* Conceptual models of immunity

Jonathan Dushoff

BIRS Canmod meeting, Nov 2023

History of this work

- Innovative influenza cross-immunity models by Julia Gog
  - *https://pubmed.ncbi.nlm.nih.gov/11942531/*
- My attempts to understand conceptual under-pinnings
- Michael (WZ) Li (PHAC) asking practical questions that made me share my ideas
- Daniel (Sang Woo) Park took the lead in making this a real project
  - With help from Jess Metcalf and Bryan Grenfell
- *https://www.medrxiv.org/content/10.1101/2023.07.14.23292670*

What do modelers assume about vaccines?

- Leaky model: 80% efficacy means that each individual is 80% protected (20% chance of infection relative to naive individual)
- Polarized model: 80% efficacy means that 80% of individuals are completely protected (20% are unprotected)

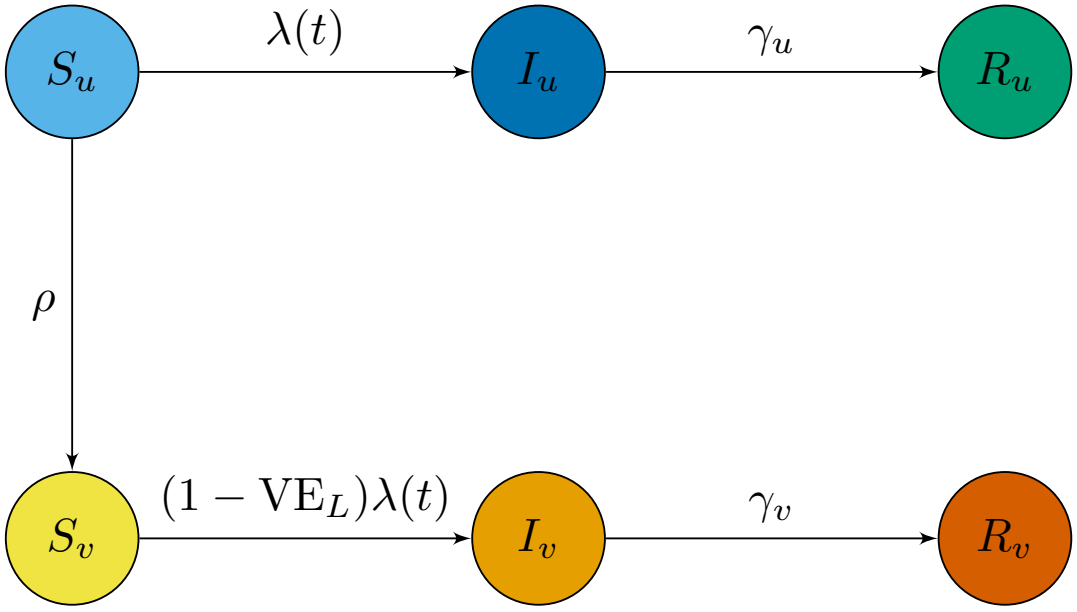
What does it mean to be protected?

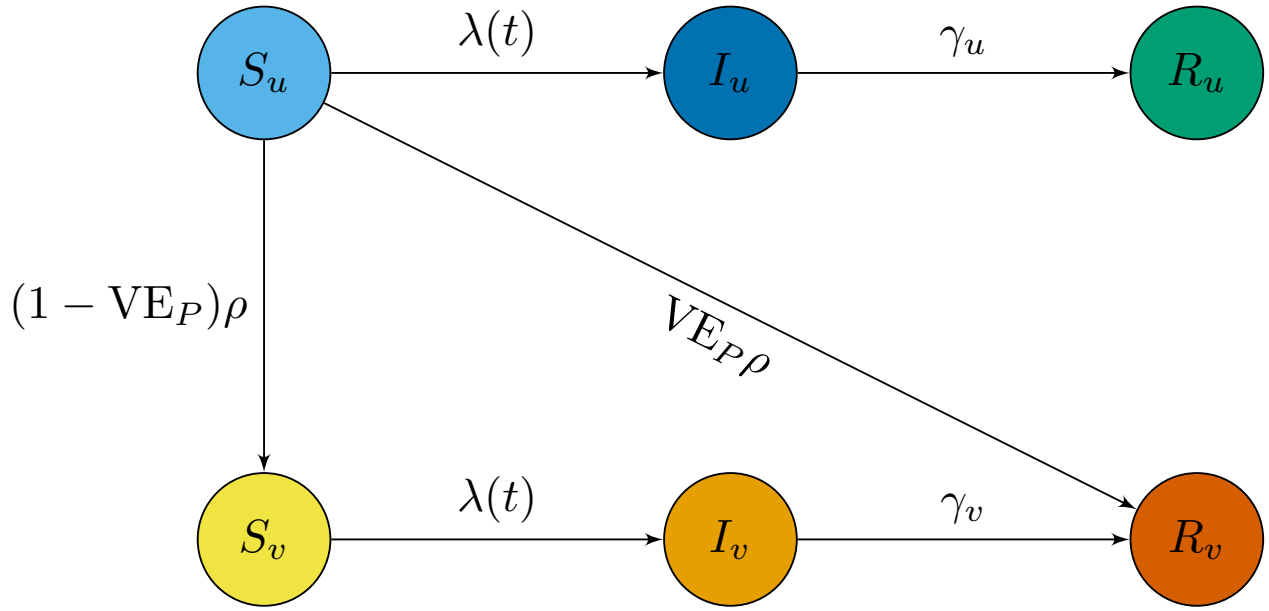
- Against death?
- Severe outcomes?
- Transmission?
- Measurable infection?
- Immune response?

How do we model immunity?

- History-based
  - What exposures has an individual had?
  - Maps naturally to leaky immunity (vaxxed individuals are all the same)
- Status-based
  - What is an individual immune to?
  - Maps naturally to polarized immunity

