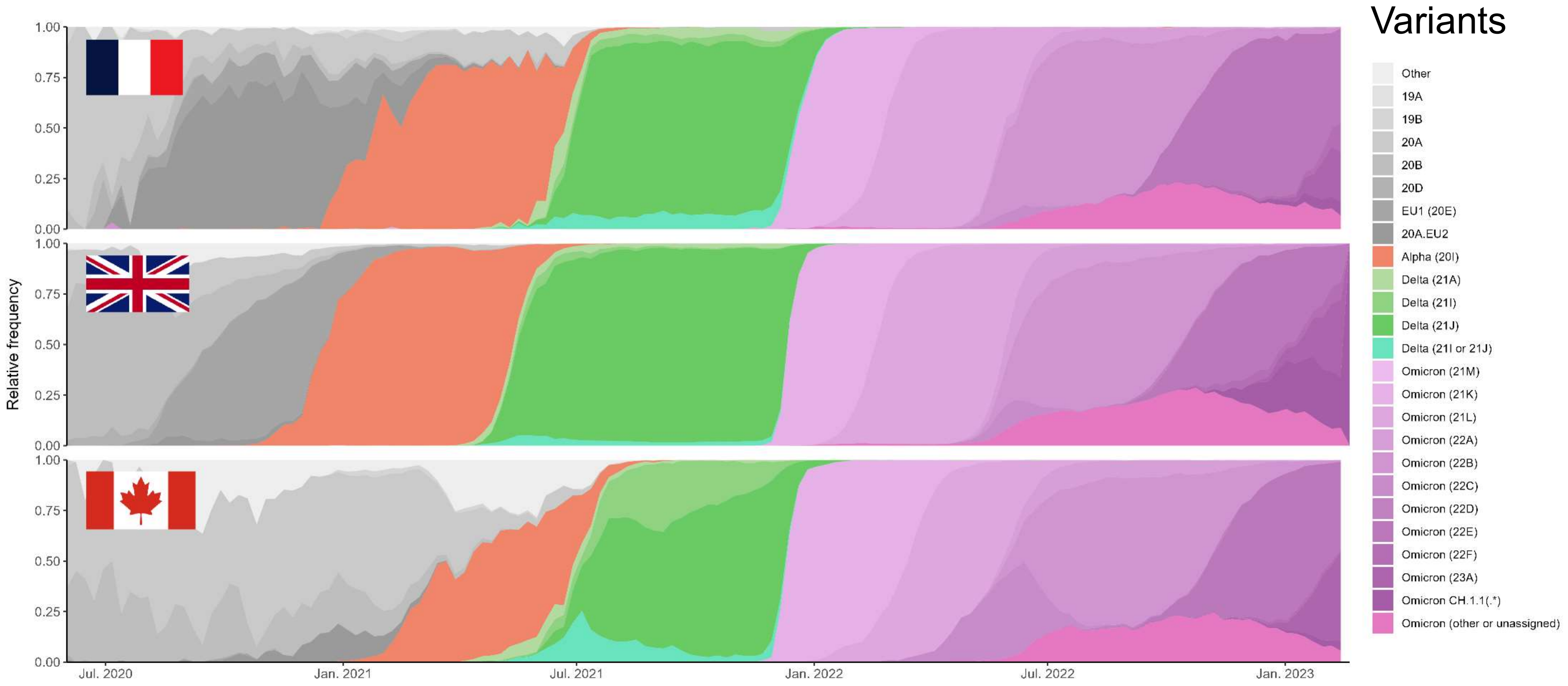
Unifying epidemiological an evolutionary dynamics
– June 13 2023 –

The speed of adaptation to vaccination

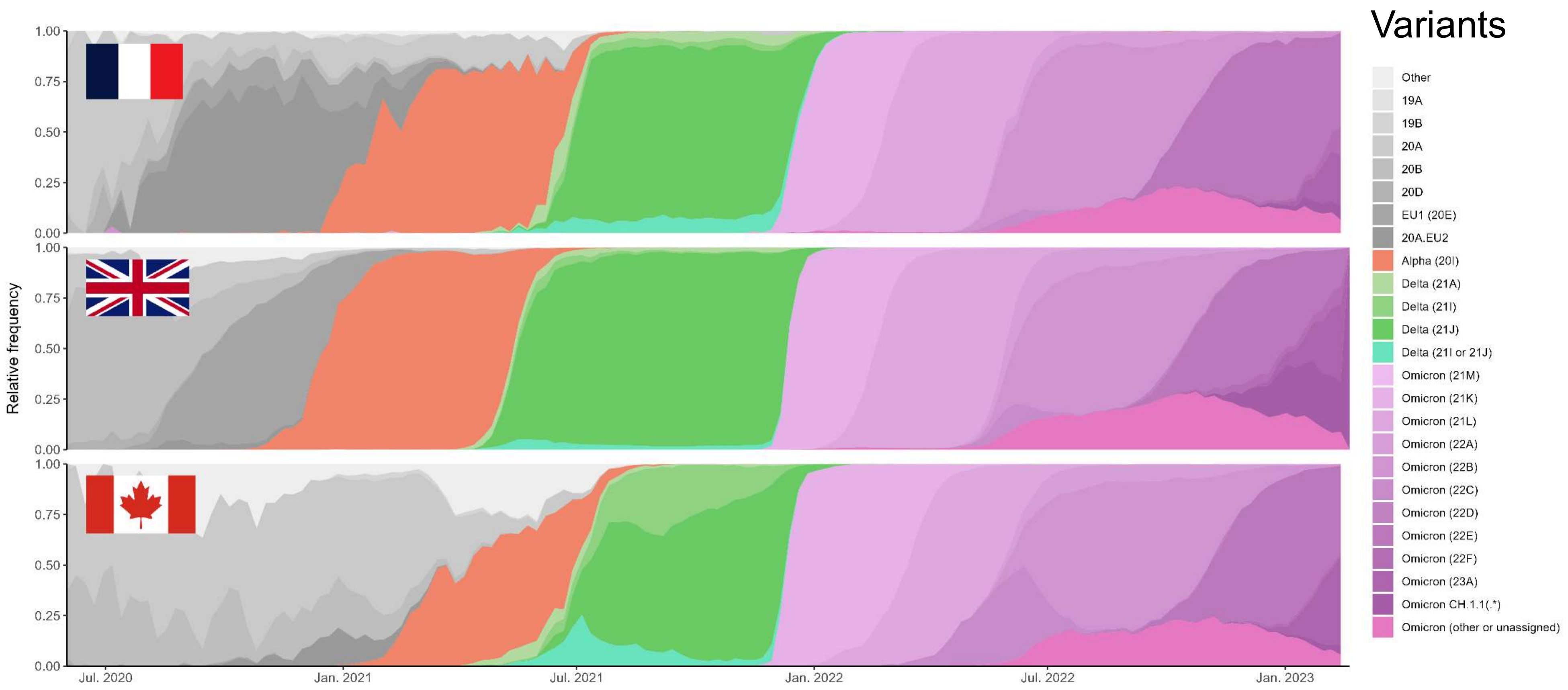
Sylvain Gandon

SARS-CoV2 evolution



GISAID data - © W. Benhamou

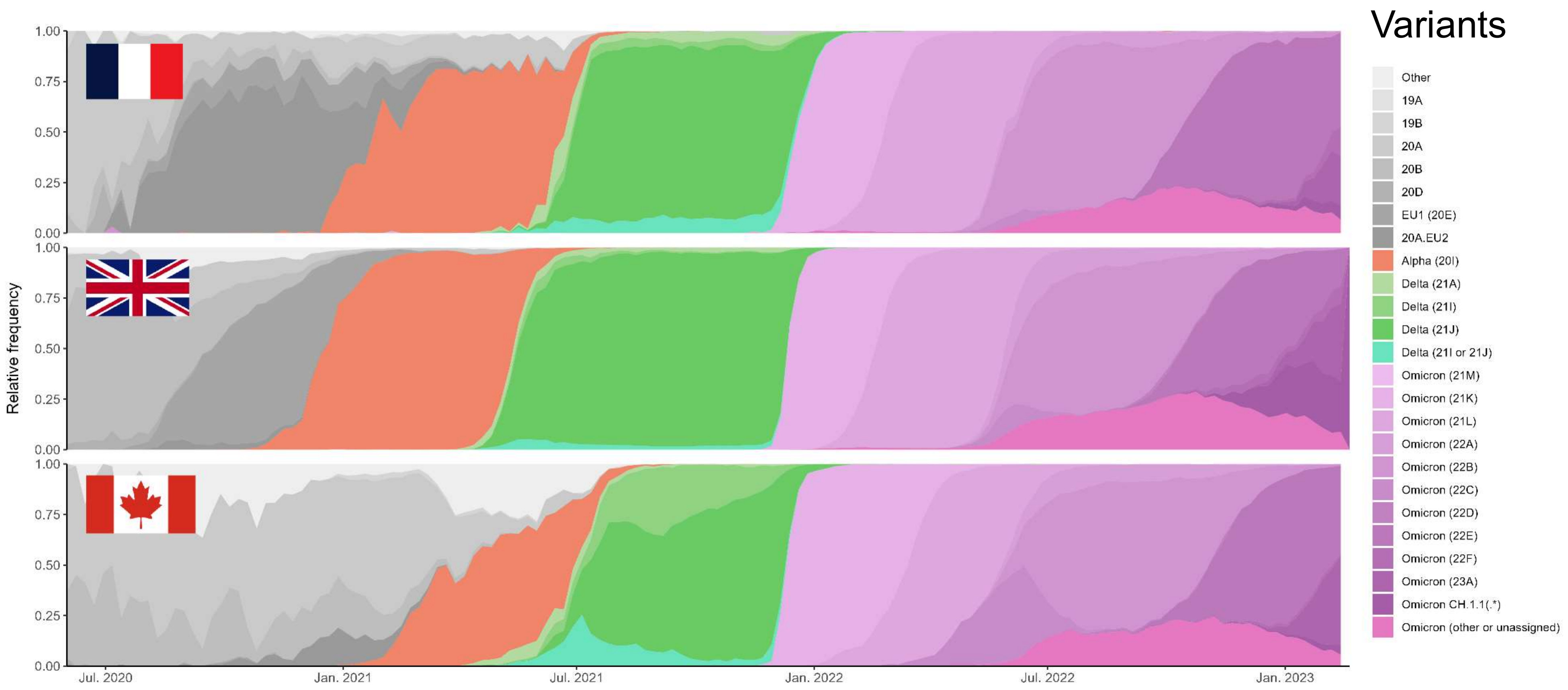
SARS-CoV2 evolution



GISAID data - © W. Benhamou

Natural immunity

SARS-CoV2 evolution

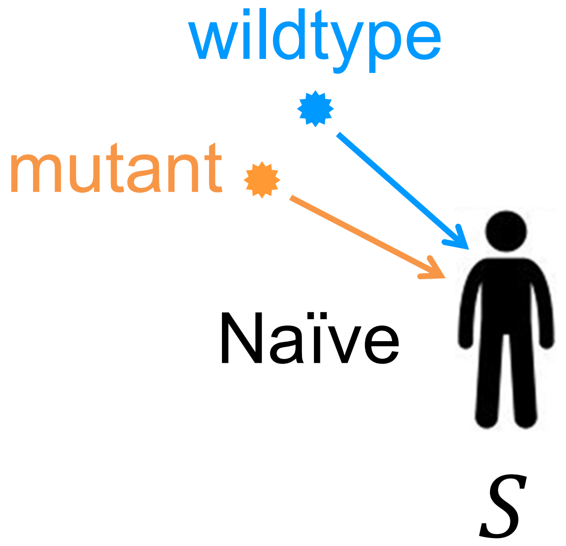


GISAID data - © W. Benhamou

Natural immunity

Vaccination

A simple vaccination model



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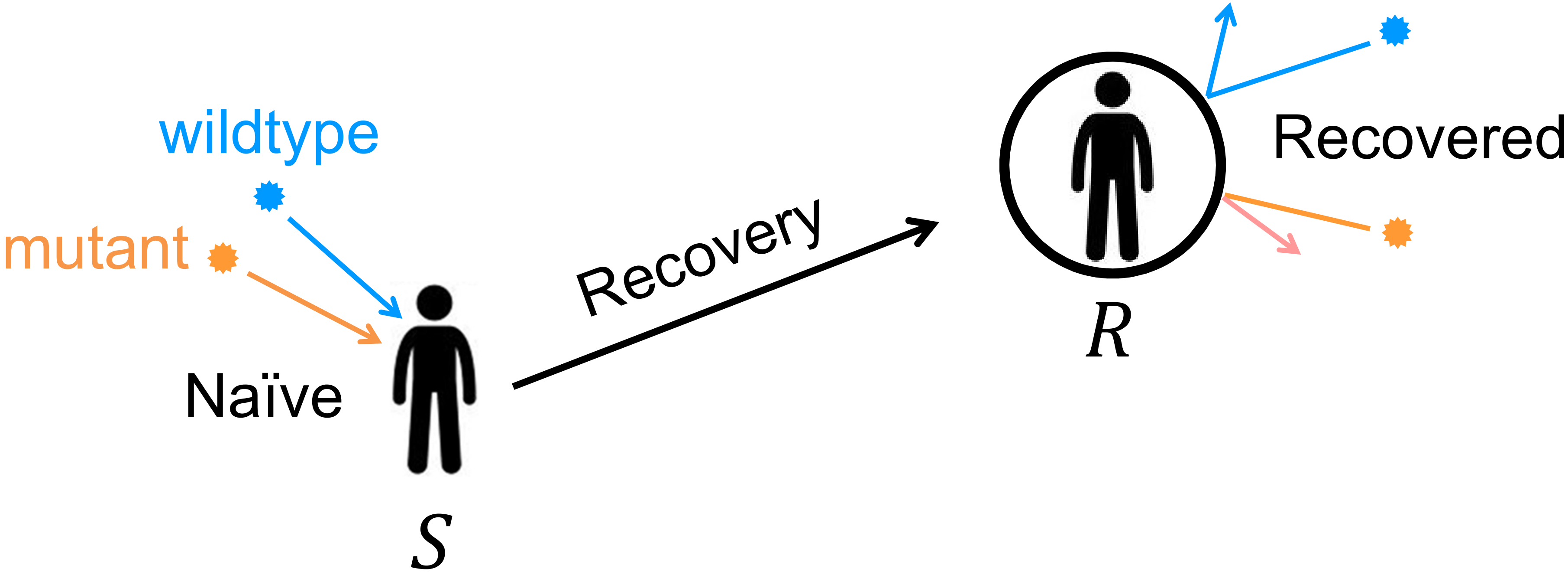

