Understanding the measles paradox: modeling host-parasite predatory feedbacks

Sinead Morris
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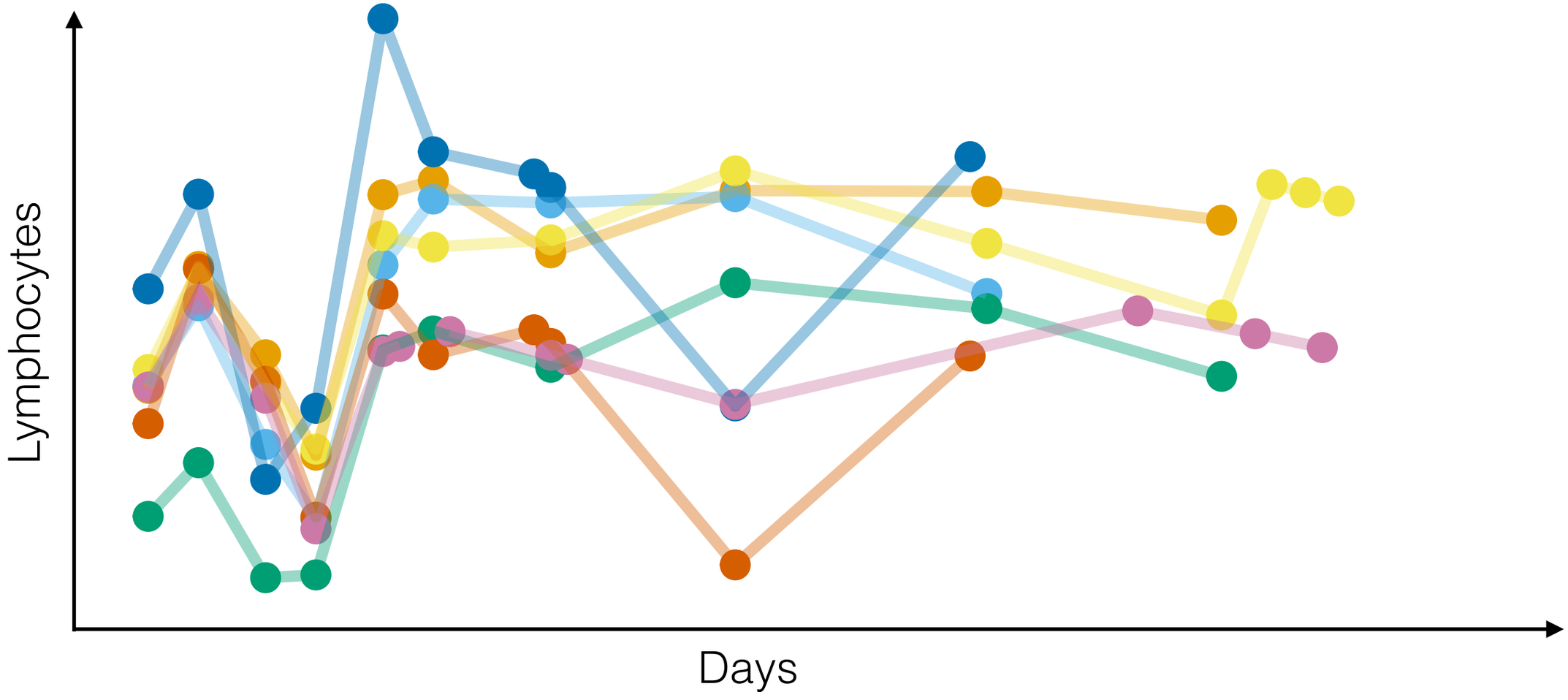
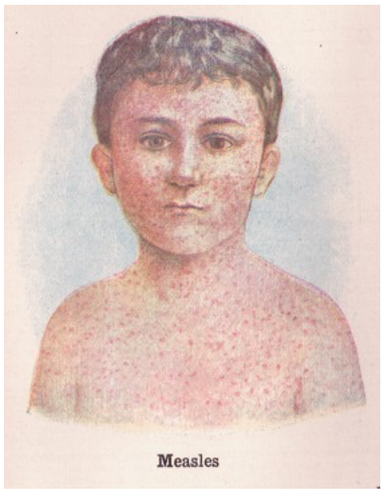
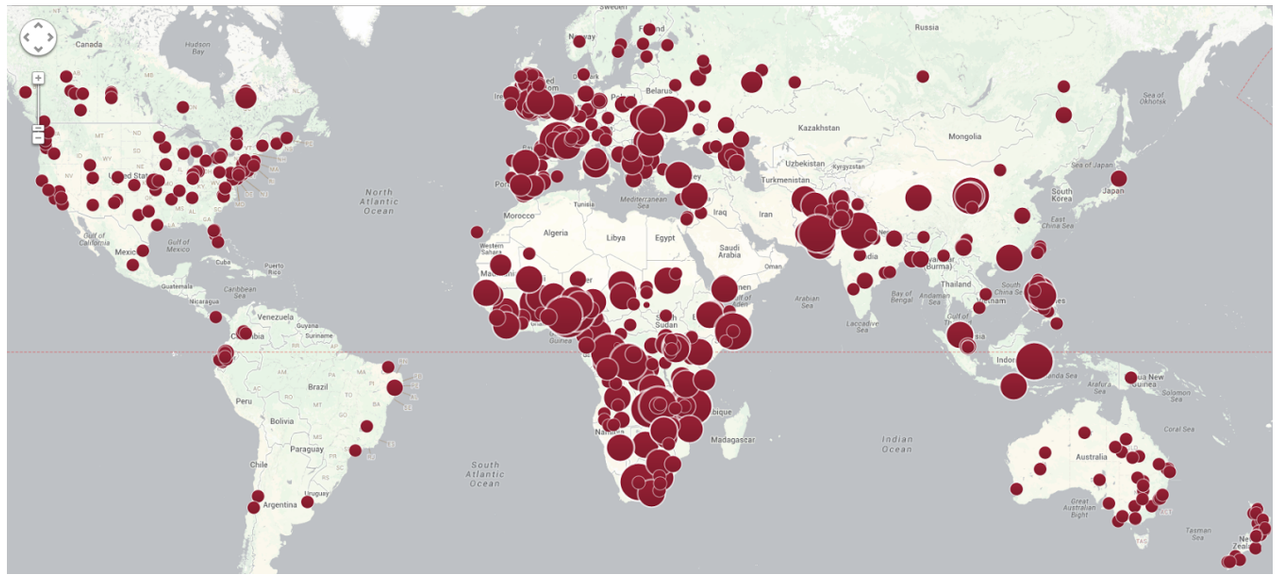
https://sineadmorris.github.io



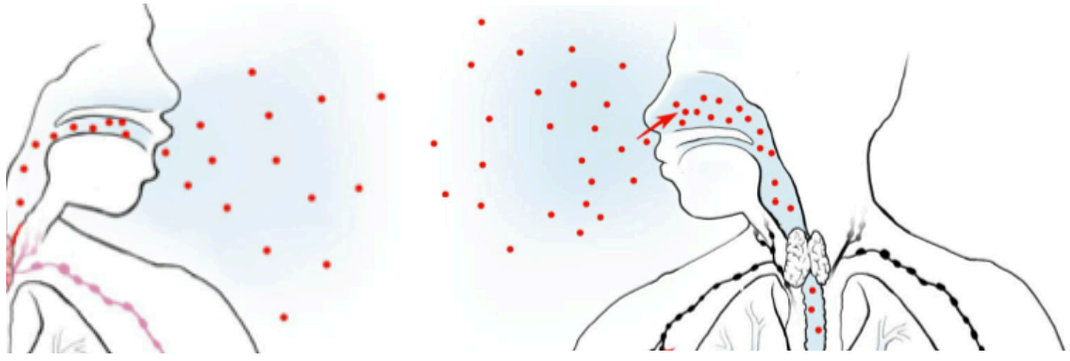
Background



serious respiratory disease



180,000 annual cases



classic respiratory infection

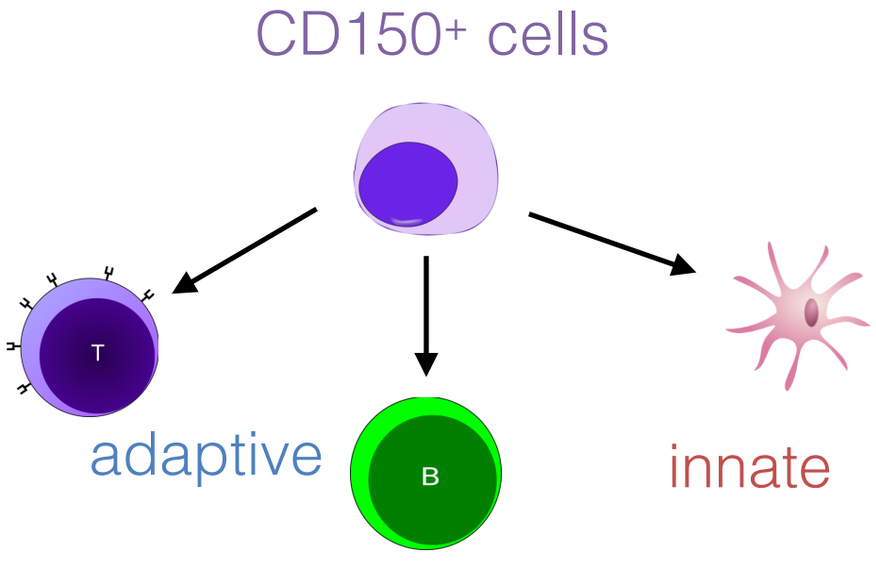
nature International weekly journal of science

Published online 20 June 2008 | Nature | doi:10.1038/news.2008.907

News

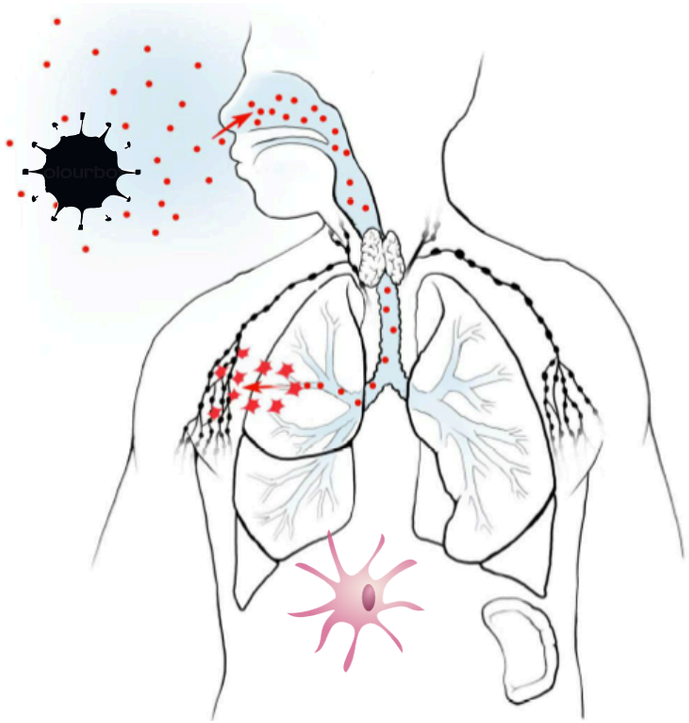
Measles doesn't work in the way we thought

Virus attacks the immune system, not the airways.

