

The Evolutionary Epidemiology of Pathogens During Vaccination Campaigns

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With the unprecedented global vaccination campaign against SARS-CoV-2 attention has now turned to the potential evolutionary consequences of this large-scale intervention. In this perspective we summarize what is currently known about evolution in the context of vaccination from research on other pathogen species, with an eye towards the future evolution of COVID-19.

It is useful to think of the temporal dynamics of evolutionary change for novel pathogens like SARS-CoV-2 as passing through two phases. In the first phase the host population is immunologically naïve and selection strongly favours adaptation to these abundant naïve hosts. In the second phase a growing proportion of the population will have an immunological history with the pathogen, either through natural infection or vaccination, and thus selection will shift, increasingly favouring adaptation to these hosts. In this article we will focus primarily on vaccine-driven evolution but return to the issue of evolution driven by immunity acquired from natural infections in our conclusions.

Pathogen adaptation to naïve and vaccinated hosts depends on the appearance of new variants as well as on their fitness in each host type. We can quantify fitness by considering both the *absolute* per capita growth rate of infections caused by a variant as well as this growth rate *relative to the growth rate of the wildtype*. The absolute growth rate will determine if the variant can spread in a population while the relative growth rate will determine if the variant can increase in frequency and thereby potentially displace the wildtype.

For a variant to spread in a population its absolute growth rate must be positive (equivalently, its reproduction number must be larger than one). The absolute growth rate, r_i , of infections caused by any pathogen variant i can be approximated as (**Appendix**)

$$r_i = (1 - p)r_{i,N} + pr_{i,V} \quad (1)$$

where p is the fraction of the population vaccinated, and $r_{i,N}$ and $r_{i,V}$ are the growth rates of infections by variant i in a fully naïve and fully vaccinated population, respectively [1, 2].

For a variant to increase in relative *frequency*, and thus potentially displace the wildtype, its selection coefficient, s , defined as the difference between its growth rate and that of the wildtype, must be positive. For the above model this is given by

$$s = (1 - p)\Delta r_N + p\Delta r_V \quad (2)$$

where Δr_N and Δr_V are the differences in growth rate between the variant and the wildtype in a fully naïve and fully vaccinated population, respectively.

With this we can give a precise definition of a variant being adapted to vaccinated or naïve host populations. If $\Delta r_V > 0$ then the variant is more fit (i.e., has a higher growth rate) than the wildtype in a population of vaccinated hosts and so we say it is adapted to vaccinated host populations (equivalently, it is vaccine-adapted). Likewise, if $\Delta r_N > 0$ then the variant is more fit (i.e., has a higher growth rate) than the wildtype in a population of naïve hosts and so we say it is adapted to naïve host populations. Thus, in the first phase of an outbreak, when the fraction of vaccinated hosts p is small, selection strongly favours variants for which $\Delta r_N > 0$ while in the second phase, when p is large, it strongly favours variants for which $\Delta r_V > 0$. In what follows we will focus on vaccine-adapted variants (i.e., those for which $\Delta r_V > 0$). Note that while there are many molecular and cellular mechanisms playing out within an infected host that can make a variant vaccine-adapted (**Box 1**), it is the impact of these mechanisms on the growth rate of the population of infected individuals that determines whether a variant spreads.

The above ideas lead to two useful ways of categorizing vaccine-adapted variants. First, if a vaccine-adapted variant is also adapted to naïve host populations (i.e., $\Delta r_N > 0$) then we refer to it as a “generalist” variant since it is better at spreading than the wildtype irrespective of host type. Conversely, if a vaccine-adapted variant is maladapted to naïve host populations (i.e., $\Delta r_N < 0$) then we refer to it as a “specialist” variant since it is specialized to have higher fitness than the wildtype in vaccinated host populations only. This categorization is useful because, for vaccine-adapted variants, generalists will increase in frequency and replace the wildtype regardless of the vaccine coverage whereas specialists require the vaccine coverage to be above a critical threshold before they will increase in frequency (**Figure 1**).

A second useful way to categorize a variant is by whether the absolute growth rate of infections that it causes is inhibited or facilitated by vaccination. The absolute growth rate of a vaccination-inhibited variant decreases as the vaccination coverage increases, whereas the absolute growth rate of a vaccination-facilitated variant increases with increasing vaccination (**Figure 1**). This categorization is useful because it speaks to whether the spread of infection will ultimately be lower or higher because of vaccination and subsequent vaccine-driven pathogen evolution. If a variant’s growth rate is vaccination-inhibited, then increasing vaccination coverage will always reduce the overall spread of infection, even if the variant ultimately replaces the wildtype (**Figure 1a,c**). However, if a variant’s growth rate is vaccination-facilitated, then if vaccination drives the variant to replace the wildtype it is possible that the overall spread of infection goes up (e.g., **Figure 1b**).

To conceptualize evolutionary change during a vaccination campaign we can begin by constructing a plot of the absolute growth rate of different possible variants in each host type, locating on the plot each of the four types of variants from Figure 1 (**Figure 2**). We can also use such a plot to illustrate how the nature of selection changes as a vaccination campaign proceeds. In Phase 1, when most hosts are naïve (i.e., p is small), selection will primarily favour variants with larger growth rates in naïve hosts (**Figure 3a**). As we move to Phase 2, however (**Figure 3b**), and an increasing fraction of hosts are vaccinated (i.e., p increases), selection shifts to primarily favouring variants with larger growth rates in vaccinated hosts (**Figure 3c**). Throughout this transition the variants that appear can be specialists or generalists, and either vaccination-inhibited or vaccination-facilitated.

Evolutionary theory makes some predictions about how we expect adaptation in novel pathogens to unfold during a vaccination campaign. As a pathogen adapts there will be occasional selective sweeps in which a new variant displaces the wildtype and becomes the new wildtype. The sequence of selective sweeps that occurs will be determined by both the direction of selection and the set of variants that happen to appear (**Box 2**). Initially, in a new host-pathogen association like SARS-COV-2, there will typically be abundant scope for adaptation to both naïve and vaccinated hosts and thus a great many of the variants that arise and sweep to fixation will be generalist variants (**Figure 4a**). Over time, as the pathogen becomes better adapted to the novel host, and as vaccination coverage increases, there will be fewer new variants that increase fitness in both host types, leaving primarily specialist variants as the source of variation for further adaptation (**Figure 4b**). Thus, as a pathogen becomes increasingly adapted to a novel host, adaptation to vaccination will tend to result in the loss of some degree of adaptation to naïve hosts.

It is not possible to make definitive predictions about whether variants are likely to be vaccination-inhibited or vaccination-facilitated, but if most variants that arise result in only relatively small changes in fitness, then we would expect primarily vaccination-inhibited variants in the early stages of a vaccination campaign. Once vaccination coverage is high enough, and the pathogen has adapted sufficiently to vaccinated hosts would it be possible for any variants to arise within the vaccination-facilitated region and spread.

Examples of Vaccine-Driven Evolution

Before considering examples of vaccine-driven evolution it is important to stress that many vaccines have not been undermined by vaccine-driven pathogen adaptation (e.g. smallpox, measles, polio). This lack of adaptation is hypothesized to result from two features commonly associated with vaccination [3]. First, because vaccination is a prophylactic intervention, it can keep pathogen numbers small within vaccinated hosts, which limits the generation and transmission of novel variants. Second, because vaccines typically induce immune responses against multiple targets on a pathogen, multiple genetic changes may be required to circumvent vaccine-mediated immunity [4]. Both features are expected to limit the ability of the pathogens to adapt to vaccination by hampering the accessibility of variants (fewer red dots in **Figure 3, Box 2**). However, for

a handful of vaccines that do not keep pathogen numbers small within infected hosts or that do not induce immunity against multiple targets, vaccine-driven adaptation has occurred [3]. Given this, we look to these previous examples for guidance on possible outcomes of vaccine-driven evolution.

The most direct way to determine how vaccines affect pathogen adaptation is through experimental evolution, yet we know of only one study that takes this approach. It involved a novel host-pathogen association of malaria parasites in laboratory mice [5]. Parasites were serially passaged for 20 generations through either vaccinated or naïve mice and allowed to evolve in response to these different treatments. The parasites became progressively better able to replicate in the host type they were evolving in, but they also evolved a better replication rate in the other host type as well. Even the evolved pathogens still had their growth inhibited by the vaccine, however, demonstrating that the variants that arose during evolution were vaccination-inhibited generalists.

Most other data are observational and focus on pathogen species that have a longer association with their host. As expected from the earlier considerations, many vaccine-adapted variants appear to be specialist variants relative to the wildtype. For example, vaccine-adapted variants of hepatitis B virus arise that have altered surface antigens, making the vaccine less effective [6]. These variants cause sporadic breakthrough infections but they have not increased in overall number at the population level even as vaccination rates have increased [7, 8]. This suggests that, although they are more fit than the wildtype within vaccinated hosts, their spread from vaccinated hosts is apparently suppressed making them vaccination-inhibited specialists. In *Bordetella pertussis*, acellular vaccines that target PRN have led to the spread of vaccine-adapted variants that no longer express PRN [9]. These variants appear to be more fit than the wildtype in vaccinated populations but less fit in naïve populations making them specialist variants [10]. Variants also arise that overexpress the immunosuppressive PTX molecule, and these appear to be more fit than non-overexpressing variants in both naïve and acellular-vaccinated hosts [30]. Notably, fitness was not assayed in whole-cell vaccinated hosts limiting our ability to definitively classify the variants as specialists or generalists. In both sets of *B. pertussis* variants, however, the ability of these variants to spread in a vaccinated population appears to be less than in naïve populations [10, 11], making them all vaccination-inhibited variants.

