Model-based optimization of vaccine inoculum dose

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Motivation

- The inoculum dose (live pathogen or antigen) is important.
- Common assumptions:
  - Higher dose leads to more symptoms and more severe outcomes (e.g. LD50).
  - Higher dose induces a stronger immune response and creates more immune memory.
- Overall goal: Investigate those assumptions and study the impact of dose, with a focus on vaccines.

Previous Work

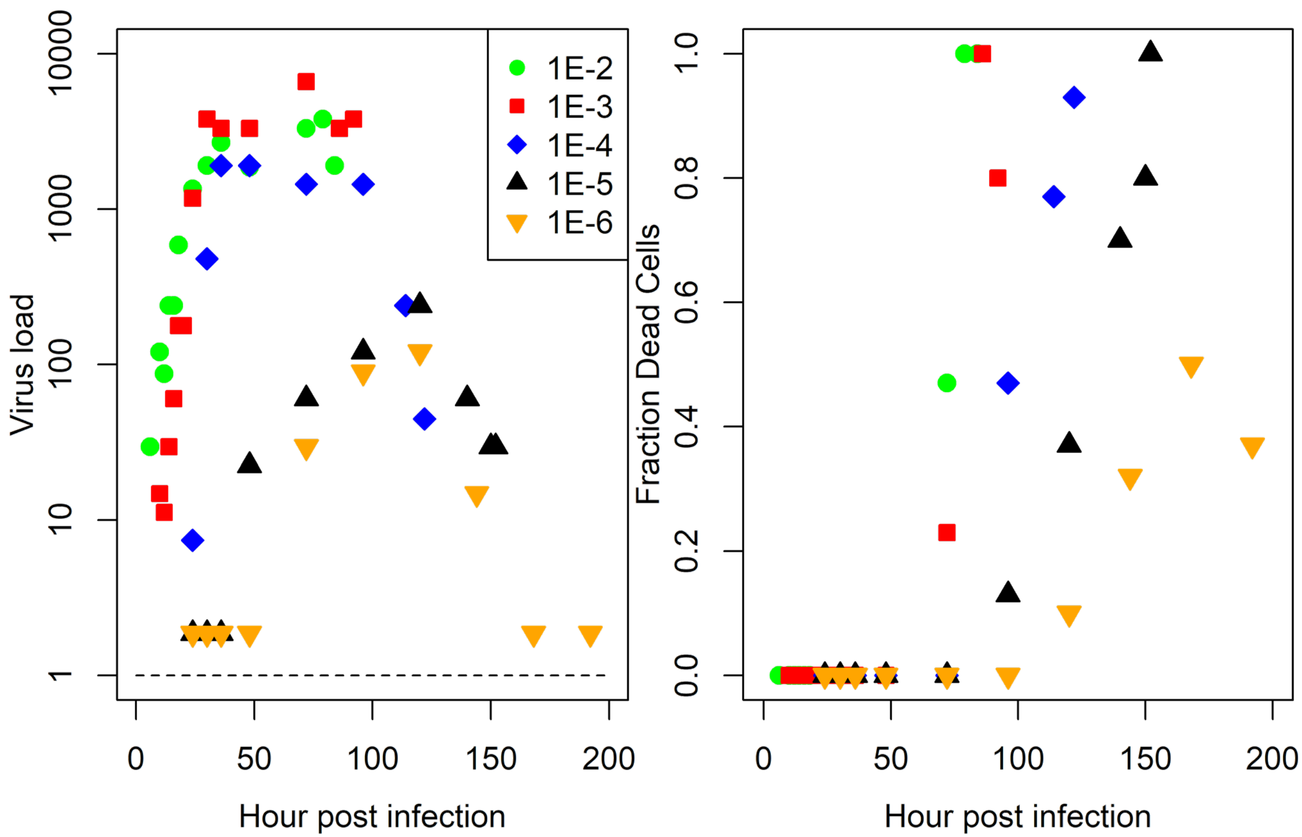
Handel et al 2018 PLoS Comp Bio

(also Li and Handel 2014 JTB, won't talk about it)

Project Aim

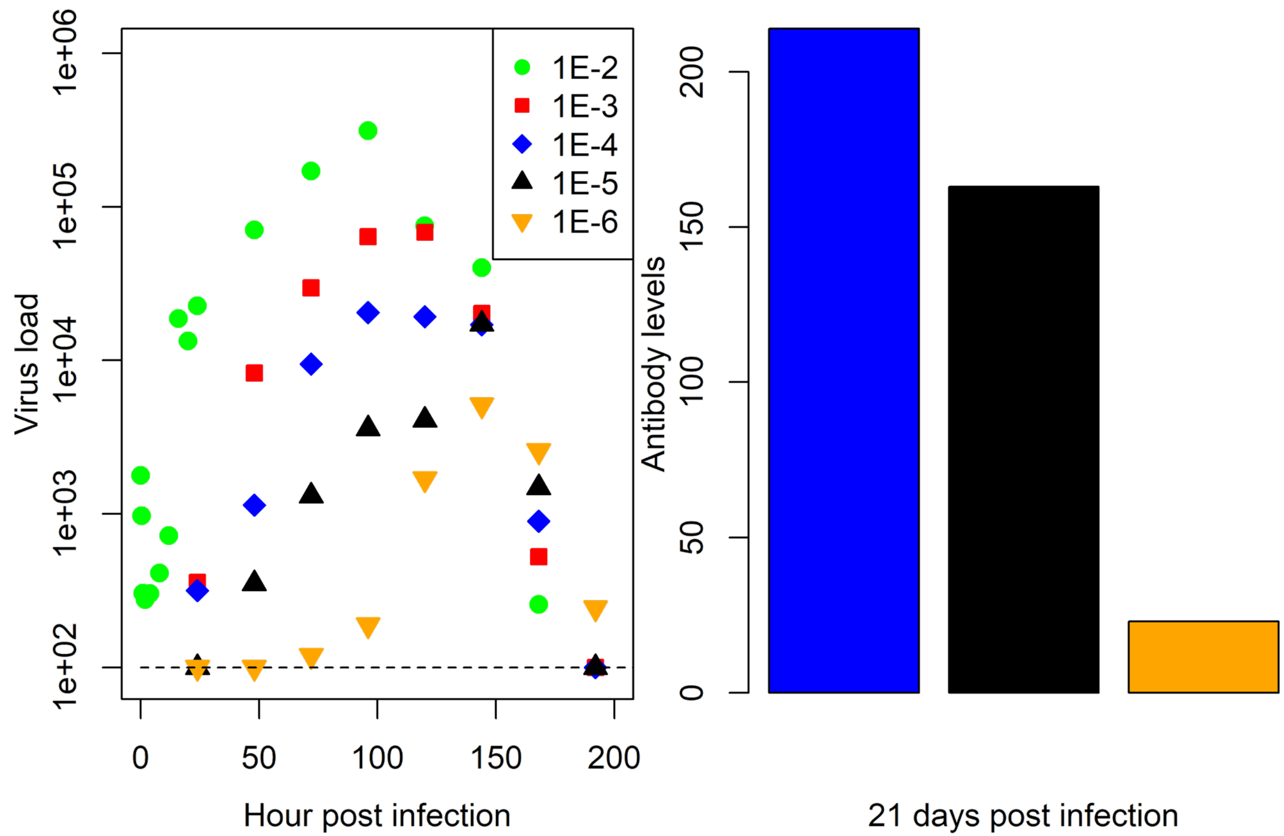
- Build a framework combining data with models to investigate the impact of inoculum dose on immune response and morbidity/symptoms.
- Illustrate how to use new framework to predict outcomes (immune response and morbidity) for a large range of inoculum doses.
- Show how one can use the framework to optimize vaccine dose.

