Mosaic vaccination: how distributing different vaccines across a population could improve epidemic control

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Abstract

Although vaccination has been remarkably effective against some pathogens, for others, rapid antigenic evolution implies that vaccination confers only weak and/or short-lived protection. Consequently, considerable effort has been invested in developing more evolutionarily robust vaccines, either by targeting highly conserved components of the pathogen (universal vaccines) or by including multiple immunological targets within a single vaccine (multi-epitope vaccines). An unexplored third possibility is to vaccinate individuals with one of a number of qualitatively different vaccines, creating a 'mosaic' of individual immunity in the population. Here we explore whether? a mosaic vaccination strategy can deliver superior epidemiological outcomes to 'conventional' vaccination, in which all individuals receive the same vaccine. We suppose vaccine doses can be distributed both between distinct vaccine 'targets' (e.g., different surface proteins against which an immune response can be generated) and across immunologically-distinct variants at these targets (e.g., strains); the pathogen can undergo antigenic evolution at both targets. Using simple mathematical models, we show that conventional vaccination is often outperformed by mosaic vaccination strategies, that is, mosaic vaccination often leads to fewer infected individuals over the course of the epidemic.

Keywords: vaccination, antigenic evolution, mosaic therapy, evolutionary epidemiology

1 Introduction

After hygiene, vaccines are arguably the greatest success story in public health to date. Vaccines are responsible for the eradication of smallpox in humans and rinderpest in livestock, and have driven substantial declines in the incidence of numerous childhood illnesses. Between 2010 and 2015, an estimated ten million lives were saved by vaccines [1]. Like vaccines, drugs have also substantially improved the management and control of infectious diseases over the last century. As the rates of drug prescriptions have increased, so too has the frequency of drug resistant pathogens in response. While the efficacy of drugs and optimism for their use into the future has declined dramatically due to pathogen evolution, many vaccines seem comparatively robust [2, 3]. As humanity heads towards a potential post-antibiotic era, the use and resilience of vaccines is becoming even more important (see, for example [4], and references therein).

Yet vaccines are not immune to the challenges posed by pathogen evolution. As a result of either high mutation rates or existing standing variation, many pathogen populations harbour diversity in relevant immune-signalling sites. If that diversity translates to relatively weak immune responses against strains other than the one to which a host was previously exposed, then vaccines—often produced from one or a few target strains—will fail to offer broad protection. It is precisely this combination of limited cross-immunity (i.e, protection against different strains), resultant strong selection [5, 6], and rapid evolution that necessitates yearly updating of the composition of influenza vaccines, for example.

Efforts are ongoing to improve vaccination strategies against evolving threats like influenza [7]. In particular, the search for more highly conserved targets of immune responses may yet produce a universal vaccine that need not be updated in the face of antigenic evolution [8–11]. Yet the consequences of such vaccines, including for pathogen evolution, have not been fully elucidated [12]. An alternative strategy is a vaccine cocktail, designed to elicit immune responses against multiple targets (i.e., epitopes) with a single vaccine [12]; much like drug cocktails, these are expected to be more robust in the face of evolution [13]. Multi-strain vaccines offer a different kind of cocktail (e.g., eliciting immune responses against different variants of the same target), which has been broadly useful for limiting disease caused by some pathogens (e.g., pneumococcal vaccines; see [14] for a discussion of success and challenges).

Here we investigate a different vaccination strategy by asking if and when vaccinating individuals with one of a number of qualitatively different vaccines—essentially a 'cocktail' at the population level— produces better epidemiological outcomes than a strategy that gives every individual the same vaccine. More accurately, in the vernacular of resistance evolution, this would be a 'mosaic' strategy [13]. The epidemiological consequences of using a mosaic vaccination strategy, to our knowledge, have not been explored. We develop and analyze a simple mathematical model of disease transmission, vaccination, and evolution to specifically ask, first, if vaccines with different targets existed, what would be the optimal way to use them? Second, we extend our model to consider the scenario of having a set of vaccines that target the same immunologic site, but different genetic (and antigenic) variants, for which limited cross-immunity may exist. Finally, we ask which source of variation across vaccine doses—targets or variants—can produce the best outcomes for controlling the spread of disease. Overall, we find that conventional vaccine programs, in which all individuals receive identical vaccines, are often outperformed by mosaic strategies that deliberately seed variation in the host population.

2 The model

Consider a pathogen modelled in a standard SIR framework (see Sup. Info.). Let β be a rate constant reflecting the number of disease transmissions caused by a single infectious individual, per unit time, in a fully susceptible population. Infections have mean duration δ such that in the absence of vaccination, $\beta\delta$ reflects the basic reproductive ratio of this pathogen in a population where the density of susceptibles is normalized to 1. Infection leads to sufficiently broad and long lasting immunity such that once infected, hosts cannot be reinfected over the timescale under consideration.

The pathogen has two potential vaccine 'targets', A and B, each of which may exhibit antigenic variation. Biologically, these 'targets' could be different surface proteins that could be used as signals to generate an immune response, or different epitopes on the same surface protein. We use 'variants' to refer to immunologically-distinct versions of these targets, and 'strains' to refer to pathogens harbouring different variants, such that A_iB_j denotes the pathogen strain with variant i at target A and variant j at target B (see Figure 1**a**). Antigenic space at each target is one dimensional [15–17], while antigenic change is cumulative

and equally likely at either target. Thus if we denote the initial pathogen strain as A_0B_0, then the next strain will be either A_1B_0 or A_0B_1 with equal probability. Antigenic change can either be generated by *de novo* mutation within the focal population, or it can be imported from an external source such as a reservoir animal population or a geographic region in which the pathogen is endemic (e.g., the annual global spread of influenza A H3N2 originates from southeast Asia [18, 19]).

A fraction p of the population will be vaccinated, and in the most general case, the vaccine doses can be distributed amongst four possible candidates (Fig. 1**b**). A fraction x of the p doses are distributed to vaccine target A, and $1-x$ to target B. Of the doses allocated to target A, a fraction y_A are distributed to the most abundant variant in the population initially, A_0, and $1-y_A$ to A_1; likewise of the doses against B, a fraction y_B will target B_0, while $1-y_B$ target B_1. Each vaccine has efficacy χ_0 against its intended target/variant combination; for example, the probability that strain A_0B_1 infects individuals vaccinated against B_1 is reduced by a factor $1-\chi_0$. More generally, a vaccine protecting against variant $j = 0, 1, ...$ of one target reduces the probability of infection by a strain with variant i of the same target by a factor $\chi_{|i-j|}$. Thus, vaccines confer cross-protection, where the degree of cross-protection depends only on the antigenic distance between variants at the vaccine target and not the variant at the other target. In contrast, infection-acquired immunity offers full protection against all strains, thus vaccine protection is inferior to infection-acquired immunity.

We treat pathogen evolution as a sequence of discrete antigenic changes, each of which may (or may not) produce a "wave" of the epidemic, such that the overall infection process consists of a series of strain-specific waves (Fig. 1**c**). To simplify the mathematical analysis, we will assume that these strain-specific waves occur sequentially, rather than simultaneously; that is, we make the approximation that a single strain dominates the infection process at any time. This assumption is valid provided that antigenic change is sufficiently infrequent such that by the time a novel strain has risen to appreciable levels in the population, the epidemic wave by the previous strain has largely concluded. In the first instance we will assume that antigenic change occurs without considering its origin (i.e., whether it is from mutation or imported). We will later discuss the implications of these assumptions for our results.

Let S_0 denote the initial density of individuals without infection-acquired immunity (susceptibles); note that population densities have been normalized such that $S_0 = 1$ implies that every individual in the population is susceptible. S_1 is then the density of susceptibles after the first wave (caused by the initial strain A_0B_0) and in general S_n denotes the susceptible density following the nth wave. These individuals can be further divided based upon whether they have been vaccinated. Let U_n denote the density of susceptible, unvaccinated individuals, and let $V_N^{k_j}$ denote the density of susceptible individuals vaccinated against variant j of target k ($k_j \in \{A_0, A_1, B_0, B_1\}$), following the nth wave. Therefore,

$$S_n = U_n + \sum_{k_j} V_n^{k_j}. \tag{1}$$

Suppose the initial densities are known, that is, $U_0 = S_0(1-p)$ and (for example) $V_0^{A_0} = S_0 p x y_A$. Then for a given sequence of antigenic changes, the remaining vaccinated individuals, after each wave, can be computed based on the sequence of remaining unvaccinated individuals. For example, suppose an epidemic occurs in three waves, $\ell = 0, 1, 2$, with dominant strains $A_0B_0 \to A_0B_1 \to A_1B_1$. Individuals vaccinated against target A_1 have vaccine protection that depends on the antigenic distance between A_1 and the circulating strains in successive waves (which we denote Δ_ℓ); in this example, these distances would be $\Delta_0 = 1$, $\Delta_1 = 1$ and $\Delta_2 = 0$. The final density of individuals vaccinated against A_1 is:

$$V_n^{A_1} = V_0^{A_1} \prod_{\ell=0}^{n-1} \left(\frac{U_{\ell+1}}{U_\ell} \right)^{1-\chi_{\Delta_\ell}}, \tag{2}$$

and similarly for the three analogous variables, $V_n^{A_0}$, $V_n^{B_0}$, and $V_n^{B_1}$ (see Sup. Info. 5.1).

In general, U_n, $V_n^{k_j}$, and S_n will depend upon which of the 2^{n-1} sequences of antigenic changes occurred. For example, if $n = 2$, the final strain could be A_1B_0 or A_0B_1 with equal probability, and so depending upon how the vaccine doses were allocated, these sequences could yield different values of S_2, U_2, and $V_2^{k_j}$.

