Complex vaccination strategies prevent the emergence of vaccine resistance

Simon A. Rella[1]*, Yuliya A. Kulikova[2,3], Aygul R. Minnegalieva[3], Fyodor A. Kondrashov[3]*

[1]*Institute of Science and Technology Austria, 1 Am Campus, Klosterneuburg, A-3400, Austria*

[2]*International Institute for Applied Systems Analysis, Schlossplatz 1, Laxenburg, A-2361, Austria*

[3]*Okinawa Institute of Science and Technology, Tancha 1919-1, Onna-son, Okinawa 904-0495, Japan*

*Corresponding SAR simon.rella@ist.ac.at, FAK fyodor.kondrashov@oist.jp

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 escape. Vaccine resistance in highly infectious pathogens was prevented by the full-epitope vaccine, that is, 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.

© The Author(s) 2024. Published by Oxford University Press on behalf of The Society for the Study of Evolution (SSE).

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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 an increase of infectivity (Y. Wang et al. 2022) and evolving vaccine resistance (Willett et al. 2022; Garcia-Beltran et al. 2021; Meijers et al. 2023). An interesting aspect of SARS-CoV-2 is its propensity for rapid evolution driven by the host immune response in immunocompromised individuals over 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 (Lee et al. 2022, Agrati et al. 2023).

The ideal goal when dealing with an emergent disease is eradication, as has been achieved in some cases (Ochmann and Roser 2018; The Lancet 2019; Breman and Arita 1980; Normile 2010). The second best option is to control the pathogen's spread and evolution that would allow it to avoid these control mechanisms. Vaccination of the entire population should reduce the rate of spread of the virus. 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 evade the vaccine-induced immune response (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).

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

A potential solution for the prevention 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) thereby allowing us 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 with 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 escape, 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 particularly relevant if the evolution of the pathogen is enhanced by selection due to the immune system in the same way as SARS-CoV-2 evolution is enhanced in immunocompromised individuals (Gandon and Day 2008; Sonnleitner et al. 2022; Lee et al. 2022; Agrati et al. 2023).

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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

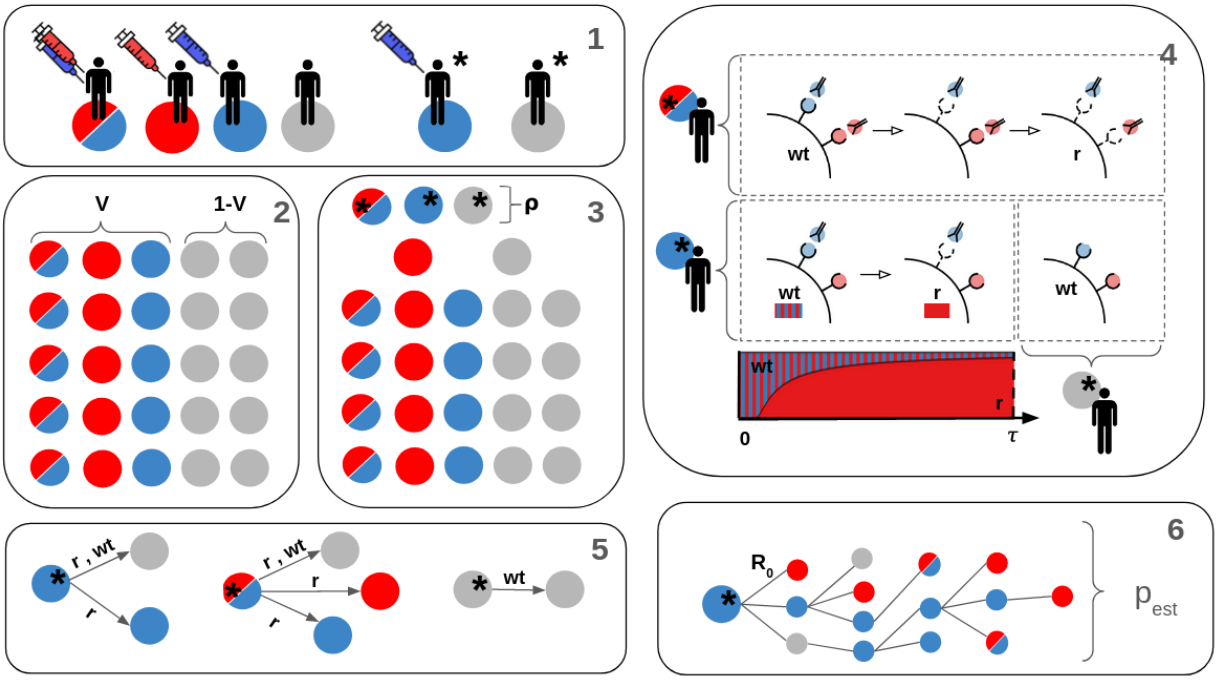
In our model, a schematic of which is shown in Fig 1, we have an infinite population size with different states assigned to individuals. Given a current snapshot of the population, the state of an individual can be unvaccinated (S), unvaccinated and infected by a pathogen φ (SP_φ) and vaccinated by a specific vaccine of type σ (V_σ). Further, some fraction of the population, hereby referred to as immunocompromised (I), experiences prolonged disease when infected. The immunocompromised can be vaccinated (IV_σ), vaccinated and infected ($IV_\sigma P_\varphi$) or unvaccinated and infected (IP_φ). In the immunocompromised vaccinated and infected individuals ($IV_\sigma P_\varphi$) the immune system can select for mutations ($\varphi \rightarrow \varphi'$) in epitopes that have been displayed by the vaccine σ to the immune system (Agrati et al. 2023). These mutations render the vaccine ineffective against the respective epitopes. Such selection is hindered in healthy individuals as vaccines effectively suppress vaccinated and infected states ($V_\sigma P_\varphi$). We later consider a variant of the model, which relaxes this assumption: Immunocompromised individuals are excluded but regular vaccinated individuals experience breakthrough infections and in these individuals the pathogen can evolve. In that case, the individual

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

states are, as before, (S), (SP_φ), (V_σ) and with an additional state of vaccinated and infected ($V_\sigma P_\varphi$). It is possible to extrapolate from one model to the other by tuning the parameters ρ (fraction of breakthrough infections) and τ (length of disease), discussed below.

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 protection against the pathogen. We review this assumption in the discussion. Using equations derived from stochastic epidemiological models we consider the probability of fixation at a given point in time of such vaccine-resistant variants in an immunocompromised individual and the probability of establishment of these variants in the entire population. Note, that we are not solving for the expected fraction of infected and susceptible, as is usually done with SIS-models, but rather we compute the probability of emergence and establishment of resistant variants for given model variables. We use the term establishment when a pathogen spreads to many individuals in the population and we talk about fixation of a variant within a host.



Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Fig 1: Overview of the model for the case of two epitopes in vaccine design. (1) The model features several states of an individual: healthy or vaccinated. Individuals can be vaccinated with a 2-epitope vaccine or one of two single-epitope vaccines (red and blue). Unvaccinated individuals are shown in gray. Further, each individual can be in a diseased state (marked by an asterisk, *). (2) All N individuals are vaccinated in accordance with the chosen vaccination strategy. (here N = 25 for visualization purposes, the actual model operates in the limit of large N). (3) Immune-driven selection in infected individuals may lead to the emergence of vaccine-resistant strains with some small probability. (4) Selection pressure drives the wild type population of pathogens (wt) to evolve resistance towards administered vaccines (r). For instance, an individual that received the blue vaccine, will only develop an immune response towards the blue epitope. Over time the pathogen population in the host will become a vaccine-resistant population from a wild type population. We assume that vaccine resistance does not emerge in unvaccinated individuals. (5) Once evolved, mutants will spread within the population of hosts. However, due to different host immune types, some variants have reduced transmissibility. (6) Using a branching process we evaluate the probability that the vaccine resistant strain infects a certain fraction of the population, not vanishing in the large N limit, which we identify as the probability of establishment.

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 creates antibodies against one epitope while 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 special case of the multi-epitope vaccine. We denote the

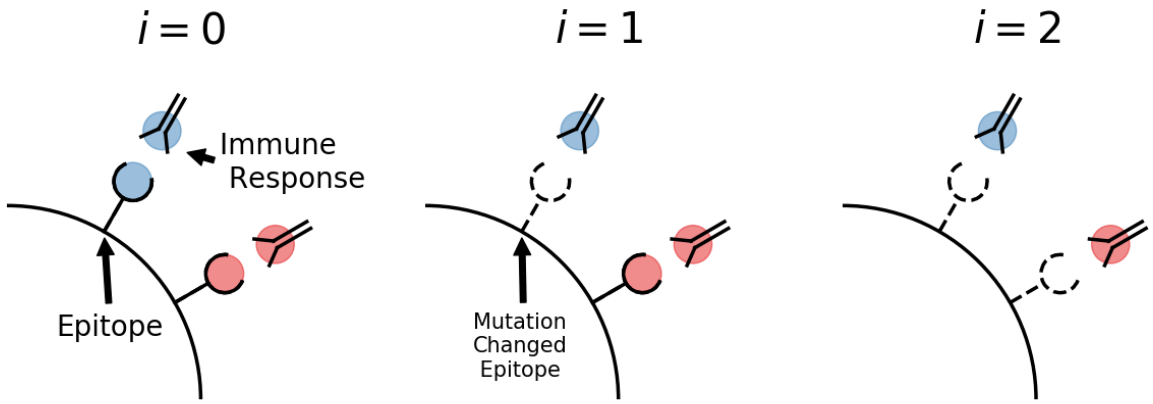
Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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 a variant φ as the set of its epitopes in the wildtype state. The initial condition starts with the wild type pathogen that carries all unmutated 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 acquire resistant mutations is denoted as i. A super resistant pathogen acquires mutations in all n epitopes (**Fig 2**), such that $\varphi = \varnothing$ and $|\varphi| = 0$. There exist $C(n, i)$ different pathogens with i mutated epitopes.



Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Fig. 2. 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, no vaccine is perfect, and a small fraction of the vaccinated population (ρ) can get infected and infect others. Further, as we will detail below, these individuals can still produce some immune response which can drive the selection of the pathogen inside the body. 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. The immunocompromised model and the model with imperfect vaccines are similar. In the former few individuals have a high probability of causing the evolution of a vaccine-resistant strain while in the latter, many individuals have a small probability of doing the same.

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, $|\sigma|$, equals the vaccine valence m.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Our model relies on the simplifying assumption that each recognized epitope contributes equally to the overall rate of pathogen clearance. Vaccines with more epitopes do not clear a recognized pathogen faster than a single-epitope vaccine, because both are assumed to induce the same total number of antibodies, but the multi-epitope vaccine induces multiple available antibody types. As described in detail within **Supp. Res. Sec. 1-2**, this symmetry assumption reduces the relevant model parameters from the full sets σ and φ to their integer set sizes, m and i.

Evolution

In each infected and vaccinated individual ($IV_{\sigma}P_{\varphi}$) we model evolution 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. A pathogen population with i mutations, in a host vaccinated against m epitopes, becomes a pathogen population with i+1 mutations with a probability p per day of infection. Always starting with the wildtype, the probability to find a pathogen with i mutated epitopes by time t, given a vaccine of valence m was administered, can be approximated with a Poisson distribution,

$$p_m(i) = (pt)^i e^{-pt}/i! \qquad \text{for i} < \text{m}. \qquad \textbf{(Eq. 1)}$$

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

$$p_m(i) = \sum_{j=m}^{\infty} (pt)^j e^{-pt}/j! \quad \text{for i = m}$$

$$p_m(i) = 0 \qquad \text{for i > m} \qquad \textbf{(Eq. 2)}$$

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Note that this simple treatment of the evolutionary process ignores any differential fitness effects between variants. Further, it requires that evolutionary trajectories always start with the wildtype. 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) in an immunodynamical setting, generates similar qualitative results (See **Supp. Res. Sec. 1-2** and **Supp. Fig. 1**). More generally speaking, the presented algorithm, as well as its more complicated variants, do not exclude the possibility that pathogen diversity has existed even prior to vaccination, which would correspond to a different initial condition.

Vaccination Strategies

When multiple epitopes can be targeted, vaccines with different valences (number of targeted epitopes) can be created (**Fig. 3**). 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, constrained by the normalization condition:

$$S + \sum_{m=1}^{n} V_m = 1 \quad \textbf{(Eq. 3)}$$

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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

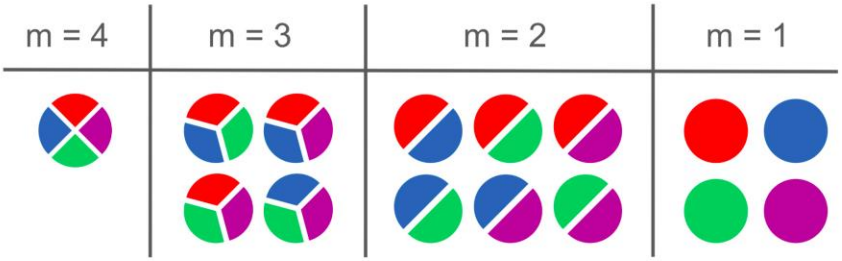


Fig. 3. Available multi-epitope vaccines for a vaccination procedure targeting n different epitopes. Different possible vaccines for the number of epitopes n = 4. Full-epitope strategy (left panel) with m = 4, where the population is inoculated with the n-epitope vaccine. A single-epitope strategy (right 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. Given one of $N\rho$ individuals, in which the pathogen can evolve if vaccinated ($IV_\sigma P_\varphi$ or $V_\sigma P_\varphi$) , the probability $p_{trans}\,(i)$ that it will transmit a pathogen variant with i mutated epitopes is

$$p_{trans}\,(i,\tau) \;=\; \sum_{m=1}^{n} \quad V_m \int_0^\tau \quad p_m(i)/\tau \; dt \qquad \textbf{(Eq. 4)}$$

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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Establishment 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. 3**),

$$R_i = R_0(1-(1-\rho)(\sum_{m=1}^{i} V_m\,(1-C(i,m)/C(n,m)) + \sum_{m=i+1}^{n} V_m)) \quad \textbf{(Eq. 5)}$$

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 is infectious, thereby contributing to population level transmissibility. Finally, establishment in a population with a large population size and random interactions can be approximated by a branching process, as $1 - 1/R_i$, where $R_i \geq 1$ (Patwa and Wahl 2008Lieberman, Hauert, and Nowak 2005) (see **Supp. Res. Sec. 5**).

Overall Probability of Pathogen Evolution

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

$$p_{est}(i,\tau) = p_{trans}(i,\tau)\,(1 - 1/R_i), \quad \text{with } R_i \geq 1 \quad . \quad \textbf{(Eq. 6)}$$

We are in particular interested in the probability p_{est} that *any* variant will establish in the population, as this signifies failure of the vaccination campaign. As a result of ρN initial transmission events (the average number of infected and immunocompromised individuals), this probability of establishment is

$$p_{est} = 1 - \prod_{i=1}^{n} (1 - p_{est}(i,\tau))^{\rho N} = 1 - exp(\rho N \sum_{i=1}^{n} log(1 - p_{est}(i)) , \quad \textbf{(Eq. 7)}$$

which, among various life-history attributes of the pathogen, will also depend on the employed vaccination strategy. Note that the presented algorithm only considers establishment as resulting from

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

two distinct and sequential processes: (1) Mutation and (2) Transmission. Any additional mutations, which might occur within the transmission chain, are neglected, as they are not expected to contribute heavily to the probability that *any* variant will establish.

Evaluation of the epidemic burden

Establishing variants will trigger an epidemic and a considerable fraction of the population will subsequently become infected. Basic epidemiology can provide estimates for the speed, size and length of an epidemic as a function of the reproductive number of a mutant. In fact, pathogens which have a high probability of establishing in a population cause relatively more secondary infections and ultimately larger epidemics. In the classical SIR model, the size of the pandemic s(i), which is the total fraction of the population which becomes infected by an establishing variant, i, can be determined by the inverse relation,

$$\mathbf{1} - \boldsymbol{s(i)} = \boldsymbol{exp}(-\boldsymbol{R_0 s(i)})\,. \qquad \textbf{(Eq. 8)}$$

It can be shown that this measure for the fraction of infected is strongly correlated with the probability of establishment of variant i with transmissibility $\boldsymbol{R_0}$ (See **Supp. Res. Sec. 5**). In this manuscript we present the probability of establishment, both as a measure for the risk of pathogen evolution, as well as a measure for the epidemic burden. In the case of Fig. 4 and Fig. 9 we also explicitly present the expected size of the epidemic resulting from vaccine resistant variants (see **Supp. Res. Sec. 4**).

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Results

General description of the model

We considered a hypothetical pathogen with 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. 1-2)** driven by the vaccine-induced immune response. The new pathogen variant created by these intra-host 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.

The ultimate goal of a successful vaccination campaign is to prevent the spread of disease and reduce the associated disease burden in the form of the number of infected, diseased or disabled

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

individuals. In this paper, we are not concerned with the complex dynamics of the disease burden, rather we study the possibility that a complex vaccination strategy can prevent the spread of vaccine-resistant variants in the first place. Therefore, we use the probability of establishment of the vaccine-resistant variant as a proxy for the success of a specific vaccination strategy, based on the following logic. If the vaccination strategy fails to prevent a vaccine-resistant variant from spreading in the population then the subsequent disease burden that will be caused by the spread of this variant will be determined by SIR-like dynamics and are not of further concern to the question whether the said strategy is successful. Furthermore, we show that the probability of establishment of a vaccine-resistant strain is correlated with the disease burden (see **Supp. Res. Sec. 5**).

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 = 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 establishment of vaccine resistance for a given set of parameters using **Eq. 7** (see the Model section). Similarly, we can compute the expected burden induced by evolving vaccine resistance for different values of α using the methods outlined in **Supp. Res. Sec. 4**. **Fig. 4** shows the results of the optimal strategy as a function of the fraction of the vaccinated population, V.

In a pure m = 1 strategy (α = 1) the probability of establishment is largest at intermediate levels of vaccination (blue line in **Fig. 4a**). However, under this strategy the probability of establishment and

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

the epidemic burden 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 (Rella et al. 2021; Chabas et al. 2018).

