

# Evolution of resistance to COVID-19 vaccination with dynamic lockdown

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## Article

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# 1 Evolution of resistance to COVID-19 vaccination with dynamic lockdown

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11

12 **The COVID-19 pandemic has led to an unprecedented global response in terms of social**  
13 **lockdown in order to slow the spread of the virus <sup>1,2</sup>. Currently the greatest hope is**  
14 **based on world-wide vaccination<sup>3,4</sup>. The expectation is that social and**  
15 **economic activities can gradually resume as more and more people become vaccinated.**  
16 **Yet, a relaxation of social distancing that allows increased transmissibility, coupled with**  
17 **selection pressure due to vaccination, will likely lead to the emergence of vaccine**  
18 **resistance <sup>5</sup>. Here we analyze the evolutionary dynamics of COVID-19 in the presence of**  
19 **dynamic lockdown and in response to vaccination. We use infection and vaccination**  
20 **data of 6 different countries (Israel, US, UK, Brazil, France and Germany) to assess the**  
21 **probability and timing for the wave of vaccine resistant mutant<sup>2</sup>. For slow vaccination**  
22 **rates, resistant mutants will appear inevitably even if strict lockdown is maintained. For**  
23 **fast vaccination rates (such as those used in Israel) the emergence of the mutant can be**  
24 **prevented if strict lockdown is maintained during vaccination. Our mathematical results**  
25 **provide quantitative guidelines for a combined vaccination and lockdown policy that**  
26 **minimizes the probability of emergence of vaccine resistance variants for current and**  
27 **future vaccination programs.**

28

29 The COVID-19 pandemic has had a devastating effect on global health and economy. Since  
30 the identification of the first SARS-COV-2 case in December 2019, 178.71 million  
31 infections have been recorded and at least 3.86 million people have died as a result of the  
32 infection (as of June 2021)<sup>2</sup>. The increased mortality and complication rates of SARS-COV-  
33 2<sup>1</sup> compared to the mild diseases caused by seasonal coronaviruses, such as HCoV-229E<sup>6</sup>,  
34 have led to unparalleled governmental and individual-level responses in order to reduce  
35 the number of SARS-COV-2 infections.

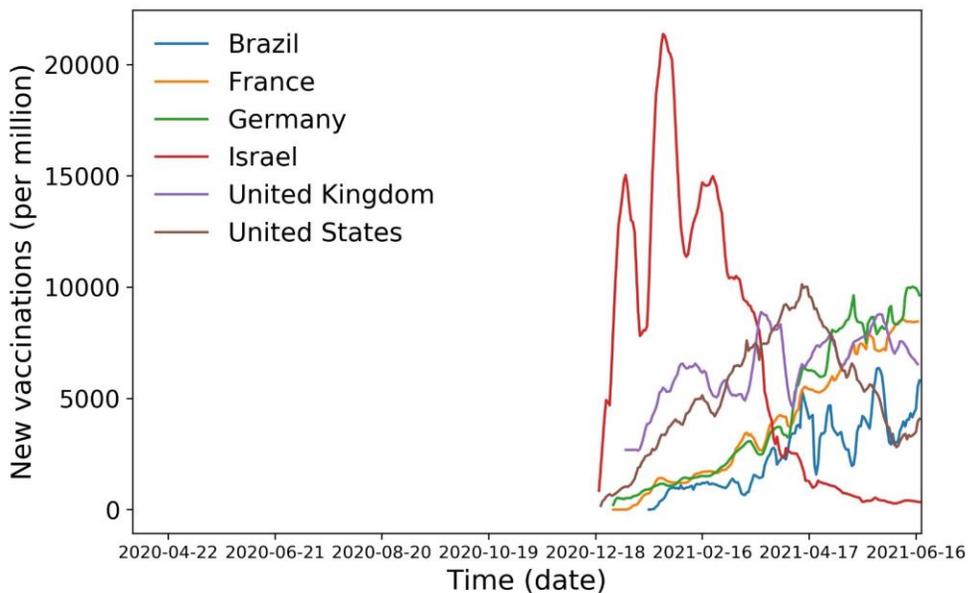
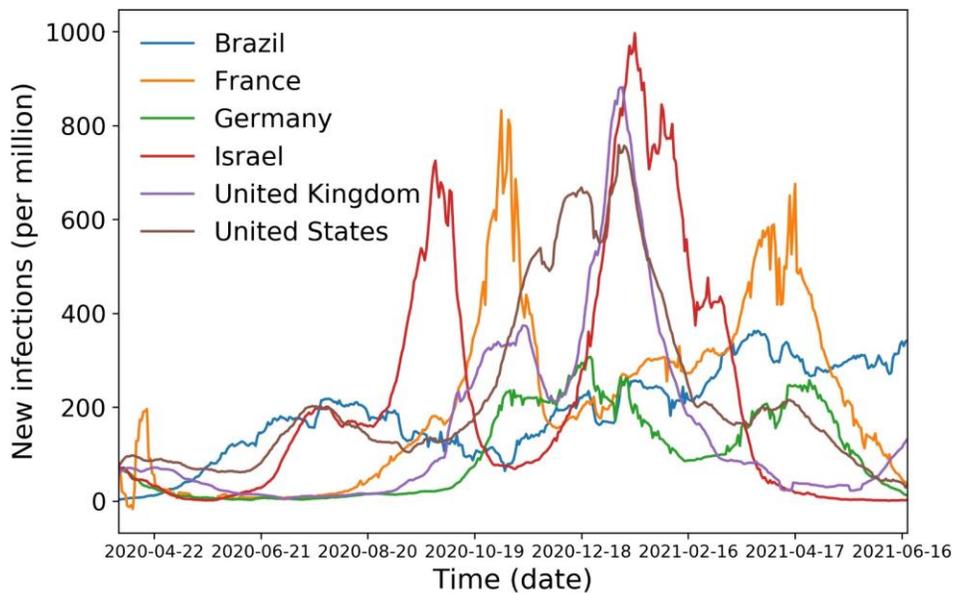
36 Since the beginning of the pandemic, it has become clear that non-pharmaceutical  
37 interventions (NPI), such as lockdowns, are economically and socially unsustainable in the  
38 long run. Periodical loosening and tightening of social distancing measures, which present  
39 an attempt at balancing economical and sanitary considerations, have led to waves of  
40 increase and decrease in the number of SARS-COV-2 infections per day<sup>2</sup> (see **Figure 1A**).  
41 Therefore, much hope has been placed on vaccine development, which would allow the  
42 immunization of a large fraction of the population, thereby substantially reducing  
43 mortality and potentially achieving herd immunity, which could in principle eradicate  
44 SARS-COV-2 altogether.

45 Mass vaccination campaigns have been launched in many countries (see **Figure 1B**), most  
46 notably Israel and the UK (both more than 60% of vaccinated population) and the US and  
47 Germany (both more than 50% of vaccinated population). Currently, four companies are  
48 producing vaccines that have been approved for emergency use either by the Food and  
49 Drug Administration (FDA)<sup>3</sup> or by the European Medicines Agency (EMA)<sup>4</sup>: Pfizer-  
50 Biontech, Moderna, AstraZeneca and Johnson & Johnson/Janssen Pharmaceuticals.  
51 Several other vaccines are also used outside of the European Union and the USA:  
52 Gamaleya (Sputnik V), Sinopharm Beijing, Sinovac, Sinopharm-Wuhan and Bharat-Biotech  
53 (Covaxin)<sup>7</sup>.

54

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56



57

58 **Figure 1: New SARS-CoV2 cases per day per million and number of vaccinations against SARS-CoV2 per**  
 59 **day per million in France, Germany, USA, Israel, Brazil and UK. (A)** In an attempt to balance economic and  
 60 sanitary considerations, these six countries have gone through several cycles of loosening and tightening  
 61 government-imposed restrictions, resulting in periodical increases and decreases in the number of SARS-  
 62 CoV2 infections per day. The so-called “British variant”, identified in November 2020, is most probably  
 63 responsible for the increase in the number of infections in the UK and Israel at that time. **(B)** Large scale  
 64 vaccination programs commenced in December 2020. At the peak, Israel vaccinated more than 20,000  
 65 people per million (2%) per day. The vaccination rate then decreased in April 2021 as most eligible  
 66 individuals had been vaccinated.

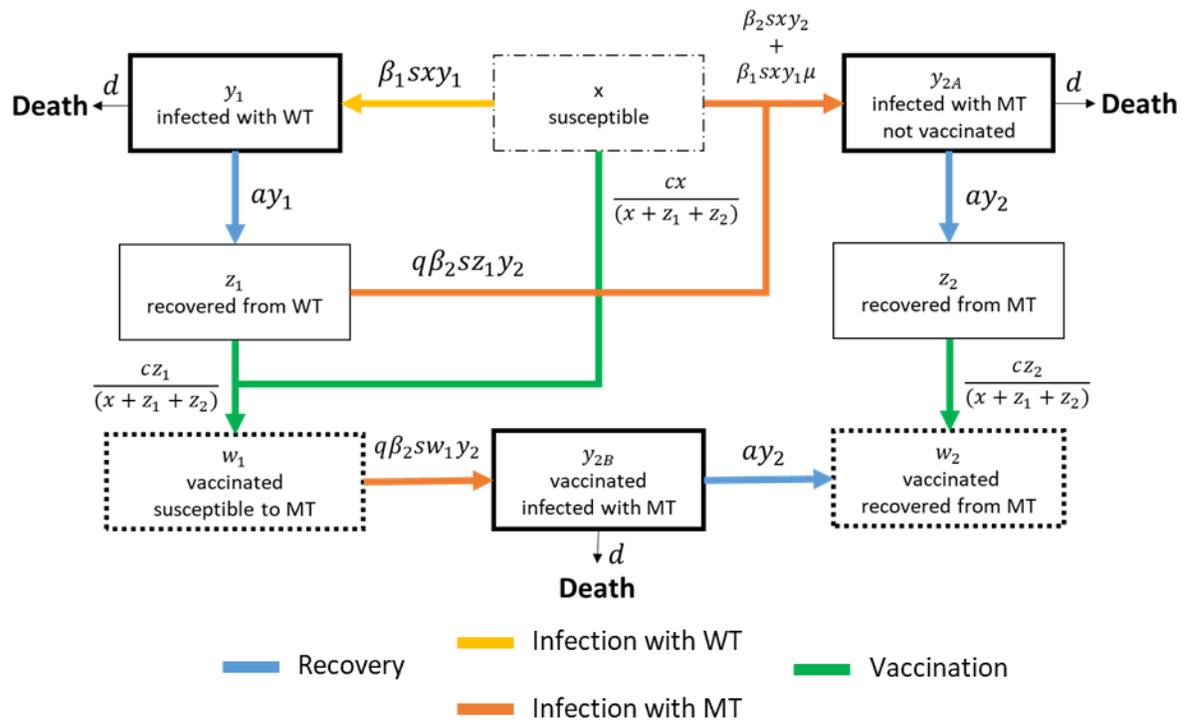
67 However, the identification of new SARS-COV-2 variants has cast a shadow over the  
68 expectation of a swift end of the pandemic<sup>8,9</sup>. The so-called “British” variant (B.1.1.7),  
69 now termed  $\alpha$ , and “South African” variant (501.V2), now termed  $\beta$ , have been shown to  
70 be neutralized to a lesser extent by convalescent and vaccinee sera<sup>10</sup>, although  
71 experiments on non-human primates have shown that this decrease might not  
72 necessarily cause a decrease in immunity<sup>11</sup>. Structural studies have mapped and  
73 predicted mutations that lead to antibody escape<sup>12-14</sup>. As vaccination around the world  
74 progresses, the continued evolution of SARS-COV-2 could eventually give rise to a fully  
75 vaccine resistant variant. Such a variant could quickly spread due to its ability to infect  
76 vaccinated and recovered in addition to fully susceptible individuals. The question of  
77 emergence of vaccine resistance has already been the subject of many research papers<sup>15-</sup>  
78 <sup>18</sup>.

79 What policy could be exercised that would minimize the chance of emergence of vaccine  
80 resistant strains? Policymakers can vary the extent of social distancing imposed and  
81 regimes of vaccine administration. The critical biological parameters on the other hand  
82 include the infectivity of the various strains and the rate of mutation of the virus that may  
83 ultimately lead to emergence of a resistant strain. Here we introduce a mathematical  
84 model that examines various combinations of these parameters. Our model helps to  
85 design optimal policies that would minimize the chance of emergence of resistant strains  
86 or maximize the time until their occurrence.

87 Our paper is an addition to the extensive body of work that has been performed in the  
88 past year in order to understand the spread and evolution of SARS-COV-2<sup>19-25</sup>. SARS-COV-  
89 2 research has drawn on a very long history of epidemiological research<sup>26,27,36-38,28-35</sup>. Due  
90 to the global and urgent nature of the pandemic, many studies that could inform policy-  
91 making have been conducted<sup>5,39,48,40-47</sup>.

92 In order to understand the evolutionary potential of the virus in response to a vaccination  
93 program we study a stochastic model for infection dynamics and virus evolution in the  
94 presence of varying degrees of social lockdown and different vaccination rates. We

95 distinguish between a wild-type virus (WT) and a vaccine resistant mutant virus (MT). The  
 96 vaccine is effective against the WT strain, while the MT strain evades immunity induced  
 97 by the vaccine either partially or completely. We build upon the mathematical framework  
 98 of the Susceptible-Infected-Removed (SIR) model from epidemiology<sup>32,49</sup>, albeit with  
 99 considerable adjustments necessitated by the specific problem at hand. Our model keeps  
 100 track of people who are susceptible, infected by WT or MT, recovered from WT or MT,  
 101 vaccinated or unvaccinated (**Figure 2**).



