Statistical power and validity of Ebola vaccine trials in Sierra Leone

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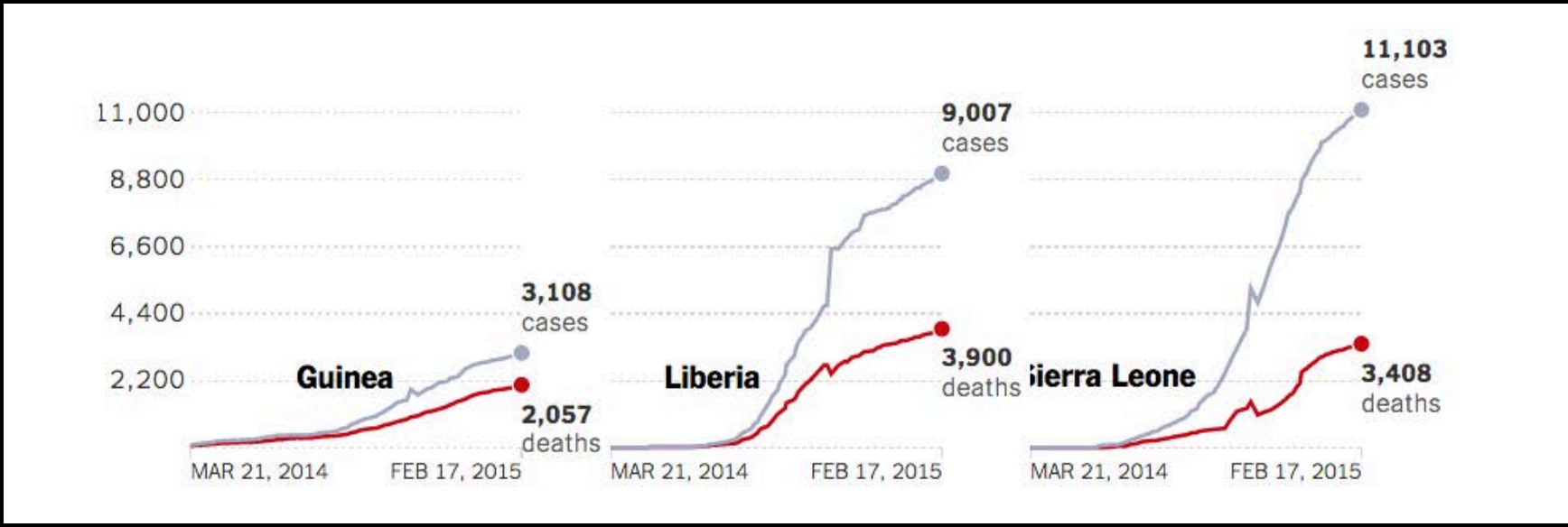
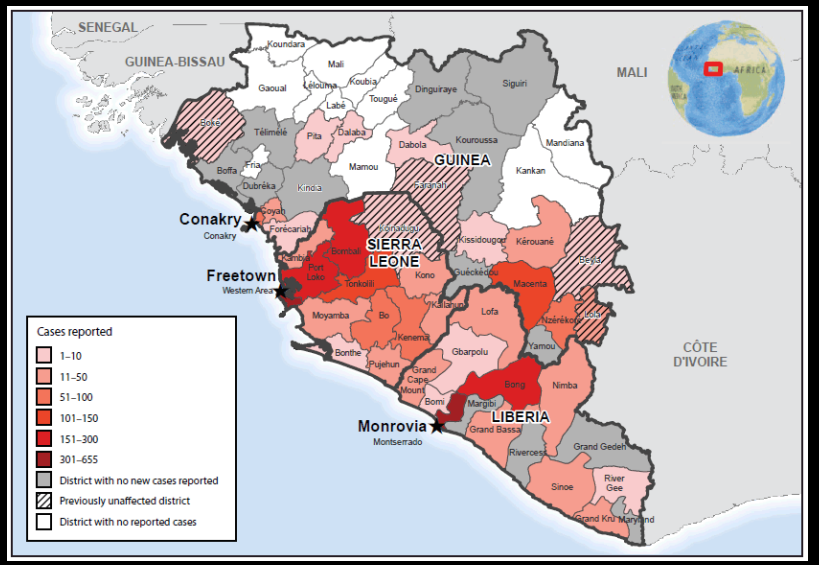
Ebola in West Africa



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,
  vaccine appears to increase risk! (confounding)

- Confounding avoided by randomization to vaccine or placebo

- Randomized double-blinded placebo-controlled trials

Is randomization ethical?

- You're a HCW in Sierra Leone with high Ebola risk.
- A vaccine appears safe and promising.
- Would you want to be randomized to placebo?

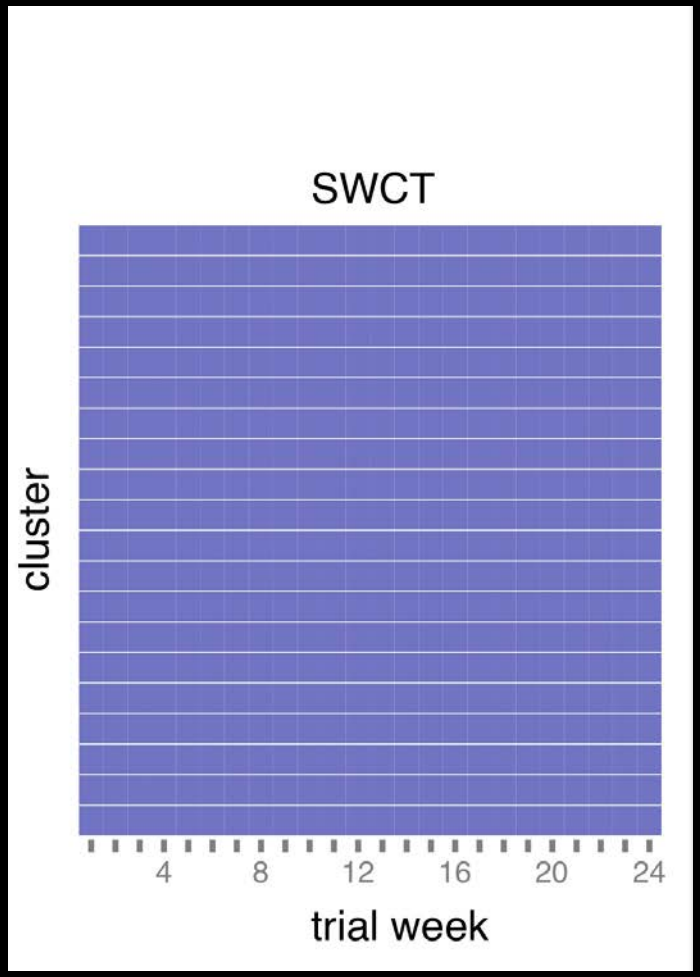
Equipoise

Uncertainty in the medical community regarding whether a participant is better off receiving the intervention or placebo.

Stepped Wedge Cluster Trial

- Evaluate an intervention when there is no equipoise
- Vaccinate everyone as fast as possible, group by group
- Randomize group-order of vaccination
- Compare infection risk between
  vaccinated & not-yet-vaccinated individuals
- Because order is randomized, confounding is avoided

Stepped Wedge Cluster Trial



24 weeks of observation

20 clusters (each row), 300 people each

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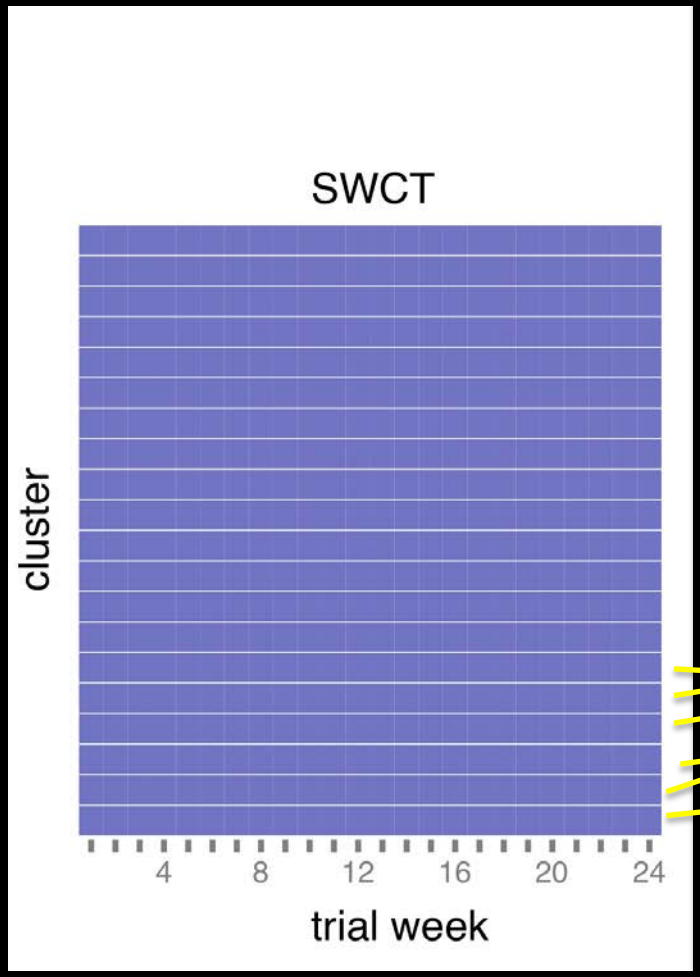

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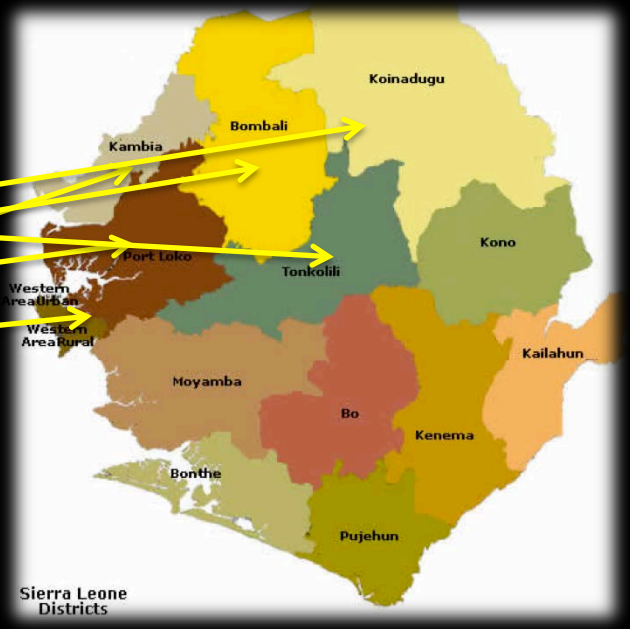

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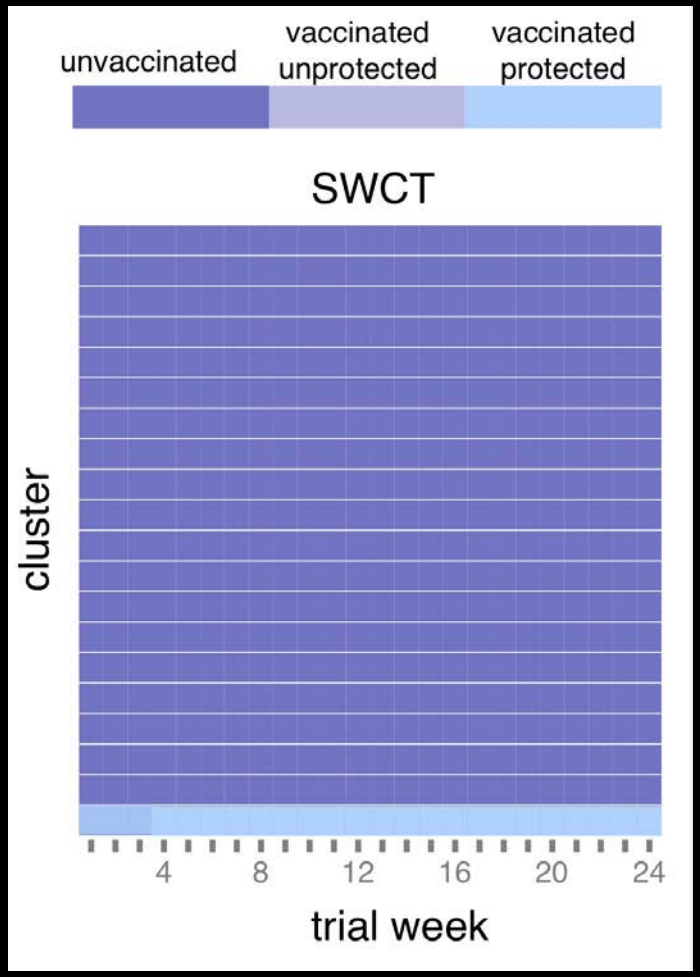

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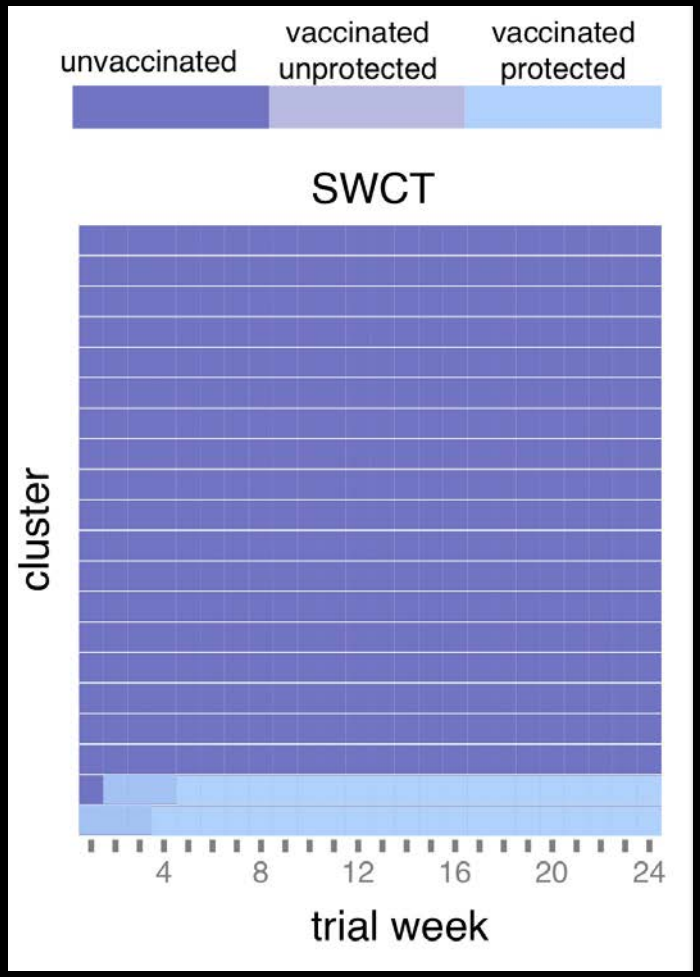

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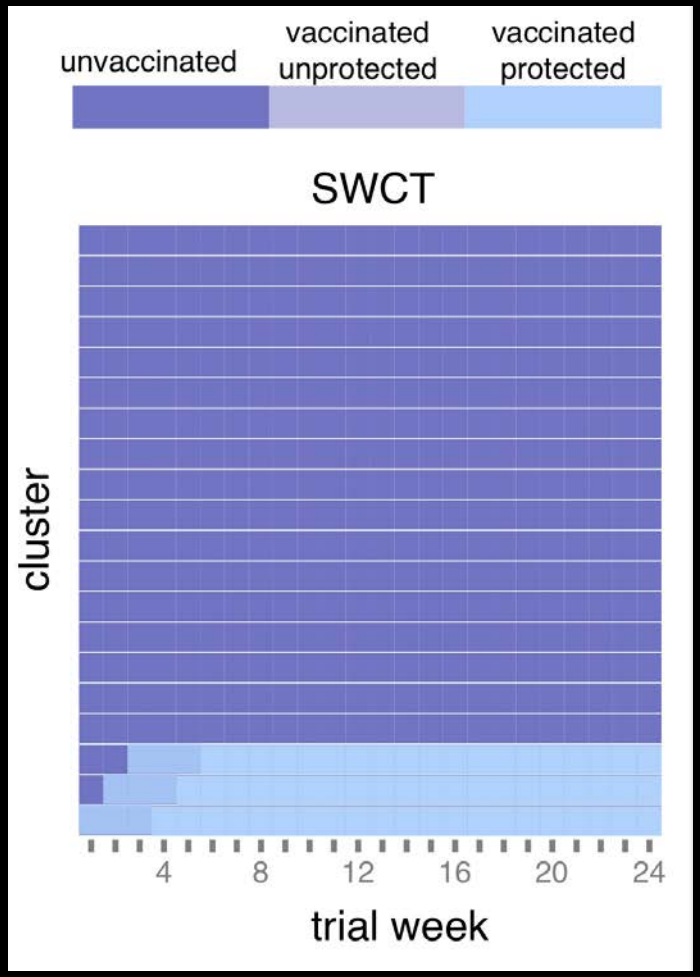

