* Conceptual models of immunity

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BIRS Canmod meeting, Nov 2023

History of this work

- Innovative influenza cross-immunity models by Julia Gog
 https://pubmed.ncbi.nlm.nih.qov/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)

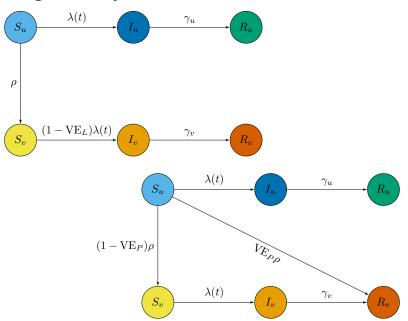
What does it mean to be protected?

- 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

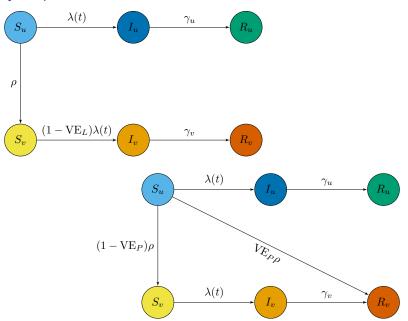
Modeling immunity



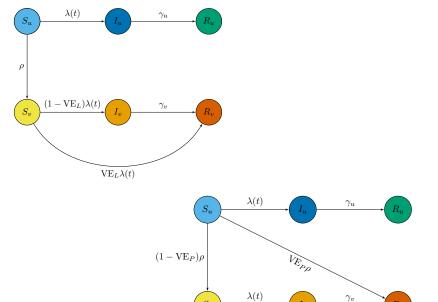
Limitations

- 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



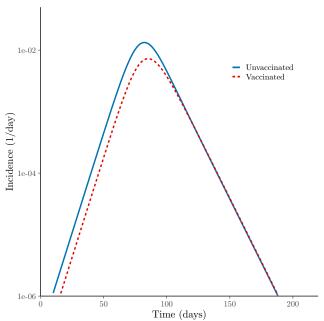
Leaky with boosting v. polarized



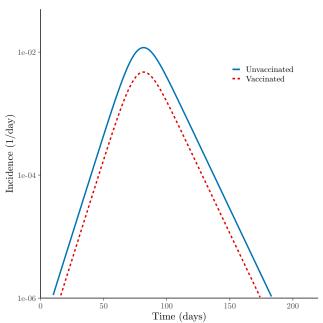
 S_v

 R_v

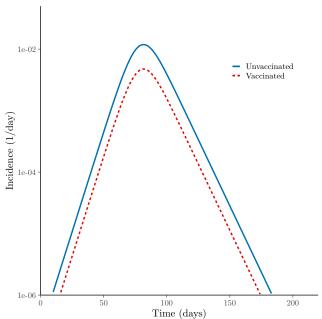
Leaky vaccine

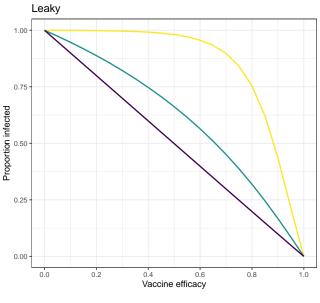


Polarized vaccine

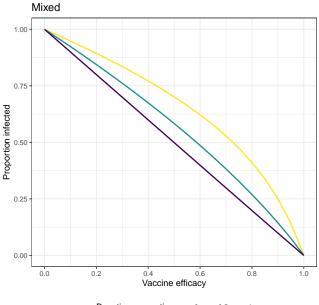


Leaky vaccine with boosting

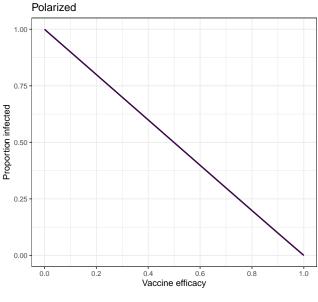




Boosting proportion — 0 — 0.5 — 1



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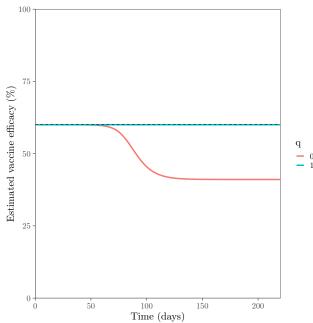


