## 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 Li 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)

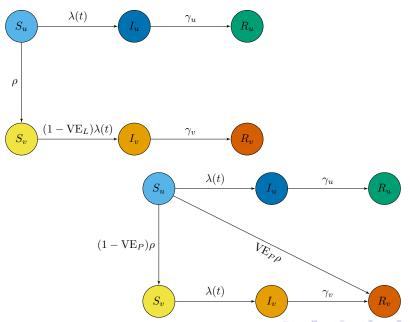
## What does it mean to be protected?

- 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

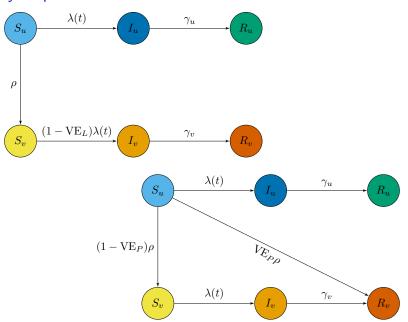
# Modeling immunity



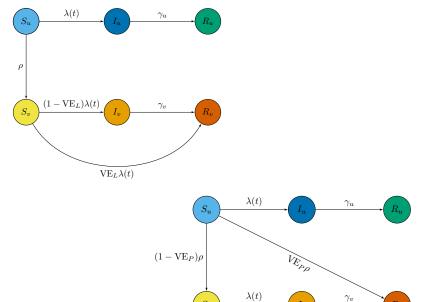
#### Limitations

- 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



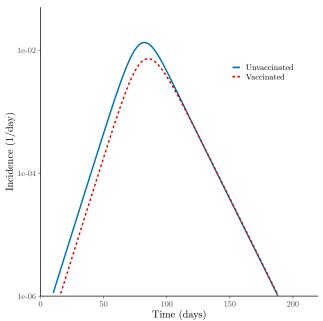
# Leaky with boosting v. polarized



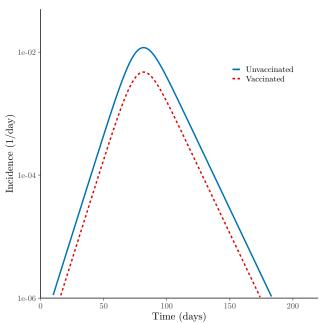
 $S_v$ 

 $R_v$ 

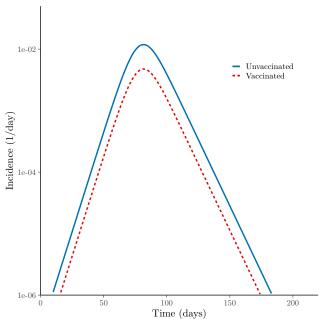
# Leaky vaccine



#### Polarized vaccine



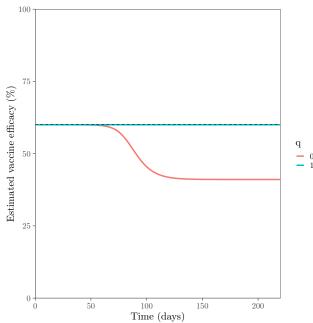
# Leaky vaccine with boosting



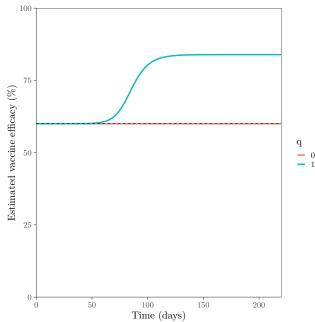
#### Vaccine effectiveness

- Efficacy: how protective the vaccine is in theory with a controlled exposure
- ▶ Effectiveness: how protective it will in a population
- We can project theoretical 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

#### 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

	Delta Predominant Period					Omicron Predominant Period				
Prior Infection, Vaccination,		Facility			Ratio of HR		Facility			Ratio of HR
and Type of Facility Exposure	! Infections	Exposures		HR (95% CI)	(Pvalue)	!Infections	Exposures		HR (95% CI)	(Pvalue)
Prior SARS-CoV-2 Infection*										
No Exposure No Prior Infection	111	10502				129	7135			
Prior Infection Cellblock Exposure	11	6522	-	0.21 (0.11, 0.39)	-	38	6329	-	0.36 (0.25, 0.54)	-
No Prior Infection	199 34	3436 2180		0.32 (0.24, 0.44)	0.216	347 155	3374 2606		0.61 (0.49, 0.75)	0.019
Cell Exposure No Prior Infection Prior Infection	41 12	179 85		0.59 (0.30, 1.16)	0.029	73 36	448 254	-	0.89 (0.58, 1.35)	
Prior Vaccination <sup>b</sup>	1					1				
No Exposure Unvaccination Vaccinated	92 30	7883 9141	•	0.32 (0.21, 0.49)	_	97 70	5771 7693	-	0.57 (0.42, 0.78)	-
Cellblock Exposure Unvaccination Vaccinated Cell Exposure	169 64	2603 3013		0.35 (0.26, 0.47)	0.727	255 247	2579 3401		0.69 (0.58, 0.83)	0.313
Unvaccination Vaccinated	36 17	155 109	-	0.74 (0.37, 1.48)	0.033	48 61	323 379	-	0.96 (0.64, 1.46)	0.041
Hybrid Immunity°										
No Exposure No Hybrid Immunity Hybrid Immunity Cellblock Exposure	85 4	5650 4289		0.05 (0.02, 0.10)	_	81 22	3537 4095	•	0.24 (0.15, 0.39)	-
No Hybrid Immunity Hybrid Immunity Cell Exposure	147 12	1802 1379		0.10 (0.05, 0.19)	0.203	190 90	1702 1729	•	0.41 (0.31, 0.55)	0.053
No Hybrid Immunity Hybrid Immunity	28 4	115 45	-	0.29 (0.07, 1.12)	0.026	36 24	237 168		0.80 (0.46, 1.39)	0.001

Lind et al., Nat Commun, 2023. https://doi.org/10.1038/s41467-023-40750-8