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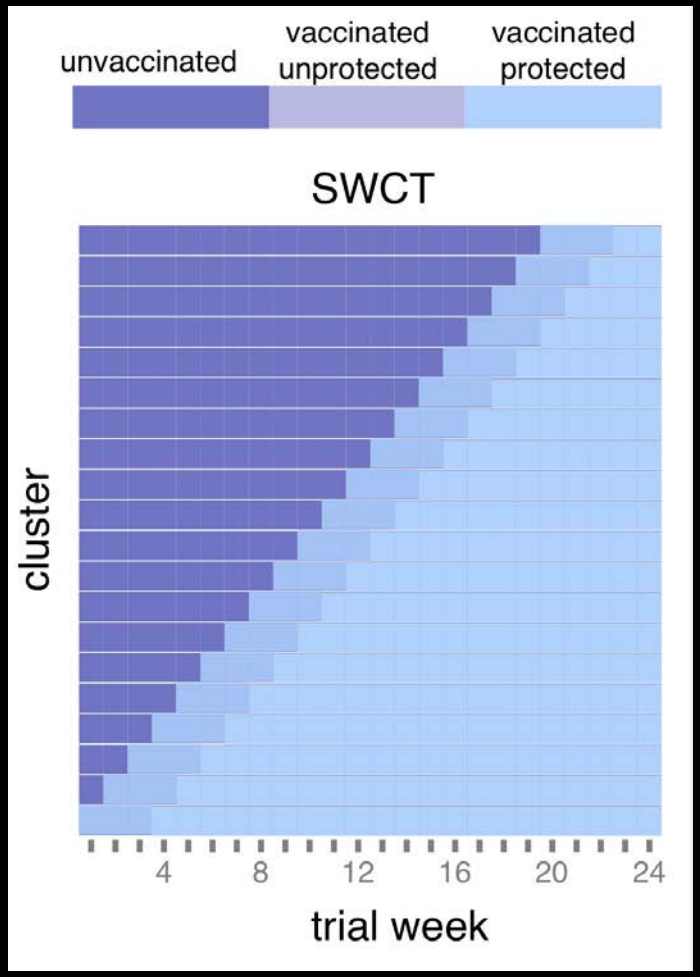

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Everyone is vaccinated (no equipoise issues)

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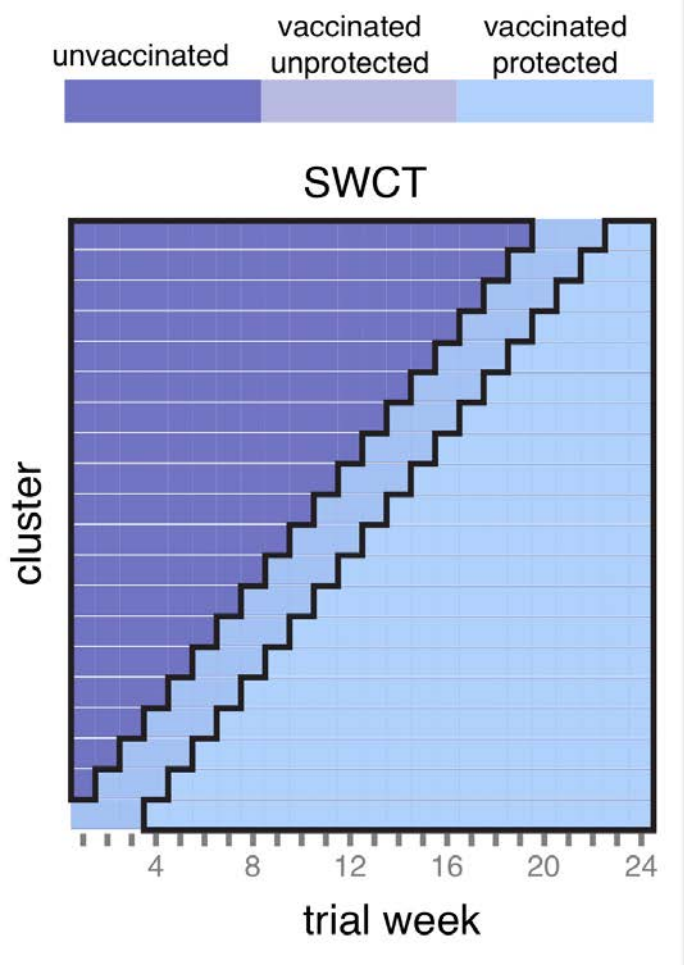

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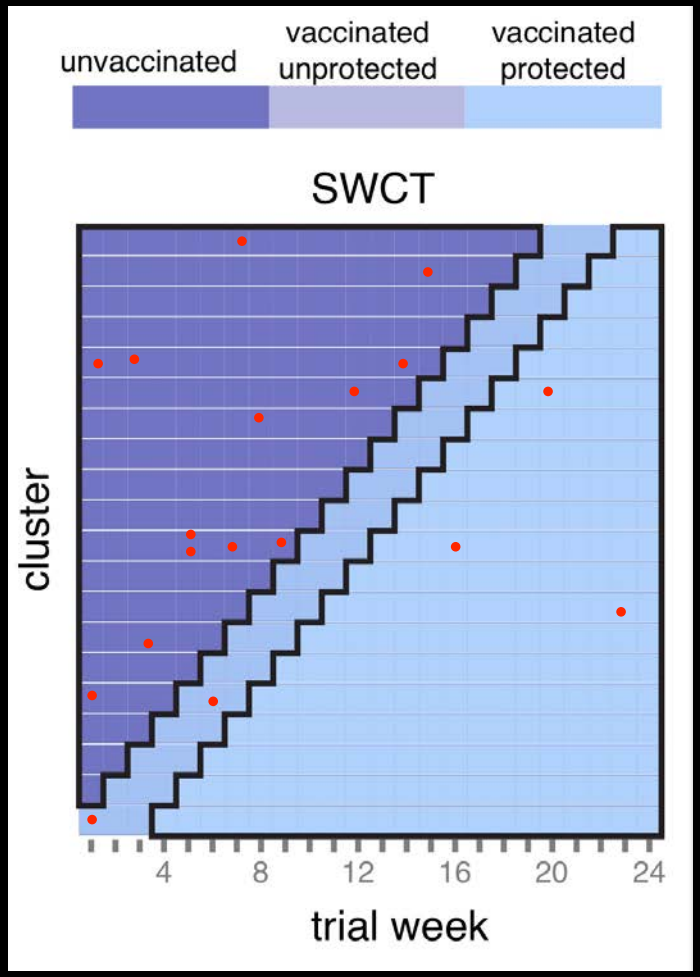

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Compare # infections between vaccinated & not-yet-vaccinated

- infected participant

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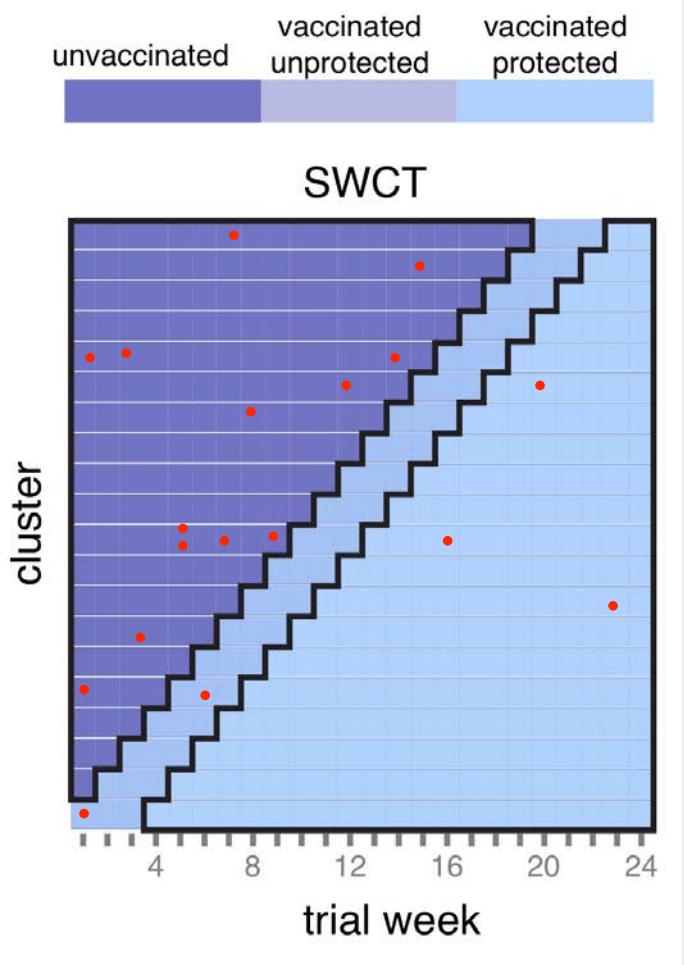
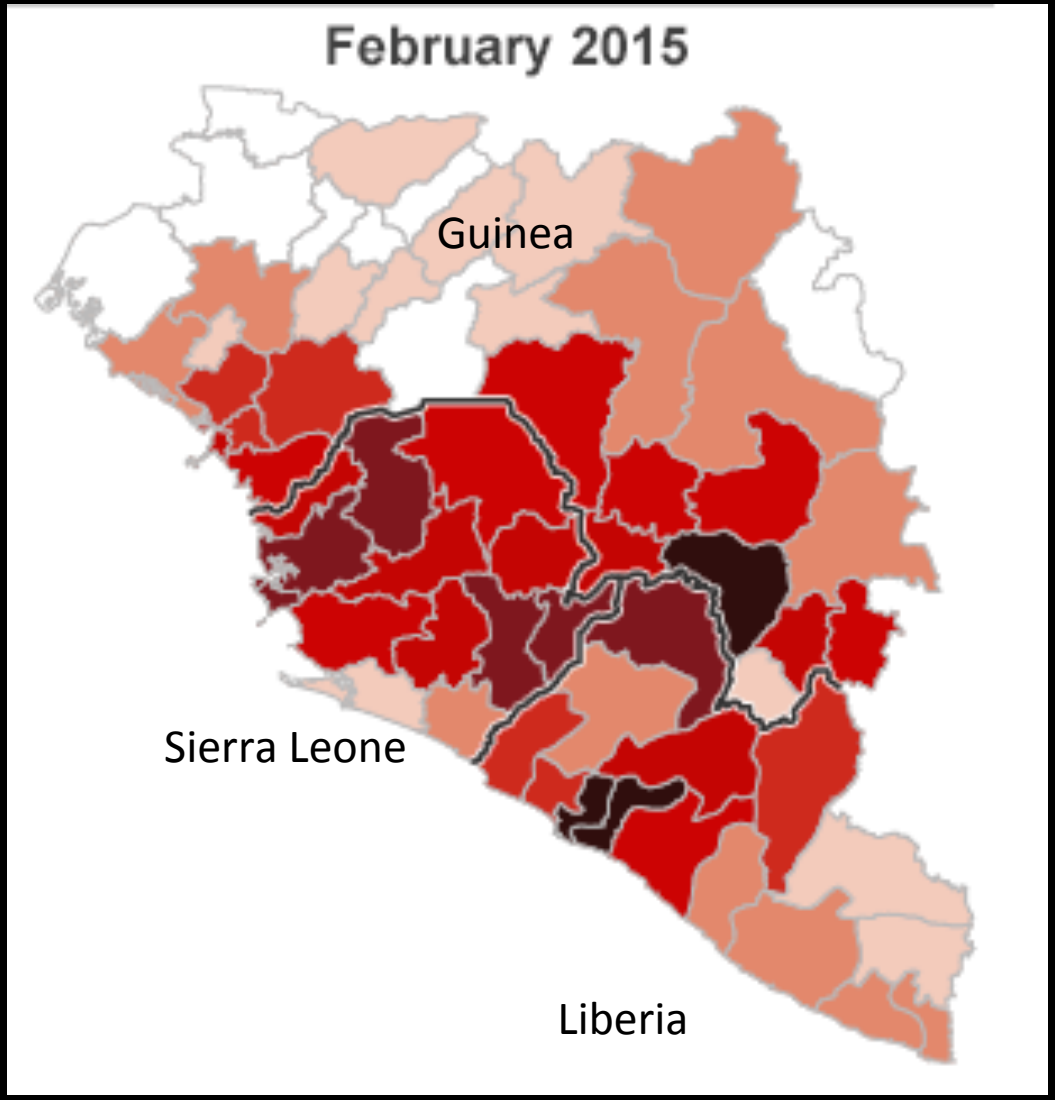


In Nov 2014, to avoid ethical issues CDC proposed this design.

Regional Variation in Ebola Cases



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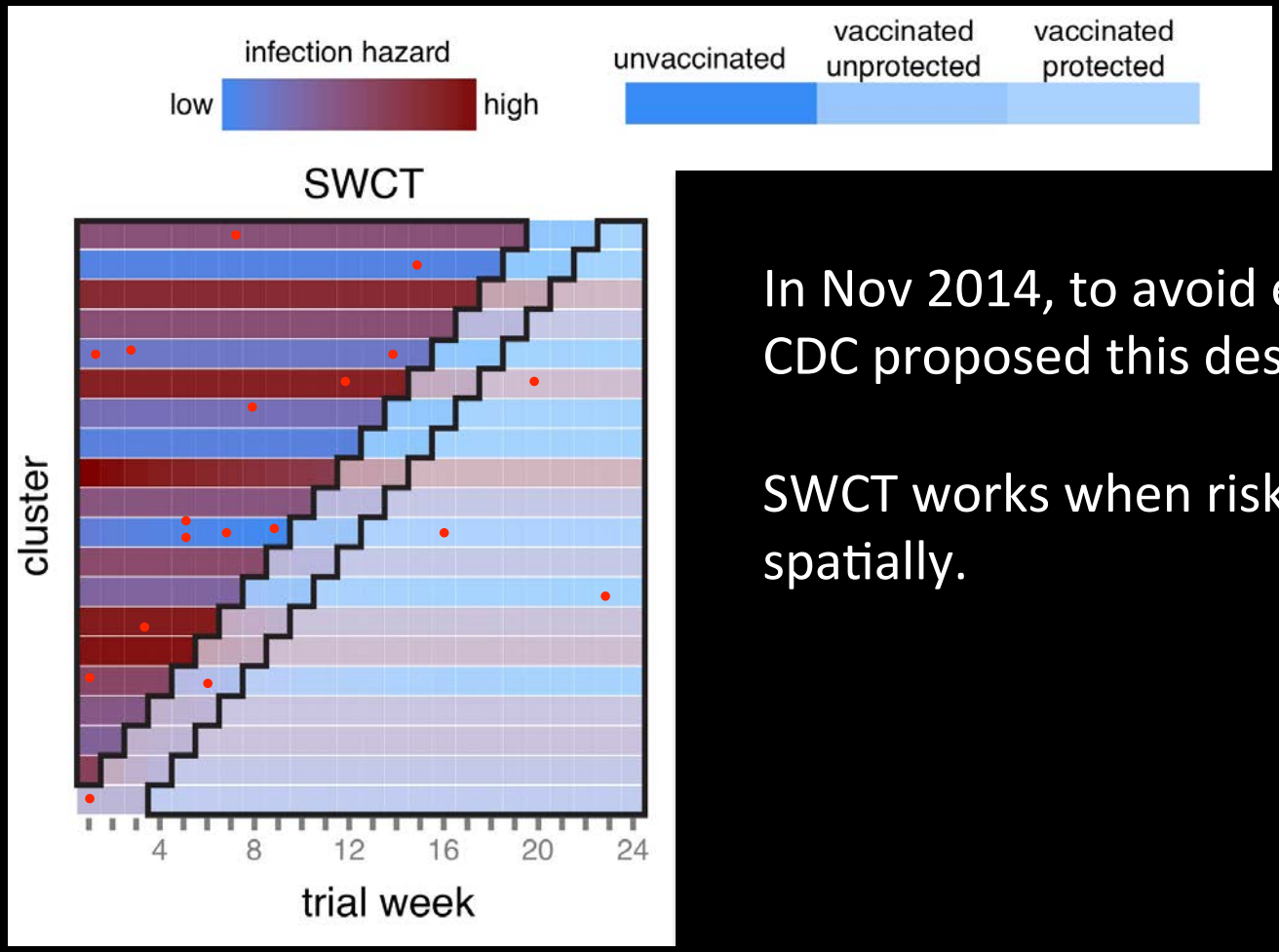

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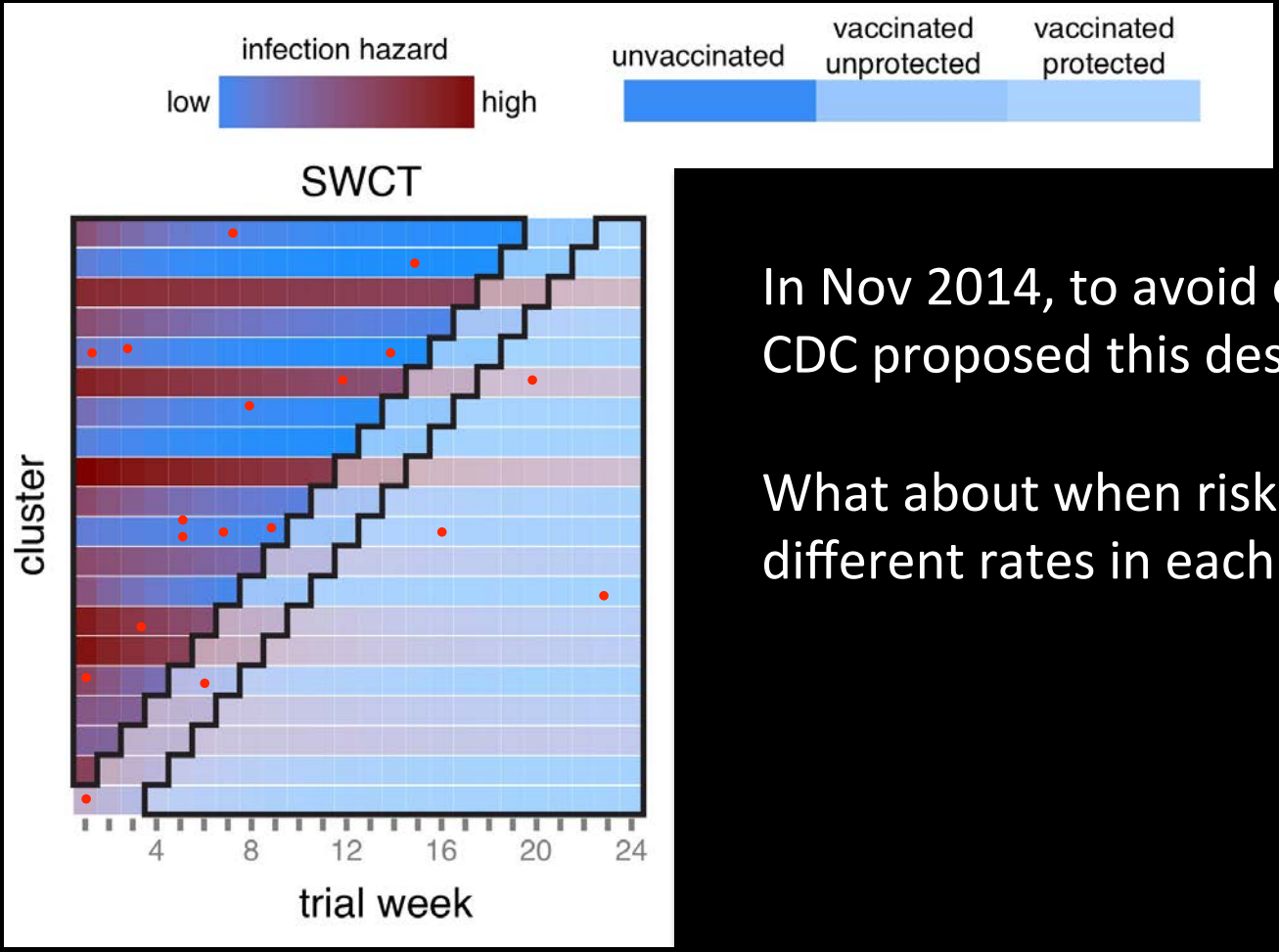
SWCT works when risk varies spatially.

