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Title: Biosurveillance Review

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70 YEARS OF CREATING TOMORROW

Los Alamos NATIONAL LABORATORY

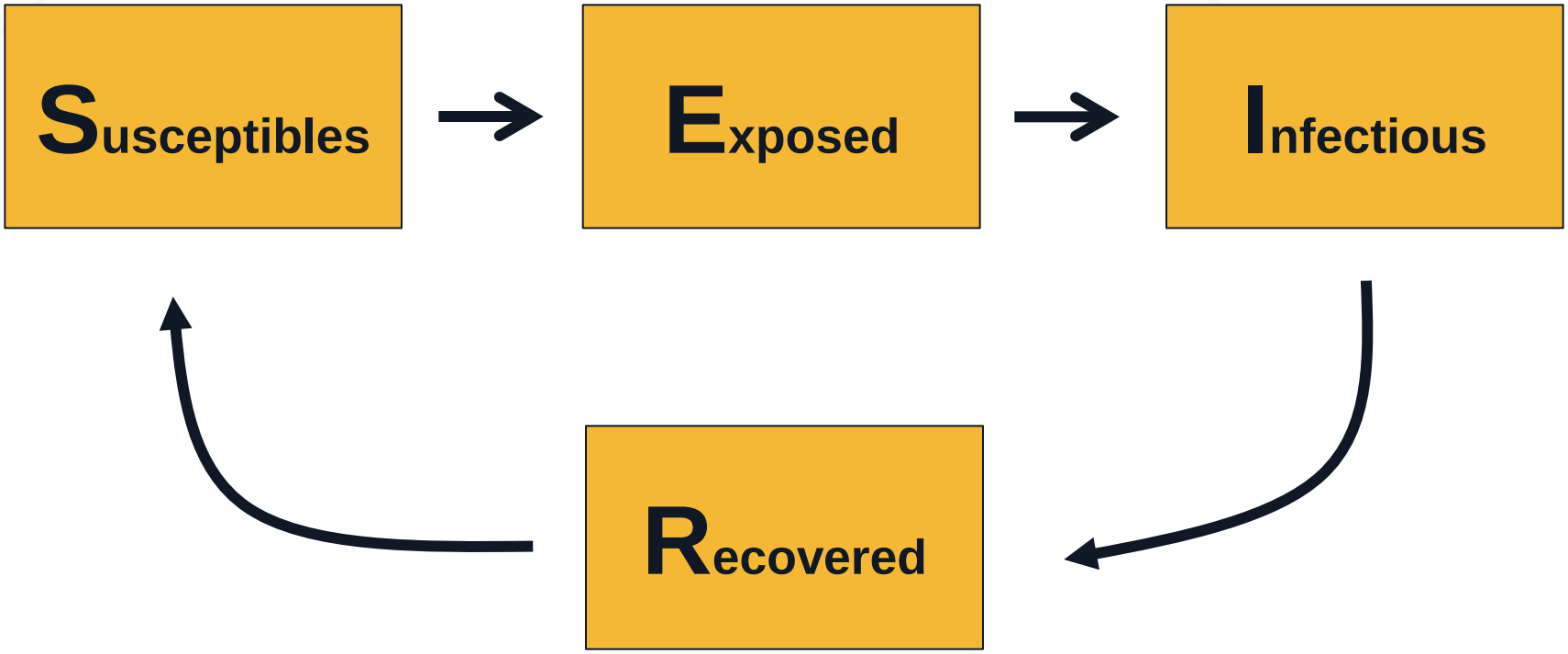
Biosurveillance Review

Ruy Ribeiro

Multiscale models of disease: from the host to the population

September 11-12, 2013

A simple epidemiological model



Within host determinants

- Pathogen
  - Load
  - Genotype/Phenotype
  - Co-infections
- Immune response
  - Right kind
  - Primed
- Host damage
- Symptoms

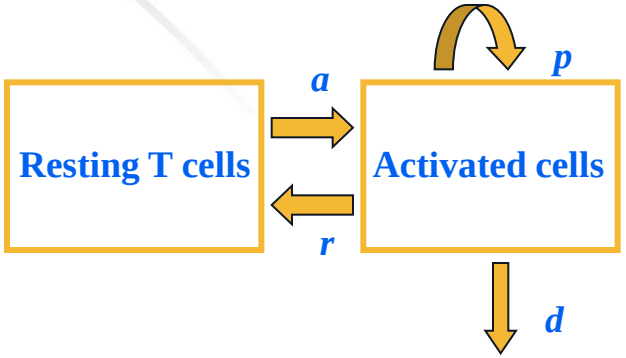
How to link multiple scales

- Research problem
- Potential approaches
  - Divide epi in sub-compartments, eg. resistance
  - Define distribution of rates based on within host models
  - Make pathogen transmission dependent on titers
  - Build agent-based models with within-host dynamics

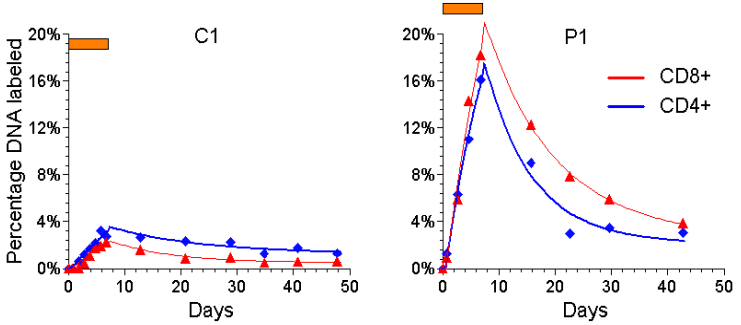
LANL capabilities

- **Technical capabilities**
  - Data analysis and interpretation
  - Statistical models and data fitting
  - Development of mechanistic models
  - Multiscale model development
    - Materials
    - Astrophysics
    - Climate/Ocean Modeling
- **Subject specific expertise**
  - Immune system
  - Chronic infections: HIV, HCV, HBV
  - Acute infections: influenza

From models….