Similar patterns often arise with vaccines used in farm animals, although the data necessary to distinguish between specialist and generalist variants are often inconclusive. For example, avian metapneumovirus vaccination suppresses virus shedding in turkeys, but less so for recent isolates of the virus than historical isolates, and no difference was detected between the isolates in non-vaccinated turkeys [12]. This difference has been credited to amino acid divergence in two genes [12]. Similarly, breakthrough against a vaccine for a fish bacterial pathogen *Yersinia ruckeri*, has been associated with a loss of the bacterial flagellum [13]. However, partial vaccine protection persists against all tested variants [14] again suggesting that these variants are vaccination-inhibited.

One strikingly different example is the chicken pathogen Marek's disease virus (MDV). MDV is an oncogenic virus that can cause paralysis and high levels of mortality [15], and a succession of vaccines have been developed and deployed in response to continual vaccine-driven evolution [16]. The vaccine-adapted variants that have been analyzed appear to be disfavoured in naïve chickens relative to the ancestral virus [17]. Nevertheless, unlike the examples described above, the vaccine-adapted variants of MDV transmit better from vaccinated chickens than from naive chickens [17]. These variants are therefore examples of vaccination-facilitated specialist variants. Notably, the overall prevalence of infection was nevertheless reduced by vaccination despite this evolution [18] (as in **Figure 1d**).

Other examples of host-pathogen associations involve the coexistence of multiple serotypes, and where the vaccines deployed target only a subset of these serotypes. These situations are more complex because the very coexistence of serotypes suggests that there are multiple host types present, possibly because of distinct immunological histories that have arisen through natural infection by the different serotypes. As a result, we would need to extend the framework in **Figures 2** and **3** by having additional axes corresponding to the different kinds of hosts. Nevertheless, we can draw an analogy to the previous examples by viewing the set of serotypes targeted by the vaccine as the 'wildtype' and the non-targeted serotypes as the 'variants'. The fact that the wildtype and variant serotypes coexist suggests that, as expected, they are specialist variants. It is more difficult to categorize them as being vaccination-inhibited or vaccination-facilitated, but in all examples that we are aware of, the total prevalence of infection has either gone down or remained unchanged after the deployment of the vaccine. For example, vaccination against *Streptococcus pneumoniae* resulted in no change in the total prevalence of bacterial carriage because non-targeted serotypes completely replaced vaccine-targeted serotypes following vaccination [19-21]. For human papillomavirus in contrast, vaccination reduced the total number of infections because non-targeted serotypes did not change in prevalence while vaccine-targeted serotypes became less common [22]. Other examples involving coexisting serotypes, including *Bordetella pertussis* [23], *Haemophilus influenzae* [24], *Neisseria meningitidis* [25], and rotavirus [26], appear to fall somewhere between these two extremes.

One final example is human influenza virus, which continually evolves in response to host immunity through a process known as antigenic drift, generating many sequential influenza variants over time [27]. To keep up with antigenic drift, flu vaccines are frequently updated. Again, this can be conceptualized in the current framework by introducing a new axis in **Figures 2** and **3** every time a new vaccine is introduced and/or a new immunological type of host arises. We were unable to find definitive data that addresses whether influenza variants tend to be generalists or specialists. Either way, existing data suggest that most novel variants arising through antigenic drift are partially inhibited by vaccination [28].

Most of the above examples are consistent with the theoretical expectation that generalist variants eventually give way to specialist variants as novel host-pathogen associations become more established during a vaccination campaign. Most of these cases are also

examples of vaccination-inhibited variants. As a result, vaccination has generally resulted in a reduced overall spread of infection, even when vaccination drove the evolutionary advantage of the variants. More worrisome are vaccination-facilitated variants because the vaccine itself then increases the absolute growth rate of infections by the variants. In such cases, vaccine-driven evolution could, in principle, undermine our control of the disease by making the prevalence of infection higher after vaccine deployment compared to what it would have been if the vaccine had never been used. Although we have identified examples of vaccination-facilitated specialist variants, it is noteworthy that even in these cases it appears that such a vaccine-driven increase in the overall prevalence of infection has never been documented [29].

Perhaps the most worrisome kind of variant would be a vaccination-facilitated generalist since it would spread regardless of vaccine coverage, and it would also necessarily completely compromise our ability to control infection using that particular vaccine (**Figure 1c**). We were unable to find any example of this from any host-pathogen interaction but such variants can readily be imagined (see **Box 1** and below). It is not clear if their rarity is because very few variants in this category are possible (**Box 2**), or if it is because generalist variants will be rare except when host-pathogen associations are new.

SARS-CoV-2

There is now substantial evidence that SARS-CoV-2 has been undergoing rapid adaptive evolution since its first appearance in humans. The first compelling data involved the spread of the Alpha variant as a result of what appears to be a transmission advantage over the original wildtype in naïve individuals [30]. What does our framework tell us about the potential for SARS-CoV-2 adaptation to vaccination? Epidemiological data from several countries suggest that, as expected, the main vaccine-adapted variants to appear so far are vaccination-inhibited generalists (**Figure 5**). It is important to stress, however, that the evolutionary advantage of Delta is not driven by vaccination. The Delta variant increased in frequency in countries with very low vaccine coverage as well as in countries with relatively high vaccination coverage, suggesting it is a generalist. Data indicating that Delta is vaccination-inhibited are less direct and come both from epidemiological studies [31] and from neutralization assays [32]. Although these data only quantify one of the three components of fitness (see section '**The Relationship Between Pathogen Fitness and Infection Characteristics**' below), they show that while Delta is vaccine-adapted, current vaccines (BNT162b2 Pfizer-BioNTech, mRNA-1273 Moderna, and ChAdOx1 nCoV-19 Oxford-AstraZeneca) nevertheless still provide considerable levels of vaccine protection [33, 34]. The case for the Alpha variant being vaccine adapted is even less direct because Alpha spread and was then largely replaced by Delta before significant vaccine coverage existed in most countries. Thus, while the epidemiological data clearly show that Alpha was advantageous relative to the wildtype in naïve hosts [30, 35, 36], estimates of its fitness in vaccinated hosts again come from proxies using vaccine efficacy. The important point for both variants is that they would have spread to near

fixation regardless of whether vaccines had been deployed because they are vaccination-inhibited generalists (**Figure 5**).

Although the above examples of evolution are not driven by vaccination, vaccine coverage is now reaching high enough levels in some countries that the possibility of vaccine-driven vaccine adaptation has become a real concern. As mentioned earlier, vaccine-driven evolution has tended to occur in other pathogens when either the benefits of prophylaxis are small (e.g., the vaccine does not significantly suppress viral replication) or when they target a small number of viral epitopes [3, 37]. Data increasingly suggest that at least the first of these is true for SARS-CoV-2 [38-41]. As SARS-CoV-2 adapts further to humans we might therefore expect that specialist variants will begin to appear that have even higher reproductive success in vaccinated populations but where this increased adaptation to the vaccine comes at a cost of reduced reproductive success in naïve populations.

So far as we know, vaccination-facilitated variants in SARS-COV-2 have not yet been reported and, depending on the available genetic variation (**Box 2**), it is possible that they will never be. That said, it is not difficult to imagine that such variants are possible. For a variant to be vaccination-facilitated the vaccine would have to either increase the rate at which the variant generates new infections and/or decrease the rate at which existing infections caused by the variant are lost from circulation through recovery, isolation, or death. Molecular processes involving antibody dependent enhancement of cell infectivity have been documented in SARS-CoV-2, providing a mechanism by which the vaccine could increase the spread of variants through a population [32, 42]. In fact, one study has even shown that as few as 4 additional mutations in the Delta variant are required for such processes to completely ameliorate the effectiveness of the vaccine in vitro [43]. Similarly, if there are variants whose transmission is curtailed because of the disease severity that they cause, then vaccination could facilitate their silent or semi-silent spread (**Box 2**; [17]).

In the longer term, if variants like those hypothesized above appear and spread, thereby compromising the utility of the vaccine, it is likely that new vaccines would be introduced. Furthermore, as SARS-CoV-2 spreads in the human population and moves towards an endemic equilibrium, the number of people with an immunological history due to natural infection will increase significantly as well. In both cases, the framework presented here will need to be extended to account for multiple host types. Making longer-term predictions for such cases is difficult at this stage because a great deal will depend on the nature of the genetic variation that is possible (**Box 2**).