Data I



- Influenza A virus (IAV) infection in mice (Ginsberg et al 1952, JEM)
- Left: Virus load for 5 inoculum doses, average of several animals per dose. Right: fraction lung damage.

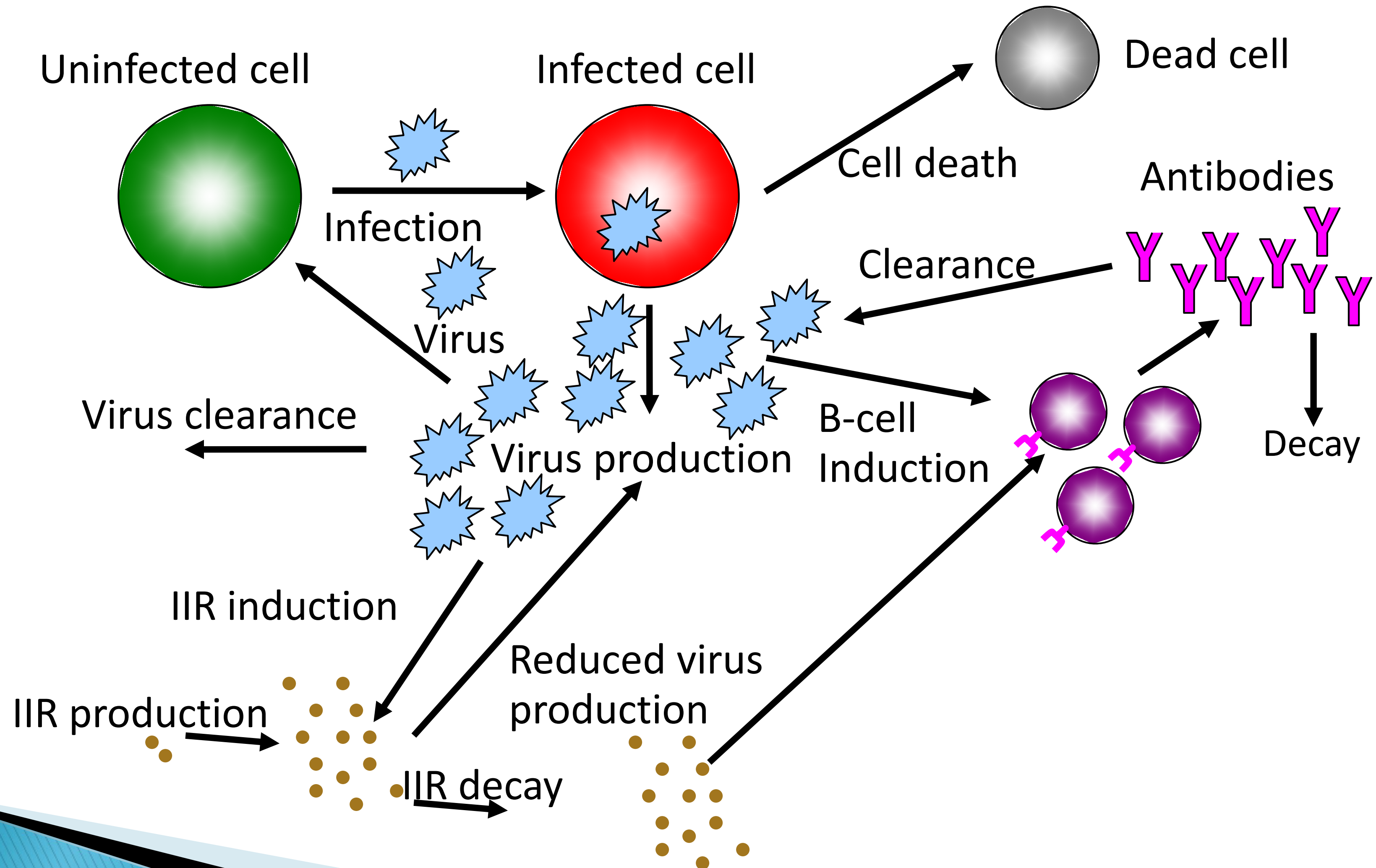
Data II



- HPIV infection in cotton rats (Ottolini et al JGV 1996)
- Left: Virus load for 5 inoculum doses, average of several animals per dose. Right: Antibody increase at end of infection for the 3 lowest doses.
- For more/similar data, see: Li & Handel 2014 JTB (or ask me).

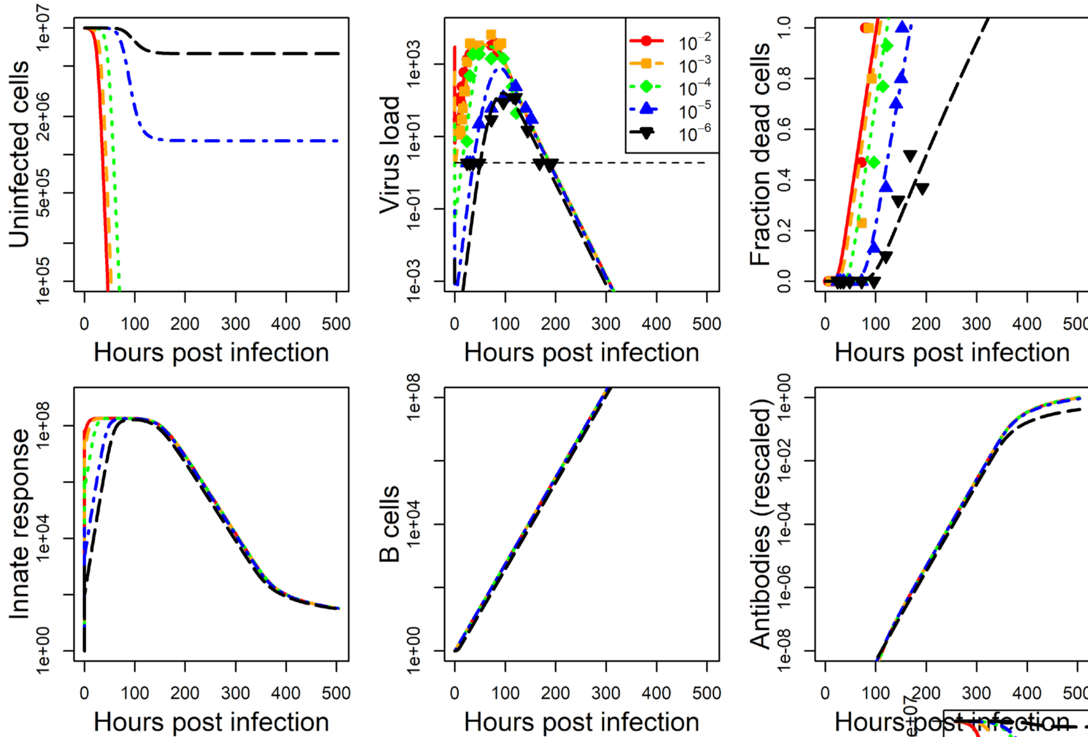
Model diagram

- A model with innate (IIR) and adaptive (B cell/antibody) immune response.