Modeling immunity

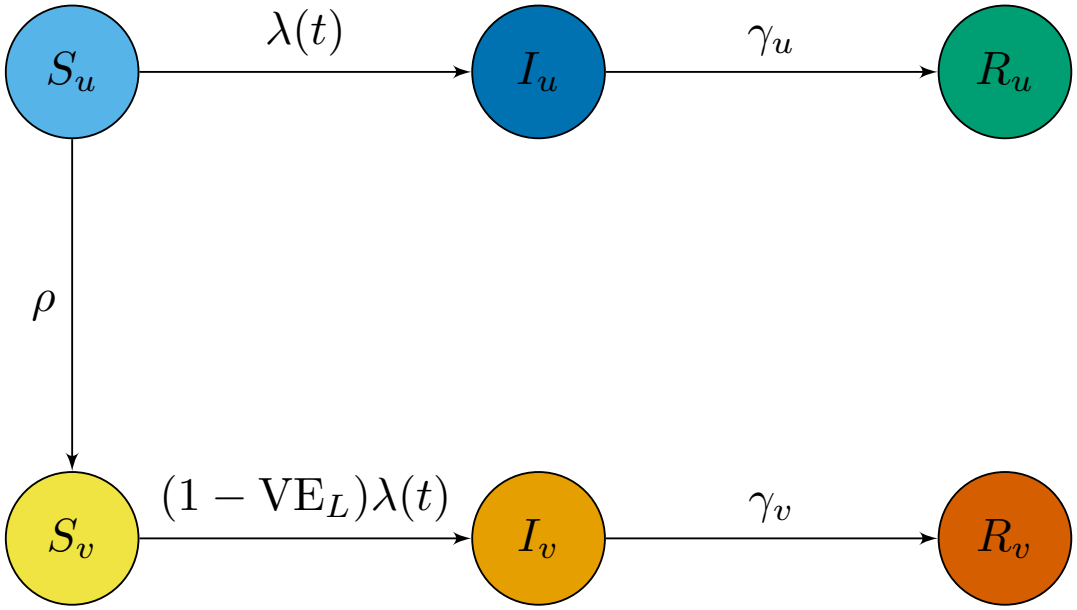


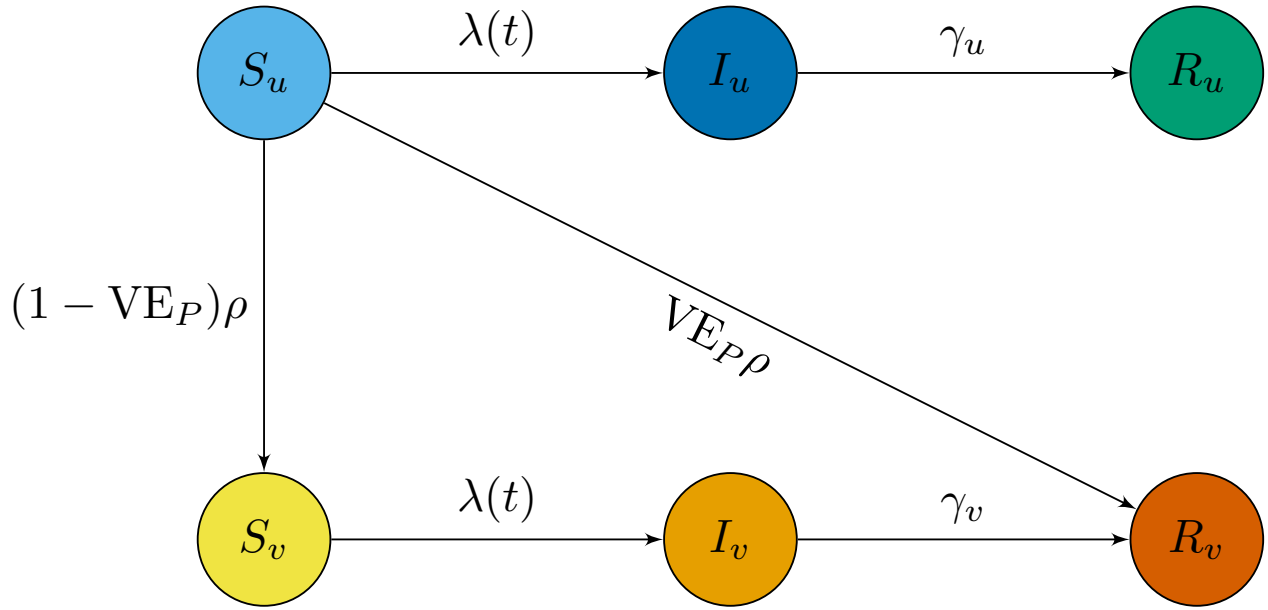


Limitations

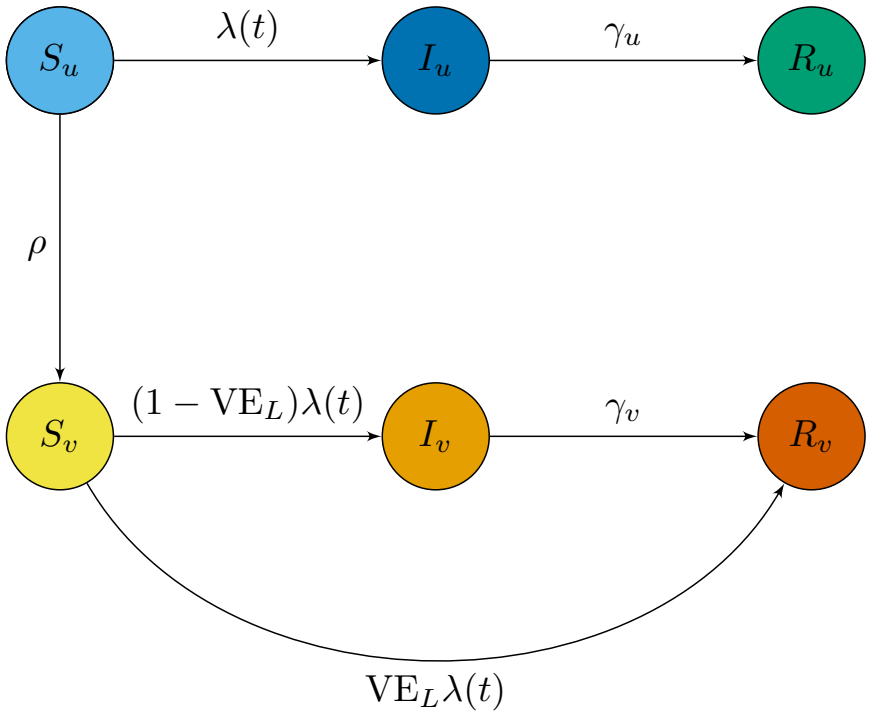
- Polarized approach assumes that a substantial proportion of the population is completely unprotected
  - Unrealistic
  - But how intrinsic is this assumption?
- Leaky approach ignores failed challenges
  - These are challenges that would counter-factually infect with protection
  - But I could resist one today and succumb next week

