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

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Introduction: A key feature of the COVID-19 pandemic has been the emergence of SARS-CoV-2 variants with different transmission characteristics. However, when a novel variant arrives in a host population, it will not necessarily lead to many cases. Instead, it may fade out, due to stochastic effects and the level of immunity in the population. Immunity against novel SARS-CoV-2 variants may be influenced by prior exposures to related viruses, such as other SARS-CoV-2 variants and seasonal coronaviruses, and the level of cross-reactive immunity conferred by those exposures.

Methods: Here, we investigate the impact of cross-reactive immunity on the emergence of SARS-CoV-2 variants in a simplified scenario in which a novel SARS-CoV-2 variant is introduced after an antigenically related virus has spread in the population. We use mathematical modelling to explore the risk that the novel variant invades the population and causes a large number of cases, as opposed to fading out with few cases.

Results: We find that, if cross-reactive immunity is complete (i.e. someone infected by the previously circulating virus is not susceptible to the novel variant), the novel variant must be more transmissible than the previous virus to invade the population. However, in a more realistic scenario in which cross-reactive immunity is partial, we show that it is possible for novel variants to invade, even if they are less transmissible than previously circulating viruses. This is because partial cross-reactive immunity effectively increases the pool of susceptible hosts that are available to the novel variant compared to complete cross-reactive immunity. Furthermore, if previous infection with the antigenically related virus assists the establishment of infection with the novel variant, as has

been proposed following some experimental studies, then even variants with very limited transmissibility are able to invade the host population.

Discussion: Our results highlight that fast assessment of the level of cross-reactive immunity conferred by related viruses against novel SARS-CoV-2 variants is an essential component of novel variant risk assessments.

KEYWORDS

cross-reactive immunity, mathematical modelling, infectious disease epidemiology, SARS-CoV-2, COVID-19, variants, emergence

1 Introduction

When a new SARS-CoV-2 variant first arrives in a host population, a key question for policy makers is whether or not it will become widespread. For this to occur, two steps are required: introduction and invasion. First, the variant must arrive in the host population, either through *de novo* mutation or importation from elsewhere (introduction). Second, the variant must then spread from person to person and cause a large number of cases, as opposed to fading out with few cases (invasion). Following introduction, a range of factors affect the risk that a novel variant will invade, including its inherent transmissibility and the connectivity of the location in which it is introduced (1, 2). An additional crucial factor in this process is the background level of immunity to the new variant in the host population. For example, a feature of the Omicron (B.1.1.529) variant that allowed it to become widespread is its ability to evade immunity from past infection or vaccination, at least partially, meaning that the background immunity level was low (3–5).

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

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

Similarly to the cross-reactive immunity conferred by other SARS-CoV-2 variants, the impact of prior infections with seasonal coronaviruses on subsequent infections by SARS-CoV-2 is also unclear. Some analyses have found that previous infections with seasonal coronaviruses are likely to be protective against SARS-CoV-2 infection. The SARS-CoV-2 spike protein can be divided into the S1 and S2 subunits. The S1 subunit contains an antigenically variable receptor binding domain, while the S2 subunit is more conserved between coronaviruses. Kaplonek et al. (19) showed that SARS-CoV-2 S2 antibody responses are associated with milder COVID-19 symptoms, suggesting that previous infection with seasonal coronaviruses may lead to COVID-19 infections being less severe. Furthermore, strong and multispecific cross-reactive T-cell responses induced by seasonal coronavirus infection prior to SARS-CoV-2 infection have been associated with protection against SARS-CoV-2 infection in seronegative healthcare workers (5, 20).

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

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

2 Methods

2.1 Epidemiological model

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

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

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

We then model the emergence of the novel variant. If an individual has previously been infected by the related virus, their susceptibility to the novel variant is assumed to be modified by a multiplicative factor $1–\alpha$ (relative to the susceptibility of a host who has not previously been infected by the related virus). Consequently, if $\alpha > 0$, prior infection with the related virus is protective against infection with the novel variant. If instead $\alpha = 0$, then earlier infection with the related virus does not affect the risk of infection with the novel variant. If $\alpha < 0$, earlier infection with the related virus promotes infection with the novel variant. Similarly, the infectiousness of a host infected with the novel variant who has previously been infected by the related virus is modified by a multiplicative factor $1–\epsilon$ (relative to the infectiousness of a host who has not previously been infected by the related virus). Again, positive (negative) values of ϵ reflect scenarios in which prior infection with the related virus reduces (increases) the infectiousness of an individual who is infected with the novel variant.

