Observed and forecasted impact of different candidate Ebola vaccines immunization strategies and target populations

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On behalf of the 3 modelling teams who presented at the SAGE Working Group of June 2018

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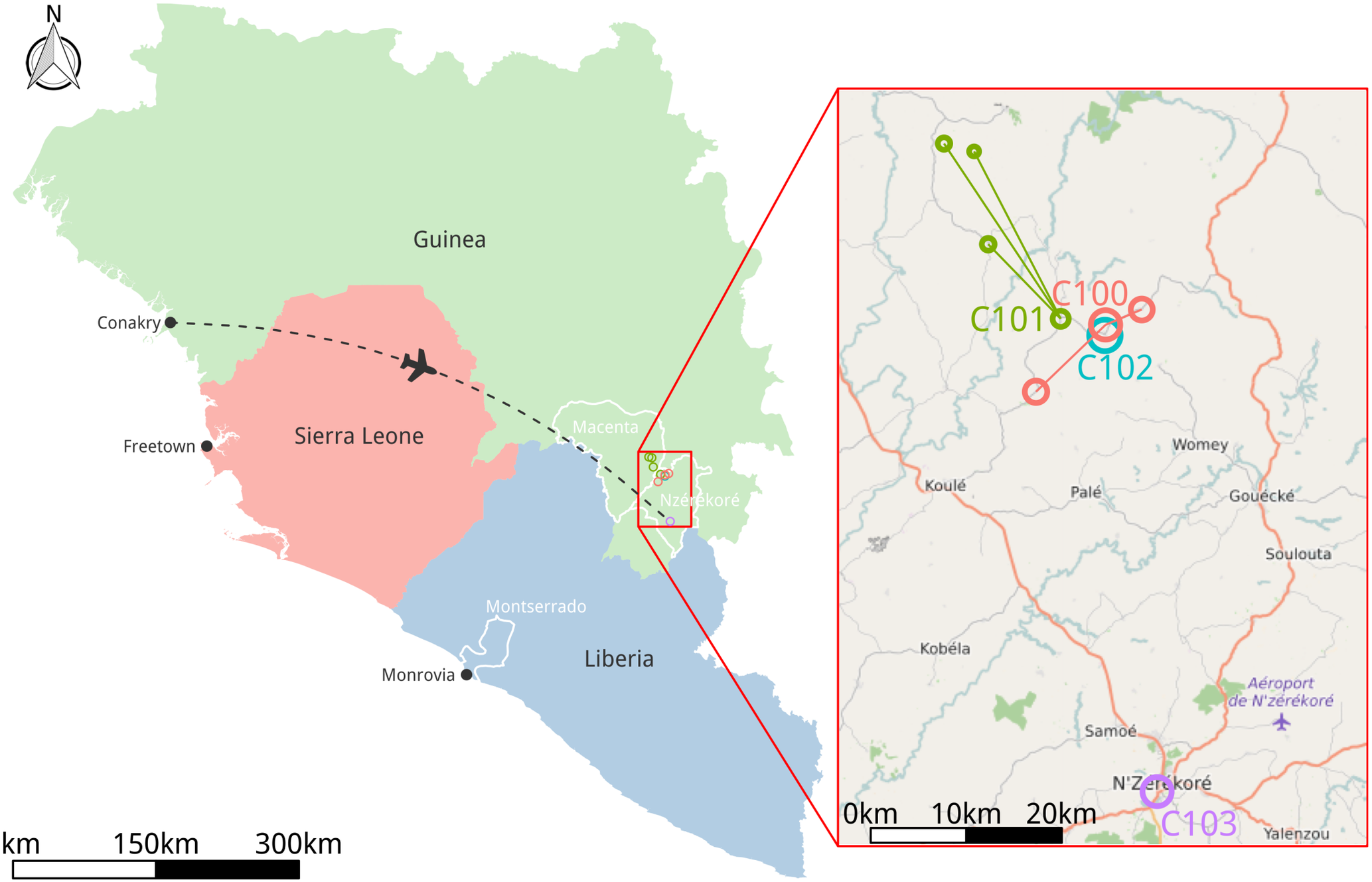
Objective

- Summarize existing evidence about the **population-level effectiveness** of Ebola virus disease (EVD) immunization of different strategies and target populations, using:
    - Observational data (following a flare-up in Guinée in March 2016)
    - **Predictions from Mathematical Models**
- Strategies & target populations tested:
    - **Pre-emptive** and/or **Reactive** vaccination
    - **Ring** vs **Targeted** vs **Mass** vaccination
    - Health-care workers; Front-line workers; Contacts and contacts of contacts of EVD cases; General population

Observational data

Ring vaccination under compassionate use following a flare-up of EVD cases in Guinée forestière in March 2016

Ring vaccination during a flare-up of EVD cases in Guinea



Findings

- **1510 individuals were vaccinated in 4 rings**, including 303 children aged between 6 and 17 and 307 front-line workers.

- The median **time from confirmation of index case to vaccination of participants in a ring decreased from 10 days** for the first EVD confirmed case (mainly due to the geographical localisation) **to 2 days** for the last EVD case reported in this outbreak.

- **No secondary EVD cases occurred among vaccinees.**

- Adverse events following vaccination were reported in 47 (16.5%) 6–17 year olds (all mild) and 408 (34.8%) adults (98% mild). **No severe vaccine-related adverse events were reported.**

- **Ring vaccination strategy can be rapidly and safely implemented at scale** in response to Ebola outbreaks in rural settings

Predictions from Mathematical Modelling

Overview of models and summary of findings

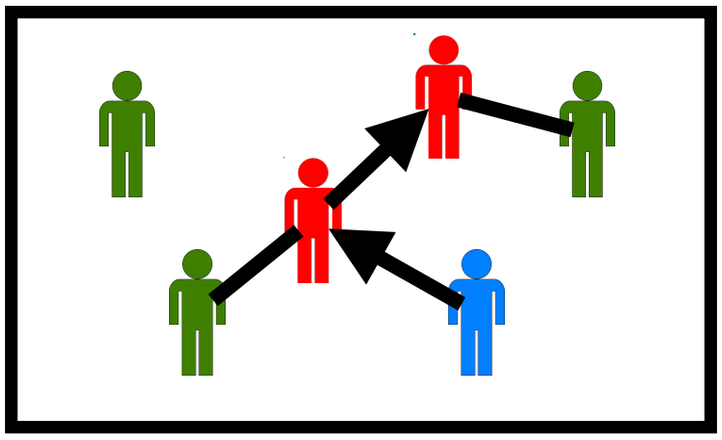
Content

1. Overview of the different models
2. Summary of the findings

Models overview

Individual based

Tracks individual status



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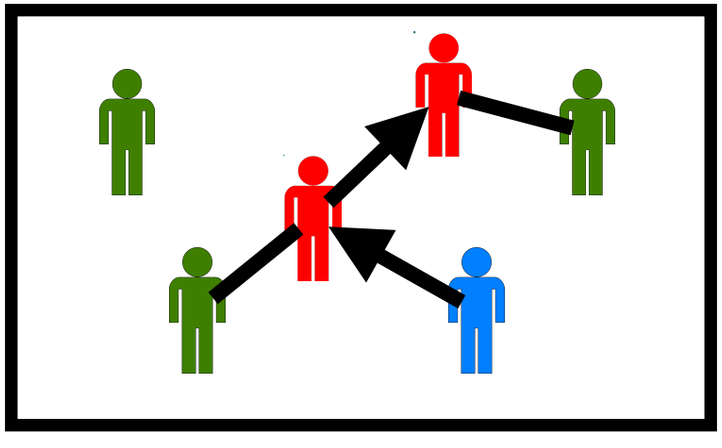
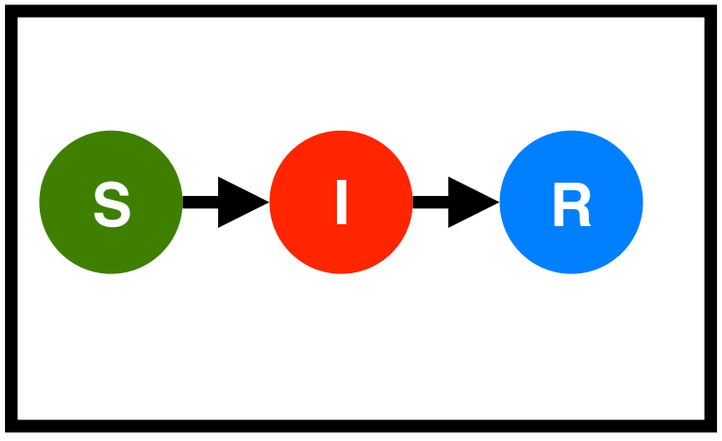


Compartmental

Tracks population status



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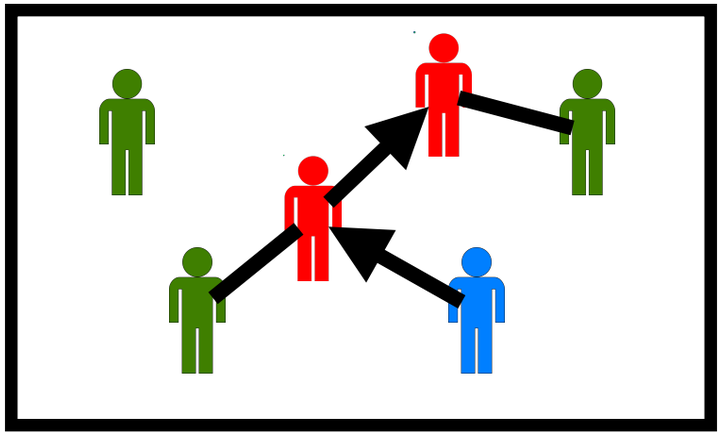

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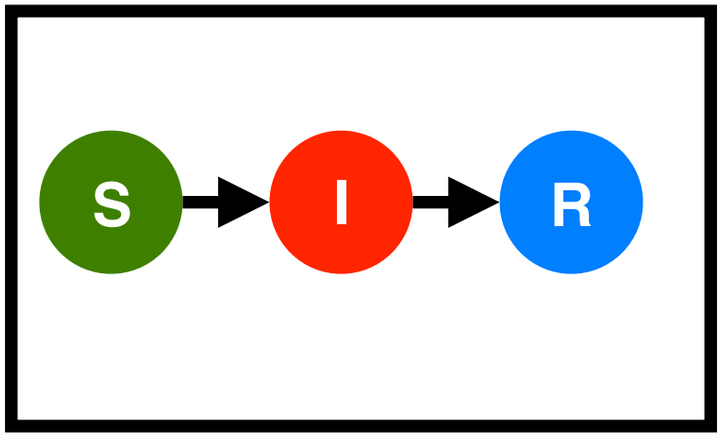
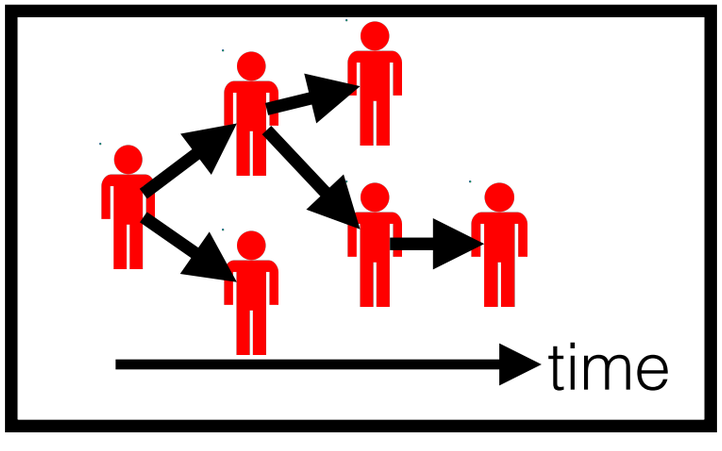


Branching process
Tracks infected individuals



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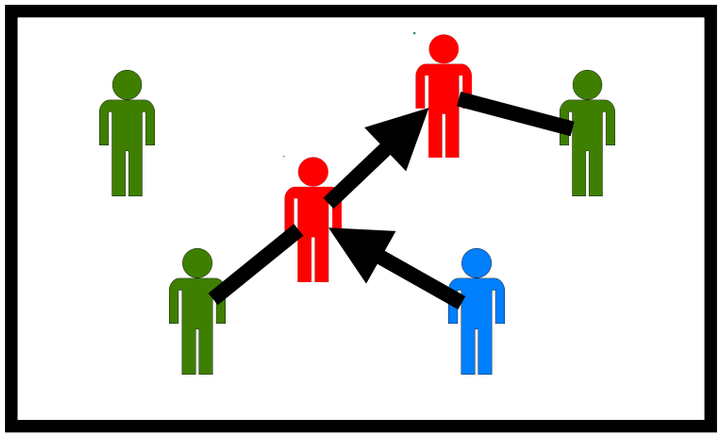

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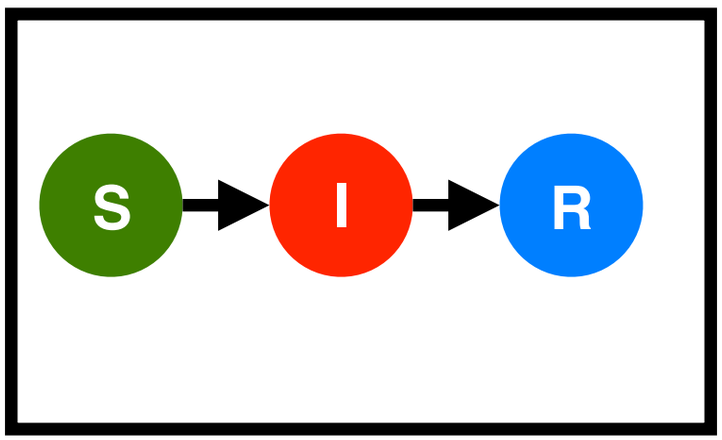

