

# Conceptual models of immunity

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# 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)

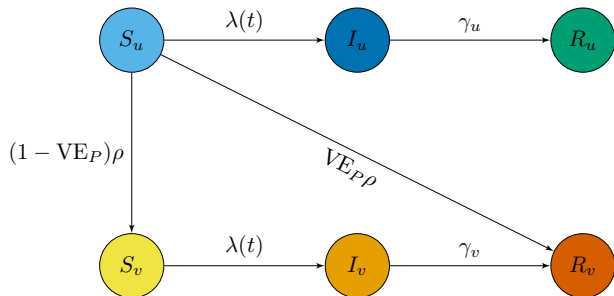
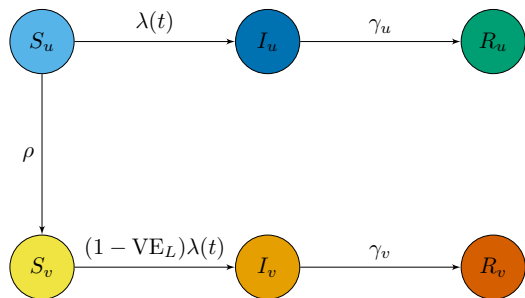
# What does it mean to be protected?

- ▶ 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

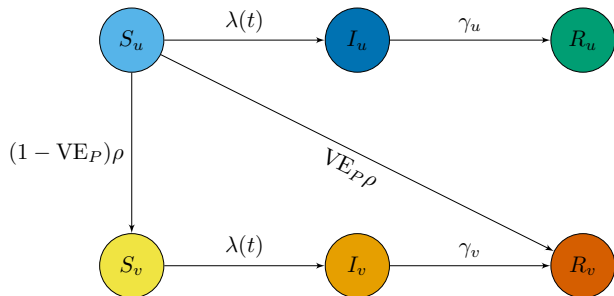
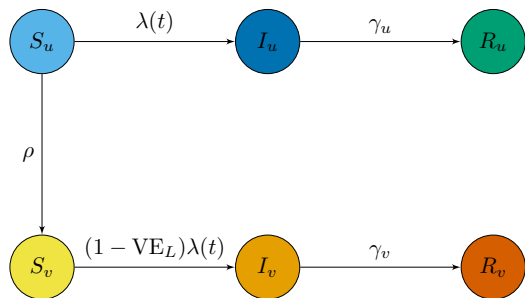
## Modeling immunity



# Limitations

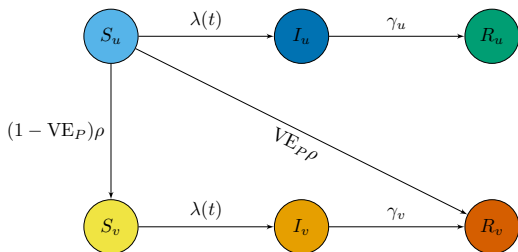
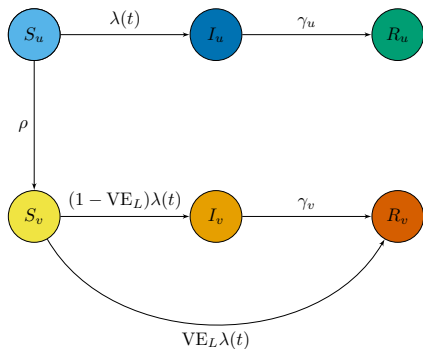
- ▶ Polarized approach assumes that a substantial proportion of the population is completely unprotected
  - ▶ Unrealistic
  - ▶ But how intrinsic is this assumption?
- ▶ Leaky approach ignores failed challenges
  - ▶ These are challenges that would counter-factually infect with protection
  - ▶ But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

