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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 vacci-2 nate older and more sensitive hosts first to minimize the disease bur-3 den. But what are the evolutionary consequences of targeted vaccination? We clarify the consequences of different vaccination strate-5 gies 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 vacci-8 nation targets individuals who are likely to be involved in a higher 9 number of contacts. We also discuss the pros and cons of dose-10 sparing strategies. Because delaying the second dose increases the 11 proportion of the population vaccinated with a single dose, this strat-12 egy can both speed up the spread of the vaccine-adapted variant and 13 14 reduce the cumulative number of deaths. Hence, strategies that are most effective at slowing viral adaptation may not always be epidemi-15 ologically optimal. A careful assessment of both the epidemiological 16 and evolutionary consequences of alternative vaccination strategies 17 is required to determine which individuals should be vaccinated first. 18

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

he development of effective vaccines against SARS-CoV-2 raises hope regarding the possibility of eventually halting 2 the ongoing pandemic. But vaccine supply shortages have 3 sparked a debate about the optimal distribution of vaccination 4 among different categories of individuals. Typically, infections 5 with SARS-CoV-2 are far more deadly in older individuals 6 than in younger ones (1). Prioritizing vaccination for older classes may thus provide a *direct* benefit in terms of mortality 8 (2, 3). Yet, younger individuals are usually more active and, 9 consequently, they may contribute more to the spread of the 10 epidemic. Prioritizing vaccination for younger and more active 11 individuals may thus provide an *indirect* benefit through a 12 reduction of the epidemic size (4, 5). Earlier studies have com-13 14 pared alternative ways to deploy vaccination in heterogeneous 15 host populations and showed that recommendation varies with the choice of the quantity one is trying to minimize (e.g., the 16 cumulative number of deaths, the remaining life expectancy or 17 the number of infections) (3, 6, 7). The recommendation also 18 varies with the properties of the pathogen and the efficacy of 19 the vaccine (3, 4, 8). For SARS-CoV-2, the increase in mor-20 tality with age is such that the direct benefit associated with 21 22 vaccinating more vulnerable individuals tends to overwhelm the indirect benefits obtained from vaccinating more active 23 individuals (2, 3, 9, 10). But some studies challenge this view 24 and identified specific conditions where vaccinating younger 25 and more active classes could be optimal (5, 7, 11, 12). A 26 similar debate emerges over the possibility to delay the second 27 vaccination dose to maximise the number of partially vacci-28 nated individuals. A quantitative exploration of alternative 29 vaccination strategies can help provide useful recommenda-30

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).

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Vaccine-driven evolution, however, could erode the benefit 34 of vaccination and alter the above recommendations which 35 are based solely on the analysis of epidemiological dynamics. 36 Given that hosts differ both in their sensitivity to the disease 37 and in their contribution to transmission, who should we vacci-38 nate first if we want to minimise the spread of vaccine-adapted 39 variants? The effect of alternative vaccination strategies on the 40 speed of pathogen adaptation remains unclear. Previous stud-41 ies of adaptation to vaccines focused on long-term evolutionary 42 outcomes (17, 18). These analyses are not entirely relevant for 43 the ongoing pandemic because what we want to understand 44 first is the short-term consequence of different vaccination 45 strategies (19). A few studies have discussed the possibility of 46 SARS-CoV-2 adaptation following different targeted vaccina-47 tion strategies but did not explicitly account for evolutionary 48 dynamics (12, 20). A recent simulation study explored the 49 effect of a combination of vaccination and social distancing 50 strategies on the probability of vaccine-driven adaptation (21). 51 This model, however, did not study the impact of targeted 52 vaccination strategies on the speed of adaptation. 53

Here, we develop a theoretical framework based on the anal-54 ysis of the deterministic dynamics of multiple variants after 55 they successfully managed to reach a density at which they are 56 no longer affected by the action of demographic stochasticity. 57 We study the impact of different vaccination strategies on 58 the rate of change of the frequency of a novel variant, which 59 allows us to quantify the speed of virus adaptation to vac-60 cines. Numerical simulations tailored to the epidemiology of 61

#### 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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<sup>62</sup> SARS-CoV-2 confirm the validity of our approximation of the

63 strength of selection for vaccine-adapted variants.

