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Working paper

Complex vaccination strategies prevent the emergence of vaccine resistance

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Table of contents

Abstract 1

1. Introduction 2
2. Methods 4
3. Results 11
4. Discussion 28
5. Supplementary Materials 37
6. Bibliography 45

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Complex vaccination strategies prevent the emergence of vaccine resistance

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Vaccination is the most effective tool to control infectious diseases. However, the evolution of vaccine resistance, exemplified by vaccine-resistance in SARS-CoV-2, remains a concern. Here, we model complex vaccination strategies against a pathogen with multiple epitopes - molecules targeted by the vaccine. We found that a vaccine targeting one epitope was ineffective in preventing vaccine resistance. Vaccine resistance in highly infectious pathogens was prevented by the full-epitope vaccine, one targeting all available epitopes, but only when the rate of pathogen evolution was low. Strikingly, a bet-hedging strategy of random administration of vaccines targeting different epitopes was the most effective in preventing vaccine resistance in pathogens with low rate of infection and high rate of evolution. Thus, complex vaccination strategies, when biologically feasible, may be preferable to the currently used single-vaccine approaches for long-term control of disease outbreaks, especially when applied to livestock with near 100% vaccination rates.

Introduction

The COVID-19 pandemic raised public awareness to the dangers and epidemiological characteristics of infectious disease. The obvious danger is that of a new disease emerging in the human population, livestock or crops impacting public health and the global food chain supply. Our experience with COVID-19 also demonstrated the danger of the emergent disease to evolve, changing our ability to contain the spread of the disease through increase of infectivity (Y. Wang et al. 2022) and evolving vaccine resistance (Willett et al. 2022; Garcia-Beltran et al. 2021). An interesting aspect of SARS-CoV-2 is its propensity for rapid evolution driven by the host immune response in immunocompromised individuals in the course of very long infection periods (Choi et al. 2020; Kemp et al. 2021; Sonnleitner et al. 2022). In such cases, the SARS-CoV-2 virus has the time to adapt to the relatively weak pressure of the compromised immune system with the resulting adapted variants posing a greater threat to the general population.

The ideal goal when dealing with an emergent disease is eradication, as has been achieved in some cases ("History of Measles | CDC" n.d.; Ochmann and Roser 2018; The Lancet 2019; Breman and Arita 1980). The second best option is to control the pathogen's spread and evolution that would allow it to avoid these control mechanisms. Widespread use of a vaccine allows the population to achieve herd immunity, reducing the rate of spread of the virus ($R_0 < 1$). However, the COVID-19 pandemic demonstrated that even the goal of containment may not be easily achieved (X. Zhang et al. 2022). SARS-CoV-2 rapidly evolved variants with a much higher infectivity (Soh et al. 2021) and showed a tendency to avoid vaccines (Planas et al. 2022; McCallum et al. 2021), both of these factors may have been driven by evolution of SARS-CoV-2 in immunocompromised patients (Sonnleitner et al. 2022).

A potential solution for the containment of pathogen evolution is a multi-epitope or mosaic vaccine (Kennedy and Read 2017; Barouch et al. 2018; Corey and McElrath 2010; Hou et al.

2019; Suhrbier 1997). Such a vaccine causes the immune system to develop antibodies against different epitopes, which are molecular targets for the immune system, frequently a part of a protein displayed on the surface of the pathogen. Their application to SARS-CoV-2 by selection of several epitopes in the Spike protein has been considered (Kar et al. 2020; J. Zhang et al. 2022) but not implemented. In theory, a vaccine that targets several epitopes at once reduces the probability of evolution of vaccine resistance (Kennedy and Read 2017) allowing to achieve the second best outcome - long-term control of the pathogen spread in the population. Furthermore, a more complex, mosaic strategy was proposed by McLeod et. al. (McLeod, Wahl, and Mideo 2021), whereby a combination of different vaccines targeting a different set of epitopes can be used in the population reducing the rate of spread of vaccine resistance.

Barring issues of the host immune response, the hypothesis that a vaccine that simultaneously targets several epitopes is better than a vaccine that targets just one seems logical. Specifically, when a multi-epitope vaccine is used, more mutations have to occur in the pathogen to evolve vaccine resistance, reducing the probability of such evolution (REX Consortium 2013; McLeod, Wahl, and Mideo 2021). On the other hand, simultaneous introduction of a vaccine against all epitopes may have a potential weakness. In the arms race between the pathogen and the immune system, massive vaccination of all individuals with a multi-epitope vaccine may be equivalent to showing all of the cards to the pathogen allowing it to simultaneously adapt to all of the epitopes presented in the vaccine and winning in the evolutionary arms race. This process may be faster if the evolution of the pathogen is accelerated by selection of the immune system in the same way as SARS-CoV-2 evolution in immunocompromised individuals (Sylvain Gandon and Day 2008; Sonnleitner et al. 2022).

Here, we consider a hypothetical model of pathogen evolution in a vaccinated population. We study the conditions under which the pathogen does not evolve vaccine resistance, in other words when the pathogen remains controlled or, in rare cases, is eradicated from the population.

We specifically focus on the efficacy of complex vaccination strategies with a combination of different vaccines targeting different epitopes to control the spread of the pathogen and to reduce the probability of evolving vaccine resistance.

Methods

Model Introduction

In our model we have an infinite population size with different states assigned to individuals. The state of an individual can be unvaccinated (S), unvaccinated and infected by a pathogen φ (SP_{φ}) and vaccinated by a specific vaccine of type σ (V_{σ}). For simplicity, we base our model on an epidemiological SIS-model with vaccination (Keeling and Rohani 2011) without a compartment of recovered individuals, therefore only vaccines provide immune memory against a pathogen. Further, some fraction of the population, hereby referred to as immunocompromised, experiences prolonged disease (I), they can be vaccinated (IV_{σ}) or vaccinated and infected ($IV_{\sigma}P_{\varphi}$). In the immunocompromised vaccinated and infected individuals the immune system can select for mutations in epitopes that have been displayed by the vaccine to the immune system. These mutations render the vaccine ineffective against the respective epitopes. We consider the probability of fixation of such vaccine-resistant variants in an immunocompromised individual and the probability of fixation of these variants in the entire population. We generally use the term fixation to signify fixation in the population and we specify cases when we talk about fixation of a variant in the body of one individual. We also consider a model when immunocompromised individuals are excluded but regular vaccinated individuals experience breakthrough infections and in these individuals the pathogen can evolve. In that case, the individual states are, as before, (S), (SP_{φ}), (V_{σ}) and with an additional state of vaccinated and infected ($V_{\sigma}P_{\varphi}$).

Epitopes

We consider the epidemiological and evolutionary dynamics of a pathogen with n epitopes, each epitope we denote as e_k, where k = {1,..,n}. We introduce vaccines that induce antibodies against these epitopes and we distinguish several different types of vaccines. A single-epitope vaccine targets one epitope. Multi-epitope vaccines create antibodies against several epitopes. A multi-epitope vaccine does not necessarily induce antibodies against all possible epitopes: this is achieved by a full-epitope vaccine, which is a unique case of the multi-epitope vaccine. We denote the number of epitopes per multi-epitope vaccine as its valence, m, where m is a discrete number ranging between {1,...n}. The binomial coefficient C(n,m), gives the number of possible types of multi-epitope vaccines with valence m. The broadest immune response will be induced by the full-epitope vaccine with valence m = n.

Pathogen Variants

In the model there are several pathogen variants, φ, where each variant carries a unique set of epitope states. We denote the variant φ as the set of epitopes all in the wildtype state. The initial condition starts with φ , the wild type pathogen that carries all epitopes $\varphi = \{e_1, \dots, e_n\}$, $|\varphi| = n$, where all e_k can be targeted by existing vaccines. New variants can emerge that carry mutations in some epitopes, rendering them undetectable by the memory immune response induced by the corresponding vaccines. The number of epitopes that acquired resistant mutations is denoted as i. A super resistant pathogen acquires mutations in all n epitopes (**Fig 1**), such that $\varphi=\varnothing$ and $|\varphi| = 0$. There exist $C(n, i)$ different pathogens with i mutated epitopes.

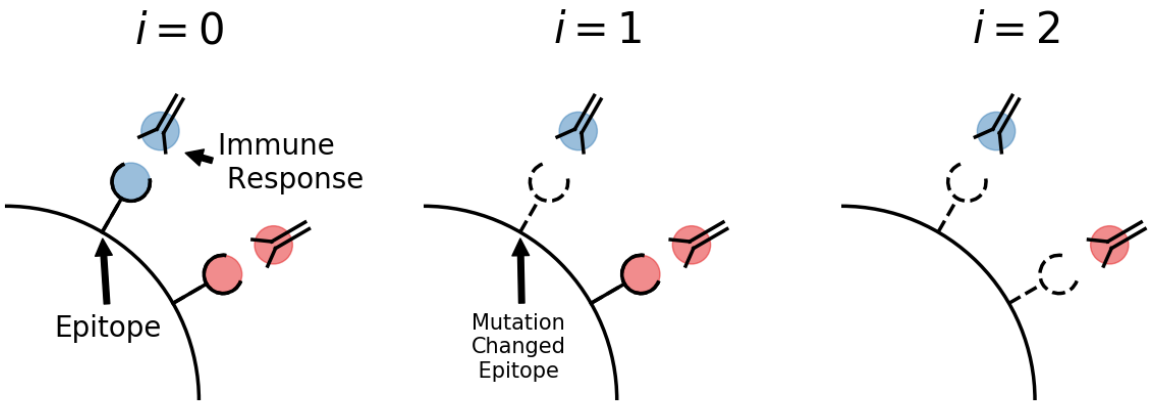


Fig. 1. An example of evolution of vaccine resistance in a pathogen with two epitopes. Starting with a pathogen displaying two epitopes (n = 2, coloured spheres), two of which are recognized by antibodies induced by a vaccine with a valence of 2 (m = 2, corresponding coloured antibodies). Mutations may render the epitopes unrecognizable by the vaccine-induced antibodies. If both of the epitopes acquire such mutations (farthest right drawing) the pathogen is no longer impaired by the vaccine.

Immunity

Ideal vaccines prevent all vaccinated individuals from becoming infected (S Gandon et al. 2001). However, a vaccine may be imperfect, and a small fraction of the vaccinated population (ρ) can get infected and infect others. The vaccinated infected individuals experience the disease for a time period τ. Under model conditions with immunocompromised individuals ρ is small and τ is large. When we model breakout infections with imperfect vaccines ρ is larger and τ is small. In our model an individual that received a vaccine containing the antigen e_k will be immune against every pathogen that carries the wild-type version of the epitope e_k. The immune state induced by a vaccine can be represented as the set of epitopes, against which immunity is generated σ = { …, e_k ,… }. In the baseline model described here, the size of σ equals the vaccine valence m.

