

Evolutionary stability of antigenically escaping viruses

Supplementary information

Appendix A: Derivation of the wave speed

1. Fitness speed relation

To derive the speed of the viral wave, we look for solutions of the form $n(x, t) = n(x - vt, t)$. To this end, we consider Eq. 5 in the frame of reference of the wave, $u = x - vt$, and we assume that it admits a stationary solution

$$D\partial_u^2 n(u) + v\partial_u n(u) + F(u)\Theta(n - n_c)n(u) = 0. \quad (\text{S.1})$$

The main assumption is that the behavior of the wave is driven only by the individuals at the front tip. If we define $u_T = x_T - vt$ the antigenic position at which $n(u_T) = n_c$, we encode this assumption by considering only the behavior around u_T . In particular, the fitness is approximated is a linear function around it: $F(u) \approx F(u_T) + \partial_u F(u_T)(u - u_T) \equiv F_T + s_T(u - u_T)$.

The next step is to solve equation S.1 on the right and on the left of u_T , and then to impose the continuity of the infected host profile and its derivative. For $u > u_T$ the equation reduces to

$$D\partial_u^2 n(u) + v\partial_u n(u) = 0. \quad (\text{S.2})$$

solving this equation and imposing $n(\infty) = 0$ and $n(u_T) = n_c$, one can find

$$n(u) = n_c \exp\left(-\frac{v}{D}(u - u_T)\right) \quad \text{for } u > u_T. \quad (\text{S.3})$$

The behavior of the wave on the left of the tip can be obtained by solving

$$D\partial_u^2 n(u) + v\partial_u n(u) + (F_T + s_T(u - u_T))n(u) = 0. \quad (\text{S.4})$$

We consider the solution as $n(u) = \exp(-vu/(2D))\psi(u)$. By plugging it into Eq. S.4, the equation to solve becomes

$$\frac{D}{s_T}\partial_u^2 \psi(u) + \left(\frac{F_T}{s_T} - u_T - \frac{v^2}{4Ds_T} + u\right)\psi(u) \equiv c_1\partial_u^2 \psi(u) + (u - c_2)\psi(u) = 0, \quad (\text{S.5})$$

where the coefficients $c_1 = D/s_T$ and $c_2 = u_T + v^2/(4Ds_T) - F_T/s_T$ are introduced for a shorter notation. One can then realize that the equation can be rewritten as an Airy equation with a simple change of variable $y = c_2 - u$. The solution can be then expressed as a linear combination of Airy functions:

$$\psi(y) = AAi\left(yc_1^{-1/3}\right) + BBi\left(yc_1^{-1/3}\right). \quad (\text{S.6})$$

However, by knowing that the function decays to zero for $u \rightarrow \infty$, the coefficient B can be set to zero. This leads to the following solution:

$$n(u) = A \exp\left(-\frac{v}{2D}u\right) Ai\left((c_2 - u)c_1^{-1/3}\right) \quad \text{for } u < u_T. \quad (\text{S.7})$$

Now we have to impose continuity and equality of the first derivative between the Eq. S.3 and Eq. S.7 at the intersection point u_T . After some algebra, the two conditions lead to the following expression:

$$\frac{Ai'\left((c_2 - u_T)c_1^{-1/3}\right)}{Ai\left((c_2 - u_T)c_1^{-1/3}\right)} = \frac{v}{2D}c_1^{1/3} = \frac{v}{2(D^2s_T)^{1/3}}. \quad (\text{S.8})$$

This dimensionless ratio diverges in the FKPP regime as the slope of the fitness profile vanishes, but could reach more moderate values in the linear fitness regime. In a first approximation we assume that it is large enough for the Airy

function at the denominator on the left-hand-side to be close to its first zero $\xi_0 \approx -2.3381$. We can then expand the function around ξ_0 :

$$\frac{\text{Ai}'(\xi_0 + \epsilon)}{\text{Ai}(\xi_0 + \epsilon)} \approx \frac{\text{Ai}'(\xi_0 + \epsilon)}{\text{Ai}(\xi_0) + \epsilon \text{Ai}'(\xi_0)} \approx \frac{1}{\epsilon} = \frac{v}{2D} c_1^{1/3}. \quad (\text{S.9})$$

The value of ϵ can be found as $\epsilon + \xi_0 = (c_2 - u_T)c_1^{-1/3}$ and, after some algebra, one can obtain

$$c_2 - u_T - \xi_0 c_1^{1/3} = \frac{2D}{v}. \quad (\text{S.10})$$

Finally, by expliciting the coefficients c_1 and c_2 , a relation between the speed of the wave, the fitness at the tip and its derivative can be obtained:

$$\frac{v^2}{4D} = F_T + \xi_0 (Ds_T^2)^{1/3} + \frac{2Ds_T}{v}. \quad (\text{S.11})$$

The third term on the right handside isn't a priori negligible in the linear-fitness regime for which we show in the next section that $v \sim (D^2 s_T)^{1/3}$. However, we tested this fitness speed relation for different values of the cutoff n_c in Fig. S1A and observed that neglecting this term provides a very good approximate relation:

$$\frac{v^2}{4D} \simeq F_T + \xi_0 (Ds_T^2)^{1/3}. \quad (\text{S.12})$$

A more thorough justification requires to calculate the exact speed in the linear-fitness regime to estimate the relative contribution of each term and is provided in the next section. Overall, Fig. S1A shows that Eq. S.12 is satisfied independently of the cutoff as well as for the stochastic model described in Sec. 4B.