…to knowledge



- Some examples of within-host modeling
  - Detailed description of the epidemiological classes according to within-host status (HIV)
  - Mechanistic models of within-host infection (influenza)

HIV vaccines: questions of interest

- Can non-sterilizing vaccines help control the epidemic?

- Which vaccine parameters are most important for this?

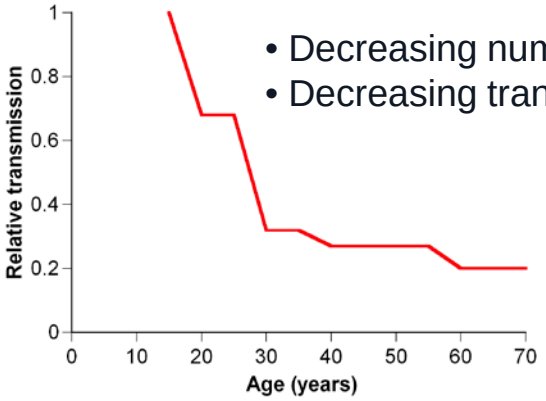
Predicting the Impact of a Nonsterilizing Vaccine against Human Immunodeficiency Virus

Miles P. Davenport,[1,2] Ruy M. Ribeiro,[2] Dennis L. Chao,[3] and Alan S. Perelson[2]*

