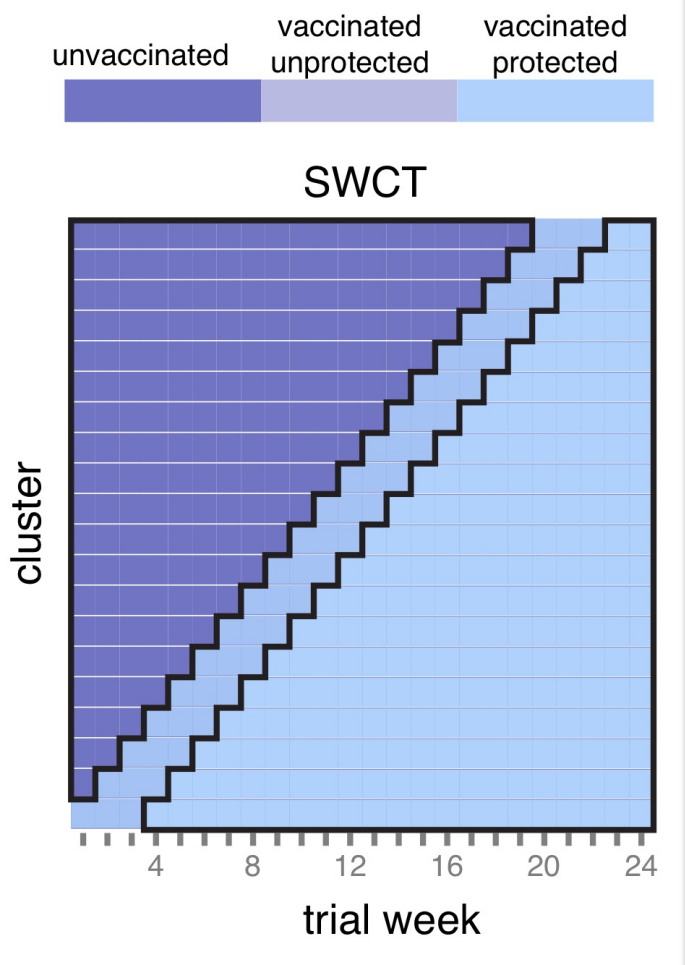

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Compare # infections between vaccinated & not-yet-vaccinated

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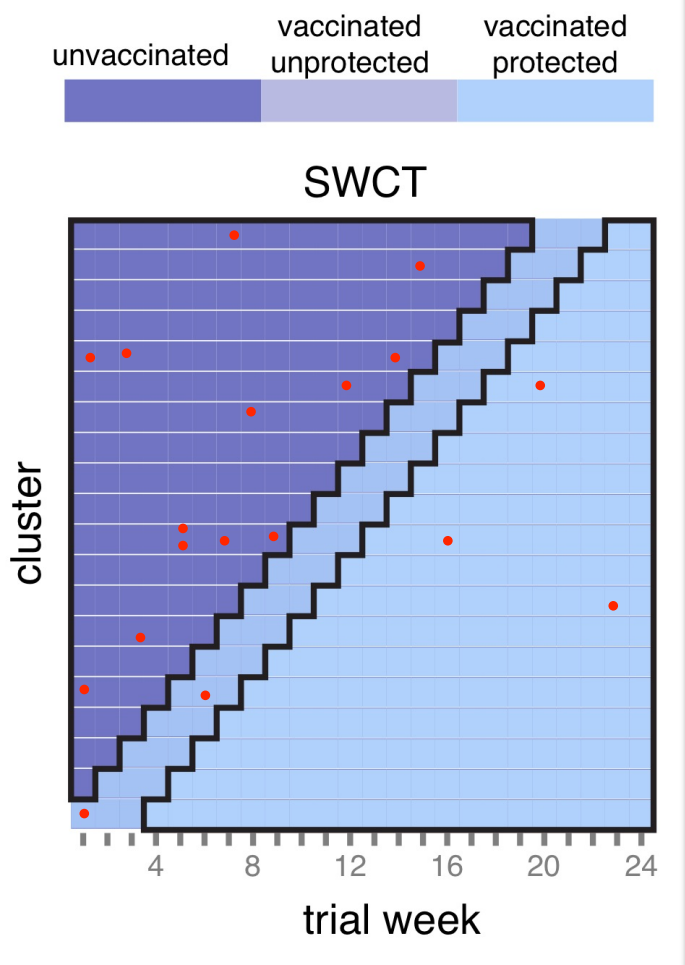

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Compare # infections between vaccinated & not-yet-vaccinated

- infected participant

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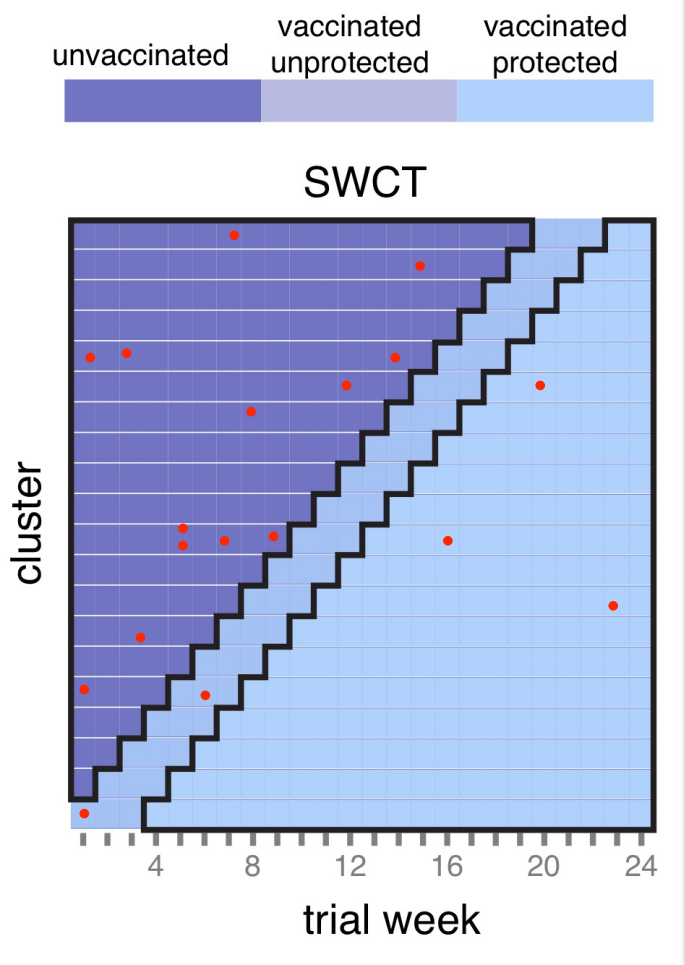
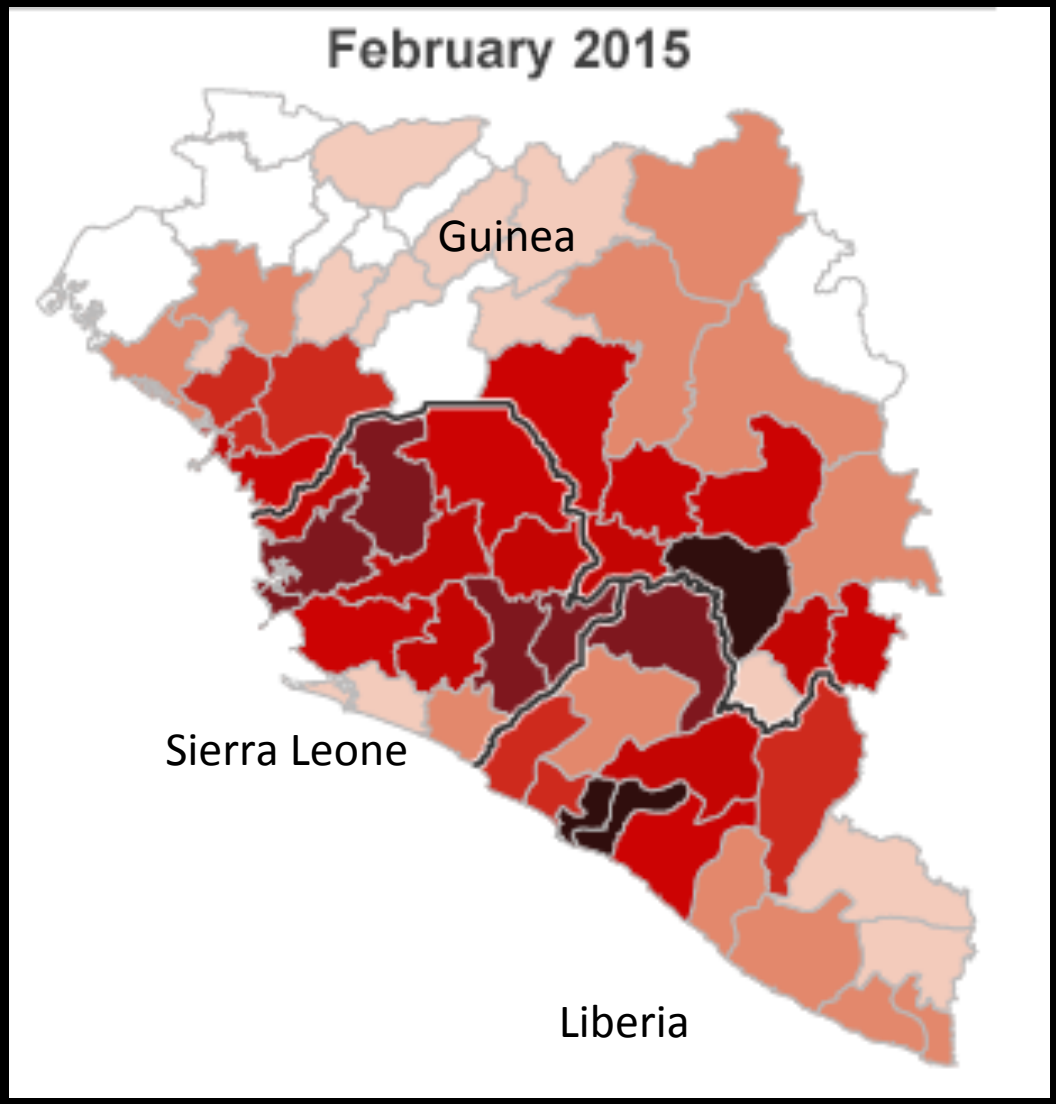


In Nov 2014, CDC proposed this design to side step ethical concerns.

Regional Variation in Ebola Cases



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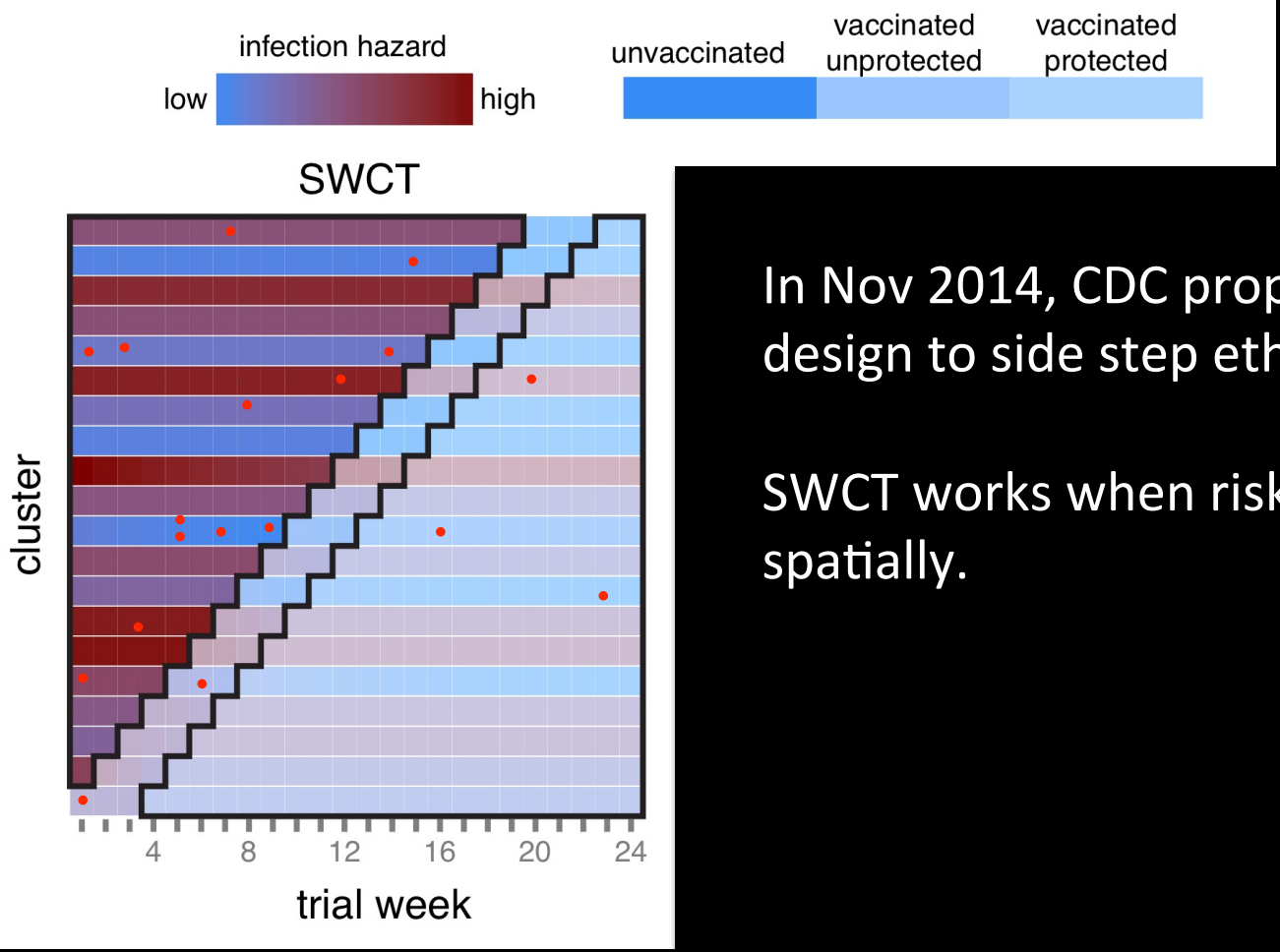

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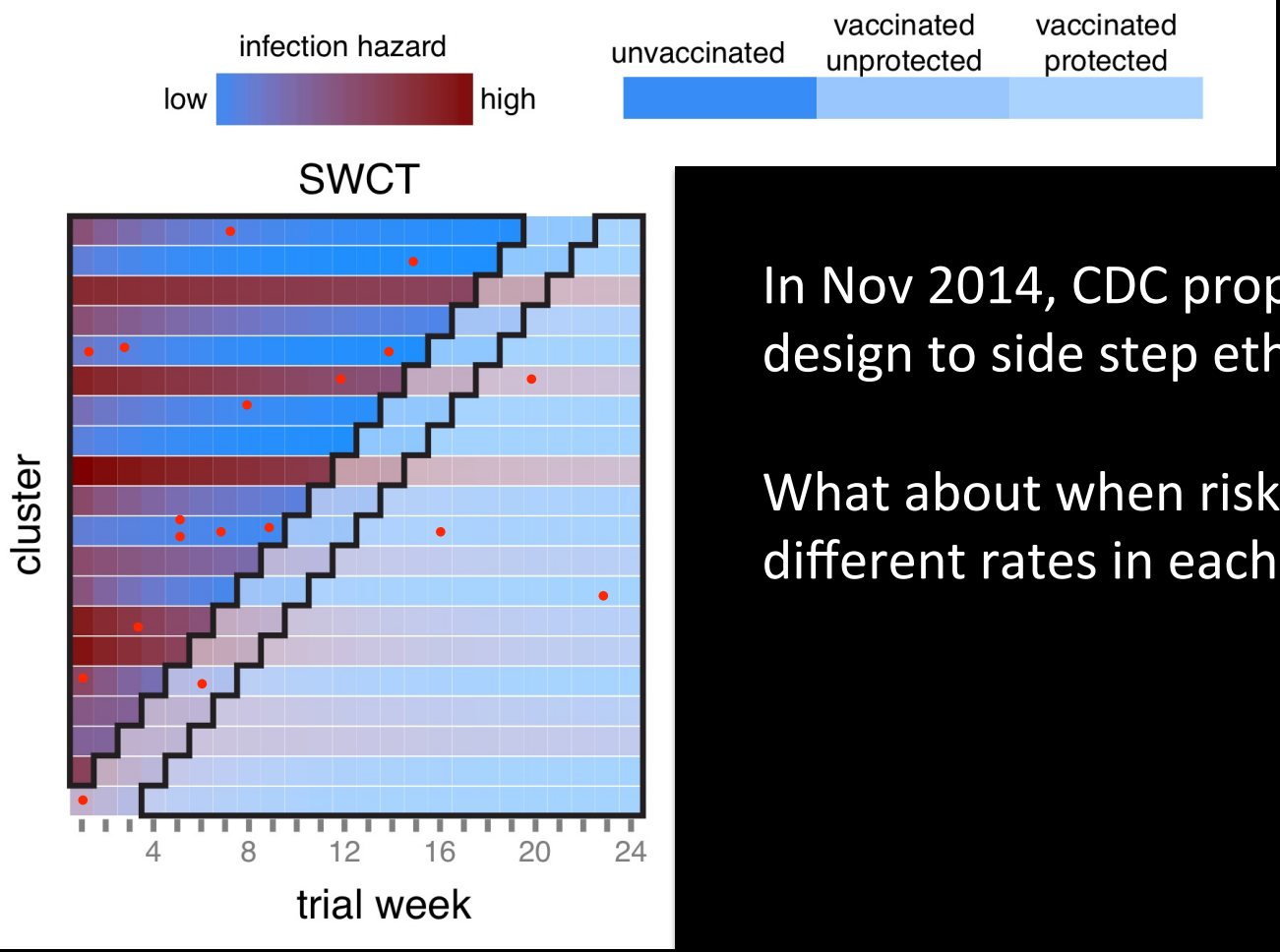
SWCT works when risk varies spatially.