The Relationship Between Pathogen Fitness and Infection Characteristics

The above analysis focuses solely on pathogen fitness and therefore on how vaccine-driven evolution might affect the spread of infection. One thing missing from this discussion is a consideration of how vaccination might drive the evolution of infection characteristics like vaccine efficacy or disease severity. To better illustrate the relationship

between the fitness of a variant and the characteristics of the infection that it causes we can decompose the absolute growth rate r_i , of a variant into three components of fitness (**Box 1 and 3**): (i) *infectivity* - the probability that, upon exposure, a variant infects either type of host; (ii) *transmissibility* - the rate at which a variant produces infectious propagules that contact uninfected individuals; and (iii) *infection duration* – how long a variant produces infectious propagules in either type of host before the infectious period ends through recovery, isolation, or death. All else equal, variants with increased infectivity, increased transmissibility, or increased duration of infection will have an increased growth rate.

Vaccine efficacy - The infectivity of a variant is often one of the main properties quantified when determining how well a vaccine works against a variant. If σ_N and σ_V denote the infectivity of a variant in naïve and vaccinated hosts respectively, then vaccine efficacy (VE) is the proportional reduction in infectivity that vaccination confers, given by $VE = 1 - \sigma_V/\sigma_N$. This highlights two important things about the utility of VE for understanding the evolutionary epidemiology of vaccine-adapted variants. First, because VE is a measure of the relative infectivity of a variant in vaccinated versus non-vaccinated hosts, a variant can have a reduced VE as a result of an increase in σ_V and/or a decrease in σ_N . Second, VE involves only one of the three different components of fitness and so it provides only partial information for determining the fate of a variant or the consequences it will have if it sweeps to fixation. For example, the Beta and Gamma variants of SARS-Cov-2 both appear to reduce VE [44] yet, to date, neither has become the dominant variant. Measures of VE that capture other components of pathogen adaptation to vaccinated hosts do exist [45].

A related issue arises in discussions of vaccination that center around so-called “escape variants”. Although this term is not always defined precisely, it is often used in reference to variants that differ in epitope and so are able to escape a specific immune response as measured in inhibition assays *in vitro* [44, 46-49]. We have purposefully avoided using this term because it conflates the mechanism through which a variant is potentially adapted to vaccinated hosts (i.e., escape from a specific immunity and so greater ability to replicate within an individual) with the source of selection that favours the variant (i.e., increased infectivity). It is useful to keep these notions distinct because there are many different mechanisms through which a variant can be adapted to vaccinated hosts (**Box 1**) and each of these can affect any of the three epidemiological components of fitness (i.e., infectivity, transmissibility, infection duration). Ideally, we would quantify multiple infection characteristics (infectivity, transmissibility, and infection duration) for variants that arise, along with a quantification of fitness. Such an approach is possible for SARS-CoV-2 using the unprecedented availability of genetically resolved, real time epidemiological data (**Box 3**).

Disease Severity - Arguably the most important infection characteristic from the standpoint of human health is the severity of disease caused by a variant. Most definitions of severity capture both the morbidity and the mortality caused by infection. As such, severity can affect all three components of fitness. For example, high disease severity might reduce infection duration through increased mortality, or it might reduce the

transmissibility through a reduction in activity level and thus the contact rate of infected individuals [50]. In most cases disease severity *per se* is disadvantageous to the pathogen and thus selected against [51]. It is nevertheless difficult to make predictions about how disease severity will evolve because variants that cause more severe disease might have increased fitness relative to the wildtype through differences in other components of fitness [52]. For example, data suggests that the Alpha variant of SARS-CoV-2 may cause more severe disease than the Wuhan wildtype [53, 54], but it nevertheless has higher fitness because its transmissibility is higher. Also, severity of the disease may be partially mediated by the host immune response and recent studies suggest that some antibodies may “enhance” the replication of the virus and may induce more symptoms [42]. A variant that could escape from neutralizing antibodies and exploit this enhancing effect could lead to greater disease severity in vaccinated hosts [43]. This illustrates that, although we can make quite robust and reliable predictions about the evolution of pathogen fitness in naïve and vaccinated hosts, it is harder to make predictions about the underlying components of fitness or disease severity since variants with very different values of the three fitness components can nevertheless have the same overall fitness (**Box 1** and **3**). This means that patterns of evolution in these infection characteristics are likely to be somewhat idiosyncratic. This is a major reason why we cannot extrapolate the evolutionary trajectories of such traits from one pathogen to another.

Despite the lack of robust theoretical predictions about disease severity, a few empirical observations can be made from other infectious diseases that could be relevant to SARS-CoV-2. First, vaccine protection tends to be even more evolutionarily robust against disease than against infection. This conclusion arises from the observation that when pathogens have evolved in response to vaccines in the past, vaccinated individuals that are infected by a pathogen tend to have better outcomes than non-vaccinated individuals [29]. A potential concern is if there are enhancing effects of antibodies on disease severity [55, 56], as there may be for COVID [42, 43]. Second, for pathogens with coexisting serotypes, vaccine-driven serotype replacement could in principle increase or decrease overall disease burdens if different serotypes have different propensities for causing disease, as they often do (for example, [57]). Rational design of variant-based vaccines must therefore consider both the current prevalence of each variant and their likelihood of causing disease given infection. Third, under certain conditions, vaccines may lead to the evolution of highly virulent variants. The best example of this is MDV in which highly virulent variants of the virus kill their hosts so quickly that they are unable to persist in the absence of vaccination [17]. Vaccines ameliorate disease severity of MDV and so they allow hosts infected by these highly virulent variants to remain alive but they do not prevent transmission. Despite this effect, however, vaccinated chickens exposed to these highly virulent variants are nevertheless better off than non-vaccinated chickens exposed to the original wildtype. On the other hand, non-vaccinated chickens are now at greater risk of infection with variants causing more severe Marek’s disease than they were prior to the introduction of the vaccine. Regardless of whether SARS-CoV-2 follows this path (**Figure 5**), vaccination remains our most effective tool to mitigate the epidemic, as was the case with MDV [58]. Vaccination also reduces the number of cases which may also slow down the flux of new mutations and thus the probability of viral adaptation (**Box 2**).

Implications

If further adaptation of SARS-CoV-2 occurs in response to vaccination, then our framework and the examination of previous experimental and empirical examples suggest that the long-term outcome will likely yield specialist variants. The path to getting there will likely involve vaccination-inhibited variants meaning that we are likely to, at least partially, retain the benefits of vaccination in the short term. In the meantime, there is an urgent need to monitor the epidemiology and evolution of the virus [37]. This will better characterize newly arising variants (**Box 3**) and make it possible to decide if, like for flu, new vaccines are needed to counteract viral adaptation.

It is also critical to stress that evolutionary concerns are not a reason to withhold currently available vaccines. First, vaccines are currently greatly reducing disease burdens and saving lives [59]. Second, as discussed above, much of the evolution currently occurring in SARS-CoV-2 involves generalist variants and so would be occurring regardless of whether we deployed existing vaccines. Third, immunity arising from natural infections will also impact on-going viral evolution. Currently, it is impossible to know whether natural immunity or vaccine-induced immunity will be the stronger evolutionary driver. Fourth, even with the Delta variant, current mRNA vaccines substantially reduce the probability of infection and infection duration compared to infections in naïve individuals [40, 41, 44]. That itself very substantially reduces evolutionary potential (**Box 2**).

Going forward, it is quite possible that new vaccine schedules (e.g., boosters, combinations of existing vaccines) or next-generation vaccines (e.g., new RNA sequences, mucosal vaccines) will be required to deal with SARS-CoV-2 evolution. The more that vaccination suppresses transmission, targets multiple epitopes, and more effectively inhibits infection and within-host replication and so mutation and recombination, the better it will be at slowing the rate of adaptation (**Box 2**) and providing sustainable long-term efficacy [37].

Summary

In the history of human and animal vaccination, there are few documented cases of vaccine-driven evolution. Yet, for situations where adaptation to vaccination occurs, we propose a typology of vaccine-adapted variants based on their fitness in naïve and vaccinated host populations (**Figure 1**).

Adaptation occurs when a novel variant is more fit than its predecessors. The fitness of a variant is measured by its per-capita growth rate of the number of infections that it causes (i.e., the number of new infections per infection per unit time).

In the early phase of pandemics, we expect the rise of variants that are better at spreading than their ancestors in both naïve and immunized hosts (generalists). Later, viral evolution

should involve specialised adaptations to immunized hosts, and so some decrease of adaptation to naïve hosts.

Both generalist and specialist variants can be inhibited by vaccination, where the growth rate of infections decrease as vaccine coverage increases. Under these circumstances, even if the impact of vaccination can be eroded by viral evolution, the overall spread of infection is still reduced by vaccination.

Vaccination-facilitated variants can arise. In this case, the overall spread of infection could theoretically go up as vaccination rates increase.

Even though the direction of selection can be predicted from our framework, the actual speed and direction of phenotypic evolution is very difficult to predict. That is because there is no way of knowing in advance what phenotypes are available to the virus genetically (via mutation or recombination) (**Box 2**) or how particular mutations relate to the multiple dimensions of the fitness landscape (**Box 1**).