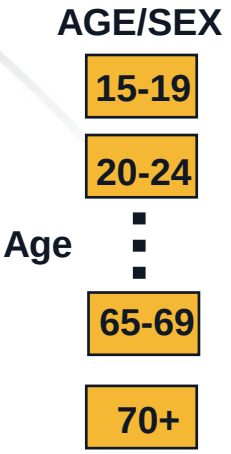
Davenport *et al.* J Virol 2004

A model of HIV-1 non-sterilizing vaccines

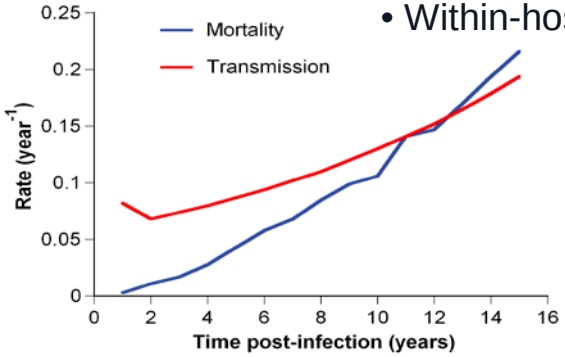
- Transmission by age & sex



- Decreasing number of sexual partners
- Decreasing transmission

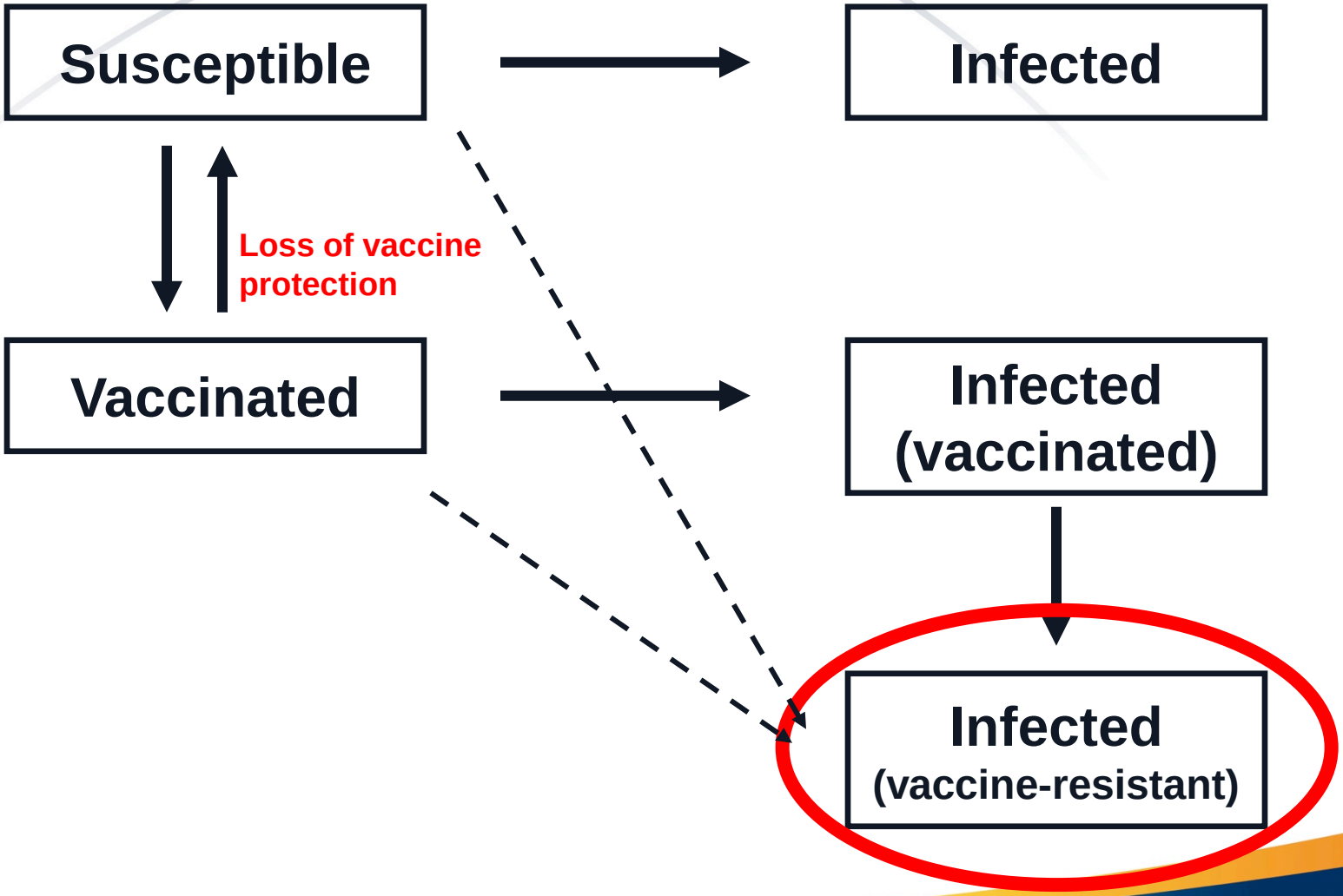


- Transmission/symptoms by duration of infection

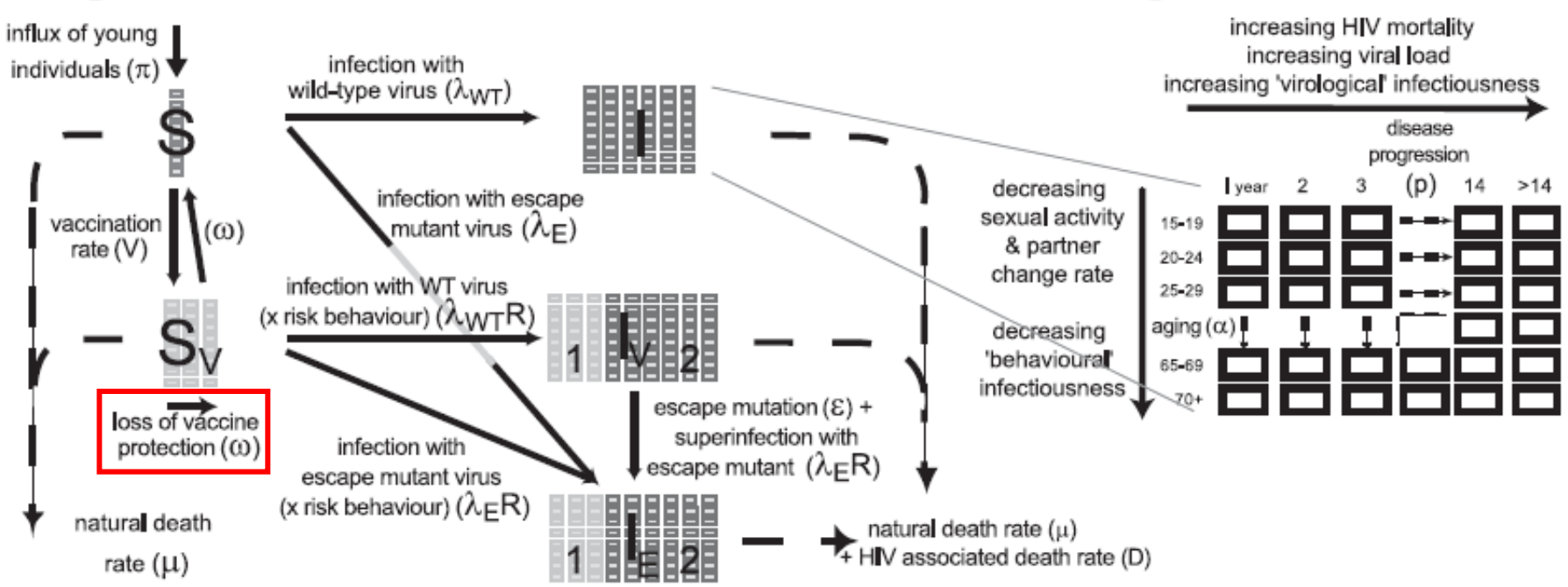


- Within-host variable

Add vaccinated class



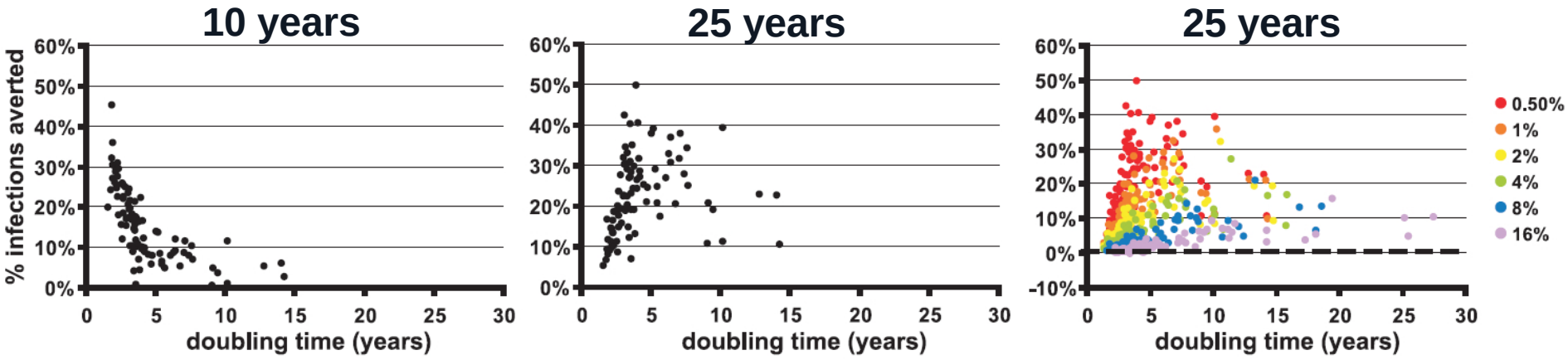
Everything together!



Davenport *et al.* J Virol 2004