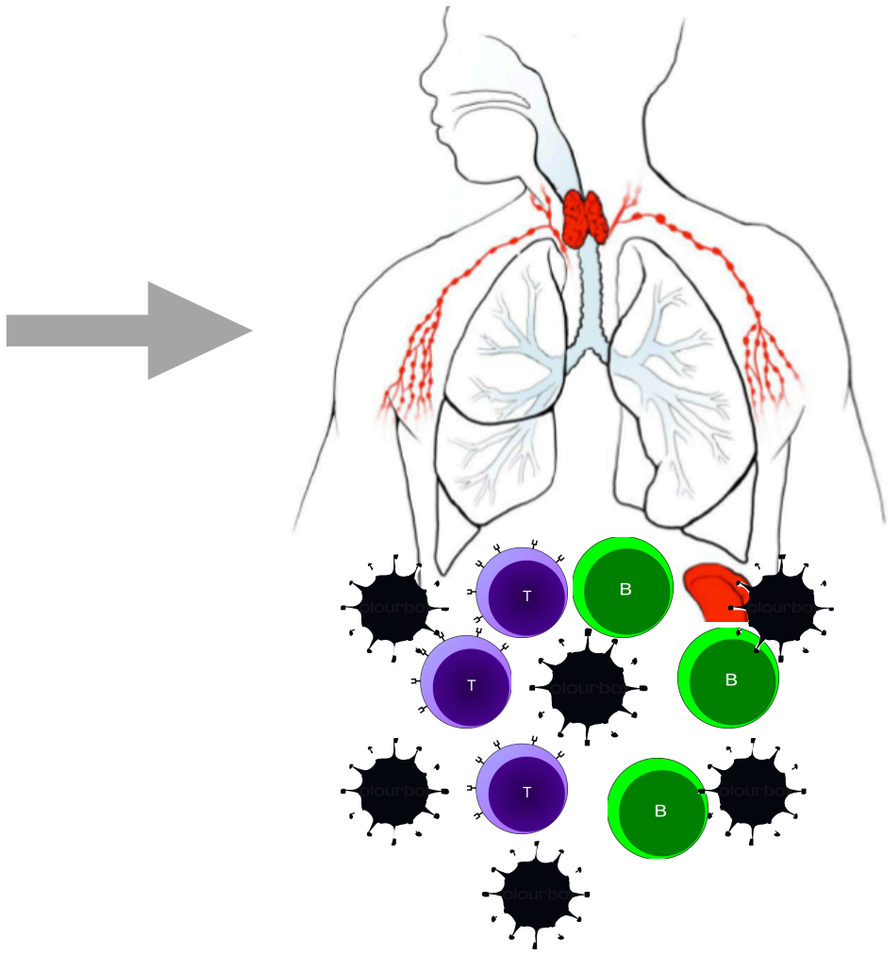


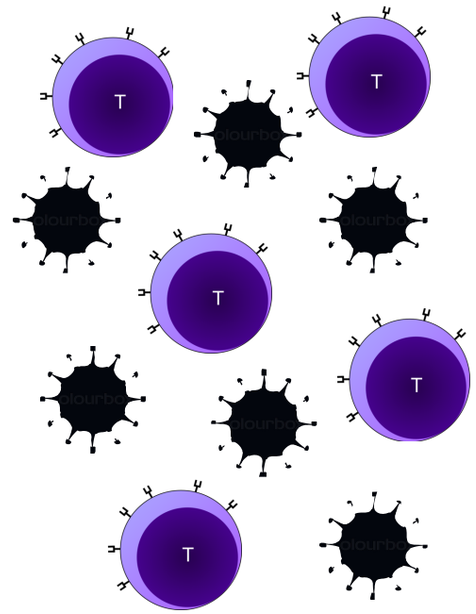
de Swart et al (2007) PLoS Pathogens

Background



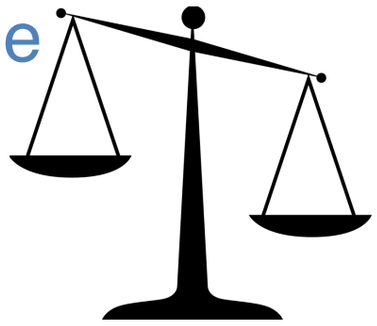
Mühlebach et al (2011) Nature



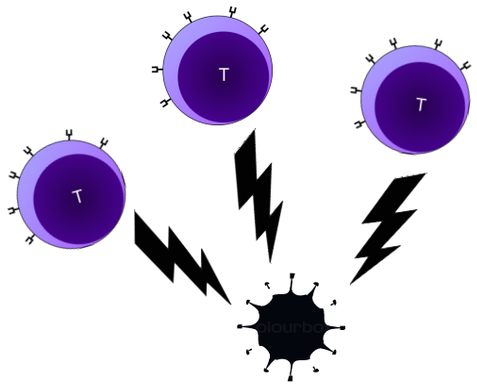


“Measles paradox”

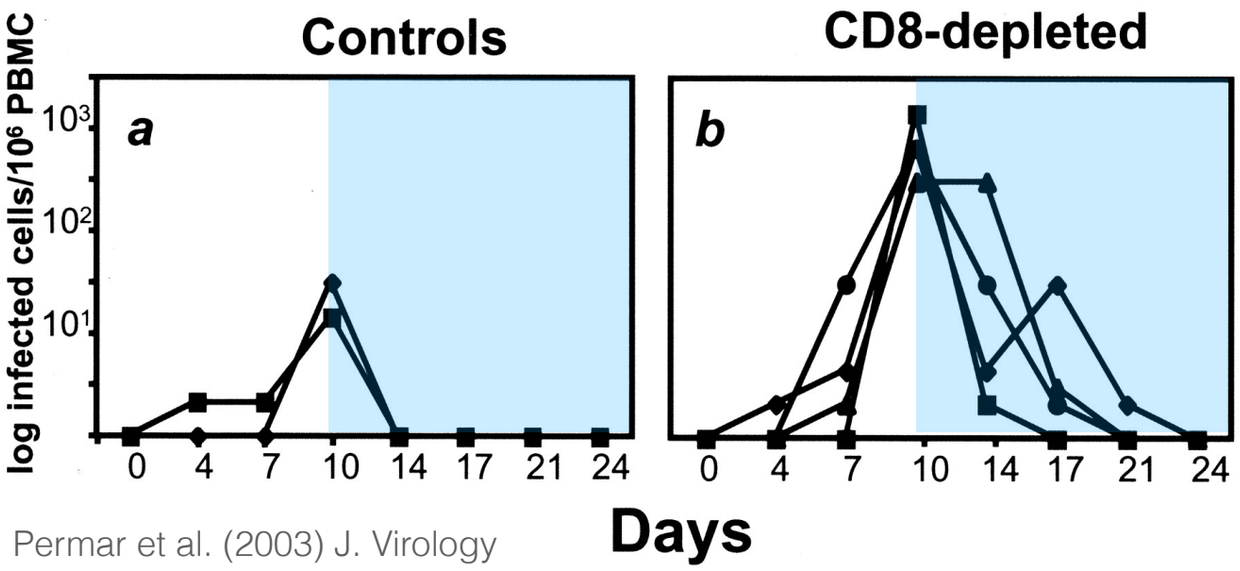
↑ strong immune response



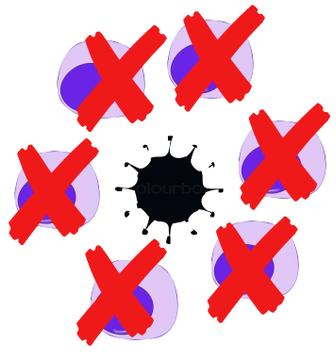
huge cell depletion ↓



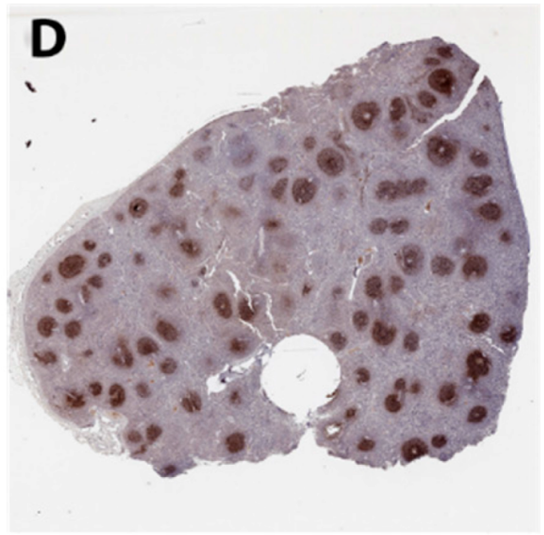
active suppression of viral growth



Permar et al. (2003) J. Virology



target cell limitation



Laksono et al. (2016) Viruses

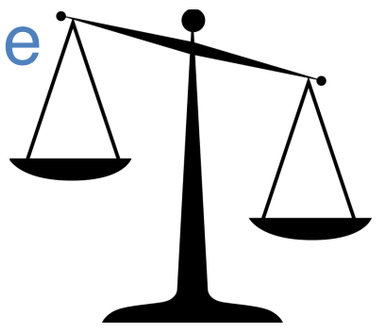
CDV: 100% mortality

Williams et al (1985) J. Wildlife Dis.

Ludlow et al (2012) J. Virology

“Measles paradox”

↑ strong immune response



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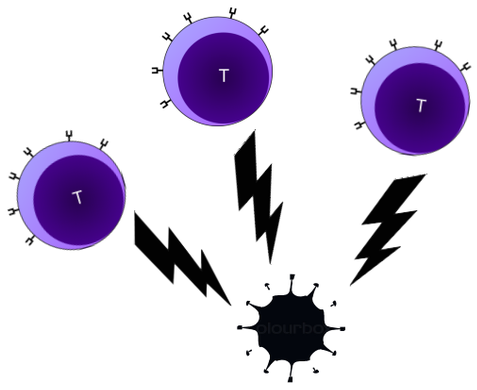
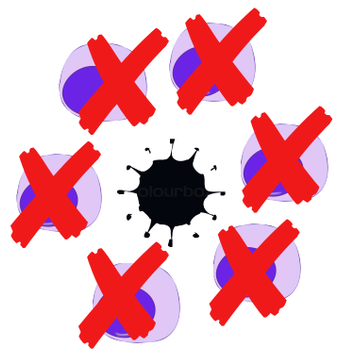