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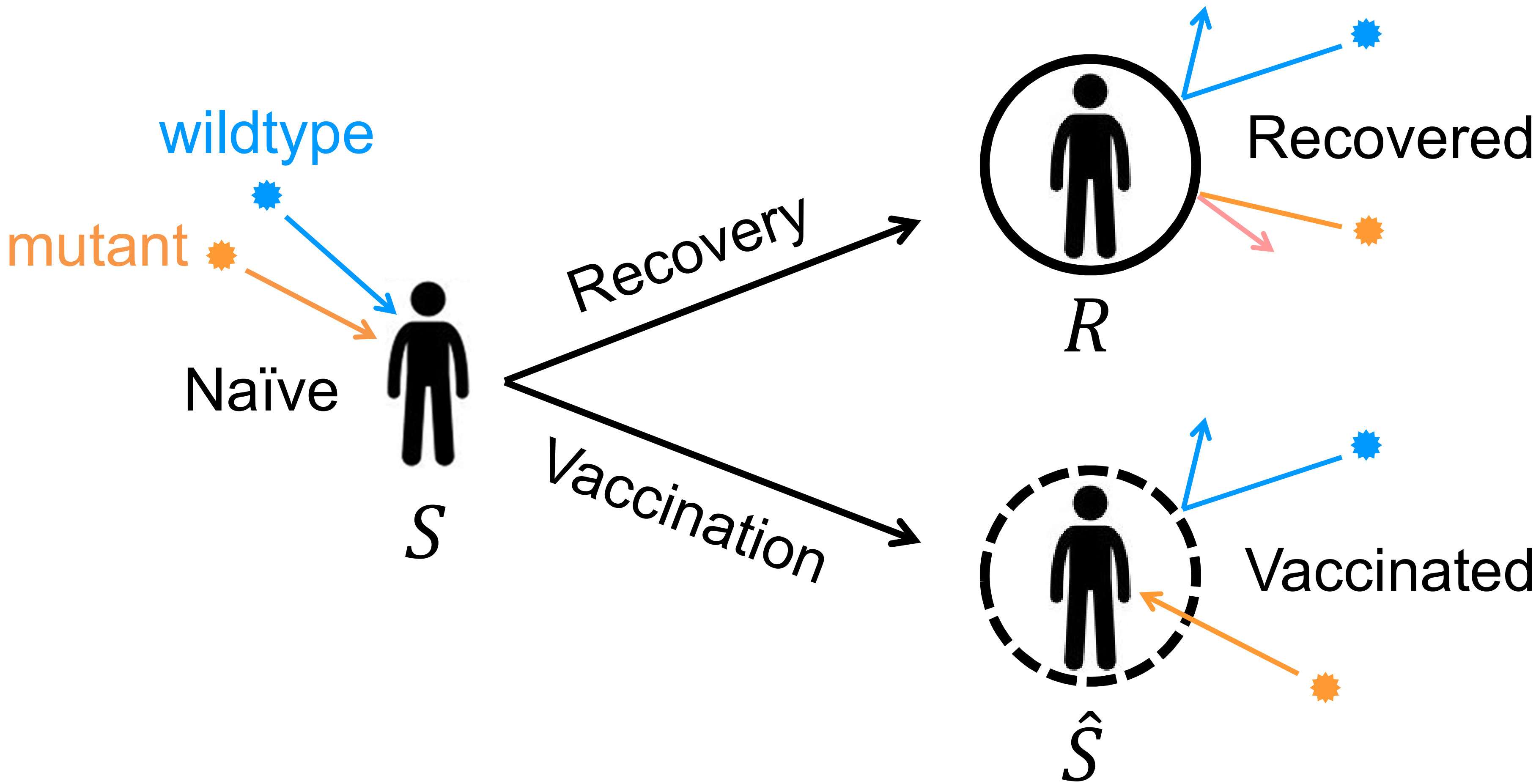

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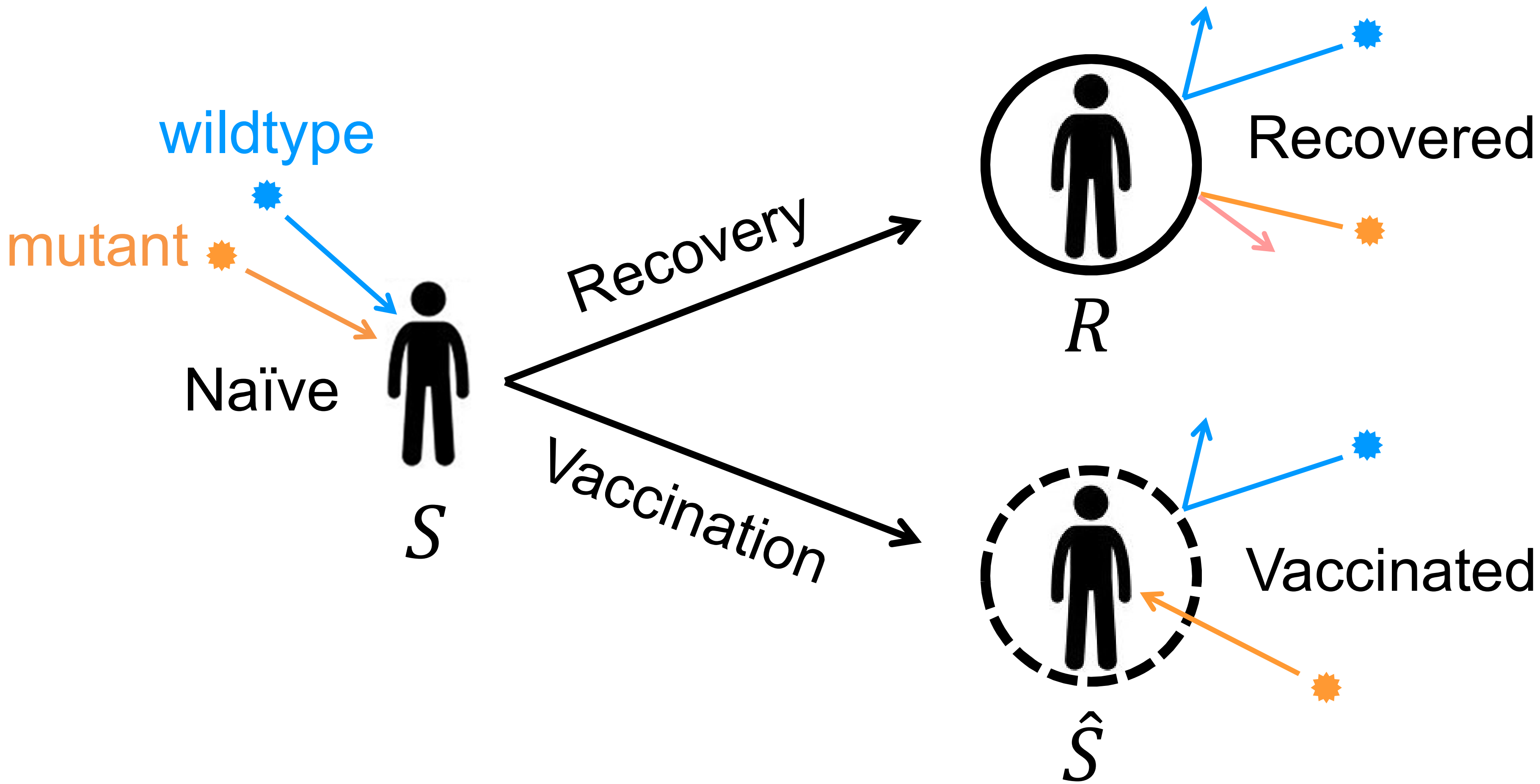

How fast will the pathogen adapt to vaccination?

Outline

(1) The invasion (or not) of escape mutations

Outline

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(2) Transient dynamics and host heterogeneity

Outline

(1) The invasion (or not) of escape mutations

(2) Transient dynamics and host heterogeneity

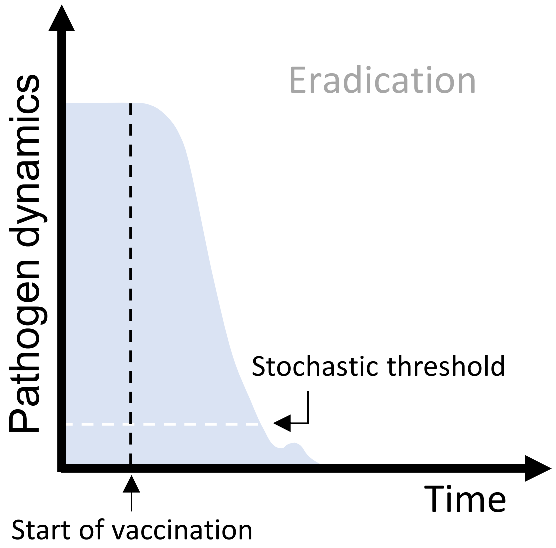
(3) Inferring variant life-history traits

(1) The invasion (or not) of escape mutations

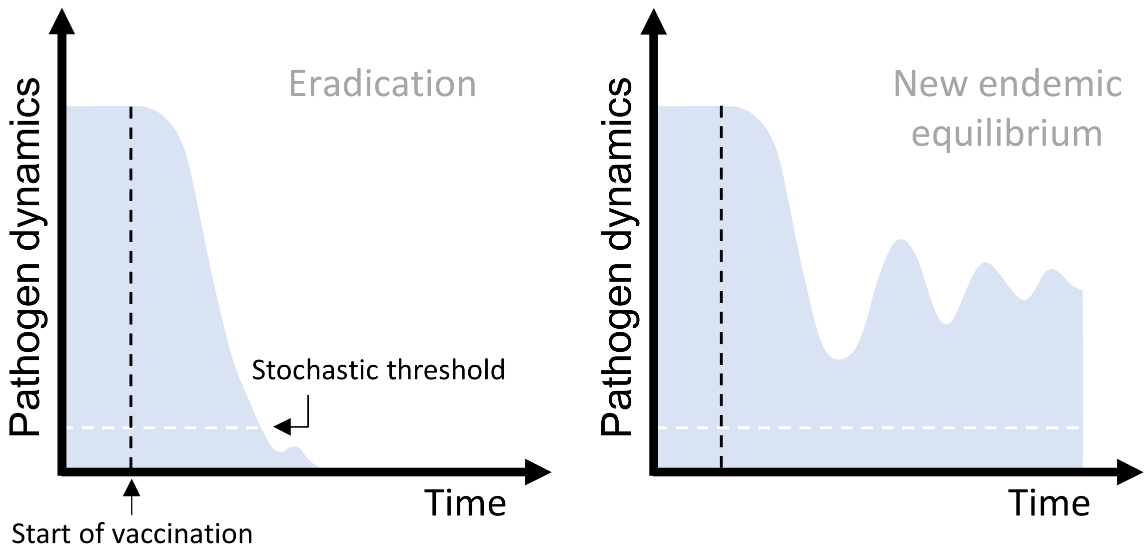
with Todd L. Parsons
M. Voinson
A. Lambert
T. Day

Can pathogens adapt to vaccination?

Can pathogens adapt to vaccination?



Can pathogens adapt to vaccination?



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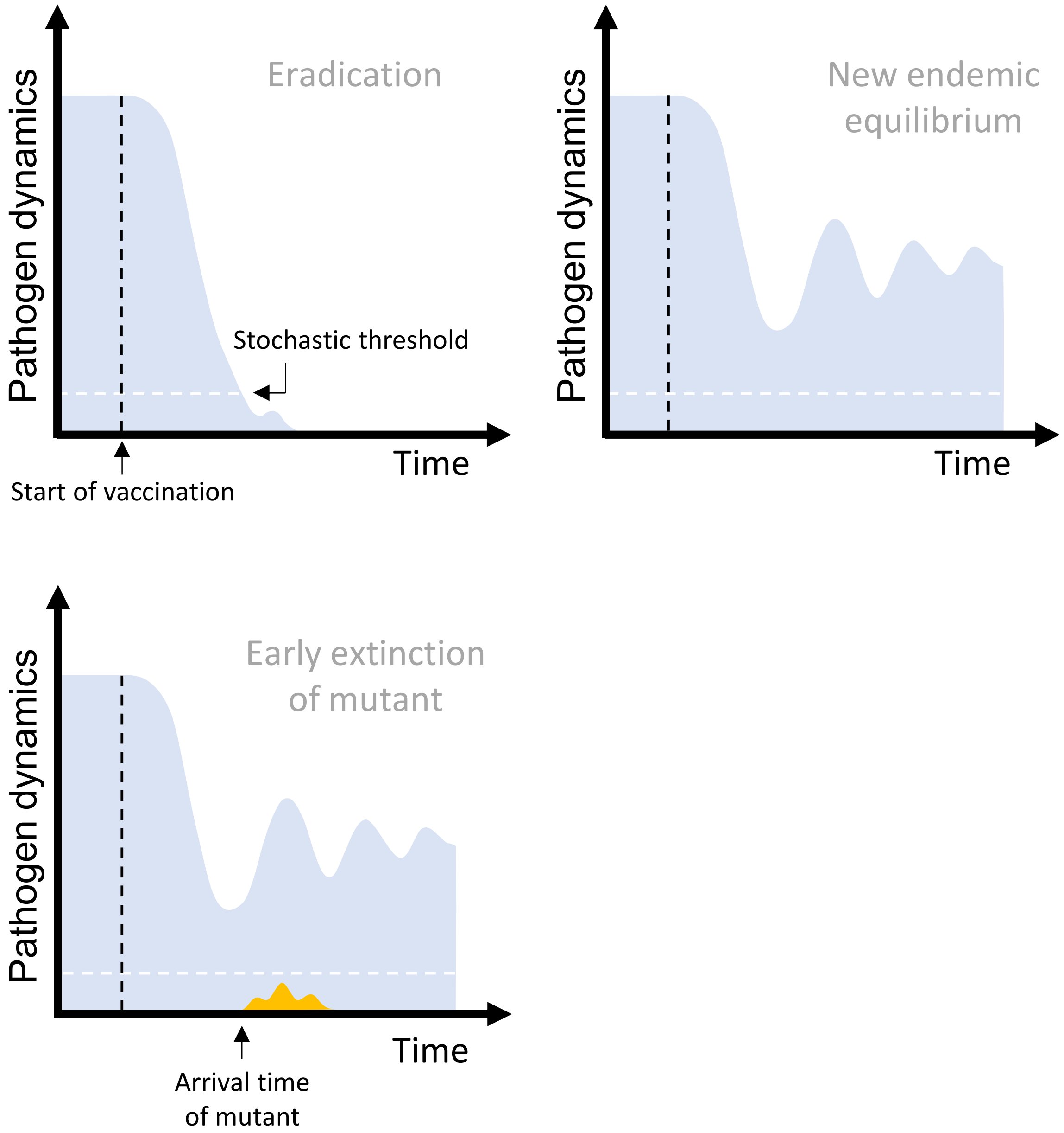

