Within Host Dynamics of SARS-CoV-2 in Humans

Physics of Life, Data and Epidemiology

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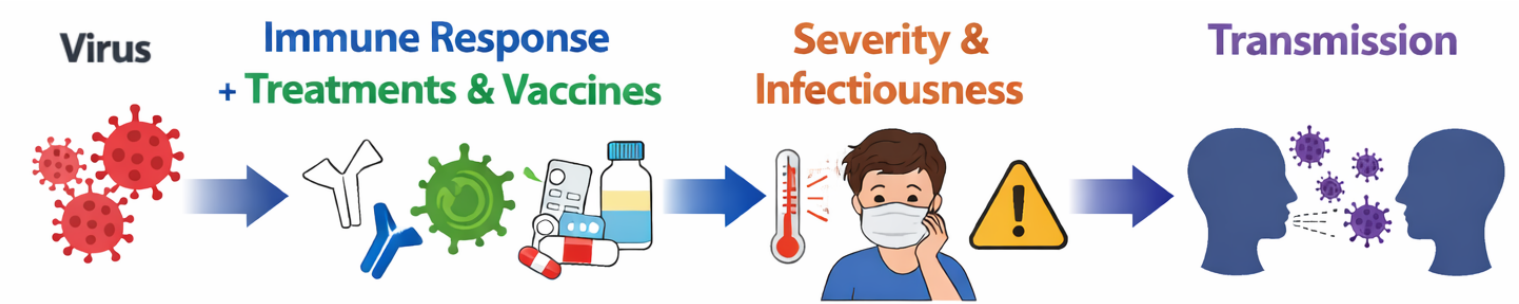
Outline

Motivation & objectives

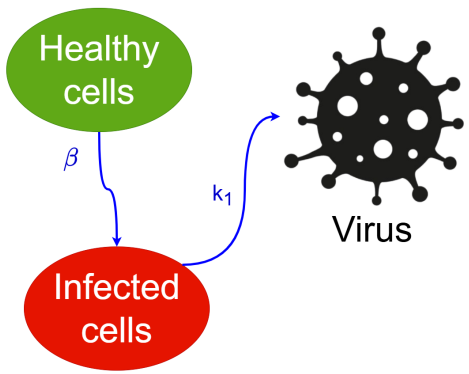


- Build up in small steps a published SARS-CoV-2 within-host model
- Analyze immune-driven viral clearance
- Compare antivirals vs vaccination effect
- Model immunodeficiency
- Link viral load to epidemiological R_0

Model adapted from Ghosh, I. Within Host Dynamics of SARS-CoV-2 in Humans: Modeling Immune Responses and Antiviral Treatments. SN COMPUT. SCI. 2, 482 (2021).

Model 1: Target-cell

$$\frac{dH}{dt} = \Pi - \beta HV - \mu_1 H$$
$$\frac{dI}{dt} = \beta HV - \mu_2 I$$
$$\frac{dV}{dt} = k_1 I - \mu_3 V$$

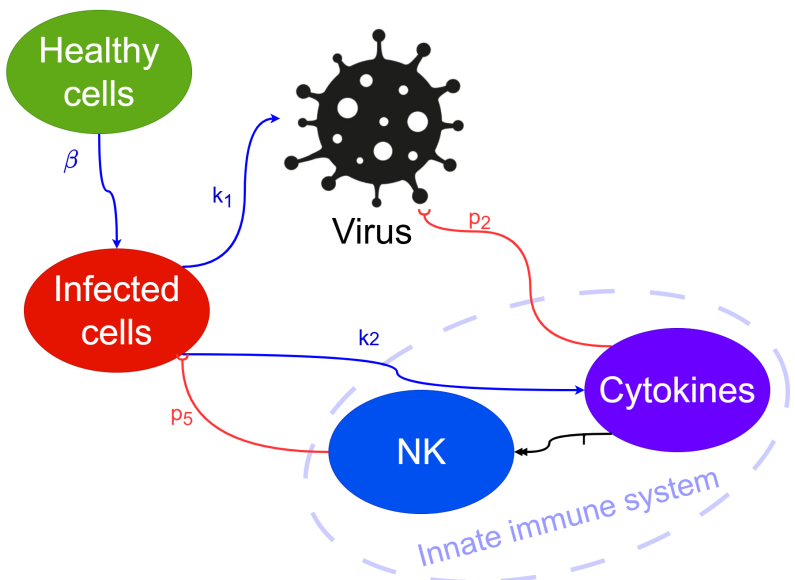


Two equilibria: disease-free and endemic

Threshold: $R_w = \frac{\Pi \beta k_1}{\mu_1 \mu_2 \mu_3}$

Model 2: Innate immunity

$$\frac{dH}{dt} = \Pi - \beta HV - \mu_1 H$$
$$\frac{dI}{dt} = \beta HV - \mu_2 I - p_5 NI$$
$$\frac{dV}{dt} = k_1 I - \mu_3 V - p_2 CV$$
$$\frac{dC}{dt} = \frac{k_2 I}{1 + \gamma V} - \mu_4 C$$
$$\frac{dN}{dt} = rC - \mu_5 N$$