We want to stress that the expression Eq. S.12 still depends on one unknown quantity: the position of the tip, u_T . As discussed also in the main text, this makes the expression only implicit and does not provide a direct prediction of the wave speed from the model parameters. However, since we do not specify the shape of $F(u)$, the validity of the equation goes beyond the presented model and can be a valuable result for other frameworks that study traveling wave dynamics, connecting the wave speed with interpretable quantities, i.e. F_T and s_T .

In general, to close this expression, one first step is to impose the normalization of the population profile

$$\int_{-\infty}^{\infty} du n(u) = N. \quad (\text{S.13})$$

This integral needs the value of the function $n(u)$ in the whole domain, which, in our case, is unknown and does not allow us to close the expression for the wave speed. However, this can be done in the extreme regimes (see also the main text): in the FKPP regime Eq. S.12 loses its dependence on u_T and does not require Eq. S.13, while, in the linear-fitness regime, the integral of Eq. S.13 can be solved. In this latter case N is still unknown, but the fitness depends on it and the chain of conditions can be closed by imposing that the average fitness is zero (see next section for the derivation).

However, in general, the value of the speed does depend on the cutoff value, as shown by Fig. S1B where the speed is plotted as a function of the cross reactivity. This dependency is weak, as proven by the fact that varying the cutoff for several order of magnitude leads to quite similar speeds. In the two limit cases, this dependency can be analytically understood. In the FKPP regime, there is no dependency on n_c , while, in the linear-fitness case, the cutoff appears as a factor dividing the population size, Eq. S.25. The stochastic simulations show a speed which is compatible with an effective value of the deterministic cutoff.

2. Wave speed in the linear-fitness regime

Here we consider the system in the linear-fitness regime, where the wave feels an approximately linear fitness profile. This regime is obtained for large values of r_0 or, more precisely, for a small adimensional coefficient $k \ll 10^{-3}$. In such a condition we assume that the fitness is linear and zero at the center of the wave: $F(u) = su$ (so that $u = 0$ is the mean viral position in the co-moving frame). The explicit expression of the fitness slope s will be found later. This allows us to write down the approximation of Eq. 5, which we consider at stationarity in the frame of reference of the moving wave

$$D\partial_u^2 n(u) + v\partial_u n(u) + su\Theta(n - n_c)n(u) = 0. \quad (\text{S.14})$$

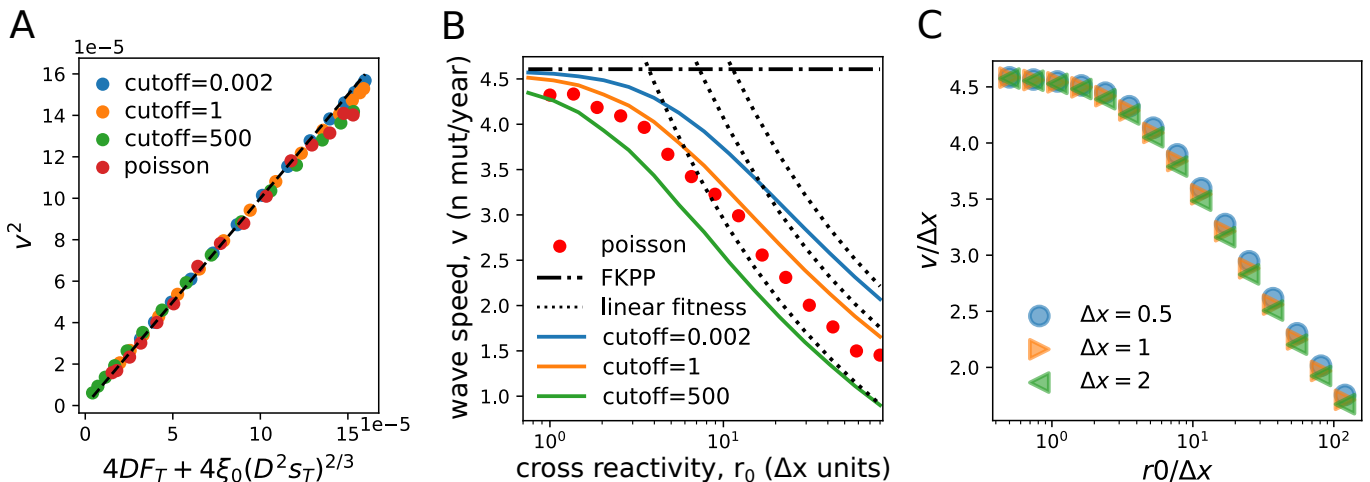


FIG. S1: (A): Testing the fitness speed relation, Eq. S.12 for different deterministic simulations of Eq. 5 having different cutoffs n_c . The relation is tested also for a stochastic simulation (red dots) whose details are described in Sec. 3B. The threshold below which the simulation is fully stochastic is $n_{stoch} = 10^5$. In this latter setting, speed, fitness and selection at the tip fluctuates, and to build the figure are averaged over a stationary trajectory. The other parameters of the simulations are: $\mu_x = 4 \cdot 10^{-3} \text{ day}^{-1}$, $\beta = 0.12 \text{ day}^{-1}$, $\gamma + \alpha = 0.1 \text{ day}^{-1}$, $M = 5$, $N_h = 10^{10}$. The panel (B) shows the wave speed as a function of r_0 . The stochastic setting behaves like a deterministic one with a proper cutoff, in this case around $n_c \sim 10$. Panel (C) tests that the value of the speed is approximately invariant for different values of Δx if the antigenic space is taken in units of Δx . This confirms that Eq. 5 is approximately invariant by change of spatial units of measures, and allows us to fix them by choosing $\Delta x = 1$.