Stepped Wedge Cluster Trial



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

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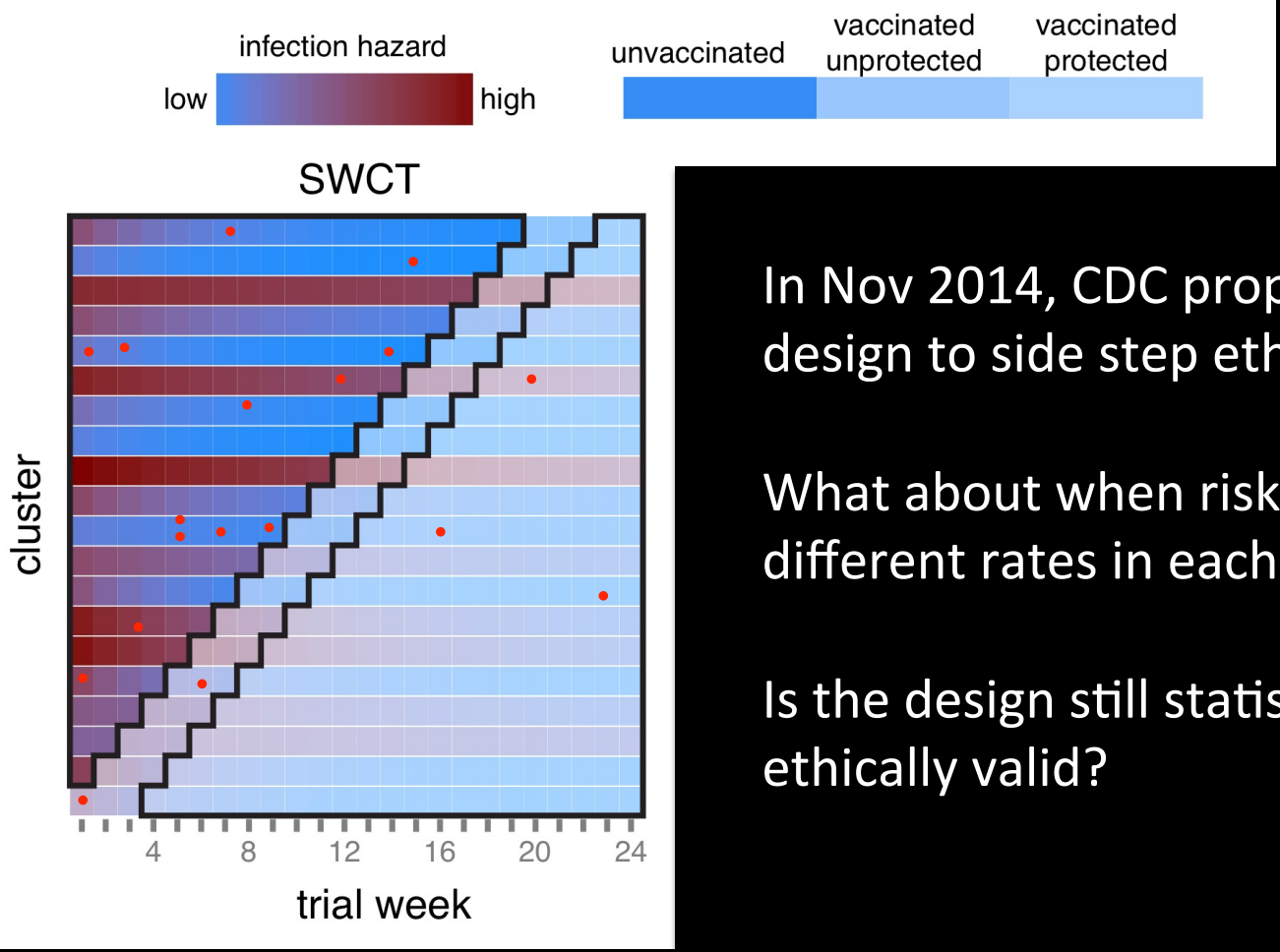

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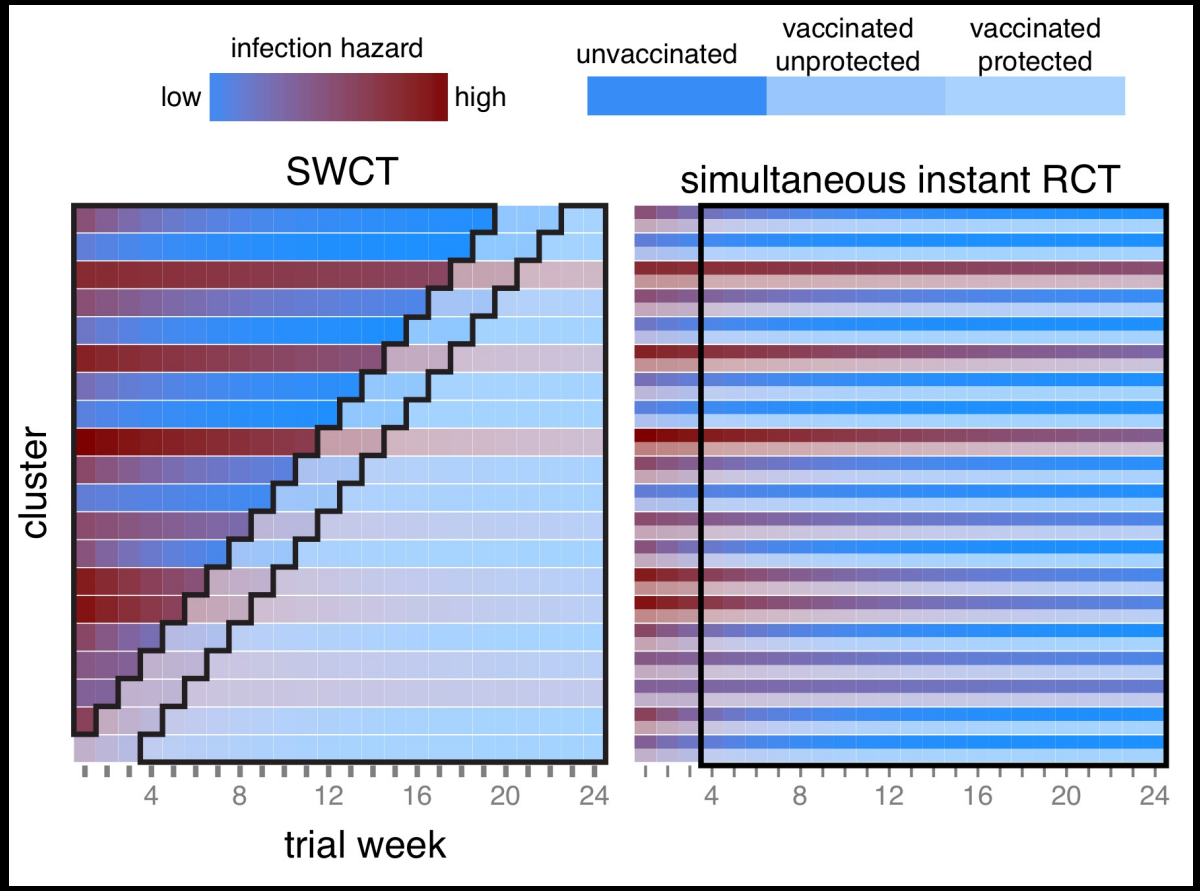
What about when risk is declining at different rates in each district?

Is the design still statistically & ethically valid?

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

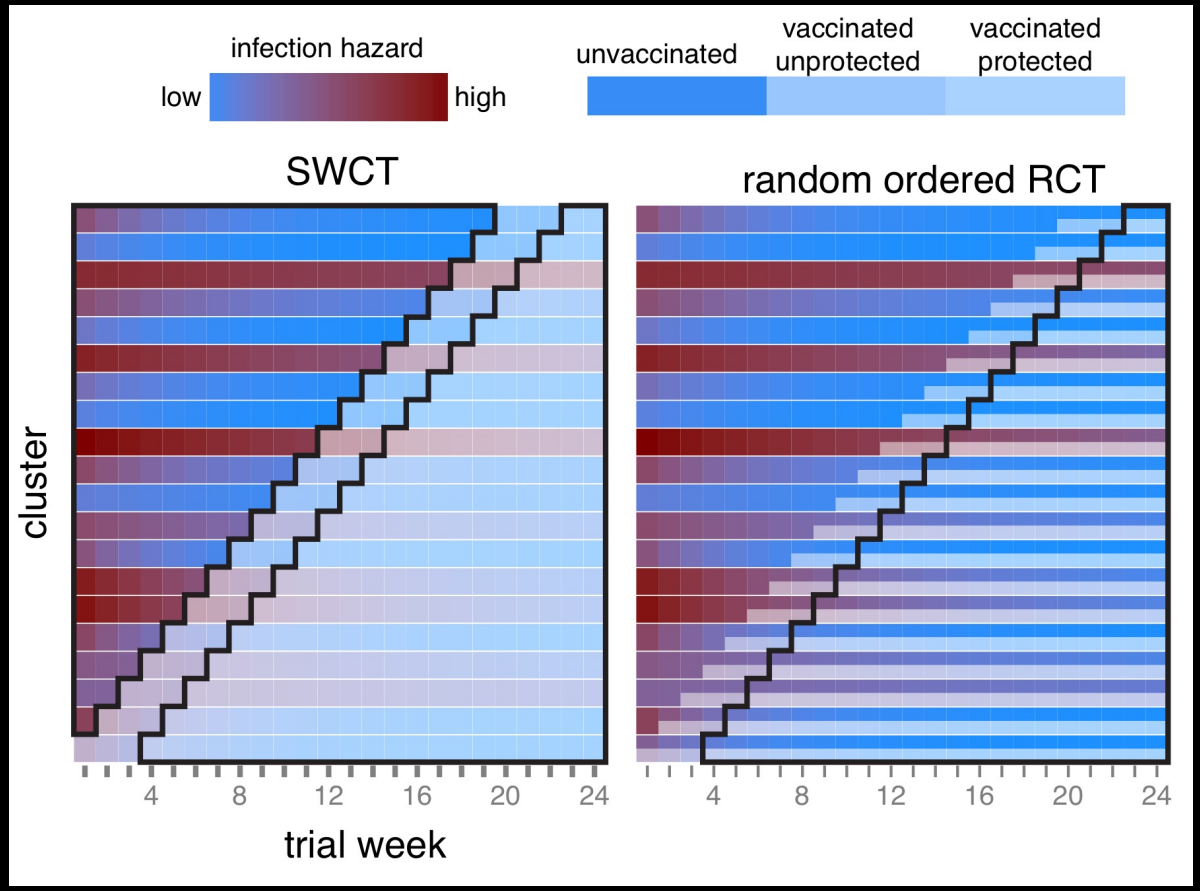
Other Options



Vaccinate half of each cluster immediately.

Not logistically feasible.

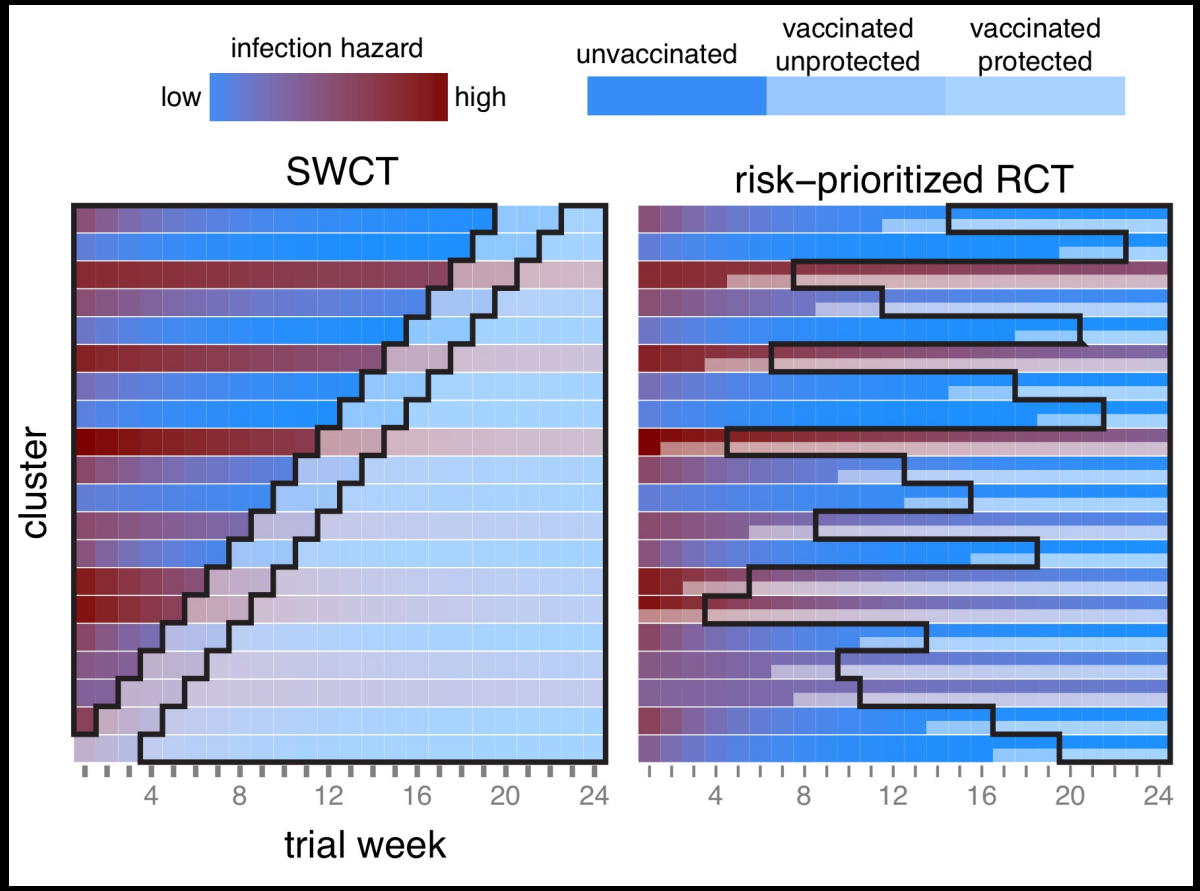
Other Options



Vaccinate half of each cluster 1 week at a time.

Comparing vaccinated & unvaccinated individuals in same risk categories.

Other Options

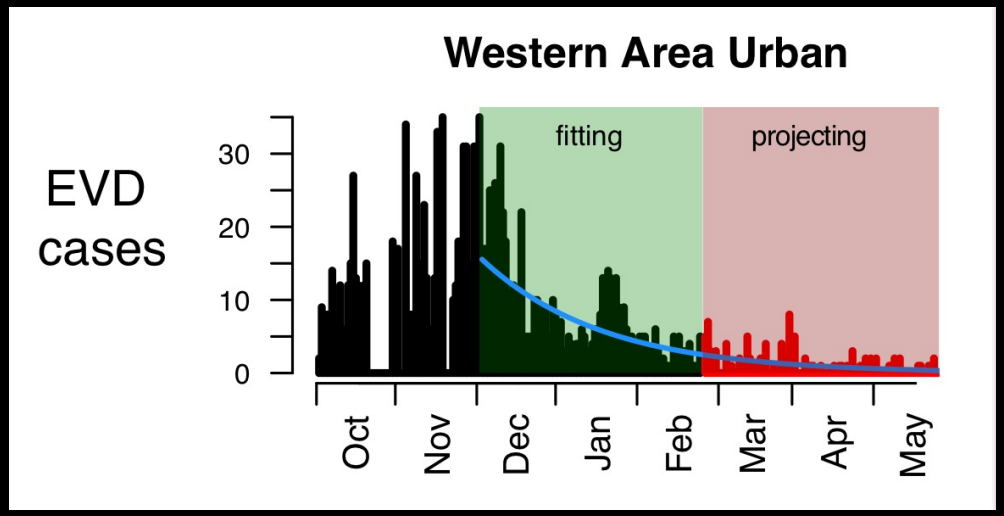


Vaccinate half of each cluster 1 week at a time.

Comparing vaccinated & unvaccinated individuals in same risk categories.

Prioritize high risk clusters.