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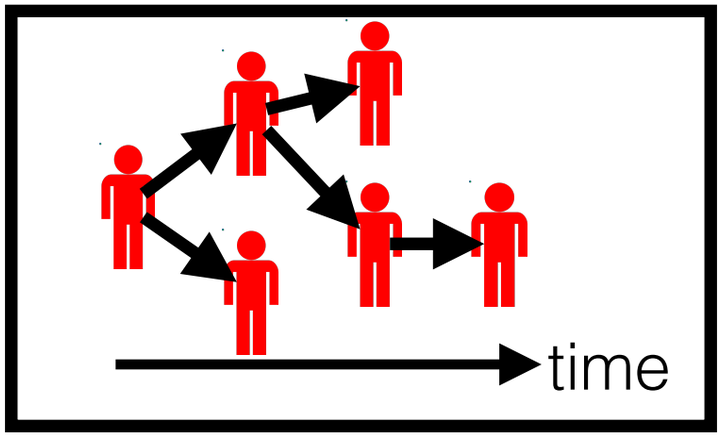

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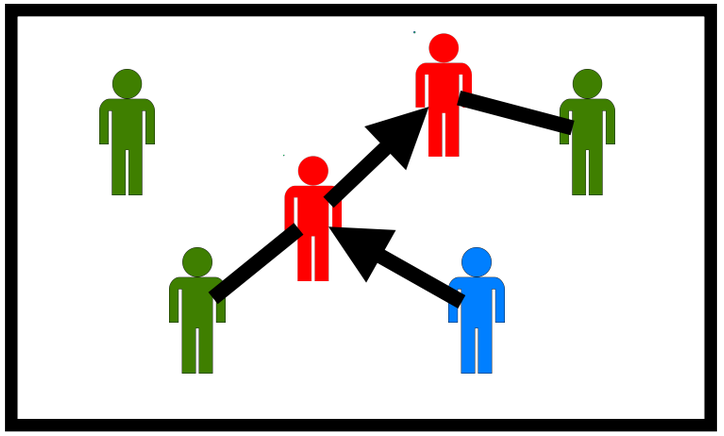

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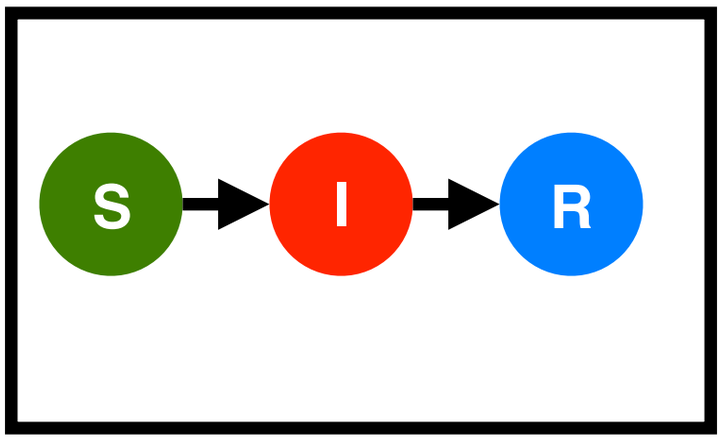

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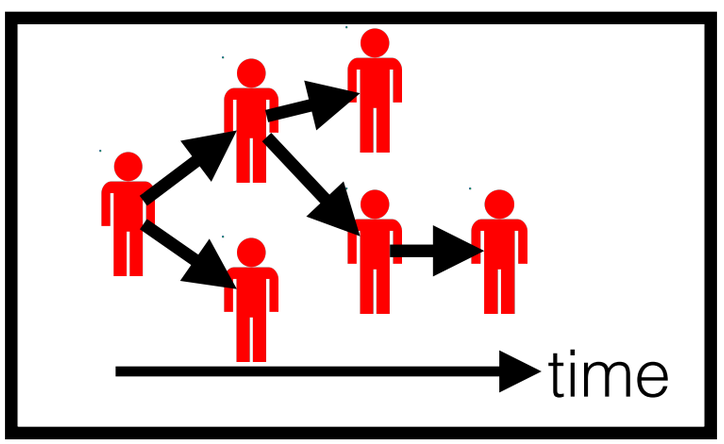

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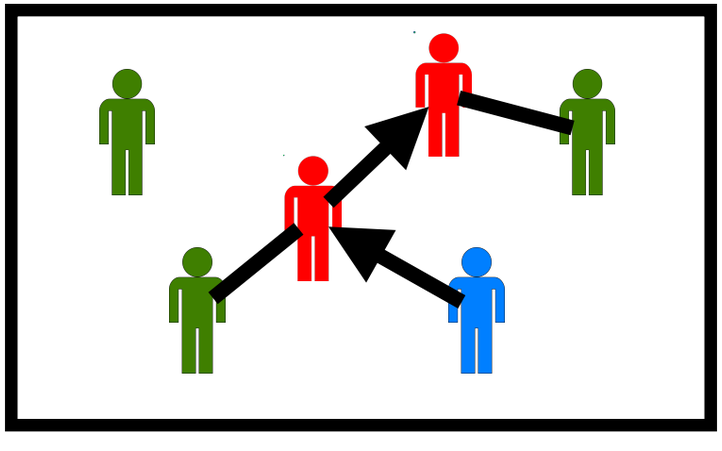

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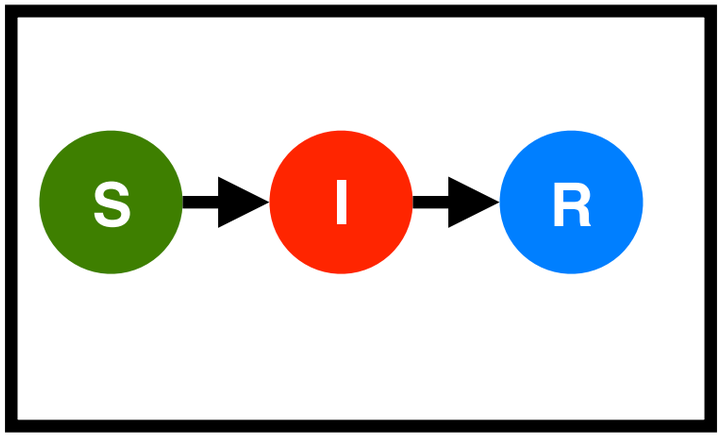

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x2

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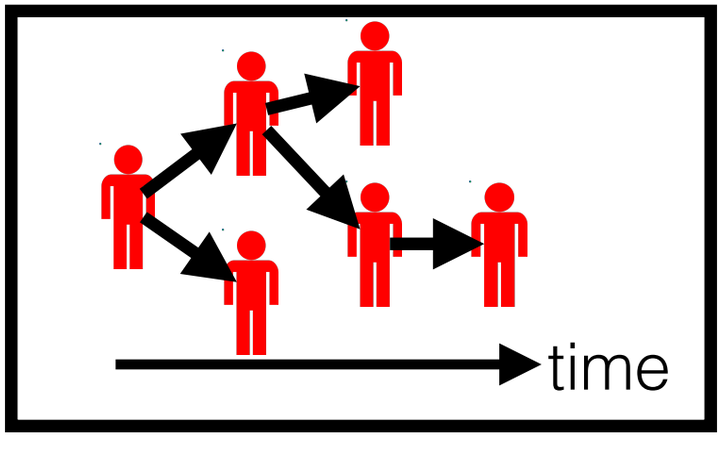

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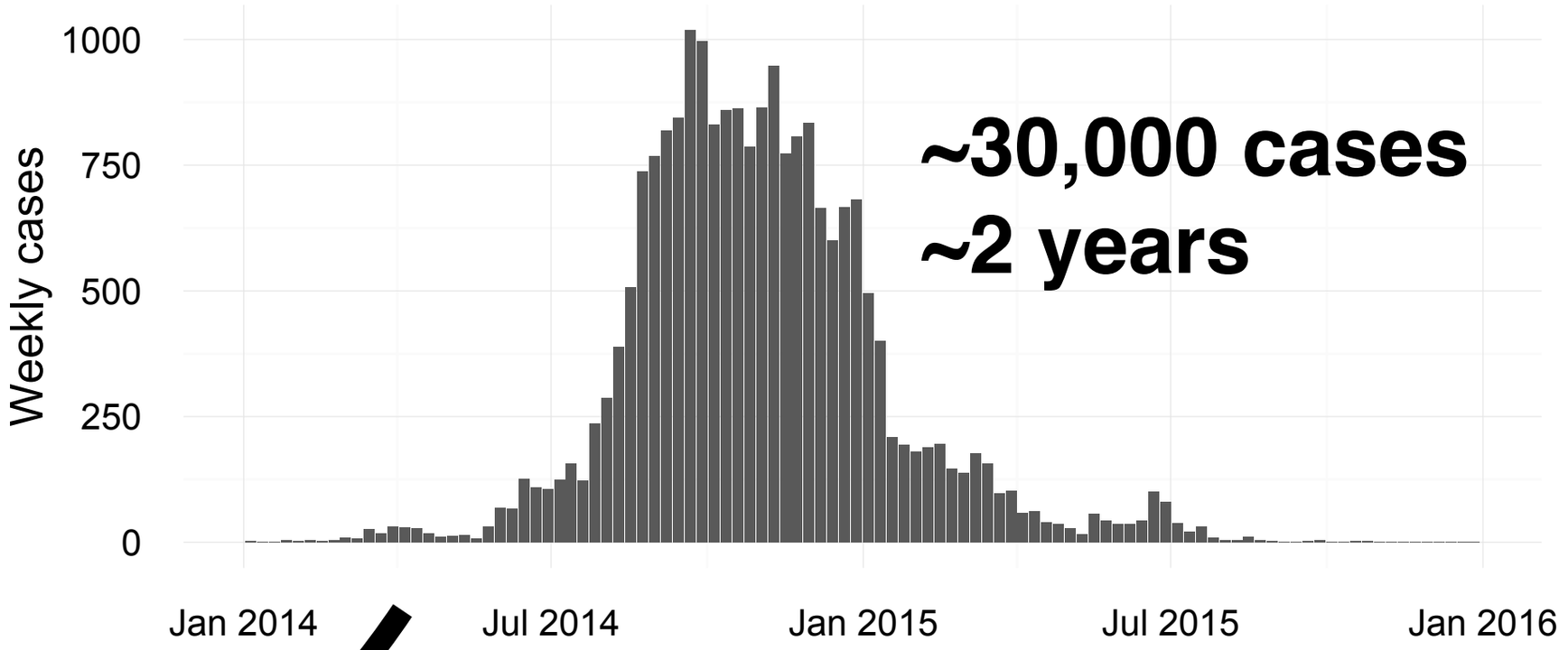
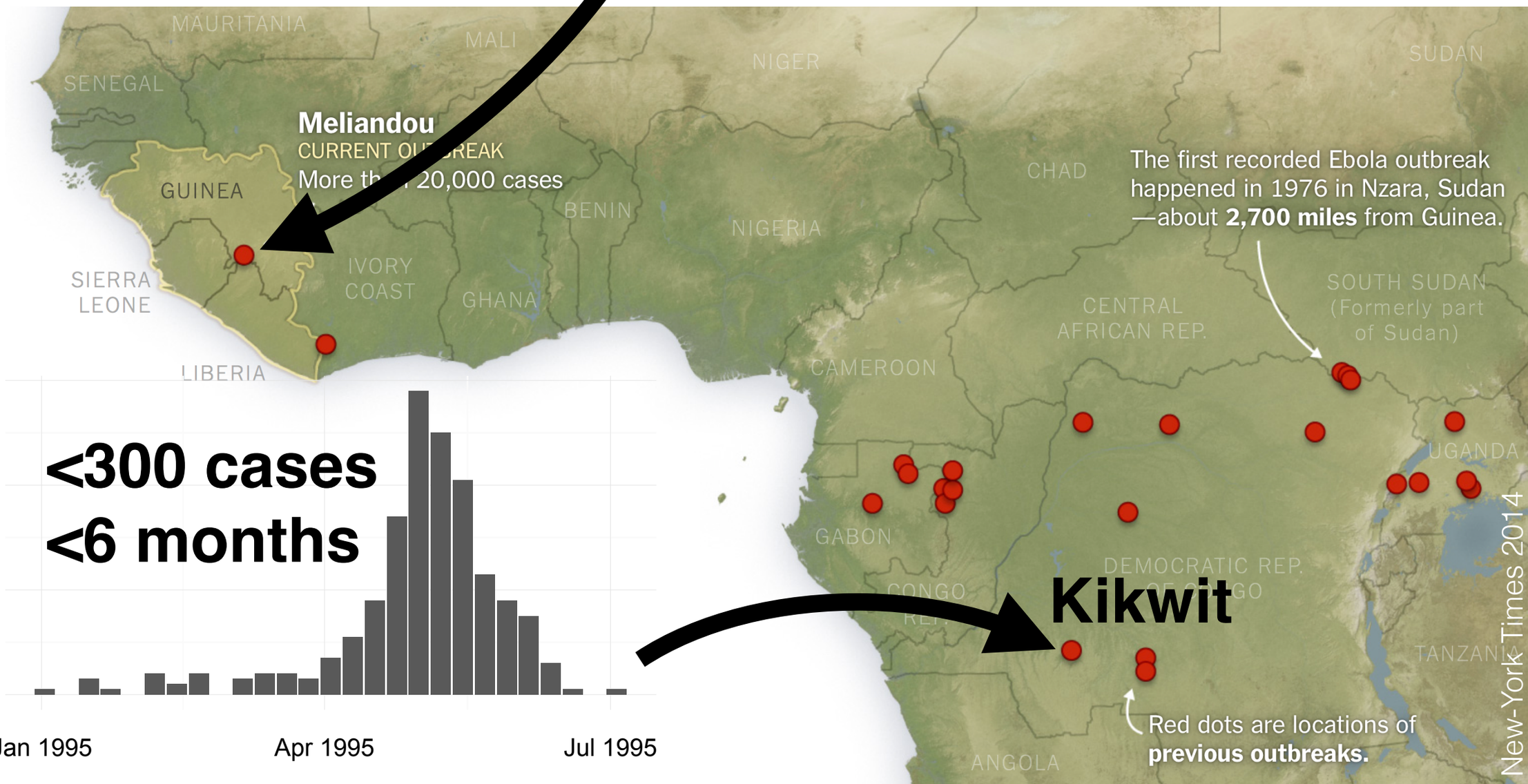
Models can reproduce both **localised** & **widespread** outbreaks





Vaccination strategies

- **Pre-emptive** vaccination:
  - **Targeted**: health-care workers (HCWs). *NB: excluding front-line workers (FLWs) as they are recruited after the outbreak is declared.*
  - **Mass** vaccination: random allocation among people living in areas at risk of Ebola.