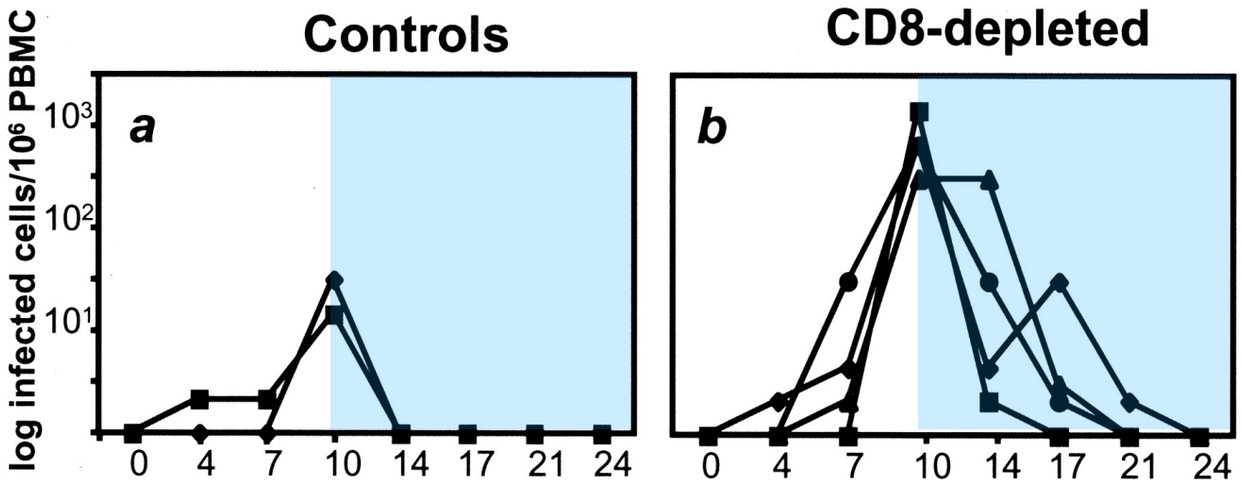
active suppression of viral growth

Aims

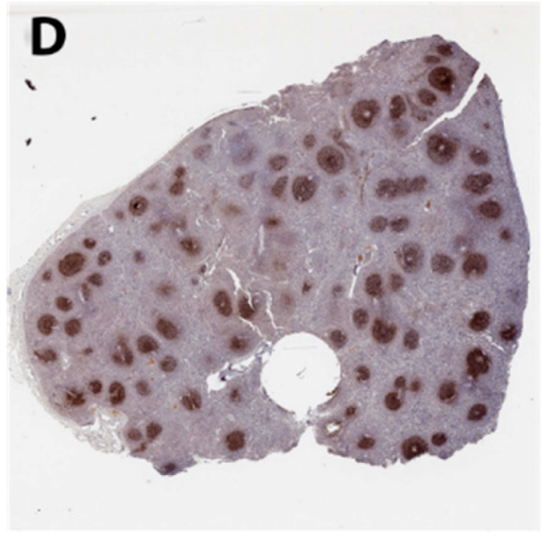
1. within-host model of predatory feedbacks
2. identify drivers of viral clearance



target cell limitation



Permar et al. (2003) J. Virology



Laksono et al. (2016) Viruses

CDV: 100% mortality

Williams et al (1985) J. Wildlife Dis.

Ludlow et al (2012) J. Virology

Data

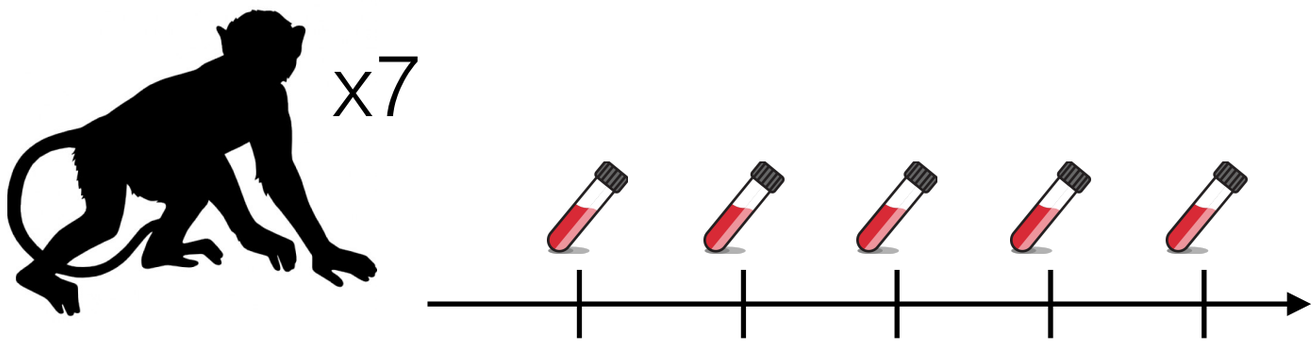
PNAS

Prolonged persistence of measles virus RNA is characteristic of primary infection dynamics

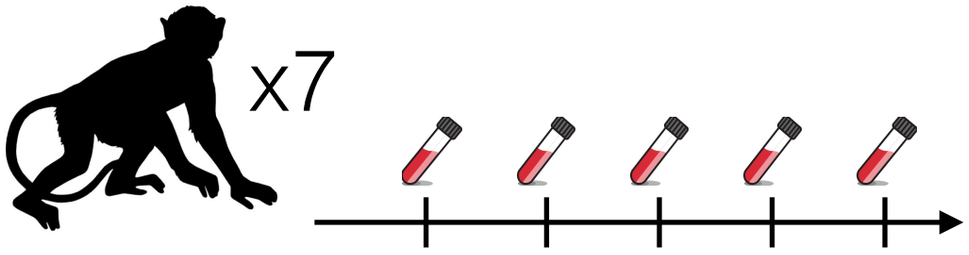
Wen-Hsuan W. Lin[a], Roger D. Kouyos[b], Robert J. Adams[c], Bryan T. Grenfell[b,d], and Diane E. Griffin[a,1]

[a]W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205; [b]Department of Ecology and Evolutionary Biology, Woodrow Wilson School of Public and International Affairs, Princeton University, Princeton, NJ 08544; [c]Department of Molecular and Comparative Pathobiology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205; and [d]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892

Contributed by Diane E. Griffin, July 2, 2012 (sent for review May 4, 2012)