## Leaky v. polarized

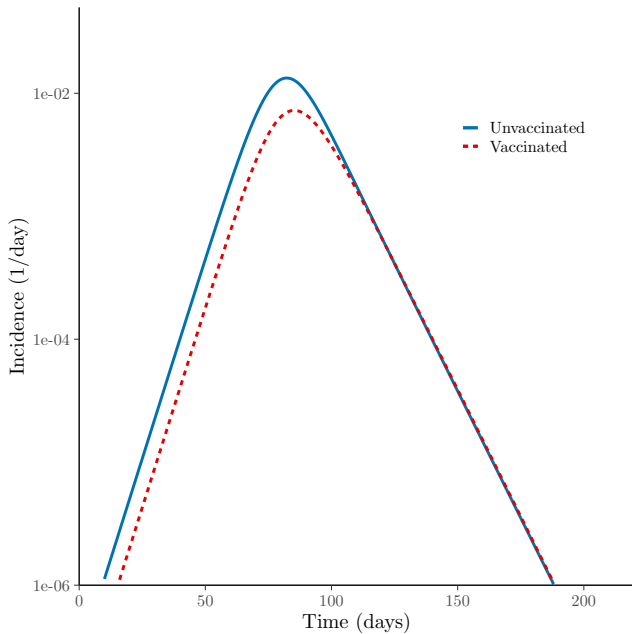




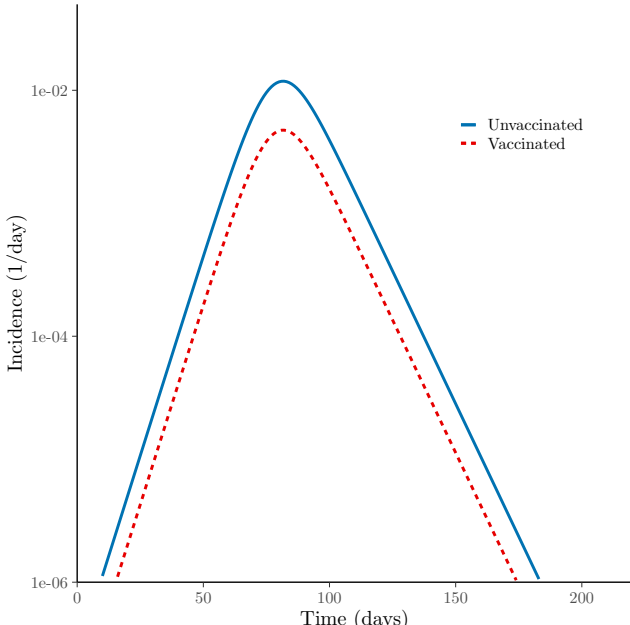
## Leaky with boosting v. polarized



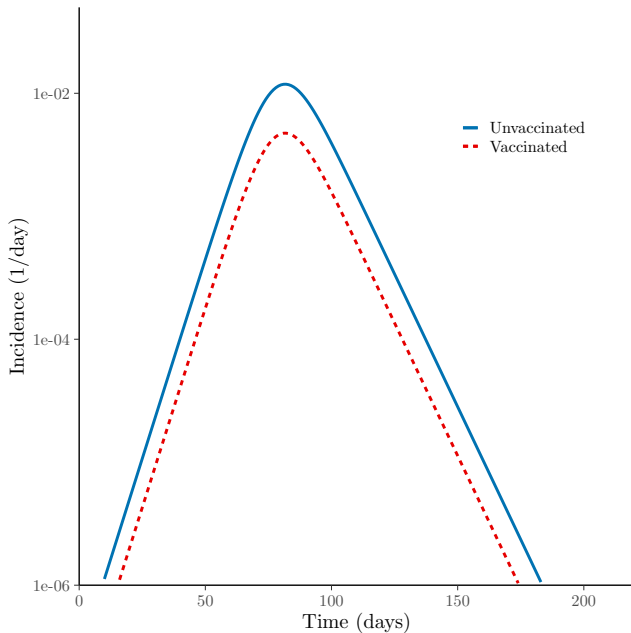
# Leaky vaccine



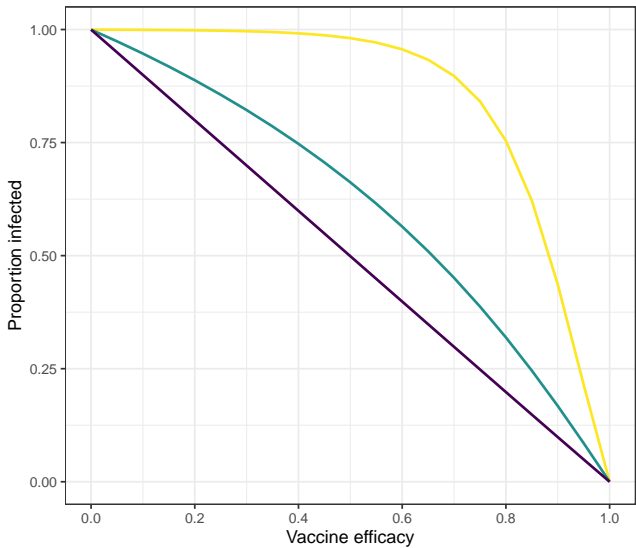
# Polarized vaccine



# Leaky vaccine with boosting

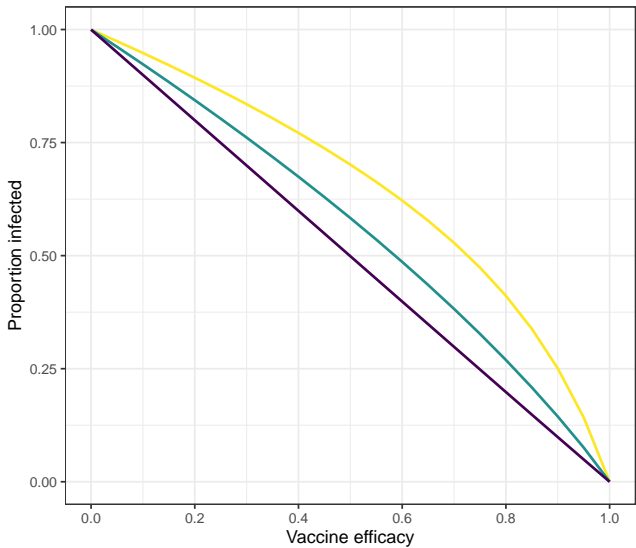


# Leaky



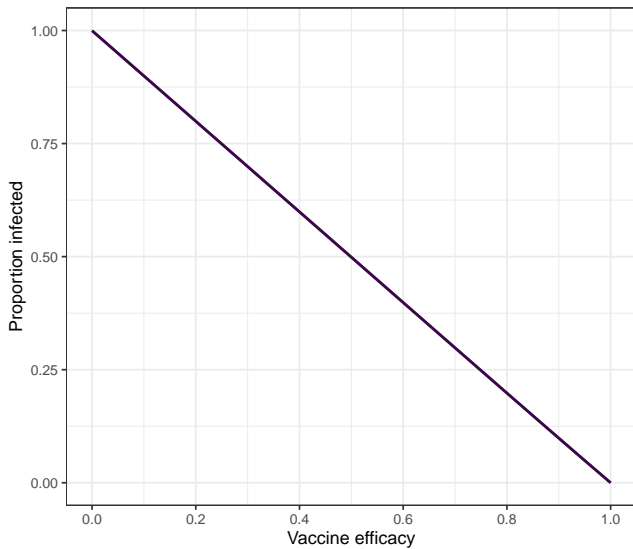
Boosting proportion — 0 — 0.5 — 1