Given a particular sequence of $n-1$ antigenic changes, from equation (1) and a set of equations like equation (2), the only unknowns are $U_1, ..., U_n$, which we now show how to compute. First, we determine whether the reproductive number of the pathogen strain with n antigenic changes is greater than one. While the basic reproductive number is given by $R = \beta\delta$ in a fully susceptible population, this value is reduced as

the fraction of susceptibles declines over successive waves. Using again the sequence $A_0B_0 \to A_0B_1 \to A_1B_1$ as an example, the potential for a third wave, $\mathcal{R}_0^{(3)}$, depends on the overall level of vaccine protection against A_1B_1 in the population after the second wave:

$$\mathcal{R}_0^{(3)} = R\Big[U_2 + (1-\chi_1)V_2^{A_0} + (1-\chi_0)V_2^{A_1} + (1-\chi_1)V_2^{B_0} + (1-\chi_0)V_2^{B_1}\Big]. \tag{3}$$

Using the same logic, a general formula for $\mathcal{R}_0^{(n)}$ is provided in the Sup. Info 5.2. If $\mathcal{R}_0^{(3)} > 1$, then an A_1B_1 wave occurs. Otherwise, either the epidemic ends or a new wave might occur if the pathogen evolves further, and strain A_2B_1 or A_1B_2 emerges. From the preceding assumptions (see Sup. Info. 5.2 for a full derivation), we find that U_n is the solution of

$$0 = \frac{1}{R}\ln\left(\frac{U_n}{U_{n-1}}\right) + U_{n-1} - U_n + \sum_{k_j}\left(V_{n-1}^{k_j} - V_n^{k_j}\right). \tag{4}$$

Once $U_1, ..., U_n$ are computed using equation (4), we can calculate S_n (using equations (1) and (2)). Although our derivation applies for any shape of cross-protection, in what follows, we will assume limited cross-protection between variants, $\chi_z \approx 0$ for $z > 0$. We will discuss the implications of this assumption for our results later.

2.1 Antigenic change scenarios

From equations (3) and (4), we see that although in an unvaccinated population there can be at most a single wave, in a vaccinated population, antigenic change may cause successive waves as strains escape vaccine coverage. Our analysis will therefore focus upon two representative scenarios of vaccine escape; in both situations we are interested in the expected remaining uninfecteds, which we will denote $\mathbb{E}[S_{\text{final}}]$. In the first scenario, we suppose the sequence of waves is limited by antigenic change. Specifically, we assume that antigenic change is rare, and so at most one antigenic change might occur over the timescale of interest. Thus, following the initial potential wave by strain A_0B_0, with probability ω a single antigenic change occurs at either target with equal probability, while with probability $1-\omega$, no antigenic change happens. If we let $S_2^{(A_jB_k)}$ denote the density of hosts without natural immunity following a second wave by strain A_jB_k, then $\mathbb{E}[S_{\text{final}}]$ is given by

$$\mathbb{E}[S_{\text{final}}] = (1-\omega)S_1 + \omega\left(\frac{1}{2}S_2^{(A_1B_0)} + \frac{1}{2}S_2^{(A_0B_1)}\right). \tag{5}$$

In the second scenario, the sequence of epidemic waves is not limited by antigenic change. Specifically, following the initial potential wave by strain A_0B_0, the pathogen will undergo successive one unit antigenic changes (and successive potential waves) until the density of remaining individuals without infection-acquired immunity is less than or equal to $1/R$; at this point, the population will have herd immunity and so any novel strains will be unable to cause an epidemic wave. In this case, $\mathbb{E}[S_{\text{final}}]$ is the average remaining uninfected individuals computed over all possible antigenic sequences terminating in $S_n \le 1/R$. For example, if we were to vaccinate exclusively against the primary variant of target A, such that $x = 1$ and $y_A = 1$, then under the assumption of limited cross-protection ($\chi_z \approx 0$ for $z > 0$), we find that $S_n \le 1/R$ the first time the variant A_1 appears. Therefore to compute $\mathbb{E}[S_{\text{final}}]$, we would take the average over all possible epidemic sequences ending with a change from $A_0 \to A_1$ (e.g., $A_0B_0 \to A_1B_0$, $A_0B_0 \to A_0B_1 \to A_1B_1, ...$).

Because $\mathbb{E}[S_{\text{final}}]$ denotes the expected density of individuals who do not contract the infection over the timescale of interest, we will take maximizing it as the metric for evaluating the efficacy of particular vaccination strategies. An important point to note is that when antigenic change is not limiting, the best outcome we can hope to achieve is $\mathbb{E}[S_{\text{final}}] = 1/R$. Thus irrespective of vaccine coverage, the population will ultimately be protected by herd immunity acquired through infection. The purpose of vaccination is then to 'ease' the population gradually down to the herd immunity threshold so that when it is reached, there are few active infections in the population. In contrast, rapid epidemic dynamics can lead to 'overshoot' [20], where many active infections exist when the herd immunity threshold is reached, meaning that although, on average, infections are not able to replace themselves through transmission, overall the susceptible fraction is reduced to below $1/R$. Consequently, the vaccine strategy that performs best (i.e., maximizes $\mathbb{E}[S_{\text{final}}]$) is that which avoids this overshoot. In contrast, when the epidemic is limited by antigenic change, considerably better outcomes than $1/R$ can be achieved; for example, it is possible under certain conditions for $\mathbb{E}[S_{\text{final}}] = S_0$.

2.2 Epidemic cases

To provide a baseline for comparison, consider 'conventional' vaccination, in which all doses are directed towards the primary variant of target A: $x = 1$ and $y_A = 1$. We note that from equation (3), $\mathcal{R}_0^{(n)}$ for any strain is at most RS_{n-1}, and thus when the density of susceptibles has been reduced to $1/R$ or less, no further waves can occur.

It is helpful to divide the space of epidemic outcomes into three qualitatively different cases, based on the expected outcome of conventional vaccination with vaccination coverage, p, and vaccine strength, χ_0; i.e., protection afforded against the vaccine strain. Case I occurs when protection is sufficiently weak, or the initial strain sufficiently strong, such that the initial wave reduces the density of susceptibles to below this critical threshold $1/R$ and no further waves can occur. Specifically, case I occurs when $\chi_0 \leq T_{\mathrm{I}/\mathrm{II}}(p)$, where

$$T_{\mathrm{I}/\mathrm{II}}(p) = 1 - \frac{1}{RS_0 - 1} \ln\left(\frac{RS_0 p}{1 - RS_0(1-p)\mathrm{e}^{-RS_0+1}}\right), \tag{6}$$

gives the threshold between cases I and II (see Sup. Info. 5.3). In this case, infection-acquired immunity (due to the large number of individuals who were infected) protects the population against further waves (Fig. 2). From equation (6), any decrease to pathogen transmissibility (β), duration of carriage (δ), or availability of hosts without natural immunity (S_0) will lower the threshold $T_{\mathrm{I}/\mathrm{II}}(p)$.

In case III, in contrast, antigenic change is necessary for an epidemic to occur. Case III occurs when vaccine protection is sufficiently strong that the reproductive number of the initial strain is less than one. In this situation, antigenic change at target A must occur before the epidemic proceeds. Thus the first wave can only be caused by a strain with variant $k \geq 1$ at target A, where the index k tends to increase with the broadness of cross-protection. Case III occurs when $\chi_0 \geq T_{\mathrm{II}/\mathrm{III}}(p)$ (see Sup. Info. 5.3), where

$$T_{\mathrm{II}/\mathrm{III}}(p) = \frac{RS_0 - 1}{RS_0 p}. \tag{7}$$

Case II occurs when coverage is of intermediate strength, specifically, $T_{\mathrm{I}/\mathrm{II}}(p) < \chi_0 \leq T_{\mathrm{II}/\mathrm{III}}(p)$. In this case, the wave caused by the initial strain is such that $S_1 > 1/R$, and so antigenic change can generate subsequent waves until $S_n \leq 1/R$ (Fig. 2). Thus, in case II, antigenic change is possible but not necessary for an epidemic. From equation (7), any decrease to pathogen transmissibility (β), duration of carriage (δ), or availability of hosts without natural immunity (S_0) will lower the threshold $T_{\mathrm{II}/\mathrm{III}}(p)$.

3 Results

3.1 Vaccines distributed across targets

First, consider distributing equally-effective vaccines between two targets: a fraction x of available vaccine doses are used against target A and $1 - x$ are used against B. All doses are to be allocated to the primary variant at each target, that is, we will vary x while $y_A = y_B = 1$. Because both vaccines offer equal protection against the initial strain A_0B_0, the choice of x will have no effect on the size of the initial wave, and will only impact subsequent waves, to which conventional vaccination provides no protection (under our assumption of limited cross-immunity). As a result, any vaccine heterogeneity ($0 < x < 1$) will be at least as good as conventional vaccination in terms of maximizing S_n; in fact, when antigenic evolution either can cause secondary waves (case II) or is necessary for an initial wave (case III), any variation in targets across vaccine doses, $0 < x < 1$, will be superior to the conventional vaccination strategy.

Perhaps more surprisingly, despite our assumptions of equivalent vaccine efficacy and mutation rates across targets, for case II and III an even distribution of doses between targets, $x = 1/2$, is rarely the best strategy for maximizing $\mathbb{E}[S_{\mathrm{final}}]$, regardless of whether antigenic change is limited or not. This is because if evolution is either limited or not by antigenic change, there are (effectively) two equally probable sequences of antigenic change, differentiated by which target changes first (i.e., is the second wave caused by A_1B_0 or A_0B_1?). We can choose x to maximize vaccine protection against either one of these sequences. In the case of limited antigenic change, if $\omega > 0$, this means choosing $x = x^*$ to block the second wave of one sequence, $\mathcal{R}_0^{(2)} = 1$, that is, x^* satisfies

$$x^* = \frac{1}{\chi_0}\left(\frac{1 - RU_1}{RS_0 p}\left(\frac{U_0}{U_1}\right)^{1-\chi_0} - 1 + \chi_0\right). \tag{8}$$

(See Sup. Info. 5.4). Since our choice of x does not affect U_1 or S_1, it follows from equation (5) that x^* will be independent of ω. In comparison with $x = 1/2$, this choice of x^* will reduce protection against the other sequence. However, for a wide range of parameter space, the average of outcomes across the two possible sequences when $x = x^*$ outperforms the expected outcome when $x = 1/2$, and will always outperform conventional vaccination (Fig. 3). Of course, by symmetry, if x^* is optimal, then so is $1 - x^*$ (Fig. 3).

