The importance of vaccinated individuals to population-level evolution of pathogens

Alternative title

Population heterogeneity in within-host evolution: consequences for vaccine escape

Maria A. Gutierrez (she/her)

PhD student, supervised by Prof. Julia Gog

Email: mag84@cam.ac.uk questions very welcomed (even if you aren't here for the talk!)

Department of Applied Mathematics and Theoretical Physics (DAMTP), University of Cambridge

Context: SARS-CoV-2 **vaccine escape**…

- Cobey et al. Concerns about SARS-CoV-2 **evolution** should not hold back efforts to expand **vaccination**. *Nature Reviews Immunology* (2021)
- Thompson et al. SARS-CoV-2 incidence and **vaccine escape**. *The Lancet Infectious Diseases* (2021)
- Saad-Roy et al. Epidemiological and **evolutionary considerations of SARS-CoV-2 vaccine** dosing regimes. *Science* (2021)
- Gog et al. **Vaccine escape** in a heterogeneous population: insights for SARS-CoV-2 from a simple model. *Royal Society Open Science* (2021)
- Rella et al. Rates of SARS-CoV-2 transmission and vaccination impact the fate of **vaccine-resistant** strains. *Scientific Reports* (2021)
- Gandon et al. Targeted **vaccination** and the speed of SARS-CoV-2 **adaptation**. PNAS (2021)
- Day, Gandon et al. Pathogen **evolution** during **vaccination** campaigns. PLOS Biology. (2022)
- Lobinska et al. Evolution of **resistance to COVID-19 vaccination** with dynamic social distancing. *Nature Human Behaviour* (2022)
- Zhang et al. A spatial vaccination strategy to reduce the risk of **vaccine-resistant variants**. *PLOS Computational Biology (2022)*

…but hopefully broadly applicable to evo-epi models

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Talk plan

1. Published work
    a. Evolutionary approach
    b. Epidemic models
    c. Escape pressure results
2. Work in progress
    a. Reinfections
    b. Immunocompromised
    c. Multi-wave evolution
3. Discussion
    a. Conclusions
    b. Applications
    c. Further ideas

Gutierrez, M. A. and Gog, J. R.
The importance of vaccinated individuals to population-level evolution of pathogens.
Journal of Theoretical Biology
(21 June 2023)