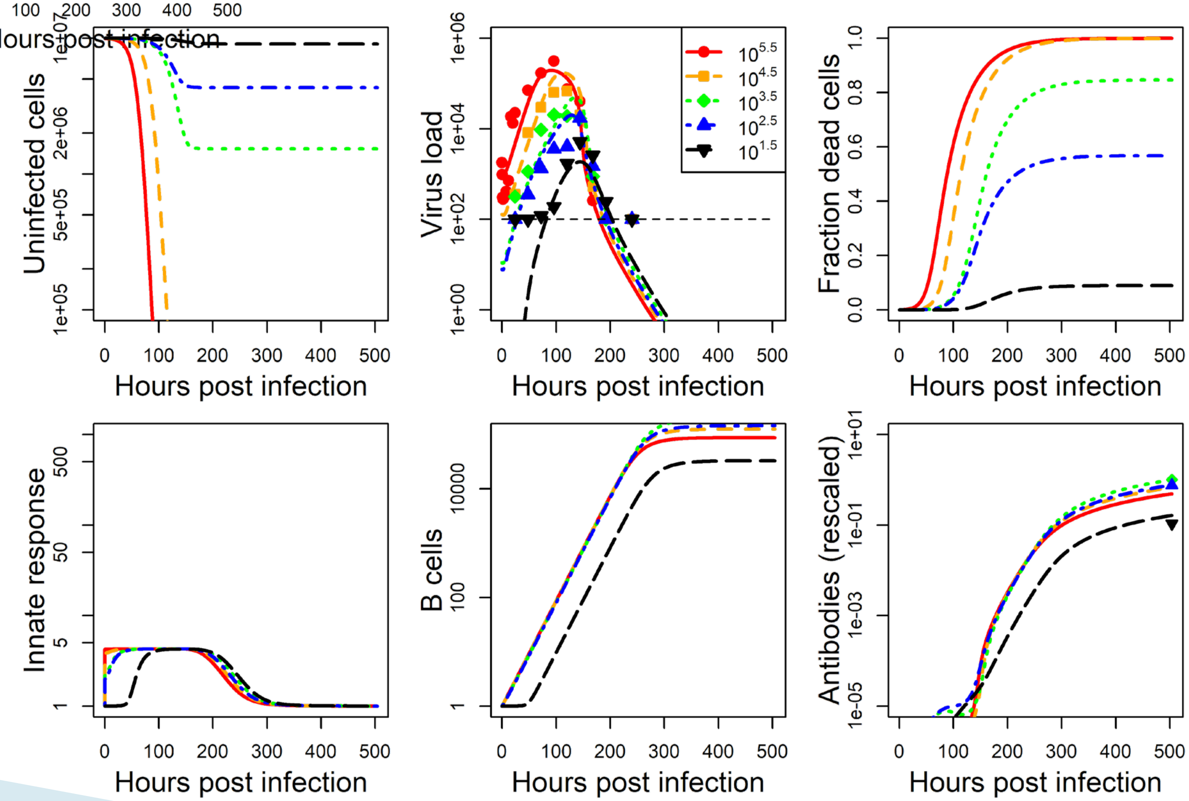


Model equations

Uninfected cells	$\dot{U} = -bUV$
Infected cells	$\dot{I} = bUV - d_I I$
Dead cells	$\dot{D} = d_I I$
Virus	$\dot{V} = \frac{p}{1+s_F F} I - d_V V - k_A AV - b_p UV$
Innate Response	$\dot{F} = p_F + g_F \frac{V}{V+h_V} (F_{max} - F) - d_F F$
B-cells	$\dot{B} = \frac{FV}{FV+h_F} g_B B$
Antibodies	$\dot{A} = r_A B - d_A A - k_A AV$



Influenza



HPIV

Immunity and Morbidity as function of Inoculum

- We want to know immune protection and morbidity as function of dose.
- We can map antibodies (A) to protection (P) and innate response (F) to morbidity (M).

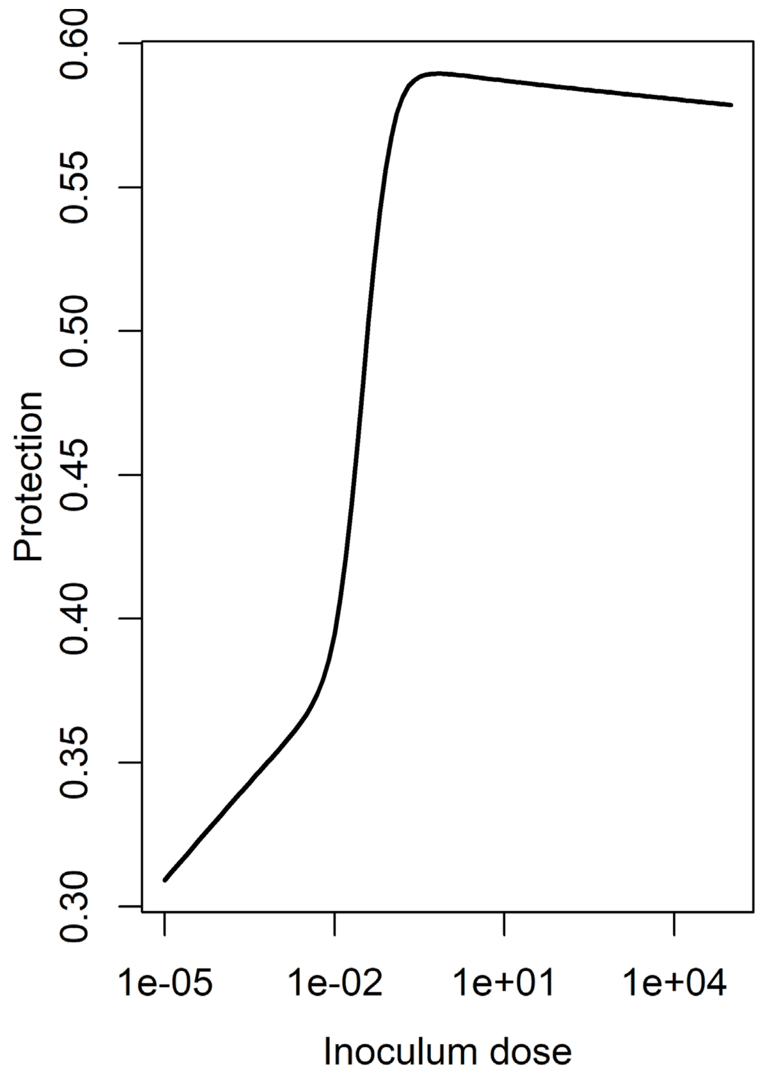
$$P = 1 - \frac{1}{1 + e^{k_1(\log(A) - k_2)}}$$