As for the previous derivation of the fitness-speed relation, we want to solve the equations on the right and on the left of the tip of the wave u_T , where $n(u_T) = n_c$, and then impose the continuity of the function and its derivative on the junction point. On the right side, $u > u_T$ the solution is exactly equal to Eq. S.3. For $u < u_T$, the structure of the equation is the same as the previous section, but with different coefficients. The solution is then the Airy function S.7 with $c_1 = D/s$ and $c_2 = v^2/(4Ds)$:

$$n(u) = A \exp\left(-\frac{v}{2D}u\right) \text{Ai}\left((c_2 - u)c_1^{-1/3}\right) \quad \text{for } u < u_T. \quad (\text{S.15})$$

Importantly, this population profile is valid in the whole antigenic space, while before we were considering only the expression close to the tip. As before, we can impose the the continuity of the function and its derivative in u_T and get

$$c_2 - u_T - \xi_0 c_1^{1/3} = \frac{v^2}{4Ds} - u_T - \xi_0 \left(\frac{D}{s}\right)^{1/3} = \frac{2D}{v}. \quad (\text{S.16})$$

This provides a first equation connecting the speed with the model parameters, however we still have the unknown u_T . To find a second condition for fixing its value, we consider the normalization of the host population

$$\int_{-\infty}^{u_T} du n(u) \approx N, \quad (\text{S.17})$$

where we consider the contribution to N given by the right side of the cutoff negligible. The expression of the number of hosts for $u < u_T$ is known in this regime, Eq. S.15 (with the previously specified coefficients c_1 and c_2). This leads to the following integral

$$\frac{n_c}{\text{Ai}\left((c_2 - u_T)c_1^{-1/3}\right)} \int_{-\infty}^{u_T} du \exp\left(-\frac{v}{2D}(u - u_T)\right) \text{Ai}\left((c_2 - u)c_1^{-1/3}\right) \approx N, \quad (\text{S.18})$$

where the coefficient A in Eq. S.15 has been fixed with $n(u_T) = n_c$.

By making a change of variable in the integral $\xi = \xi_0 + (u_T - u)/c_1^{1/3}$ and using expression S.16 one obtains

$$\int_{\xi_0}^{\infty} d\xi c_1^{1/3} \exp\left(\frac{vc_1^{1/3}}{2D}\xi\right) \text{Ai}\left(\xi + \frac{2D}{vc_1^{1/3}}\right) = \frac{N}{n_c} \exp\left(\frac{vc_1^{1/3}}{2D}\xi_0\right) \text{Ai}\left(\frac{2D}{vc_1^{1/3}} + \xi_0\right), \quad (\text{S.19})$$

$$\int_{\xi_0}^{\infty} d\xi \exp\left(\frac{\xi}{\eta}\right) \text{Ai}(\eta + \xi) = \frac{N}{n_c c_1^{1/3}} \exp\left(\frac{\xi_0}{\eta}\right) \text{Ai}(\eta + \xi_0), \quad (\text{S.20})$$

where in the second equation we just substituted $\eta = 2Dc_1^{-1/3}/v$ which is a small quantity since the diffusion coefficient is much smaller than the speed. The next approximation is to extend the limit of integration from the first zero of the Airy function to $-\infty$, by knowing that in this domain the function is oscillating around 0 and therefore is expected to give a negligible contribution. This allows us to use the following equality involving the Airy function [1]

$$\int_{-\infty}^{\infty} e^{pt} \text{Ai}(t) dt = \exp(p^3/3) \quad (\text{S.21})$$

which leads to the following expression if we neglect η in the Airy function argument

$$\exp(\eta^{-3}/3) = \frac{Nc_1^{-1/3}}{n_c} \exp\left(\frac{\xi_0}{\eta}\right) \text{Ai}(\eta + \xi_0). \quad (\text{S.22})$$

The next steps is to take the logarithm of this expression and expand the Airy function around its zero

$$\frac{\eta^{-3}}{3} = \log\left(\frac{Nc_1^{-1/3}}{n_c}\right) + \xi_0\eta^{-1} + \log(\eta \text{Ai}'(\xi_0)). \quad (\text{S.23})$$

We now consider the leading term η^{-3} and the logarithmic term containing the population size. This gives us the following estimate of the speed in the linear fitness regime (shown in the main text)

$$v \approx 2 \left(3sD^2 \ln\left(\frac{N}{n_c} \frac{s^{1/3}}{D^{1/3}}\right) \right)^{1/3}. \quad (\text{S.24})$$

At this stage we can see that for a large enough population size $N \gg n_c(D/s)^{1/3}$ the third term on the right-hand-side of Eq. S.11 is negligible with respect to the second term $\xi_0(Ds^2)^{1/3}$ and Eq. S.12 is a good approximation to the fitness speed relation. This condition is verified for the range of parameters considered in this paper as shown in Fig. S1A.