#### 64 Results

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

$$\dot{p}_m \approx p_m (1 - p_m) \mathcal{S}(t) \tag{1}$$

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

Targeted vaccination strategies aim to preferentially vacci-76 nate hosts according to specific epidemiological characteristics. 77 For instance, we could target hosts that have more contacts, 78 or are more at risk of a severe disease. In our model, we 79 therefore introduce some heterogeneity among hosts. As a 80 result, from the point of view of the parasite, the quality of 81 the host may differ among infected hosts, and this variation 82 is likely to affect the dynamics of vaccine-adapted variants. 83 To quantify host quality, we use the concept of reproductive 84 value, a key concept in demography and evolutionary biol-85 ogy (22-24). Reproductive value measures how much a virus 86 infecting a given class of hosts will contribute to the future 87 of the viral population. Our general mathematical analysis 88 allows us to take the difference in host quality into account 89 when calculating the selection coefficient  $\mathcal{S}(t)$  (see Methods). 90 We use this approach to analyse the speed of adaptation 91 during the ongoing pandemic of SARS-CoV-2 under different 92 scenarios. We use an epidemiological model tailored to the 93 biology of SARS-CoV-2 (see Methods). However, it is impor-94 95 tant to keep in mind that, due to simplifying assumptions and uncertainty about parameter values, our results cannot 96 be translated directly into public-health recommendations 97 without further investigations (see Discussion). Nonetheless, 98 our theoretical framework gives clear foundations for future 99 100 applied work, and captures some of the most salient features of the COVID-19 pandemic. In particular, we introduce a 101 time-varying parameter c(t) which measures the intensity of 102 Non-Pharmaceutical Interventions (NPI). We assume that the 103 epidemic is initially controlled by NPI which yields succes-104 sive epidemic waves before the deployment of vaccination at 105 t = 150 days. We use this model to explore the effect of two 106 different forms of heterogeneity on the speed of SARS-CoV-2 107 108 adaptation.

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

2 | www.pnas.org/cgi/doi/10.1073/pnas.XXXXXXXXXXX

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

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

$$\mathcal{S}(t) = (1 - c(t)) \beta \Delta E \left( \hat{S}^L + \mathcal{M}^2 \hat{S}^H \right)$$
 [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 for intermediate values of the speed of the vaccination rollout
because when vaccine rollout is very fast the vaccine-adapted
variant is rapidly favoured, whatever the targeted vaccination
strategy (Figure S3). Finally, we note that maintaining social
distancing for longer can substantially decrease the speed of
adaptation (Figure S4).

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

$$\mathcal{S}(t) = (1 - c(t)) \beta \left( \Delta E^{\mathrm{I}} \hat{S}^{\mathrm{I}} + \Delta E^{\mathrm{II}} \hat{S}^{\mathrm{II}} \right)$$

[3]

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

#### 226 Discussion

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

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

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

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



**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).

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

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

Hence, as for any therapeutic interventions that may result 315 in the evolution of pathogen resistance, the identification of 316 an optimal vaccination strategy that reduces the death toll 317 of the pandemic requires specific models accounting for both 318 the epidemiology and the evolution of the virus (31-33). Be-319 cause our model relies on several simplifying assumptions and 320 because our knowledge of the biology of SARS-Cov-2 and of 321 several key parameter values (e.g., vaccine efficacy, virulence, 322 contact rates...) remain imperfect, our model cannot be used 323 directly to make quantitative public-health recommendations. 324 Nonetheless, our framework lays a clear conceptual foundation 325 to analyse the consequences of targeted vaccination strate-326 gies. In order to make more precise applied predictions, it 327 would be interesting to investigate how other realistic factors 328 (such as age structure, difference in transmissibility among 329 А



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 where 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).

