

* 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.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)

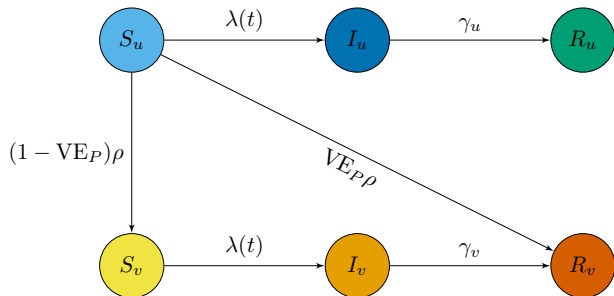
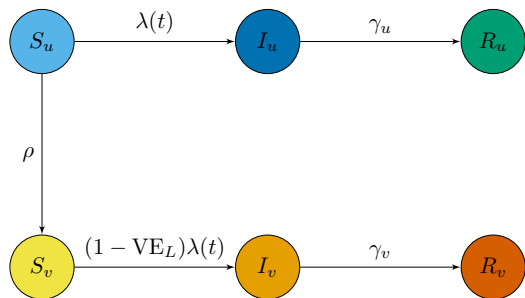
What does it mean to be protected?

- ▶ 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

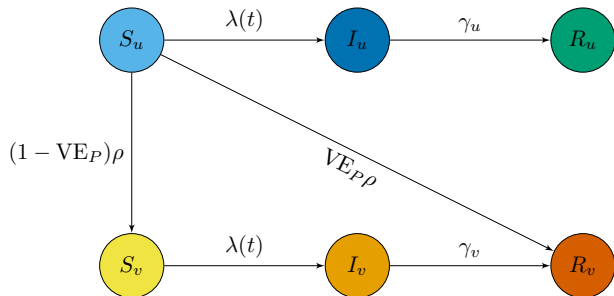
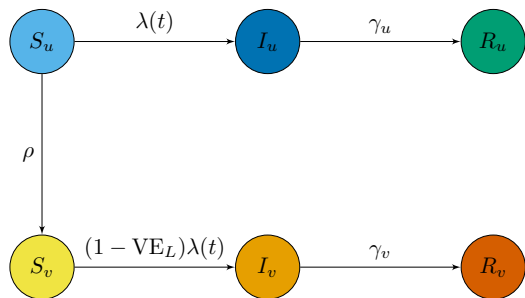
Modeling immunity



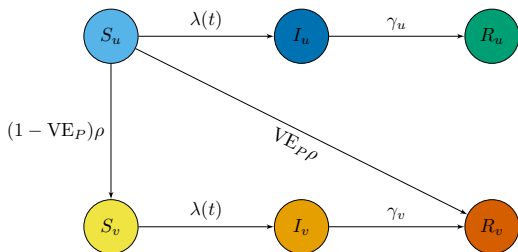
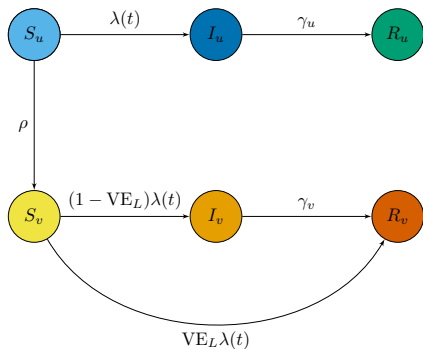
Limitations

