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# Targeted vaccination and the speed of SARS-CoV-2 adaptation

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**The limited supply of vaccines against SARS-CoV-2 raises the question of targeted vaccination. Many countries have opted to vaccinate older and more sensitive hosts first to minimize the disease burden. But what are the evolutionary consequences of targeted vaccination? We clarify the consequences of different vaccination strategies through the analysis of the speed of viral adaptation measured as the rate of change of the frequency of a vaccine-adapted variant. We show that such a variant is expected to spread faster if vaccination targets individuals who are likely to be involved in a higher number of contacts. We also discuss the pros and cons of dose-sparing strategies. Because delaying the second dose increases the proportion of the population vaccinated with a single dose, this strategy can both speed up the spread of the vaccine-adapted variant and reduce the cumulative number of deaths. Hence, strategies that are most effective at slowing viral adaptation may not always be epidemiologically optimal. A careful assessment of both the epidemiological and evolutionary consequences of alternative vaccination strategies is required to determine which individuals should be vaccinated first.**

Evolutionary epidemiology | Vaccination | Adaptation | COVID-19 | SARS-CoV 2

The development of effective vaccines against SARS-CoV-2 raises hope regarding the possibility of eventually halting the ongoing pandemic. But vaccine supply shortages have sparked a debate about the optimal distribution of vaccination among different categories of individuals. Typically, infections with SARS-CoV-2 are far more deadly in older individuals than in younger ones (1). Prioritizing vaccination for older classes may thus provide a *direct* benefit in terms of mortality (2, 3). Yet, younger individuals are usually more active and, consequently, they may contribute more to the spread of the epidemic. Prioritizing vaccination for younger and more active individuals may thus provide an *indirect* benefit through a reduction of the epidemic size (4, 5). Earlier studies have compared alternative ways to deploy vaccination in heterogeneous host populations and showed that recommendation varies with the choice of the quantity one is trying to minimize (e.g., the cumulative number of deaths, the remaining life expectancy or the number of infections) (3, 6, 7). The recommendation also varies with the properties of the pathogen and the efficacy of the vaccine (3, 4, 8). For SARS-CoV-2, the increase in mortality with age is such that the direct benefit associated with vaccinating more vulnerable individuals tends to overwhelm the indirect benefits obtained from vaccinating more active individuals (2, 3, 9, 10). But some studies challenge this view and identified specific conditions where vaccinating younger and more active classes could be optimal (5, 7, 11, 12). A similar debate emerges over the possibility to delay the second vaccination dose to maximise the number of partially vaccinated individuals. A quantitative exploration of alternative vaccination strategies can help provide useful recommenda-

tions: a two-dose strategy is recommended when the level of protection obtained after the first dose is low and/or when vaccine supply is large (13–16).

Vaccine-driven evolution, however, could erode the benefit of vaccination and alter the above recommendations which are based solely on the analysis of epidemiological dynamics. Given that hosts differ both in their sensitivity to the disease and in their contribution to transmission, who should we vaccinate first if we want to minimise the spread of vaccine-adapted variants? The effect of alternative vaccination strategies on the speed of pathogen adaptation remains unclear. Previous studies of adaptation to vaccines focused on long-term evolutionary outcomes (17, 18). These analyses are not entirely relevant for the ongoing pandemic because what we want to understand first is the short-term consequence of different vaccination strategies (19). A few studies have discussed the possibility of SARS-CoV-2 adaptation following different targeted vaccination strategies but did not explicitly account for evolutionary dynamics (12, 20). A recent simulation study explored the effect of a combination of vaccination and social distancing strategies on the probability of vaccine-driven adaptation (21). This model, however, did not study the impact of targeted vaccination strategies on the speed of adaptation.

Here, we develop a theoretical framework based on the analysis of the deterministic dynamics of multiple variants after they successfully managed to reach a density at which they are no longer affected by the action of demographic stochasticity. We study the impact of different vaccination strategies on the rate of change of the frequency of a novel variant, which allows us to quantify the speed of virus adaptation to vaccines. Numerical simulations tailored to the epidemiology of

## Significance Statement

The ongoing pandemic of SARS-CoV-2 raises an important question: who should we vaccinate first? Answering this question requires an analysis of both the short-term (epidemiological) and the long-term (evolutionary) consequences of targeted vaccination strategies. We analyse the speed of pathogen adaptation and the cumulative number of deaths in heterogeneous host populations to shed light on the effects of alternative vaccination strategies. This analysis shows that minimizing the speed of pathogen adaptation does not always minimize the number of deaths. This evaluation of both the epidemiological and evolutionary consequences of public-health policies provides a practical tool to identify the best vaccination strategy.

The authors have no competing interests.

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62 SARS-CoV-2 confirm the validity of our approximation of the  
63 strength of selection for vaccine-adapted variants.

## 64 Results

65 We are interested in tracking the frequency  $p_m$  of hosts infected  
66 by the vaccine-adapted variant among all the infected hosts. It  
67 is possible to show that under a broad range of conditions one  
68 can approximate the dynamics of the vaccine-adapted variant  
69 frequency as:

$$70 \quad \dot{p}_m \approx p_m(1 - p_m)\mathcal{S}(t) \quad [1]$$

71 where  $\mathcal{S}(t)$  is the selection coefficient on the vaccine-escape  
72 mutation. This selection coefficient measures the rate of change  
73 of the logit of the frequency of the vaccine-adapted variant  
74 (i.e.,  $\ln(p_m/(1 - p_m))$ ) and provides a relevant measure for the  
75 speed at which the viral population is adapting (see Methods).

76 Targeted vaccination strategies aim to preferentially vacci-  
77 nate hosts according to specific epidemiological characteristics.  
78 For instance, we could target hosts that have more contacts,  
79 or are more at risk of a severe disease. In our model, we  
80 therefore introduce some heterogeneity among hosts. As a  
81 result, from the point of view of the parasite, the *quality* of  
82 the host may differ among infected hosts, and this variation  
83 is likely to affect the dynamics of vaccine-adapted variants.  
84 To quantify host quality, we use the concept of reproductive  
85 value, a key concept in demography and evolutionary biol-  
86 ogy (22–24). Reproductive value measures how much a virus  
87 infecting a given class of hosts will contribute to the future  
88 of the viral population. Our general mathematical analysis  
89 allows us to take the difference in host quality into account  
90 when calculating the selection coefficient  $\mathcal{S}(t)$  (see Methods).