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

#### 343 Materials and Methods

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

$$\frac{\mathrm{d}p_m}{\mathrm{d}t} = \varepsilon p_m (1 - p_m) \, \mathbf{v}^\top \frac{\mathrm{d}\mathbf{R}_m}{\mathrm{d}e_m} \mathbf{f} + O(\varepsilon^2) \qquad [4] \quad \text{351}$$

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

$$\frac{\mathrm{d}\mathbf{f}}{\mathrm{d}t} = \mathbf{R}_w \mathbf{f} - \lambda(t)\mathbf{f}$$
<sup>[5]</sup>

$$\frac{\mathrm{d}\mathbf{v}^{\top}}{\mathrm{d}t} = -\mathbf{v}^{\top}\mathbf{R}_{w} + \lambda(t)\mathbf{v}^{\top}$$
[6]

where  $\mathbf{R}_{w}$  is the transition matrix for the wild-type strain and 352 353  $\lambda(t)$  is the per-capita growth rate of the resident population at time t (see (24, 35) for a more detailed description). The 354  $\mathrm{d}\mathbf{R}_m/\mathrm{d}e_m$  term in Eq. (6) refers to the differentiation of each 355 356 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 357 358 slowly compared to the ecological variables  $\mathbf{f}$  and  $\mathbf{v}$ , and we can use a quasi-equilibrium approximations obtained by setting the 359 right-hand-sides of equations Eq. (5) and Eq. (6) to zero. This 360 361 allows us to obtain analytical expressions for the class frequencies and reproductive values and thus to calculate the selection 362 coefficient for a specific life cycle (scenario 1 vs scenario 2). Note 363 that, although the weak selection assumption (small  $\varepsilon$ ) is driving 364 the separation of time scale, the approximation remains good when 365 366 selection is strong as discussed in the two scenarios below and shown in the figures. The Mathematica notebooks used to generate 367 the figures will be accessible from a data repository upon publication. 368 369

Scenario 1: should we preferentially vaccinate individuals with more 370 **contacts?.** We assume that susceptible hosts in class k (where k = L371 or H) are vaccinated at rate  $\nu^k$  representing the speed of vaccination 372 rollout in that host class. We note  $\mathcal{M} > 1$  the relative number of 373 contacts of H hosts compared to L hosts and  $\rho_{\tau}$  (resp.  $\rho_{\sigma}$ ) the 374 relative transmissibility (resp. susceptibility) of vaccinated hosts 375 compared to naive hosts of the same class. Both  $\rho_{\tau}$  and  $\rho_{\sigma}$  are 376 functions of the vaccine escape trait. With these assumptions, the 377 force of infection of a pathogen strain i due to naive infected hosts 378 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 379 380 by a "hat" (denoting protection). Hosts in class k infected by 381 pathogen strain *i* eventually leaves the class at rate  $\delta_i^k$  (resp.  $\hat{\delta}_i^k$  for 382 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. 383 384  $\hat{I}_{i}^{k}$ ) may depend on the host class k and pathogen strain i. We track 385 the cumulative number of deaths D. This quantity can be used 386 to compare the efficacy of different vaccination strategies. Note 387 that the probabilities  $\mu_i^k$  and  $\hat{\mu}_i^k$  have no impact on evolutionary 388 dynamics because these events occur when the host is assumed to be 389 no longer infectious and consequently they do not affect pathogen 390 391 fitness.

<sup>392</sup> This yields the following dynamical system (see also figure 1A):