102

103 **Figure 2: Infection dynamics, vaccination and resistance.** Susceptible individuals ( $x$ ) can be infected by  
 104 wildtype (WT) or mutant (MT) virus. Infected people ( $y_1, y_{2A}, y_{2B}$ ) can die (with rate  $d$ ) or recover (with  
 105 rate  $a$ ). People recovered from WT or vaccinated against WT can be infected by MT. People recovered from  
 106 MT cannot be infected by WT. We assume equal infectivity, recovery and death rates for both WT and MT.  
 107 Vaccination occurs at rate  $c$  per day for all unvaccinated individuals (excluding those that are currently in  
 108 active infection). Mutation happens (at rate  $\mu$ ) when exposure to a WT infected individual ( $y_1$ ) results in  
 109 the generation of a MT infected individual. Since  $\mu$  is small, we neglect the term  $1 - \mu$ . The rates of these  
 110 events are indicated on the arrows and are used in the Gillespie algorithm implementing the stochastic  
 111 dynamics.

112 Crucially, we assume there is a dynamic lockdown guided by the number of new infections  
113 per day. As that number exceeds a threshold, governmental rules and individual  
114 responses reduce social activity. If the number of new infections falls below this  
115 threshold, the lockdown is somewhat relaxed and some people stop following the rules,  
116 thereby allowing higher transmission of the virus. We simulate these dynamics as a  
117 stochastic process. In consequence, we obtain fluctuating numbers of new infections per  
118 day. We introduce mass vaccination at alternative fixed rates. Then we compute the  
119 probability and timing of the wave of infection caused by the spontaneous emergence of  
120 a vaccine resistant virus.

121 In our approach, the mutation rate  $\mu$  denotes the probability that a WT-infected individual  
122 will infect a susceptible individual with the MT strain. The exact value of this probability  
123 is currently unknown and complex to obtain empirically. For the simulations and  
124 calculations reported in this paper we therefore consider a wide range of mutation rates.  
125 From our model, we also derive an upper bound for the mutation rate using the fact that  
126 no wave of a vaccine-resistant variant has occurred up until now. Note that this rate can  
127 be very different from the per-base mutation rate of SARS-COV-2, which is about  $10^{-5}$ .

128

## 129 DYNAMICS OF VIRAL INFECTION AND EVOLUTION

130 Our model keeps track of eight different variable states: individuals who are susceptible  
131 ( $x$ ), infected with WT ( $y_1$ ), non-vaccinated and infected with MT ( $y_{2A}$ ), vaccinated and  
132 infected with MT ( $y_{2B}$ ), recovered from WT ( $z_1$ ), recovered from MT ( $z_2$ ), vaccinated but  
133 susceptible to MT ( $w_1$ ), vaccinated and recovered from MT ( $w_2$ ); see **Figure 2**.

134 The WT strain can infect susceptible individuals ( $x$ ), converting them to individuals  
135 infected with WT ( $y_1$ ) at rate  $\beta_1$ . A mutation can occur with probability  $\mu$ . In this case, a  
136 WT infected individual infects a susceptible individual ( $x$ ) with a mutated version of the  
137 virus, in a mutation that have taken place in the infecting individual, thus converting the  
138 susceptible to a MT infected individual ( $y_{2A}$ ). WT infected individuals either recover with

139 rate  $a$  and become immune to future WT infection ( $z_1$ ) or die at rate  $d$ . Susceptible  
140 individuals ( $x$ ) and individuals recovered from WT ( $z_1$ ) can become vaccinated individuals  
141 ( $w_1$ ). The parameter  $c$  denotes the number of individuals vaccinated per day. Hence, the  
142 rates of vaccination of  $x$ ,  $z_1$  and  $z_2$  are respectively  $cx/(x + z_1 + z_2)$ ,  $cz_1/(x + z_1 + z_2)$   
143 and  $cz_2/(x + z_1 + z_2)$ . For simplicity we assume single-dose vaccination; for a double  
144 dose vaccine our model would describe the application of the second dose ignoring partial  
145 immunity caused by the first dose; extension of our model to a full two dose vaccination  
146 protocol is straightforward.

147 At rate  $\beta_2$ , the MT strain infects susceptible individuals ( $x$ ), WT recovered individuals ( $z_1$ )  
148 and vaccinated individuals who are not immune to MT ( $w_1$ ). MT infected individuals either  
149 recover with rate  $a$  and become immune to future MT and WT infection ( $z_2$ ) or die at  
150 same death rate  $d$  as with the WT strain, i.e. assuming no difference in lethality between  
151 the two strains. We assume one-way cross-immunity induced by the viral strains: the MT  
152 strain can infect individuals that have recovered from WT or that have been vaccinated  
153 against WT, but the WT strain cannot infect individuals that have recovered from the MT.  
154 In practice, the WT strain becomes extinct soon after the appearance of the MT strain,  
155 meaning that the number of individuals recovered from MT that could become infected  
156 with WT is negligible. We note that our MT strain escapes both from the immunity that is  
157 induced by natural infection with WT and the immunity induced by vaccination against  
158 WT.

159 We need to distinguish between MT infected individuals that are or are not vaccinated:  
160  $y_{2B}$  and  $y_{2A}$ , respectively. Upon recovery the former will not be vaccinated (again), while  
161 the latter will be vaccinated.

162 We also study partial immunity to the MT strain which can be acquired by recovery from  
163 WT infection or by vaccination. For partial immunity, the corresponding infection rates  
164 are multiplied by a parameter  $q$ , which is between 0 and 1. If  $q = 1$  then WT infection or  
165 vaccination confers no immunity to MT at all; the mutant escapes completely. For  $0 <$   
166  $q < 1$ , the MT is a partial escape mutant. For  $q = 0$ , the MT does not escape at all.

167 Lockdown measures are implemented by multiplying the infectivity coefficients of each  
168 strain by a social activity parameter  $s$  which ranges in  $[0,1]$ . Unconstrained social  
169 interaction means  $s = 1$ , while  $s = 0$  would be complete lockdown. The population  
170 tolerates a certain number of new infections,  $L$ , per day. Each day, if the number of new  
171 infections exceeds  $L$ , then  $s$  is decreased by a random, uniformly distributed number  
172 between 0 and 0.1. If the number of new infections is less than  $L$ , then  $s$  is increased by  
173 a random, uniformly distributed number between 0 and 0.1. In any case,  $s$  cannot  
174 decrease below 0.05 or increase above 1.

175 As an example, the rate of infection of the recovered from WT  $z_1$  by the MT strain infected  
176 individuals  $y_2$  is multiplied both by the lockdown coefficient  $s$  and the partial immunity  
177 coefficient  $q$  – hence this rate is given by  $q\beta_2sw_1y_2$ .

#### 178 COMPUTATIONAL IMPLEMENTATION AND DATA

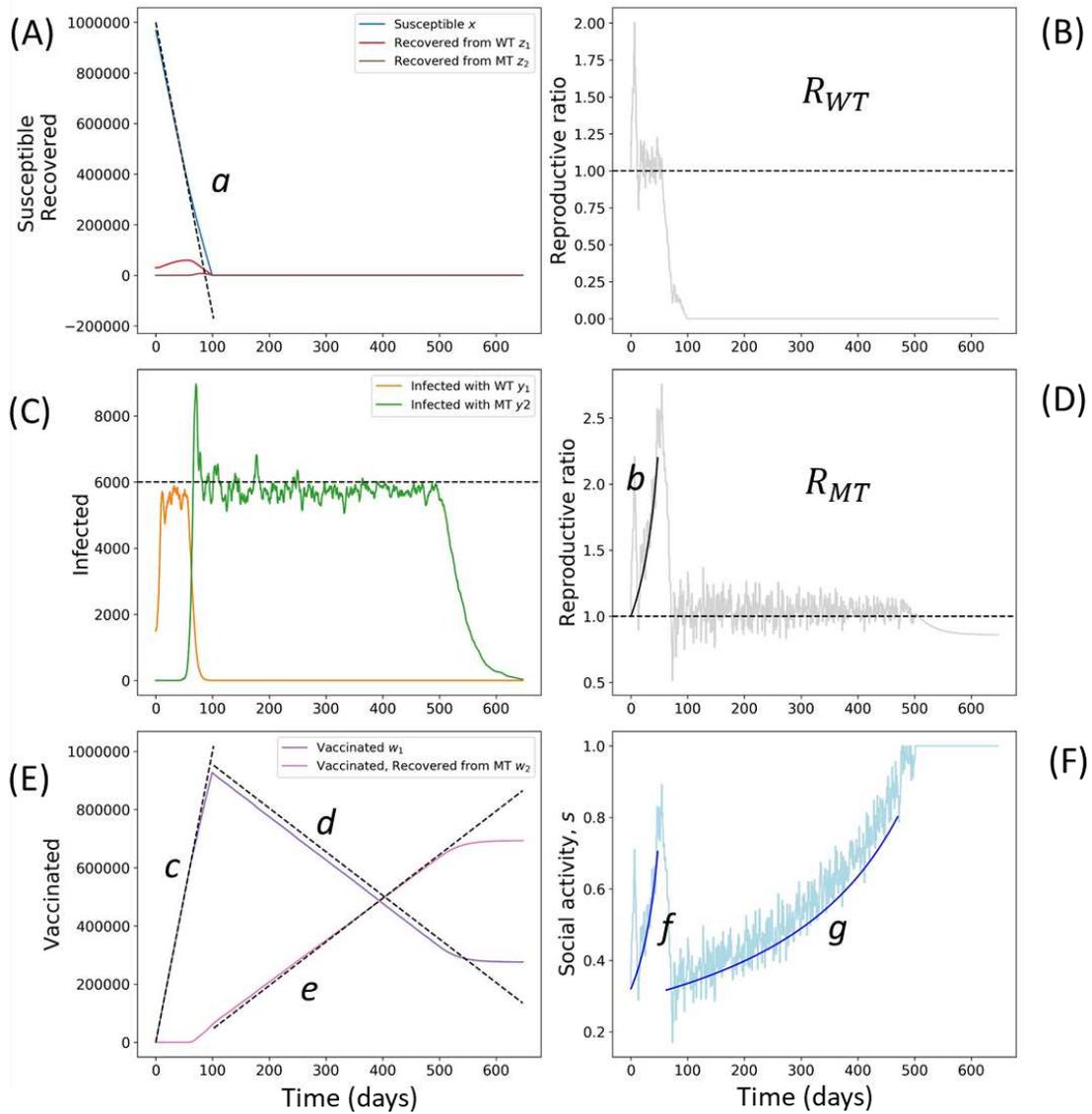
179 A Gillespie algorithm is commonly used to simulate stochastic systems with high variation  
180 in waiting times between consecutive events<sup>50–53</sup>. In our model the population is  
181 represented as a vector of length eight, corresponding to the eight categories. The rates  
182 of all possible events (infection, recovery, death, mutation and vaccination) are  
183 calculated. The time of the next event in the model is drawn from an exponential  
184 distribution, with parameter dependent on the sum of all event rates and an event is  
185 chosen, with probability proportional to its rate. The population is updated according to  
186 the event that occurred. The simulation is stopped when there are no more infected  
187 individuals in the population. The algorithm is presented in pseudocode in the **Appendix**,  
188 along with a table of the possible events of the model and their default rates.

189 In order to achieve feasible computation time and resources, we simulated populations  
190 of size up to  $N = 10^6$ . The results of those simulations can be scaled to larger population  
191 sizes by considering a population of for example  $N = 10^7$  as  $m = 10$  “batches” of  $10^6$   
192 individuals, and computing the results for  $N = 10^7$  as  $1 - (1 - p)^m$ , where  $p$  is the  
193 proportion of runs where the MT strain took over. **Figure S1** shows the strong agreement

194 between simulated results and the results scaled from simulations with smaller  
195 population sizes.

196 For all our simulations, we have endeavored to use real world data for all model  
197 parameters. In particular, infection and vaccination data has been obtained from the  
198 database *Our World in Data* <sup>2</sup> (OWID) and downloaded on June 19<sup>th</sup>, 2021.

199 In our simulation, since the number of new infections each day is constant, the number  
200 of susceptible individuals decreases linearly with slope  $-L/a$ . Vaccination of both  
201 susceptible and recovered individuals proceeds at rate  $c$ . The social activity parameter,  $s$ ,  
202 increases as more and more individuals become immunized either by infection or by  
203 vaccination. The WT reproductive rate,  $R_{WT}$ , is maintained at 1 as long as the MT has not  
204 appeared. The MT reproductive rate,  $R_{MT}$ , increases with the social activity parameter  $s$   
205 until the MT strain takes over. After MT takeover, the MT reproductive rate  $R_{MT}$  is  
206 buffered at 1 by the dynamic lockdown (see **Figure 3** and **Methods**).