Data



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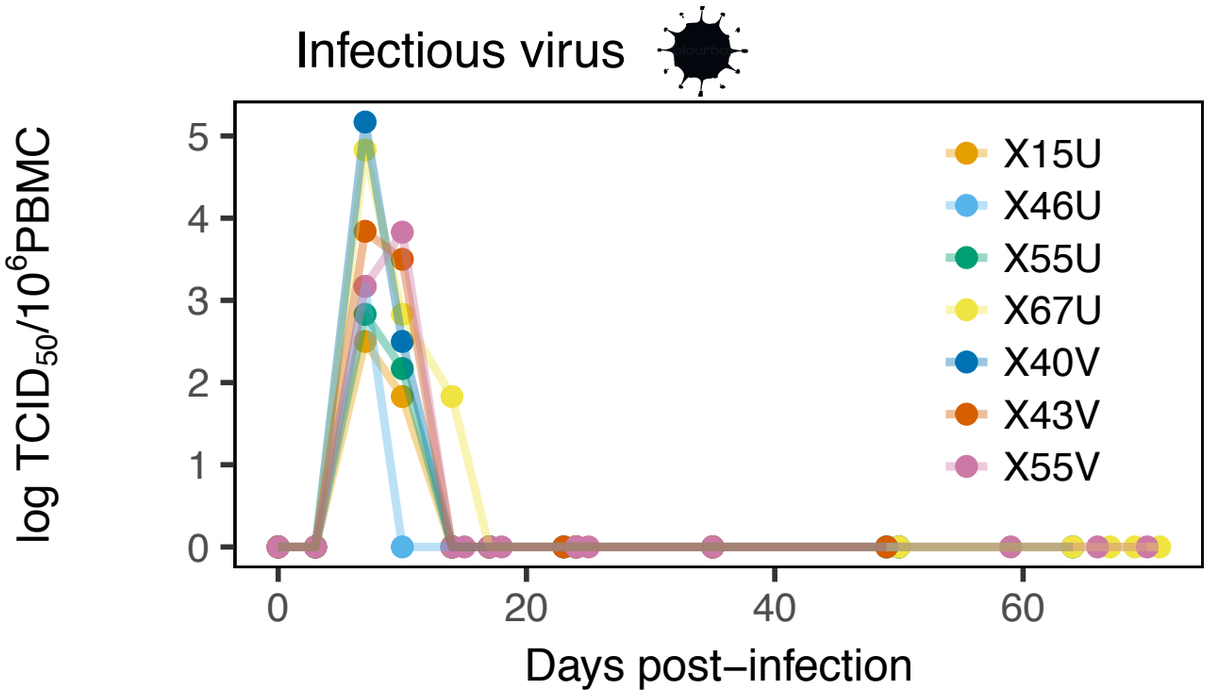
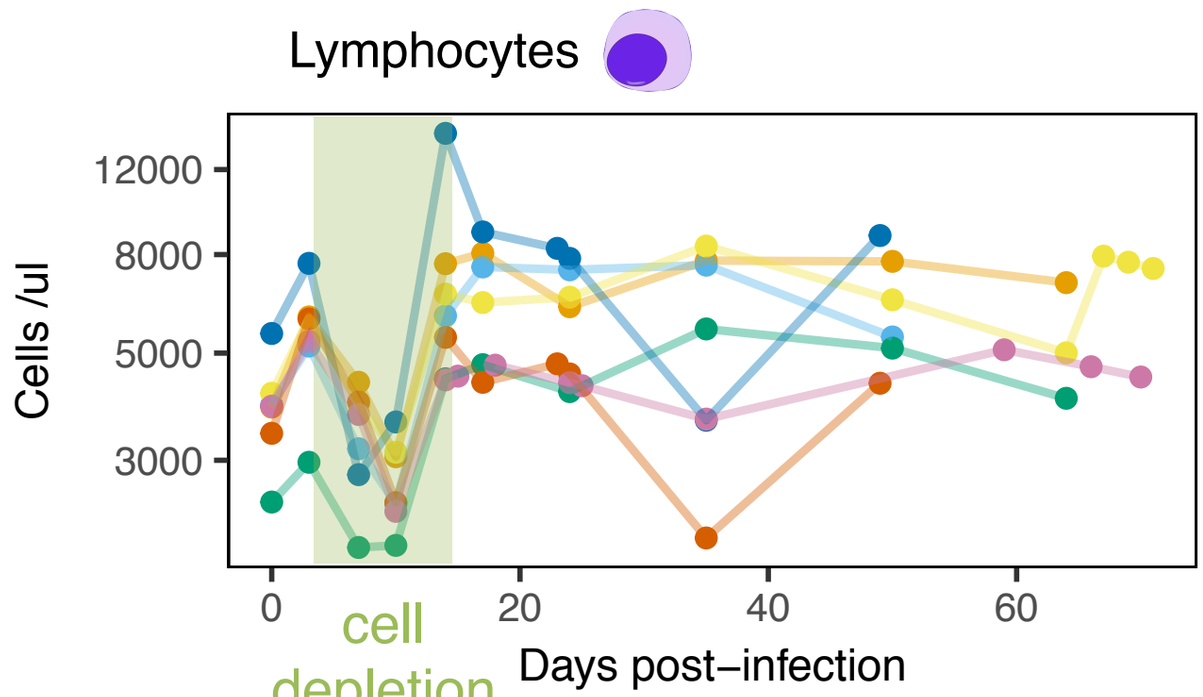
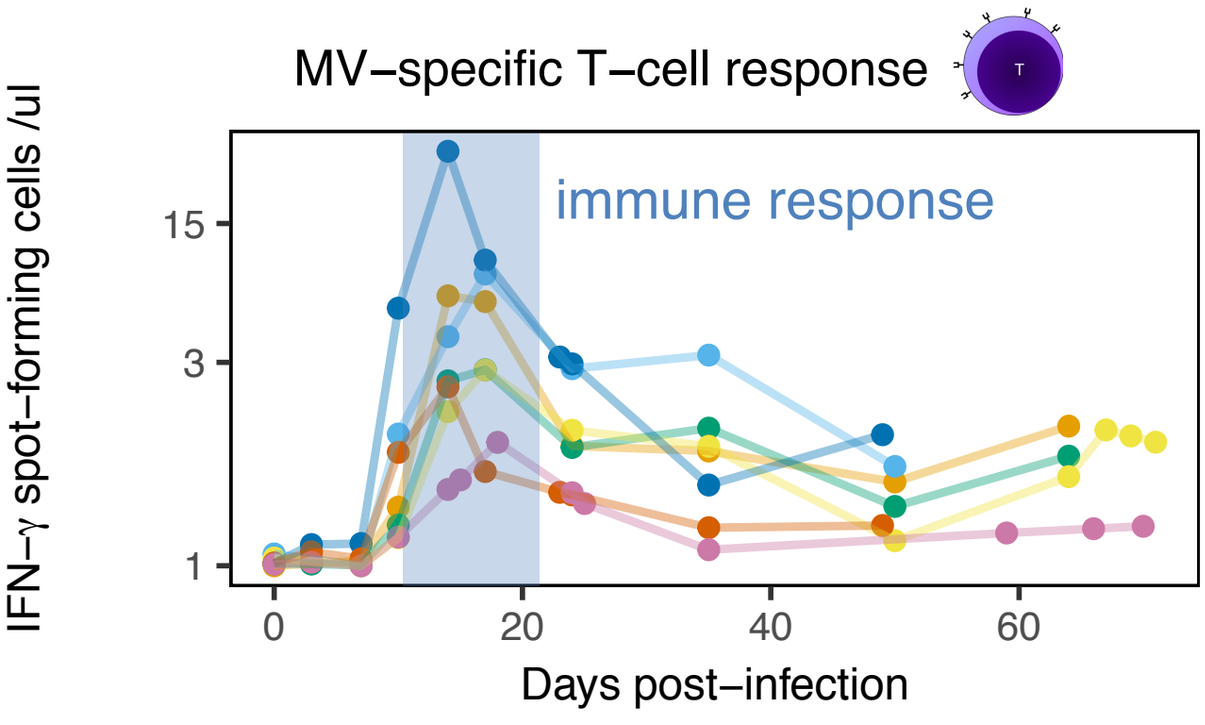
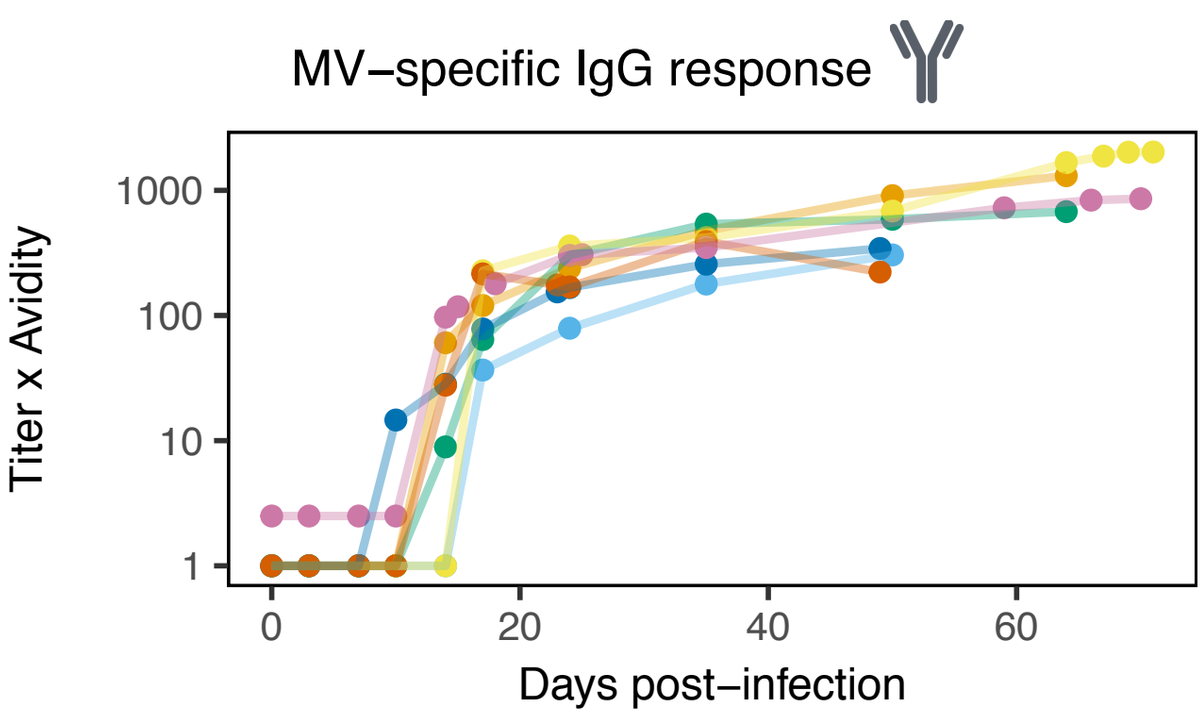
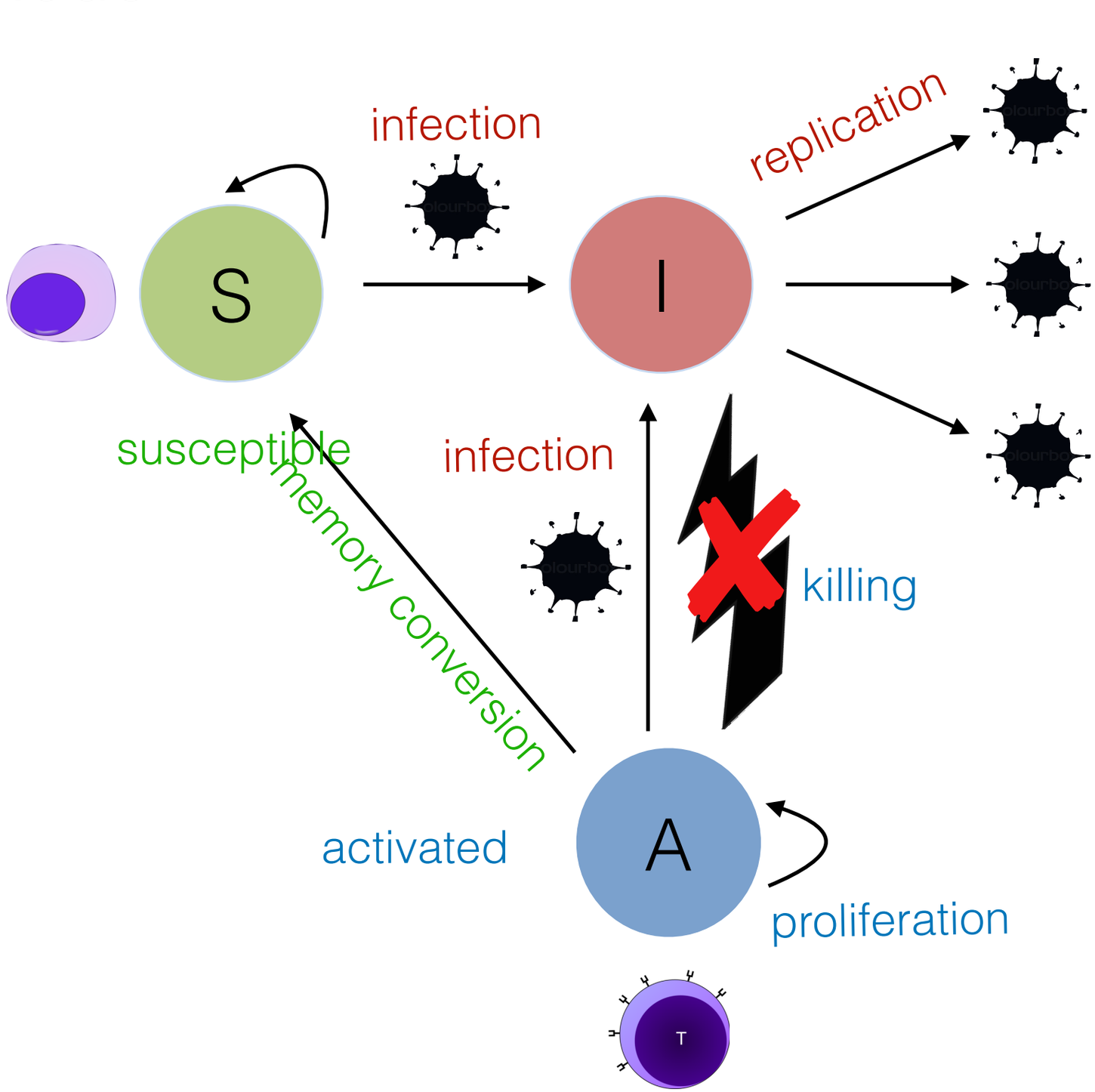