If instead pathogen evolution is not limited by antigenic change, maximizing protection against one sequence of antigenic changes means choosing x so that for one of the sequences, $S_{\text{final}} = 1/R$. Again, this means reduced protection against the other sequence of antigenic change, but the average of these two outcomes, $\mathbb{E}[S_{\text{final}}]$, generally outperforms $x = 1/2$, and always outperforms conventional vaccination. As before, if x^* is optimal, then so is $1 - x^*$ (Fig. 3).

3.2 Vaccines distributed across variants

Next, we consider distributing equally-effective vaccines between two variants of target A, that is, setting $x = 1$ and varying y_A. Clearly, any $y_A < 1$ will reduce the protection against the initial strain, and so if vaccine coverage is sufficiently weak (case I), all doses should be allocated to the primary variant, $y_A = 1$ (conventional vaccination). In case II and III, however, conventional vaccination performs poorly because the population is effectively unvaccinated against any variation at target A (Fig. 2). Therefore we might expect that some doses should be allocated to provide protection against the secondary variant.

If evolution is severely limited by antigenic change ($\omega \to 0$), then it is optimal to maximize protection against the primary variant, A_0; we denote this choice y_{A_0}. In case II, because conventional vaccination is not sufficiently strong to block the initial A_0B_0 epidemic wave, we should simply maximize protection against this strain by choosing $y_{A_0} = 1$. In case III, because conventional vaccination is more than strong enough to completely block the A_0B_0 epidemic wave, we can divert vaccine doses toward A_1B_0. In particular, we can choose y_A such that the reproductive number for the first wave is reduced to one, i.e., y_{A_0} satisfies $\mathcal{R}_0^{(1)} = 1$ ($y_{A_0} = \frac{RS_0-1}{RS_0p\chi_0}$), and so blocks the wave by the initial strain. In this strategy, any excess doses not needed to block the A_0B_0 epidemic wave are diverted to protect against the (rare) possibility that a strain carrying the variant A_1 emerges (red surface in Fig. 4**a**; see also Sup. Info. 5.5).

When the likelihood of antigenic change is high ($\omega \to 1$), then so is the threat of a potential second wave by strain A_1B_0. In this circumstance it is optimal to maximize protection against the secondary variant at target A, that is, given the next strain is A_1B_0, choose y_{A_1} to satisfy $\mathcal{R}_0^{(2)} = 1$ so as to block the potential wave by A_1B_0. Varying the likelihood of antigenic change (i.e., varying ω) tips the balance between the conservative strategy of focusing upon the primary variant, y_{A_0}, and instead shifting resources to target the secondary variant, y_{A_1}, even though doing so will yield a larger epidemic wave by the initial strain (Fig. 4**c**,**d**). Additionally, increasing RS_0 favours targeting the primary variant over the secondary (y_{A_0} over y_{A_1}) because the initial wave is more likely to deplete the remaining uninfecteds, S_1, such that further waves pose little additional threat. Note as well that the switch between y_{A_0} and y_{A_1} is sensitive to the level of vaccine coverage, and so for a given ω and RS_0, y_{A_1} may be favoured in some regions of case II or case III whereas y_{A_0} may be favoured in others; but in general, the closer we are to $T_{I/II}(p)$, the more likely y_{A_1} is favoured.

When evolution is not limited by antigenic change (and so is limited by infection-acquired immunity), we can always choose y_A to ensure that $\mathbb{E}[S_{\text{final}}] = 1/R$. Thus in contrast to distributing vaccine doses between targets, when distributing across variants we can, in theory, always attain the optimum ($\mathbb{E}[S_{\text{final}}] = 1/R$). This can be achieved with two values of y_A: when we choose $y_A = y^*$,

$$y^* = \frac{1 - RS_0 e^{-RS_0+1}}{RS_0 p e^{-RS_0+1}\left(e^{\chi_0(RS_0-1)} - 1\right)} \tag{9}$$

which provides sufficiently weak protection against the initial strain such that $S_1 = 1/R$ (Sup. Info. 5.5). Second, we can choose $y_A = y^\bullet$, where $y^\bullet > y^*$ such that only after antigenic change at target A will $\mathbb{E}[S_{\text{final}}] = 1/R$ (Fig. 4**b**,**e**). Although both y^* and $y^\bullet$ maximize $\mathbb{E}[S_{\text{final}}]$, from a public health perspective $y^\bullet$ is the superior option as it maximizes $\mathbb{E}[S_{\text{final}}]$ after at least one antigenic change, and so two waves, rather than one epidemic and no antigenic change. By staggering the waves, the peak burden on the healthcare system will be reduced (e.g., [21]). Indeed, the less desirable outcome of y^* could simply be achieved using conventional vaccination with artificially lowered coverage.

3.3 Distributing across targets and variants simultaneously

Next, consider distributing vaccines across both targets and variants. When we are free to choose all three of (x, y_A, y_B), many different combinations can lead to similar S_n. For example, when antigenic change is not limiting, we have already shown that when only manipulating y_A (with $x = 1$) there are two values of y_A which ensure the optimal outcome, $\mathbb{E}[S_{\text{final}}] = 1/R$. Therefore we have the opportunity to apply further constraints to identify optimal combinations. One approach would be to apply additional metrics. For example, in addition to maximizing S_n we could also seek to maximize the average n at which S_n is first equal to $1/R$ (this was what separated $y^\bullet$ from y^*), or minimize the variance between epidemic sequences (when $x = 1/2$ and $y_A = y_B$). Alternatively, we may impose the constraint that we are free to distribute across targets (x) and then across both variants in the same way; that is, we take $y_A = y_B = y$ and so we are choosing the pair (x, y) rather than the triplet (x, y_A, y_B). The motivation for imposing this constraint is that doing so allows us to see when either distribution dimension has primacy. Specifically, when distributing between targets is more important, then the optimal (x, y) will show variation between targets as coverage (p and χ_0) changes, while all the doses will be allocated towards the primary variant, $y = 1$. In particular, we expect to see optimal values x^* and $1 - x^*$ where $x^* \neq 1/2$, as observed when distributing across targets only. When distributing between variants is more important, then we should expect y to vary with vaccine coverage while doses will be evenly allocated across targets, $x = 1/2$.

Since for epidemics not limited by antigenic change the optimal vaccination strategy satisfies $\mathbb{E}[S_{\text{final}}] = 1/R$, and as we have previously shown that this is always (theoretically) possible when we can vary doses between variants, it logically follows that if we can vary doses between both targets and variants we can similarly achieve the optimum. Therefore we will restrict our attention to when the epidemic is limited by antigenic change. Under these circumstances, the outcome is as we would expect from consideration of our previous results. When the likelihood of antigenic change is low ($\omega \to 0$) the optimal solution is to rely upon distributing doses between targets (varying x) while targeting the primary variant, $y = 1$. As the likelihood of antigenic change increases ($\omega \to 1$), the optimal strategy is to distribute between variants (varying y), while keeping doses equally divided across targets, $x = 1/2$ (Fig. 5; Sup. Info. 5.6). The reason for this is intuitive: when there is a low probability of a second wave, we want to maintain maximum protection against the initial strain ($y = 1$), while we are free to distribute between targets so as to block one of the epidemic sequences (i.e., choose x to satisfy equation (8)). As the likelihood of antigenic change increases ($\omega \to 1$), a wave by a secondary variant is increasingly likely, and so we are more willing to sacrifice protection against the initial strain to allocate doses against the secondary variants. Because each epidemic sequence is equally likely, when relying upon distributing between variants it makes sense to distribute equally between targets ($x = 1/2$; Fig. 5; Sup. Info. 5.6). Incidentally, this strategy also minimizes the variance in epidemic size across the two sequences.

3.4 Mutations, cross-protection, and multi-strain epidemics

The preceding analysis made three key assumptions. First, antigenic change was assumed to arise without consideration of its source. This is reasonable if antigenic novelty originates outside the focal population. For example, it may come from a reservoir animal population or be otherwise imported from a source population (e.g., influenza A H3N2 from southeast Asia [18, 19]). If instead we focused strictly on antigenic change from *de novo* mutation in the focal population, then unless mutations are very likely, conventional vaccination tends to perform better than our results show; in this case it is typically better to 'hit hard' in the hopes of preventing antigenic change, rather than to distribute vaccine doses in anticipation of an unlikely mutation. This is particularly true in case III. The other complicating factor when explicitly considering mutation is whether or not vaccination can induce within-host evolution, biasing which target is most likely to generate novel variants. Although consideration of this possibility is beyond the scope of the current work, in at least some relevant diseases (e.g., influenza A), modelling suggests within-host evolution due to vaccination plays a limited role [22–24].

Second, we assumed cross-protection was limited. The shape, or 'broadness' (i.e., how slow the decay of χ_z is for increasing z), of the cross-protection function is of no consequence in case I. In cases II and III, however, the primary role of the broadness of vaccine cross-immunity is that it determines the reduction in vaccine protection against new strains. If vaccine cross-immunity is broad, antigenic change will cause a small reduction in vaccine protection, and so a smaller subsequent wave. If, however, cross-immunity is narrow, antigenic change will cause a large reduction in vaccine protection, and so potentially a large wave.