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

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

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

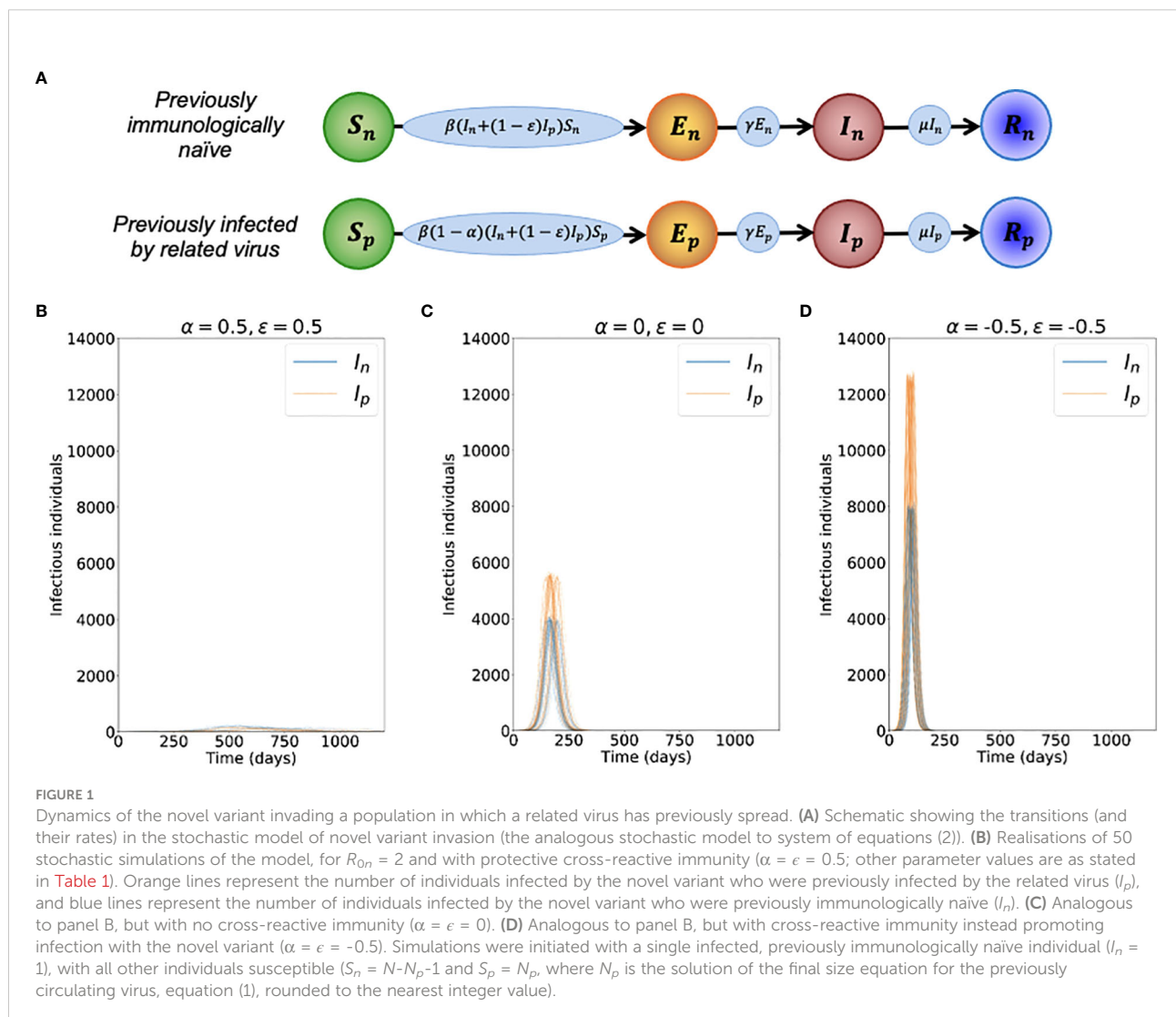$$\frac{dI_n}{dt} = \gamma E_n - \mu I_n,$$