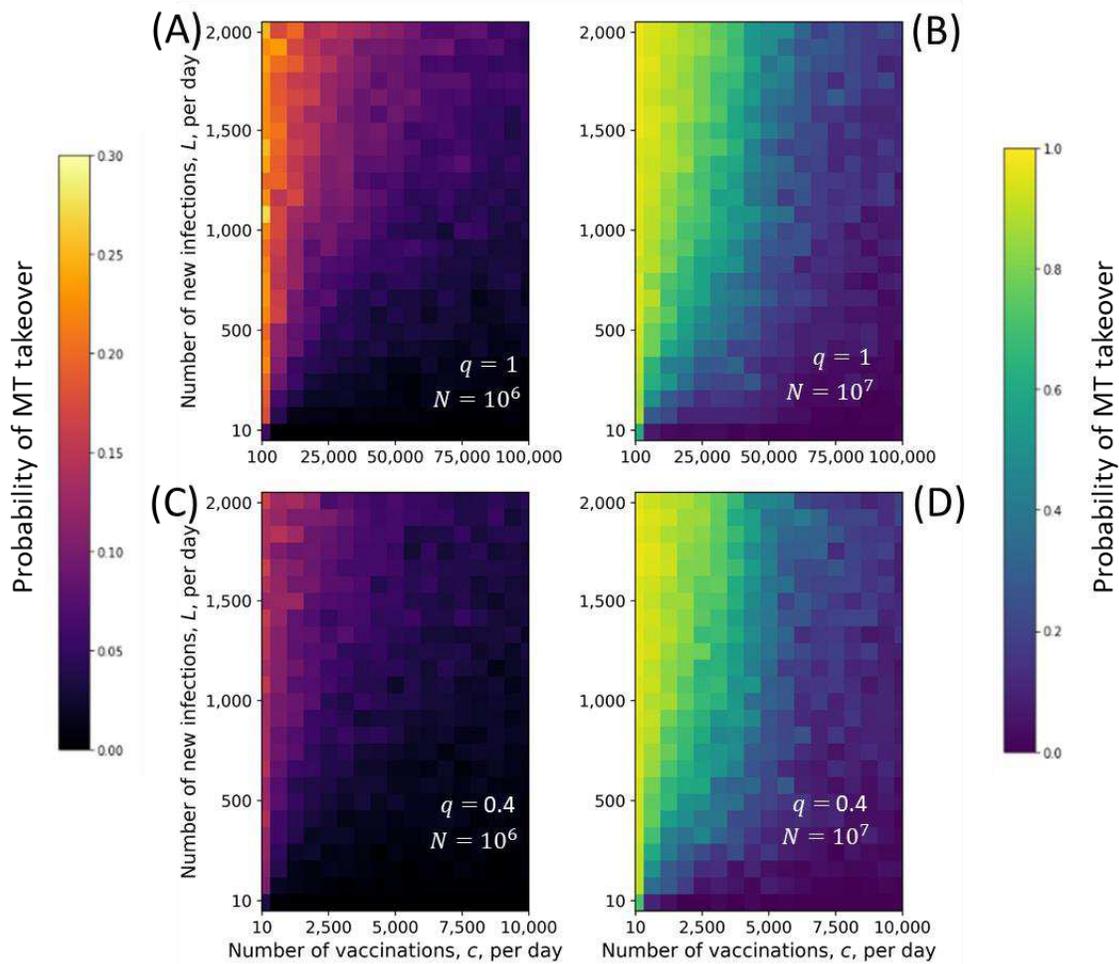


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208 **Figure 3: Evolution of resistance in presence of vaccination.** (A) Before MT takeover, the decline in  
 209 susceptible individuals ( $x$ ) can be approximated by a linear function with slope equal to the vaccination  
 210 rate  $c$ . Since vaccination is fast, individuals recovered from WT and non-vaccinated individuals recovered from  
 211 MT are few. The equation of line (a) is  $x(t) = x(0) - ct$  for  $t < t^*$  where  $t^*$  is the time of takeover of the  
 212 MT. (B) The reproductive rate  $R_{WT}$  is maintained at around 1 by dynamic lockdown. After mutant takeover,  
 213  $R_{WT}$  is less than 1, since the lockdown is now adjusted to the population susceptible to the MT strain. (C)  
 214 The number of active WT infections before takeover and of active MT infections after takeover, is  
 215 fluctuating around  $L/a$  until herd immunity to the MT is reached. (D) Before MT takeover, the reproductive  
 216 rate of the MT grows as (b)  $R_{MT} = \beta_2(x(t) + z_1(t) + w_1(t))/a$ . After takeover,  $R_{MT}$  is maintained around  
 217 1. (E) The number of vaccinated individuals ( $w_1$ ) first increases linearly with slope equal to the vaccination  
 218 rate. After MT takeover, the number of individuals vaccinated to the WT and recovered from MT ( $w_2$ )

219 increased linearly with slope  $L$ . The equations of the lines are given by (c)  $w_1(t) = ct$  for  $t < t^*$  (d)  $w_1(t) =$   
220  $w_1(t^*) - L(t - t^*)$  for  $t > t^*$  (e)  $w_2(t) = L(t - t^*)$  for  $t > t^*$ . (F) Before MT takeover, the dynamic  
221 lockdown is adjusted to the WT. As the number of individuals immune to WT grows, social activity increases.  
222 When the MT emerges, lockdown measures are reinstated. Subsequently, social activity increases as the  
223 population immune to the MT grows. The equations for the lines given by (f)  $s(t) = a/\beta_1 x(t)$  for  $t < t^*$   
224 ; (g)  $s(t) = a/\beta_2(x(t) + z_1(t) + w_1(t))$  for  $t > t^*$ .

225 We performed 1000 runs of the stochastic simulation for each combination of parameters  
226 reflecting realistic values of the two model parameters determined by governmental  
227 policy: the tolerated number of infections per day,  $L$ , and the vaccination rate per day,  $c$ .  
228 Each square of the color map shown in **Figure 4** reflects the average value of these 1000  
229 runs, which were performed for a population of  $N = 10^6$  and then scaled to  $N = 10^7$   
230 and  $N = 10^8$ . At each combination of  $L$  and  $c$  the color maps denote the predicted  
231 probability of a mutant take over. We perform computations using  $q = 1$  and  $q = 0.4$  for  
232 complete and partial immune evasion by the mutant.



233

234 **Figure 4: Probability of emergence of resistance.** For each square of the color maps, the proportion of runs  
 235 (out of 1000 runs) where the number of individuals infected with the MT strain exceeded the number of  
 236 individuals infected with the WT strain is recorded. All simulations are run for a population size of  $N = 10^6$ ,  
 237 then scaled to obtain the results shown for  $N = 10^7$ . Results for color maps (B) and (D) were scaled  
 238 according to  $(1 - (1 - p)^{10})$ , where  $p$  is the proportion of runs where the MT strain took over. We observe  
 239 a triangular shape of  $(L, c)$  parameter sets for which the MT strain takes over, indicating that high  
 240 vaccination rates can be safely associated with more lenient social distancing measures. On the other hand,  
 241 very slow vaccination cannot be compensated by any strength of lockdown. Partial immunity to the WT  
 242 strain (panels (A) and (C)) does not affect the shape of the parameter space where we observe MT takeover,  
 243 but reduces its probability.

244

245 Allowing a large amount of infection cases and slow vaccination results is almost certain  
 246 takeover of the MT strain. On the other hand, very fast vaccination coupled with a low  
 247 number of tolerated new infections per day can prevent emergence of the MT. Partial  
 248 immune evasion ( $q = 0.4$ ) of the mutant slightly reduces the probability of its takeover.  
 249 Note that the shape of the parameter space where we observe takeover is similar for  $q =$   
 250  $1$  and  $q = 0.4$ .

## 251 REPRODUCTIVE RATIO OF THE MUTANT AND PROBABILITY OF TAKEOVER

252 In **Figure 5** we show detailed data from 6 countries together with the estimated  
 253 reproductive ratio,  $R_{MT}$ , of a vaccine resistant mutant and the probability of generating a  
 254 wave of resistant virus. Data for the number of susceptible individuals  $x(t)$ , vaccinated  
 255 individuals  $w(t)$ , recovered individuals  $z(t)$ , newly infected individuals  $L(t)$ , and an  
 256 estimate for the reproductive rate  $R_{WT}$  of the WT can be obtained from *OWID* <sup>2</sup>. The  
 257 reproductive rate  $R_{MT}$  of the escape mutant can be calculated according to:

$$R_{MT}(t) = R_{WT}(t)[x(t) + qw(t) + qz(t)]/x(t) \quad (1)$$

258 The probability of not producing an escape mutant in a given day is  $(1 - \mu)^{L(t)}$ . The  
 259 probability of not producing a surviving escape mutant is  $(1 - \rho(t)\mu)^{L(t)}$ , where  $\rho(t)$  is  
 260 the survival probability of a mutant generated on that day. If  $R_{MT}(t) < 1$  then  $\rho(t) = 0$ .  
 261 If  $R_{MT}(t) > 1$  we assume  $\rho(t) = 1 - 1/R_{MT}(t)$ . The probability that no surviving mutant  
 262 is generated between time 0 and time  $t$  is given by

$$P(t) = \prod_{\tau=0}^t [1 - \mu\rho(\tau)]^{L(\tau)} \quad (2)$$

263 In **Figure 5** we show the reproductive rate of the mutant  $R_{MT}(t)$  and the probability  $P(t)$   
 264 of generating a surviving escape mutant as a function of time. Prior to vaccination the  
 265 reproductive rate of a potential escape mutant tracks closely that of the WT. As people  
 266 become vaccinated in large numbers,  $R_{MT}$  starts to increase significantly above  $R_{WT}$ .  
 267 Nevertheless, it is possible to keep  $R_{MT}$  below one by maintaining some measures of  
 268 lockdown. (This is the case for Israel and UK). Overall, the probability that Israel generated  
 269 a vaccine escape mutant (before June 2021) is of order of 1-2 percent (assuming  $\mu =$

270  $10^{-7}$ ). For the same mutation rate the corresponding probability for the United States is  
271 32 percent; the United States have a much larger total population size but also many more  
272 infections per million people. The corresponding probabilities for Brazil, France, Germany,  
273 and UK are 17, 8, 4 and 6 percent (see **Table 1**).

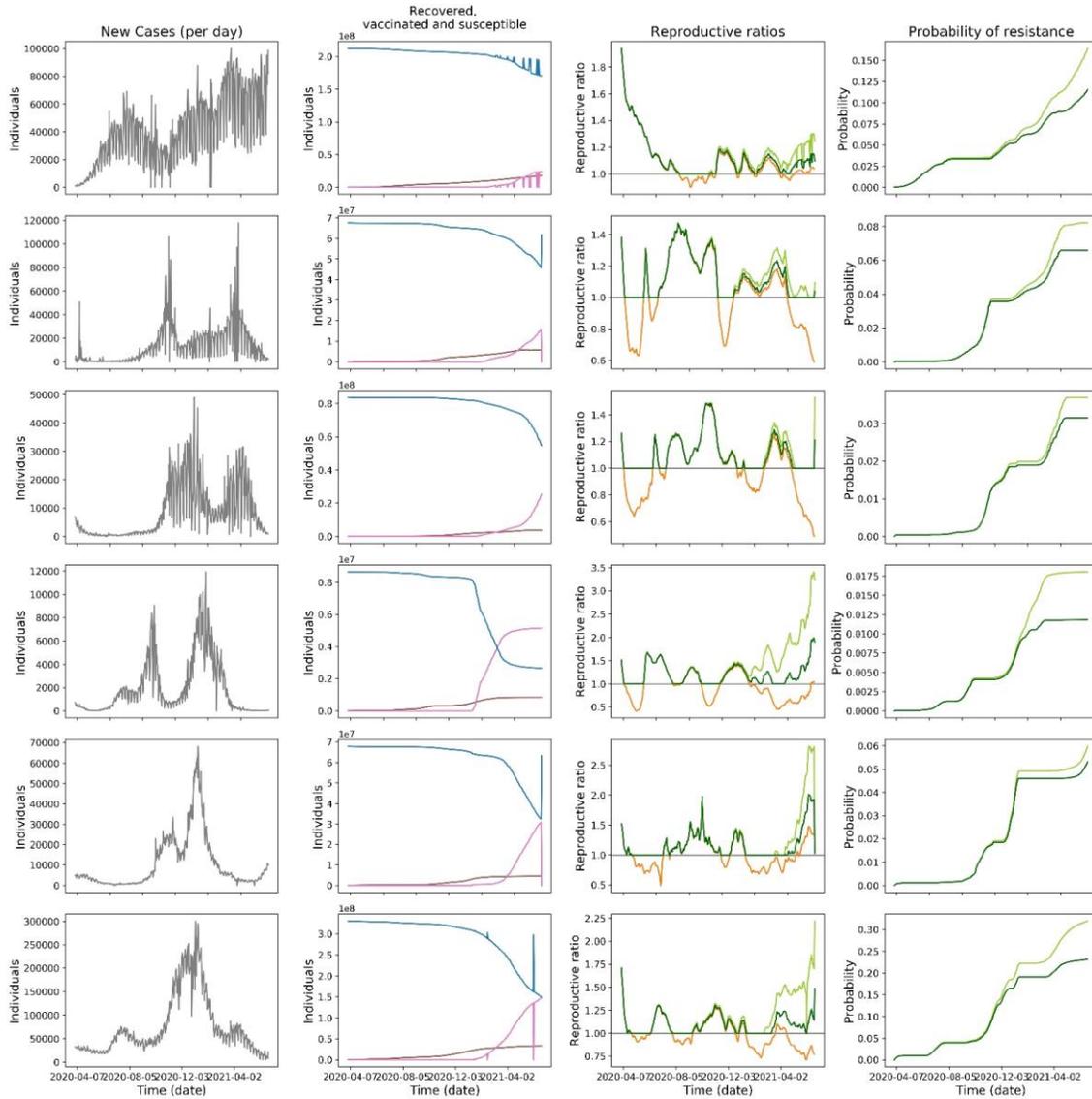
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280 **Figure 5: Infection, vaccination data and estimates for reproductive ratios and probability of resistance**  
 281 **for Brazil, France, Germany, Israel, the United Kingdom, and the United States.** The total number of new  
 282 cases per day (leftmost column), number of susceptible,, recovered, and vaccinated individuals (second  
 283 column from left) was downloaded from the *OWID* (Our World In Data) database. We used the *OWID*  
 284 estimate for the WT reproductive coefficient  $R_{WT}$  to calculate the potential MT reproductive coefficient  
 285  $R_{MT}$  for a full escape mutant ( $q = 1$ ) and a partial escape mutant ( $q = 0.4$ ), (third column). We use Eq. 2  
 286 to estimate the probability that an escape mutant would have emerged until a certain date assuming  $\mu =$   
 287  $10^{-7}$  (fourth column).

288

289

Country	Population size ( $\times 10^6$ )	Average rate of infection per day per person before vaccination ( $\times 10^{-6}$ )	Average rate of infection per day per person after vaccination ( $\times 10^{-6}$ )	Average rate of vaccination per day per person ( $\times 10^{-6}$ )	Probability of resistance ( $\mu = 10^{-7}$ )
Brazil	212.6	132	294	2946	0.166
France	68.1	120	319	4440	0.082
Germany	83.8	67	135	4878	0.037
Israel	8.7	120	412	9181	0.018
United Kingdom	67.9	109	187	6358	0.060
United States	331.0	173	246	5533	0.320

290

291 **Table 1: Calculated probability of emergence of vaccine resistance using real-world data from six**  
 292 **countries: Brazil, France, Germany, Israel, the United Kingdom and the United States.** The probability of  
 293 vaccine resistance was calculated using the product formula in Eq. 2 and the data presented in **Figure 5**  
 294 assuming  $\mu = 10^{-7}$ .

