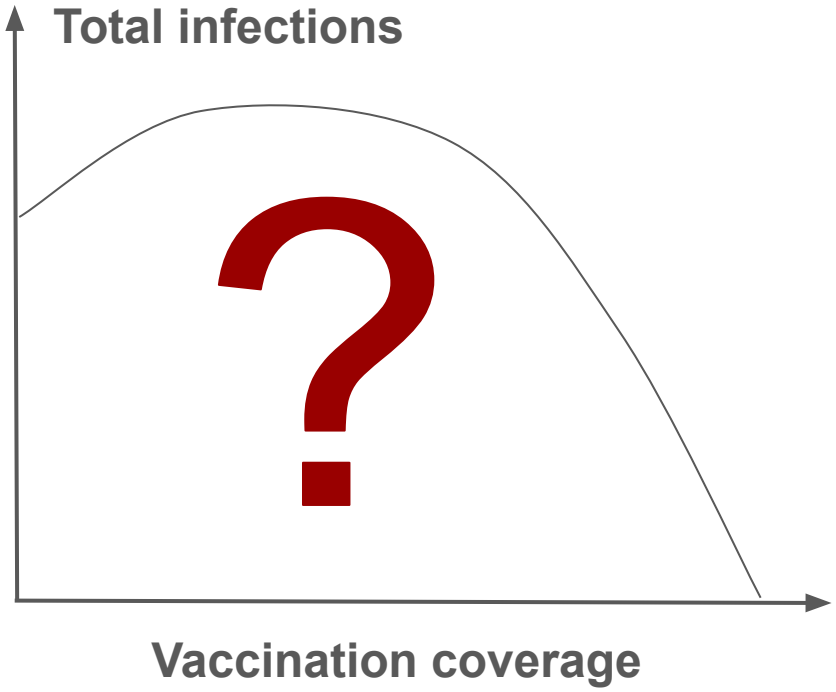
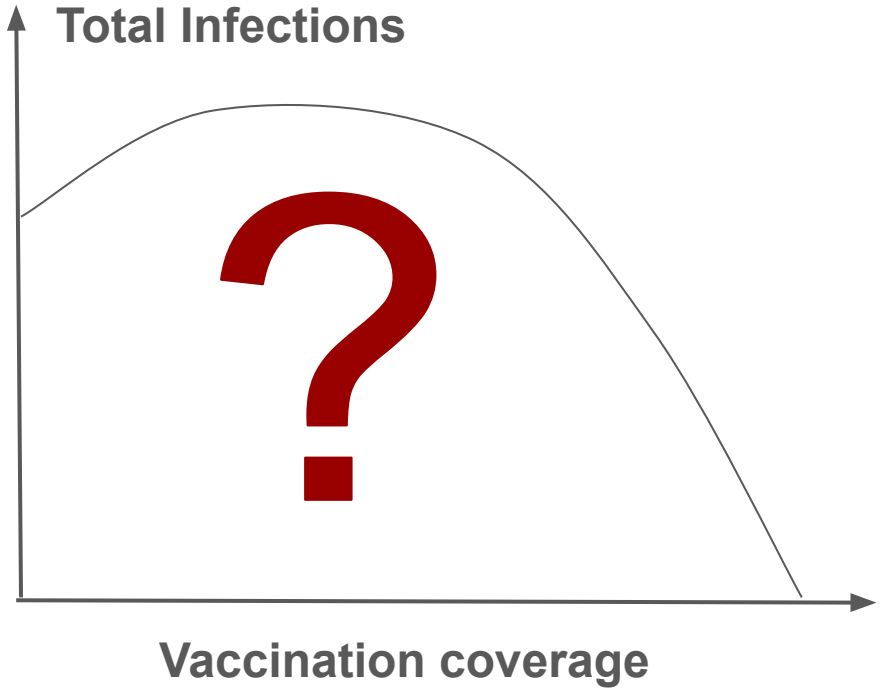
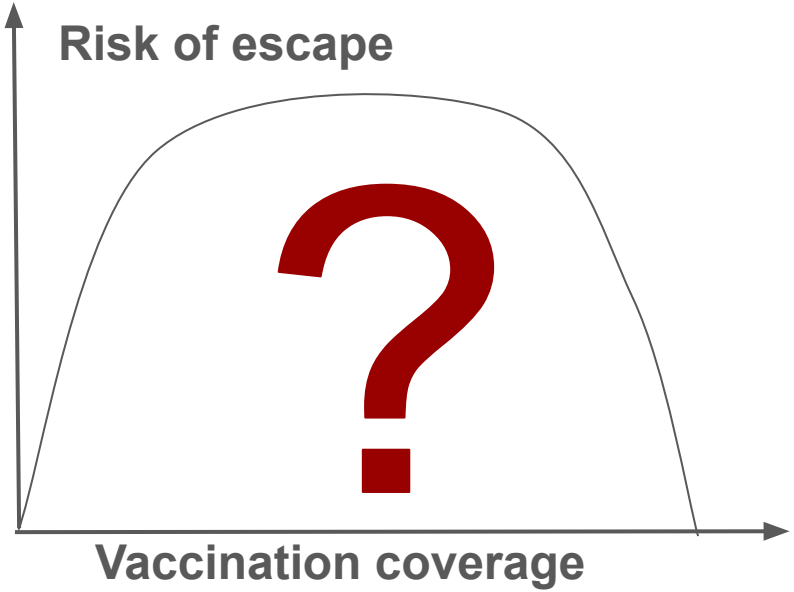
Modelling **vaccine escape** in a population



Maria A. Gutierrez
University of Cambridge


Total Infections
?
Vaccination coverage



Vaccine escape in a heterogeneous population insights for SARS-CoV-2 from a simple model