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 establishment 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. 4a,b**).

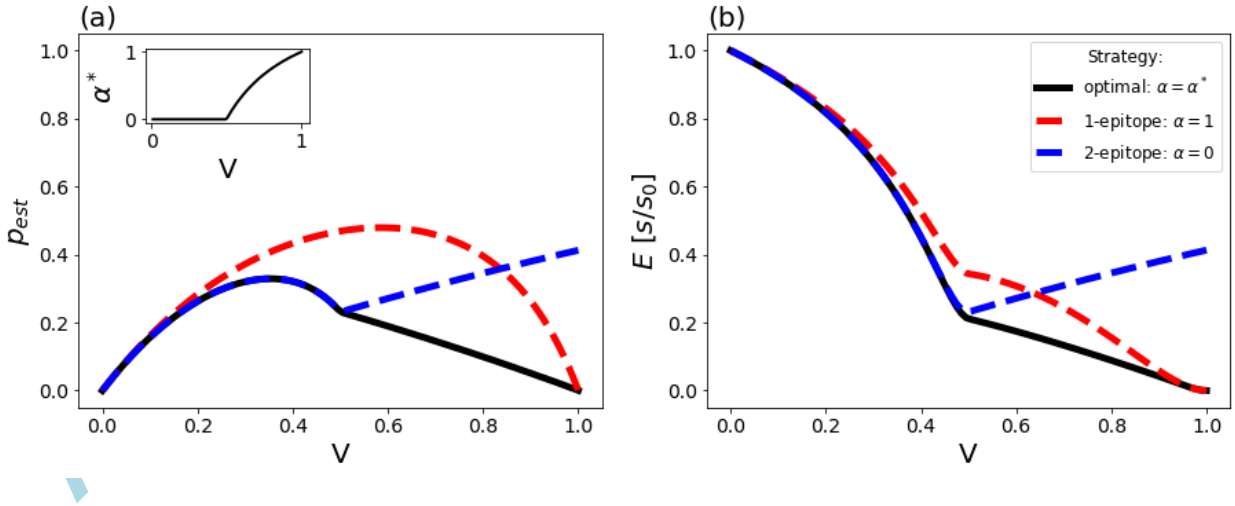


Fig. 4. Optimal vaccination strategy to prevent evolution of vaccine resistance in the 2 epitope scenario. **a**) The probability of establishment of a vaccine resistant variant (p_{est}) as a function of V for three different vaccination strategies, full-epitope vaccination (blue line), single-epitope vaccination (red line) and for an optimal mixed vaccination strategy (black line). The black line of the inlay plot shows the

Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

optimal α*, share of individuals vaccinated with a single-epitope vaccine, as a function of the fraction of the vaccinated population V. 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 (back line). **b)** The expected epidemic burden, E[s/s0], which is the average fraction of affected individuals in the population compared to the unvaccinated scenario, as a function of V for the same three strategies as in (a). 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. 5** 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 establishment 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. 5a**). The pure full-epitope strategy is only optimal for high levels of R_0. However, even 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. 5b**).

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

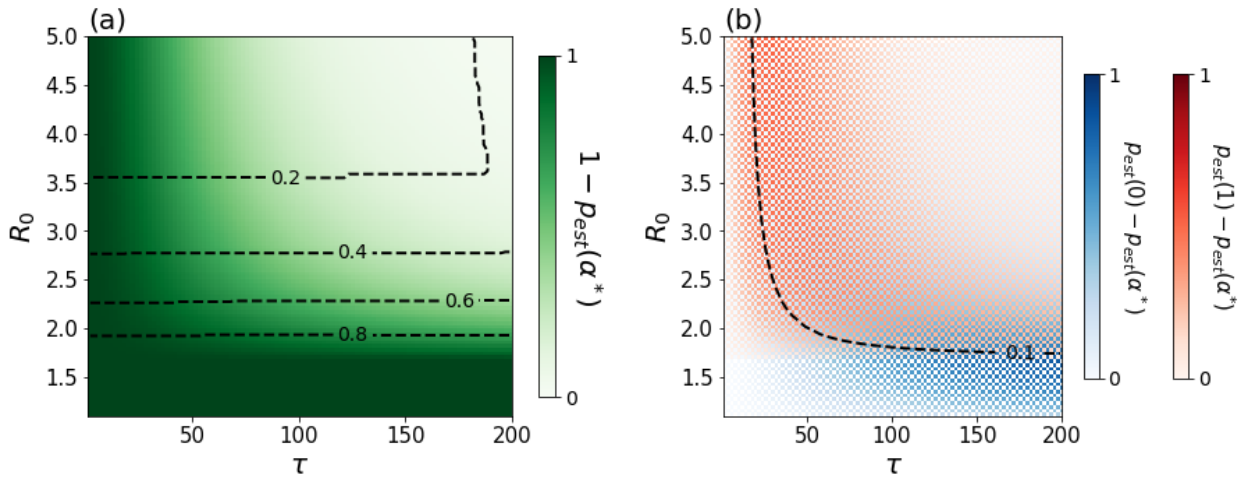


Fig. 5. Optimal vaccination strategy as a function of pathogen infectivity and disease duration in an immunocompromised individual. Share of vaccinated individuals in population, V = 0.8, initial number of immunocompromised individuals, ρN = 1, τ - disease duration of immunocompromised individuals, R_0 - transmissibility of the pathogen. **a**) The probability of preventing the establishment 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 establishment 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 establishment 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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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. 3**). 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. 5)**:

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

In an infinite population and at the limit of strong selection, in the host vaccinated with an m-epitope, the establishment 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-

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

resistant variant (**Fig. 6a**). 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. 6b**).

If evolution within the immunocompromised individual is rapid, and consequently the probability of establishment 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. 6c,** probability of establishment derived from **Eq. 6** 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 establishment 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 establishment of the resistant variant (**Fig. 6c**). 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 establishment decreases until it saturates at the level of $1 - 1/(R_0(1-V))$, which is the probability of establishment of a wildtype in a vaccinated population. . This threshold is approached fastest when m = $[(n+1)/2]$ (**Fig. 6d**).