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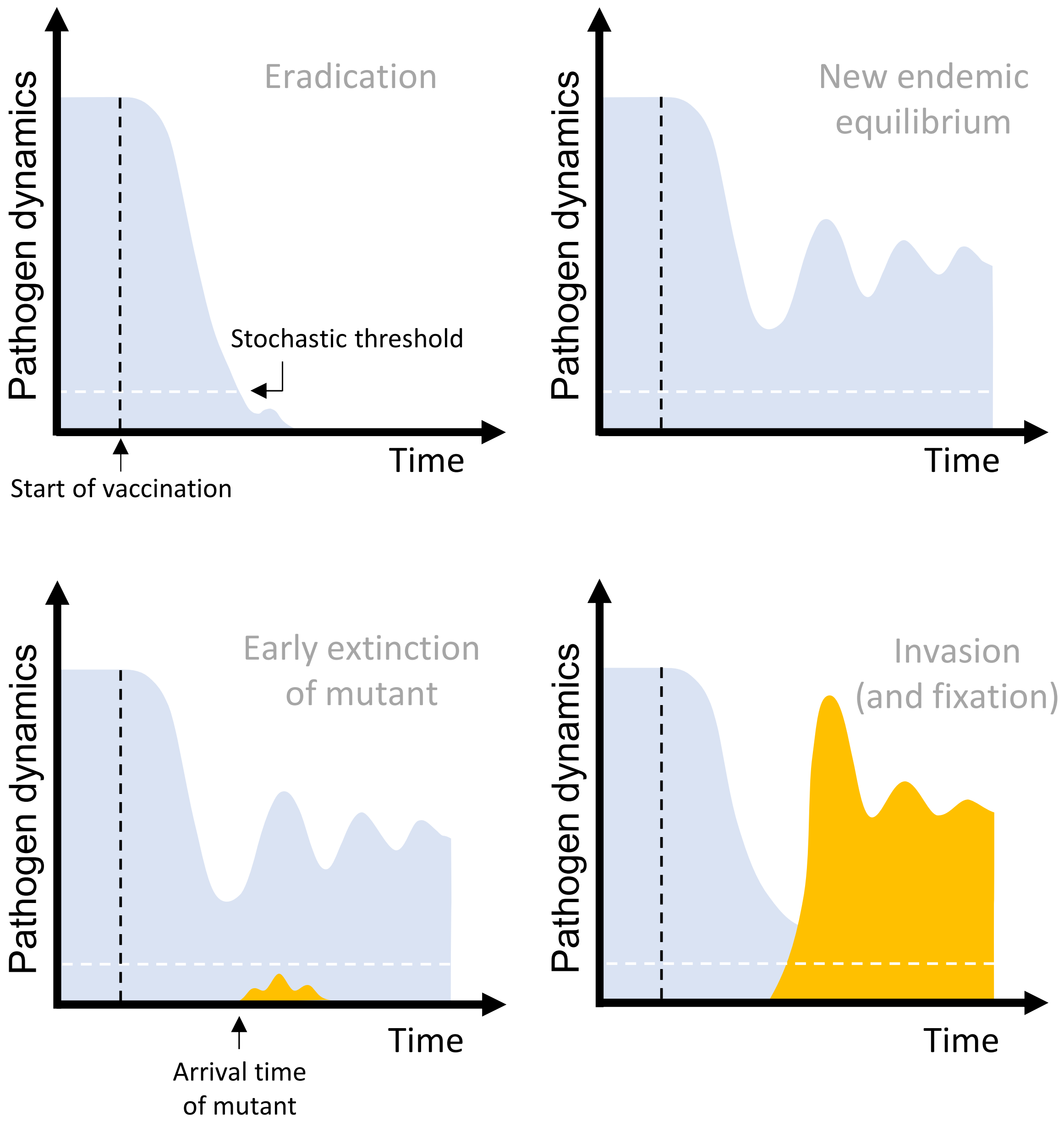
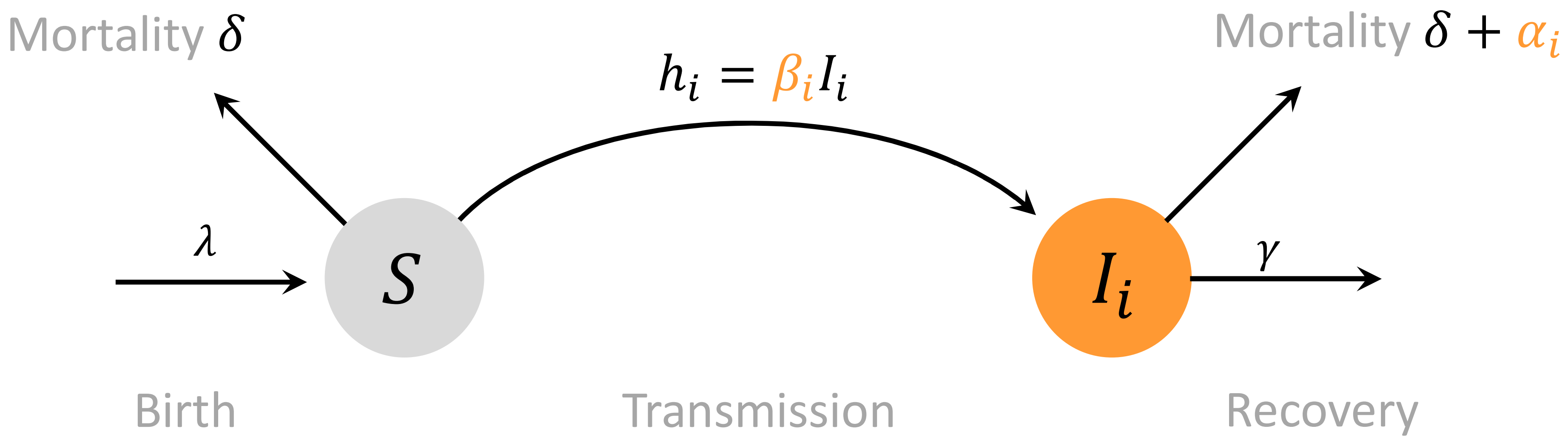
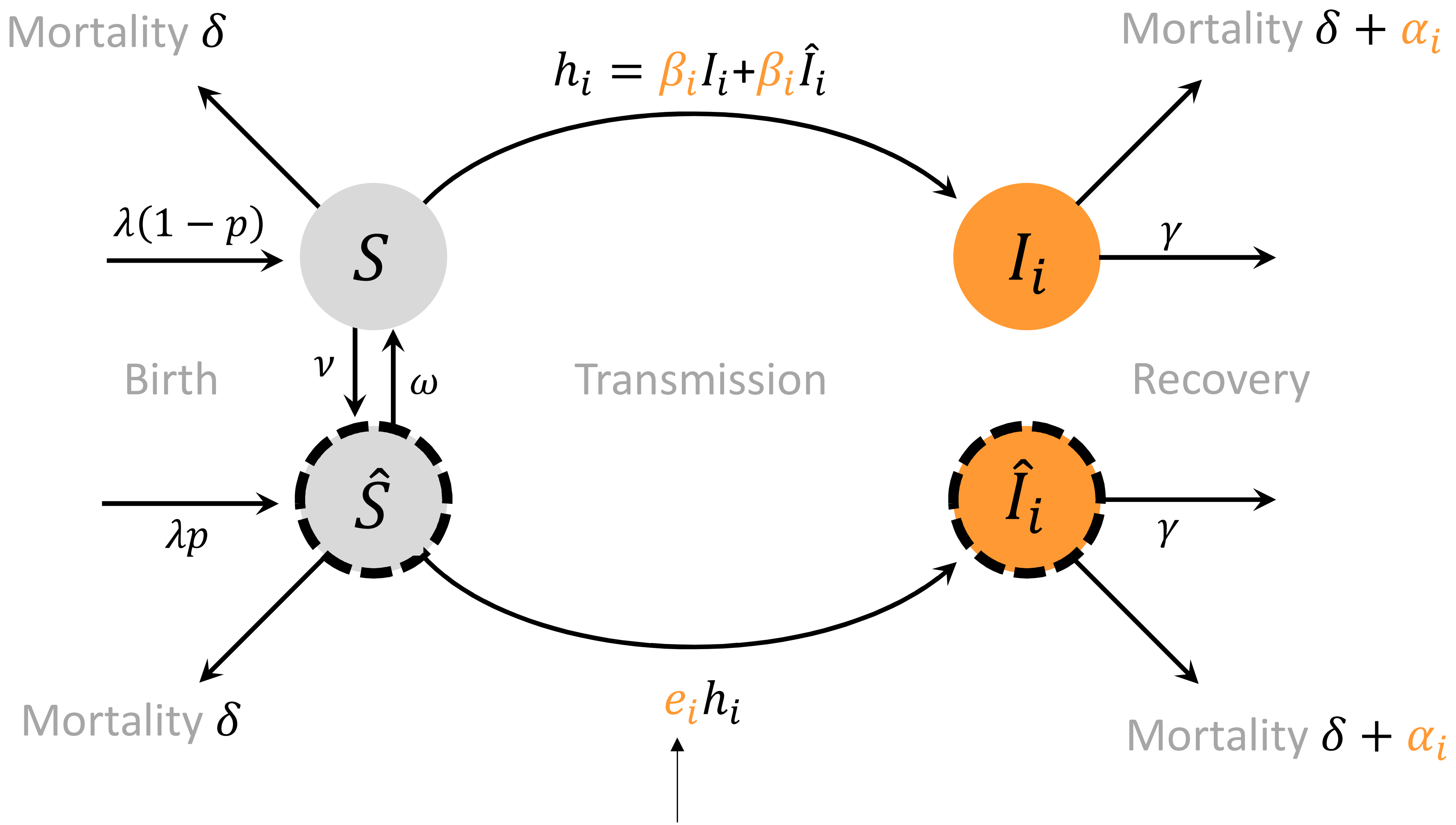


A toy model



Mortality δ
$h_i = \beta_i I_i$
Mortality $\delta + \alpha_i$
λ
S
I_i
γ
Birth
Transmission
Recovery

A toy model



Ability to escape immunity triggered by vaccination

A toy model

Epidemiology & evolution

$$\dot{S} = \lambda(1-p) - \left(\frac{\beta_w}{N}(I_w + \hat{I}_w) + \frac{\beta_m}{N}(I_m + \hat{I}_m) + \delta\right)S - \nu S + \omega\hat{S} + \omega_R R$$

$$\dot{\hat{S}} = \lambda p - \left(e_w\frac{\beta_w}{N}(I_w + \hat{I}_w) + e_m\frac{\beta_m}{N}(I_m + \hat{I}_m) + \delta\right)\hat{S} + \nu S - \omega\hat{S}$$

$$\dot{I}_w = \frac{\beta_w S}{N}(I_w + \hat{I}_w) - (\delta + \alpha_w + \gamma)I_w$$

$$\dot{I}_m = \frac{\beta_m S}{N}(I_m + \hat{I}_m) - (\delta + \alpha_m + \gamma)I_m$$

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$$\dot{\hat{I}}_m = e_m\frac{\beta_m \hat{S}}{N}(I_m + \hat{I}_m) - (\delta + \alpha_m + \gamma)\hat{I}_m$$

$$\dot{R} = \gamma(I_w + \hat{I}_w + I_m + \hat{I}_m) - (\delta + \omega_R)R$$

A toy model

Epidemiology & evolution

$$\dot{S} = \lambda(1-p) - \left(\frac{\beta_w}{N}(I_w + \hat{I}_w) + \frac{\beta_m}{N}(I_m + \hat{I}_m) + \delta\right)S - \nu S + \omega \hat{S} + \omega_R R$$

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Evolution

$$p_m = \frac{I_m + \hat{I}_m}{I_w + \hat{I}_w + I_m + \hat{I}_m}$$

$$\dot{p}_m = p_m(1 - p_m)s_m$$

selection

A toy model

Epidemiology & evolution

$$\dot{S} = \lambda(1-p) - \left(\frac{\beta_w}{N}(I_w + \hat{I}_w) + \frac{\beta_m}{N}(I_m + \hat{I}_m) + \delta\right)S - \nu S + \omega \hat{S} + \omega_R R$$

$$\dot{\hat{S}} = \lambda p - \left(e_w \frac{\beta_w}{N}(I_w + \hat{I}_w) + e_m \frac{\beta_m}{N}(I_m + \hat{I}_m) + \delta\right)\hat{S} + \nu S - \omega \hat{S}$$

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Evolution

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selection

$$s_m = r_m - r_w$$

$$r_i = \underbrace{\beta_i(S + e_i\hat{S})/N}_{birth} - \underbrace{(\mu + \alpha_i + \gamma)}_{death}$$

Effect of vaccination speed on adaptation

Mutation

Effect of vaccination speed on adaptation

Mutation

Flux of escape mutant:

$$\mu_m \left(I_w(t) + \theta \hat{I}_w(t) \right)$$

Effect of vaccination speed on adaptation

Mutation

Flux of escape mutant:

$$\mu_m \left(I_w(t) + \theta \hat{I}_w(t) \right)$$

↑ Mutation rate

Effect of vaccination speed on adaptation

Mutation

Flux of escape mutant:

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Density of unvaccinated infected hosts

Effect of vaccination speed on adaptation

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Flux of escape mutant:

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Density of vaccinated infected hosts

Effect of vaccination speed on adaptation

Mutation

Flux of escape mutant:

$$\mu_m \left(I_w(t) + \theta \hat{I}_w(t) \right)$$

↑

$\theta > 1$

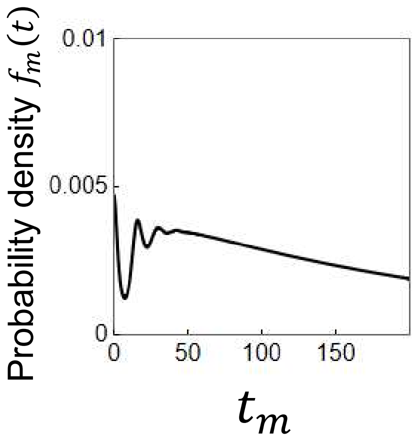
if within-host selection favors escape mutations in vaccinated hosts

Effect of vaccination speed on adaptation

$\mu_m = 0.1, \theta = 1, \omega = 0.05, \omega_R = 0$

Mutation

ν=0.1



Flux of escape mutant:

$$\mu_m \left(I_w(t) + \theta \hat{I}_w(t) \right)$$

$\theta > 1$

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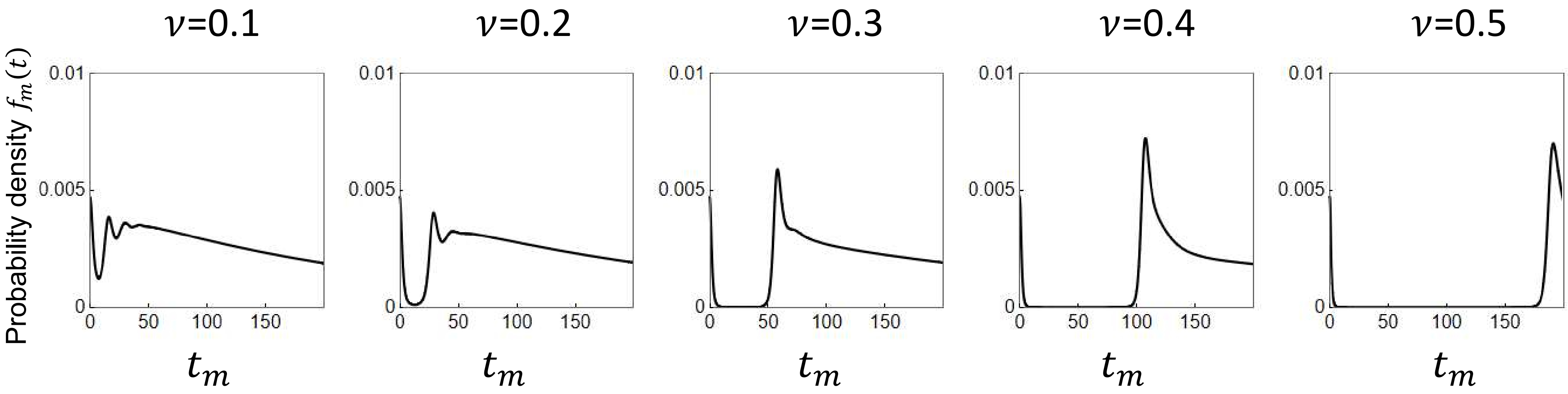
Effect of vaccination speed on adaptation