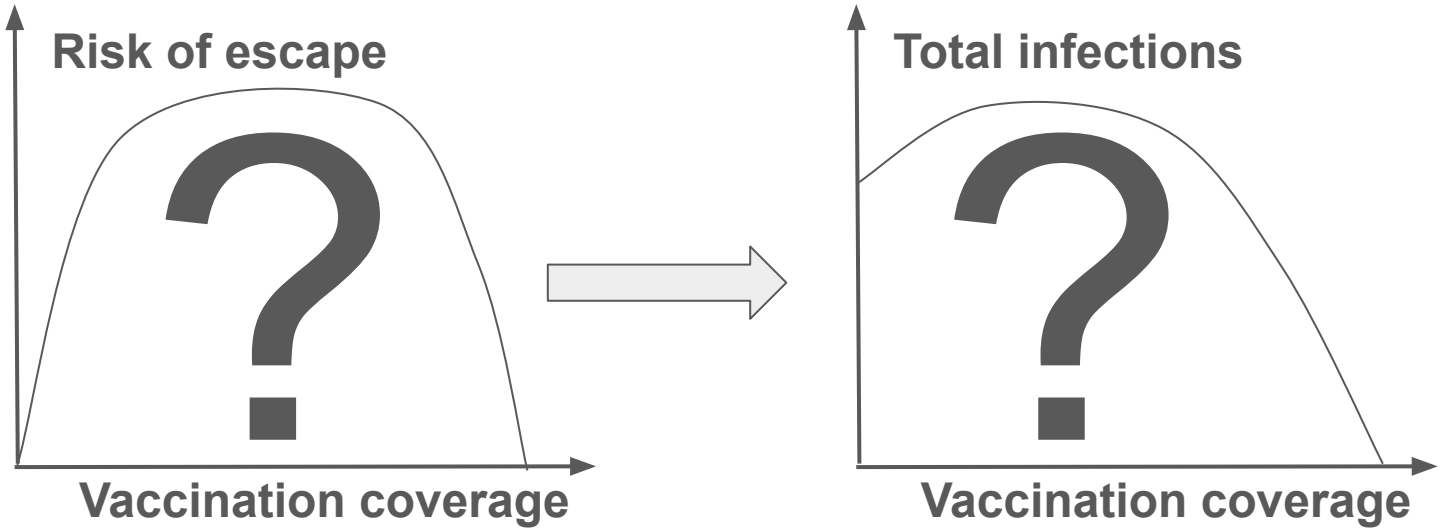
Julia R. Gog[1,2], Edward M. Hill[2,3,4,5], Leon Danon and Robin N. Thompson[2,3,4]

Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes

Chadi M. Saad-Roy[1]*, Sinead E. Morris[2], C. Jessica E. Metcalf[3,4], Michael J. Mina[5], Rachel E. Baker[3,6], Jeremy Farrar[7], Edward C. Holmes[8], Oliver G. Pybus[9], Andrea L. Graham[3], Simon A. Levin[3], Bryan T. Grenfell[3,4,10]*, Caroline E. Wagner[11]*

Rates of SARS-CoV-2 transmission and vaccination impact the fate of vaccine-resistant strains

Simon A. Rella[1], Yuliya A. Kulikova[2], Emmanouil T. Dermitzakis[3]✉ & Fyodor A. Kondrashov[1]✉



Goals for today:

1. Do intermediate vaccination levels always lead to the **highest risk of vaccine escape**?

2. If so, might the risk of vaccine escape result in **more total infections** at intermediate vaccination levels?

Modelling vaccine escape in a population

GATES Cambridge

Final-year of PhD with **Julia Gog**

Slides at
mariaalegriagutierrez.com/talks

Questions/comments/feedback:
mag84@cam.ac.uk

I'm looking for a **postdoc position:**

from Summer/Fall 2025

(evolutionary epidemiology and/or infectious disease math-modelling)

1. Vaccine breakthrough infections

Gutierrez & Gog 2023, *J. Theoretical Biology*

2. Partial immunity & reinfections

4. Stochastic emergence

Unpublished work, in preparation for PhD thesis

3. Infections in vulnerable hosts

5. Impact of escape strain

1. Vaccine breakthrough infections

Gutierrez & Gog 2023, *J. Theoretical Biology*

2. Partial immunity & reinfections

4. Stochastic emergence

Unpublished work, in preparation for PhD thesis

3. Infections in vulnerable hosts

5. Impact of escape strain

Simplified scales of selection

not explicitly within-host,
but vaccination status matters!

Individual

generation of strains,
(emergence not yet)

Population

$$P(t) \propto (I_U(t) + \theta_E I_V(t))$$

Escape pressure

infections in unvaccinated hosts

Relative selection in vaccinated hosts

infections in vaccinated hosts

Others use just I_V or I_U or a fixed linear combination.

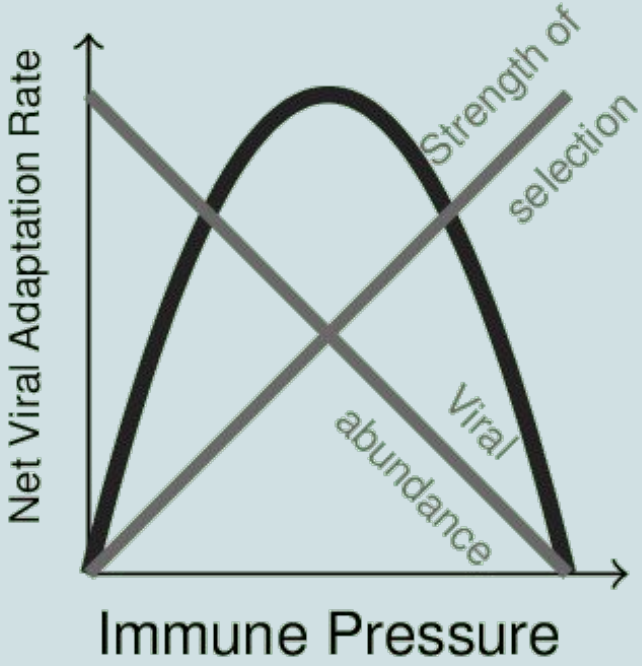
Gog et al 2021, Saad-Roy et al 2021, Thompson et al 2021, Rella et al 2021, Zhang et al 2022

Within-host selection by vaccination status

$$P(t) = I_U(t) + \theta_E I_V(t)$$

$\theta_E > 1?$

If infected, **who is more likely to generate an escape strain?** Vaccinated or unvaccinated?



Grenfell et al, *Science* 2004

Transient SIR epidemic wave

vaccination coverage *c*:
vaccines given before outbreak,
permanent partial immunity
against infection θ_S and transmission θ_I

Initial conditions

$$S_U(0) = 1 - c$$
$$S_V(0) = c\theta_S$$

Polarised protection against infection

$$\dot{S}_U = -S_U\lambda$$
$$\dot{S}_V = -S_V\lambda$$
$$\dot{I}_U = S_U\lambda - I_U$$
$$\dot{I}_V = S_V\lambda - I_V$$

SIR dynamics

Force of infection

$$\lambda = R_0(I_U + \theta_I I_V)$$

reduced transmissibility

Further assumptions:
well-mixing,
homogeneity,
no reinfections,
constant R0,
not time-since-infection,
same infectious period,
no births and deaths.