Project Declining Epidemics



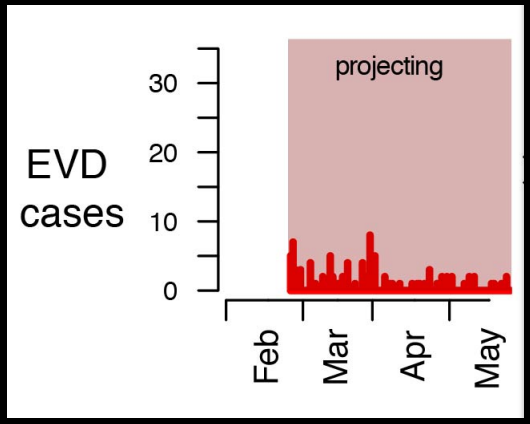
Exponential decay models fit to district-level incidence

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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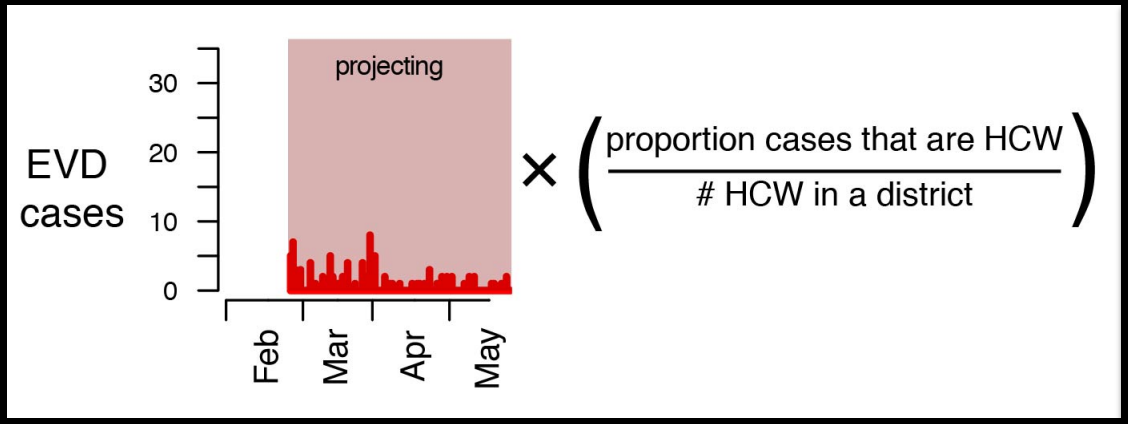

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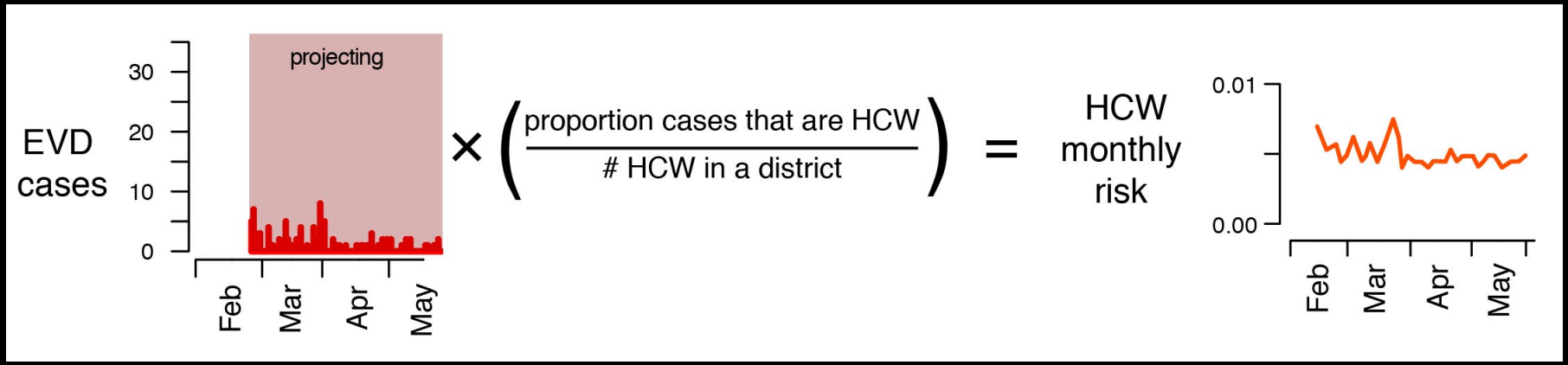


Example

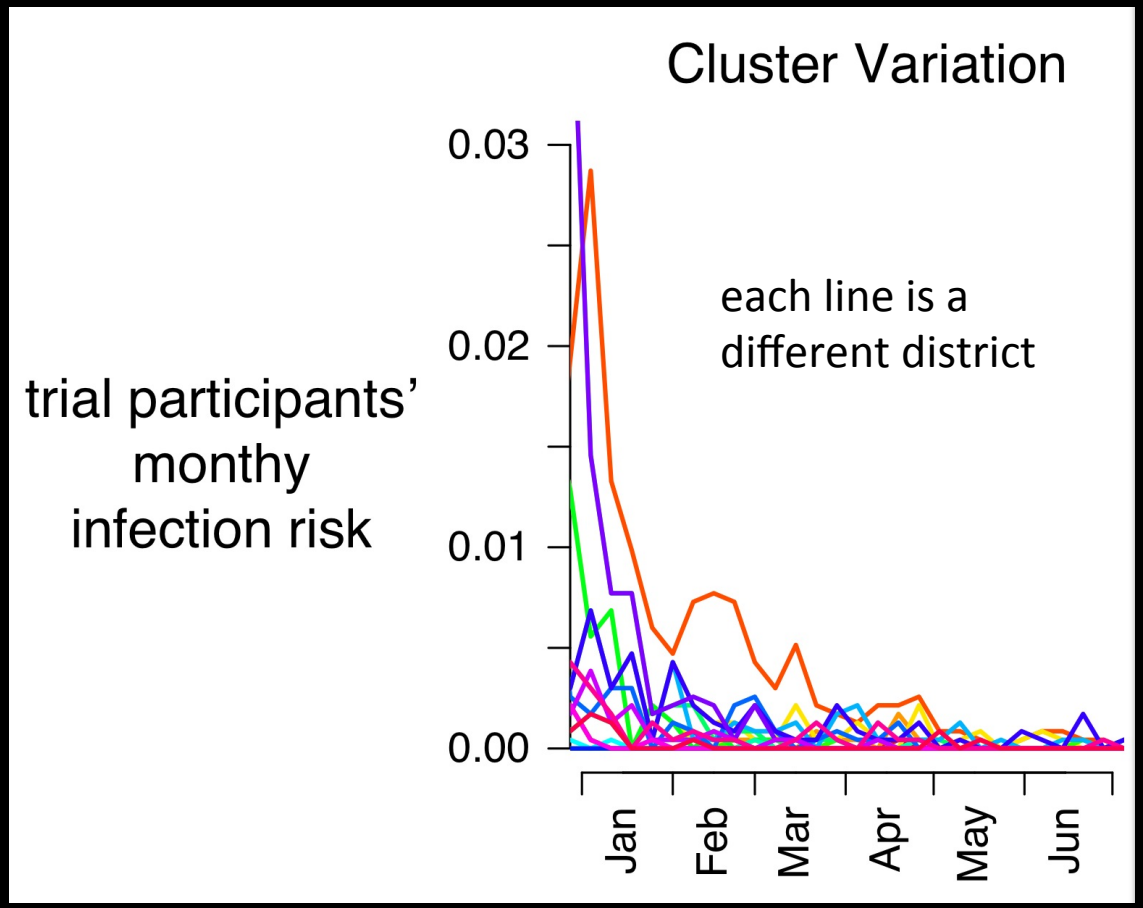
100 cases in a district in March ➔ 5 cases in HCW

If there are

5 HCW cases/500 HCW = 0.01 risk per month

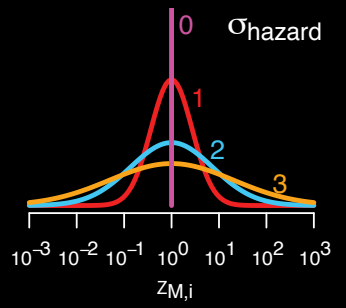
Modeling Ebola Risk

HCW risk varies by district

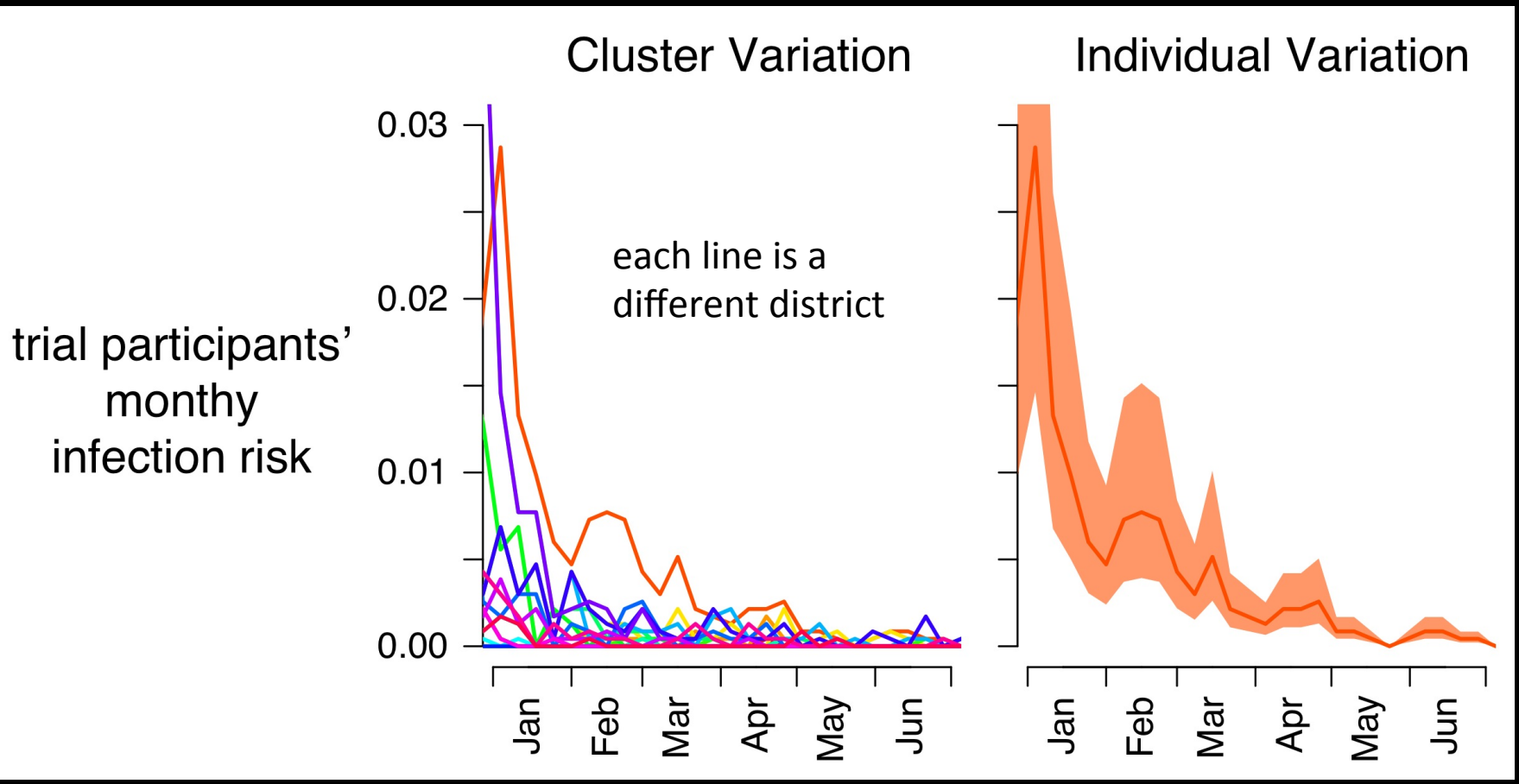


Modeling Ebola Risk

HCW risk varies by district and individually



Heterogeneity



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

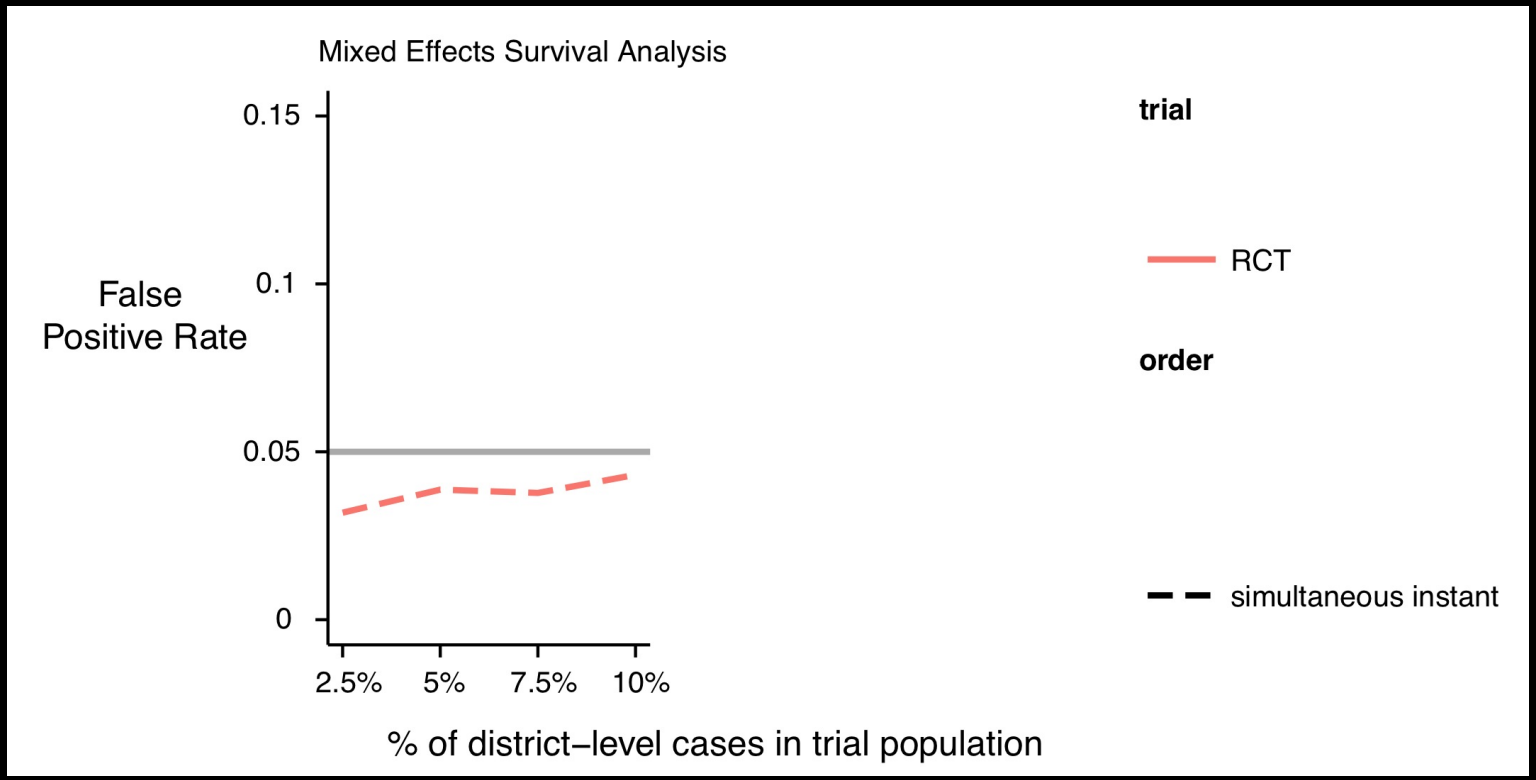
False Positive Rate

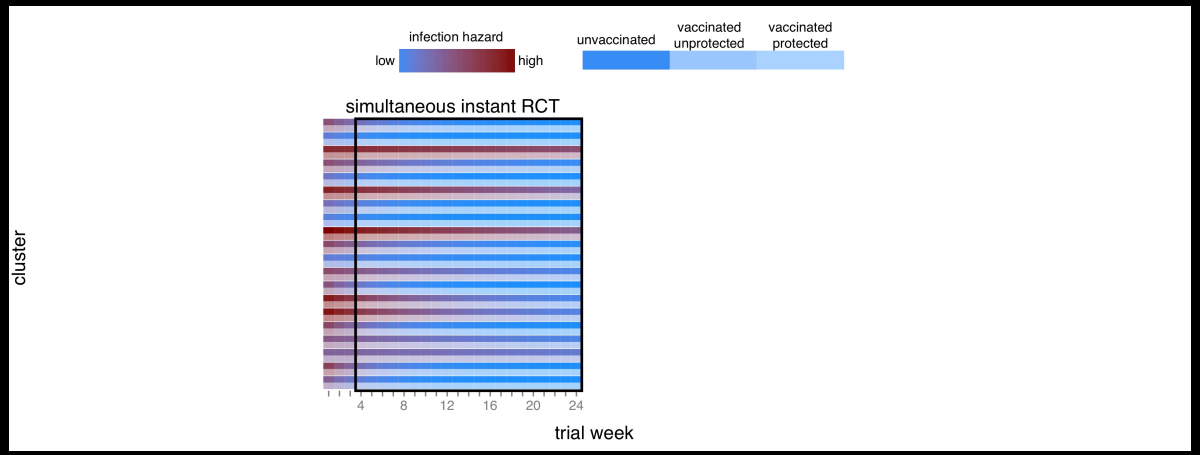
If vaccine does not affect Ebola risk, % times we incorrectly conclude it does.