- ▶ 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

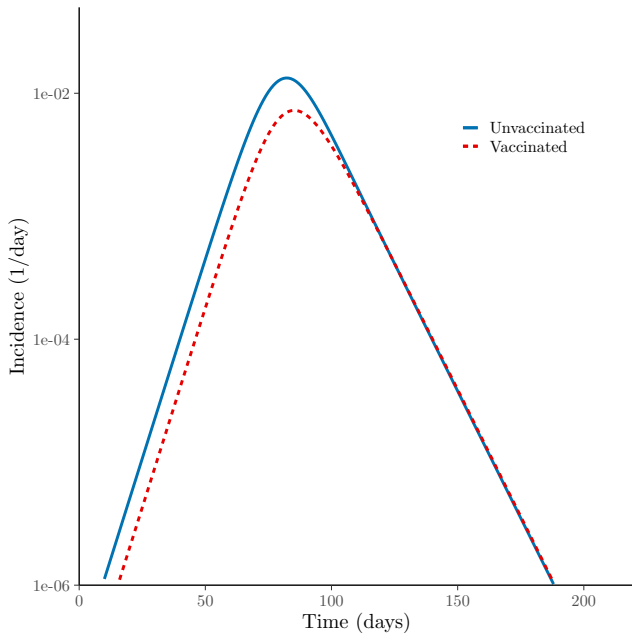
Leaky v. polarized



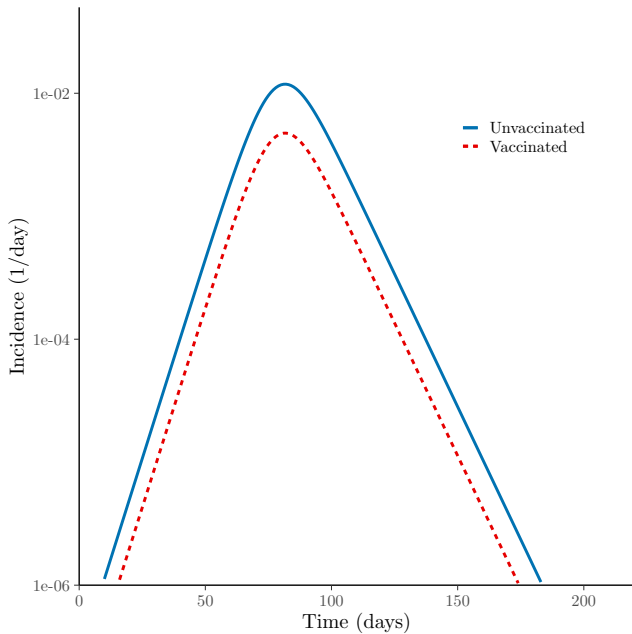
Leaky with boosting v. polarized



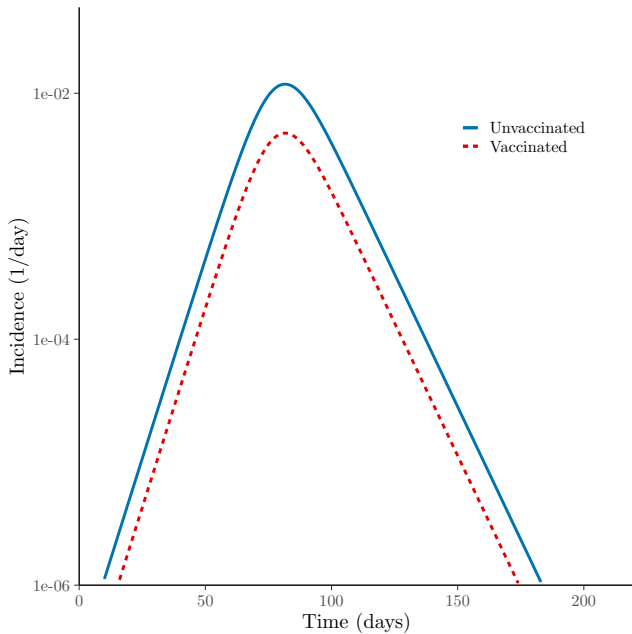
Leaky vaccine



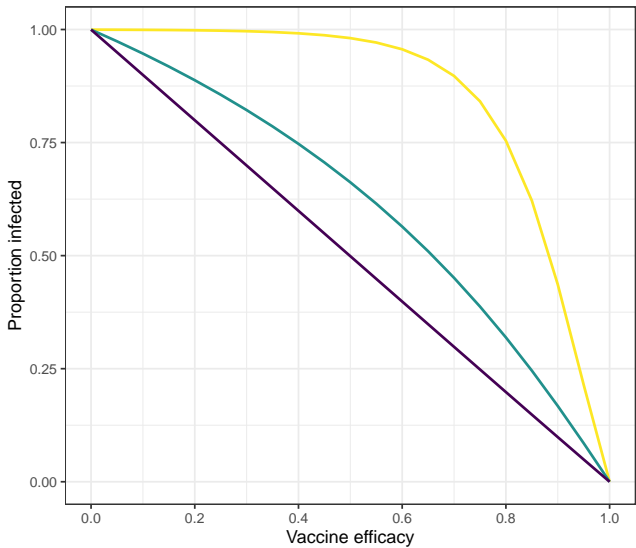
Polarized vaccine



Leaky vaccine with boosting

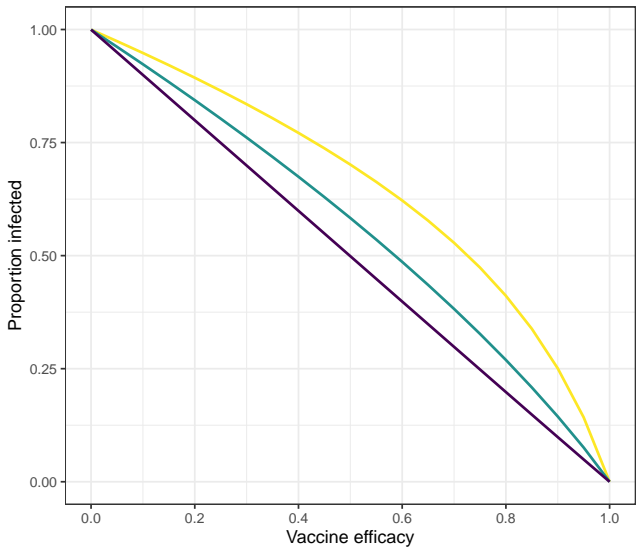


Leaky



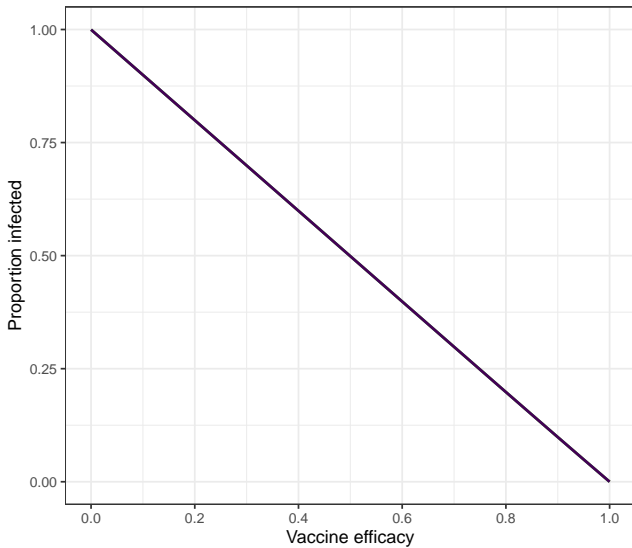
Boosting proportion — 0 — 0.5 — 1

Mixed



Boosting proportion — 0 — 0.5 — 1

Polarized

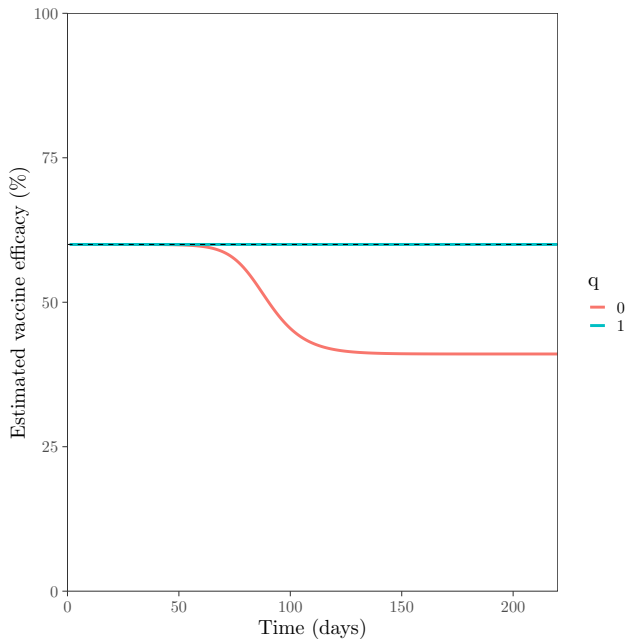


Boosting proportion 0 0.5 1

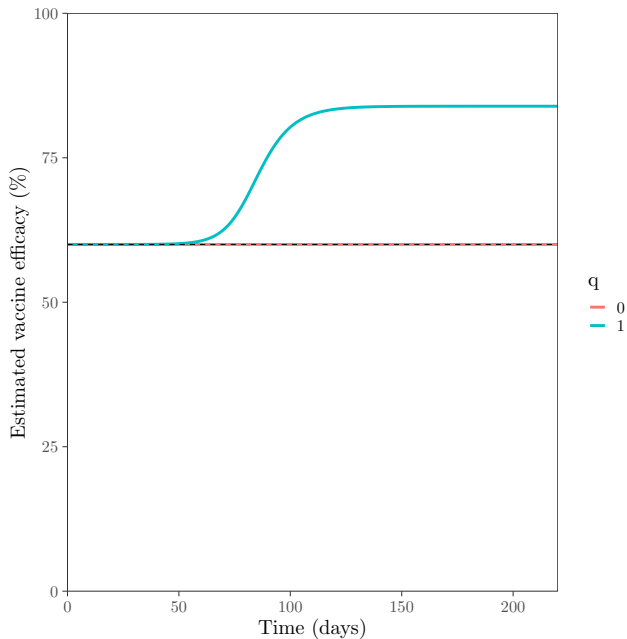
Vaccine effectiveness