Thus increasing cross-protection increases the efficacy of conventional vaccination in case II and III. For example, if antigenic change is not limiting, conventional vaccination is more likely to achieve the optimum of $\mathbb{E}[S_{\text{final}}] = 1/R$ with broad cross-immunity, whereas with narrow cross-immunity, substantial overshoot is more likely (Fig. 2). In our model, the shape of cross-immunity will ultimately depend upon the units of antigenic space. For example, if k_i and k_{i+1} differ by a single, nearly-neutral mutation, cross-protection will tend to be broad. If instead antigenic variation arises in a source population with pre-existing immunity, large differences between k_i and k_{i+1} may be necessary to escape extinction in the source population, and so cross-protection may be narrow.

Third, we assumed each wave consists of a single strain. Although this may be reasonable if antigenic variation originates elsewhere, it is less likely when variation is generated by *de novo* mutation. If our results were extended to include multi-strain waves, the predicted efficacy of conventional vaccination would be weakened, since whenever an escape mutant arises during an ongoing wave, there are more individuals without infection-acquired immunity and so available to be infected by the escape mutant. This would lead to a larger wave by the strain with limited vaccine protection.

4 Discussion

We have used a simple model to explore the optimal distribution of vaccines that differ in antigenic targets and/or specific variants at those targets (i.e., strains). We show that with weak vaccines (either low coverage or strength), evolutionary change in the pathogen population does not alter epidemiological outcomes and so a mosaic vaccination strategy, in which individuals receive one of a set of possible vaccines, is not better than a conventional, homogeneous strategy. In cases where pathogen evolution can lead to successive waves of an epidemic, or is required for an initial wave, using a mosaic vaccination strategy often leads to better outcomes than giving all individuals identical vaccines.

By assuming that vaccines designed to elicit immunity against different targets are equally effective, we assume that distributing vaccine doses between those targets leads to no decline in initial protection relative to conventional vaccines. The benefit of a mosaic strategy is that should there be any antigenic evolution at either target that renders one vaccine ineffective (assuming limited cross-immunity between variants), the other vaccine will still provide protection to the individuals that received it, and hence the population. Perhaps surprisingly, the optimal distribution of vaccine doses between targets is not 50:50—better outcomes can be achieved on average with unequal allocation, which will provide more protection in cases where the target that is rarer among vaccine doses is the one that undergoes antigenic change.

It is interesting to consider our results in the context of the ongoing COVID-19 pandemic, given the rapid and parallel development of dozens of vaccines against SARS-CoV-2 [25–27]. While many COVID-19 vaccines in development target the same spike protein, some target epitopes in other genes [26] and the potential for multi-epitope (i.e., cocktail) vaccines is being investigated (e.g., [28–31]). If in the future multiple COVID-19 vaccines were approved with similar efficacies (i.e., roughly equal protection against the predominant circulating strain), then our results suggest that to minimize the risk of evolutionary escape and reduce the total number of individuals who get infected, the vaccines should be used in a mosaic strategy (*sensu* [13]). Multiple plausible vaccine targets exist for other infectious diseases (e.g., hemagglutinin (HA) and neuraminidase (NA) in influenza [32]), but whether each target would induce equal efficacy protection and is subject to an equal likelihood of mutation remain open questions (though see [6] for similar estimates of non-synonymous mutation rates in HA and NA within hosts). Our model provides a framework for building in these details and evaluating the efficacy of mosaic vaccination strategies for specific diseases.

What happens when vaccines are distributed across variants of a given target is perhaps more subtle. If evolutionary change in antigens is unlikely, then diverting any vaccine doses away from the predominant strain can lead to worse epidemiological outcomes. However, even if antigenic change is unlikely, if vaccine efficacy (χ_0) is sufficiently strong or coverage (p) is sufficiently high (i.e., our case III), then from a population perspective better outcomes can be achieved by vaccinating a fraction of the population against a secondary variant. As the likelihood of waves from antigenically-distinct strains increases, then a trade-off emerges between protection in an initial wave versus subsequent ones. Put simply, a small initial wave due to strong vaccine protection against an initial variant leaves a large pool of susceptible individuals that could be exploited by a subsequent strain (assuming weak cross-immunity from vaccination), while a large initial wave due to poor vaccine protection leaves few individuals susceptible to future waves (assuming strong cross-immunity from natural infections). The optimal strategy essentially titrates between these scenarios,

offering intermediate protection against initial and subsequent strains and dampening—but not eliminating—individual waves. This intermediate strength optimal strategy echoes results from previous work: in an explicit two-strain epidemiological model, if vaccination disproportionately impacts one strain (and vaccine-induced immunity is weaker than natural immunity), then increasing vaccine coverage or strength can lead to outgrowth of infections with the second strain and worse outcomes overall [33, 34].

Distributing across variants seems intuitively risky. For influenza, for example, substantial work goes into choosing which variant of each flu subtype will be included in a vaccine in a given year (e.g., [35]). Part of the decision is based on the frequency of circulating variants and the likelihood that any one variant will seed the coming year's seasonal epidemic. If there is good reason to expect some variant, k_j, will circulate predominantly, it would seem unethical to allocate any vaccine doses to a different variant. Yet our results show that over a considerable range of parameters (i.e., vaccine efficacy and coverage, likelihood of antigenic change), the conventional strategy does not give rise to the best outcomes and so the principle of equipoise would not be breached by distributing vaccines across variants. Of course, our model assumes that the second, dominant strain to circulate in a given epidemic can be predicted. For influenza, evolutionary predictions are improving (e.g., [36, 37]; reviewed in [35]); our results suggest a novel way of using those predictions for vaccine design, assuming any practical barriers can be overcome.

Though not exploring the consequences of variable vaccines *per se*, previous work has explored the epidemiological and evolutionary consequences of vaccines that produce variable effects across hosts. First, using a data-driven model of a viral disease of fish, Langwig et al. [38] showed that vaccines which induce variation in susceptibility across hosts can lead to better epidemiological outcomes than vaccines that have individually-invariant effects (analogous to theoretical results exploring the effects of natural variation in susceptibility [39–41]). This is because with variation, average susceptibility declines over the course of the epidemic, since hosts that are the most susceptible get infected earlier on average. Likewise, in our model, distributing vaccine doses across targets or variants changes the landscape of host susceptibility both initially and as circulating pathogens evolve. In our case, distributing across targets mitigates the increase in susceptibility that would occur with conventional vaccines following antigenic evolution, while distributing across variants can actually reverse it. Second, as an explanation for why few vaccines have failed in the face of pathogen evolution, relative to the alarming rise and spread of drug resistance, Kennedy & Read [2] argue that individual variation in response to vaccination, e.g., generating immunity against different antigens, may lead to more diverse selection pressures acting on pathogens. In practice, for influenza at least, there is strong evidence that individuals do respond qualitatively differently to the same vaccine, due to differences in past history of exposure (e.g., [42]; reviewed in [43]). Our work reinforces the idea that, in some cases, this variation can be beneficial from a public health perspective [2] and so generating such variation could be an explicit aim of vaccination.

Our model and analyses come with a number of caveats and limitations, in addition to those already mentioned above. For example, we use only one metric, i.e., the fraction of the population that remains uninfected, to assess epidemiological outcomes. Our analysis of the effect of targeting different variants incorporated the idea that more waves in an epidemic—in effect, expanding the duration of the epidemic, while achieving the same outcome—is beneficial from a public health perspective. But this is true more broadly: the value of 'flattening the curve' and reducing peak demands on the health care system is now widely appreciated [21], and our model does not explicitly compare the peak infection burden. Further, we assume that vaccination has only one protective effect, i.e., reducing susceptibility to infection. Vaccines may additionally (or instead) reduce the duration of infection or infectiousness of a vaccinated (and infected) host. These choices are likely to influence our results. In particular, the optimal outcomes for vaccines distributed across variants depend on the rate at which different vaccinated susceptible groups are depleted and so a vaccine that impacts, for example, the duration of infection, will change the rate at which those susceptible individuals are depleted.

While the evolutionary and epidemiological consequences of universal vaccines have received some theoretical attention (e.g., [44]), as far as we are aware, no previous study explores the potential for vaccination strategies to essentially generate universal coverage at the host population level by delivering variable vaccines to individuals. This mosaic strategy generates heterogeneity in the host population (and, thus, the fitness landscape for pathogens), which has long been thought to be protective against disease outbreaks [45]. Theory predicts that 'naturally' variable host populations are less likely to experience sustained disease spread (e.g., [40, 41]), and the protective effect of host variation has been empirically demonstrated in a number of experimental (e.g., *Daphnia*-microsporidium [46]; bacteria-phage [47]), as well as natural systems [48], especially those in which rapid host evolution is unlikely [49]. Our work suggests that vaccination

strategies that harness—and, in fact, generate—variation can often outperform conventional vaccines.

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5 Supplementary Information

5.1 Single epidemic wave

We consider a pathogen with two vaccine targets, A and B, each of which can exhibit antigenic variation. We let A_iB_j denote a pathogen strain with variant i at target A and variant j at target B. At each target, antigenic space is one dimensional, such that as i (or j) increases, we move further away from the reference strain, which we denote A_0B_0. Using this reference strain, we will refer to the variant indexed 0 as the 'primary' variant and the variant indexed 1 as the 'secondary' variant, e.g., strain A_1B_0 has the secondary variant for target A and primary variant for target B.