Statistical Power

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

False Positive Rates





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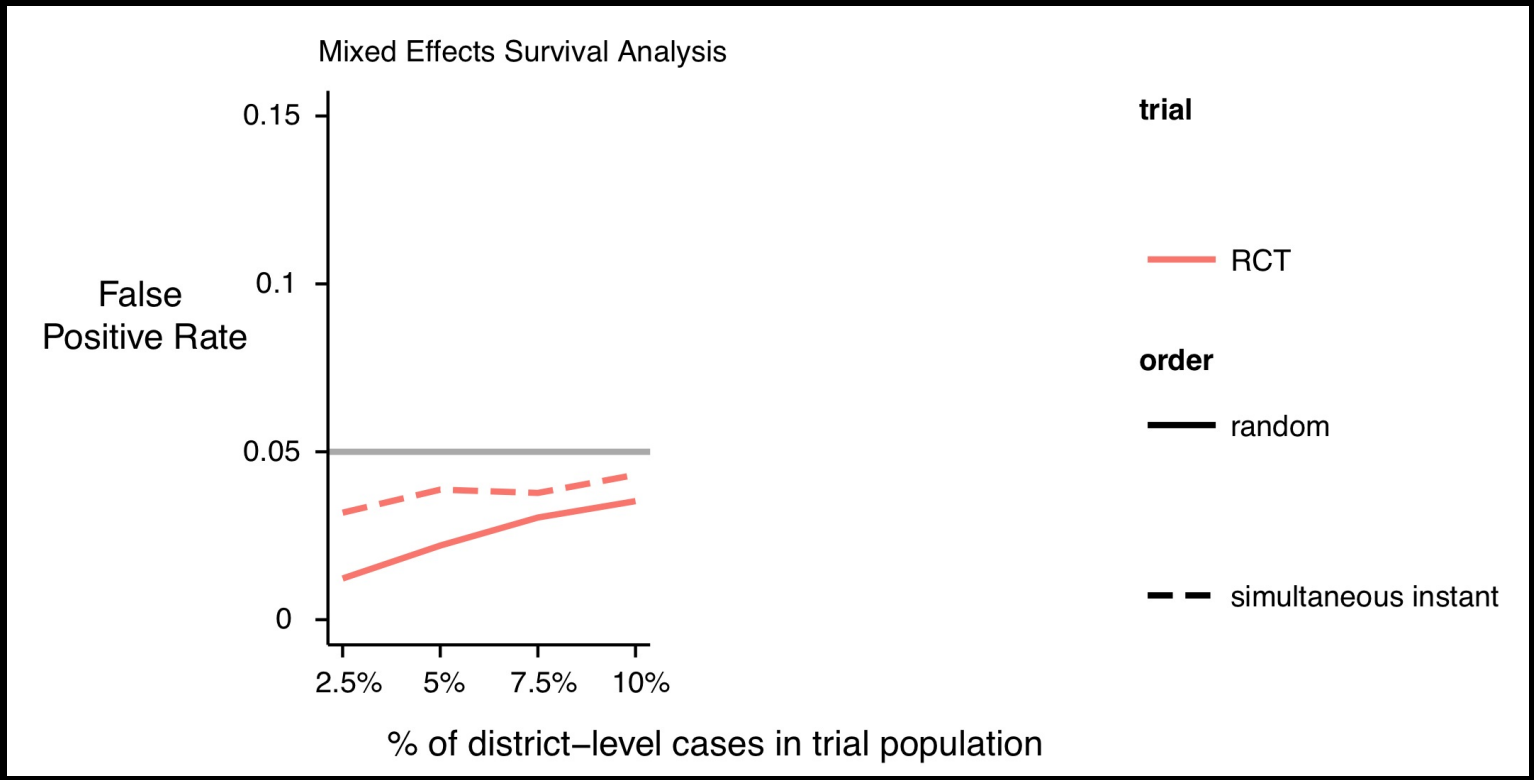

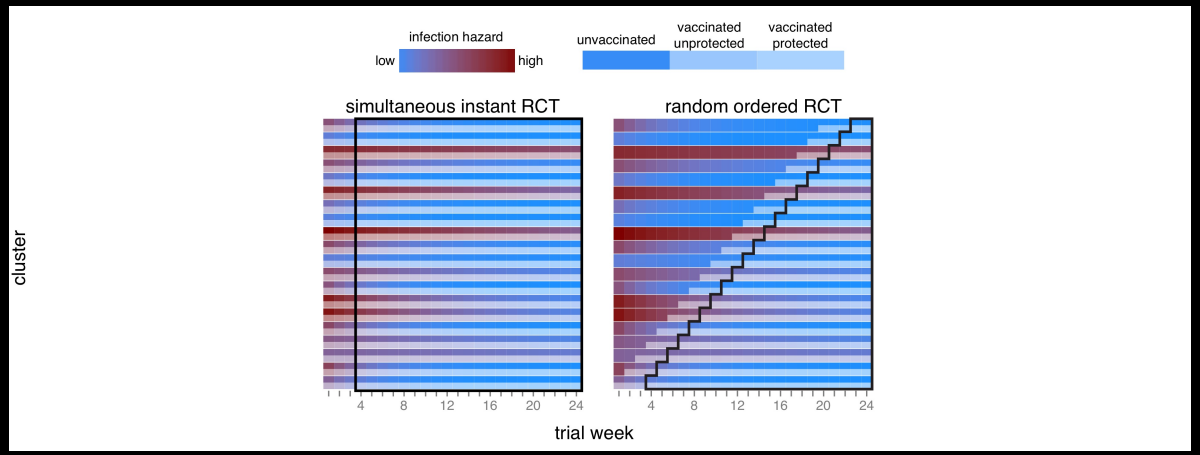

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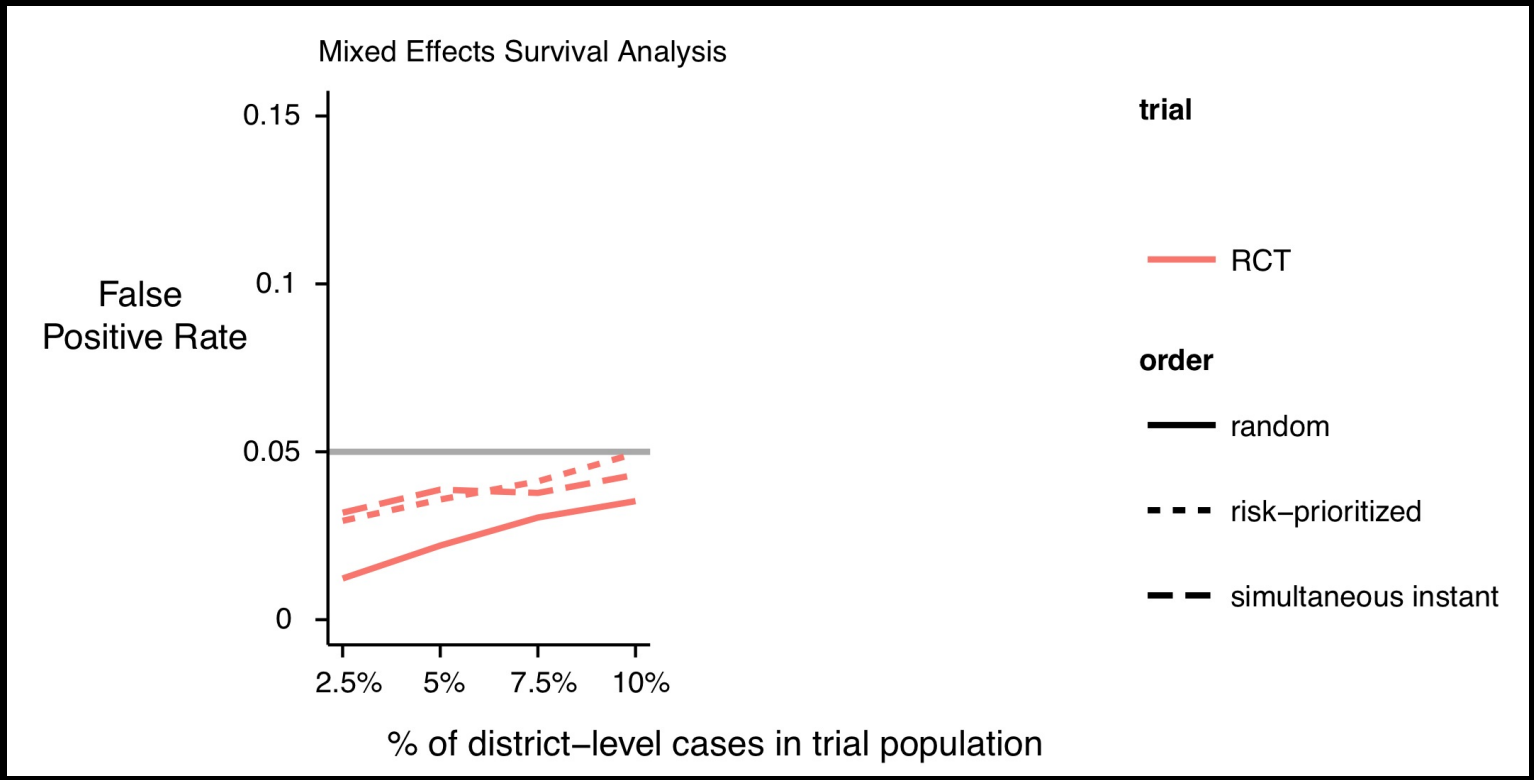

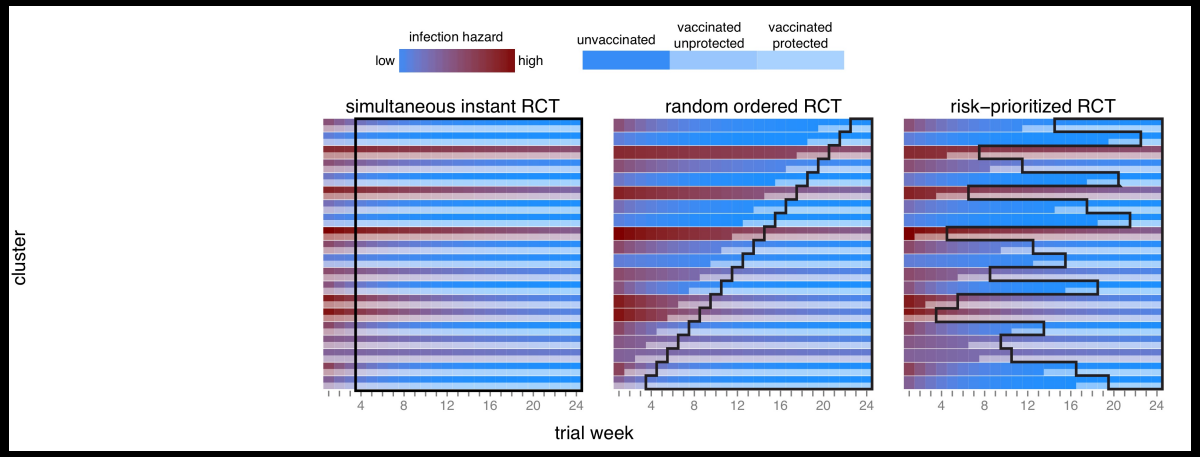

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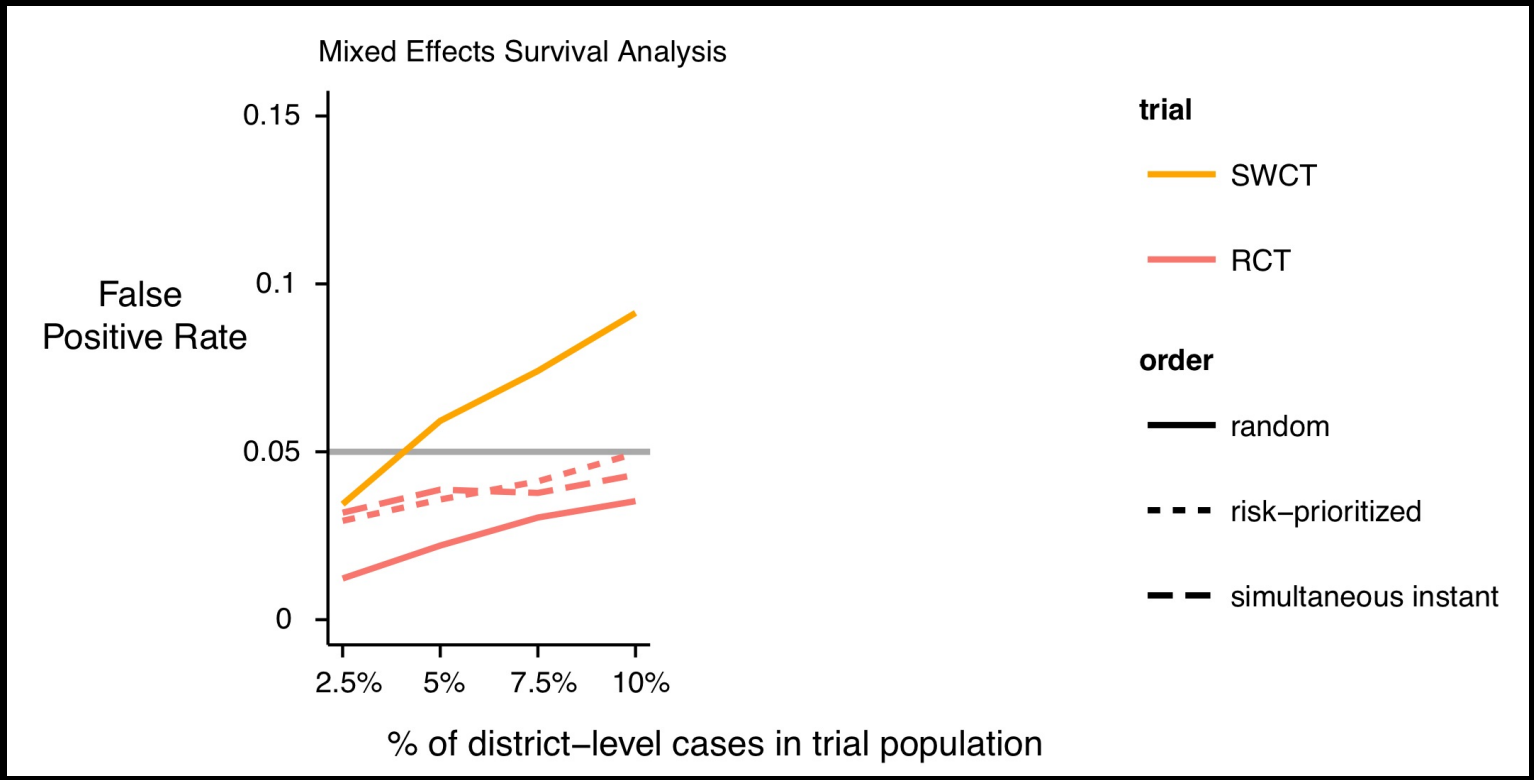