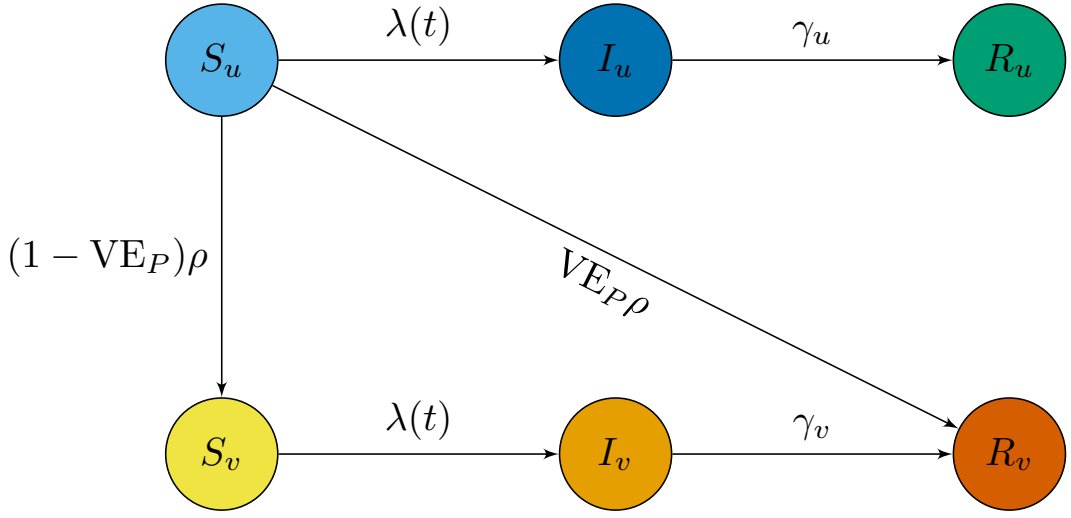
Leaky v. polarized



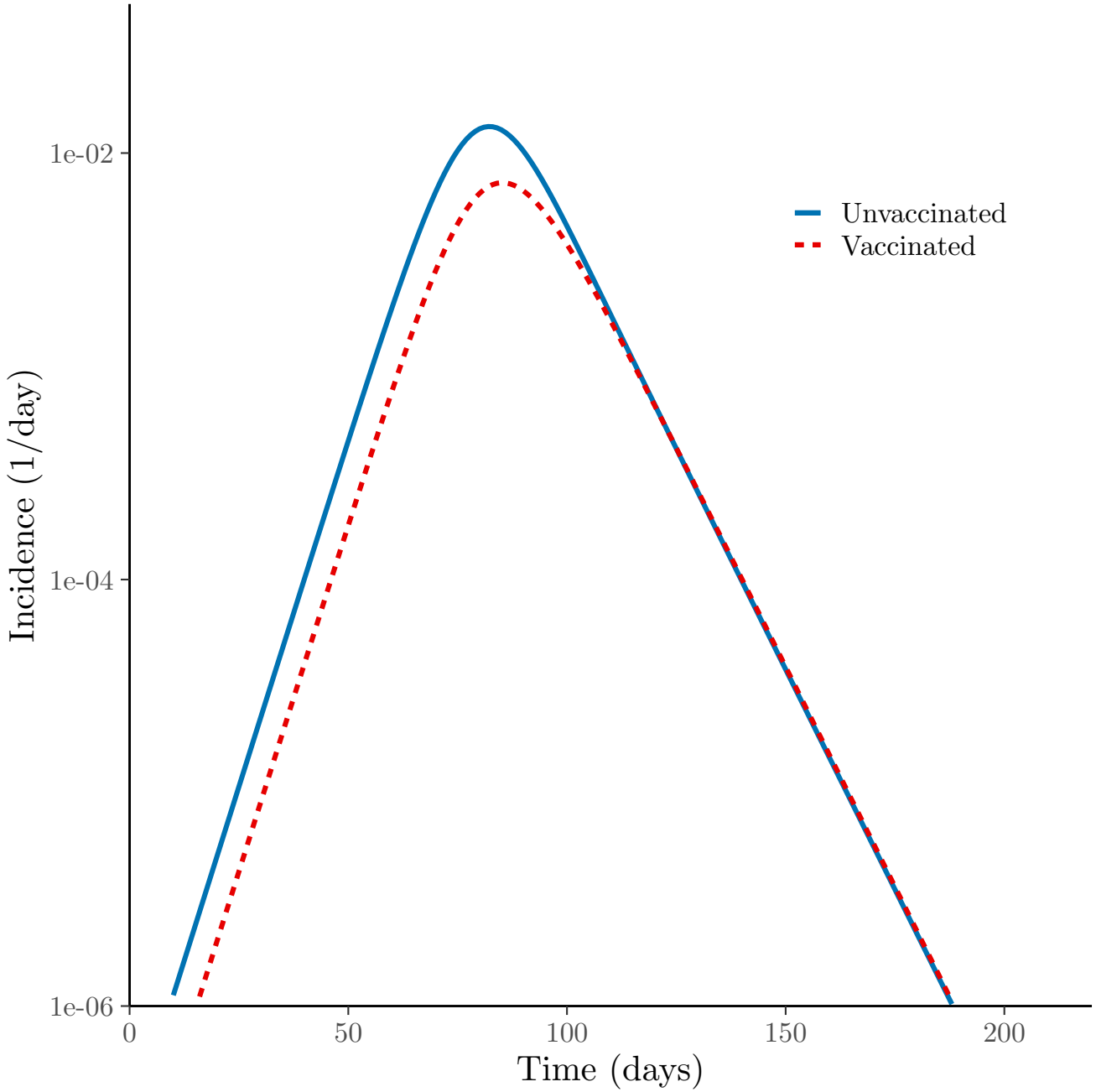


Leaky with boosting v. polarized

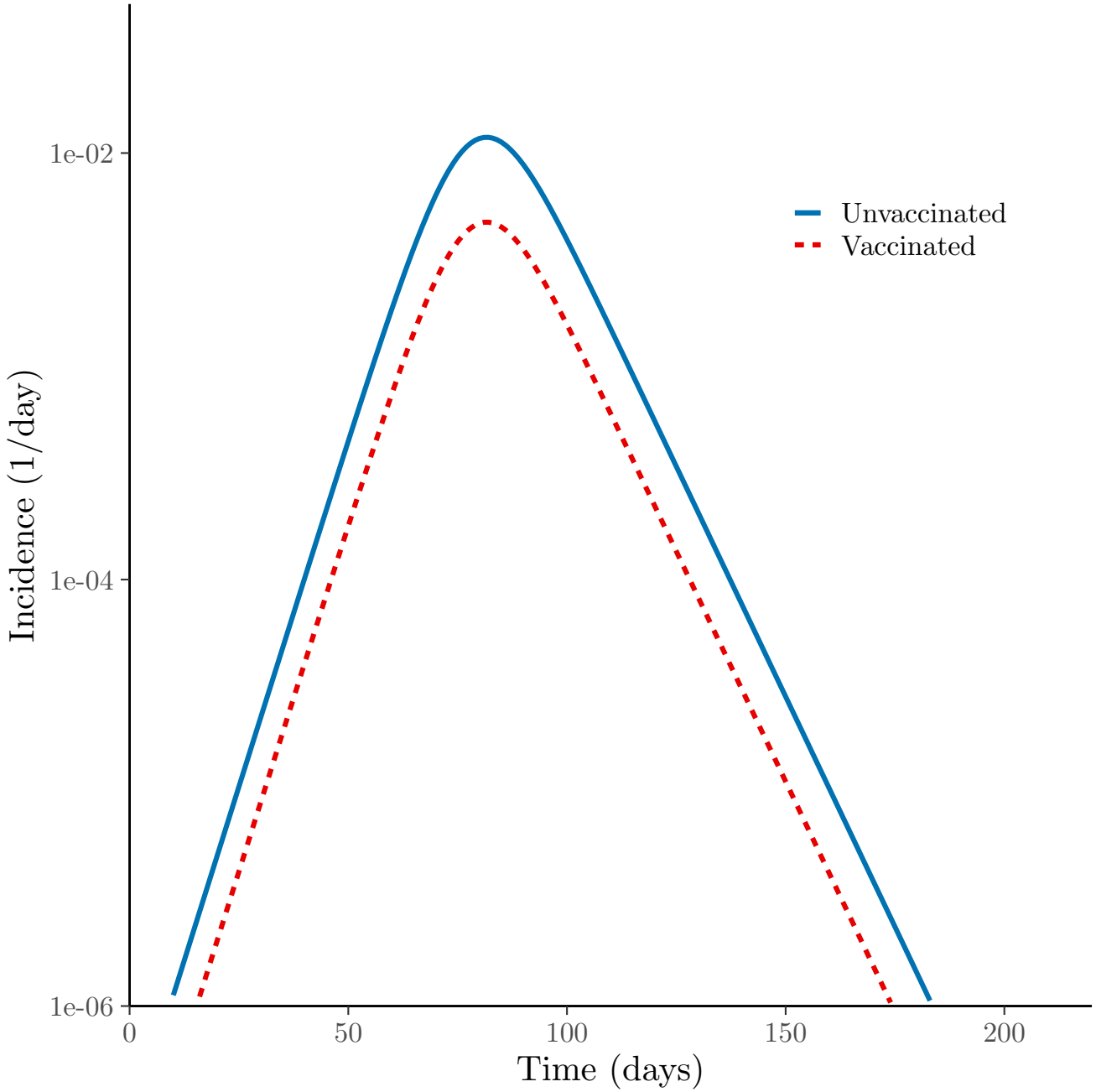




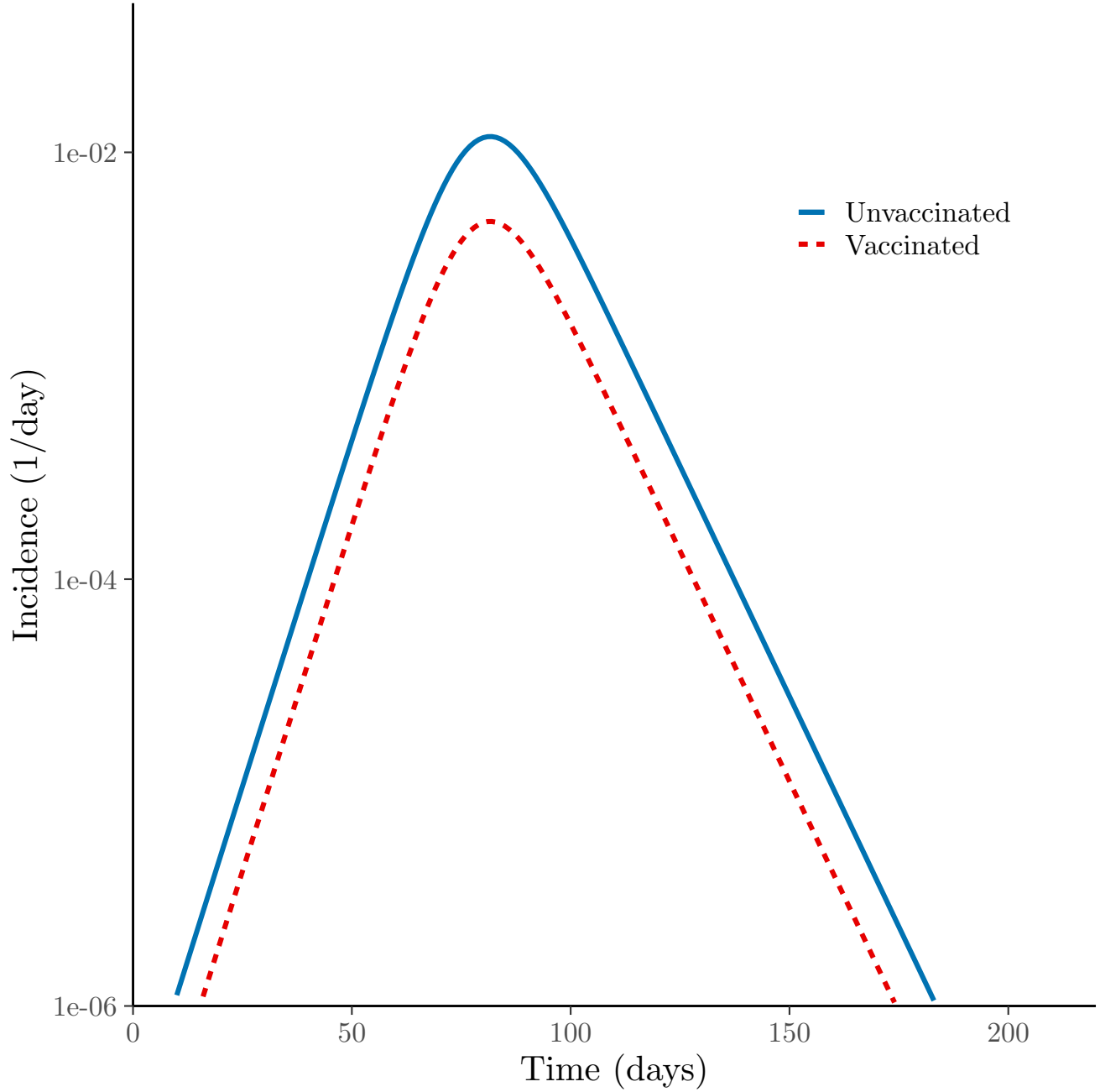
Leaky vaccine

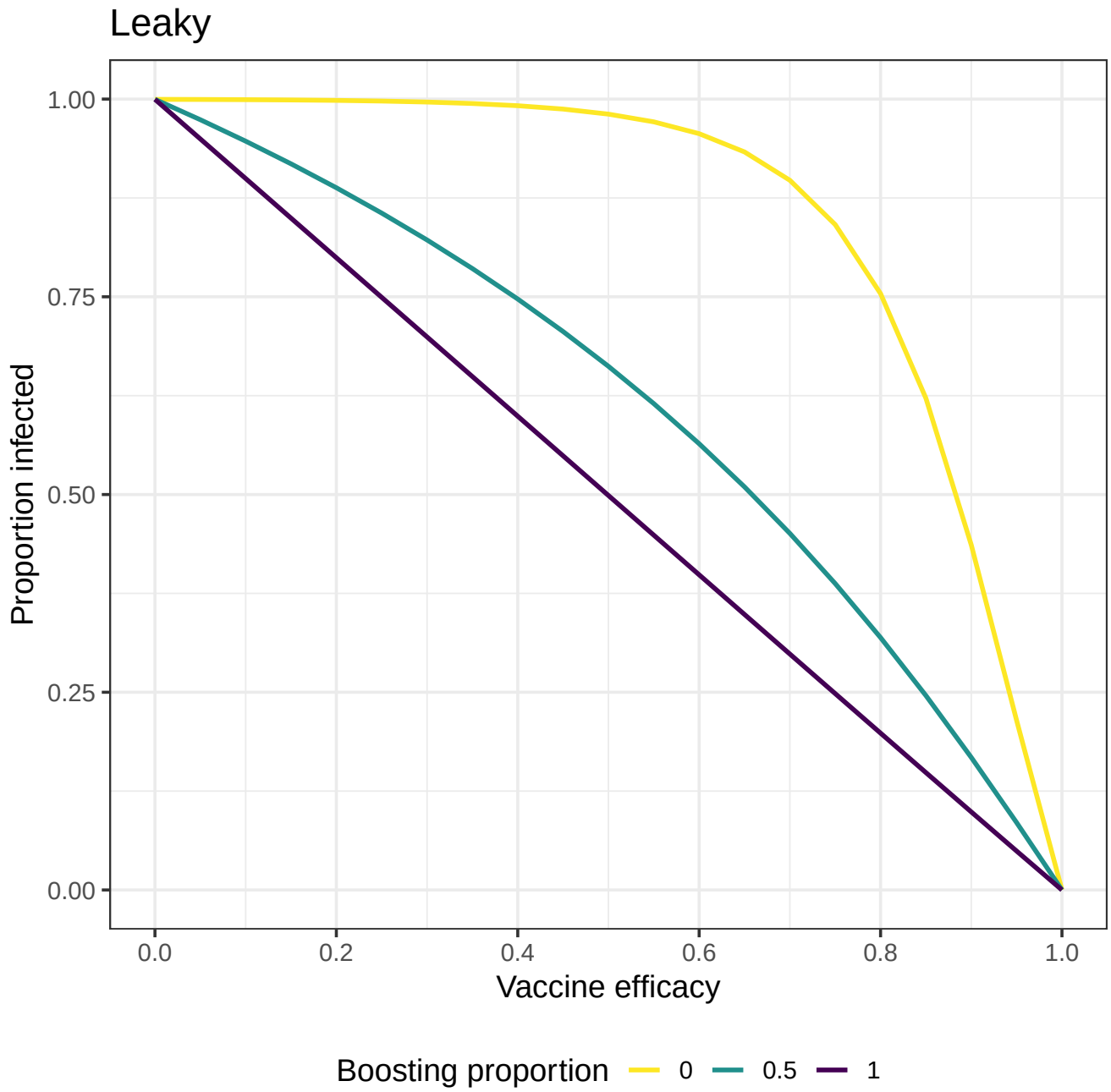