Immunodynamics

To obtain estimates for the rate of pathogen evolution within a patient, we use a basic model of how the immune system reacts towards different pathogen variants. Drawing inspiration from basal formulations of immunodynamics (Nowak and May 2000) we denote the growth rates of the infected cell population x_φ with pathogen φ by the differential equation

$$dx_\varphi/dt = r\,x_\varphi - (a + z_\sigma(x_\varphi))x_\varphi \qquad \textbf{(Eq. 1)}$$

where $z_\sigma(x)$ corresponds to the strength of the immune response towards pathogen xφ if the immune type of the patient is σ, a is the baseline decay rate and r the growth rate of infected cells. If $r/(a + z_\sigma(x_\varphi)) < 0$, the population of infected cells cannot grow, ultimately leading to the clearance of the pathogen. This is the case for a healthy individual and an infection blocking vaccine. Individuals with prolonged diseased state will have $r/a > r/(a + z_\sigma(x_\varphi)) > 1$ and the pathogen can not be cleared from the patient's system. This provides the pathogen with an environment that can select for resistance mutations. Note, that the absence of an immune response $z_\sigma(x_\varphi) = 0$ as well as a strong immune system with $r < (a + z_\sigma(x_\varphi))$ will not provide such a selective environment (Kennedy and Read 2017; Bonhoeffer et al. 1997).

Evolution

We model evolution within a patient as a Bernoulli process, later referred to as the Bernoulli Model. Mutation, selection and fixation occur at once and immediately change the state of the whole pathogen population in a patient from one variant to another. At each day of the prolonged disease and with probability p a patient vaccinated against m epitopes and infected with a pathogen with i mutated epitopes can potentially change to a patient carrying a pathogen population with i+1 mutated epitopes. Starting with the wildtype, the probability to find a pathogen

with i mutated epitopes at time t, given a vaccine of valence m was administered, can be approximated with a Poisson distribution.

$p_m(i) = (pt)^i e^{-pt}/i!$ for i < m **(Eq. 2)**

If we ignore any adaptive immune response that goes beyond the epitopes that were targeted by the vaccine, we further set:

$$p_m(m) = \sum_{i=m}^{\infty} (p\tau)^i e^{-pt}/i!$$

$$p_m(i) = 0 \text{ for i> m} \quad \textbf{3)}$$

Note that this simple treatment of the evolutionary process ignores any differential fitness effects between variants. Employing more complicated evolutionary algorithms, such as the infinite population model of population genetics or the Wright-Fisher model with mutation and selection (Hartl and Clark 2006), generates similar qualitative results (See **Supp. Res. Sec. 2** and **Supp. Fig. 1**).

Vaccination Strategies

When multiple epitopes can be targeted, vaccines with different valences (number of targeted epitopes) can be created (**Fig. 2**). If a combination of different vaccines can be used, four different vaccination strategies become possible: 1) a full-epitope vaccination strategy, in which a fraction V_n of the population receives a vaccine of valence m = n, 2) a single-epitope vaccination strategy, in which a fraction V_1 of the total population receives one of n different vaccines with valence m = 1 at random (thus, a fraction V_1/n is vaccinated with one of the n vaccines), 3) an m-epitope vaccination scheme, in which each vaccinated individual in a fraction

V_m of the total population receives one of C(n,m) possible combinations of epitopes at random, and 4) a mixture of the strategies 1-3, confined by the normalization condition:

$$S + \sum_{m=1}^{n} V_m = 1$$

Under all strategies, a fraction S of the population remains unvaccinated, which ultimately is an important parameter for the observed dynamics in our model.

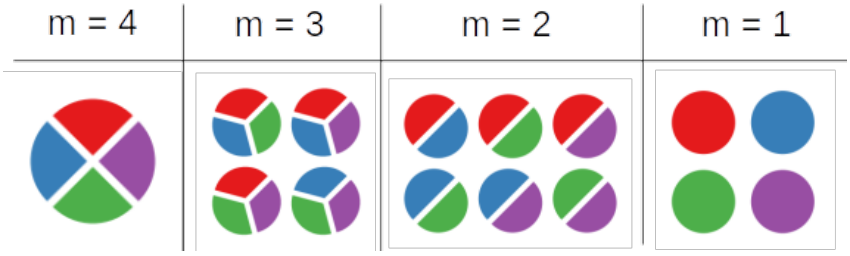


Fig. 2. Available multi-epitope vaccines for a vaccination procedure targeting n different epitopes. Different possible vaccines for the number of epitopes n = 4. Full-epitope strategy (left panel) with m = 4, where the population is inoculated with the n-epitope vaccine. A single-epitope strategy (right panel) with m = 1, where the population is inoculated with 4 different vaccines, each of them against a single epitope. The intermediate, m-epitope strategy (two middle panels) with inoculation by multiple vaccines, against 2 or 3 different epitopes. A mixed strategy can have vaccines containing a combination of all 4 different vaccine types (n-epitope, m-epitope and single-epitope).

Transmission

We assume a finite number of infected individuals N, out of which a fraction ρ, are infectious and the pathogen is subjected to selection by the immune system. Given one of $N\rho$ individuals, in which the pathogen can evolve, the probability $p_{trans}(i)$ that it will transmit a pathogen variant with i mutated epitopes is

$$p_{trans}(i,t) = \sum_{m=1}^{n} V_m \int_0^{\tau} p_m(i)\, dt\, /\tau \qquad \textbf{(Eq. 5)}$$

where p_m is a Poisson distribution as defined before and V_m the fraction of the population vaccinated with any m-epitope vaccine. The equation contains the cumulative distribution of $p_m(i)$ normalized by the disease duration, which corresponds to the probability of a variant i being transmitted at any time *t* from the beginning of the disease to its end at $t = \tau$.

All $N\rho$ individuals will have the same probability to transmit new variants. It is therefore a sufficient condition for pathogen fixation to occur as a result of at least one transmission attempt.

Fixation within the Population

To understand whether a pathogen variant is fixed in the population, we first derive the basic reproductive number for a pathogen with i mutations, R_i (see **Supp. Res. Sec. 1**),

$$R_i = R_0(1-(1-\rho)(\sum_{m=1}^{i} V_m\,(1-C(i,m)/C(n,m)\,) + \sum_{m=i+1}^{n} V_m)) \text{ . } \textbf{(Eq. 6)}$$

R_0 denotes the basic reproductive number, that is the expected number of secondary infections induced by the wildtype pathogen in an unvaccinated population, and ρ is the fraction of the vaccinated population that becomes diseased, thereby contributing to population level transmissibility. Finally, fixation in a population with a large population size, at equilibrium and random interactions (Patwa and Wahl 2008; Lieberman, Hauert, and Nowak 2005) is $1 - 1/R_i$.

Overall Probability of Pathogen Evolution

A new variant can potentially emerge in one of the $N\rho$ individuals with prolonged diseased state, be transmitted and ultimately be fixed in the population. The probability for the combined outcome is given by

$$p_{fix}(i) = p_{trans}(i)\,(1 - 1/R_i), \qquad \textbf{(Eq. 7)}$$

the probability p_{fix} that any variant will fix in the population in ρN transmission events

$$p_{fix} = 1 - \prod_{i=1}^{n} (1 - p_{fix}(i))^{\rho N} = 1 - exp(\rho N \sum_{i=1}^{n} log(1 - p_{fix}(i)) , \quad \textbf{(Eq. 8)}$$

which, among various properties of the pathogen, will also depend on the employed vaccination strategy.

Results

General description of the model

We considered a hypothetical pathogen with multiple (n) epitopes, which are targets of vaccines. Thus, a vaccine may target any number of m ={1… n} epitopes, with the full-epitope vaccine causing an effective immune response against all n epitopes. The effect of the vaccine epitopes is not cumulative, in other words a single-epitope vaccine is just as effective as the full-epitope vaccine against a pathogen with all n epitopes. The pathogen evolves by accumulating mutations that change the epitope in a way that renders the antibody against this epitope produced by any vaccine ineffective. For example, an individual vaccinated by a single-epitope vaccine with epitope e_3 can still be infected by a pathogen in which the epitope e_3 has been mutated. In the extreme case, a pathogen variant in which all epitopes were mutated can infect an individual vaccinated by any vaccine, including the full-epitope vaccine.

The population has a fraction of individuals (V) that are vaccinated by a random vaccine from the pool of vaccines that is being used. Initially we consider vaccines to be perfect so that all vaccinated non-immunocompromised individuals cannot be infected and transmit the pathogen. However, a small fraction of immunocompromised individuals (ρ) can get infected even

though they are vaccinated. When that happens, the pathogen in the body of the vaccinated and infected individual is subjected to mutation and selection **(Eq. 2-3)** driven by the vaccine-induced immune response. The new pathogen variant created by these intra-body processes has some probability to be transmitted to other susceptible individuals. The transmitted pathogen variant may become extinct or may spread in the population and eventually become fixed.

Model with 2 epitopes

We first consider the case of a pathogen carrying only two epitopes (n = 2). The population may be vaccinated by the full-epitope vaccine (m=2) or each individual may receive one of the two single-epitope vaccines (m =1). The complete set of strategies is determined by the parameter α, such that some proportion, α, of the vaccinated individuals receive one of the single-epitope vaccines, while the rest of the vaccinated individuals, 1- α, receive the full-epitope vaccine. When α is 0 or 1 the strategy is reduced to the simple cases, when α = 0 all administered vaccinations are full-epitope, while when α = 1 all administered vaccinations are single-epitope.

It is straightforward to evaluate the optimal strategy, α, that minimizes the fixation of vaccine resistance for a given set of parameters using **Eq. 8** (see the Model section). **Fig. 3a** shows the results of the optimal strategy as a function of the fraction of the vaccinated population, V. When more individuals are vaccinated, the probability of fixation is high regardless of the vaccine strategy, since vaccine administration coupled with high transmission selects for resistance (Rella et al. 2021; Chabas et al. 2018). In a pure m = 1 strategy (α = 1) the probability of fixation is largest at intermediate levels of vaccination (green line in **Fig. 3b**). However, under this strategy the probability of fixation of a resistant variant is much lower for higher values of V when most individuals are vaccinated with one of the two single-epitope vaccines because the rate of transmission is lower.

The full-epitope vaccine strategy (α = 0) corresponds to the optimal strategy when vaccination rates are below the herd immunity threshold ($V_H = 1 - 1/R_0$). For vaccination rates higher than the herd immunity threshold the full-epitope vaccine strategy loses its efficacy and becomes less effective than a mixed strategy due to the small probability of fixation of super-resistant variants. Thus, for V>V_H, the optimal mixing strategy α* outperforms the strategy relying on a single full-epitope vaccine (**Fig. 3b**).