Model

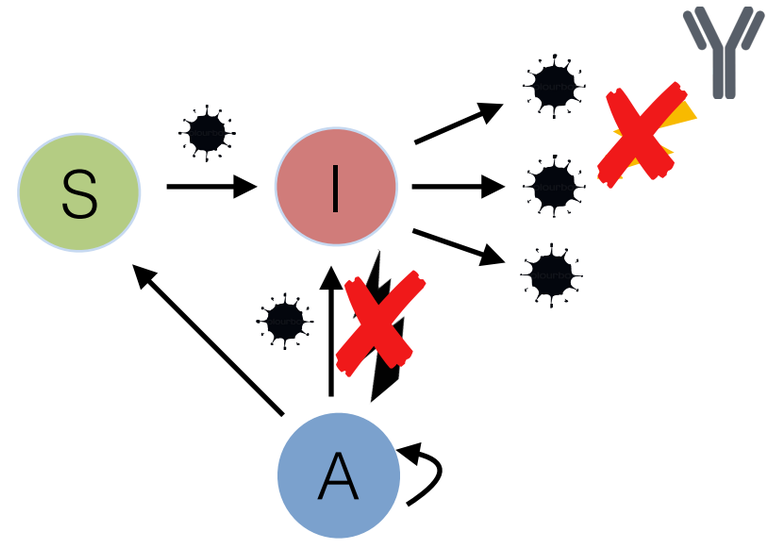


Target cells

Target cells + T-cells

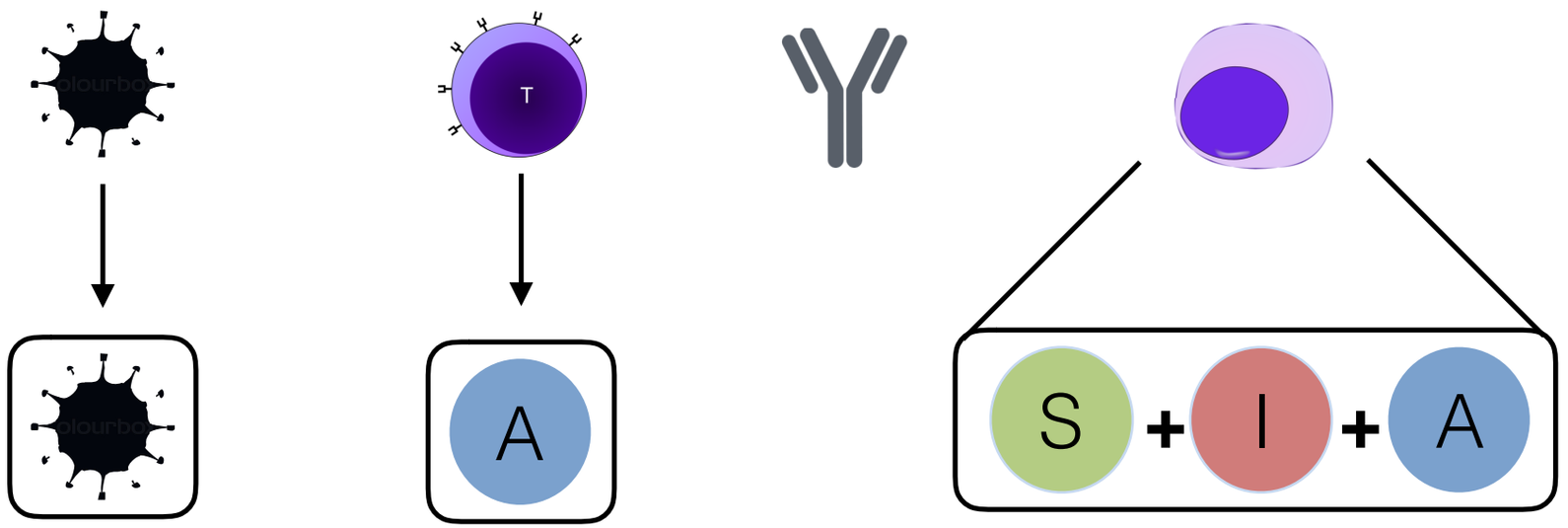
Target cells + T-cells + **Y**s

Model



Data

Model

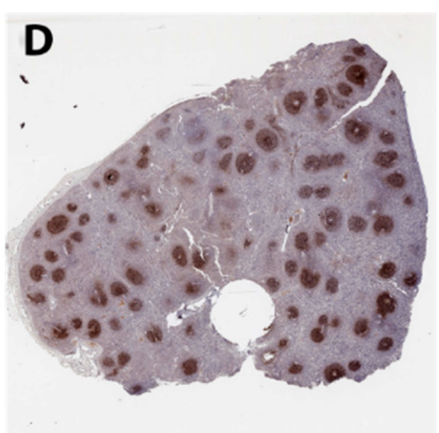


Caveats

Parameter specification

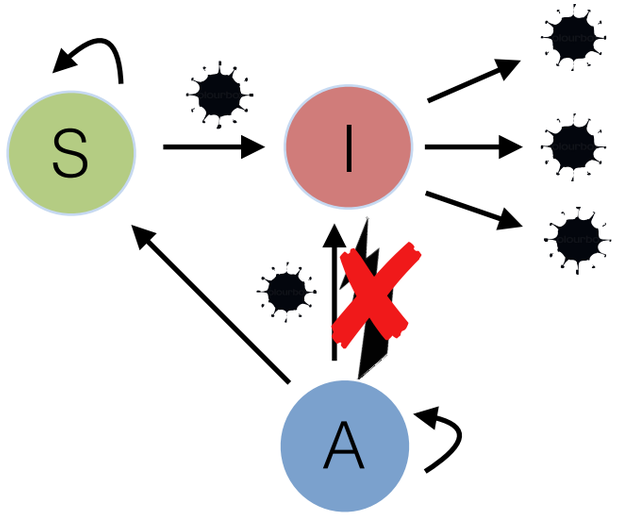
Data from blood, not lymphoid tissues

vs

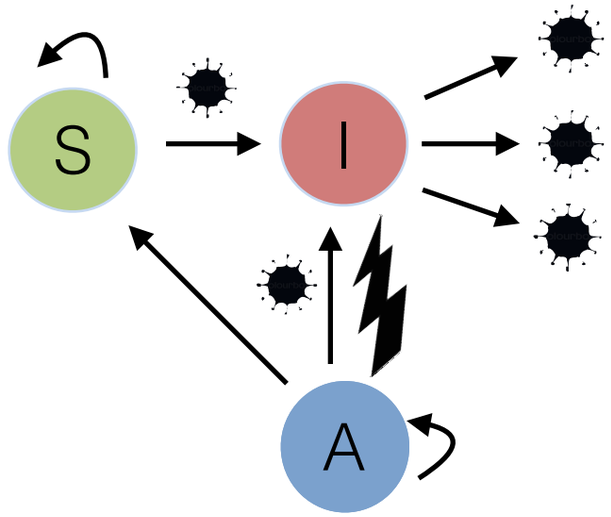


Laksono et al. (2016)