91 We use this approach to analyse the speed of adaptation  
92 during the ongoing pandemic of SARS-CoV-2 under different  
93 scenarios. We use an epidemiological model tailored to the  
94 biology of SARS-CoV-2 (see Methods). However, it is impor-  
95 tant to keep in mind that, due to simplifying assumptions  
96 and uncertainty about parameter values, our results cannot  
97 be translated directly into public-health recommendations  
98 without further investigations (see Discussion). Nonetheless,  
99 our theoretical framework gives clear foundations for future  
100 applied work, and captures some of the most salient features  
101 of the COVID-19 pandemic. In particular, we introduce a  
102 time-varying parameter  $c(t)$  which measures the intensity of  
103 Non-Pharmaceutical Interventions (NPI). We assume that the  
104 epidemic is initially controlled by NPI which yields succes-  
105 sive epidemic waves before the deployment of vaccination at  
106  $t = 150$  days. We use this model to explore the effect of two  
107 different forms of heterogeneity on the speed of SARS-CoV-2  
108 adaptation.

109 **Heterogeneity in contact numbers and vulnerability:** In the first  
110 scenario we assume that hosts differ in their ability to mix and  
111 thus to transmit the disease. More specifically, following the  
112 model used by (12), we assume that some hosts ( $L$ ) have a  
113 low number of social interactions, while other hosts ( $H$ ) have  
114 a higher number of contacts. These two types of hosts can  
115 be thought as corresponding to the older and younger halves  
116 of the population. The increased rate of social interactions  
117 among  $H$  hosts is captured by a parameter  $\mathcal{M} \geq 1$ . Susceptible  
118 hosts are initially naive ( $S^L$  and  $S^H$ ) but they can become  
119 vaccinated ( $\hat{S}^L$  and  $\hat{S}^H$ ) at rates  $\nu^L$  and  $\nu^H$ , respectively.  
120 When vaccinated, hosts have a lower probability to become

121 infected ( $r_\sigma$  measures the efficacy at blocking infection) and if  
122 they become infected they have a lower probability to transmit  
123 the virus ( $r_\tau$  measures the efficacy at blocking transmission)  
124 and to die from the infection ( $r_\mu$  measures the efficacy at  
125 reducing mortality). Viral adaptation, however, can erode  
126 these benefits. We consider different viral strains characterised  
127 by an escape trait  $e$  which takes values between 0 (no escape)  
128 and 1 (full escape). The capacity of a variant to reduce the  
129 effect of the vaccine on transmissibility (resp. infectivity) is  
130 captured by a function  $E_\tau(e)$  (resp.  $E_\sigma(e)$ ), which allows us to  
131 quantify the overall ability of the virus to escape the protective  
132 effects of the vaccine as  $E(e) = E_\tau(e)E_\sigma(e)$ . Note that the  
133 capacity of a variant to reduce mortality does not affect the  
134 strength of selection in our model (i.e., the duration of infection  
135 is affected neither by the variant nor by the vaccine).

136 In the Methods, we derive a simple approximation for the  
137 strength of selection acting on the vaccine-adapted variant:

$$S(t) = (1 - c(t))\beta \Delta E (\hat{S}^L + \mathcal{M}^2 \hat{S}^H) \quad [2]$$

138 where  $\Delta E$  refers to the change in vaccine escape ability caused  
139 by the mutation. This tells us that the intensity of selection  
140 depends on (i) the ability of the virus mutant to escape the  
141 protective effects of vaccine, (ii) the densities of uninfected  
142 hosts (both  $L$  and  $H$ ) who have been vaccinated and (iii) the  
143 relative number of contacts of each class of hosts. Note that  
144 the epidemiological impact of a higher contact rate ( $\mathcal{M} > 1$ )  
145 translates into a magnified selective impact ( $\mathcal{M}^2$ ). Thus,  
146 if we have to choose between vaccinating  $L$  and  $H$  hosts,  
147 targeting  $H$  hosts is expected to select more strongly for  
148 the vaccine-adapted variant. Figure 1B confirms that this  
149 approximation captures very well the temporal dynamics of  
150 the vaccine-adapted variant. In particular, the simulations  
151 confirm that targeted vaccination of the  $L$  hosts slows down  
152 the rate of adaptation of the virus.

153 Of course, the choice of the vaccination strategy should not  
154 be based solely on the reduction of the speed of adaptation to  
155 vaccines. Indeed, the best way to limit the spread of vaccine-  
156 escape mutations would be to adopt the worst epidemiological  
157 strategy: avoiding the use of vaccines. Yet, we urgently need  
158 vaccines to save lives and halt the current pandemic. We can  
159 use our numerical simulations to study the consequences of  
160 distinct targeted vaccination strategies on the total number of  
161 cases and on mortality (see Methods). Figure 1C shows that  
162 targeting  $L$  hosts is expected to increase the number of cases  
163 because  $H$  hosts contribute more to the spread of the disease.  
164 Yet, Figure 1D shows that targeting  $L$  hosts is expected to  
165 decrease the cumulative number of deaths after some time  
166 because  $L$  hosts (i.e., older individuals) are also associated  
167 with higher risks of dying from the infection. Hence, targeting  
168  $L$  hosts makes sense both for epidemiological and evolutionary  
169 reasons.

170 We explored the robustness of the above results for a range  
171 of alternative scenarios. First, we note that, as expected from  
172 our analytic approximation, the use of a transmission-blocking  
173 vaccine (instead of an infection-blocking vaccine) yields very  
174 similar outcomes (compare Figure 1 and S1). Second, we show  
175 in Figure S2 that evolution amplifies the increase in the cumu-  
176 lative number of deaths when  $H$  hosts are vaccinated compared  
177 to a scenario without viral adaptation. Indeed, the spread  
178 of a vaccine-adapted variant drives a large epidemic wave in  
179 vaccinated populations. This evolutionary effect is maximized  
180

181 for intermediate values of the speed of the vaccination rollout  
182 because when vaccine rollout is very fast the vaccine-adapted  
183 variant is rapidly favoured, whatever the targeted vaccination  
184 strategy (Figure S3). Finally, we note that maintaining social  
185 distancing for longer can substantially decrease the speed of  
186 adaptation (Figure S4).

187 **Heterogeneity in the number of vaccination doses:** In our second  
188 scenario, we assume that the heterogeneity among hosts is  
189 determined by differential strength of immunity induced by  
190 distinct vaccination status. We distinguish between unvac-  
191 cinated hosts ( $S$ ), hosts partially vaccinated with one dose ( $\hat{S}^I$ )  
192 and hosts fully vaccinated with two doses ( $\hat{S}^{II}$ ). Using the  
193 same approach as before, we obtain the following expression  
194 for the strength of selection acting on the strength of selection  
195 on the vaccine-adapted variant:

$$196 \quad \mathcal{S}(t) = (1 - c(t))\beta (\Delta E^I \hat{S}^I + \Delta E^{II} \hat{S}^{II}) \quad [3]$$