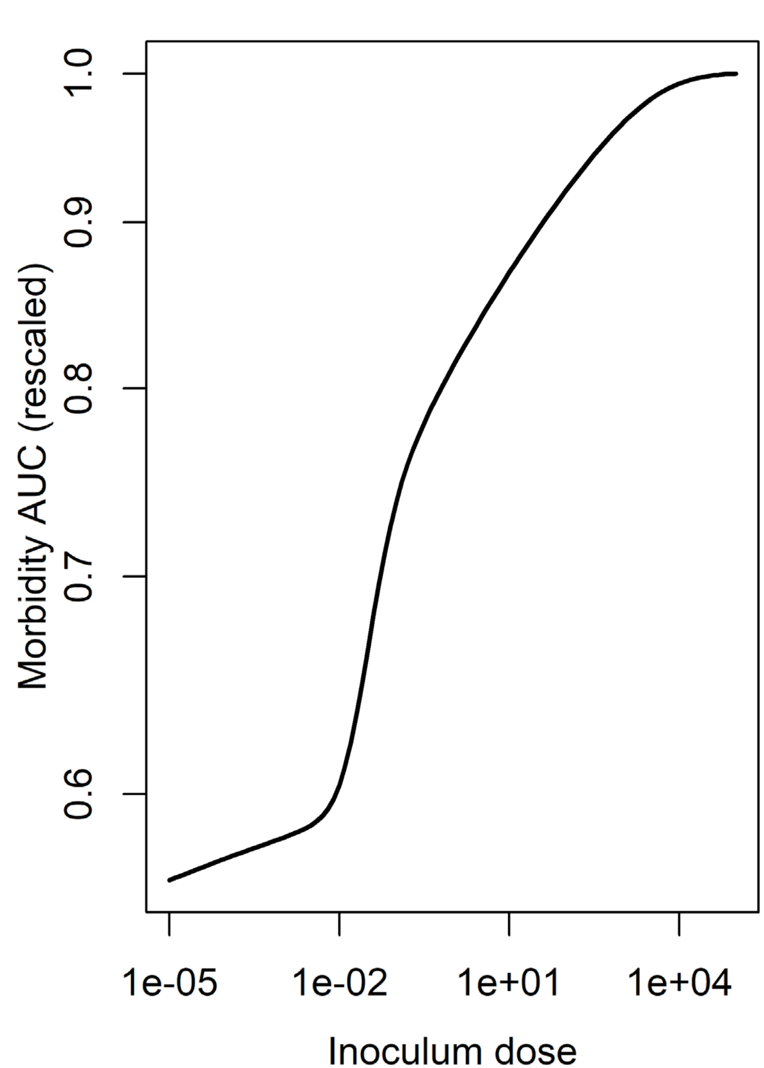
Coudeville et al 2010 BMC Med Res Meth

$$M = \int \frac{aF^c}{b + F^c}$$

Hayden et al 1998 JCI

Impact of inoculum on immunity/morbidity - flu





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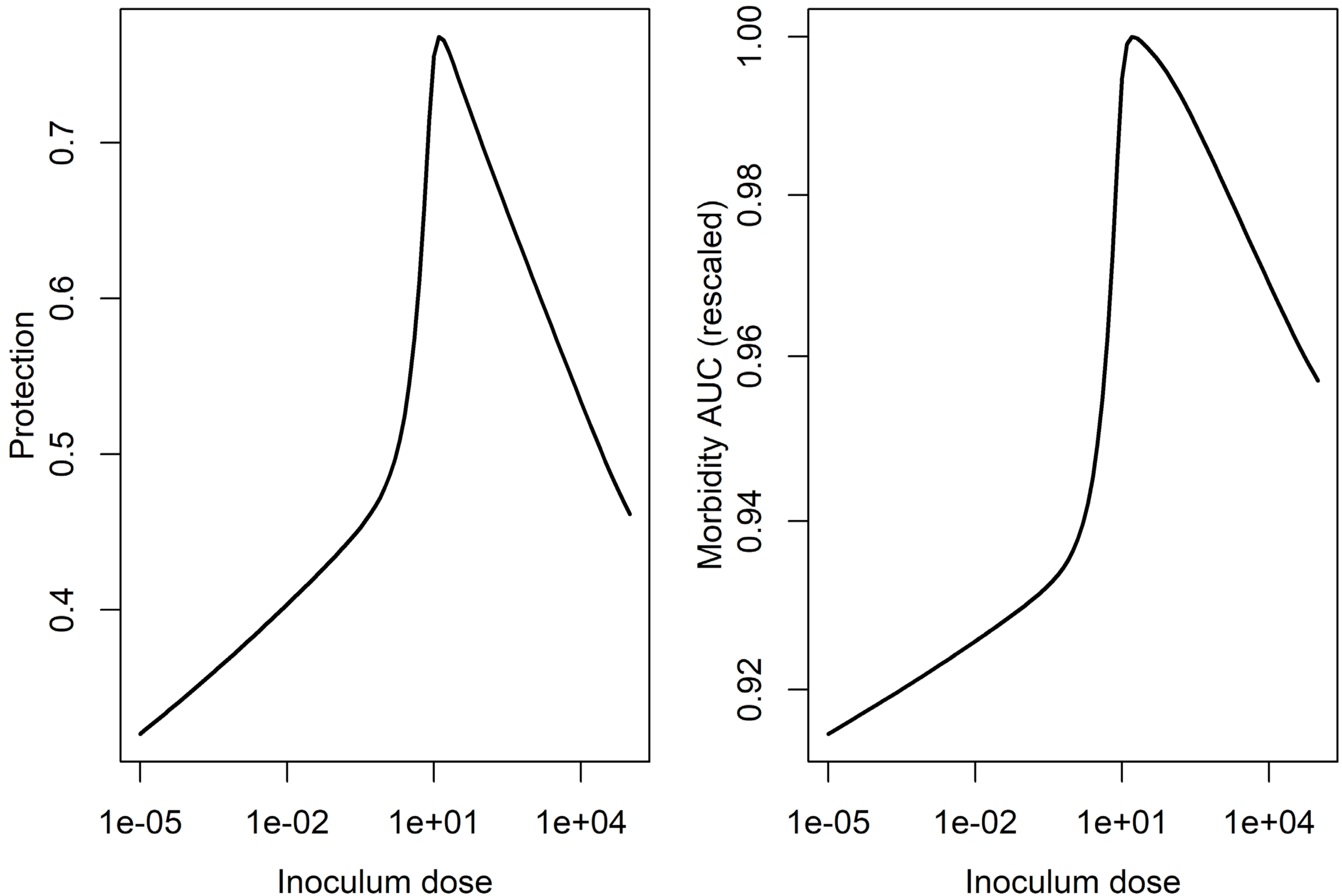
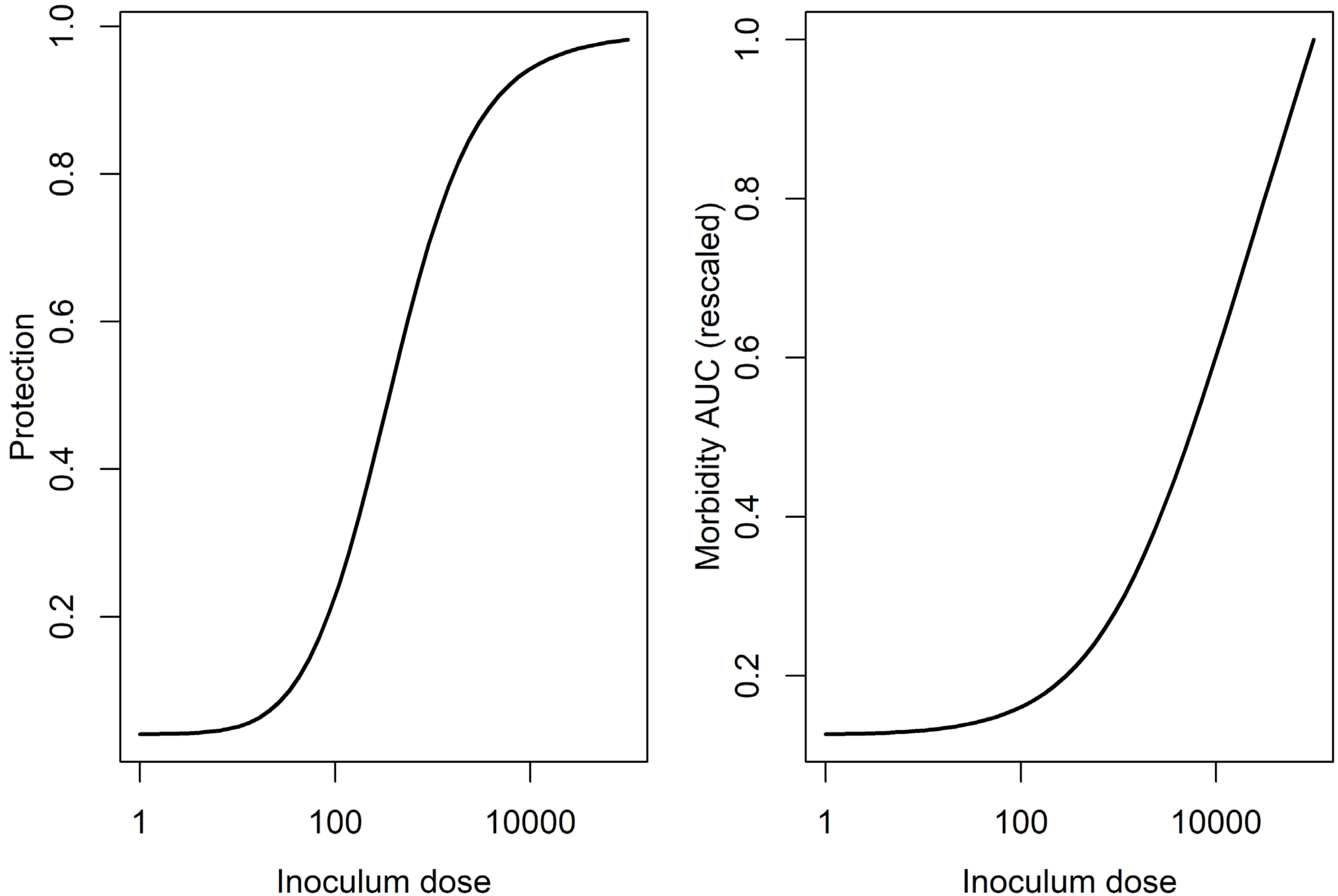
Impact of inoculum on immunity/morbidity - HPIV