$$\begin{split} \dot{S}^{L} &= -\nu^{L}S^{L} - (h_{i} + \hat{h}_{i})S^{L} \\ \dot{\hat{S}}^{L} &= \nu^{L}S^{L} - (h_{i} + \hat{h}_{i})\rho_{\sigma}(e_{i})\hat{S}^{L} \\ \dot{\hat{S}}^{H} &= -\nu^{H}S^{H} - \mathcal{M}(h_{i} + \hat{h}_{i})S^{H} \\ \dot{\hat{S}}^{H} &= \nu^{H}S^{H} - \mathcal{M}(h_{i} + \hat{h}_{i})\rho_{\sigma}(e_{i})\hat{S}^{H} \\ \dot{\hat{I}}_{i}^{L} &= (h_{i} + \hat{h}_{i})S^{L} - \delta_{i}^{L}I_{i}^{L} \\ \dot{\hat{I}}_{i}^{L} &= (h_{i} + \hat{h}_{i})\rho_{\sigma}(e_{i})\hat{S}^{L} - \delta_{i}^{L}\hat{I}_{i}^{L} \\ \dot{\hat{I}}_{i}^{H} &= \mathcal{M}(h_{i} + \hat{h}_{i})S^{H} - \delta_{i}^{H}I_{i}^{H} \\ \dot{\hat{I}}_{i}^{H} &= \mathcal{M}(h_{i} + \hat{h}_{i})\rho_{\sigma}(e_{i})\hat{S}_{i}^{H} - \delta_{i}^{H}\hat{I}_{i}^{H} \\ \dot{\hat{I}}_{i}^{H} &= \mathcal{M}(h_{i} + \hat{h}_{i})\rho_{\sigma}(e_{i})\hat{S}_{i}^{L} - \hat{\delta}_{i}^{L}\hat{I}_{i}^{L} \\ \dot{D} &= \sum_{i} \left( \mu_{i}^{L}\delta_{i}^{L}I_{i}^{L} + \hat{\mu}_{i}^{L}\delta_{i}^{L}\hat{I}_{i}^{L} + \mu_{i}^{H}\delta_{i}^{H}I_{i}^{H} + \hat{\mu}_{i}^{H}\delta_{i}^{J}\hat{I}_{i}^{H} \right) \end{split}$$

$$\begin{bmatrix} 7 \end{bmatrix}$$

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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).

$$\mathbf{R}_{i} = \begin{pmatrix} \beta^{L} S^{L} - \delta^{L} & \beta^{L} \rho_{\tau}(e_{i}) S^{L} \\ \beta^{L} \rho_{\sigma}(e_{i}) \hat{S}^{L} & \beta^{L} \rho_{\tau}(e_{i}) \rho_{\sigma}(e_{i}) \hat{S}^{L} - \hat{\delta}^{L} \\ \mathcal{M} \beta^{L} S^{H} & \mathcal{M} \beta^{L} \rho_{\tau}(e_{i}) S^{H} \\ \mathcal{M} \beta^{L} \rho_{\sigma}(e_{i}) \hat{S}^{H} & \mathcal{M} \beta^{L} \rho_{\tau}(e_{i}) \rho_{\sigma}(e_{i}) \hat{S}^{H} \end{pmatrix}$$

2. We assume that host classes L and H only differ through their 400 number of contacts, so that  $\delta_i^L = \hat{\delta}_i^L = \delta_i^H = \hat{\delta}_i^H = \delta$  and 401  $\beta_i^L = \beta_i^H = \beta(1 - c(t))$  where  $\beta$  is the baseline transmissibility 402 and 1 - c(t) captures the effect of Non-Pharmaceutical Inter-403 ventions (NPI) aimed at controlling the epidemic by reducing 404 transmission. The parameter c(t) varies between 0 and 1 and 405 quantifies the intensity of the control, which may vary over 406 time as observed during the COVID-19 pandemic. 407

The latter assumption implies that the duration of infection is the 408 same in all classes, but the effect of vaccination on the mortality 409 of the different classes of hosts can be captured through the proba-410 bilities  $\mu^L$ ,  $\hat{\mu}^L$ ,  $\mu^H$ ,  $\hat{\mu}^H$  (again, note that there is no influence of 411 the pathogen genotype on disease outcome). For instance, in our 412 simulations, we assume that L hosts tend to have fewer contacts 413 but a higher mortality risk, while H hosts have more contacts but 414 a lower mortality risk. This may reflect the observed differences 415 between age classes. 416

The transition matrix  $\mathbf{R}_i$  is the 4×4 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 vaccineescape mutant, which is:

p

$${}_{m} = \frac{I_{m}^{L} + I_{m}^{H} + \hat{I}_{m}^{L} + \hat{I}_{m}^{H}}{\sum_{i} \left( I_{i}^{L} + I_{i}^{H} + \hat{I}_{i}^{L} + \hat{I}_{i}^{H} \right)}$$
[9] 422