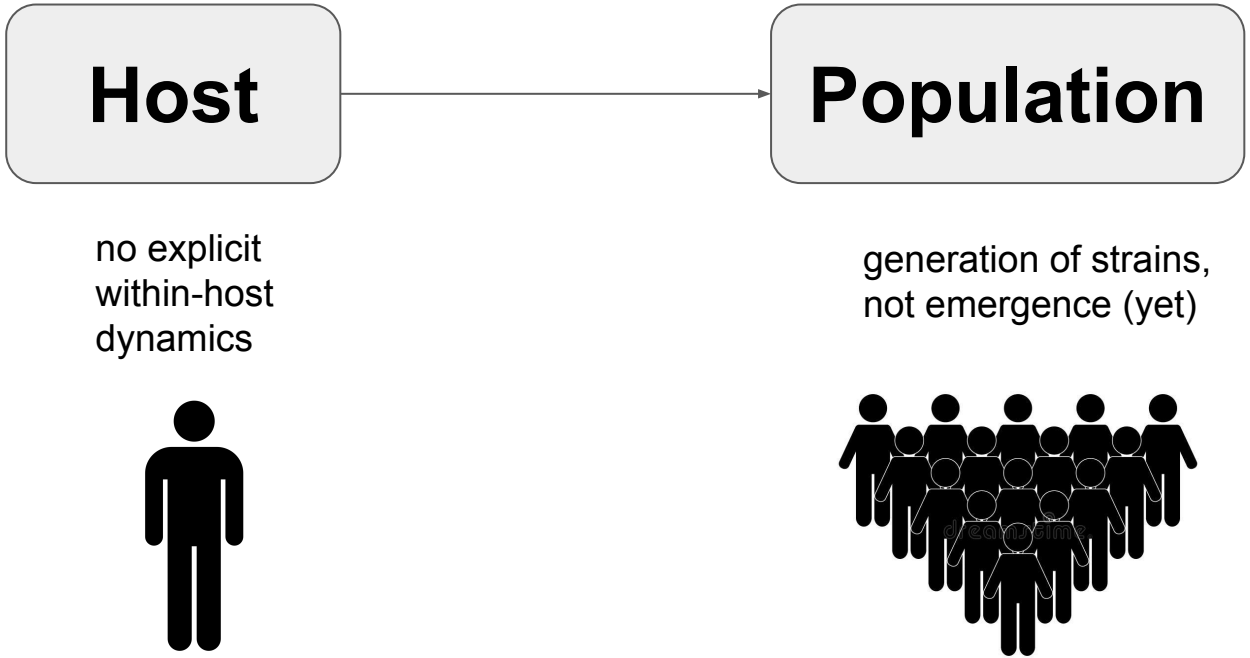
Published work

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Evolutionary approach

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Simplified scales of selection



Population level

[overall constant of proportionality unimportant, focus on relative pressure]

Escape pressure (rate)

key parameter!

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

infections in unvaccinated hosts

infections in vaccinated hosts

Epidemic wave

Cumulative escape pressure (time integral of above)

$$P' = C_U + \theta_E C_V$$

[assumes wave unaffected by new strain(s)]

Endemic equilibrium

Escape pressure rate at equilibrium

$$P^* = I_U^* + \theta_E I_V^*$$

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Gutierrez & Gog, JTB 2023

Within-host level

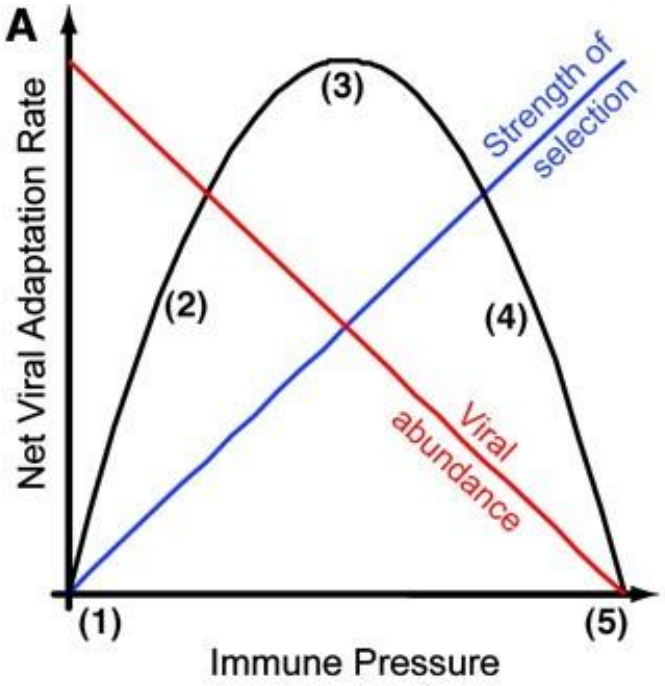
Q: Do infections in vaccinated hosts contribute more or less to the escape pressure than infections in unvaccinated hosts?

$\theta_E > 1?$

$\theta_E < 1?$

vaccines =>

- more within-host selection for escape
- BUT lower viral load, so less mutations

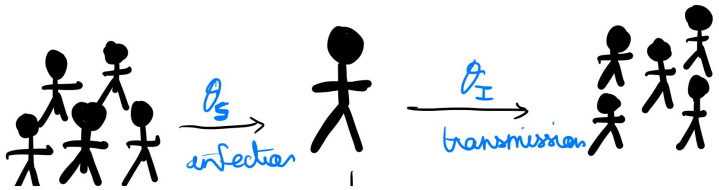


Grenfell et al, Science 2004 (*Phylodynamics*)

Epidemic model

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Transient SIR epidemic wave (endemic also in paper)



c: vaccination coverage in population,
- vaccines given before wave
- no waning of immunity
- no reinfections