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

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

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

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

$$\frac{dR_p}{dt} = \mu I_p. \tag{2}$$

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

2.2 Risk of invasion

As noted above, since we are interested in the risk of invasion of the novel variant, we use the analogous stochastic

FIGURE 1
Dynamics of the novel variant invading a population in which a related virus has previously spread. **(A)** Schematic showing the transitions (and their rates) in the stochastic model of novel variant invasion (the analogous stochastic model to system of equations (2)). **(B)** Realisations of 50 stochastic simulations of the model, for $R_{0n} = 2$ and with protective cross-reactive immunity ($\alpha = \epsilon = 0.5$; other parameter values are as stated in Table 1). Orange lines represent the number of individuals infected by the novel variant who were previously infected by the related virus (I_p), and blue lines represent the number of individuals infected by the novel variant who were previously immunologically naïve (I_n). **(C)** Analogous to panel B, but with no cross-reactive immunity ($\alpha = \epsilon = 0$). **(D)** Analogous to panel B, but with cross-reactive immunity instead promoting infection with the novel variant ($\alpha = \epsilon = -0.5$). Simulations were initiated with a single infected, previously immunologically naïve individual ($I_n = 1$), with all other individuals susceptible ($S_n = N-N_p-1$ and $S_p = N_p$, where N_p is the solution of the final size equation for the previously circulating virus, equation (1), rounded to the nearest integer value).

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

When the novel variant is introduced, we also approximate the probability that it invades the population analytically. To do this, we assume that infections occur according to a branching process (32–35). Specifically, we denote by q_{ij} the probability that the novel variant fails to invade the host population, starting from i currently infected individuals who are immunologically naïve and j currently infected individuals who were previously infected by the related virus. In this analysis, "currently infected" individuals refer to those who are either exposed or infectious, since exposed and infectious individuals are each expected to infect the same number of other hosts in future. This is because exposed individuals are not yet infectious, and only start generating infections when they move into the infectious states in the model.

We then consider the probability of the novel variant failing to invade the host population starting from a single currently infected individual who was previously immunologically naïve, q_{10}. As in similar previous branching process analyses (36–39), we consider the various possibilities for what happens next: either that individual infects another individual who was also previously immunologically naïve (with probability $\frac{\beta(N-N_p)}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu}$); or, that individual infects someone 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 individual recovers without infecting anyone else (with probability $\frac{\mu}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu}$). Applying the

law of total probability therefore gives $q_{10} = \frac{\beta(N-N_p)}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu}$
$q_{20} + \frac{\beta(1-\alpha)N_p}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu} q_{11} + \frac{\mu}{\beta(N-N_p)+\beta(1-\alpha)N_p+\mu} q_{00}.$

Instead starting from a single currently infected individual who was previously infected by the related virus gives $q_{01} =$
$\frac{\beta(1-\varepsilon)(N-N_p)}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu} q_{11} + \frac{\beta(1-\varepsilon)(1-\alpha)N_p}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu} q_{02} +$
$\frac{\mu}{\beta(1-\varepsilon)(N-N_p)+\beta(1-\varepsilon)(1-\alpha)N_p+\mu} q_{00}.$

We then assume that infections occur according to a branching process (so that $q_{20} = q_{10}^2$; as infection lineages failing to establish starting from two currently infected hosts requires the infection lineages from both currently infected hosts to fail independently (36–38)). Making similar approximations throughout the equations above, and noting that $q_{00} = 1$ (since the novel variant will not invade if there are no currently infected individuals) gives

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

$$q_{01} = \frac{\beta(1-\epsilon)(N-N_p)}{\beta(1-\epsilon)(N-N_p)+\beta(1-\epsilon)(1-\alpha)N_p+\mu} \; q_{10}q_{01}$$
$$+ \frac{\beta(1-\alpha)N_p}{\beta(1-\epsilon)(N-N_p)+\beta(1-\epsilon)(1-\alpha)N_p+\mu} q_{01}^2 + \frac{\mu}{\beta(1-\epsilon)(N-N_p)+\beta(1-\epsilon)(1-\alpha)N_p+\mu}.$$