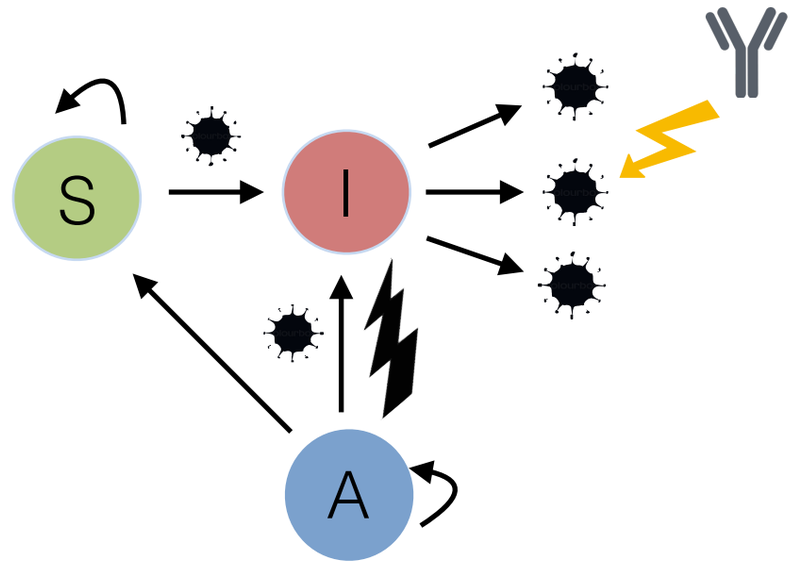
Results: AIC



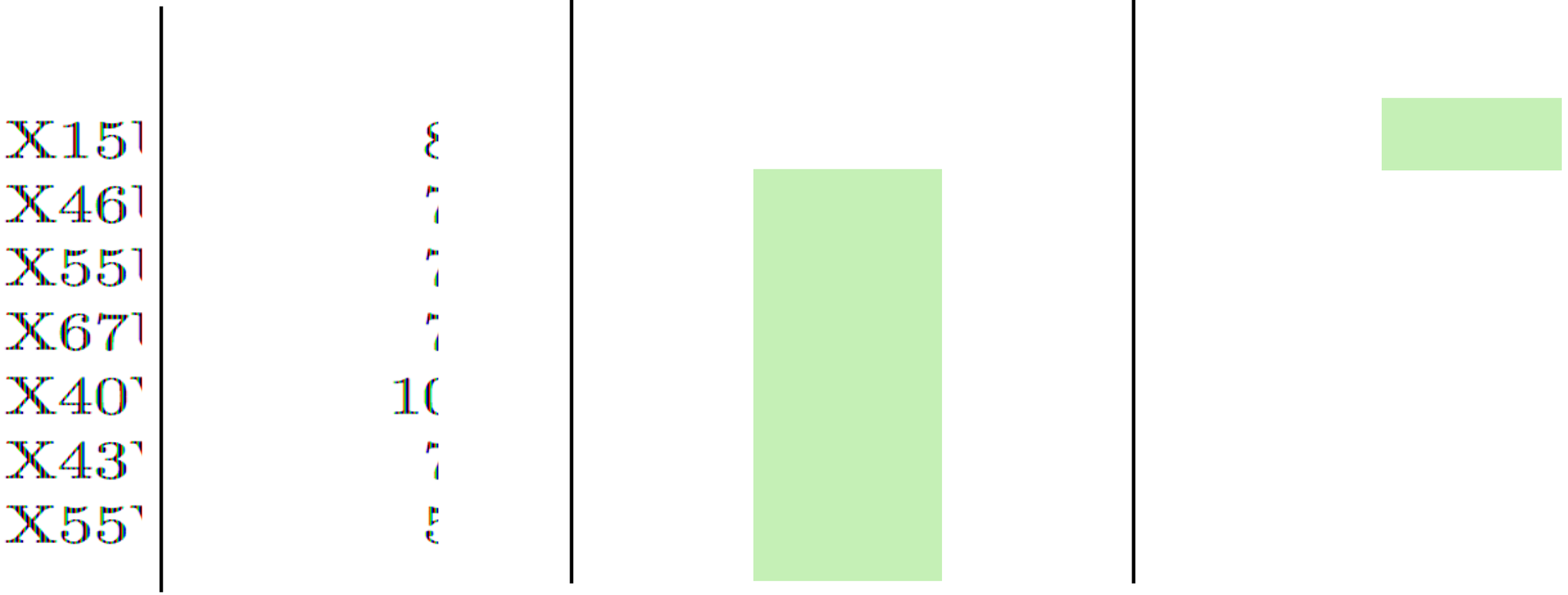
Target cells



Target cells + T-cells

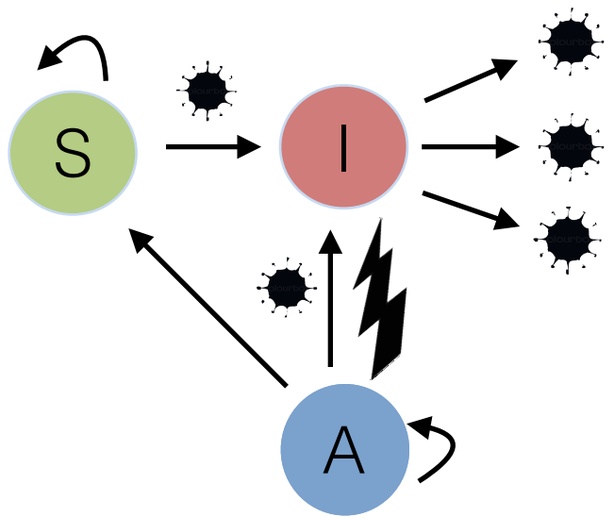


Target cells + T-cells + **Y**s



Results: AIC

Target cells



Target cells + T-cells

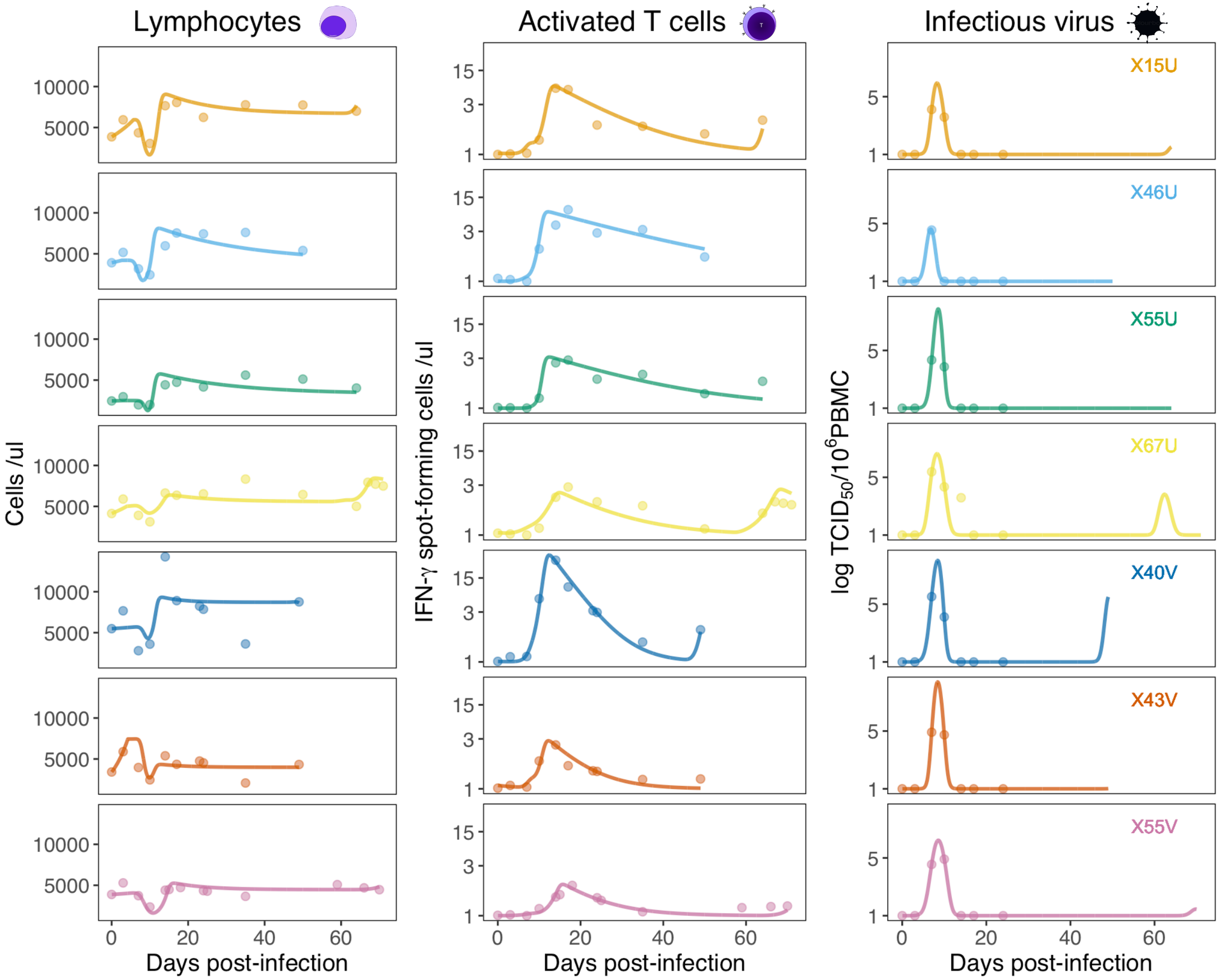
Target cells + T-cells + **Y**s

X15
X46
X55
X67
X40
X43
X55

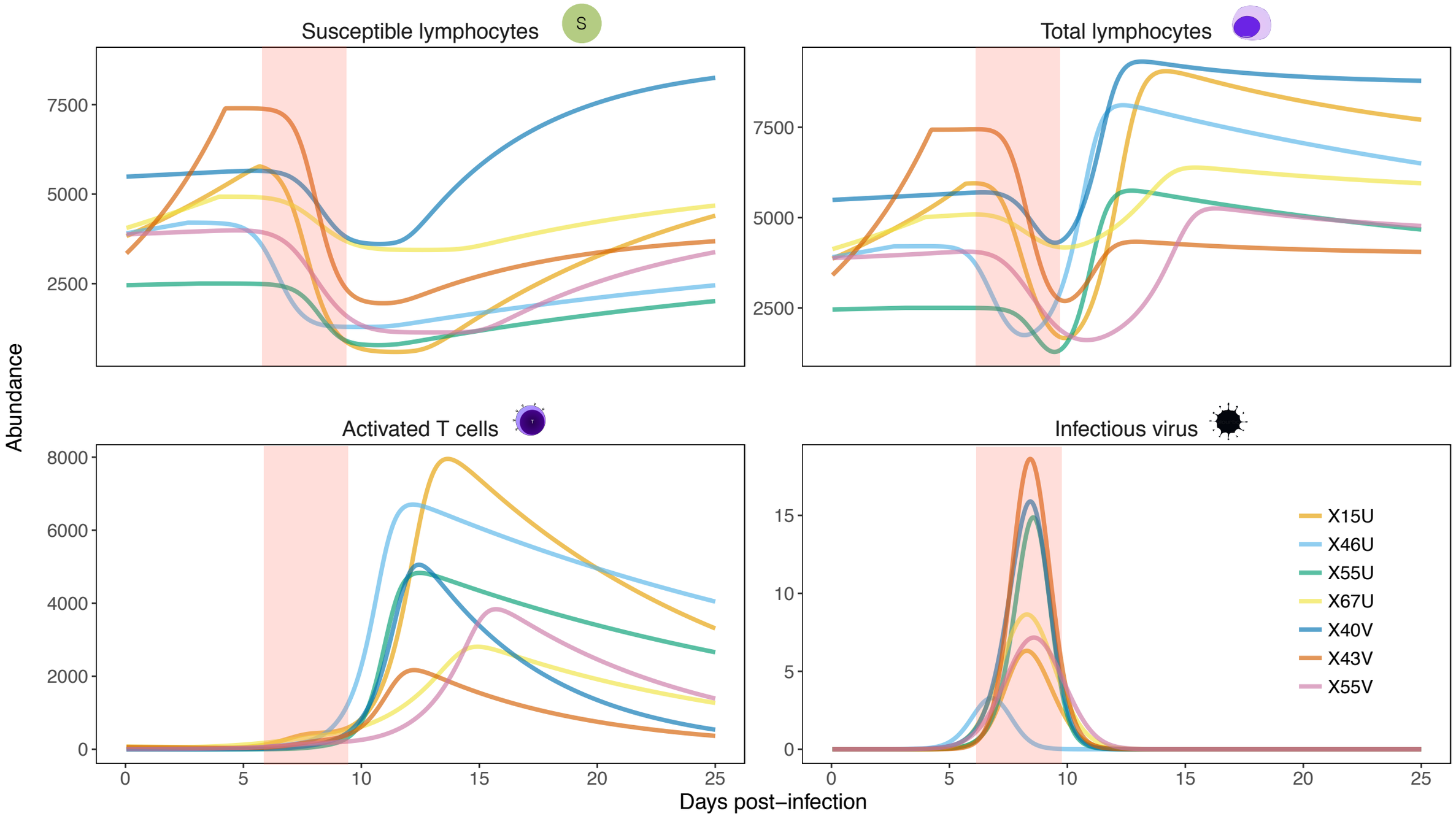
immune response

cell depletion

Results: model fits



