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The impact of cross-reactive immunity on the emergence of SARS-CoV-2 variants

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18 **Abstract**

19 A key feature of the COVID-19 pandemic has been the emergence of SARS-CoV-2 variants with
20 different transmission characteristics. However, when a novel variant arrives in a host population, it
21 will not necessarily lead to many cases. Instead, it may fade out, due to stochastic effects and the
22 level of immunity in the population. Immunity against novel SARS-CoV-2 variants may be
23 influenced by prior exposures to related viruses, such as other SARS-CoV-2 variants and seasonal
24 coronaviruses, and the level of cross-reactive immunity conferred by those exposures. Here, we
25 investigate the impact of cross-reactive immunity on the emergence of SARS-CoV-2 variants in a
26 simplified scenario in which a novel SARS-CoV-2 variant is introduced after an antigenically related
27 virus has spread in the population. We use mathematical modelling to explore the risk that the novel
28 variant invades the population and causes a large number of cases, as opposed to fading out with few
29 cases. If cross-reactive immunity is complete (i.e. someone infected by the previously circulating
30 virus is not susceptible to the novel variant), the novel variant must be more transmissible than the
31 previous virus to invade the population. However, in a more realistic scenario in which cross-reactive
32 immunity is partial, we show that it is possible for novel variants to invade, even if they are less
33 transmissible than previously circulating viruses. This is because partial cross-reactive immunity
34 effectively increases the pool of susceptible hosts that are available to the novel variant compared to
35 complete cross-reactive immunity. Furthermore, if previous infection with the antigenically related
36 virus assists the establishment of infection with the novel variant, as has been proposed following
37 some experimental studies, then even variants with very limited transmissibility are able to invade
38 the host population. Our results highlight that fast assessment of the level of cross-reactive immunity

39 conferred by related viruses on novel SARS-CoV-2 variants is an essential component of novel
40 variant risk assessments.

41

42 **1 Introduction**

43 When a new SARS-CoV-2 variant first arrives in a host population, a key question for policy makers
44 is whether or not it will become widespread. For this to occur, two steps are required: introduction
45 and invasion. First, the variant must arrive in the host population, either through de novo mutation or
46 importation from elsewhere (introduction). Second, the variant must then spread from person to
47 person and cause a large number of cases, as opposed to fading out with few cases (invasion).

48 Following introduction, a range of factors affect the risk that a novel variant will invade, including its
49 inherent transmissibility and the connectivity of the location in which it is introduced [1,2]. An
50 additional crucial factor in this process is the background level of immunity to the new variant in the
51 host population. For example, a feature of the Omicron (B.1.1.529) variant that allowed it to become
52 widespread is its ability to evade immunity from past infection or vaccination, at least partially,
53 meaning that the background immunity level was low [3–5].

54 Mathematical modelling has often been used to explore the impact of cross-reactive immunity
55 between pathogen strains on the dynamics of infectious disease outbreaks [6–11]. During the
56 COVID-19 pandemic, models have provided real-time insights into the risk posed by novel variants.
57 For example, Bhatia *et al.* [12] extended existing methods for estimating pathogen transmissibility
58 [13–15] to enable the transmissibility of novel variants to be assessed, including estimating the
59 infectiousness of the Alpha (B.1.1.7), Beta (B.1.351) and Gamma (P.1) variants relative to the wild
60 type virus (the SARS-CoV-2 virus that first emerged in Wuhan, China). Dyson *et al.* [16] analysed
61 epidemiological data from England, and projected the course of the outbreak in that country if a
62 variant emerged with different transmission characteristics. They warned that a variant with high

63 transmissibility or substantial immune escape properties had the potential to generate large numbers
64 of infections and hospitalisations.

65 Meanwhile, experimental and statistical studies have explored the effects of prior infections with
66 related viruses on infections with different SARS-CoV-2 variants. Some studies have found previous
67 infections with other SARS-CoV-2 variants to have a protective effect. For example, Wratil *et al.*
68 [17] demonstrated that a combination of infection and vaccination induced hybrid immunity is
69 protective against SARS-CoV-2 variants including the Omicron variant. A recent analysis of
70 infection data from Portugal found that previous SARS-CoV-2 infections were protective against
71 infection with the BA.5 Omicron subvariant, with the level of protection particularly high in
72 individuals who were previously infected by the BA.1 or BA.2 Omicron subvariants [18]. However,
73 some studies have indicated that prior infection with other SARS-CoV-2 variants may instead have a
74 detrimental effect on subsequent infections with novel SARS-CoV-2 variants. For example, earlier
75 infection with the SARS-CoV-2 wild type was found to inhibit the immune response to infections
76 with the Omicron variant among triple vaccinated healthcare workers [5].

77 Similarly to the cross-reactive immunity conferred by other SARS-CoV-2 variants, the impact of
78 prior infections with seasonal coronaviruses on subsequent infections by SARS-CoV-2 is also
79 unclear. Some analyses have found that previous infections with seasonal coronaviruses are likely to
80 be protective against SARS-CoV-2 infection. The SARS-CoV-2 spike protein can be divided into the
81 S1 and S2 subunits. The S1 subunit contains an antigenically variable receptor binding domain, while
82 the S2 subunit is more conserved between coronaviruses. Kaplonek *et al.* [19] showed that SARS-
83 CoV-2 S2 antibody responses are associated with milder COVID-19 symptoms, suggesting that
84 previous infection with seasonal coronaviruses may lead to COVID-19 infections being less severe.
85 Furthermore, strong and multispecific cross-reactive T-cell responses induced by seasonal

86 coronavirus infection prior to SARS-CoV-2 infection have been associated with protection against
87 SARS-CoV-2 infection in seronegative healthcare workers [5,20].