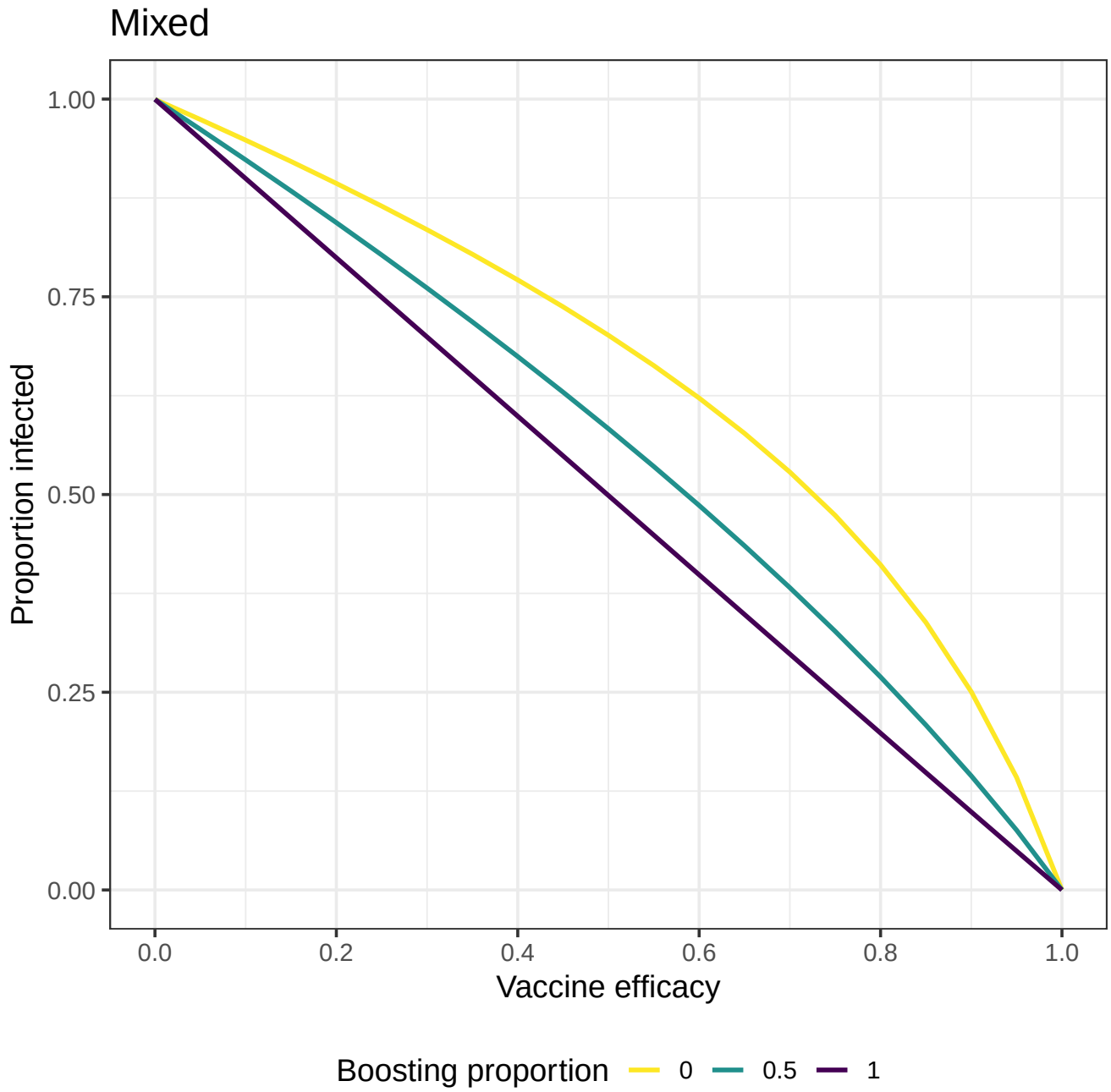
Polarized vaccine

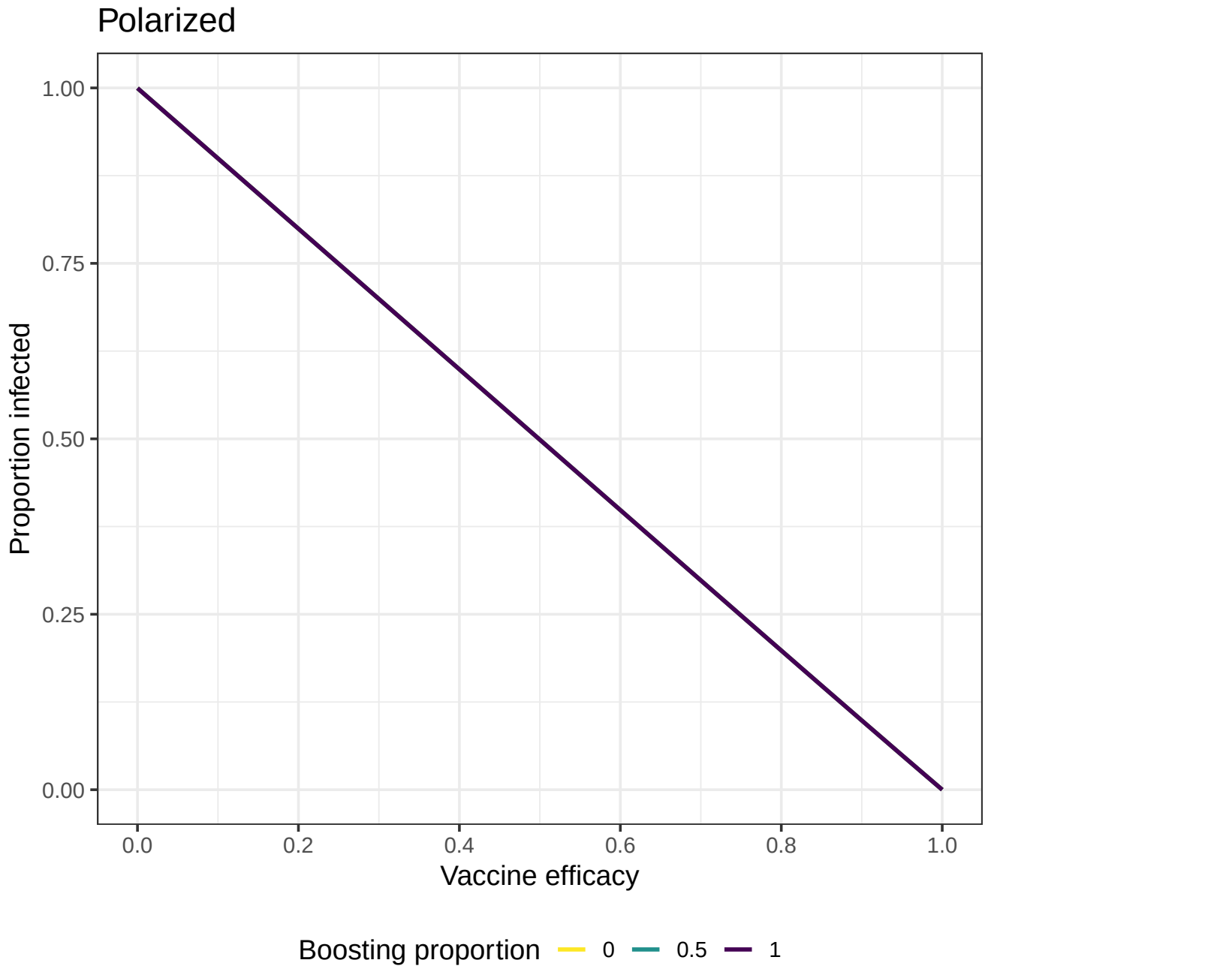


Leaky vaccine with boosting




Leaky
1.00
0.75
0.50
0.25
0.00
Proportion infected
0.0
0.2
0.4
0.6
0.8
1.0
Vaccine efficacy
Boosting proportion
0
0.5
1