Results: model predictions



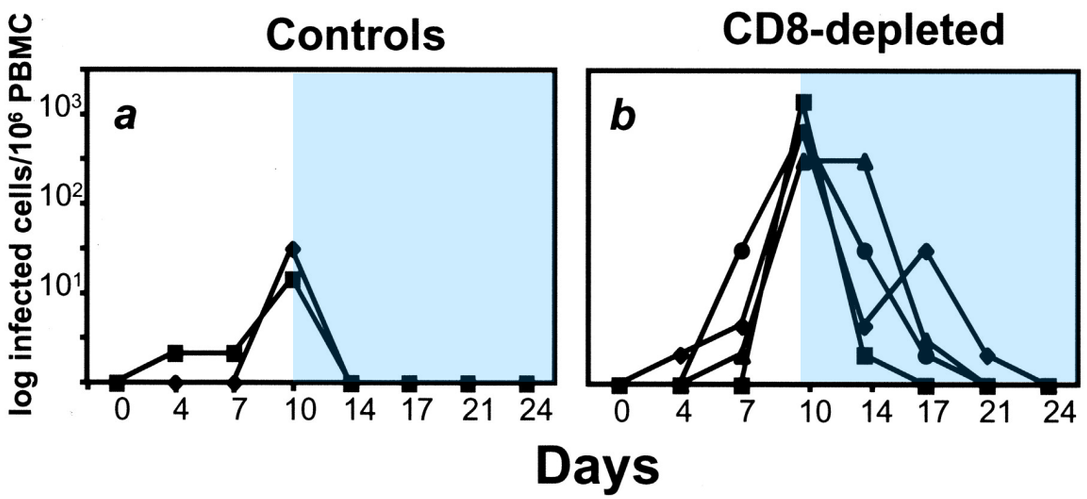
immune response

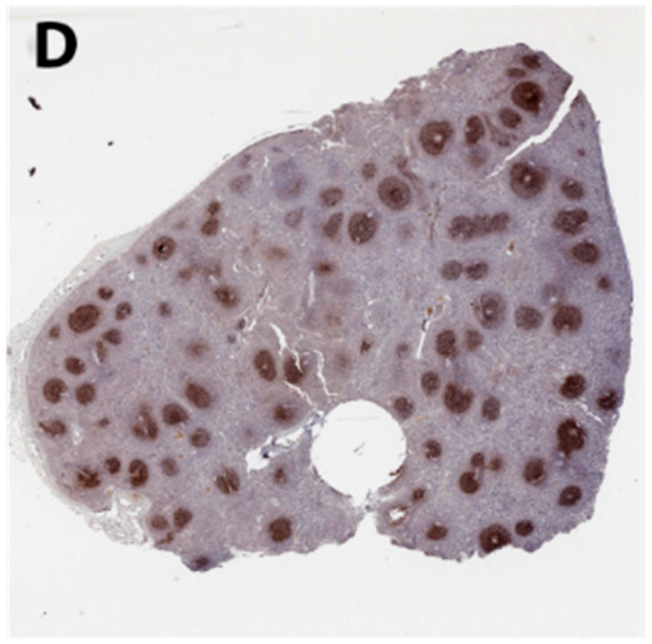
cell depletion

Simulation experiments

1

2





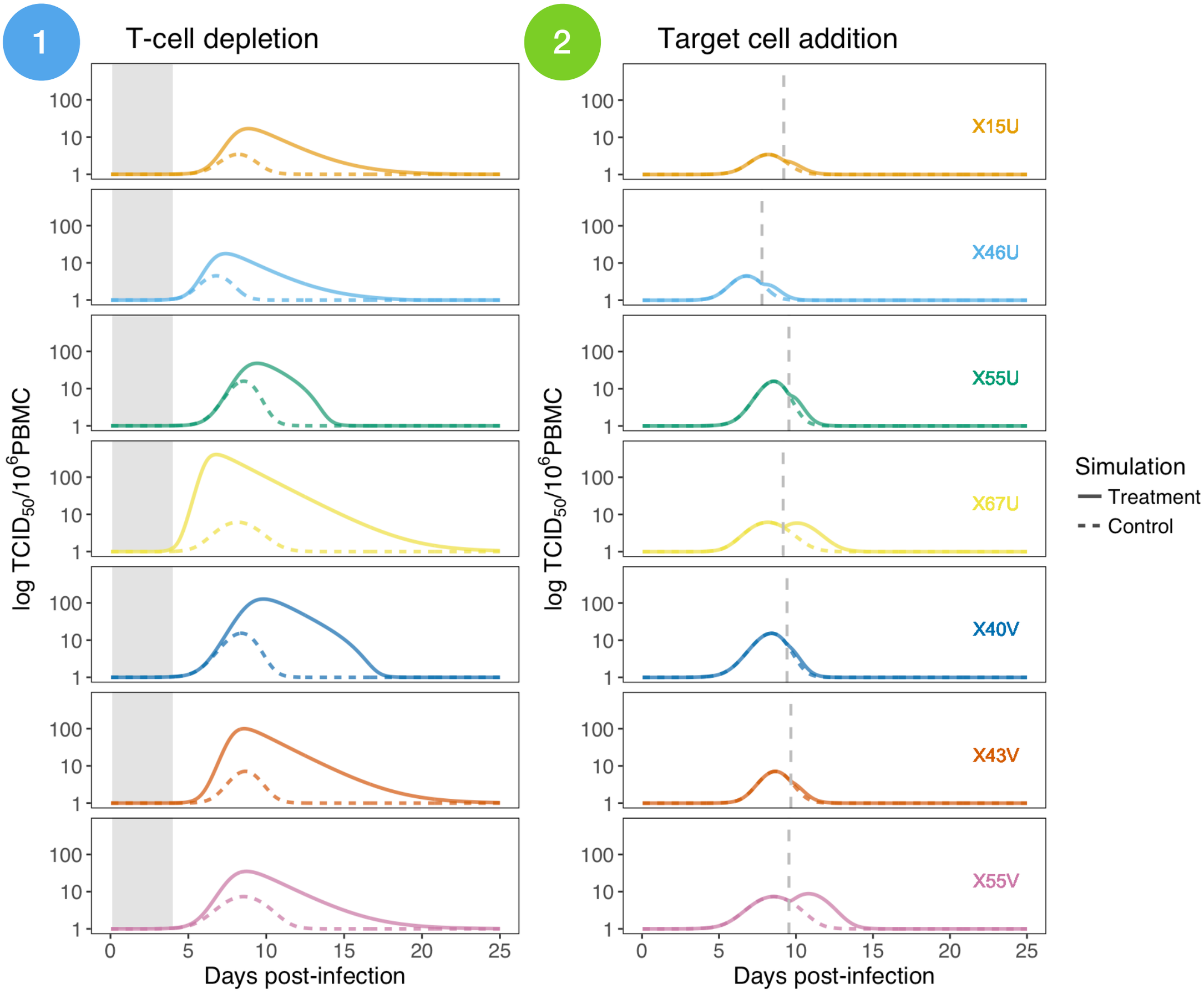
- t = 0: deplete T-cells
- t < 4d: suppress activation/ proliferation

Is viral clearance delayed?

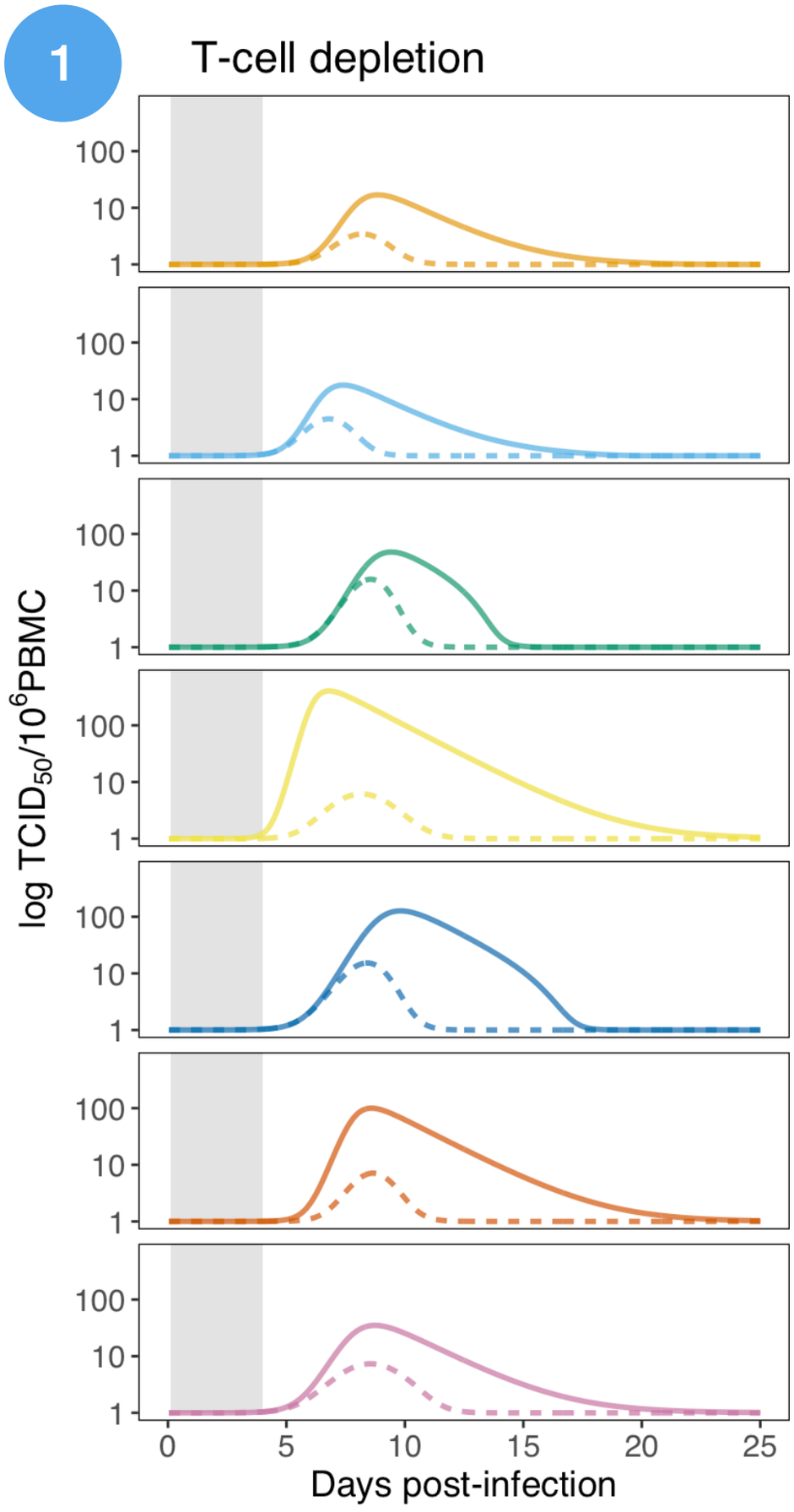
- peak + 1d: add new S cells

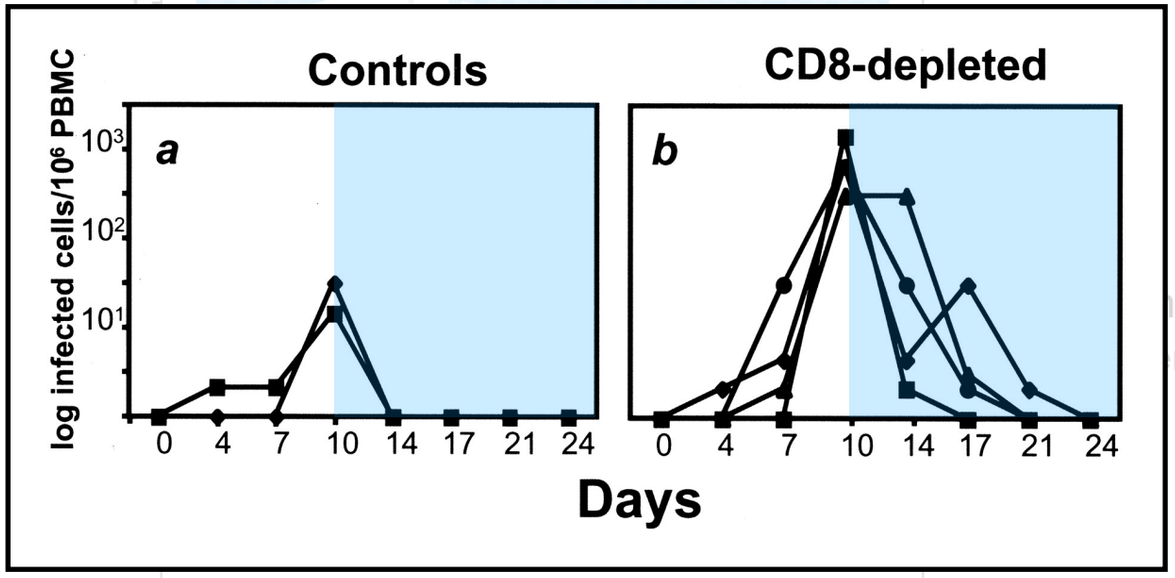
Does viral load resurge?