Analytical final-size solution leads to escape pressure

Initial effective R-number $R_e = R_0(1 - c(1 - \theta_S\theta_I))$

vaccine transmission-blocking

Same ratio vaccinated:unvaccinated through all compartments

$$(S_V, I_V, R_V) = \frac{c\theta_S}{1-c}(S_U, I_U, R_U)$$

Integrated escape pressure $P = \int_0^\infty (I_U + \theta_E I_V)dt = C_U + \theta_E C_V$

Cumulative final-sizes

…similar to standard SIR final-size

$$P = (1 - c(1 - \theta_S\theta_E))(1 + R_e^{-1}W(-R_e e^{-R_e}))$$

"escape-blocking factor"

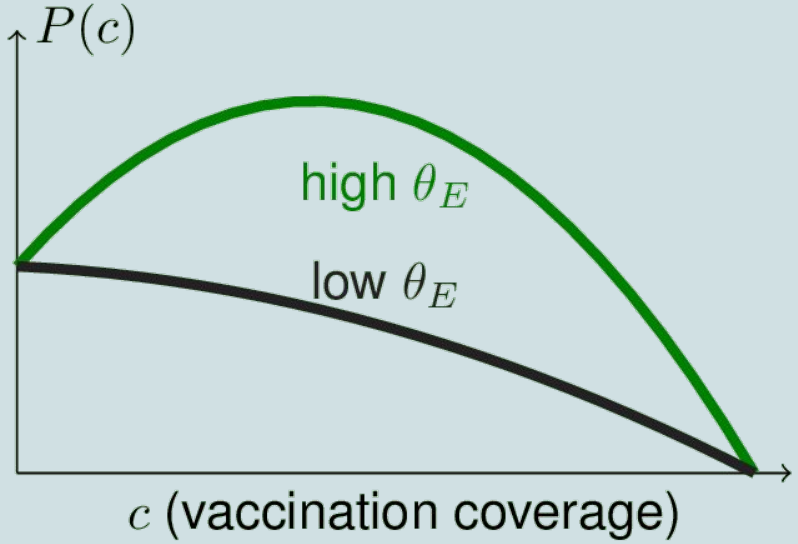
Lambert W function

Escape pressure *P* as a function of vaccination coverage *c*

$$P = C_U + \theta_E C_V$$

Behaviour of *P* depends on the relative escape contribution of vaccinees, θ_E

- Unimodal if θ_E above threshold
- Decreasing if θ_E below threshold



P always decreases to zero if vaccination coverage is near herd immunity threshold

Gutierrez and Gog, 2023, *JTB*

1. Vaccine breakthrough infections

Gutierrez & Gog 2023, *J. Theoretical Biology*

2. Partial immunity & reinfections

4. Stochastic emergence

Unpublished work, in preparation for PhD thesis

3. Infections in vulnerable hosts

5. Impact of escape strain

Are **reinfections** important for vaccine escape?

Before: $P = C_U + \theta_E C_V$

Now: separate hosts by immune status

Escape pressure

$$P = C_N + \theta_E C_P$$

Infections in immunologically **naïve hosts**

Infections in hosts with **partial immunity**

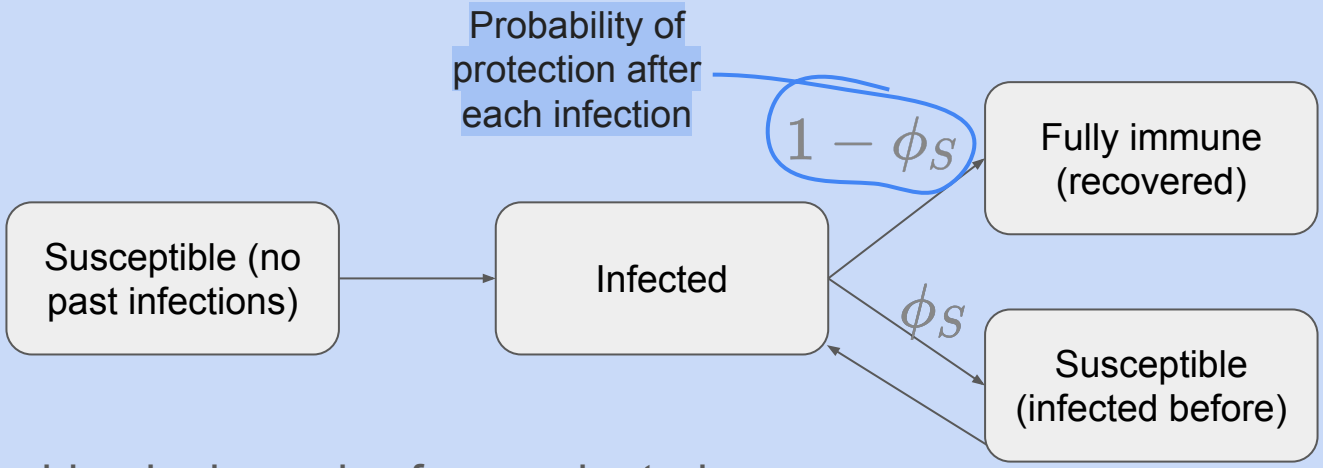
Relative selection in partially immune hosts

Within-host selection for escape might also be stronger (or weaker) **in reinfections,** relative to naïve hosts, due to **partial immunity** in the host.

Grouped together in C_P: reinfections in unvaccinated & all infections in vaccinated

In general, could have different relative selection instead of all θ_E

SIR with **lifelong partial immunity** from infections



Same epidemic dynamics for vaccinated

As before: $1-\theta_S$ probability of protection after vaccination

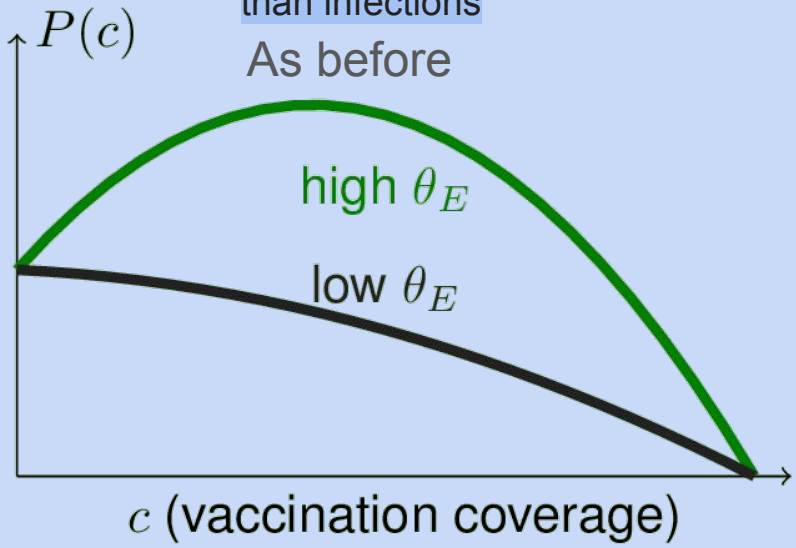
(All hosts equally infectious, allows to find P(c) analytically)

