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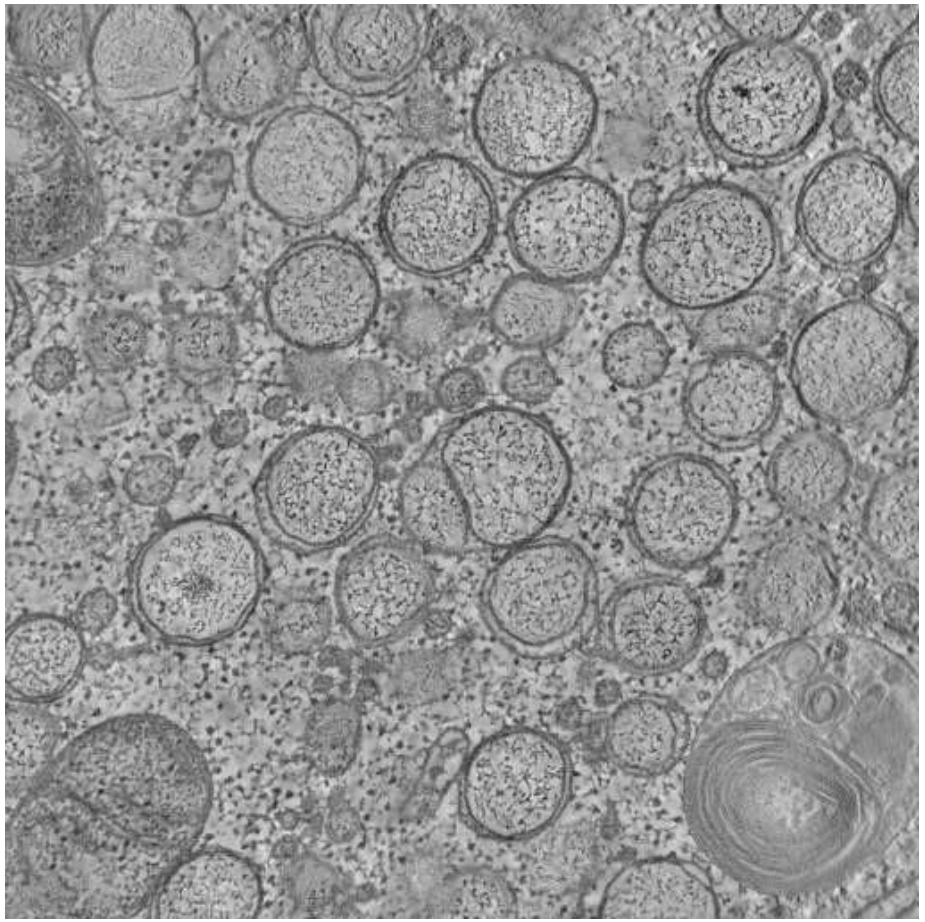
In-host modelling of SARS-CoV-2

The intersection of epidemiological and immunological domains

Thomas Finnie
Emergency Preparedness, Resilience and Response, UKHSA, Porton Down, UK

In host modelling



Kèvin Knoops, Abraham J. Koster, A. Mieke Mommaas, Eric J. Snijder (2012) CIL:40178, Chlorocebus pygerythrus, epithelial cell. CIL. Dataset. https://doi.org/doi:10.7295/W9CIL40178

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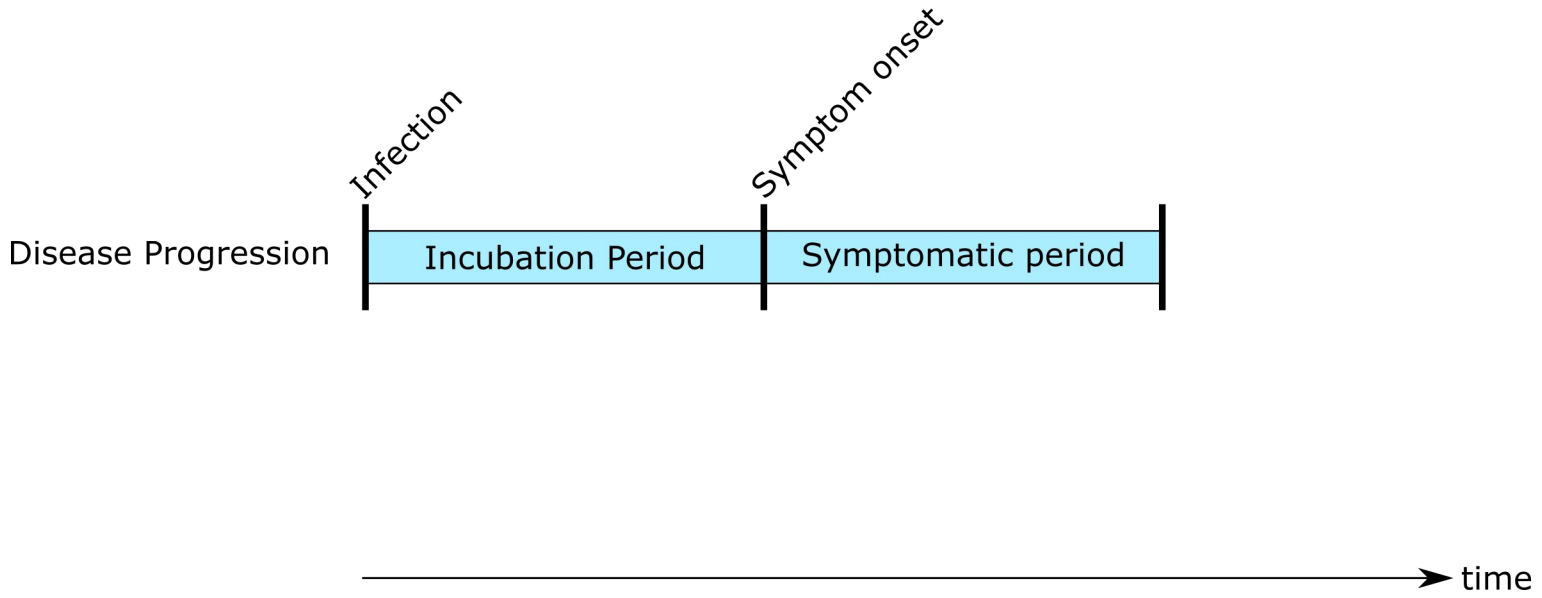
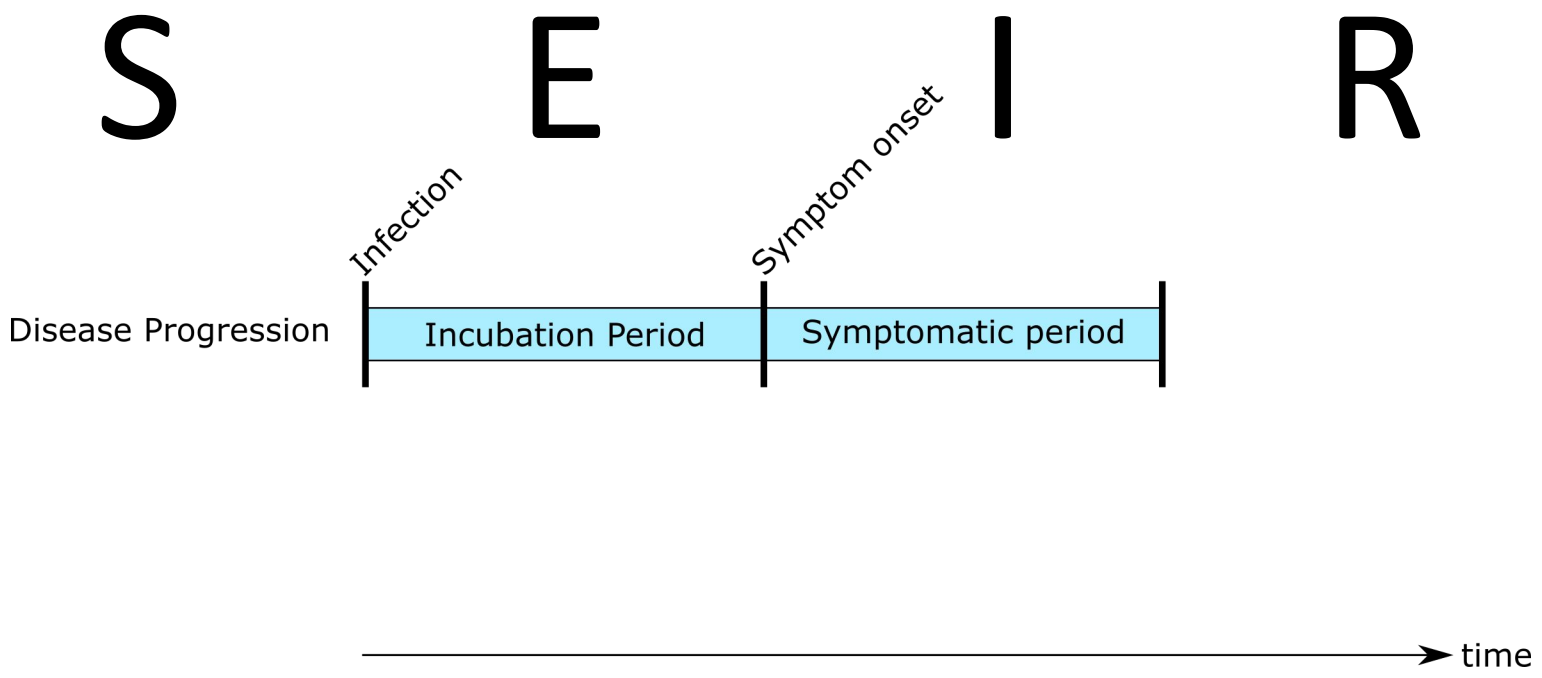
Human challenge and in-host model