(3)

The probability of invasion starting from one currently infected individual who was previously immunologically naïve, p_{10}, and the probability of invasion starting from one currently infected individual who was previously infected by the related virus, p_{01}, are then given by $p_{10} = 1-q_{10}$ and $p_{01} = 1-q_{01}$, where q_{10} and q_{01} are the minimal non-negative solutions of system of equations (3) (40).

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 (27, 28)
$1/\mu$	Mean infectious period of novel variant	8 days (29–31)
R_{0p}	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_{0n}	Reproduction number of novel variant (accounting for interventions)	Varies (see figures)
β	Transmission rate of novel variant	Set so that $R_{0n} = \frac{\beta N}{\mu}$
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)

2.3 Special cases

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

For example, in a scenario in which previous infection with the related virus is entirely protective against infection with the novel variant, then $\alpha = 1$. In that case, since a previously infected individual cannot be infected with the novel variant, then p_{01} does not apply. However, in that 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 the host population). This can be seen by substituting $\alpha = 1$ into the first equation of system of equations (3), solving the resulting quadratic equation for q_{10} (taking the minimal non-negative solution (40)), and then calculating $p_{10} = 1 - q_{10}$. In a scenario in which the related virus has not previously spread in the host population, then this solution for p_{10} is identical to the classic branching process estimate for the probability of a major outbreak, $p_{10} = 1 - \frac{1}{R_{0n}}$ (33, 41, 42).

Alternatively, we can consider a scenario in which prior infection with the related virus eliminates the infectiousness of a host infected by the novel variant (i.e. the individual can become infected, but the virus cannot then establish, so onwards transmission cannot occur). In that case, $\epsilon = 1$ and so, in 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 $p_{01} = 0$. Again, in a scenario in which a related virus has not previously spread in the population, this is the classic estimate for the probability of a major outbreak, $p_{10} = 1 - \frac{1}{R_{0n}}$ (33, 41, 42).

Finally, in a scenario in which previous infection by the related virus does not affect the dynamics of the novel variant (so that $\alpha = \epsilon = 0$), we expect the risk of novel variant invasion to be independent of whether or not the initial infected individual has previously been infected by the related virus. In other words, we expect $q_{10} = q_{01}$. In this case, system of equations (3) reduces to a single quadratic equation for q_{10}. Taking the minimal non-negative solution of that equation (40) indicates that $p_{10} = p_{01} = 1 - q_{10} = 1 - \frac{1}{R_{0n}}$ (whenever $R_{0n} > 1$; otherwise the novel variant will never invade the host population).

3 Results

To investigate the effects of prior infection by an antigenically related virus on the epidemiological dynamics of a newly emerged variant, we first ran stochastic simulations of the analogous stochastic model to system of equations (2). Representative time series of the dynamics illustrate that, if the novel variant successfully spreads in the host population, outbreaks tend to have a lower peak number of infections and

have a longer duration when cross-reactive immunity has a protective effect (Figure 1B), compared to when prior infection by the related virus has no effect (Figure 1C). In contrast, if prior infection by the related virus instead promotes infection by the novel variant, outbreaks tend to have a higher peak number of infections and a shorter duration (Figure 1D).