So far, SARS-CoV-2 variants of concern are vaccination-inhibited generalists that would have spread independent of vaccination. We expect more such variants, depending on mutational availability. Vaccination-enhanced specialists should also begin to appear, again depending on mutational availability.

Beyond those expectations, a priori prediction about future vaccine efficacy and disease severity for SARS-CoV-2 is not possible. Molecular epidemiological surveillance will be critical for detecting adaptation as it unfolds.

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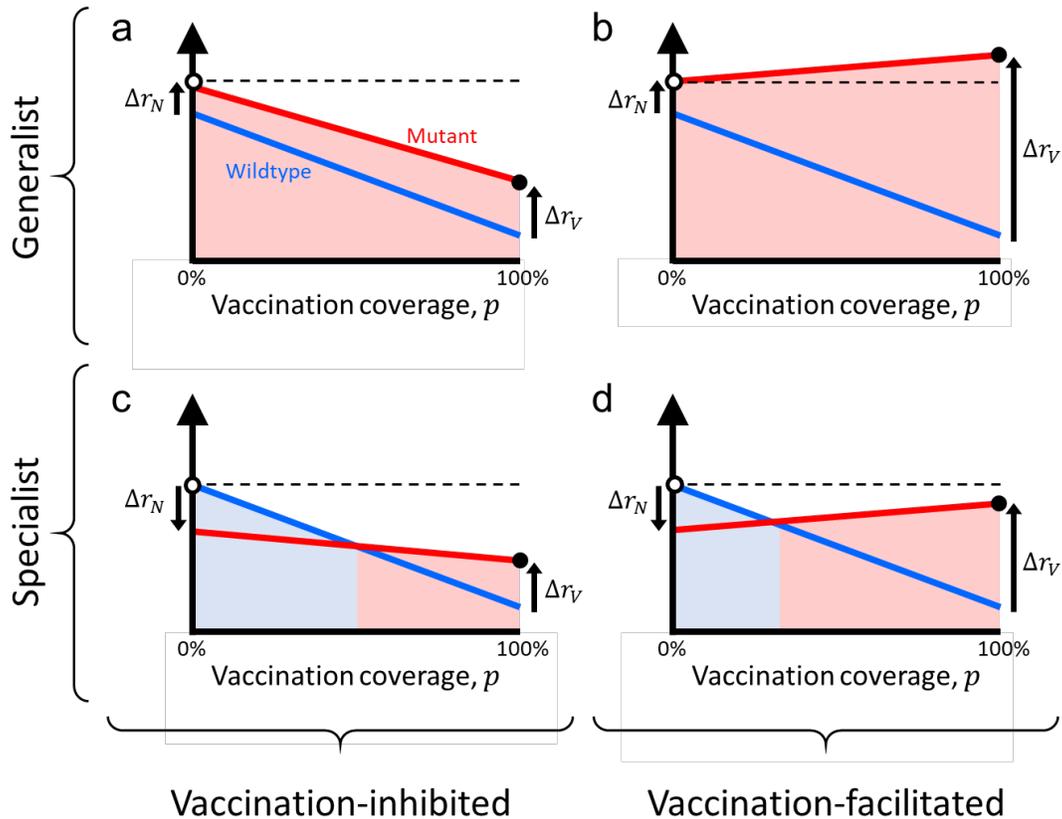


Figure 1: Four types of vaccine-adapted variants. Solid lines depict the growth rate of the population of infected individuals for the wildtype (blue) and for a variant (red) as a function of vaccination coverage. Vaccination decreases the growth rate of the wildtype ($r_N > r_V$). Quantities Δr_N and Δr_V are the differences in growth rate between the variant and the wildtype in naïve and vaccinated hosts, respectively. Colored shading indicates which type prevails evolutionarily: the wildtype (light blue shading) or the variant (light red shading). Panels **(a)** and **(b)** are generalists - the variant is also better adapted to naïve hosts ($\Delta r_N > 0$). Generalist variants will outcompete the wildtype even in the absence of vaccination. Panels **(c)** and **(d)** are specialists – the variant is maladapted to naïve hosts ($\Delta r_N < 0$). Specialist variants will outcompete the wildtype only above a critical vaccination threshold. Panels **(a)** and **(c)** are vaccination-inhibited variants - the growth rate of the variant decreases with increasing vaccination. As a result, the growth rate of infections after adaptation (i.e., after fixation of the fittest type) in a fully vaccinated population (black dot) is always lower than that in a fully naïve population (white dot & dashed line). Panels **(b)** and **(d)** are vaccination-facilitated variants - the growth rate of the variant increases with increasing vaccination. As a result, the growth rate of infections after adaptation in a fully vaccinated population (black dot) is always higher than that in a fully naïve population (white dot) for generalist variants (panel **(c)**) but it can go either way for specialists (panel **(d)** - only the case where it is lower is shown).

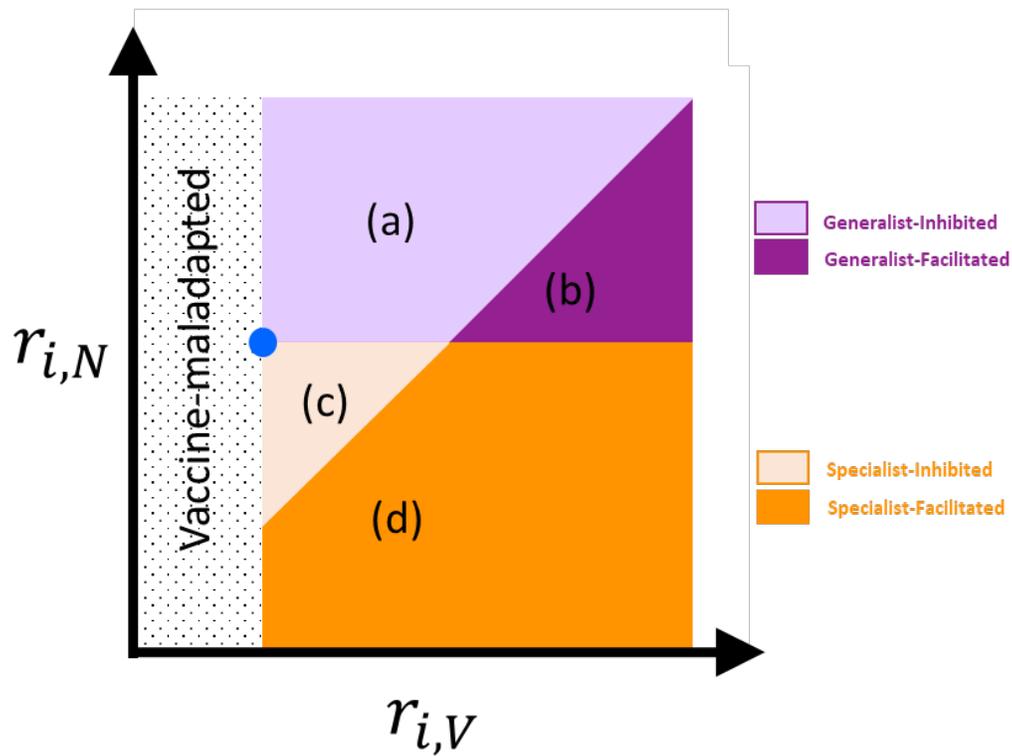


Figure 2: Four types of vaccine-adapted variants. A plot of the growth rate of variants in a fully naïve, $r_{i,N}$, and a fully vaccinated, $r_{i,V}$, population. Blue dot indicates location of the wildtype. Uncolored region corresponds to variants whose growth rate in vaccinated hosts is less than that of the wildtype and so are vaccine-maladapted (and so ignored in our discussion). Different coloured regions correspond to the 4 types of variants from **Figure 1** (labels **(a)**-**(d)** correspond to panels **(a)**-**(d)** from **Figure 1**). Additional types of variants are presented in **Figure S1**.