197 Equation Eq. (3) is very similar to equation Eq. (2), but now  
198 we have to account for the fact that the escape mutation  
199 has different effects in each class. Hence, the influence of an  
200 increase in the densities of hosts vaccinated by a single or two  
201 doses of vaccines are weighted by  $\Delta E^I$  and  $\Delta E^{II}$ , respectively.  
202 A single vaccine dose is likely to induce a lower protection  
203 against the virus (i.e.  $E^I > E^{II}$ ) but this does not necessarily  
204 imply that  $\Delta E^I > \Delta E^{II}$ . In fact, we can show that if the  
205 vaccine is acting on a single step of the virus' life cycle (e.g.,  
206 only blocking infection) we expect  $\Delta E^{II} > \Delta E^I$ . Delaying the  
207 acquisition of the second dose will have two effects: (i) a lower  
208 density  $\hat{S}^{II}$  of fully vaccinated hosts decreases the more intense  
209 selection imposed by these hosts, (ii) but delaying the second  
210 dose allows for more hosts to be vaccinated and the increase  
211 in  $\hat{S}^I$  may result in stronger selection for the vaccine-adapted  
212 variant. We show in Figure 2B that this second effect can be  
213 more important than the first one and delaying the second dose  
214 can result in faster adaptation. However, Figure 2D shows  
215 that delaying the second dose may reduce the cumulative  
216 number of deaths because a larger fraction of the population  
217 would benefit from the protection of the vaccine (but higher  
218 rates of vaccination rollout can reverse this effect on mortality,  
219 see Figures S5 and S6). Hence, in contrast to the previous  
220 scenario, the strategy that maximises the speed of adaptation  
221 may result in a lower mortality. The contrast between our  
222 two scenarios illustrates the necessity to quantify both the  
223 epidemiological and the evolutionary consequences of different  
224 targeted vaccination strategies to identify the optimal way to  
225 distribute vaccines.

## 226 Discussion

227 The speed of the spread of SARS-CoV-2 variants has baffled  
228 the scientific community (25, 26). In spite of a relatively  
229 small mutation rate (27, 28) SARS-CoV-2 has the ability to  
230 produce mutations with variable phenotypic effects that fuel  
231 the adaptation to human populations. The growing concern  
232 regarding the ability of the virus to escape host immunity calls  
233 for tools allowing us to anticipate the speed of the spread of  
234 vaccine-escape mutants. We show here that heterogeneity in  
235 the behaviour (scenario 1) and/or immune status (scenario 2)  
236 can induce variation in the strength of selection for vaccine-  
237 escape mutations. We contend that it is important to quantify  
238 this variation because it could be used to carry out targeted

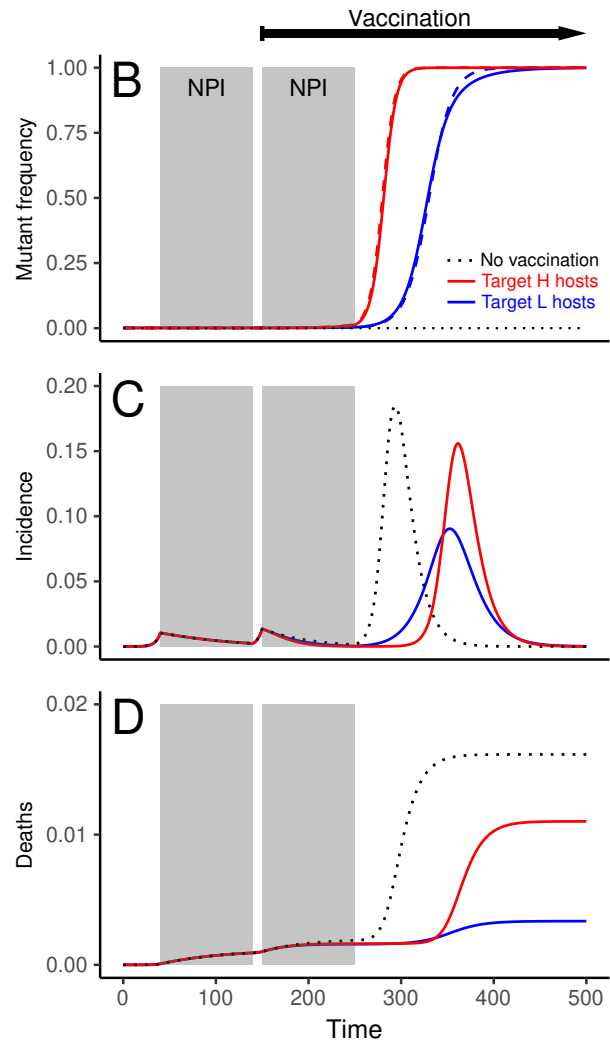
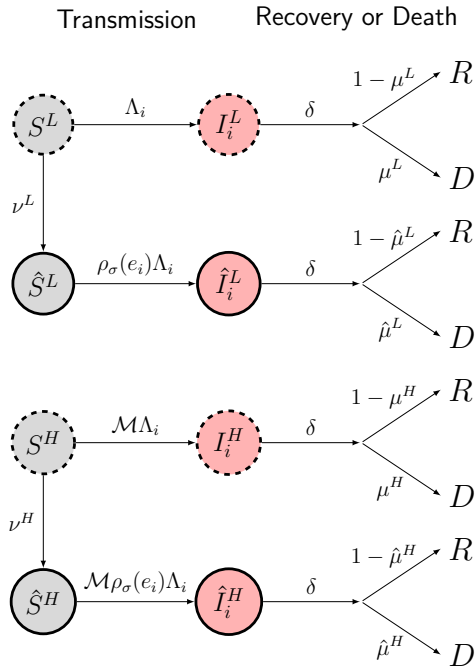
239 vaccination strategies that, for a given vaccination coverage,  
240 could limit the speed of adaptation of the virus.

241 We show that targeted vaccination on older hosts which  
242 are associated with lower number of contacts but higher risks  
243 of mortality may be a good strategy to reduce both the spread  
244 of the vaccine-escape variant and the cumulative number of  
245 deaths. (12) used a different approach to identify vaccination  
246 strategies that could reduce what they call 'vaccine escape pres-  
247 sure', a quantity proportional to the density of *infected* hosts  
248 who are vaccinated. In contrast, we show that the strength of  
249 selection on the vaccine-adapted mutant is proportional to the  
250 density of *susceptible* hosts who are vaccinated. Their analysis  
251 relies on the assumption that the incidence of the infection  
252 remains small (i.e., no depletion of susceptible hosts) and they  
253 do not track explicitly the rate of spread of a vaccine-adapted  
254 variant. They conclude that vaccinating most of the vulnerable  
255 hosts and few of the mixers could be the most risky for vaccine  
256 escape. Yet, it is difficult to evaluate how the 'vaccine escape  
257 pressure' criteria used in (12) may affect the speed of viral  
258 adaptation. A high incidence among vaccinated hosts may  
259 speed up viral adaptation because a vaccine-adapted variant  
260 generated by mutation is more likely to escape extinction in  
261 a vaccinated host. But a quantification of this effect would  
262 require an explicit description of the interplay between within-  
263 host selection and demographic stochasticity. In other words,  
264 their model focuses on the process that limits the emergence  
265 of vaccine-adapted variants while our analysis focuses on the  
266 strength of selection after emergence. It would thus be partic-  
267 ularly interesting to explore the robustness of our results with  
268 a model that would account for the effects of demographic  
269 stochasticity and within-host selection on the emergence of  
270 new variants.