Impact of inoculum on immunity/morbidity - vaccine



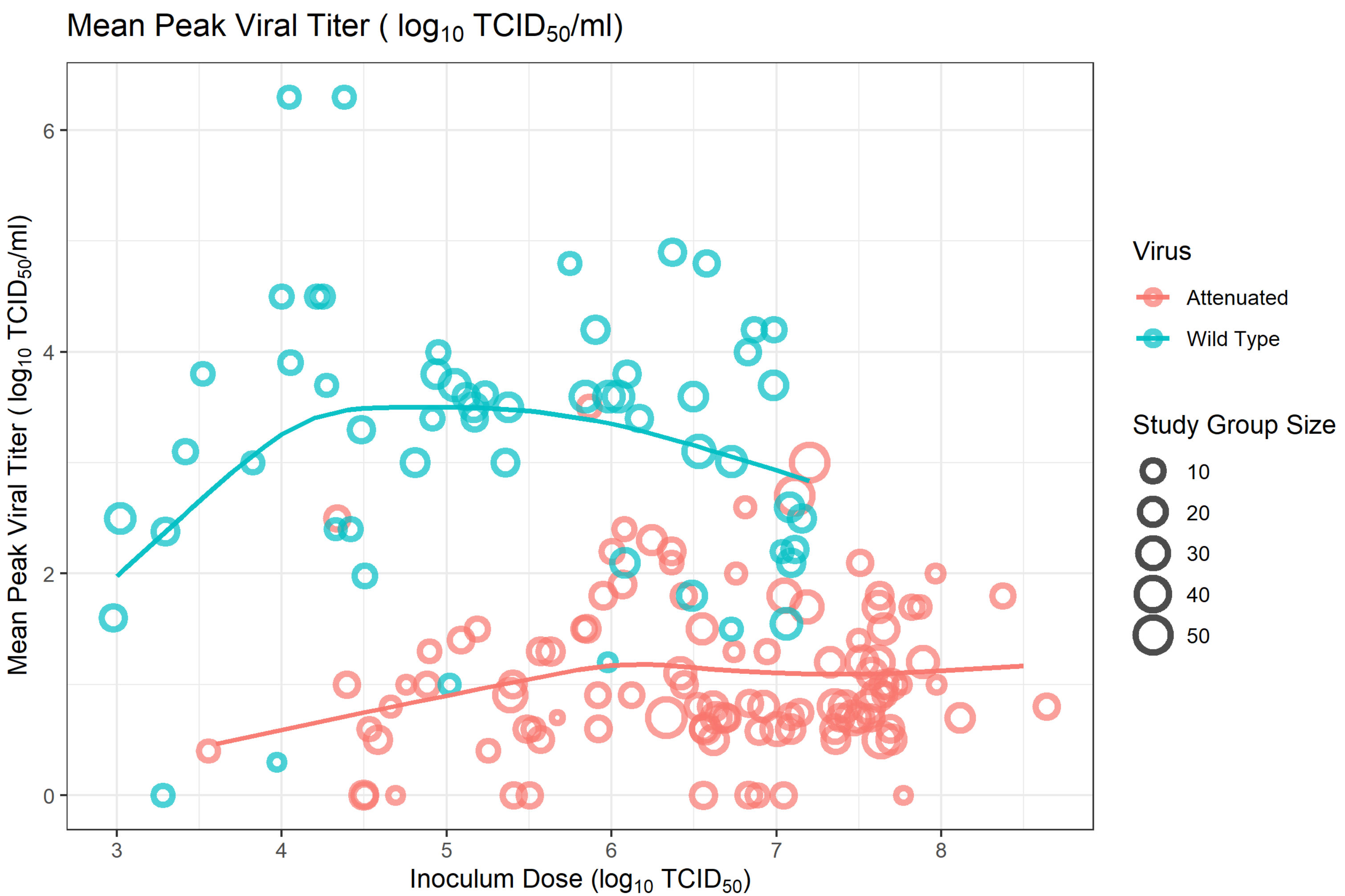
Summary so far

- We proposed a framework that combines data and models to study the impact of dose.
- We used animal data to show how this framework could be applied.
- With this framework, one could potentially determine important outcomes for any dose and pick the optimal dose based on those considerations.
- The data was not too meaningful and thus results can only be considered conceptual.