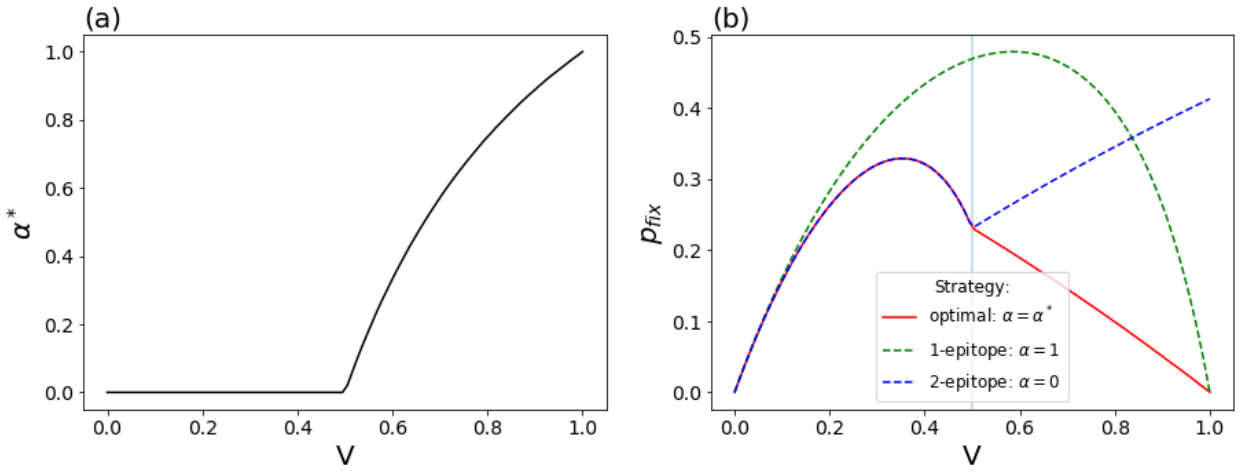


Fig. 3. Optimal vaccination strategy to prevent evolution of vaccine resistance in the 2 epitope scenario. **a**) The black line shows the optimal α*, share of individuals vaccinated with a single-epitope vaccine, as a function of the fraction of the vaccinated population V. **b**) The probability of fixation of a vaccine resistant variant (p_{fix}) as a function of V for three different vaccination strategies, full-epitope vaccination (blue line), single-epitope vaccination (green line) and for an optimal mixed vaccination strategy (red line). The full-epitope vaccination strategy matches the mixed optimal strategy below herd immunity (V= 1- 1/R_0 = 0.5), after which the mixed strategy is best (blue line). Other parameters for this figure were $\rho N = 10$, R_0 = 2, τ = 200, p = 10^{-3}.

The optimal strategy does not only depend on the vaccination rates, V, but is also strongly affected by the infectivity of the pathogen (R_0) and its persistence and evolution in the immunocompromised individual (τ, p, ρ). In **Fig. 4** we show the probability of establishment of a

vaccine resistant variant as a function of R_0 and the length of the disease duration τ of the immunocompromised individuals (we obtained similar results for p as we do for τ). For an optimal vaccine strategy (α^*), when R_0 and τ are small, vaccine resistance does not evolve. When both R_0 and τ are large, a pathogen is highly infectious and spends a long time in an immunocompromised individual making the fixation of the vaccine-resistant variant inevitable. For the intermediate ranges of R_0 and τ, an optimal vaccination strategy mostly does not depend on τ (**Fig. 4a**). The pure full-epitope strategy is only optimal for high levels of R_0. However, eve n the straightforward single-epitope strategy outperforms the full-epitope strategy when τ is large and R_0 is small. Across a large range of parameters a mixed optimal strategy outperforms both the straightforward single-epitope and the full-epitope strategies (**Fig. 4b**).

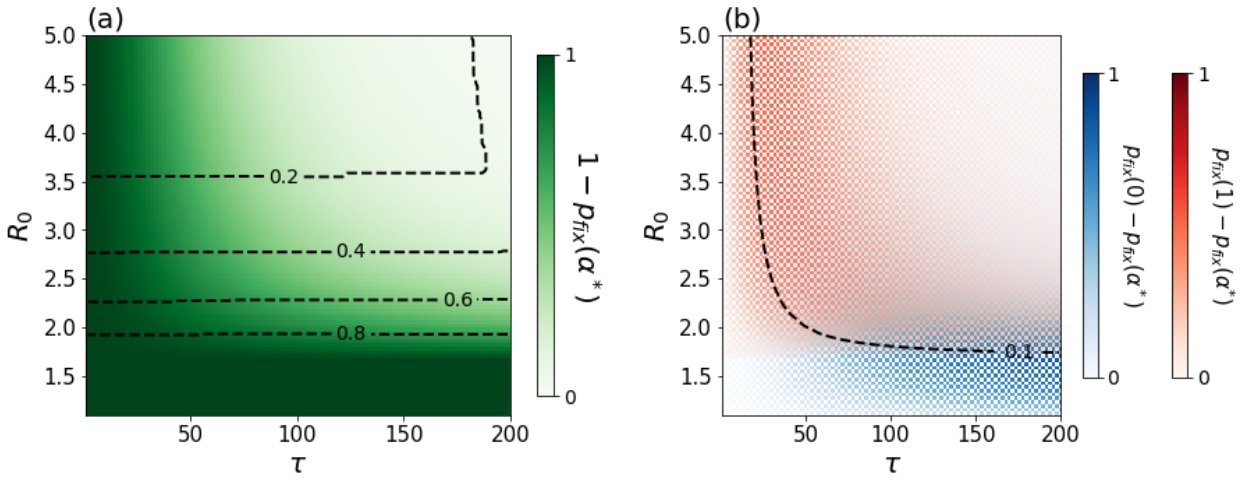


Fig. 4. Optimal vaccination strategy as a function of pathogen infectivity and disease duration in an immunocompromised individual. Share of vaccinated individuals in population, V = 0.8, initial number of immunocompromised individuals, ρN = 1, τ - disease duration of immunocompromised individuals, R_0 - transmissibility of the pathogen.**a**) The probability of preventing the fixation of a resistant variant (green) for optimal vaccination strategy (α^*) is shown. Dotted contour lines show the fraction of single-epitope vaccines (0.8, 0.6, 0.4 and 0.2) in the optimal solution α^* for different levels of R_0 and τ. **b**) Difference in the probability of fixation of a vaccine resistant strain for the optimal strategy α^* and the single-epitope vaccination strategy

(blue) and the full-epitope strategy (red). Parameter space above the contour line corresponds to the probability of fixation of a vaccine resistant variant above 10% for the optimal strategy α^* (see **a**).

Model with n-epitopes

The case with a large number of epitopes is more complex due to the combinatorially large number of mixed vaccination strategies. An optimal vaccination strategy may be similar to the one we observed in the 2-epitope case: a combination of multi-epitope vaccines with different valences m. Such a mixed use of multi-epitope vaccines may simultaneously reduce transmission at the population level and reduce the probability of fixation of vaccine-resistant variants in immunocompromised individuals. However, for a case with several epitopes such a strategy may be unrealistic to implement in practice and we show later that considering a mix of vaccines of different valences in the same vaccination campaign does not provide substantial advantages (**SFig. 2**). We therefore primarily consider a simpler set m-epitope mixed vaccination strategy, whereby all individuals are vaccinated by different vaccines with the same valence, m. Thus, individuals receive a vaccine against a different set of epitopes but always the same number of epitopes. Under such strategy the herd immunity threshold in the population is achieved through the vaccination of individuals by vaccines protecting against different pathogen variants (related to the concept of the diversity threshold introduced by (King and Lively 2012)). The n epitopes can be distributed to a total of C(n,m) groups of m epitopes per vaccine, thereby generating a high diversity of individuals inoculated by different vaccines, with different individuals protected against and susceptible to infection by different variants. We can define the m-epitope herd immunity threshold towards a variant with i mutant epitopes, by calculating the threshold for which $R_i \geq 1$ **(Eq. 6)**:

$$V_H(m,i) = (1 - 1/R_0)/(1 - C(i,m)/C(n,m)) \qquad \textbf{(Eq.9)}\ .$$

In an infinite population and at the limit of strong selection in the body of an individual vaccinated with an m-epitope, the fixation of a variant that carries all m resistance mutations, m = i is guaranteed. Therefore, we first looked at the efficacy of different vaccination strategies against vaccine-resistant variants when mutant epitopes were already present in the population. The variants spread faster in populations vaccinated with low-epitope vaccines, however, all vaccines were equally good at preventing the spread of the wildtype pathogen and all were equally ineffective against the super-resistant variant (**Fig. 5a**). Similarly, high-epitope vaccines lead to a lower herd immunity threshold when the population is infected with variants with an intermediate number of mutated epitopes (**Fig. 5b**).

If evolution within the immunocompromised individual is rapid, and consequently the probability of fixation of the super-resistant variant is high, the best vaccination strategy is the one that diversifies the immune response types in the population and uses the m-epitope vaccine strategy with optimal valence $m = [(n+1)/2]$, where [(n + 1)/2] denotes the floor function (**Fig. 5c,** probability of fixation derived from **Eq. 7** in the limit of m = i and conditioned on transmission $p_{trans}(m) = 1$). At the extreme cases of m = 0 no vaccines are administered, and when the vaccine is completely ineffective (m = n), the probability of fixation of the strain will be driven purely by genetic drift, as follows from **Eq. 6**, independent of V. For intermediate values of m, higher vaccination rates can greatly reduce, and even eliminate (when V = 1) the probability of fixation of the resistant variant (**Fig. 5c**). This is due to the different ways intermediate valence vaccines with 1 < m < n can be combined (**Fig. 2**), whereby the evolution of resistance towards one such combination of epitopes, does not imply resistance to all combinations. In the same limit, increasing the total number of epitopes n, the probability of fixation decreases until it saturates at the level of 1 - 1/(R_0(1-V)), which is the probability of fixation of a wildtype in a vaccinated population. . This threshold is approached fastest when m = $[(n+1)/2]$ (**Fig. 5d**).