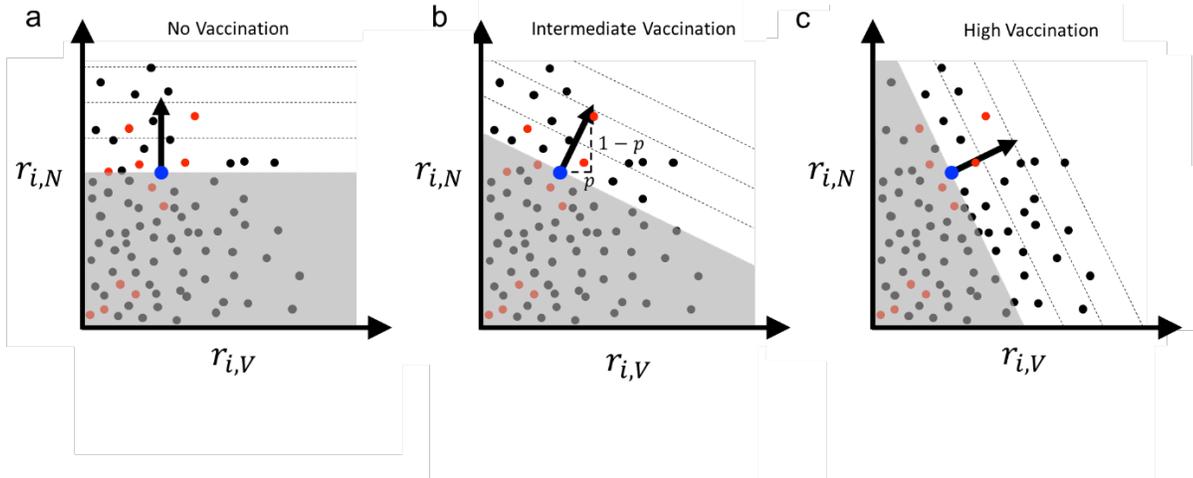


Figure 3: Selection and genetic variation. A plot of the growth rate of all viable variants i in a fully naïve and a fully vaccinated population (black dots). Large blue dot denotes the current wildtype. Red dots are those variants that are most accessible from the wildtype (see **Box 2**). Note that the location of all variants along the $r_{i,V}$ axis is specific to a vaccine and will be different for different vaccines. All variants in white region are selectively advantageous but variants in the direction of the selection arrow are most strongly favoured (dashed lines indicate contours of increasing fitness). Variants in the grey region are disfavoured by selection. The direction of selection arrow is upwards in a fully naïve population ($p = 0$) (panel **(a)**) and shifts towards the right as the level of vaccination (and/or fraction of hosts with exposure to the wildtype through natural infection) increases (panels **(b)** and **(c)**).

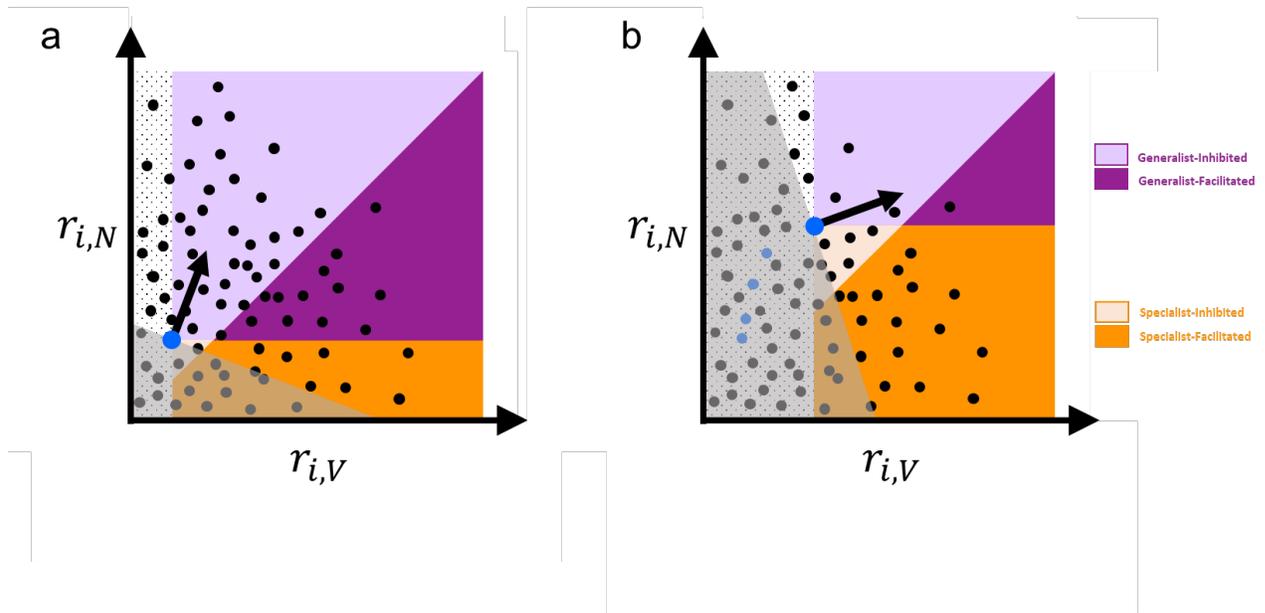


Figure 4: Pathogen adaptation during vaccination. A plot of the growth rate of all viable variants in a fully naïve and a fully vaccinated population (dots). Large blue dot denotes the phenotype of the current wildtype and black arrow indicates direction of selection (variants in the grey region are disfavoured by selection). Note that the location of all variants along the $r_{i,V}$ axis is specific to a vaccine and will be different for different vaccines. Coloured regions indicate the four different kinds of variants. **(a)** Early in a novel host-pathogen association (and in the first phase of the vaccination campaign). Many potential new variants will be better adapted to both host types (i.e., they will be generalists). **(b)** Later in the association, when the pathogen is better adapted to its novel host (and vaccination levels are higher). The evolutionary trajectory of successive fixation events leading to the new wildtype variant is indicated with the succession of blue dots. Note how the change in the location of the blue dot can affect the typology of some variants (i.e., a variant that was identified as a generalist in the early stage of adaption could later become a specialist relative to the more recent form of the virus). Once the level of adaptation is high (panel **b**) most selectively advantageous variants that appear will tend to be specialists. Even though generalists are still more strongly favoured by selection there are fewer of them that can arise.

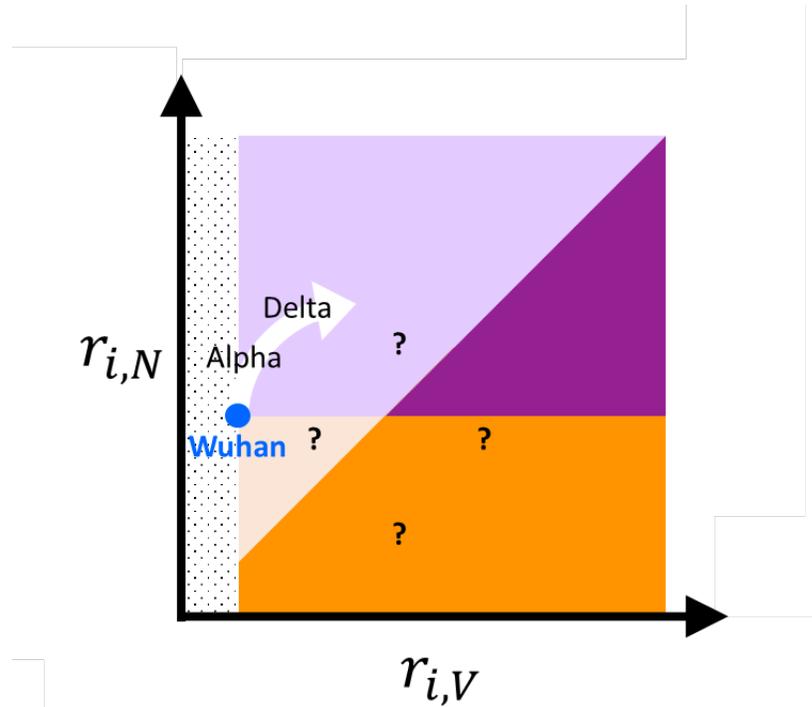


Figure 5: Graphical representation of SARS-CoV-2 adaptation to naïve and vaccinated hosts. Blue dot denotes location of the Wuhan wildtype, which is relatively poorly adapted to both naïve and vaccinated hosts. The Alpha and Delta variants are both vaccination-inhibited generalists relative to the wildtype. Question marks indicate uncertainty in where the next vaccine-adapted variants will lie.

Box 1 – Mechanisms of vaccine adaptation

Our focus is on the ability of a variant to spread between hosts, and this ability can arise from several different mechanisms operating within an infected individual. Pathogens have evolved a vast diversity of countermeasures against natural immunity, many of which will also be highly effective against vaccine-induced immunity and so are expected to be involved in adaptation to vaccination. The list below is intended to be illustrative of the diversity of possible within-host adaptations, rather than comprehensive.

Immune evasion (avoiding anti-pathogen responses).

- Antigenic change.
- Antigenic loss. Inactivation or deletion of molecules targeted by host responses. Examples include loss of toxins (diphtheria, pertussis).
- Antigenic repertoires. Changes in genes controlling the rates at which pathogens generate and expose novel antigens (e.g. trypanosomes, malaria).
- Increased cell-cell infection to evade antiviral humoral immunity which threatens cell-free infection [49].
- Altered tissue tropism to immune-privileged sites.

Immune suppression (dampening or mis-directing anti-pathogen responses).

- Up-regulation of enzymes to degrade effector molecules (e.g., ptxP3 in pertussis)
- Production of immune-regulatory molecules such as cytokine mimics (e.g. pox viruses) and immune antagonists (e.g. Orf9b and Orf6 in Alpha variant of SARS-CoV-2, [60]).
- Production of substances that drive inappropriate responses (e.g. helminths)
- Production of 'smoke screen' molecules, which distract immune effector molecules (e.g. malaria, [61])

Immune exploitation (utilizing host responses)

- Antibody-dependent enhancement (e.g. [42, 43])

Life-history mediated countermeasures against immunity

Direct countermeasures against immunity, such as those listed above, are not the only possible within-host mechanisms of vaccine adaptation. A very different suite of potential mechanisms has to do with where, when, and how fast pathogens replicate.