To model the epidemiological dynamics of a single epidemic wave, we use a standard SIR model with a single strain, say $A_\ell B_m$, present. Let $I_i(t)$ denote the density of infected individuals with strain $i = A_\ell B_m$ at time t. Infections are transmitted with rate constant β, and are cleared at a per-capita rate $1/\delta$. Let $U(t)$ denote the density of unvaccinated individuals in the population at time t, and $V^{k_j}(t)$ denote the density of individuals vaccinated against target k and variant j ($k_j \in \{A_0, A_1, B_0, B_1\}$). Then the epidemiological dynamics are given by the system of ordinary differential equations

$$\begin{aligned}
\frac{\mathrm{d}U}{\mathrm{d}t} &= -\beta U I_i \\
\frac{\mathrm{d}V^{k_j}}{\mathrm{d}t} &= -\beta(1-\chi_{|j-i_k|})V^{k_j} I_i, \quad k_j \in \{A_0, A_1, B_0, B_1\} \\
\frac{\mathrm{d}I_i}{\mathrm{d}t} &= \Big(\beta U + \beta \sum_{k_j}(1-\chi_{|j-i_k|})V^{k_j} - \frac{1}{\delta}\Big) I_i
\end{aligned} \tag{10}$$

where i_k is the variant of strain $A_\ell B_m$ at target k, i.e., $i_A = \ell$ and $i_B = m$, and so $|j - i_k|$ is the distance in antigenic space between the variant targeted by the vaccine, j, and strain i variant, i_k. From system (10), the basic reproductive number of pathogen strain i is

$$\mathcal{R}_0 = R\Big(U(0) + \sum_{k_j}(1-\chi_{|j-i_k|})V^{k_j}(0)\Big), \tag{11}$$

where $R \equiv \beta\delta$. It follows that if $\mathcal{R}_0 > 1$, then an initially rare strain i will cause an epidemic.

The density of individuals who have not been infected by time t is

$$S(t) = U(t) + \sum_{k_j} V^{k_j}(t). \tag{12}$$

Our objective is to derive from system (10) an expression for the remaining uninfected individuals, $S(t)$, after sufficient time has elapsed for the epidemic wave to conclude, that is, we are interested in $S(\infty)$. To do so, notice in system (10) that U is a monotonically decreasing function of time. Therefore, we can rescale time by U, which will give the reduced system

$$\begin{aligned}
\frac{\mathrm{d}V^{k_j}}{\mathrm{d}U} &= (1-\chi_{|j-i_k|})\frac{V^{k_J}}{U}, \\
\frac{\mathrm{d}I_i}{\mathrm{d}U} &= -1 - \sum_{k_j}(1-\chi_{|j-i_k|})\frac{V^{k_j}}{U} + \frac{1}{RU}.
\end{aligned} \tag{13}$$

From (13), we can directly solve for V^{k_j}, that is,

$$V^{k_j} = V^{k_j}(0)\left(\frac{U}{U(0))}\right)^{1-\chi_{|j-i_k|}}. \tag{14}$$

Using this result, we are left with the differential equation

$$\frac{\mathrm{d}I_i}{\mathrm{d}U} = -1 - \sum_{k_j}\frac{(1-\chi_{|j-i_k|})V^{k_j}(0)}{U}\left(\frac{U}{U(0)}\right)^{1-\chi_{|j-i_k|}} + \frac{1}{RU}. \tag{15}$$

Using the condition that strain i is initially rare, that is, $I_i(0) \approx 0$, this has solution

$$I_i(U) = \frac{1}{R}\ln\left(\frac{U}{U(0)}\right) + U(0) - U + \sum_{k_j} V^{k_j}(0)\left(1 - \left(\frac{U}{U(0)}\right)^{1-\chi_{|j-i_k|}}\right). \tag{16}$$

As $t \to \infty$, we know that $I_i \to 0$, that is, the wave of strain i will eventually burn itself out of the host population. Therefore $U(\infty)$ is the solution of

$$0 = \frac{1}{R}\ln\left(\frac{U(\infty)}{U(0)}\right) + U(0) - U(\infty) + \sum_{k_j} V^{k_j}(0)\left(1 - \left(\frac{U(\infty)}{U(0)}\right)^{1-\chi_{|j-i_k|}}\right), \tag{17}$$

which can be written, using Equation (14), as

$$0 = \frac{1}{R}\ln\left(\frac{U(\infty)}{U(0)}\right) + U(0) - U(\infty) + \sum_{k_j}\left(V^{k_j}(0) - V^{k_j}(\infty)\right). \tag{18}$$

Therefore, there are two possibilities: if $\mathcal{R}_0 \le 1$, $U(\infty) = U(0)$, otherwise $U(\infty)$ is the solution of equation (18) satisfying $0 < U(\infty) < U(0)$. Once we have $U(\infty)$, we can then plug it into equation (12) to obtain $S(\infty)$.

5.2 Successive epidemic waves

We now extend equation (18) to consider a sequence of successive epidemic waves starting from the initial strain A_0B_0. To do so, let U_n and $V_n^{k_j}$ denote the density of susceptible, unvaccinated individuals and susceptible individuals vaccinated against k_j, following the nth epidemic wave. This epidemic wave will have been due to a strain $n-1$ antigenic changes from the initial strain. Before any epidemic waves (or antigenic changes), i.e., $n = 0$, we have S_0 susceptible individuals without infection-acquired immunity. We vaccinate a fraction p of these. Of the vaccinated individuals, a fraction x vaccines are directed towards target A and $1-x$ directed towards target B. A fraction y_k of the doses for target k are used against the primary variant, k_0, while the remaining $1-y_k$ are used against the secondary variant, k_1. Therefore we initially have a density of $U_0 = S_0(1-p)$ unvaccinated, susceptible individuals, while the initial density of individuals vaccinated against each target and variant combination is:

$$V_0^{A_0} = S_0 pxy_A, \qquad V_0^{A_1} = S_0 px(1-y_A),$$
$$V_0^{B_0} = S_0 p(1-x)y_B, \qquad V_0^{B_1} = S_0 p(1-x)(1-y_B).$$

After the nth epidemic wave, the next pathogen strain, $A_\ell B_m$, will have undergone $n = \ell + m$ antigenic changes. There are 2^n possible antigenic sequences and $n+1$ possible $A_\ell B_m$ strains. For a given sequence of antigenic changes culminating in strain $A_\ell B_m$ following the nth epidemic wave, the basic reproductive number of strain $A_\ell B_m$ is

$$\mathcal{R}_0^{(n+1)} = R\big(U_n + (1-\chi_\ell)V_n^{A_0} + (1-\chi_{|\ell-1|})V_n^{A_1} + (1-\chi_m)V_n^{B_0} + (1-\chi_{|m-1|})V_n^{B_1}\big), \tag{19}$$

that is, $\mathcal{R}_0^{(n+1)}$ indicates whether or not the $(n+1)^{\text{th}}$ epidemic wave will occur. Note that, in general, U_n and $V_n^{k_j}$ will be specific to the sequence of antigenic changes.

If $\mathcal{R}_0^{(n+1)} \le 1$, then $U_{n+1} = U_n$, otherwise from equation (18), U_{n+1} is the solution of

$$0 = \frac{1}{R}\ln\left(\frac{U_{n+1}}{U_n}\right) + U_n - U_{n+1} + \sum_{k_j}\left(V_n^{k_j} - V_{n+1}^{k_j}\right) \tag{20}$$

satisfying $0 < U_{n+1} < U_n$. Then using Equation (14) we have

$$V_n^{k_j} = V_0^{k_j}\prod_{i=0}^{n-1}\left(\frac{U_{i+1}}{U_i}\right)^{1-\chi_{|j-i_k|}} \tag{21}$$

where i_k is the variant at target k of the strain causing epidemic wave i, and

$$S_n = U_n + \sum_{k_j} V_n^{k_j} \tag{22}$$

is the remaining uninfected individuals after the nth epidemic wave. We are therefore equipped to compute the remaining uninfected individuals after the nth epidemic wave for a given sequence of antigenic changes.

Because the outcome, S_n, will depend upon the sequence of antigenic changes, in the main text we focus upon comparing the expected remaining uninfecteds, $\mathbb{E}[S_{\text{final}}]$ for two different scenarios. Specifically, the scenarios we consider are (i) epidemics that are limited by antigenic change, and (ii) epidemics that are not.

For epidemics limited by antigenic change, we let ω denote the probability of a single antigenic change, and $S_2^{(A_jB_k)}$ denote the remaining uninfected individuals following a second epidemic wave by strain A_jB_k. Then the expected remaining uninfected individuals following $\omega \in [0,1]$ antigenic changes is

$$\mathbb{E}[S_{\text{final}}] = (1-\omega)S_1 + \frac{\omega}{2}(S_2^{(A_1B_0)} + S_2^{(A_0B_1)}). \tag{23}$$

For epidemics not limited by antigenic change, the successive epidemic waves will continue until the remaining uninfected individuals satisfies $S_{\text{final}} \leq 1/R$. In general this threshold will be reached within 1 or 2 antigenic changes (under the assumption of limited cross-protection, $\chi_{|z|} \approx 0$ for $z > 0$). For epidemics not limited by antigenic change, we restrict our attention to situations in which we either distribute vaccines between targets, but not variants, (so vary x while fixing $y_k = 1$) or between variants, but not targets (so vary y_A with $x = 1$). If we are distributing between targets, a single antigenic change is required to escape vaccination at a given target; after this initial change, any subsequent antigenic change at that target will have no effect. Therefore it suffices to consider two possible epidemic sequences, (i) $A_0B_0 \to A_1B_0 \to A_1B_1$, and (ii) $A_0B_0 \to A_0B_1 \to A_1B_1$. Therefore,

$$\mathbb{E}[S_{\text{final}}] = \frac{1}{2}S_3^{(\text{i})} + \frac{1}{2}S_3^{(\text{ii})}, \tag{24}$$

where $S_3^{(\ell)}$ is the remaining individuals without infection acquired immunity following the third epidemic wave for epidemic sequence $\ell = \text{i}$ or $\ell = \text{ii}$. If we are instead distributing between variants, since all vaccine doses are directed at target A any antigenic change at target B will have no effect; moreover, it is possible (depending upon y_A) that two antigenic changes at target A will be required to sufficiently deplete the remaining uninfecteds. In combination, this means that $S_3^{(A_2B_0)} = S_4^{(A_2B_1)} = \cdots = S_{3+j}^{(A_2B_j)}$. Thus there is only one antigenic sequence that matters: $A_0B_0 \to A_1B_0 \to A_2B_0$, and so $\mathbb{E}[S_{\text{final}}] = S_3^{(A_2B_0)}$.