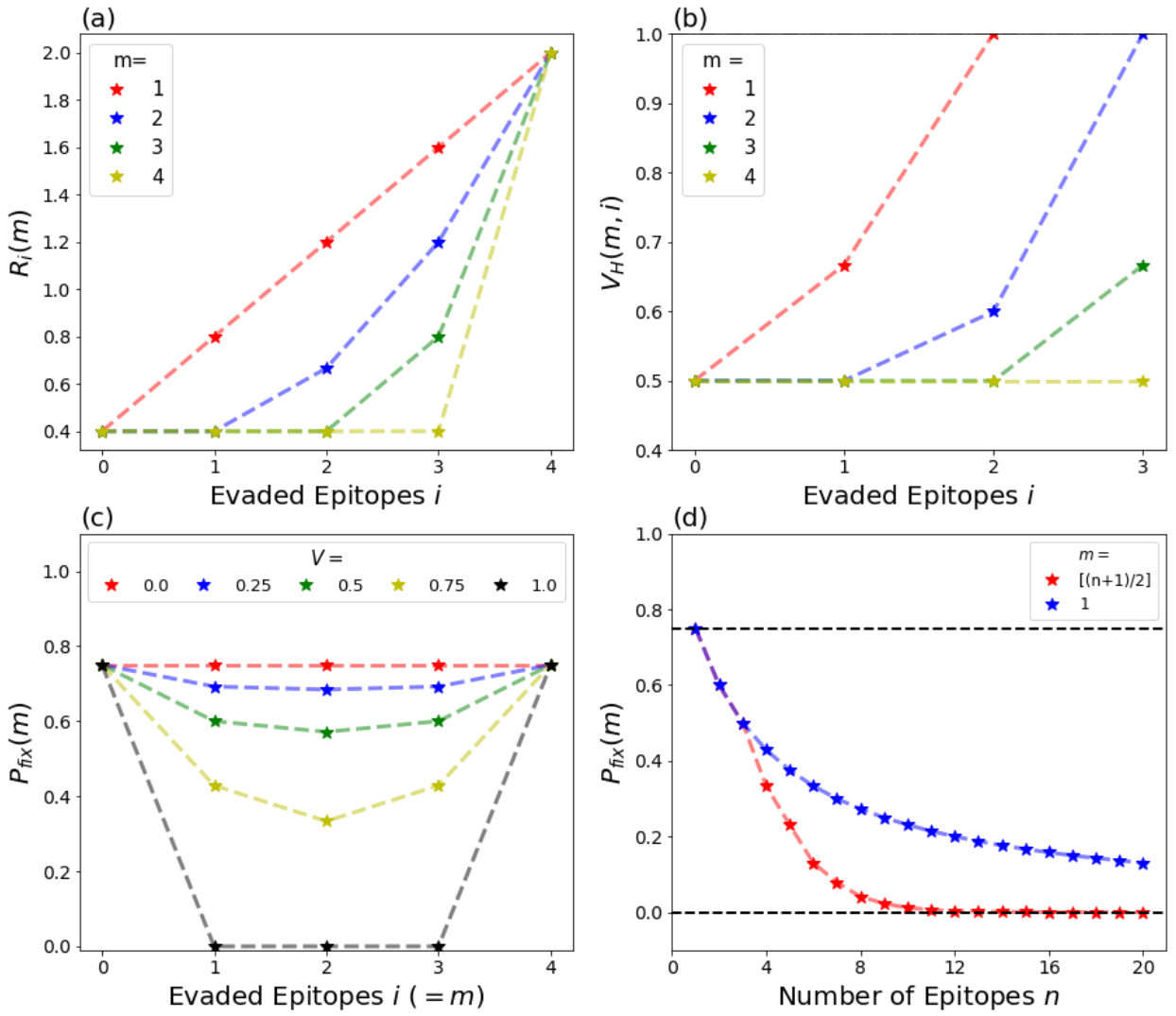


Fig. 5. Effect of different vaccine strategies in preventing the fixation of vaccination-resistant variants. a) The rate of spread of a pathogen with i mutations, indicated by the reproductive number $R_i(m)$, of variants carrying i mutant epitopes (X-axis) (**Eq. 6**) for different valencies m of the vaccination strategy (in color). R_0 = 2 for wild-type. **b**) The herd immunity threshold ($V_H(m,i)$), **Eq. 8**, for the number of mutant epitopes in the variant present in the population (X-axis). R_0 = 2 for wild type. **c**) The probability of fixation at the population level ($p_{fix}(m)$) of a pathogen resistant to one of the vaccines of valence m (X-axis), for different levels of vaccination in population (in color). **d**) Probability of fixation at the population level ($P_{fix}(m)$) of a pathogen that developed full resistance to one of the vaccines of valence m as a function of number of epitopes n: single-epitope vaccine, m=1 (blue) and optimal vaccine valence, $m_{n/2}$ = floor$[(n+1)/2]$ (red). For panels (a) and (d) V=0.75.

We then considered the model with only the wildtype pathogen was present initially in the population. As in the case of 2-epitopes, the optimal vaccination strategy in the case of n-epitopes depends on the properties of the pathogen and its evolution in the immunocompromised host. Having more than 2 epitopes has two effects on pathogen fixation as a function of population level transmissibility and within body evolution: 1) it is harder to evolve resistance to an n-epitope vaccine as it will take longer for variants with a mutation in all epitopes to fix and 2) m-epitope vaccines can be combined to create versatile combinations that reduce the probability of fixation in the population by diversifying the immune response of the individuals in the population. Thus, pathogens with faster rates of evolution in the immunocompromised individuals and higher rates of transmission may be contained by vaccines targeting m out of n epitopes. The best protection against pathogens with fast rate of evolution in the immunocompromised individuals is achieved when $m_{n/2} = [(n+1)/2]$, while highly transmissible diseases with low rates of evolution are best counteracted with a full-epitope vaccine (**Fig. 6**).

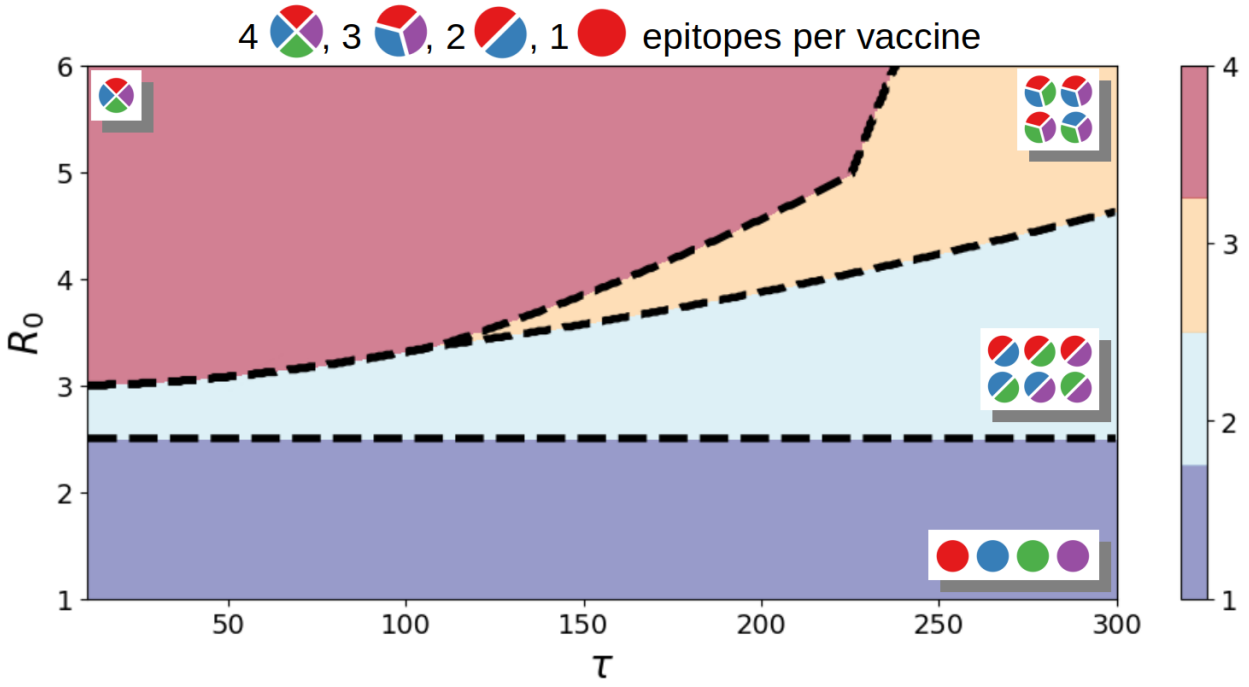


Fig. 6. The optimal choice of epitopes per vaccine (m, vaccine valence) as a function of disease duration τ and transmissibility R_0. Optimal choice of m* minimizes $p_{fix}(m^*)$, the probability of a pathogen fixation at the population level. For R_0 below ~2.5, single epitopes are sufficient, for low τ and high R_0 full-epitope vaccines provide the lowest probability of mutant fixation within the population. Intermediate, m-valence vaccine strategies are best for other values of τ and R_0. Importantly, there are areas in which all vaccine strategies have approximately equal efficacy, either equally high for low τ and R_0 or equally low for high τ and R_0 (see **Fig. 7**).

When R_0 and τ are high, no vaccination strategy prevents the fixation of a resistant variant (**Fig. 7a**). The benefits of optimal vaccination strategies are apparent only within certain ranges of R_0 and τ parameters. Specifically, the optimal strategy is substantially better than the single-epitope vaccine when R_0 is high and τ is low and better than the full-epitope vaccine when R_0 is low and τ is high (**Fig. 7b**). Any vaccination strategy contains pathogen spread when both R_0 and τ are low (**Fig. 7b**).

For many parameter combinations the optimal vaccine strategy may not be very different from other strategies. Therefore, we determined the near-optimal scenarios with the fewest epitopes per vaccine (the minimal valence strategy) and the near-optimal scenario with the most epitopes per vaccine (the maximum valence strategy), that result in the probability of fixation of a mutated pathogen within 10% of the optimal vaccination strategy m*, $p_{fix}(m) < p_{fix}(m^*) + 0.1$. For the minimal strategy a single-epitope vaccine was efficient for low values of R_0 (**Fig. 7d**) and a higher valence vaccine was always as good as a single-epitope vaccine (**Fig. 7c**). For the maximal valence strategy, the full-epitope approach was efficient when R_0 was high (**Fig. 7d,7c**). For a very specific range of R_0 values, around 2.5, a 2-valent vaccine strategy was always the optimal one (**Fig. 7d,7c**). The efficacy of the optimal vaccination strategy was higher when the number of epitopes in the pathogen was high (**Fig. 7e**) and when the population had more vaccinated individuals (**Fig. 7f**).