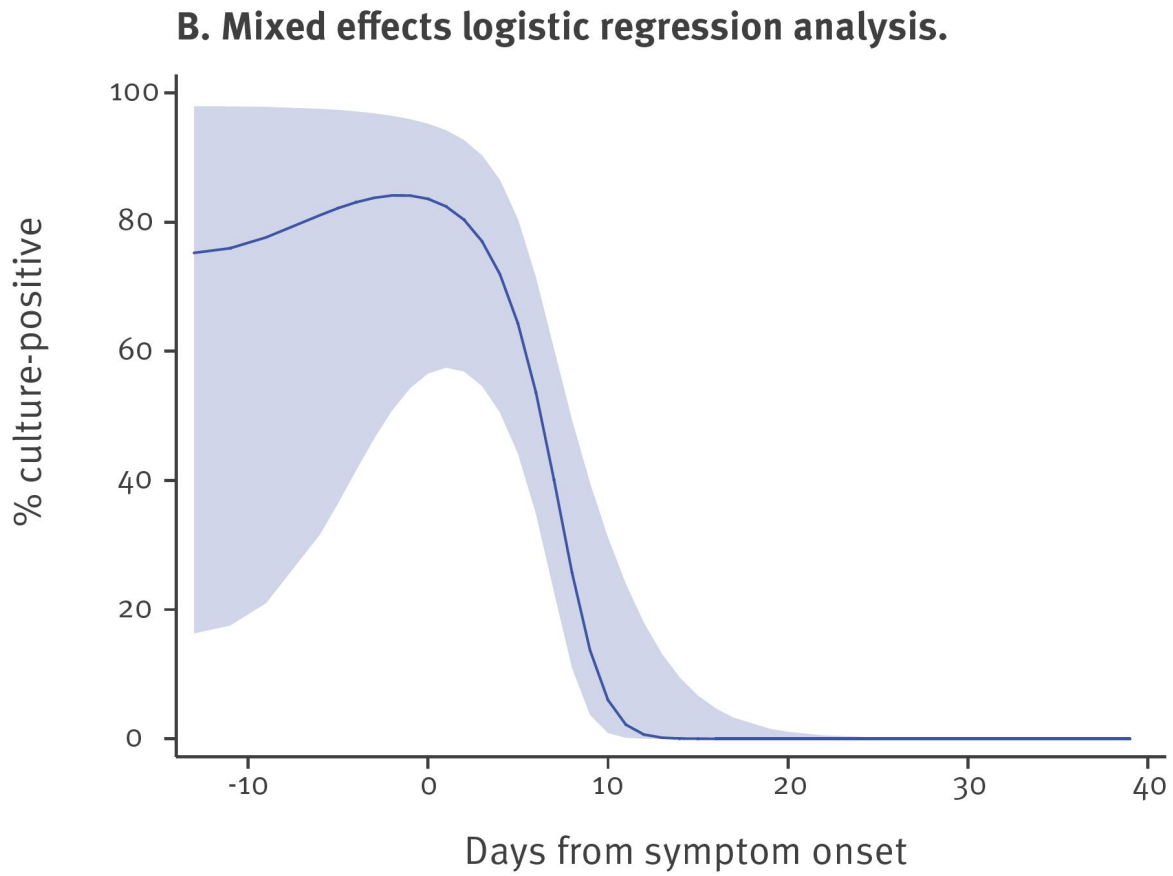
Disease process overview



Disease process overview

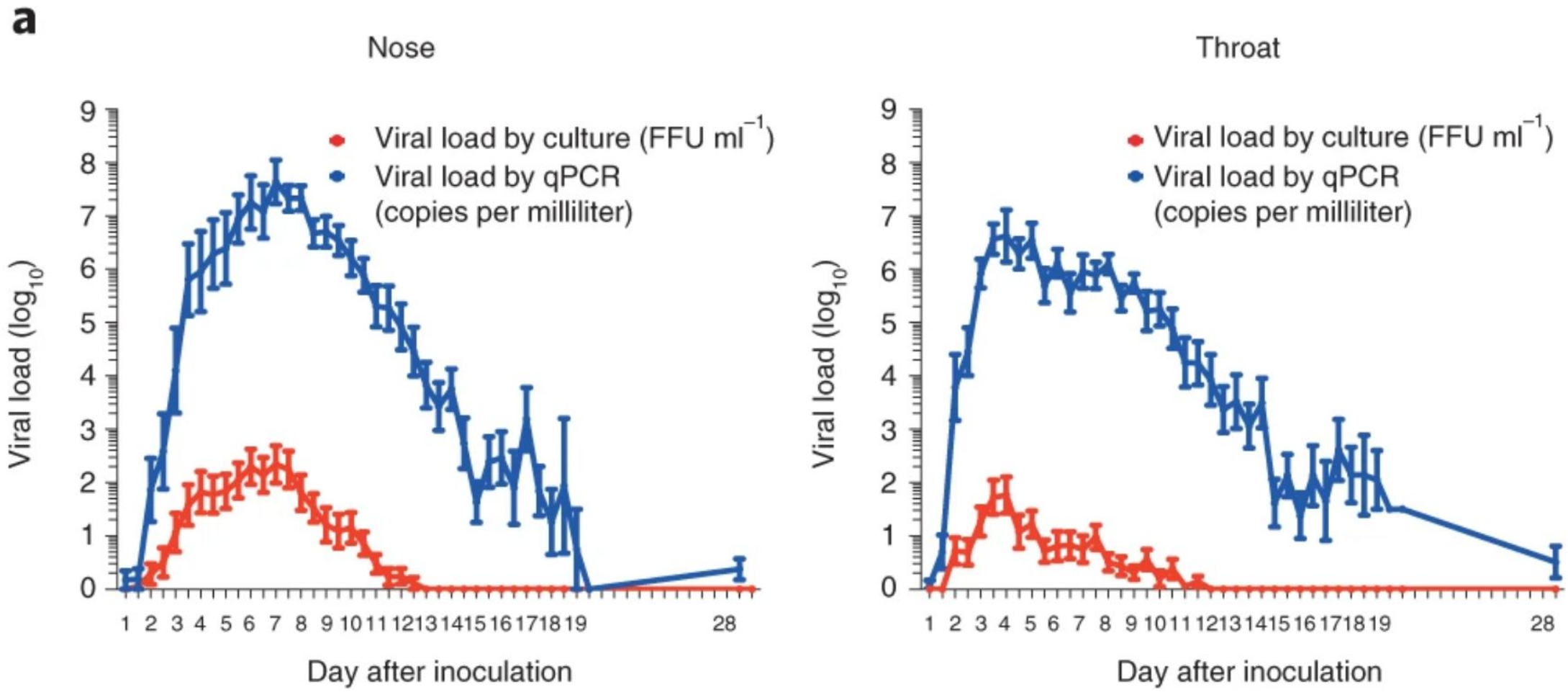


Symptomatic period distribution



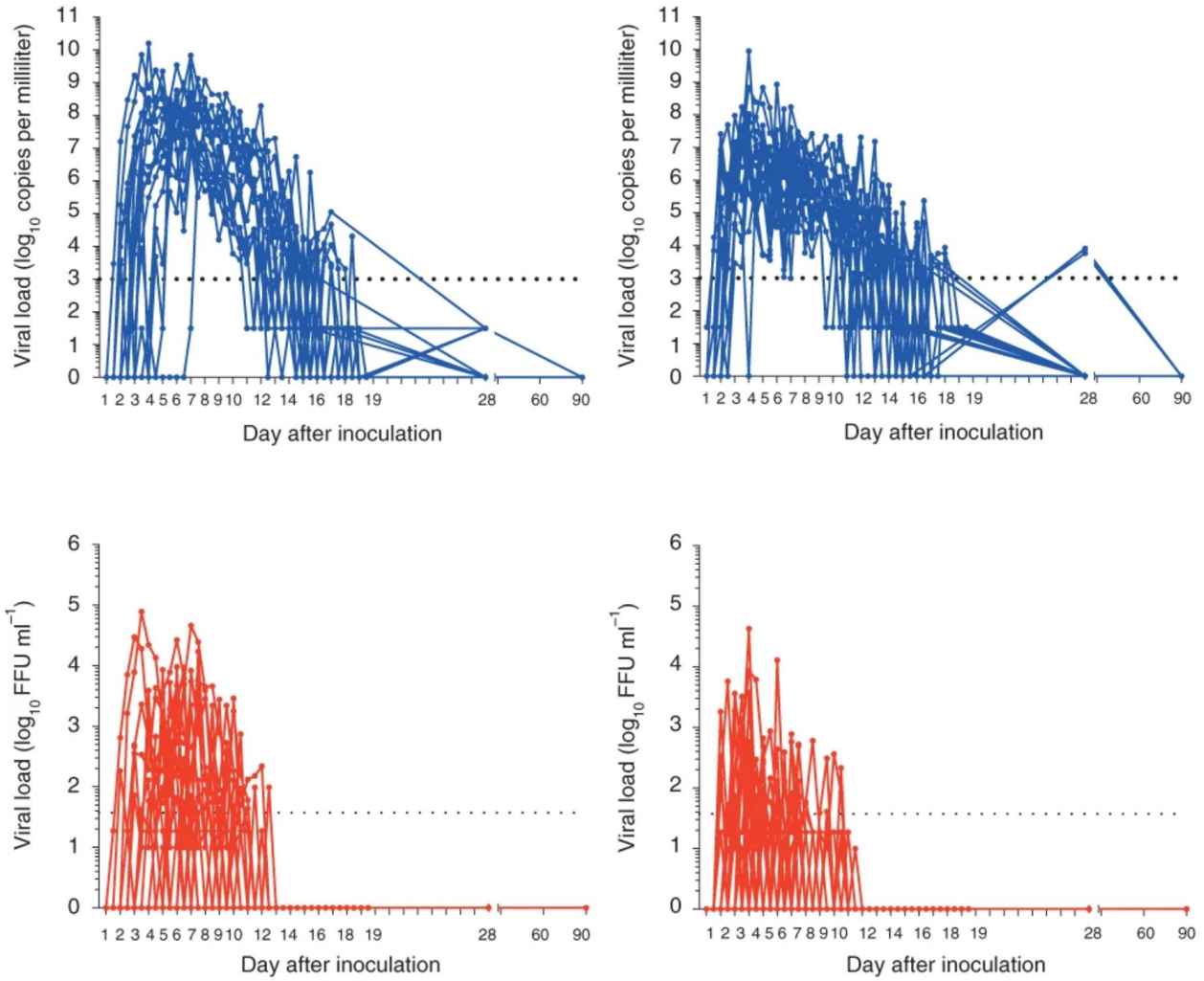
Singanayagam, A., Patel, M., Charlett, A., Bernal, J. L., Saliba, V., Ellis, J., Ladhani, S., Zambon, M., & Gopal, R. (2020). Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Eurosurveillance*, *25*(32), 2001483.

Human challenge data



Killingley, B., Mann, A. J., Kalinova, M., Boyers, A., Goonawardane, N., Zhou, J., Lindsell, K., Hare, S. S., Brown, J., Frise, R., Smith, E., Hopkins, C., Noulin, N., Löndt, B., Wilkinson, T., Harden, S., McShane, H., Baillet, M., Gilbert, A., … Chiu, C. (2022). Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. *Nature Medicine*, 1–11.

Human challenge data



In host model

Tissue Cells

$$\frac{dT}{dt} = -\beta T V_{\text{inf}}$$

$$\frac{dE}{dt} = \beta T V_{\text{inf}} - kE$$

$$\frac{dI}{dt} = kE - \delta I - k_C C I$$

Virus

$$\frac{dV_{\text{inf}}}{dt} = p_{\text{inf}} I - c_{\text{inf}} V_{\text{inf}}$$

$$\frac{dV_{\text{tot}}}{dt} = p_{\text{tot}} I - c_{\text{tot}} V_{\text{tot}}$$

Immune effector cells

$$\frac{dC}{dt} = \frac{r C V_{\text{tot}}}{V_{\text{tot}} + s} - \delta_C C$$