Model 3: Adaptive immunity

$$\frac{dH}{dt} = \Pi - \beta HV - \mu_1 H$$

$$\frac{dI}{dt} = \beta HV - \mu_2 I - p_5 NI - p_1 TI$$

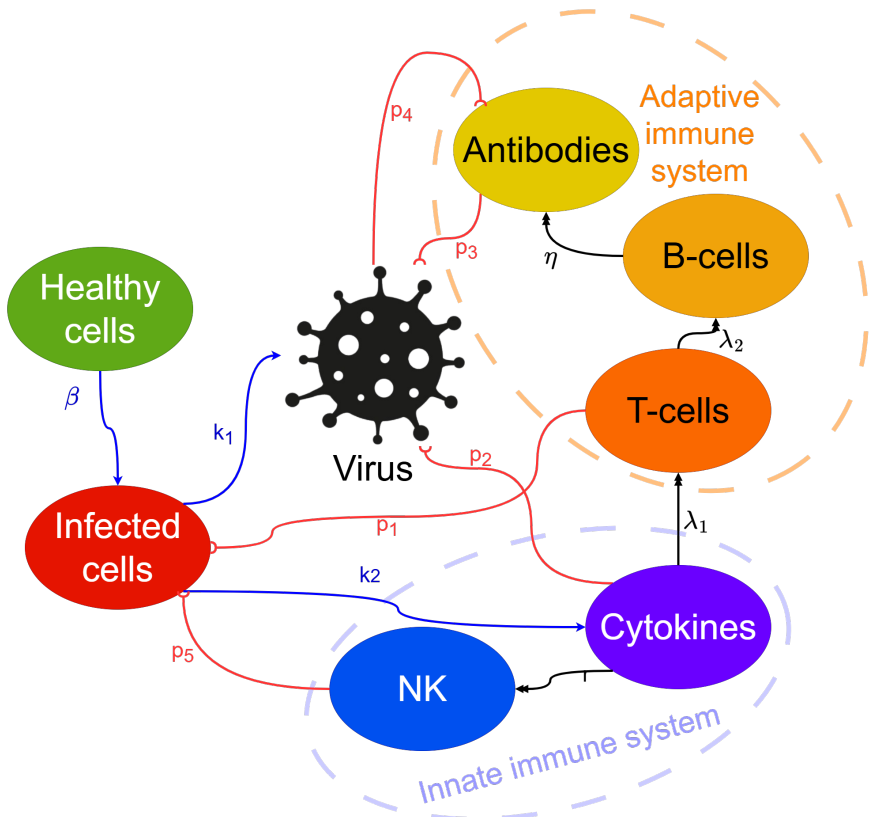
$$\frac{dV}{dt} = k_1 I - \mu_3 V - p_2 CV - p_3 AV$$

$$\frac{dC}{dt} = \frac{k_2 I}{1+\gamma V} - \mu_4 C$$

$$\frac{dN}{dt} = rC - \mu_5 N$$

$$\frac{dT}{dt} = \lambda_1 CT - \mu_6 T \qquad \frac{dB}{dT} = \lambda_2 TB - \mu_7 B$$

$$\frac{dA}{dt} = G(t-\tau)\eta B - p_4 AV - \mu_8 A$$

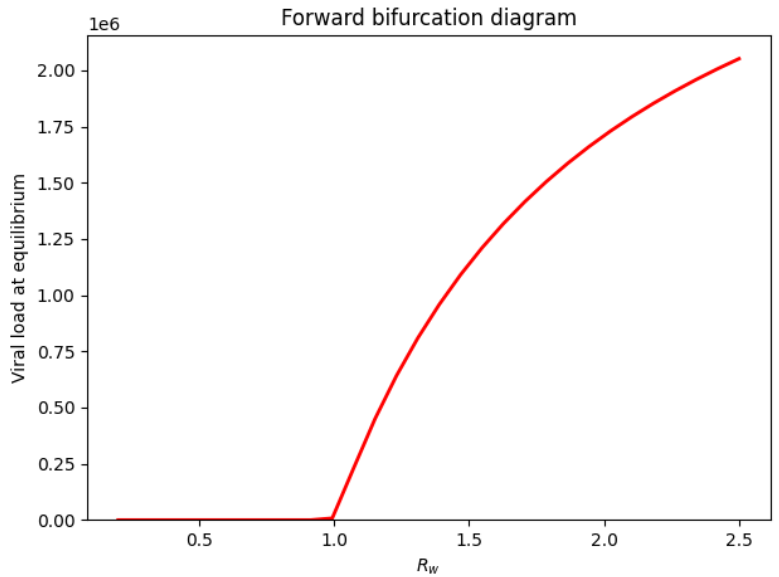


Model 3: Adaptive immunity

Four equilibria:

- Disease-free (DFE)
- Virus persistence without immune reponses
- Virus persistence without adaptive immunity
- Full virus-immune coexistence

The DFE is locally asymptotically stable when $R_w < 1$, exhibiting a forward bifurcation at the critical threshold. This threshold determines whether the virus will be cleared or persist in the long term.



Interventions

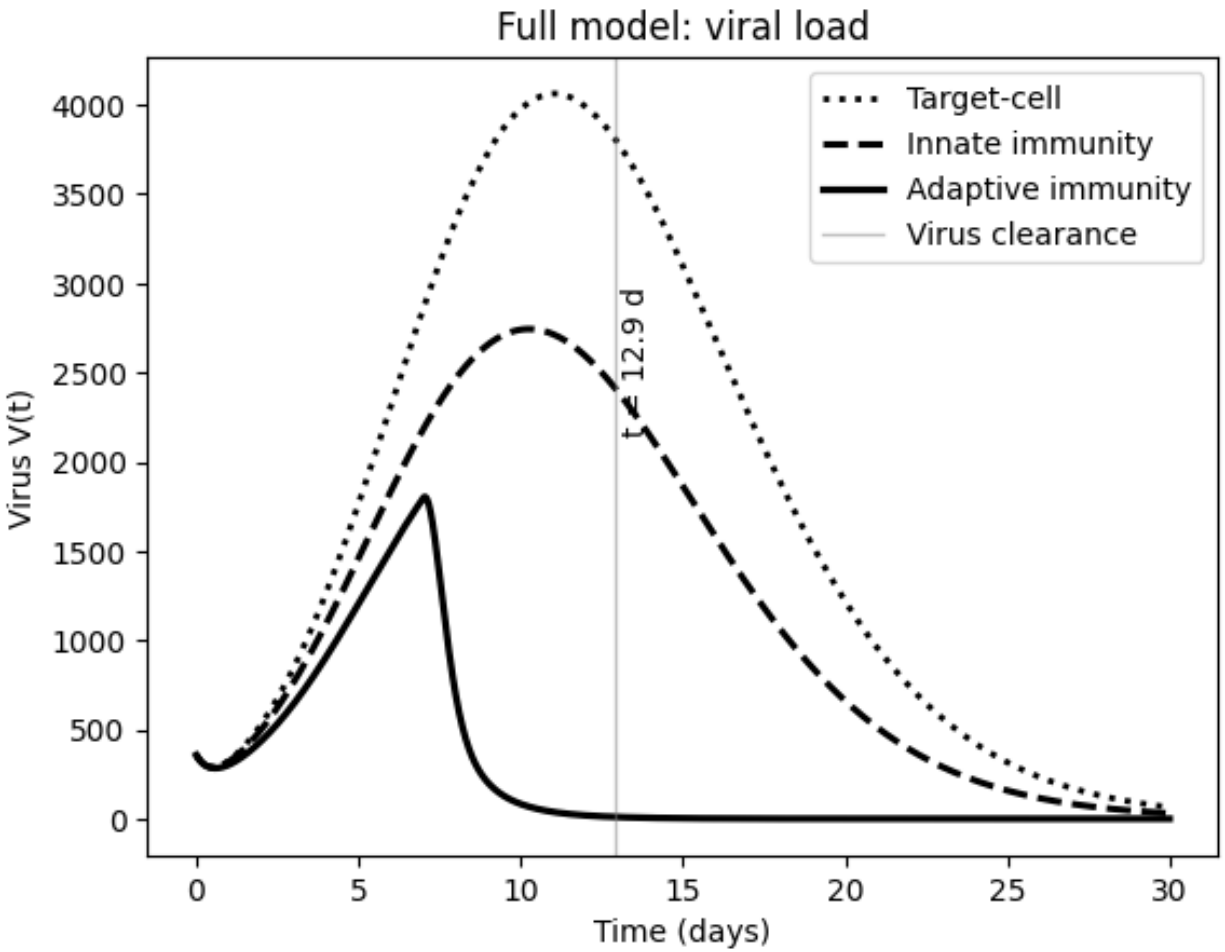
Vaccination Assuming the person is fully vaccinated a sufficiently long time ago, vaccination eliminates the delay in antibody development ($\tau = 0$) as the body has already developed antibodies against SARS-CoV-2. Optional: antibodies already present in initial values.