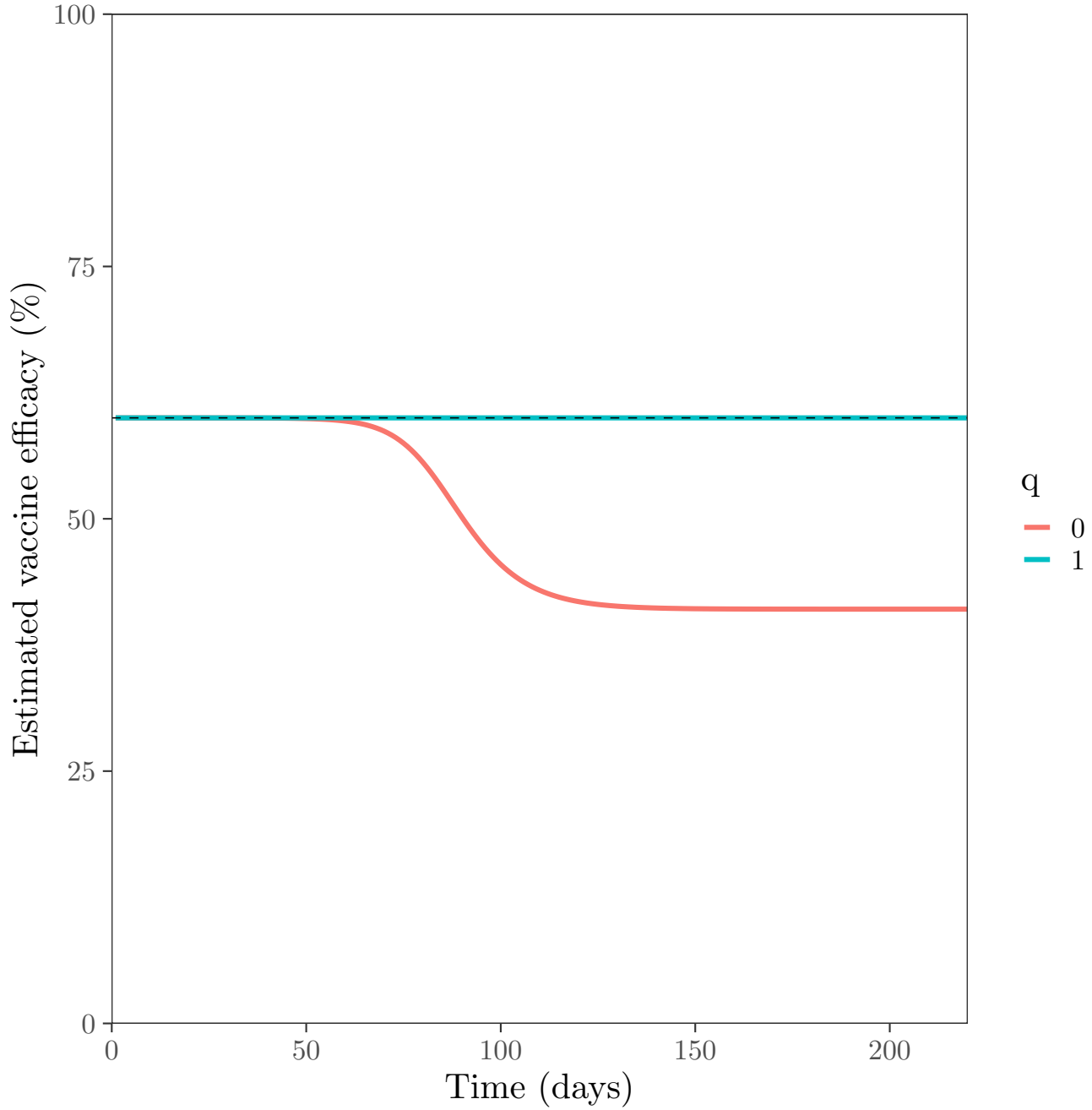

Mixed
1.00
0.75
0.50
0.25
0.00
Proportion infected
0.0
0.2
0.4
0.6
0.8
1.0
Vaccine efficacy
Boosting proportion
0
0.5
1


Polarized
1.00
0.75
0.50
0.25
0.00
Proportion infected
0.0
0.2
0.4
0.6
0.8
1.0
Vaccine efficacy
Boosting proportion
0
0.5
1

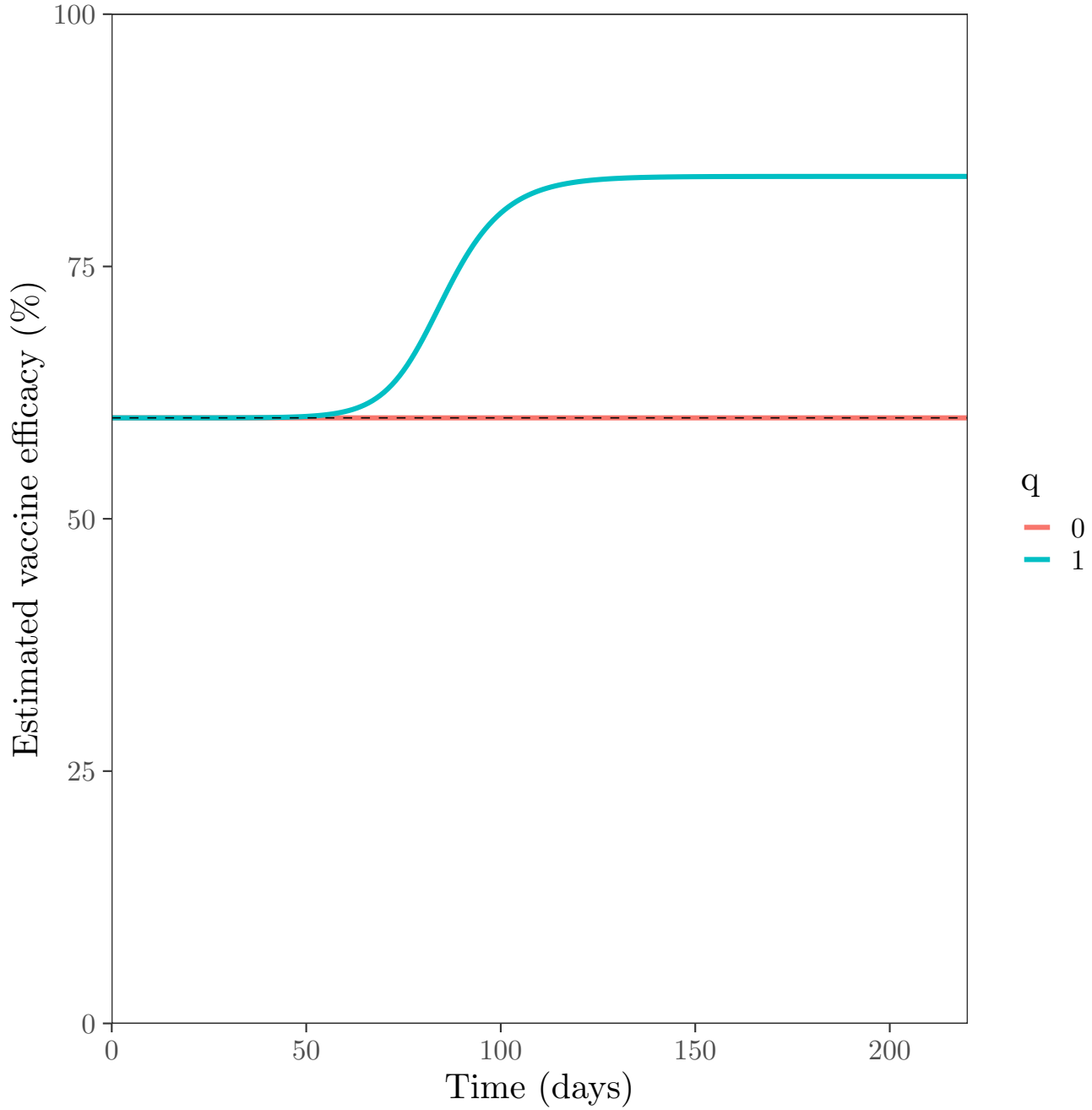
Vaccine effectiveness

- Efficacy: protection with a controlled exposure
- Effectiveness: protection in a population
- Project effectiveness under different assumptions
  - Cumulative incidence
  - Instantaneous hazard