88 In contrast, there is also evidence that previous infections with seasonal coronaviruses can have
89 detrimental effects on susceptibility to and outcomes of infection with SARS-CoV-2. With respect to
90 disease outcomes, McNaughton *et al.* [21] showed that prior immunity to seasonal coronaviruses was
91 positively associated with fatal outcomes in individuals with severe COVID-19. Similar results were
92 found by Smit *et al.* [22] in an independent cohort. Conflicting results to Kaplonek *et al.* [19] were
93 found by Garrido *et al.* [23], who found that S2 antibody responses were associated with greater
94 disease severity. With respect to susceptibility, Wratil *et al.* [24] demonstrated that cross-reactive
95 immunity imparted by seasonal coronaviruses may increase susceptibility to SARS-CoV-2.
96 Additionally, a modelling analysis by Pinotti *et al.* [25] has suggested that the general trend of
97 increased severity of SARS-CoV-2 infections in older individuals may be explained by an increased
98 chance that older individuals have been exposed to seasonal coronaviruses.

99 Given this conflicting evidence in the literature, and to help understand the possible effects of prior
100 infections on the risk of emergence of SARS-CoV-2 variants, in this study we develop a
101 mathematical model considering two viruses: a novel SARS-CoV-2 variant and an antigenically
102 related virus that has previously spread in the population. We investigate the factors affecting the risk
103 that the novel variant invades the host population. We assume that infection with the previously
104 circulating virus affects the chance of successful infection with, and subsequent transmission of, the
105 novel variant, considering scenarios in which prior infection is either protective (partially or
106 completely) or detrimental. We show that the level of cross-reactive immunity between novel SARS-
107 CoV-2 variants and antigenically related viruses is a key factor determining
108 whether or not a novel variant will invade the host population. This highlights the need to conduct a
109 rapid assessment of the level of cross-reactive immunity between previously circulating viruses and

110 newly emerged SARS-CoV-2 variants whenever a novel SARS-CoV-2 variant is introduced into a
111 new host population.

112

113 **2 Methods**

114 **2.1 Epidemiological model**

115 We consider the introduction of a novel variant to a population consisting of N hosts. We assume that
116 prior immunity has been conferred by infections with a related virus that has already spread within
117 the host population. Assuming that this previously circulating virus follows dynamics that are
118 characterised by the standard (deterministic) SEIR model, the number of individuals in the
119 population who have been previously infected by that virus is given by the solution, N_p , to the final
120 size equation [8],

$$121 \quad N_p = N - Ne^{-\frac{R_{0p}N_p}{N}}. \quad (1)$$

122 In this expression, R_{0p} is the reproduction number of the previously circulating virus, which we
123 assume accounts for any interventions that were introduced (prior to, or immediately after, its arrival
124 in the host population) to limit its spread. We assume that N_p individuals were previously infected by
125 that virus (we round N_p to the nearest integer value), and the remaining $N - N_p$ individuals in the
126 population are immunologically naïve (i.e. they do not carry any immunity against the novel variant).
127 The dependence of N_p on R_{0p} is shown in Fig S1.

128 We then model the emergence of the novel variant. If an individual has previously been infected by
129 the related virus, their susceptibility to the novel variant is assumed to be modified by a
130 multiplicative factor $1 - \alpha$ (relative to the susceptibility of a host who has not previously been
131 infected by the related virus). Consequently, if $\alpha > 0$, prior infection with the related virus is

132 protective against infection with the novel variant. If instead $\alpha = 0$, then earlier infection with the
 133 related virus does not affect the risk of infection with the novel variant. If $\alpha < 0$, earlier infection
 134 with the related virus promotes infection with the novel variant. Similarly, the infectiousness of a
 135 host infected with the novel variant who has previously been infected by the related virus is modified
 136 by a multiplicative factor $1 - \varepsilon$ (relative to the infectiousness of a host who has not previously been
 137 infected by the related virus). Again, positive (negative) values of ε reflect scenarios in which prior
 138 infection with the related virus reduces (increases) the infectiousness of an individual who is infected
 139 with the novel variant.

140 Transmission dynamics for the novel variant are also modelled using an SEIR model, but with two
 141 main differences compared to the dynamics of the previously circulating virus. First, the SEIR model
 142 for the novel variant is extended to account for cross-reactive immunity conferred by the related
 143 virus. Second, since we are modelling invasion, we use a stochastic model in which, in each
 144 simulation of the model, the novel variant may either invade the host population or fade out with few
 145 infections. The analogous deterministic model to the stochastic model that we consider for the novel
 146 variant is given by:

$$147 \quad \frac{dS_n}{dt} = -\beta I_n S_n - \beta(1 - \varepsilon) I_p S_n,$$

$$148 \quad \frac{dE_n}{dt} = \beta I_n S_n + \beta(1 - \varepsilon) I_p S_n - \gamma E_n,$$

$$149 \quad \frac{dI_n}{dt} = \gamma E_n - \mu I_n,$$

$$150 \quad \frac{dR_n}{dt} = \mu I_n,$$

$$151 \quad \frac{dS_p}{dt} = -\beta(1 - \alpha) I_n S_p - \beta(1 - \varepsilon)(1 - \alpha) I_p S_p,$$

$$152 \quad \frac{dE_p}{dt} = \beta(1 - \alpha) I_n S_p + \beta(1 - \varepsilon)(1 - \alpha) I_p S_p - \gamma E_p,$$

$$153 \quad \frac{dI_p}{dt} = \gamma E_p - \mu I_p,$$

154 $\frac{dR_p}{dt} = \mu I_p.$ (2)

155 In these equations, the variables S_n , E_n , I_n and R_n refer to the infection status (with the novel variant)
156 of individuals who have not been infected previously by the related virus, and S_p , E_p , I_p and R_p refer
157 to the infection status of individuals who have previously been infected by the related virus. A
158 schematic illustrating the transitions of individuals between these states, and the rates at which those
159 transitions occur, is shown in Fig 1A. The parameter β is the infection rate parameter, and the mean
160 latent period and infectious period are $1/\gamma$ days and $1/\mu$ days, respectively. We define the
161 reproduction number of the novel variant to be $R_{0n} = \frac{\beta N}{\mu}$, reflecting the transmission potential of the
162 novel variant if the host population is entirely immunologically naïve. For a full description of the
163 stochastic model, see Text S1.