To get a more precise estimate of the speed, one can consider also the order η^{-1} , leading to

$$v = 2 (sD^2)^{1/3} \left[\left(3 \ln\left(\frac{N}{n_c} \frac{s^{1/3}}{D^{1/3}}\right) \right)^{1/3} + \xi_0 \left(3 \ln\left(\frac{N}{n_c} \frac{s^{1/3}}{D^{1/3}}\right) \right)^{-1/3} \right]. \quad (\text{S.25})$$

In fact, these expressions still depends on N and s which we derive in the following. We start by integrating the equation for the density of immune receptors, Eq. 2, with a stationary number of infected hosts $N(t) = N$ and defining $\tau = MN_h/N$:

$$h(x, t) = \frac{1}{N} \int_{-\infty}^t \frac{dt'}{\tau} \exp\left(-\frac{t-t'}{\tau}\right) n(x, t'). \quad (\text{S.26})$$

Then one makes the approximation that the wave has a very small width compared with the spatial scale $v\tau$, which characterizes the decay of the immune density. This allows us to consider $n(x)$ as a delta function at $u = 0$: $n(u) = \delta(u)/N$, where $u = x - vt$, leading to the following expression

$$h(u) = \frac{1}{v\tau} \exp\left(\frac{u}{v\tau}\right) \Theta(-u), \quad (\text{S.27})$$

where $\Theta(u)$ is the Heaviside function. With such an expression, the coverage, Eq. 3, can be computed explicitly, leading to (for $u > 0$)

$$c(u) = \frac{r_0 e^{-u/r_0}}{v\tau + r_0}. \quad (\text{S.28})$$

We can then compute the fitness felt by the wave

$$F(u) = \beta \left(1 - \frac{r_0 e^{-u/r_0}}{v\tau + r_0} \right)^M - \alpha - \gamma. \quad (\text{S.29})$$

In this regime the fitness is assumed to be linear, $F(u) \approx F(0) + \partial_u F(0)u$, which is justified if the width of the wave is much smaller than r_0 . By having assumed the stationary condition, we expect the fitness of the bulk of the wave to be zero, i.e. $F(0) = 0$. This leads to the following condition that connects the wave speed with the population size N and, together with Eq. S.25, closes the system having v and N as unknown

$$v\tau = \frac{vMN_h}{N} = r_0 \left(R_0^{1/M} - 1 \right)^{-1}. \quad (\text{S.30})$$

Finally, the explicit value of the fitness slope s can be obtained from $s = \partial_u F(0)$

$$s = \frac{\beta M}{r_0 + v\tau} \left(\frac{v\tau}{r_0 + v\tau} \right)^{M-1} = \frac{\alpha + \gamma}{r_0} M \left(R_0^{1/M} - 1 \right). \quad (\text{S.31})$$

Appendix B: Derivation of the mutational load

To obtain the effect of deleterious mutations in our epidemiological context, we follow the approach proposed in [2], which, in turn, refers to the classical results of mutation selection balance of population genetics [3, 4]. We consider a population in which $n_k(t)$ is the number of individuals carrying k deleterious mutations. Mutations are assumed to occur during the bottleneck of a transmission event. This is because harmful mutations arising within the very few individuals that are transmitted are weakly subject to purifying selection, while, if they occur during the course of an in-host infection, selection will tend to remove them. The number of mutations that can occur per genome at transmission are assumed to follow a Poisson distribution with rate U_d . Moreover, we assume that each single deleterious mutation affects the transmissibility of the population by a multiplicative factor $(1 - s_d)$, leading to the following transmissibility for the population having k mutations:

$$\beta_k = \beta_0 (1 - s_d)^k. \quad (\text{S.1})$$

Putting all the assumptions together, one obtains the following temporal evolution for the number of infected hosts:

$$\partial_t n_k = S \sum_{j=0}^k \beta_j n_j \text{Pois}(k-j|U_d) - \gamma n_k = S \beta_0 e^{-U_d} \sum_{j=0}^k (1 - s_d)^j n_j \frac{U_d^{k-j}}{(k-j)!} - \gamma n_k \quad (\text{S.2})$$

where, for simplicity, the virulence α and the recovery rate γ are condensed together in a single parameter.

At equilibrium, one can impose the stationarity of the equation above and find the number of infected hosts

$$n_k^* = N \frac{e^{-U_d/s_d}}{k!} \left(\frac{U_d}{s_d} \right)^k. \quad (\text{S.3})$$

This expression can be verified by substituting it in Eq. S.2 and using the relation $\beta_0 S = e^{U_d} \gamma$ that can be obtained from $\partial_t n_0 = 0$.

As a final step, we can compute the average transmission rate that such a population has

$$\langle \beta \rangle = \sum_k \beta_k \frac{n_k^*}{N} = \beta_0 e^{-U_d/s_d} \sum_k \frac{(1 - s_d)^k}{k!} \left(\frac{U_d}{s_d} \right)^k = \beta_0 e^{-U_d} \approx \beta_0 (1 - U_d). \quad (\text{S.4})$$

Using this expression, one can then obtain an effective growth rate for the population having a given deleterious mutation rate

$$F(x) = \langle \beta \rangle S(x) - \gamma = \beta_0 S(x) e^{-U_d} - \gamma \approx \beta_0 S(x) (1 - U_d) - \gamma. \quad (\text{S.5})$$

In the main text, to discuss about evolutionary stability of the beneficial mutation rate or selection coefficient, the deleterious mutation coefficient is expressed as the product of a constant and the beneficial mutation rate

$$U_d = a \mu_x = \lambda D \quad (\text{S.6})$$

where $a = \Delta x^2 \lambda / 2$ can be interpreted as a ratio between deleterious and beneficial mutations which cannot be changed. What can be changed by viruses is the global mutation rate, which would increase the antigenic mutation rate μ_x but, at the same time, would increase the deleterious rate through the relation above, leading to the mutational trade-off.