Incidence-based effectiveness



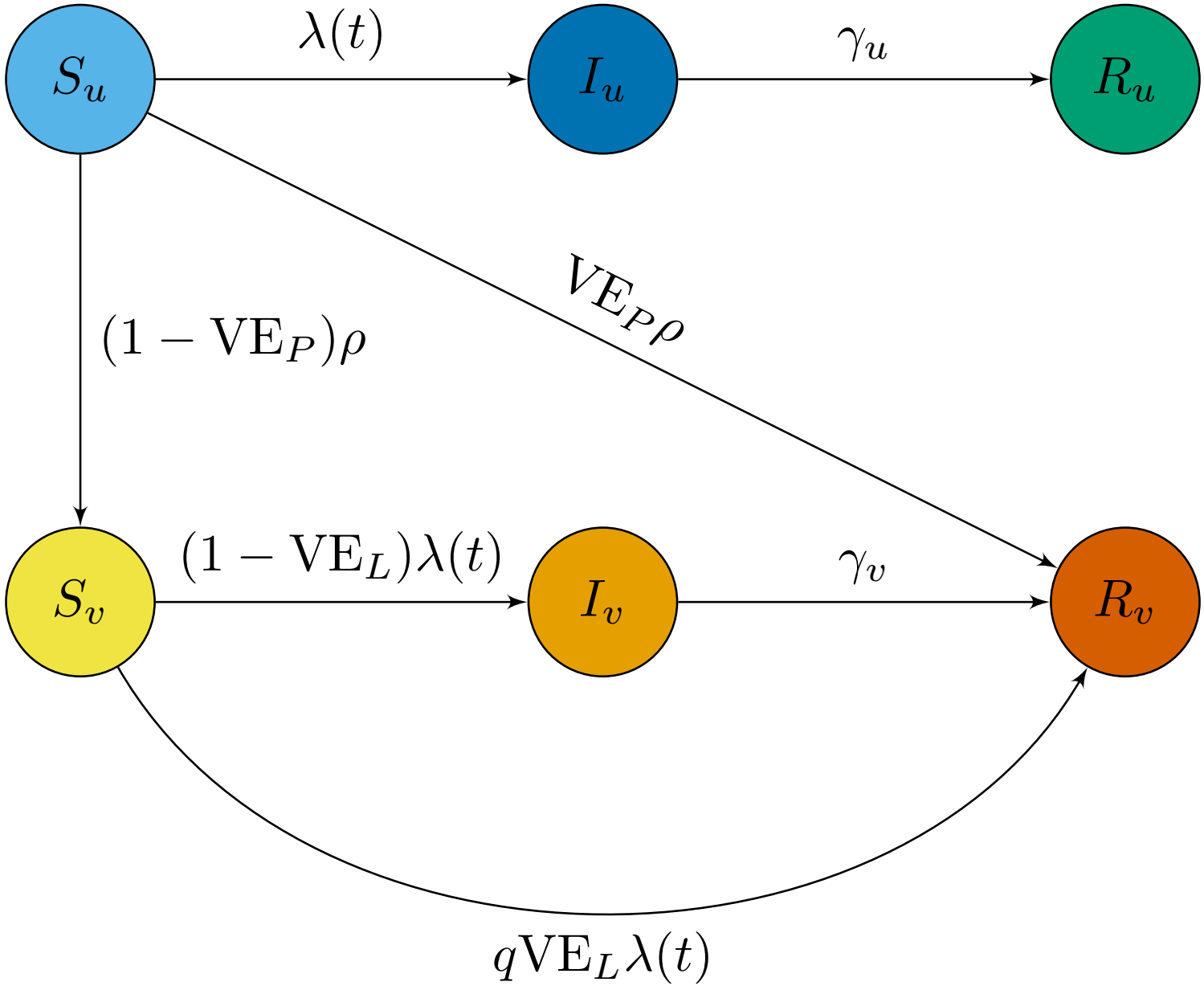
Hazard-based effectiveness



Questions going forward

- Vaccine vs infection-driven immunity
- Protection against what?
- Immune waning
- A broader view of leakiness

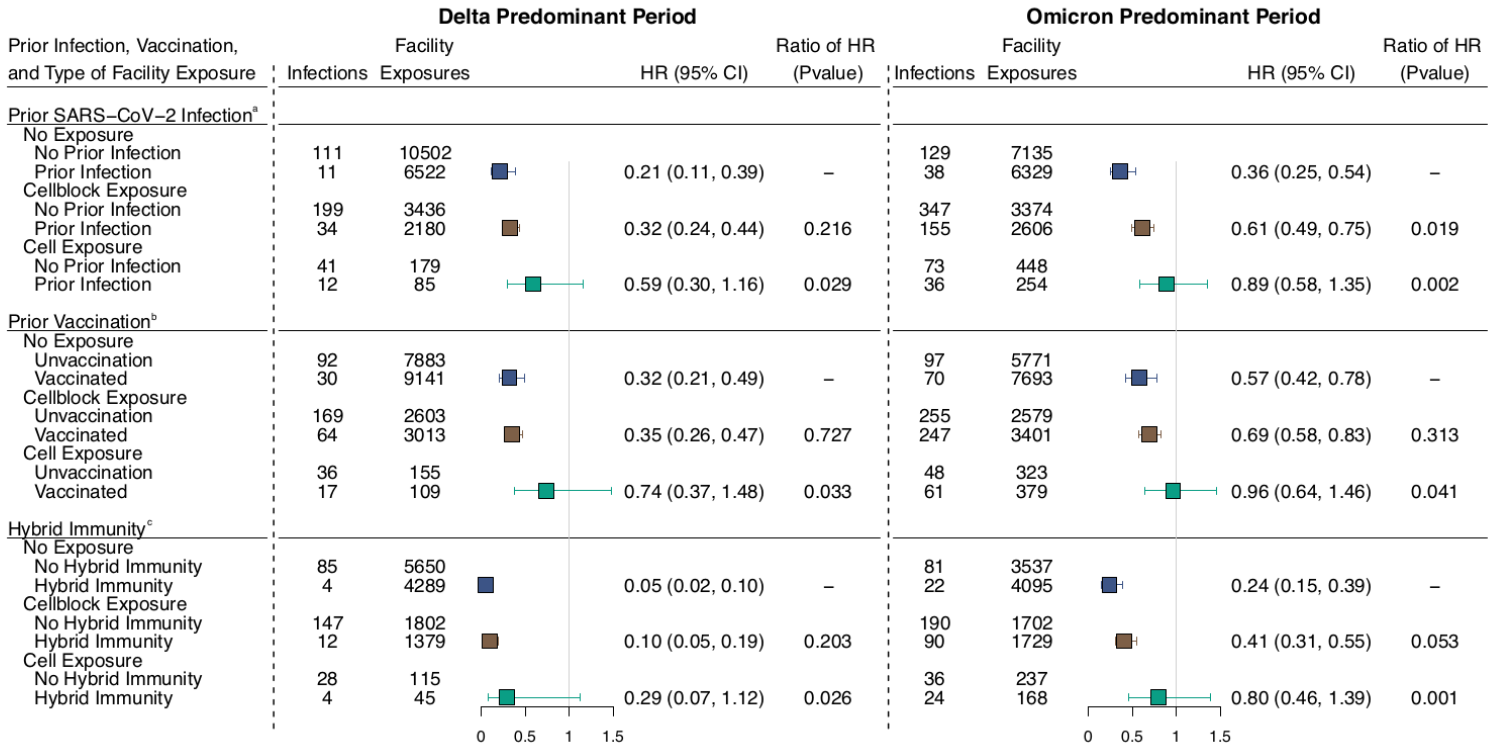
Transmission reduction



Doses and timing

- We can define leakiness as any gap between efficacy and effectiveness
  - We can imagine different standard challenges for efficacy
- Should we be thinking only about number of challenges?
  - What about dose-dependence?
  - Can these be cleanly disentangled?