$\mu_m = 0.1, \theta = 1, \omega = 0.05, \omega_R = 0$

Mutation

Faster rollout of vaccination



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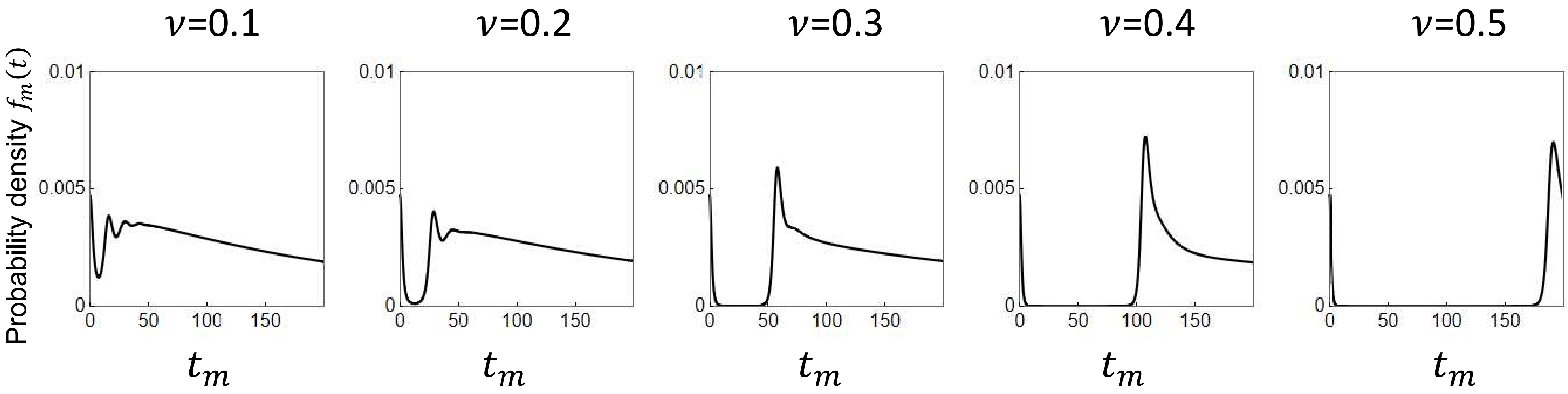
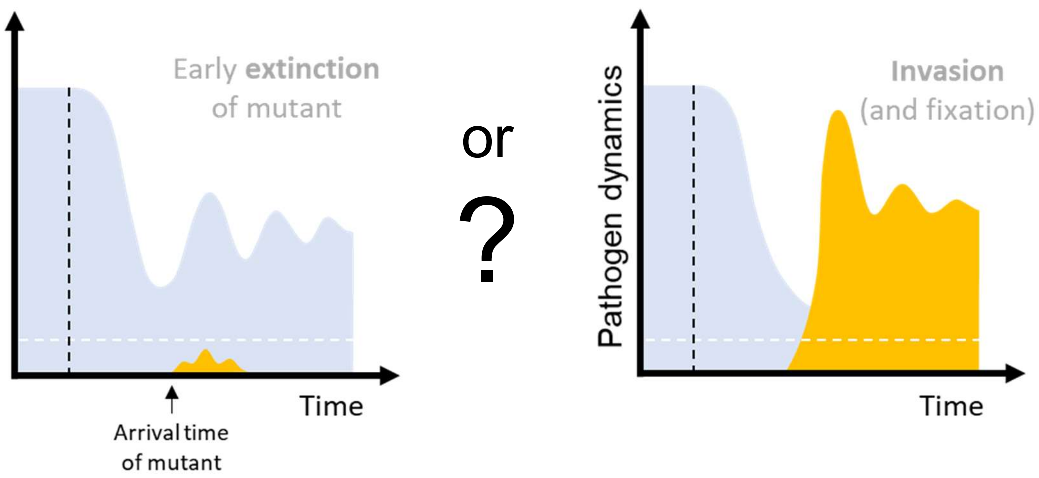


Invasion



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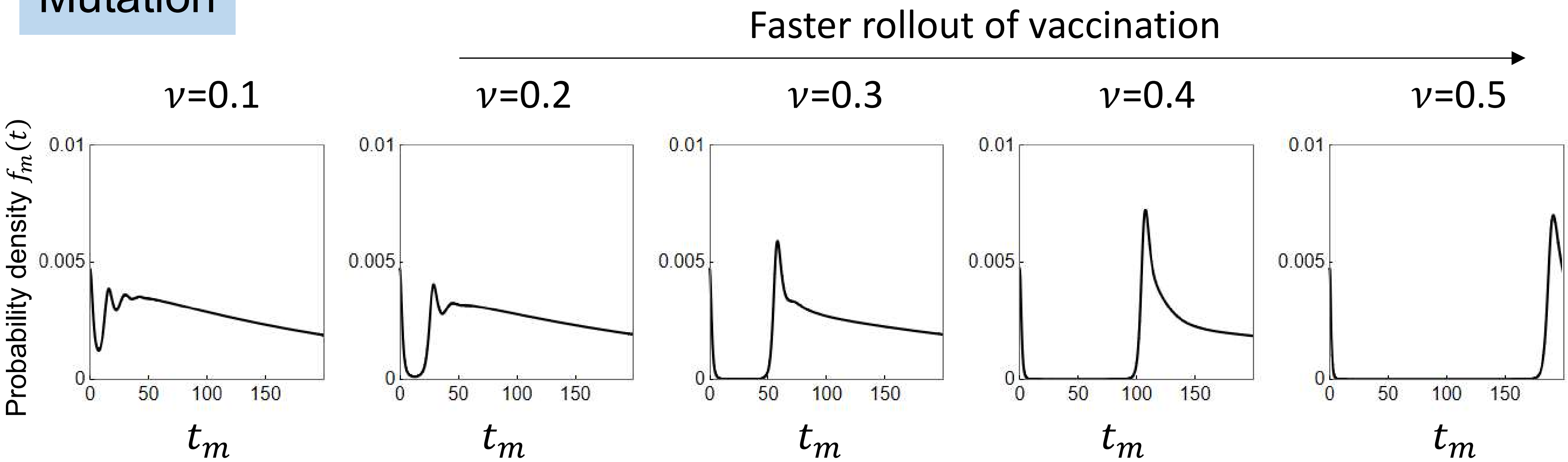
Mutation



Invasion

$$P_m^{t_m} = \frac{1}{1 + \int_{t_m}^{\infty} d_m e^{-\int_{t_m}^{t} (b_m(s) - d_m) ds} dt}$$

Birth:

$$b_m(t) = \beta_m \left(S(t) + e_m \hat{S}(t) \right) / N(t)$$

Death:

$$d_m = \delta + \alpha_m + \gamma$$

Kendall (1948)

Effect of vaccination speed on adaptation

$\mu_m = 0.1, \theta = 1, \omega = 0.05, \omega_R = 0$

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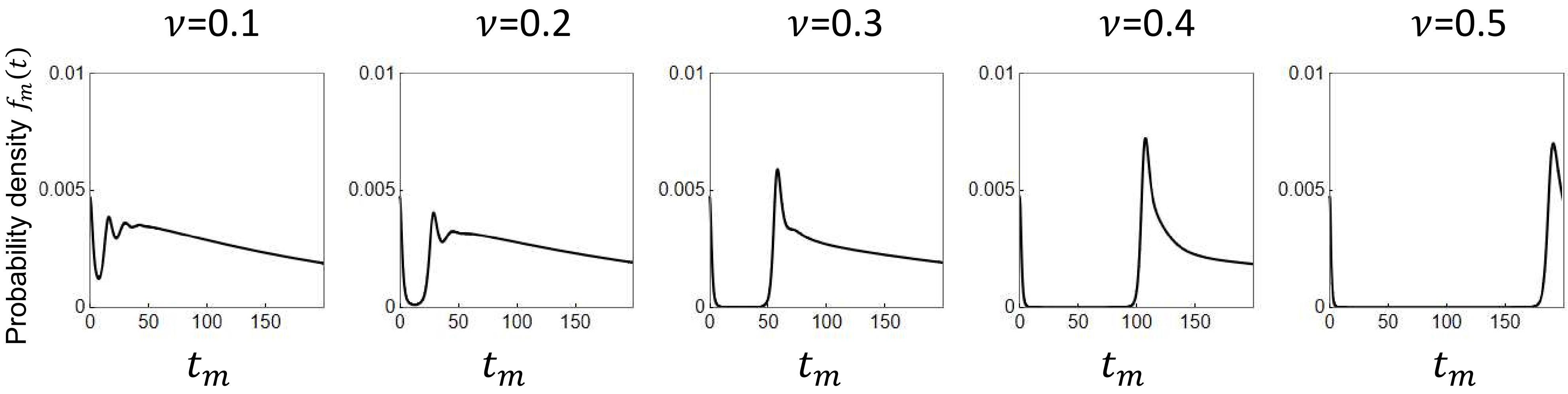
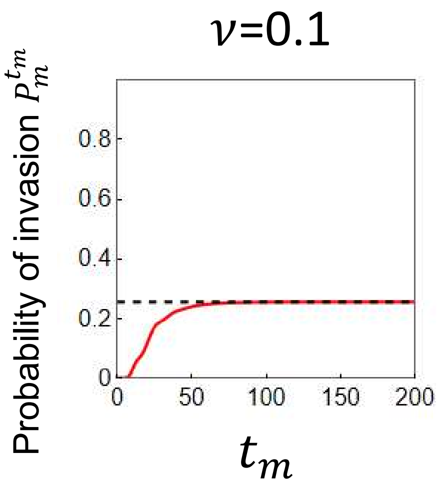
Faster rollout of vaccination



Invasion



Life-history traits:

$e_w = 0.03, \beta_w = 20, \alpha_w = 1$

$e_m = 1, \beta_m = 15, \alpha_m = 1$

Birth:

$$b_m(t) = \beta_m \left(S(t) + e_m \hat{S}(t)\right)/N(t)$$

Death:

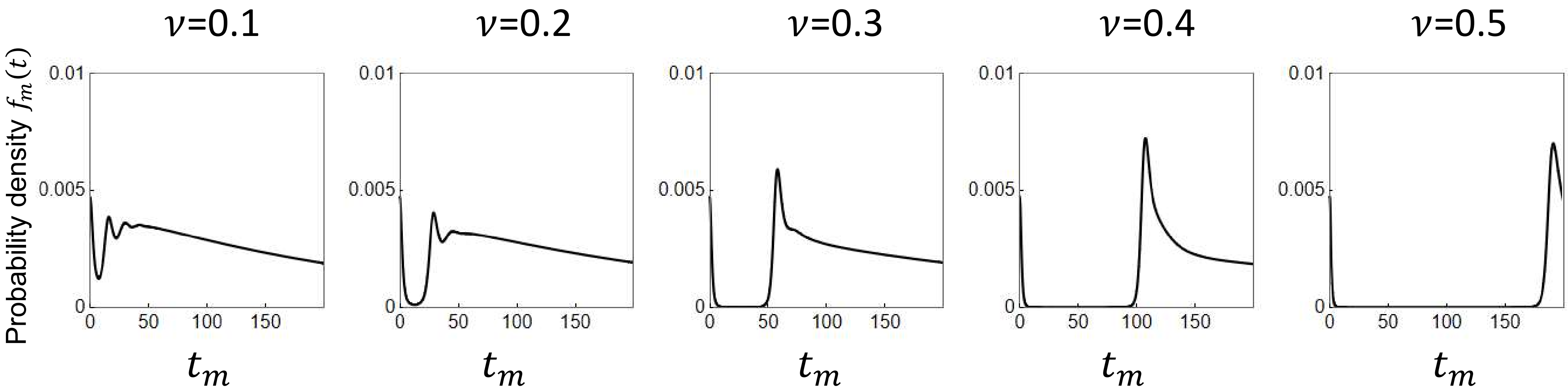
$$d_m = \delta + \alpha_m + \gamma$$

Effect of vaccination speed on adaptation

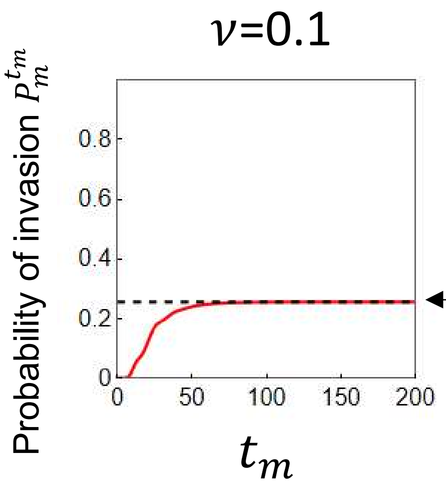
$\mu_m = 0.1, \theta = 1, \omega = 0.05, \omega_R = 0$