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

Incidence-based effectiveness



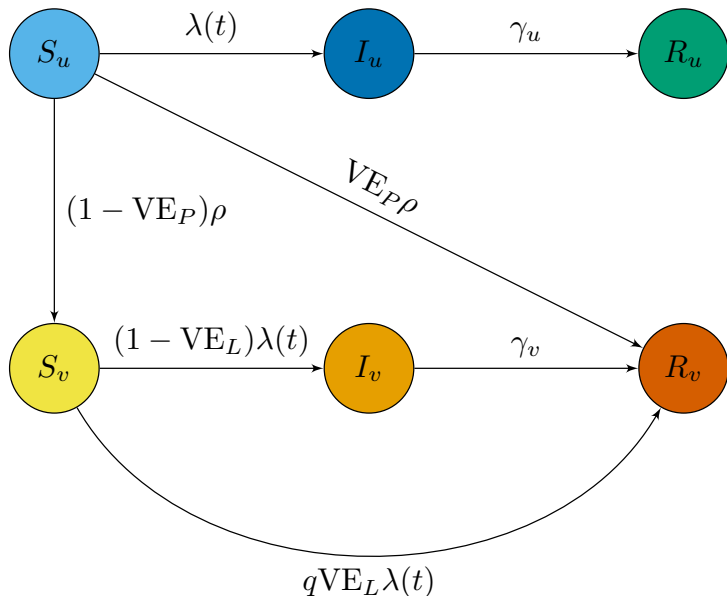
Hazard-based effectiveness



Questions going forward

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

Transmission reduction



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

Prior Infection, Vaccination, and Type of Facility Exposure	Delta Predominant Period				Omicron Predominant Period			
	Facility		Ratio of HR (95% CI)	(Pvalue)	Facility		Ratio of HR (95% CI)	(Pvalue)
Infections	Exposures	Infections			Exposures			
Prior SARS-CoV-2 Infection^a								
No Exposure								
No Prior Infection	111	10502			129	7135		