Different behaviour possible if reinfections are likely

Escape pressure P(c) depends on relative protection from vaccines vs infections

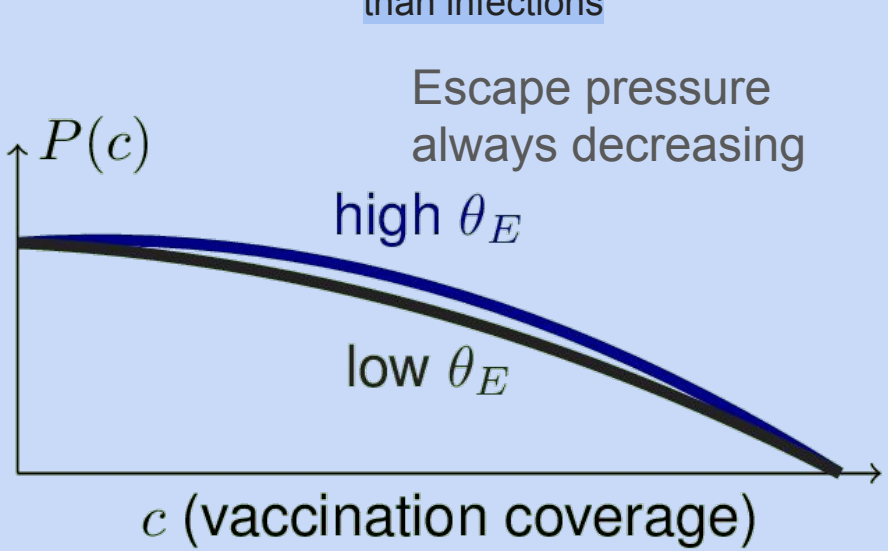
$\theta_S > \phi_S$

Vaccines *less* protective than infections



$\theta_S < \phi_S$

Vaccines *more* protective than infections



1. Vaccine breakthrough infections

Gutierrez & Gog 2023, *J. Theoretical Biology*

2. Partial immunity & reinfections

4. Stochastic emergence

Unpublished work, in preparation for PhD thesis

3. Infections in vulnerable hosts

5. Impact of escape strain

How do **immunocompromised hosts** affect escape?

Immunocompromised hosts (chronic infections) are likely source of antigenic evolution (eg, Omicron)

Split population in **two groups,** with different levels of selection.

(In general, could do n>2 groups)

Before:

$$P = C_U + \theta_E C_V$$

Relative selection $\alpha > 1$ in immunocompromised hosts

Now:

Escape pressure

Infections in **"healthy"** hosts

Infections in **immunocompromised** hosts

$$P = C_{U,H} + \theta_E C_{V,H} + \alpha(C_{U,I} + \theta_E C_{V,I})$$

Same factor θ_E for infections in vaccinees

SIR dynamics with **population heterogeneity**

Assortative mixing

→ Analytic final-size

$$\begin{bmatrix} m^2 & m \\ m & 1 \end{bmatrix}$$

Contact matrix

Relative **contact rate m>1** in healthy hosts

Vaccinating first healthy hosts with more contacts might be best to reduce overall mortality (Gog 2021)

Different vaccination coverages c_H, c_I for each group

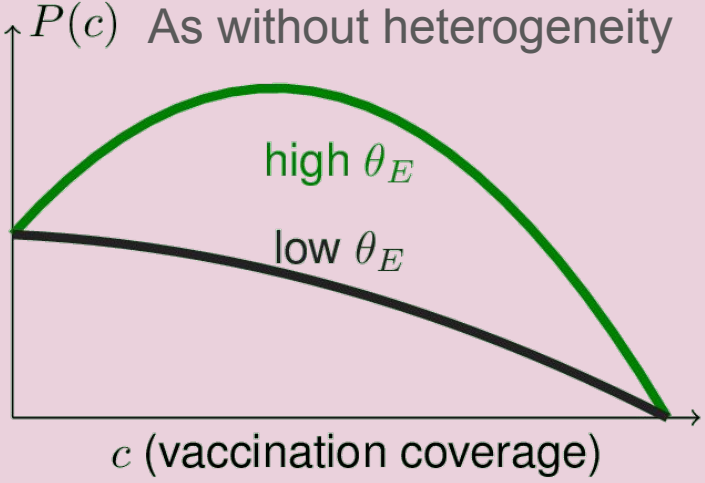
Escape pressure P(c) depends on total coverage $c = c_H + c_I$

But **order of vaccination matters!**

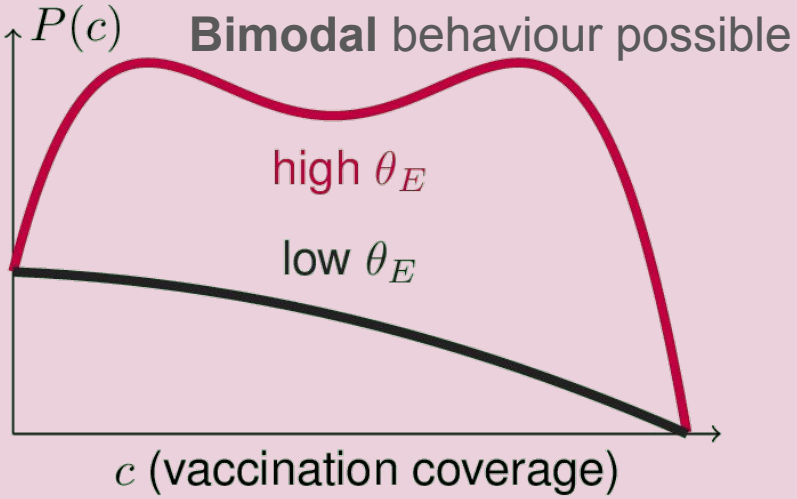
Immunocompromised infections impact the shape of P(c)

Escape pressure P(c) at high θ_E depends on vaccination strategy

Vaccinating **first immunocompromised** (higher within-host selection)