Mutation

Faster rollout of vaccination →



Invasion



$$P_m^* = 1 - \frac{1}{R_m^*} \quad \text{with } R_m^* = \frac{b_m^*}{d_m^*}$$

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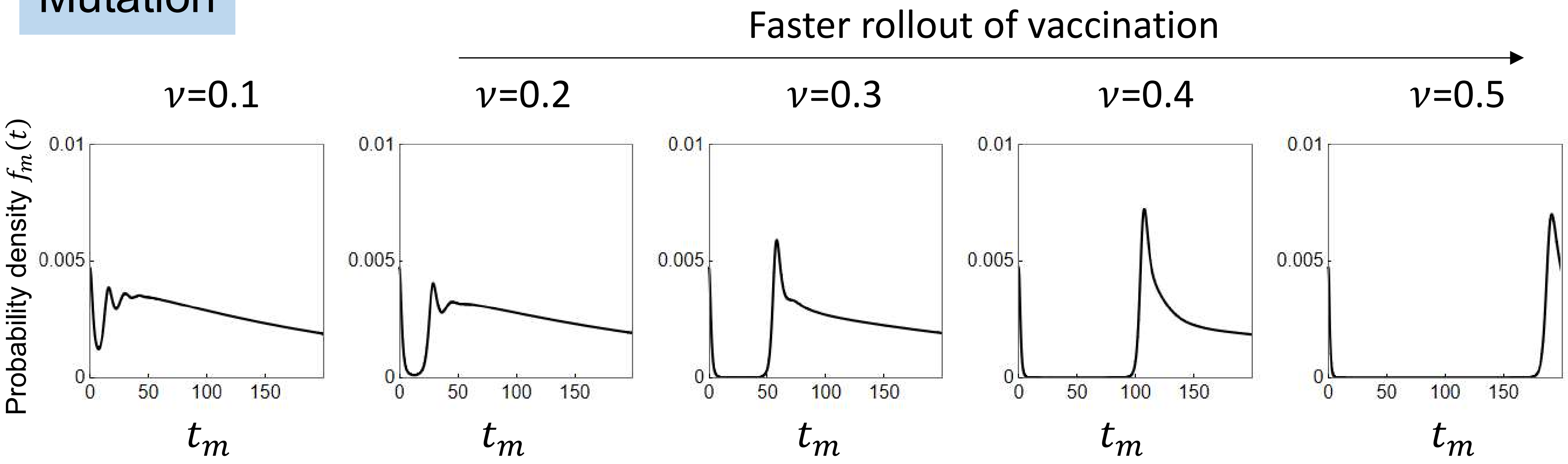
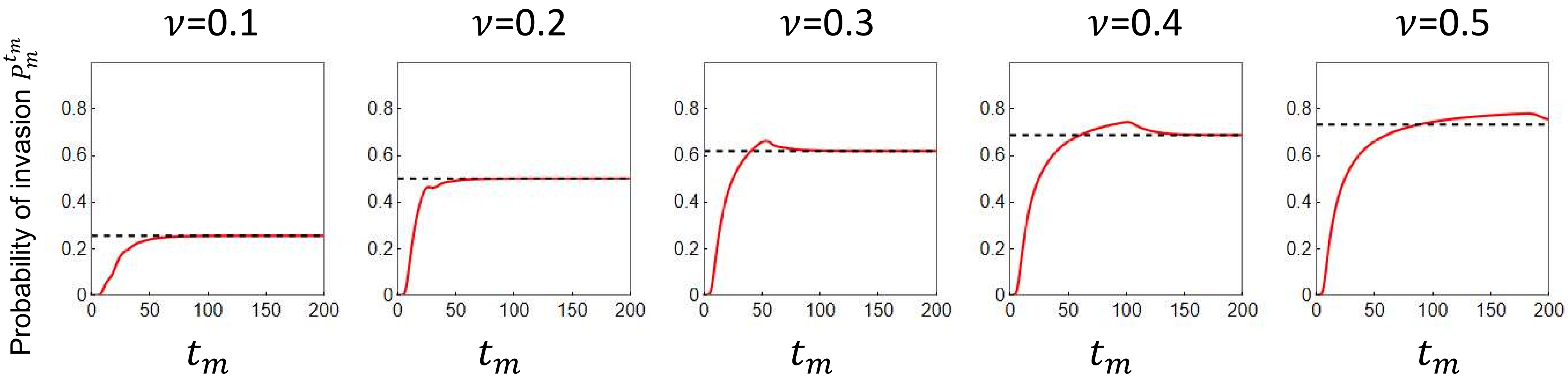


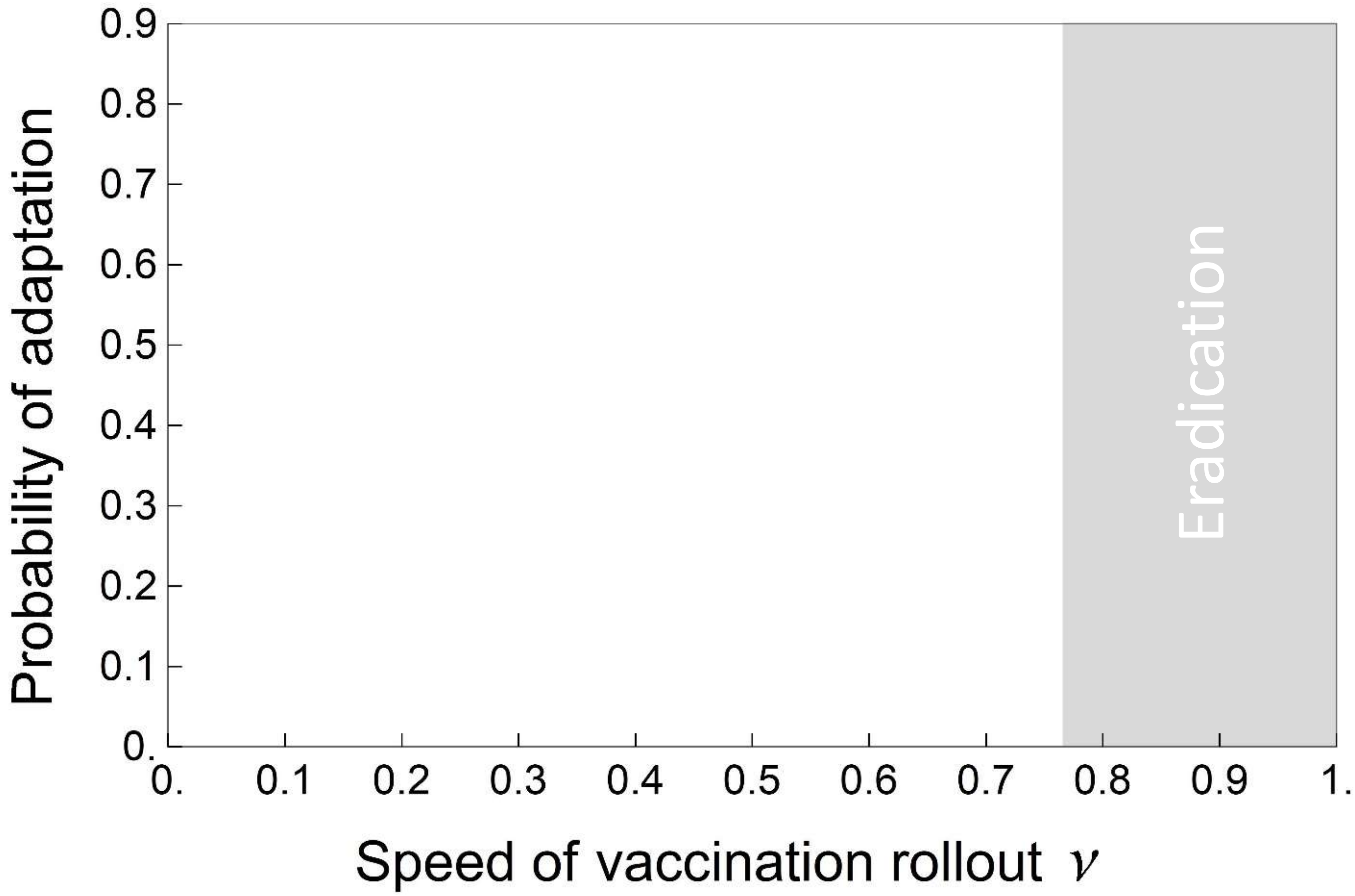
Invasion



Effect of vaccination speed on adaptation

Mutation + Invasion

$\mu_m = 0.1, \theta = 1, \omega = 0.05, \omega_R = 0.05$

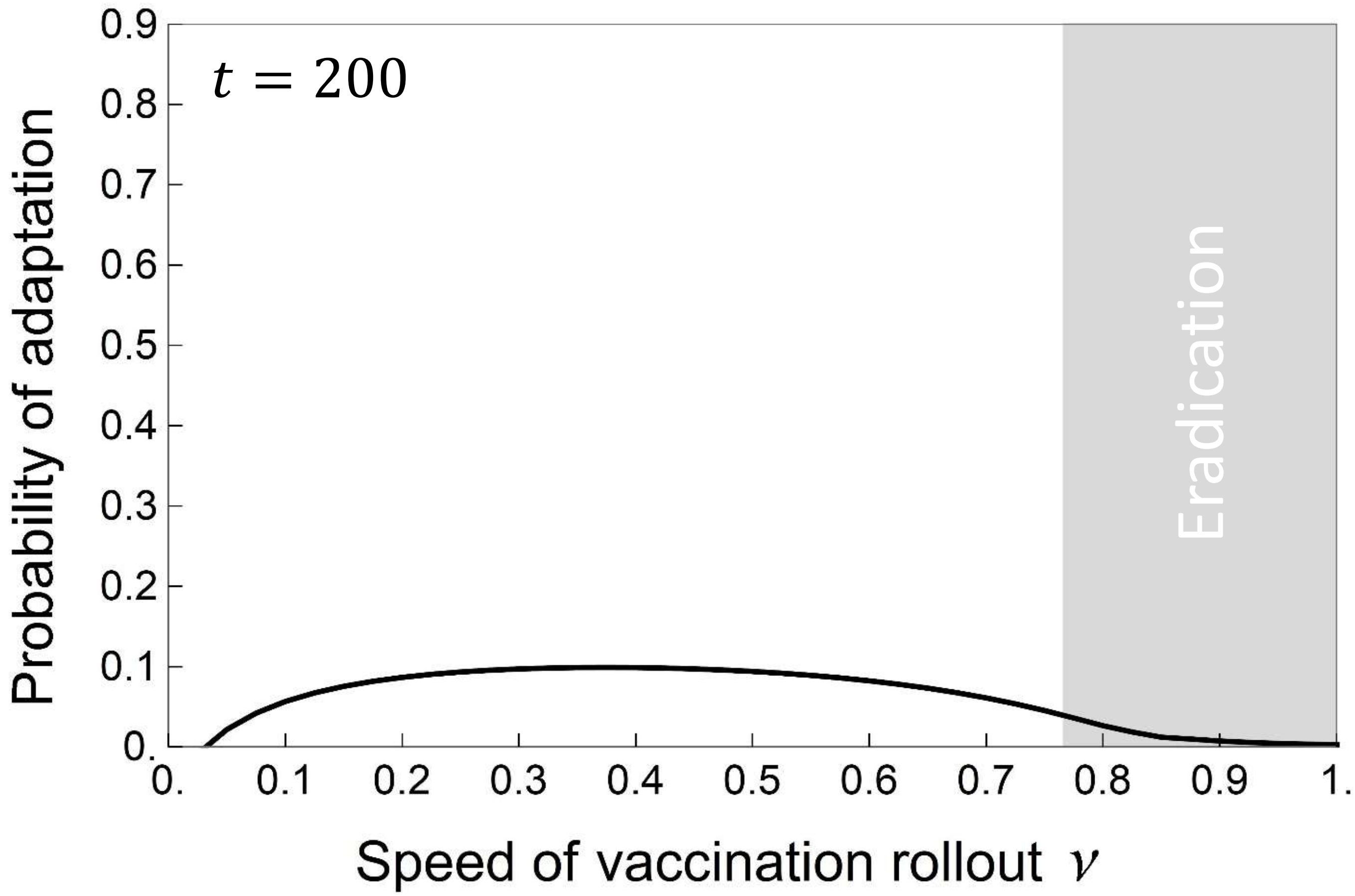


Effect of vaccination speed on adaptation

Mutation + Invasion

$$A_m^t = 1 - e^{-\int_0^t \mu_m (I_w(s) + \theta \hat{I}_w(s)) \, P_m^s \, ds}$$

$\mu_m = 0.1, \theta = 1, \omega = 0.05, \omega_R = 0.05$



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$$A_m^t = 1 - e^{-\int_0^t \mu_m (I_w(s)+\theta \hat{I}_w(s)) \, P_m^s \, ds}$$

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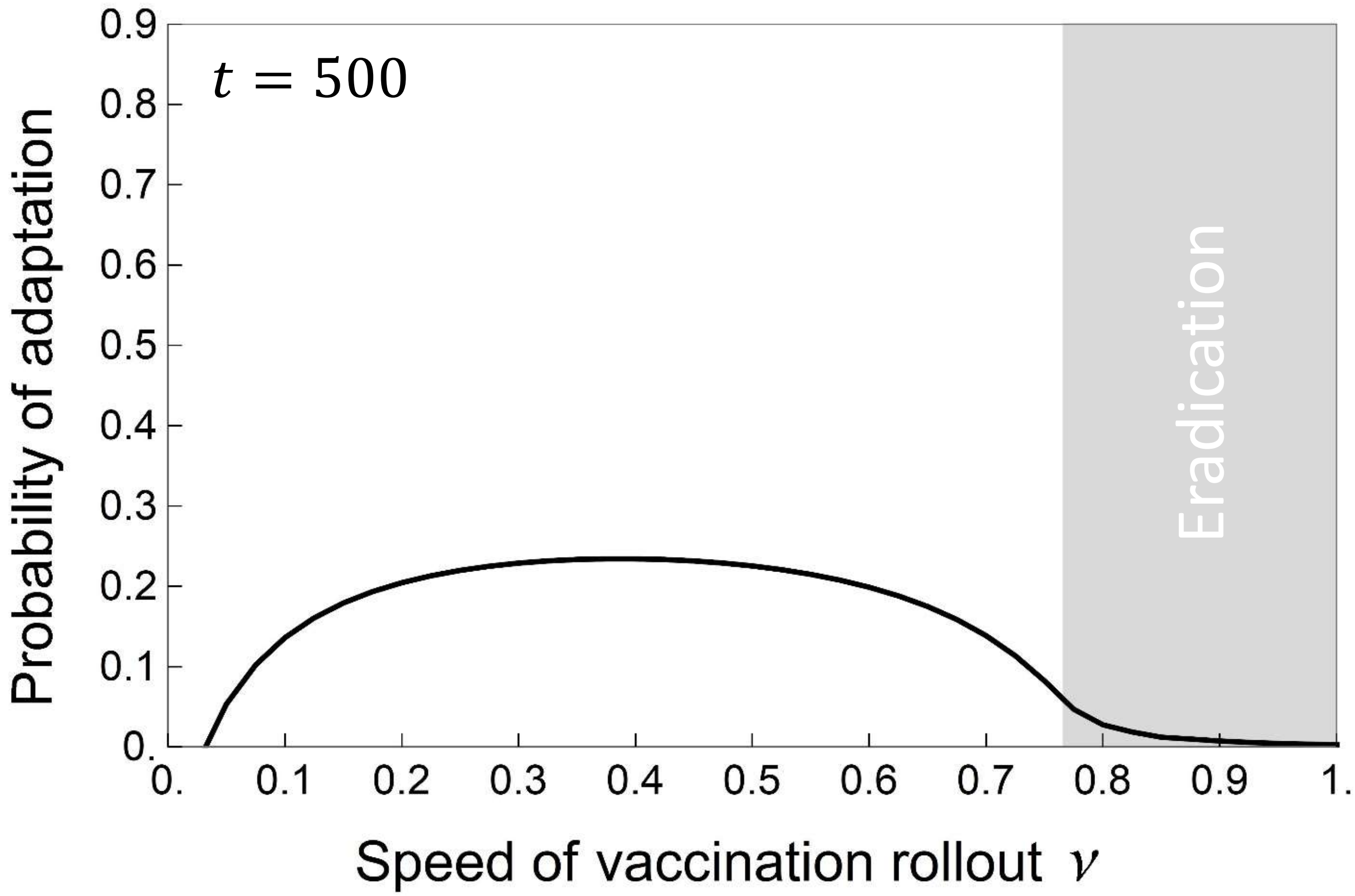