Carruthers, J., Xu, J., Finnie, T., & Hall, I. (2022). *A within-host model of SARS-CoV-2 infection* (p. 2022.04.22.22274137). medRxiv. https://doi.org/10.1101/2022.04.22.22274137

Parameter estimation

- An Approximate Bayesian Computation Sequential Monte Carlo (ABC-SMC)
  - Parameter sets are sampled from the intermediate distribution of the previous generation and perturbed using a multivariate normal kernel
  - An adaptive algorithm is used to decrease acceptance tolerance
  - Solutions of the mathematical model are compared to human challenge data using the distance function:

$$d(\mathrm{MM},\mathrm{HC})^2 = \sum_{t\in\mathcal{T}} \left[\log_{10}(V_{\mathrm{inf}}^{(\mathrm{MM})}(t)) - \log_{10}(V_{\mathrm{inf}}^{(\mathrm{HC})}(t))\right]^2 + \left[\log_{10}(V_{\mathrm{tot}}^{(\mathrm{MM})}(t)) - \log_{10}(V_{\mathrm{tot}}^{(\mathrm{HC})}(t))\right]^2$$

- Fix $\delta_C = 0$ and $k = 3$ day^{-1}
- Prior distributions:

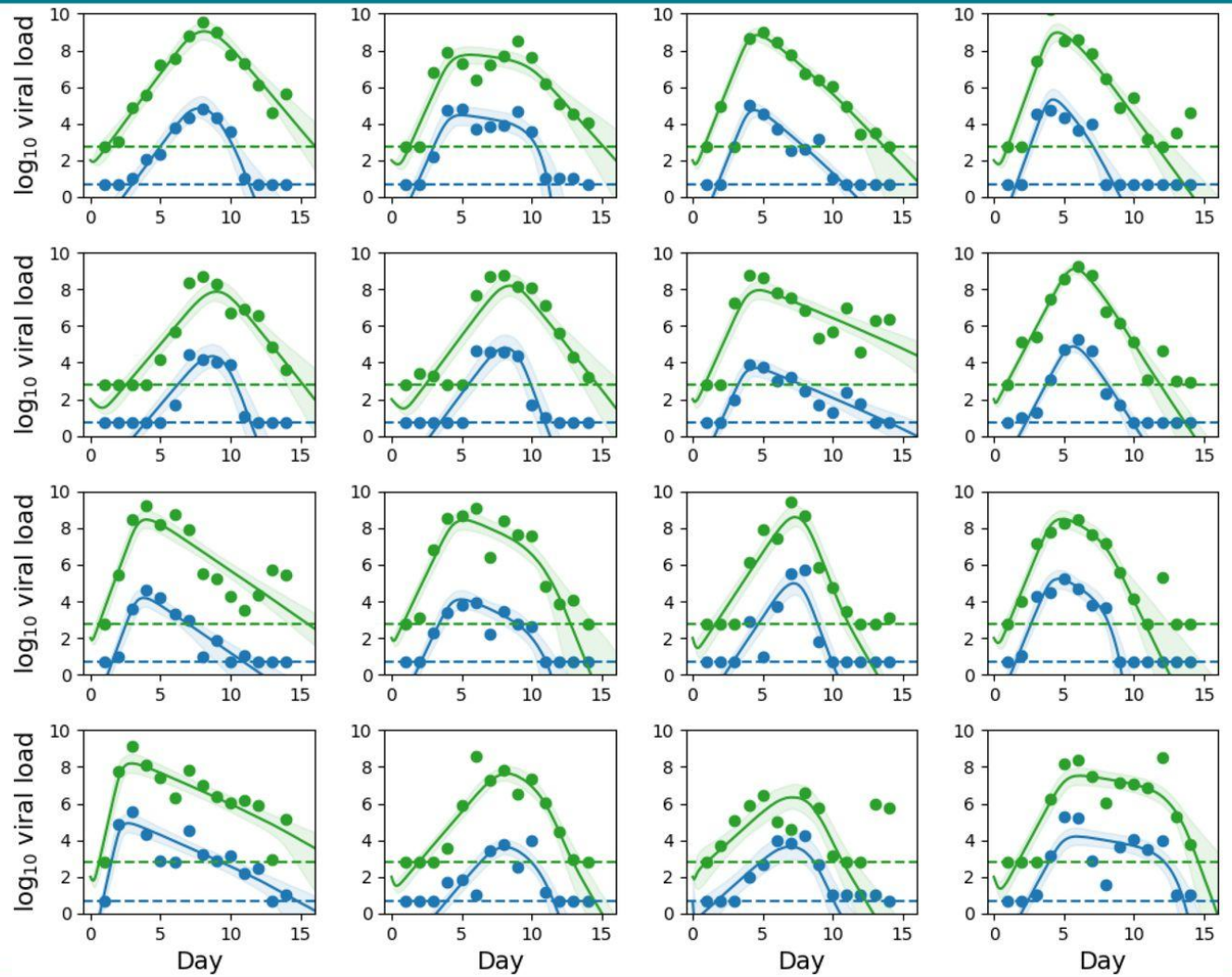
$$\log_{10}\beta \sim U(-7,-2) \qquad \delta \sim U(0,5) \qquad \log_{10} p_{\mathrm{inf}} \sim U(-1,3) \qquad \log_{10} p_{\mathrm{tot}} \sim U(1,6)$$
$$c_{\mathrm{inf}} \sim U(0,50) \qquad c_{\mathrm{tot}} \sim U(0,10) \qquad r \sim U(0,2) \qquad \log_{10} k_C \sim U(-5,-2)$$