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

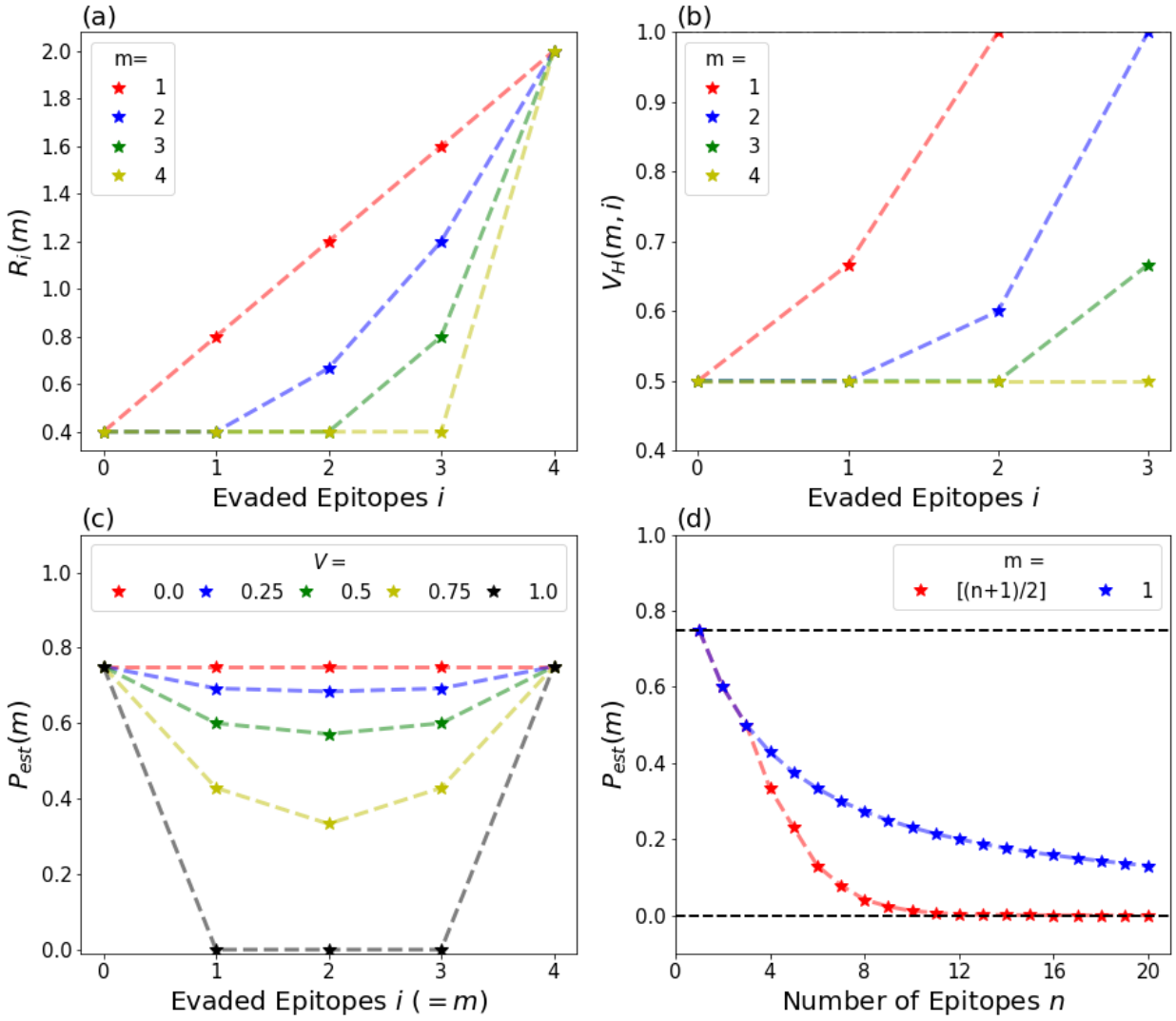


Fig. 6. Effect of different vaccine strategies in preventing the establishment of vaccination-resistant variants. a) The rate of spread of a pathogen with i mutations, indicated by the reproductive number $R_i(m)$, of variants carrying i mutant epitopes (X-axis) (**Eq. 5**) for different valencies m of the vaccination strategy (in color). $R_0 = 2$ for wild-type. **b**) The herd immunity threshold ($V_H(m,i)$), **Eq. 9**, 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 establishment at the population level ($p_{est}(m)$) 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 establishment at the population level ($P_{est}(m)$) of a pathogen that developed full resistance to one of the

Accepted

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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 when 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 life-history attributes of the pathogen and its evolution in the immunocompromised host. Having more than 2 epitopes has two effects on pathogen establishment as a function of population level transmissibility and within host 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 establishment 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 a 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. 7**).

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

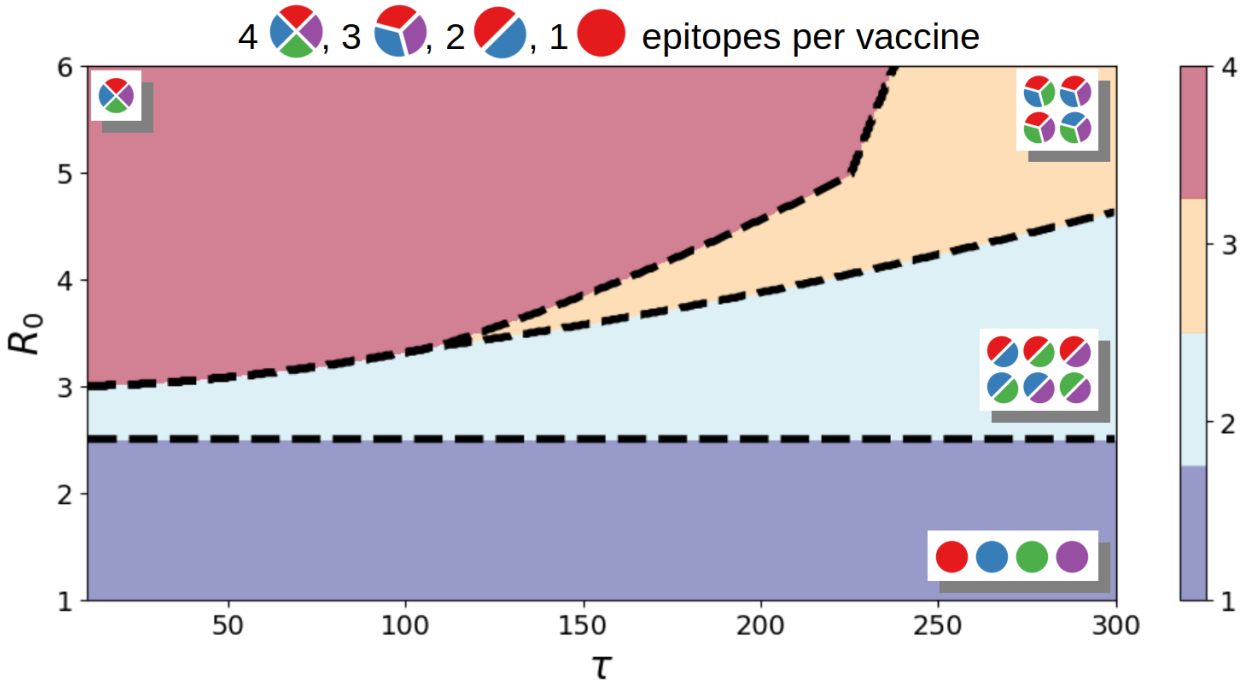


Fig. 7. The optimal choice of epitopes per vaccine (m, vaccine valence) as a function of disease duration τ and transmissibility R_0. The graph illustrates the split of the hyper parameter space for an optimal vaccine strategy for vaccines with m=4 epitopes. Optimal choice of m* minimizes $p_{est}(m^*)$, the probability of a pathogen establishment 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 establishment 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. 8**).

When R_0 and τ are high, no vaccination strategy prevents the establishment of a resistant variant (**Fig. 8a**). 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

Accepted Ma

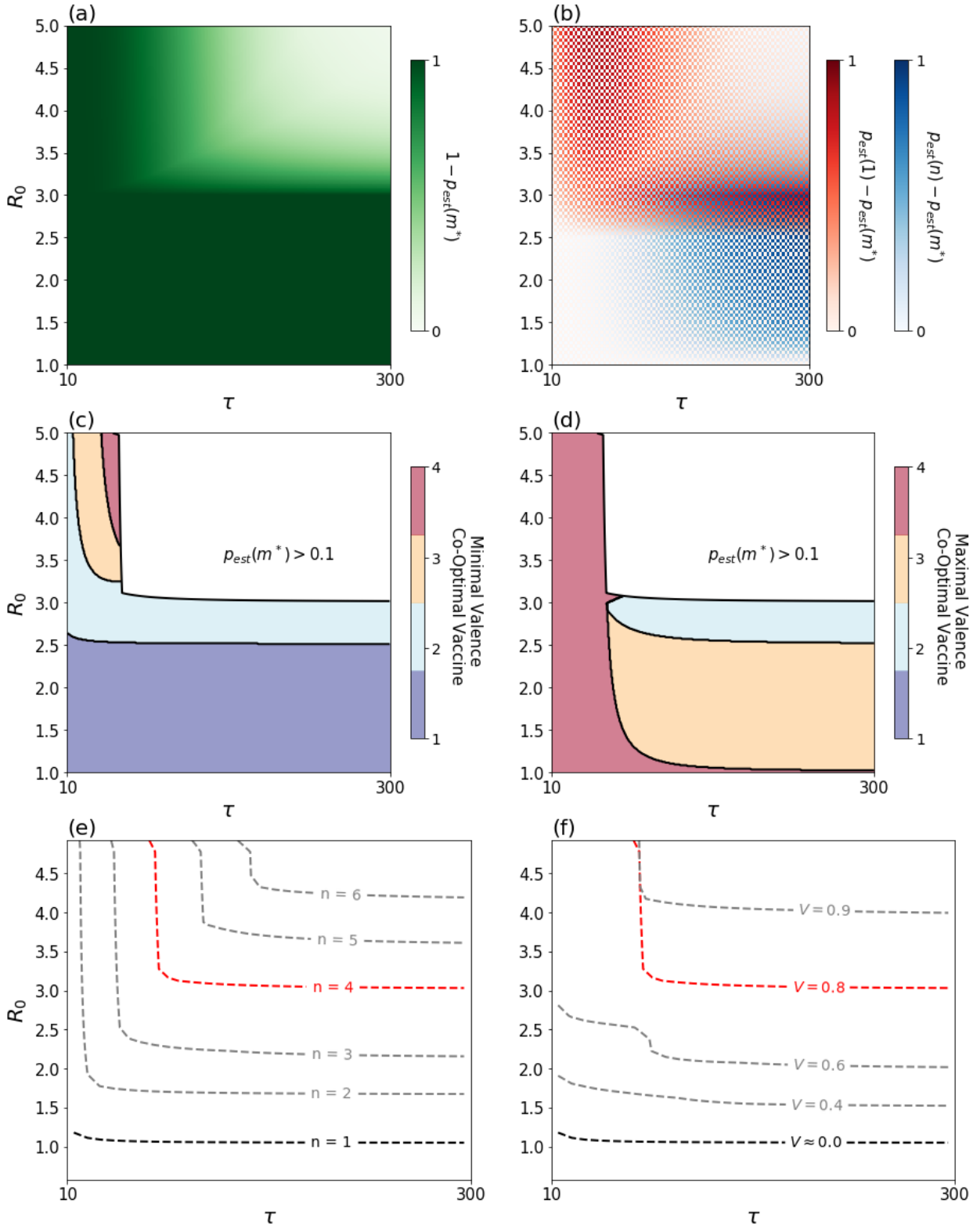
Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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. 8b**). Any vaccination strategy contains pathogen spread when both R_0 and τ are low (**Fig. 8b**).