Antivirals Antiviral drugs target SARS-CoV-2 infection through two mechanisms: blocking infection (ϵ_1), which modifies the infection term to $(1 - \epsilon_1)\beta \mathrm{HV}$, and blocking viral production (ϵ_2), which changes the viral production term to $(1 - \epsilon_2)\mathrm{k_1 I}$.

Numerical methods

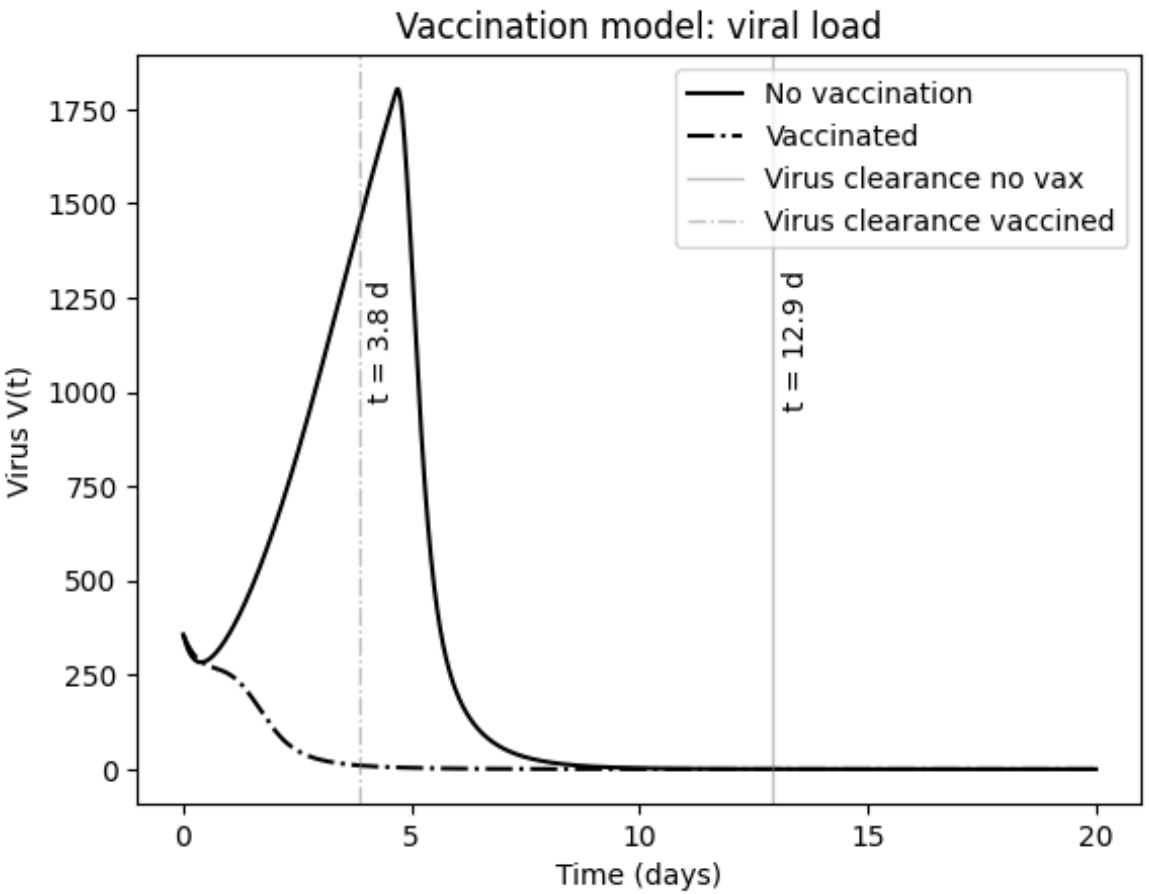
- ODE Solver: Used `solve_ivp` with BDF method (Backward Differentiation Formula)
  - Appropriate for stiff differential equations
- Time Domain: Simulated viral dynamics over 30 days
  - t_eval = np.linspace(0, 30, 1500) high-resolution output
- Virus Clearance Detection: Below 10 RNA copies/ml, virus is experimentally undetectable and usually non-infectious
  - Custom algorithm to determine viral clearance time
  - Defined as viral load remaining below threshold (10.0) for a minimum duration (0.5 days)
  - Prevents false detection of temporary viral load fluctuations
- Initial values and parameters taken from Ghosh et al. (2021).