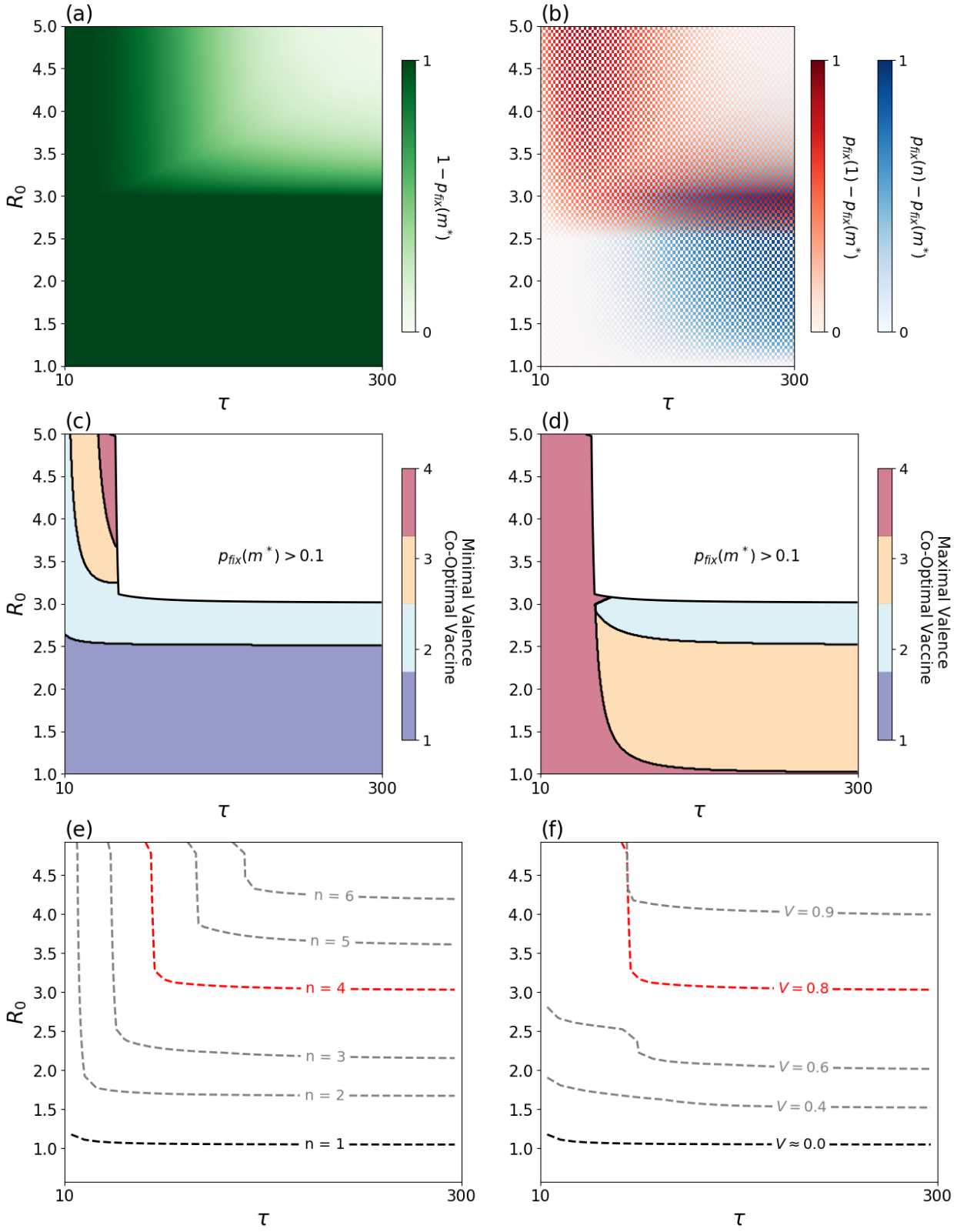

(a)
(b)
(c)
(d)
(e)
(f)
R_0
τ
$1 - p_{fix}(m^*)$
$p_{fix}(1) - p_{fix}(m^*)$
$p_{fix}(n) - p_{fix}(m^*)$
$p_{fix}(m^*) > 0.1$
Minimal Valence Co-Optimal Vaccine
Maximal Valence Co-Optimal Vaccine
n = 6
n = 5
n = 4
n = 3
n = 2
n = 1
$V = 0.9$
$V = 0.8$
$V = 0.6$
$V = 0.4$
$V \approx 0.0$

Fig. 7. Optimal vaccination strategies countering a 4-epitope pathogen. a) The probability of preventing the fixation of a resistant variant (green) when the optimal vaccination strategy was applied, for different disease duration, τ, and rate of spread, R_0. **b**) The difference between the optimal vaccination strategy and the single-valence vaccine strategy (red) and the full-epitope vaccine strategy (blue). In the overlap region the optimal strategy outperforms both the single-valence and the full-valence vaccine strategies. The near-optimal minimal (**c**) and near-optimal maximal (**d**) vaccination strategy. Coloured regions define areas where the different strategies were minimally (**c**) or maximally (**d**) near-optimal. The area in white shows the region where the optimal vaccine strategy has a lower than 90% chance to prevent the fixation of a resistant strain ($p_{fix}(m^*) > 0.1$). The same threshold, $p_{fix}(m^*) = 0.1$, is shown as a function of n, the number of epitopes (**e**) , for V = 0.8, and (**f**) as a function of V, with n = 4 . For all figures, p = 0.02.

Imperfect vaccine model

Not all pathogens lead to the same type of evolution in immunocompromised individuals as we see in SARS-CoV-2. Similarly, as observed in SARS-CoV-2, vaccines may not be 100% effective in preventing transmission, so they can be imperfect (Sylvain Gandon et al. 2003; S Gandon et al. 2001; Kissler et al. 2021). Thus, we used our model to study the optimal vaccination strategy without immunocompromised individuals, but with imperfect vaccines. Under this scenario vaccinated individuals have a chance (ρ) to get infected and have a short period of infection during which they can transmit the virus to others. The same principle of evolution in the vaccinated but infected individuals as in the immunocompromised individuals was applied. Broadly speaking, only a few immunocompromised individuals ($\rho N \sim 1$) were in the population and the pathogen had a substantial time (τ) in these immunocompromised hosts. With imperfect vaccines the time the pathogen spends evolving in a vaccinated individual is short, however, depending on the degree of imperfection of the vaccine, the number of infected vaccinated individuals in which the pathogen evolves can be large.

Considering the 2-epitope scenario, when the vaccine is completely ineffective, $\rho > 0.5$, it does not matter which vaccine strategy is employed because the probability of fixation of a resistant variant will be high. By contrast, when the imperfection of the vaccines is small the optimal strategy greatly reduces the probability of fixation of resistant variants (**Fig. 8**). The admixture of fill-epitope (2-epitope in this case) vaccines has a strong effect even for very small values of ρ (**Fig. 8b**) even though for these small values of ρ the share of 2-epitope vaccine admixture into the optimal vaccine mix is low (**Fig. 8a**). Thus, when breakout infections are rare (low values of ρ) the best strategy is close to a single-epitope strategy and requires administering only a small number of full-epitope vaccines in the population but following a pure single-epitope strategy even when breakout infections are rare almost certainly will lead to the fixation of a resistant strain (**Fig 8b**). The reason for this is because mixing a small fraction of a full-epitope into a population otherwise vaccinated with single-epitopes diversifies the population and pushes the herd immunity threshold below 1. This radically decreases the probability of fixation if the number of transmission attempts is high, as in this case ($N = 10^5$). When ρ is higher, the best strategy requires a higher dose of administered full-epitope vaccines.

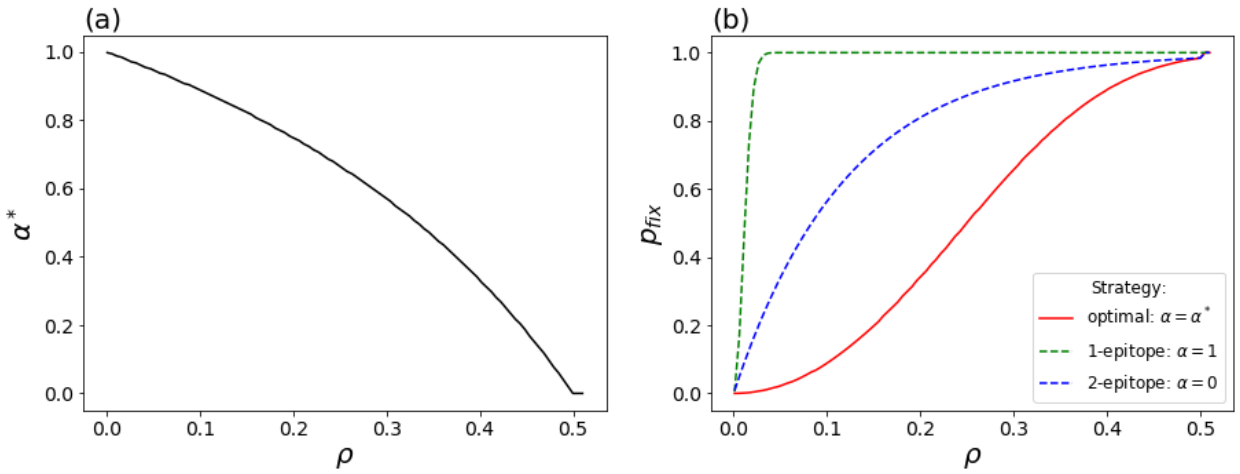


Fig. 8. Optimal vaccination strategy to reduce evolution of vaccine resistance in the 2-epitope scenario and imperfect vaccination. (**a)** The optimal vaccination strategy, characterized by α*, share of single-epitope vaccines, as a function of vaccine imperfection ρ (fraction of breakthrough infections). (**b**) The probability of fixation of a vaccine resistant variant as a function of ρ for 2-epitope vaccination (blue line), single-epitope vaccination (green line) and optimal mixed vaccination(red line) strategies. Initially infected population N = 10^5, full vaccine rollout (V=1), R_0 = 2, p= 10^{-3}.

In the n-epitope scenario we derive the optimal vaccination strategy (m*) where all individuals in the population receive different vaccines with the same valence. We study the probability of fixation of a vaccine-resistant variant for the optimal vaccination strategy as a function of the degree of imperfection of the vaccine (ρ) and the number of infected individuals in the population (N). When the number of infected individuals and vaccine imperfection are high the optimal vaccination strategy does not prevent the fixation of a vaccine-resistant strain (**Fig. 9a**). Similarly, when N and ρ are low, any vaccine strategy is effective (**Fig. 9b**). The optimal strategy outperforms the single-epitope vaccine strategy when N is high (red in **Fig. 9b**) and outperforms the full-epitope vaccine strategy when ρ is low (blue in **Fig. 9b**).

Similarly to the previous section, we determine near-optimal minimal (the fewest number of epitopes) and maximal (the maximum number of epitopes) vaccination strategies. The solution space for these near-optimal strategies shows a straightforward pattern, with the single-epitope vaccine being the minimum near-optimal strategy for low values of ρ (**Fig. 9c**) while the full-epitope vaccine strategy being maximum near-optimal strategy for low values of N (**Fig. 9d**). The optimal vaccine model better reduces resistant variant fixation when there are multiple epitopes in the pathogen (**Fig. 10a**), when the disease duration in individuals is short (**Fig. 10b**), when the pathogen is not highly infectious (**Fig. 10c**) and when a large proportion of the population is vaccinated (**Fig. 10d**). We did not investigate the interaction of these parameters.