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

$$\begin{aligned} \mathcal{S}(t) &= \frac{\mathrm{d}\rho_{\sigma}}{\mathrm{d}e_{m}} h_{w} \left( \hat{v}^{L} \hat{S}^{L} + \mathcal{M} \hat{v}^{H} \hat{S}^{H} \right) \\ &+ \frac{\mathrm{d}\rho_{\tau}}{\mathrm{d}e_{m}} \hat{h}_{w} \left( v^{L} S^{L} + \rho_{\sigma}(e_{w}) \hat{v}^{L} \hat{S}^{L} + \mathcal{M} v^{H} S^{H} + \mathcal{M} \rho_{\sigma}(e_{w}) \hat{v}^{H} \hat{S}^{H} \right) \end{aligned}$$

$$\tag{10}$$

where the vector  $\mathbf{v} = \begin{pmatrix} v^L & \hat{v}^L & v^H & \hat{v}^H \end{pmatrix}$  collects the reproductive values of an individual resident pathogen in classes  $I^L$ ,  $\hat{I}^L$ , 428  $I^H$  and  $\hat{I}^H$  respectively. Note that this result only depends on assumption (i) above. 430

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:

$$\frac{\hat{v}^L}{v^L} = \frac{\hat{v}^H}{v^H} = \rho_\tau(e_w), \qquad \frac{v^H}{v^L} = \mathcal{M}, \qquad \frac{\hat{v}^H}{v^L} = \mathcal{M}\rho_\tau(e_w) \quad [11] \quad \text{435}$$

Similarly, we have the following quasi-equilibrium approximations for the class frequencies, which give the fraction of infected individuals in a given class: 438

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

$$[12]$$
 439  
 $f^{H}f^{H}$  + 440

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Together with the normalisation condition  $v^L f^L + \hat{v}^L \hat{f}^L + v^H f^H + 440$  $\hat{v}^H \hat{f}^H = 1$ , we can use these relationships to obtain:

$$S(t) = \varepsilon \beta (1 - c(t)) \left( \hat{S}^L + \mathcal{M}^2 \hat{S}^H \right) \left. \frac{\mathrm{d}(\rho_\sigma \rho_\tau)}{\mathrm{d}e_m} \right|_{e_m = e_w}$$
[13] 442

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 444

$$\Delta E = \varepsilon \left. \frac{\mathrm{d}E}{\mathrm{d}e_m} \right|_{e_m = e_w} \tag{445}$$

which is the first order approximation of the difference  $E(e_m) - 446 E(e_w)$ .

$$\begin{array}{cccc}
\mathcal{M}\beta^{H}S^{L} & \mathcal{M}\beta^{H}\rho_{\tau}(e_{i})S^{L} \\
\mathcal{M}\beta^{H}\rho_{\sigma}(e_{i})\hat{S}_{I} & \mathcal{M}\beta^{H}\rho_{\tau}(e_{i})\rho_{\sigma}(e_{i})\hat{S}^{L} \\
\mathcal{M}^{2}\beta^{H}S^{H} - \delta^{H} & \mathcal{M}^{2}\beta^{H}\rho_{\tau}(e_{i})S^{H} \\
\mathcal{M}^{2}\beta^{H}\rho_{\sigma}(e_{i})\hat{S}^{H} & \mathcal{M}^{2}\beta^{H}\rho_{\tau}(e_{i})\hat{\rho}_{\sigma}(e_{i})\hat{S}^{H} - \hat{\delta}^{H}
\end{array}\right)$$
[8]

