Maths & the Evolution of Viruses

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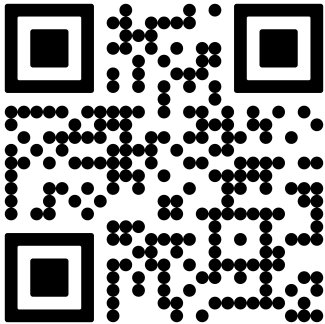
Christ's Maths Society

November 23, 2022

Overview



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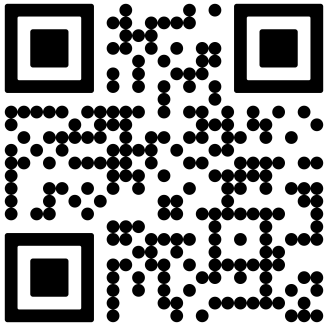
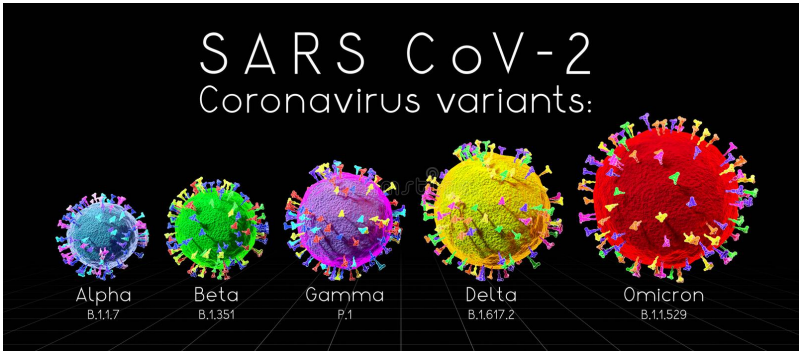
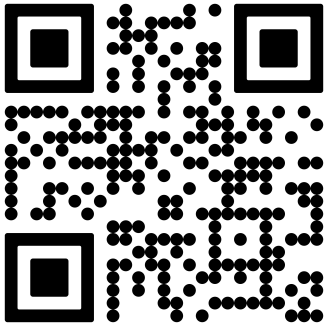


Motivation


SARS CoV-2
Coronavirus variants:
Alpha
B.1.1.7
Beta
B.1.351
Gamma
P.1
Delta
B.1.617.2
Omicron
B.1.1.529

Overview



Measuring escape: it's difficult!

Quantify the **"immune/antigenic/vaccine escape pressure"** exerted on the virus towards mutations with the ability to escape immunity (eg antibodies).

Can think of it as the probability that an escape variant appears during the epidemic:

- Escape at probability $p_U \ll 1$ per infection in the unvaccinated.
- Escape at probability $p_V \ll 1$ per infection in the vaccinated.

$$P = 1 - (1 - p_U)^{N_U}(1 - p_V)^{N_V} \approx p_U N_U + p_V N_V$$

Measuring escape: the unknowns

Only care about **relative escape pressur**e (relative to epidemic without vaccination). Define $\theta_E = p_V/p_U$, so

$$\boxed{P \propto N_U + \theta_E N_V}$$

Is $\theta_E < 1$ or $\theta_E > 1$?

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$$\boxed{P \propto N_U + \theta_E N_V}$$

Is $\theta_E < 1$ or $\theta_E > 1$? We have no idea, θ_E could be in any value in $[0, \infty)$!!

- Unvaccinated individuals have higher viral load $\implies$ more mutations
- Escape variants evade immunity in vaccinated individuals $\implies$ more selection pressure

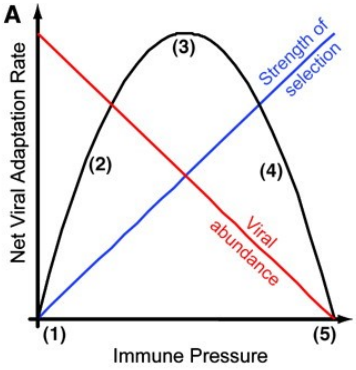
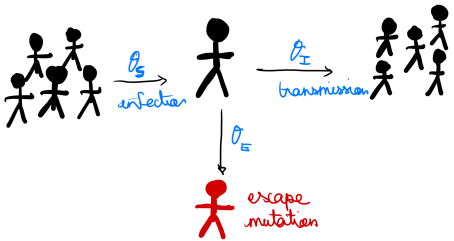


Figure 1: *Phylodynamics* (Grenfell et al. Science)