# Mixed



Boosting proportion — 0 — 0.5 — 1

## Polarized



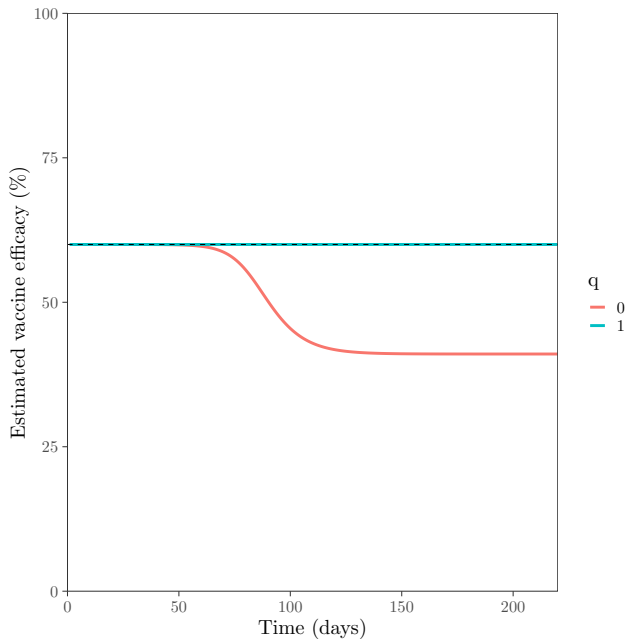
Boosting proportion 0 0.5 1

# Vaccine effectiveness

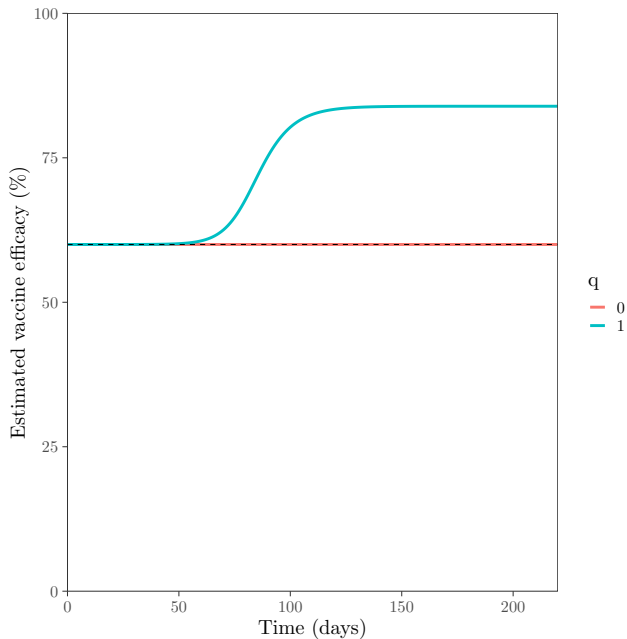
- ▶ Efficacy: protection with a controlled exposure
- ▶ Effectiveness: protection in a population
- ▶ Project effectiveness under different assumptions
  - ▶ Cumulative incidence
  - ▶ Instantaneous hazard