Results: full model

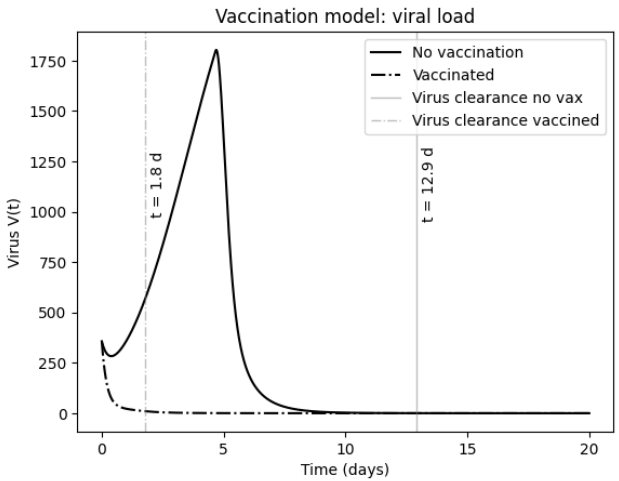


- viral load as metric
- immune response reduces peak and virus clearance time
- $R_w \approx 0.25 \rightarrow$ DFE

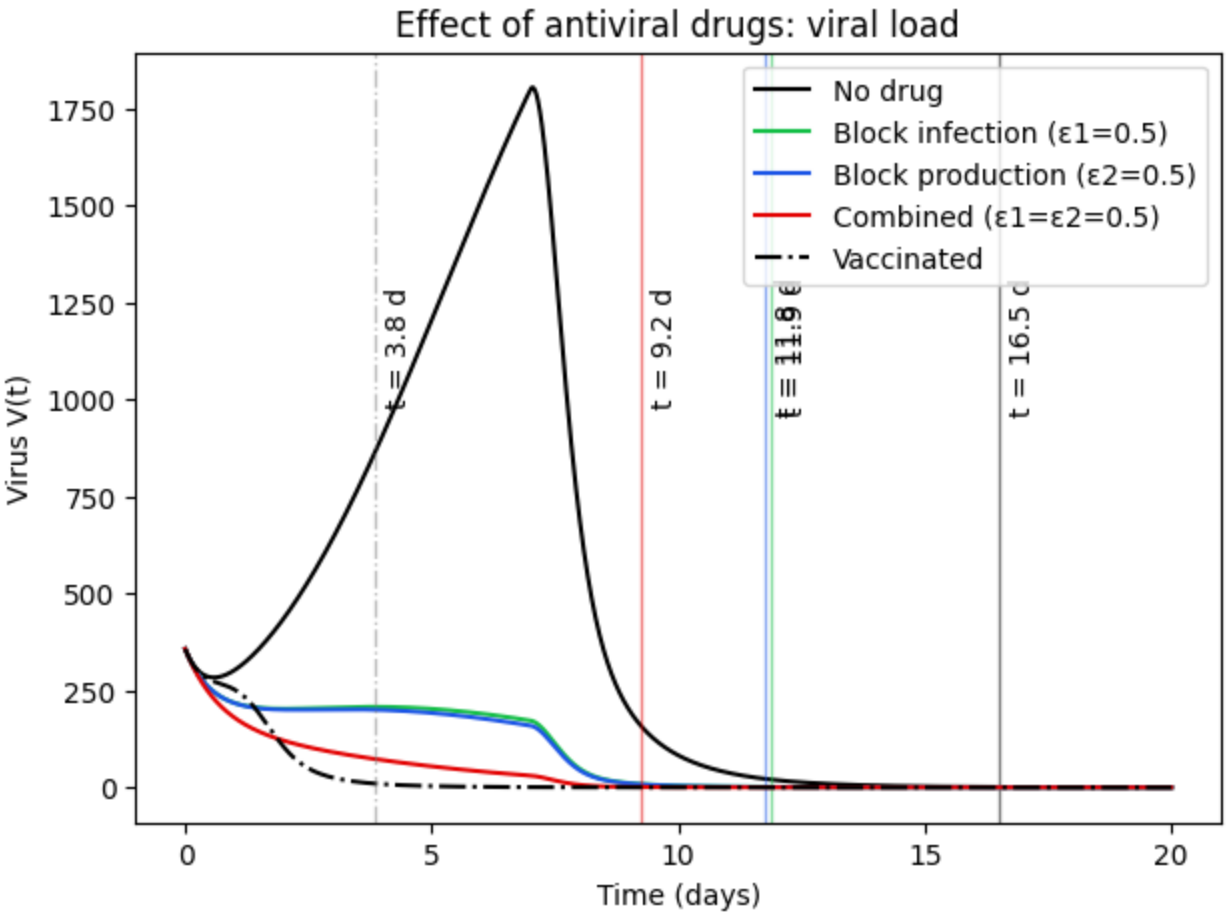
Results: vaccination



- reduced viral peak
- faster clearance time
- optional: antibodies already present, even faster clearance (immune system already triggered - recent infection or vax)



Results: antivirals



- reduced viral peak $\rightarrow$ save the lives of many severely ill patients and will reduce the time spent in intensive care units
- reduced $R_w = \frac{\Pi(1-\epsilon_1)\beta(1-\epsilon_2)k_1}{\mu_1\mu_2\mu_3}$
- slower than vaccination for clearance

Modeling Immunodeficiency

Type	Clinical Examples
Innate Immunity	- Elderly - Sepsis
B-cell Deficiency	- Chemotherapy
T-cell Deficiency	- HIV/AIDS - Transplant recipients - Chronic corticosteroid use
B+T Deficiency	- Severe combined immunodeficiency (SCID) - Advanced hematologic malignancies - Post-bone marrow transplantation
Drug-induced	- Chemotherapy agents - Transplant medications - Corticosteroids