An aside on model selection

- A second model without immune response was built (omitting the ODE on effector cells)
- Models compared at end of each ABC generation using Bayes factor
  - Six individuals - very strong evidence for including immune response
  - One individual - there was positive evidence for inclusion
  - Nine participants - there was not sufficient evidence in favour of either model

- Model with immune response used

Posterior predictions



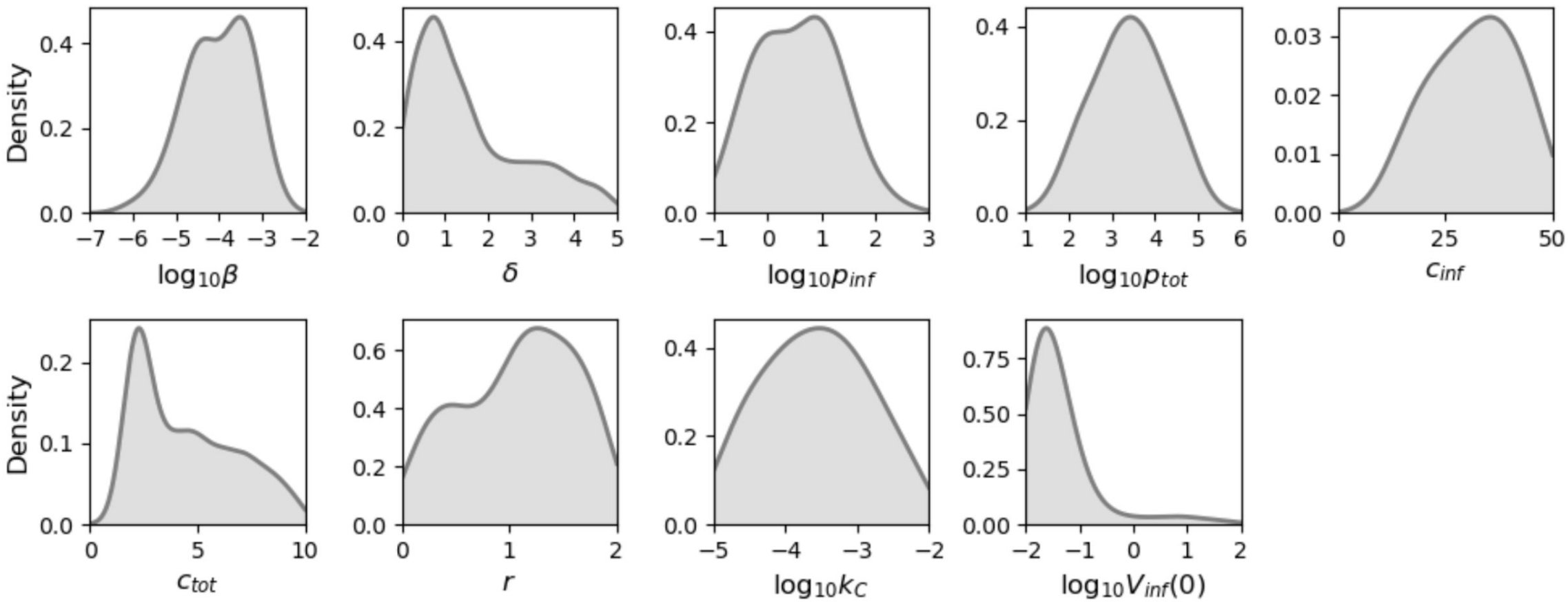
Predicted viral dynamics of infectious virus (blue) and total virus (green) for participants of the human challenge study

From individual to experimental population

- Construct a mixture distribution:

$$m(\boldsymbol{\theta}) = \sum_{i=1}^{P} w_i f_i(\boldsymbol{\theta})$$

Mixture distribution posteriors

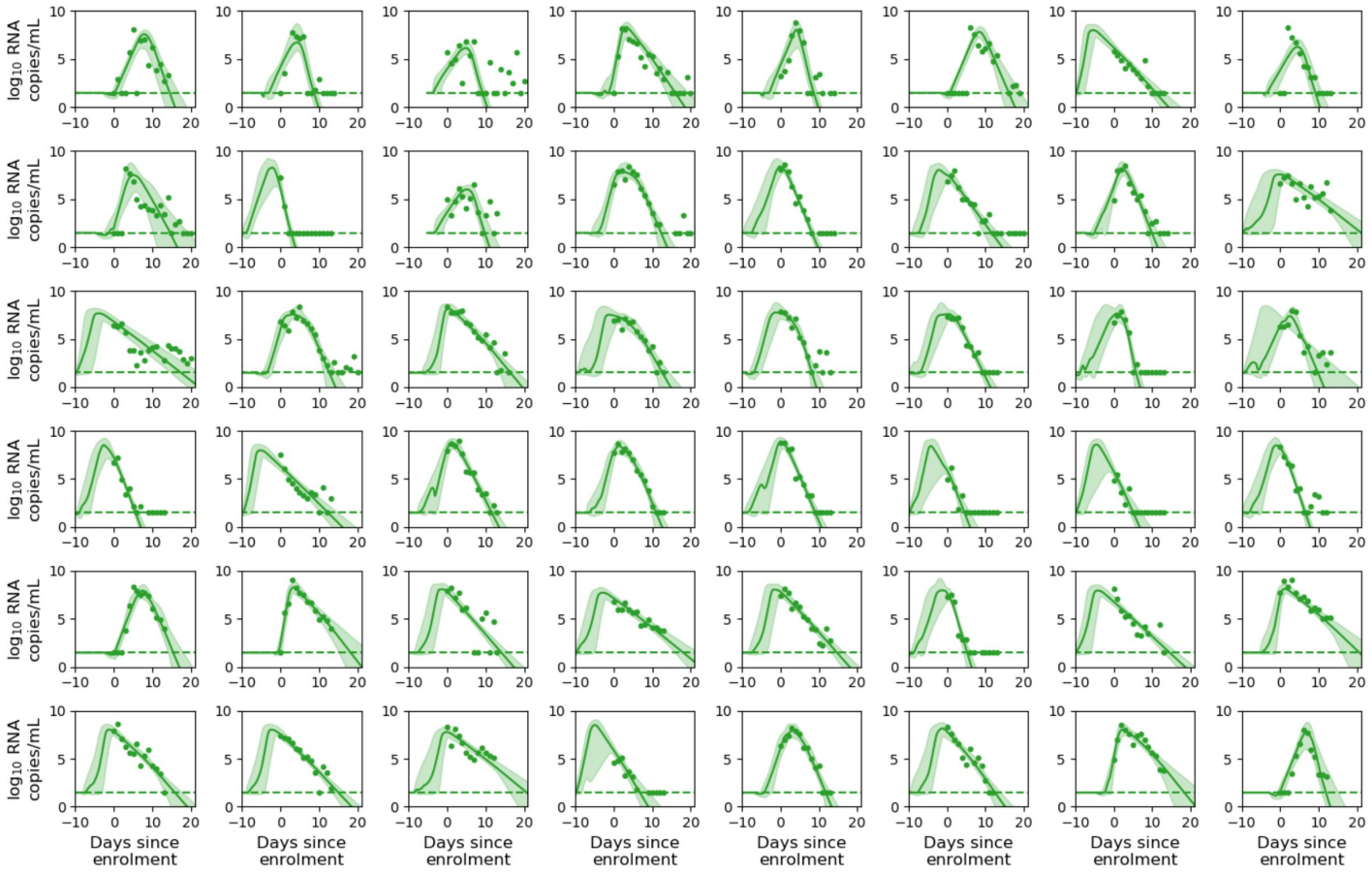


Comparing experimental population to general

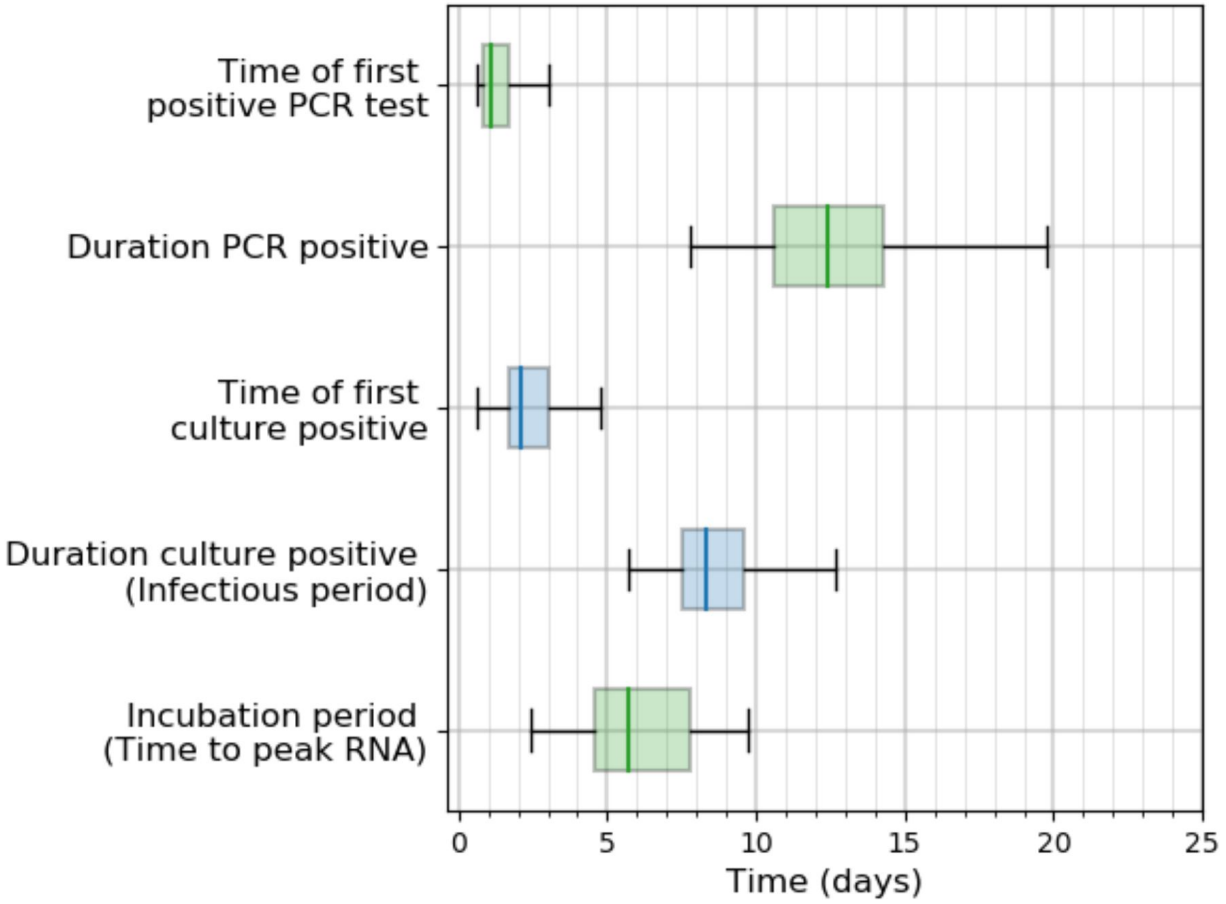
- Challenge study participants unusual compared to general population
- Compare modelled viral dynamics to those observed in a study (ATACCC*)of the wider population

*Singanayagam A, Hakki S, Dunning J, Madon KJ, Crone MA, Koycheva A, Derqui-Fernandez N, Barnett JL, Whitfield MG, Varro R et al.. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B. 1.617. 2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. The Lancet Infectious Diseases. 2021; 22: 183–195

Existing model parameterisation with fit to ATACCC data



Timescales of infection



Estimates for the time of first positive test and the duration an individual remains positive. The timescales are derived from model predictions of both total (green) and infectious (blue) virus

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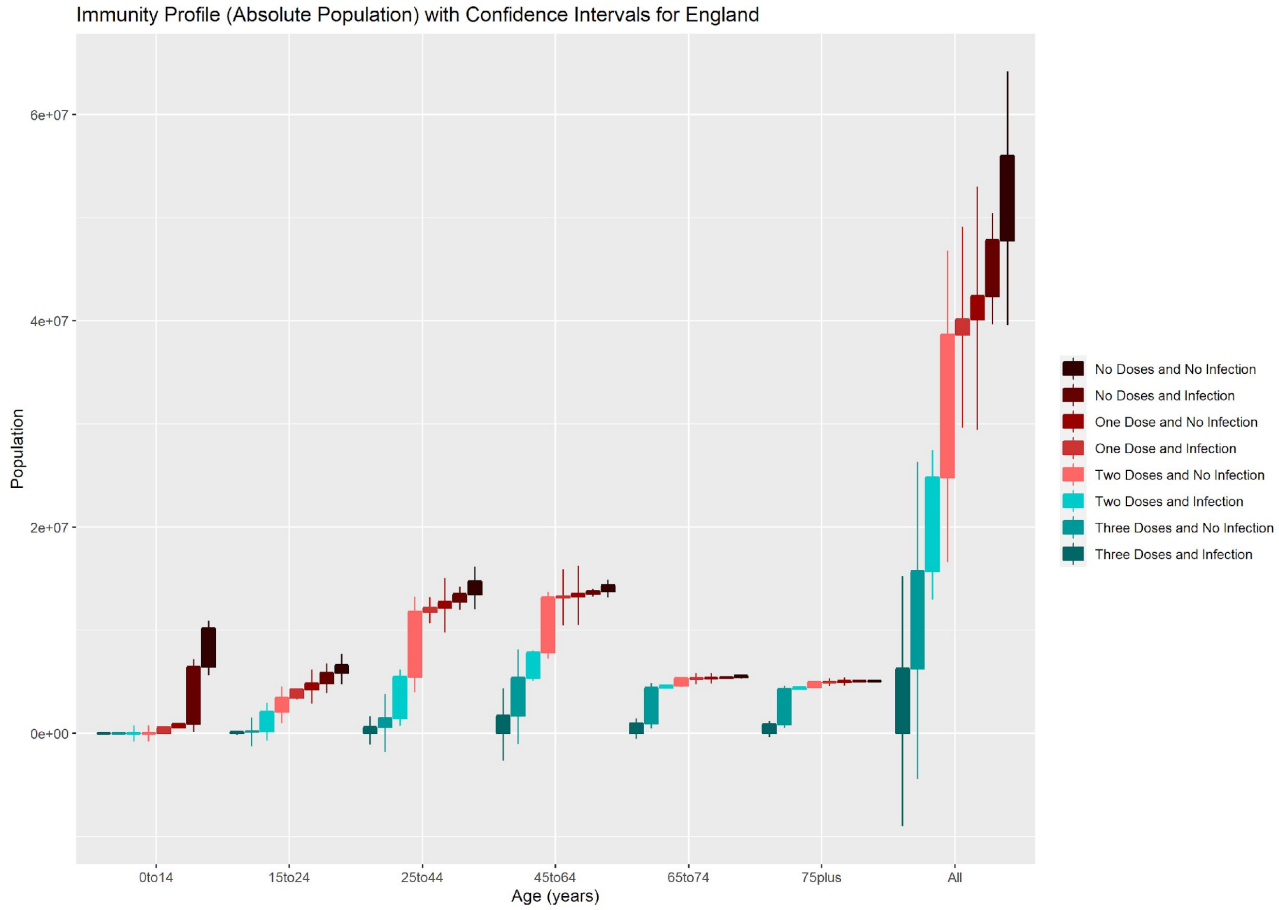
Where next?