Simulation experiments



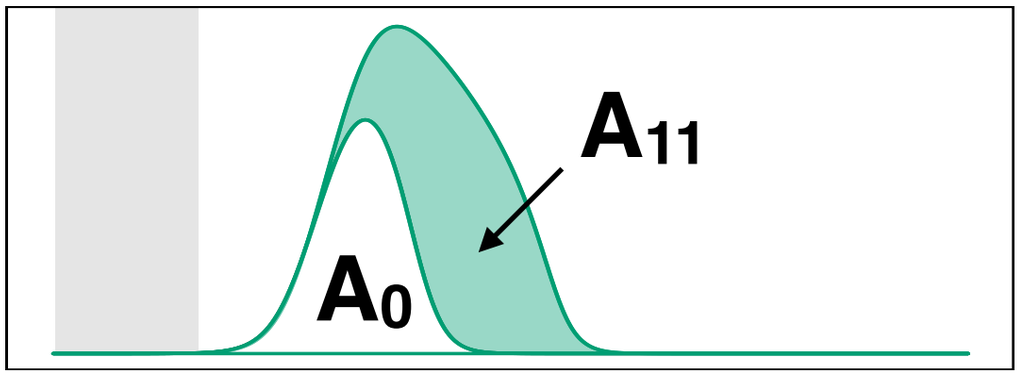
Simulation experiments



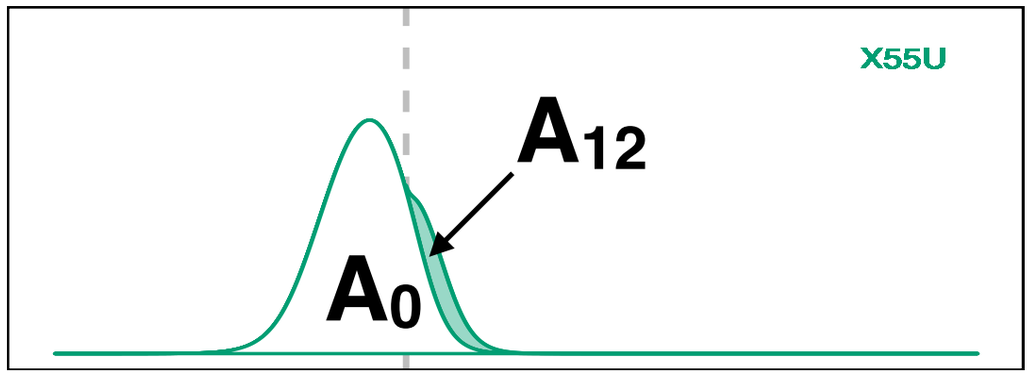


Simulation experiments

1 T–cell depletion

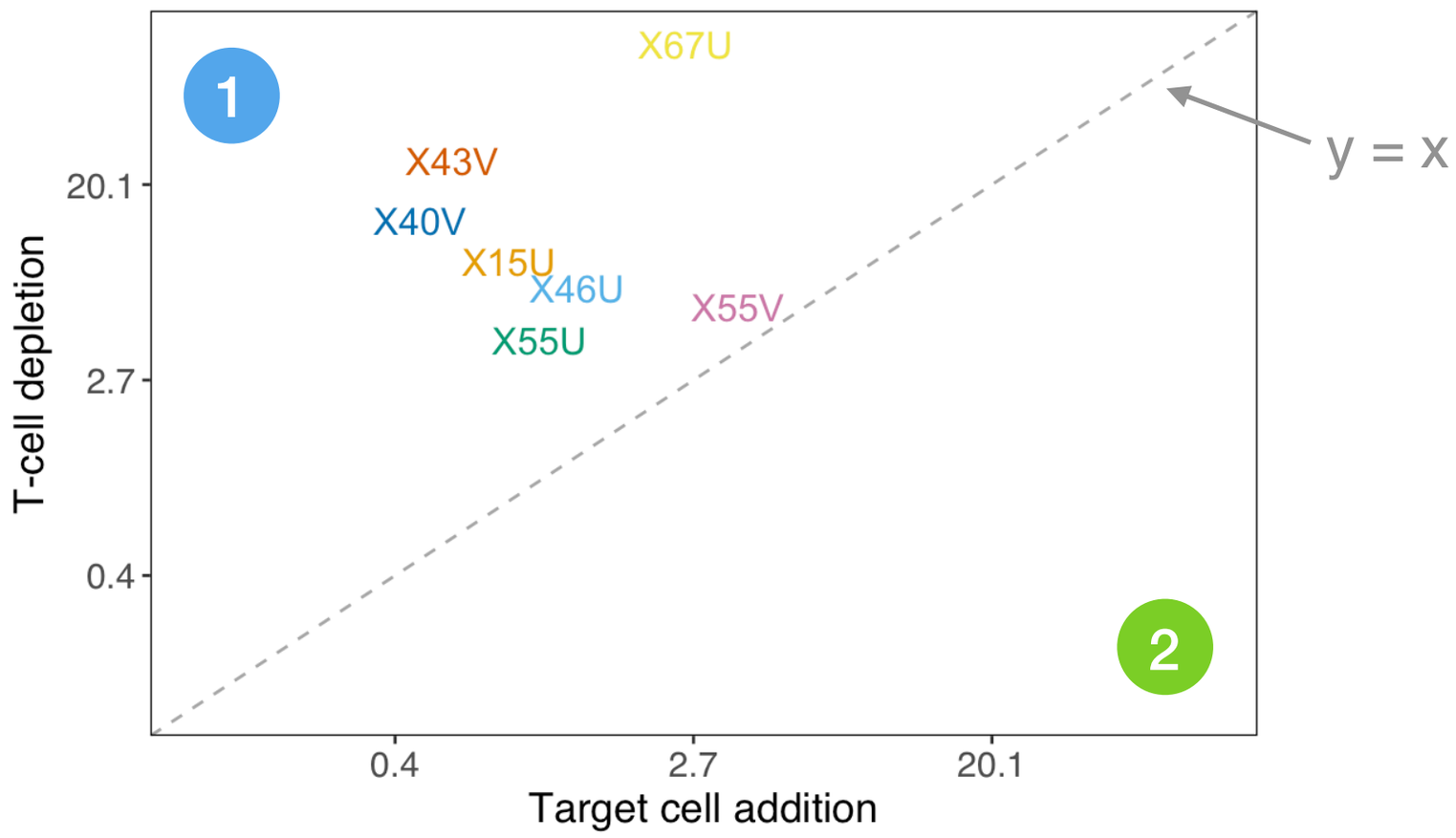


2 Target cell addition



$$\text{Effect}_1 = \frac{A_{11}}{A_0}$$

$$\text{Effect}_2 = \frac{A_{12}}{A_0}$$



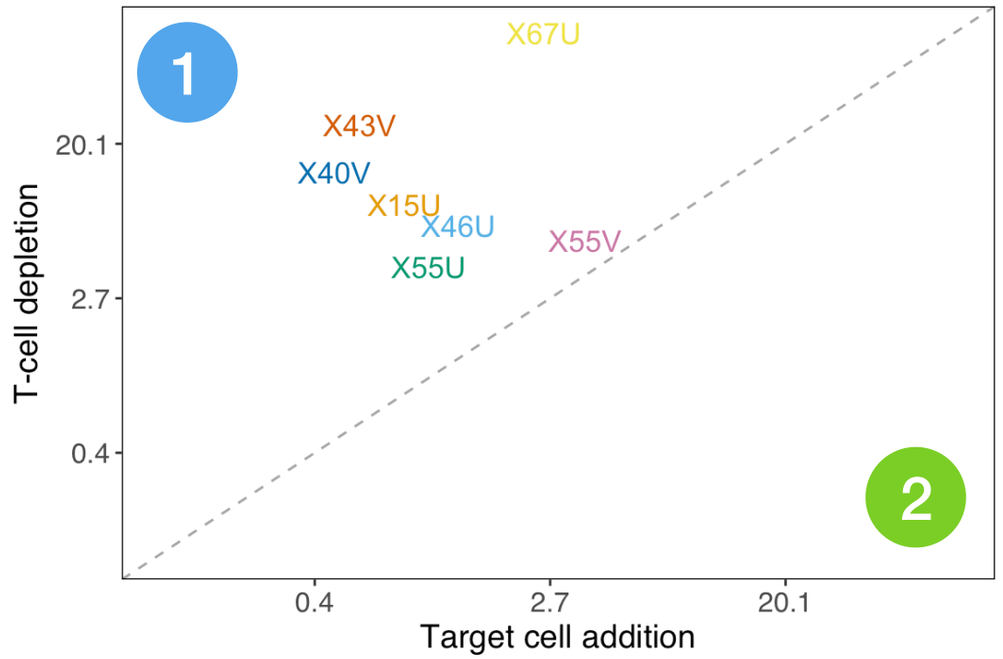
Extension to other systems

Measles

immune response

cell depletion

Rik de Swart,
Erasmus MC

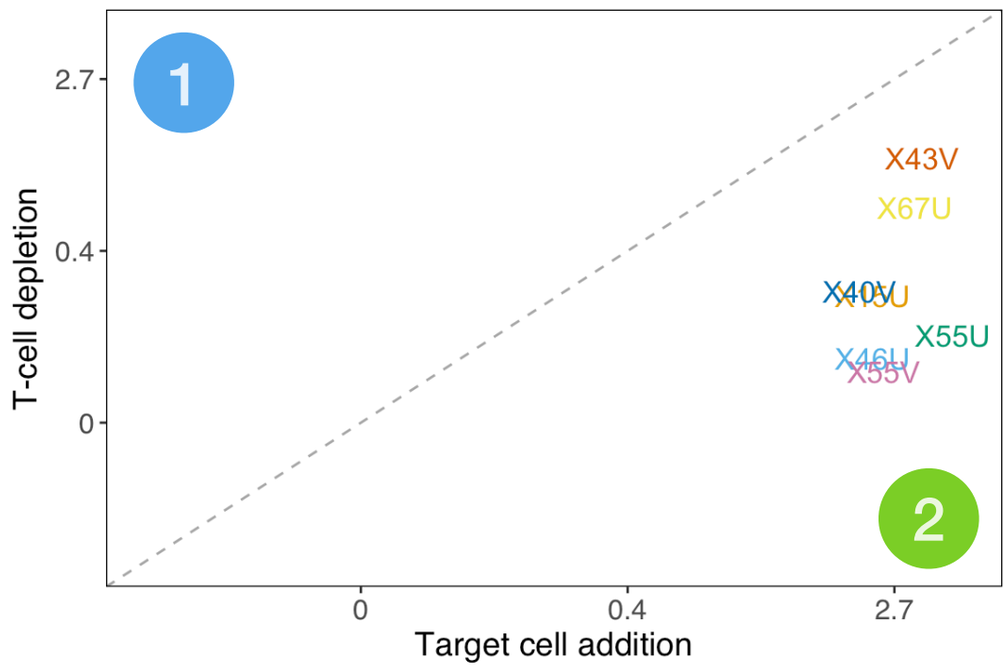


2 x replication rate

CDV

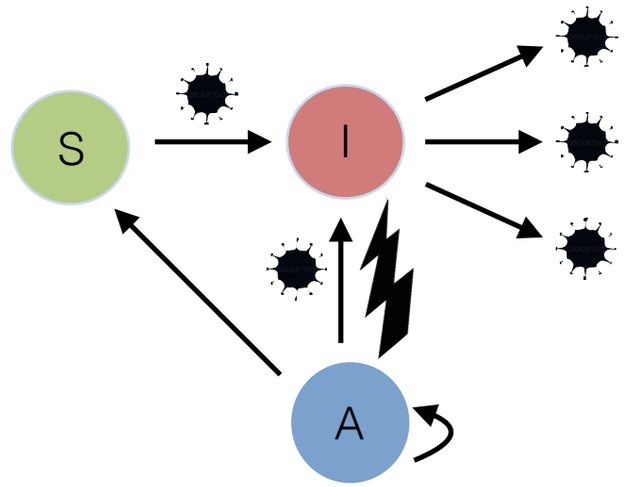
immune response

cell depletion

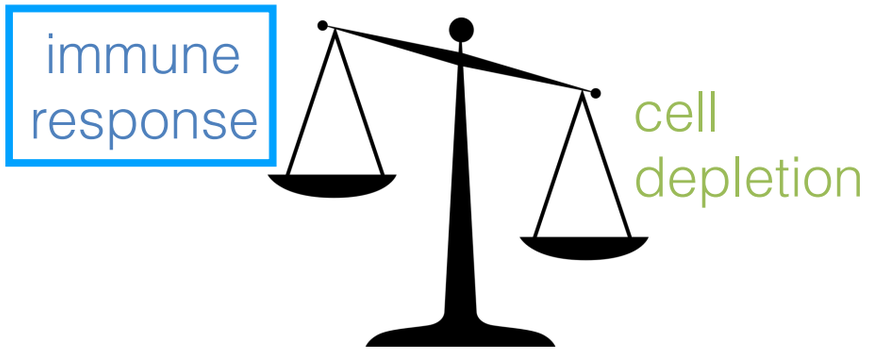


Conclusions

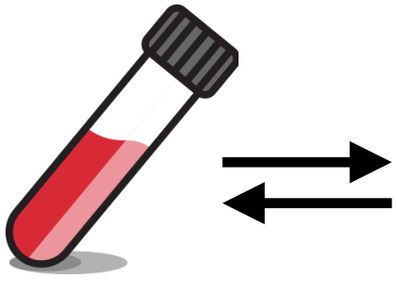
1. within-host model of predatory feedbacks

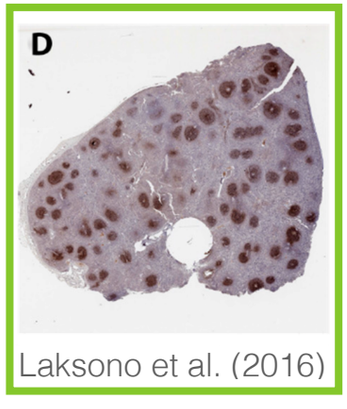


2. identify drivers of viral clearance



Next steps





Laksono et al. (2016)

Thanks

Bryan Grenfell
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Diane Griffin
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Erasmus MC

And:
Andrew Yates, Columbia University
Michael Mina, Harvard Medical School
Rory de Vries, Erasmus MC
Wen-Hsuan Lin, Columbia University
Roger Kouyos, University Hospital Zurich

PhD committee:
Jessica Metcalf, Princeton University
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Department of
Ecology and Evolutionary Biology