Appendix C: Evolutionary stability analysis

1. General stability condition

To derive the condition for the invasion of a mutant, we start by considering a resident population at a stationary-wave state. We also consider a generic mutant that can have, in general, a new set of parameters labeled with a prime, e.g. β' , D' , \dots , which are assumed to be close to the parameters of the resident. In the frame of reference of the resident wave moving at speed v , the equation for the mutant dynamics reads

$$\begin{aligned}\partial_t n'(u, t) &= D' \partial_u^2 n'(u, t) + v \partial_u n'(u, t) + F'(u) \Theta(n + n' > n_c) n'(u) \\ F'(u) &= \beta' S(u) - \gamma' - \alpha' \approx F'_T + s'_T (u - u_T).\end{aligned}\quad (\text{S.1})$$

Note that the quantities not labeled with a prime are the wave speed v and the susceptibility of the resident population $S(u)$. We assume that the mutant is rare enough that it does not generate any significant immune response, and, therefore, it does not contribute to the susceptibility. Moreover, the resident population number appears within the theta function, which imposes the cutoff when the total number of individuals, $n + n'$, is smaller than the threshold n_c . This assumption allows us to identify the tip of the wave at the same position both for the resident and the invading populations, greatly simplifying the calculations. Finally, as for the previous calculations, the fitness is linearized around the tip, implying that, also for this derivation, the success or failure of an invasion depends only on what happens at the tip.

We are going to look for solutions $n'(u, t) = e^{\rho t} \phi(u)$, i.e. a stationary profile that would grow or decay at rate ρ . Here we also make the approximation that success or failure in the invasion depends only on the sign of this rho. That is to say that we identify a successful mutant only by looking at its initial growth rate. By substituting this solution in the equation above with a linearized tip we can solve the equation on the right and on the left of the tip as performed in the previous paragraphs. For $u > u_T$ one has to solve

$$D' \partial_u^2 \phi(u) + v \partial_u \phi(u) - \rho \phi(u) = 0, \quad (\text{S.2})$$

which leads to the solution

$$\phi(u) = n_c \exp\left(-\frac{v}{2D'} \left(1 + \sqrt{1 + \frac{4D'}{v^2} \rho}\right) (u - u_T)\right) \approx n_c \exp\left(-\left(\frac{v}{D'} + \frac{\rho}{v}\right) (u - u_T)\right) \quad (\text{S.3})$$

On the left side of the tip, we can find an Airy equation like Eq. S.5 (but different coefficients c_1 and c_2)

$$\frac{D'}{s'_T} \partial_u^2 \phi(u) + \left(\frac{F'_T - \rho}{s'_T} - u_T - \frac{v^2}{4D' s'_T} + u\right) \phi(u) \equiv c_1 \partial_u^2 \phi(u) + (u - c_2) \phi(u) = 0. \quad (\text{S.4})$$

Therefore leading to the solution S.7. As before we impose the continuity of the function and the derivative at the intersection, leading to

$$\frac{\text{Ai}'(\xi_0 + \epsilon)}{\text{Ai}(\xi_0 + \epsilon)} = \left(\frac{v}{2D'} + \frac{\rho}{v}\right) c_1^{1/3} \approx \frac{v}{2D'} c_1^{1/3}. \quad (\text{S.5})$$

where ρ is considered to be small. We can then carry out all the procedure of the sections before of approximating the Airy function around its zero. This leads to

$$c_2 - u_T - \xi_0 c_1^{1/3} = \frac{\rho - F'_T}{s'_T} + \frac{v^2}{4D' s'_T} - \xi_0 \left(\frac{D'}{s'_T}\right)^{1/3} = 0, \quad (\text{S.6})$$

$$\rho = F'_T + \xi_0 \left(D' s'_T{}^2\right)^{1/3} - \frac{v^2}{4D'} = 0. \quad (\text{S.7})$$

If this last expression is larger than zero, we then expect a mutant that grows and invades the resident population, Eq. 10 of the main text. This condition has been tested in figure S2, where, given a mutation coefficient D' for the mutant, we looked for the value of transmissibility $\tilde{\beta}'$ such that the mutant invades for $\beta' > \tilde{\beta}'$ or does not for $\beta' < \tilde{\beta}'$. The equation above, i.e. $\rho(\tilde{\beta}', D') = 0$, provides a prediction for this value $\tilde{\beta}'$ as a function of D' . Despite the numerous approximations in the computation above, the prediction of this transition point is very accurate. More details on how the simulations are performed are in the caption of the figure.