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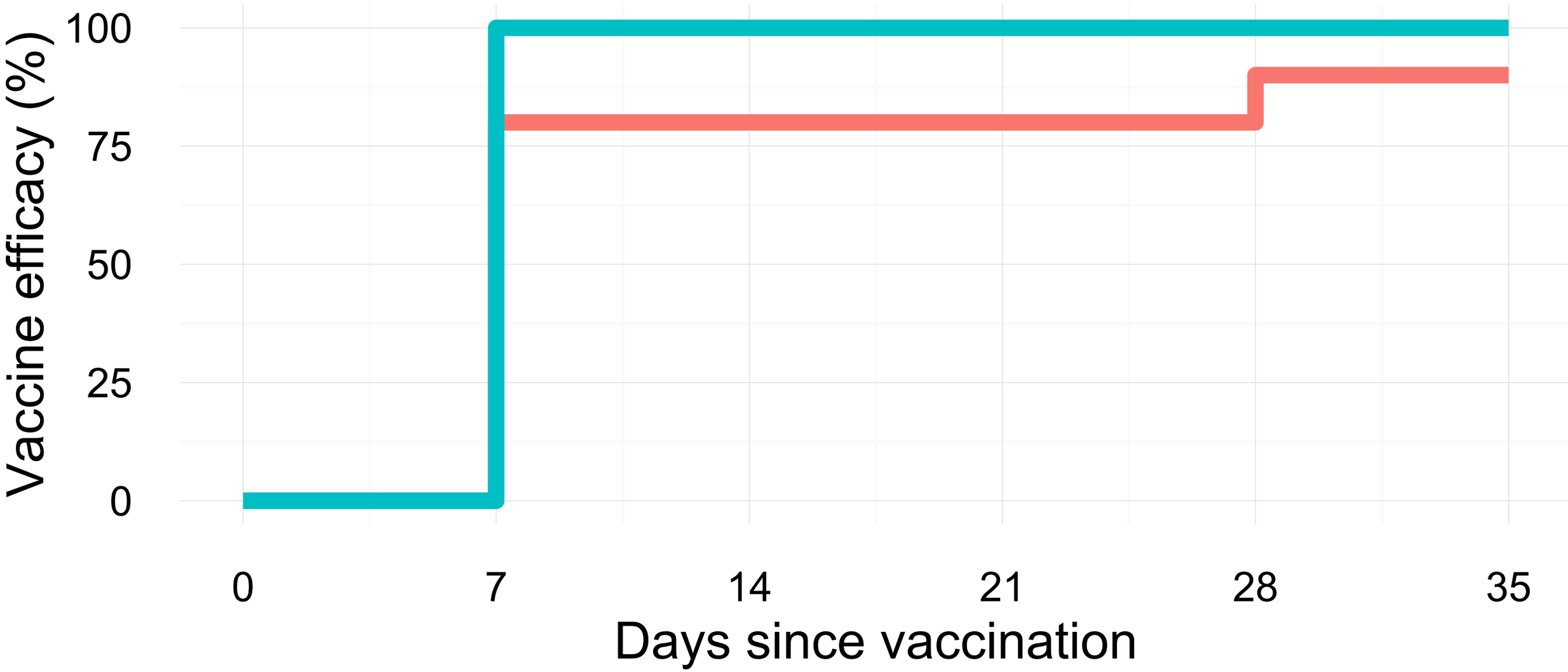
- **Reactive** vaccination:
  - **Ring** vaccination: contacts and contacts of contacts (CCCs) of EVD cases. *Parameters based on Ebola ça Suffit ring trial data.*
  - **Targeted** vaccination: HCWs and/or FLWs
  - **Mass** vaccination: random allocation among people living in areas reporting EVD cases.

		Branching process	Comp. 1 Kikwit	Comp. 2 West-Africa	IBM	IBM
Pre-emptive	HCW		✔		✔	
Pre-emptive	Mass	✔	✔	✔	✔	
Reactive	Ring	✔			✔	✔
Reactive	Targeted		✔		✔	
Reactive	Mass		✔	✔	✔	

Vaccine efficacy

Single-dose:
VE = 100% (CI: 64-100%)
after day 7 post-vaccination

Prime-boost:
VE = 80% after day 7 and 90%
after day 28 post-vaccination



Models limitations

- Models do not explicitly account for spontaneous **human behavioural changes**
- **Data used for calibration** might be incomplete thus introducing potential biases
- Several **unknown parameters** are based on assumptions:
  - Efficacy of prime-boost vaccine (no phase 3 trial yet)
  - Duration of immunity (>1 year for single dose and prime-boost)
  - Capacity on the field for mass vaccination (e.g. number of doses distributed per day)

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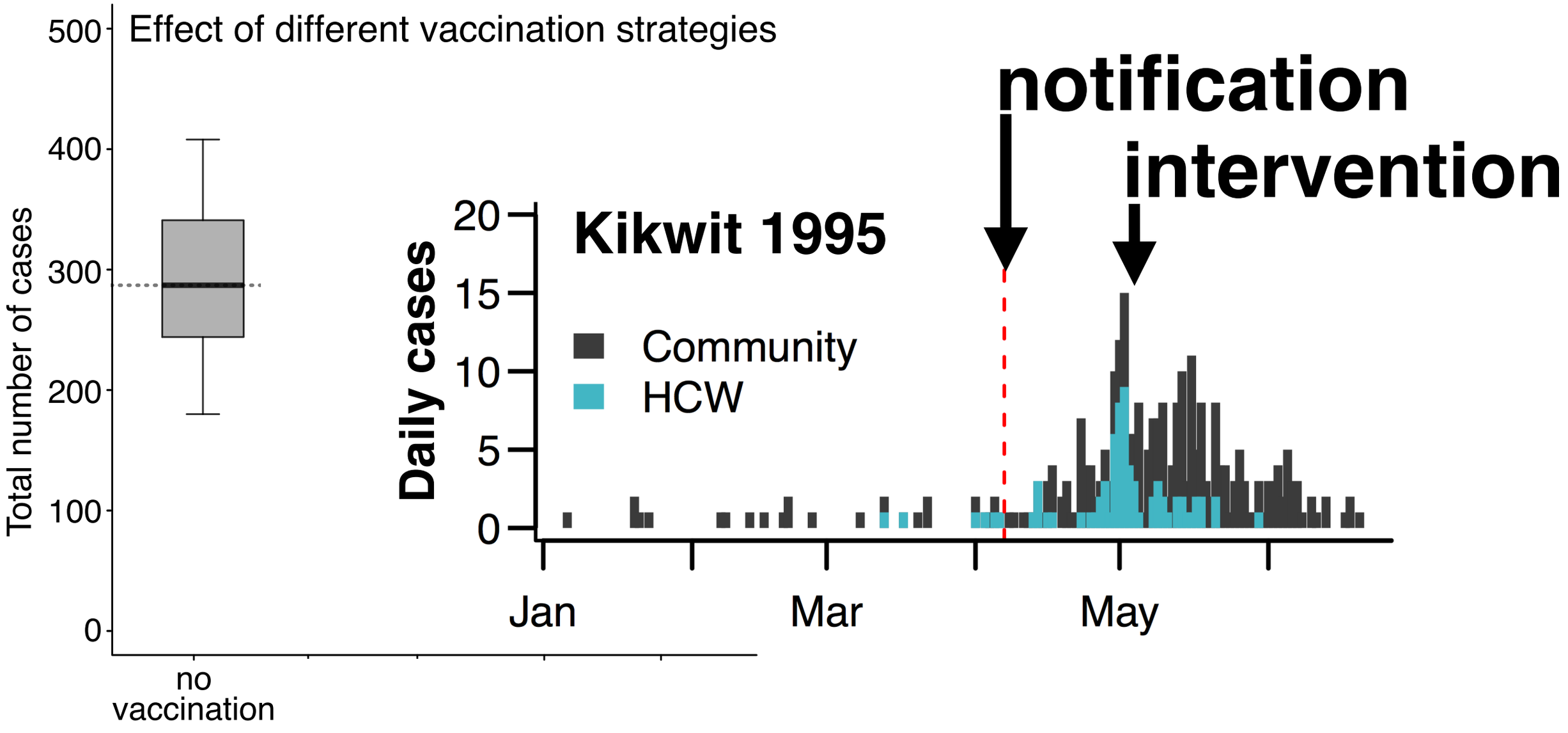
Impact of health-care workers vaccination



<u>Note:</u> this model reproduces the 1995 EVD outbreak in Kikwit and accounts for classical control measures that were implemented at that time.

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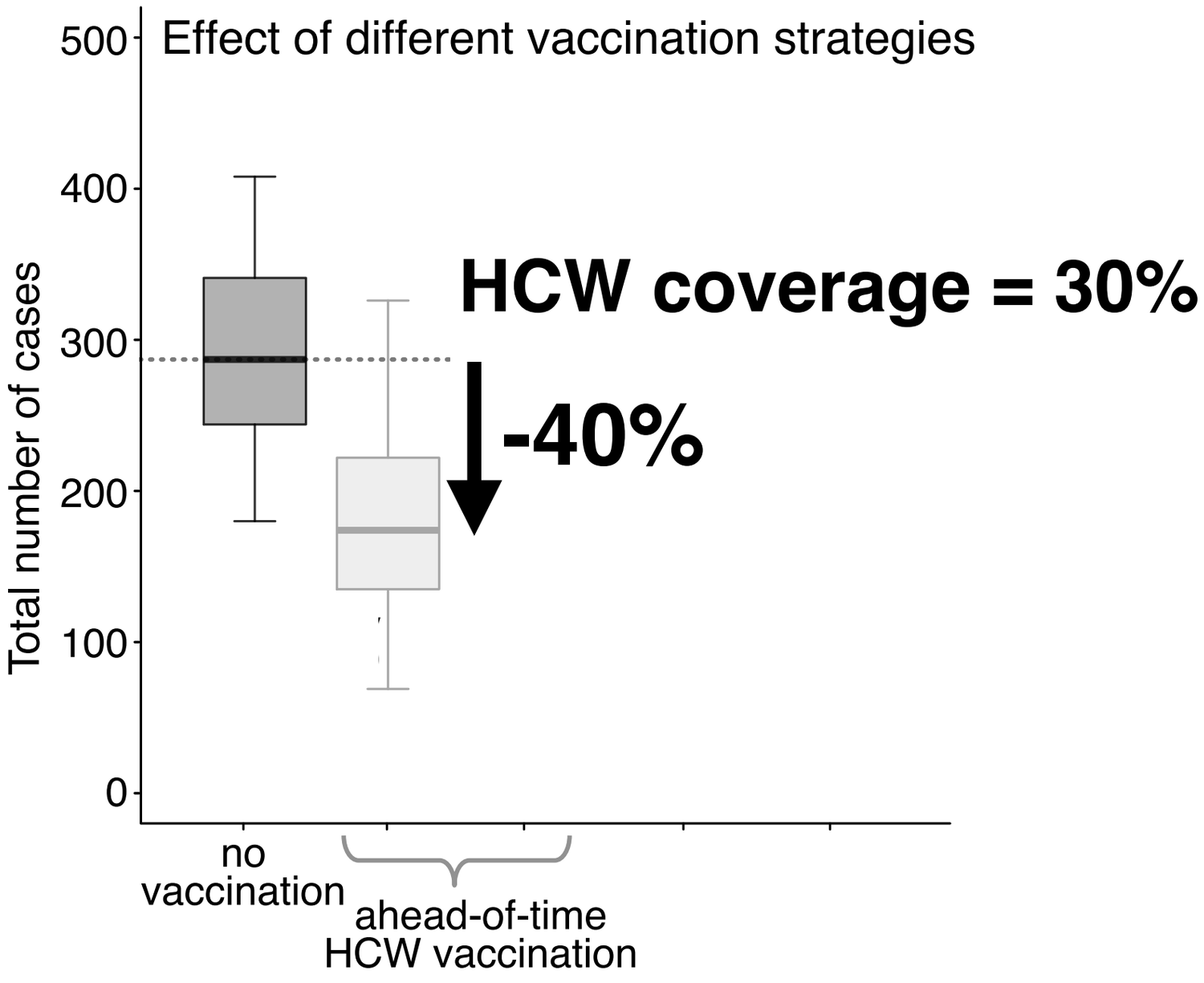