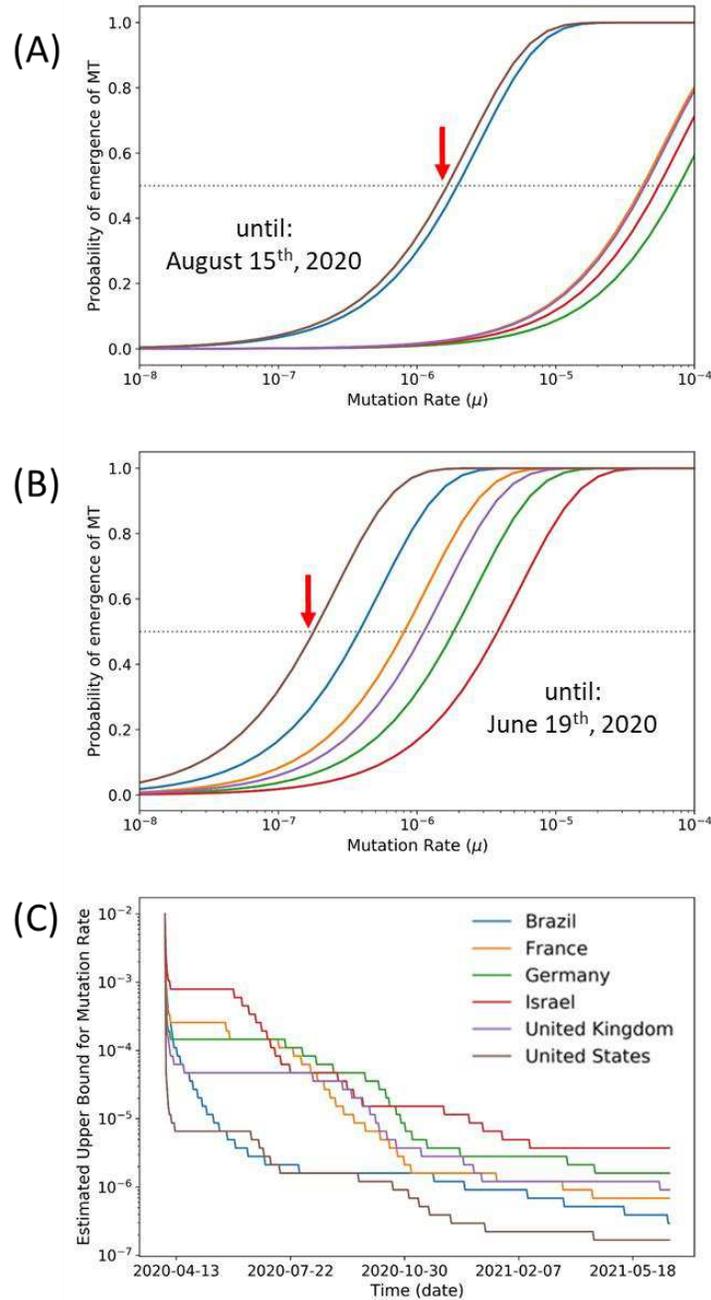
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296 ESTIMATING THE MUTATION RATE  $\mu$

297 We suggest a method to estimate an upper bound of the mutation rate  $\mu$  from WT to MT  
298 based on the observation that despite a large number of infections since the beginning of  
299 the pandemic and including recent vaccination campaigns, no immune evasive mutant  
300 has yet taken over. Our method for calculating an upper bound of the mutation rate is  
301 potentially applicable for estimating any mutation rate between two phenotypes in an  
302 evolving population. The upper bound is computed at any given time point, and can be  
303 updated and become tighter if in future evasive strain still does not appear.

304 For each country, we use Eq. (2) to compute the probability of takeover using data from  
305 the beginning of the pandemic up until June 19<sup>th</sup> 2021 for a wide range of mutation rates.  
306 We assume  $q = 1$ , which means the MT strain is fully immune evasive.

307 The resulting function for probability of mutant take over (for a given time point) versus  
308 mutation rate has a sigmoidal shape, with its midpoint corresponding to the mutation  
309 rate for which it is equally probable that the MT strain would have taken over or not.  
310 Plugging in data on number of infections in several countries gives an upper bound on the  
311 probability of mutant take over and a corresponding estimation of mutation rate per  
312 transmission that will result in the emergence of such a mutant. This estimated upper  
313 bound on the mutation rate decreases over time as long as more infections do not give  
314 rise to a MT strain (see **Figure 6**).



315

316 **Figure 6: Estimation of mutation rate given that no vaccine resistant mutant has yet taken over. (A,B)**

317 Using Eq. 2, we calculate the probability of MT strain takeover for a range of mutation rate values. The

318 probability of MT strain takeover follows a sigmoidal function, where the midpoint is reached for the value

319 of  $\mu$  where MT strain takeover becomes more probable than not. (C) The midpoint of the function

320 (indicated by a red arrow) describing the probability of MT strain takeover will decrease in value as more

321 and more time passes without the takeover of an MT strain. We can use this value as an upper bound of

322 the mutation rate for our model.

323

324 Since the probability of MT takeover (Eq. (2)) is strongly dependent on the number of  
325 infections, significant decreases in the estimated values correspond to periods with high  
326 infection rates in which, nonetheless, a mutant did not appear. The estimate for the upper  
327 bound of the mutation rate is expected to plateau as vaccination campaigns lead to a  
328 decrease in the number of infection cases. The estimate of  $10^{-6}$  will decrease further if  
329 and when large countries such as the US will advance in the vaccination campaign with  
330 no mutant takeover. Using the world infection and vaccination data, we obtain  $\mu = 10^{-7}$   
331 as the order of magnitude for the upper bound for the rate at which immune evasive  
332 mutants appear. But estimates based on individual countries may be more informative  
333 since the world data reflects the average over an extremely heterogeneous population  
334 subject to very different policies.

#### 335 A SIMPLE FORMULA FOR THE ESCAPE PROBABILITY

336 The dynamic lockdown captured by the social activity parameter  $s(t)$  maintains the  
337 number of new infections per day fluctuating around a fixed value and thereby buffers  
338 the reproductive ratio of the wildtype  $R_{WT}$  around 1. The number of active infections is  
339 roughly constant and given by  $L/a$ , where  $a$  is the recovery rate (see **Figure 3**). If  
340 vaccination is slow,  $c \ll L$ , then the change in the number of susceptible,  $x(t)$ , and  
341 recovered individuals,  $z_1(t)$ , over time can be described by linear functions with slopes  
342 proportional to  $L$  (see **Methods and Figure S2A**).

343 Alternatively, for fast vaccination,  $c \gg L$ , the change in the number of susceptible  $x(t)$   
344 and vaccinated individuals  $w_1(t)$  can be described by linear functions with slopes  
345 proportional to  $c$  before MT takeover, and with slopes proportional to  $L$  after MT  
346 takeover (see **Methods and Figure 3E**). Neglecting vaccination of recovered individuals  
347 (which is a reasonable approximation for  $c \gg L$ ) we can write  $x(t) = N - Lt - ct$ ,  $z(t) =$   
348  $Lt$  and  $w(t) = ct$ . The time when herd immunity against the WT is reached is given by

$$T_H = \frac{N}{c + L} \left(1 - \frac{1}{R_0}\right) \quad (3)$$

349 During vaccination the reproductive rate of the mutant increases as (see **Methods**)

$$R_{MT}(t) = \frac{N}{N - (L + c)t} \quad (4)$$

350 The reproductive rate of the MT is initially 1 and increases to  $R_0$  as people recover from  
 351 WT infection or are vaccinated (see **Figure 3D**). Once a mutant has been generated, the  
 352 probability of its survival depends on the value of the reproductive rate,  $R_{MT}(t)$ . The  
 353 probability that no surviving mutant has appeared before time  $t$ , where  $t \leq T_H$ , can be  
 354 calculated to be (see **Methods**):

$$P(t) = \exp\left[-\left(\frac{\mu N}{2}\right)\left(\frac{L}{N}\right)\left(\frac{c + L}{N}\right)t^2\right] \quad (5)$$

355 The probability that no surviving mutant has appeared until herd immunity is

$$P(T_H) = \exp\left[-\left(\frac{\mu N}{2}\right)\left(\frac{L}{c + L}\right)\left(1 - \frac{1}{R_0}\right)^2\right] \quad (6)$$

356 Here  $R_0 = \beta N/a$  is the basic reproductive ratio of the WT. The corresponding formulas  
 357 for partial immune escape mutants are given in the **Methods**. Eq. (6) is in good agreement  
 358 with the results of exact stochastic simulations (**Figure S3**).

359 In **Table 2**, we show how the probability and timing of resistance depends on the  
 360 vaccination rate and the number of new infections per day. We first consider a large  
 361 country of  $N = 10^8$  inhabitants and a mutation rate of  $\mu = 10^{-7}$ . If 10,000 new infections  
 362 occur per day and 1 million people are vaccinated per day, then herd immunity is reached  
 363 in 66 days and the probability of generating a vaccine resistant mutant is about 2 percent.  
 364 For the same vaccination rate, if 50,000 new infections are tolerated each day, then the  
 365 probability of generating an escape mutant increases to 10 percent. If 10,000 new  
 366 infections occur per day but only 100,000 people are vaccinated every day, then the  
 367 probability of generating vaccine resistance increases to 18 percent.

368

(A)

Rate of infection $l$ per day per person ( $\times 10^{-6}$ )	Rate of vaccination $c$ per day per person ( $\times 10^{-6}$ )	Time to herd immunity, $T_H$ (in days)	Probability of resistance			
			t = 50 days	t = 100 days	t = 200 days	t = $T_H$
100	1000	606	0.001	0.005	0.022	0.183
100	5000	131	0.006	0.025	-	0.043
200	5000	128	0.013	0.051	-	0.082
500	5000	121	0.034	0.128	-	0.183
100	10,000	66	0.013	-	-	0.022
200	10,000	65	0.025	-	-	0.043
500	10,000	63	0.064	-	-	0.100

$$N = 10^8 \quad \mu = 10^{-7}$$

(B)

Rate of infection $l$ per day per person ( $\times 10^{-6}$ )	Rate of vaccination $c$ per day per person ( $\times 10^{-6}$ )	Time to herd immunity, $T_H$ (in days)	Probability of resistance			
			t = 50 days	t = 100 days	t = 200 days	t = $T_H$
100	1000	606	0.013	0.053	0.197	0.867
100	5000	131	0.062	0.225	-	0.353
200	5000	128	0.122	0.405	-	0.575
500	5000	121	0.291	0.747	-	0.867
100	10,000	66	0.119	-	-	0.197
200	10,000	65	0.225	-	-	0.353
500	10,000	63	0.481	-	-	0.653

$$N = 10^9 \quad \mu = 10^{-7}$$

369

370 **Table 2: Calculated probability of vaccine resistance for a range of vaccination rates and infection rates.**

371 We observe of counterintuitive effect of higher probability of resistance along time for higher vaccination

372 rates, but lower probability of resistance overall. See also **Figure S4**.

373

374

375 As the proportion of vaccinated individuals grows, social distancing measures relax, and  
376 the probability of emergence of resistance increases. Hence, higher vaccination rates are  
377 associated with higher probabilities of resistance after 50, 100 and 200 days (see **Table**  
378 **2**). However, faster vaccination leads to earlier herd immunity. When herd immunity is  
379 reached, there are no more new infections and the cumulative probability of resistance  
380 plateaus. Therefore, we observe an interesting counterintuitive effect: the probability of  
381 resistance until a fixed time  $t$  increases with the vaccination rate  $c$ , but the probability of  
382 resistance until time  $T_H$  when herd immunity is achieved decreases with the vaccination  
383 rate  $c$ . (see **Table 2 and Figure S4**).

384 We can derive estimates for the emergence of vaccine resistant strains using current  
385 vaccination and infection rates from around the world. If the whole world ( $N = 8 \cdot 10^9$ )  
386 vaccinated as fast as the US ( $c = 5000$  per day per million) and had slightly lower  
387 infection rates than Germany ( $L = 100$  per day per million) then herd immunity would  
388 be achieved in  $T_H = 131$  days; the probability that a resistant virus was generated and  
389 survived by that time would be 0.97 (for  $\mu = 10^{-7}$ ) and 0.29 (for  $\mu = 10^{-8}$ ). If the whole  
390 world vaccinated as fast as Brazil ( $c = 3000$  per day per million) and had infection rates  
391 like the US ( $L = 250$  per day per million) then herd immunity would be achieved in  $T_H =$   
392 205 days; the probability that a resistant virus was generated and survived by that time  
393 would be 0.999 (for  $\mu = 10^{-7}$ ) and 0.75 (for  $\mu = 10^{-8}$ ). Our results underline the  
394 importance of maintaining lockdown measures while herd immunity is not achieved and  
395 timely distribution of vaccines around the world.

## 396 SUMMARY

397 We have studied evolution of resistance to COVID-19 vaccination in the presence of  
398 dynamic lockdown. We use real world data to simulate the spread of the SARS-COV-2  
399 virus. We have performed stochastic simulations and obtained analytical results. In  
400 particular, we have derived a simple intuitive formula for the probability of emergence of  
401 a vaccine resistant strain over time (Eqs. (5) and (6)).

402 Our model most closely corresponds to the assumption that immune evasion could be  
403 due to a single point mutation. Nevertheless, our estimates of the mutation rate between  
404 the wild-type and immune evasive strains could signify that a combination of mutations  
405 is needed to achieve immune evasion. Therefore, we have explored lower effective  
406 mutation rates than the current estimation for the per-base mutation rate of the SARS-  
407 COV-2 virus.

408 The probability of takeover of an immune evasive strain is mostly dependent on the  
409 number of total infection cases that occur during the pandemic. Social distancing  
410 measures, such as lockdowns, can delay or event prevent the emergence of the MT strain.  
411 Each natural infection is an opportunity for the MT strain to appear and possibly take  
412 over. Hence, the main policy goal should be to maximize the proportion of the population  
413 which will be immunized to the virus through vaccination as opposed to natural infection.