- Variants that replicate earlier or faster can overwhelm the immune response, at least initially.
- Variants that replicate more slowly can potentially remain below immune detection for longer (e.g., many chronic viral infections).
- Variants which can exploit altered host cell invasion pathways can have an advantage when primary pathways are blocked by host immunity.

Traits underpinning these mechanisms can include higher binding affinity to host receptors, large burst sizes (number of pathogen progeny released from a host cell), altered latency (dormancy in host cell) and changes in the investment of within-host replication relative to transmission stage production (e.g., malaria).

Finally, where transmission is restricted by disease severity (for instance, via host death or hospitalization), vaccination, can enhance pathogen transmission by reducing disease severity (e.g., Marek's disease).

Most of the traits listed above can be studied in a variety of *in vitro* and *in vivo* models, with native pathogens or novel expression systems like pseudoviruses. Often, *in vivo* studies are also possible, using animal models and, in some cases, human subjects. In most cases, it is very challenging to link within-host mechanisms to between-host fitness because individual traits are often, at best, correlates or partial determinants of one or more of infectivity, transmissibility and infection duration (which are the three key components of fitness). Fitness *per se* (i.e., the growth rate of the number of infections) and other components of fitness can also be inferred in real time from rates at which the different variants spread in the human population (**Box 3**).

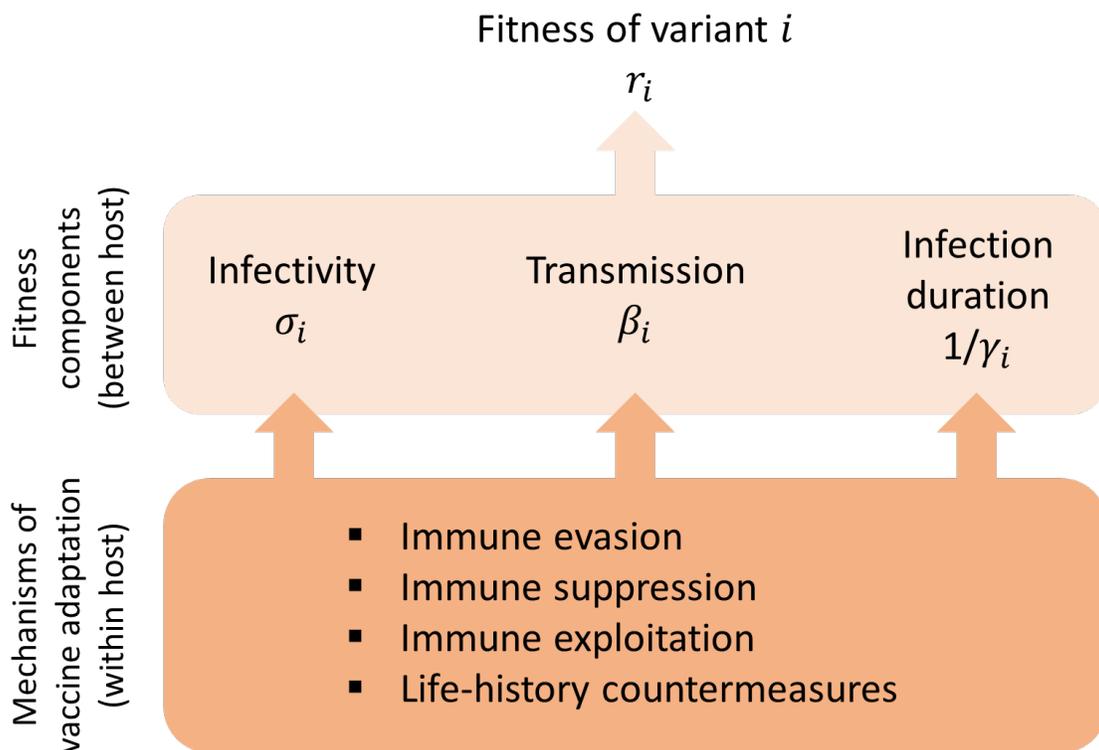


Figure Box 1: The fate of a variant i within a host population is determined by three key components of fitness, each of which can be affected by several within-host mechanisms of adaptation. All else equal, variants with increased infectivity, increased transmissibility, or increased duration of infection will have an increased fitness (rate of spread in a population). As indicated in equation (1) fitness depends on both the amount of adaptation to naïve and vaccinated hosts. Within-host processes impact those three components of fitness to varying extents and, in turn, individual viral mutations can affect those processes to varying extent. Some within-host mechanisms of adaptation can be measured directly in *in vitro* assays. Some components of viral fitness can be inferred from evolutionary epidemiological studies (**Box 3**).

Box 2 – Mutation and adaptation to vaccination

Pathogen adaptation requires variation in fitness among variants. New variants arise from mutation during replication and from recombination when distinct variants coinfect the same host. It is important to distinguish between the rate at which new variants arise and how their fitness differs from the wildtype.

The rate at which variants arise

Mutations are continuously generated during the replication of the virus within infected hosts. The rate at which this occurs is proportional to the rate at which genomic changes occur during replication, and the amount of replication that is taking place. Vaccination reduces the amount of replication taking place in two ways. First, at the within-host level, if a vaccinated host is infected, a vaccine-primed immune response is expected to reduce the viral load and to clear the infection faster. Second, at the between-host level, the rollout of vaccination is expected to reduce the number of infected hosts (both naïve and vaccinated). These effects are tempered for imperfect (or leaky) vaccines, however, because they have a lower ability to reduce pathogen replication and to prevent infection.

The fitness effects of variants

The fate of a new variant is determined by how the rate of change of number of infections it causes differs from that of the wildtype in both naïve and vaccinated populations (i.e., where it falls in **Figure 3** relative to the wildtype). To this end it is useful to distinguish between the set of variants that are *possible* (all the dots in **Figure 3**) and the set of variants that are easily *accessible* from the wildtype (the subset of red dots in **Figure 3**). There will be biological constraints on the magnitude of growth rate that is possible in the two host types and therefore all the dots in **Figure 3** will fall within some specific region of plane. Most mutations are expected to be deleterious or have little effect, but some may result in a larger growth rate than the wildtype [62, 63]. Hence, we expect a higher density of possible phenotypes (black dots in **Figure 3**) with low fitness and only few variants are expected to increase fitness in all dimensions of the fitness landscape. Within this set of possible variants, some will be more readily accessible from the current wildtype than others for several reasons. First, some variants might be multiple mutational or recombinational steps away from the wildtype and so will be exceedingly unlikely to arise. For example, the lack of adaptation of measles virus to vaccines despite decades of global vaccination is potentially because variants that can escape a polyclonal antibody response require at least five new mutations to the H glycoprotein [4]. Second, competition between the variant and the wildtype within an infection can promote (or hamper) the variant's ability to reach a density high enough for onward transmission to occur. For example, in novel host-pathogen associations, mutations that are beneficial for within-host competition are also likely to be beneficial in other respects, including their ability to spread at the between-host level simply because more generalist variants are accessible when the wildtype is poorly adapted to its host (see **Figure 4a** but when axes are within- and between-host fitness). As the association becomes more established, however, variants that are successful within hosts will tend to have reduced success at the between-host level. This effect of within-host selection biasing the set of variants that

are accessible to between-host selection is likely also modulated by the leakiness of the vaccine [64].

Vaccination and the speed of pathogen adaptation

Faster rollout and more effective vaccines will, all else equal, limit the emergence of new variants. Hence, the use of leaky vaccines (and the occurrence of chronic infections in immunocompromised hosts) could speed up pathogen adaptation both because they increase the flux of mutation and because they facilitate the within-host rise of some vaccine-adapted variants. Once a vaccine-adapted variant is circulating in the population, the influence on evolutionary adaptation of the rate at which it arises through mutation is negligible compared to the selection acting on the variant (e.g. the dynamics of the Alpha variant at the end of 2020 in UK is only driven by selection, not by the flux of mutations). In this case, the speed of pathogen adaptation is mainly driven by selection and different targeted vaccination strategies may provide ways to slow down this adaptation [65-67].

Box 3 – How to characterise the fitness of SARS-CoV-2 variants?

The ongoing pandemic of SARS-CoV-2 is characterised by an unprecedented access to incidence and sequencing data in real time. This data provides a unique opportunity for quantifying the underlying components of viral fitness (infectivity, transmissibility, and infection duration) related to adaptation to naïve and vaccinated hosts. Three main dynamical variables carry useful information about these components of fitness (**Appendix**).

First, the per capita growth rate of the epidemic during vaccination provides information about the potential emergence and the spread of new variants. Any deviation from the predicted drop in incidence of the wildtype due to increasing vaccination coverage could signal the spread of a vaccine-adapted variant ($\Delta r_V > 0$).

Second, analysis of the change in frequency of a variant allows some inference to be made about which components of fitness underly adaptation to vaccination. We show in the appendix that the magnitude of change in the frequency of a variant will be proportional to the availability of susceptible hosts if the variant obtains its advantage through increased transmissibility, β , or infectivity, σ , but this change will be independent of susceptible hosts if the variant obtains its advantage through a longer infection duration. Therefore, as the availability to susceptible hosts varies with lockdowns and other NPIs, tracking how this affects the change in variant frequency can inform us about the mechanism underlying the variant's success = [52, 68] = [52, 68].