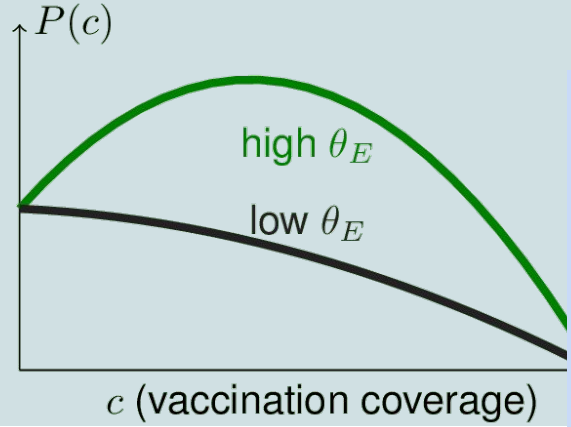


Vaccinating **first healthy host** (with more contacts)

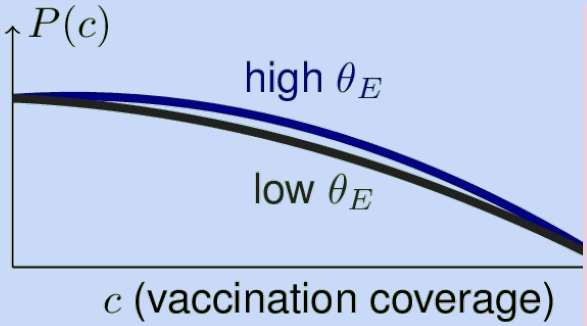


Recap:
Possible “shapes” for the escape pressure P(c)

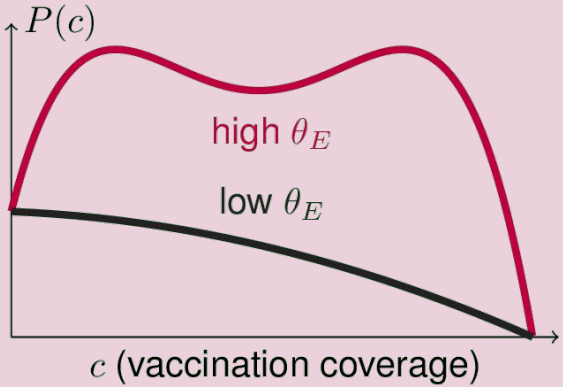
Relative host selection is key.



The relative protection from infection vs vaccines matters.



With immunocompromised, the vaccination order matters.



1. Vaccine breakthrough infections

Gutierrez & Gog 2023, *J. Theoretical Biology*

2. Partial immunity & reinfections

4. Stochastic emergence

Unpublished work, in preparation for PhD thesis

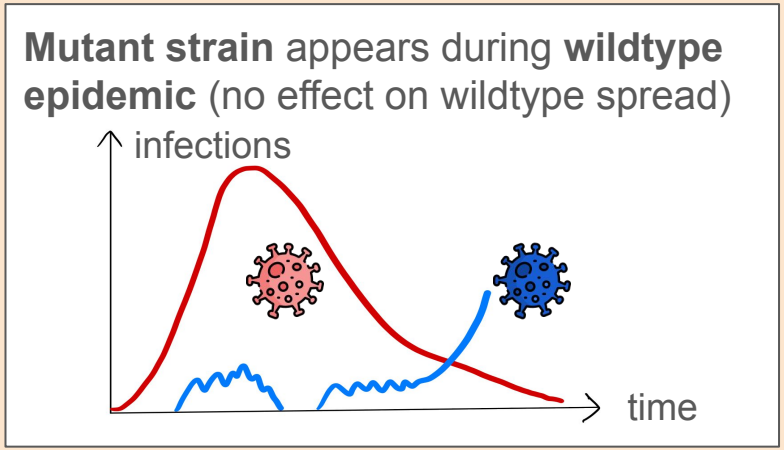
3. Infections in vulnerable hosts

5. Impact of escape strain

After an escape mutant *appears,* can it spread & emerge?

Stochastic dynamics for early mutant spread

Emergence probability p(t) changes with time:
Few hosts remain susceptible late in the epidemic



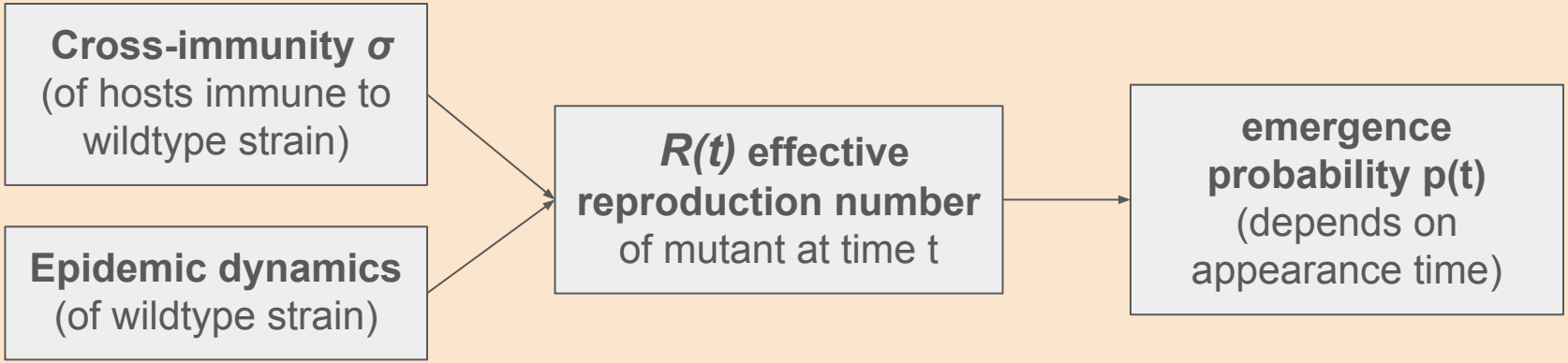
Escape pressure rate
for appearance and emergence

Emergence probability
for mutants that appear at time t

$$P(t) = (I_U(t) + \theta_E I_V(t))p(t)$$

Rate at which mutants appear (as before)

Time-inhomogeneous emergence branching process



Susceptible depletion (from wildtype strain)
→ traditional branching process (e.g., p=1-1/R) not valid
→ a **time-dependent transmission rate R(t)** in "birth-death" process