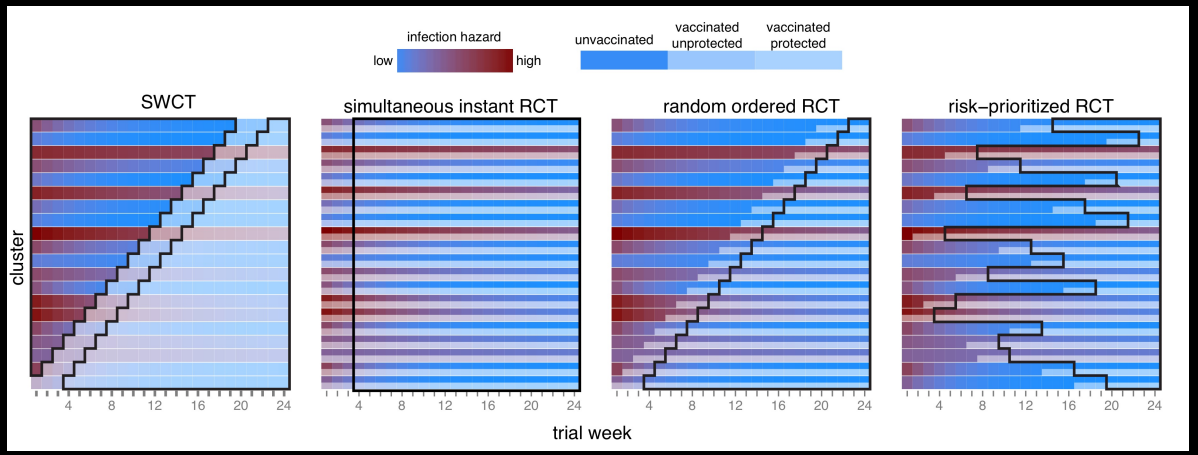

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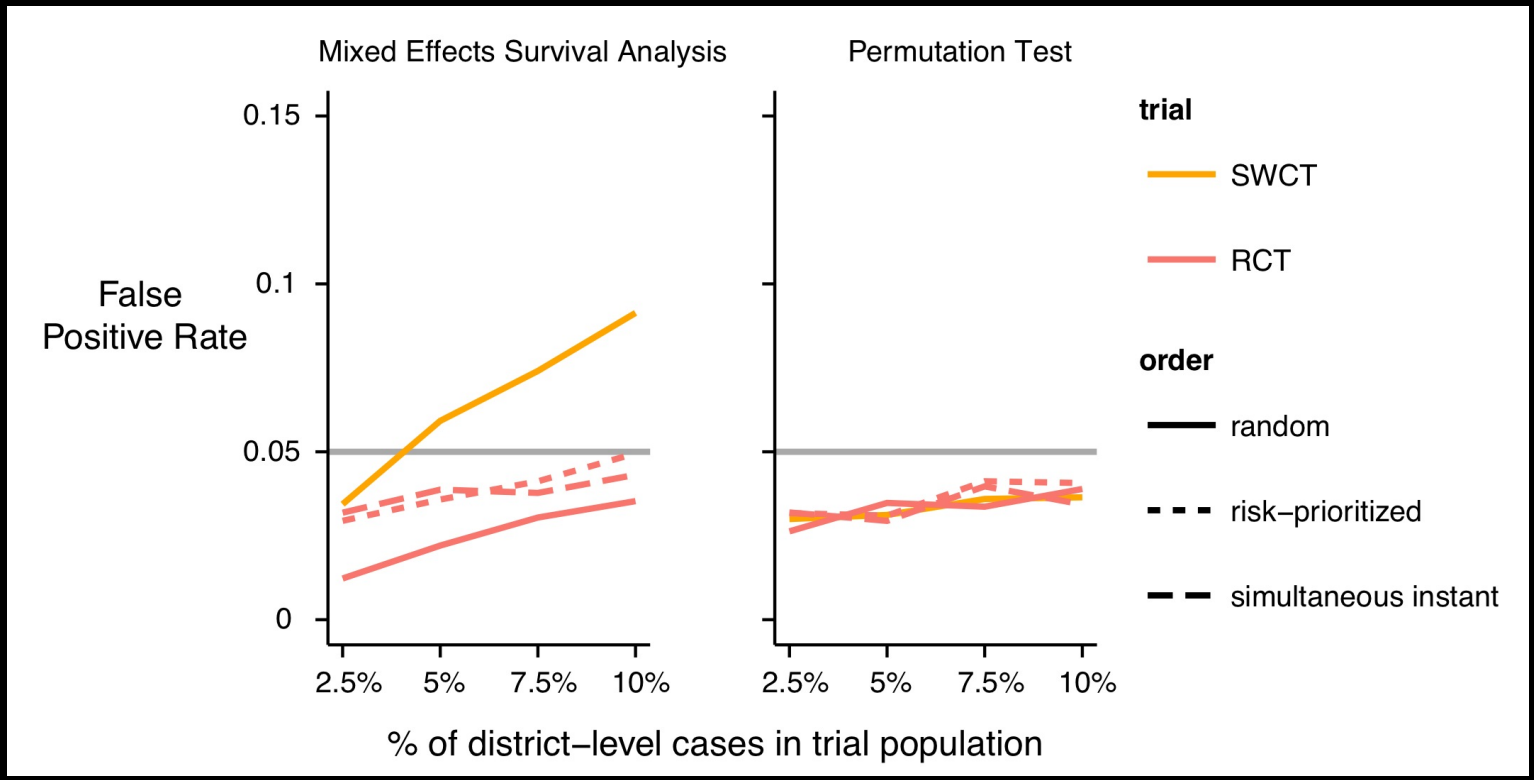

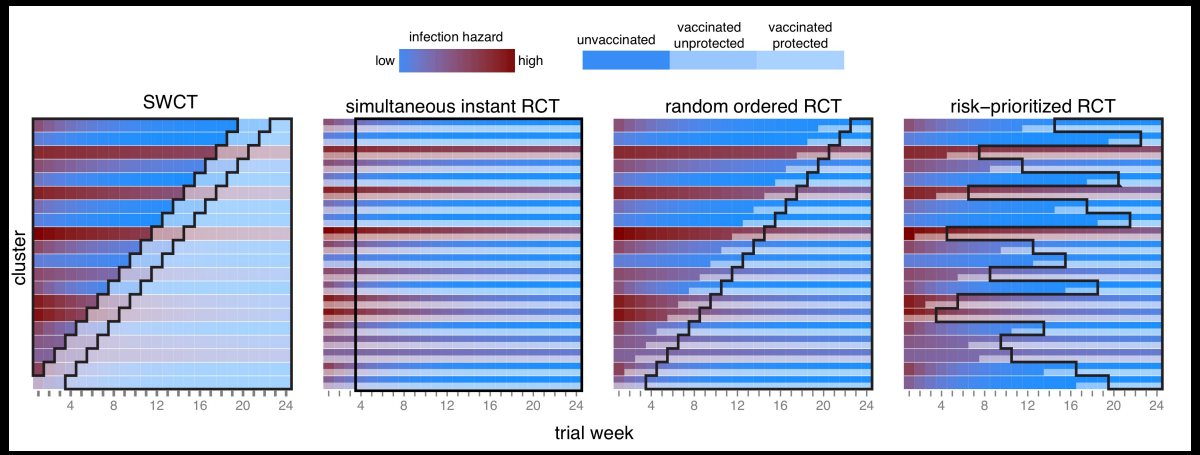

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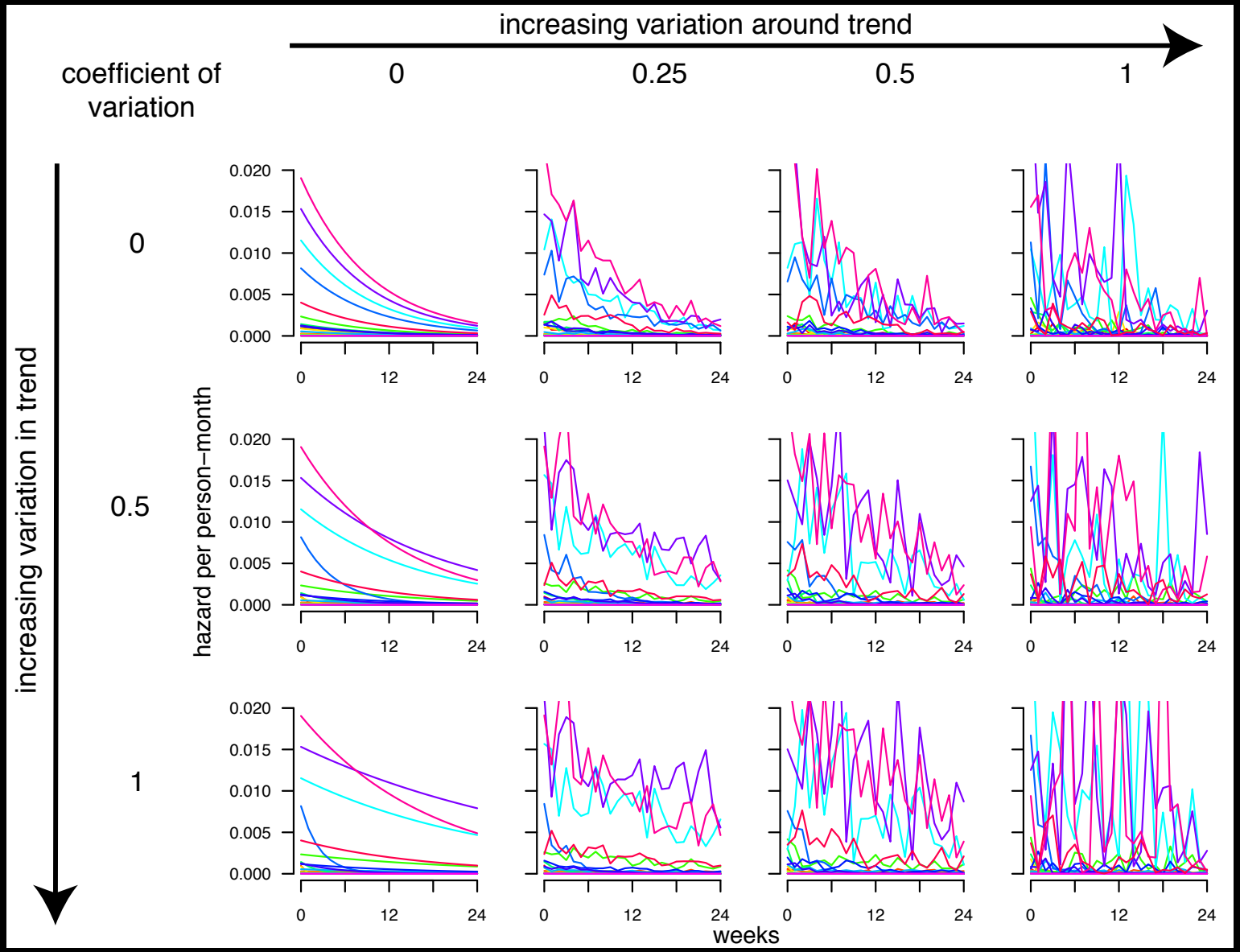

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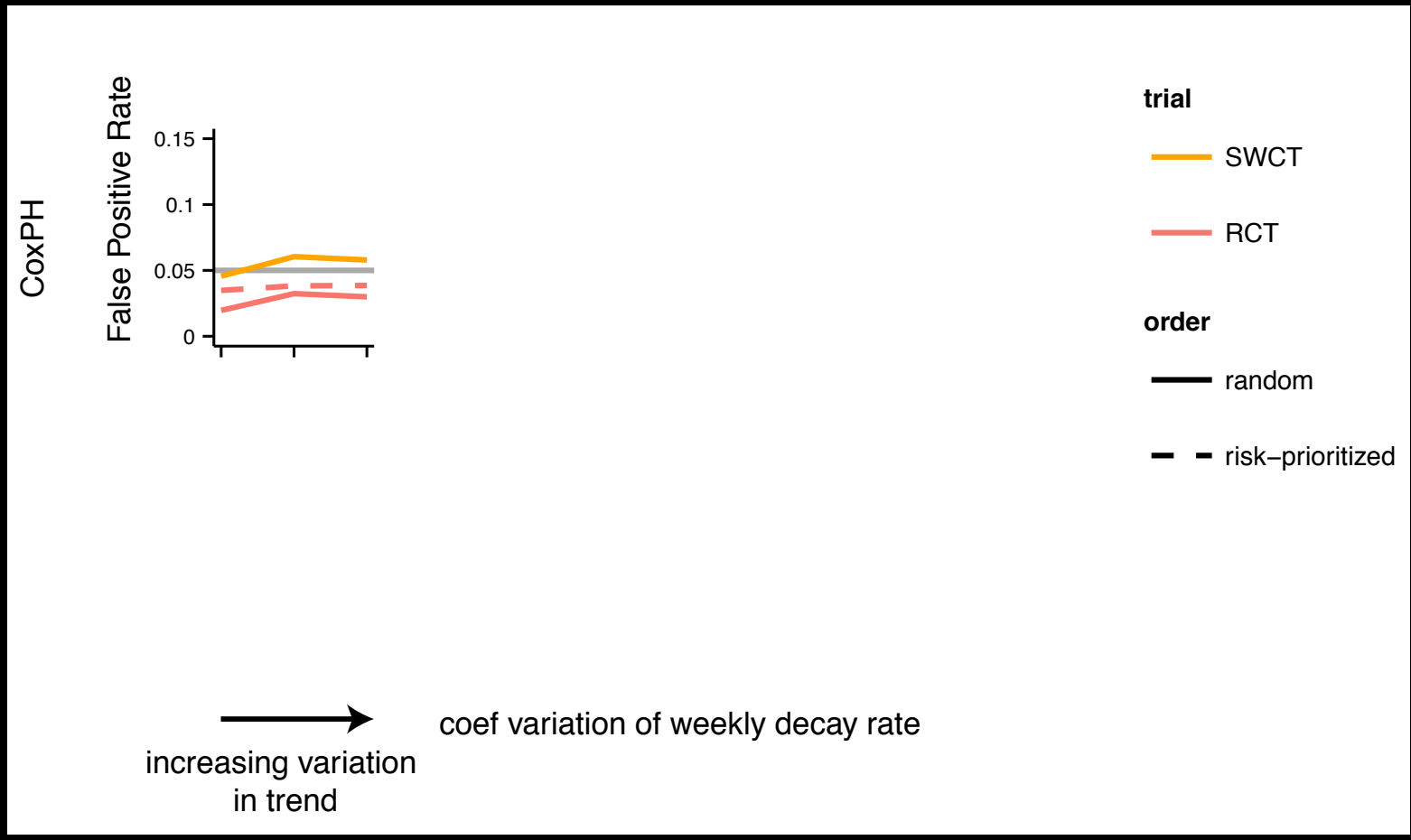

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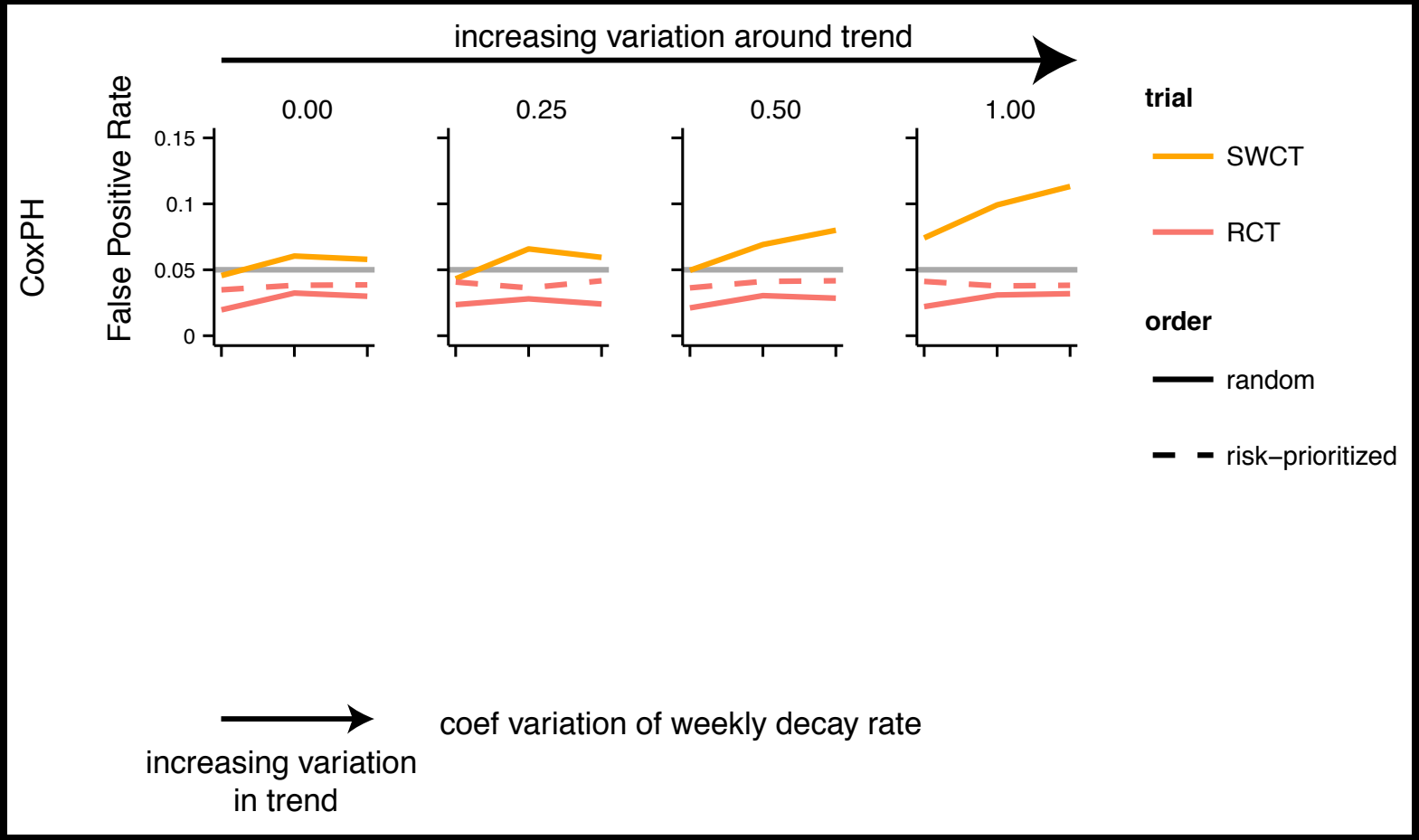