Connecticut correctional study



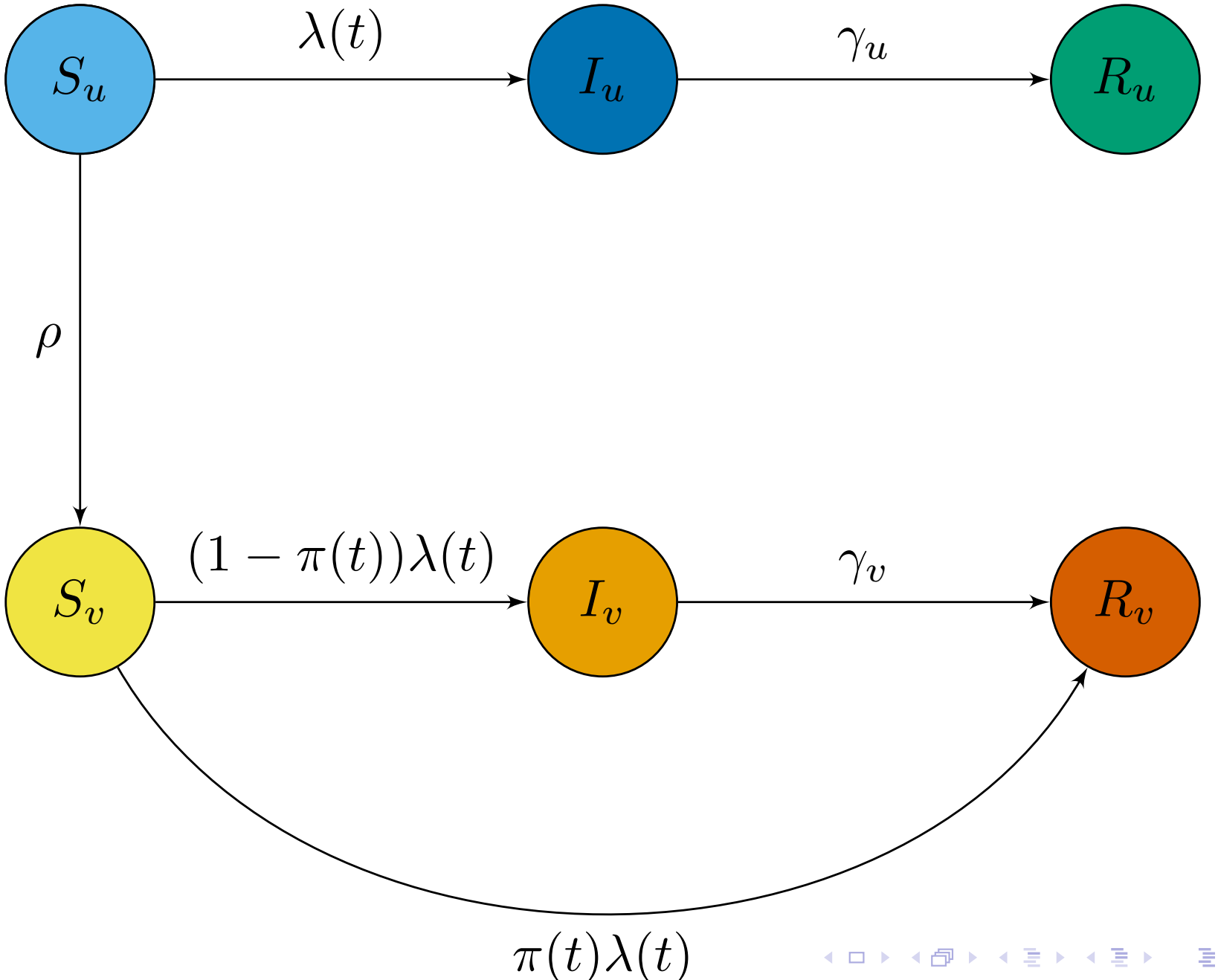
Lind et al., Nat Commun, 2023.

https://doi.org/10.1038/s41467-023-40750-8

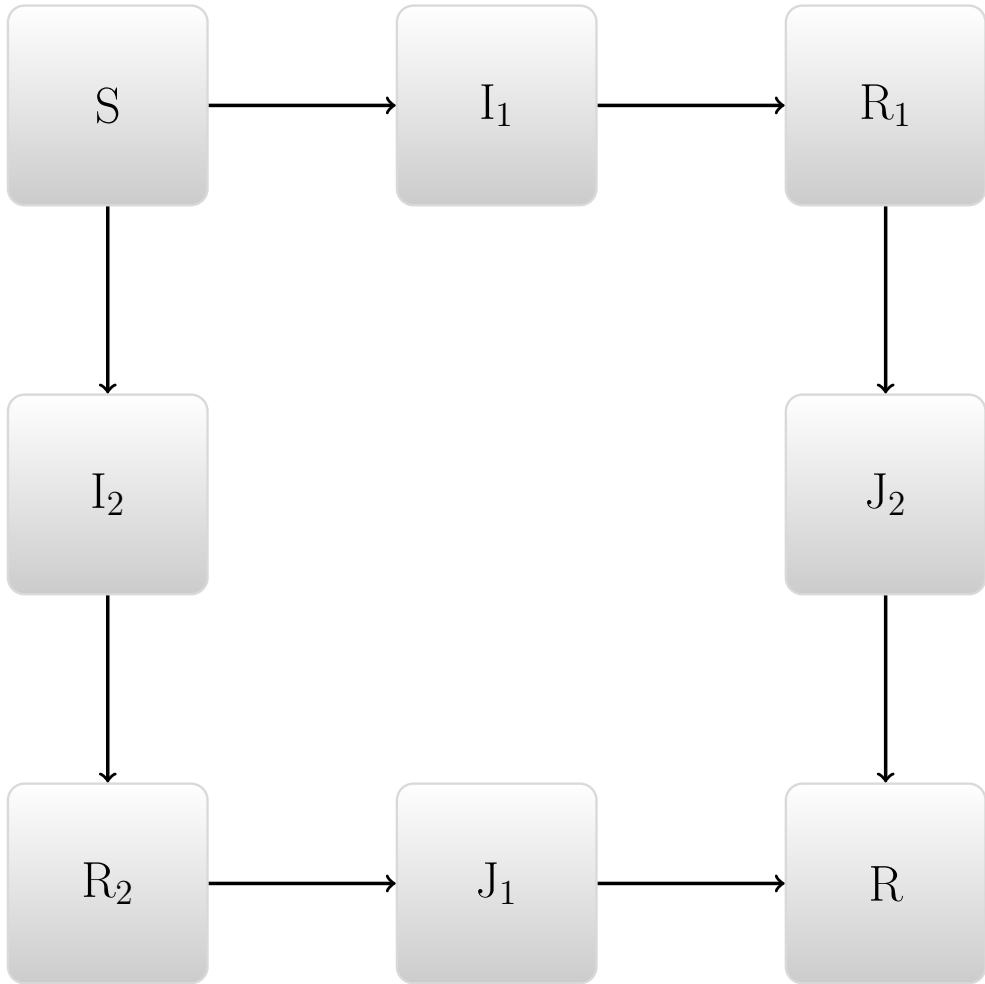
Time scales of challenge

- Challenges a week apart are likely antagonistic
  - Immune boosting, polarized-like dynamics
- Challenges an hour apart are likely *synergistic*
  - Potentially overwhelming, leaky-like dynamics
- These are questions for Jane!