Measuring escape: imperfect vaccines

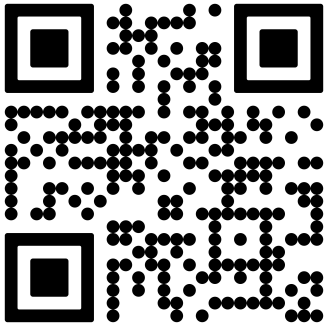


Probability of infection reduced by a factor θ_S (susceptibility reduction)

Probability of transmission reduced by a factor θ_I (infectivity reduction)

Probability of escape mutation changed by a factor θ_E

Overview



Background: the SIR model

Use proportions of the total population, start with everyone susceptible $S(0) = 1$, except an infinitesimal proportion of infected $I(0) = \epsilon$, $R_0 > 1$ (initial outbreak will grow)

Susceptible	$\dot{S} = -R_0 SI$
Infectious	$\dot{I} = R_0 SI - I$
Recovered	$\dot{R} = +I$

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Can eliminate $R = 1 - S - I$, and solve the 2D system:

$$\frac{dI}{dS} = \frac{\dot{I}}{\dot{S}} = \frac{R_0 SI - I}{-R_0 SI} = -1 + \frac{1}{R_0 S} \implies I = 1 - S + R_0^{-1} \log S$$

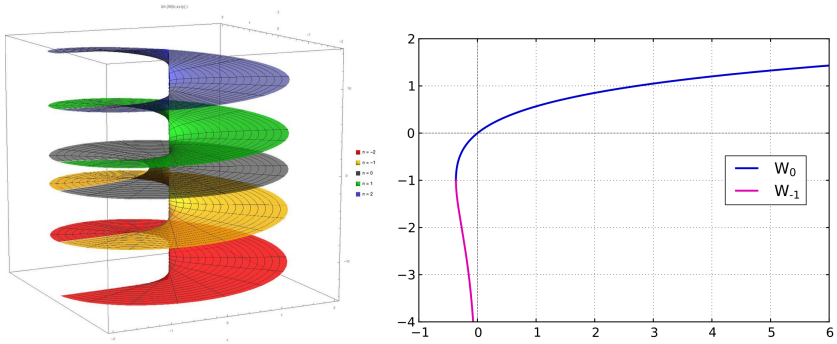
For final size, take $I \to 0$: $S_\infty = 1 - R_0 \log S_\infty^{-1}$ (implicit), total infections is

$$\boxed{N = 1 - S_\infty = 1 + \frac{W[-R_0 e^{-R_0}]}{R_0}}$$

where W is the Lambert W function.

Aside: the Lambert W function

$W(z)$ solves $We^W = z$ in the complex plane, has multiple branches!



For real numbers, only need two branches, W_0 and W_{-1}

For the SIR model, only need principal branch $W_0(x) \in [-1, 0)$ for $x \in [-e^{-1}, 0)$

Transient scenario: setting up the system

Duplicated compartments for vaccinated or unvaccinated

Full permanent immunity from vaccines or infections

Vaccination before the outbreak, a proportion c of the population:

$S_U(0) = (1-c) \leftarrow$ susceptible unvaccinated, $S_V(0) = c\theta_S \leftarrow$ susceptible vaccinated

	Unvaccinated	Vaccinated
Susceptible	$\dot{S}_U = -R_0 S_U \lambda(t)$	$\dot{S}_V = -R_0 S_V \lambda(t)$
Infectious	$\dot{I}_U = R_0 S_U \lambda(t) - I_U$	$\dot{I}_V = R_0 S_V \lambda(t) - I_V$
Recovered	$\dot{R}_U = I_U$	$\dot{R}_V = I_V$

$\lambda(t) = I_U + \theta_I I_V$ (effective number of infectious individuals)

Transient scenario: solving the system 1/2

Claim: $(S_V, I_V, R_V) = \frac{c\theta_S}{1-c}(S_U, I_U, R_U)$ at all times.

Proof: For $\mathbf{u}^T = (S_U(t), I_U(t), R_U(t))$ and $\mathbf{v}^T = (S_V(t), I_V(t), R_V(t))$,

$$\dot{\mathbf{u}} = \mathbf{M}\mathbf{u} \qquad\qquad \dot{\mathbf{v}} = \mathbf{M}\mathbf{v}$$

with $\mathbf{M}(t) = \begin{pmatrix} -R_0\lambda(t) & 0 & 0 \\ R_0\lambda(t) & -1 & 0 \\ 0 & +1 & 0 \end{pmatrix}$ and $\mathbf{v}(0) = \frac{c\theta_S}{1-c}\mathbf{u}(0)$.