164 **2.2 Risk of invasion**

165 As noted above, since we are interested in the risk of invasion of the novel variant, we use the
166 analogous stochastic model to system of equations (2) rather than solving the differential equations
167 numerically. When we compute the risk of invasion by simulation, we run model simulations using
168 the direct method version of the Gillespie stochastic simulation algorithm ([26]; see Text S1) until
169 the novel variant fades out (i.e. $E_n + I_n + E_p + I_p$ reaches zero). The parameter values used in our
170 main analyses are given in Table 1.

171 When the novel variant is introduced, we also approximate the probability that it invades the
172 population analytically. To do this, we assume that infections occur according to a branching process
173 [27–30]. Specifically, we denote by q_{ij} the probability that the novel variant fails to invade the host
174 population, starting from i currently infected individuals who are immunologically naïve and j
175 currently infected individuals who were previously infected by the related virus. In this analysis,
176 “currently infected” individuals refer to those who are either exposed or infectious, since exposed and

177 infectious individuals are each expected to infect the same number of other hosts in future. This is
 178 because exposed individuals are not yet infectious, and only start generating infections when they
 179 move into the infectious states in the model.

180 We then consider the probability of the novel variant failing to invade the host population starting
 181 from a single currently infected individual who was previously immunologically naïve, q_{10} . As in
 182 similar previous branching process analyses [31–34], we consider the various possibilities for what
 183 happens next: either that individual infects another individual who was also previously
 184 immunologically naïve (with probability $\frac{\beta(N-N_p)}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu}$); or, that individual infects someone
 185 who was previously infected with the related virus (with probability $\frac{\beta(1-\alpha)N_p}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu}$); or, that
 186 individual recovers without infecting anyone else (with probability $\frac{\mu}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu}$). Applying
 187 the law of total probability therefore gives

$$188 \quad q_{10} = \frac{\beta(N-N_p)}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu} q_{20} + \frac{\beta(1-\alpha)N_p}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu} q_{11} + \frac{\mu}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu} q_{00}.$$

189 Instead starting from a single currently infected individual who was previously infected by the related
 190 virus gives

$$191 \quad q_{01} = \frac{\beta(1-\varepsilon)(N-N_p)}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu} q_{11} + \frac{\beta(1-\varepsilon)(1-\alpha)N_p}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu} q_{02} +$$

$$192 \quad \frac{\mu}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu} q_{00}.$$

193 We then assume that infections occur according to a branching process (so that $q_{20} = q_{10}^2$; as
 194 infection lineages failing to establish starting from two currently infected hosts requires the infection
 195 lineages from both currently infected hosts to fail independently [31–33]). Making similar

196 approximations throughout the equations above, and noting that $q_{00} = 1$ (since the novel variant will
 197 not invade if there are no currently infected individuals) gives

$$198 \quad q_{10} = \frac{\beta(N-N_p)}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu} q_{10}^2 + \frac{\beta(1-\alpha)N_p}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu} q_{10}q_{01} + \frac{\mu}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu},$$

$$199 \quad q_{01} = \frac{\beta(1-\varepsilon)(N-N_p)}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu} q_{10}q_{01} + \frac{\beta(1-\varepsilon)(1-\alpha)N_p}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu} q_{01}^2 + \frac{\mu}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu}. \quad (3)$$

200 The probability of invasion starting from one currently infected individual who was previously
 201 immunologically naïve, p_{10} , and the probability of invasion starting from one currently infected
 202 individual who was previously infected by the related virus, p_{01} , are then given by $p_{10} = 1 - q_{10}$ and
 203 $p_{01} = 1 - q_{01}$, where q_{10} and q_{01} are the minimal non-negative solutions of system of equations (3)
 204 [35].

205 **2.3 Special cases**

206 In general, we solve system of equations (3) numerically. However, an analytic solution can be
 207 obtained straightforwardly in some special cases.

208 For example, in a scenario in which previous infection with the related virus is entirely protective
 209 against infection with the novel variant, then $\alpha = 1$. In that case, since a previously infected
 210 individual cannot be infected with the novel variant, then p_{01} does not apply. However, in that

211 scenario, $p_{10} = 1 - \frac{\mu}{\beta(N-N_p)}$ (whenever $\frac{\beta(N-N_p)}{\mu} > 1$; otherwise, the novel variant will never invade

212 the host population). This can be seen by substituting $\alpha = 1$ into the first equation of system of
 213 equations (3), solving the resulting quadratic equation for q_{10} (taking the minimal non-negative

214 solution [35]), and then calculating $p_{10} = 1 - q_{10}$. In a scenario in which the related virus has not

215 previously spread in the host population, then this solution for p_{10} is identical to the classic branching

216 process estimate for the probability of a major outbreak, $p_{10} = 1 - \frac{1}{R_{0n}}$ [28,36,37].

217 Alternatively, we can consider a scenario in which prior infection with the related virus eliminates
218 the infectiousness of a host infected by the novel variant (i.e. the individual can become infected, but
219 the virus cannot then establish, so onwards transmission cannot occur). In that case, $\varepsilon = 1$ and so – in
220 a similar fashion to above – we obtain $p_{10} = 1 - \frac{\mu}{\beta(N-N_p)}$ (whenever $\frac{\beta(N-N_p)}{\mu} > 1$) and $p_{01} = 0$.