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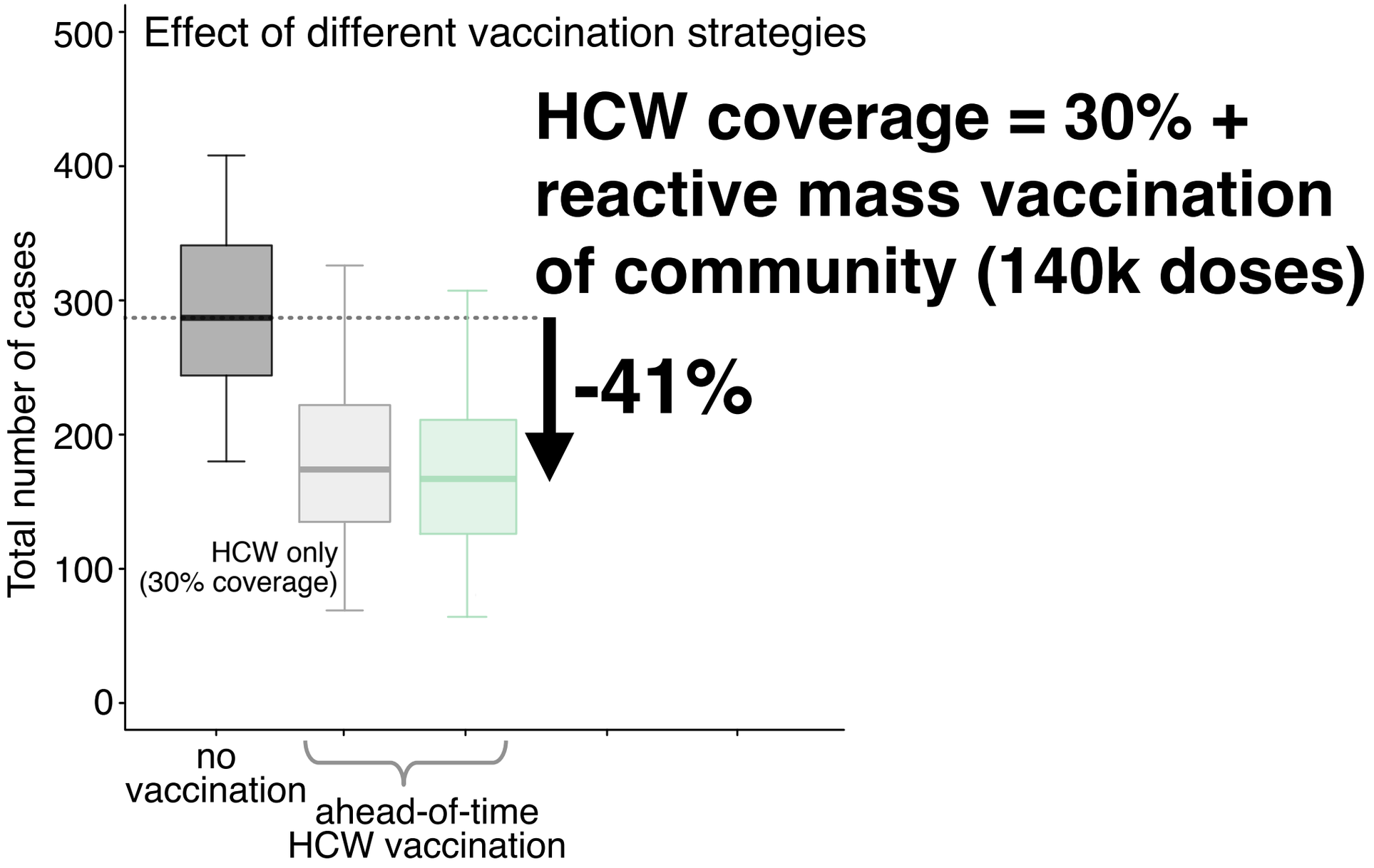

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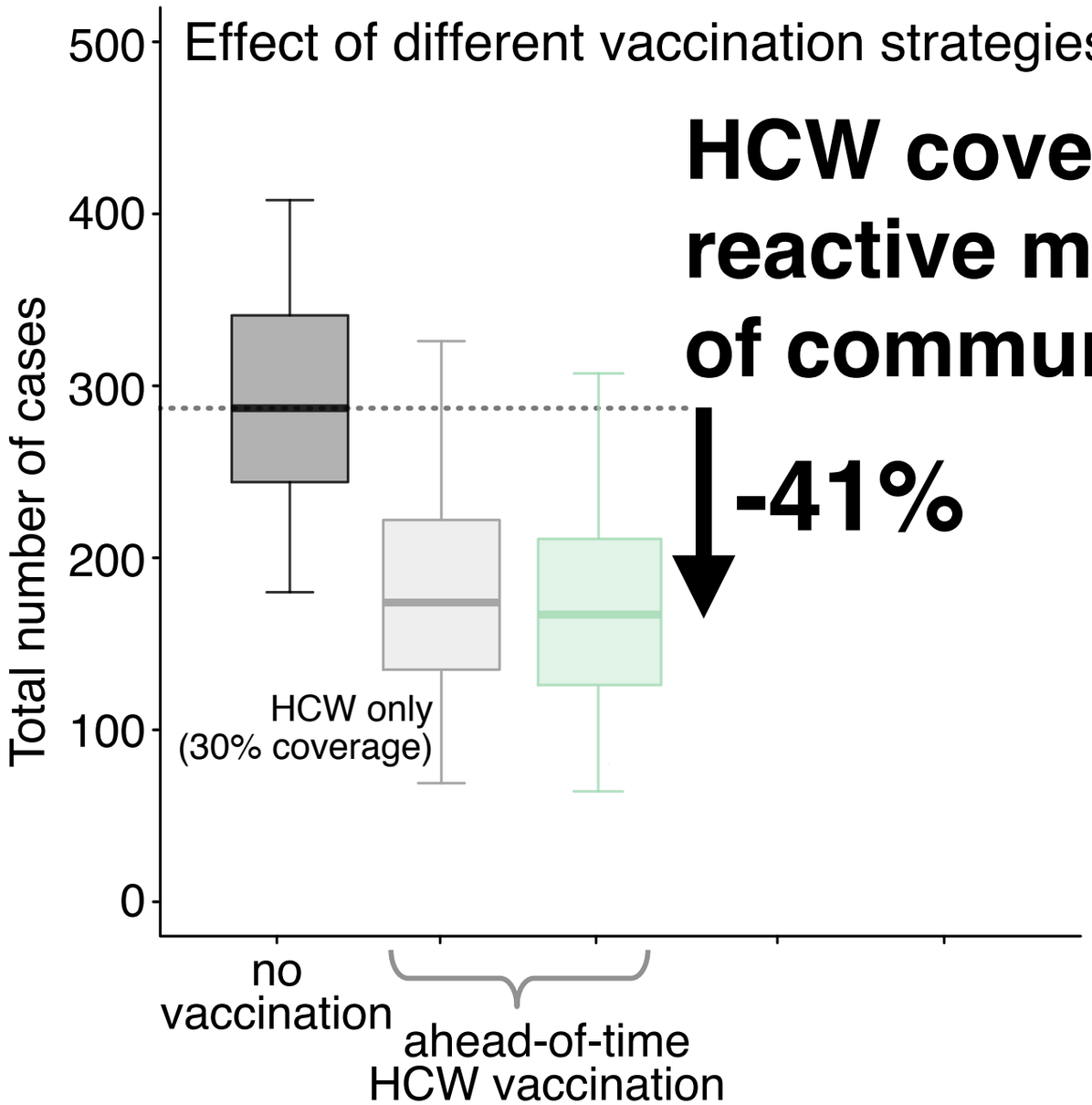

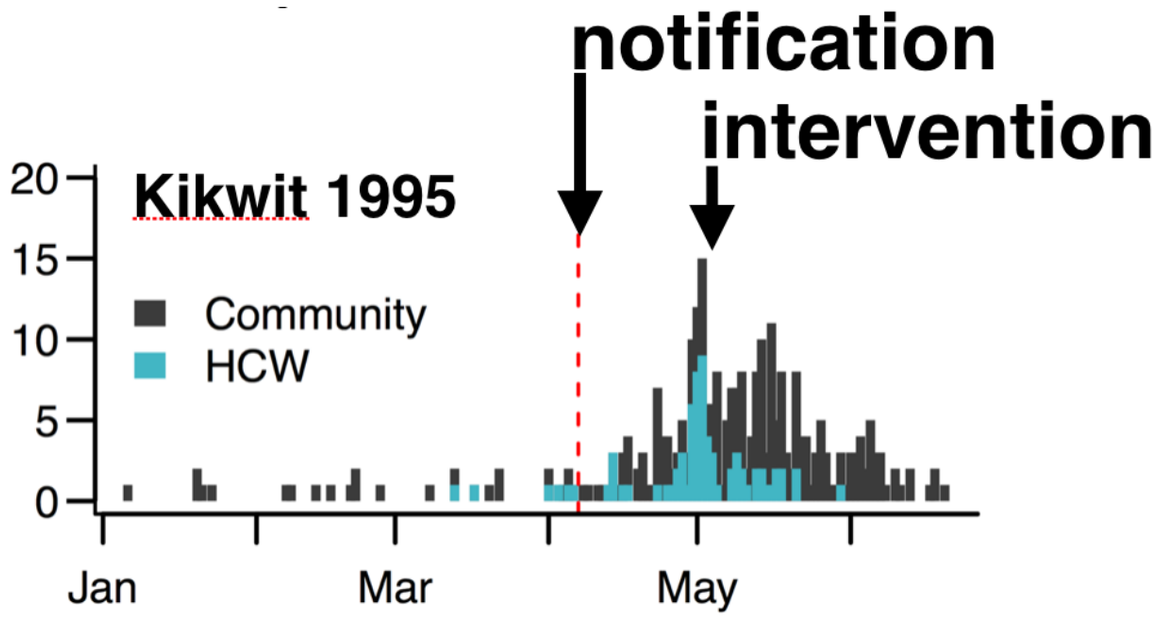

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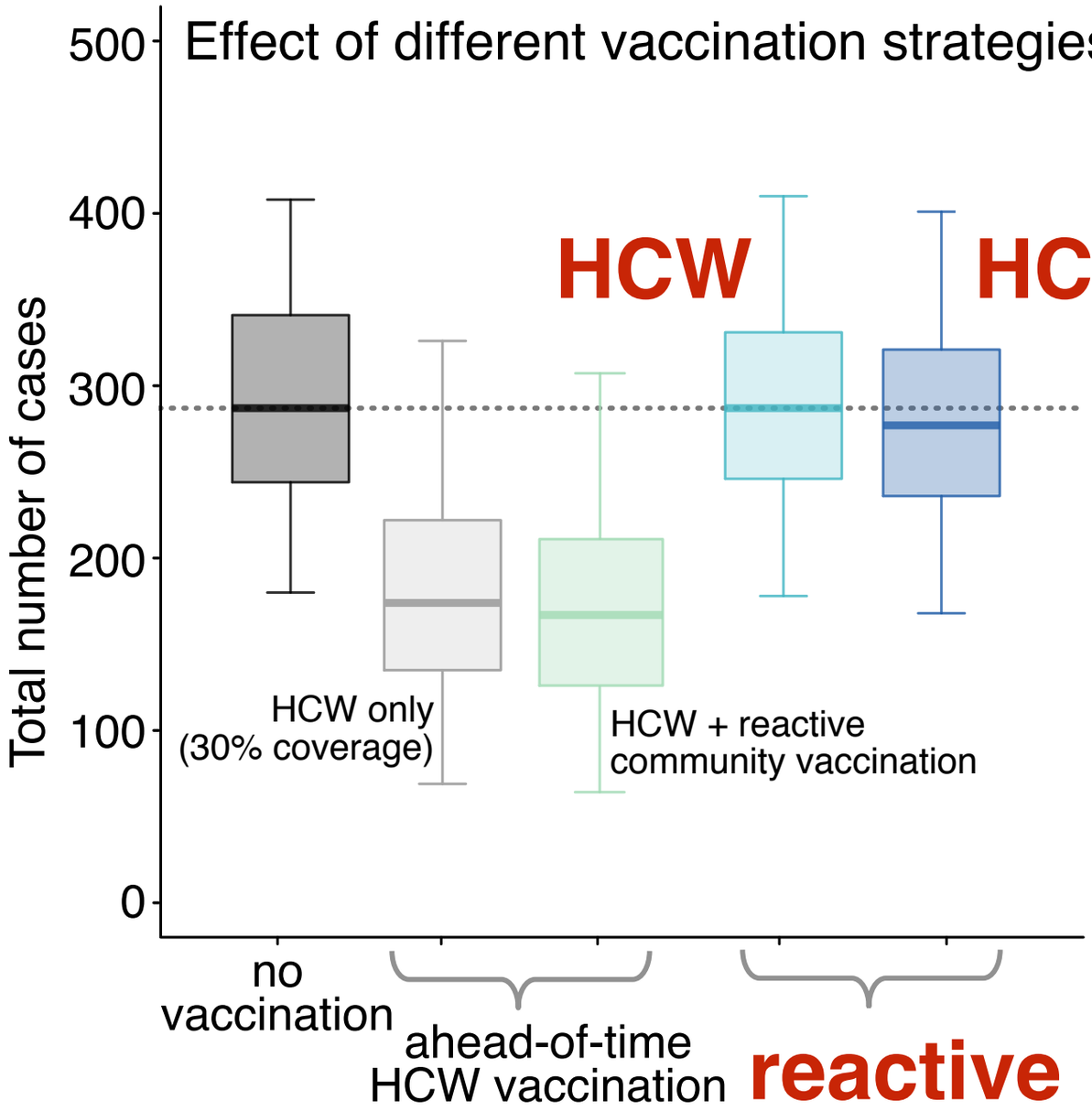