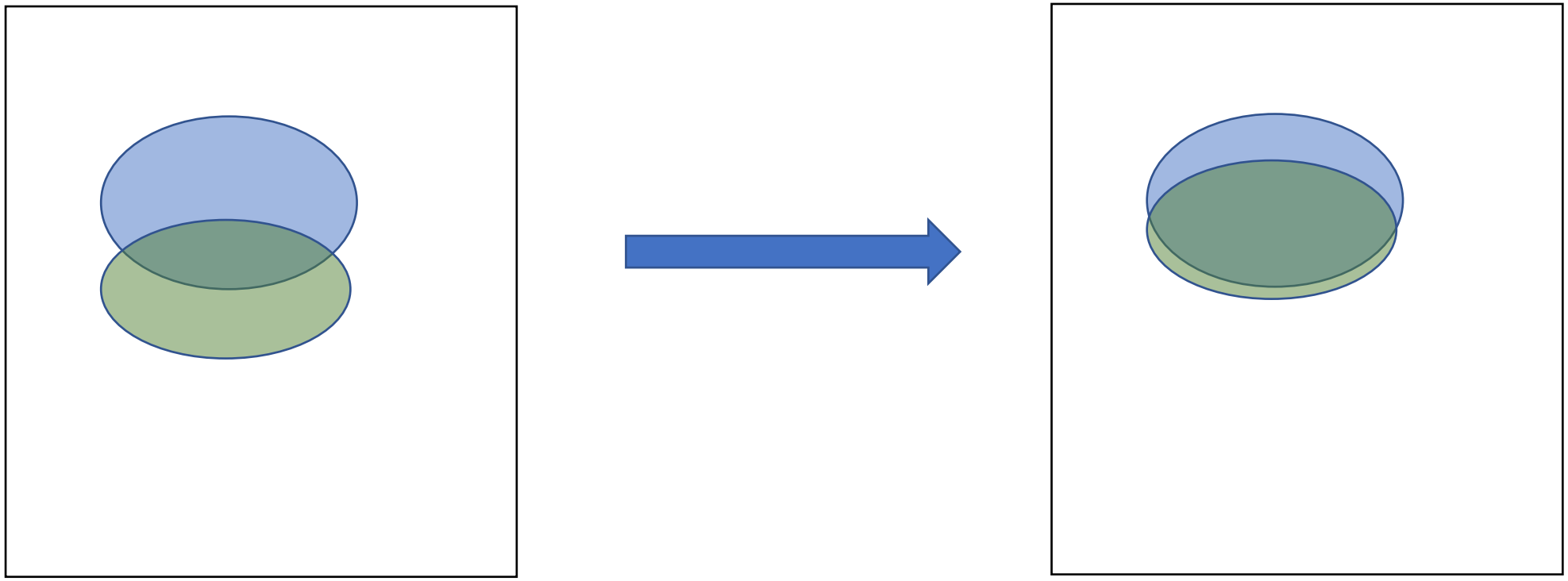
Mid to late epidemic question

- How much more disease is there going to be?

- How many more healthcare admissions and deaths does this disease have the potential to cause?


Immunity Profile (Absolute Population) with Confidence Intervals for England
Population
6e+07
4e+07
2e+07
0e+00
0to14
15to24
25to44
45to64
65to74
75plus
All
Age (years)
No Doses and No Infection
No Doses and Infection
One Dose and No Infection
One Dose and Infection
Two Doses and No Infection
Two Doses and Infection
Three Doses and No Infection
Three Doses and Infection

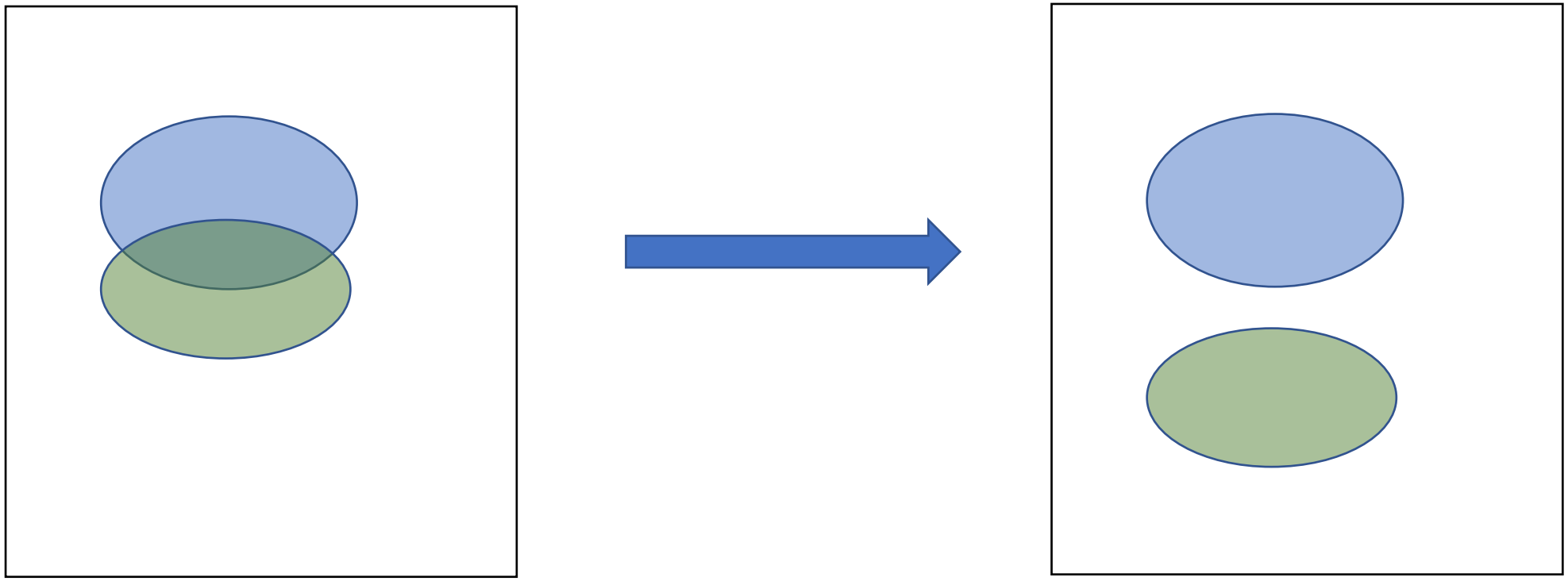
Genetic vs. Immunological space



Viral genetic space

Immunological space

Genetic vs. Immunological space



Viral genetic space

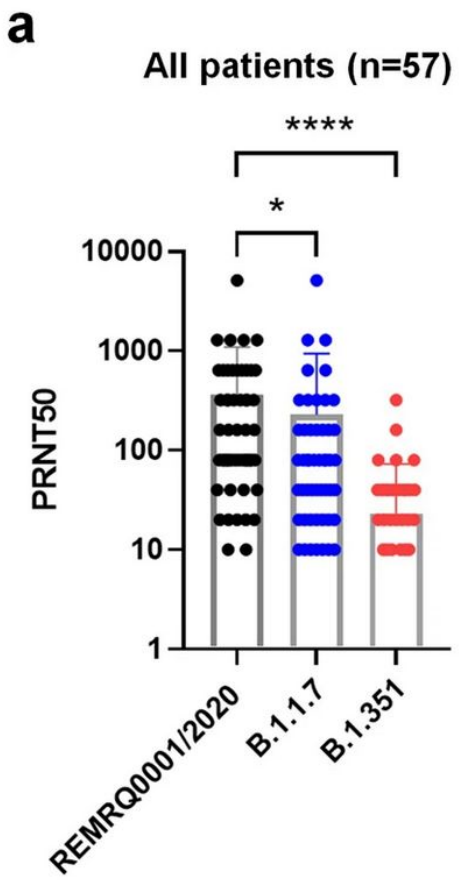
Immunological space

Genetic space

```yaml
unique-id: denture-daughter
phe-label: VOC-20DEC-01
who-label: Alpha
alternate-names:
- VOC202012/01
- UK variant
- Kent variant
- VOC1
belongs-to-lineage:
- PANGO: B.1.1.7
- nextstrain: N501Y.V1
description: This variant became widespread in the UK in the Winter of 2021 and is characterised by increased transmissibility.
information-sources:
- https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201
- https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563
variants:
- gene: S
  one-based-reference-position: 21764
  protein: surface glycoprotein
  reference-base: ATACATG
  type: deletion
  variant-base: A
- gene: S
  one-based-reference-position: 21990
  protein: surface glycoprotein
  reference-base: TTTA
  type: deletion
  variant-base: T
- amino-acid-change: N501Y
  codon-change: AAT-TAT
  gene: S
  one-based-reference-position: 23063
```