221 Again, in a scenario in which a related virus has not previously spread in the population, this is the
222 classic estimate for the probability of a major outbreak, $p_{10} = 1 - \frac{1}{R_{0n}}$ [28,36,37].

223 Finally, in a scenario in which previous infection by the related virus does not affect the dynamics of
224 the novel variant (so that $\alpha = \varepsilon = 0$), we expect the risk of novel variant invasion to be independent
225 of whether or not the initial infected individual has previously been infected by the related virus. In
226 other words, we expect $q_{10} = q_{01}$. In this case, system of equations (3) reduces to a single quadratic
227 equation for q_{10} . Taking the minimal non-negative solution of that equation [35] indicates that
228 $p_{10} = p_{01} = 1 - q_{10} = 1 - \frac{1}{R_{0n}}$ (whenever $R_{0n} > 1$; otherwise the novel variant will never invade
229 the host population).

230 **3 Results**

231 To investigate the effects of prior infection by an antigenically related virus on the epidemiological
232 dynamics of a newly emerged variant, we first ran stochastic simulations of the analogous stochastic
233 model to system of equations (2). Representative time series of the dynamics illustrate that, if the
234 novel variant successfully spreads in the host population, outbreaks tend to have a lower peak
235 number of infections and have a longer duration when cross-reactive immunity has a protective effect
236 (Fig 1B), compared to when prior infection by the related virus has no effect (Fig 1C). In contrast, if
237 prior infection by the related virus instead promotes infection by the novel variant, outbreaks tend to
238 have a higher peak number of infections and a shorter duration (Fig 1D).

239 However, rather than focusing on the dynamics of outbreaks once the novel variant has invaded the
240 host population, our main goal was to quantify the risk of the novel variant successfully invading in
241 the first place (as opposed to fading out with few cases). We therefore calculated the risk of the novel
242 variant invading the population, starting from the introduction of a single case to the population (Fig
243 2). We not only calculated this quantity by numerically solving system of equations (3) (Fig 2 - red
244 dotted and dashed lines), but also confirmed that these numerical approximations matched estimates
245 of the invasion probability obtained using large numbers of simulations of the stochastic model (Fig
246 2 - black dots and crosses).

247 We found that, when previous infection with the related virus is completely protective against the
248 novel variant (i.e. $\alpha = \varepsilon = 1$), then the reproduction number of the novel variant must be higher than
249 the reproduction number of the antigenically related virus in order for the novel variant to invade.
250 Specifically, in Fig 2A (in which $R_{0p} = 1.5$, as marked by the vertical blue dotted line), the
251 probability of the novel variant invading the host population is zero unless $R_{0n} > R_{0p}$, and indeed
252 remains zero whenever R_{0n} is only slightly larger than R_{0p} . This can be explained analytically as
253 follows. The previously circulating virus will spread around the population until sufficiently many
254 individuals have been infected that herd immunity (to the previous virus) is reached. This occurs
255 when $N \left(1 - \frac{1}{R_{0p}}\right)$ individuals have become infected [38]. However, at this point, infections do not
256 stop immediately: there is an “overshoot” in infections while transmission slows and the previously
257 circulating virus fades out. As a result, a lower bound on the final size of the outbreak caused by the
258 previously circulating virus is $N_p > N \left(1 - \frac{1}{R_{0p}}\right)$. As noted in the Methods (Special cases), in a
259 scenario involving complete cross-reactive immunity, the novel variant can only invade the
260 population if $\frac{\beta(N-N_p)}{\mu} > 1$, or equivalently $R_{0n} > \frac{N}{N-N_p}$. Substituting the lower bound for N_p into this
261 expression shows that invasion of the novel variant requires $R_{0n} > R_{0p}$.

262 In contrast, if cross-reactive immunity is only partial, then the novel variant may invade for lower
263 values of R_{0n} than when cross-reactive immunity is complete (Fig 2B). This can include scenarios in
264 which $R_{0n} < R_{0p}$ (in some cases lying between those shown in Fig 2B and Fig 2C). As noted in the
265 Methods, when previous infection by the antigenically related virus does not affect the
266 epidemiological dynamics of the novel variant, then the novel variant can only invade if $R_{0n} > 1$
267 (Fig 2C), mirroring the classical result for models in which cross-reactive immunity is not accounted
268 for [36]. Finally, in scenarios in which prior infection by the related virus promotes infection with the
269 novel variant, the novel variant can invade even if R_{0n} is small. This includes scenarios in which
270 $R_{0n} < 1$ (Fig 2D).

271 In Fig 2, we note that the immune status of the initial infected individual affects the risk that the
272 novel variant will invade the host population. In particular, when cross-reactive immunity is
273 protective, we found that the probability of invasion is higher if the initially infected host had not
274 previously been infected by the related virus (Fig 2B). In contrast, if cross-reactive immunity
275 promotes infection with the novel variant, then the probability of the novel variant invading is higher
276 if the initial infection arose in an individual who had previously been infected with the related virus
277 (Fig 2D).

278 We then explored how the probability of invasion of the novel variant depends on the susceptibility-
279 and infectiousness-modifying effects of cross-reactive immunity individually (Fig 3). We found that
280 the values of α and ε affect the probability of a major outbreak differently. This is because, starting
281 from a single infected individual, the number of infections generated by that individual is crucial in
282 determining whether or not a novel variant will invade. If the first infected host infects multiple
283 others, then all of those individuals' transmission lineages must fade out in order for invasion to fail
284 to occur. Hence, invasion is more likely to occur if the first infected individual infects many
285 individuals. Starting from a single infected individual who was not previously infected by the related

286 virus, only susceptibility-modifying immunity (characterised by α) affects the number of infections
287 generated by the first infected individual. As such, the probability of invasion in this case is more
288 sensitive to α than to ε (Fig 3A).