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

We found that, when previous infection with the related virus is completely protective against the novel variant (i.e. $\alpha = \epsilon = 1$), then the reproduction number of the novel variant must be higher than the reproduction number of the antigenically related virus in order for the novel variant to invade. Specifically, in Figure 2A (in which $R_{0p} = 1.5$, as marked by the vertical blue dotted line), the probability of the novel variant invading the host population is zero unless $R_{0n} > R_{0p}$, and indeed remains zero whenever R_{0n} is only slightly larger than R_{0p}. This can be explained analytically as follows. The previously circulating virus will spread around the population until sufficiently many individuals have been infected that herd immunity (to the previous virus) is reached. This occurs when $N(1 - \frac{1}{R_{0p}})$ individuals have become infected (43). However, at this point, infections do not stop immediately: there is an "overshoot" in infections while transmission slows and the previously circulating virus fades out. As a result, a lower bound on the final size of the outbreak caused by the previously circulating virus is $N_p > N(1 - \frac{1}{R_{0p}})$. As noted in the Methods (Special cases), in a scenario involving complete cross-reactive immunity, the novel variant can only invade the 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 expression shows that invasion of the novel variant requires $R_{0n} > R_{0p}$. In contrast, if cross-reactive immunity is only partial, then the novel variant may invade for lower values of R_{0n} than when cross-reactive immunity is complete (Figure 2B). This can include scenarios in which $R_{0n} < R_{0p}$ (in some cases lying between those shown in Figures 2B, C). As noted in the Methods, when previous infection by the antigenically related virus does not affect the epidemiological dynamics of the novel variant, then the novel variant can only invade if $R_{0n} > 1$ (Figure 2C), mirroring the classical result for models in which cross-reactive immunity is not accounted for (41). Finally, in scenarios in which prior infection
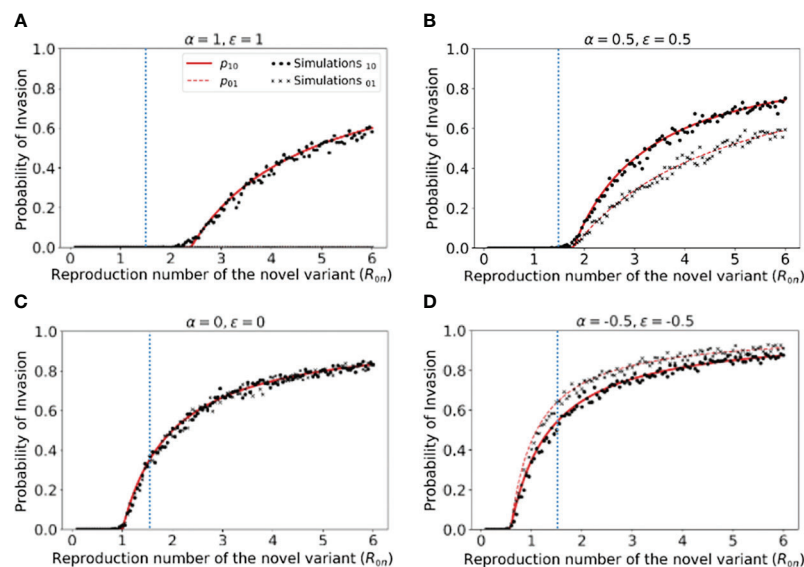
FIGURE 2

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

by the related virus promotes infection with the novel variant, the novel variant can invade even if R_{0n} is small. This includes scenarios in which $R_{0n} < 1$ (Figure 2D).

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

We then explored how the probability of invasion of the novel variant depends on the susceptibility- and infectiousness-modifying effects of cross-reactive immunity individually (Figure 3). We found that the values of α and ϵ affect the probability of a major outbreak differently. This is because, starting from a single infected individual, the number of infections generated by that individual is crucial in

determining whether or not a novel variant will invade. If the first infected host infects multiple others, then all of those individuals' transmission lineages must fade out in order for invasion to fail to occur. Hence, invasion is more likely if the first infected individual infects many individuals. Starting from a single infected individual who was not previously infected by the related virus, only susceptibility-modifying immunity (characterised by α) affects the number of infections generated by the first infected individual. As such, the probability of invasion in this case is more sensitive to α than to ϵ (Figure 3A).