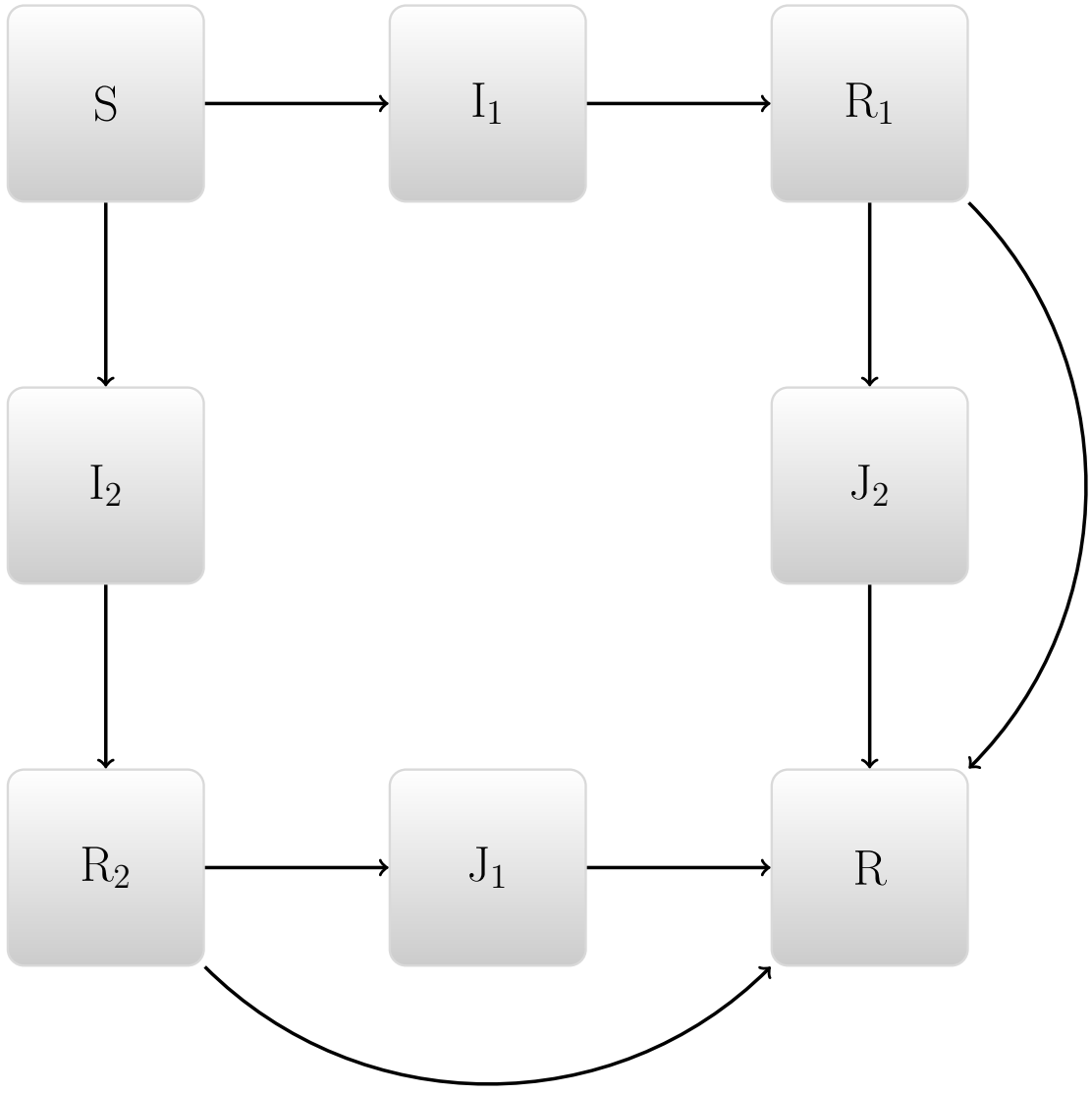
Dose dependence



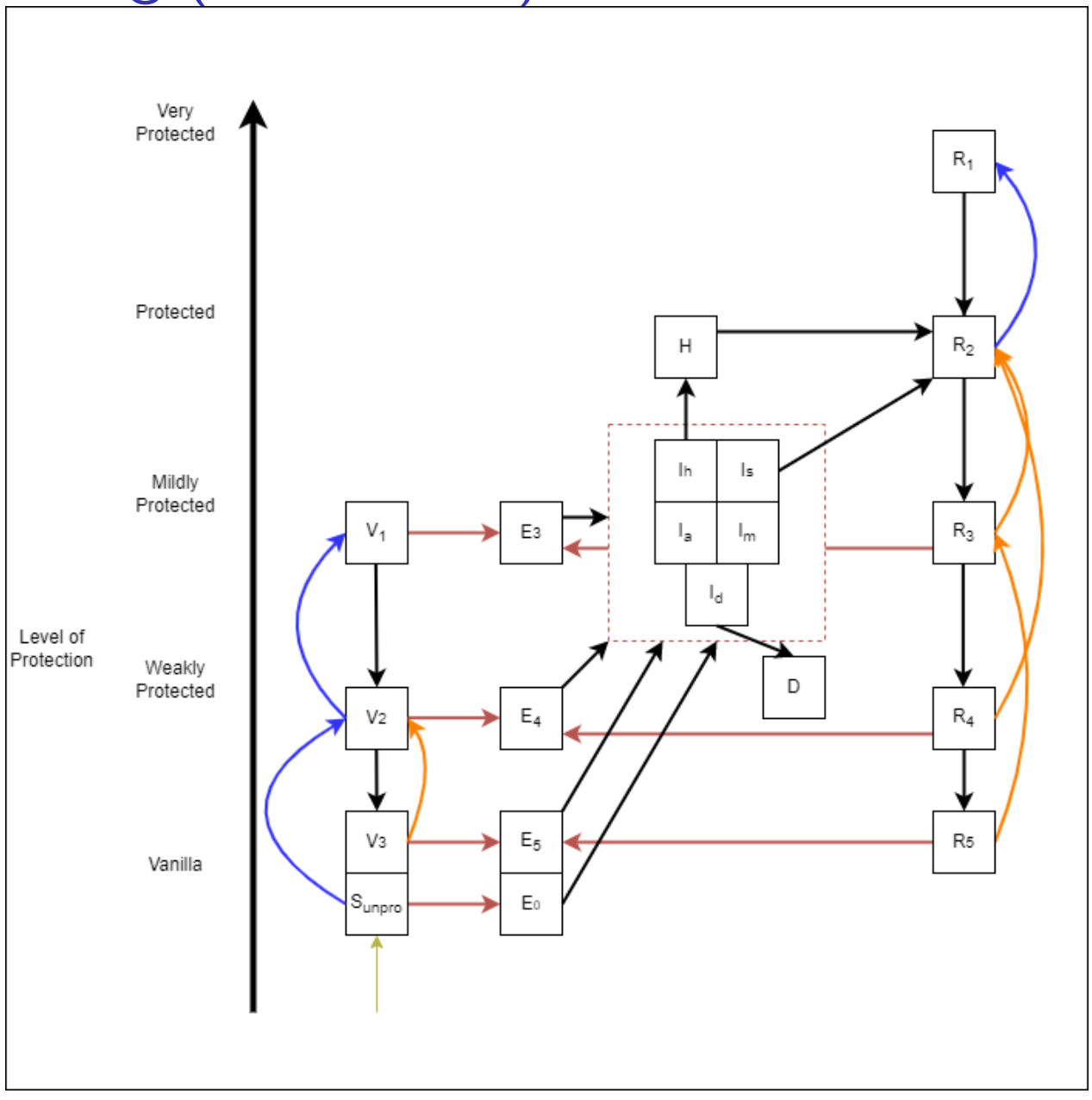
Interacting strains



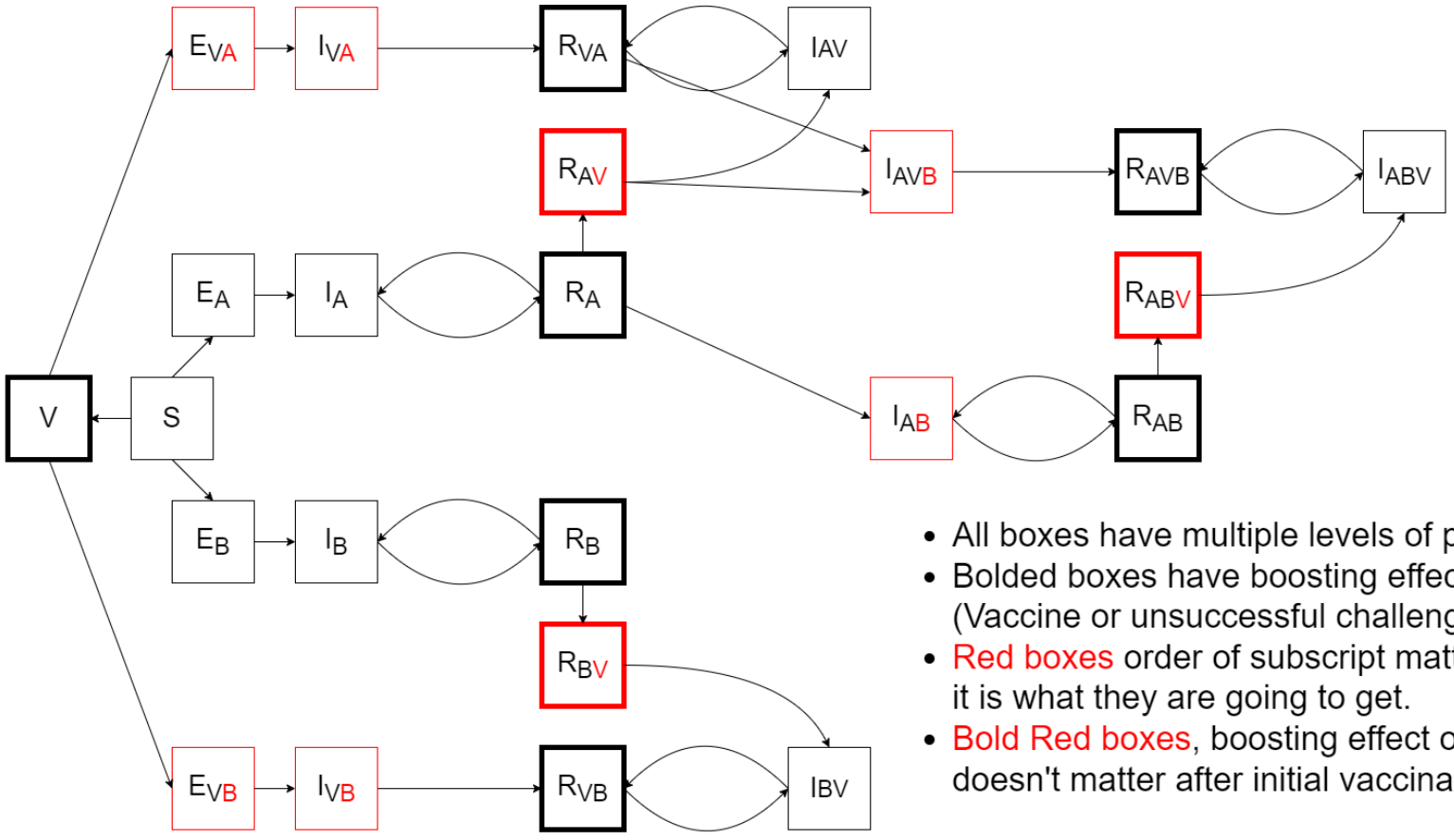
Interacting strains



Immune waning (whiteboard)



Cross immunity (whiteboard)



- All boxes have multiple levels of protection
- Bolded boxes have boosting effect (Vaccine or unsuccessful challenge)
- Red boxes order of subscript matters and it is what they are going to get.
- Bold Red boxes, boosting effect order doesn't matter after initial vaccination.

Michael WZ Li, PHAC

Thanks

- Organizers and audience
- Daniel, Mike and other collaborators
- PHAC, CIHR