HIV vaccines: results

- The vaccine has different effect in different populations
  - Prevalence is important
  - Rate of growth of the epidemic is important



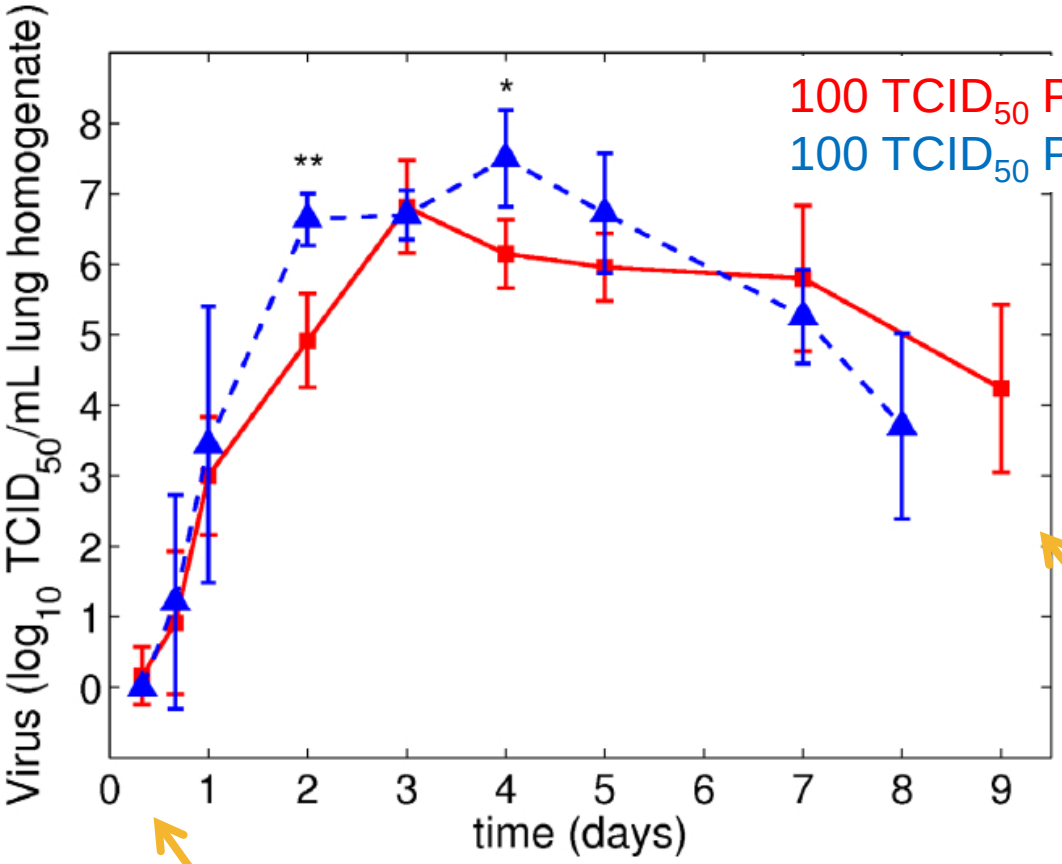
Davenport *et al.* J Virol 2004

- Influenza infection in mice
  - To study pathogenesis
  - To study immunology

Effect of 1918 PB1-F2 Expression on Influenza A Virus Infection Kinetics

Amber M. Smith[1], Frederick R. Adler[2], Julie L. McAuley[3], Ryan N. Gutenkunst[4], Ruy M. Ribeiro[1], Jonathan A. McCullers[5], Alan S. Perelson[1]*