289 In contrast, if the first infected individual was previously infected by the related virus, then
290 infectiousness-modifying immunity (characterised by ε) also affects the probability of this individual
291 infecting any other member of the population. In fact, ε then affects all potential transmissions
292 generated by the first infected individual, whereas α only affects potential transmissions to part of the
293 population (those individuals who were previously infected by the related virus). In that scenario, the
294 probability of a major outbreak is therefore slightly more sensitive to ε than α (Fig 3B). The different
295 effects of susceptibility-modifying and infectiousness-modifying cross-reactive immunity therefore
296 explain the asymmetric nature of the contours about the diagonal $\varepsilon = \alpha$ in Fig 3.

297

298 **4 Discussion**

299 The epidemiological dynamics of the COVID-19 pandemic have been shaped by the emergence of
300 different SARS-CoV-2 variants. However, not all variants that have appeared have spread widely and
301 caused a large number of cases. Most novel variants have faded out, with relatively few variants
302 being responsible for the vast majority of SARS-CoV-2 infections.

303 Here, we have developed a mathematical model to investigate the impact of cross-reactive immunity
304 (generated by previous infections by related viruses) on the probability that a newly introduced
305 variant will invade the host population. We found that, if prior infection with a related virus has a
306 strong protective effect, then the novel variant must be more infectious than the related virus to be
307 able to invade the host population (Fig 2A). If instead, however, the previously circulating virus has a
308 very weak protective effect or no protective effect on infection with the novel variant, then the risk of

309 invasion of the novel variant is unaffected by the outbreak of the related virus, and so the invasion
310 probability matches the well-known estimate for the “probability of a major outbreak” (Fig 2C)
311 [28,36,37]. If prior infection with the related virus promotes infection by the novel variant, as has
312 been indicated as possible in some studies exploring the impact of prior infections by SARS-CoV-2
313 or seasonal coronaviruses on infections with SARS-CoV-2 variants, then even novel variants with
314 limited transmissibility are able to invade (Fig 2D).

315 We further showed that the immune status of the first individual in the population infected by the
316 novel variant affects the probability that the novel variant invades (Figs 2 and 3). This is in turn
317 influenced by the pathway by which the novel variant is introduced into the host population. If the
318 variant is introduced from elsewhere, for example by an incoming traveller [1,15], then it may be
319 introduced by someone who was not previously infected by the related virus. If instead it appears as a
320 result of mutation from a related virus within the local population (as was likely the case for the
321 emergence of the Alpha variant in Kent, England [39]), then the initial infected case would be an
322 individual who was previously infected by the related virus.

323 Previous modelling studies have explored the risk of a novel virus invading when it is introduced to a
324 host population, including scenarios in which the pathogen evolves to facilitate emergence [40–44].
325 Of significant relevance to our study, Hartfield and Alizon [45] applied a branching process model to
326 investigate the invasion probability in a scenario in which a resident pathogen strain that confers
327 cross-reactive immunity is spreading in the host population, and considered Chikungunya virus as a
328 case study. Those authors demonstrated that the standard estimate for the probability of a major
329 outbreak overestimates the invasion probability in that scenario, due to the potential for depletion of
330 susceptible individuals by the resident strain over the timescale of invasion of the novel virus.
331 Echoing this result in a single strain setting, Sachak-Patwa *et al.* [46] showed that simple estimates
332 for the probability of a major outbreak are overestimates if the pathogen enters the host population

333 during a vaccination campaign, again due to depletion of susceptible individuals occurring within the
334 period of the pathogen either invading or fading out. Other researchers have investigated the
335 emergence of a novel pathogen strain that is introduced to the population when a resident strain is
336 endemic [47]. In contrast to previous studies, we focus on a scenario in which a related virus has
337 already spread widely around the host population and caused a completed outbreak, rather than being
338 resident in the host population. An additional novel aspect of the current study is that we conduct a
339 thorough investigation of the effects of different levels of cross-reactive immunity, including
340 scenarios in which prior infection with an antigenically related virus can promote infection with the
341 novel variant. Although such scenarios may seem counterintuitive, recent evidence suggests that
342 there is a clear possibility that infection-promoting cross-reactivity may occur, as described in the
343 Introduction.

344 To understand general principles governing the relationship between cross-reactive immunity and the
345 risk of invasion of a novel variant, we constructed the simplest possible model in this study. Further
346 developments could involve including additional epidemiological and evolutionary detail in our
347 transmission model, particularly if it is to be used to predict emergence of specific variants rather
348 than to understand general principles. For example, in the model considered here, the infectious
349 period of individuals infected by the novel variant is assumed to follow an exponential distribution.
350 However, gamma distributions have been found to represent observed epidemiological periods more
351 accurately than exponential distributions [48–50], and gamma-distributed infectious periods can be
352 incorporated into calculations of invasion probabilities [51,52]. We also assumed a fixed level of
353 cross-reactive immunity for all individuals who were previously infected by the related virus. In
354 reality, immunity is heterogeneous between previously infected hosts, and is likely to wane over time
355 [53,54]. The level of cross-reactive immunity in any individual may depend on a range of factors,
356 including whether or not the individual is immunocompromised or has underlying comorbidities