Stepped Wedge Cluster Trial



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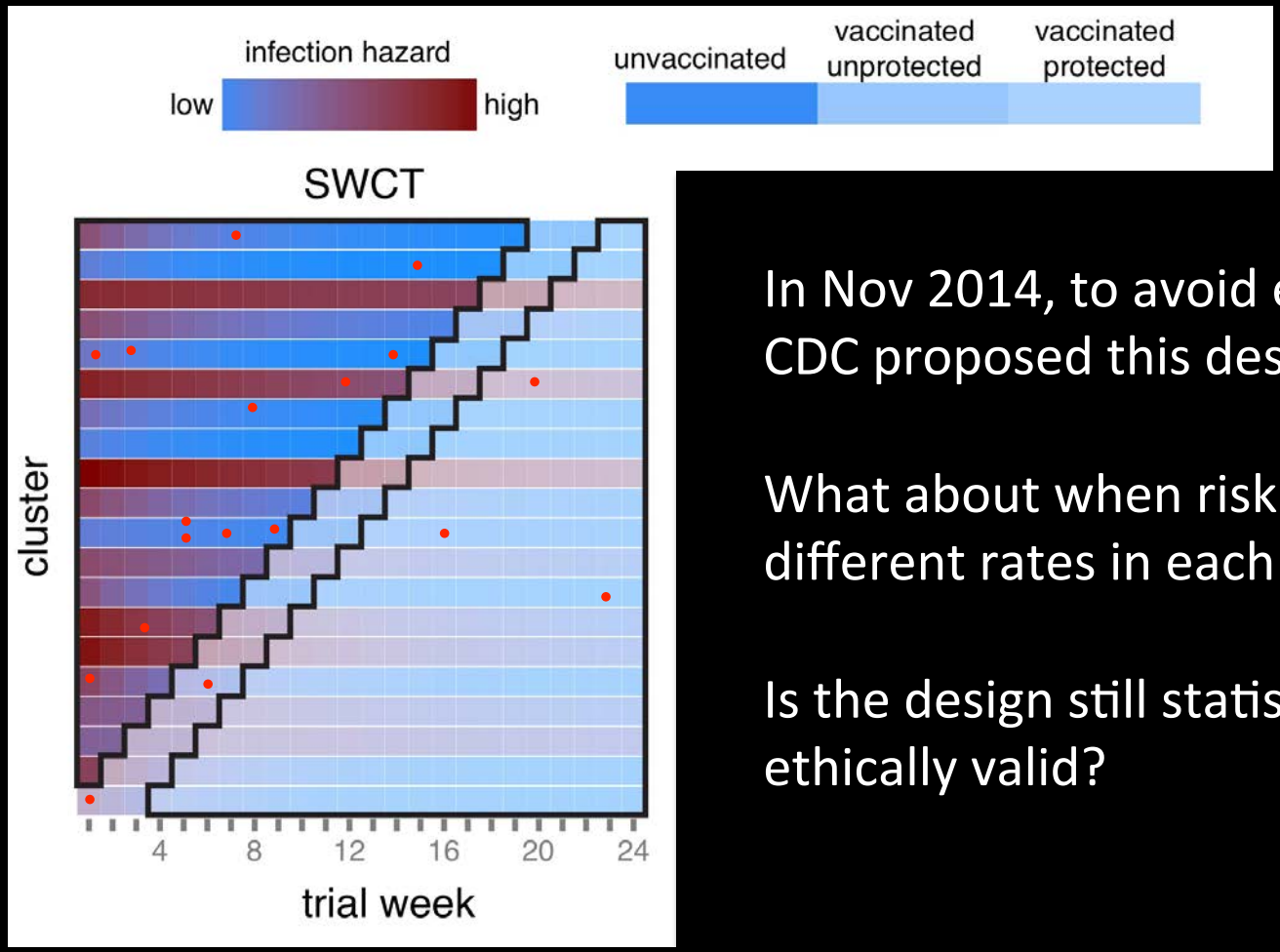
What about when risk is declining at different rates in each district?

Stepped Wedge Cluster Trial



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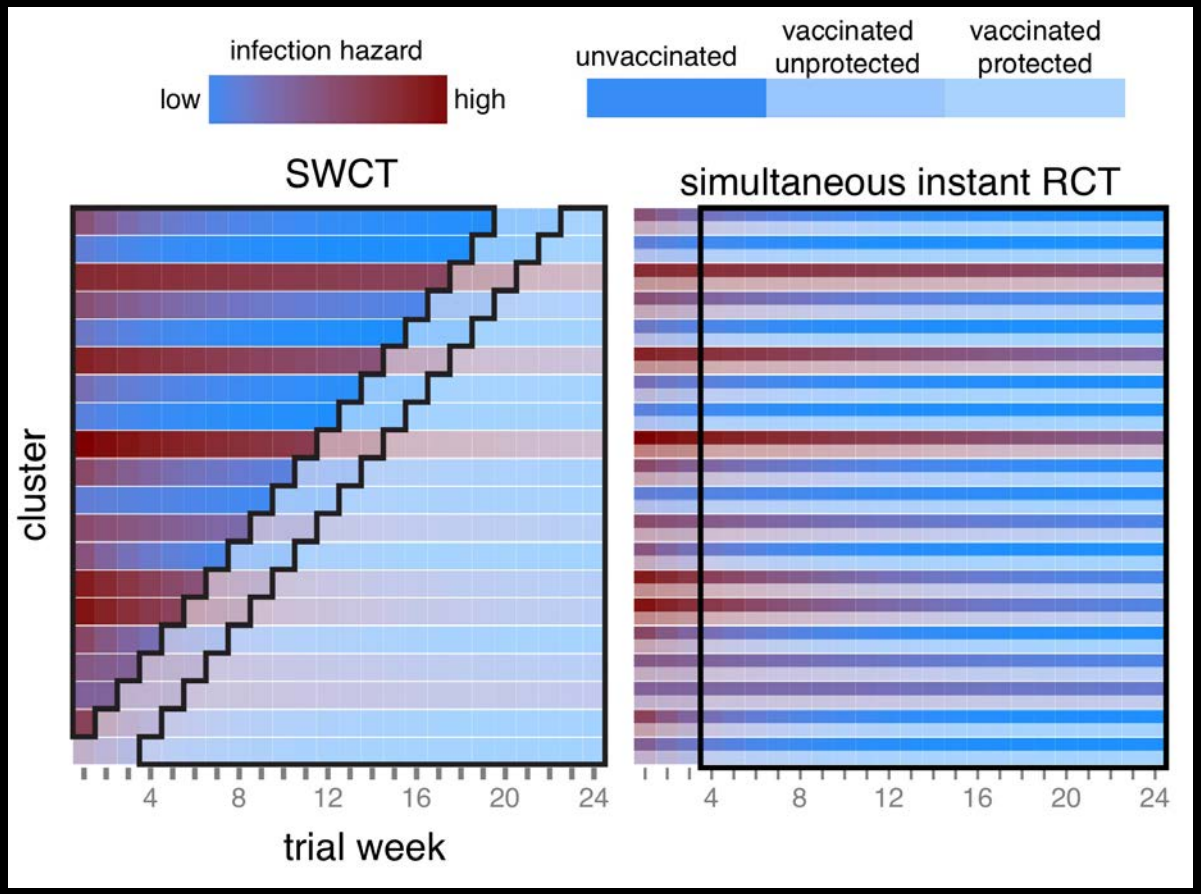
What about when risk is declining at different rates in each district?

Is the design still statistically & ethically valid?

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

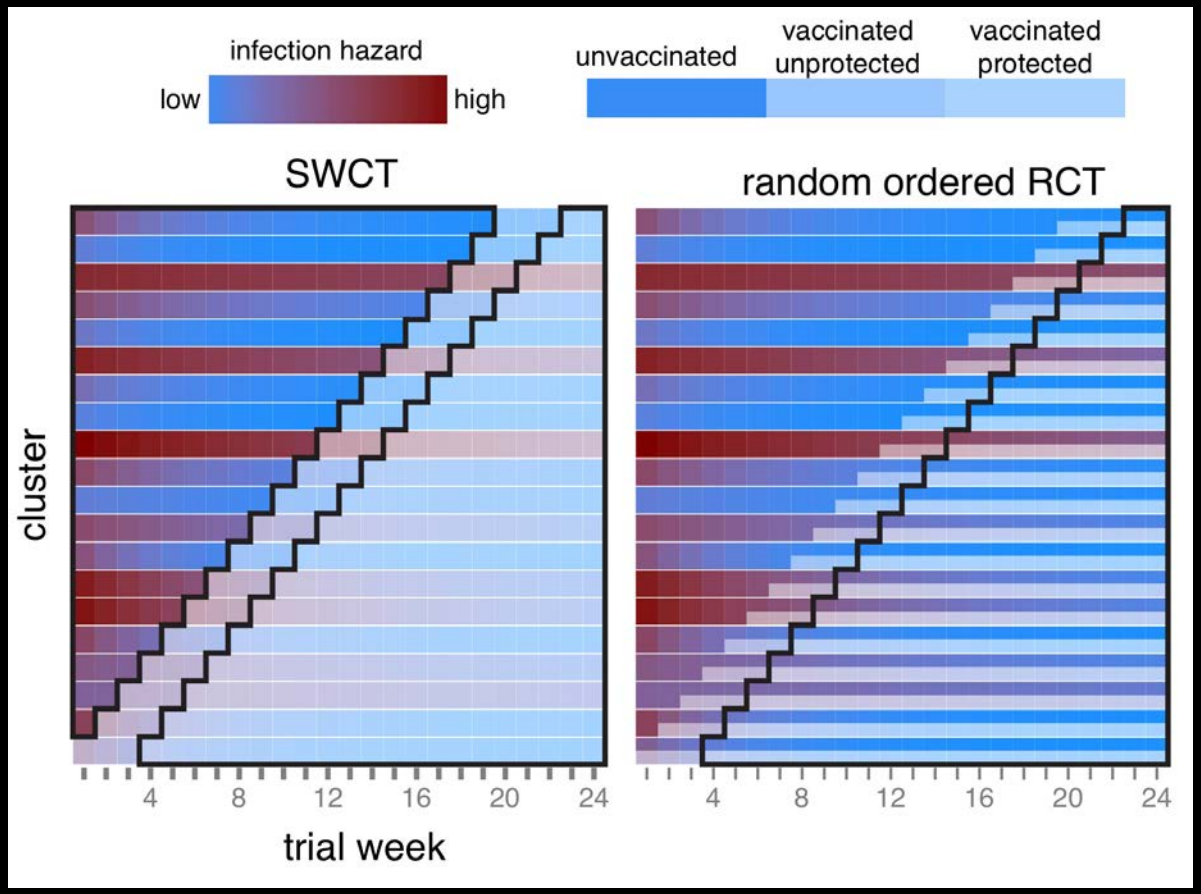
Other Options



Vaccinate half of each cluster immediately.

Not logistically feasible.

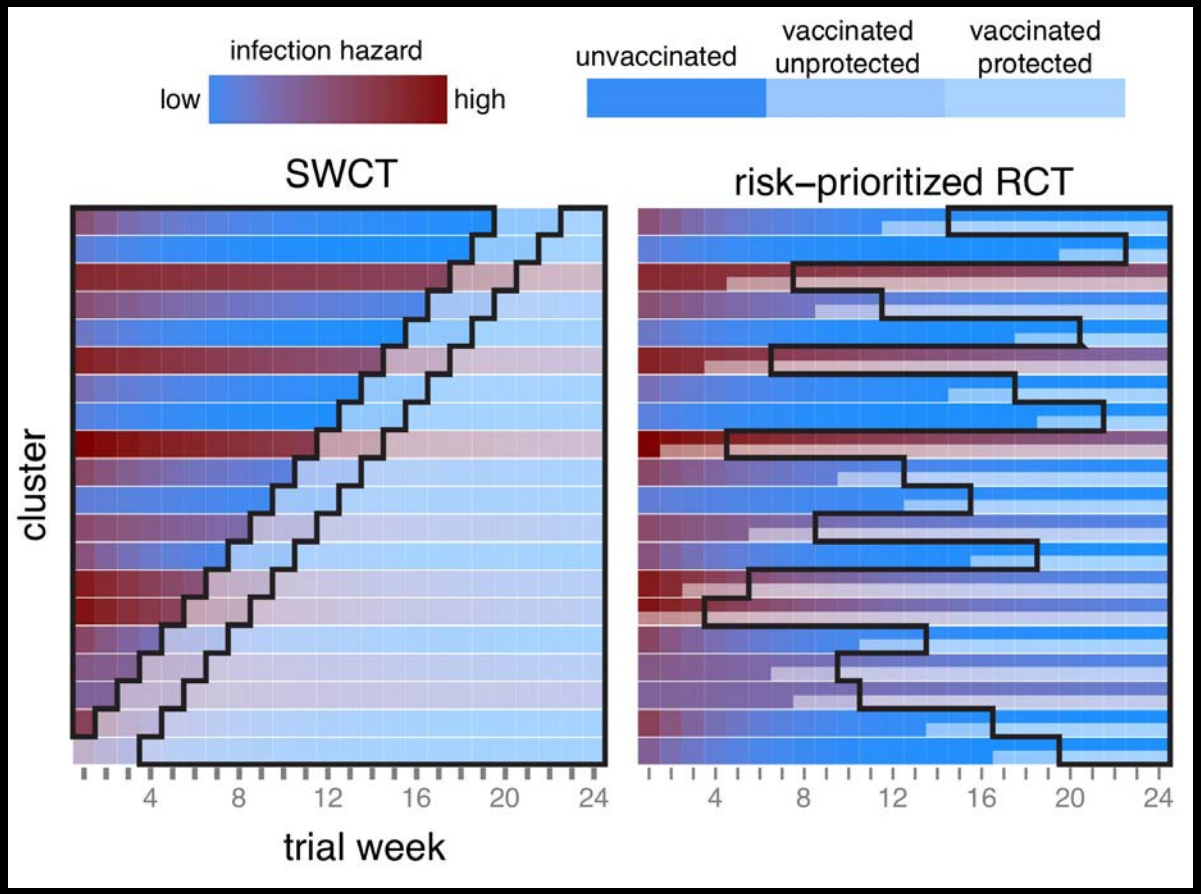
Other Options



Vaccinate half of each cluster 1 week at a time.

Comparing vaccinated & unvaccinated individuals in same risk categories.

Other Options

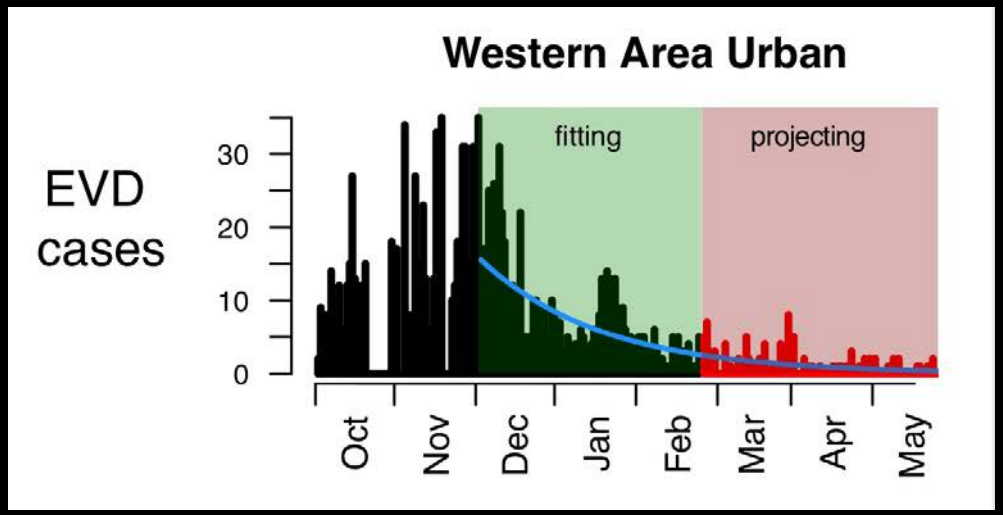


Vaccinate half of each cluster 1 week at a time.