Key Clinical Scenarios

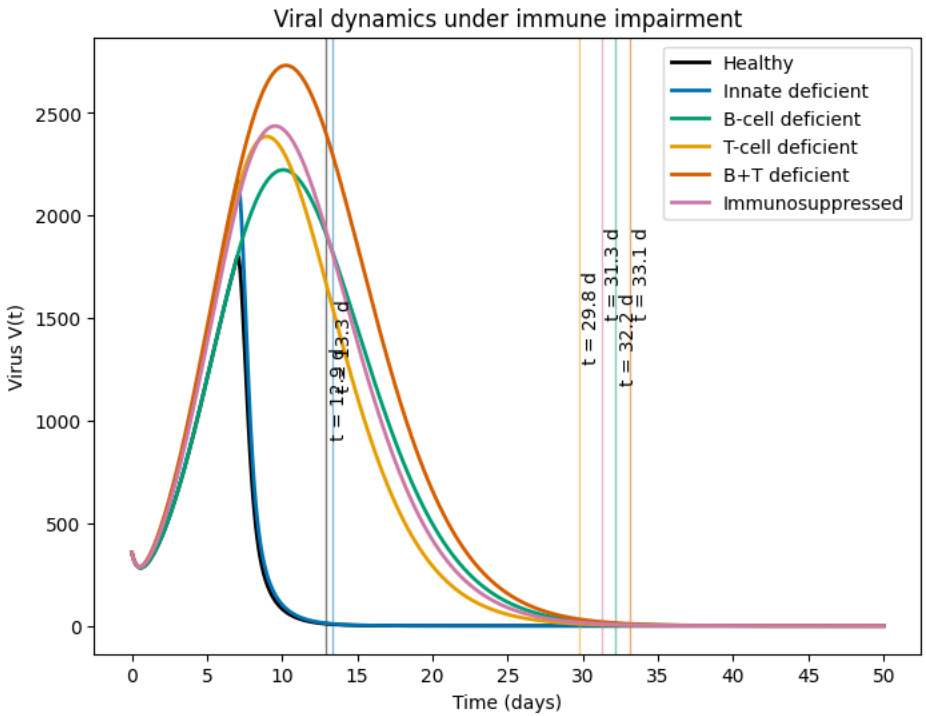
- HIV/AIDS: Progressive T-cell depletion leads to opportunistic infections
- Transplantation: Intentional immunosuppression increases viral persistence
- Chemotherapy: Affects multiple immune components, particularly B-cells

Immunodeficiency results

Model implementation preserves equation structure while modifying immune-related parameters

Table: Summary of Immunodeficiency Scenarios

Condition	Modified parameters
Healthy	Baseline
Innate deficient	$p_5 \downarrow$, $k_2 \downarrow$
B-cell deficient	$\eta \downarrow$, $B(0) \approx 0$
T-cell deficient	$p_1 \downarrow$, $\lambda_1 \downarrow$
B+T deficient	$p_1 \downarrow$, $\eta \downarrow$, $\lambda_1 \downarrow$, $\lambda_2 \downarrow$
Immunosuppressed	All immune parameters $\times \alpha$



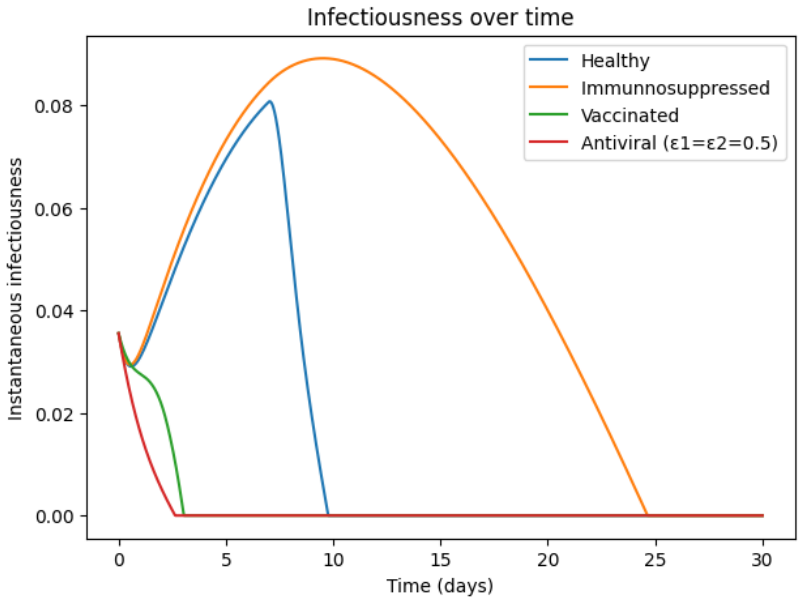
Longer simulation time window: 50 days

Viral load as a proxy for infectiousness

- Experimental evidence shows viral load strongly correlates with transmission
- Log(VL) better predicts transmission probability
- Instantaneous infectiousness model:

  $\beta(t) = \beta_0 \log_{10}(V(t) + 1)$
- Total infectiousness over infection course:

  $I = \int_0^T \beta(t)dt$



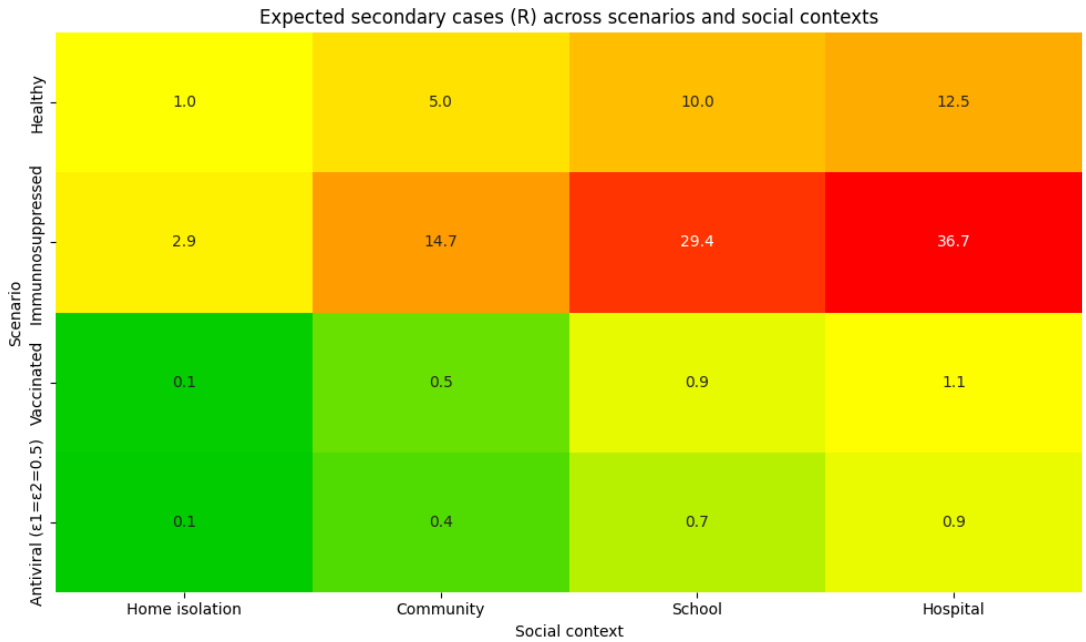
Scenario	Total I	Clearance
Healthy	0.50	16.5d
Immunosupp.	1.47	>30d
Vaccinated	0.05	6.6d
Antiviral	0.04	9.2d