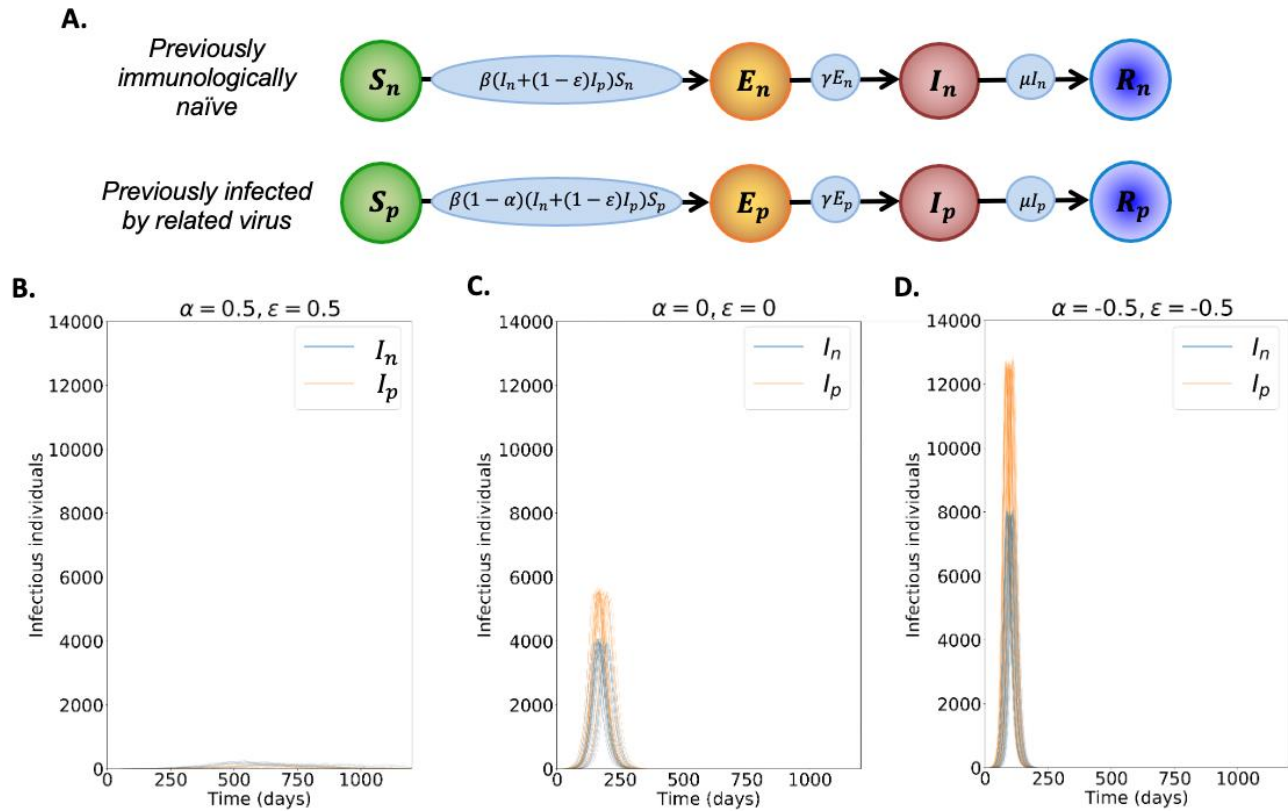
357 [55], and the characteristics of their previous infection [56]. Waning immunity has been included
358 previously in a range of epidemiological models [57,58], and is a target for future addition to the
359 modelling framework presented here, along with consideration of heterogeneity in immunity between
360 previously infected hosts. Additionally, similar investigations to those conducted here could be
361 undertaken for scenarios in which multiple viruses are co-circulating (potentially allowing for
362 superinfection [59]). This could include analyses of epidemiological dynamics beyond the early
363 phase of the outbreak of the novel variant, after it has invaded the host population.

364 A key challenge going forwards is to develop reliable approaches for inferring the level of cross-
365 reactive immunity between previously circulating viruses and newly emerged SARS-CoV-2 variants
366 (i.e. the values of the parameters α and ε in our model). Serological studies measuring correlates of
367 immune responses in infected patients (e.g. ELISA analyses of cross-reactive antibody responses
368 [21]) have the potential to determine broadly whether previous infections might be protective or
369 detrimental. This may be sufficient to approximate the risk that a new variant will invade host
370 populations in which it is not yet widespread (in Fig 3A, for example, if the values of α and ε are
371 both negative, then the probability of the novel variant invading if it is introduced to new host
372 populations is high). More precise estimates of the level of cross-reactive immunity may require
373 substantial epidemiological investigations. As an example, Altarawneh *et al.* [60] used data from
374 national databases in Qatar to estimate the effect of previous SARS-CoV-2 infection on the risk of
375 symptomatic reinfection by specific SARS-CoV-2 variants. If similar analyses can be carried out in
376 locations in which novel variants first emerge, then estimates of the probability of those variants
377 invading other locations can be refined. We note, however, that there is currently substantial
378 uncertainty in estimates of the level of cross-reactive immunity between different viruses.
379 Altarawneh *et al.* estimated that previous infection with other SARS-CoV-2 variants has around 56%
380 effectiveness at preventing symptomatic reinfection by the Omicron variant [60], whereas other

381 analyses have suggested that previous infections by other variants have only a limited effect on
382 reinfection rates by the Omicron variant [3]. This uncertainty needs to be resolved before the
383 modelling approach described here can be used to make precise quantitative predictions rather than
384 demonstrating qualitative principles about the general impacts of cross-reactive immunity.

385 In summary, understanding the risk posed by a novel variant requires the degree of cross-reactive
386 immunity between previously circulating viruses and the new variant to be assessed. In scenarios in
387 which previous infections by antigenically related viruses have a limited effect, or promote infection
388 with the novel variant, then the risk of the variant invading the host population is substantially higher
389 than in scenarios in which previous infections by related viruses are protective. Given the impact that
390 different variants have had on transmission and control during the COVID-19 pandemic, fast
391 detection and analyses of novel variants is essential for both national and global public health.