5.3 Epidemic cases

There are two thresholds which delineate the qualitatively different epidemic regimes discussed in the main text. The first is when the epidemic wave by the initial strain, A_0B_0, reduces the remaining uninfecteds to exactly $1/R$, that is, $S_1 = 1/R$. To obtain the threshold value of χ_0 for which this occurs (which we denote $T_{I/II}(p)$), we simultaneously solve equation (20) when $n = 0$ and equation (22) when $n = 1$ and $S_1 = 1/R$, that is, we solve

$$\begin{aligned} 0 &= \frac{1}{R}\ln\left(\frac{U_1}{U_0}\right) + U_0 - U_1 + S_0 p\left(1 - \left(\frac{U_1}{U_0}\right)^{1-\chi_0}\right) \\ \frac{1}{R} &= U_1 + S_0 p\left(\frac{U_1}{U_0}\right)^{1-\chi_0} \end{aligned} \tag{25}$$

for U_1 and χ_0, then set $\chi_0 = T_{I/II}(p)$, which yields

$$T_{\text{I}/\text{II}}(p) = 1 - \frac{1}{RS_0 - 1}\ln\left(\frac{RS_0 p}{1 - RS_0(1-p)\mathrm{e}^{-RS_0+1}}\right). \tag{26}$$

The second threshold occurs when the epidemic wave by the initial strain A_0B_0 is blocked, $\mathcal{R}_0^{(1)} = 1$. To obtain the threshold value of χ_0 for which this occurs (which we denote $T_{II/III}(p)$), we solve

$$\mathcal{R}_0^{(1)} = R(S_0(1-p) + (1-\chi_0)S_0 p) = 1 \tag{27}$$

for χ_0 and set $\chi_0 = T_{II/III}(p)$ which yields

$$T_{II/III}(p) = \frac{RS_0 - 1}{RS_0 p}. \tag{28}$$

5.4 Vaccines distributed across targets

When we distribute vaccines across targets, there are two sets of sequences of antigenic changes of interest, $A_0B_0 \to A_1B_0 \to \cdots$ and $A_0B_0 \to A_0B_1 \to \cdots$ (recall that cross-protection is assumed to be limited). The optimal vaccination strategy, x^*, is to distribute vaccine doses so as to maximize protection against one of these sequences. Without loss of generality, focus upon the set of sequences in which the first antigenic change occurs at target A, that is, $A_0B_0 \to A_1B_0 \to \cdots$.

When we are considering epidemics limited by antigenic change, this means choosing $x = x^*$ to block the second epidemic wave by A_1B_0, that is, x^* satisfies $\mathcal{R}_0^{(2)} = 1$. Therefore we solve equation (20) with $n = 0$ for U_1, that is, we solve

$$0 = \frac{1}{R}\ln\left(\frac{U_1}{U_0}\right) + U_0 - U_1 + S_0 p\left(1 - \left(\frac{U_1}{U_0}\right)^{1-\chi_0}\right) \tag{29}$$

for U_1 and then use that value in

$$1 = R\left(U_1 + S_0 p\left(\frac{U_1}{U_0}\right)^{1-\chi_0}(x^* + (1-x^*)(1-\chi_0))\right) = \mathcal{R}_0^{(2)}, \tag{30}$$

to solve for x^*. Solving the second expression for x^* as a function of U_1 gives

$$x^* = \frac{1}{\chi_0}\left(\frac{1 - RU_1}{RS_0 p}\left(\frac{U_0}{U_1}\right)^{1-\chi_0} - 1 + \chi_0\right), \tag{31}$$

while the first equation can be numerically solved for U_1 (there is no analytic solution of U_1 in this case). Of course if x^* is a solution then so to is $1 - x^*$.

If instead we are considering epidemics with unlimited antigenic change (and so limited by infection-acquired immunity), then we want to choose x^* to satisfy $S_2^{(A_1B_0)} = 1/R$. Therefore we solve

$$\begin{aligned}
0 &= \frac{1}{R}\ln\left(\frac{U_1}{U_0}\right) + U_0 - U_1 + S_0 p\left(1 - \left(\frac{U_1}{U_0}\right)^{1-\chi_0}\right) \\
0 &= \frac{1}{R}\ln\left(\frac{U_2}{U_1}\right) + U_1 - U_2 + S_0 p\left(\frac{U_1}{U_0}\right)^{1-\chi_0}\left(1 - x^*\frac{U_2}{U_1} - (1-x^*)\left(\frac{U_2}{U_1}\right)^{1-\chi_0}\right) \\
\frac{1}{R} &= U_2 + S_0 p\left(\frac{U_1}{U_0}\right)^{1-\chi_0}\left(x^*\frac{U_2}{U_1} + (1-x^*)\left(\frac{U_2}{U_1}\right)^{1-\chi_0}\right) = S_2^{(A_1B_0)}
\end{aligned} \tag{32}$$

for x^*, U_1, and U_2. Note that if we are in case III, that is, $\chi_0 > T_{II/III}(p)$, then $U_1 = U_0 = S_0(1-p)$, and we only need to solve for x^* and U_2.

5.5 Vaccines distributed across variants

When we distribute vaccines across variants, the two scenarios of evolutionary limitations are slightly different. First, for epidemics limited by antigenic change, there are two candidate solutions, $y_A = y_{A_0}$, in which we maximize protection against the primary variant at target A, and $y_A = y_{A_1}$, in which we maximize protection against the secondary variant at target A. Specifically,

$$y_{A_0} = \min\left(1, \frac{RS_0 - 1}{RS_0 p\chi_0}\right), \tag{33}$$

that is, in case II, $y_{A_0} = 1$, while in case III, since $U_1 = U_0$, y_{A_0} is the solution of

$$\mathcal{R}_0^{(1)} = R\left(S_0(1-p) + (1-\chi_0)S_0 p y_{A_0} + S_0 p(1 - y_{A_0})\right) = 1. \tag{34}$$

When we maximize protection against the secondary variant, $y_A = y_{A_1}$, this means choosing y_{A_1} to satisfy $\mathcal{R}_0^{(2)} = 1$, given the next strain is A_1B_0. That is, we solve

$$\begin{aligned} 0 &= \frac{1}{R}\ln\left(\frac{U_1}{U_0}\right) + U_0 - U_1 + S_0 p y_{A_1}\left(1 - \left(\frac{U_1}{U_0}\right)^{1-\chi_0}\right) + S_0 p(1 - y_{A_1})\left(1 - \frac{U_1}{U_0}\right) \\ 1 &= R\left(U_1 + S_0 p y_{A_1}\left(\frac{U_1}{U_0}\right)^{1-\chi_0} + (1-\chi_0) S_0 p (1 - y_{A_1})\frac{U_1}{U_0}\right) = \mathcal{R}_0^{(2)} \end{aligned} \tag{35}$$

for y_{A_1} and U_1. Which of y_{A_1} or y_{A_0} performs the best will depend upon the values of ω and R.

Second, for epidemics not limited by antigenic change (and so limited by infection-acquired immunity), we can always choose y_A to ensure $\mathbb{E}[S_{\text{total}}] = 1/R$. First, we can choose $y_A = y^*$ such that after the first epidemic $S_1 = 1/R$. To do so, we solve

$$\begin{aligned} 0 &= \frac{1}{R}\ln\left(\frac{U_1}{U_0}\right) + U_0 - U_1 + S_0 p y^*\left(1 - \left(\frac{U_1}{U_0}\right)^{1-\chi_0}\right) + S_0 p(1 - y^*)\left(1 - \frac{U_1}{U_0}\right) \\ \frac{1}{R} &= U_1 + S_0 p y^*\left(\frac{U_1}{U_0}\right)^{1-\chi_0} + S_0 p(1 - y^*)\frac{U_1}{U_0} \end{aligned} \tag{36}$$

for U_1 and y^*; doing so gives

$$y^* = \frac{1 - RS_0 e^{-RS_0+1}}{RS_0 p e^{-RS_0+1}\left(e^{\chi_0(RS_0-1)} - 1\right)}. \tag{37}$$

Second, we can choose $y_A = y^\bullet$ such that $S_2 = 1/R$, if we assume the first antigenic change is A_1B_0 (note that this is justified since $U_1 = U_2 = \cdots = U_j$ for A_0B_j, and so we can ignore all antigenic changes to target B). Therefore, we solve

$$\begin{aligned} 0 &= \frac{1}{R}\ln\left(\frac{U_1}{U_0}\right) + U_0 - U_1 + S_0 p y^\bullet\left(1 - \left(\frac{U_1}{U_0}\right)^{1-\chi_0}\right) + S_0 p(1 - y^\bullet)\left(1 - \frac{U_1}{U_0}\right) \\ 0 &= \frac{1}{R}\ln\left(\frac{U_2}{U_1}\right) + U_1 - U_2 + S_0 p y^\bullet\left(\frac{U_1}{U_0}\right)^{1-\chi_0}\left(1 - \frac{U_2}{U_1}\right) + S_0 p(1 - y^\bullet)\frac{U_1}{U_0}\left(1 - \left(\frac{U_2}{U_1}\right)^{1-\chi_0}\right) \\ \frac{1}{R} &= U_2 + S_0 p y^\bullet\left(\frac{U_1}{U_0}\right)^{1-\chi_0}\frac{U_2}{U_1} + S_0 p(1 - y^\bullet)\frac{U_1}{U_0}\left(\frac{U_2}{U_1}\right)^{1-\chi_0} \end{aligned}$$

for U_1, U_2 and $y^\bullet$.

5.6 Vaccines distributed across targets and variants simultaneously

Finally, consider a vaccine which can be distributed across both targets and variants, but distribution across variants must be the same across targets. That is, we are free to vary x and $y_A = y_B = y$. Here we focus upon the situation in which antigenic change is limited, since we know from our previous results that when antigenic change is not limiting, we can always reach the optimum $\mathbb{E}[S_{\text{final}}] = 1/R$ by varying between variants alone.