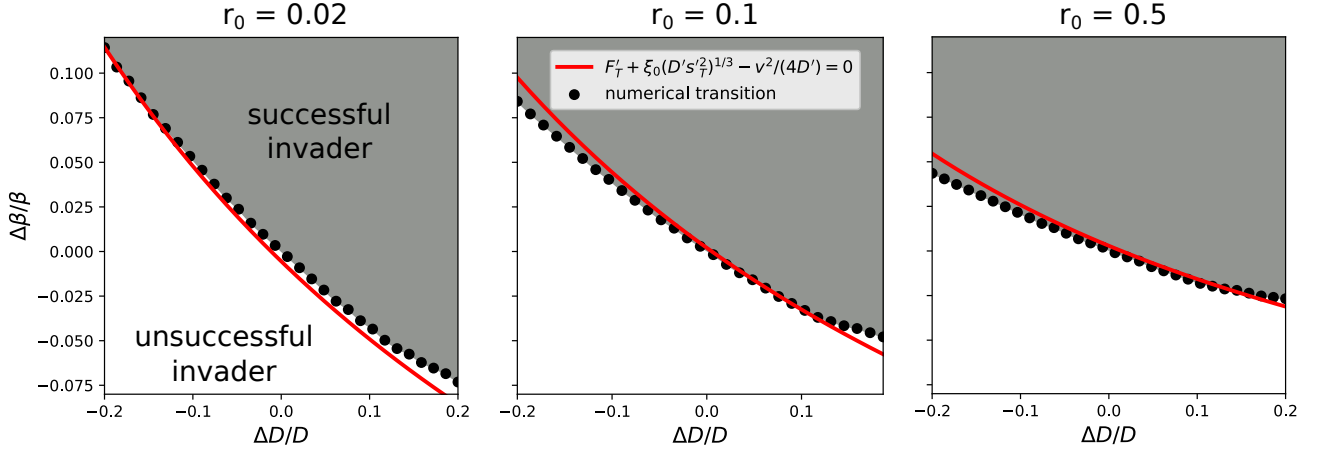


FIG. S2: Testing the invasion criteria S.7. A given resident population is first simulated in isolation until it reaches stationarity with parameters $D = 5 \cdot 10^{-6}$, $\beta = 2$, $\gamma + \alpha = 1$, $M = 5$, $N_h = 10^{12}$ and r_0 is indicated in the plot title. Then, a mutant with given $D' = D + \Delta D$ and $\beta' = \beta + \Delta\beta$ is introduced with $n'(x) = \epsilon n(x)$, $\epsilon = 0.05$ (all the other mutant parameters are the same of the resident). The system evolves until one of the two populations becomes $10/\epsilon$ times bigger than the other or after 6000 units of time. This is repeated for different values of β' using a bisection-like iteration until the point of transition, $\tilde{\beta}$, between a successful or unsuccessful invader is found. Each black point in the plot is $(\beta^* - \beta)/\beta$ for a given D' . The red line is the prediction of Eq. S.7 equal to zero.

The invasion condition S.7 simplifies considerably in the limits of small and large r_0 . For small r_0 , the fitness is saturated, so that $F'_T = F'_{\max} = \beta' - \alpha' - \gamma'$ and $\sigma'_T = 0$. Using $F'_{\max} = v^2/4D'$, the invasion condition becomes:

$$\frac{v'^2 - v^2}{4D'} > 0. \quad (\text{S.8})$$

The evolutionary stable solution is the one that maximizes the speed of the wave.

For large r_0 the fitness profile is approximately linear, so that $s'_T = s'$ and $F'_T = F(0)' + s'x_T$, $F_T = sx_T$. By plugging these equations into the invasion condition one has

$$F(0)' + s'x_T + \xi_0 (D's'^2)^{1/3} - \frac{v^2}{4D'} > 0. \quad (\text{S.9})$$

We can now use the speed-fitness relation, Eq. 7, and $F_T = sx_T$ to obtain

$$F(0)' + x_T \left(s' - \frac{D}{D'} s \right) + \xi_0 \left((D's'^2)^{1/3} - \frac{D}{D'} (Ds^2)^{1/3} \right) > 0. \quad (\text{S.10})$$

The selection terms in s and s' are subdominant, since $s \propto r_0^{-1}$. The dominant term is therefore the fitness of the mutant at the center of the wave,

$$F(0)' = \beta' S(0) - \alpha' - \gamma' = \frac{\beta'(\alpha + \gamma)}{\beta} - \alpha' - \gamma' > 0. \quad (\text{S.11})$$

Using the definition of the reproductive ratio $R_0 = \beta/(\alpha + \gamma)$, this yields the condition

$$R'_0 > R_0. \quad (\text{S.12})$$

To find a general criterion for the evolutionary stability of the viral population, we assume that the evolution acts on a generic parameter θ from which all the other parameters can depend on: $\beta(\theta)$, $\alpha(\theta)$, $\gamma(\theta)$, $D(\theta)$. As before, we label with a prime the parameter of a mutant θ' . We also indicate the fitness and its derivative at the tip as $F_T(\theta)$, $s_T(\theta)$ for the resident population and $F'_T(\theta', \theta) = \beta(\theta')S(\theta) - \alpha(\theta') - \gamma(\theta')$, $s'_T(\theta', \theta) = \beta(\theta')\partial_x S(\theta)$ for the mutant growing in the resident θ . The growth rate of a mutant can be then expressed as a function of θ and θ' : $\rho(\theta', \theta)$. The evolutionary stability is reached at a value θ^* such that the growth rate of a mutant having a slightly different value is no larger. As shown in the main text, this translates into the condition $\partial_{\theta'} \rho(\theta', \theta)|_{\theta'=\theta=\theta^*} = 0$, where the derivative acts only on the parameters labeled with a prime in equation S.7,

$$\left[\partial_{\theta'} F'_T(\theta', \theta) + \frac{2\xi_0}{3} \left(\frac{D(\theta')}{s'_T(\theta', \theta)} \right)^{1/3} \partial_{\theta'} s'_T(\theta', \theta) + \left(\frac{v(\theta)^2}{4D(\theta)^2} + \frac{\xi_0}{3} \left(\frac{s'_T(\theta', \theta)}{D(\theta')} \right)^{2/3} \right) \partial_{\theta'} D(\theta') \right] \Big|_{\theta'=\theta=\theta^*} = 0. \quad (\text{S.13})$$