Reference: R. Ke et al., In vivo kinetics of SARS-CoV-2 infection and its relationship with a person's infectiousness, PNAS (2021)

Contact Rates and Reproduction Number

- Expected secondary cases → Basic reproduction number: $R_0 = c \cdot I$
- Different social contexts → different c values (contacts/day)

Setting	c
Home isolation	1-2
General community	8-12
School	15-25
Hospital ward	20-30



Key Insight

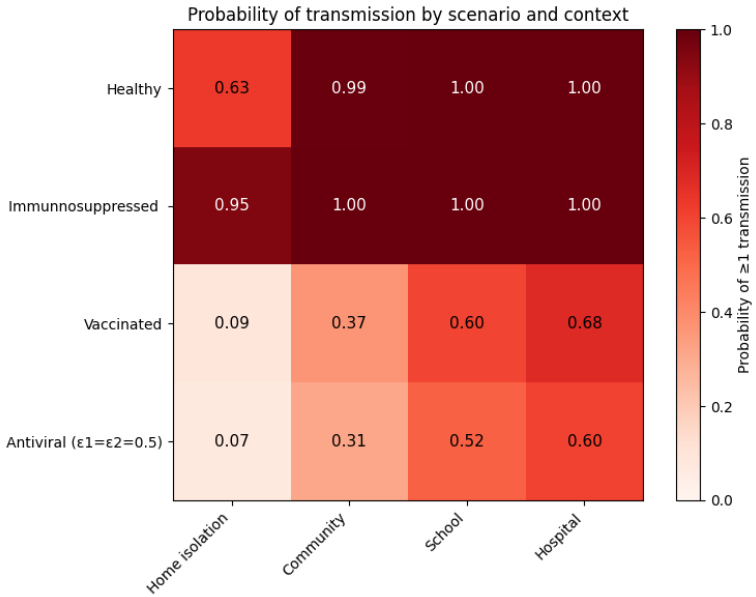
Public health interventions (isolation) and biomedical interventions (vaccines, antivirals) act on different components (c vs I) but combine multiplicatively in reducing R.

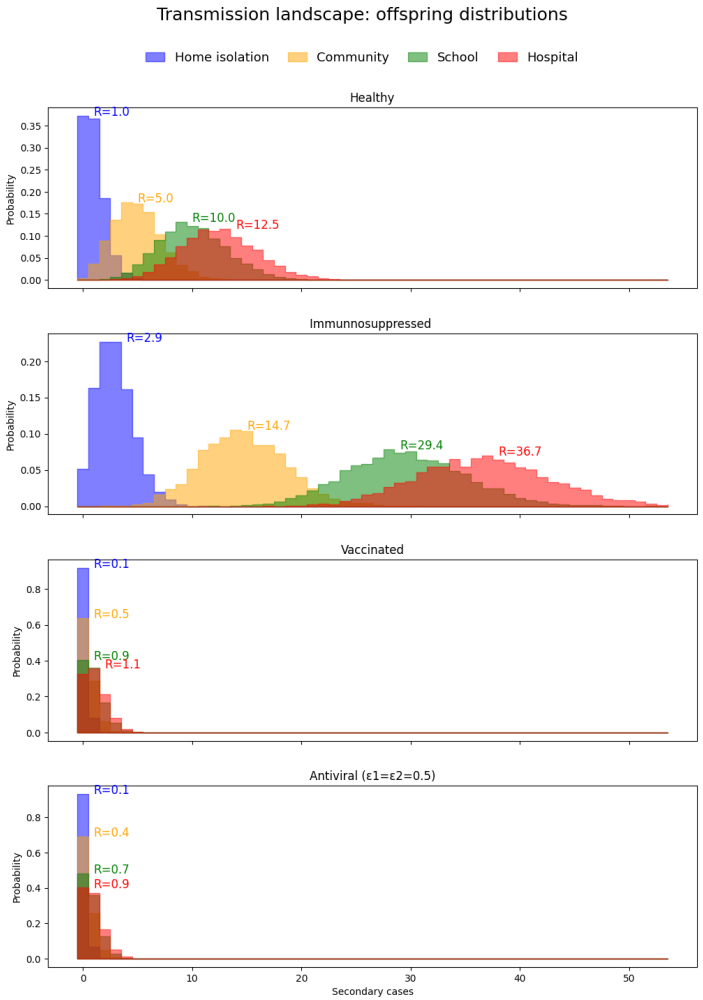
Offspring distribution: from mean to variability

Actual transmission is stochastic → number of secondary cases: Z∼Poisson(R)

This assumes:

- homogeneous susceptibility among contacts
- independent transmission events





Multiscale Impact of Interventions

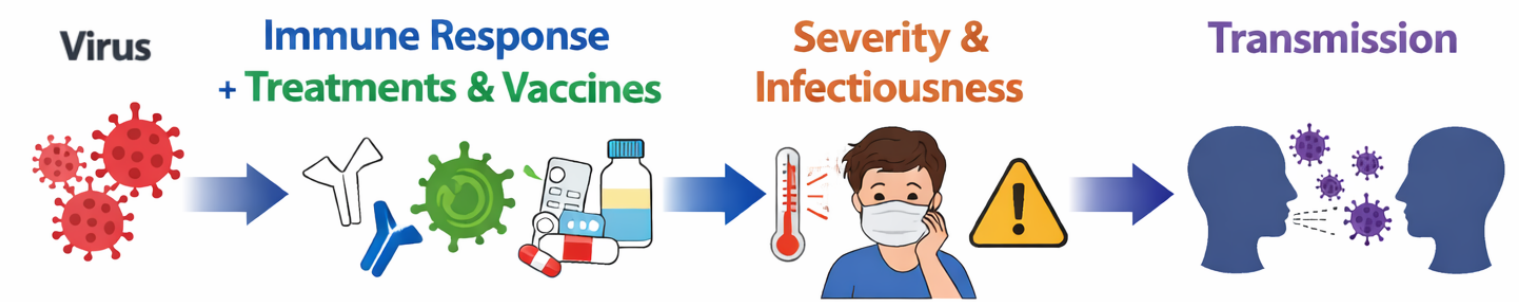
Immunodeficiency: Higher, longer viral load, larger I, heavier tail in offspring distribution (superspreaders)

Vaccination: Shorter duration of high viral load, reduced I even if early growth occurs, $R < 1$ in community settings

Antiviral treatment: Strong suppression of viral production, sharp reduction in I, similar effect as vaccination

Home isolation: Reduction in c, independent of immune status, multiplicative effect with other interventions

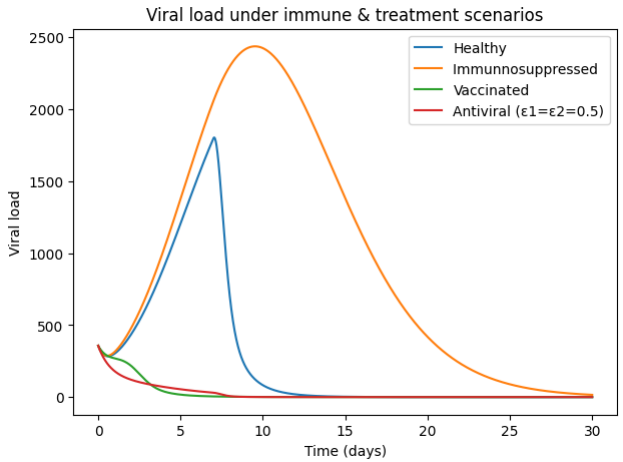
Discussion

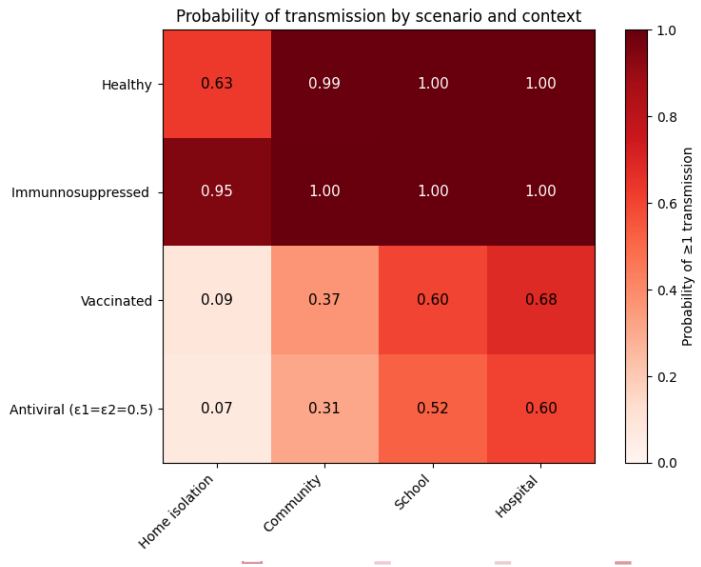


Limitations	Strengths
Deterministic, no stochasticity	Mechanistic immune modeling
No spatial lung structure	Stability and threshold analysis
No patient-specific calibration	Interventions in a unified framework
Simplified immune memory	Viral load $\rightarrow$ transmission link
No viral evolution or reinfection	Biologically interpretable parameters

Conclusions

- Within-host dynamics link immunology to epidemiology
- Immune responses shape both viral load and transmission
- Vaccines and antivirals shorten infectiousness
- Immunodeficiency amplifies epidemic risk
- Biomedical and behavioral interventions act synergistically on R_0





Thanks for your attention!

References

1. Ghosh, I. Within Host Dynamics of SARS-CoV-2 in Humans: Modeling Immune Responses and Antiviral Treatments. SN COMPUT. SCI. 2, 482 (2021).
2. R. Ke, C. Zitzmann, D.D. Ho, R.M. Ribeiro, & A.S. Perelson, In vivo kinetics of SARS-CoV-2 infection and its relationship with a person's infectiousness, Proc. Natl. Acad. Sci. U.S.A. 118 (49) e2111477118, https://doi.org/10.1073/pnas.2111477118 (2021).
3. Ke R, Romero-Severson E, Sanche S, Hengartner N. Estimating the reproductive number R0 of SARS-CoV-2 in the United States and eight European countries and implications for vaccination. J Theor Biol. 2021

Model 1: Target-cell, equilibria

$$\frac{dH}{dt} = \Pi - \beta HV - \mu_1 H$$
$$\frac{dI}{dt} = \beta HV - \mu_2 I$$
$$\frac{dV}{dt} = k_1 I - \mu_3 V$$

Two equilibria:

Disease-free $\quad H_0 = \frac{\Pi}{\mu_1} \qquad I_0 = 0 \qquad V_0 = 0$

Endemic $\quad H_1 = \frac{\mu_2 \mu_3}{\beta k_1} \qquad I_1 = \frac{\Pi \beta k_1 - \mu_1 \mu_2 \mu_3}{\beta k_1 \mu_2} \qquad V_1 = \frac{\Pi \beta k_1 - \mu_1 \mu_2 \mu_3}{\beta \mu_2 \mu_3}$