Both $\hat{\mathbf{u}}(t) := \frac{1-c}{c\theta_S}\mathbf{v}(t)$ and $\mathbf{u}(t)$ obey the same first order ODE and IC $\mathbf{u}(0) = \hat{\mathbf{u}}(0)$. Hence (by uniqueness of solutions), $\hat{\mathbf{u}}(t) = \mathbf{u}(t)$. Thus $\mathbf{v}(t) = \frac{c\theta_S}{1-c}\mathbf{u}(t)$. □

Transient scenario: solving the system 2/2

This proportion reduces the system to a standard SIR model

$$\dot{S}_U = -S_U I_U R_0 \left(1 + \frac{c\theta_S\theta_I}{1-c}\right) \qquad \dot{I}_U = +S_U I_U R_0 \left(1 + \frac{c\theta_S\theta_I}{1-c}\right) - I_U$$

$$S_U(0) = 1 - c \qquad I_U(0) = \epsilon \ll 1$$

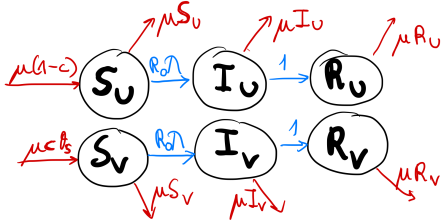
with effective $R-$number $R_e = R_0(1 - c + c\theta_S\theta_I)$.
$R_e = 1$ gives herd-immunity threshold $\tilde{c} = (1 - R_0^{-1})/(1 - \theta_S\theta_I)$.
For $c < \tilde{c}$, get $N_U = (1-c)\left(1 + W(-R_e e^{-R_e})/R_e\right) = (1-c)(c\theta_S)^{-1}N_V$

$$\boxed{P = N_U + \theta_E N_V = (1 - c + \theta_S\theta_E c)\left(1 + \frac{1}{R_e} W\left(-R_e e^{-R_e}\right)\right)}$$

Endemic scenario: setting up the system

	Unvaccinated	Vaccinated
Susceptible	$\dot{S}_U = \mu(1-c) + R_0 S_U \lambda - \mu S_U$	$\dot{S}_V = \mu c \theta_S - R_0 S_V \lambda - \mu S_V$
Infectious	$\dot{I}_U = R_0 S_U \lambda - I_U - \mu I_U$	$\dot{I}_V = R_0 S_V \lambda - I_V - \mu I_V$
Recovered	$\dot{R}_U = I_U - \mu R_U$	$\dot{R}_V = I_V - \mu R_V$

μ is per capita birth/death rate, vaccinate proportion c of births



Endemic scenario: solving the system

Claim: $(S_V, I_V, R_V) = \frac{c\theta_S}{1-c}(S_U, I_U, R_U)$ at all times.

Proof: $\dot{\mathbf{u}} = \mathbf{x}_U + \mathbf{M}(t)\mathbf{u}$, $\dot{\mathbf{v}} = \mathbf{x}_V + \mathbf{M}(t)\mathbf{v}$, with $\mathbf{M}(t) = \begin{pmatrix} -R_0\lambda(t) - \mu & 0 & 0 \\ R_0\lambda(t) & -1-\mu & 0 \\ 0 & +1 & -\mu \end{pmatrix}$
and $\mathbf{x}_U^T = (\mu(1-c), 0, 0) = \frac{1}{\alpha}\mathbf{x}_V^T$, $\mathbf{v}(0) = \alpha\mathbf{u}(0)$ for $\alpha = c\theta_S/(1-c)$.
Both $\mathbf{u}(t), \hat{\mathbf{u}}(t) := \alpha^{-1}\mathbf{v}(t)$ solve the IVP:
$\dot{\mathbf{y}}(t) = \mathbf{F}(t, \mathbf{y}(t)) = \mathbf{M}(t)\mathbf{y}(t) + \mathbf{x}_U, \mathbf{y}(0) = \mathbf{u}(0)$, so $\mathbf{u}(t) = \hat{\mathbf{u}}(t)$ □

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Endemic equilibrium: Set derivatives to zero, look for $(S_U^*, I_U^*, R_U^*) = \frac{1-c}{c\theta_S}(S_V^*, I_V^*, R_V^*)$

For $R_e > 1 + \mu$, $I_U^* = \mu(1-c)\left[1/(1+\mu) - 1/R_e\right] = (1-c)I_V^*/c\theta_S$.