In contrast, if the first infected individual was previously infected by the related virus, then infectiousness-modifying immunity (characterised by ϵ) also affects the probability of this individual infecting any other member of the population. In fact, ϵ then affects all potential transmissions generated by the first infected individual, whereas α only affects potential transmissions to part of the population (those individuals who were previously infected by the related virus). In that scenario, the probability of a major outbreak is therefore slightly more sensitive to ϵ than α (Figure 3B). The different effects of
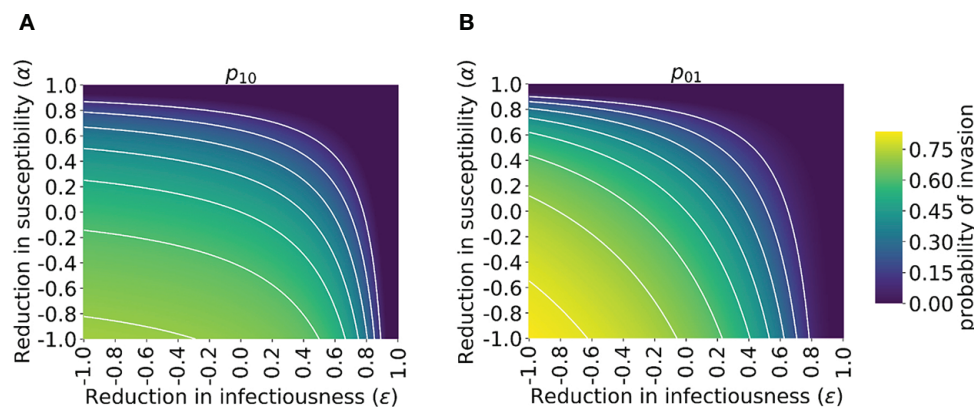
FIGURE 3
Probability of the novel variant invading the host population, starting from the introduction of a single infectious individual, for different levels of cross-reactive immunity affecting susceptibility and infectiousness individually. The invasion probability is approximated analytically by solving system of equations (3) numerically. **(A)** The probability of the novel variant invading, starting from a single infected individual who was previously immunologically naïve. **(B)** Analogous to panel A, but starting from a single infected individual who was previously infected by the related virus. White lines represent contours of constant probability of invasion of the novel variant. As in Figure 1, the division of the host population between individuals who were previously immunologically naïve and those who were previously infected by the related virus was calculated based on the final size equation for the previously circulating 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 Figure S4). Other parameter values used are shown in Table 1.

susceptibility-modifying and infectiousness-modifying cross-reactive immunity therefore explain the asymmetric nature of the contours about the diagonal $\epsilon = \alpha$ in Figure 3.

4 Discussion

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

Here, we have developed a mathematical model to investigate the impact of cross-reactive immunity (generated by previous infections by related viruses) on the probability that a newly introduced variant will invade the host population. We found that, if prior infection with a related virus has a strong protective effect, then the novel variant must be more infectious than the related virus to be able to invade the host population (Figure 2A). If instead, however, the previously circulating virus has a very weak protective effect or no protective effect on infection with the novel variant, then the risk of invasion of the novel variant is unaffected by the outbreak of the related virus, and so the invasion probability matches the well-known estimate for the "probability of a major outbreak" (Figure 2C) (33, 41, 42). If prior infection with the related virus promotes infection by the novel variant, as has been indicated as possible

in some studies exploring the impact of prior infections by SARS-CoV-2 or seasonal coronaviruses on infections with SARS-CoV-2 variants, then even novel variants with limited transmissibility are able to invade (Figure 2D).

We further showed that the immune status of the first individual in the population infected by the novel variant affects the probability that the novel variant invades (Figures 2, 3). This is in turn influenced by the pathway by which the novel variant is introduced into the host population. If the variant is introduced from elsewhere, for example by an incoming traveller (1, 15), then it may be introduced by someone who was not previously infected by the related virus. If instead it appears as a result of mutation from a related virus within the local population (as was likely the case for the emergence of the Alpha variant in Kent, England (44)), then the initial infected case would be an individual who was previously infected by the related virus.