Polarised ("all-or-nothing") vaccine immunity
(leaky immunity also in paper)

unvaccinated (fraction) $S_U(0) = 1 - c$

vaccinated (fraction) $S_V(0) = c\theta_S$

Force of infection

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

^reduced infectivity

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

Assumptions:
well-mixing
constant R0,
not time-since-infection,
same infectious period,
not SEIR/SIAR,
no quarantined hosts…

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Gutierrez & Gog, JTB 2023

Analytical final size solution leads to escape pressure

Same ratio of vaccinated to unvaccinated maintained in each stage

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

$$R_e = R_0(1 - c(1 - \theta_S\theta_I))$$

Vaccine transmission-blocking factor appears on R number

Can integrate SIR for final sizes C_U, C_V needed in escape pressure

$$P = C_U + \theta_E C_V$$

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

"Escape blocking factor"

Lambert W function

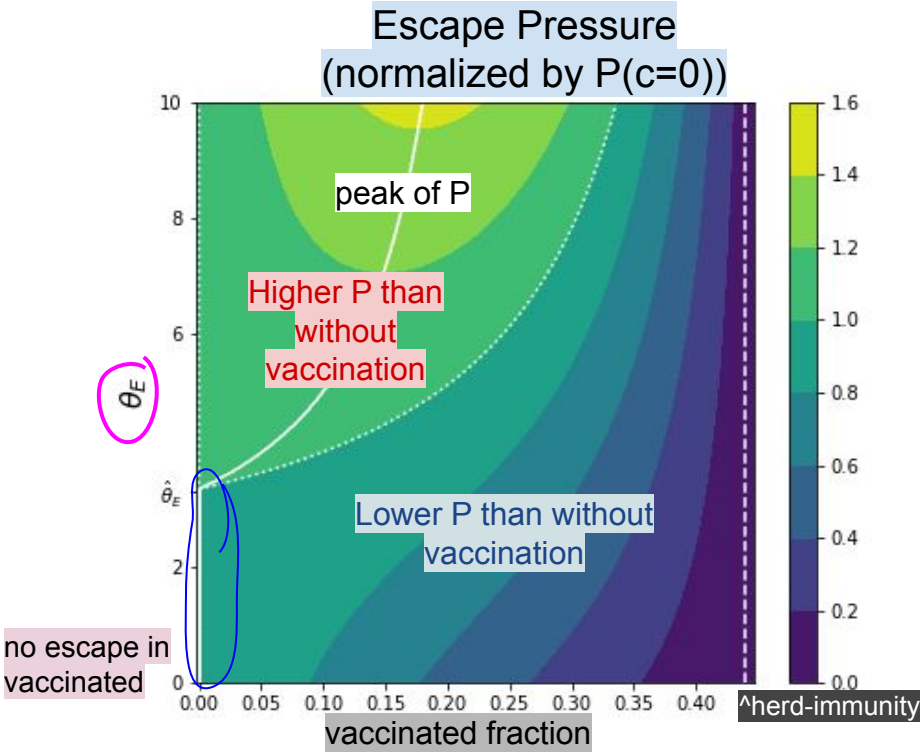
Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