# Incidence-based effectiveness



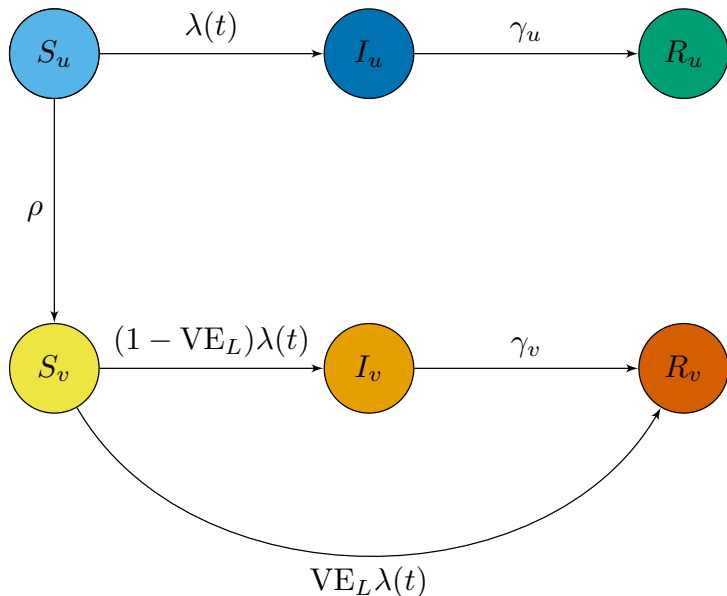
# Hazard-based effectiveness



## Questions going forward

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

## Transmission reduction



# Leakiness

- ▶ 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

Prior Infection, Vaccination, and Type of Facility Exposure	Delta Predominant Period				Omicron Predominant Period				
	Facility		Ratio of HR		Facility		Ratio of HR		
	Infections	Exposures	HR (95% CI)	(Pvalue)	Infections	Exposures	HR (95% CI)	(Pvalue)	
<b>Prior SARS-CoV-2 Infection<sup>a</sup></b>									
No Exposure									
Prior Infection	111	10502		0.21 (0.11, 0.39)	-	129	7135		0.36 (0.25, 0.54)
Cellblock Exposure	11	6522		0.32 (0.24, 0.44)	0.216	38	6329		0.61 (0.49, 0.75)
No Prior Infection	199	3436		0.59 (0.30, 1.16)	0.029	347	3374		0.89 (0.58, 1.35)
Prior Infection	34	2180		0.29 (0.07, 1.12)	0.026	155	2606		0.80 (0.46, 1.39)
Cell Exposure	41	179		0.05 (0.02, 0.10)	-	73	448		0.24 (0.15, 0.39)
No Prior Infection	12	85		0.10 (0.05, 0.19)	0.203	36	254		0.41 (0.31, 0.55)
Prior Infection									
<b>Prior Vaccination<sup>b</sup></b>									
No Exposure									
Unvaccination	92	7883		0.05 (0.02, 0.10)	-	97	5771		0.24 (0.15, 0.39)
Vaccinated	30	9141		0.10 (0.05, 0.19)	0.203	70	7693		0.41 (0.31, 0.55)