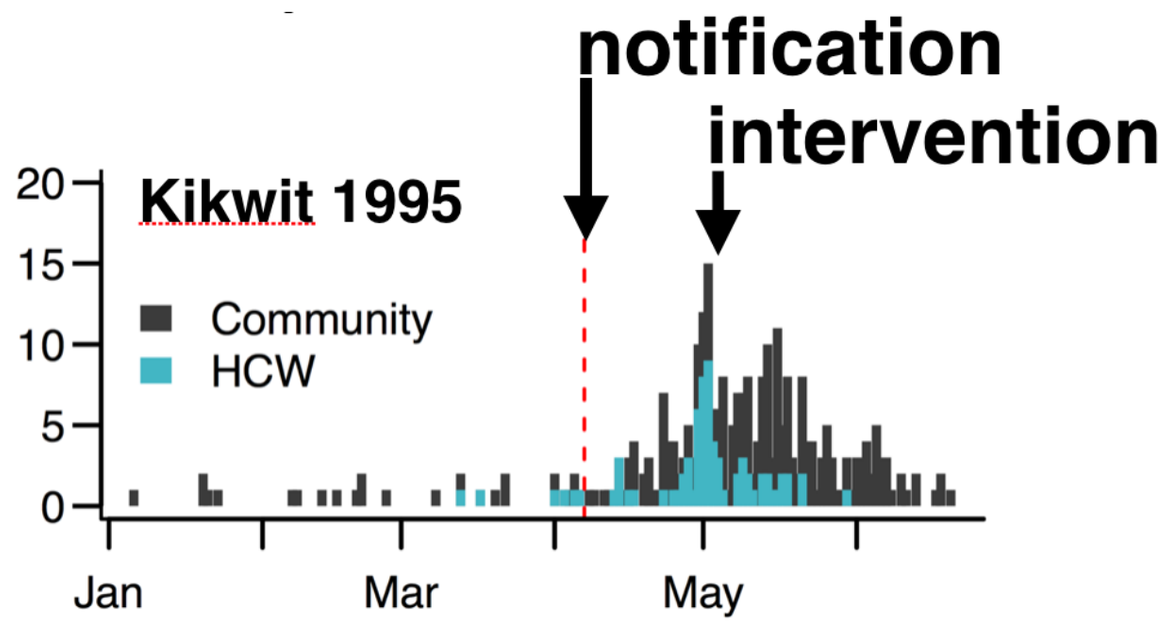

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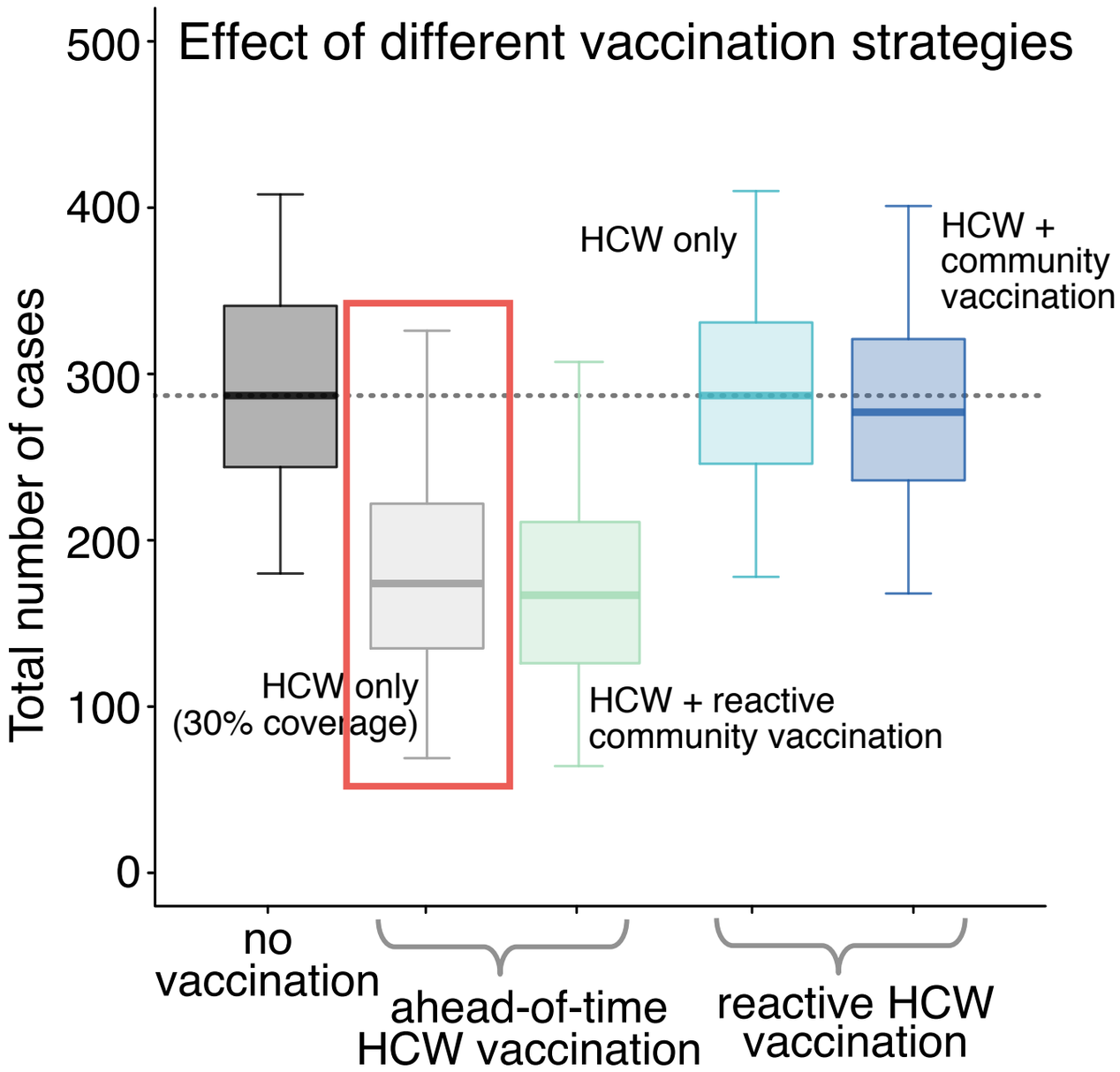

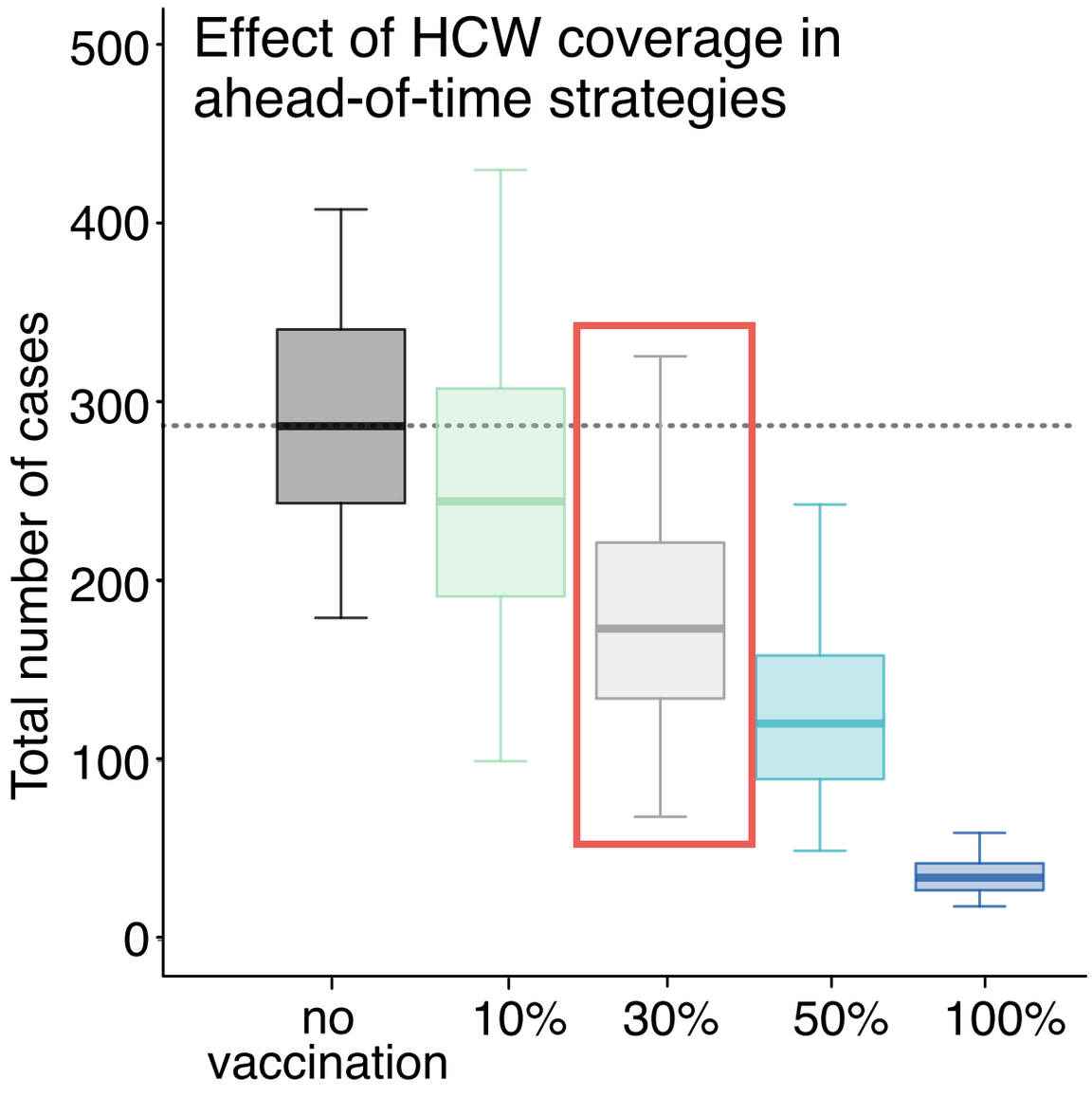

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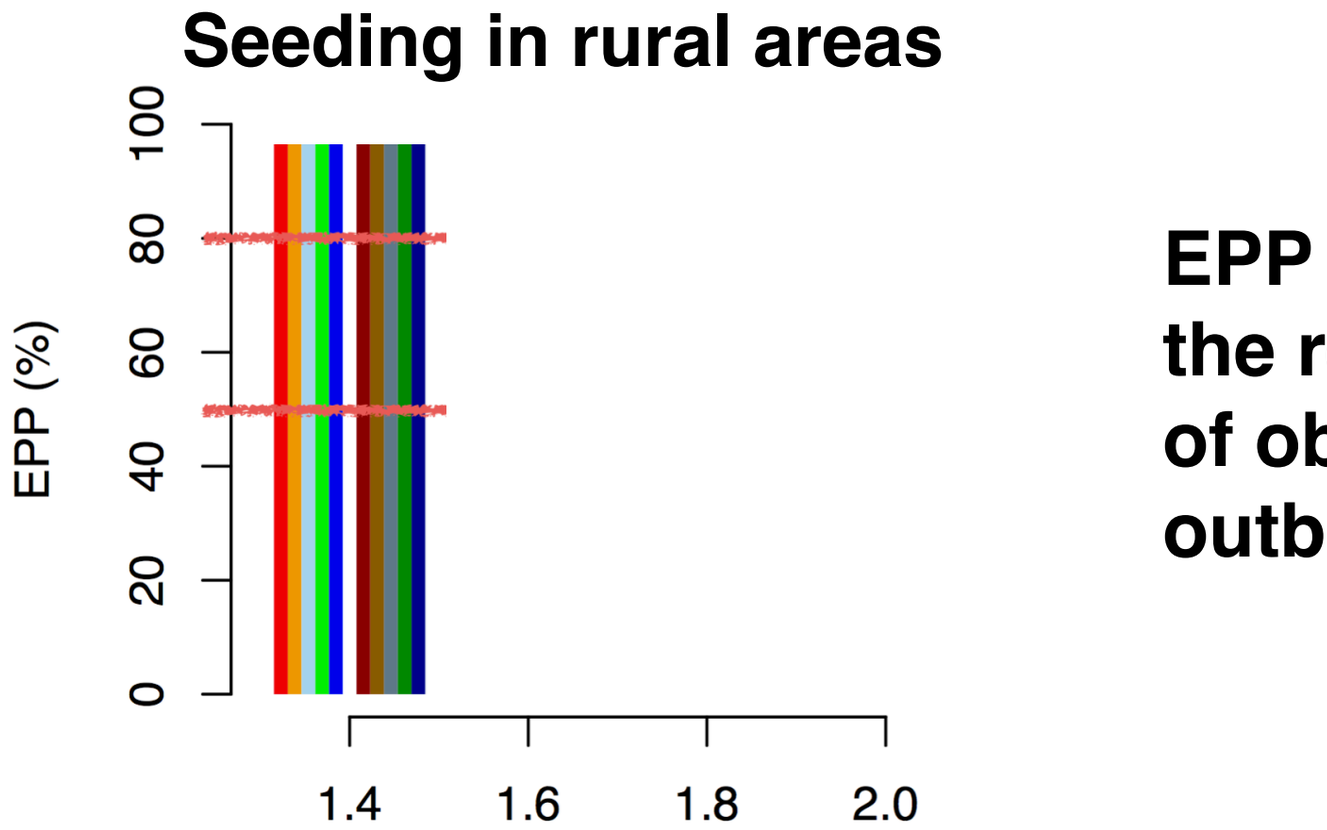
Health-care workers

- **HCWs are at high-risk of infection** during EVD outbreaks, especially at the outset of the outbreak when **they can amplify the spread** of the disease.

- Models suggest that pre-emptive vaccination of HCW may be an **effective strategy with both direct and indirect protective effects** to limit the spread to the community and avoid depletion of HCWs in areas with limited health-resources.

- The number of doses needed depends on the number of HCW in areas at risk of EVD outbreaks, their turnover and the **(unknown) duration of vaccine-induced immunity**.

Impact of ring vaccination + pre-emptive/ reactive HCW/FLW vaccination



EPP is defined as the reduction of the risk of observing a large outbreak (>300 cases).