271 We also discuss the effect of delaying the second dose of  
272 the vaccine on viral adaptation and on mortality. In a recent  
273 model, (29) found that imperfect immunity induced by a  
274 single dose may lead to stronger within-host selection for  
275 vaccine-escape variants. This is the same argument used  
276 by (12) where the infection of imperfectly immunized hosts  
277 may speed up viral adaptation. But, as discussed above, this  
278 effect relies on the interplay between demographic stochasticity  
279 and within-host selection. In contrast, we focus on between-  
280 host selection and ask whether vaccine-adapted variants can  
281 increase in frequency at the population level. We contend  
282 that once vaccine-adapted variants reach a significant fraction  
283 of the population, the fate of those mutations will be driven  
284 by between-host selection. Our analysis clarifies the balance  
285 between the effects of mutations in different types of hosts (i.e.  
286 the relative magnitudes of  $\Delta E^I$  and  $\Delta E^{II}$ ) and the quantity of  
287 the different types of hosts (i.e. the relative densities of hosts  
288 with one or two doses of the vaccine). We show that a higher  
289 speed of adaptation may be the price to pay for a reduced  
290 number of deaths (Figure 2B). Indeed, delaying the second  
291 dose allows for protecting (albeit partially) a larger fraction  
292 of the population (see (15) for an exploration of this effect).  
293 This positive effect can outweigh the negative consequences of  
294 an erosion of vaccine efficacy due to viral adaptation.

295 Interestingly, we found that combining vaccination and  
296 NPI can delay the rise of vaccine-adapted variant (Figures S4  
297 and S7). Our analysis clarifies the origin of the positive effect  
298 of NPI discussed in previous studies (21, 30). In our deter-  
299 ministic model, this effect emerges from the reduction in the

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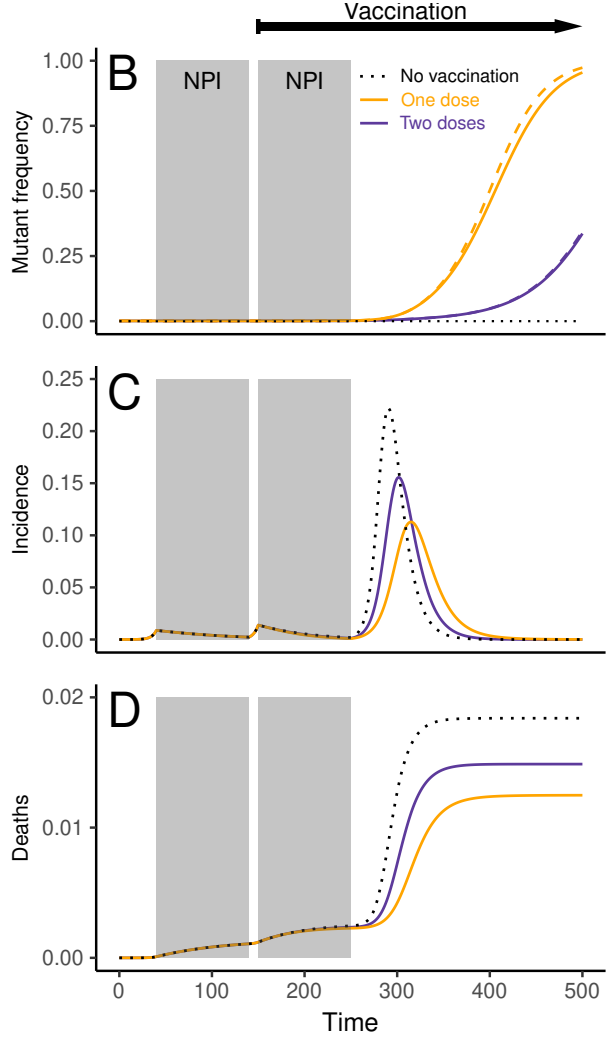
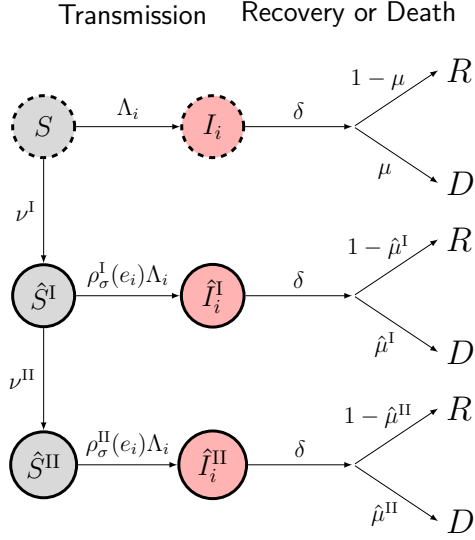
**Fig. 1. Scenario 1 – heterogeneity in contact numbers and vulnerability.** (A) A graphical presentation of the epidemiological life-cycle with  $L$  hosts who are more vulnerable to the disease and  $H$  hosts who have a higher number of contacts. Infected hosts are indicated with a light-red shading and vaccination with a bold circle border. The force of infection on naïve hosts is noted  $\Lambda_i = h_i + \hat{h}_i$  (see Methods and Table 1 for additional details on this model). (B) Dynamical change of the frequency  $p_m$  of the vaccine-adapted mutant for two distinct targeted vaccination strategies: (i) mostly  $L$  hosts are vaccinated (blue lines), (ii) mostly  $H$  hosts are vaccinated (red lines). The full lines indicate the exact numerical computation and the dashed line indicates the approximation obtained from (2). The gray areas indicate the period where Non-Pharmaceutical Interventions were used to control the epidemic ( $c(t) = 0.7$  with NPI). (C) Incidence of the epidemic (fraction of the total host population that is infected) in the absence of vaccination (dotted black line) or under the two alternative vaccination strategies used in (B) (blue and red lines). (D) Cumulative number of deaths (fraction of the total host population) in the absence of vaccination (dotted black line) or under the two alternative vaccination strategies used in (B) (blue and red lines).

300 strength of between-host selection due to lower opportunities  
 301 of transmission (i.e., see the effect of larger values of  $c(t)$  in  
 302 equations (2) and (3)).

303 Vaccination is urgently needed to control the SARS-CoV-2  
 304 pandemic but the limited supply of vaccines is raising major  
 305 ethical and practical issues. Public health policies need to  
 306 strike a balance between social, ethical and short-term epi-  
 307 demiological considerations. Our work illustrates that the  
 308 long-term evolutionary consequences of specific vaccination  
 309 strategies also need to be considered and evaluated using  
 310 quantitative models. Indeed, viral adaptation could erode the  
 311 efficacy of vaccines and targeted vaccination may provide a way  
 312 to delay this adaptation. Yet, as illustrated with the second  
 313 scenario, a strategy that minimizes the cumulative number of  
 314 deaths may not necessarily minimize the speed of adaptation.