Previous modelling studies have explored the risk of a novel virus invading when it is introduced to a host population, including scenarios in which the pathogen evolves to facilitate emergence (45–49). Of significant relevance to our study, Hartfield and Alizon (50) applied a branching process model to investigate the invasion probability in a scenario in which a resident pathogen strain that confers cross-reactive immunity is spreading in the host population, and considered Chikungunya virus as a case study. Those authors demonstrated that the standard estimate for the probability of a major outbreak overestimates the invasion probability in that scenario, due to the potential for depletion of susceptible individuals by the

resident strain over the timescale of invasion of the novel virus. Echoing this result in a single strain setting, Sachak-Patwa et al. (51) showed that simple estimates for the probability of a major outbreak are overestimates if the pathogen enters the host population during a vaccination campaign, again due to depletion of susceptible individuals occurring within the period of the pathogen either invading or fading out. Other researchers have investigated the emergence of a novel pathogen strain that is introduced to the population when a resident strain is endemic (52). In contrast to previous studies, we focussed on a scenario in which a related virus has already spread widely around the host population and caused a completed outbreak, rather than being resident in the host population. An additional novel aspect of the current study is that we conducted a thorough investigation of the effects of different levels of cross-reactive immunity, including scenarios in which prior infection with an antigenically related virus can promote infection with the novel variant. Although such scenarios may seem counterintuitive, recent evidence suggests that there is a clear possibility that infection-promoting cross-reactivity may occur, as described in the Introduction.

To understand general principles governing the relationship between cross-reactive immunity and the risk of invasion of a novel variant, we constructed the simplest possible model in this study. Further developments could involve including additional epidemiological and evolutionary detail in our transmission model, particularly if it is to be used to predict emergence of specific variants rather than to understand general principles. For example, in the model considered here, the infectious period of individuals infected by the novel variant is assumed to follow an exponential distribution. However, gamma distributions have been found to represent observed epidemiological periods more accurately than exponential distributions (53–55), and gamma-distributed infectious periods can be incorporated into calculations of invasion probabilities (56, 57). We also assumed a fixed level of cross-reactive immunity for all individuals who were previously infected by the related virus. In reality, immunity is heterogeneous between previously infected hosts, and is likely to wane over time (58, 59). The level of cross-reactive immunity in any individual may depend on a range of factors, including whether or not the individual is immunocompromised or has underlying comorbidities (60), and the characteristics of their previous infection (61). Waning immunity has been included previously in a range of epidemiological models (62, 63), and is a target for future addition to the modelling framework presented here, along with consideration of heterogeneity in immunity between previously infected hosts. Additionally, similar investigations to those conducted here could be undertaken for scenarios in which multiple viruses are co-circulating (potentially allowing for superinfection (64)). This could include analyses of epidemiological dynamics beyond the early phase of the

outbreak of the novel variant, after it has invaded the host population.

A key challenge going forwards is to develop reliable approaches for inferring the level of cross-reactive immunity between previously circulating viruses and newly emerged SARS-CoV-2 variants (i.e. the values of the parameters α and ϵ in our model). Serological studies measuring correlates of immune responses in infected patients (e.g. ELISA analyses of cross-reactive antibody responses (21)) have the potential to determine broadly whether previous infections might be protective or detrimental. This may be sufficient to approximate the risk that a new variant will invade host populations in which it is not yet widespread (in Figure 3A, for example, if the values of α and ϵ are both negative, then the probability of the novel variant invading if it is introduced to new host populations is high). More precise estimates of the level of cross-reactive immunity may require substantial epidemiological investigations. As an example, Altarawneh et al. (65) used data from national databases in Qatar to estimate the effect of previous SARS-CoV-2 infection on the risk of symptomatic reinfection by specific SARS-CoV-2 variants. If similar analyses can be carried out in locations in which novel variants first emerge, then estimates of the probability of those variants invading other locations can be refined. We note, however, that there is currently substantial uncertainty in estimates of the level of cross-reactive immunity between different viruses. Altarawneh et al. estimated that previous infection with other SARS-CoV-2 variants has around 56% effectiveness at preventing symptomatic reinfection by the Omicron variant (65), whereas other analyses have suggested that previous infections by other variants have only a limited effect on reinfection rates by the Omicron variant (3). This uncertainty needs to be resolved before the modelling approach described here can be used to make precise quantitative predictions rather than demonstrating qualitative principles about the general impacts of cross-reactive immunity.

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

Data availability statement

The datasets presented in this study can be recreated using code in online repositories. The names of the repository/

repositories can be found below: https://github.com/yairdaon/waning.

Author contributions

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.1049458/full#supplementary-material

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