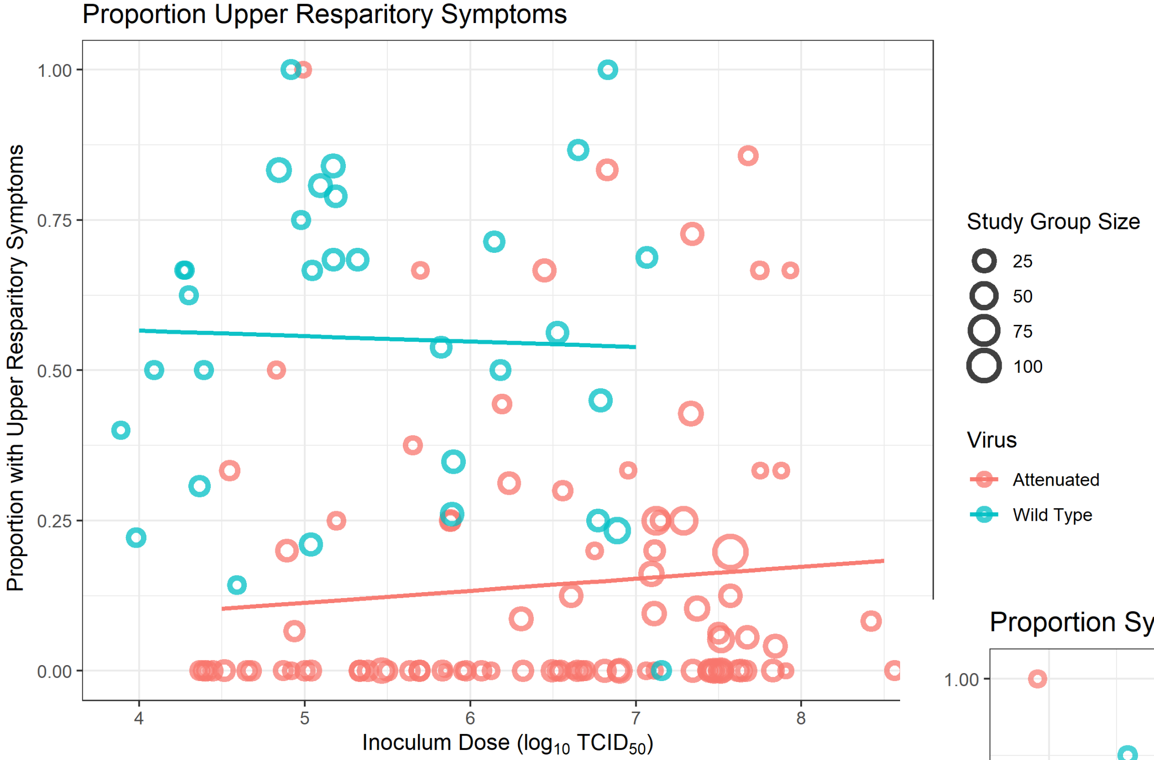
Current work

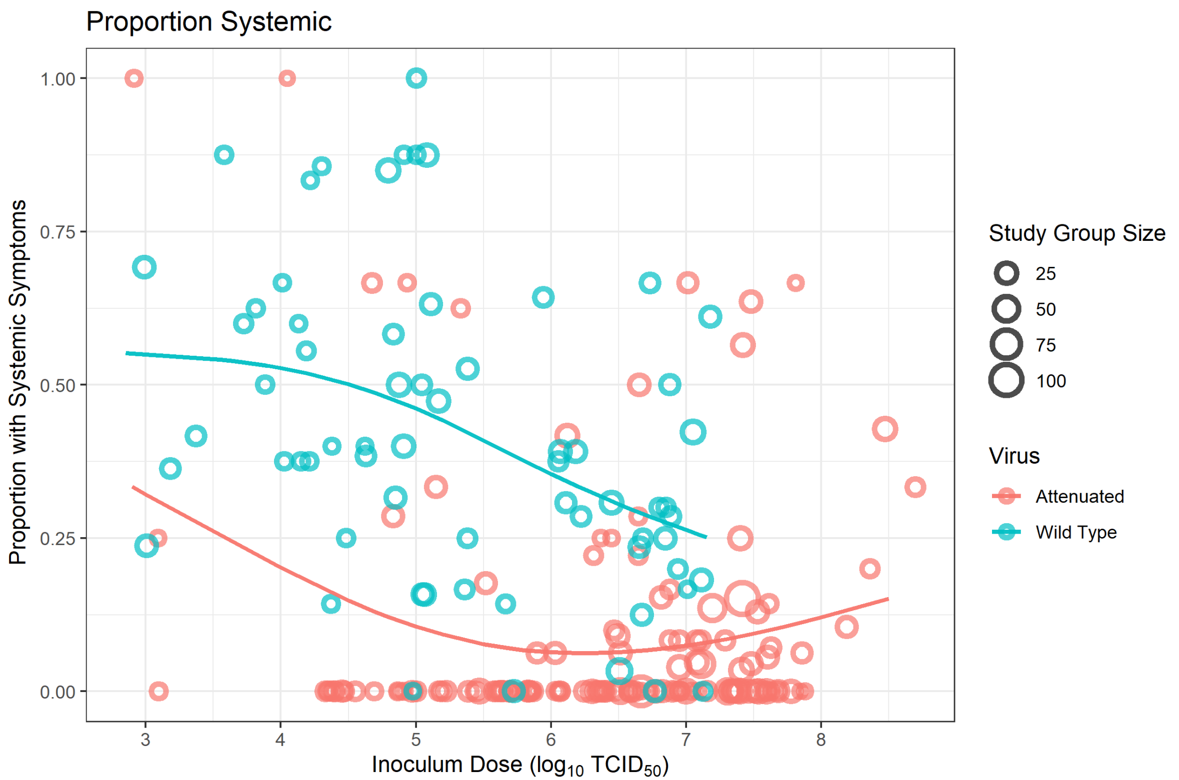
Human influenza challenge studies

- Systematic review of human challenge studies (similar to Carrat et al 2008).