Third, the over representation of a variant in vaccinated hosts can be used as an early signal that the variant is adapted to the vaccine. We show in the appendix that the difference in variant frequency between naïve and vaccinated hosts (i.e., the genetic differentiation of the viral populations in the two types of hosts) is mainly governed by the relative infectivity of the variant in vaccinated hosts, but not by its transmissibility. Hence, the analysis of these three dynamical variables provides a way to begin disentangling the three major components of fitness.

Appendix

In this appendix we derive the expressions presented in the main text, and we also show how changes in the three main components of fitness of a variant affect the evolutionary dynamics.

1. The model

We track the dynamics of variant i in a host population with a density S_N of naïve hosts and a density S_V of vaccinated hosts using the following system of differential equations:

$$\begin{aligned} \dot{I}_i^N &= h_i \sigma_i^N S_N - \gamma_i^N I_i^N \\ \dot{I}_i^V &= h_i \sigma_i^V S_V - \gamma_i^V I_i^V \\ h_i &= \beta_i^N I_i^N + \beta_i^V I_i^V \end{aligned}$$

The reproductive success of a variant is determined by three components of fitness:

- β_i^N and β_i^V : the transmission rate of variant i from naïve and vaccinated hosts
- σ_i^N and σ_i^V : the infectivity of variant i in naïve and vaccinated hosts
- γ_i^N and γ_i^V : the infection duration of variant i in naïve and vaccinated hosts

Below we present the derivation of the three dynamical variables mentioned in Box 3 that capture the epidemiological and evolutionary dynamics during adaptation to vaccination (equations (S1), (S2) and (S3) below).

2. The growth rate of the epidemic

In the initial phase of the epidemic the prevalence is low and both S_N and S_V are then approximately constant. The prevalence of variant i is therefore expected to increase exponentially and its growth rate is given by the dominant eigenvalue r_i of the matrix:

$$\mathbf{R}_i = \begin{pmatrix} r_i^{NN} & r_i^{VN} \\ r_i^{NV} & r_i^{VV} \end{pmatrix}$$

where

$$\begin{aligned} r_i^{NN} &= \beta_i^N \sigma_i^N S_N - \gamma_i^N \\ r_i^{VN} &= \beta_i^V \sigma_i^N S_N \\ r_i^{VV} &= \beta_i^V \sigma_i^V S_V - \gamma_i^V \\ r_i^{NV} &= \beta_i^N \sigma_i^V S_V \end{aligned}$$

If we further define $\delta_i = \gamma_i^V - \gamma_i^N$ then we can write

$$r_i = (1 - p)r_{i,N} + pr_{i,V} - \frac{S_V \beta_i^V \sigma_i^V}{S_N \beta_i^N \sigma_i^N + S_V \beta_i^V \sigma_i^V} \delta_i + O[\delta_i]^2$$

with: $r_{i,N} = S \beta_i^N \sigma_i^N - \gamma_i^N$, $r_{i,V} = S \beta_i^V \sigma_i^V - \gamma_i^N$, and where $S = S_N + S_V$ and $p = \frac{S_V}{S_N + S_V}$ is the coverage of vaccination (i.e., the fraction of the uninfected population that is vaccinated).

When $\delta_i = 0$ this simplifies to:

$$r_i = (1 - p)r_{i,N} + pr_{i,V}$$

which is equation (1) of the main text.

In the following, for simplicity, the effects of the mutation on the different viral components of fitness in host X (where $X = N$ or V) will be assumed to be small and will be denoted:

- $\Delta\beta_X = \beta_m^X - \beta_w^X$
- $\Delta\sigma_X = \sigma_m^X - \sigma_w^X$
- $\Delta\gamma_X = \gamma_m^X - \gamma_w^X$

and the components of fitness of the wildtype will be noted:

- $\delta = \delta_w$
- $\beta_X = \beta_w^X$
- $\sigma_X = \sigma_w^X$
- $\gamma_X = \gamma_w^X$

Using this notation the growth rate of the wildtype population is:

$$r = (1 - p)r_N + pr_V$$

and the growth rate of the novel variant is $r + \Delta r$ where:

$$\Delta r = (1 - p) \underbrace{(S(\Delta\beta_N\sigma_N + \beta_N\Delta\sigma_N) - \Delta\gamma_N)}_{\Delta r_N} + p \underbrace{(S(\Delta\beta_V\sigma_V + \beta_V\Delta\sigma_V) - \Delta\gamma_V)}_{\Delta r_V}$$

The growth rate of the whole population of all infected individuals is simply:

$\bar{r} = r + f_m\Delta r$	(S1)
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where f_m is the frequency of the novel variant:

$$f_m = \frac{I_m^N + I_m^V}{I_w^N + I_w^V + I_m^N + I_m^V}$$

Thus, a variant with a higher growth rate will spread when $\Delta r > 0$ and the subsequent increase in mutant frequency will affect the growth rate of the whole pathogen population.

3. The dynamics of variant frequency

The dynamics of the variant frequency f_m depends on the distribution of the variant in naïve and vaccinated hosts (Gandon & Day 2007). But if the phenotype of the variant is not very different from that of the wildtype we can obtain a very good approximation of these dynamics using (Otto & Day 2007):

$$\dot{f}_m \approx f_m(1 - f_m)\mathbf{V}^T \Delta \mathbf{R}_m \mathbf{F}$$

where \mathbf{V}^T is the vector of reproductive values and \mathbf{F} is the vector of class frequencies which correspond to the conormalised (i.e. $\mathbf{V}^T \mathbf{F} = \mathbf{1}$) left and right eigenvectors of \mathbf{R}_w , respectively:

$$\mathbf{F} \propto \left\{ \frac{S_N \sigma_N}{S_V \sigma_V} \left(1 + \frac{\delta}{S_N \beta_N \sigma_N + S_V \beta_V \sigma_V} \right) + O(\delta^2), 1 \right\}$$

$$\mathbf{V}^T \propto \left\{ \frac{\beta_N}{\beta_V} \left(1 + \frac{\delta}{S_N \beta_N \sigma_N + S_V \beta_V \sigma_V} \right) + O(\delta^2), 1 \right\}$$

and selection on the different transitions is given by:

$$\Delta \mathbf{R}_m = \begin{pmatrix} S_{NN} & S_{VN} \\ S_{NV} & S_{VV} \end{pmatrix}$$

where:

$S_{NN} = (\Delta \beta_N \sigma_N + \beta_N \Delta \sigma_N) S_N - \Delta \gamma_N$	Selection coefficient (when N infect N)
$S_{NV} = (\Delta \beta_N \sigma_V + \beta_N \Delta \sigma_V) S_V$	Selection coefficient (when N infect V)
$S_{VV} = (\Delta \beta_V \sigma_V + \beta_V \Delta \sigma_V) S_V - \Delta \gamma_V$	Selection coefficient (when V infect V)
$S_{VN} = (\Delta \beta_V \sigma_N + \beta_V \Delta \sigma_N) S_N$	Selection coefficient (when V infect N)

After some calculation this yields:

$$\dot{f}_m \approx f_m(1 - f_m)s$$

where:

$$s \propto (1 - p)S(\beta_N \Delta \sigma_N + \sigma_N \Delta \beta_N) + pS(\beta_V \Delta \sigma_V + \sigma_V \Delta \beta_V) - (1 - q)\Delta \gamma_N - q\Delta \gamma_V + \delta K + O(\delta^2)$$

$$q = \frac{S_V \beta_V \sigma_V}{S_N \beta_N \sigma_N + S_V \beta_V \sigma_V}$$

$$K = \frac{S_N S_V \beta_N \beta_V \sigma_N \sigma_V}{(S_N \beta_N \sigma_N + S_V \beta_V \sigma_V)^2} \left(\left(\frac{\Delta \beta_N}{\beta_N} - \frac{\Delta \beta_V}{\beta_V} \right) + \left(\frac{\Delta \sigma_N}{\sigma_N} - \frac{\Delta \sigma_V}{\sigma_V} \right) - \frac{2}{(S_N \beta_N \sigma_N + S_V \beta_V \sigma_V)} (\Delta \gamma_N - \Delta \gamma_V) \right)$$

When $\delta = 0$ this simplifies as:

$s \propto \underbrace{(1 - p)S(\beta_N \Delta \sigma_N + \sigma_N \Delta \beta_N) - (1 - q)\Delta \gamma_N}_{\text{selection in naive hosts}} + \underbrace{pS(\beta_V \Delta \sigma_V + \sigma_V \Delta \beta_V) - q\Delta \gamma_V}_{\text{selection in vaccinated hosts}} \quad (\text{S2})$
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Note how selection for higher values of transmission β and infectivity σ depend on the density of susceptible hosts S while selection on the duration of infection γ does not (Day et al 2020).