Threshold: $R_w = \frac{\Pi \beta k_1}{\mu_1 \mu_2 \mu_3}$

Model 3: Adaptive immunity, equilibria

- Disease-Free Equilibrium (DFE): $E_0 = \left(\frac{\Pi}{\mu_1}, 0, 0, 0, 0, 0, 0, 0\right)$
  Stable when $R_w < 1$, where $R_w = \frac{\Pi \beta k_1}{\mu_1 \mu_2 \mu_3}$
- Virus Persistence Without Immune Response:
  $E_1 = \left(\frac{\Pi}{\mu_1 R_w}, \frac{\mu_1 \mu_3}{\beta k_1}(R_w - 1), \frac{\mu_1}{\beta}(R_w - 1), 0, 0, 0, 0, 0\right)$
  Exists when $R_w > 1$
- Virus Persistence With Innate Immunity: $E_2 = (H_2, I_2, V_2, C_2, N_2, 0, 0, 0)$
  With $Q = \beta H_2 V_2$
  $H_2 = \frac{\Pi - Q}{\mu_1}, \quad I_2 = \frac{Q}{\mu_2 + p_5 N_2}, \quad N_2 = \frac{r C_2}{\mu_5}, \quad V_2 = \frac{1}{\gamma}\left(\frac{k_2 I_2}{\mu_4 C_2} - 1\right)$
  The innate immune response is sufficiently strong to sustain immune activation but insufficient to clear the virus.
- Full Virus-Immune Coexistence: $E_3 = (H_3, I_3, V_3, C_3, N_3, T_3, B_3, A_3)$

$$C_3 = \frac{\mu_6}{\lambda_1}, \quad V_3 = \frac{1}{\gamma}(R_1 - 1), \quad I_3 = \frac{\mu_4 \mu_6 R_1}{\lambda_1 k_2}, \quad N_3 = \frac{r C_3}{\mu_5}$$

$$T_3 = \frac{\mu_7}{\lambda_2}, \quad A_3 = \frac{1}{p_3 V_3}(R_2 - 1), \quad B_3 = \frac{A_3}{\eta(p_4 V_3 + \mu_8)}, \quad H_3 = \frac{\Pi - \beta H_3 V_3}{\mu_1}$$

Exists when $R_1 > 1$ and $R_2 > 1$

Model Parameters

Symbol	Description	Value and Unit
Π	Production rate of healthy cells	4×10^{3} cells ml^{-1} day^{-1}
β	Infection rate	2×10^{-8} ml (RNA copies)$^{-1}$ day^{-1}
γ	Immunosuppression strength	0.5 ml (RNA copies)$^{-1}$
μ_1	Death rate of healthy cells	0.14 day^{-1}
μ_2	Death rate of infected cells	0.65 day^{-1}
μ_3	Clearance rate of virus	0.9004 day^{-1}
μ_4	Death rate of cytokines	0.7 day^{-1}
μ_5	Death rate of NK cells	0.07 day^{-1}
μ_6	Death rate of T cells	1.0 day^{-1}
μ_7	Death rate of B cells	0.2 day^{-1}
μ_8	Death rate of antibodies	0.07 day^{-1}
k_1	Virus production rate	253.5 day^{-1}
k_2	Cytokines production rate	5.0 day^{-1}
p_1	T cell killing rate	0.001 ml cells^{-1} day^{-1}
p_2	Cytokine neutralization rate	0.6104 ml molecules^{-1} day^{-1}
p_3	Antibody neutralization rate	0.01865 ml molecules^{-1} day^{-1}
p_4	Antibody production rate	3×10^{-7} ml (RNA copies)$^{-1}$ day^{-1}
p_5	NK cell killing rate	5.74×10^{-4} ml cells^{-1} day^{-1}
r	NK cell activation rate	0.52 day^{-1}
λ_1	T cell activation rate	0.1 ml cells^{-1} day^{-1}
λ_2	B cell activation rate	0.01 ml cells^{-1} day^{-1}
η	Antibody production rate	0.05 day^{-1}
τ	Antibody production delay	7.0 days

Initial Values

Variable	Description	Initial Value	Unit
H	Healthy cells	4×10^5	cells ml^{-1}
I	Infected cells	3×10^{-4}	cells ml^{-1}
V	Viral load	357	RNA copies ml^{-1}
C	Cytokines	0	molecules ml^{-1}
N	NK cells	100	cells ml^{-1}
T	T cells	500	cells ml^{-1}
B	B cells	100	cells ml^{-1}
A	Antibodies	0	molecules ml^{-1}

Source: Ghosh, I. Within Host Dynamics of SARS-CoV-2 in Humans (2021)

Immunodeficiency parameters

Scenario	Parameter Modifications
Healthy (Baseline)	No modifications
Innate Deficient	$k_2 \times 0.2$ (cytokine production) $r \times 0.2$ (NK activation) $\mu_5 \times 2.0$ (NK decay rate)
B-cell Deficient	$\eta = 0.001$ (antibody production) $B(0) = 10$ cells ml^{-1} (initial B cells)
T-cell Deficient	$p_1 \times 0.2$ (T-cell killing) $\lambda_1 \times 0.2$ (T activation) $\lambda_2 \times 0.2$ (B activation)
B+T Deficient	$p_1 \times 0.2$ (T-cell killing) $\lambda_1 \times 0.2$ (T activation) $\lambda_2 \times 0.2$ (B activation) $\eta = 0.001$ (antibody production) $B(0) = 10$ cells ml^{-1} (initial B cells) $T(0) = 50$ cells ml^{-1} (initial T cells)
Immunosuppressed	All immune parameters (k_2, p_1, p_3, r, λ_1, λ_2, η) $\times 0.3$

Calibrating Transmission Parameter

- Need to link within-host viral load to population-level R_0
- Use empirical R estimates from literature
- Solve for β_0 in the equation:

$$R_0^{\text{empirical}} = c \cdot \int_0^T \beta_0 \log_{10}(V(t) + 1) dt$$

Reference Data

- R_0 estimates from Ke et al. (2021)
- US and European countries: $R_0 \approx 5$
- Assumed contact rate: $c = 10$ contacts/day (general commuting)
- Healthy host viral dynamics as baseline

Reference: Ke R, Romero-Severson E, Sanche S, Hengartner N. Estimating the reproductive number R of SARS-CoV-2 in the United States and eight European countries and implications for vaccination. J Theor Biol. 2021;517:110621.