Comparing vaccinated & unvaccinated individuals in same risk categories.

Prioritize high risk clusters.

Project Declining Epidemics



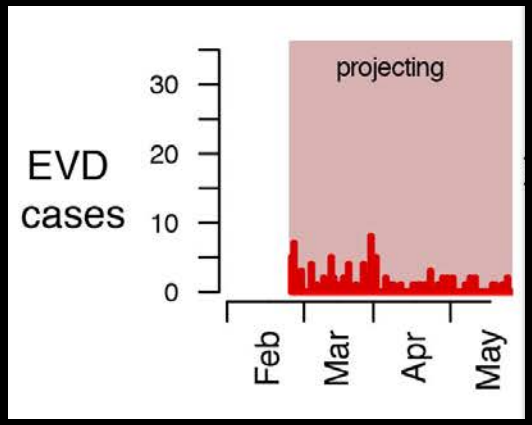
Exponential decay models fit to district-level incidence

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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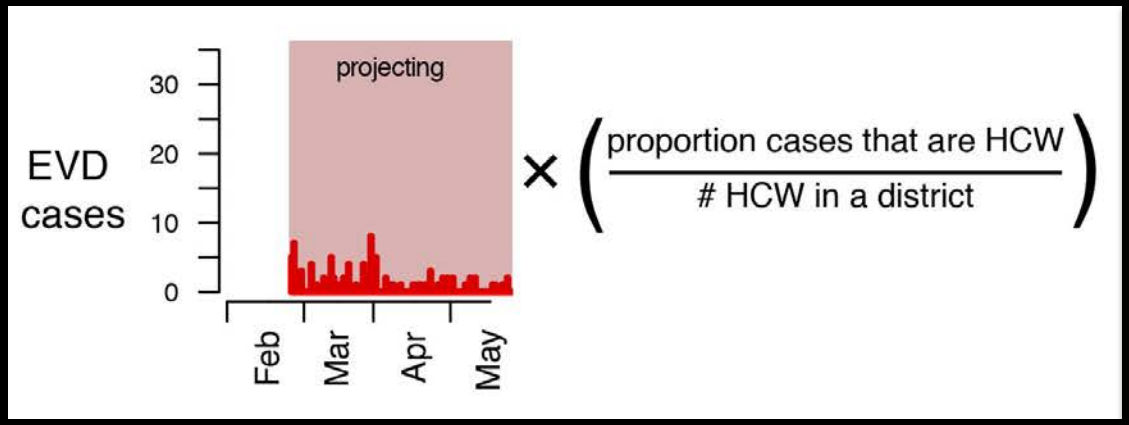

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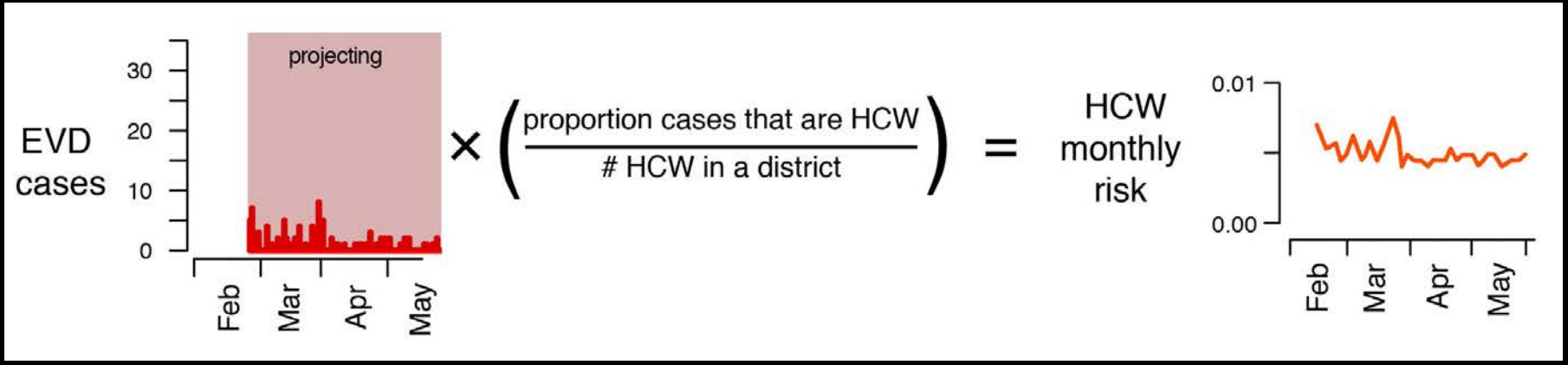


Example

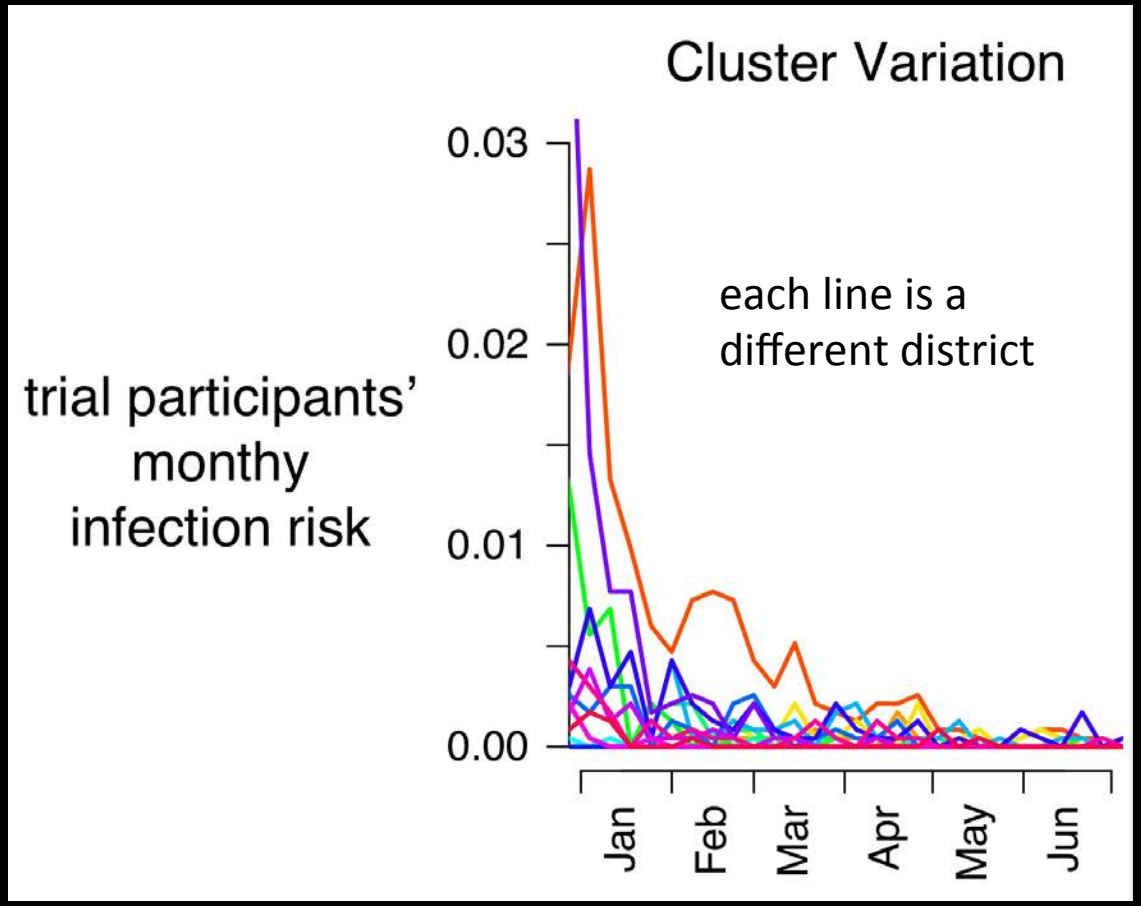
100 cases in a district in March ➔ 5 cases in HCW

If there are

5 HCW cases/500 HCW = 0.01 risk per month

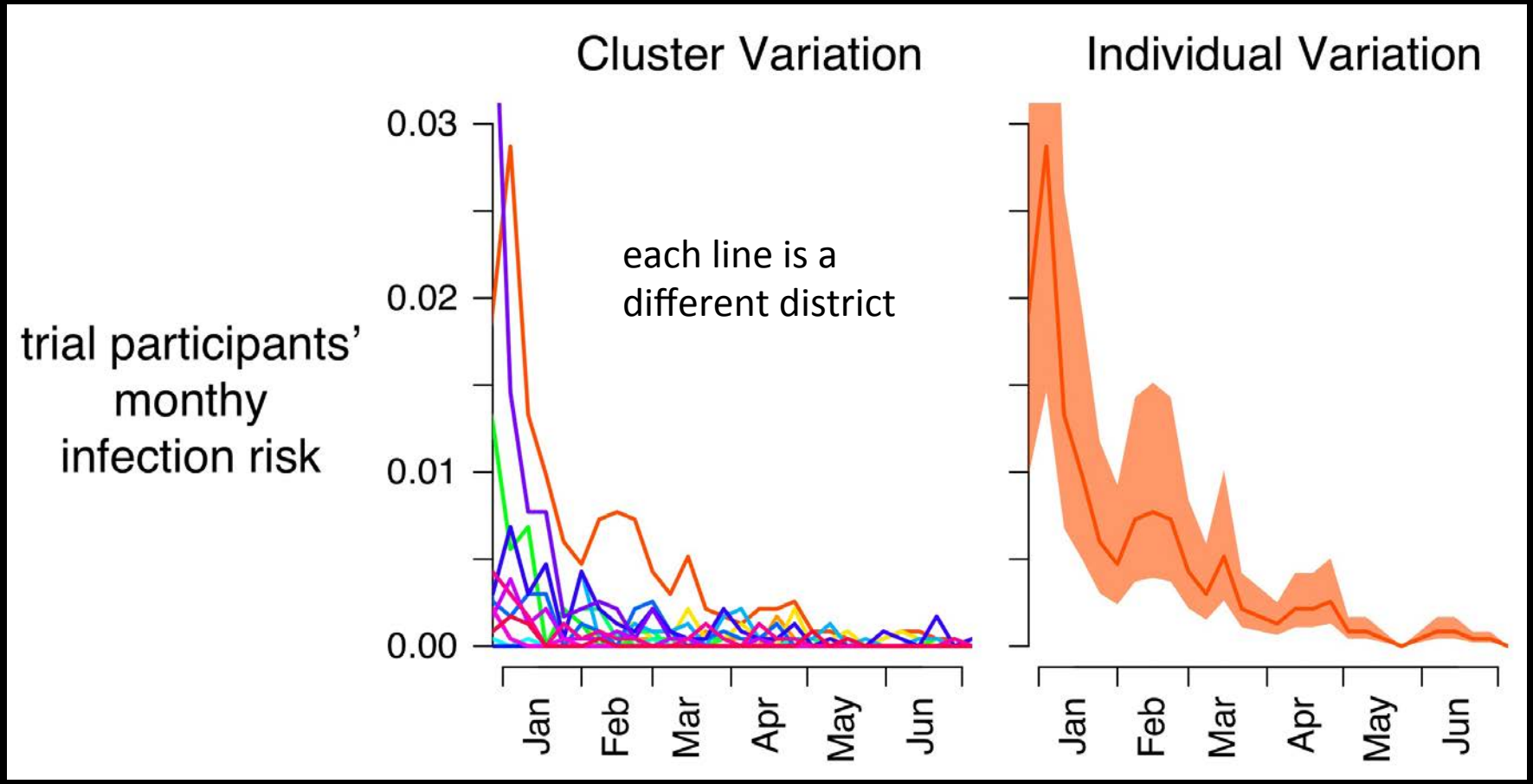
Modeling Ebola Risk

HCW risk varies by district



Modeling Ebola Risk

HCW risk varies by district and individually



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

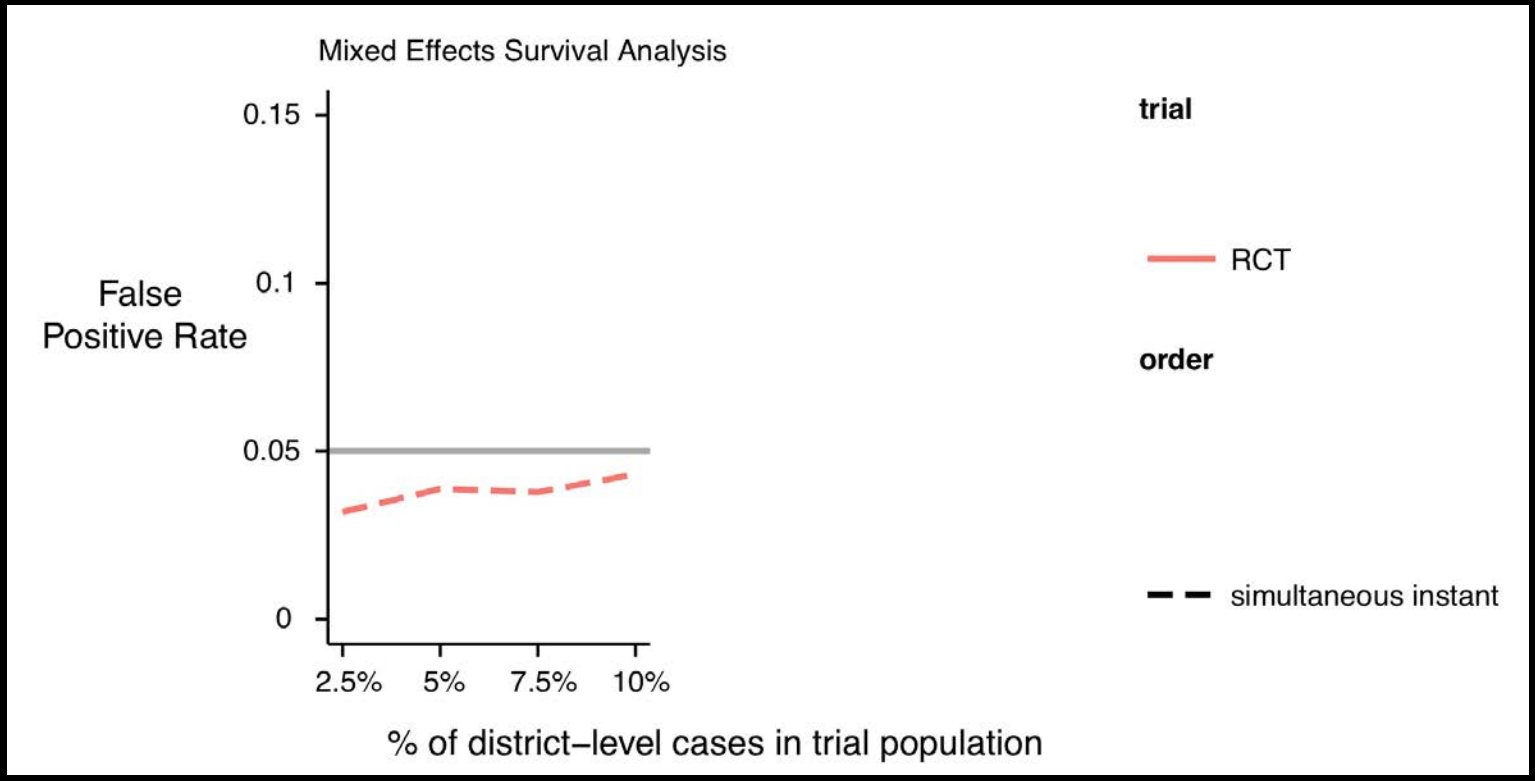
False Positive Rate

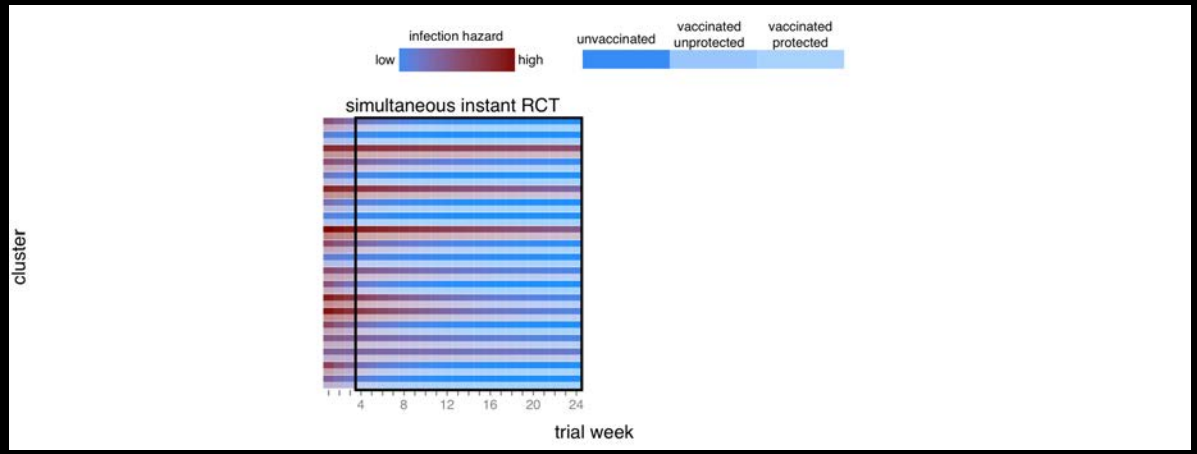
If vaccine does not affect Ebola risk, % times we incorrectly conclude it does.