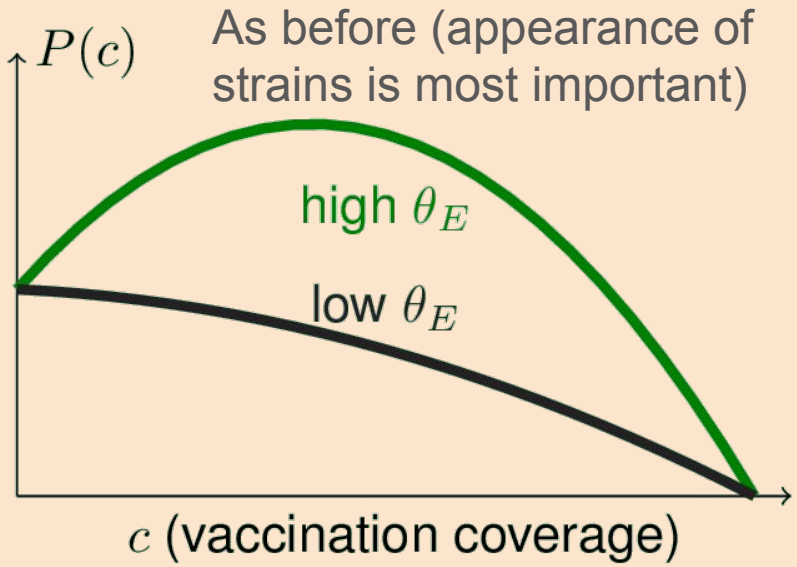
$$\dot{p} = p(1 - (1 - p)R(t))$$

(Recent preprint with similar approach for p(t): Gandon et al, 2024)

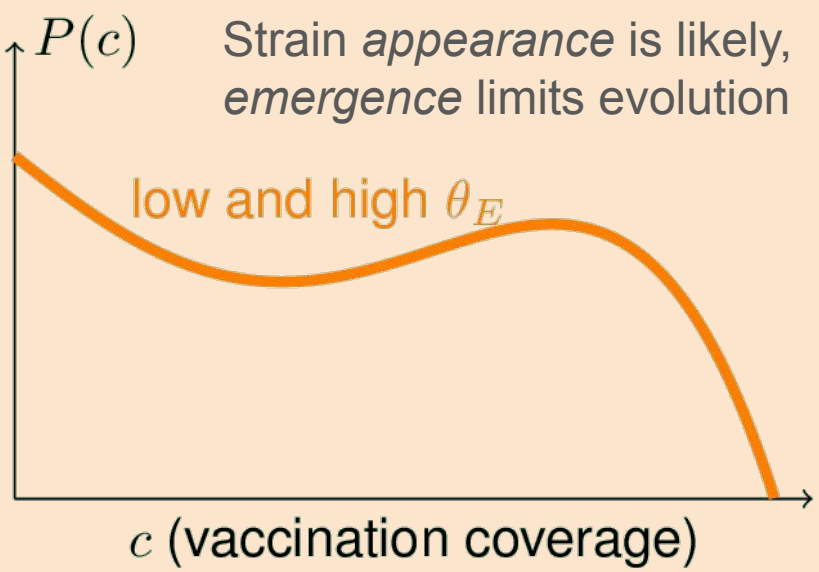
High cross-immunity leads to new behaviours

The shape of the **cumulative escape pressure P(c)** depends on the **cross-immunity σ** between the wildtype and mutant strains.

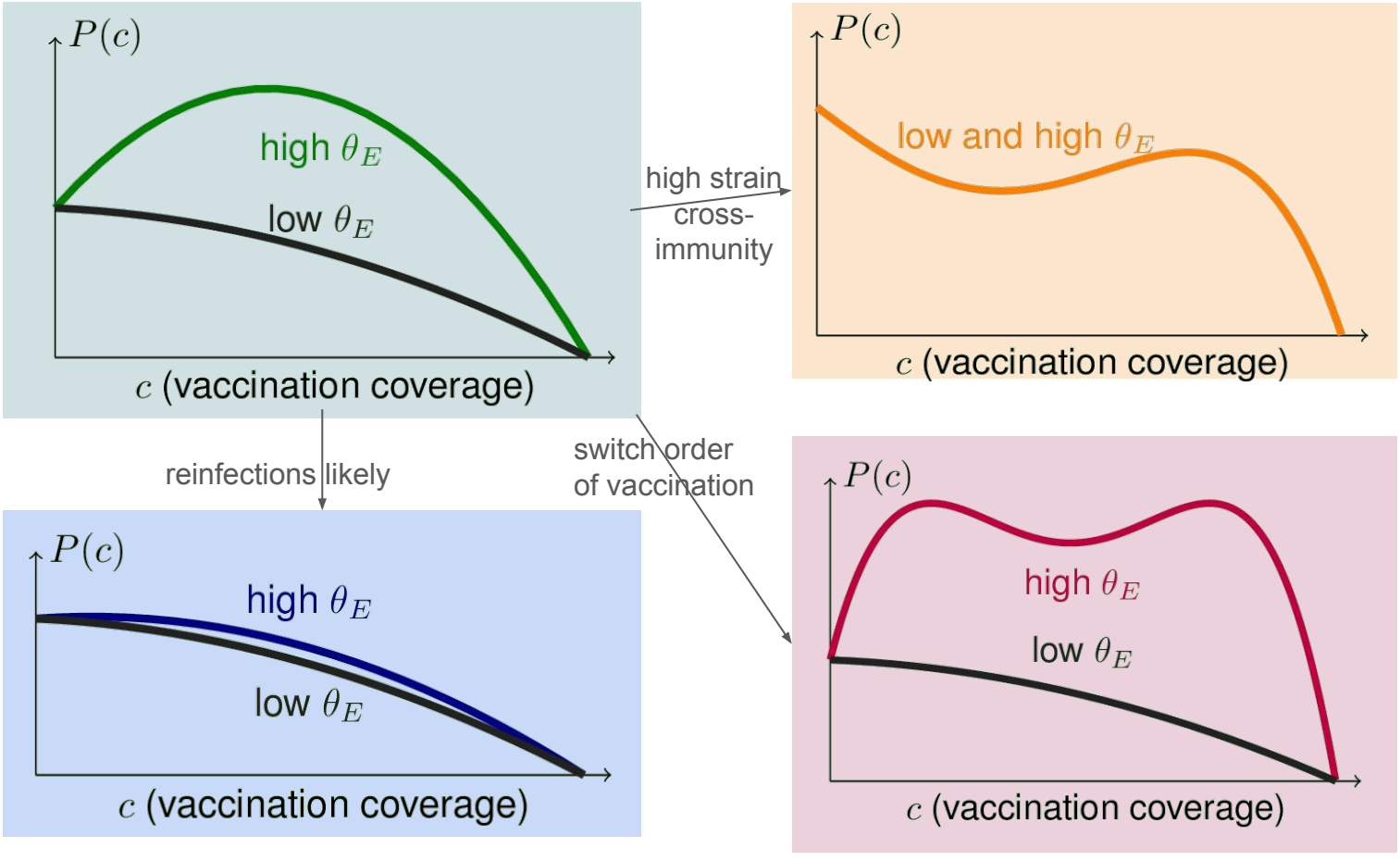
Low cross-immunity
(high emergence probability)



High cross-immunity
(low emergence probability)



Recap: Possible “shapes” for the escape pressure P(c)



Goals for today:

1. Do intermediate vaccination levels always lead to the **highest risk of vaccine escape**? Sometimes, but not for all scenarios.