Hence, as for any therapeutic interventions that may result  
 in the evolution of pathogen resistance, the identification of  
 an optimal vaccination strategy that reduces the death toll  
 of the pandemic requires specific models accounting for both  
 the epidemiology and the evolution of the virus (31–33). Be-  
 cause our model relies on several simplifying assumptions and  
 because our knowledge of the biology of SARS-Cov-2 and of  
 several key parameter values (e.g., vaccine efficacy, virulence,  
 contact rates...) remain imperfect, our model cannot be used  
 directly to make quantitative public-health recommendations.  
 Nonetheless, our framework lays a clear conceptual foundation  
 to analyse the consequences of targeted vaccination strategies.  
 In order to make more precise applied predictions, it  
 would be interesting to investigate how other realistic factors  
 (such as age structure, difference in transmissibility among

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**Fig. 2. Scenario 2 – heterogeneity in the number of vaccination doses.** (A) A graphical presentation of the epidemiological life-cycle where the superscripts  $I$  and  $II$  refer to the first and second doses of vaccine. Infected hosts are indicated with a light-red shading and vaccination with a bold circle border. The force of infection on naïve hosts is noted  $\Lambda_i = h_i + \hat{h}_i$  (see Methods and Table 2 for additional details on this model). (B) Dynamical change of the frequency  $p_m$  of the vaccine-adapted mutant for two distinct targeted vaccination strategies: (i) vaccinated hosts receive two doses sequentially (purple lines), (ii) a single dose is used for each host (orange lines). The full lines indicate the exact numerical computation and the dashed line indicates the approximation obtained from (3). The gray areas indicate the period where Non-Pharmaceutical Interventions were used to control the epidemic ( $c(t) = 0.7$  with NPI). (C) Incidence of the epidemic (fraction of the total host population that is infected) in the absence of vaccination (dotted black line) or under the two alternative vaccination strategies used in (B) (purple and orange lines). (D) Cumulative number of deaths (fraction of the total host population) in the absence of vaccination (dotted black line) or under the two alternative vaccination strategies used in (B) (purple and orange lines).

330 hosts classes, or alternative vaccination schedules) may affect  
 331 our results. Furthermore, the present work could be readily  
 332 extended to combine the two forms of heterogeneities in the  
 333 same model to allow for alternative ways to distribute the  
 334 vaccines (e.g., two doses for  $L$  individuals and one dose for  
 335  $H$  individuals). It would also be possible to use the same  
 336 framework to account for other factors that have been shown  
 337 to affect the outcome of vaccination strategy like assortative  
 338 mixing (4) and compensatory behavior after vaccination (34).  
 339 In all these scenarios, our framework could be used to identify  
 340 which strategy manages to strike the right balance between the  
 341 epidemiological and the evolutionary consequences of targeted  
 342 vaccination strategies.

343 **Materials and Methods**

**General approach.** We first give a general overview of the method  
 344 used to calculate the selection coefficient in structured host popula-  
 345 tions. The dynamics of hosts infected by pathogen strain  $i$  can be  
 346 captured by a matrix  $\mathbf{R}_i$  collecting the transition rates between host  
 347 classes. Assuming that mutations have small phenotypic effects (i.e.  
 348  $e_m = e_w + \varepsilon$ ), we can write the change in frequency of the mutant  
 349 strain as  
 350

$$\frac{dp_m}{dt} = \varepsilon p_m (1 - p_m) \mathbf{v}^\top \frac{d\mathbf{R}_m}{de_m} \mathbf{f} + O(\varepsilon^2) \quad [4] \quad 351$$

where  $\mathbf{v}^\top$  is the vector of reproductive values and  $\mathbf{f}$  is the vector of  
 344 class frequencies. These vectors are conormalised such that  $\mathbf{v}^\top \mathbf{f} = 1$   
 345 and satisfy the following dynamical equations

$$\frac{d\mathbf{f}}{dt} = \mathbf{R}_w \mathbf{f} - \lambda(t) \mathbf{f} \quad [5]$$

$$\frac{d\mathbf{v}^\top}{dt} = -\mathbf{v}^\top \mathbf{R}_w + \lambda(t) \mathbf{v}^\top \quad [6]$$

where  $\mathbf{R}_w$  is the transition matrix for the wild-type strain and  $\lambda(t)$  is the per-capita growth rate of the resident population at time  $t$  (see (24, 35) for a more detailed description). The  $d\mathbf{R}_m/de_m$  term in Eq. (6) refers to the differentiation of each elements of the transition matrix  $\mathbf{R}_m$  with respect to the effect of the mutant. For small  $\varepsilon$ , the mutant frequency  $p_m$  changes slowly compared to the ecological variables  $\mathbf{f}$  and  $\mathbf{v}$ , and we can use a quasi-equilibrium approximations obtained by setting the right-hand-sides of equations Eq. (5) and Eq. (6) to zero. This allows us to obtain analytical expressions for the class frequencies and reproductive values and thus to calculate the selection coefficient for a specific life cycle (scenario 1 vs scenario 2). Note that, although the weak selection assumption (small  $\varepsilon$ ) is driving the separation of time scale, the approximation remains good when selection is strong as discussed in the two scenarios below and shown in the figures. The Mathematica notebooks used to generate the figures will be accessible from a data repository upon publication.

**Scenario 1: should we preferentially vaccinate individuals with more contacts?** We assume that susceptible hosts in class  $k$  (where  $k = L$  or  $H$ ) are vaccinated at rate  $\nu^k$  representing the speed of vaccination rollout in that host class. We note  $\mathcal{M} > 1$  the relative number of contacts of  $H$  hosts compared to  $L$  hosts and  $\rho_\tau$  (resp.  $\rho_\sigma$ ) the relative transmissibility (resp. susceptibility) of vaccinated hosts compared to naive hosts of the same class. Both  $\rho_\tau$  and  $\rho_\sigma$  are functions of the vaccine escape trait. With these assumptions, the force of infection of a pathogen strain  $i$  due to naive infected hosts is  $h_i = \beta_i^L I_i^L + \mathcal{M}\beta_i^H I_i^H$ , and  $\hat{h}_i = \rho_\tau(e_i)(\beta_i^L \hat{I}_i^L + \mathcal{M}\beta_i^H \hat{I}_i^H)$  for vaccinated infected hosts. Note that vaccinated hosts are indicated by a "hat" (denoting protection). Hosts in class  $k$  infected by pathogen strain  $i$  eventually leaves the class at rate  $\delta_i^k$  (resp.  $\hat{\delta}_i^k$  for vaccinated hosts) and can either recover or die. We assume that the probability  $\mu_i^k$  (resp.  $\hat{\mu}_i^k$ ) of dying after leaving the class  $I_i^k$  (resp.  $\hat{I}_i^k$ ) may depend on the host class  $k$  and pathogen strain  $i$ . We track the cumulative number of deaths  $D$ . This quantity can be used to compare the efficacy of different vaccination strategies. Note that the probabilities  $\mu_i^k$  and  $\hat{\mu}_i^k$  have no impact on evolutionary dynamics because these events occur when the host is assumed to be no longer infectious and consequently they do not affect pathogen fitness.