414 In terms of policy implications, our result supports the maintenance of social distancing  
415 measures until the daily number of infections decreases substantially. Allowing a large  
416 number of infections can only be counterbalanced by very high vaccination rates, which  
417 ensure that herd immunity is reached before the MT strain can appear and takeover.  
418 Furthermore, our result underlines the importance of a worldwide effort to quickly  
419 vaccinate as many individuals as possible, especially in highly populated countries with  
420 low access to vaccines. Slow, or no vaccination, results in a large number of total cases in  
421 these areas and hence the emergence of an MT strain which could then spread over the  
422 whole world.

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## 425 **AUTHOR CONTRIBUTIONS**

426 All authors conceived the project and designed the study. GL have written all the code and ran  
427 analysis. All authors have written the paper. MN has supervised the project.

## 428 **CODE AND DATA AVAILABILITY**

429 Available upon request.

430 REFERENCES

- 431 1. Wu, J. T. *et al.* Estimating clinical severity of COVID-19 from the transmission  
432 dynamics in Wuhan, China. *Nat. Med.* (2020). doi:10.1038/s41591-020-0822-7
- 433 2. COVID-19 Data Explorer - Our World in Data. Available at:  
434 [https://ourworldindata.org/explorers/coronavirus-data-](https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&country=USA~GBR~CAN~DEU~ITA~IND&region=World&pickerMetric=location&pickerSort=asc&Metric=Confirmed+cases&Interval=7-day+rolling+average&Align+outbreaks=false&Relative+to+Population=true)  
435 [explorer?zoomToSelection=true&time=2020-03-](https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&country=USA~GBR~CAN~DEU~ITA~IND&region=World&pickerMetric=location&pickerSort=asc&Metric=Confirmed+cases&Interval=7-day+rolling+average&Align+outbreaks=false&Relative+to+Population=true)  
436 [01..latest&country=USA~GBR~CAN~DEU~ITA~IND&region=World&pickerMetric=l](https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&country=USA~GBR~CAN~DEU~ITA~IND&region=World&pickerMetric=location&pickerSort=asc&Metric=Confirmed+cases&Interval=7-day+rolling+average&Align+outbreaks=false&Relative+to+Population=true)  
437 [ocation&pickerSort=asc&Metric=Confirmed+cases&Interval=7-](https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&country=USA~GBR~CAN~DEU~ITA~IND&region=World&pickerMetric=location&pickerSort=asc&Metric=Confirmed+cases&Interval=7-day+rolling+average&Align+outbreaks=false&Relative+to+Population=true)  
438 [day+rolling+average&Align+outbreaks=false&Relative+to+Population=true.](https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&country=USA~GBR~CAN~DEU~ITA~IND&region=World&pickerMetric=location&pickerSort=asc&Metric=Confirmed+cases&Interval=7-day+rolling+average&Align+outbreaks=false&Relative+to+Population=true)  
439 (Accessed: 19th June 2021)
- 440 3. Different COVID-19 Vaccines | CDC. Available at:  
441 [https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html.](https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html)  
442 (Accessed: 19th March 2021)
- 443 4. Safe COVID-19 vaccines for Europeans | European Commission. Available at:  
444 [https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-](https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-19-vaccines-europeans_en)  
445 [19-vaccines-europeans\\_en.](https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-19-vaccines-europeans_en) (Accessed: 19th March 2021)
- 446 5. Böttcher, L. & Nagler, J. Decisive Conditions for Strategic Vaccination against  
447 SARS-CoV-2. *medRxiv* 2021.03.05.21252962 (2021).  
448 doi:10.1101/2021.03.05.21252962
- 449 6. Walsh, E. E., Shin, J. H. & Falsey, A. R. Clinical impact of human coronaviruses  
450 229E and OC43 infection in diverse adult populations. *J. Infect. Dis.* (2013).  
451 doi:10.1093/infdis/jit393
- 452 7. Vaccines – COVID19 Vaccine Tracker. Available at:  
453 [https://covid19.trackvaccines.org/vaccines/.](https://covid19.trackvaccines.org/vaccines/) (Accessed: 19th March 2021)
- 454 8. Tegally, H. *et al.* Emergence and rapid spread of a new severe acute respiratory  
455 syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike  
456 mutations in South Africa. *medRxiv* **10**, 2020.12.21.20248640 (2020).

- 457 9. Rambaut, A. *et al.* Preliminary genomic characterisation of an emergent SARS-  
458 CoV-2 lineage in the UK defined by a novel set of spike mutations - SARS-CoV-2  
459 coronavirus / nCoV-2019 Genomic Epidemiology - Virological. (2020). Available at:  
460 [https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-](https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563)  
461 [sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563](https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563).  
462 (Accessed: 16th April 2021)
- 463 10. Wang, P. *et al.* Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7  
464 to Antibody Neutralization. *bioRxiv Prepr. Serv. Biol.* (2021).  
465 doi:10.1101/2021.01.25.428137
- 466 11. Luchsinger, L. L. & Hillyer, C. D. Vaccine efficacy probable against COVID-19  
467 variants. *Science (80-. )*. **371**, 1116 LP – 1116 (2021).
- 468 12. Starr, T. N. *et al.* Prospective mapping of viral mutations that escape antibodies  
469 used to treat COVID-19. *Science (80-. )*. **371**, 850–854 (2021).
- 470 13. Starr, T. N. *et al.* Deep Mutational Scanning of SARS-CoV-2 Receptor Binding  
471 Domain Reveals Constraints on Folding and ACE2 Binding. *Cell* **182**, 1295-  
472 1310.e20 (2020).
- 473 14. Greaney, A. J. *et al.* Complete Mapping of Mutations to the SARS-CoV-2 Spike  
474 Receptor-Binding Domain that Escape Antibody Recognition. *Cell Host Microbe*  
475 **29**, 44-57.e9 (2021).
- 476 15. Thompson, R. N., Hill, E. M. & Gog, J. R. SARS-CoV-2 incidence and vaccine escape.  
477 *Lancet Infect. Dis.* (2021). doi:10.1016/S1473-3099(21)00202-4
- 478 16. Gerrish, P. J. *et al.* How unequal vaccine distribution promotes the evolution of  
479 vaccine escape. *medRxiv* (2021).
- 480 17. Cobey, S., Larremore, D. B., Grad, Y. H. & Lipsitch, M. Concerns about SARS-CoV-2  
481 evolution should not hold back efforts to expand vaccination. *Nature Reviews*  
482 *Immunology* 1–6 (2021). doi:10.1038/s41577-021-00544-9

- 483 18. Geoffroy, F., Traulsen, A. & Uecker, H. Vaccination strategies when vaccines are  
484 scarce: On conflicts between reducing the burden and avoiding the evolution of  
485 escape mutants. *medRxiv* 2021.05.04.21256623 (2021).  
486 doi:10.1101/2021.05.04.21256623
- 487 19. Baker, R. E., Yang, W., Vecchi, G. A., Metcalf, C. J. E. & Grenfell, B. T. Assessing the  
488 influence of climate on wintertime SARS-CoV-2 outbreaks. *Nat. Commun.* **12**, 1–7  
489 (2021).
- 490 20. Geoghegan, J. L. *et al.* Genomic epidemiology reveals transmission patterns and  
491 dynamics of SARS-CoV-2 in Aotearoa New Zealand. *Nat. Commun.* **11**, 1–7 (2020).
- 492 21. Komissarov, A. B. *et al.* Genomic epidemiology of the early stages of the SARS-  
493 CoV-2 outbreak in Russia. *Nat. Commun.* **12**, 1–13 (2021).
- 494 22. Faria, N. R. *et al.* Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in  
495 Manaus, Brazil. *Science (80-. )*. eabh2644 (2021). doi:10.1126/science.abh2644
- 496 23. Lythgoe, K. A. *et al.* SARS-CoV-2 within-host diversity and transmission. *Science*  
497 (80-. ). **372**, eabg0821 (2021).
- 498 24. Komarova, N. L., Schang, L. M. & Wodarz, D. Patterns of the COVID-19 pandemic  
499 spread around the world: Exponential versus power laws: Patterns of the COVID-  
500 19 pandemic spread around the world: Exponential versus power laws. *J. R. Soc.*  
501 *Interface* **17**, (2020).
- 502 25. Saad-Roy, C. M. *et al.* Immune life history, vaccination, and the dynamics of SARS-  
503 CoV-2 over the next 5 years. *Science (80-. )*. **370**, 811–818 (2020).
- 504 26. BERNOULLI & D. Essai d’une nouvelle analyse de la mortalite causee par la petite  
505 verole, et des avantages de l’inoculation pour la prevenir. *Hist. l’Acad., Roy. Sci.*  
506 *avec Mem* 1–45 (1760).
- 507 27. Kermack, W. O & Mckendrick, A. G. A contribution to the mathematical theory of  
508 epidemics. *Proc. R. Soc. London. Ser. A, Contain. Pap. a Math. Phys. Character*

- 509           **115**, 700–721 (1927).
- 510   28.   Diekmann, O., Heesterbeek, J. A. P. & Metz, J. A. J. On the definition and the  
511           computation of the basic reproduction ratio  $R_0$  in models for infectious diseases  
512           in heterogeneous populations. *J. Math. Biol.* **28**, 365–382 (1990).
- 513   29.   Dietz, K. The estimation of the basic reproduction number for infectious diseases.  
514           *Stat. Methods Med. Res.* **2**, 23–41 (1993).
- 515   30.   Nowak, M. A. & May, R. M. Superinfection and the evolution of parasite  
516           virulence. *Proc. R. Soc. B Biol. Sci.* **255**, 81–89 (1994).
- 517   31.   Nowak, M. A. & Bangham, C. R. M. Population dynamics of immune responses to  
518           persistent viruses. *Science (80-. )*. **272**, 74–79 (1996).
- 519   32.   Hethcote, H. W. Mathematics of infectious diseases. *SIAM Rev.* **42**, 599–653  
520           (2000).
- 521   33.   Brauer, F. & Castillo-Chavez, C. *Mathematical Models in Population Biology and*  
522           *Epidemiology.* **40**, (Springer New York, 2012).
- 523   34.   Hamer, W. The Milroy Lectures ON EPIDEMIC DISEASE IN ENGLAND-THE  
524           EVIDENCE OF VARIABILITY AND OF PERSISTENCY OF TYPE. *The Lancet* **167**, 569–  
525           574 (1906).
- 526   35.   Bailey, N. *The Mathematical Theory of Infectious Diseases and its applications.*  
527           *Immunology* **34**, (Wiley-Blackwell, 1978).
- 528   36.   Tillett, H. E. Infectious Diseases of Humans; Dynamics and Control. *Epidemiol.*  
529           *Infect.* **108**, 211 (1992).
- 530   37.   Nowak, M. & May, R. M. Virus Dynamics: Mathematical Principles of Immunology  
531           And Virology. Available at:  
532           [https://www.researchgate.net/publication/48378467\\_Virus\\_Dynamics\\_Mathema](https://www.researchgate.net/publication/48378467_Virus_Dynamics_Mathematical_Principles_of_Immunology_And_Virology)  
533           [tical\\_Principles\\_of\\_Immunology\\_And\\_Virology.](https://www.researchgate.net/publication/48378467_Virus_Dynamics_Mathematical_Principles_of_Immunology_And_Virology) (Accessed: 30th March 2021)

- 534 38. Diekmann, O. & Heesterbeek, J. A. P. Mathematical Epidemiology of Infectious  
535 Diseases: Model Building, Analysis and Interpretation. Available at:  
536 [https://www.researchgate.net/publication/48376881\\_Mathematical\\_Epidemiology\\_of\\_Infectious\\_Diseases\\_Model\\_Building\\_Analysis\\_and\\_Interpretation](https://www.researchgate.net/publication/48376881_Mathematical_Epidemiology_of_Infectious_Diseases_Model_Building_Analysis_and_Interpretation).  
537  
538 (Accessed: 30th March 2021)
- 539 39. Ragonnet-Cronin, M. *et al.* Genetic evidence for the association between COVID-  
540 19 epidemic severity and timing of non-pharmaceutical interventions. *Nat. Commun.* **12**, 2188 (2021).  
541
- 542 40. Rossman, H. *et al.* Hospital load and increased COVID-19 related mortality in  
543 Israel. *Nat. Commun.* **12**, 1904 (2021).
- 544 41. Saad-Roy, C. M. *et al.* Epidemiological and evolutionary considerations of SARS-  
545 CoV-2 vaccine dosing regimes. *Science (80-. )*. eabg8663 (2021).  
546 doi:10.1126/science.abg8663
- 547 42. Saad-Roy, C. M. *et al.* Immune life history, vaccination, and the dynamics of SARS-  
548 CoV-2 over the next 5 years. *Science (80-. )*. **370**, 811–818 (2020).
- 549 43. Ashcroft, P., Lehtinen, S., Angst, D. C., Low, N. & Bonhoeffer, S. Quantifying the  
550 impact of quarantine duration on covid-19 transmission. *Elife* **10**, 1–33 (2021).
- 551 44. Komarova, N. L., Azizi, A. & Wodarz, D. Network models and the interpretation of  
552 prolonged infection plateaus in the COVID19 pandemic. *Epidemics* 100463 (2021).  
553 doi:10.1016/j.epidem.2021.100463
- 554 45. Castro, M., Ares, S., Cuesta, J. A. & Manrubia, S. The turning point and end of an  
555 expanding epidemic cannot be precisely forecast. *Proc. Natl. Acad. Sci.* **117**,  
556 26190–26196 (2020).
- 557 46. Stich, M., Manrubia, S. C. & Lázaro, E. Variable mutation rates as an adaptive  
558 strategy in replicator populations. *PLoS One* (2010).  
559 doi:10.1371/journal.pone.0011186

- 560 47. Yagan, O. *et al.* Modeling and Analysis of the Spread of COVID-19 Under a  
561 Multiple-Strain Model with Mutations. *Harvard Data Sci. Rev.* (2021).  
562 doi:10.1162/99608f92.a11bf693
- 563 48. Lehtinen, S., Ashcroft, P. & Bonhoeffer, S. On the relationship between serial  
564 interval, infectiousness profile and generation time. *J. R. Soc. Interface* (2021).  
565 doi:10.1098/rsif.2020.0756
- 566 49. Hethcote, H. W. Three Basic Epidemiological Models. in (1989). doi:10.1007/978-  
567 3-642-61317-3\_5
- 568 50. Gillespie, D. T. A general method for numerically simulating the stochastic time  
569 evolution of coupled chemical reactions. *J. Comput. Phys.* **22**, 403–434 (1976).
- 570 51. Gillespie, D. T. Exact stochastic simulation of coupled chemical reactions. in  
571 *Journal of Physical Chemistry* **81**, 2340–2361 (American Chemical Society, 1977).
- 572 52. Cota, W. & Ferreira, S. C. Optimized Gillespie algorithms for the simulation of  
573 Markovian epidemic processes on large and heterogeneous networks. *Comput.*  
574 *Phys. Commun.* **219**, 303–312 (2017).
- 575 53. Mukhamadiarov, R. I. *et al.* Social distancing and epidemic resurgence in agent-  
576 based susceptible-infectious-recovered models. *Sci. Rep.* **11**, 130 (2021).