Table 1. Main	parameters and	default values	used in scen	nario 1
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Virus parameters	Symbol	Values
Basic reproduction ratio	$R_0$	3
Transmission	$\beta$	0.12 day <sup>-1</sup>
Recovery rate	$\delta$	0.1 day-1
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	$\nu^L$	$0.02 \text{ day}^{-1}$ (blue) $0.002 \text{ day}^{-1}$ (red)
Vaccination rate of $H$ hosts	$\nu^H$	$0.002 \text{ day}^{-1}$ (blue) $0.02 \text{ day}^{-1}$ (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:

$$\rho_{\tau}(e_i) = 1 - r_{\tau}(1 - e_i)$$
[14]

$$\rho_{\sigma}(e_i) = 1 - r_{\sigma}(1 - e_i) \tag{15}$$

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

$$egin{aligned} \mu^L &= \mathcal{D} \ \mu \ \hat{\mu}^L &= 
ho_\mu \ \mathcal{D} \ \mu \ \mu^H &= \mu \ \hat{\mu}^H &= 
ho_\mu \ \mu \end{aligned}$$

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

Scenario 2: should we delay the second dose?. For our second sce-455 nario, we consider three classes of susceptible hosts: unvaccinated 456 (S), vaccinated with 1 dose  $(S^{I})$  and vaccinated with 2 doses  $(S^{II})$ . 457 Unvaccinated susceptible hosts can be given a first dose of vaccine 458 at rate  $\nu^{I}$ . Susceptible hosts that have received one dose can be 459 given a second dose at rate  $\nu^{\text{II}}$ . With one dose, the relative trans-460 missibility (resp. susceptibility) of vaccinated hosts with respect to 461 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 462 463 life cycle is similar to the one used for scenario 1, and we have the 464

following dynamics (see also figure 2A):

where the forces of infection by virus strain i are  $h_i = \beta_i I_i$  and  $\hat{h}_i = \rho_{\tau}^{\rm I}(e_i)\beta_i^{\rm I} \hat{I}_i^{\rm I} + \rho_{\tau}^{\rm II}(e_i)\beta_i^{\rm II} \hat{I}_i^{\rm II}$ . For simplicity, we will also assume, as in scenario 1, that  $\beta_i = \beta_i^{\rm I} = \beta_i^{\rm II} = \beta(1 - c(t))$  and  $\delta_i = \hat{\delta}_i^{\rm I} = \hat{\delta}_i^{\rm II} = \delta$ , 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  $\mu_i = \mu$ ,  $\hat{\mu}_i^{\rm I} = \hat{\mu}^{\rm I}$  and  $\hat{\mu}_i^{\rm II} = \hat{\mu}^{\rm II}$  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

$$\mathbf{R}_{i} = \begin{pmatrix} \beta S - \delta & \rho_{\tau}^{\mathrm{I}}(e_{i})\beta^{\mathrm{I}}S & \rho_{\tau}^{\mathrm{II}}(e_{i})\beta^{\mathrm{II}}S \\ \beta \rho_{\sigma}^{\mathrm{II}}(e_{i})\hat{S}^{\mathrm{II}} & \rho_{\tau}^{\mathrm{II}}(e_{i})\beta^{\mathrm{II}}\rho_{\sigma}^{\mathrm{II}}(e_{i})\hat{S}^{\mathrm{II}} - \delta^{\mathrm{II}} & \rho_{\tau}^{\mathrm{II}}(e_{i})\beta^{\mathrm{II}}\rho_{\sigma}^{\mathrm{II}}(e_{i})\hat{S}^{\mathrm{II}} \\ \beta \rho_{\sigma}^{\mathrm{II}}(e_{i})\hat{S}^{\mathrm{III}} & \rho_{\tau}^{\mathrm{II}}(e_{i})\beta^{\mathrm{I}}\rho_{\sigma}^{\mathrm{II}}(e_{i})\hat{S}^{\mathrm{III}} & \rho_{\tau}^{\mathrm{II}}(e_{i})\hat{S}^{\mathrm{III}} - \delta^{\mathrm{III}} \end{pmatrix}$$