Mouse model of influenza infection



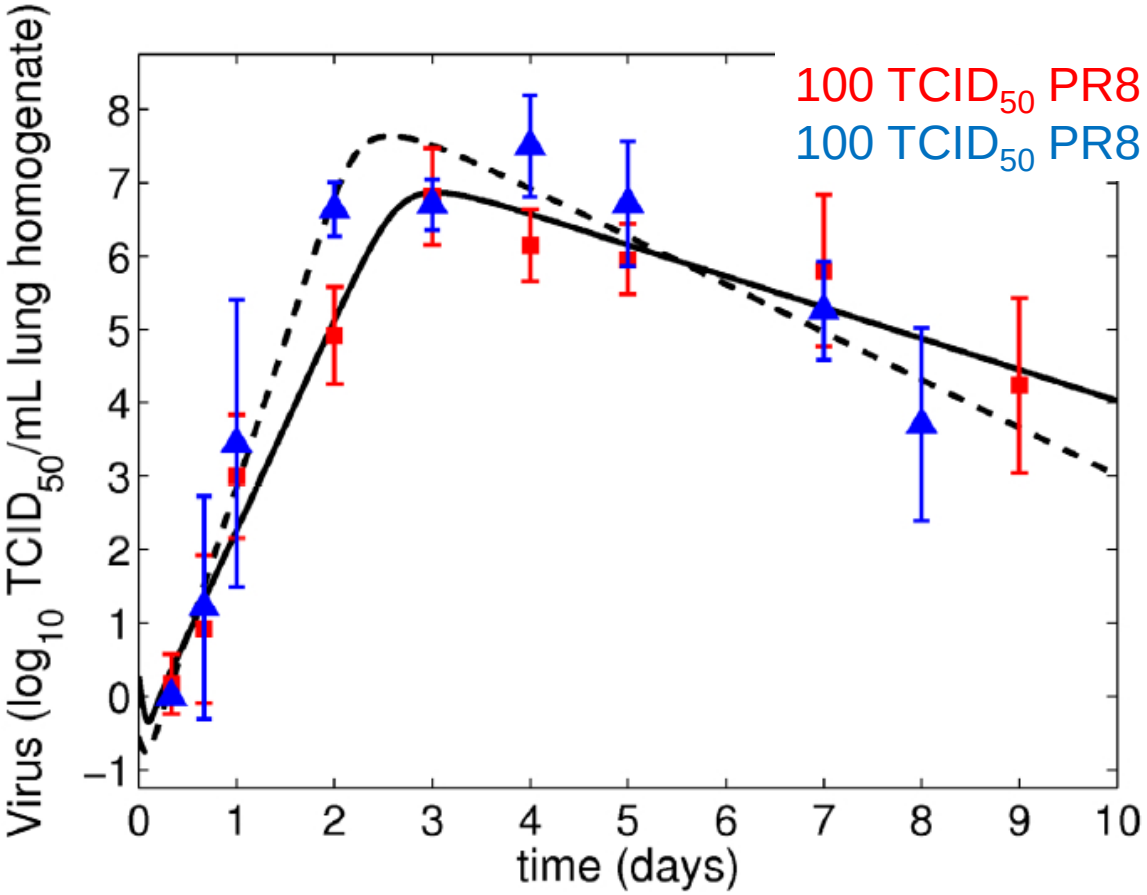
Fits to influenza infection in mice

$$\frac{dT}{dt} = -\beta TV$$

$$\frac{dI_1}{dt} = \beta TV - kI_1$$

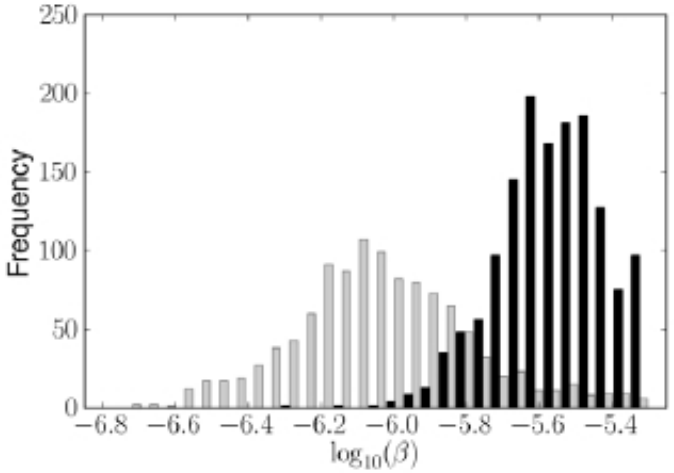
$$\frac{dI_2}{dt} = kI_1 - \delta I_2$$

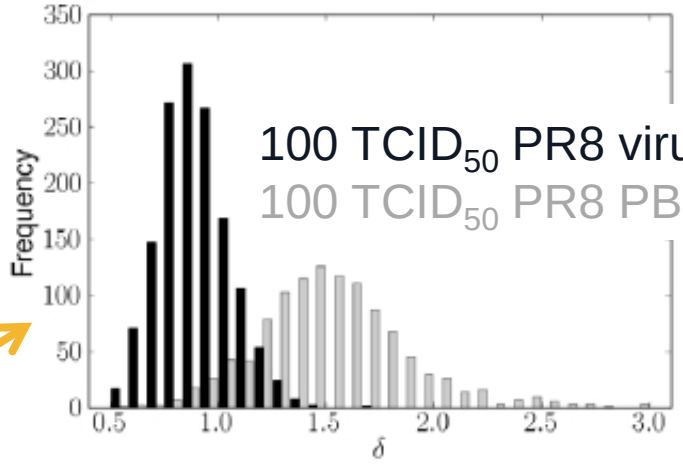
$$\frac{dV}{dt} = pI_2 - cV$$



Smith *et al.* PLoS Comp Biol 2011