Prior Infection	11	6522	■		38	6329	■	
Cellblock Exposure			0.21 (0.11, 0.39)	-			0.36 (0.25, 0.54)	-
No Prior Infection	199	3436			347	3374		
Prior Infection	34	2180	■	0.216	155	2606	■	0.019
Cell Exposure			0.32 (0.24, 0.44)				0.61 (0.49, 0.75)	
No Prior Infection	41	179			73	448		
Prior Infection	12	85	■	0.029	36	254	■	0.002
			0.59 (0.30, 1.16)				0.89 (0.58, 1.35)	
Prior Vaccination^b								
No Exposure								
Unvaccination	92	7883			97	5771		
Vaccinated	30	9141	■		70	7693	■	
Cellblock Exposure			0.32 (0.21, 0.49)	-			0.57 (0.42, 0.78)	-
Unvaccination	169	2603			255	2579		
Vaccinated	64	3013	■	0.727	247	3401	■	0.313
Cell Exposure			0.35 (0.26, 0.47)				0.69 (0.58, 0.83)	
Unvaccination	36	155			48	323		
Vaccinated	17	109	■	0.033	61	379	■	0.041
			0.74 (0.37, 1.48)				0.96 (0.64, 1.46)	
Hybrid Immunity^c								
No Exposure								
No Hybrid Immunity	85	5650			81	3537		
Hybrid Immunity	4	4289	■		22	4095	■	
Cellblock Exposure			0.05 (0.02, 0.10)	-			0.24 (0.15, 0.39)	-
No Hybrid Immunity	147	1802			190	1702		
Hybrid Immunity	12	1379	■	0.203	90	1729	■	0.053
Cell Exposure			0.10 (0.05, 0.19)				0.41 (0.31, 0.55)	
No Hybrid Immunity	28	115			36	237		
Hybrid Immunity	4	45	■	0.026	24	168	■	0.001
			0.29 (0.07, 1.12)				0.80 (0.46, 1.39)	

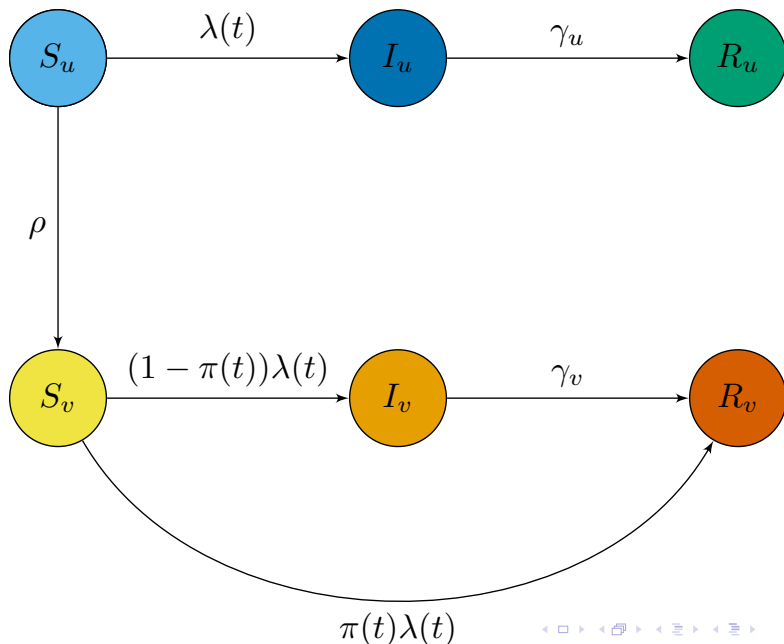
Lind et al., Nat Commun, 2023.