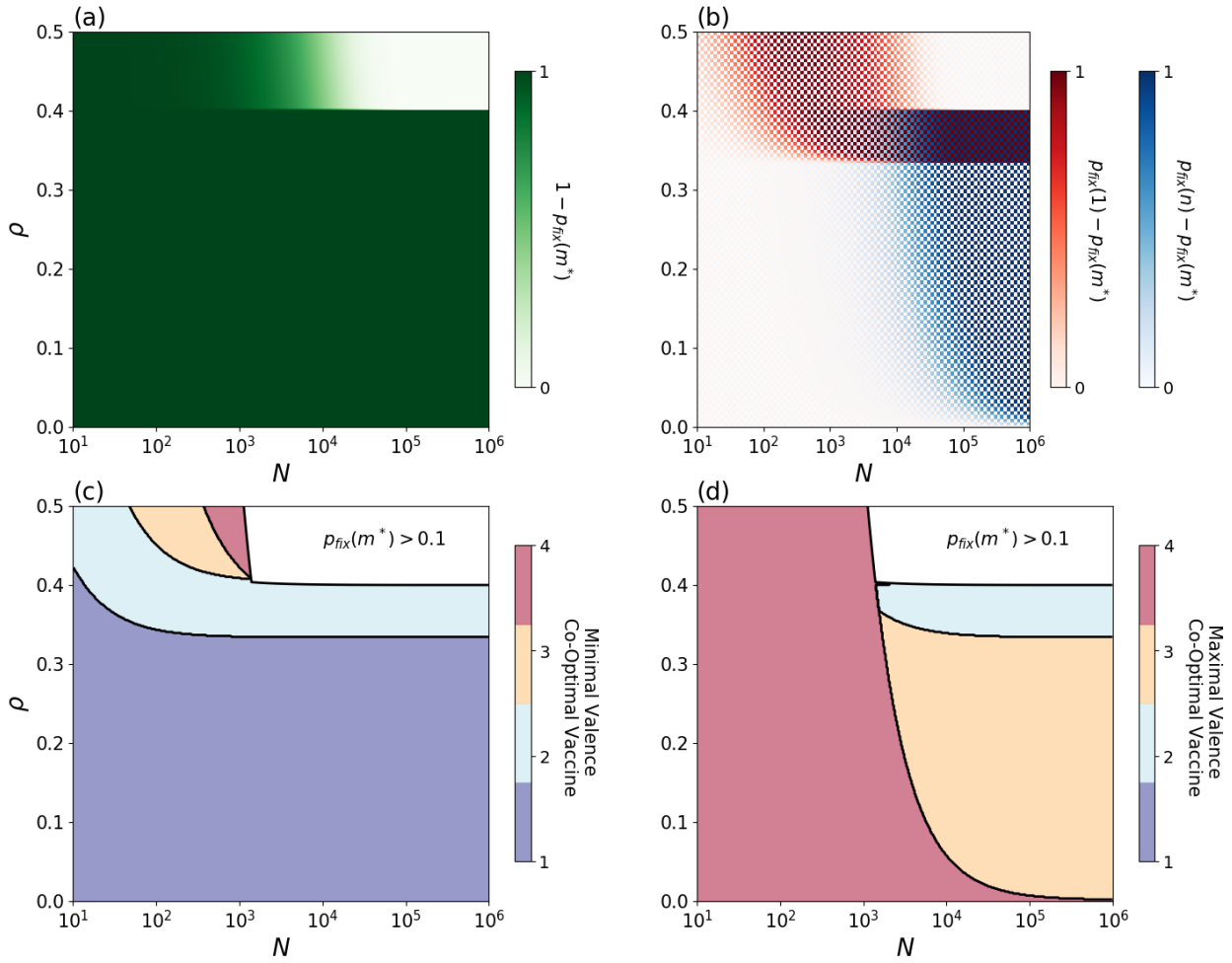


Fig. 9. Optimal vaccination strategy for imperfect vaccines. a) The probability of preventing the fixation of a resistant variant when the optimal vaccination strategy is applied. **b**) The difference between the single-epitope and the optimal (red) and the full-epitope and the optimal (blue) vaccination strategies. The dark region in the overlapping region is an area of parameter space where the optimal strategy is better than both the single-epitope and the full-epitope vaccination strategies. The parameter values showing the (**c**) minimal and (**d**) maximal valence of near-optimal vaccination strategies. Coloured regions define areas where the different m-epitope strategies were (**c**) minimally or (**d**) maximally near-optimal. Within the white area the optimal vaccine strategy has a lower than 90% chance to prevent the fixation of a resistant strain ($p_{fix}(m^*) > 0.1$). For this Figure τ = 10, p = 0.05 and R_0 = 2, ρ - degree of imperfection of the vaccine, N - number of infected individuals. When $\rho \geq 1 - (1 - 1/R_0)/V$, no variant, not even the wildtype, can be contained so we show ρ ranging from 0 to $1/R_0$ (V=1).

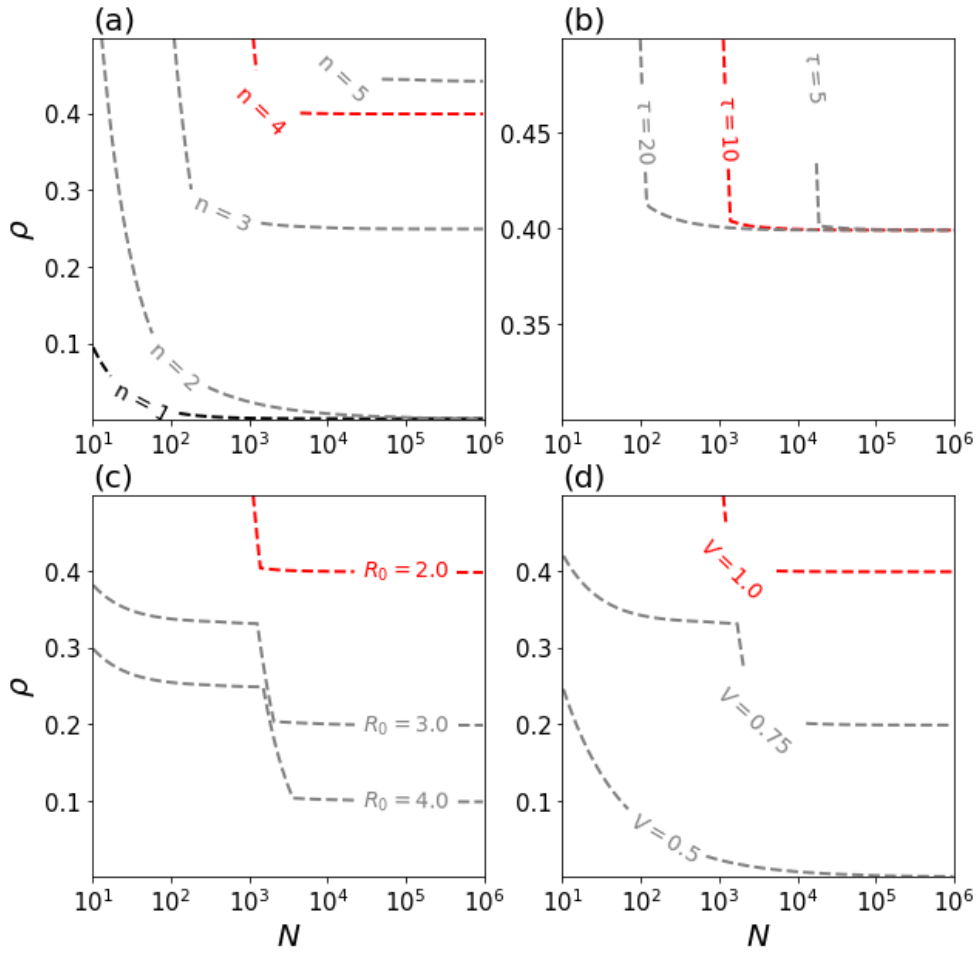


Fig. 10. Efficacy of optimal vaccination strategy in preventing the fixation of resistant strains. Above the dashed contour lines the optimal vaccine strategy has a lower than 90% chance to prevent the fixation of a resistant strain. The figure shows the probability of fixation of a resistant strain as a function of N and ρ for n (**a**), τ (**b**), R_0 (**c**) and V (**d**). All red lines correspond to a base parameter choice in the model of n = 4, V = 1, τ = 10, R_0 = 2. Across panels, each parameter **(a)** n, **(b)** τ, **(c)** R_0 and **(d)** V are varied keeping all the other three parameters constant at the base value.

Discussion

It has been previously suggested that the application of multiple epitopes, both distributed across the population (McLeod, Wahl, and Mideo 2021) and within the same individual (Suhrbier 1997), can be a way of preventing evolution of a vaccine-resistant pathogen. The rationale for their use is that a pathogen will have a harder time adapting to such vaccines. We struggled to come up with a simple term describing the complex vaccination strategies we propose here. In the literature of pesticide and antibiotic resistance the equivalent of a vaccination strategy of inoculating individuals with different single-epitope vaccines is called a *mosaic vaccination* approach, with this term used by McLeod *et al*. (McLeod, Wahl, and Mideo 2021) for the same approach in a 2-epitope model. The full-epitope strategy, also in the antibiotic resistance literature, is referred to as *pyramid* or *combination* approach (REX Consortium 2016; 2013). Meanwhile, *mosaic vaccines* or *multi-epitope vaccines* are those that target more than one epitope, different strains or even different pathogens (Suhrbier 1997). The strategies we consider in our model do not fit into any of these definitions and for lack of a better word we just refer to them as complex strategies.

Among the goals of a vaccination campaign against a pathogen is to prevent its evolution towards vaccine resistance. Our results suggest that the optimal vaccination strategy utilizing a combination of different epitope vaccines, is better at reducing the emergence of vaccine resistance than the traditional approach of using one single-epitope vaccine and the full-epitope vaccine strategy when there is considerable selection against vaccine-induced antibodies. This may have broad practical implications for immunologists and policymakers tackling emergent and established pathogens but our results come with a set of caveats. The assumptions and simplifications in our model were motivated either by a reasonable approximation of biological reality or by mathematical simplicity. We prioritized the exploration of the model with a perfect

vaccine and very few immunocompromised individuals over the model where all individuals in the population were the same but the vaccine was imperfect. This was done because we were initially motivated by the phenomenon of rapid pathogen evolution in immunocompromised individuals seen in SARS-CoV-2 patients but also because in our analytical model we have an infinite population size, making it mathematically more convenient to deal with a set small number of immunocompromised individuals. However, since all vaccines have less than 100% efficacy (Lipsitch et al. 2022; S Gandon et al. 2001), the model analyzing imperfect vaccines is arguably applicable to a wider range of pathogens.

Perhaps the greatest simplification in our model, driven by lack of collective knowledge of the relevant biological processes, is the process of selection of pathogens in an infected individual driven by the immune system. By parsimony we assume that selection against all presented epitopes is equal and that all mutations have an equal probability of emergence. We also assume that selection by the immune system can be mathematically described by a simple Bernoulli process. We explored three different ways of modeling the selection in the individual driven by the immune system: the Bernoulli model, the Infinite model and the Wright-Fisher model (Hartl and Clark 2006). We obtained broadly similar results on a set of test parameters for these three models (**SFig. 1**) and we selected the Bernoulli model for its mathematical simplicity.

We also assumed that vaccine resistance is caused by a single mutation rather than by a series of mutations on a complex protein fitness landscape of the epitope, as observed in the Spike protein of SARS-CoV-2 (Starr et al. 2020). However, there is no general biological understanding of a generic fitness landscape of an epitope that could be used as a model template. Roughly the accumulation of several mutations to achieve resistance should be mathematically equivalent to reducing the mutation rate of a single mutant. Therefore, exploring complex intra-protein fitness landscapes of epitopes should lead to qualitatively different results. However, the fitness landscape of the interacting epitopes may have an influence on our results.