Hence $P^* = I_S^* + \theta_E I_U^* = (1 - c(1-\theta_E\theta_S))\mu\left[1/(1+\mu) - 1/R_e\right]$. Take limit $\mu \ll 1$

$$\boxed{P^* \propto (1 - c(1-\theta_E\theta_S))\left(1 - R_e^{-1}\right)}$$

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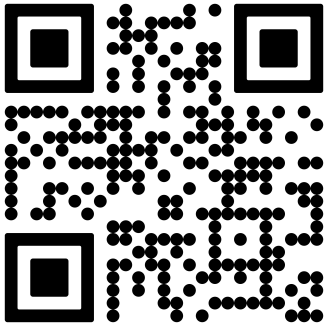
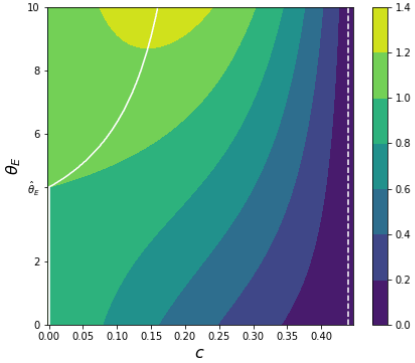
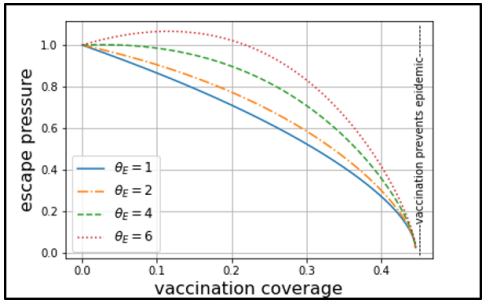


Results: escape pressure as a function of c

- Peaks at intermediate vaccination c for θ_E above a threshold $\hat{\theta}_E$: this is when vaccinated individuals contribute a lot to escape
- Monotonically decreasing with c for $\theta_E < \hat{\theta}_E$





Finding the maximiser and the bifurcation point

$P^* = (1 + c(\theta_S\theta_E - 1))(1 - R_e^{-1})$, $R_e = R_0(1 - c(1 - \theta_S\theta_I))$

Differentiate to find gradient and evaluate at $c = 0$:

$$\frac{dP}{dc} = (\theta_S\theta_E - 1)(1 - R_e^{-1}) - (1 + c(\theta_S\theta_E - 1))R_e^{-2}R_0(1 - \theta_S\theta_I)$$

$$\left.\frac{dP}{dc}\right|_{c=0} = (\theta_S\theta_E - 1)(1 - R_0^{-1}) - R_0^{-1}(1 - \theta_S\theta_I)$$

This is negative ($P(c)$ decreasing $\forall c$) iff $(\theta_E\theta_S - 1) < (1 - \theta_S\theta_I)/(R_0 - 1)$

Else maximiser is $c_m = (1 - \theta_S\theta_I)^{-1}\left[1 - \sqrt{1 + (1 - \theta_S\theta_I)/(\theta_S\theta_E - 1)}/\sqrt{R_0}\right]$

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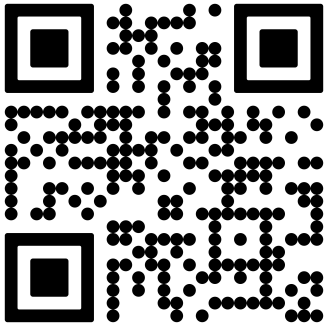

Conclusion and takeaways

- θ_E is key in regulating how vaccination affects escape
  - Intermediate levels of vaccination can be the most dangerous
  - But also possible that any vaccination level decreases escape
- Other evo-epi models should not neglect θ_E!
- Would be very helpful to empirically estimate θ_E
- At some point, vaccines could also be evaluated based on their θ_E
- While θ_E remains unknown, keep vaccinating to reduce escape pressure
- Perhaps escape variants more likely to come from countries with lower vaccination rates (so donate vaccines!)
- Maths is super useful in this context

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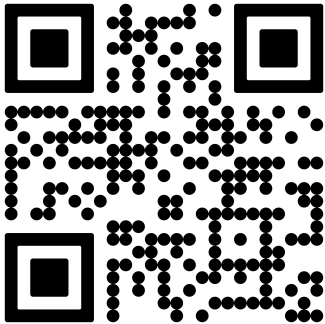

Where's my model going wrong or what is missing?

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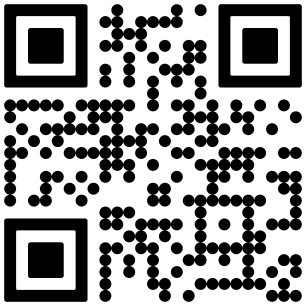
- Transmission of escape variants
- Reinfections
- Waning immunity
- Different individuals likely contribute differently to escape
- Multiple vaccine doses
- Multiple vaccine types
- Multiple variants in circulation

All models are wrong, but some are useful...(George Box)

Any questions?

Thank you for listening

and thanks to my PhD supervisor, Prof. Julia Gog



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