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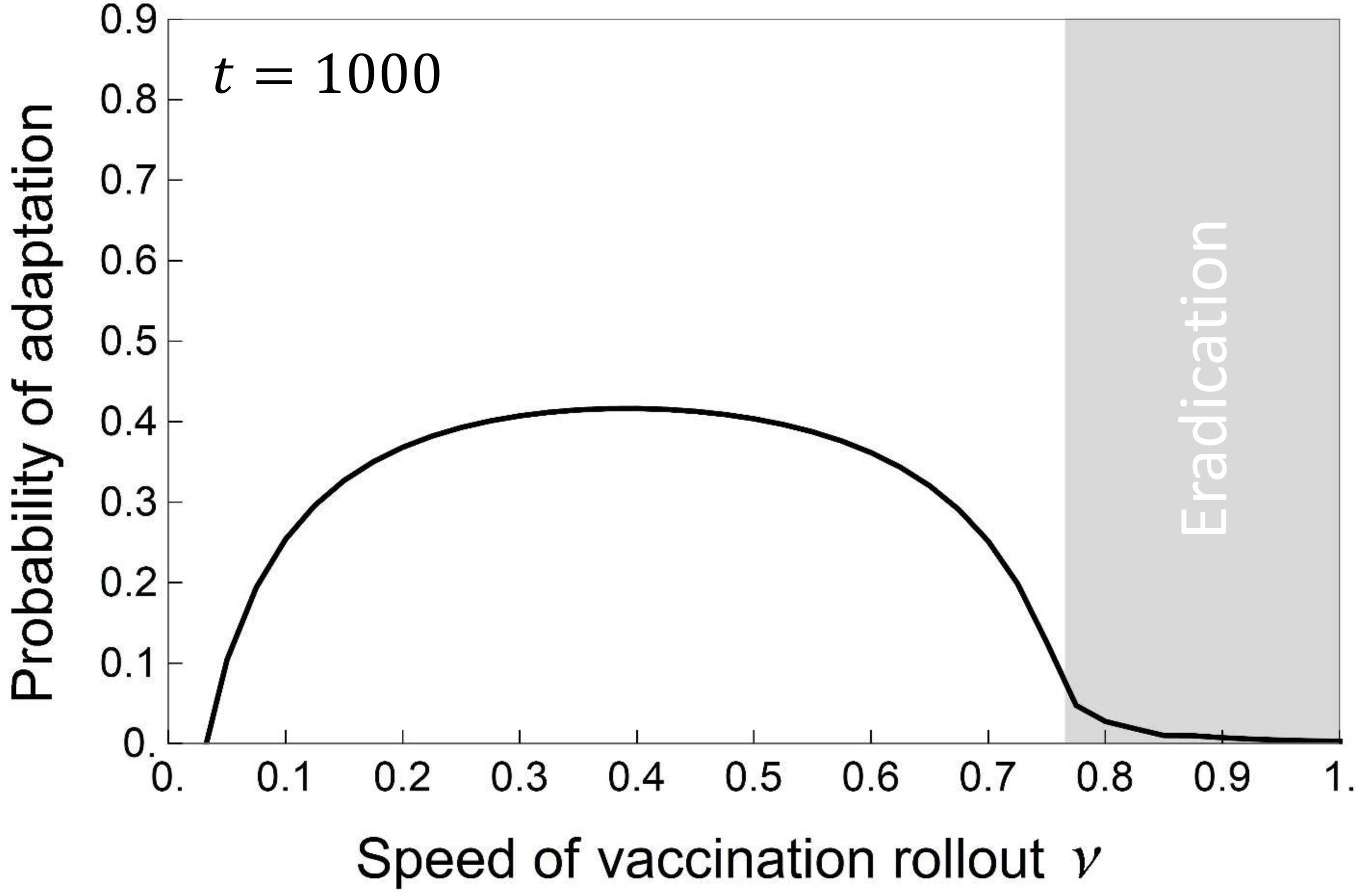

Effect of vaccination speed on adaptation

Mutation + Invasion

$$A_m^t = 1 - e^{-\int_0^t \mu_m\left(I_w(s)+\theta \hat{I}_w(s)\right) P_m^s \, ds}$$

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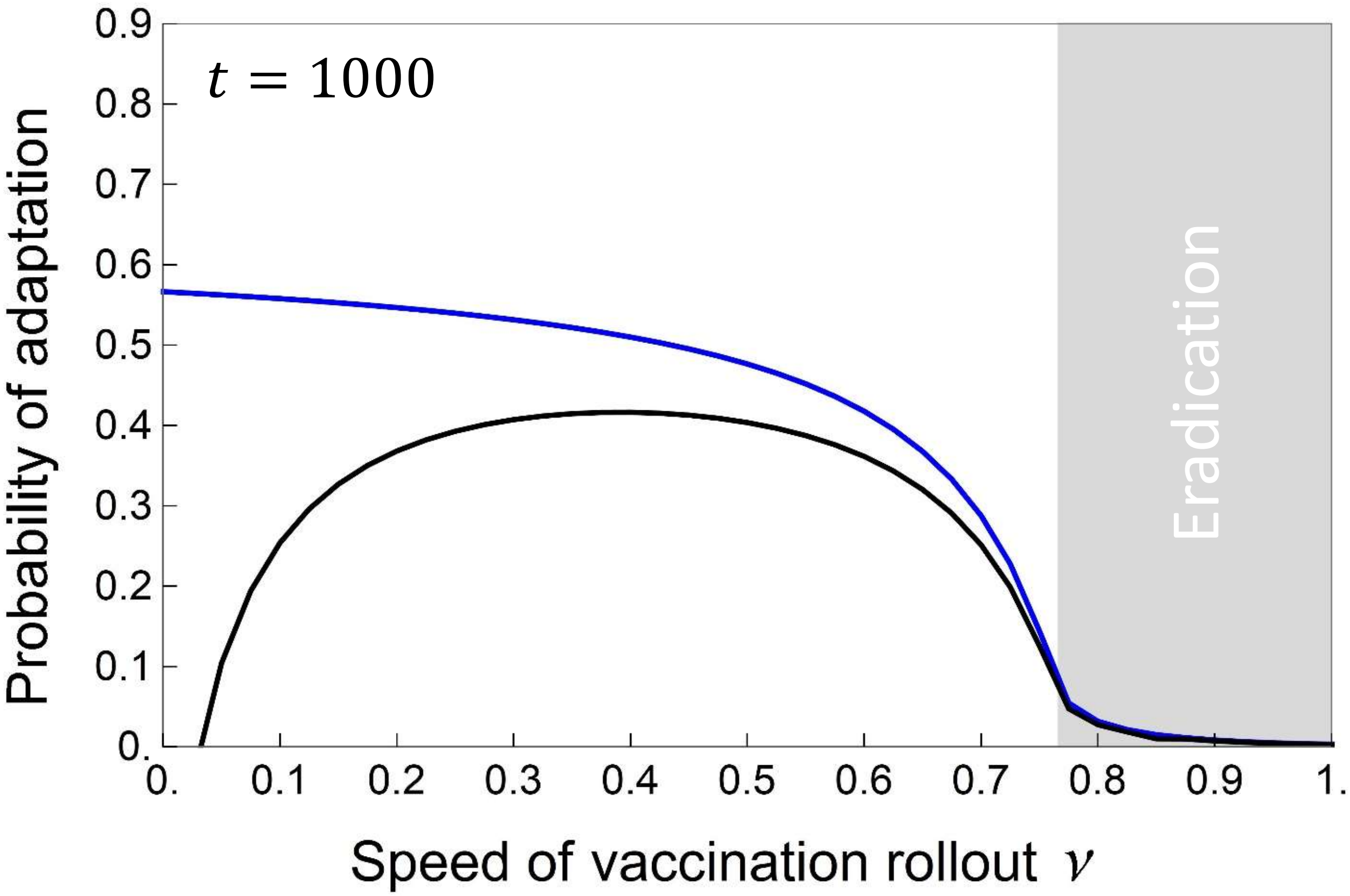

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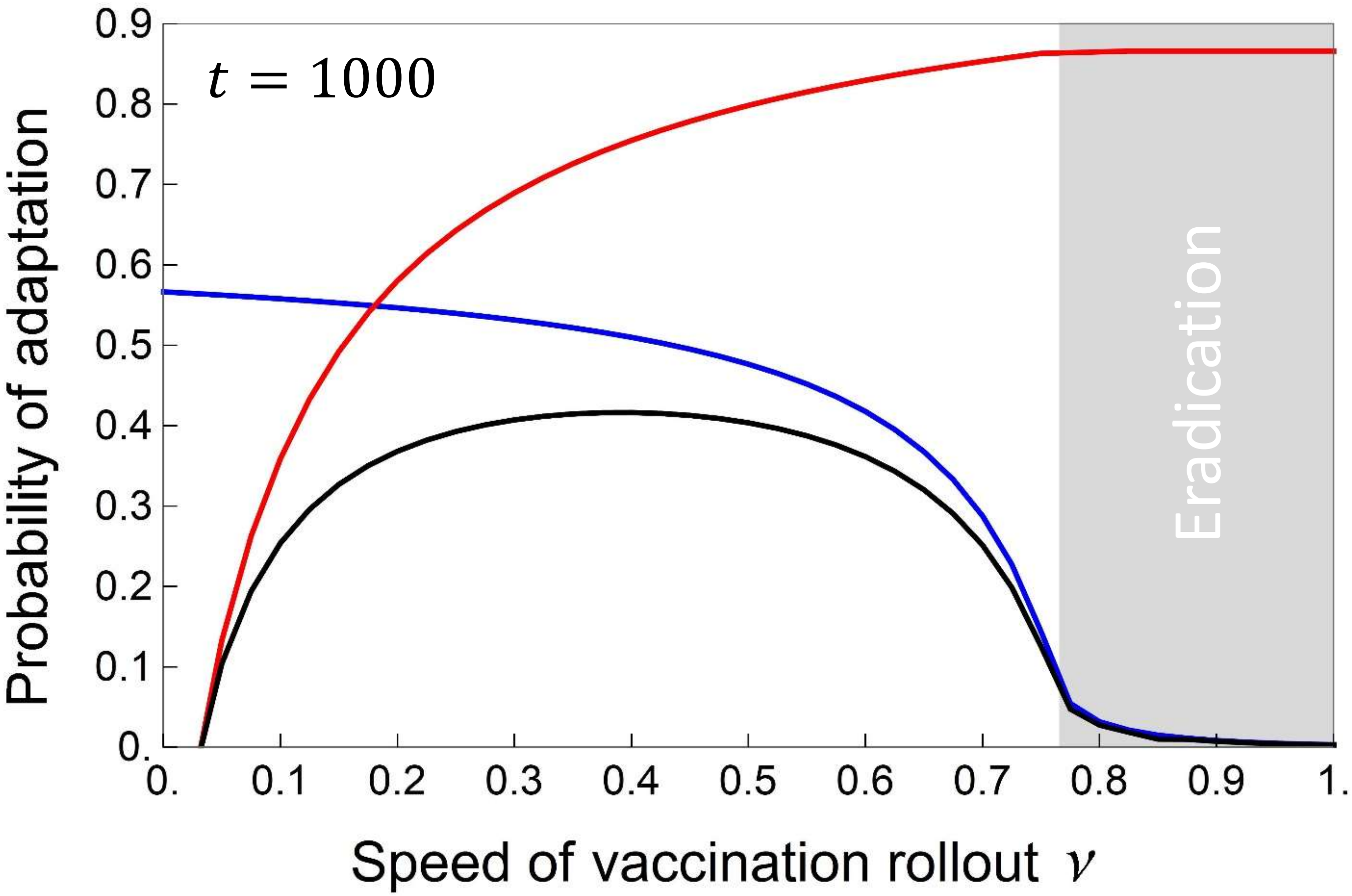
$$P_m^s \approx 1 - 1/\, R_m^*$$

$\mu_m = 0.1, \theta = 1, \omega = 0.05, \omega_R = 0.05$



Effect of vaccination speed on adaptation

Mutation + Invasion

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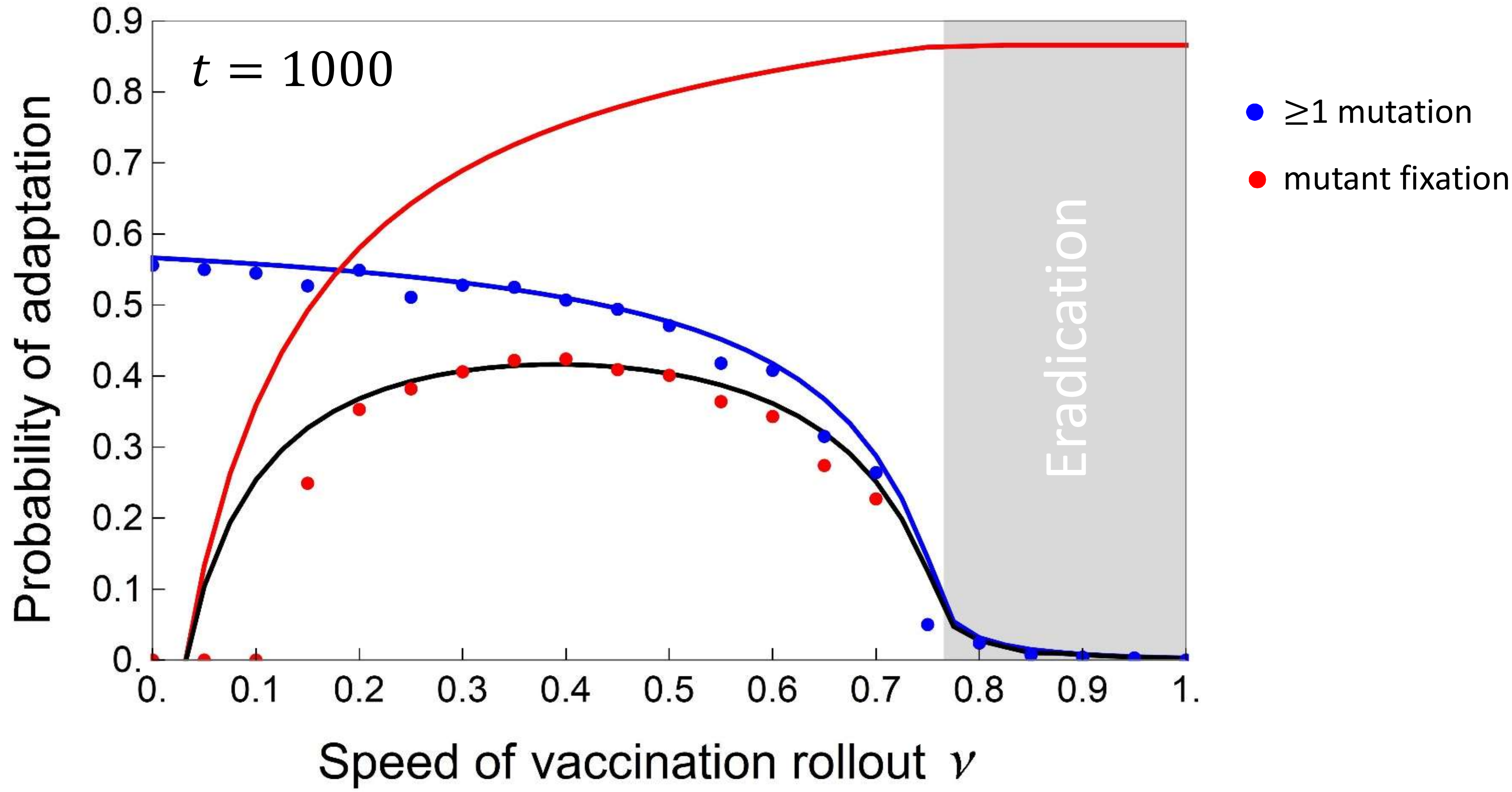