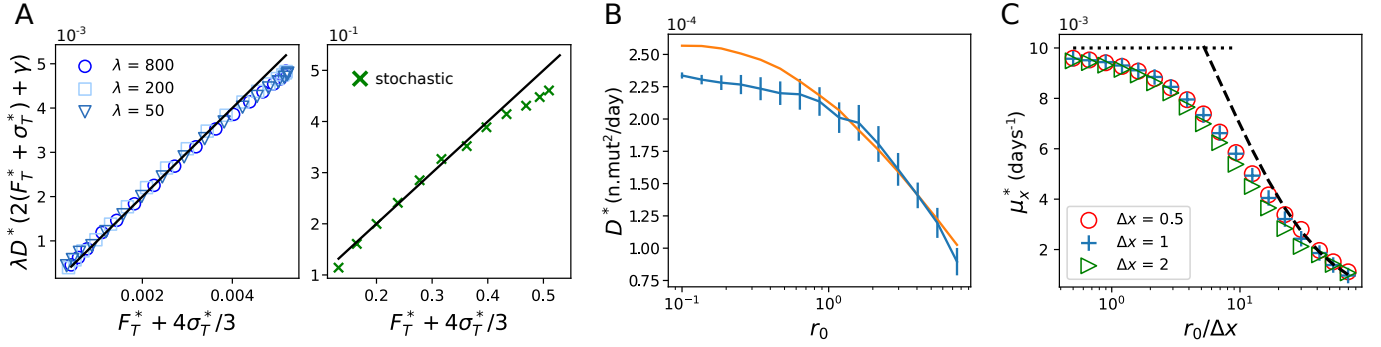


FIG. S3: Panel (A): test of the evolutionary stability equation Eq. S.17. The left panel shows the deterministic setting with cutoff with parameters $\beta_0 = 0.05 \text{ days}^{-1}$, $\gamma + \alpha = 0.04 \text{ days}^{-1}$, $M = 5$, $N_h = 10^{10}$. The right panel A tests the equation for the stochastic simulations as described in Sec. 4B with $n_{stoch} = 10^4$ and parameters $\lambda = 250 \text{ days/n.mutations}^2$, $\beta = 2 \text{ days}^{-1}$, $\gamma + \alpha = 1 \text{ days}^{-1}$, $M = 5$, $N_h = 10^{10}$. (B): same stochastic simulations of panel A-right but plotted as a function of r_0 . The blue line is the temporal average over D^* which fluctuates with a standard deviation of the error bar. The continuous line is the prediction of Eq. S.17. Panel (C) checks that the evolutionary stable antigenic mutation rate is independent of Δx after a proper rescaling of r_0 . This confirms that Eq. 5 is approximately invariant by spatial re-scaling. Parameters: $\beta_0 = 0.05 \text{ days}^{-1}$, $\gamma + \alpha = 0.04 \text{ days}^{-1}$, $a = 100 \text{ days}$, $M = 5$, $N_h = 10^{10}$.

We now want to express the equation only as a function of the fitness and the selection at the tip by using Eq. S.12 for $v(\theta)$. We will also use the fact that $D(\theta)|_{\theta=\theta^*} = D(\theta')|_{\theta'=\theta^*}$

$$\left[\partial_{\theta'} F_T'(\theta', \theta) + \frac{2\xi_0}{3} \left(\frac{D(\theta')}{s_T'(\theta', \theta)} \right)^{1/3} \partial_{\theta'} s_T'(\theta', \theta) + \left(F_T'(\theta', \theta) + \frac{4\xi_0}{3} \left(s_T'(\theta', \theta)^2 D(\theta') \right)^{1/3} \right) \frac{\partial_{\theta'} D(\theta')}{D(\theta')} \right] \Big|_{\theta'=\theta=\theta^*} = 0. \quad (\text{S.14})$$

This expression can be rewritten in a more compact form by introducing $\sigma_T'(\theta', \theta) = \xi_0 (D(\theta') s_T'(\theta', \theta)^2)^{1/3}$, which leads to

$$\left[\frac{\partial_{\theta'} F_T'(\theta', \theta) + \partial_{\theta'} \sigma_T'(\theta', \theta)}{F_T'(\theta', \theta) + \sigma_T'(\theta', \theta)} + \frac{\partial_{\theta'} D(\theta')}{D(\theta')} \right] \Big|_{\theta'=\theta=\theta^*} = 0. \quad (\text{S.15})$$

Recognizing logarithmic derivatives, this condition is equivalent to:

$$\partial_{\theta'} [(F_T'(\theta', \theta) + \sigma_T'(\theta', \theta)) D(\theta')] \Big|_{\theta'=\theta=\theta^*} = 0. \quad (\text{S.16})$$

2. Evolutionary stability of the mutation rate

The evolutionary stable antigenic diffusion coefficient D^* under mutational load trade-off, where the fitness is $F(u) = \beta_0 S(u)(1 - \lambda D) - \gamma - \alpha$, from Eq. S.5, can be obtained by identifying $\theta = D$ in Eq. S.15. Note that the choice $\Delta x = 1$ allows us to get the evolutionary stable antigenic mutation rate as $U_x^* = 2D^*$. After some algebra, one can get the following formula

$$F_T^*(1 - 2\lambda D^*) + \sigma_T^* \left(\frac{4}{3} - 2\lambda D^* \right) - \gamma \lambda D^* = 0, \quad (\text{S.17})$$

where for simplicity we put $\alpha = 0$ and we dropped the dependencies from θ^* , writing, for example, $F_T^* = F_T(\theta^*)$. This expression provides D^* as a function of the fitness value and slope at the tip and it is tested in Fig. 3 and S3, that prove its validity also in the stochastic setting.