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 establishment of a mutated pathogen within 10% of the optimal vaccination strategy m*, $p_{est}(m) < p_{est}(m^*) + 0.1$. For the minimal strategy a single-epitope vaccine was efficient for low values of R_0 (**Fig. 8d**) and a higher valence vaccine was always as good as a single-epitope vaccine (**Fig. 8c**). For the maximal valence strategy, the full-epitope approach was efficient when R_0 was high (**Fig. 8d,8c**). For a very specific range of R_0 values, around 2.5, a 2-valent vaccine strategy was always the optimal one (**Fig. 8d,8c**). The efficacy of the optimal vaccination strategy was higher when the number of epitopes in the pathogen was high (**Fig. 8e**) and when the population had more vaccinated individuals (**Fig. 8f**).

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024



Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Fig. 8. Optimal vaccination strategies countering a 4-epitope pathogen. a) The probability of preventing the establishment 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 establishment of a resistant strain ($p_{est}(m^*) > 0.1$). The same threshold, $p_{est}(m^*) = 0.1$, 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 infection, 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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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 ineffective and herd immunity can not be reached, $\rho > 0.5$ for $R_0 = 2$, it does not matter much which vaccine strategy is employed because the probability of establishment of a resistant variant will be close to 1. By contrast, when the imperfection of the vaccines is small the optimal strategy greatly reduces the probability of establishment of resistant variants (**Fig. 8a**) and the expected size of the epidemic (**Fig. 9b**). The admixture of full-epitope (2-epitope in this case) vaccines has a strong effect even for very small values of ρ (**Fig. 9b**) even though for these small values of ρ the share of 2-epitope vaccine admixture into the optimal vaccine mix is low (**Fig. 9a**). 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 establishment of a resistant strain (**Fig 9b**). 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 establishment 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.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

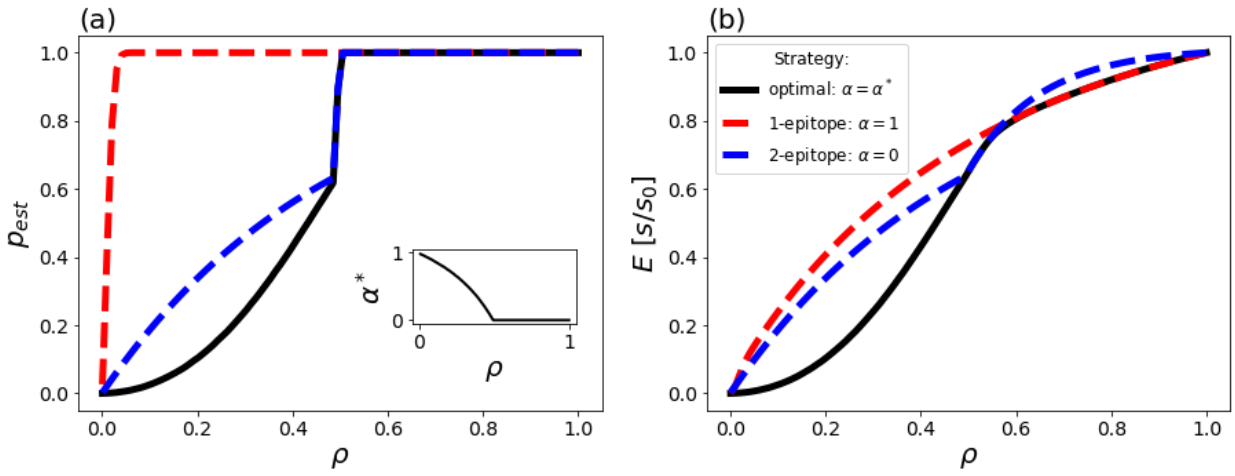


Fig. 9. Optimal vaccination strategy to reduce evolution of vaccine resistance in the 2-epitope scenario and imperfect vaccination. (**a**) The probability of establishment of a vaccine resistant variant as a function of ρ for 2-epitope vaccination (blue line), single-epitope vaccination (red line) and optimal mixed vaccination(black line) strategies. The inlay graph represents the optimal vaccination strategy, for which p_{est} is minimal, characterized by α^*, share of single-epitope vaccines, as a function of vaccine imperfection ρ (fraction of breakthrough infections). (b) The expected epidemic burden, E[s/s0], which is the average fraction of affected individuals in the population compared to the unvaccinated scenario, as a function of ρ for the same three strategies as in (a). For small values of ρ admixture can considerably reduce the burden. Fixed parameters in these plots: Initially infected population N = 10^5, full vaccine rollout (V=1), R_0 = 2, p= 10^{-3}, τ = 5.

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 establishment 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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

strategy does not prevent the establishment of a vaccine-resistant strain (**Fig. 10a**). Similarly, when N and ρ are low, any vaccine strategy is effective (**Fig. 10b**). The optimal strategy outperforms the single-epitope vaccine strategy when N is high (red in **Fig. 10b**) and outperforms the full-epitope vaccine strategy when ρ is low (blue in **Fig. 10b**).

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. 10c**) while the full-epitope vaccine strategy being maximum near-optimal strategy for low values of N (**Fig. 10d**). The optimal vaccine model better reduces resistant variant establishment when there are multiple epitopes in the pathogen (**Fig. 11a**), when the disease duration in individuals is short (**Fig. 11b**), when the pathogen is not highly infectious (**Fig. 11c**) and when a large proportion of the population is vaccinated (**Fig. 11d**). We did not investigate the interaction of these parameters.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

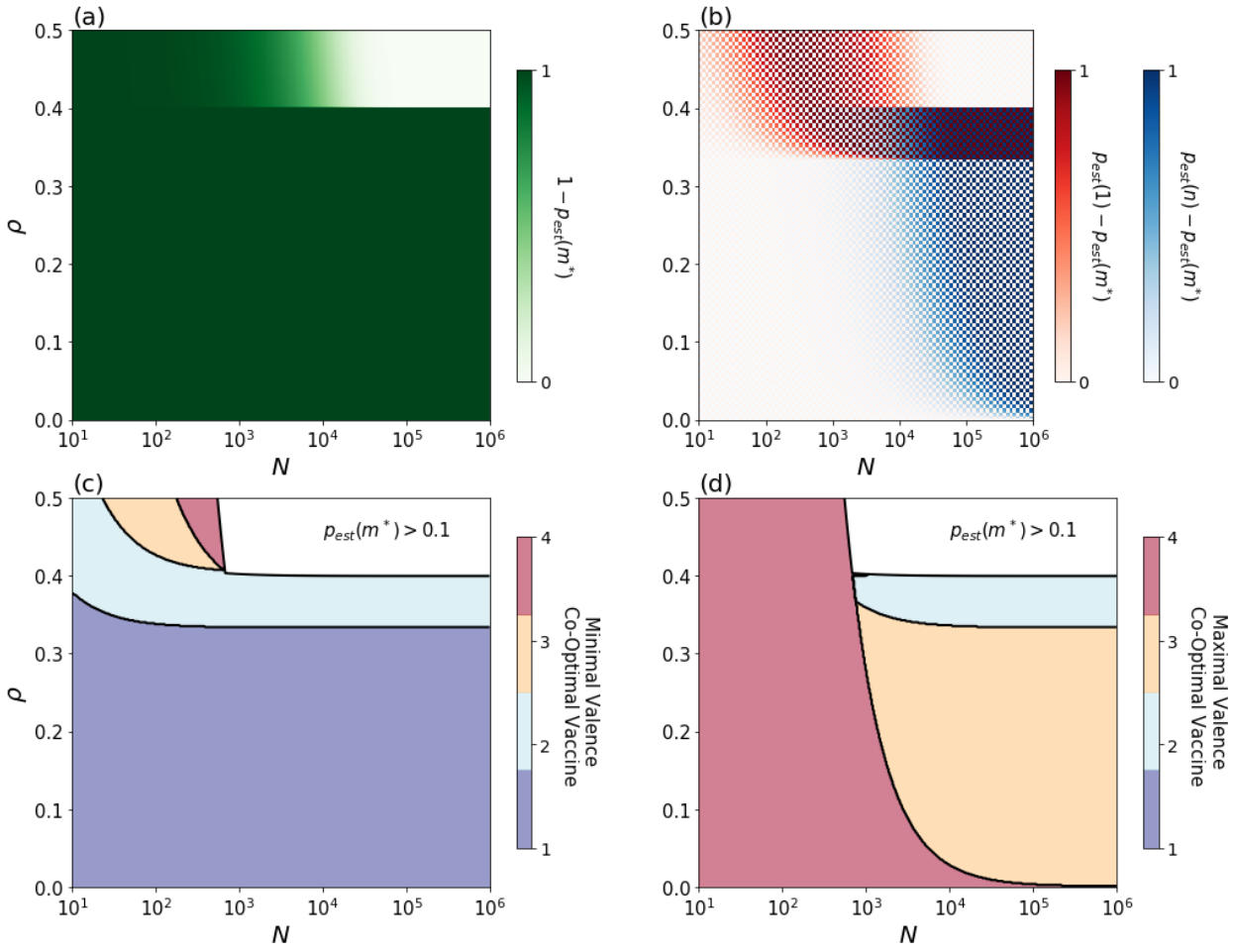


Fig. 10. Optimal vaccination strategy for imperfect vaccines. a) The probability of preventing the establishment of a resistant variant when the optimal vaccination strategy is applied. **b**) The difference between the single-epitope and the optimal (red) and the full-epitope and the optimal (blue) 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 establishment of a resistant strain ($p_{est}(m^*) > 0.1$). 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 $\rho \geq 1 -$

Accepted

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

$(1 - 1/R_0)/V$, no variant, not even the wildtype, can be contained so we show ρ ranging from 0 to $1/R_0$ (V=1).