This yields the following dynamical system (see also figure 1A):

$$\begin{aligned} \dot{S}^L &= -\nu^L S^L - (h_i + \hat{h}_i) S^L \\ \dot{\hat{S}}^L &= \nu^L S^L - (h_i + \hat{h}_i) \rho_\sigma(e_i) \hat{S}^L \\ \dot{S}^H &= -\nu^H S^H - \mathcal{M}(h_i + \hat{h}_i) S^H \\ \dot{\hat{S}}^H &= \nu^H S^H - \mathcal{M}(h_i + \hat{h}_i) \rho_\sigma(e_i) \hat{S}^H \\ \dot{I}_i^L &= (h_i + \hat{h}_i) S^L - \delta_i^L I_i^L \\ \dot{\hat{I}}_i^L &= (h_i + \hat{h}_i) \rho_\sigma(e_i) \hat{S}^L - \hat{\delta}_i^L \hat{I}_i^L \\ \dot{I}_i^H &= \mathcal{M}(h_i + \hat{h}_i) S^H - \delta_i^H I_i^H \\ \dot{\hat{I}}_i^H &= \mathcal{M}(h_i + \hat{h}_i) \rho_\sigma(e_i) \hat{S}^H - \hat{\delta}_i^H \hat{I}_i^H \\ \dot{D} &= \sum_i (\mu_i^L \delta_i^L I_i^L + \hat{\mu}_i^L \hat{\delta}_i^L \hat{I}_i^L + \mu_i^H \delta_i^H I_i^H + \hat{\mu}_i^H \hat{\delta}_i^H \hat{I}_i^H) \end{aligned} \quad [7]$$

We analyse this general model under two simplifying but reasonable assumptions.

1. We assume that the pathogen strains only differ through their effect on the parameters  $\rho_\tau$  and  $\rho_\sigma$  (that is, we only look at vaccine escape mutations, not mutations that can also affect transmissibility or virulence).

$$\mathbf{R}_i = \begin{pmatrix} \beta^L S^L - \delta^L & \beta^L \rho_\tau(e_i) S^L & \mathcal{M} \beta^H S^L & \mathcal{M} \beta^H \rho_\tau(e_i) S^L \\ \beta^L \rho_\sigma(e_i) \hat{S}^L & \beta^L \rho_\tau(e_i) \rho_\sigma(e_i) \hat{S}^L - \hat{\delta}^L & \mathcal{M} \beta^H \rho_\sigma(e_i) \hat{S}^L & \mathcal{M} \beta^H \rho_\tau(e_i) \rho_\sigma(e_i) \hat{S}^L \\ \mathcal{M} \beta^L S^H & \mathcal{M} \beta^L \rho_\tau(e_i) S^H & \mathcal{M}^2 \beta^H S^H - \delta^H & \mathcal{M}^2 \beta^H \rho_\tau(e_i) S^H \\ \mathcal{M} \beta^L \rho_\sigma(e_i) \hat{S}^H & \mathcal{M} \beta^L \rho_\tau(e_i) \rho_\sigma(e_i) \hat{S}^H & \mathcal{M}^2 \beta^H \rho_\sigma(e_i) \hat{S}^H & \mathcal{M}^2 \beta^H \rho_\tau(e_i) \rho_\sigma(e_i) \hat{S}^H - \hat{\delta}^H \end{pmatrix} \quad [8]$$

2. We assume that host classes  $L$  and  $H$  only differ through their number of contacts, so that  $\delta_i^L = \hat{\delta}_i^L = \delta_i^H = \hat{\delta}_i^H = \delta$  and  $\beta_i^L = \beta_i^H = \beta(1 - c(t))$  where  $\beta$  is the baseline transmissibility and  $1 - c(t)$  captures the effect of Non-Pharmaceutical Interventions (NPI) aimed at controlling the epidemic by reducing transmission. The parameter  $c(t)$  varies between 0 and 1 and quantifies the intensity of the control, which may vary over time as observed during the COVID-19 pandemic.

The latter assumption implies that the duration of infection is the same in all classes, but the effect of vaccination on the mortality of the different classes of hosts can be captured through the probabilities  $\mu^L, \hat{\mu}^L, \mu^H, \hat{\mu}^H$  (again, note that there is no influence of the pathogen genotype on disease outcome). For instance, in our simulations, we assume that  $L$  hosts tend to have fewer contacts but a higher mortality risk, while  $H$  hosts have more contacts but a lower mortality risk. This may reflect the observed differences between age classes.

The transition matrix  $\mathbf{R}_i$  is the  $4 \times 4$  matrix of per-capita transition rates of the pathogen between the 4 different types of hosts, given by equation Eq. (8) (see page bottom).

We are interested in the dynamics of the frequency of the vaccine-escape mutant, which is:

$$p_m = \frac{I_m^L + I_m^H + \hat{I}_m^L + \hat{I}_m^H}{\sum_i (I_i^L + I_i^H + \hat{I}_i^L + \hat{I}_i^H)} \quad [9]$$

The dynamics of  $p_m$  can be calculated by plugging the expressions of  $\mathbf{R}_w$  and  $\mathbf{R}_m$  into equations Eq. (4), Eq. (5) and Eq. (6). After some rearrangements, we obtain

$$\begin{aligned} \dot{S}(t) &= \frac{d\rho_\sigma}{de_m} h_w (\hat{v}^L \hat{S}^L + \mathcal{M} \hat{v}^H \hat{S}^H) \\ &+ \frac{d\rho_\tau}{de_m} \hat{h}_w (v^L S^L + \rho_\sigma(e_w) \hat{v}^L \hat{S}^L + \mathcal{M} v^H S^H + \mathcal{M} \rho_\sigma(e_w) \hat{v}^H \hat{S}^H) \end{aligned} \quad [10]$$

where the vector  $\mathbf{v} = (v^L \quad \hat{v}^L \quad v^H \quad \hat{v}^H)$  collects the reproductive values of an individual resident pathogen in classes  $I^L, \hat{I}^L, I^H$  and  $\hat{I}^H$  respectively. Note that this result only depends on assumption (i) above.