577

## 578 METHODS

### 579 [Derivation of mathematical results](#)

#### 580 [1. No Vaccination](#)

581 First we consider the case without vaccination. We denote by  $x$  the number of susceptible  
582 individuals; by  $y$  the number of individuals infected with wildtype (WT); by  $z$  the number  
583 of individuals recovered from WT. The infection rate is  $\beta$ ; the recovery rate  $a$ ; the  
584 mutation rate  $\mu$ ; the population size  $N$ . The social activity parameter  $s(t)$  captures the

585 extent of imposed lockdown that varies over time. For simplicity, we neglect the number  
586 of individuals who die, hence the population size  $N$  is assumed to be constant.

587 Deterministic WT infection dynamics are given by the system of differential equations:

$$\begin{aligned}\dot{x} &= -\beta sxy \\ \dot{y} &= \beta sxy - ay \\ \dot{z} &= ay\end{aligned}\tag{7}$$

588 Initially, all of the population is susceptible to the WT strain, and no individuals are  
589 infected with or recovered from the WT strain. Therefore, we have:  $x(0) = N$ ,  $y(0) = 0$   
590 and  $z(0) = 0$ . Social activity,  $s(t)$ , is adjusted such that  $y(t) = L/a$  is constant (see  
591 **Figure S2C**).  $L$  is the number of new infections per day.

592 Without lockdown,  $s = 1$ , the basic reproductive ratio of the WT is given by  $R_0 = \beta N/a$ .  
593 If  $R_0 > 1$ , the number of infected individuals grows initially. With lockdown,  $s < 1$ , the  
594 reproductive ratio is  $R_{WT} = \beta Ns/a$ . Since the social distancing measures maintain  
595  $y(t) = L/a$  at a constant value, we have  $R_{WT} = 1$  and  $\beta s(t)x(t) = a$  (see **Figure S2**).  
596 The parameter  $s$  can vary between 0 and 1.

597 Each day,  $L$  individuals become infected and  $L$  individuals recover. Therefore, we have:

$$\begin{aligned}\dot{x} &= -L \\ \dot{y} &= 0 \\ \dot{z} &= L\end{aligned}\tag{8}$$

598 The solution to this system of differential equations is

$$\begin{aligned}x(t) &= N - Lt \\ z(t) &= Lt\end{aligned}\tag{9}$$

599 Hence, the number of susceptible individuals decreases linearly with slope  $L$  while the  
600 number of recovered individuals increases linearly with slope  $L$ . (See **Figure S2** for  
601 agreement with the stochastic simulation).

602 When  $x(t)$  has declined such that  $R_{WT} < 1$  and  $s = 1$ , there are not enough susceptible  
 603 individuals to sustain the infection. This herd immunity is achieved when  $x(t) < a/\beta$ .  
 604 Thus, the time  $T_H$  until herd immunity is given by  $\beta(N - Lt) = a$ . We obtain:

$$T_H = \frac{N}{L} \left( 1 - \frac{1}{R_0} \right) \quad (10)$$

### 605 *1.1 Rate of generating mutants*

606 Each day,  $L$  new individuals become infected. Each of these infections has probability  $\mu$   
 607 to be a vaccine-resistant MT. Hence, the rate of producing a mutant is  $L\mu$  per day. Let  
 608  $P(t)$  denote the probability that no mutant has been produced until time  $t$ . We have  
 609  $\dot{P}(t) = -L\mu P(t)$ , which leads to  $P(t) = e^{-L\mu t}$ .

610 The MT strain can be generated only during infection. Hence, if the MT strain has not  
 611 been generated until the time when there are no more WT infections – that is,  
 612 approximately when herd immunity is reached – it will never be generated. We neglect  
 613 here the time of exponential decrease in the number of WT infections between time  $T_H$   
 614 (when herd immunity is reached) and the time when the number of WT infections has  
 615 reached zero. The probability that no mutant will appear before time  $T_H$  is  $P(T_H) =$   
 616  $e^{-L\mu T_H}$ . Inserting from eq (4) we obtain

$$P(T_H) = \exp(-N\mu(1 - 1/R_0)) \quad (11)$$

### 617 *1.1 Rate of generating surviving mutants*

618 In order to calculate the probability that the MT strain will be generated and survive, we  
 619 need to multiply the rate of generation of the MT strain with the probability that it will  
 620 not become extinct by random drift. If  $\rho(t)$  is the survival probability of the MT, then the  
 621 rate of producing a surviving mutant is  $L\mu\rho(t)$  per day. We approximate  $\rho(t) = 1 -$   
 622  $1/R_{MT}(t)$ , where  $R_{MT}(t)$  is the reproductive ratio of the mutant at time  $T$ .

623 We have

$$R_{MT}(t) = \beta s(t)N/a \quad (12)$$

624 Since  $s(t) = a/\beta x(t)$  and using Eq. (9) we obtain

$$R_{MT}(t) = \frac{N}{N - Lt} \quad (13)$$

625 And therefore we have  $\rho(t) = Lt/N$ .

626 Let  $P(t)$  denote the probability that not surviving mutant has been produced until time  
 627  $t$ . We have  $\dot{P}(t) = -L\mu\rho(t)P(t) = -L^2\mu tP(t)/N$ . We can solve this differential  
 628 equation to obtain  $P(t) = \exp(-\mu L^2 t^2/2N)$ . The probability that no surviving mutant  
 629 has been produced until herd immunity, which is reached at time  $T_H$ , is given by

$$P(T_H) = \exp\left(-\frac{\mu N}{2}\left(1 - \frac{1}{R_0}\right)^2\right) \quad (14)$$

## 630 2. With Vaccination

631 Let us now add vaccination. Denote by  $w$  the number of vaccinated people. If both  
 632 recovered and susceptible individuals are vaccinated at a total rate of  $c$  per day then  
 633 deterministic infection and vaccination dynamics are given by

$$\begin{aligned} \dot{x} &= -\beta sxy - \frac{cx}{x+z} \\ \dot{y} &= \beta sxy - ay \\ \dot{z} &= ay - \frac{cz}{x+z} \\ \dot{w} &= c \end{aligned} \quad (15)$$

634 The initial condition is  $x(0) = N$ ,  $y(0) = 0$ ,  $z(0) = 0$ ,  $w(0) = 0$ ,  $s(0) = 1$  and  $R_0 =$   
 635  $\beta N/a$ . As before, we adjust  $s(t)$  such that  $y(t) = L/a$  is constant (see **Figure 3**).

636 Each day,  $L$  susceptible individuals become infected and  $cx(x+z)$  susceptible individuals  
 637 become vaccinated. Also,  $L$  infected individuals recover, and  $cx(x+z)$  of recovered  
 638 individuals become vaccinated. We have:

$$\begin{aligned}
\dot{x} &= -L - \frac{cx}{x+z} \\
\dot{y} &= 0 \\
\dot{z} &= L - \frac{cz}{x+z} \\
\dot{w} &= c
\end{aligned}
\tag{16}$$

639 For simplicity let us assume that we only vaccinate susceptible people. This assumption  
640 is a reasonable approximation if  $c \gg L$ . In this case, we can write

$$\begin{aligned}
\dot{x} &= -L - c \\
\dot{y} &= 0 \\
\dot{z} &= L \\
\dot{w} &= c
\end{aligned}
\tag{17}$$

641

642 The solution to this system of differential equations is

$$\begin{aligned}
x(t) &= N - Lt - ct \\
z(t) &= Lt \\
w(t) &= ct
\end{aligned}
\tag{18}$$

643 Hence, the number of susceptible individuals decreases linearly with slope  $L + c$ , while  
644 the number of recovered individuals increases linearly with slope  $L$ , and the number of  
645 vaccinated individuals increases linearly with slope  $c$ .

646 The time  $T_H$  until herd immunity is given by

$$T_H = \frac{N}{c + L} (1 - 1/R_0)
\tag{19}$$

647 [2.1 Rate of generating mutants](#)

648 The rate of producing a mutant is  $L\mu$  per day. Let  $P(t)$  denote the probability that no  
649 mutant has been produced until time  $t$ . We have  $\dot{P}(t) = -L\mu P(t)$ , which gives  $P(t) =$   
650  $\exp(-L\mu t)$ .

651 The MT strain can be generated only during infection. Hence, if the MT strain has not  
652 been generated until the time when there are no more WT infections – that is, when herd  
653 immunity is reached – it will never be generated. Again we neglect here the time of  
654 exponential decrease in the number of WT infections between the time  $T_H$  when herd  
655 immunity is reached and the time where the number of WT infections reaches 0. Hence,  
656 the probability that no mutant will appear is  $P(T_H) = \exp(-L\mu T_H)$ . Using Eq. (19), the  
657 probability that no mutant has appeared until herd immunity is:

$$P(T_H) = \exp\left(-N\mu\left(\frac{L}{c+L}\right)\left(1 - \frac{1}{R_0}\right)\right) \quad (20)$$

658 [2.2 Rate of generating surviving mutants](#)

659 In order to calculate the probability that surviving mutants are generated, we again  
660 consider the survival probability  $\rho(t) = 1 - 1/R_{MT}(t)$ , where  $R_{MT}(t)$  is the reproductive  
661 ratio of the mutant at time  $t$ . The rate of producing a surviving mutant is then  $L\mu\rho(t)$  per  
662 day. We have:

$$R_{MT}(t) = \frac{\beta s(t)N}{a} \quad (21)$$

663 As explained above,  $s(t) = a/\beta x(t)$ . Using Eq. (18) we obtain

$$R_{MT}(t) = \frac{N}{N - (L + c)t} \quad (22)$$

664 And therefore  $\rho(t) = (L + c)t/N$ .

665 Let  $P(t)$  denote the probability that not surviving mutant has been produced until time  
 666  $t$ . We have  $P'(t) = -L\mu\rho(t)P(t) = -L\mu(c + L)tP(t)/N$ . Let  $v = c/N$  and  $l = L/N$ .  
 667 We can solve this differential equation to obtain:

$$P(t) = \exp\left(-\frac{\mu N}{2}l(v + l)t^2\right) \quad (23)$$

668 The probability that no surviving mutant has been produced until herd immunity, which  
 669 is reached at time  $T_H$ , is:

$$P(T_H) = \exp\left(-\frac{\mu N}{2}\left(\frac{l}{v + l}\right)\left(1 - \frac{1}{R_0}\right)^2\right) \quad (24)$$

670

### 671 [2.3 Rate of generating surviving mutants with partial immune escape](#)

672 We can also study the case where the infectivity of the mutants is reduced by a factor  
 673  $q \in [0,1]$  when infecting recovered or vaccinated people. For  $q = 1$  we obtain full  
 674 escape, while  $q = 0$  means that the mutant does not escape at all.

675 A similar derivation to the one above leads to the following result. The probability that  
 676 no surviving mutant with partial escape  $q$  has appeared until herd immunity is given by:

$$P(T_H) = \exp\left(-\frac{\mu N}{2}\left(\frac{l}{v + l}\right)A\right)$$

with

$$A = \frac{2q}{1-q}\left(-\frac{R_0-1}{R_0} + \frac{1}{1-q}\log\frac{R_0}{1+q(R_0-1)}\right) \quad (25)$$

677 For  $q = 1$  we obtain  $A = (1 - (1/R_0))^2$  leading to Eq. (23) above.

678

679 Relationship between the product formula and the exponential formula

680

681 Each day,  $L$  new WT infections occur. Each new infection has a probability of  $\mu$  to be the  
682 MT strain. The survival probability of the mutant is approximately  $1 - 1/R_m(t)$  where  
683  $R_m(t)$  is the basic reproductive ratio of the MT appearing at time  $t$ .

684 Hence, the probability that none of the  $L$  new WT infections in a day will generate a  
685 surviving mutant is  $(1 - \mu(1 - 1/R_m(t)))^L$ . Then, we can write the probability  $P$  that no  
686 surviving mutant will be produced between time  $t = 0$  and the time  $T_H$  when herd  
687 immunity is reached as the product

$$P = \prod_{\tau=0}^{T_H} \left[ 1 - \mu \left( 1 - \frac{1}{R_{MT}(\tau)} \right) \right]^L \quad (26)$$

688 We have  $T_H = [N/(c + L)](1 - 1/R_0)$  and  $R_{MT}(t) = N/[N - (c + L)t]$ .

689 Since  $\rho(t) = 1 - 1/R_m(t) = (c + L)t/N$  we can write:

$$P = \prod_{\tau=0}^{T_H} \left( 1 - \frac{\mu(c + L)\tau}{N} \right)^L$$

691 Let us use the abbreviation  $u = \mu(c + L)/N$ . Then

$$\begin{aligned} 692 \quad P &= \prod_{\tau=0}^{T_H} (1 - u\tau)^L \\ 693 \quad &= \exp\left[\log \prod_{\tau=0}^{T_H} (1 - u\tau)^L\right] \\ 694 \quad &= \exp\left[L \log \prod_{\tau=0}^{T_H} (1 - u\tau)\right] \\ &= \exp\left[L \sum_{\tau=0}^{T_H} \log(1 - u\tau)\right] \quad (27) \end{aligned}$$

695 Note that Eq. (26) is exactly equivalent to Eq. (23). Assuming  $uT_H \ll 1$  which is the same  
696 as  $\mu(1 - (1/R_0)) \ll 1$  we obtain

697 
$$P = \exp[-uL \sum_{\tau=0}^{T_H} \tau]$$

698 
$$= \exp\left[-\frac{uLT_H(T_H + 1)}{2}\right]$$

699 Assuming  $T_H \gg 1$  which is  $N\left(1 - \frac{1}{R_0}\right) \gg c + L$ , we obtain

700 
$$P = \exp\left[-\frac{uLT_H^2}{2}\right]$$

701 
$$= \exp\left[-\frac{(\mu(c + L)/N)LT_H^2}{2}\right]$$

702 Finally, inserting  $T_H = (N/(c + L))(1 - 1/R_0)$  we get:

$$P(T_H) = \exp\left(-\frac{\mu N}{2} \left(\frac{l}{v + l}\right) \left(1 - \frac{1}{R_0}\right)^2\right) \quad (28)$$

703 Which is equivalent to Eq.(24) (see above).

704

705 [Dynamics after appearance of the MT strain](#)

706 [1. No Vaccination](#)

707 After the MT strain has taken over, social distancing measures will continue maintaining  
708 the number of daily infections at  $L$ , which implies that  $(y_1 + y_2) = L/a$  (see **Figure S2**).