Statistical Power

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

False Positive Rates





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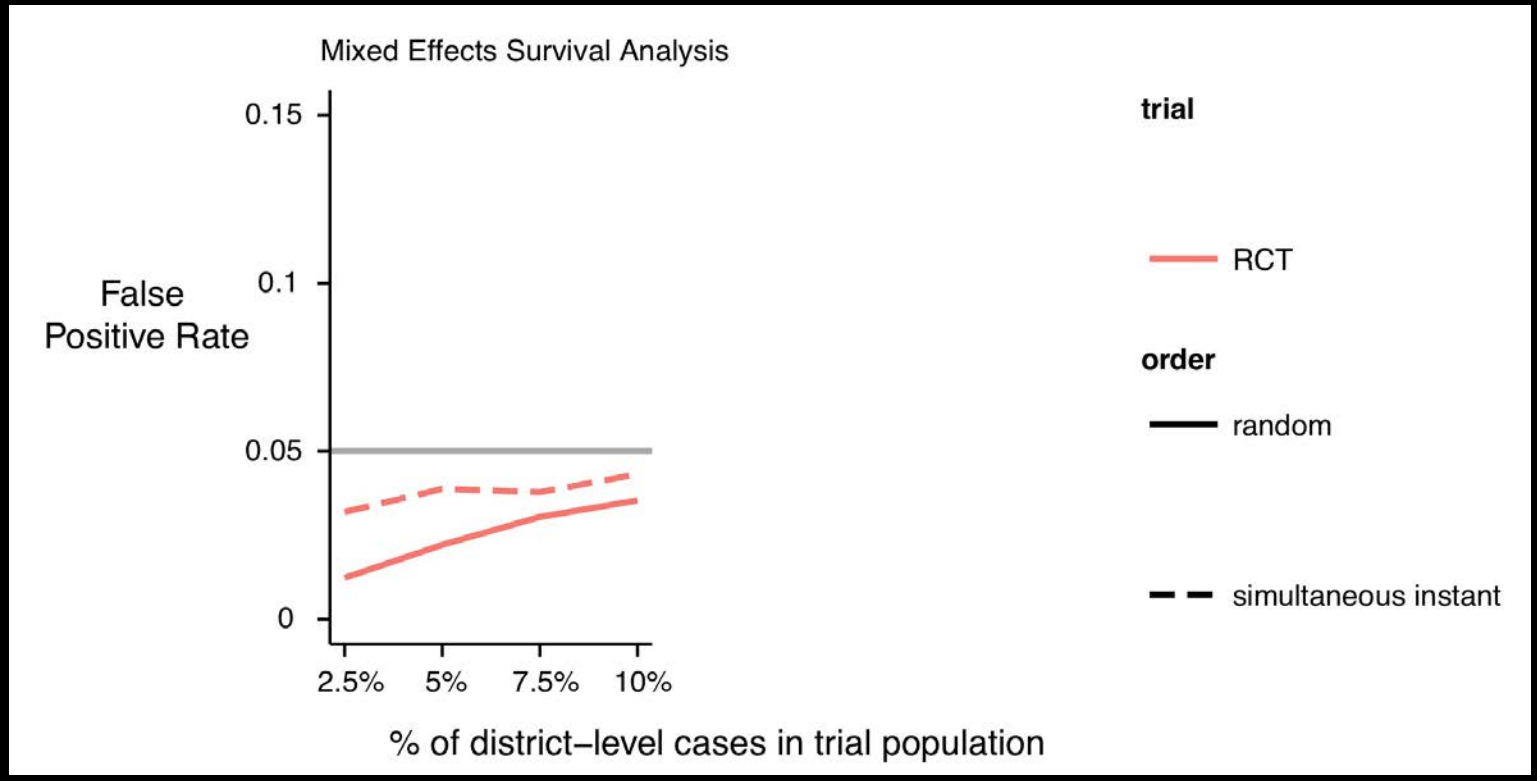

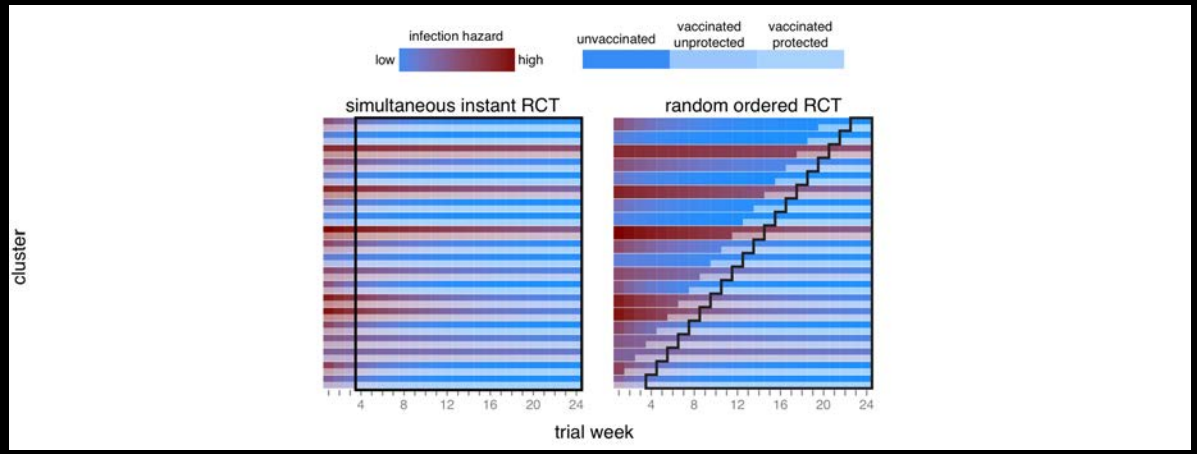

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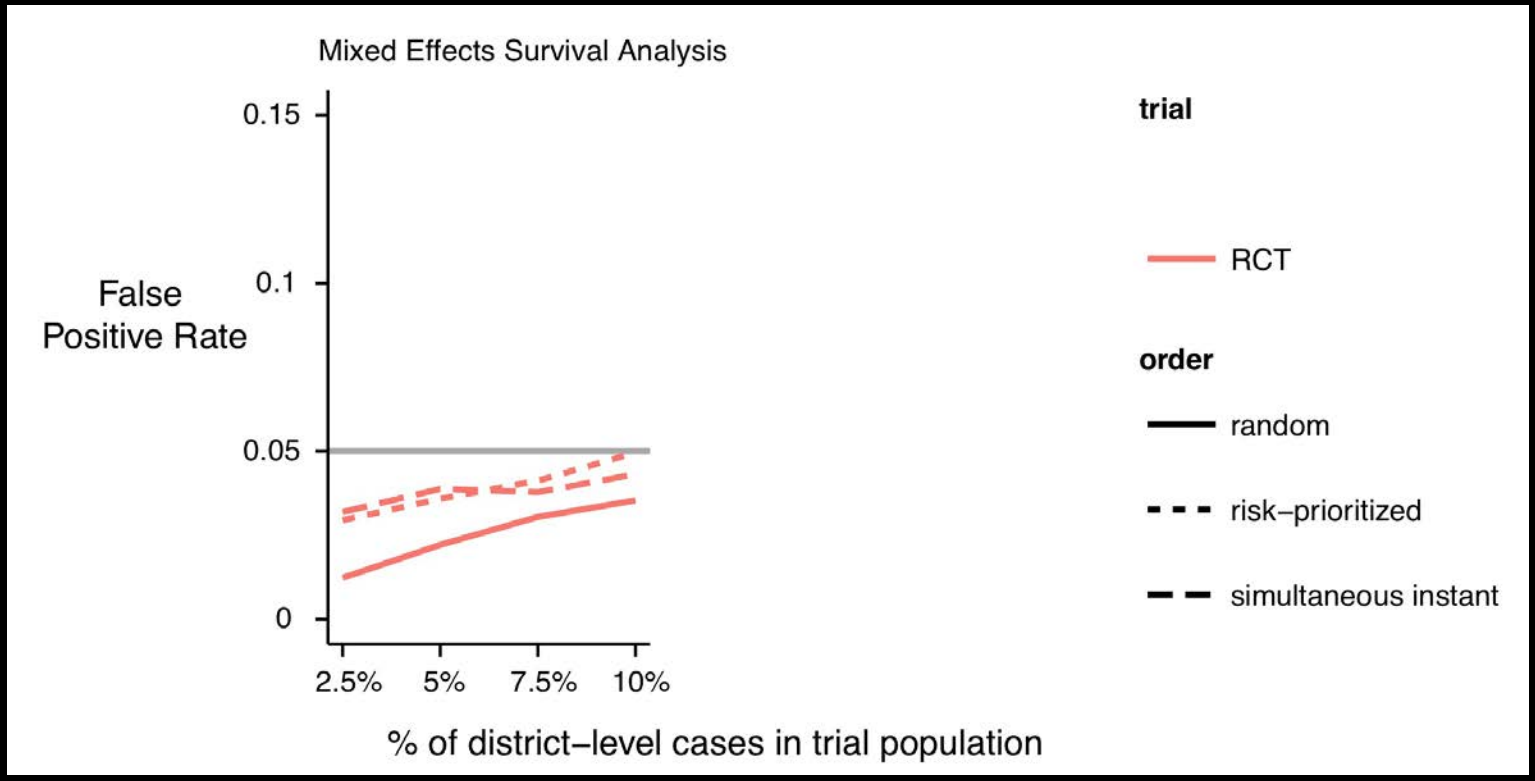

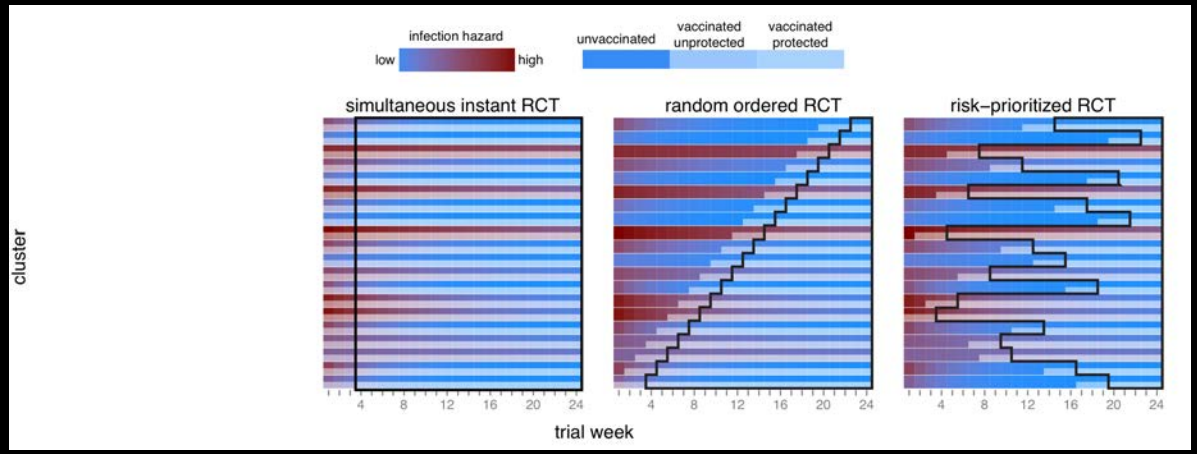

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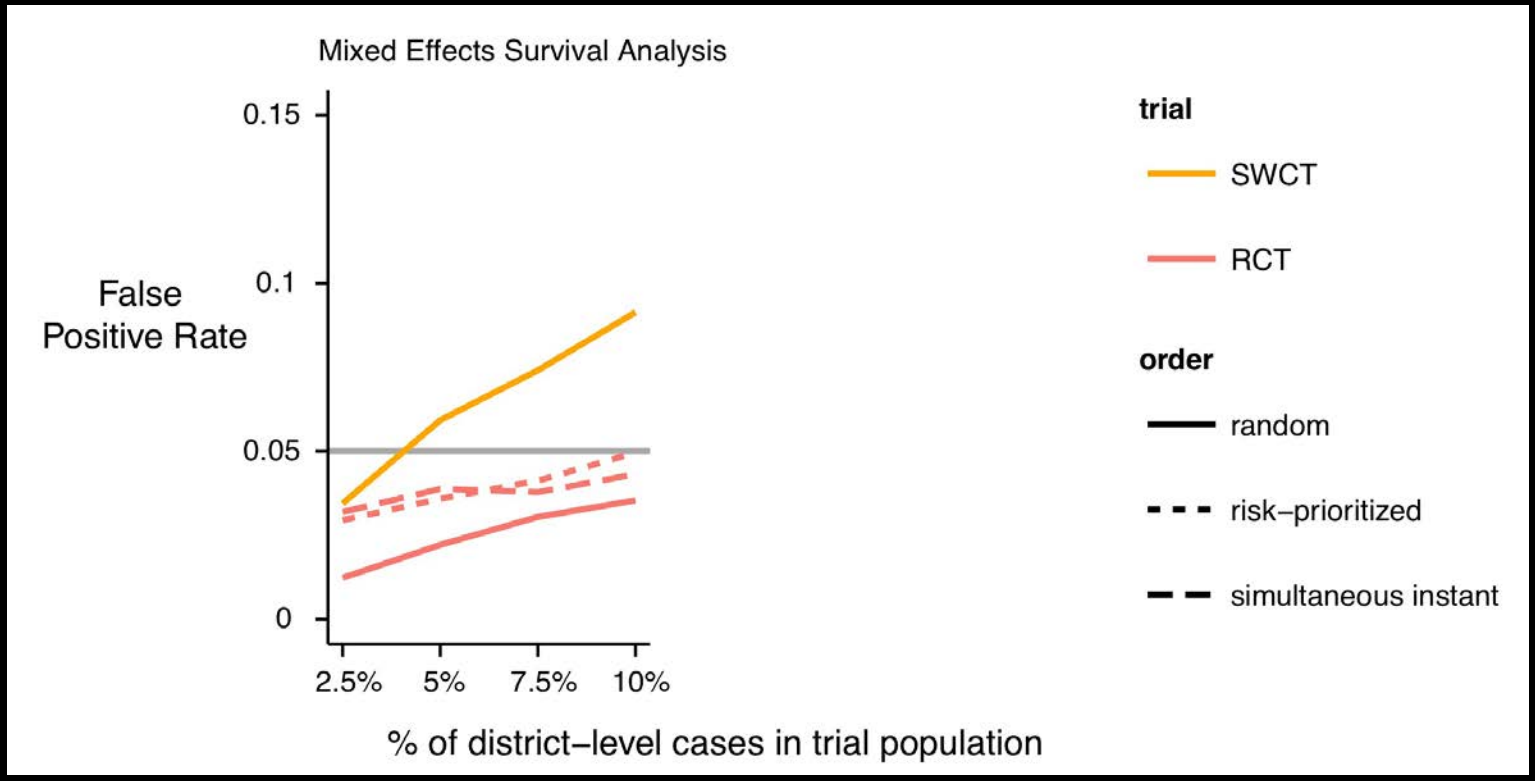

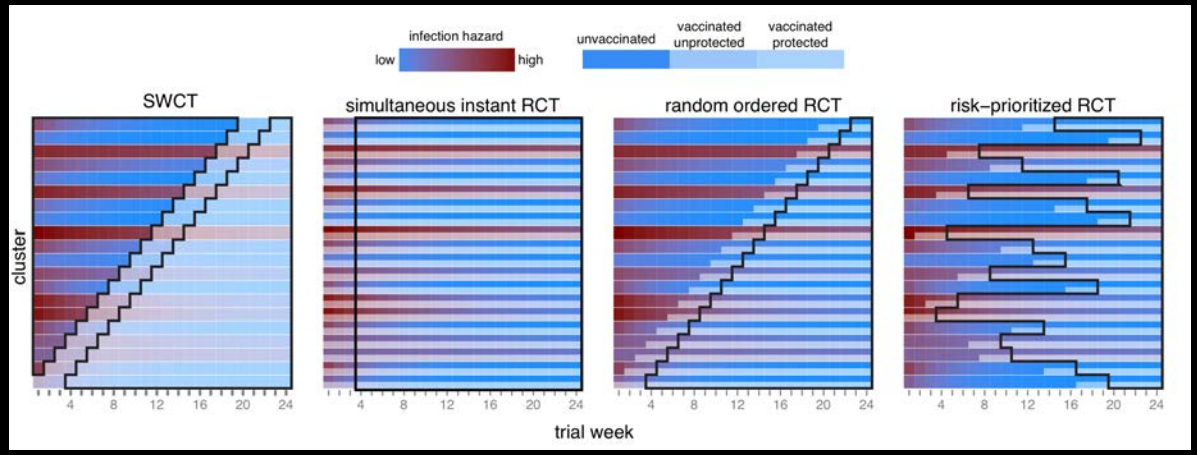

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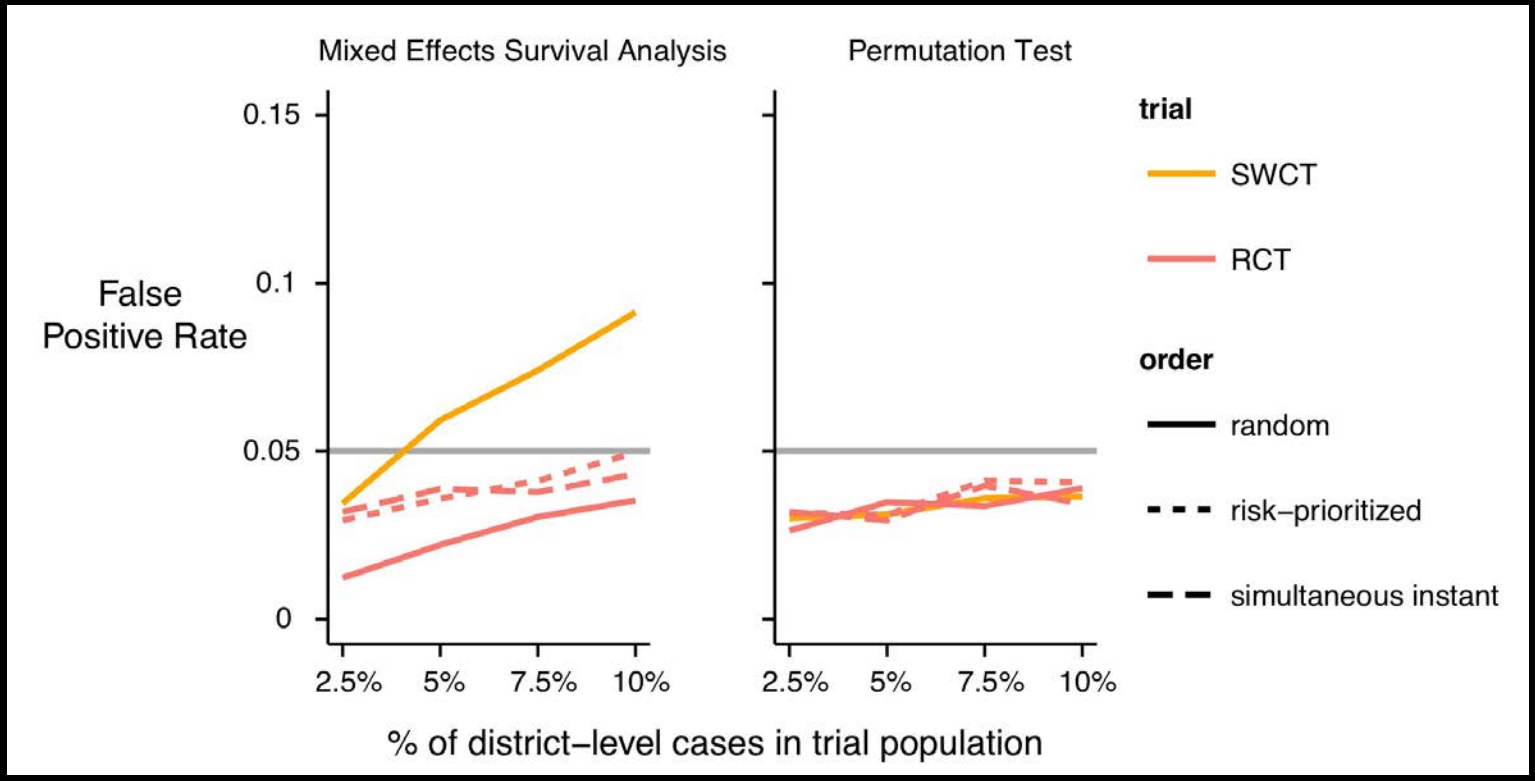