It is possible to simplify the expression of the selection coefficient by treating the reproductive values as fast variables. In particular, using our assumption (ii), this leads to the following quasi-equilibrium approximations:

$$\frac{\hat{v}^L}{v^L} = \frac{\hat{v}^H}{v^H} = \rho_\tau(e_w), \quad \frac{v^H}{v^L} = \mathcal{M}, \quad \frac{\hat{v}^H}{\hat{v}^L} = \mathcal{M} \rho_\tau(e_w) \quad [11]$$

Similarly, we have the following quasi-equilibrium approximations for the class frequencies, which give the fraction of infected individuals in a given class:

$$\frac{f^L}{f^L} = \rho_\sigma(e_w) \frac{\hat{S}^L}{S^L}, \quad \frac{f^H}{f^L} = \mathcal{M} \frac{S^H}{S^L}, \quad \frac{\hat{f}^H}{\hat{f}^L} = \mathcal{M} \rho_\sigma(e_w) \frac{\hat{S}^H}{\hat{S}^L}. \quad [12]$$

Together with the normalisation condition  $v^L f^L + \hat{v}^L \hat{f}^L + v^H f^H + \hat{v}^H \hat{f}^H = 1$ , we can use these relationships to obtain:

$$S(t) = \varepsilon \beta (1 - c(t)) (\hat{S}^L + \mathcal{M}^2 \hat{S}^H) \left. \frac{d(\rho_\sigma \rho_\tau)}{de_m} \right|_{e_m=e_w} \quad [13]$$

To recover equation Eq. (2) in the main text, we use the notations  $E_\tau = \rho_\tau$ ,  $E_\sigma = \rho_\sigma$ ,  $E = E_\tau E_\sigma$  and

$$\Delta E = \varepsilon \left. \frac{dE}{de_m} \right|_{e_m=e_w}$$

which is the first order approximation of the difference  $E(e_m) - E(e_w)$ .

**Table 1. Main parameters and default values used in scenario 1**

Virus parameters	Symbol	Values
Basic reproduction ratio	$R_0$	3
Transmission	$\beta$	0.12 day <sup>-1</sup>
Recovery rate	$\delta$	0.1 day <sup>-1</sup>
Baseline probability of death	$\mu$	0.001
Increased contact rate of $H$ hosts	$\mathcal{M}$	2
Increased mortality of $L$ hosts	$\mathcal{D}$	20
Infectivity of wild type on vaccinated hosts	$e_w$	0
Infectivity of mutant type on vaccinated hosts	$e_m$	0.8

Vaccine parameters	Symbol	Values
Vaccination rate of $L$ hosts	$\nu^L$	0.02 day <sup>-1</sup> (blue)    0.002 day <sup>-1</sup> (red)
Vaccination rate of $H$ hosts	$\nu^H$	0.002 day <sup>-1</sup> (blue)    0.02 day <sup>-1</sup> (red)
Efficacy at blocking infection	$r_\sigma$	0.9
Efficacy at blocking transmission	$r_\tau$	0
Efficacy at reducing mortality	$r_\mu$	0.9

**Numerical simulations:** In our applications, we use a linear model of vaccine escape:

$$\begin{aligned} \rho_\tau(e_i) &= 1 - r_\tau(1 - e_i) & [14] \\ \rho_\sigma(e_i) &= 1 - r_\sigma(1 - e_i) & [15] \end{aligned}$$

where  $r_\tau$  and  $r_\sigma$  give the vaccine efficacy in the absence of vaccine escape mutation (i.e.  $e_i = 0$ ). When  $e_i = 1$  (full vaccine escape), the vaccine offers no reduction in transmissibility and susceptibility ( $\rho_\sigma = \rho_\tau = 1$ ). As explained above, we assume that  $L$  hosts have a higher risk of mortality due to the disease, and note  $\mathcal{D}$  the relative increase in mortality of  $L$  hosts vs  $H$  hosts,  $\mu$  the baseline mortality probability, and  $\rho_\mu = 1 - r_\mu$  the reduction in mortality due to the vaccine (which we assume independent of host classes and of pathogen genotype). We thus have

$$\begin{aligned} \mu^L &= \mathcal{D} \mu \\ \hat{\mu}^L &= \rho_\mu \mathcal{D} \mu \\ \mu^H &= \mu \\ \hat{\mu}^H &= \rho_\mu \mu \end{aligned}$$

with  $\mathcal{D} > 1$  and  $0 < \rho_\mu < 1$ .

Initial conditions used in Figure 1B-D:  $S^L(0) = S^H(0) = 1/2$ ,  $\hat{S}^L = \hat{S}^H = 0$ ,  $I^L(0) = I^H(0) = 10^{-6}$ ,  $\hat{I}^L(0) = \hat{I}^H(0) = 10^{-6}$ ,  $D(0) = 0$ ,  $p_m(0) = 10^{-3}$ . The intensity of Non-Pharmaceutical Interventions varies with time ( $c(t) = 0.7$  when  $t \in [40, 140]$  and  $t \in [150, 250]$ ,  $c(t) = 0$  otherwise). Vaccination starts at  $t = 150$  and the other parameters used in Figure 1B-D are listed in Table 1.

**Scenario 2: should we delay the second dose?** For our second scenario, we consider three classes of susceptible hosts: unvaccinated ( $S$ ), vaccinated with 1 dose ( $S^I$ ) and vaccinated with 2 doses ( $S^{II}$ ). Unvaccinated susceptible hosts can be given a first dose of vaccine at rate  $\nu^I$ . Susceptible hosts that have received one dose can be given a second dose at rate  $\nu^{II}$ . With one dose, the relative transmissibility (resp. susceptibility) of vaccinated hosts with respect to pathogen strain  $e_i$  is  $\rho_\tau^I(e_i)$  (resp.  $\rho_\sigma^I(e_i)$ ). With two doses, we use the notation  $\rho_\tau^{II}(e_i)$  and  $\rho_\sigma^{II}(e_i)$ . Apart from these assumptions, the life cycle is similar to the one used for scenario 1, and we have the

following dynamics (see also figure 2A):

$$\begin{aligned} \dot{S} &= -\nu^I S - (h_i + \hat{h}_i) S \\ \dot{S}^I &= \nu^I S - \nu^{II} \hat{S}^I - (h_i + \hat{h}_i) \rho_\sigma^I(e_i) \hat{S}^I \\ \dot{S}^{II} &= \nu^{II} \hat{S}^I - (h_i + \hat{h}_i) \rho_\sigma^{II}(e_i) \hat{S}^{II} \\ \dot{I}_i &= (h_i + \hat{h}_i) S - \delta_i I_i \\ \dot{\hat{I}}_i^I &= (h_i + \hat{h}_i) \rho_\sigma^I(e_i) \hat{S}^I - \delta_i^I \hat{I}_i^I \\ \dot{\hat{I}}_i^{II} &= (h_i + \hat{h}_i) \rho_\sigma^{II}(e_i) \hat{S}^{II} - \delta_i^{II} \hat{I}_i^{II} \\ \dot{D} &= \sum_i (c_i \delta_i I_i + \hat{c}_i^I \delta_i^I \hat{I}_i^I + \hat{c}_i^{II} \delta_i^{II} \hat{I}_i^{II}) \end{aligned} \quad [16]$$

where the forces of infection by virus strain  $i$  are  $h_i = \beta_i I_i$  and  $\hat{h}_i = \rho_\tau^I(e_i) \beta_i^I \hat{I}_i^I + \rho_\tau^{II}(e_i) \beta_i^{II} \hat{I}_i^{II}$ . For simplicity, we will also assume, as in scenario 1, that  $\beta_i = \beta_i^I = \beta_i^{II} = \beta(1 - c(t))$  and  $\delta_i = \delta_i^I = \delta_i^{II} = \delta$ , so that (1) hosts only differ through the parameters  $\rho_\tau$  and  $\rho_\sigma$ , and (2) the viral strains only differ through the parameters  $\rho_\tau$  and  $\rho_\sigma$ . We also assume that  $\mu_i = \mu$ ,  $\hat{\mu}_i^I = \hat{\mu}^I$  and  $\hat{\mu}_i^{II} = \hat{\mu}^{II}$  to account for potential differences between mortality rates between different classes of hosts (but no influence of the pathogen genotype).