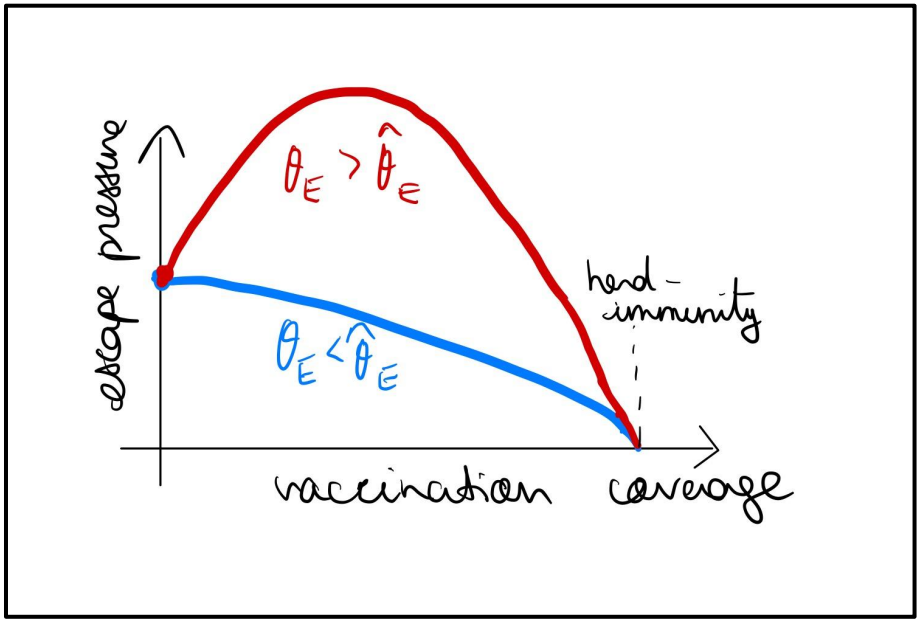
Gutierrez & Gog, JTB 2023

Results

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

The **relative escape contribution** (ThetaE) of vaccinated hosts regulates the shape of the escape pressure