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

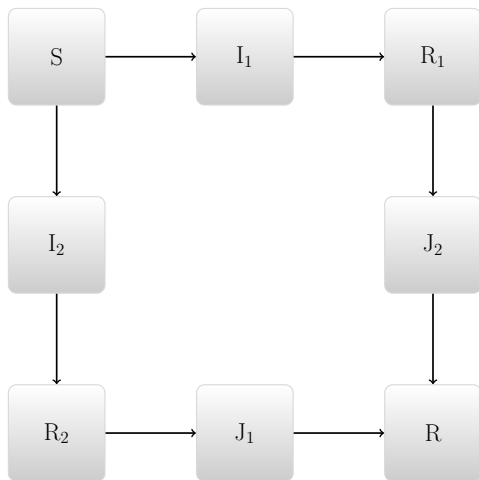
Time scales of challenge

- ▶ 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!

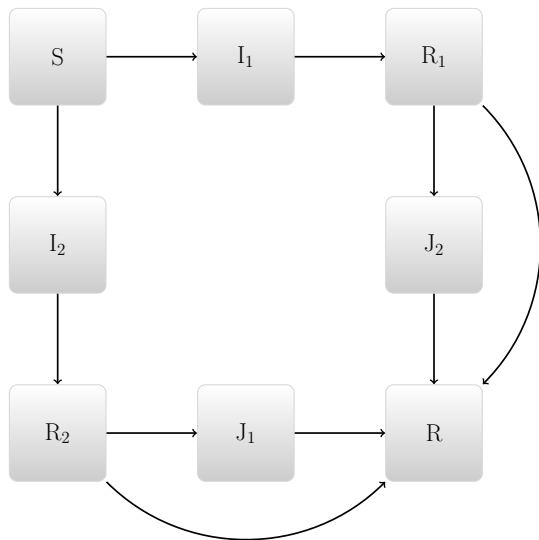
Dose dependence



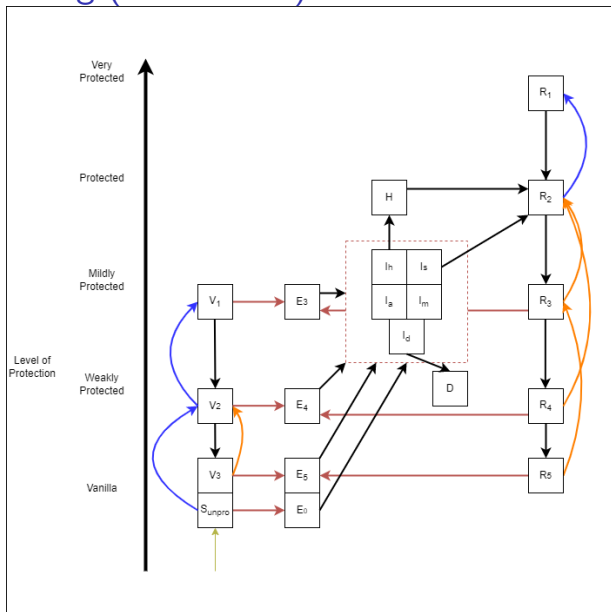
Interacting strains



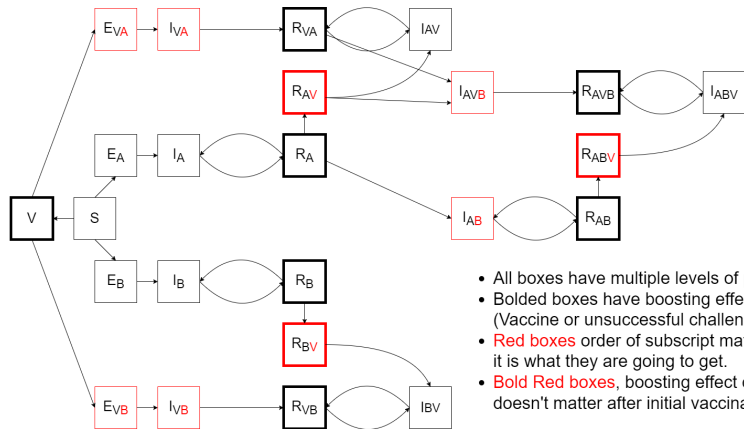
Interacting strains



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