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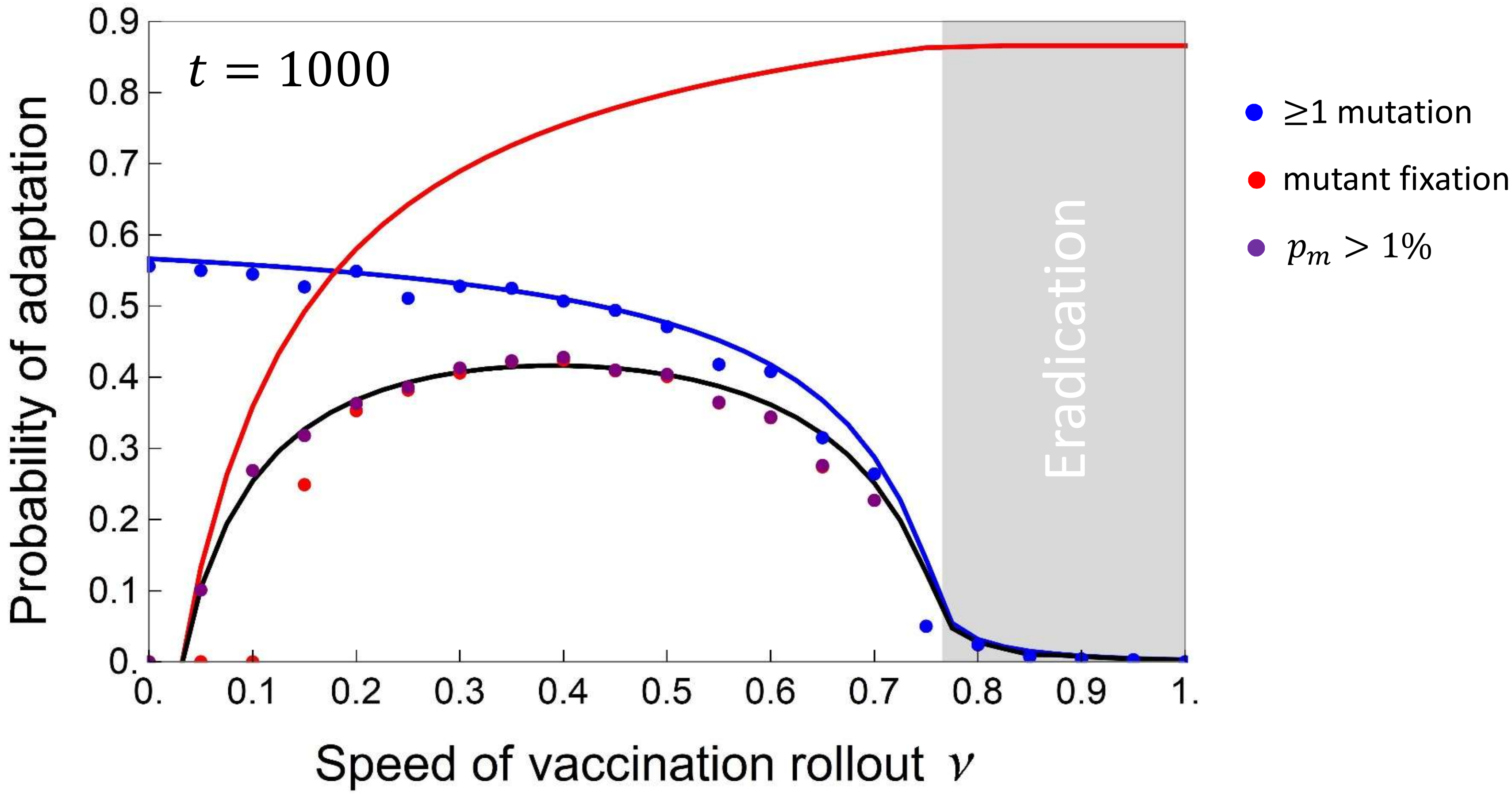

Conclusions (1)

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Adaptation to vaccination is driven by:

- **Introduction of escape variants by mutation**
  - Mutation rate
  - Vaccination speed
  - Non Pharmaceutical Interventions

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But invasion does not imply fixation

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But invasion does not imply fixation

If there is invasion, what is the speed of adaptation?

(2) Transient dynamics in heterogeneous host populations

with S. Lion

Gandon, S., & Lion, S. (2022). Targeted vaccination and the speed of SARS-CoV-2 adaptation. *PNAS*, *119*(3)

Speed of adaptation

The frequency of a vaccine-adapted variant changes as follows

$$\dot{p}_m = p_m(1 - p_m)s_m$$

Where:

$p_m(1 - p_m)$ is the genetic variance

$s_m = r_m - r_w$ is the selection coefficient

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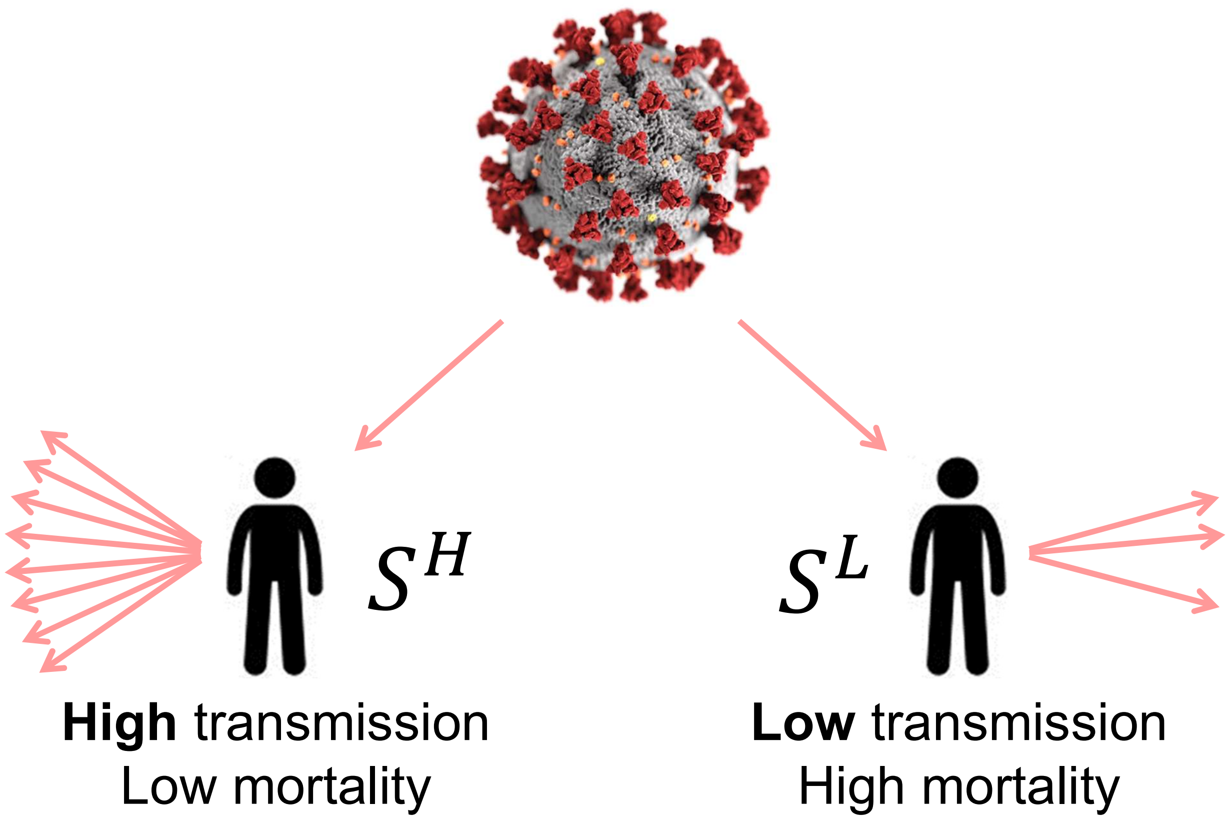
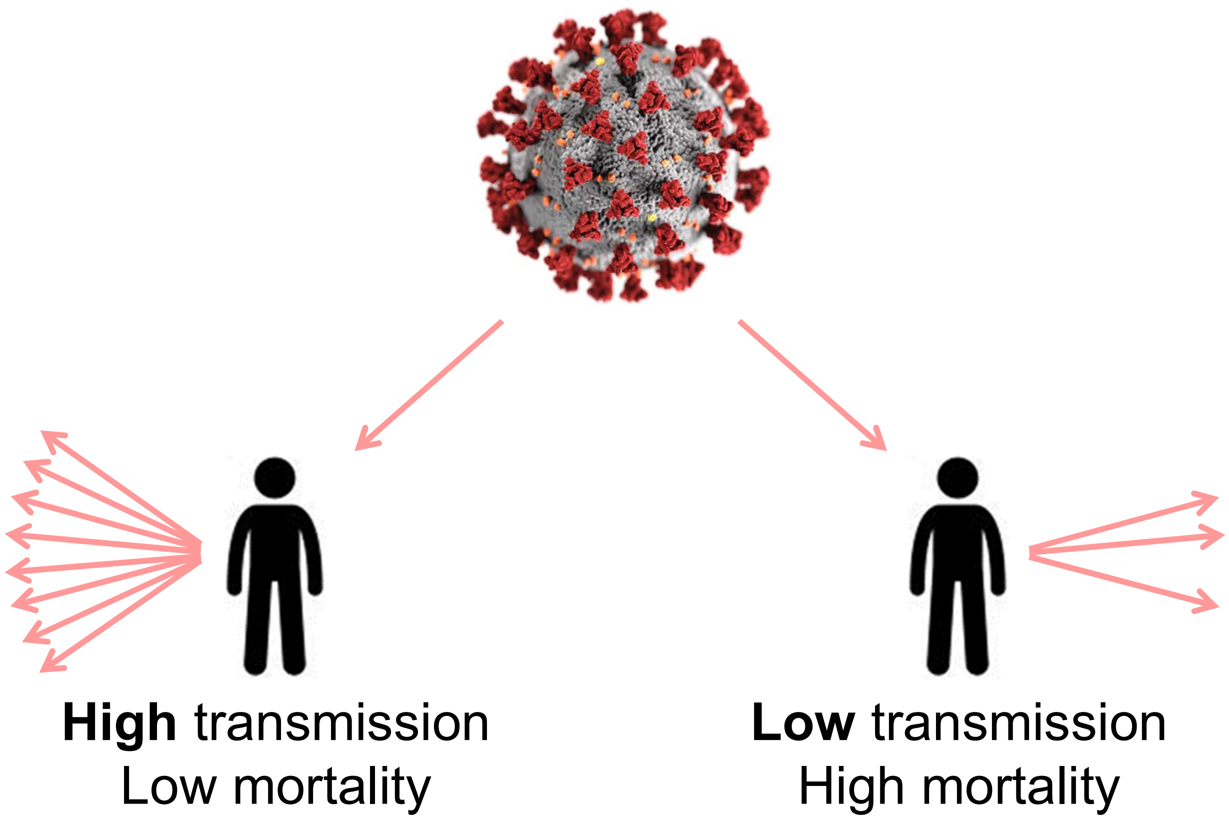
How to account for host heterogeneities in s_m?

Host heterogeneity

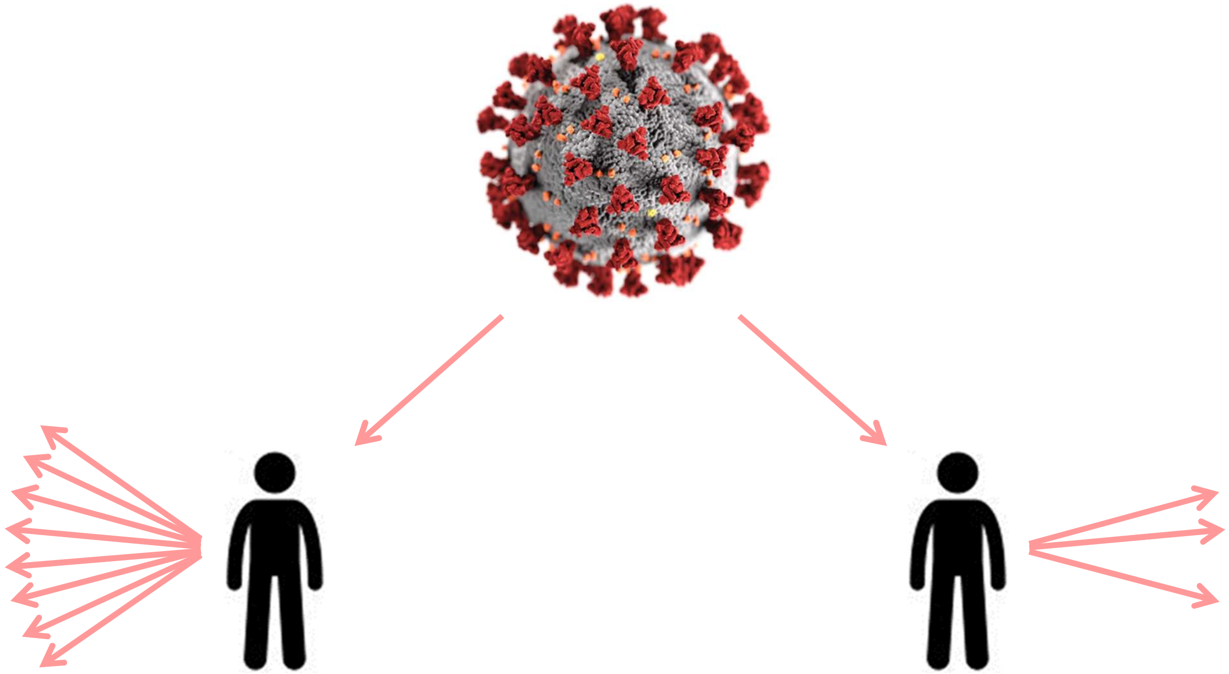


Host heterogeneity



Who should we vaccinate?