392 **Figures**



393

394 Figure 1. Dynamics of the novel variant invading a population in which a related virus has previously spread. A.

395 Schematic showing the transitions (and their rates) in the stochastic model of novel variant invasion (the analogous

396 stochastic model to system of equations (2)). B. Realisations of 50 stochastic simulations of the model, for $R_{0n} = 2$ and

397 with protective cross-reactive immunity ($\alpha = \epsilon = 0.5$; other parameter values are as stated in Table 1). Orange lines

398 represent the number of individuals infected by the novel variant who were previously infected by the related virus (I_p),

399 and blue lines represent the number of individuals infected by the novel variant who were previously immunologically

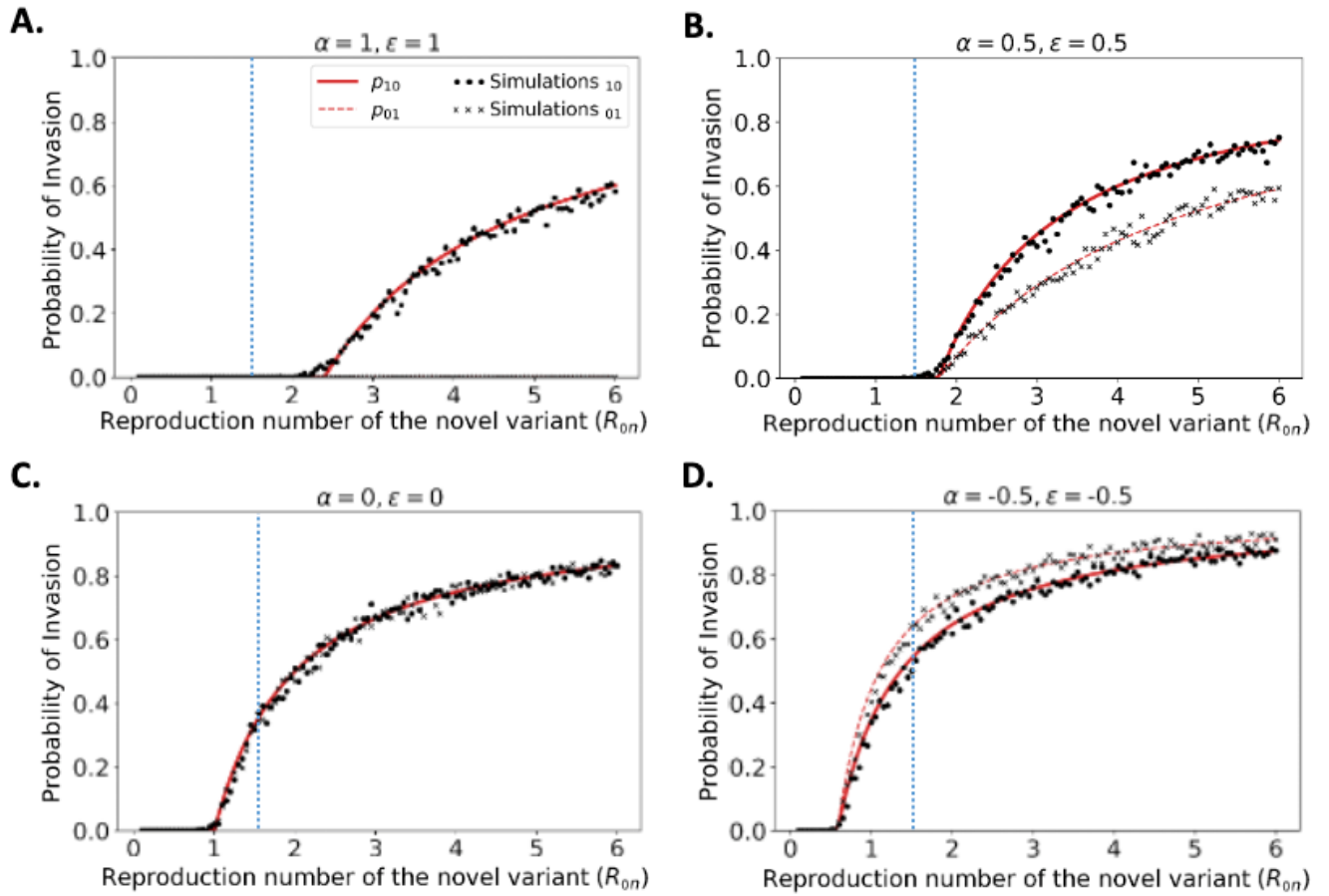
400 naïve (I_n). C. Analogous to panel B, but with no cross-reactive immunity ($\alpha = \epsilon = 0$). D. Analogous to panel B, but with

401 cross-reactive immunity instead promoting infection with the novel variant ($\alpha = \epsilon = -0.5$). Simulations were initiated

402 with a single infected, previously immunologically naïve individual ($I_n = 1$), with all other individuals susceptible ($S_n =$

403 $N - N_p - 1$ and $S_p = N_p$, where N_p is the solution of the final size equation for the previously circulating virus, equation

404 (1), rounded to the nearest integer value).