It is interesting to study the limits of this expression in the FKPP and linear fitness regime. In the first, setting $\sigma_T = 0$ and $F_T = \beta_0(1 - \lambda D) - \gamma$, one can obtain

$$D^* = \frac{\beta_0 - \gamma}{2\beta_0\lambda}, \quad (\text{S.18})$$

under the condition that $1 - \lambda D = 1 - U_d \neq 0$, which is satisfied since the deleterious mutation rate is a small quantity.

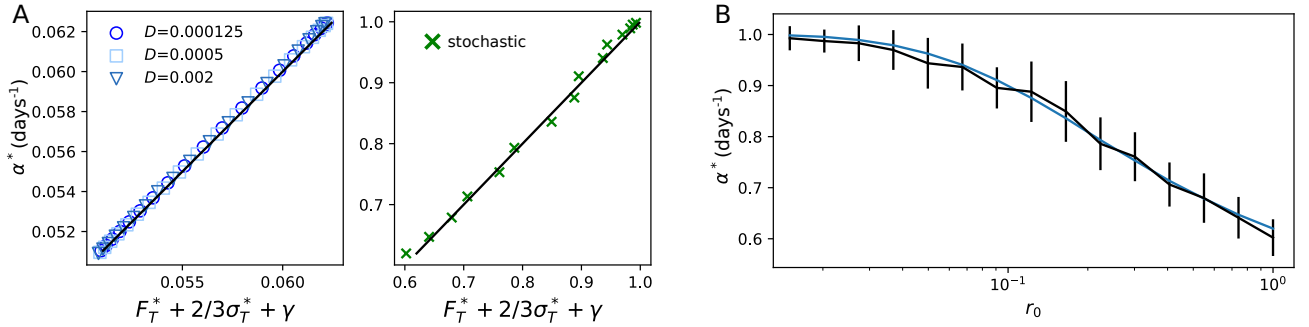


FIG. S4: Panel (A): test of Eq. S.21. On the left in the deterministic setting with cutoff, where the transmissibility reads $\beta(\alpha) = b\sqrt{\alpha}$ and the parameters are $b = 0.5 \text{ days}^{-1/2}$, $\gamma = 0.05 \text{ days}^{-1}$, $M = 5$, $N_h = 10^{10}$. On the right in the stochastic setting with parameters: $D = 10^{-5} \text{ n.mutations}^2/\text{days}$, $b = 2 \text{ days}^{-1/2}$, $\gamma = 0.5 \text{ days}^{-1}$, $M = 5$, $N_h = 10^{12}$. The simulations are performed as described in Sec. 3B and Sec. 3C with $n_{stoch} = 10^5$. The points are temporal averages of the quantity. Panel (B): same stochastic simulation shown as a function of r_0 . The error bars quantifies the standard deviations of the temporal fluctuations of α^* . The blue line is the prediction of Eq. S.21.

In the linear fitness regime, an explicit expression can be obtained only by considering $\lambda D \ll 1$, which leads to

$$F_T^* + \sigma_T^* \frac{4}{3} - \gamma \lambda D^* = \frac{v^{*2}}{4D^*} + \frac{\sigma_T^*}{3} - \gamma \lambda D^* = 0, \quad (\text{S.19})$$

where we used the fitness-speed relation. We can now express the speed as $v = A s^{1/3} D^{2/3}$ using Eq. S.25, where A contains logarithmic dependencies. This allows us to make also the approximation of considering A constant in D and get

$$D^* = \frac{M\gamma}{r_0} \left(\left(\frac{\beta_0}{\gamma} \right)^{1/M} - 1 \right) \left(\frac{1}{\gamma\lambda} \left(\frac{A^2}{4} - \frac{\xi_0}{3} \right) \right)^{3/2}, \quad (\text{S.20})$$

where we used Eq. S.31 for the selection coefficient.

3. Evolutionary stability of the virulence

In a similar way of what we did for the evolutionary stable mutation rate, we can obtain the equation for the evolutionary stable virulence, i.e. $\theta = \alpha$ in Eq. S.15,

$$\frac{\partial_\alpha \beta(\alpha^*)}{\beta(\alpha^*)} \left(F_T^* + \alpha^* + \gamma + \frac{2}{3} \sigma_T^* \right) = 1, \quad \alpha^* = F_T^* + \gamma + \frac{2}{3} \sigma_T^*, \quad (\text{S.21})$$

where the expression on the right assumes the transmissibility trade-off as $\beta(\alpha) = b\sqrt{\alpha}$. The validity of this expression is tested in Fig. 5 in a deterministic setting and Fig. S4 for a stochastic simulation.

We can also write explicitly the expression in the FKPP regime (in a general way and with our specific assumption on the trade-off):

$$\partial_\alpha \beta(\alpha^*) = 1, \quad \alpha^* = b^2/4. \quad (\text{S.22})$$

Finally, in the linear fitness regime one can simply use the fitness-speed relation to express F_T as a function of the speed and get

$$\frac{\partial_\alpha \beta(\alpha^*)}{\beta(\alpha^*)} \left(\frac{v^{*2}}{4D^*} + \alpha + \gamma - \frac{\sigma_T^*}{3} \right) = 1. \quad (\text{S.23})$$

One can then express v from Eq. S.25, use s_T^* given by Eq. S.31 and numerically solve for α^* (which is the procedure used to get the linear-fitness predictions in -Fig.5.)

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