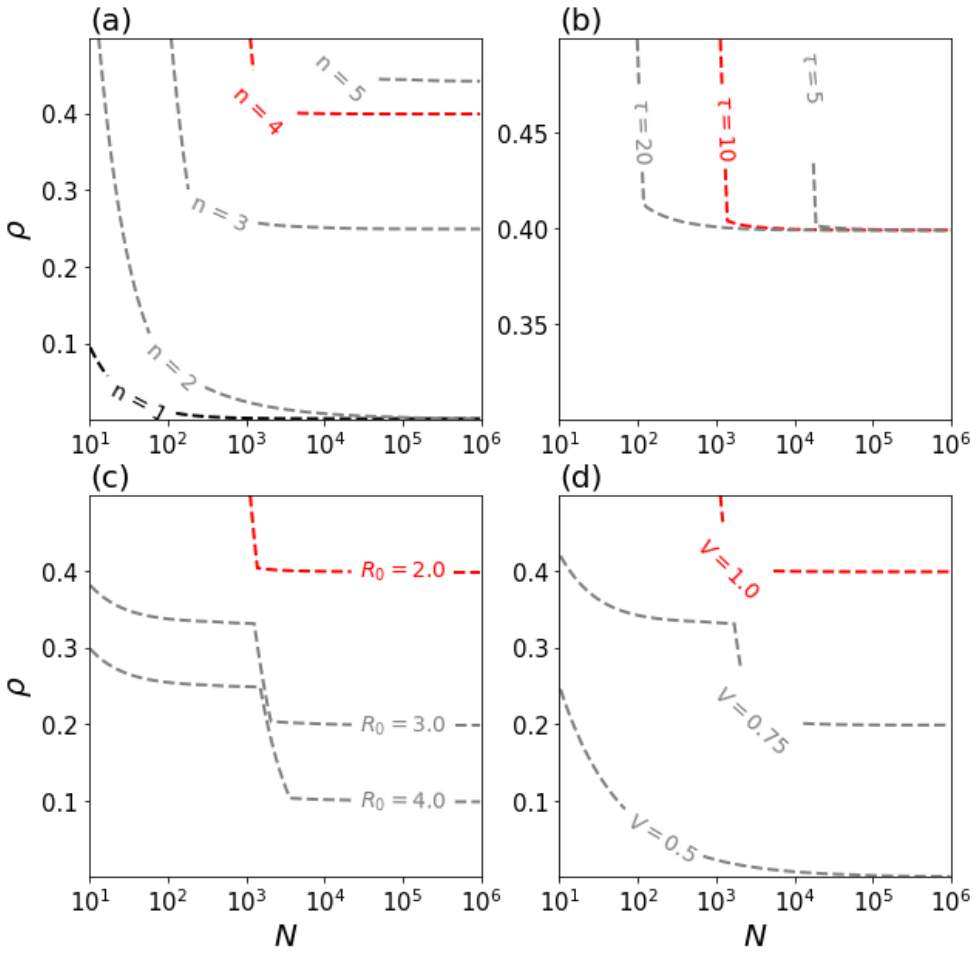


Fig. 11. Efficacy of optimal vaccination strategy in preventing the establishment of resistant strains. Above the dashed contour lines the optimal vaccine strategy has a lower than 90% chance to prevent the establishment of a resistant strain. The figure shows the probability of establishment of a resistant 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.

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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. Our model assumes that all different immune types, regardless of the number of immunized epitopes n, clear the pathogen within the same time. Put differently, we treat all vaccines as equally strong, as long as they provide immunity against the pathogen. 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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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. 4 and SEq. 5**). 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, the number of presented epitopes. 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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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. The immune response triggered by a natural infection is expectedly similar to that of a high m-epitope vaccine. Therefore, previous mosaic vaccination might direct natural population level immune protection to become more diverse and resilient in the light of immunodominance.

In the absence of vaccines or for small vaccine rollouts, natural immunity is expectedly the major driver of antigenic evolution. The applicability of our model to scenarios of low vaccine rollout is therefore limited, as natural immunity is not explicitly included in the analysis. Knowledge about the distribution of immune response profiles induced by natural infections could however be implemented in the presented modeling procedure with relative ease. Here we refrained from making any detailed assumptions about such profiles.

In the limit of high vaccine rollout, in particular if V, fraction of vaccinated individuals in the population, is above the herd immunity threshold, classical epidemiology predicts pathogen extinction. We argue that our model stays relevant even within this “safe” regime for the following reasons: (1) An immunocompromised individual could remain infected, even if all contacts have recovered or otherwise immune, (2) vaccines often obey limited effectivity, rendering herd immunity to become unachievable and (3) vaccine hesitancy, slow vaccine rollout and local reservoirs remain as barriers to high levels of population immunity.

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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

multiple epitopes within the host, 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 (Torbitt 1880; DeArce 2008). 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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

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

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

may be simpler than researching a complex full-epitope vaccine. A mixed single-epitope strategy while having the benefit of reducing the establishment 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 (Franzo et al. 2019).

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Data Availability statement: All data in this study derives from the model, described in detail in the main text. The code is available at github.com/Simon-Re/complex-vaccination.

Author contributions: S.A.R. and F.A.K. formulated the question. S.A.R., F.A.K, Y.A.K. and A.R.M. formulated the model. S.A.R. programmed and ran the model. All authors jointly analyzed the results and wrote the manuscript.

Funding: We received no funding for this work.

Conflict of Interest statement: The authors declare no competing interests.

Acknowledgements: We thank Raimundo Julian Saona Urmeneta, Maike Morrison, Sergey Kryazhimskiy, Hiroki Ishikawa, Simone Pigolotti and Shingo Miyauchi for fruitful discussions. We also thank participants of the FRISBI seminar at ISTA for useful comments.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Bibliography

Adorini, Luciano. 1998. “Immunodominance.” In *Encyclopedia of Immunology*, 1290–92. Elsevier. https://doi.org/10.1006/rwei.1999.0331.

Akram, Ali, and Robert D Inman. 2012. “Immunodominance: A Pivotal Principle in Host Response to Viral Infections.” *Clinical Immunology* 143 (2): 99–115. https://doi.org/10.1016/j.clim.2012.01.015.

Altman, Meghan O, Davide Angeletti, and Jonathan W Yewdell. 2018. “Antibody Immunodominance: The Key to Understanding Influenza Virus Antigenic Drift.” *Viral Immunology* 31 (2): 142–49. https://doi.org/10.1089/vim.2017.0129.

Ashby, B, and K C King. 2015. “Diversity and the Maintenance of Sex by Parasites.” *Journal of Evolutionary Biology* 28 (3): 511–20. https://doi.org/10.1111/jeb.12590.

Barouch, Dan H, Frank L Tomaka, Frank Wegmann, Daniel J Stieh, Galit Alter, Merlin L Robb, Nelson L Michael, et al. 2018. “Evaluation of a Mosaic HIV-1 Vaccine in a Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 1/2a Clinical Trial (APPROACH) and in Rhesus Monkeys (NHP 13-19).” *The Lancet* 392 (10143): 232–43. https://doi.org/10.1016/S0140-6736(18)31364-3.

Bashirova, Arman A, Wanjing Zheng, Marjan Akdag, Danillo G Augusto, Nicolas Vince, Krista L Dong, Colm O’hUigin, and Mary Carrington. 2021. “Population-Specific Diversity of the Immunoglobulin Constant Heavy G Chain (IGHG) Genes.” *Genes and Immunity* 22 (7–8): 327–34. https://doi.org/10.1038/s41435-021-00156-2.

Bonhoeffer, S, R M May, G M Shaw, and M A Nowak. 1997. “Virus Dynamics and Drug Therapy.” *Proceedings of the National Academy of Sciences of the United States of America* 94 (13): 6971–76. https://doi.org/10.1073/pnas.94.13.6971.

Breman, J G, and I Arita. 1980. “The Confirmation and Maintenance of Smallpox Eradication.” *The New England Journal of Medicine* 303 (22): 1263–73. https://doi.org/10.1056/NEJM198011273032204.

Chabas, Hélène, Sébastien Lion, Antoine Nicot, Sean Meaden, Stineke van Houte, Sylvain Moineau, Lindi M Wahl, Edze R Westra, and Sylvain Gandon. 2018. “Evolutionary Emergence of Infectious Diseases in Heterogeneous Host Populations.” *PLoS Biology* 16 (9): e2006738. https://doi.org/10.1371/journal.pbio.2006738.

Childs, Dylan Z, C J E Metcalf, and Mark Rees. 2010. “Evolutionary Bet-Hedging in the Real World: Empirical Evidence and Challenges Revealed by Plants.” *Proceedings. Biological Sciences / the Royal Society* 277 (1697): 3055–64. https://doi.org/10.1098/rspb.2010.0707.