Boosting proportion — 0 — 0.5 — 1

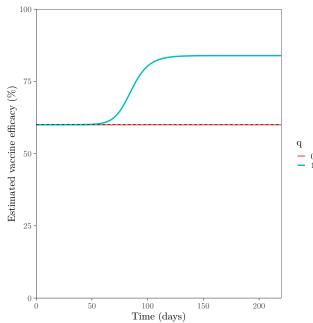
Vaccine effectiveness

- ▶ 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

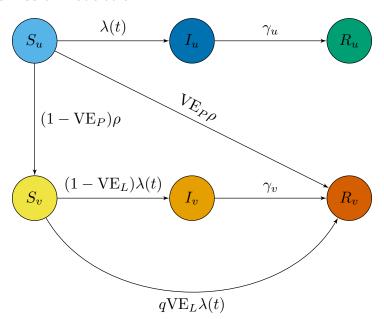




Questions going forward

- ► 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

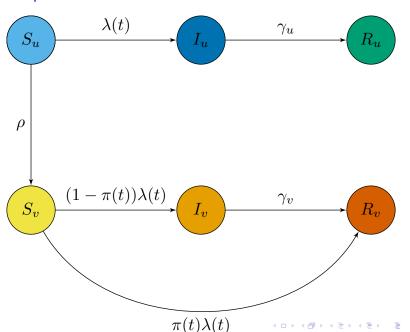
	Delta Predominant Period					Omicron Predominant Period				
Prior Infection, Vaccination.	Facility Ratio of HR									Ratio of HR
and Type of Facility Exposure	Infections	Exposures		HR (95% CI)	(Pvalue)	Infections	Exposures		HR (95% CI)	(Pvalue)
Prior SARS-CoV-2 Infection*										
No Exposure No Prior Infection	111	10502				129	7135			
Prior Infection	11	6522	6 4	0.21 (0.11, 0.39)	_	38	6329	-	0.36 (0.25, 0.54)	_
Cellblock Exposure	; "	0322	-	0.21 (0.11, 0.39)	-	. 30	0329	_	0.30 (0.23, 0.34)	-
No Prior Infection	199	3436				347	3374			
Prior Infection	34	2180		0.32 (0.24, 0.44)	0.216	; 155	2606	-	0.61 (0.49, 0.75)	0.019
Cell Exposure No Prior Infection	41	179				73	448			
Prior Infection	12	179 85	-	0.59 (0.30, 1.16)	0.029	36	448 254		0.89 (0.58, 1.35)	0.002
r noi miecion	12	00		0.35 (0.30, 1.10)	0.025	. 30	204		0.05 (0.30, 1.30)	0.002
Prior Vaccination ⁶	1					1				
No Exposure						1				
Unvaccination	92	7883	_			97	5771	_		
Vaccinated Cellblock Exposure	30	9141	-	0.32 (0.21, 0.49)	-	70	7693	-	0.57 (0.42, 0.78)	-
Unvaccination	169	2603				255	2579			
Vaccinated	64	3013		0.35 (0.26, 0.47)	0.727	247	3401		0.69 (0.58, 0.83)	0.313
Cell Exposure			_	, , , , , , , , , , , , , , , , , , , ,				_		
Unvaccination	36	155	_			48	323	_	_	
Vaccinated	17	109	_	0.74 (0.37, 1.48)	0.033	; 61	379	-	0.96 (0.64, 1.46)	0.041
Hybrid Immunity ^c	1					1				
No Exposure	-									
No Hybrid Immunity	85	5650				81	3537			
Hybrid Immunity	4	4289		0.05 (0.02, 0.10)	-	22	4095		0.24 (0.15, 0.39)	-
Cellblock Exposure	447	4000					4700			
No Hybrid Immunity Hybrid Immunity	147	1802 1379		0.10 (0.05, 0.19)	0.203	190	1702 1729		0.41 (0.31, 0.55)	0.053
Cell Exposure	12	1375		0.10 (0.00, 0.18)	0.203		1725	-	0.41 (0.31, 0.33)	0.033
No Hybrid Immunity	28	115				36	237			
Hybrid Immunity	4	45	_	0.29 (0.07, 1.12)	0.026	24	168		0.80 (0.46, 1.39)	0.001
	1					1				
			0 0.5	1.5				0 0.5	1 1.5	

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

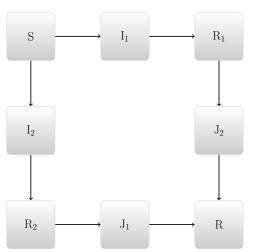
Time scales of challenge

- 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!

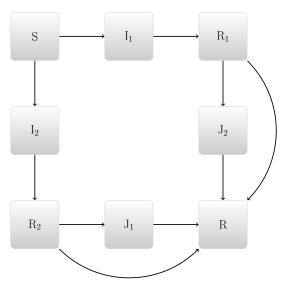
Dose dependence



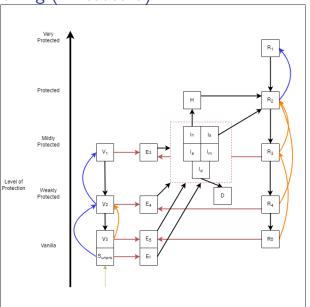
Interacting strains



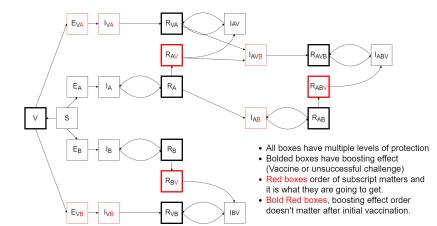
Interacting strains



Immune waning (whiteboard)



Cross immunity (whiteboard)



Michael WZ Li, PHAC

Thanks

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