Host heterogeneity



High transmission
Low mortality

Low transmission
High mortality

Who should we vaccinate?

Aim #1: reduce mortality (epidemiology)

Aim #2: slow down adaptation (evolution)

Speed of adaptation

Consider a mutation of small effect: $\varepsilon = e_m - e_w$

The selection coefficient can be approximated by:

$$s_m = \varepsilon\, \mathbf{v} \frac{\mathrm{d}\boldsymbol{R}_m}{\mathrm{d}e_m} \mathbf{f}$$

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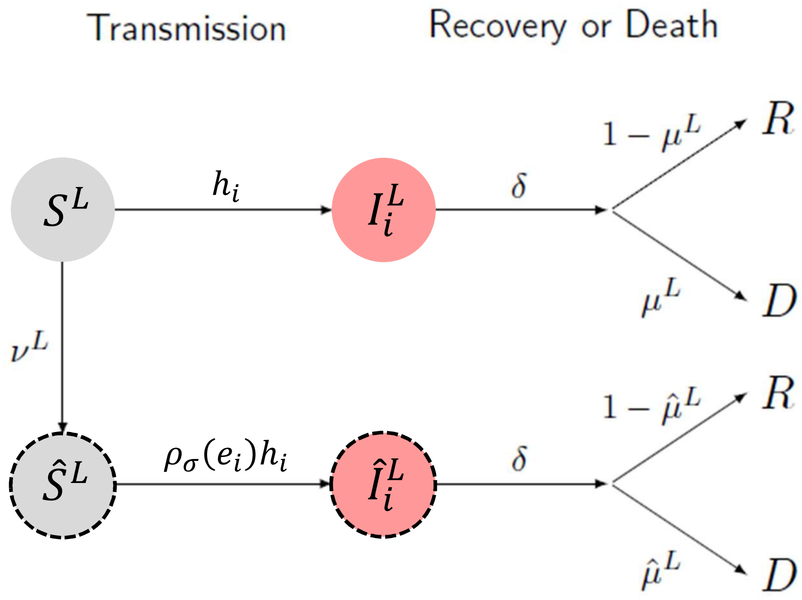
- $\mathbf{f}$ is a vector of class frequencies: host class « **quantity** » (fraction of the pathogen population in a given class)
- $\mathbf{v}$ is a vector of reproductive values: host class « **quality** » (contribution to the future of the pathogen population)

Another toy model

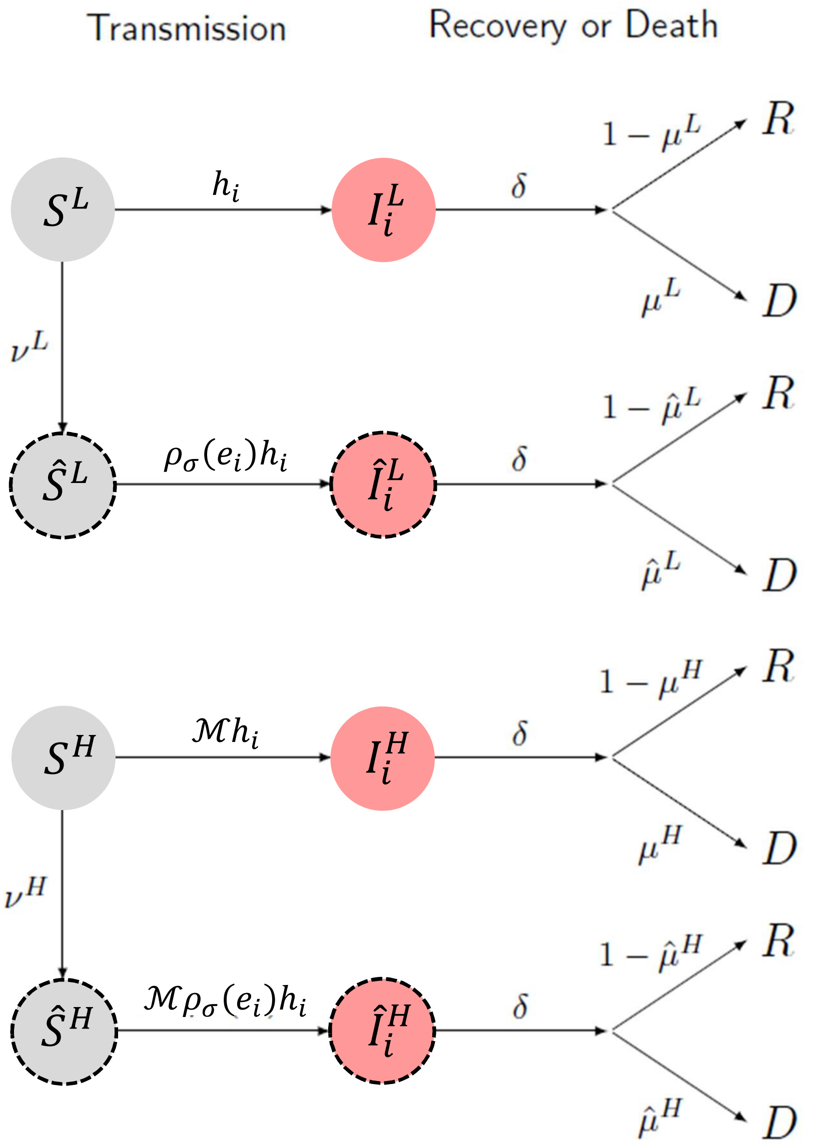
Low-transmission hosts (high risk)



Another toy model

Low-transmission hosts (high risk)

High-transmission hosts (low risk)



$\mathcal{M} > 1$
Contact rate

$\mu^L > \mu^H$ $\hat{\mu}^L > \hat{\mu}^H$
Mortality

Approximate speed of adaptation

$$s_m = \varepsilon\, \mathbf{v} \frac{\mathrm{d}\boldsymbol{R}_m}{\mathrm{d}e_m} \mathbf{f}$$

$$\begin{cases} \dfrac{v^H}{v^L} = \mathcal{M}, & \dfrac{\hat{v}^H}{v^L} = \mathcal{M}\rho_\tau \\ \dfrac{f^H}{f^L} = \mathcal{M}\dfrac{S^H}{S^L}, & \dfrac{\hat{f}^H}{f^L} = \mathcal{M}\rho_\sigma \dfrac{\hat{S}^H}{S^L} \end{cases}$$

Approximate speed of adaptation

$$s_m = \beta\left(1 - c(t)\right)\Delta E\left(\hat{S}^L + \mathcal{M}^2\hat{S}^H\right)$$

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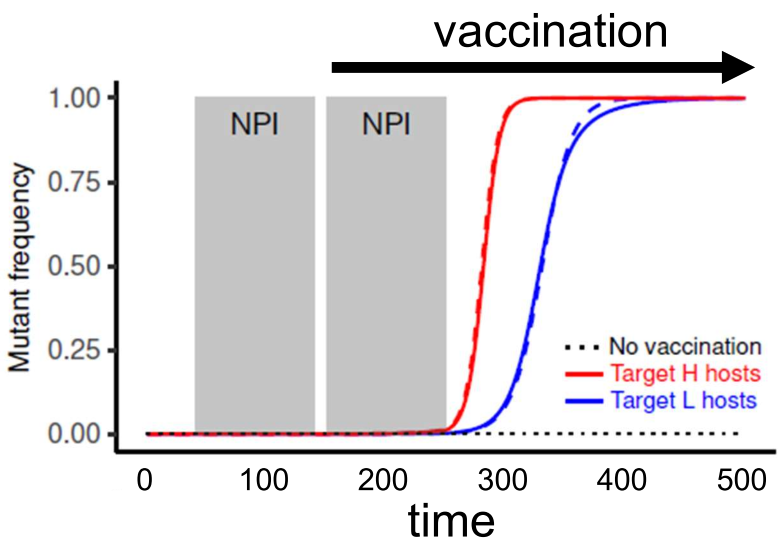
In addition, the evolutionary weight of hosts with more contacts is $\mathcal{M}^2$, so a 2-fold increase in contact number translates into a 4-fold increase in evolutionary quality (for the pathogen).

Targeted vaccination



Targeting hosts with more contacts speeds up the spread of vaccine-adapted variant

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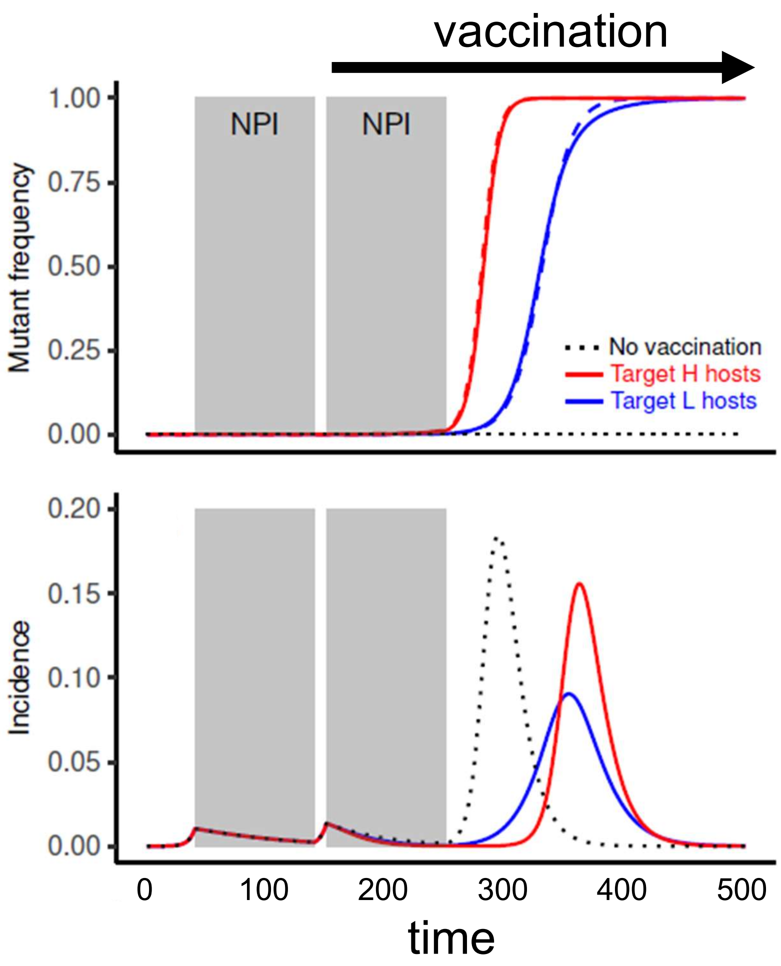

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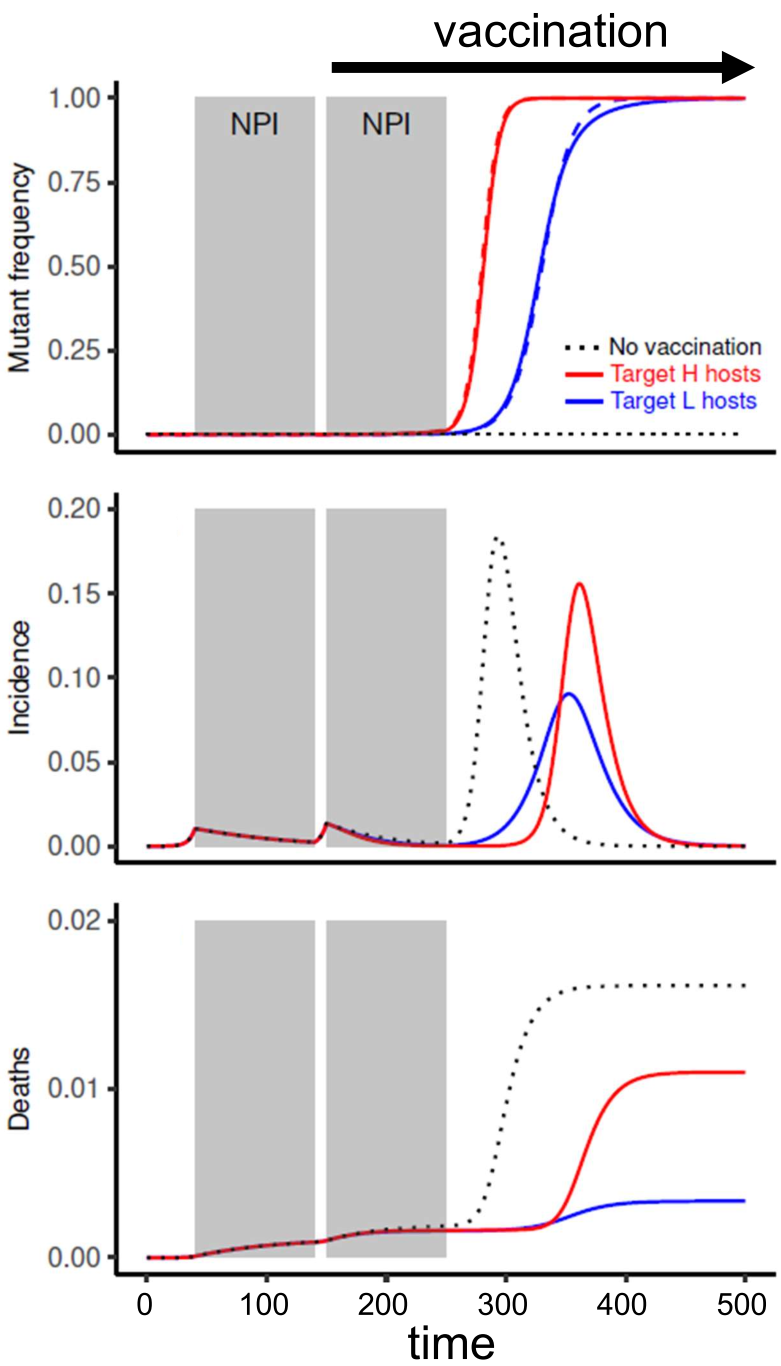

Targeting hosts with more contacts speeds up the spread of vaccine-adapted variant

Targeting hosts with more contacts delays the epidemic but yields higher epidemic peak

Targeting hosts with more contacts yields a higher cumulated number of death

Conclusions (2)

The analysis of deterministic models can be used to understand the transient (and long-term) **evolutionary impact of public health interventions** in heterogeneous host populations

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The analysis of deterministic models can be used to understand the transient (and long-term) **evolutionary impact of public health interventions** in heterogeneous host populations

Public health recommendations need to integrate not only **epidemiological** and **social** dimensions, but also their potential **evolutionary** consequences

Numerous **extensions towards further biological realism** are possible: natural immunity, age structure, spatial structure, number of vaccine doses, multilocus dynamics...

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