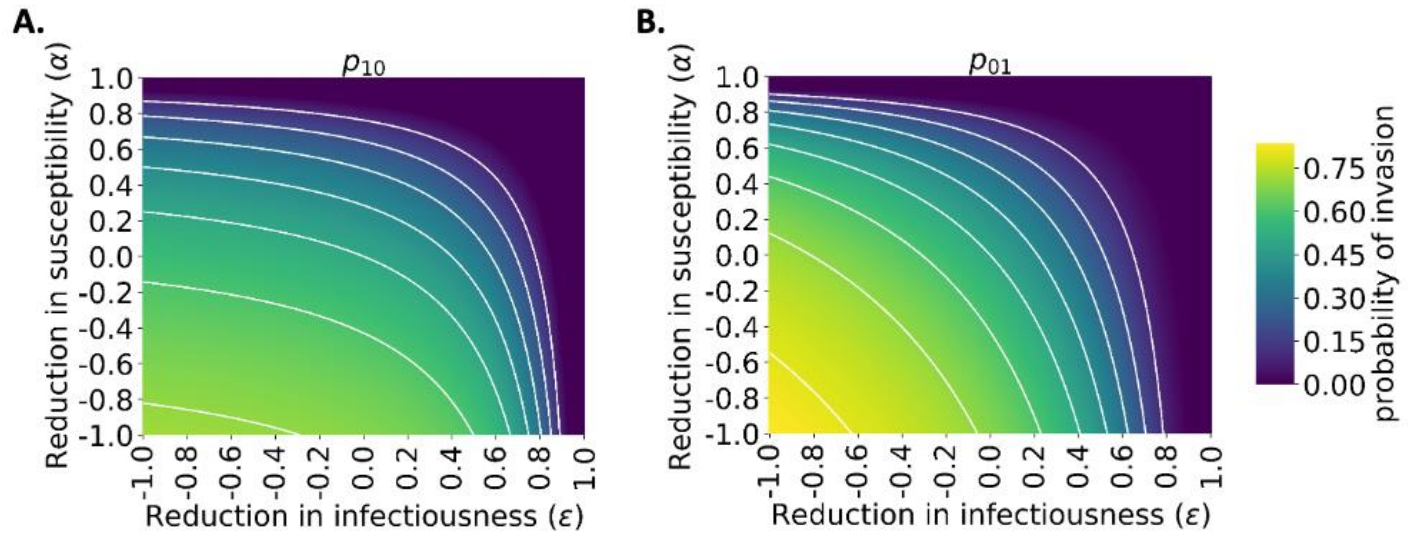


405

406 Figure 2. Probability of the novel variant invading the host population, starting from the introduction of a single
 407 infectious individual. A. The probability of the novel variant invading under an assumption of perfectly protective cross-
 408 reactive immunity ($\alpha = \epsilon = 1$). Results are shown both for analytic approximations of the invasion probability calculated
 409 using system of equations (3) (either starting from a single infected individual who was previously immunologically
 410 naïve (red solid) or starting from a single infected individual who was previously infected by the related virus (red
 411 dashed)) and for the invasion probability calculated using stochastic simulations (either starting from a single infected
 412 individual who was previously immunologically naïve (black dots) or starting from a single infected individual who was
 413 previously infected by the related virus (black crosses)). The vertical blue dotted line represents the reproduction number
 414 of the previously circulating virus ($R_{0p} = 1.5$). B. Analogous results to panel A, but with partial protective cross-reactive
 415 immunity ($\alpha = \epsilon = 0.5$). C. Analogous results to panel A, but with no cross-reactive immunity ($\alpha = \epsilon = 0$). D.
 416 Analogous to panel A, but with cross-reactive immunity instead promoting infection with the novel variant ($\alpha = \epsilon =$
 417 -0.5). In the simulations, the probability of invasion was calculated as the proportion of simulations in which the number
 418 of simultaneously infected individuals ($I_n + I_p$) exceeded 15 at any time (analyses for different values of this threshold
 419 are shown in Figs S2 and S3, with similar results). As in Fig 1, the division of the host population between individuals

420 who were previously immunologically naïve and those who were previously infected by the related virus was calculated
 421 based on the final size equation for the previously circulating virus (equation (1)). Other parameter values used are shown
 422 in Table 1.

423



424

425 Figure 3. Probability of the novel variant invading the host population, starting from the introduction of a single
 426 infectious individual, for different levels of cross-reactive immunity affecting susceptibility and infectiousness
 427 individually. The invasion probability is approximated analytically by solving system of equations (3) numerically. A.
 428 The probability of the novel variant invading, starting from a single infected individual who was previously
 429 immunologically naïve. B. Analogous to panel A, but starting from a single infected individual who was previously
 430 infected by the related virus. White lines represent contours of constant probability of invasion of the novel variant. As in
 431 Fig 1, the division of the host population between individuals who were previously immunologically naïve and those who
 432 were previously infected by the related virus was calculated based on the final size equation for the previously circulating
 433 virus (equation (1)). In this figure, $R_{0p} = 1.5$ and $R_{0n} = 2$ (analyses for other values of R_{0p} and R_{0n} are shown in Fig
 434 S4). Other parameter values used are shown in Table 1.

435

436

437

438 **Table**

439 Table 1. Illustrative parameter values used in model simulations.

Parameter	Meaning	Value used
N	Size of local host population	100,000
$1/\gamma$	Mean latent period of novel variant	5 days [61,62]
$1/\mu$	Mean infectious period of novel variant	8 days [63–65]
R_{op}	Reproduction number of previously circulating virus (accounting for interventions)	1.5, so that $N_p = 58,281$ individuals are assumed to have been infected by the previously circulating virus (approximately 58% of the population)
R_{on}	Reproduction number of novel variant (accounting for interventions)	Varies (see figures)
β	Transmission rate of novel variant	Set so that $R_{on} = \frac{\beta N}{\mu}$
α	Reduction (positive) or increase (negative) in susceptibility due to cross-reactive immunity	Varies (see figures)
ε	Reduction (positive) or increase (negative) in infectiousness due to cross-reactive immunity	Varies (see figures)

440

441 **Conflict of Interest**

442 The authors declare that the research was conducted in the absence of any commercial or financial
443 relationships that could be construed as a potential conflict of interest.

444 **Author Contributions**

445 Conceptualisation: RNT, CPT, SI, UO; Methodology: RNT, UO, ES, FLR; Formal analysis: RNT,
446 ES, YD, UO; Supervision: RNT, UO; Writing – Original draft: RNT, CPT, UO; Writing – Review
447 and editing: All authors.

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459 **Data Availability Statement**

460 Computing code developed to generate the results in the manuscript is available at
461 <https://github.com/yairdaon/waning>

462

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