In our model, we assume a specific relationship between pathogen fitness and the number of non-mutated epitopes. For example, consider a 2-epitope pathogen case, with an infected individual vaccinated with a 2-epitope vaccine. We assume that in this individual a variant with a mutation in one epitope has a fitness advantage over the wildtype because the mutant pathogen will be recognized by fewer antibodies. More generally, we assume that the relationship between the fitness of the pathogen and the number of mutated epitopes is linear (**SEq. 3 and SEq. 4**). However, if this relationship is different, our results may be affected. Specifically, if the immune system is just as effective against a pathogen with a single functional epitope as against the wildtype with multiple functional epitopes, it is likely that the full-epitope vaccination strategy may be optimal in a much larger range of parameter values.

Due to differences in immune detection and presentation (Bashirova et al. 2021; Russell et al. 2022), imprinting (Safonova et al. 2022; Yewdell and Santos 2021) and immunodominance (Havenar-Daughton, Lee, and Crotty 2017; Altman, Angeletti, and Yewdell 2018; Adorini 1998; He et al. 2022) the actual memory immunity induced by a multi-epitope vaccine may be smaller than m. Immunodominance, the tendency of the immune system to prioritize producing antibodies to one epitope over others (Adorini 1998; Akram and Inman 2012), may have a particularly strong effect on the dynamics of the model. First, the relationship between fitness and the number of mutated epitopes will not be linear. Second, this relationship may be different in different infected individuals. In either case, immunodominance is expected to further reduce the relative efficacy of the full-epitope vaccination strategy: in the extreme case of strong immunodominance and when all individuals are vaccinated with a full-epitope vaccine, such a strategy can cause individual immune systems to choose the same single immune response to a dominant epitope (Altman, Angeletti, and Yewdell 2018). However, an intermediate m-epitope vaccination strategy under immunodominance will force some immune systems to produce an immune response to a

non-dominant epitope, diversifying the immune system responses in the population and ultimately leading to a reduction of the probability of spread of a vaccine-resistant variant.

Finally, we assumed no recombination in the pathogen, which is not applicable in many pathogens (Pérez-Losada et al. 2015), and relaxing this assumption will influence the results of the model. On an intuitive level, recombination will lead to a faster rate of emergence of strains resistant to multiple epitopes within the body, potentially canceling any fitness reducing effects of resistance mutations (Cong, Heneine, and García-Lerma 2007). In our model, this is equivalent to a larger τ (see **Fig. 7**), thus, we anticipate that an intermediate m-epitope vaccination strategy would be optimal for a greater set of parameters for a pathogen with recombination. It would be interesting to consider a formal model that incorporates recombination, however, it is beyond the scope of our current work.

In sum, different levels of preexisting immunity due to infection, immunodominance, adaptivity, crossimmunity, mutation rates, recombination and pathogen clearance, will influence the results of the basic model, potentially violating assumptions and change the symmetrical outcomes driven by equal use of different vaccines in the population. Consequently, under more complex real scenarios the best vaccination strategy may not treat all epitopes equally.

The strategy of vaccination of a population with different vaccines to control for risks of evolution of resistant strains has not been studied in detail, however, the concept of controlling risk by diversifying the solution strategy has been used in a wide variety of fields. Perhaps the most impactful example is that of the Modern Portfolio Theory (Markowitz 1952) that defined the practical diversification of stocks and securities in investment portfolios in a broadly similar manner. The benefits of genetically diverse crops over the genetically uniform monoculture has been appreciated for well over a century (“Unable to Find Information for 14632411,” n.d.). The use of genetically diverse crops leads to higher yields, less damage from parasites (Y.-P. Wang

et al. 2021) and ensures overall food supply stability (Renard and Tilman 2019). At the extreme, monocultures are susceptible to drastic out of control epidemics, with the Irish potato famine (Gibson 2022) and the Panama disease, that struck banana production in the 1950's and with an evolved strain threatening banana production today (Ploetz 2015) being notable examples. In fact, similar results to ours were obtained in modeling studies tailored to agricultural systems (Djidjou-Demasse, Moury, and Fabre 2017; Rimbaud et al. 2018; Mikaberidze, McDonald, and Bonhoeffer 2015). Diversification on a genetic level is also common in nature, with many species practicing a bet-hedging strategy (Grimbergen et al. 2015), (Simons 2011; Childs, Metcalf, and Rees 2010) to minimize the risk associated with uncertainties in the future. These bet-hedging strategies allow the species to deal with uncertainties of progeny dispersal or environmental variability, but perhaps the most pertinent examples are of disease-host interactions. The benefits of genetic diversity of immune response of the population have been the subject of study for many species, which show that increased diversity of immune response increases the chances to control the spread of the disease in the population (Sommer 2005), (Chabas et al. 2018),(Ashby and King 2015; van Houte et al. 2016),(Ashby and King 2015; King and Lively 2012), (Ugelvig et al. 2010) and within whole ecosystems (Haas et al. 2011), (Schmidt and Ostfeld 2001), ultimately shaping the co-evolution of pathogens and hosts (Schmidt and Ostfeld 2001; Lively and Dybdahl 2000; S Gandon and Michalakis 2002), (Ashby and King 2015; van Houte et al. 2016)).

We are not aware of any ongoing efforts using a mixed vaccine approach, whereby different individuals in the population would receive a vaccine tailored to different epitopes. For some pathogens there may be biological limitations in creating such mixed vaccine batches, therefore, here we will discuss the potential benefits of a mixed vaccination approach only in hypothetical terms. The specific application of such an approach to thwart a particular pathogen would require detailed expertise in that particular pathogen, which is outside our area of expertise.

However, if a mixed vaccine strategy is technically feasible to apply against a specific pathogen, the experts working on this pathogen may consider the following conceptual advantages.

Many of the potential benefits of mixed vaccine strategy could be obtained by a single-epitope mixed vaccine approach, whereby the population is inoculated by different vaccines with each inducing an immune response to a single epitope. The R&D and manufacturing of several single-epitope vaccines may be simpler than researching a complex full-epitope vaccine. A mixed single-epitope strategy while having the benefit of reducing the fixation probability of vaccine-resistant strains can also be quickly adapted to evolving threats. Consider a 5-epitope pathogen and a population that is vaccinated by a mix of 5 single-epitope vaccines. If vaccine-resistance to one of the epitopes evolves, the failed vaccine can be discontinued until it can be updated to be effective against the evolved epitope. Meanwhile, an all out outbreak in the population is prevented by the four other still functional single-epitope vaccines and eventually the updated single-epitope vaccine is reintroduced. In case of vaccination of the population with a single 5-epitope vaccine, when it fails it can lead to a serious global infection event that cannot be controlled until a new 5-epitope vaccine is updated. Updating a 5-epitope vaccine may also take a long time, exacerbating the effects of the ongoing outbreak.

Our results show that the advantage of using complex strategies of vaccination is substantially stronger when a high fraction of the population is vaccinated, we believe that the most likely application of such strategies will be outside the human population due to vaccination hesitancy. Furthermore, many people may hesitate receiving a random vaccine, especially if there are any differences, however minor, in their efficacy. Perhaps people will have different reasons to choose different vaccines and the necessary vaccine diversity can be maintained. However, none of these issues apply to animals and it seems likely that initially the application of such complex mosaic vaccinations may be in livestock.

Supplementary Materials

Alternative Models of Within Body Evolution

In addition to the Bernoulli model, we also utilize the infinite model of population genetics and the Wright-Fisher model in order to situate our results within a traditional framework of population genetics. We conclude that the results of all three models are fairly similar. While the infinite model and especially the Wright-Fisher model both add considerable complexity to the dynamics, including both the probability of extinction and mutant interactions (eg. clonal interference), these effects do not change the qualitative behavior of the model and can be readily approximated with an appropriately tuned Bernoulli model.

In the infinite model and the Wright-Fisher model, we are required to define a phenotypic fitness landscape. Assuming additivity of fitness effects in different resistance mutants leads to very similar results to the Bernoulli process. Epistatic effects can however delay or accelerate evolution within a patient. The infinite model with mutations and selection is evaluated according to the differential equation (Hartl and Clark 2006) :

$$dx_\varphi/dt = (\sum_{\varphi'} \; Q(\varphi,\varphi')\, f(\sigma,\varphi')\, x_\varphi \,) / (\sum_{\varphi'} \; f(\sigma,\varphi')\, x_{\varphi'}) \qquad \textbf{(SEq 1)}$$

Here x_φ denotes the fraction of cells infected with pathogen φ. Both sums iterate through all pathogen variants φ' in the powerset $\boldsymbol{\mathcal{P}}(\{e_1,..,e_n\})$, which contains all pathogens that can be constructed with at most n epitopes. Further the sum over all pathogens in the powerset must obey the normalization condition:

$$\sum_{\varphi} \; x_\varphi = 1$$

$Q(\varphi, \varphi')$ is the mutation matrix, containing the mutation rates between pathogen φ and φ', which is defined as follows:

$$Q(\varphi, \varphi') = 1 - q \quad \text{if} \quad \varphi' = \varphi \qquad \textbf{(SEq 2)}$$

$$Q(\varphi, \varphi') = q \ /n \quad \text{if} \quad \varphi' \text{ differs from } \varphi \text{ by exactly 1 epitope}$$

$$Q(\varphi, \varphi') = 0 \quad \text{if} \quad \varphi' \text{ differs from } \varphi \text{ by more than 1 epitope}$$

q is the mutation rate in the infinite population limit, which is typically very small. $f(\sigma, \varphi)$ is the within body fitness of pathogen φ in an individual with immune state σ, which is defined as the set of epitopes, against which an individual shows a memory immune response.
Here, we model fitness as the expected number of secondary infections per infected cell obtained in the infinite population limit of **Eq. 1** in the main text.

$$f(\sigma, \varphi) = r/(a + z_\sigma(x_\varphi)). \qquad \textbf{(SEq 3)}$$

We assume $z_\sigma(x_\varphi)/a$ to be small in an individual with a weak immune system. This allows us to operate on the linearized approximation for fitness $f(\sigma, \varphi) \approx r/a \cdot (1 - z_\sigma(x_\varphi))$. Further assuming an equal memory immune response towards all presented epitopes, the response is chosen to be linearly dependent on the number of evaded epitopes $z_\sigma(x_\varphi) = z' \cdot (|\sigma| - |\varphi|) = z' \cdot (m - i)$. Thus fitness, in this simplified limit, is a linear function of i,

$$f(i, m) = f_0 + z \cdot i \quad , \ i \leq m \, , \qquad \textbf{(SEq 4)}$$

where $z = z'/a$ and $f_0 = r/a \cdot (1 - z' m)$ is the wildtype fitness in a vaccinated individual. This derivation is meant to guide intuition, but ultimately we also choose a linear function for reasons of simplicity and lack of better knowledge.