[17] 476

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

$$\frac{v^{\mathrm{II}}}{v^{0}} = \rho_{\tau}^{\mathrm{II}}(e_{w}), \qquad \frac{v^{\mathrm{II}}}{v^{0}} = \rho_{\tau}^{\mathrm{II}}(e_{w})$$
 479

and

$$\frac{f^{\rm I}}{f^0} = \rho^{\rm I}_{\sigma}(e_w) \frac{\hat{S}^{\rm I}}{S}, \qquad \frac{f^{\rm II}}{f^0} = \rho^{\rm II}_{\sigma}(e_w) \frac{\hat{S}^{\rm II}}{S} \tag{480}$$

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

$$\mathcal{S}(t) = \varepsilon \beta (1 - c(t)) \left( \hat{S}^{\mathrm{I}} \left. \frac{\mathrm{d}(\rho_{\sigma}^{\mathrm{I}} \rho_{\tau}^{\mathrm{I}})}{\mathrm{d}e_{m}} \right|_{e_{m} = e_{w}} + \hat{S}^{\mathrm{II}} \left. \frac{\mathrm{d}(\rho_{\sigma}^{\mathrm{II}} \rho_{\tau}^{\mathrm{II}})}{\mathrm{d}e_{m}} \right|_{e_{m} = e_{w}} \right)$$

$$[18] \quad 485$$

which is equation Eq. (3) in the main text using the same notations 486 as in Scenario 1. 487

Table 2. Main parameters and default va	alues used in scenario 2
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Virus parameters	Symbol	Values	
Basic reproduction ratio	$R_0$	3	
Transmission	$\beta$	0.3 day <sup>-1</sup>	
Recovery rate	δ	0.1 day-1	
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	$\nu^{I}$	$0.002 \text{ day}^{-1} \text{ (purple)}  0.004 \text{ day}^{-1} \text{ (orange)}$	
Vaccination rate for 2 <sup>nd</sup> dose	$ u^{  }$	$0.002 \text{ day}^{-1}$ (purple) $0.0002 \text{ day}^{-1}$ (orange)	
Efficacy at blocking infection (1 <sup>st</sup> and 2 <sup>nd</sup> dose)	$r^{ }$ , $r^{  }$	0.6 (1 <sup>st</sup> dose) and 0.9 (2 <sup>nd</sup> dose)	

 $r_{\tau}^{\mathsf{I}}, r_{\tau}^{\mathsf{II}}$ 

 $r^{I}_{\mu}, r^{I}_{\mu}$ 

0 (1<sup>st</sup> dose) and 0 (2<sup>nd</sup> dose)

0.5 (1st dose) and 0.95 (2nd 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:

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

Efficacy at blocking transmission (1st and 2nd dose)

Efficacy at reducing mortality (1st and 2nd dose)

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

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

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

where  $r_{\tau}$  and  $r_{\sigma}$  give the vaccine efficacy in the absence of vaccine 488 escape mutation (i.e.  $e_i = 0$ ). When  $e_i = 1$  (full vaccine escape), 489 the vaccine offers no reduction in transmissibility and susceptibility 490  $(\rho_{\sigma} = \rho_{\tau} = 1)$ . We assume that vaccination can also protect against disease induced mortality and we define  $r_{\mu}^{\rm I}$  and  $r_{\mu}^{\rm II}$  so that 491 492  $\hat{\mu}_{i}^{\text{I}} = \mu(1 - r_{\mu}^{\text{I}}) \text{ and } \hat{\mu}_{i}^{\text{II}} = \mu(1 - r_{\mu}^{\text{II}}).$ 493

Initial conditions used in Figure 2B-D: S(0) = 1,  $\hat{S}^{I}(0) = \hat{S}^{II}(0) = 0$ , 494  $I(0) = \hat{I}^{I}(0) = \hat{I}^{II}(0) = 10^{-6}, D(0) = 0, p_m(0) = 10^{-3}.$  The 495

intensity of Non-Pharmaceutical Interventions varies with time 496

- $(c(t) = 0.7 \text{ when } t \in [40, 140] \text{ and } t \in [150, 250], c(t) = 0 \text{ otherwise}).$ 497 498 Vaccination starts at t = 150 and the other parameters used in
- Figure 2B-D are listed in Table 2. 499

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