4. The dynamics of differentiation

Next, we use Gandon & Day (2007) to track the difference in variant frequency between vaccinated and naïve hosts. The dynamics of variant frequencies in naïve and vaccinated hosts in a well-mixed population is:

$$\begin{aligned}\dot{f}_m^N &= v_N s_{NN} + v_V \frac{I_V}{I_N} s_{VN} + \frac{I_V}{I_N} \bar{r}_{VN} D \\ \dot{f}_m^V &= v_V s_{VV} + v_N \frac{I_N}{I_V} s_{NV} - \frac{I_N}{I_V} \bar{r}_{NV} D\end{aligned}$$

where:

$D = f_m^V - f_m^N$	Differentiation
$v_N = f_m^N(1 - f_m^N)$	Genetic variance in naïve hosts
$v_V = f_m^V(1 - f_m^V)$	Genetic variance in vaccinated hosts

$$\begin{aligned}\bar{r}_{VN} &= f_m^V((\beta_V + \Delta\beta_V)(\sigma_N + \Delta\sigma_N) S_N) + (1 - f_m^V)(\beta_V \sigma_N S_N) \\ &= \beta_V \sigma_N S_N + f_m^V(\beta_V \Delta\sigma_N + \Delta\beta_V \sigma_N) S_N = \beta_V \sigma_N S_N + f_m^V s_{VN} \\ \bar{r}_{NV} &= f_m^N((\beta_N + \Delta\beta_N)(\sigma_V + \Delta\sigma_V) S_V) + (1 - f_m^N)(\beta_N \sigma_V S_V) \\ &= \beta_N \sigma_V S_V + f_m^N(\beta_N \Delta\sigma_V + \Delta\beta_N \sigma_V) S_V = \beta_N \sigma_V S_V + f_m^N s_{NV}\end{aligned}$$

The dynamics of differentiation D is therefore given by:

$$\dot{D} = v_V \left(s_{VV} - \frac{I_V}{I_N} s_{VN} \right) - v_N \left(s_{NN} - \frac{I_N}{I_V} s_{NV} \right) - D \left(\frac{I_N}{I_V} \bar{r}_{NV} + \frac{I_V}{I_N} \bar{r}_{VN} \right)$$

If we assume there is no differentiation initially ($D = f_m^V - f_m^N = 0$, which also means genetic variance is the same in the two environments, $v_N = v_V = v = f_m(1 - f_m)$) then the dynamics of differentiation are:

$$\begin{aligned}\dot{D} &= v \left(s_{VV} - s_{NN} - \frac{I_V}{I_N} s_{VN} + \frac{I_N}{I_V} s_{NV} \right) \\ \dot{D} &= v \left((\Delta\beta_V \sigma_V + \beta_V \Delta\sigma_V) S_V - \Delta\gamma_V - (\Delta\beta_N \sigma_N + \beta_N \Delta\sigma_N) S_N + \Delta\gamma_N \right. \\ &\quad \left. - \frac{I_V}{I_N} (\Delta\beta_V \sigma_N + \beta_V \Delta\sigma_N) S_N + \frac{I_N}{I_V} (\Delta\beta_N \sigma_V + \beta_N \Delta\sigma_V) S_V \right)\end{aligned}$$

If we further assume that the prevalence is low so that S_N and S_V remains constant during the early stage of the epidemic the prevalence will grow exponentially and the ratio $\frac{I_N}{I_V}$ will remain constant. The value of this ratio can be computed from the vector \mathbf{F} of class frequencies given above:

$$\frac{I_N}{I_V} = \frac{S_N \sigma_N}{S_V \sigma_V} \left(1 + \frac{\delta}{S_N \beta_N \sigma_N + S_V \beta_V \sigma_V} \right) + O(\delta^2)$$

The dynamics of differentiation therefore becomes:

$$\dot{D} = v \left((S_N \beta_N \sigma_N + S_V \beta_V \sigma_V) \left(\frac{\Delta \sigma_V}{\sigma_V} - \frac{\Delta \sigma_N}{\sigma_N} \right) + \Delta \gamma_N - \Delta \gamma_V + \frac{s_{NV} \frac{\sigma_V S_V}{\sigma_N S_N} + s_{VN} \frac{\sigma_N S_N}{\sigma_V S_V}}{S_N \beta_N \sigma_N + S_V \beta_V \sigma_V} \delta \right) + O(\delta^2)$$

When $\delta = 0$ this simplifies as:

$$\dot{D} = v \left(S((1-p)\beta_N \sigma_N + p\beta_V \sigma_V) \left(\frac{\Delta \sigma_V}{\sigma_V} - \frac{\Delta \sigma_N}{\sigma_N} \right) - (\Delta \gamma_V - \Delta \gamma_N) \right) \quad (S3)$$

Note how differentiation is not driven by the transmission rates of the mutant but by its relative infectivity in naïve and vaccinated hosts.

References:

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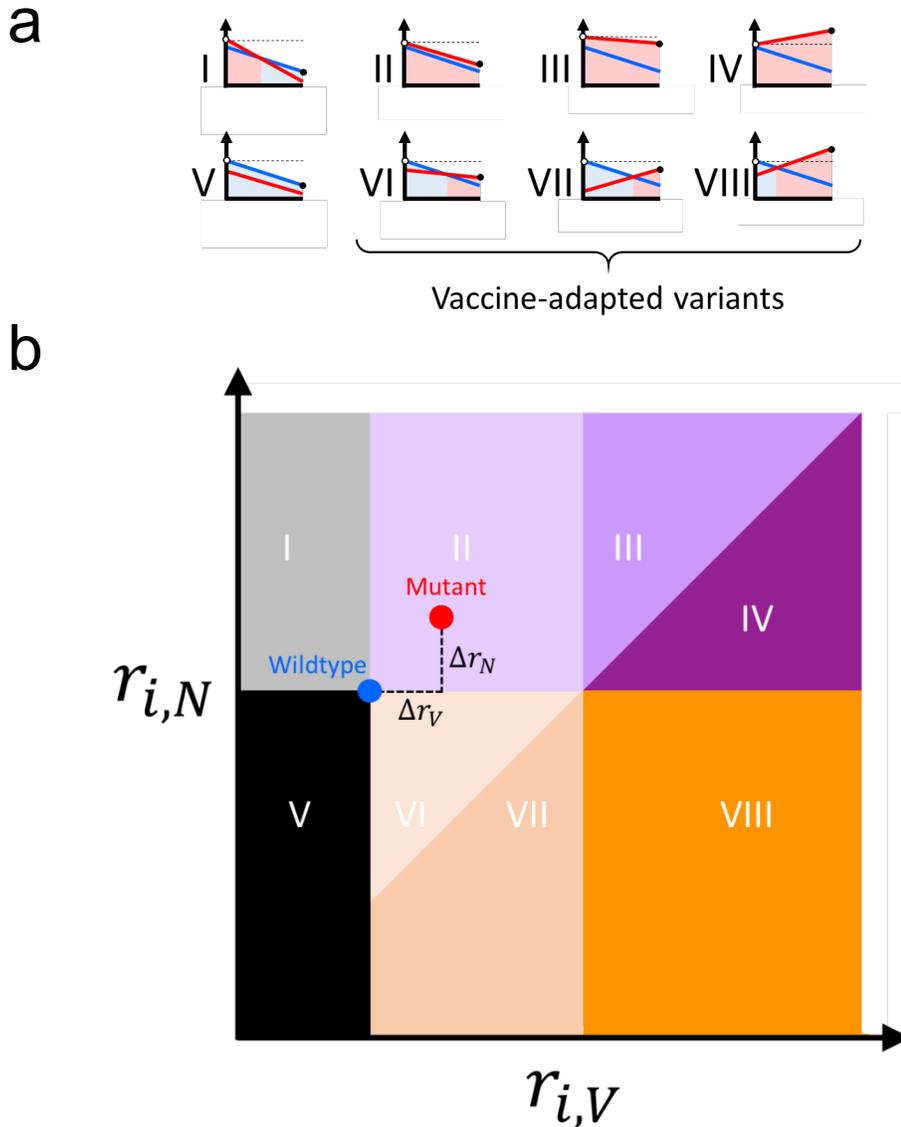


Figure S1: Typology of pathogen variants after vaccination. We can identify 8 different types of variants. The panel (a) is expanding the description of **Figure 1** and the panel (b) is indicating the location of these 8 types as in **Figure 2**. Variant type I is adapted to naïve hosts but maladapted on vaccinated hosts. Variant type V is maladapted on both types of hosts. We focus on the 6 vaccine-adapted variants with $\Delta r_V > 0$. Variants II, III and IV are generalist variants (i.e., $\Delta r_N > 0$) and the magnitude of Δr_V explains the difference between these 3 variants. Variants VI, VII and VIII are specialist variants (i.e., $\Delta r_N < 0$) and the magnitude explains the difference between these 3 variants. Note that variants IV, VII and VIII have a growth rate that increases with vaccination coverage. This increased growth rate can have major public health implications. In particular, with variants IV and VIII, evolution is expected to yield a higher pathogen growth rate after 100% vaccination (the evolved growth rate r_V is indicated with the black dot) than after 0% vaccination (the evolved growth rate r_N indicated with the white dot).