Cellblock Exposure	169	2603		0.29 (0.07, 1.12)	0.026	255	2579		0.80 (0.46, 1.39)
Unvaccination	64	3013		0.05 (0.02, 0.10)	-	247	3401		0.24 (0.15, 0.39)
Vaccinated	36	155		0.10 (0.05, 0.19)	0.203	48	323		0.41 (0.31, 0.55)
Cell Exposure	17	109		0.29 (0.07, 1.12)	0.026	61	379		0.80 (0.46, 1.39)
Unvaccination									
Vaccinated									
<b>Hybrid Immunity<sup>c</sup></b>									
No Exposure									
No Hybrid Immunity	85	5650		0.05 (0.02, 0.10)	-	81	3537		0.24 (0.15, 0.39)
Hybrid Immunity	4	4289		0.10 (0.05, 0.19)	0.203	22	4095		0.41 (0.31, 0.55)
Cellblock Exposure	147	1802		0.29 (0.07, 1.12)	0.026	190	1702		0.80 (0.46, 1.39)
No Hybrid Immunity	12	1379		0.05 (0.02, 0.10)	-	90	1729		0.24 (0.15, 0.39)
Hybrid Immunity	28	115		0.10 (0.05, 0.19)	0.203	36	237		0.41 (0.31, 0.55)
Cell Exposure	4	45		0.29 (0.07, 1.12)	0.026	24	168		0.80 (0.46, 1.39)
No Hybrid Immunity									
Hybrid Immunity									

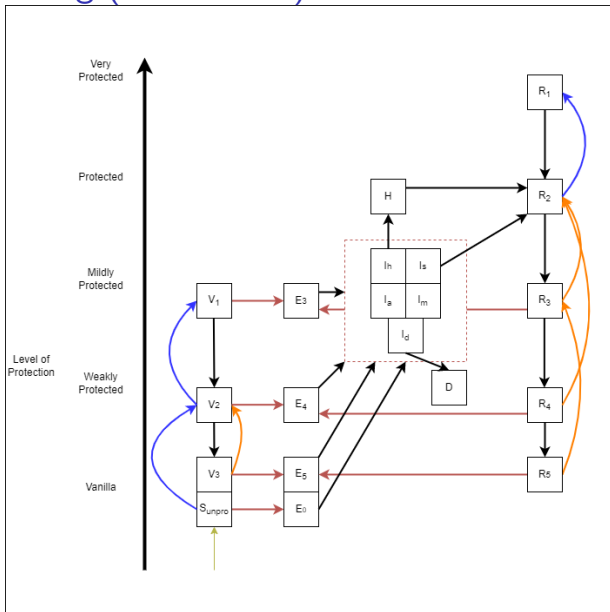
Lind et al., Nat Commun, 2023.

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

# Time scales of challenge

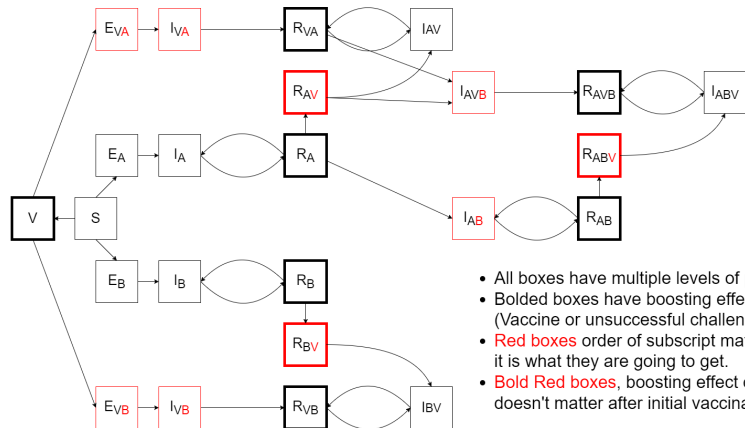
- ▶ Challenges a week apart are likely antagonistic
  - ▶ Immune boosting, polarized-like dynamics
- ▶ Challenges an hour apart are likely *synergistic*
  - ▶ Potentially overwhelming, leaky-like dynamics

# 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