Choi, Bina, Manish C Choudhary, James Regan, Jeffrey A Sparks, Robert F Padera, Xueting Qiu, Isaac H Solomon, et al. 2020. “Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host.” *The New England Journal of Medicine* 383 (23): 2291–93. https://doi.org/10.1056/NEJMc2031364.

Cong, Mian-er, Walid Heneine, and J Gerardo García-Lerma. 2007. “The Fitness Cost of Mutations Associated with Human Immunodeficiency Virus Type 1 Drug Resistance Is Modulated by Mutational Interactions.” *Journal of Virology* 81 (6): 3037–41. https://doi.org/10.1128/JVI.02712-06.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Corey, Lawrence, and M Juliana McElrath. 2010. “HIV Vaccines: Mosaic Approach to Virus Diversity.” *Nature Medicine* 16 (3): 268–70. https://doi.org/10.1038/nm0310-268.

DeArce, M. 2008. “Correspondence of Charles Darwin on James Torbitt’s Project to Breed Blight-Resistance Potatoes.” *Archives of Natural History* 35 (2): 208–22. https://doi.org/10.3366/E0260954108000351.

Djidjou-Demasse, Ramses, Benoît Moury, and Frédéric Fabre. 2017. “Mosaics Often Outperform Pyramids: Insights from a Model Comparing Strategies for the Deployment of Plant Resistance Genes against Viruses in Agricultural Landscapes.” *The New Phytologist* 216 (1): 239–53. https://doi.org/10.1111/nph.14701.

Gandon, S, M J Mackinnon, S Nee, and A F Read. 2001. “Imperfect Vaccines and the Evolution of Pathogen Virulence.” *Nature* 414 (6865): 751–56. https://doi.org/10.1038/414751a.

Gandon, S, and Y Michalakis. 2002. “Local Adaptation, Evolutionary Potential and Host-Parasite Coevolution: Interactions between Migration, Mutation, Population Size and Generation Time.” *Journal of Evolutionary Biology* 15 (3): 451–62. https://doi.org/10.1046/j.1420-9101.2002.00402.x.

Gandon, Sylvain, and Troy Day. 2008. “Evidences of Parasite Evolution after Vaccination.” *Vaccine* 26 Suppl 3 (July): C4-7. https://doi.org/10.1016/j.vaccine.2008.02.007.

Gandon, Sylvain, Margaret Mackinnon, Sean Nee, and Andrew Read. 2003. “Imperfect Vaccination: Some Epidemiological and Evolutionary Consequences.” *Proceedings. Biological Sciences / the Royal Society* 270 (1520): 1129–36. https://doi.org/10.1098/rspb.2003.2370.

Garcia-Beltran, Wilfredo F, Evan C Lam, Kerri St Denis, Adam D Nitido, Zeidy H Garcia, Blake M Hauser, Jared Feldman, et al. 2021. “Multiple SARS-CoV-2 Variants Escape Neutralization by Vaccine-Induced Humoral Immunity.” *Cell* 184 (9): 2372-2383.e9. https://doi.org/10.1016/j.cell.2021.03.013.

Gibson, Amanda Kyle. 2022. “Genetic Diversity and Disease: The Past, Present, and Future of an Old Idea.” *Evolution* 76 (S1): 20–36. https://doi.org/10.1111/evo.14395.

Grimbergen, Ard Jan, Jeroen Siebring, Ana Solopova, and Oscar P Kuipers. 2015. “Microbial Bet-Hedging: The Power of Being Different.” *Current Opinion in Microbiology* 25 (June): 67–72. https://doi.org/10.1016/j.mib.2015.04.008.

Haas, Sarah E, Mevin B Hooten, David M Rizzo, and Ross K Meentemeyer. 2011. “Forest Species Diversity Reduces Disease Risk in a Generalist Plant Pathogen Invasion.” *Ecology Letters* 14 (11): 1108–16. https://doi.org/10.1111/j.1461-0248.2011.01679.x.

Hartl, Daniel L., and Andrew G. Clark. 2006. *Principles of Population Genetics*. 4th ed. Sunderland, Mass: Sinauer Associates is an imprint of Oxford University Press.

Havenar-Daughton, Colin, Jeong Hyun Lee, and Shane Crotty. 2017. “Tfh Cells and HIV BnAbs, an Immunodominance Model of the HIV Neutralizing Antibody Generation Problem.” *Immunological Reviews* 275 (1): 49–61. https://doi.org/10.1111/imr.12512.

He, Wan-Ting, Meng Yuan, Sean Callaghan, Rami Musharrafieh, Ge Song, Murillo Silva, Nathan Beutler,

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

et al. 2022. “Broadly Neutralizing Antibodies to SARS-Related Viruses Can Be Readily Induced in Rhesus Macaques.” *Science Translational Medicine* 14 (657): eabl9605. https://doi.org/10.1126/scitranslmed.abl9605.

“History of Measles | CDC.” n.d. Accessed April 10, 2023. https://www.cdc.gov/measles/about/history.html.

Hou, Jue, Shubham Shrivastava, Christopher C Fraser, Hooi Linn Loo, Lan Hiong Wong, Victor Ho, Katja Fink, Eng Eong Ooi, and Jianzhu Chen. 2019. “Dengue Mosaic Vaccines Enhance Cellular Immunity and Expand the Breadth of Neutralizing Antibody against All Four Serotypes of Dengue Viruses in Mice.” *Frontiers in Immunology* 10 (June): 1429. https://doi.org/10.3389/fimmu.2019.01429.

Houte, Stineke van, Alice K E Ekroth, Jenny M Broniewski, Hélène Chabas, Ben Ashby, Joseph Bondy-Denomy, Sylvain Gandon, et al. 2016. “The Diversity-Generating Benefits of a Prokaryotic Adaptive Immune System.” *Nature* 532 (7599): 385–88. https://doi.org/10.1038/nature17436.

Kar, Tamalika, Utkarsh Narsaria, Srijita Basak, Debashrito Deb, Filippo Castiglione, David M Mueller, and Anurag P Srivastava. 2020. “A Candidate Multi-Epitope Vaccine against SARS-CoV-2.” *Scientific Reports* 10 (1): 10895. https://doi.org/10.1038/s41598-020-67749-1.

Keeling, Matt J., and Pejman Rohani. 2011. *Modeling Infectious Diseases in Humans and Animals*. Illustrated. Princeton University Press.

Kemp, Steven A, Dami A Collier, Rawlings P Datir, Isabella A T M Ferreira, Salma Gayed, Aminu Jahun, Myra Hosmillo, et al. 2021. “SARS-CoV-2 Evolution during Treatment of Chronic Infection.” *Nature* 592 (7853): 277–82. https://doi.org/10.1038/s41586-021-03291-y.

Kennedy, David A, and Andrew F Read. 2017. “Why Does Drug Resistance Readily Evolve but Vaccine Resistance Does Not?” *Proceedings. Biological Sciences / the Royal Society* 284 (1851). https://doi.org/10.1098/rspb.2016.2562.

King, K C, and C M Lively. 2012. “Does Genetic Diversity Limit Disease Spread in Natural Host Populations?” *Heredity* 109 (4): 199–203. https://doi.org/10.1038/hdy.2012.33.

Kissler, Stephen M, Joseph R Fauver, Christina Mack, Caroline G Tai, Mallery I Breban, Anne E Watkins, Radhika M Samant, et al. 2021. “Viral Dynamics of SARS-CoV-2 Variants in Vaccinated and Unvaccinated Persons.” *The New England Journal of Medicine* 385 (26): 2489–91. https://doi.org/10.1056/NEJMc2102507.

Lieberman, Erez, Christoph Hauert, and Martin A Nowak. 2005. “Evolutionary Dynamics on Graphs.” *Nature* 433 (7023): 312–16. https://doi.org/10.1038/nature03204.

Lipsitch, Marc, Florian Krammer, Gili Regev-Yochay, Yaniv Lustig, and Ran D Balicer. 2022. “SARS-CoV-2 Breakthrough Infections in Vaccinated Individuals: Measurement, Causes and Impact.” *Nature Reviews. Immunology* 22 (1): 57–65. https://doi.org/10.1038/s41577-021-00662-4.

Lively, C M, and M F Dybdahl. 2000. “Parasite Adaptation to Locally Common Host Genotypes.” *Nature* 405 (6787): 679–81. https://doi.org/10.1038/35015069.

Markowitz, Harry. 1952. “Portfolio Selection.” *The Journal of Finance* 7 (1): 77.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

https://doi.org/10.2307/2975974.

McCallum, Matthew, Jessica Bassi, Anna De Marco, Alex Chen, Alexandra C Walls, Julia Di Iulio, M Alejandra Tortorici, et al. 2021. “SARS-CoV-2 Immune Evasion by the B.1.427/B.1.429 Variant of Concern.” *Science* 373 (6555): 648–54. https://doi.org/10.1126/science.abi7994.

McLeod, David V, Lindi M Wahl, and Nicole Mideo. 2021. “Mosaic Vaccination: How Distributing Different Vaccines across a Population Could Improve Epidemic Control.” *Evolution Letters* 5 (5): 458–71. https://doi.org/10.1002/evl3.252.