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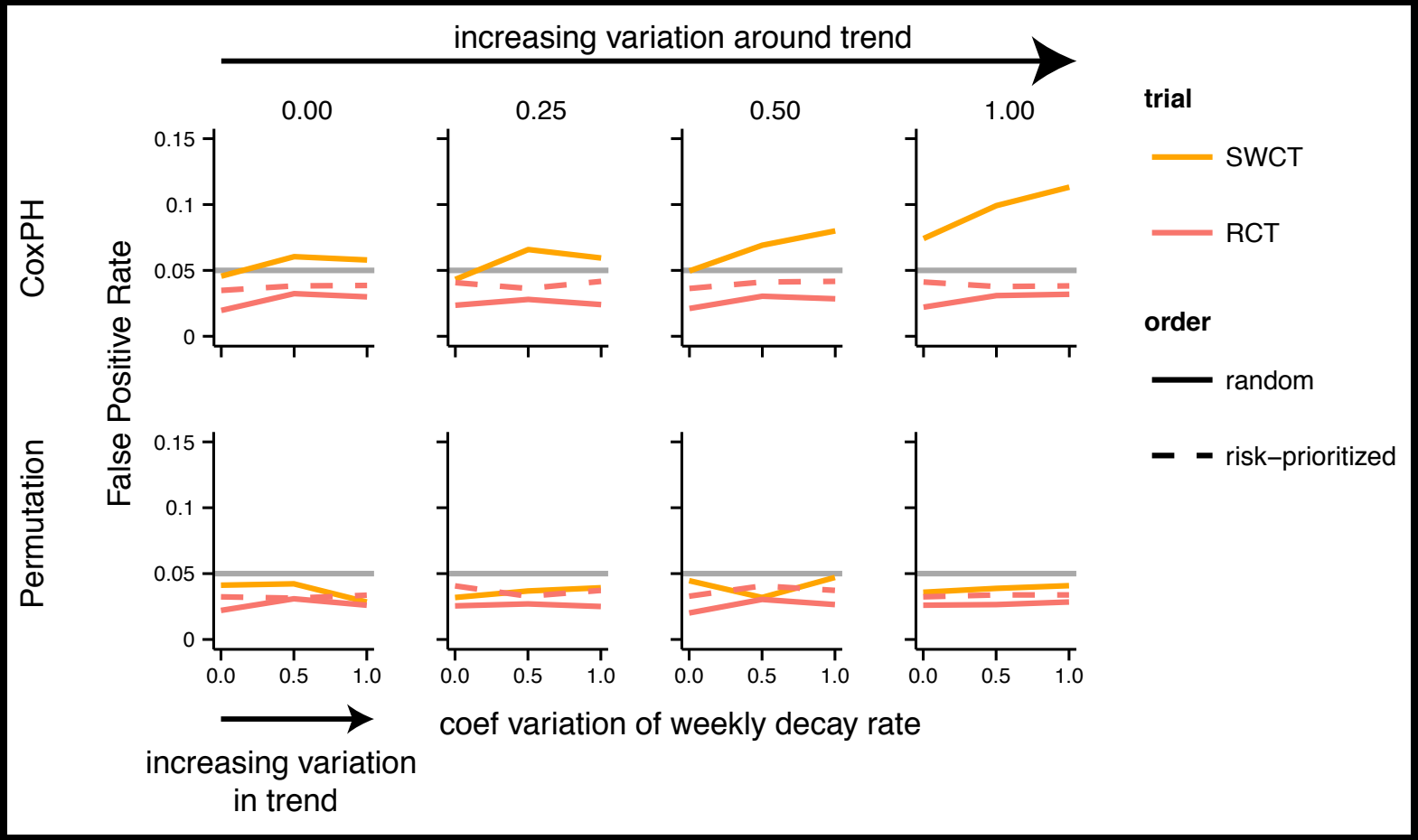
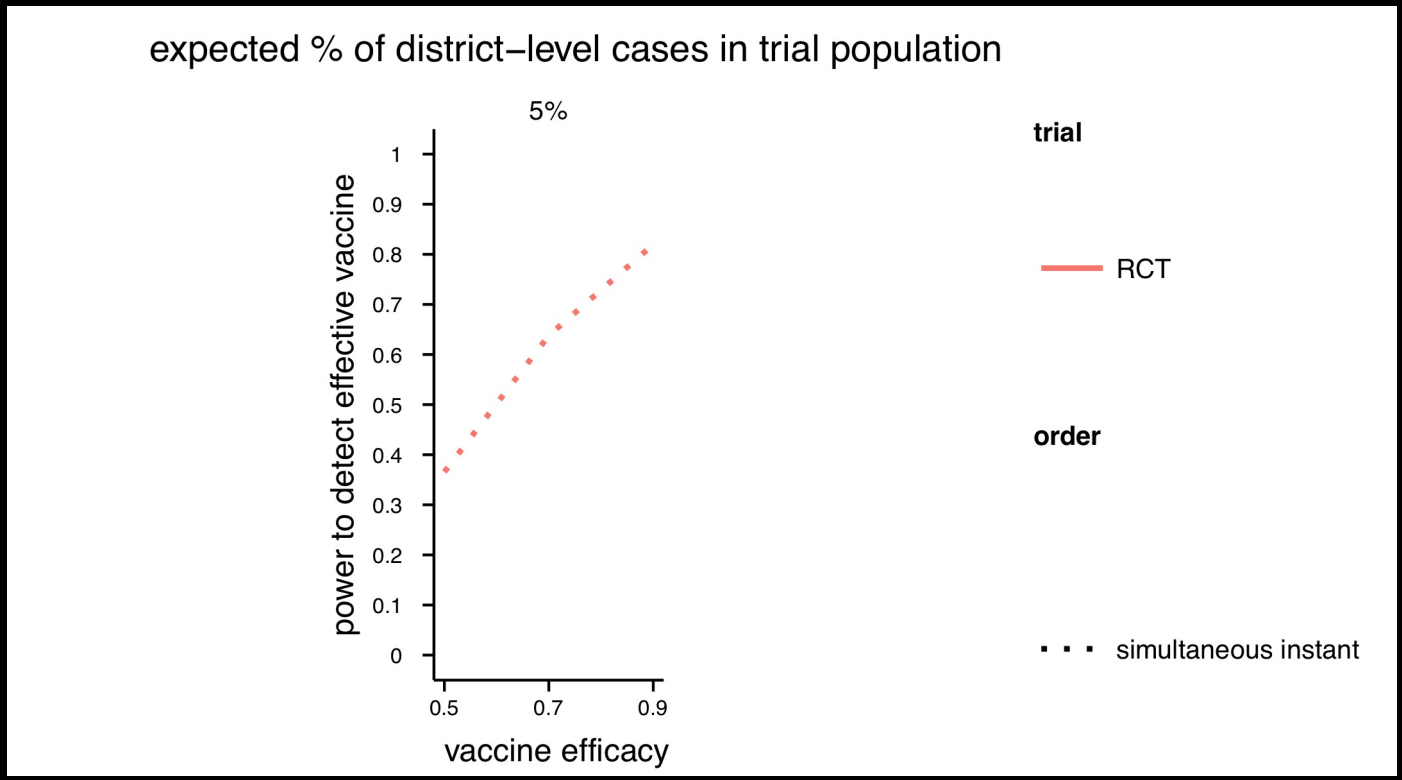
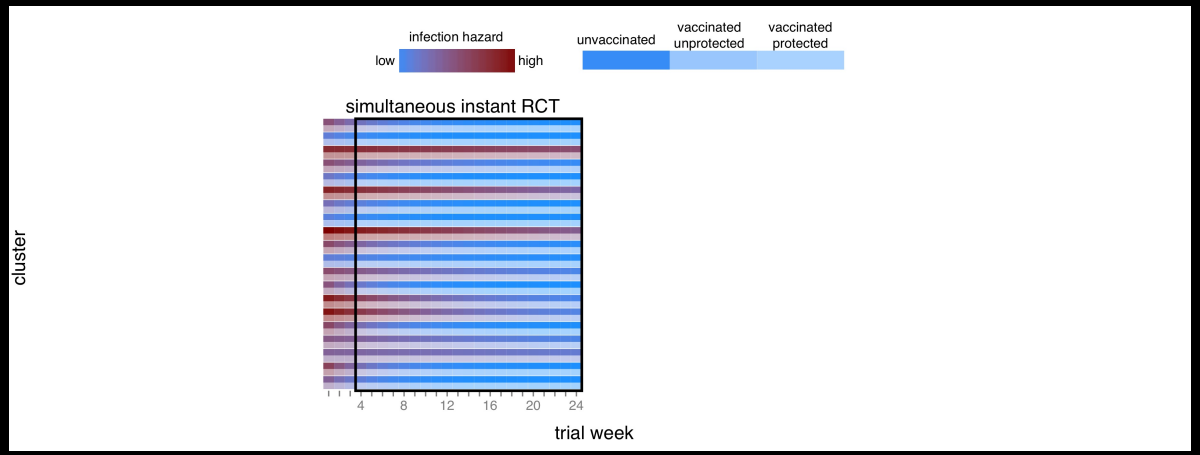


Statistical Power





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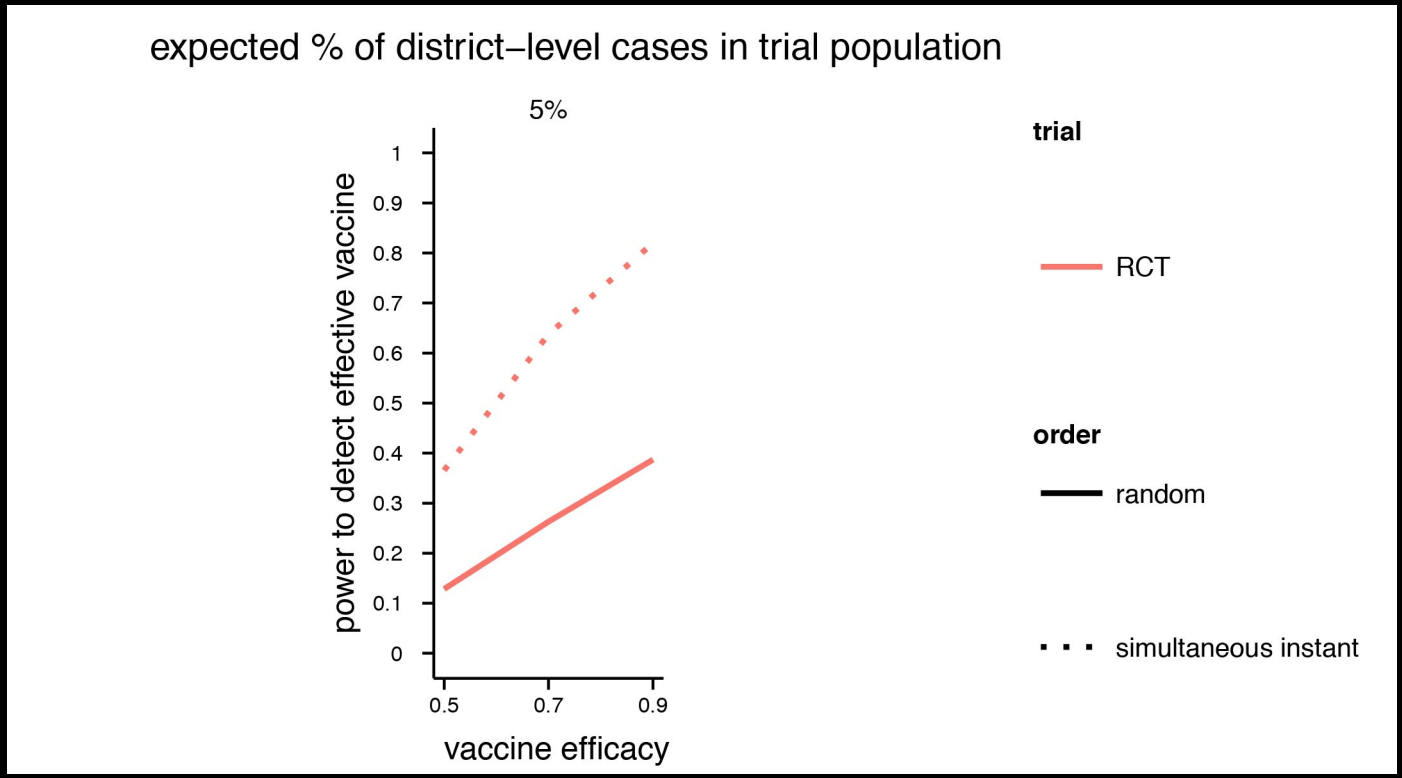