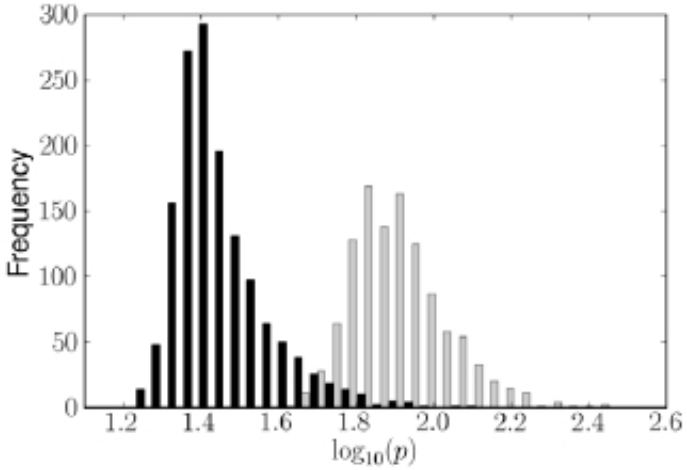
Fits to influenza infection in mice

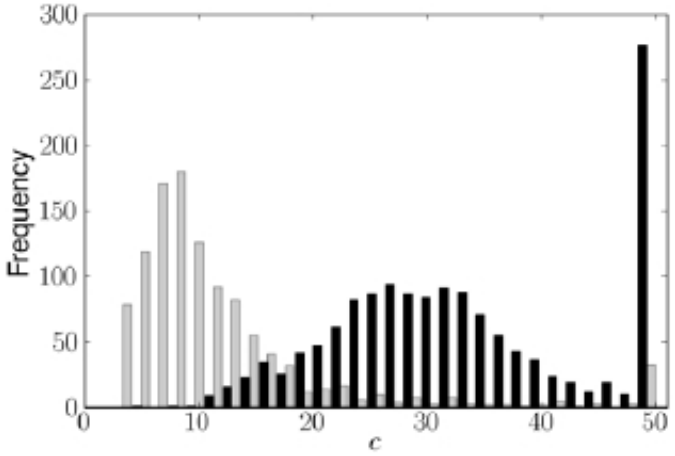




100 $TCID_{50}$ PR8 virus

100 $TCID_{50}$ PR8 PB1-F2(1918)





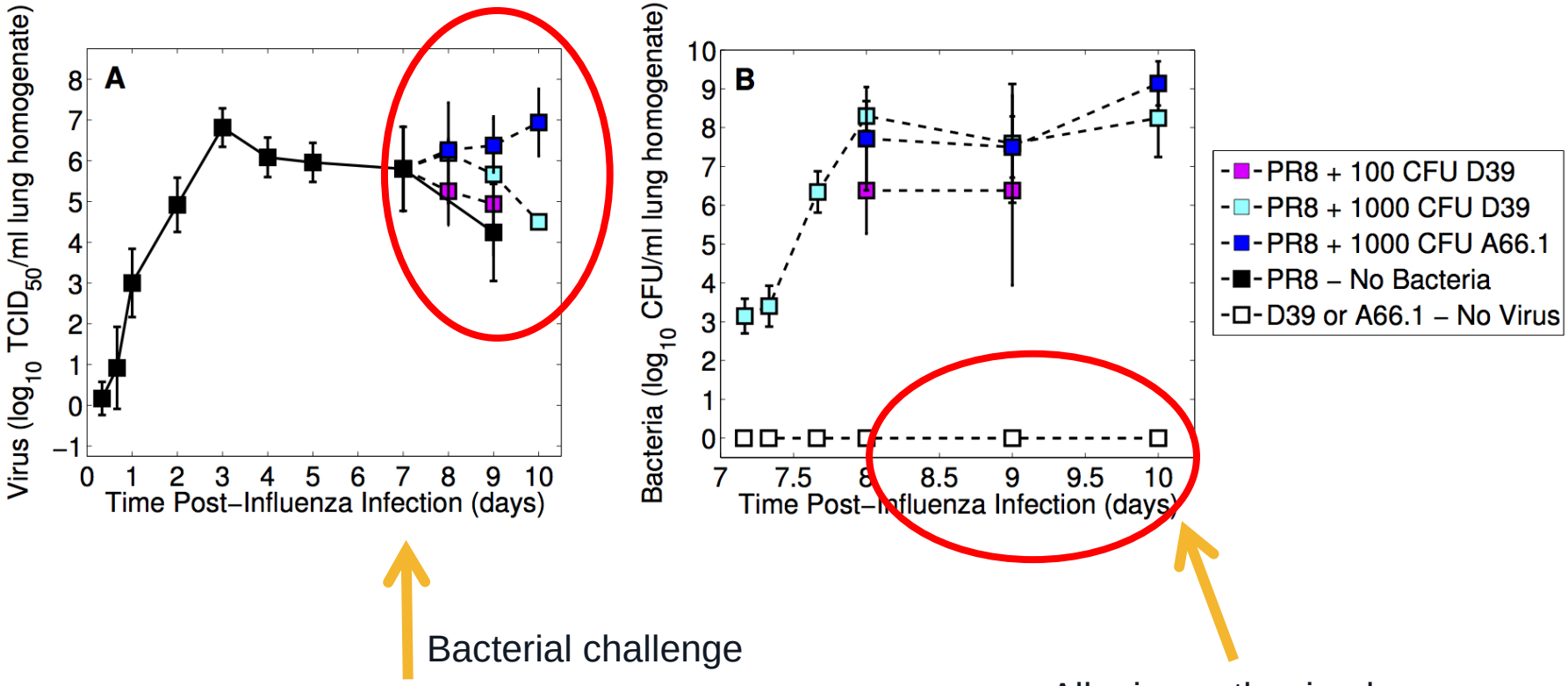
- Influenza & *S. pneumonia* co-infection
  - An important cause of morbidity / mortality
  - Synergy mechanisms not well understood