2. If so, might the risk of vaccine escape result in **more total infections** at intermediate vaccination levels?

1. Vaccine breakthrough infections

Gutierrez & Gog 2023, *J. Theoretical Biology*

2. Partial immunity & reinfections

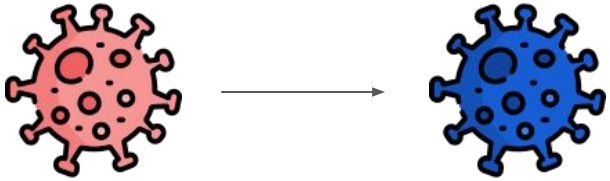
4. Stochastic emergence

Unpublished work, in preparation for PhD thesis

3. Infections in vulnerable hosts

5. Impact of escape strain

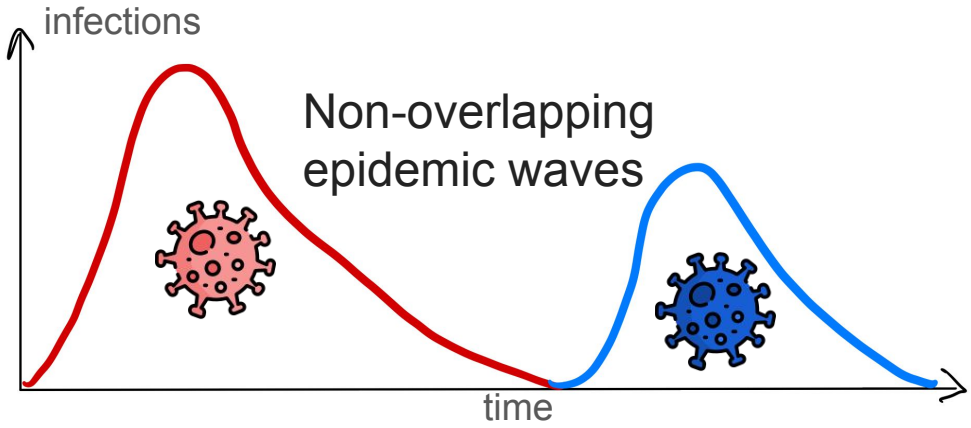
What are the consequences of a high escape pressure?



antigenic distance
d between strains

$$d = \delta + bP$$

Escape pressure



$P = C_U + \theta_E C_V$ so the **antigenic distance d is linear on the infections**

in each group, weighted by θ_E (relative selection in vaccinees vs unvaccinated)

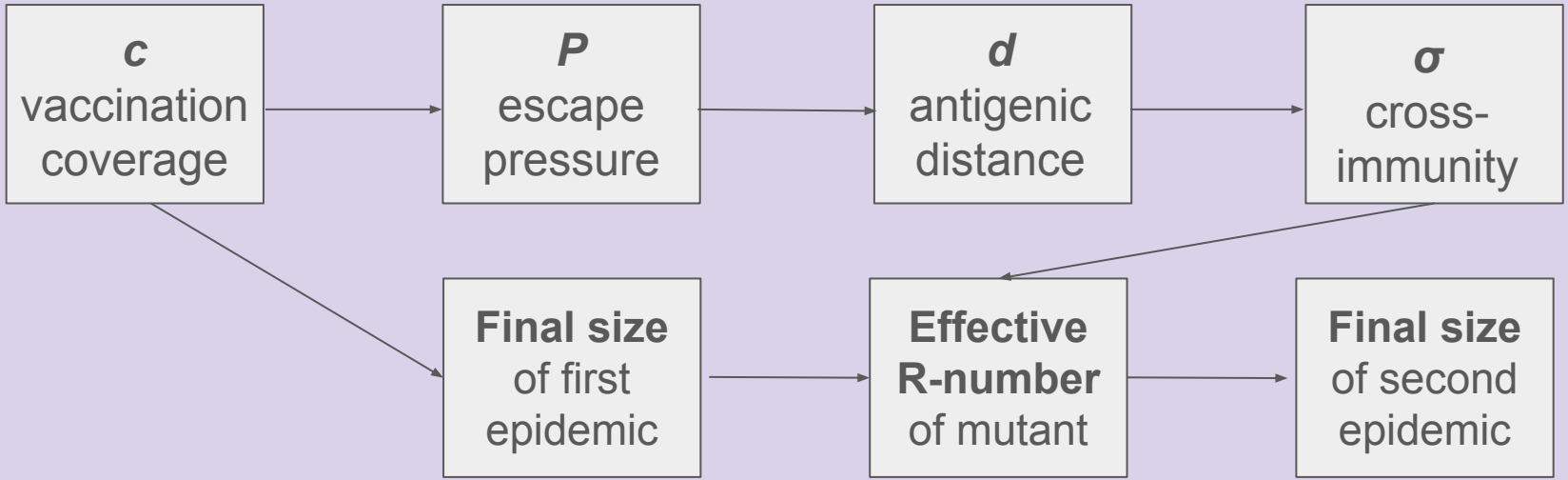
Adapted to include vaccination from Boni et al 2004

The **antigenic distance** determines the **cross-immunity**

$$\sigma = \exp(-ad)$$

Boni et al 2004

Cross-immunity σ between strains decays exponentially with the antigenic distance