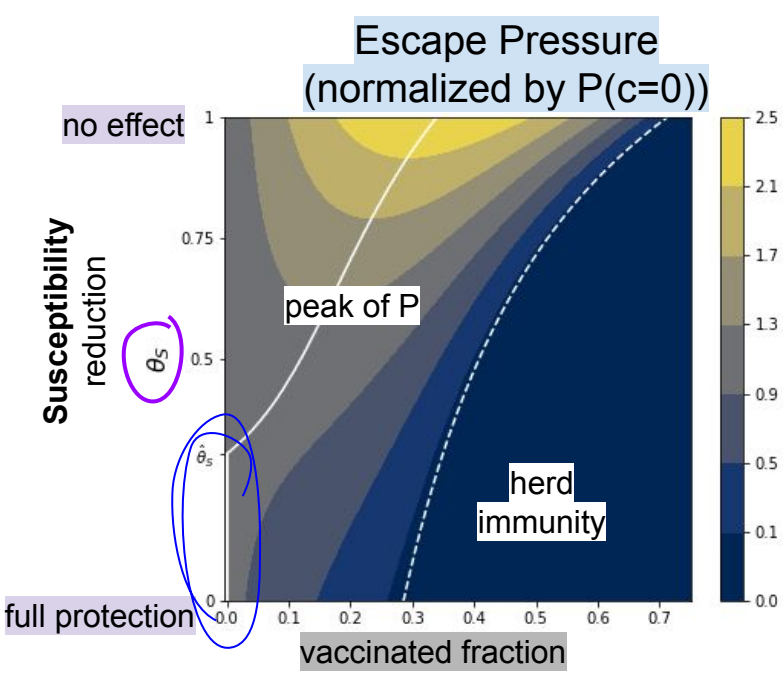


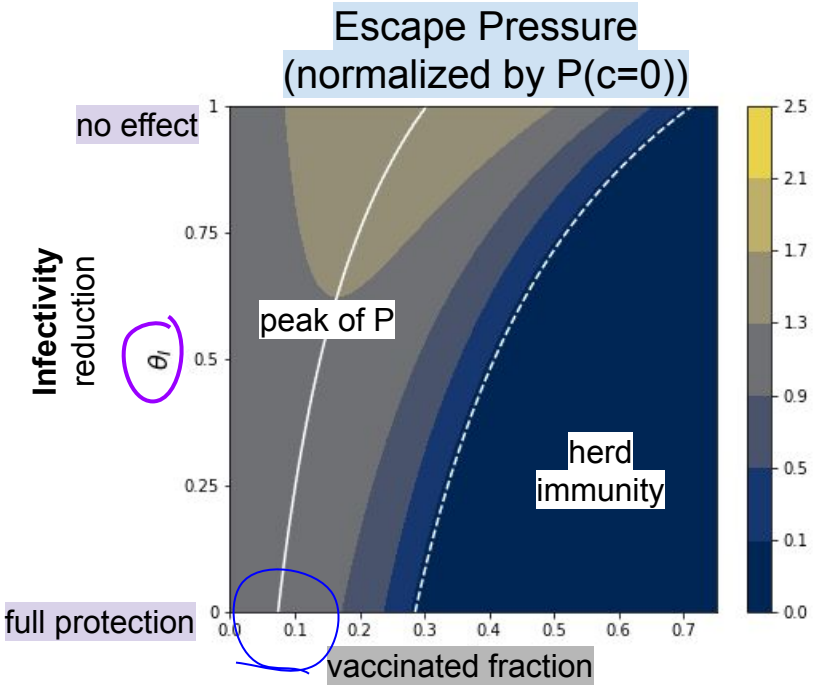


Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Gutierrez & Gog, JTB 2023

The **vaccine efficacies** (thetaS, thetaI) are also important





Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Gutierrez & Gog, JTB 2023

Work in progress

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Reinfections

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

What if infections only protect give **partial immunity?**

primary cases in unvaccinated

reinfections in unvaccinated

primary cases in vaccinated

reinfections in vaccinated

$$P = (C_U^{(1)} + \theta_E(C_U^{(2)} + C_V^{(1)} + C_V^{(2)}))$$

all infections in hosts with prior immunity

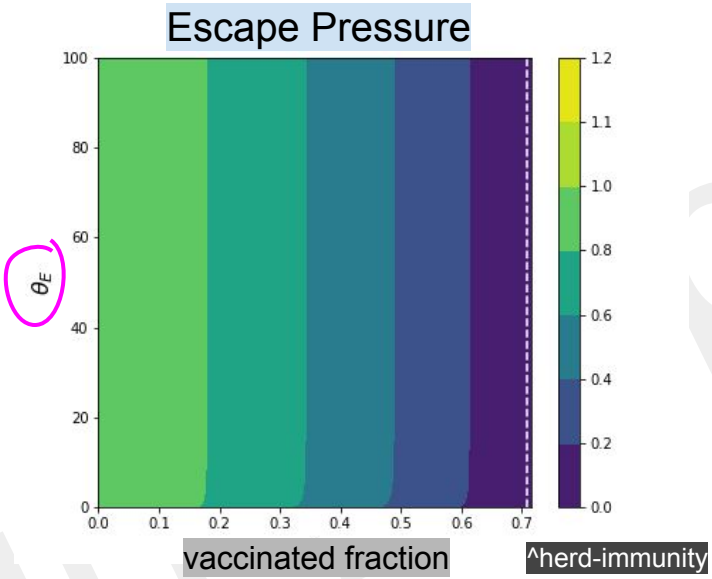
Modified model to allow for **reinfections**

Vaccinated individuals have reduced susceptibility (θ_S) and recovered individuals also have reduced susceptibility (θ'_S)

Still can find final size analytically!

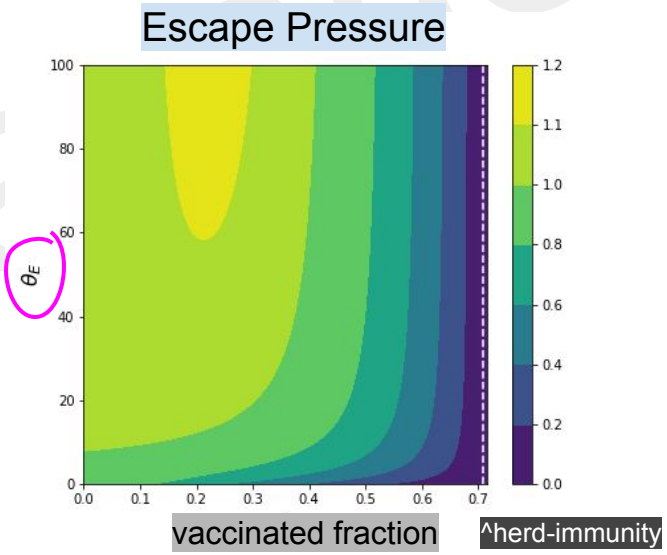
Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

If vaccines give equal or more protection than infection, the escape pressure always decreases with the vaccination coverage



$\theta_S < \theta'_S$

If vaccines give less protection than infection, the escape of hosts with prior immunity determines the shape of the escape pressure



$\theta_S > \theta'_S$

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Population heterogeneity (eg, immunocompromised)