<u>Note</u>: this model assumes poor or zero initial infrastructure for classical control measures.

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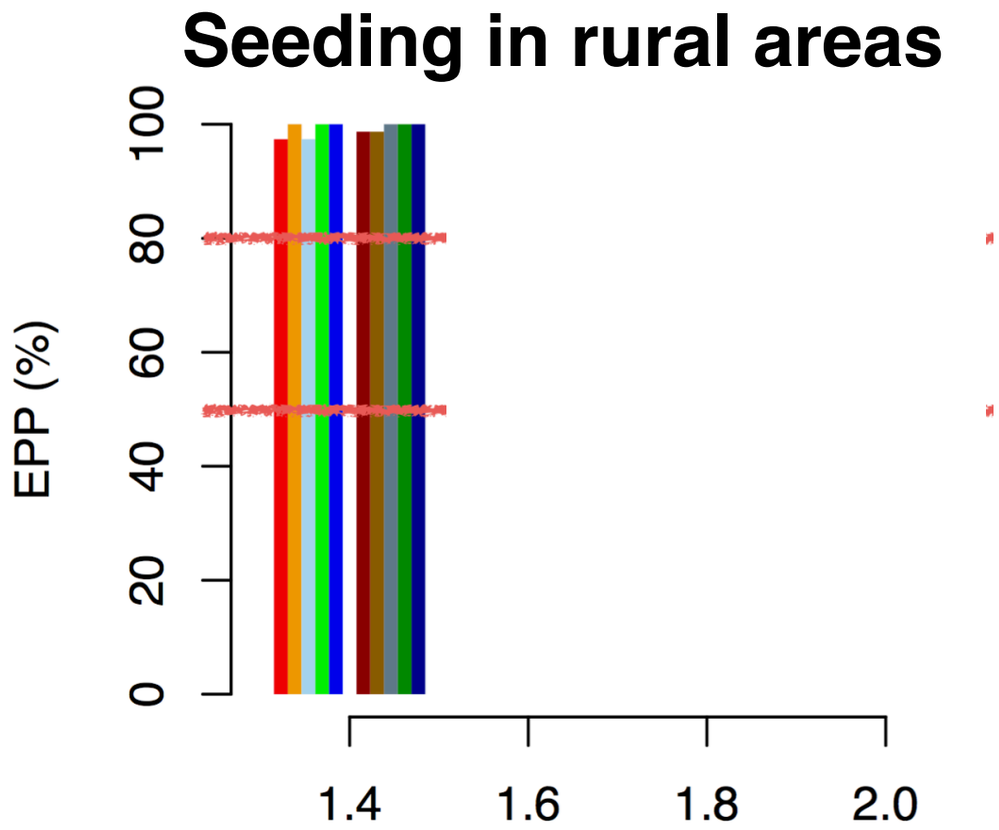

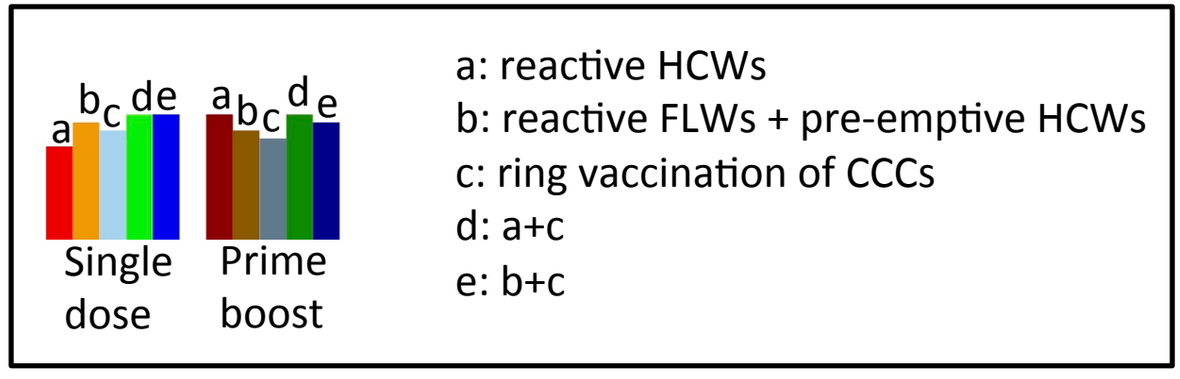

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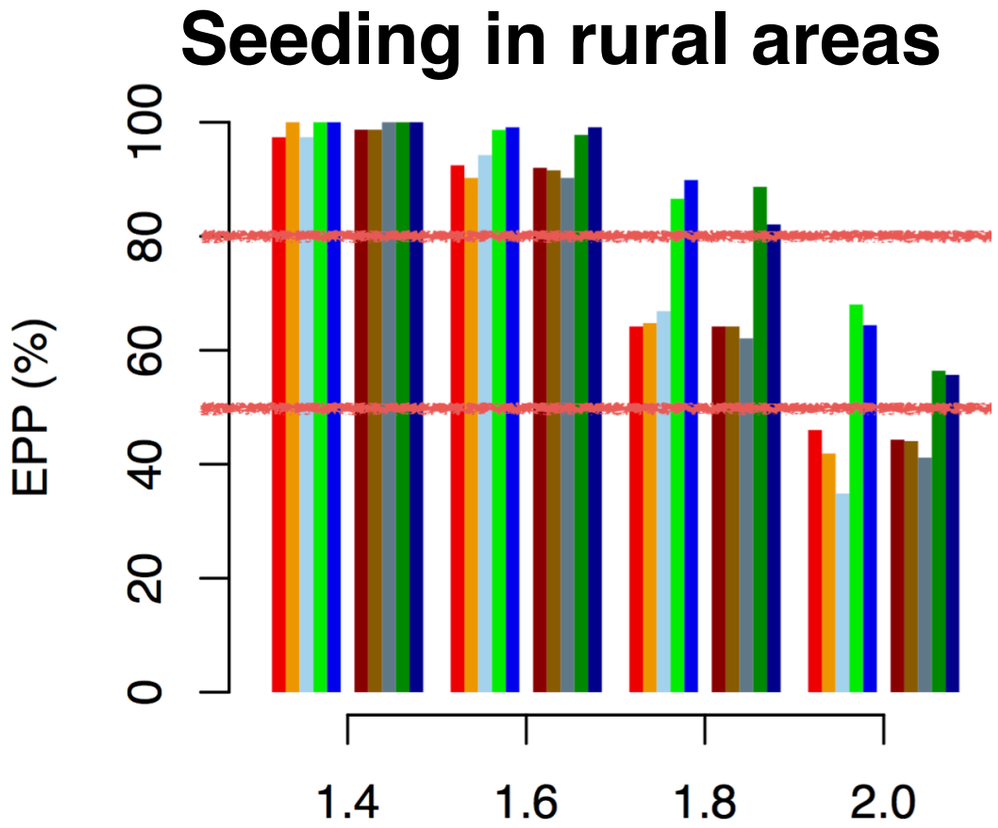

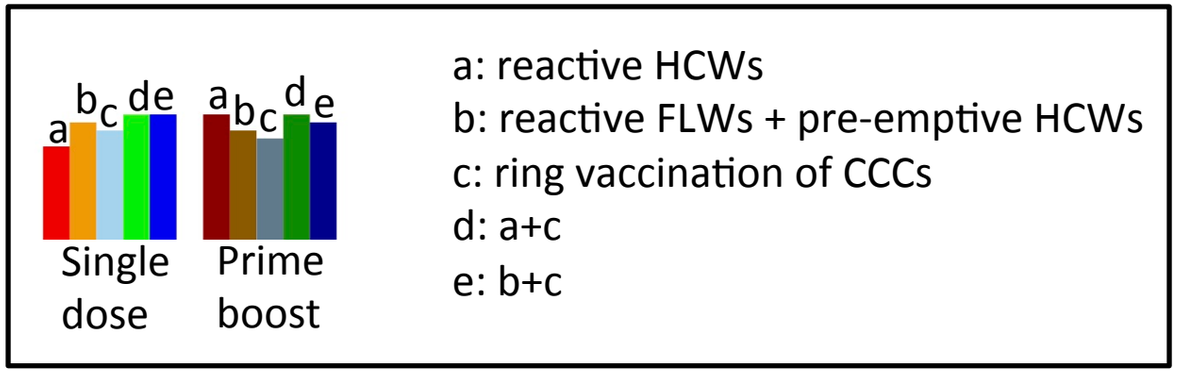

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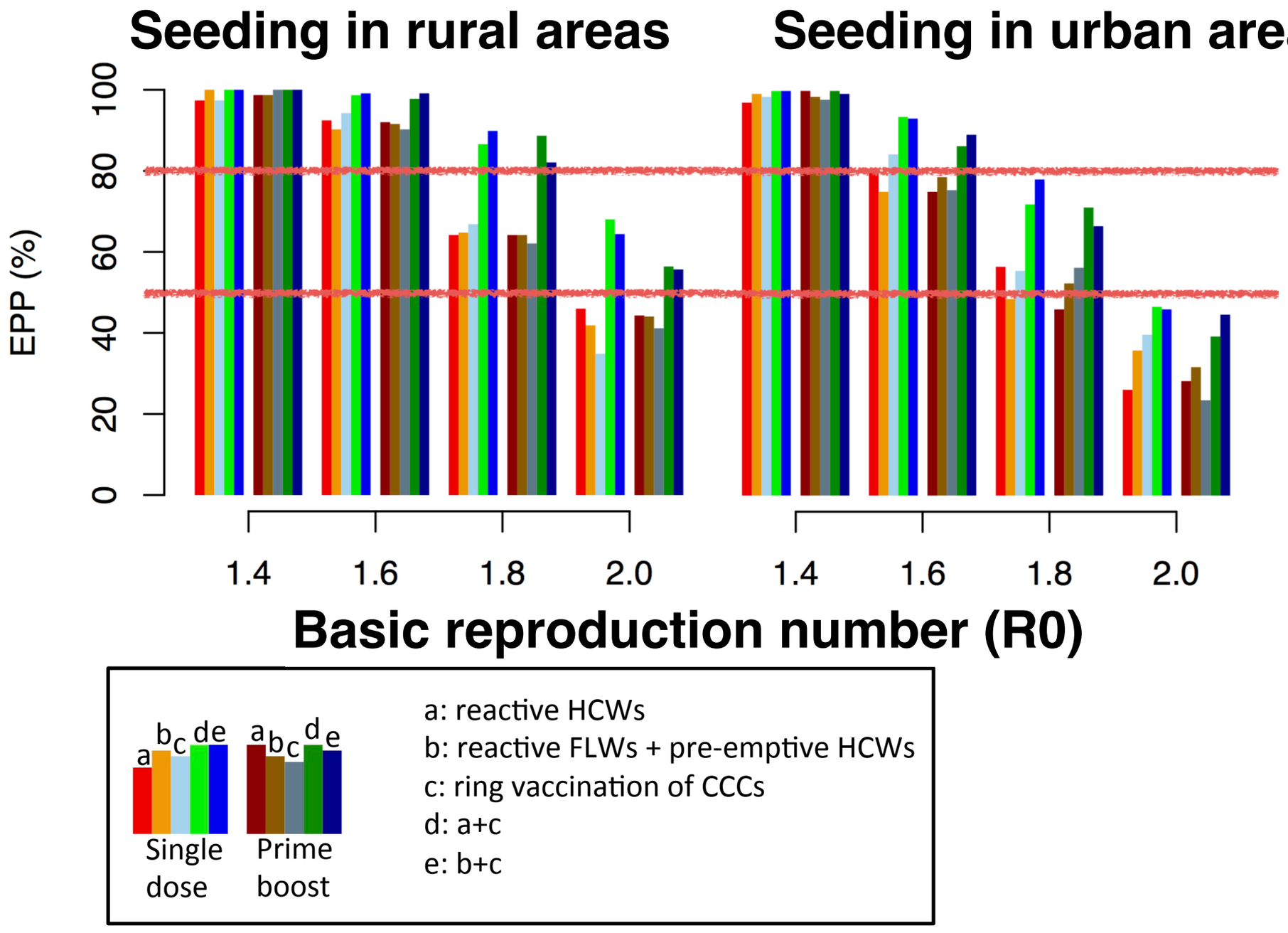

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Ring vaccination of contacts and contacts of contacts (1/2)

- **Ring vaccination may be an effective reactive strategy** to contain Ebola outbreaks because **it tracks the transmission dynamics** and target the CCCs who are the most at risk of being infected.

- **Effectiveness of this strategy has been demonstrated** during the *Ebola ça Suffit* ring vaccination trial in Guinea as well as during the flare-up in Guinea.

- Models suggest that ring vaccination may be **more effective in rural than in urban areas**, due to higher population density in cities.

Ring vaccination of contacts and contacts of contacts (2/2)

- Models suggest that ring vaccination should work best in **conjunction** with pre-emptive/reactive vaccination of HCWs/FLWs as well as with **classic control measures**.

- In particular, **comprehensive contact tracing is essential** for effective ring vaccination since missed infected contacts can seed the epidemic to new areas.

- Models results suggest that **localised Ebola outbreaks can be contained with 10,000 doses** whereas more widespread epidemics can be contained with 50,000 doses.

Mass vaccination

- **In case of poor case detection and contact tracing**, models suggest that ring vaccination should be supplemented by more geographically targeted mass vaccination.

- Targeting villages of patients would require a **tenfold increase of doses** to be effective (~100,000 doses).

- Targeting regions reporting cases would require a **hundredfold increase of doses** (~1,000,000 doses) but would have little impact in case of late vaccination.

Thank you!