The results are much as we would expect. When the probability of antigenic change is low (ω small), it is best to distribute between targets while focusing upon the primary antigen, that is, choose $y = 1$ and $x = x^*$ where x^* is provided in equation (31). As the likelihood of antigenic change increases, however, it becomes optimal to distribute doses between variants, that is, $y < 1$, with doses equally allocated between targets, $x = 1/2$. Specifically, if allocating between variants is the preferred strategy (and so $x = 1/2$), then the optimal choice of y will block the next epidemic wave by either strain A_1B_0 or A_0B_1, that is, y satisfies $\mathcal{R}_0^{(2)} = 1$ (since $x = 1/2$, $\mathcal{R}_0^{(2)}$ is not sensitive to which strain emerges). Therefore we solve

$$0 = \frac{1}{R}\ln\left(\frac{U_1}{U_0}\right) + U_0 - U_1 + S_0 p y\left(1 - \left(\frac{U_1}{U_0}\right)^{1-\chi_0}\right) + S_0 p(1 - y)\left(1 - \frac{U_1}{U_0}\right) \tag{38}$$

$$1 = R\left(U_1 + (1-\chi_0)\frac{S_0 p y}{2}\left(\frac{U_1}{U_0}\right)^{1-\chi_0} + \frac{S_0 p y}{2}\left(\frac{U_1}{U_0}\right)^{1-\chi_0} + (1-\chi_0)\frac{S_0 p(1-y)}{2}\frac{U_1}{U_0} + \frac{S_0 p(1-y)}{2}\frac{U_1}{U_0}\right) = \mathcal{R}_0^{(2)} \tag{39}$$

for U_1 and y (note the 1/2 multiplier is because it is equally likely that strain A_1B_0 or A_0B_1 will emerge). This can be done with a computer algebra package, but as the answer can only be expressed in terms of the Lambert W function, we do not show it here. Note that as we approach the threshold between case I and II, that is, $T_{I/II}(p)$, the solution of (38) in terms of y will exceed 1; in this case the optimal solution is $y = 1$ and we resort to varying x (i.e., choosing x^* from equation (31)).

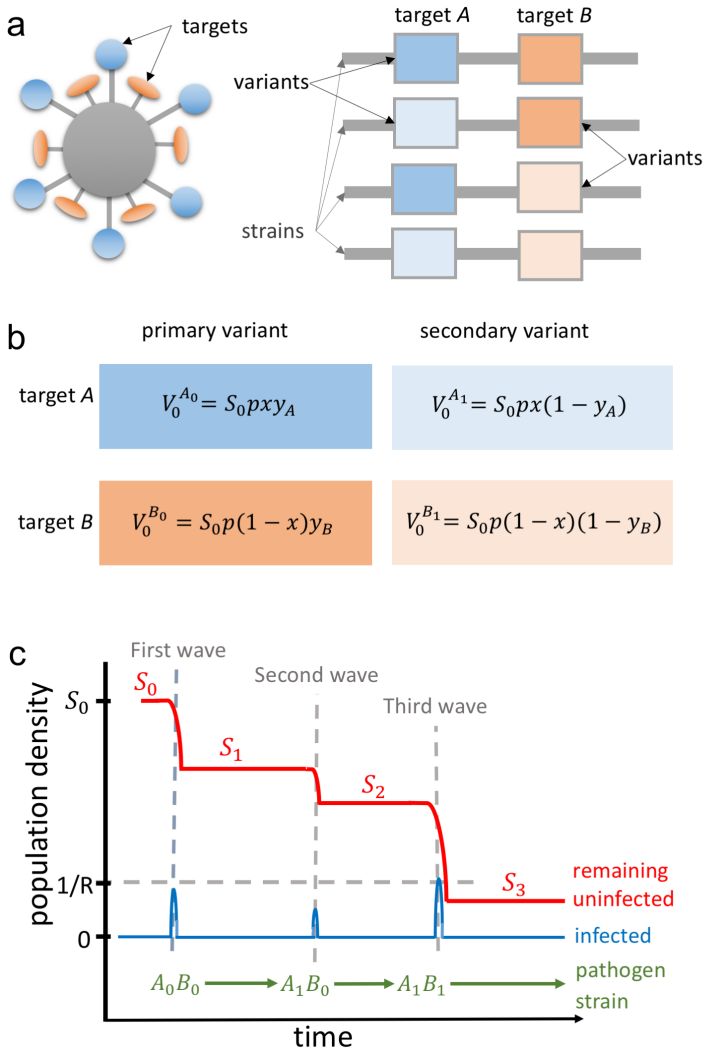

Figure 1: Model schematics. Subplot **a** illustrates assumptions about pathogen structure (left) and genome (right; each line represents a unique pathogen genome, or 'strain'). We use 'targets' to describe different surface proteins (or, equally, different epitopes on the same surface protein). We use 'variants' to capture genetically (and more crucially, antigenically) distinct versions of a given antigenic target. Subplot **b** gives the density of individuals vaccinated against different pathogen strains. A fraction p of all individuals in a population, S_0, receive a vaccine. Vaccine doses are distributed across targets (a fraction, x, focus on target A, while $1-x$ focus on target B) and variants (a fraction, y_A or y_B, focus on the primary variant of the given target). Subplot **c** illustrates the typical dynamics of our model, where S_n denotes the density of susceptible individuals (red curve) remaining after the nth wave of the epidemic. The blue curve captures our assumption that each wave reaches its epidemiological conclusion before another can begin, if the density of susceptibles is above $1/R$. One possible epidemic sequence of strains is shown in green.

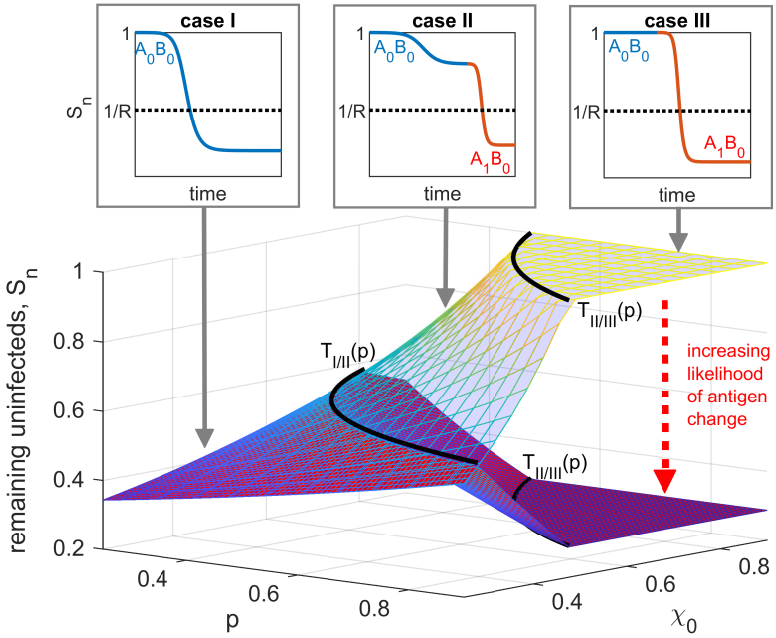

Figure 2: The three qualitatively different epidemic regimes under conventional vaccination. In case I, a single epidemic by the initial strain A_0B_0 occurs. In case II, there can be two epidemics, one by the initial strain, and one by the strain A_iB_j (here assumed to be A_1B_0). In case III, the initial strain is blocked and a single epidemic wave occurs by a secondary (antigenically novel) strain (again, assumed here to be A_1B_0). Here we show the outcome in terms of the remaining uninfected individuals, S_n, as we vary vaccine coverage, p, and vaccine strength, χ_0, where the upper translucent surface is what occurs with no antigenic change, whereas the lower surface is what occurs when antigenic change is a certainty. The curves delineating the thresholds between cases, $T_{I/II}(p)$ and $T_{II/III}(p)$, are shown for reference, while the insets show examples of the epidemic dynamics for each case.