https://github.com/phe-genomics/variant_definitions

Immunological space



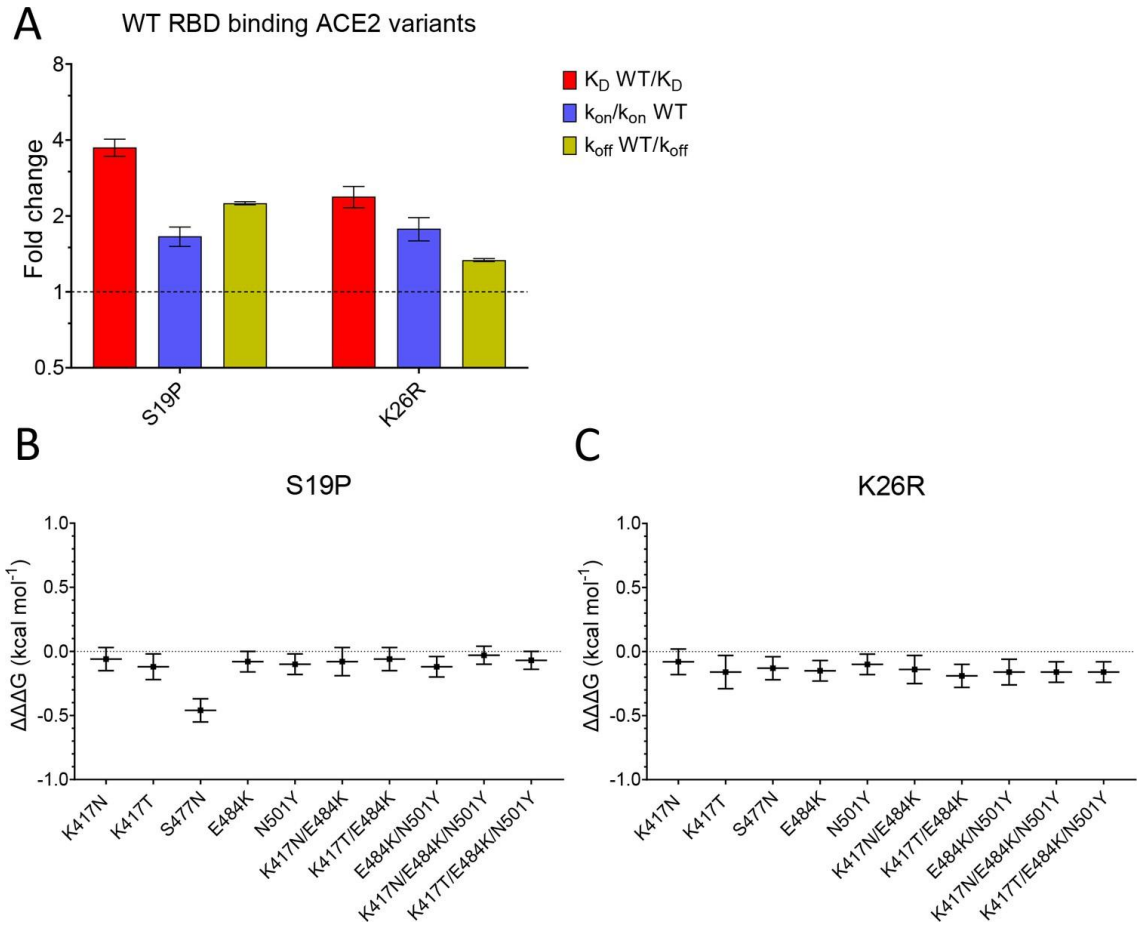
Wang, B., Goh, Y.S., Prince, T. *et al.* Resistance of SARS-CoV-2 variants to neutralization by convalescent plasma from early COVID-19 outbreak in Singapore. *npj Vaccines* **6,** 125 (2021). https://doi.org/10.1038/s41541-021-00389-2

T-Cell Repertoire

TRAV	TRA-CDR3	TRAJ	TRAC	TRBV	TRB-CDR3	TRBJ	TRBC	Ratio
TRAV26-1	CIVRSPTGDSWGKLQF	TRAJ24	TRAC	TRBV4-1	CASSQDRGNMNTEAFF	TRBJ1-1	TRBC1	0.44%
TRAV8-3	CAVGAKGYQKVTF	TRAJ13	TRAC	TRBV27	CASSLSNPRDEQFF	TRBJ2-1	TRBC2	0.37%
TRAV27	CAGHNAGNNRKLIW	TRAJ38	TRAC	TRBV4-1	CASSQGLAGANEQFF	TRBJ2-1	TRBC2	0.29%
TRAV16	CALSRGSNYKLTF	TRAJ53	TRAC	TRBV5-6	CASSPWRLDSLWGGYTF	TRBJ1-2	TRBC1	0.18%
TRAV27	CAGAKGNNDMRF	TRAJ43	TRAC	TRBV13	CASSFQGRGTEAFF	TRBJ1-1	TRBC1	0.18%
TRAV3	CADYYGQNFVF	TRAJ26	TRAC	TRBV28	CASSFQGFTEAFF	TRBJ1-1	TRBC1	0.17%
TRAV1-2	CAVWDSNYQLIW	TRAJ33	TRAC	TRBV6-2	CASSYGGDTGELFF	TRBJ2-2	TRBC2	0.15%
TRAV5	CAESIRRDKIIF	TRAJ30	TRAC	TRBV4-1	CASSWDPTGNTEAFF	TRBJ1-1	TRBC1	0.15%
TRAV20	CAVLSGAGSYQLTF	TRAJ28	TRAC	TRBV9	CASSVESGTGWGKLFF	TRBJ1-4	TRBC1	0.13%
TRAV10	CVVSGGGADGLTF	TRAJ45	TRAC	TRBV29-1	CSGTGANSYEQYF	TRBJ2-7	TRBC2	0.11%

Luo, L., Liang, W., Pang, J. *et al.* Dynamics of TCR repertoire and T cell function in COVID-19 convalescent individuals. *Cell Discov* **7,** 89 (2021). https://doi.org/10.1038/s41421-021-00321-x

Receptor binding affinity *vs.* viral genetics



Michael I Barton, Stuart A MacGowan, Mikhail A Kutuzov, Omer Dushek, Geoffrey John Barton, P Anton van der Merwe (2021) Effects of common mutations in the SARS-CoV-2 Spike RBD and its ligand, the human ACE2 receptor on binding affinity and kinetics eLife 10:e70658https://doi.org/10.7554/eLife.70658

Discrete space model

$$\frac{dT}{dt} = \lambda T \left(1 - \frac{T + I_0 + I_1}{K}\right) - \beta T V_0 - \beta T V_1$$
$$\frac{dI_0}{dt} = \beta T V_0 \mu_{0,0} + \beta T V_1 \mu_{1,0} - \delta I_0 - k_0 I_0 A_0$$
$$\frac{dI_1}{dt} = \beta T V_1 \mu_{1,1} + \beta T V_0 \mu_{0,1} - \delta I_1 - k_1 I_1 A_1$$
$$\frac{dV_0}{dt} = p_0 I_0 - c V_0$$
$$\frac{dV_1}{dt} = p_1 I_1 - c V_1$$
$$\frac{dA_0}{dt} = r A_0 \frac{V_0}{h + V_0} - \gamma A_0$$
$$\frac{dA_1}{dt} = r A_1 \frac{V_1}{h + V_1} - \gamma A_1$$