709 In practice, the WT strain rapidly goes extinct upon emergence of the MT strain; so we  
710 can consider  $y_2 = L/a$ . The mutant strain can infect susceptible individuals  $x$ , and

711 recovered individuals,  $z_1$ . The mutant strain infects those individuals with probabilities

712 proportional to their frequencies at the time  $t^*$  of mutant takeover. Hence, for times  $t >$

713  $t^*$  we have:

$$\begin{aligned} x(t) &= x(t^*) - \frac{x(t^*)}{z_1(t^*) + x(t^*)} L(t^* - t) \\ z_1(t) &= z_1(t^*) - \frac{z_1(t^*)}{z_1(t^*) + x(t^*)} L(t^* - t) \end{aligned} \quad (29)$$

714 After mutant takeover, the social distancing measures need to be readjusted to the  
 715 mutant strain. Since more individuals are susceptible to it,  $s(t)$  has to decrease (see  
 716 **Figure S2F**):

$$s(t) = \frac{aN}{\beta(x(t) + qz_1(t))} \quad (30)$$

717 Which implies that  $R_{MT} = 1$ .

718

## 719 2. With vaccination

720 As for the case without vaccination, if the mutant strain survives, it will quickly replace  
 721 the wild-type strain such that  $y_2 = L/a$  (see **Figure 3C**). The number of susceptible  
 722 individuals  $x(t^*)$  at time of mutant takeover can be neglected for large enough  
 723 vaccination rates. The number of vaccinated individuals, susceptible to the mutant strain  
 724  $w_1$  will hence decrease linearly with the number of tolerated cases per day  $L$ , and the  
 725 number of vaccinated individuals, recovered from the mutant strain  $w_2$  will increase  
 726 complementarily linearly with  $L$ . If the mutant takes over at time  $t^*$ , we have for all times  
 727  $t > t^*$ :

$$\begin{aligned} w_1(t) &= w_1(t^*) - L(t^* - t) \\ w_2(t) &= L(t^* - t) \end{aligned} \quad (31)$$

728 The social activity parameter  $s$  needs readjustment to consider the additional groups of  
 729 individuals that are now susceptible to the infecting strain. We have:

$$s(t) = \frac{a}{\beta} \frac{x(t) + q(z_1(t) + w_1(t))}{x(t) + q(z_1(t) + w_1(t)) - w_2(t)} \quad (32)$$

730 Which ensures that  $R_{MT} = 1$ . Here the parameter  $q$  in  $[0,1]$  denotes the extent of escape.

731

732 [Estimating the evolutionary potential of the virus](#)

733 If  $\mu$  is the mutation rate as described above and  $L(t)$  is the time series giving the  
734 number of new infections on day  $t$ , then the probability that no mutant has been  
735 produced between time 0 and time  $T_H$  is given by:

$$P(T_H) = \prod_{\tau=0}^{T_H} [1 - \mu]^{L(\tau)} \quad (33)$$

736 This probability will overestimate the evolutionary potential of the virus to escape from  
737 vaccination because many mutants do not survive the initial random drift. The probability  
738 that no surviving mutant has been produced between time 0 and time  $T_H$  can be written  
739 as:

$$P(T_H) = \prod_{\tau=0}^{T_H} [1 - \mu\rho(\tau)]^{L(\tau)} \quad (34)$$

740 Here  $\rho(t)$  is the survival probability of an escape mutant produced at time  $t$ . This  
741 probability depends on the basic reproductive ratio of the mutant on the day it is being  
742 produced (and the next few days until random drift is negligible). Approximately we can  
743 write:

$$\rho(t) = \min\left\{0, 1 - \frac{1}{R_M(t)}\right\} \quad (35)$$

744 For the potential of the virus to generate mutants (irrespective of whether they survive)  
745 what matters most is the total number of infections,  $\sum_{\tau} L(\tau)$ . But for the potential of the  
746 virus to generate surviving mutants one must also consider the time periods when  
747 lockdown is relaxed such that  $R_{MT}$  is above 1.

748

749 GILLESPIE PSEUDOCODE

750

751 Time = 0

```

752     Day = 0
753     Initialize population
754     Initialize reaction rates
755     while ( $y_1 + y_{2A} + y_{2B} > 0$ ):
756         if day passed:
757             day = day + 1
758             if number infections in previous day > L:
759                 s = s - random number, uniform
760                 distribution [0, 0.1]
761             if number infections in previous day < L:
762                 s = s + random number, uniform
763                 distribution [0, 0.1]
764             r1 = random number from uniform distribution
765             between 0 and 1
766             r2 = random number from uniform distribution
767             between 0 and 1
768             alpha = sum(reaction_rates)
769             tau =  $\frac{1}{\alpha} \ln\left(\frac{1}{r1}\right)$ 
770             time = time + tau
771             choose reaction, probability proportional to
772             their rates and r2*alpha
773             update population according to chosen reaction
774             update reaction rates
775             record population

```

776

777

778 TABLE OF REACTIONS AND THEIR RATES

779

<u>Infection</u>		
WT Infected Infects Susceptible	$y_1 + 1; x - 1$	$\beta_1 s x y_1$
VR (unvaccinated) Infects Susceptible	$y_{2A} + 1; x - 1$	$\beta_2 s x y_{2A}$
VR (unvaccinated) Infects Recovered from WT	$y_{2A} + 1; z_1 - 1$	$q \beta_2 s z_1 y_{2A}$
VR (unvaccinated) Infects Vaccinated	$y_{2B} + 1; w_1 - 1$	$q \beta_2 s w_1 y_{2A}$
VR (vaccinated) Infects Susceptible	$y_{2A} + 1; x - 1$	$\beta_2 s x y_{2B}$
VR (vaccinated) Infects Recovered from WT	$y_{2A} + 1; z_1 - 1$	$q \beta_2 z_1 s y_{2B}$
VR (vaccinated) Infects Vaccinated	$y_{2B} + 1; w_1 - 1$	$q \beta_2 w_1 s y_{2B}$
<u>Mutation</u>		

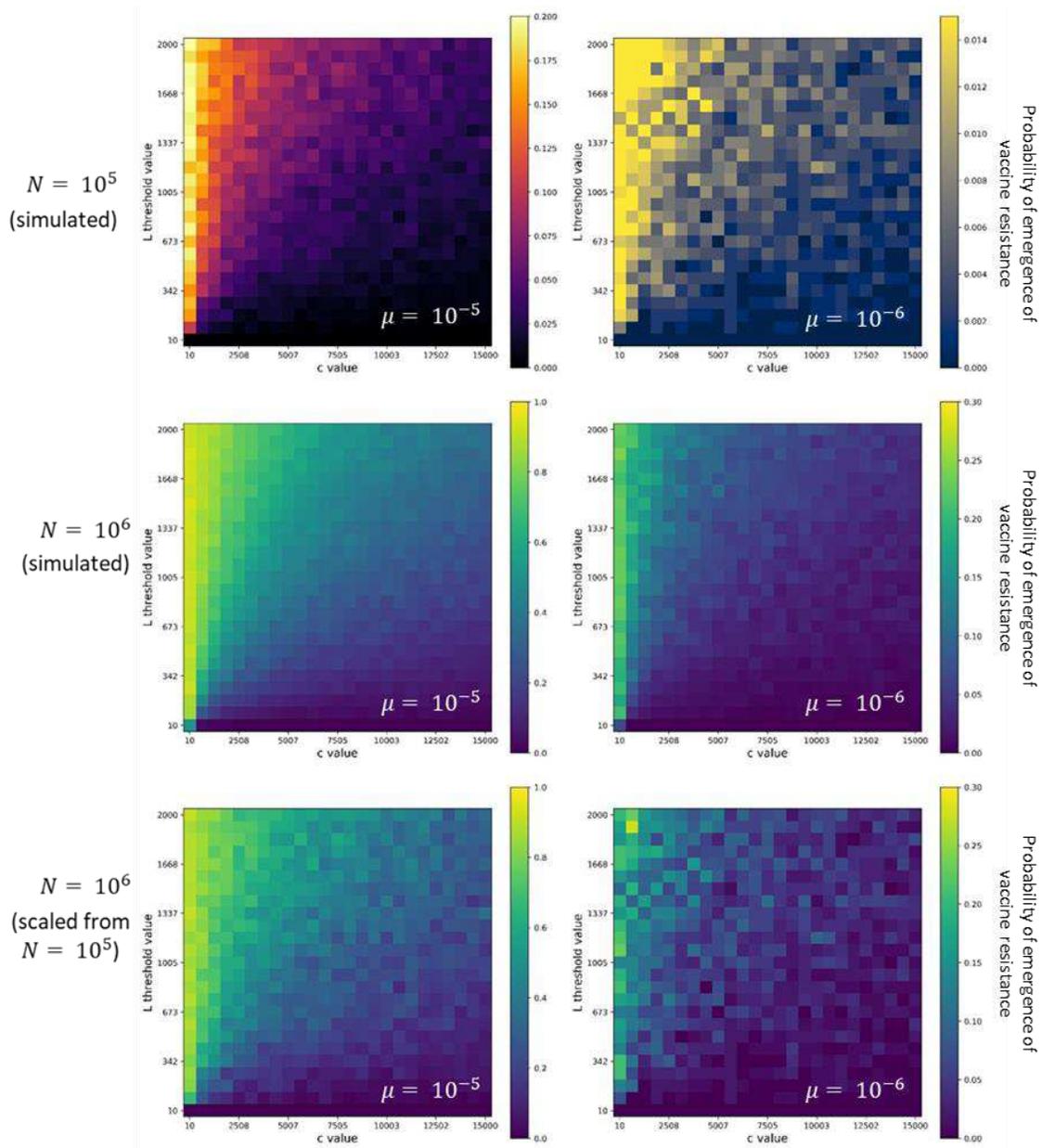
WT Mutates into VR	$x - 1; y_{2A} + 1$	$\beta_1 s x y_1 \mu$
<b><u>Recovery</u></b>		
WT Infected Recovers	$y_1 - 1; z_1 + 1$	$ay_1$
VR unvaccinated Recovers	$y_{2A} - 1; z_2 + 1$	$ay_{2A}$
VR vaccinated Recovers	$y_{2B} - 1; w_2 + 1$	$ay_{2B}$
<b><u>Death</u></b>		
WT Infected Dies	$y_1 - 1$	$dy_1$
VR unvaccinated Dies	$y_{2A} - 1$	$dy_{2A}$
VR vaccinated Dies	$y_{2B} - 1$	$dy_{2B}$
<b><u>Vaccination</u></b>		
Susceptible Gets Vaccinated	$x - 1; w_1 + 1$	$\frac{cx}{(x + z_1 + z_2)}$
WT Recovered Gets Vaccinated	$z_1 - 1; w_1 + 1$	$\frac{cz_1}{(x + z_1 + z_2)}$
WT and VR Recovered Gets Vaccinated	$z_2 - 1; w_2 + 1$	$\frac{cz_2}{(x + z_1 + z_2)}$