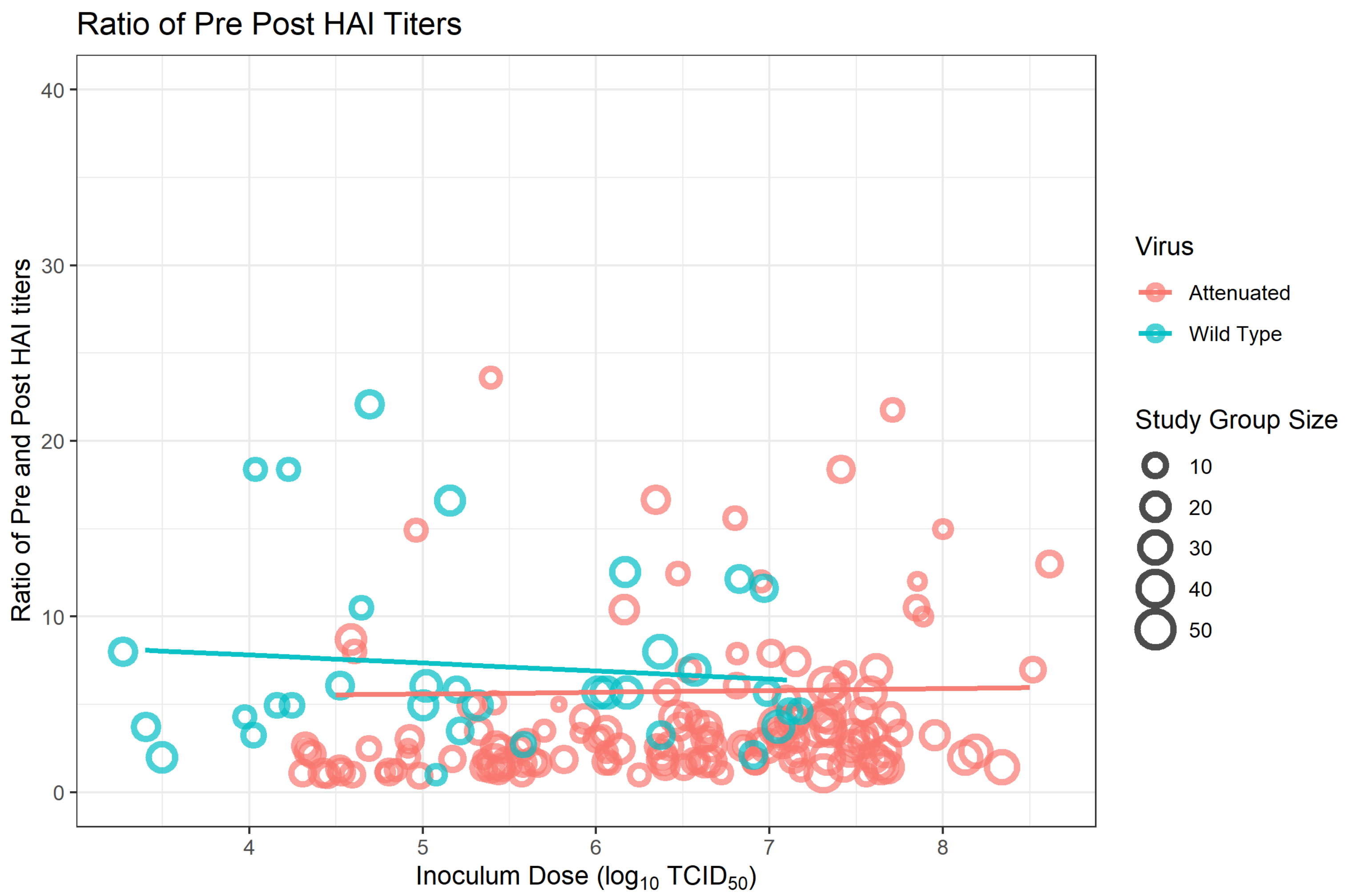


Human influenza challenge studies



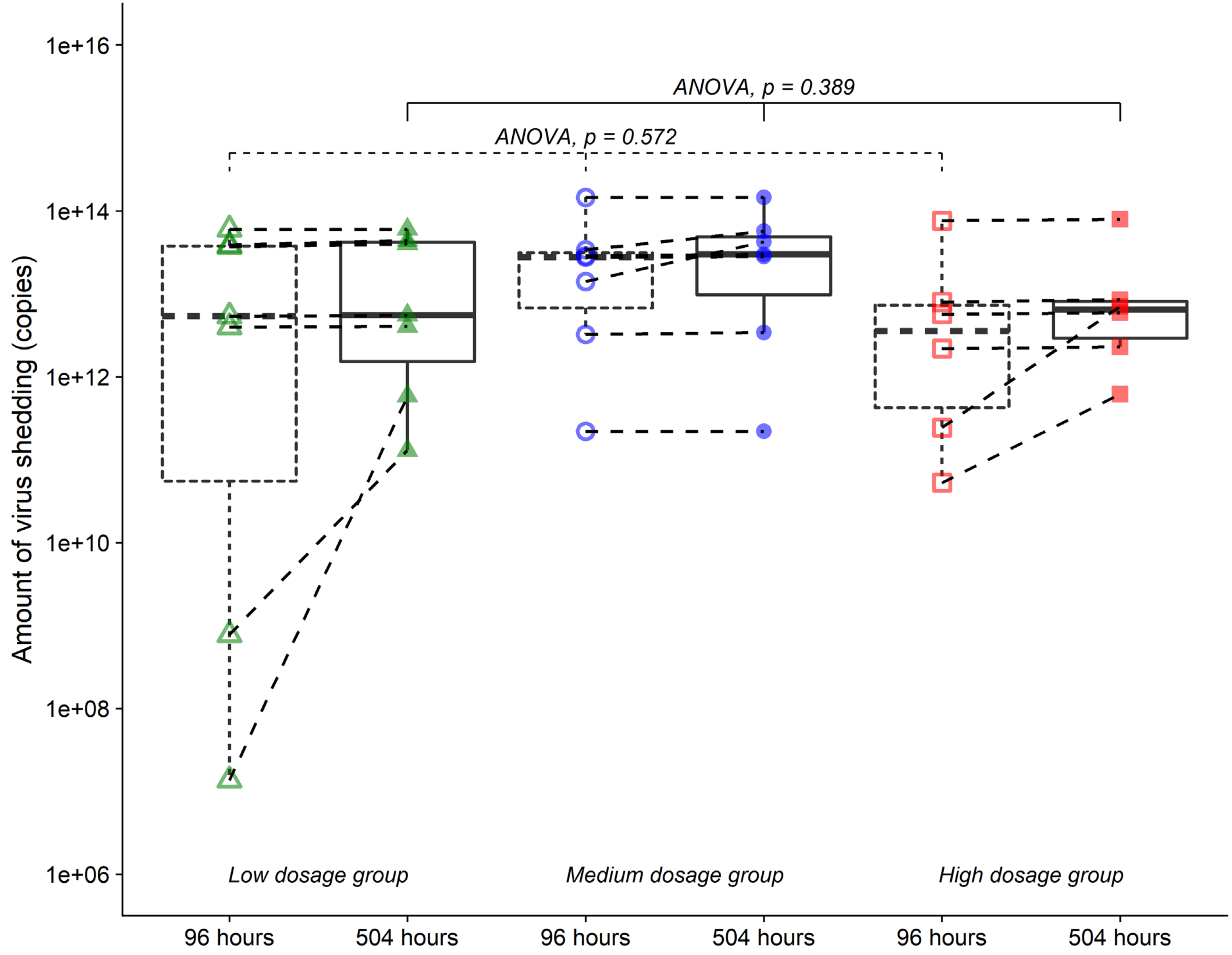


Human influenza challenge studies



Human norovirus challenge studies

- Individual patient data from a human norovirus challenge study.



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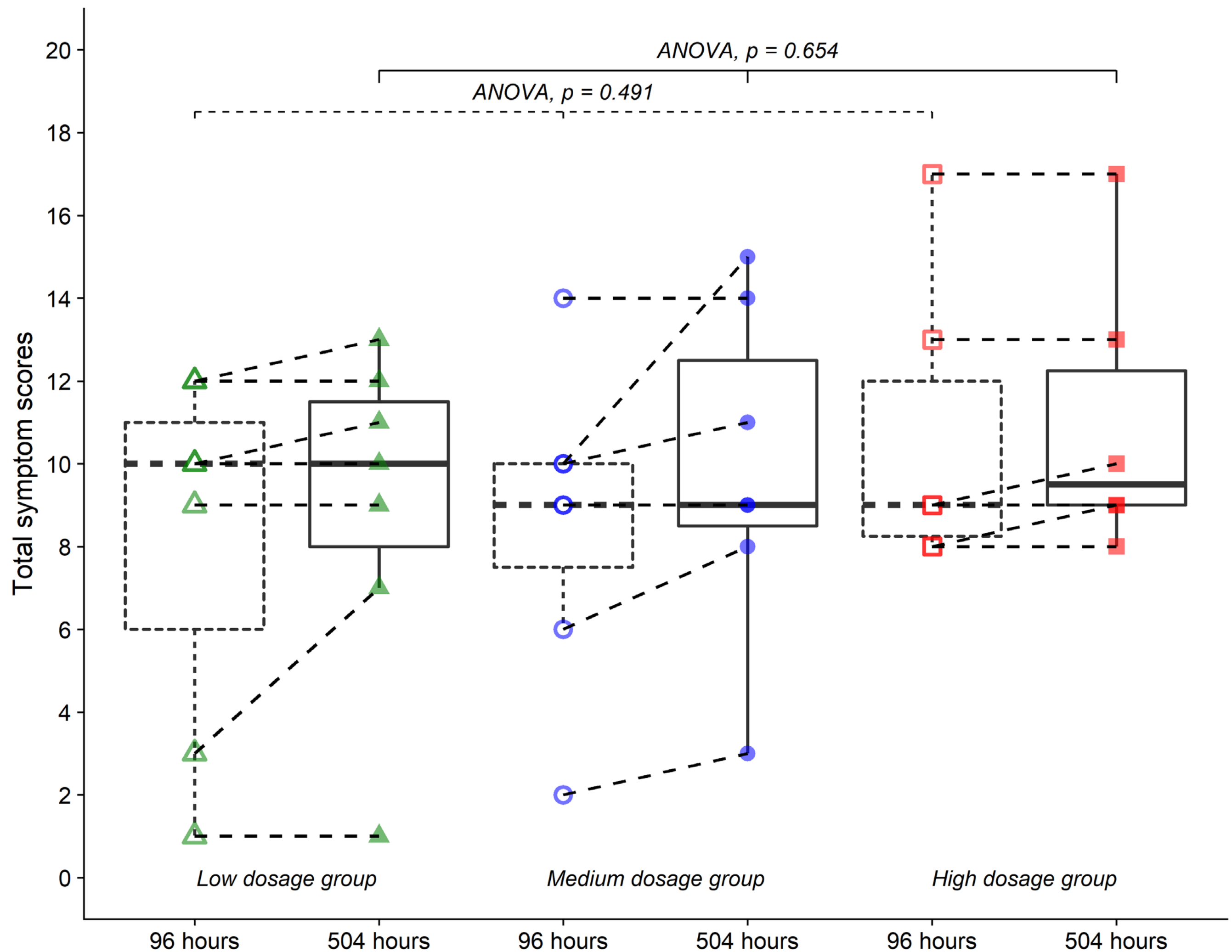