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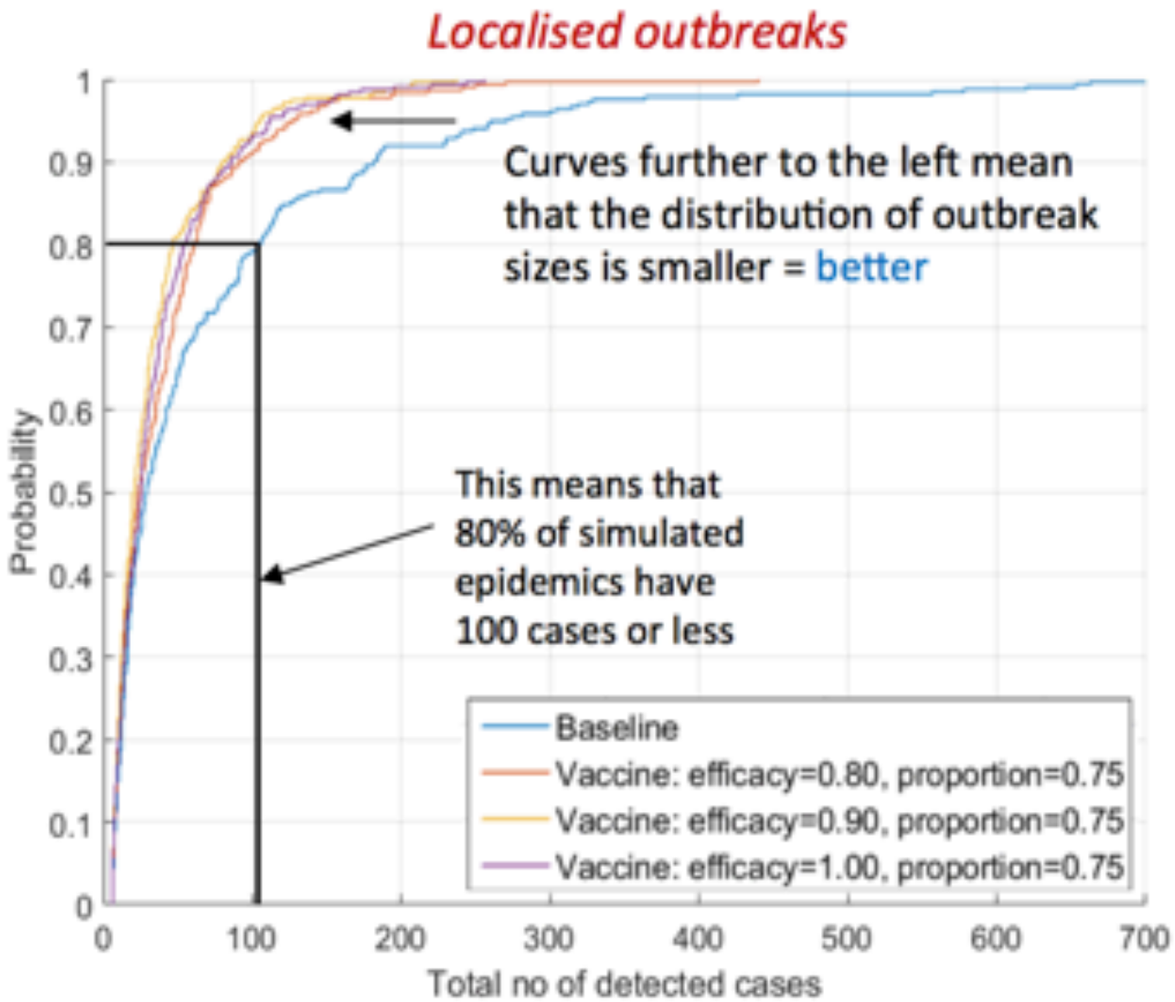
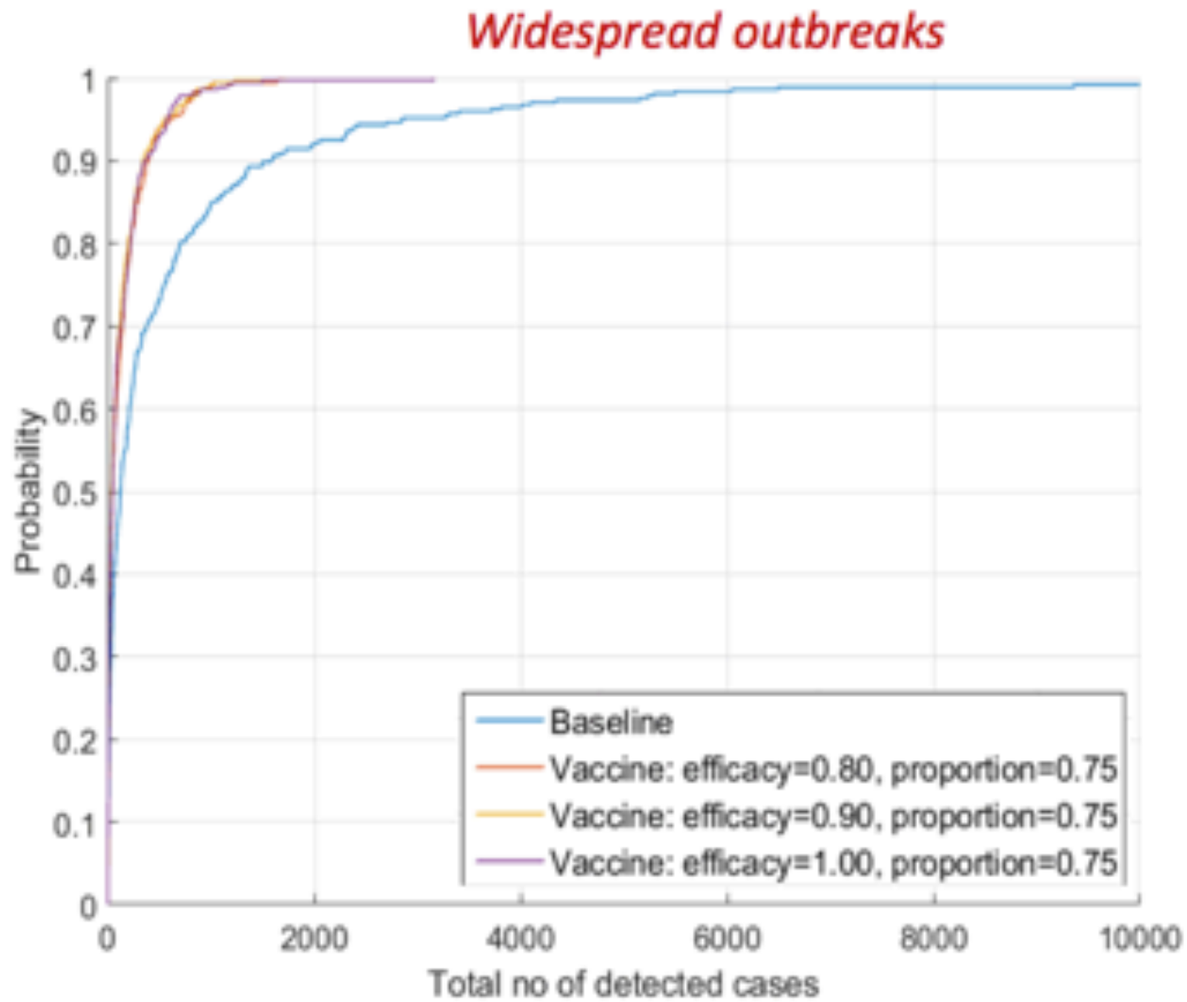
A. Kucharski
A. Robert
C. Watson

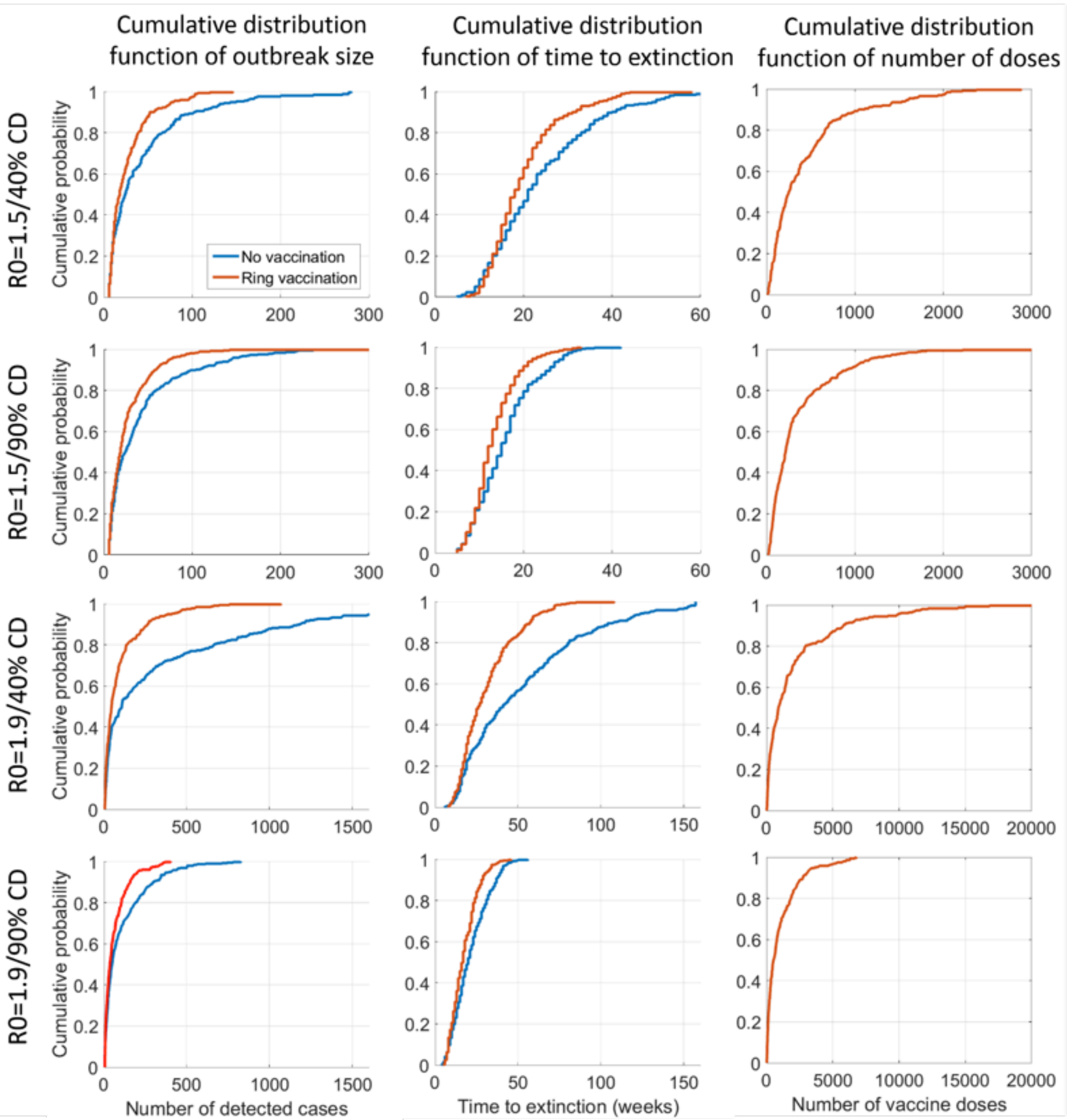
C. Donnelly
N. Ferguson
W. Hinsley
G. Nedjati-Gilani
S. Riley

Impact of ring vaccination

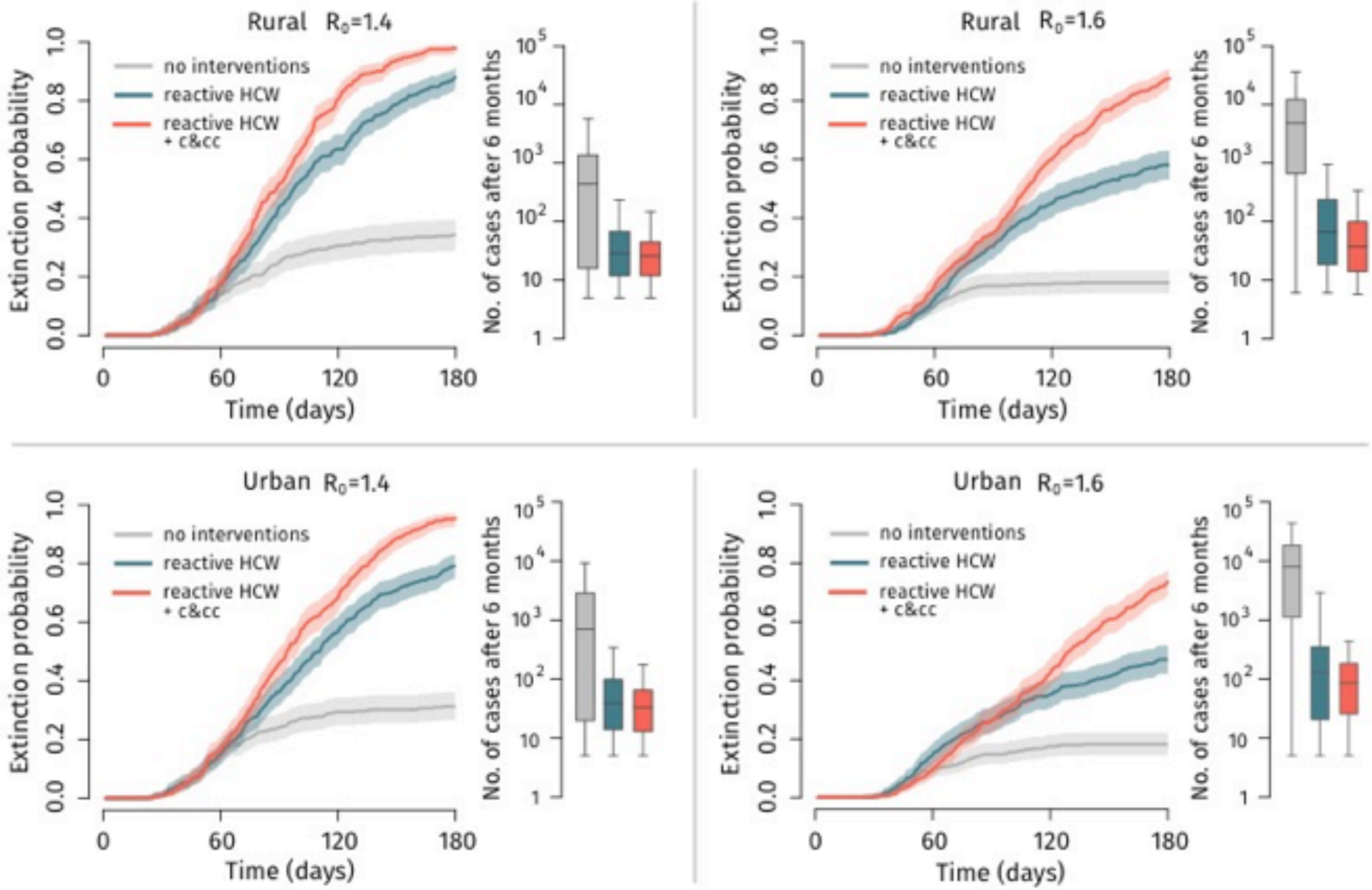




Note: classical control measures are also implemented in this model


Cumulative distribution function of outbreak size
Cumulative distribution function of time to extinction
Cumulative distribution function of number of doses
R0=1.5/40% CD
R0=1.5/90% CD
R0=1.9/40% CD
R0=1.9/90% CD
Cumulative probability
No vaccination
Ring vaccination
Number of detected cases
Time to extinction (weeks)
Number of vaccine doses