Total infections *C* as a function of vaccination coverage *c*

1st wave: decreasing

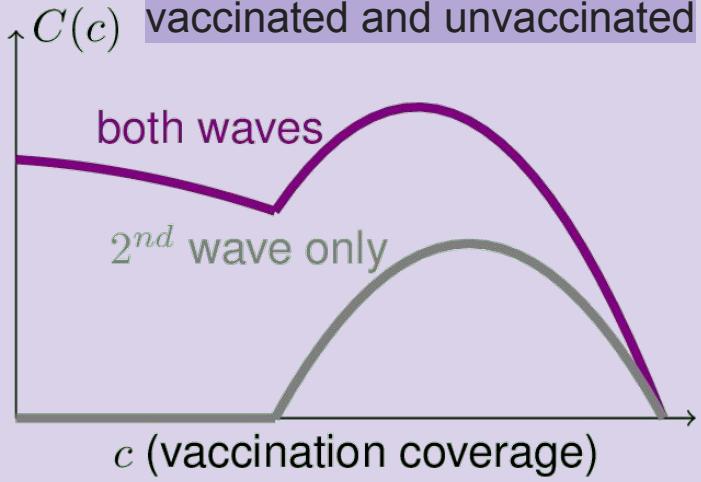
+

2nd wave: unimodal (high θ_E)

Total infections (both waves):

1. initially decreasing (no 2nd wave)
2. increasing as 2nd wave becomes possible
3. local maximum at intermediate vaccination
4. decreases for large vaccination coverages

cumulative infections in both vaccinated and unvaccinated

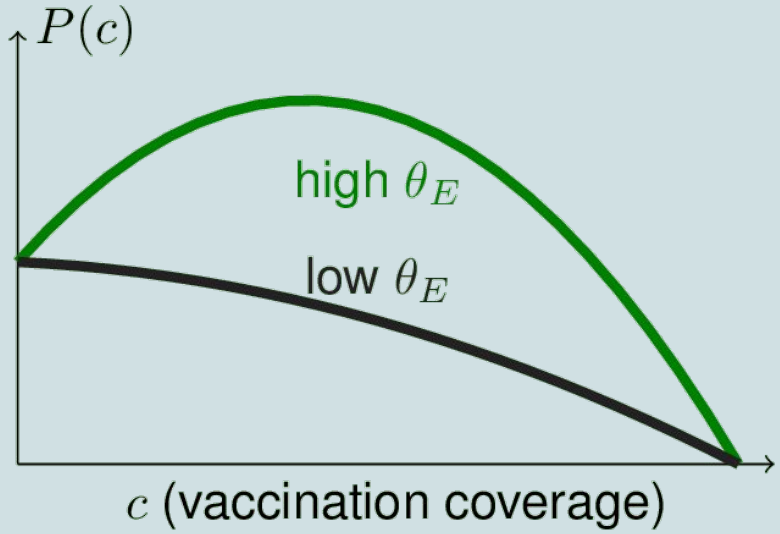


Caveat: slightly different overall balance depending on the drift rate *a* for the cross-immunity $\sigma = \exp(-ad)$

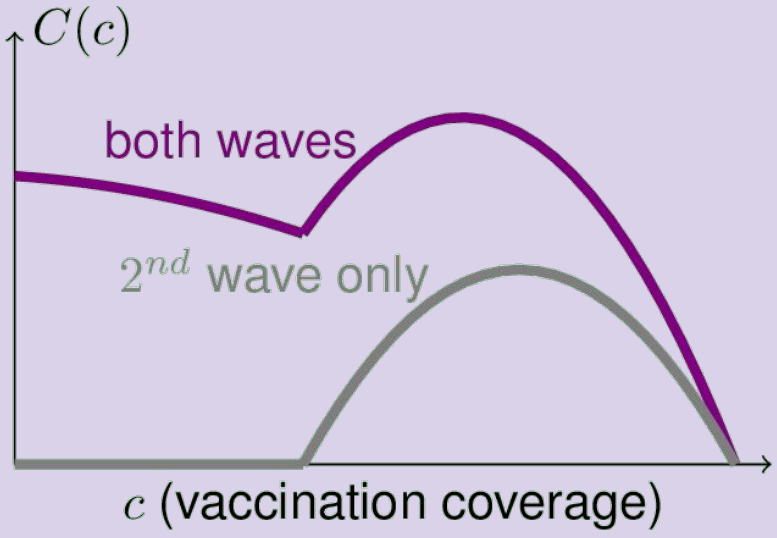
Summary: other phylodynamic shapes are possible, but

Escape risk and total infections may be highest at intermediate vaccination.

Total **escape pressure** from a single epidemic wave, without escape strain.



Total **infections** including a second epidemic wave with an escape strain.

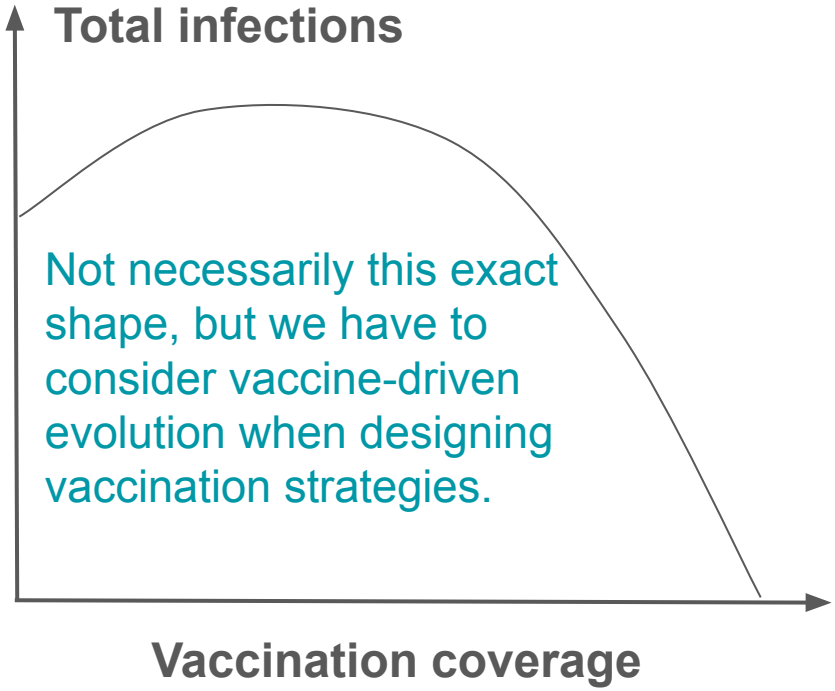


Escape risk and total infections may be highest at intermediate vaccination.

Goals for today:

1. Do intermediate vaccination levels always lead to the **highest risk of vaccine escape**? Sometimes yes, but not for all scenarios.

2. If so, might the risk of vaccine escape result in **more total infections** at intermediate vaccination levels? Yes, but we can find a reasonable tradeoff.



I'm looking for a postdoc position mag84@cam.ac.uk