Mikaberidze, A, B A McDonald, and S Bonhoeffer. 2015. “Developing Smarter Host Mixtures to Control Plant Disease.” *Plant Pathology* 64 (4): 996–1004. https://doi.org/10.1111/ppa.12321.

Normile, Dennis. 2010. “Rinderpest, Deadly for Cattle, Joins Smallpox as a Vanquished Disease.” *Science* 330 (6003): 435–435. https://doi.org/10.1126/science.330.6003.435.

Nowak, M, and R M May. 2000. “Chapter 3-4.” In *Virus Dynamics: Mathematical Principles of Immunology and Virology*, 16.

Ochmann, Sophie, and Max Roser. 2018. “Smallpox - Our World in Data.” *Our World in Data*, June.

Patwa, Z, and L M Wahl. 2008. “The Fixation Probability of Beneficial Mutations.” *Journal of the Royal Society, Interface* 5 (28): 1279–89. https://doi.org/10.1098/rsif.2008.0248.

Pérez-Losada, Marcos, Miguel Arenas, Juan Carlos Galán, Ferran Palero, and Fernando González-Candelas. 2015. “Recombination in Viruses: Mechanisms, Methods of Study, and Evolutionary Consequences.” *Infection, Genetics and Evolution* 30 (March): 296–307. https://doi.org/10.1016/j.meegid.2014.12.022.

Planas, Delphine, Nell Saunders, Piet Maes, Florence Guivel-Benhassine, Cyril Planchais, Julian Buchrieser, William-Henry Bolland, et al. 2022. “Considerable Escape of SARS-CoV-2 Omicron to Antibody Neutralization.” *Nature* 602 (7898): 671–75. https://doi.org/10.1038/s41586-021-04389-z.

Ploetz, Randy C. 2015. “Fusarium Wilt of Banana.” *Phytopathology* 105 (12): 1512–21. https://doi.org/10.1094/PHYTO-04-15-0101-RVW.

Rella, Simon A, Yuliya A Kulikova, Emmanouil T Dermitzakis, and Fyodor A Kondrashov. 2021. “Rates of SARS-CoV-2 Transmission and Vaccination Impact the Fate of Vaccine-Resistant Strains.” *Scientific Reports* 11 (1): 15729. https://doi.org/10.1038/s41598-021-95025-3.

Renard, Delphine, and David Tilman. 2019. “National Food Production Stabilized by Crop Diversity.” *Nature* 571 (7764): 257–60. https://doi.org/10.1038/s41586-019-1316-y.

REX Consortium. 2013. “Heterogeneity of Selection and the Evolution of Resistance.” *Trends in Ecology & Evolution* 28 (2): 110–18. https://doi.org/10.1016/j.tree.2012.09.001.

———. 2016. “Combining Selective Pressures to Enhance the Durability of Disease Resistance Genes.” *Frontiers in Plant Science* 7 (December): 1916. https://doi.org/10.3389/fpls.2016.01916.

Rimbaud, Loup, Julien Papaïx, Luke G Barrett, Jeremy J Burdon, and Peter H Thrall. 2018. “Mosaics,

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Mixtures, Rotations or Pyramiding: What Is the Optimal Strategy to Deploy Major Gene Resistance?" *Evolutionary Applications* 11 (10): 1791–1810. https://doi.org/10.1111/eva.12681.

Russell, Magdalena L, Aisha Souquette, David M Levine, Stefan A Schattgen, E Kaitlynn Allen, Guillermina Kuan, Noah Simon, et al. 2022. "Combining Genotypes and T Cell Receptor Distributions to Infer Genetic Loci Determining V(D)J Recombination Probabilities." *ELife* 11 (March). https://doi.org/10.7554/eLife.73475.

Safonova, Yana, Sung Bong Shin, Luke Kramer, James Reecy, Corey T Watson, Timothy P L Smith, and Pavel A Pevzner. 2022. "Variations in Antibody Repertoires Correlate with Vaccine Responses." *Genome Research* 32 (4): 791–804. https://doi.org/10.1101/gr.276027.121.

Schmidt, Kenneth A., and Richard S. Ostfeld. 2001. "Biodiversity and the Dilution Effect in Disease Ecology." *Ecology*, March.

Simons, Andrew M. 2011. "Modes of Response to Environmental Change and the Elusive Empirical Evidence for Bet Hedging." *Proceedings. Biological Sciences / the Royal Society* 278 (1712): 1601–9. https://doi.org/10.1098/rspb.2011.0176.

Soh, Sandrine M, Yeongjun Kim, Chanwoo Kim, Ui Soon Jang, and Hye-Ra Lee. 2021. "The Rapid Adaptation of SARS-CoV-2-Rise of the Variants: Transmission and Resistance." *Journal of Microbiology* 59 (9): 807–18. https://doi.org/10.1007/s12275-021-1348-5.

Sommer, Simone. 2005. "The Importance of Immune Gene Variability (MHC) in Evolutionary Ecology and Conservation." *Frontiers in Zoology* 2 (October): 16. https://doi.org/10.1186/1742-9994-2-16.

Sonnleitner, Sissy Therese, Martina Prelog, Stefanie Sonnleitner, Eva Hinterbichler, Hannah Halbfurter, Dominik B C Kopecky, Giovanni Almanzar, et al. 2022. "Cumulative SARS-CoV-2 Mutations and Corresponding Changes in Immunity in an Immunocompromised Patient Indicate Viral Evolution within the Host." *Nature Communications* 13 (1): 2560. https://doi.org/10.1038/s41467-022-30163-4.

Starr, Tyler N, Allison J Greaney, Sarah K Hilton, Daniel Ellis, Katharine H D Crawford, Adam S Dingens, Mary Jane Navarro, et al. 2020. "Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding." *Cell* 182 (5): 1295-1310.e20. https://doi.org/10.1016/j.cell.2020.08.012.

Suhrbier, A. 1997. "Multi-Epitope DNA Vaccines." *Immunology and Cell Biology* 75 (4): 402–8. https://doi.org/10.1038/icb.1997.63.

The Lancet. 2019. "Measles Eradication: A Goal within Reach, Slipping Away." *The Lancet* 393 (10182): 1669. https://doi.org/10.1016/S0140-6736(19)30903-1.

Torbitt, James. 1880. "Letter from J. Torbitt 'Letter No. 12728' ." *Darwin Correspondence Project*, September.

Ugelvig, Line V, Daniel J C Kronauer, Alexandra Schrempf, Jürgen Heinze, and Sylvia Cremer. 2010. "Rapid Anti-Pathogen Response in Ant Societies Relies on High Genetic Diversity." *Proceedings. Biological Sciences / the Royal Society* 277 (1695): 2821–28. https://doi.org/10.1098/rspb.2010.0644.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024

Wang, Yan-Ping, Zhe-Chao Pan, Li-Na Yang, Jeremy J Burdon, Hanna Friberg, Qi-Jun Sui, and Jiasui Zhan. 2021. “Optimizing Plant Disease Management in Agricultural Ecosystems Through Rational In-Crop Diversification.” *Frontiers in Plant Science* 12 (December): 767209. https://doi.org/10.3389/fpls.2021.767209.

Wang, Yifan, Caixuan Liu, Chao Zhang, Yanxing Wang, Qin Hong, Shiqi Xu, Zuyang Li, Yong Yang, Zhong Huang, and Yao Cong. 2022. “Structural Basis for SARS-CoV-2 Delta Variant Recognition of ACE2 Receptor and Broadly Neutralizing Antibodies.” *Nature Communications* 13 (1): 871. https://doi.org/10.1038/s41467-022-28528-w.

Willett, Brian J, Joe Grove, Oscar A MacLean, Craig Wilkie, Giuditta De Lorenzo, Wilhelm Furnon, Diego Cantoni, et al. 2022. “SARS-CoV-2 Omicron Is an Immune Escape Variant with an Altered Cell Entry Pathway.” *Nature Microbiology* 7 (8): 1161–79. https://doi.org/10.1038/s41564-022-01143-7.

Yewdell, Jonathan W, and Jefferson J S Santos. 2021. “Original Antigenic Sin: How Original? How Sinful?” *Cold Spring Harbor Perspectives in Medicine* 11 (5). https://doi.org/10.1101/cshperspect.a038786.

Zhang, Jing, Zi Bo Han, Yu Liang, Xue Feng Zhang, Yu Qin Jin, Li Fang Du, Shuai Shao, et al. 2022. “A Mosaic-Type Trimeric RBD-Based COVID-19 Vaccine Candidate Induces Potent Neutralization against Omicron and Other SARS-CoV-2 Variants.” *ELife* 11 (August). https://doi.org/10.7554/eLife.78633.

Zhang, Xiyun, Zhongyuan Ruan, Muhua Zheng, Jie Zhou, Stefano Boccaletti, and Baruch Barzel. 2022. “Epidemic Spreading under Mutually Independent Intra- and Inter-Host Pathogen Evolution.” *Nature Communications* 13 (1): 6218. https://doi.org/10.1038/s41467-022-34027-9.

Accepted Manuscript

Downloaded from https://academic.oup.com/evolut/advance-article/doi/10.1093/evolut/qpae106/7712376 by guest on 15 July 2024