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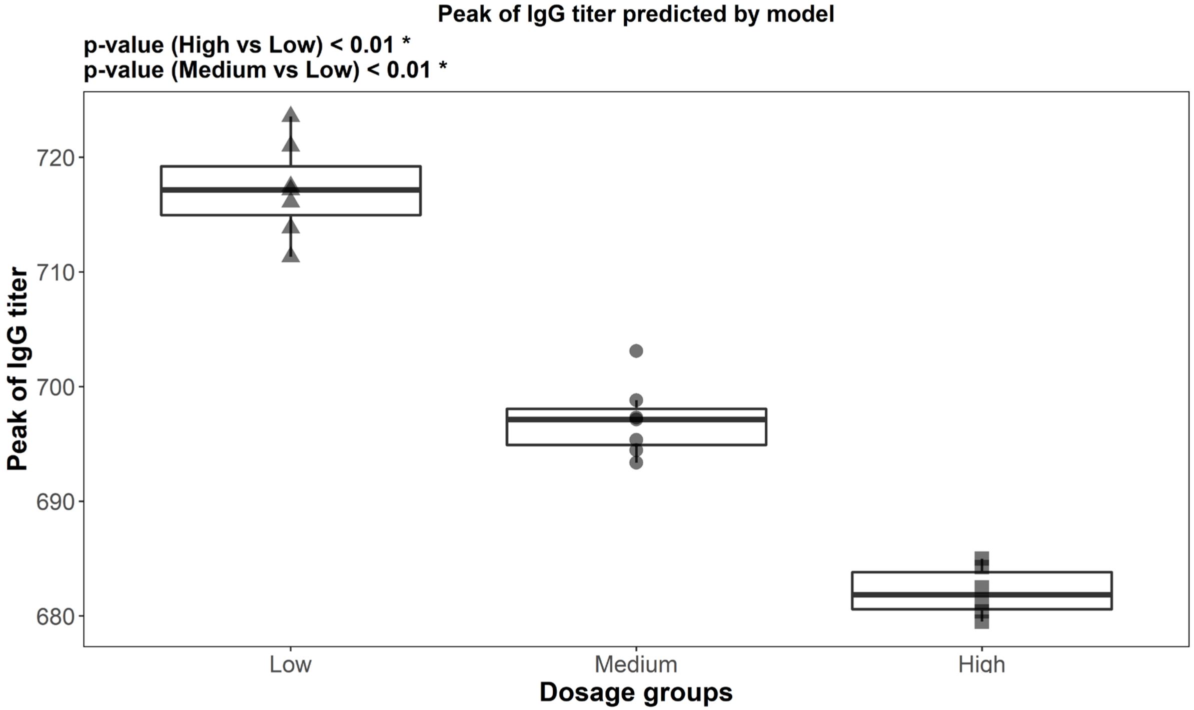
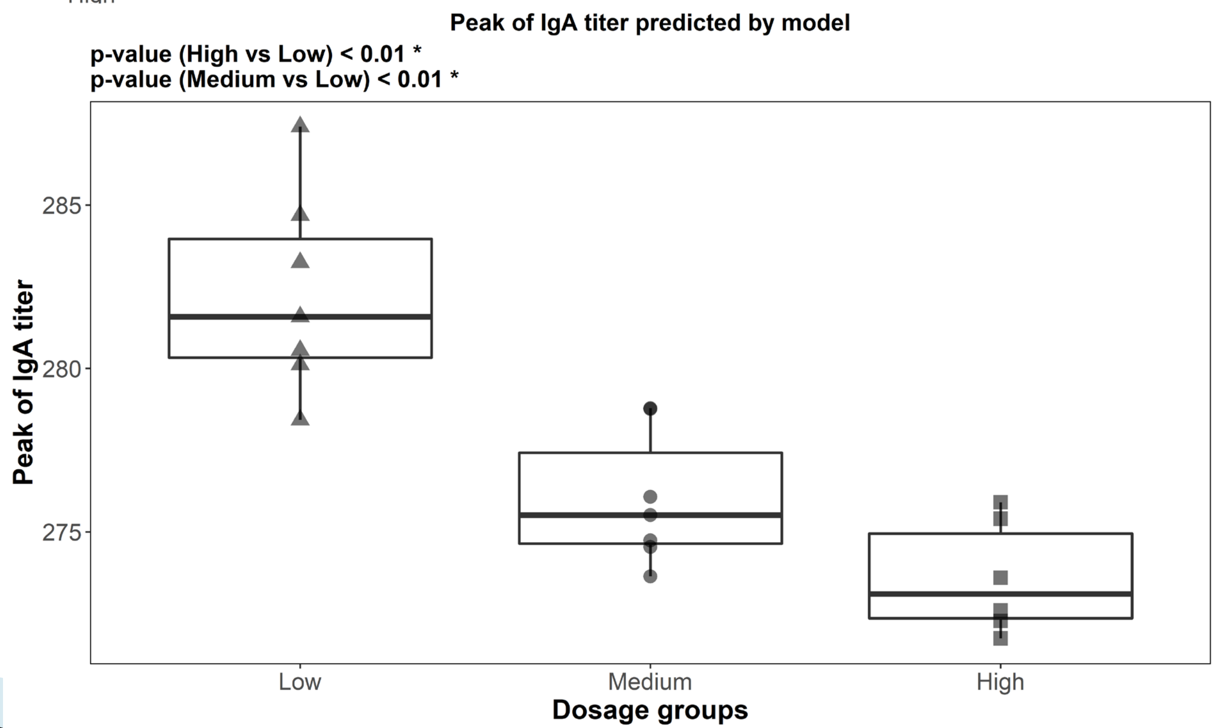


IgG peak titer

IgA peak titer



Future work

- Human norovirus vaccine candidate studies
  - Individual patient data from phase 1+2 trials of a norovirus vaccine candidate (thanks to Takeda). Infections at 3 different doses, killed vaccine, larger sample size.
- Influenza animal studies
  - Impact of dose on infection of a live attenuated vaccine in ferrets (Mark Tompkins).
- Human influenza studies
  - Existing data from individuals receiving either regular or high-dose influenza vaccine (Ted Ross).
  - New data as part of a large "Universal" influenza vaccine project. (Ted Ross, Stacey Schultz-Cherry, and 40 (or so?) co-Investigators).

Acknowledgements

- This work was done with the following collaborators


Yan Li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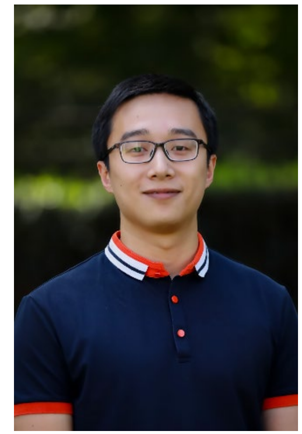
Yang Ge


Kasia Pawelek


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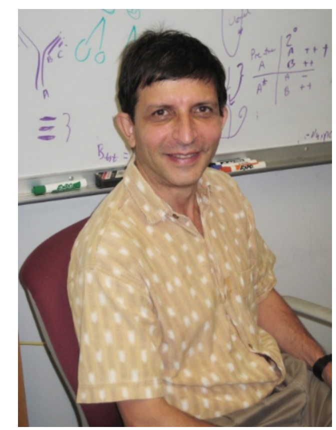
Rustom Antia

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