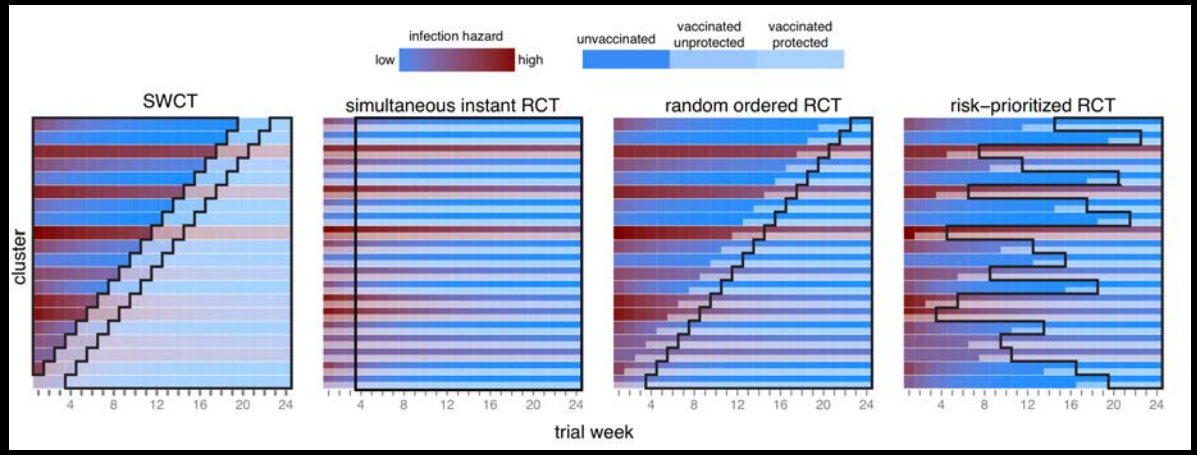

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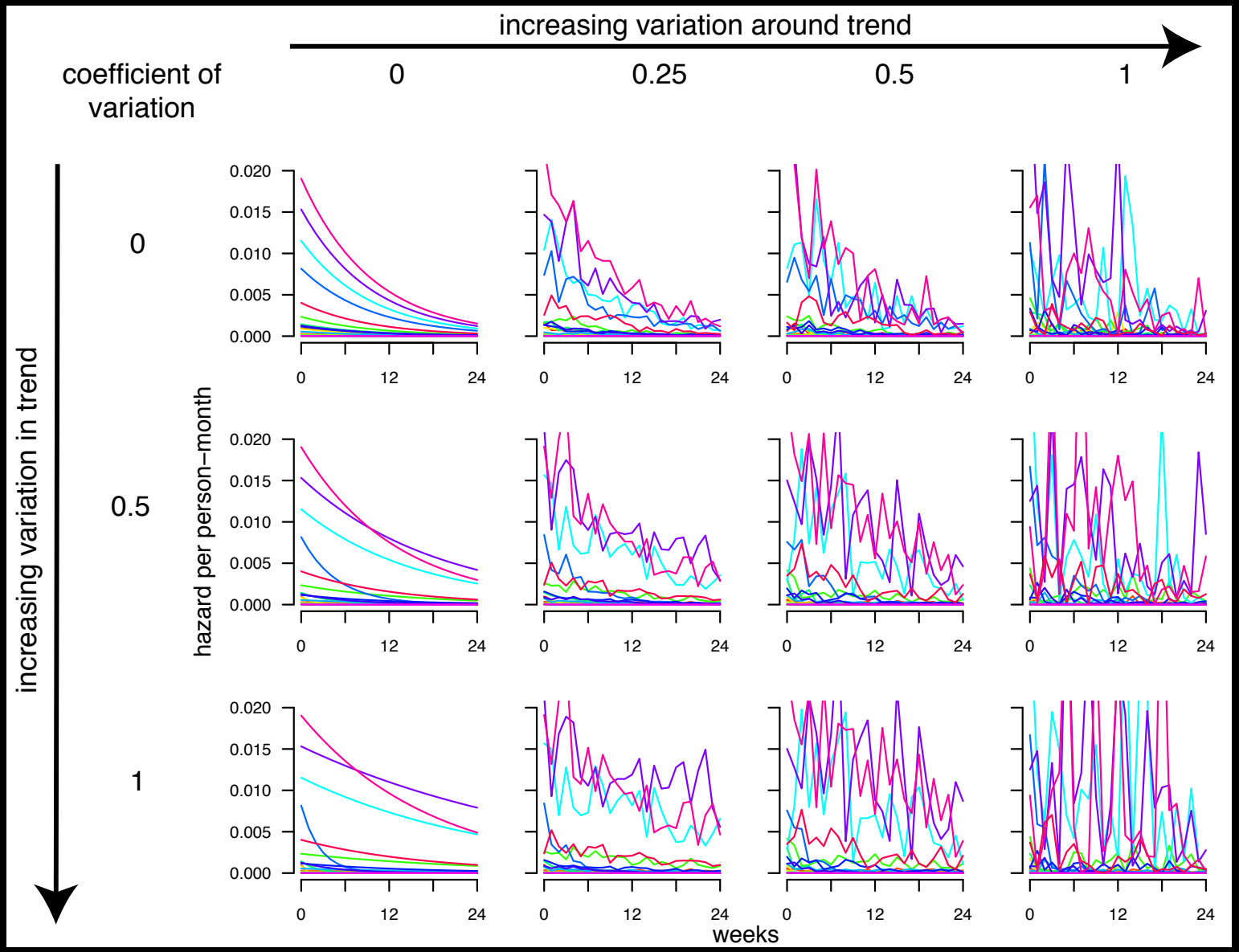

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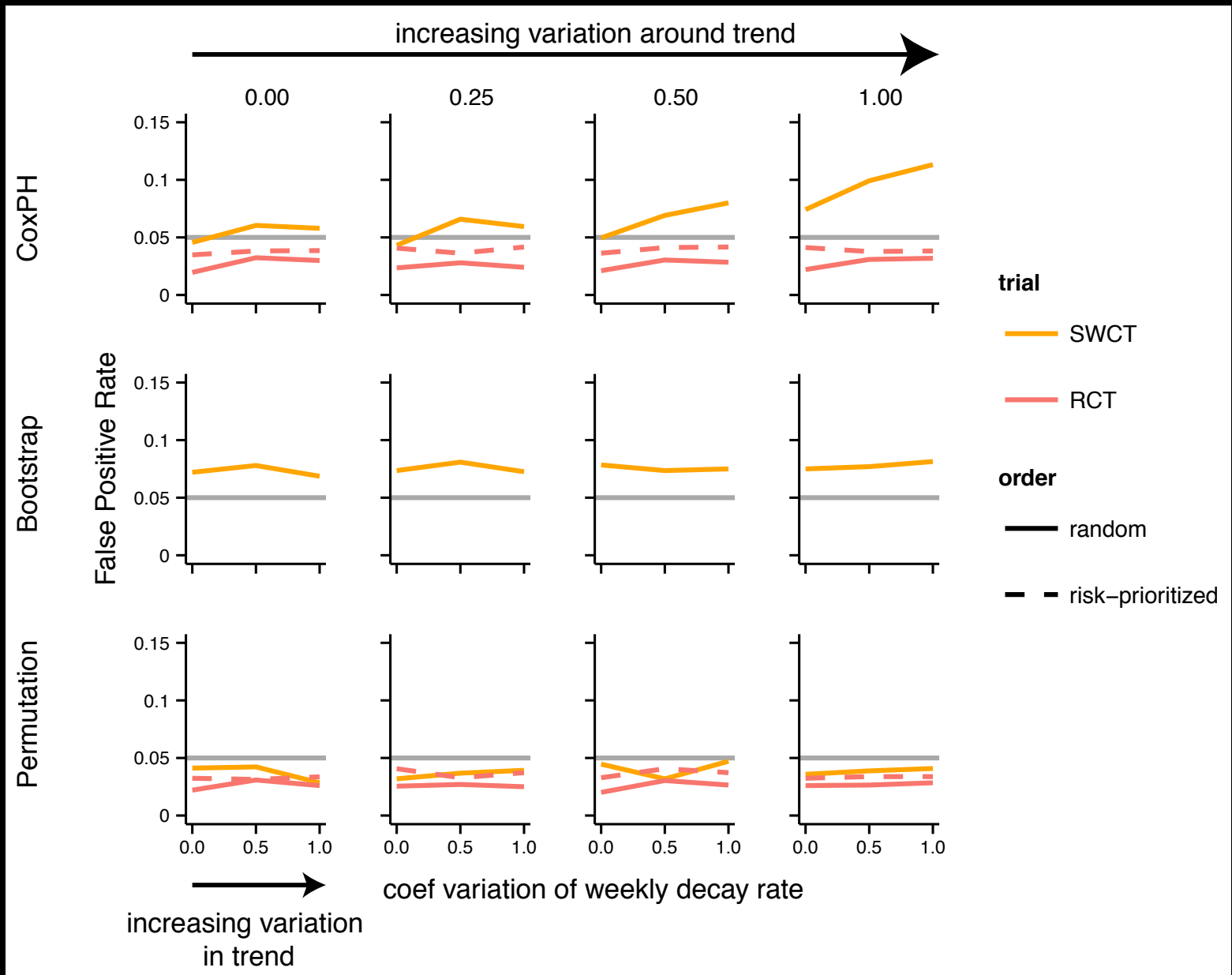

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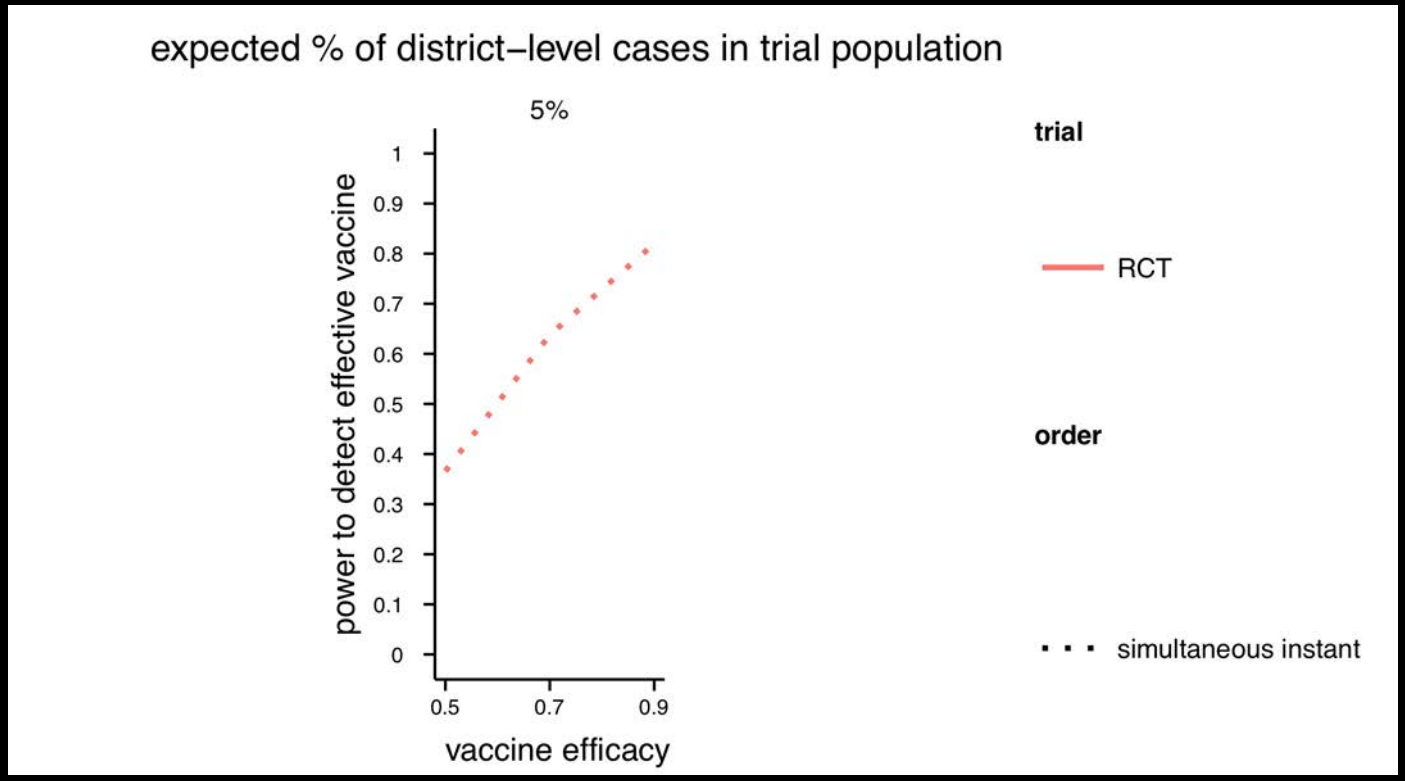