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Population heterogeneity

$$R_e = R_0 \frac{(x - c_1(1-\theta_S\theta_I)) + m^2(1-x-c_2(1-\theta_S\theta_I))}{x + m^2(1-x)}$$

Two population groups (as in Gog et al 2021)

#1, size x: **high escape contribution p>1** (“vulnerable”/ immunocompromised) ,
#2, size 1-x: larger contact rate m>1 (“mixers”/youth)

$$P = pC_1 + C_2$$

Add vaccination in:

$$P = p(C_{U,1} + \theta_E C_{V,1}) + C_{U,2} + \theta_E C_{V,2}$$

Adapt SIR model from before

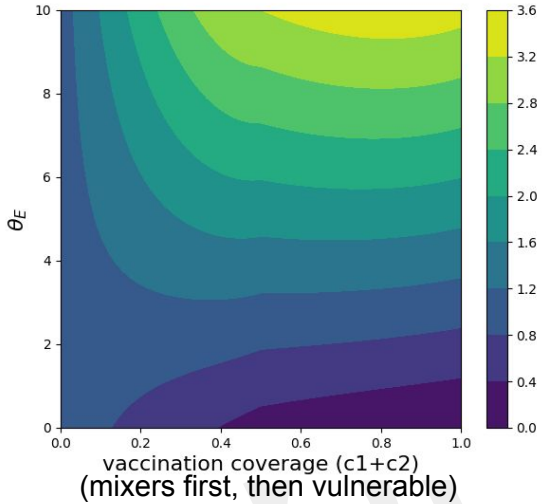
Can still solve analytically

$$P = (p(x - c_1(1 - \theta_S\theta_E)) + m(1 - c_2(1 - \theta_S\theta_E))\left(1 + \frac{W(-R_e e^{-R_e})}{R_e}\right)$$

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Best strategy to minimise escape.. (and maybe also severe disease outcomes!) is to **vaccinate first the group with more contacts**…can get **bimodal shape**

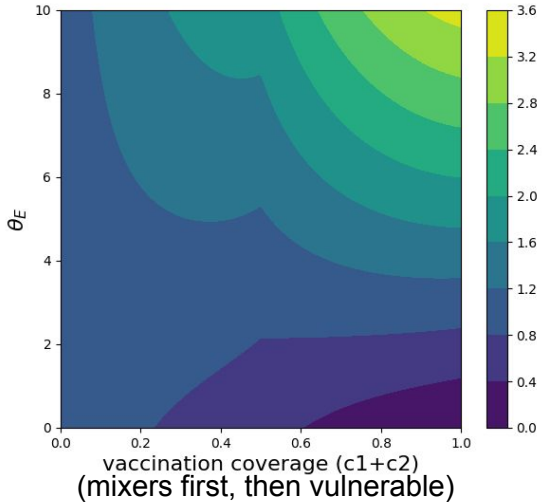
Escape Pressure



p=1

m=2 in both plots

Escape Pressure



p=5

Higher p (increased escape in immunocompromised) leads to bimodality

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Multi-wave evolution

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Single-strain waves, cross-immunity from escape pressure

Cross-immunity: **exponentially decaying** with antigenic distance (escape pressure here) [Boni, Andreasen et al 2004]

Original transient model for each wave, effective susceptible size changes

Results 1D map for effective susceptible size S, gives effective R=S*R0

$$S' = S\left(1 - (1 + W/R)\exp\left[-\frac{\mu}{1+\theta_E}\frac{(1 - c(1 - \theta_S\theta_E))}{1 - c(1 - \theta_S)}S(1 + W/R)\right]\right)$$

(W:=W[-Rexp(-R)])

[weight and normalization factors]

[final size]

If R'=S'*R0 >1, continue to new wave (can include stochastic extinction)