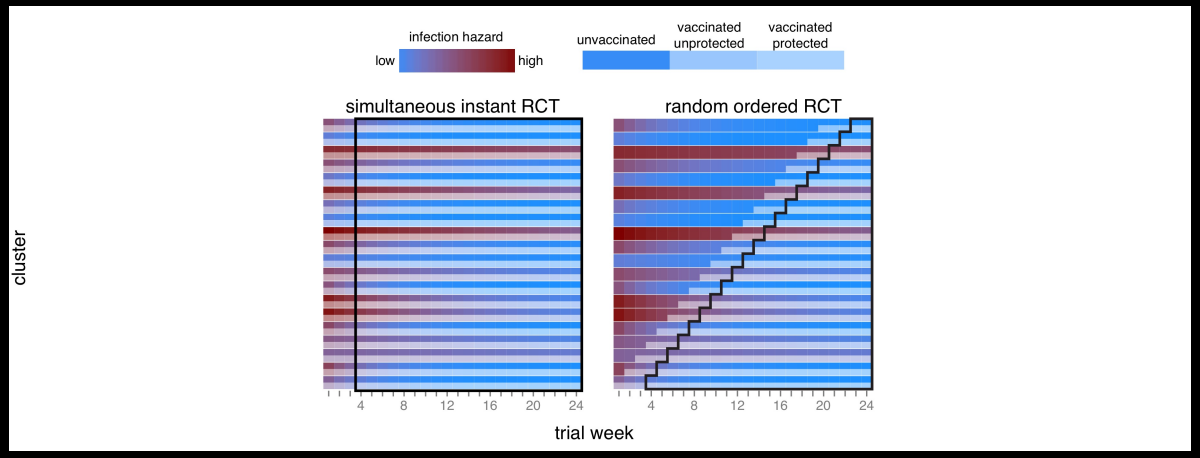

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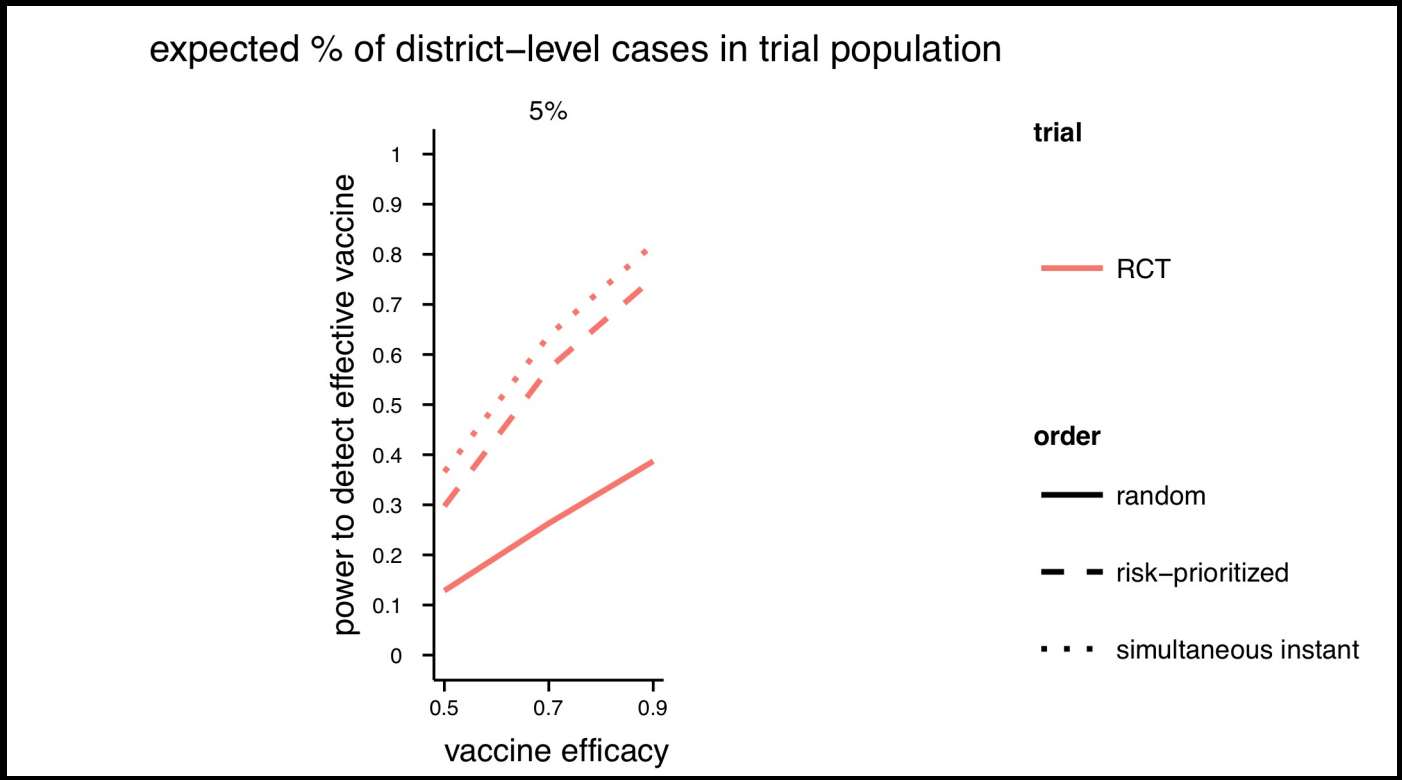
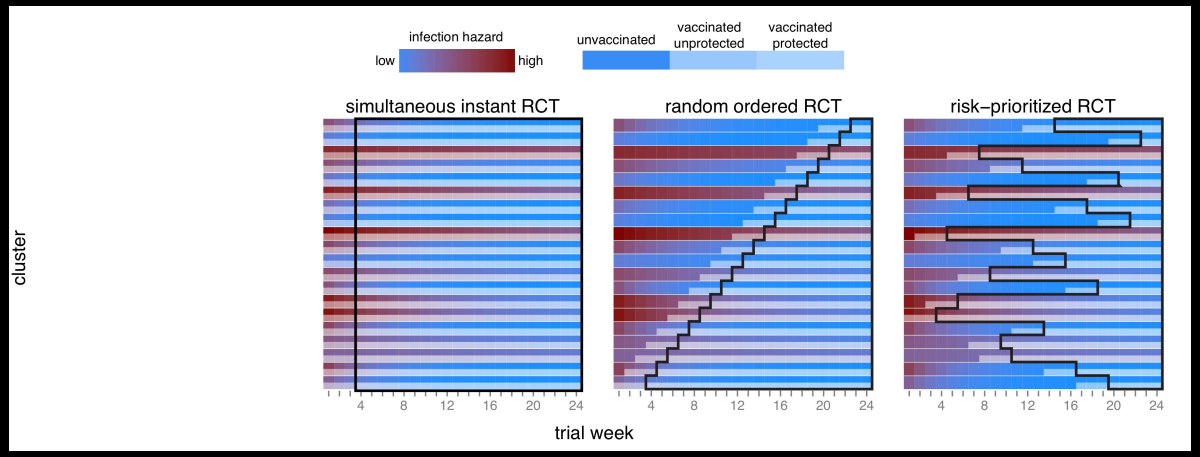
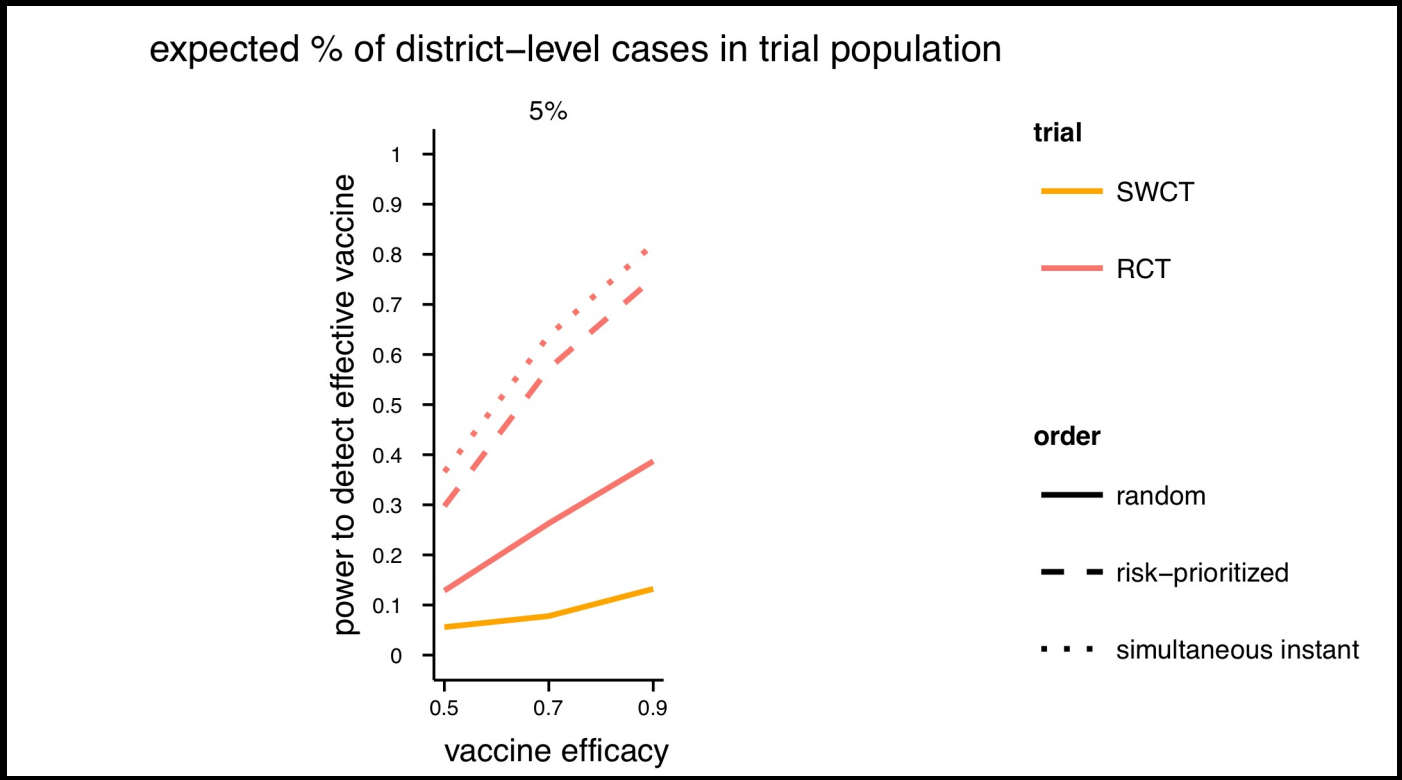
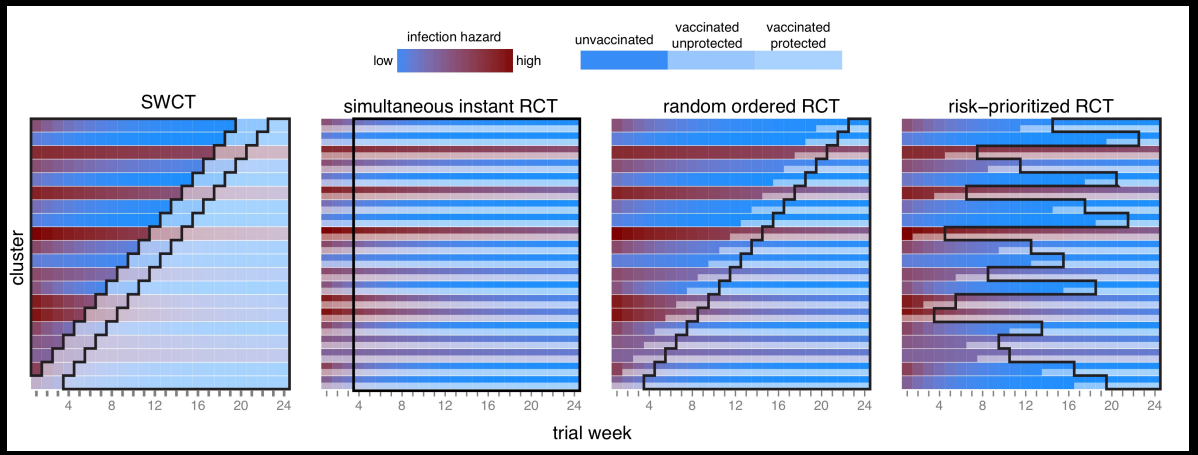