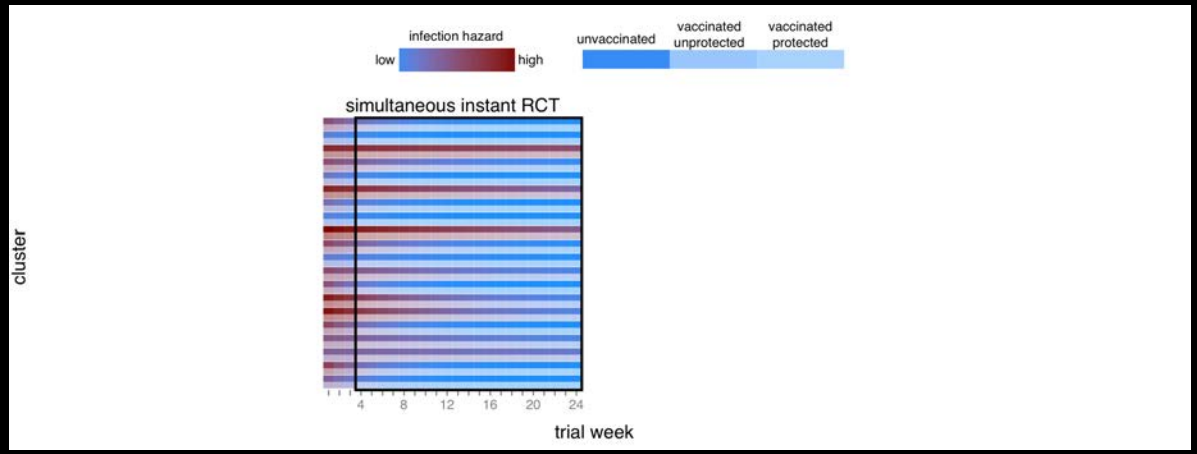

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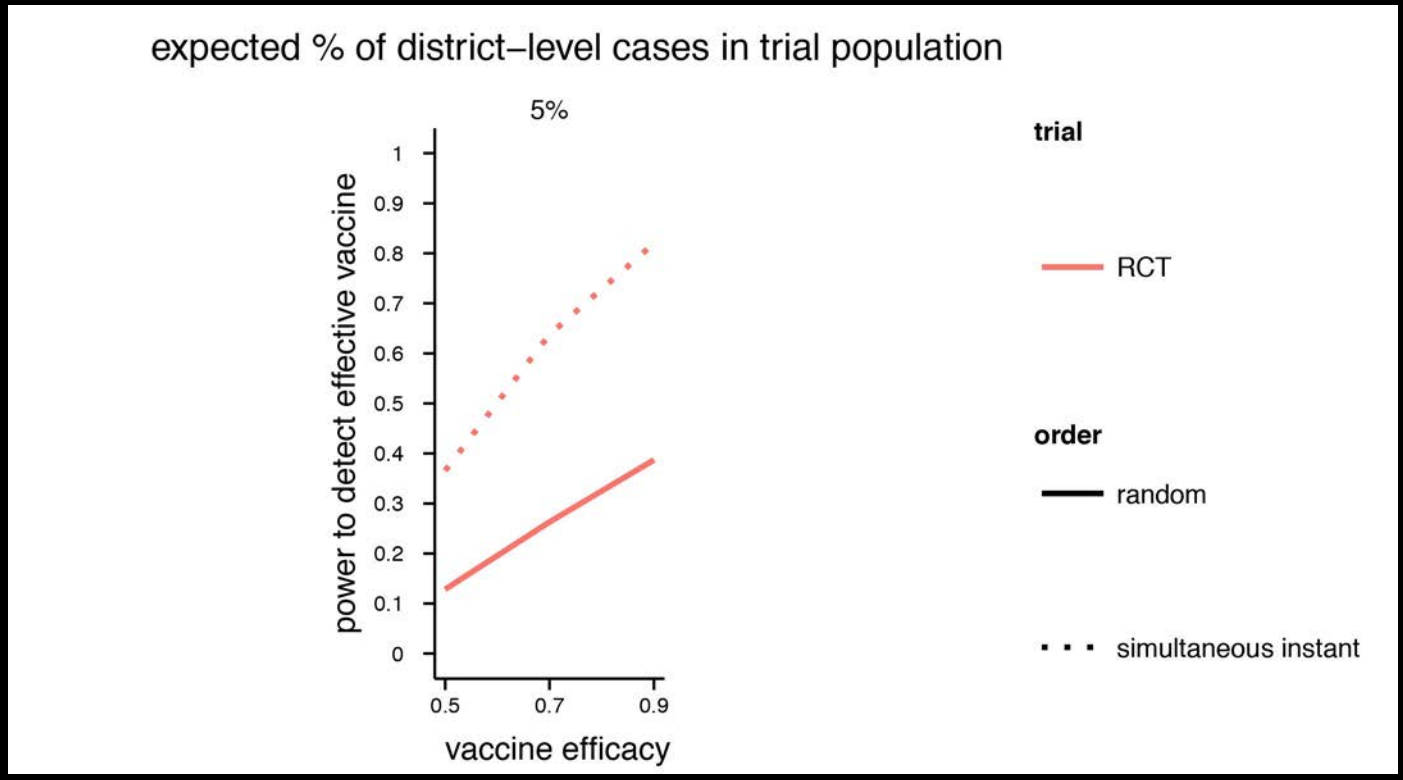

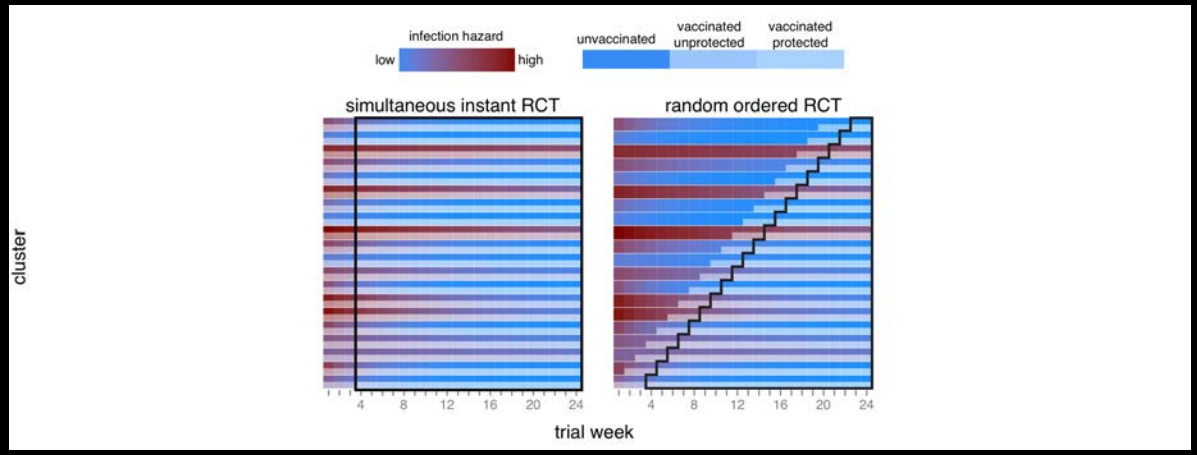

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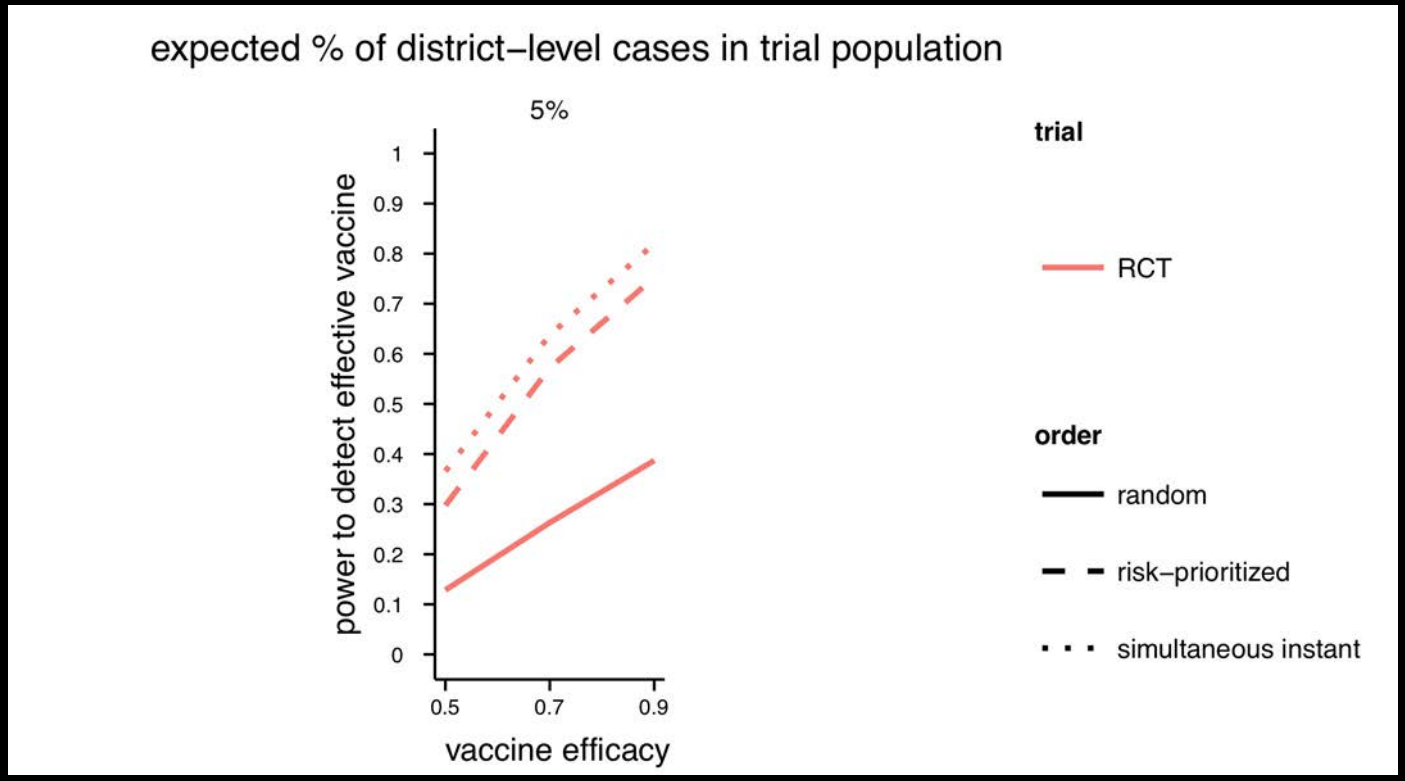

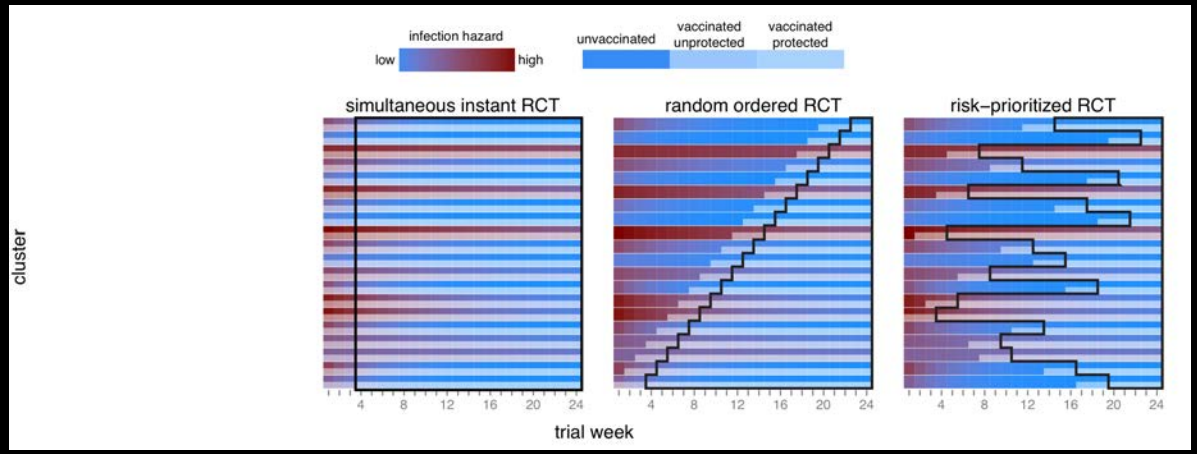

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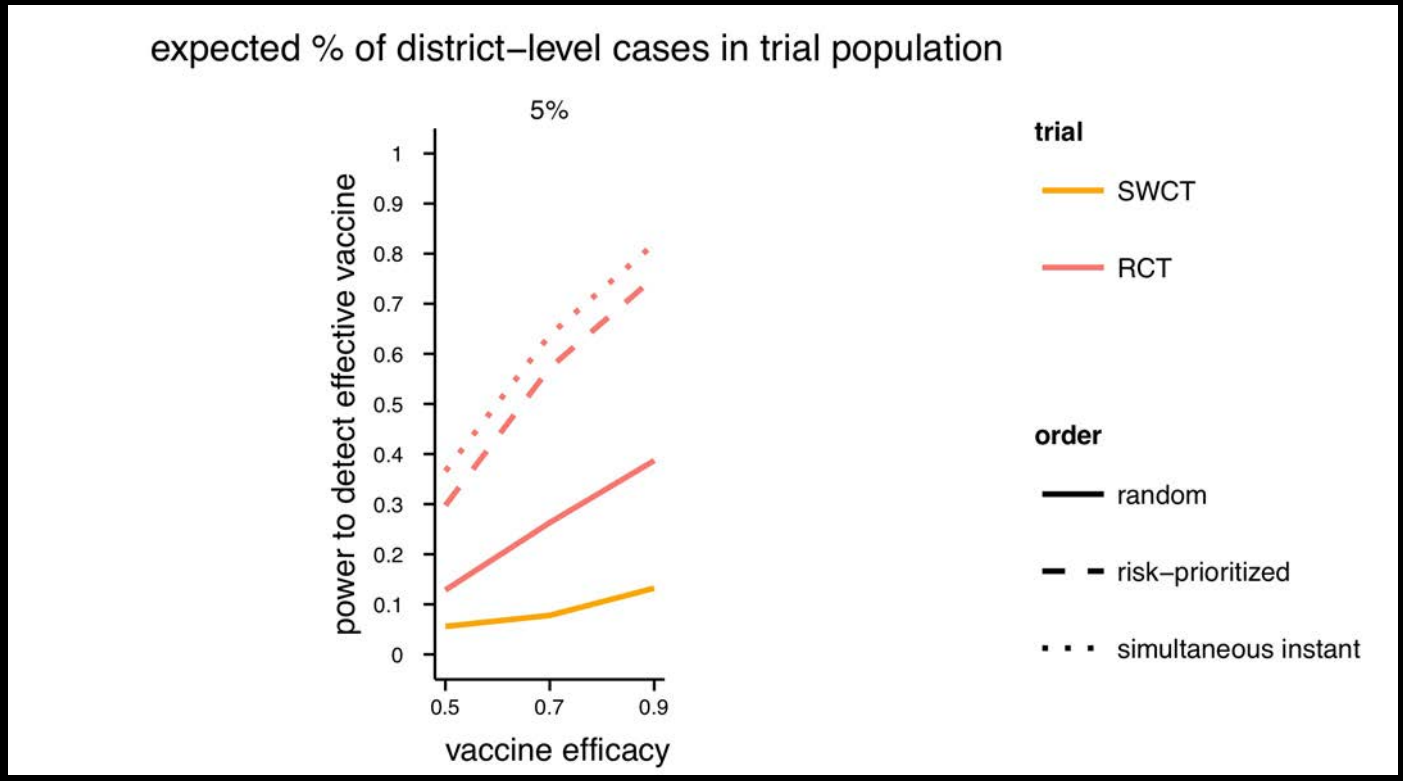

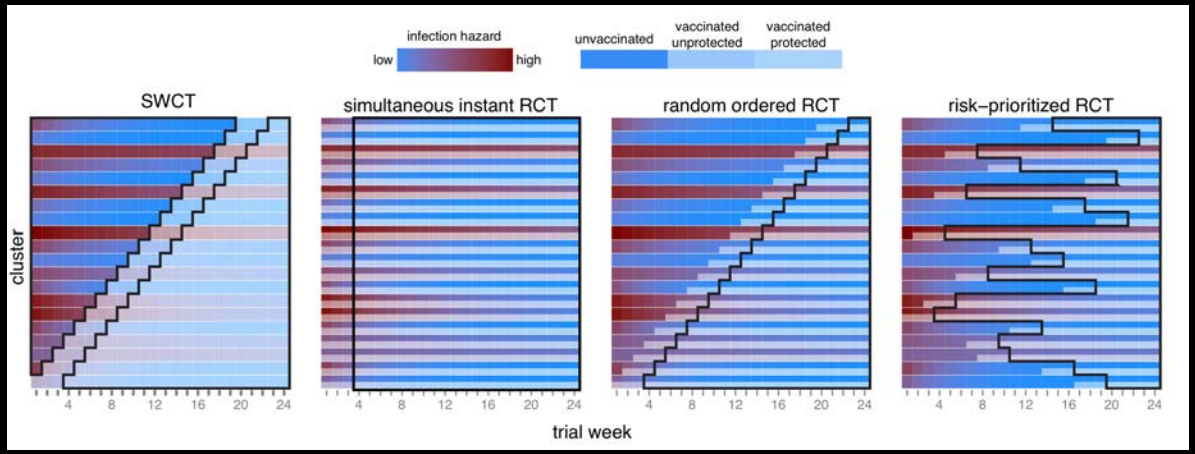

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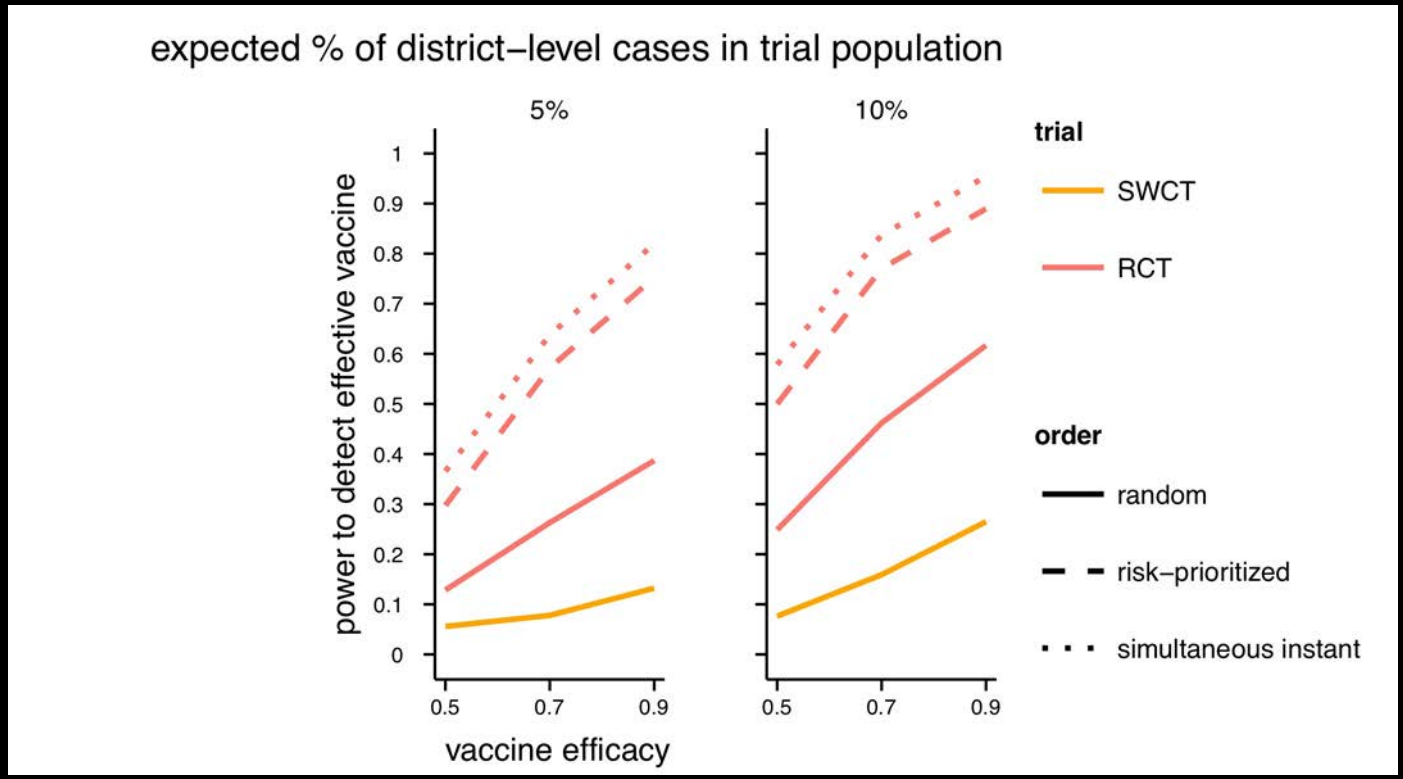