Impact of ring vaccination + reactive HCW vaccination



Note: this model is gauged to a baseline with
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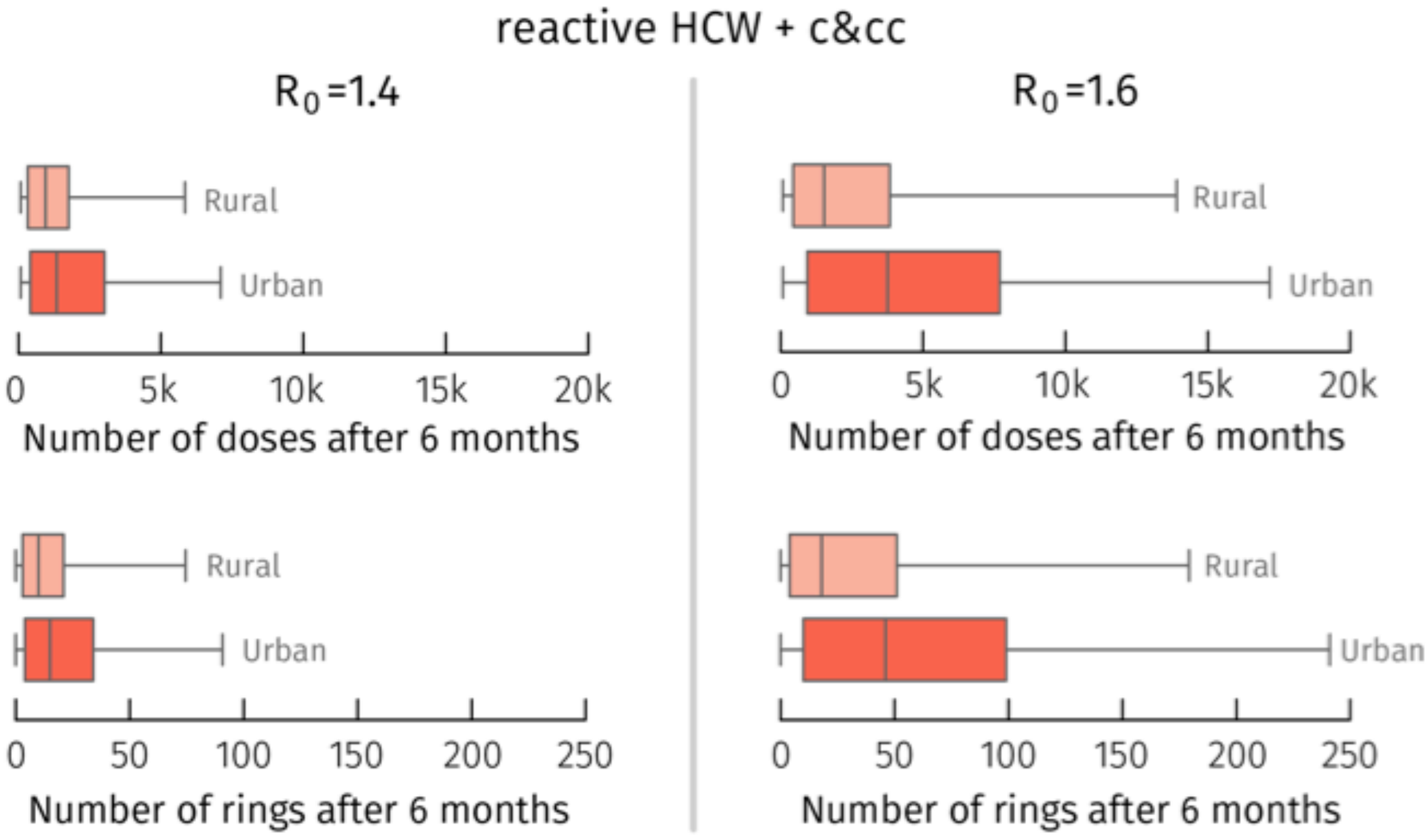
Number of doses/rings after 6 months



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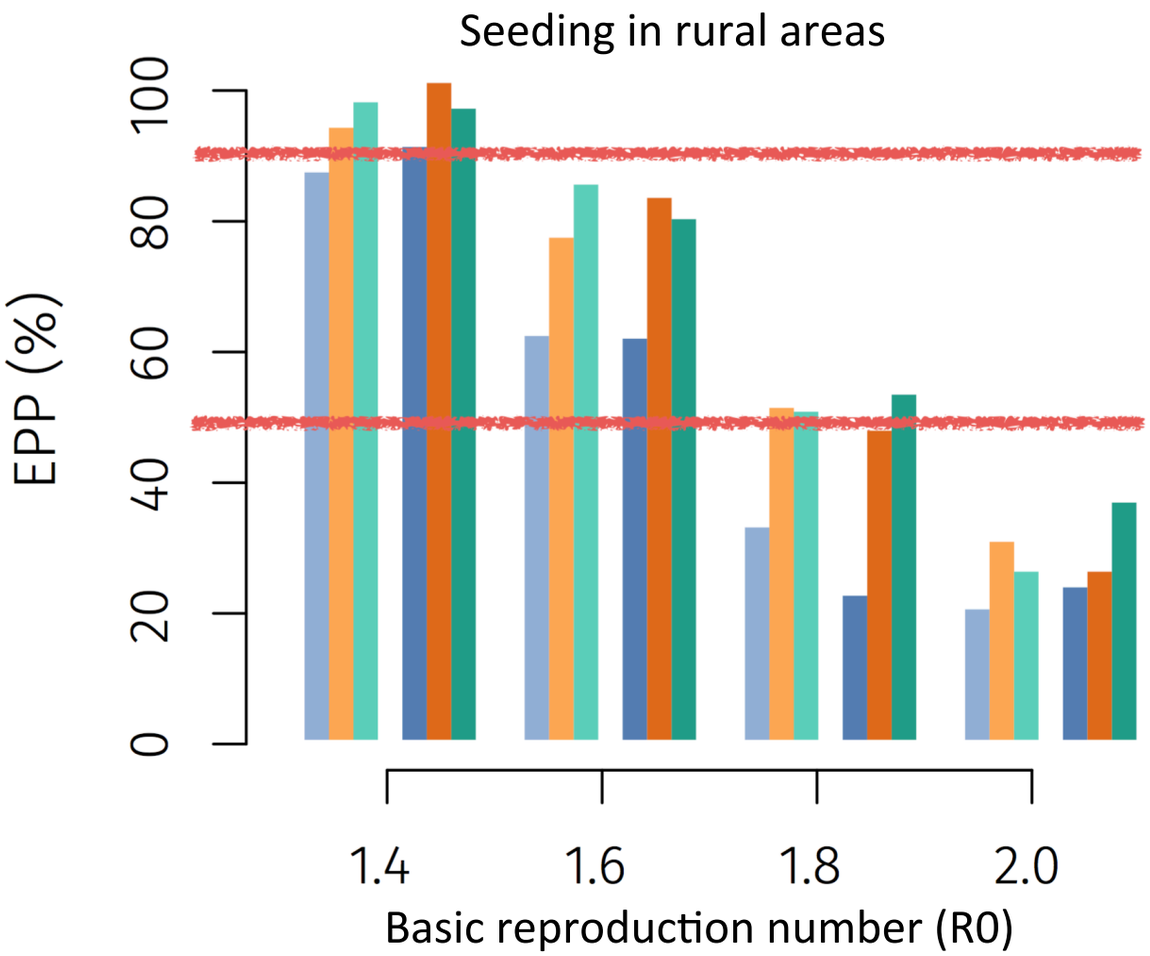
Impact of mass vaccination (village)



a b c — Single dose

a b c — Prime boost

a: mass vaccination
(village of patients + random component)
b: a + reactive HCWs
c: a + pre-emptive HCWs + reactive FLWs

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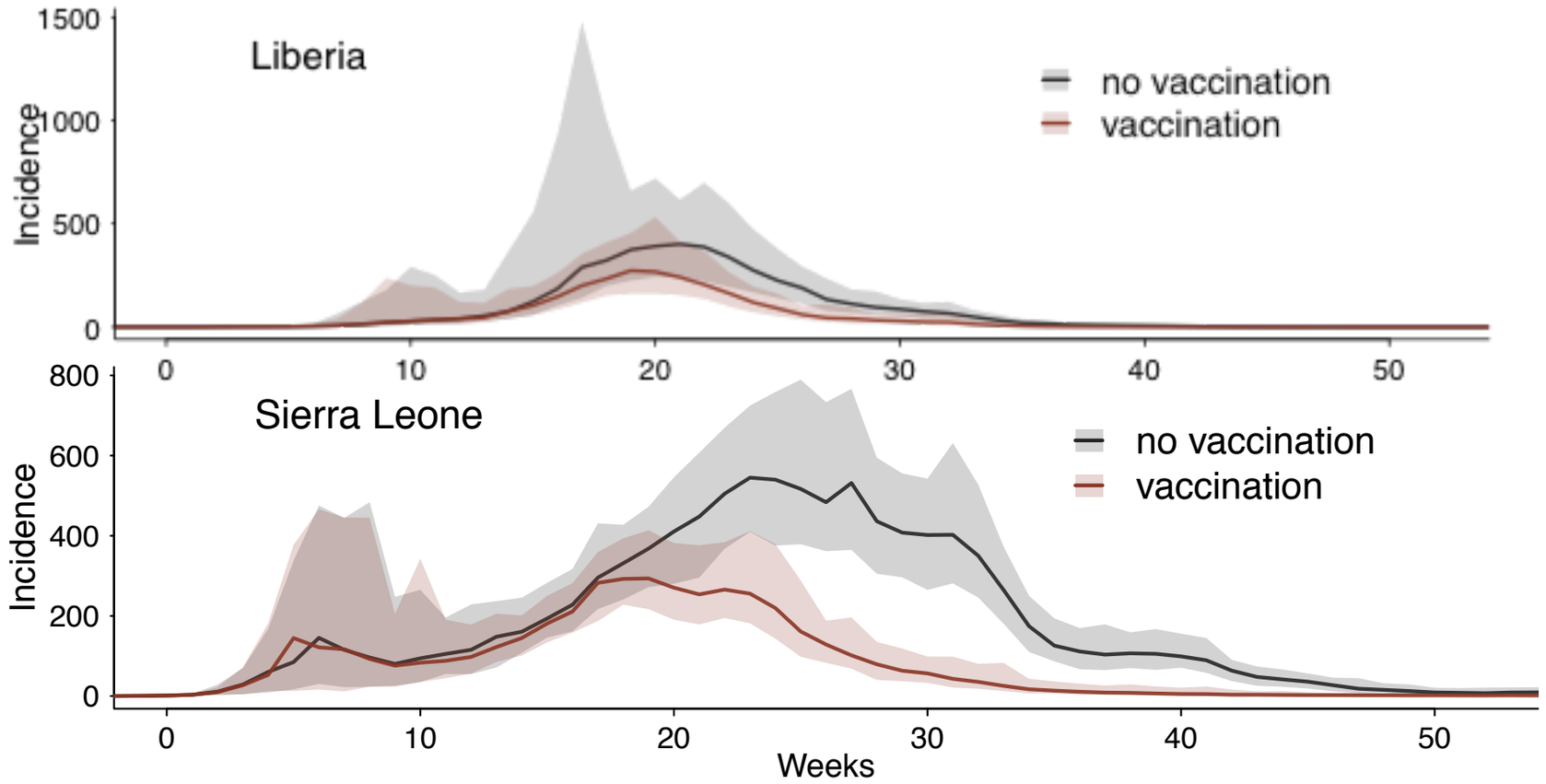
Note: this model is gauged to a baseline with poor or zero initial infrastructure for classical control measures.

Impact of mass vaccination (region)



These campaigns can reduce transmission and shorten the outbreak, but use 1-3 million doses (per country) to decrease the number of cases by approximately 50%

Note: this model reproduces the 2013-2016 EVD outbreak in Liberia and Sierra-Leone and accounts for classical control measures that were implemented at that time.