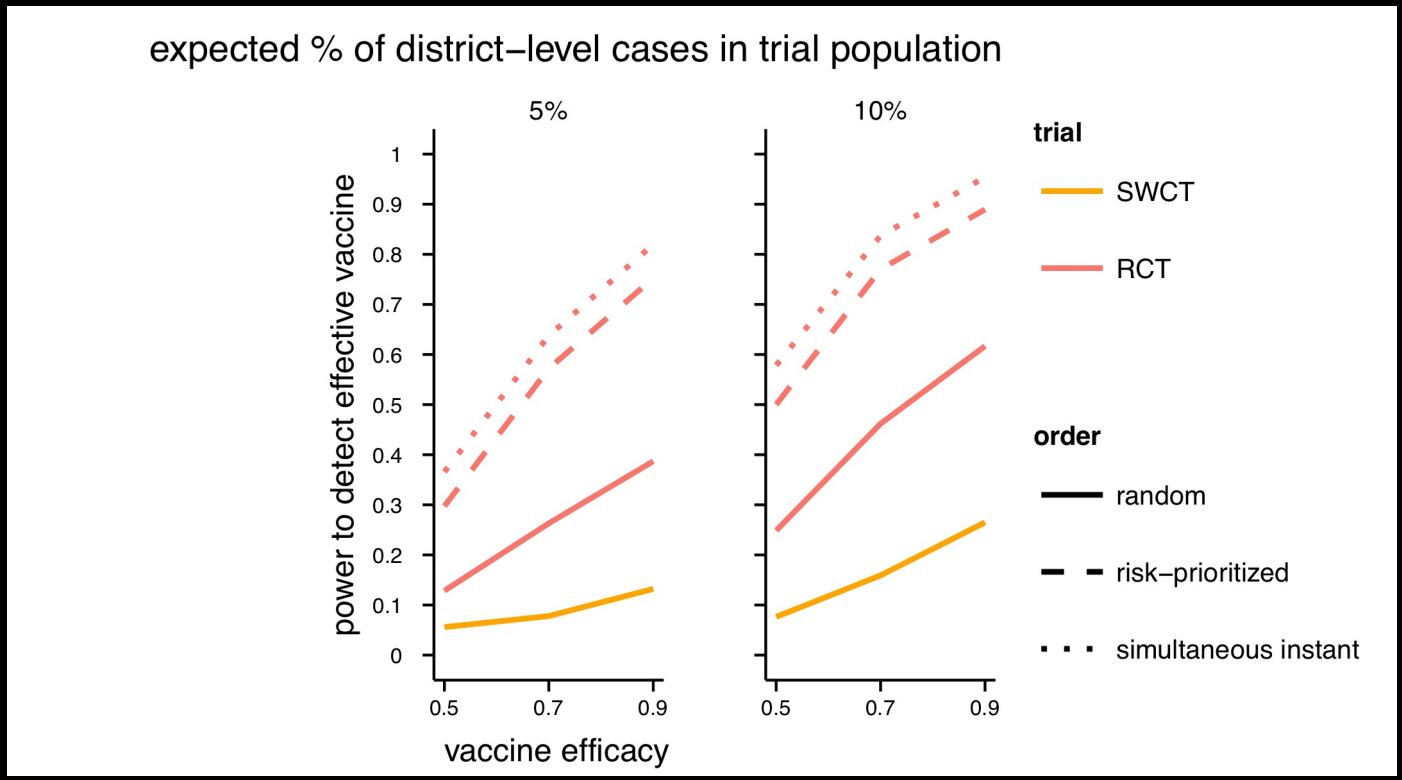


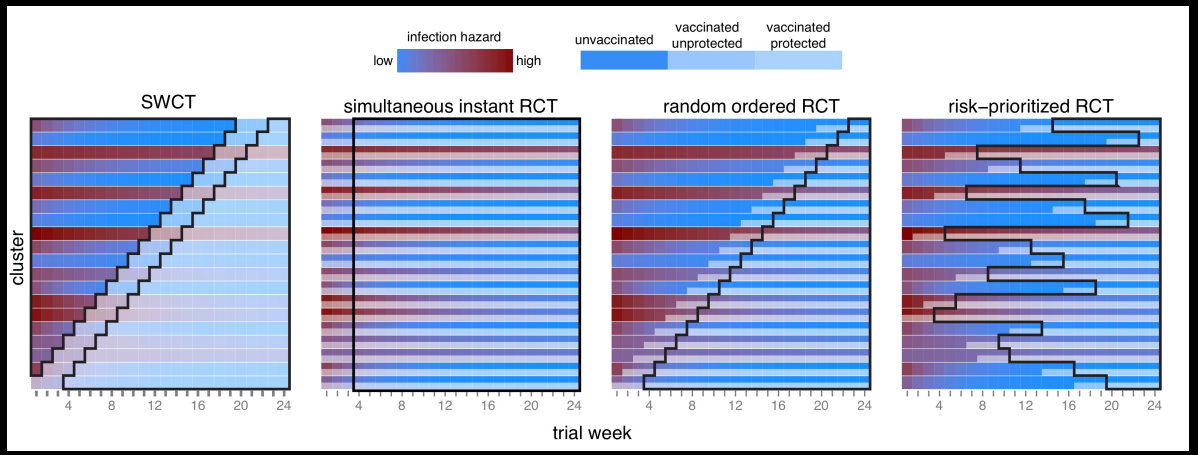
Statistical Power



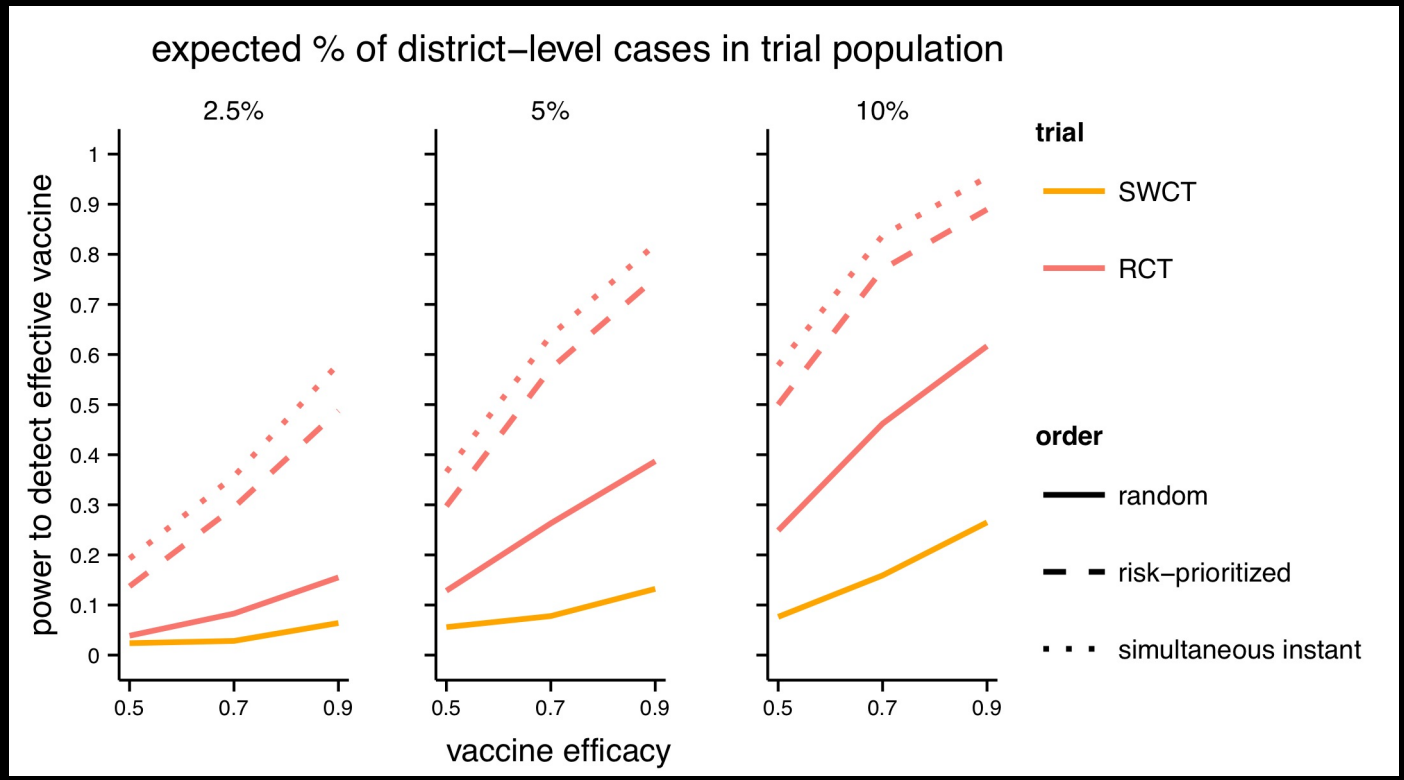


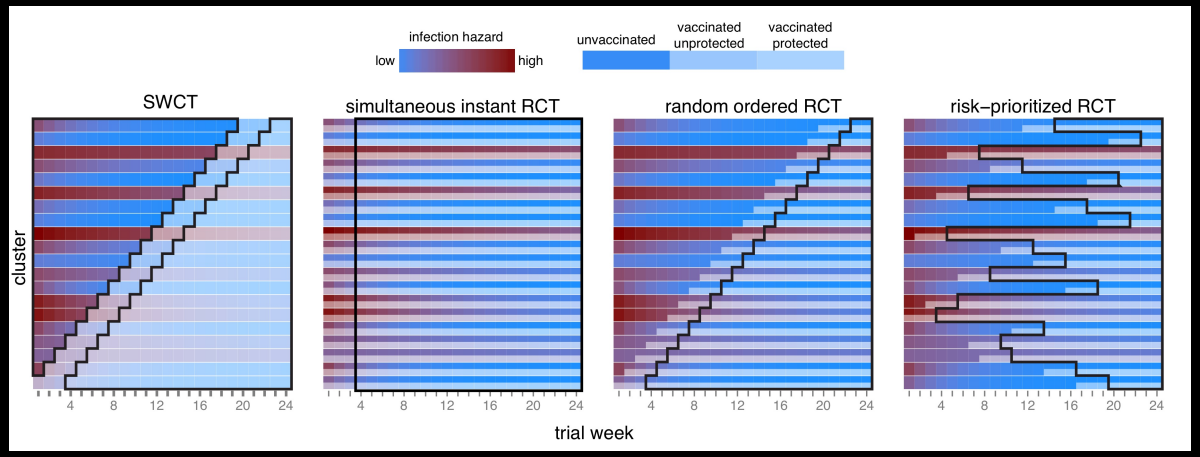
Statistical Power



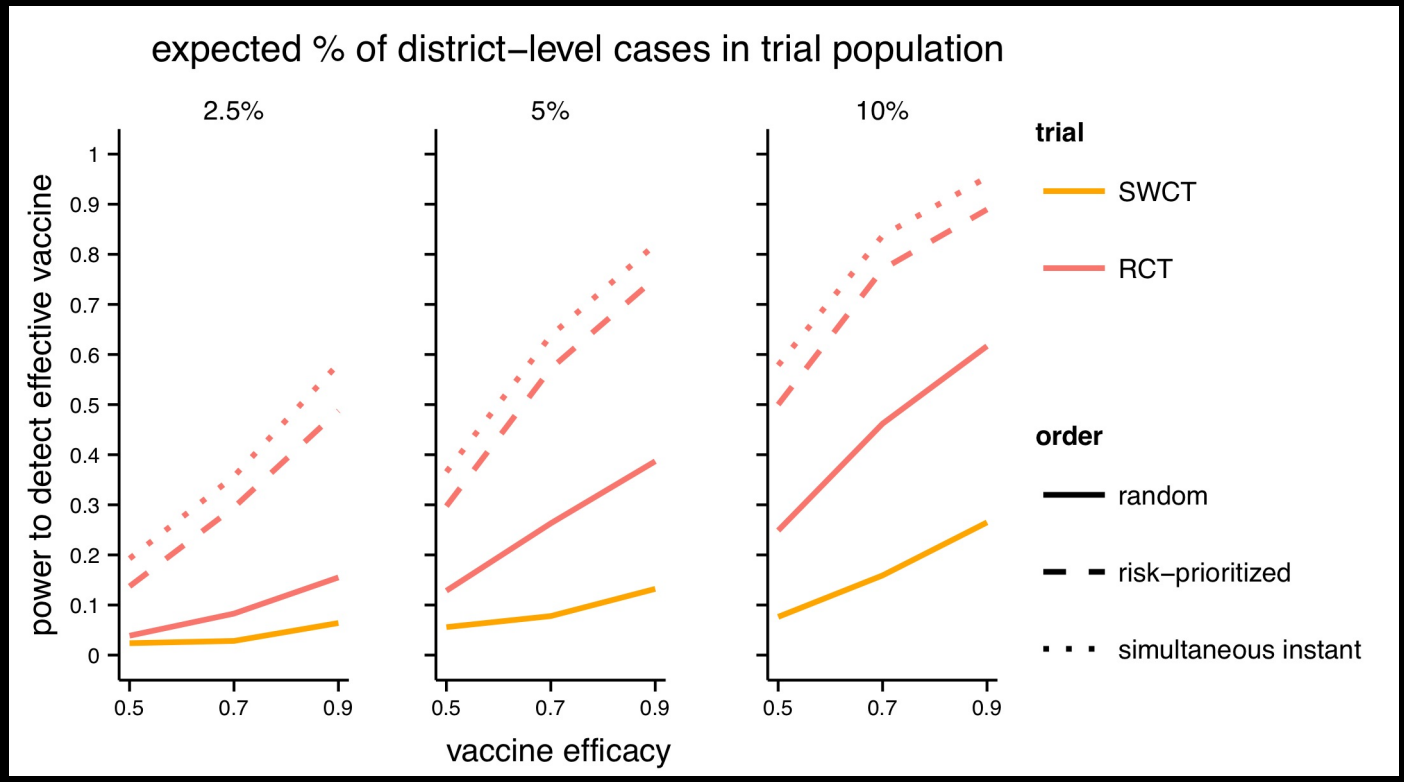


Statistical Power





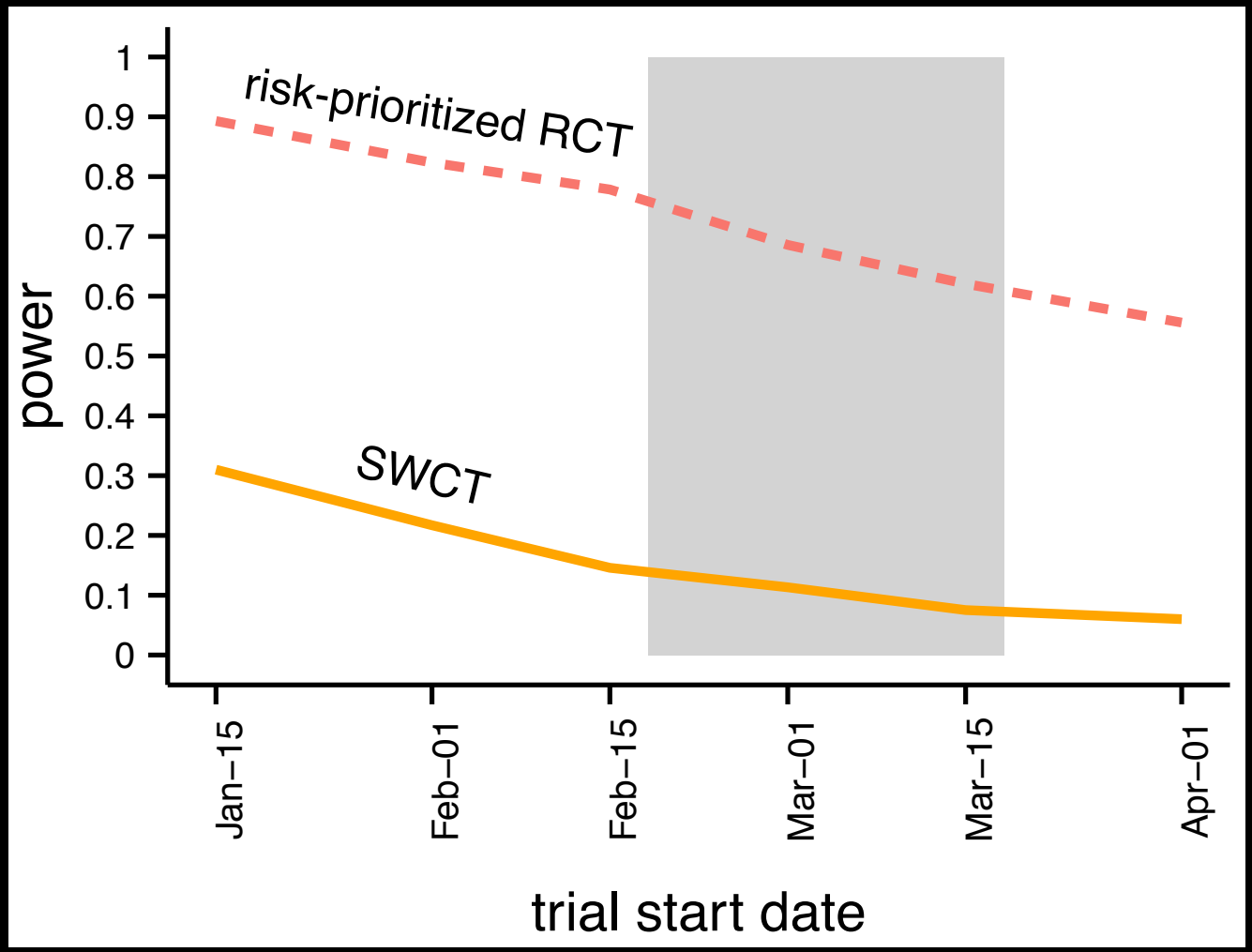
Statistical Power



Stepped wedge cluster trials have <30% of detecting an efficacious vaccine.

Risk-prioritized RCTs nearly as good as simultaneous instant RCTs.

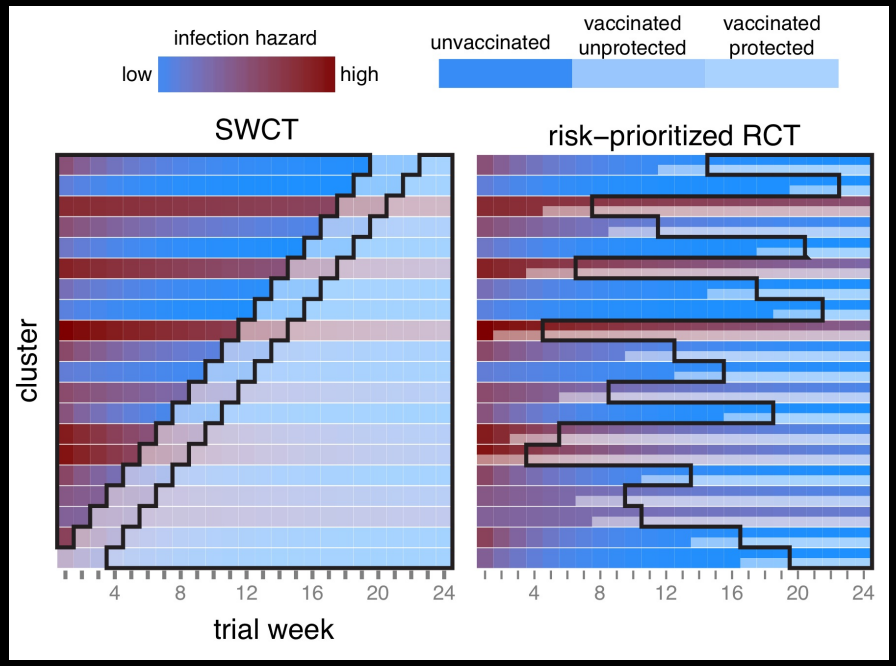
Statistical Power



Speed is a priority!

What about ethics?

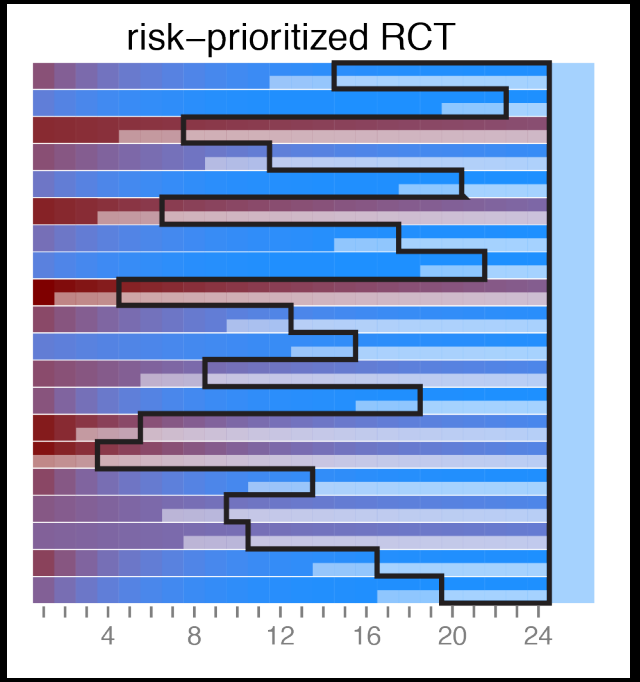
- SWCT: vaccinate everyone ASAP
- Uses random, NOT risk-prioritized, ordering to allow
- High risk people should be vaccinated first



CDC

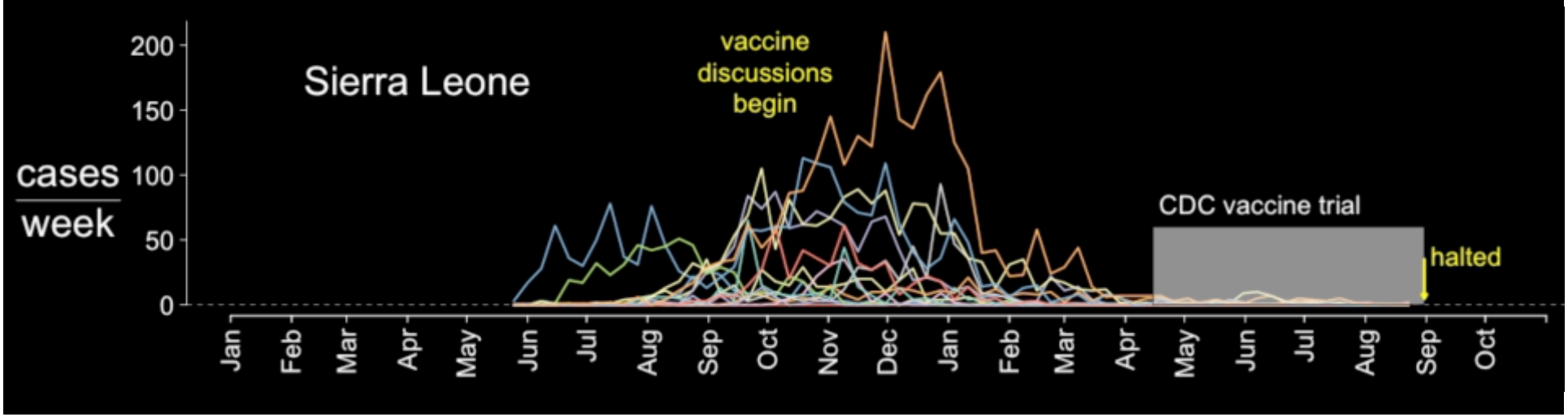
STRIVE

Sierra Leone Trial to Introduce a Vaccine against Ebola



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

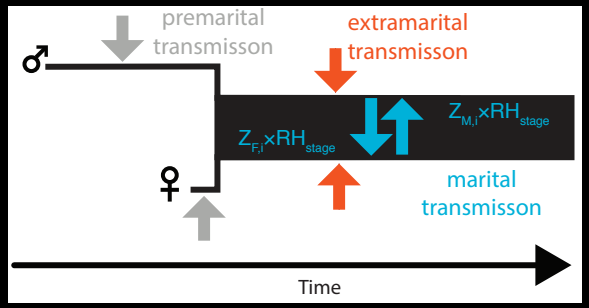
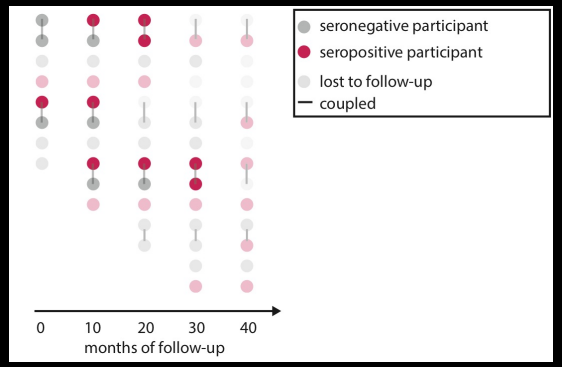
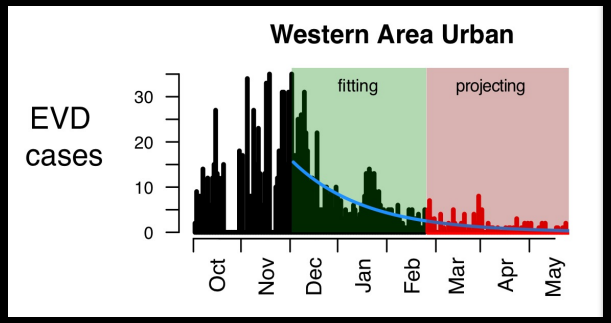
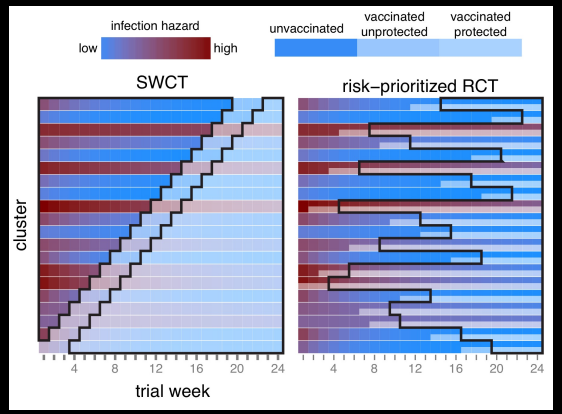
Vaccinated everyone at the end.



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

Integrative Approach

	process-centric	data-centric
acute HIV (data interpretation)		
Ebola vaccine (study planning)		

Acknowledgements

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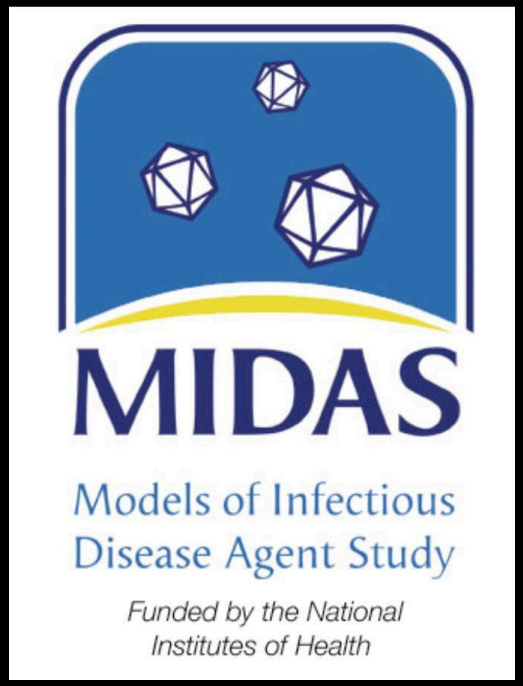
- NIH R25GM102149 to JRC Pulliam and A Welte
- Canadian Institute of Health Research (CIHR)
- Natural Sciences and Engineering Research Council of Canada (NSERC)



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Title: Statistical power and validity of Ebola vaccine trials in Sierra Leone

Attribution:
Bellan, SE, JRC Pulliam, CAB Pearson, DChampredon, SJ Fox, L Skrip, AP Galvani, M Gambhir, BA Lopman, TC Porco, LA Meyers, J Dushoff (2015) Statistical power and validity of Ebola vaccine trials in Sierra Leone. *Lancet Inf Dis*.

Code: http://ebola.ici3d.org/

For further information please contact Steve Bellan (steve.bellan@gmail.com).