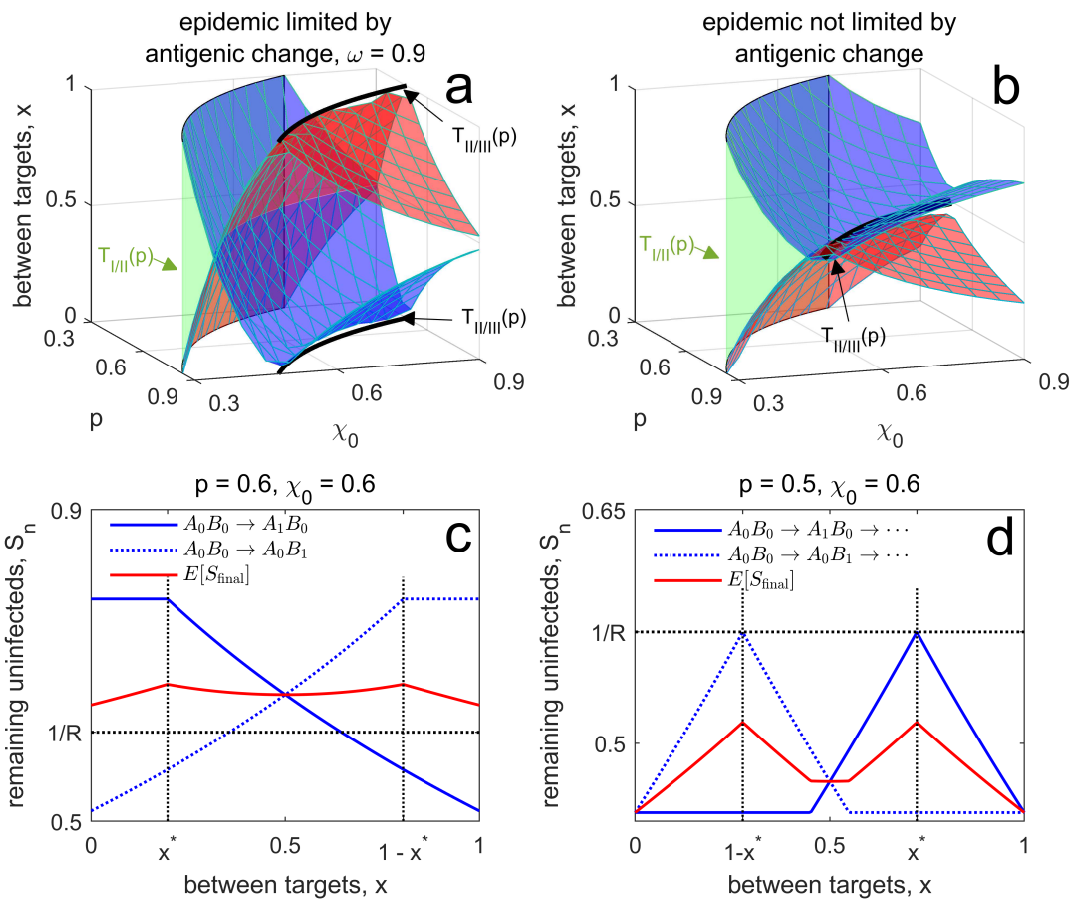

Figure 3: Optimal distribution of vaccines between targets when antigenic change is either limiting (with probability $\omega = 0.9$, subplots **a**,**c**) or is not limiting (subplots **b**,**d**). Subplots **a**,**b** show the optimal distribution as vaccine coverage, p, and strength, χ_0, vary. Note that when x^* is optimal (blue surface), $1 - x^*$ is also optimal (red surface). The thresholds $T_{I/II}(p)$ and $T_{II/III}(p)$ are also included for reference; beyond the green surface, vaccine efficacy is sufficiently low that evolution has no effect on the epidemic, and any distribution of vaccines between targets will produce the same outcome (for a given p and χ_0). Subplots **c** and **d** reveal the logic. Consider epidemics limited by antigenic change (subplot **c**). When x is small, most vaccine doses are distributed against target B. Consequently, antigenic change at target A can only slightly reduce vaccine protection, and so the potential epidemic wave by strain A_1B_0 will be blocked (solid blue line). As x increases to x^*, the potential epidemic wave by A_1B_0 remains blocked, while protection against strain A_0B_1 increases, reducing the size of the potential epidemic wave by A_0B_1 (dotted blue line). At x^*, $\mathcal{R}_0^{(2)} = 1$ for strain A_1B_0, and so although any further increases to x will increase protection against A_0B_1, it will do so by reducing protection against strain A_1B_0. Therefore, x^* is optimal, i.e., it maximizes the density of individuals who remain uninfected on average ($\mathbb{E}[S_{\text{final}}]$, red line). A similar argument holds if we focus upon the sequence $A_0B_0 \to A_0B_1$ and the optimal strategy $1 - x^*$. Next, consider epidemics not limited by antigenic change (subplot **d**); as before, focus upon the sequence $A_0B_0 \to A_1B_0 \to \cdots$. When x is small, although the epidemic wave by strain A_1B_0 will be blocked, eventually there will be antigenic change at target B. This new strain, say A_jB_1 with $j \geq 1$, will have escaped all vaccine protection (since antigenic change is cumulative and cross-protection is limited), and so will cause a large epidemic and substantial overshoot. As x increases, eventually $\mathcal{R}_0^{(2)} > 1$ for strain A_1B_0, that is, strain A_1B_0 will cause a (small) epidemic wave. In turn, this will deplete the available susceptibles and so reduce the size of any subsequent epidemic wave by strain A_jB_1, limiting overshoot. When $x = x^*$, vaccine protection against strain A_1B_0 is sufficiently weakened such that following an epidemic wave by strain A_1B_0, $S_{\text{final}} = 1/R$. Any further increase to x will reduce protection against A_1B_0 such that it causes overshoot. Similar logic follows for the sequence $A_0B_0 \to A_0B_1 \to \cdots$ and the optimal solution $1 - x^*$.

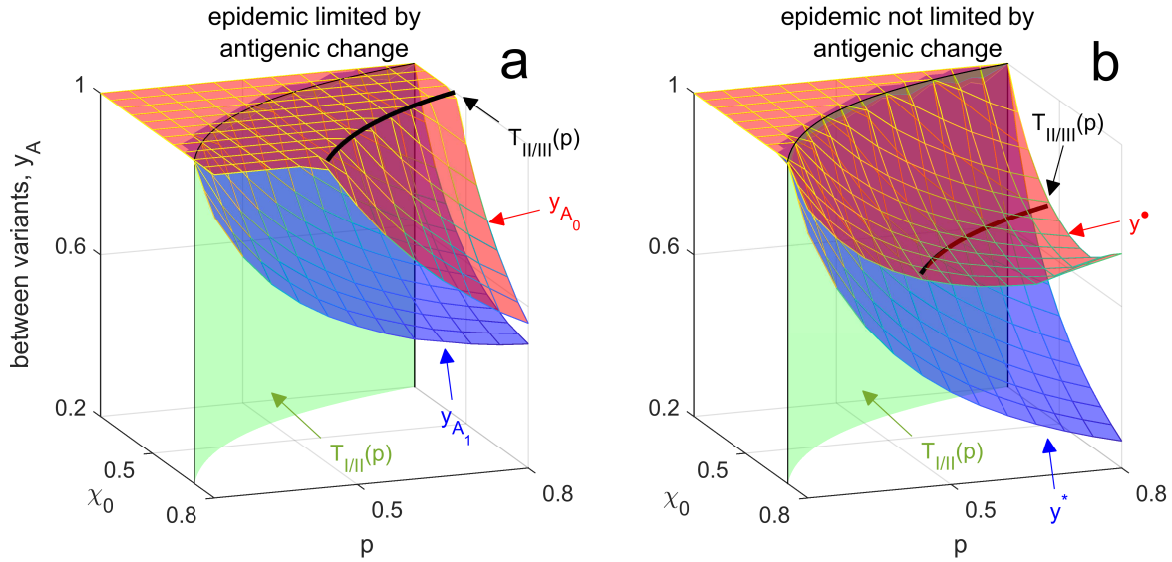

Figure 4: Optimal distribution of vaccines between variants when antigenic change is either limiting (subplot **a**) or is not limiting (subplot **b**). In subplot **a**, y_{A_0} and y_{A_1} represent the optimal strategy protecting against either the primary (y_{A_0}) or secondary (y_{A_1}) variant at target A; as the likelihood of antigenic change increases, then the likelihood y_{A_1} is the optimal strategy increases. In subplot **b**, the red and blue surface represent the two optimal strategies, y^* and $y^\bullet$ when the epidemic is limited by infection-acquired immunity. Both satisfy $\mathbb{E}[S_{\text{final}}] = 1/R$, however y^* satisfies $S_1 = 1/R$, while $y^\bullet$ requires at least one antigen change, which would result in more than one epidemic peak and overall slower spread in the host population. As in Figure 3, beyond the green surface, vaccine efficacy is sufficiently low that evolution has no effect on the epidemic outcome, so the best vaccination strategy is to focus on the primary variant.

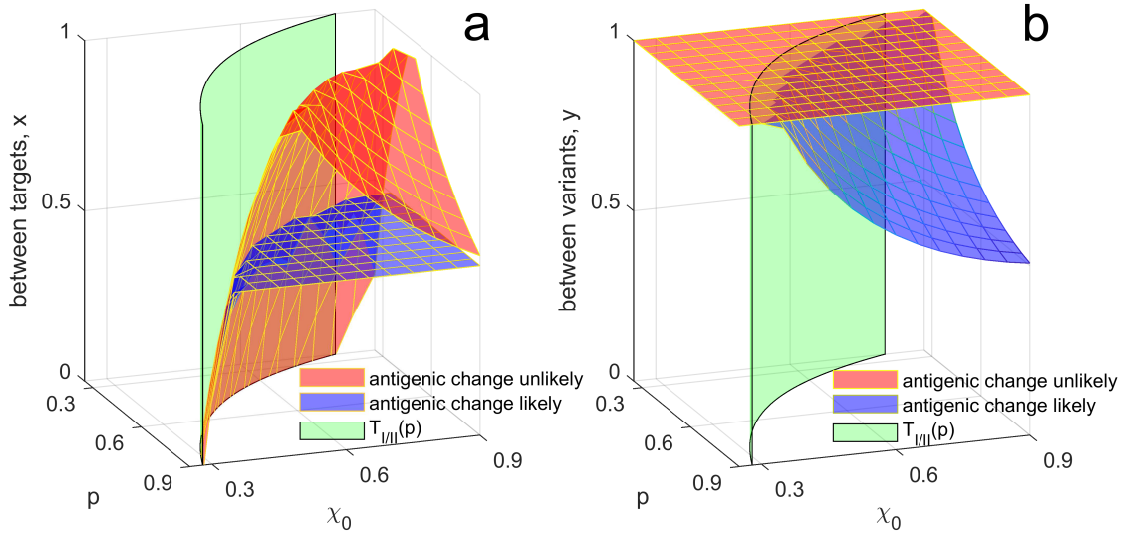

Figure 5: Optimal distribution of vaccines between targets (panel **a**) and variants (panel **b**) under limited antigenic change. In both panels, the red surface corresponds to the optimal distribution when antigenic change is unlikely (i.e., ω is small) while the blue surface corresponds to the optimal distribution when antigenic change is likely (i.e., ω approaches 1). As before, beyond the green surface, vaccine efficacy is sufficiently low that evolution has no effect on the epidemic outcome. In general, when antigenic change is unlikely (red surfaces) we should distribute between targets and protect against primary variant ($y = 1$), whereas when antigenic change is likely (blue surfaces) we should distribute between variants with doses evenly allocated between targets ($x = 1/2$). Note that for visual clarity in panel **a**, we have only shown one possible optimal solution; but if x is optimal, then so is $1 - x$. See Sup. Info. 5.6 for full derivation.