With these assumptions, the matrix  $\mathbf{R}_i$  is

$$\mathbf{R}_i = \begin{pmatrix} \beta S - \delta & \rho_\tau^I(e_i) \beta^I S & \rho_\tau^{II}(e_i) \beta^{II} S \\ \beta \rho_\sigma^I(e_i) \hat{S}^I & \rho_\tau^I(e_i) \beta^I \rho_\sigma^I(e_i) \hat{S}^I - \delta^I & \rho_\tau^{II}(e_i) \beta^{II} \rho_\sigma^I(e_i) \hat{S}^I \\ \beta \rho_\sigma^{II}(e_i) \hat{S}^{II} & \rho_\tau^I(e_i) \beta^I \rho_\sigma^{II}(e_i) \hat{S}^{II} & \rho_\tau^{II}(e_i) \beta^{II} \rho_\sigma^{II}(e_i) \hat{S}^{II} - \delta^{II} \end{pmatrix} \quad [17]$$

and the quasi-equilibrium relationships for class frequencies and reproductive values, when  $\beta^I = \beta^{II} = \beta$  and  $\delta_i^k = \delta$  are:

$$\frac{v^I}{v^0} = \rho_\tau^I(e_w), \quad \frac{v^{II}}{v^0} = \rho_\tau^{II}(e_w)$$

and

$$\frac{f^I}{f^0} = \rho_\sigma^I(e_w) \frac{\hat{S}^I}{S}, \quad \frac{f^{II}}{f^0} = \rho_\sigma^{II}(e_w) \frac{\hat{S}^{II}}{S}$$

where  $\mathbf{v} = (v^0 \ v^I \ v^{II})$  and  $\mathbf{f} = (f^0 \ f^I \ f^{II})$ . Together with the normalisation condition  $v^0 f^0 + v^I f^I + v^{II} f^{II} = 1$ , these relationships allow us to rearrange equation Eq. (4) to obtain

$$\mathcal{S}(t) = \varepsilon \beta (1 - c(t)) \left( \hat{S}^I \frac{d(\rho_\sigma^I \rho_\tau^I)}{de_m} \Big|_{e_m=e_w} + \hat{S}^{II} \frac{d(\rho_\sigma^{II} \rho_\tau^{II})}{de_m} \Big|_{e_m=e_w} \right) \quad [18]$$

which is equation Eq. (3) in the main text using the same notations as in Scenario 1.



**Table 2. Main parameters and default values used in scenario 2**

Virus parameters	Symbol	Values
Basic reproduction ratio	$R_0$	3
Transmission	$\beta$	0.3 day <sup>-1</sup>
Recovery rate	$\delta$	0.1 day <sup>-1</sup>
Baseline probability of death	$\mu$	0.01
Infectivity of wild type on vaccinated hosts	$e_w$	0
Infectivity of mutant type on vaccinated hosts	$e_m$	0.8

Vaccine parameters	Symbol	Values
Vaccination rate for 1 <sup>st</sup> dose	$\nu^I$	0.002 day <sup>-1</sup> (purple) 0.004 day <sup>-1</sup> (orange)
Vaccination rate for 2 <sup>nd</sup> dose	$\nu^{II}$	0.002 day <sup>-1</sup> (purple) 0.0002 day <sup>-1</sup> (orange)
Efficacy at blocking infection (1 <sup>st</sup> and 2 <sup>nd</sup> dose)	$r_{\sigma}^I, r_{\sigma}^{II}$	0.6 (1 <sup>st</sup> dose) and 0.9 (2 <sup>nd</sup> dose)
Efficacy at blocking transmission (1 <sup>st</sup> and 2 <sup>nd</sup> dose)	$r_{\tau}^I, r_{\tau}^{II}$	0 (1 <sup>st</sup> dose) and 0 (2 <sup>nd</sup> dose)
Efficacy at reducing mortality (1 <sup>st</sup> and 2 <sup>nd</sup> dose)	$r_{\mu}^I, r_{\mu}^{II}$	0.5 (1 <sup>st</sup> dose) and 0.95 (2 <sup>nd</sup> dose)

**Numerical simulations:** We use the same linear model of vaccine escape as in scenario 1, but we allow for different vaccine efficacies depending on the number of doses:

$$\rho_{\tau}^I(e_i) = 1 - r_{\tau}^I(1 - e_i) \quad [19]$$

$$\rho_{\sigma}^I(e_i) = 1 - r_{\sigma}^I(1 - e_i) \quad [20]$$

$$\rho_{\tau}^{II}(e_i) = 1 - r_{\tau}^{II}(1 - e_i) \quad [21]$$

$$\rho_{\sigma}^{II}(e_i) = 1 - r_{\sigma}^{II}(1 - e_i) \quad [22]$$

where  $r_{\tau}$  and  $r_{\sigma}$  give the vaccine efficacy in the absence of vaccine escape mutation (i.e.  $e_i = 0$ ). When  $e_i = 1$  (full vaccine escape), the vaccine offers no reduction in transmissibility and susceptibility ( $\rho_{\sigma} = \rho_{\tau} = 1$ ). We assume that vaccination can also protect against disease induced mortality and we define  $r_{\mu}^I$  and  $r_{\mu}^{II}$  so that  $\hat{\mu}_i^I = \mu(1 - r_{\mu}^I)$  and  $\hat{\mu}_i^{II} = \mu(1 - r_{\mu}^{II})$ .

Initial conditions used in Figure 2B-D:  $S(0) = 1, \hat{S}^I(0) = \hat{S}^{II}(0) = 0, I(0) = \hat{I}^I(0) = \hat{I}^{II}(0) = 10^{-6}, D(0) = 0, p_m(0) = 10^{-3}$ . The intensity of Non-Pharmaceutical Interventions varies with time ( $c(t) = 0.7$  when  $t \in [40, 140]$  and  $t \in [150, 250]$ ,  $c(t) = 0$  otherwise). Vaccination starts at  $t = 150$  and the other parameters used in Figure 2B-D are listed in Table 2.

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