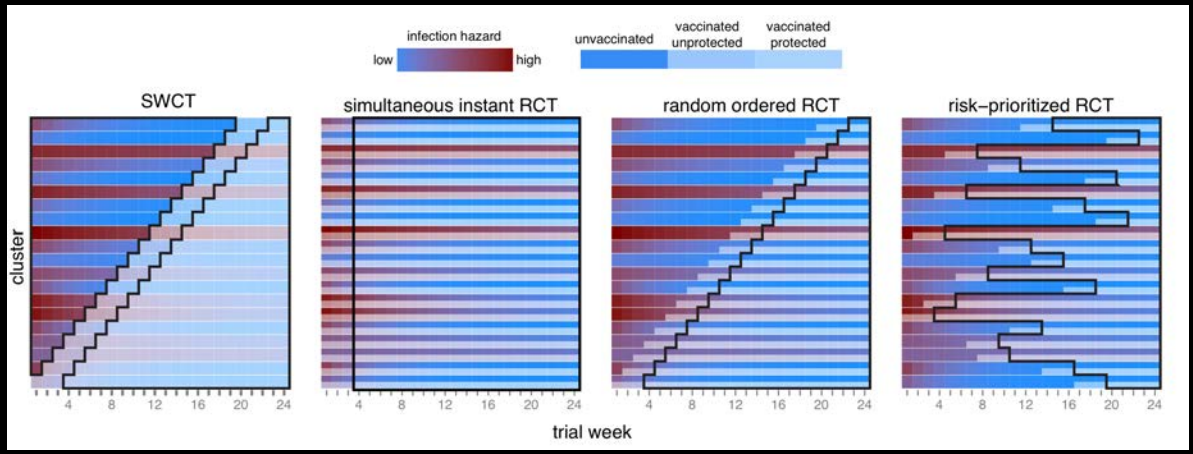

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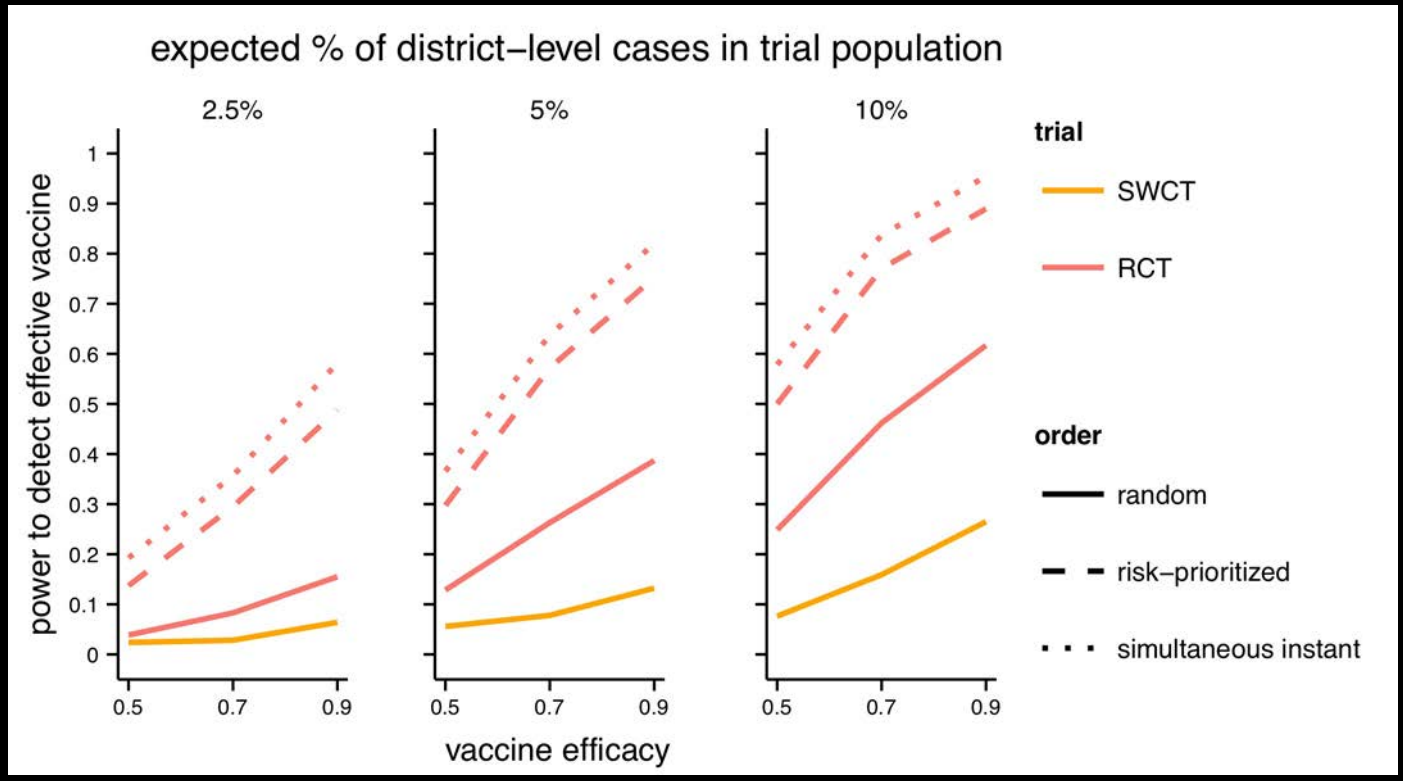

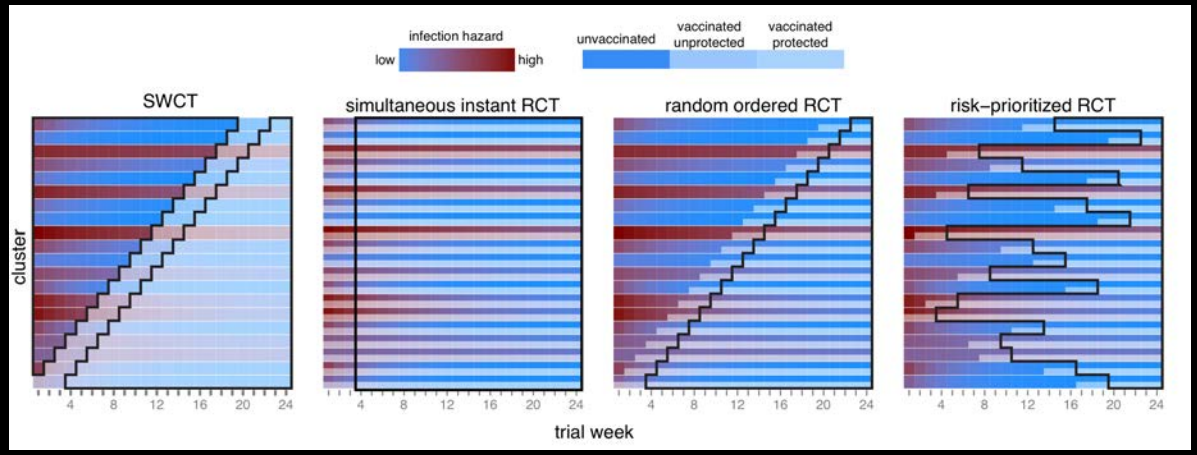

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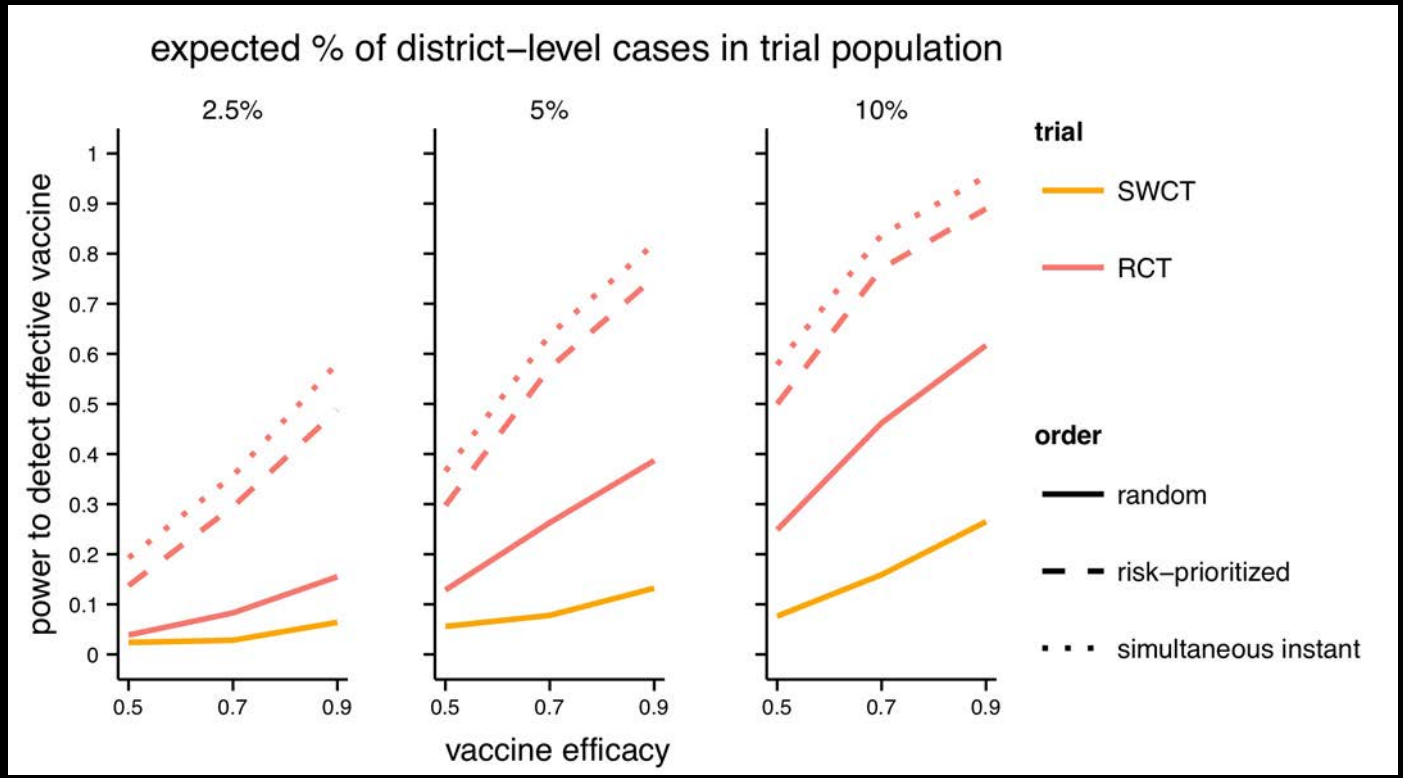
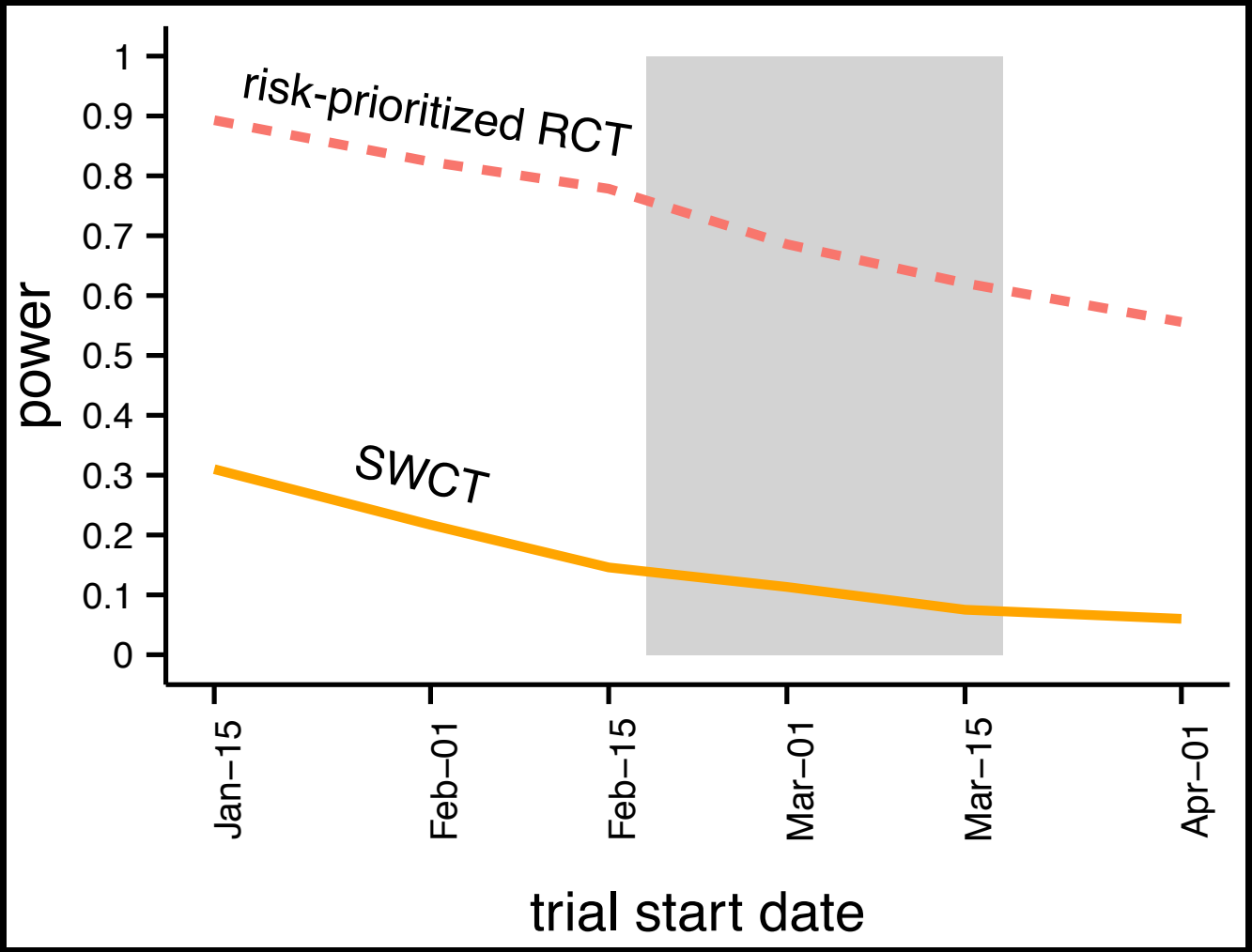


Stepped wedge cluster trials have <30% of detecting an efficacious vaccine.

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

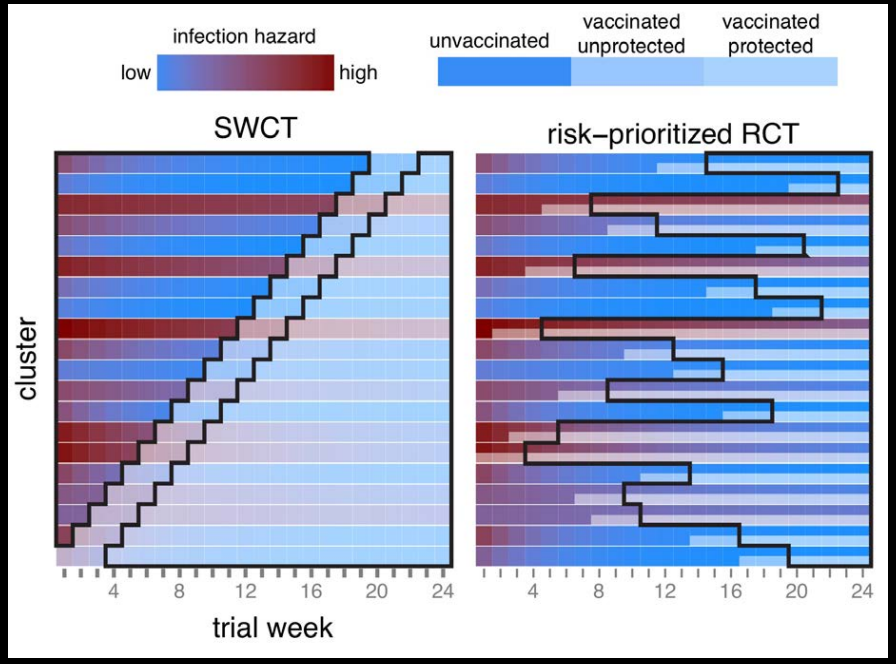
Statistical Power



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



Computational Resources

- 600,000 simulated trials (2K for 300 scenarios)
- 480 million statistical models fit
- 250 days on 12-core nodes of TX Advanced Computing Cluster
- Simulation of designs can save money/lives by helping plan

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MIDAS
Models of Infectious Disease Agent Study
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Instituts de recherche en santé du Canada

FOGARTY

NSERC CRSNG

Title: Subclinical Infections and Acquired Immunity

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

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