How to quantify escape over multiple waves? **Total (expected) number of cases**

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

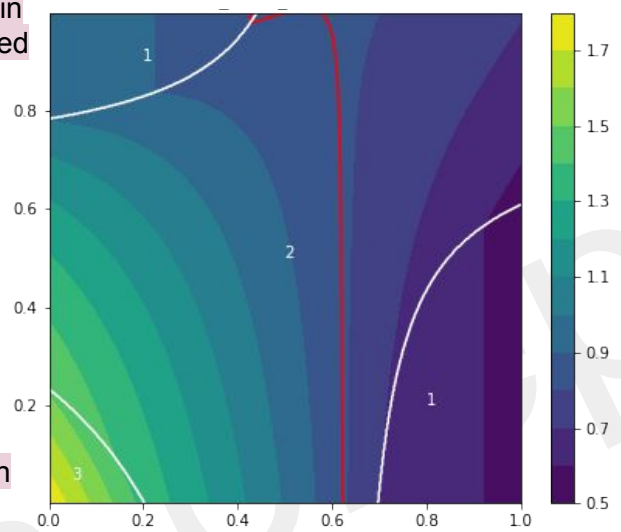
New patterns; stochastic extinction matters

Without stochastic extinction

Total infections (per individual)

no escape in unvaccinated

$$\frac{\theta_E}{1+\theta_E}$$



no escape in vaccinated

vaccinated fraction

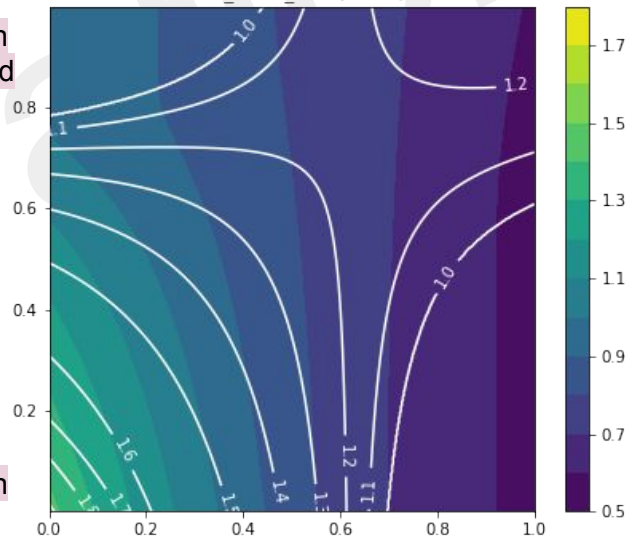
white contours: number of waves

With stochastic extinction

Expected total infections (per individual)

no escape in unvaccinated

$$\frac{\theta_E}{1+\theta_E}$$



no escape in vaccinated

vaccinated fraction

white contours: expected number of waves

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Discussion

Conclusions

1. Importance of **relative escape from vaccinated individuals**:

We shouldn't make uninformed assumptions about its value!

2. More generally, importance of **heterogeneous escape**
    a. immunocompromised
    b. reinfections
3. **Vaccine efficacies** also matter for escape; especially susceptibility VE
4. More possibilities for escape pressure than "peak at intermediate values of immunity" (described by others)
    a. monotonically decreasing
    b. bimodal

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Applications

1. Value in measuring or estimating (or modelling?) the relative escape contribution from each host type?
2. Vaccine design – to minimise escape
3. Vaccination strategies – given a vaccine, to minimise escape (& disease)
4. Target genomic sequencing at populations with highest escape pressure

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Further ideas – suggestions encouraged!

1. **Invasion** dynamics
   a. Stochastic extinction - changing susceptible size due to original strain
   b. Replacement or coexistence?
   c. Fitness cost from escape?
2. **Multiple strains**: mutation rates dependent on immune history
3. **Within-host** dynamics and selection…estimate ThetaE
4. **Waning** immunity
   a. from infection and/or vaccination
   b. within wave or across waves
5. Recombination / multiple infections

A final thought: ThetaE depends on “escape strain” of interest and specific vaccine(s)

Maria A. Gutierrez (Cambridge) - mag84@cam.ac.uk

Acknowledgements

Many thanks to my supervisor **Julia Gog** and the rest of the group in Cambridge.

Email: mag84@cam.ac.uk

Questions?

Funding:

Paper

Gutierrez, M. A. and Gog, J. R. (2023). The importance of vaccinated individuals to population-level evolution of pathogens. *Journal of Theoretical Biology*