780

781

782

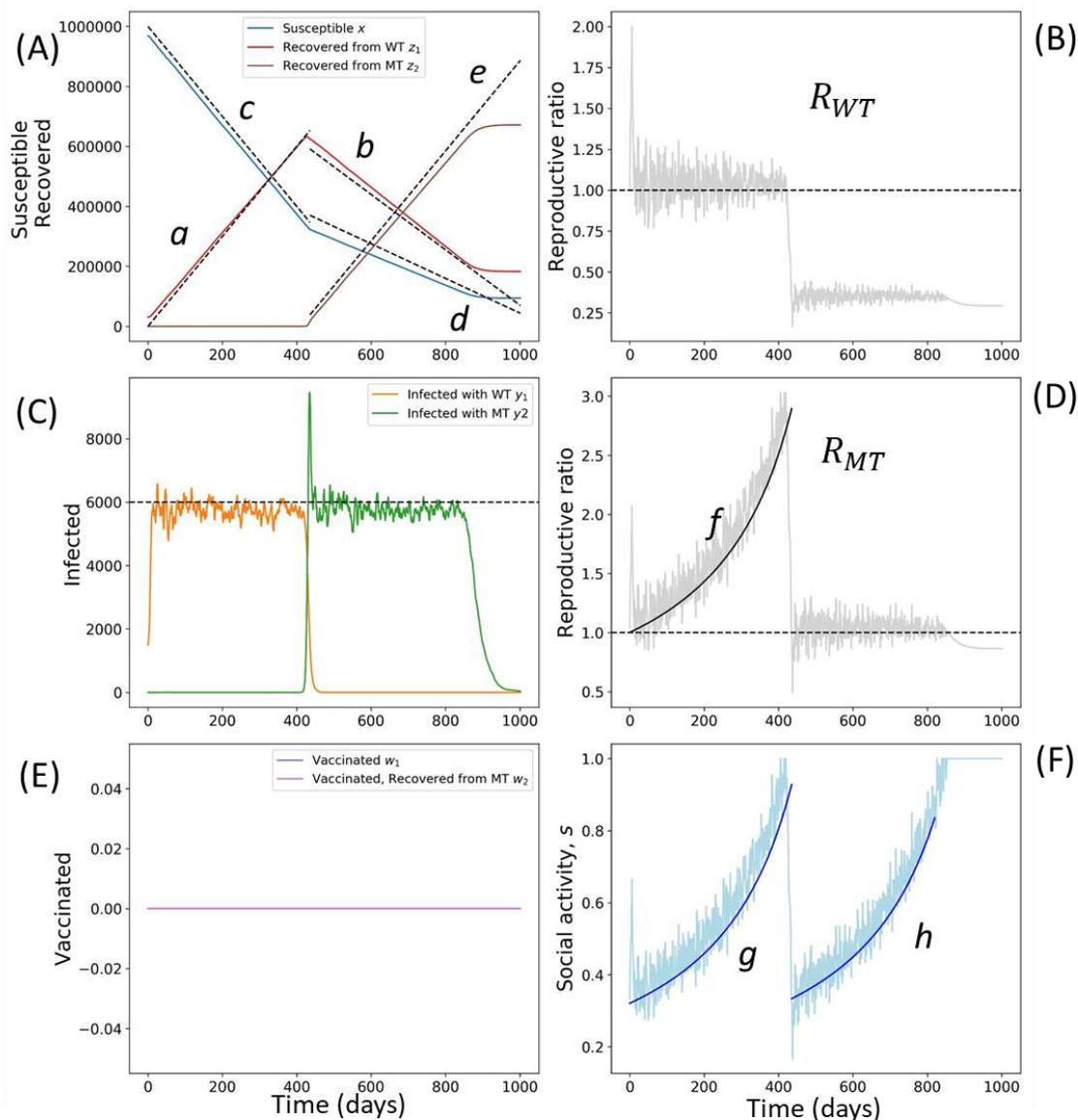
783 SUPPLEMENTARY FIGURES



784

785 **Figure S1: Scaling simulation results to larger population sizes.** Results of simulations for a given population  
786 size can be scaled to larger population size according to  $1 - (1 - p)^m$ , where  $p$  is the proportion of runs  
787 where the MT strain took over and  $m$  the ratio of the scaled population size to the simulated population  
788 size. (A) (B) Each square of the color map is colored according to the proportion of runs (out of 100) where  
789 the MT strain took over for  $N = 10^5$ . (C) (D) Each square of the color map is colored according to

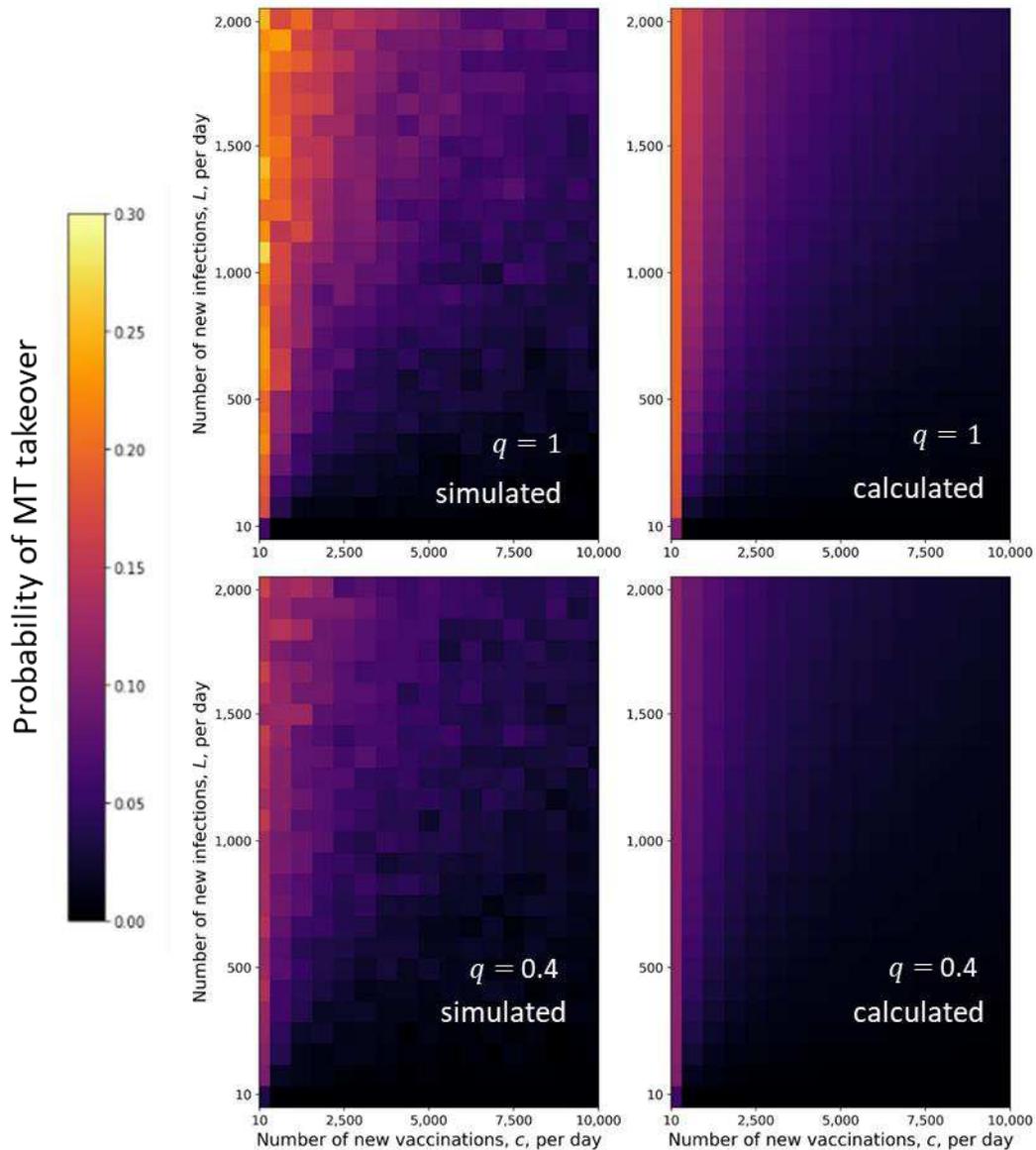
790  $1 - (1 - p)^{10}$ , where  $p$  is the proportion of runs where the MT strain took over in simulations presented in  
 791 (A) and (B). (E) (F) Each square of the color map is colored according to the proportion of runs (out of 100)  
 792 where the MT strain took over for  $N = 10^6$ . We observe a good agreement between the scaled results and  
 793 the simulated results.



794

795 **Figure S2: Evolution of resistance in absence of vaccination.** (A) Before MT takeover, the decline in  
 796 susceptible individuals ( $x$ ) along time can be approximated by a linear function with slope equal to  $L$ . Since  
 797 we assume no vaccination, the number of individuals recovered from WT grows linearly with slope equal  
 798 to  $L$ . After MT takeover, the number of individuals recovered from MT grows linearly slope equal to  $L$ , while  
 799 the number of susceptible individuals ( $x$ ) and individuals recovered from WT ( $z_1$ ) declines linearly with a  
 800 slope proportional to their frequencies at the moment of MT takeover. The equations of the lines (a), (b),

801 (c), (d) and (e) are given by, with  $t^*$  the time of takeover by the mutant strain: (a)  $z_1(t) = z_1(0) + Lt, t <$   
 802  $t^*$  (b)  $z_1(t) = (z_1(t^*) - z_1(t^*)/(z_1(t^*) + x(t^*)))L(t^* - t), t > t^*$  (c)  $x(t) = x(0) - Lt, t < t^*$  (d)  $x(t) =$   
 803  $x(t^*) - (x(t^*)/(z_1(t^*) + x(t^*)))L(t^* - t), t > t^*$  (e)  $z_2(t) = L(t^* - t), t > t^*$ . (B) The reproduction  
 804 coefficient of the wild-type  $R_{WT}$  is maintained at 1 by the dynamic lockdown. After mutant takeover,  $R_{WT}$   
 805 is less than 1, since the lockdown is now adjusted to the population susceptible to the MT strain. (C) The  
 806 number of active cases of WT ( $y_1$ ) and after mutant takeover, MT ( $y_1$ ) is constant at  $L/a$  until herd immunity  
 807 to the MT strain is reached. (D) Before MT takeover, the reproductive rate of the MT grows as (b)  $R_{MT} =$   
 808  $\beta_2(x(t) + z_1(t))/a$ . After takeover,  $R_{MT}$  is maintained around 1. (E) In this run, there was no vaccination  
 809 ( $c = 0$ ), hence  $w_1 = w_2 = 0$  for each time  $t$ . (F) Before MT takeover, the dynamic lockdown is adjusted to  
 810 the WT. As the number of individuals immune to WT grows, social activity increases. When the MT emerges,  
 811 lockdown measures are reinstated. Subsequently, social activity increases as the population immune to the  
 812 MT grows. The equations of the lines are given by (g)  $s(t) = a/(\beta_1 x(t)), t < t^*$  (h)  $s(t) = a/(\beta_2(x(t) +$   
 813  $qz_1(t))), t > t^*$ .



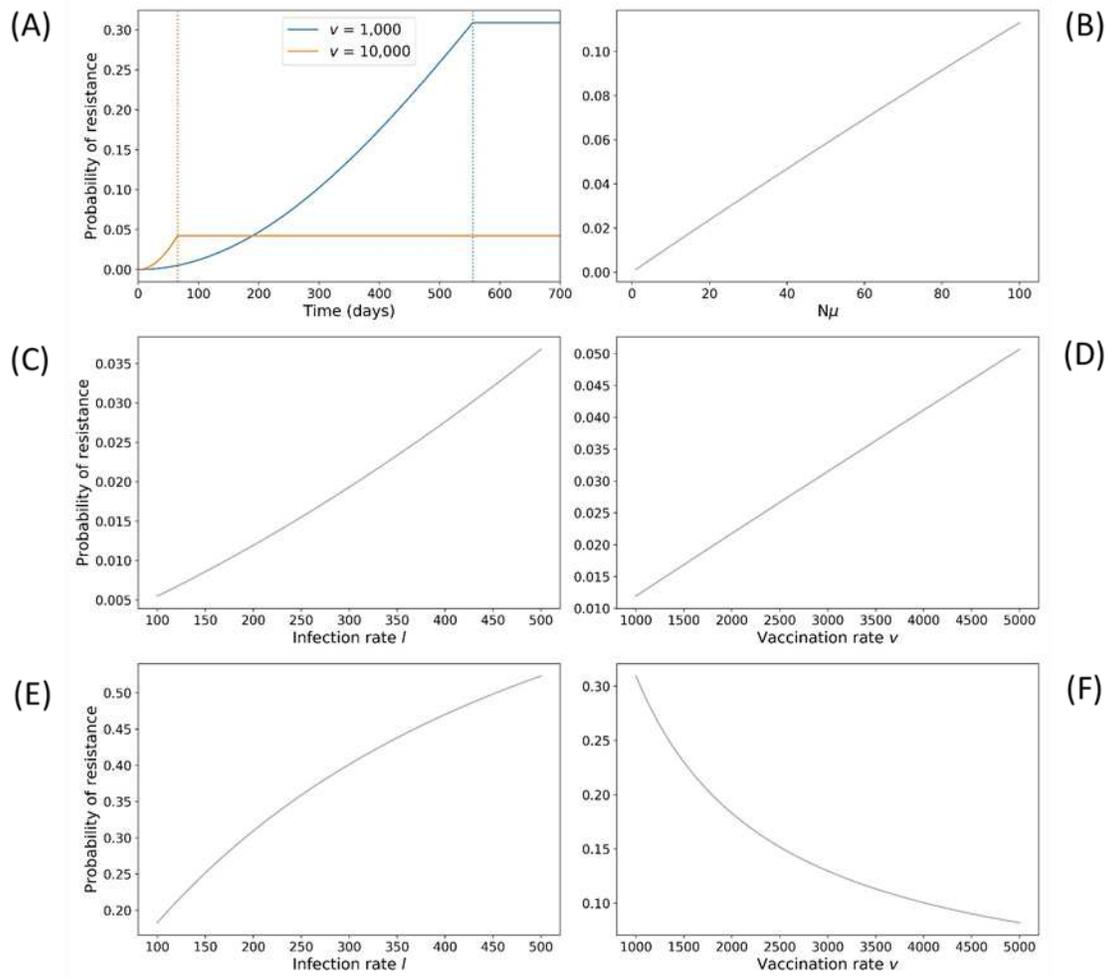
814

815 **Figure S3: Analytical approximation of the simulation results.** The probability of MT takeover before herd  
 816 immunity is reached can be calculated according to Eq. 5. We observe a good agreement between our  
 817 calculations and the results of the stochastic simulations. (A) (C) Each square of the color map is colored  
 818 according to the probability of take over calculated with Eq. (5). (B) (D) Each square of the color map is  
 819 colored according to the proportion of runs (out of 1000) where the MT strain took over. The population  
 820 size was  $N = 10^6$ .

821

822

823



824

825 **Figure S4: Counterintuitive effect of the vaccination rate on the probability of resistance.** Increasing the  
 826 population size  $N$ , the mutation rate  $\mu$  and the infection rate  $l$  all increase the probability of generating a  
 827 mutant before herd immunity is reached (B and C). We define  $v = c/N$  and  $l = L/N$ . Increasing the  
 828 vaccination rate  $v$  leads to a counterintuitive effect: the probability for a fixed time increases with  $v$  since  
 829 it leads to faster relaxation of social distancing measures, but it also leads to faster achievement of herd  
 830 immunity (A). Hence the probability of resistance until herd immunity decreases with  $v$  (F). Parameter  
 831 values:  $\mu = 10^{-7}$  (A):  $N = 10^8$ ,  $l = 200 \cdot 10^{-6}$ ; (B):  $l = 200 \cdot 10^{-6}$ ,  $v = 1000 \cdot 10^{-6}$ , (C)(E):  $N = 10^8$ ,  $v =$   
 832  $1000 \cdot 10^{-6}$ ; (D)(F):  $N = 10^8$ ,  $l = 200 \cdot 10^{-6}$ .