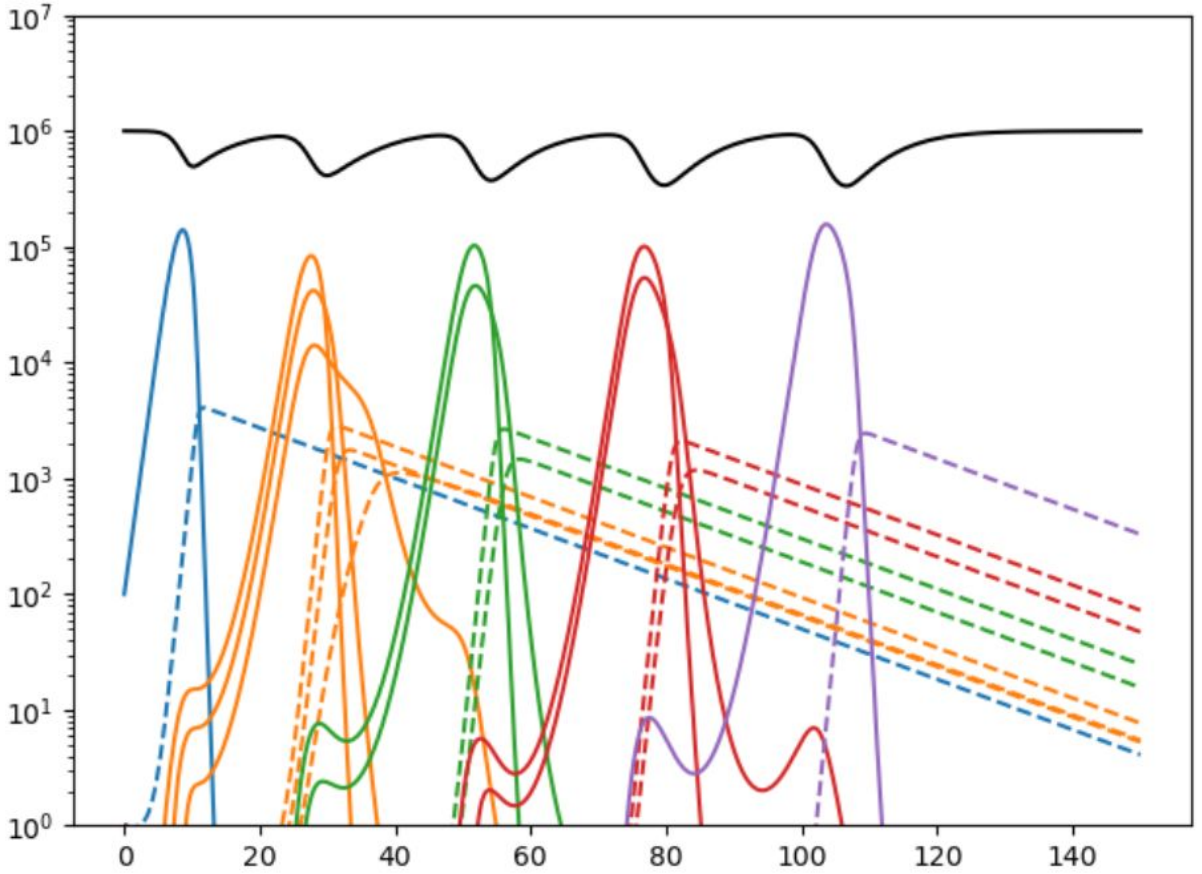
Discrete space model – updated for multiple loci

$$\frac{dT}{dt} = \lambda T \left(1 - \frac{T + \sum_{j=0}^{N}}{K}\right) - \beta T \sum_{i=0}^{N} s_i I_i$$

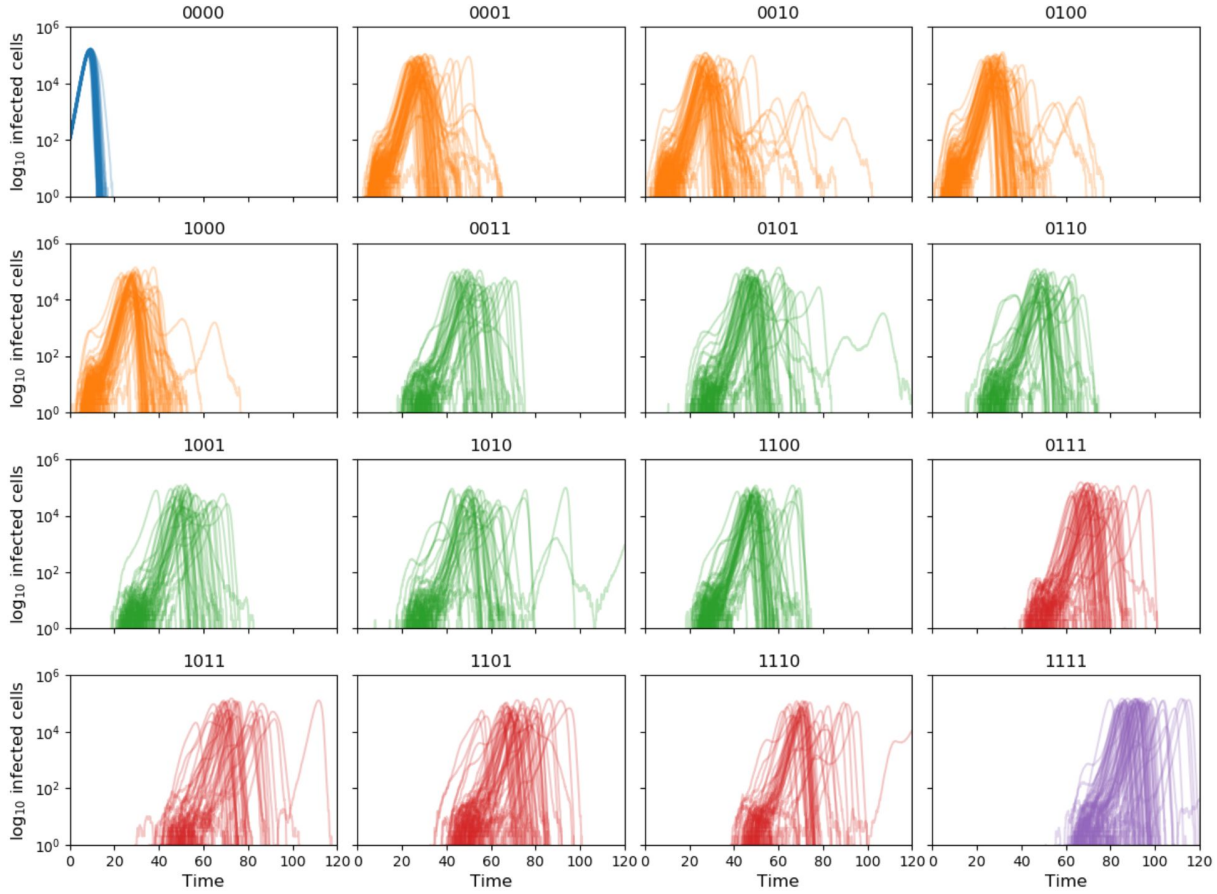
$$\frac{dI_i}{dt} = \beta T \sum_{j=0}^{N} s_j \mu_{j,i} I_j - \delta I_i - k_i I_i A_i$$

$$\frac{dA_i}{dt} = r A_i \frac{I_i}{h + I_i} - \gamma A_i$$

Viral evolution



A solution of the discrete space model for M = 4 possible mutation sites and N = 2^4 = 16 unique infected cell populations. Solid lines represent numbers of target cells (black) and infected cells (coloured), dashed lines indicate the immune response. The colours are infected cells infected with virus with 0 (blue), 1 (orange), 2 (green), 3(red) or 4 (purple) point mutations.


0000
0001
0010
0100
1000
0011
0101
0110
1001
1010
1100
0111
1011
1101
1110
1111
log10 infected cells
Time

Further development

- Increased genetic realism
- Increased immunological realism
- Lessons from influenza (but it is a very different system)

Final Thoughts

- In-host dynamics matter
  - Sometimes worth considering them directly
- Big, open questions remain on SARS-CoV-2
- How much is transferable to the “next” one?

Thanks to…

- Jonathan Carruthers
- Jingsi Xu
- Ian Hall

- Declan Bays
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- Brodie Walker
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- Nick Gent

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- PROTECT project