Kinetics of Coinfection with Influenza A Virus and *Streptococcus pneumoniae*

Amber M. Smith[1]*, Frederick R. Adler[2], Ruy M. Ribeiro[3,4], Ryan N. Gutenkunst[5], Julie L. McAuley[6], Jonathan A. McCullers[1], Alan S. Perelson[3]

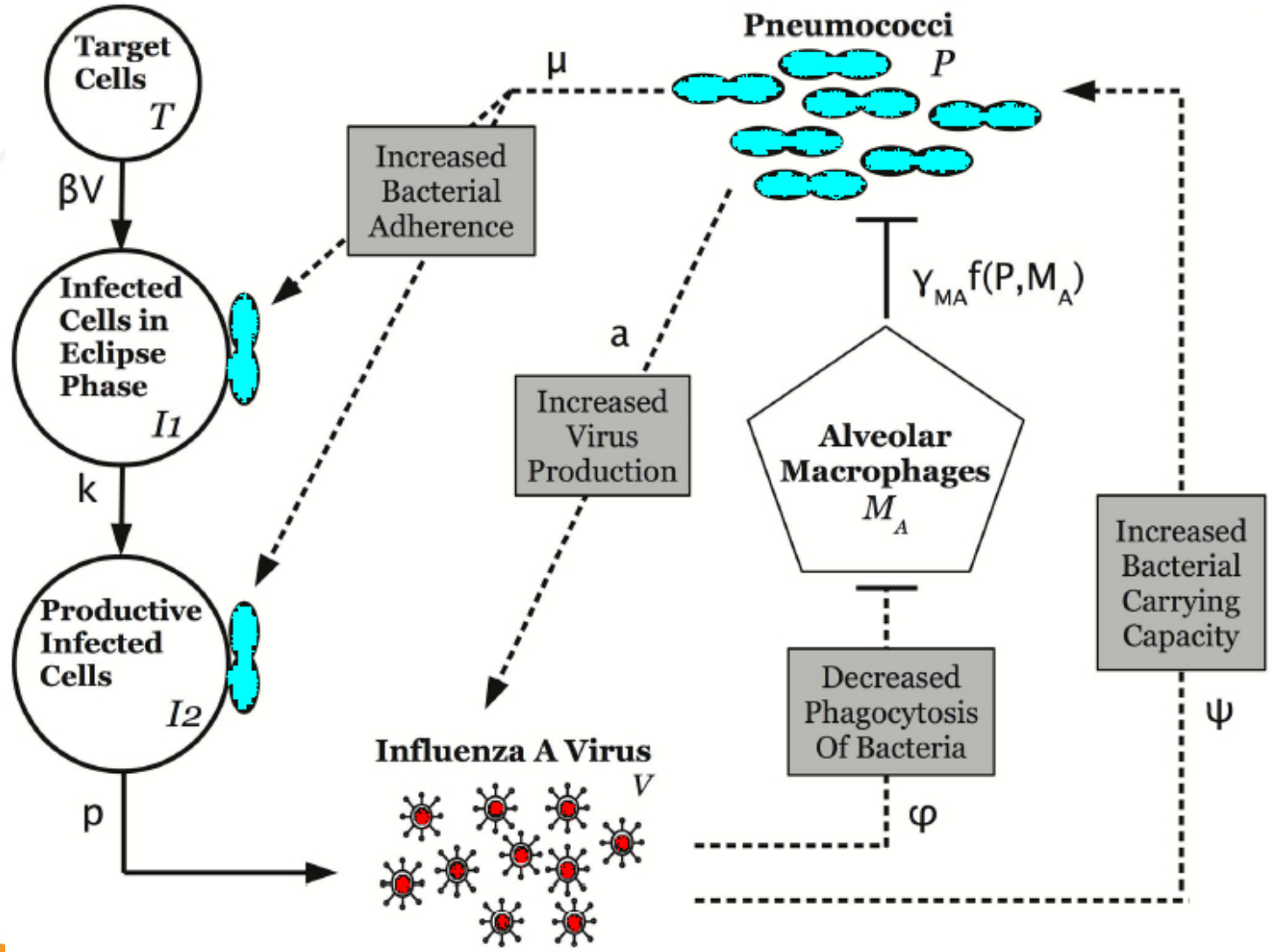
Smith *et al.* PLoS Pathogens 2013

Effect of co-infection on titers

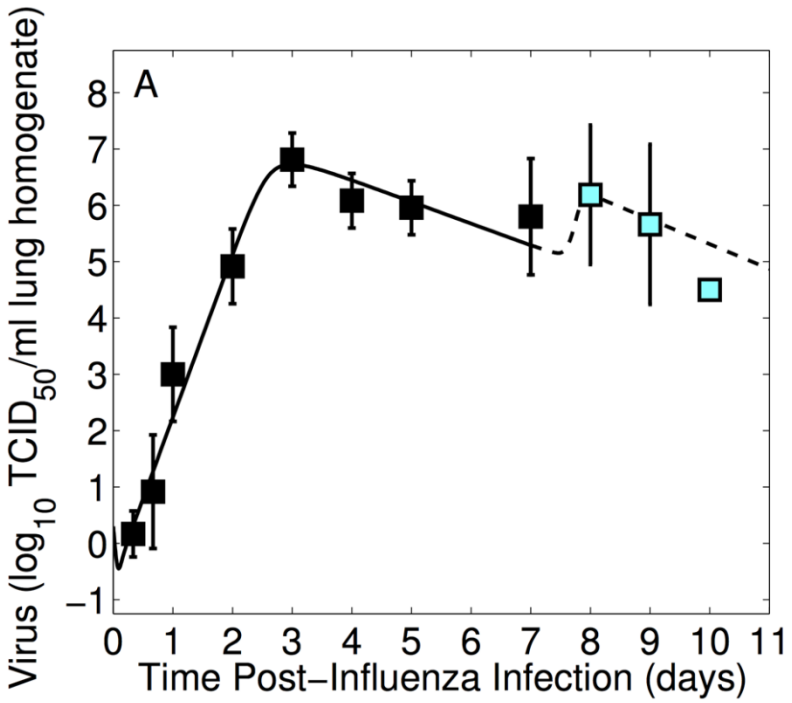


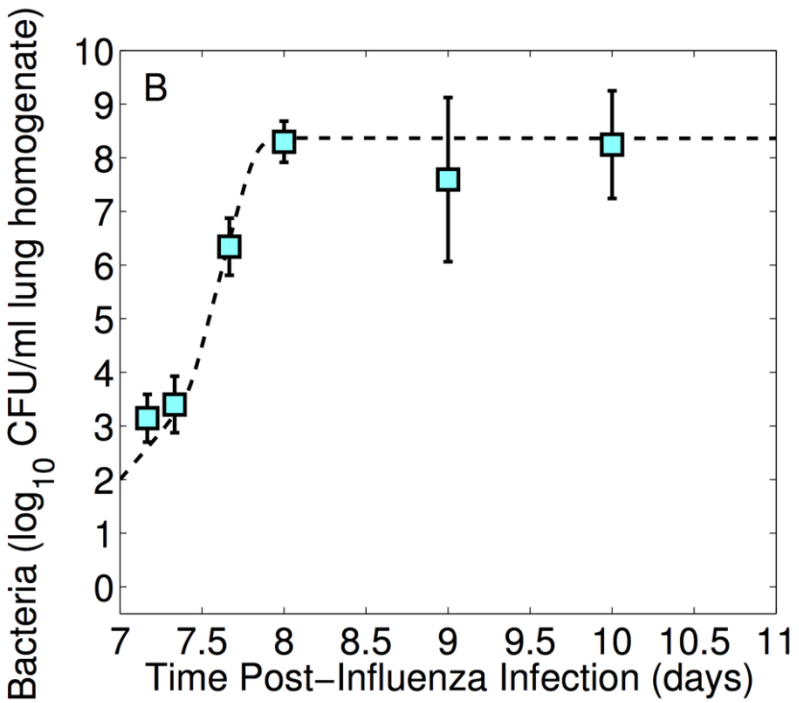
Smith *et al.* PLoS Pathogens 2013

Modeling possible mechanisms



Model fits: PR8 and *S. pneumonia*





Smith *et al.* PLoS Pathogens 2013

Analysis and Results

- Bayesian ensemble analysis
- Parameter perturbation
- Sensitivity analysis
- Model comparison (AIC)

- **RESULTS**
  - Alveolar Macrophage dysfunction (Ghoneim et al, J. Immunol 2013)
  - Enhanced viral release from infected cells

Future perspective

- Further develop within-host models
  - Integrate more immune response information
    - Incorporate (i) host defense pathways (e.g., interferon, apoptosis, autophagy, etc.) that are induced early (innate immunity)
    - Incorporate the role of neutralizing antibodies and cytotoxic T cells in pathogen clearance (acquired immunity)
    - Include pathogen pathways that have evolved to counter immune defenses
  - Develop a model of host damage / symptoms
    - Link host cell death and damage to disease symptoms
    - Identify deleterious effects the immune system has on the host
  - Leverage new ‘omics data
    - Devise a strategy to integrate data stream at different time and length scales

Future perspective

- Develop multiscale epidemiological models
  - Use a partial differential equation approach
    - Similar to the HIV work discussed
    - Besides the time variable, we will have the internal status of the host as a second variable, eg. pathogen load
    - We are doing this to link within-host (systemic) and intracellular models
  - Build agent-based models, with agent within-host dynamics
    - Each host is an agent in the model with certain properties, these should include within-host dynamics of pathogen and immunity
    - We are working on such a model for HIV infection to analyze viral evolution at the population level (NIH funded)