For very large population sizes, the resulting dynamics of the infinite model are equivalent to the Wright-Fisher model, which we evaluate with a stochastic simulation. In the Wright-Fisher model, a finite population of size N_{WF} consists of infected cells. We denote the number of cells infected with variant φ as n_φ and require the normalization condition

$\sum_\varphi \quad n_\varphi = N_{WF}$.

The population evolves by generation-wise random replacements. Define the probability of $p_\varphi(t+1)$ that an infected cell with variant φ will induce a secondary infection,

$p_\varphi(t) = (\sum_{\varphi'} \quad Q(\varphi, \varphi')\, f(\sigma, \varphi')\, n_\varphi(t)) \,/\, (\sum_{\varphi'} \quad f(\sigma, \varphi')\, n_{\varphi'}(t))$, **(SEq 5)**

in analogy to SEq. 1, where $Q(\varphi, \varphi')$ and $f(\sigma, \varphi')$ are defined as above. At each timestep the distribution of cells present in the system is evaluated by a multinomial distribution, where a cell of type φ is "drawn" with probability $p_\varphi(t)$ out of N_{WF} possible cells.

Note that for $N_{WF} = 1$, $q = p$ and z large, the Wright-Fisher model behaves closely to the Bernoulli model with mutation rate p. For N_{WF} large, the Wright-Fisher model behaves closely to the Infinite model. Different choices of N_{WF} and q in the Wright-Fisher model therefore allow a form of interpolation between the infinite model and the Bernoulli model.

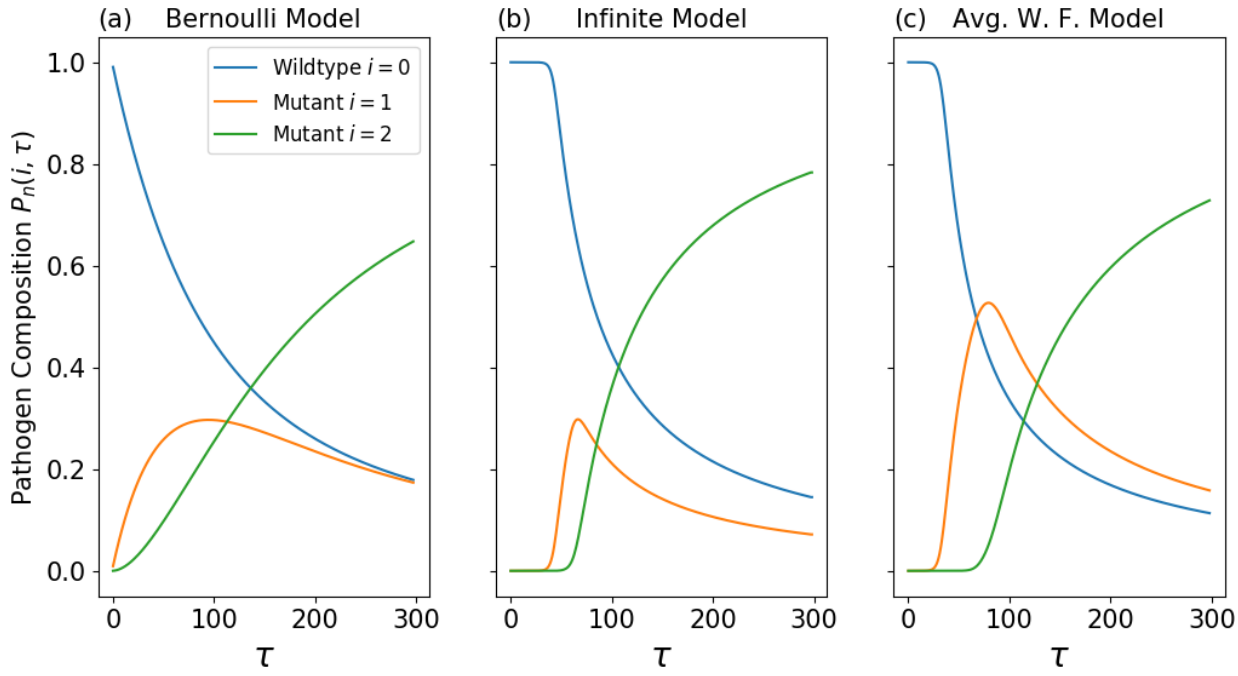
As outlined in the main text, transmission occurs at random times during the evaluation of the simulation. The probability that a certain mutation is transmitted by a patient, measured throughout the whole disease duration, has to be evaluated as the full disease population average, for the Wright-Fisher model

$p_{trans} = \sum_{t=0}^{\tau} \quad n_\varphi(t)/(N_{WF}\tau)$ **(SEq 6)**

and for the infinite model

$$p_{trans} = \int_0^{\tau} x_{\varphi}(t)\, dt\, /\tau \quad . \quad \textbf{(SEq 7)}$$

The results for the probabilities of pathogen occurrence with $|\varphi|$= i for different mutants and different times can be seen in **SFig. 1**. Given the right rescaling p = p(q), the Bernoulli model shows similar evolutionary infection profiles as the infinite model and the average Wright-Fisher Model.



SFig 1. Population genetics of within body mutation and selection. The figure shows the probability that an individual vaccinated with a 2-epitope vaccine, transmits the wildtype i = 0 (blue), a variant with one mutated epitope (i = 1) (orange), or a fully resistant variant with i = 2 mutated epitopes (green). These results are presented for **(a)** the Bernoulli model (**SEq. 3**), **(b)** the Infinite Model (**SEq. 6**) and (**c**) the Wright-Fisher model (**SEq. 7**). The infinite model was run with parameters $q_{IF} = 10^{-8}$ and z = 1. The Bernoulli model used the value p = - log(1 +z)/(2 log(q_{IF})) ≈ 0.018. The Wright-Fisher model is run with parameters $q_{WF} = q_{IF}/p \approx 5\ 10^{-7}$ and N = [p/q_{IF}] $\approx 10^6$. The right tuning of model parameters leads to a qualitative match between all three models.

Derivation of Eq. 6 (Reproductive Number)

A wildtype pathogen can spread in a naive host population with initial reproductive number R_0. In a partially vaccinated population and in the absence of natural immunity, the transmission will be reduced. Let us begin with the case of a strategy employing equal proportions of m-epitope vaccines (the total number of epitopes is n). A fraction V_m of the population is vaccinated with one of $C(n,m)$ m-epitope vaccines, while the remaining fraction is unvaccinated, S.

$S + V_m = 1, V_k = 0 \; for \; k \neq m$

We may also denote the vector $V = (S, 0, .., V_m, \ldots, 0)^T$ as the strategy. Then, the basic reproductive rate of the wildtype is given by:

$$R_{wt}[V] = R_0(1 - V_m) = R_0 S$$

A mutant that is immune to the vaccine, will again have the reproductive success of a wildtype in an unvaccinated population, R_0. A mutant with i mutations will be able to infect $C(i,m)$ types of vaccines, that is a fraction $C(i,m)/C(i,m)$ of all $C(i,m)$ vaccines. Therefore

$R_i[V] = R_0(S + V_m \, C(i,m)/C(n,m))$ **(SEq. 8)**

In case of a general strategy we can write:

$R_i[V] = R_0 \, (S + \sum_{m=1}^{i} \; V_m \, C(i,m)/C(n,m)) = R_0(1 - \sum_{m=1}^{i} \; V_m \, (1 - C(i,m)/C(n,m)) - \sum_{m=i+1}^{n} \; V_m)$ **(SEq. 9)**

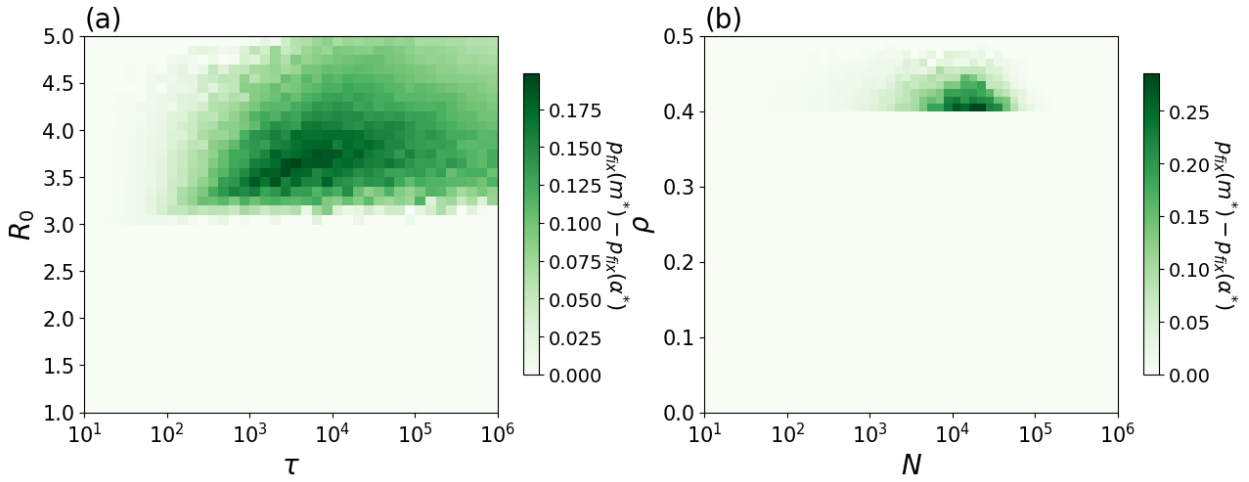
If vaccines are not perfect, a fraction ρ experiences wildtype transmission R_0, while the remainder (1-ρ) has transmission (SEq. 9), therefore

$$R_i[V] = R_0(\rho + (1-\rho)(S + \sum_{m=1}^{i} \; V_m \, C(i,m)/C(n,m)))$$

After simple reformulations:

$$R_i[V] = R_0(1-(1-\rho)(\sum_{m=1}^{i} V_m\,(1-C(i,m)/C(n,m)) + \sum_{m=i+1}^{n} V_m\,)$$

Vaccination with different vaccine valences and the global optimum solution



SFig. 2. Probability of fixation of a vaccine resistant variant for a model with a mixture of vaccines with different valences. The difference in the probability of fixation of a vaccine resistant variant between a strategy close to the global optimum $\alpha^* = (\alpha_1, \ldots, \alpha_m, \ldots, \alpha_n)$ and a discrete strategy, for which $\alpha_m = 1$ and $\alpha_k = 0$ for all $k \neq m$, for which a fraction $\alpha_m V$ receives one of C(n,m) m-epitope vaccines. The global optimal strategy outperforms the discrete strategy by up to 25% for high values of R_0, τ, N and ρ. For most other parameter values we explored, the probability of fixation in a discrete vaccination strategy was close to the globally optimal strategy. To find the global optimal strategy, we used a Monte Carlo approach, in which a strategy vector α is drawn from a Dirichlet distribution (with uniform concentration parameters all being equal to 1) several times (1000 runs per parameter choice) and the best strategy corresponds to the instance of V, which minimizes p_{fix} (**Eq. 8**). For comparison see **Fig. 7** and **Fig. 9**, which have the same parameters.

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