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The shape of waning vaccinal immunity: Implications for control

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Abstract

The COVID-19 pandemic and current uncertainties about H5N1 influenza underscore the importance of vaccination for both community immunity and to prevent pathogen invasion. While the duration of a fully-immune period is often included in epidemiological models with waning immunity, the relative susceptibility to infection in fully-waned individuals and moreover their interplay that determines the shape of the trajectory of waning vaccinal immunity also may have important impacts on pathogen invasion potential. In this paper, we examine pathogen invasion outcomes with a simple mathematical framework that embeds the shape of vaccinal immunity within a buffered susceptibility framework. Using illustrative examples, we show pathogen invasion hinges on the characteristics of this shape, resulting in a large variation in outcomes. A key result is that stronger immunity (i.e. a smaller relative susceptibility in fully-waned individuals) can have a dramatic impact on such invasion characteristics, but the magnitude of this effect crucially depends on the underlying shape of immunity: the initial rate of waning is critical to the outcome. Our results highlight the importance of measuring the relative susceptibility of infection in fully-waned individuals. Additionally, they illustrate the importance of characterising host immune responses granularly and of taking this into account in pathogen-specific epidemiological models.

Author summary

Vaccine protection often wanes over time and we therefore require repeated vaccination in order to ensure high enough levels of protection for community immunity. While waning immunity is complex, classic epidemiological models often simplify this process. In this paper, we present a mathematical model of community vaccination where

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vaccinated individuals flow through a number of compartments with changing relative susceptibility to reinfection; this allows us to examine the impact of more realistic patterns of the loss of immunity. We find that the relative susceptibility of a vaccinated individual after protection wanes and the shape of the waning process itself both have implications for the resulting level of community protection. Our results therefore show the importance of accurately modeling host immune responses and the need for more empirical work that examines the shape of vaccinal waning immunity. We also require more data on the susceptibility of infection in individuals whose protection has fully waned after vaccination.

Introduction

The COVID-19 pandemic highlighted the importance of waning immunity on epidemiological dynamics and public health interventions (e.g. [1–4]) not least in the context of proposed nonpharmaceutical interventions that hinge on individual immune status, such as 'shield immunity' [5,6]. The watershed moment during the COVID-19 pandemic was the development and deployment of safe vaccines [7–9] and while current formulations of COVID-19 vaccines only transiently prevent infection, effective transmission-blocking vaccines can result in pathogen control (see e.g. [10–12]). However, for SARS-CoV-2 and other antigenically variable pathogens such as influenza, protective immunity from vaccinations is known to wane over time [13,14]. This can be due to numerous factors including antigenic changes in the pathogen but also the waning of antibodies to vaccine strains following vaccination [15, 16]. There have been important recent efforts to generate pan-coronavirus/pan-sarbecovirus vaccines that would provide broad immunological protection (see e.g. [17–20]) and similarly, the development of 'Universal Influenza Vaccines (UIVs)' has been an important focus (see e.g. [21–26]). Such broadly-protective vaccines will be crucial to prevent the next pandemic and given the current situation with H5N1 influenza, it is important for us to better understand the epidemiological dynamics of vaccination in the context of waning immunity (see e.g. [27]).

Clearly, whether community immunity prevents pathogen establishment (or whether elimination is achieved if vaccination begins after establishment) crucially hinges on the strength and duration of vaccinal immunity. Furthermore, it may depend on the way in which immunity is lost through time, i.e. the shape of waning immunity. Thus, an important question is how immunity wanes, in addition to the rate at which it is lost. For example, does it matter if immunity remains relatively high and then falls off rapidly (an accelerating loss of immunity), or if there is an initial loss followed by a slow decline (a decelerating loss)? It seems clear that the duration and shape of waning immunity are likely to be important to epidemiological dynamics and control through vaccination.

Classic susceptible-infected-recovered-susceptible (SIRS) models capture waning immunity by using a single waning rate or immunity period, after which the host is fully susceptible again [28]. Throughout the paper when we refer to susceptibility we are only considering susceptibility to transmission, although previous models have investigated the waning of severity blocking immunity [29]. As such these classic models assume individuals are either fully susceptible or fully immune, but it is clear that individuals may never return to full susceptibility. To capture this effect, Morris et al. [30] developed a model with buffered susceptibility, where individuals wane to a different, but also susceptible, class. Recent work has leveraged simple mathematical models with buffered susceptibility to investigate the impacts of immune uncertainties on potential future SARS-CoV-2 trajectories [4,29,31–33] and have showed

that the characteristics of buffered immunity can lead to a large range of future immuno-epidemiological outcomes. For example it has been shown that structured immunity can cause backwards bifurcations or multiple equilibria in epidemiological models [34]. Simulation work has shown the importance of explicitly modeling the within host process [35] and variation in individual waning [36]. Together, this work shows that careful modeling of the immune processes is key to understanding population level dynamical implications of immune interactions.

In other work, El Khalifi and Britton [37,38] have examined gradual waning (i.e. regaining progressively stronger partial susceptibility during waning) in a variety of contexts. To model gradual waning in an SIRS model, they considered individuals flowing through a series of partially immune (and thus partially susceptible) classes until returning to complete susceptibility, and they compared linear and exponential waning with classical assumptions [37]. As a calibration method, they assumed that the cumulative immunity during the waning period was constant. In subsequent work [38], these authors further developed this framework to include heterogeneous waning among groups. While El Khalifi and Britton [37,38] showed the effects of gradual waning in SIRS frameworks, and Saad-Roy, Wagner et al. [4] examined the case where individuals wane to a partially susceptible class (i.e. 'buffered susceptibility), the effects of the shape of immunity with buffered susceptibility remain unknown.

In this paper, we develop a framework to examine the effects of the shape of waning vaccinal immunity on pathogen control. We use a buffered susceptible approach and consider multiple susceptible classes, each with their own relative susceptibility to infection, with the last (fully-waned) state (potentially) preserving some immunity (i.e. having lower susceptibility to infection than a never-exposed individual, see [4,29–33]). Thus, our mathematical model consists of a series of partially susceptible classes, which extends (and generalizes) previous analyses with two 'susceptible' classes (see [4]). We capture waning immunity with different shapes and examine how this impacts epidemiological dynamics and in particular pathogen control through vaccination. Furthermore, while El Khalifi and Britton [37,38] calibrated their model based on cumulative immunity, we assume here that the duration until individuals are fully-waned is the same, and vary the relative susceptibility as they progress through multiple partially immune states. Thus, the cumulative immunity for particular schemes may vary, and future work should examine the effects of keeping this constant in a buffered susceptibility framework.

Model framework

We extend the model of Saad-Roy, Wagner et al. [4] to include multiple partially susceptible classes. However, to focus on the waning process, we ignore characteristics of infections in priorly-immune individuals (which was modelled in [4]). Thus, in our model, S_0 is the class of completely naive hosts, S_1 describes the class of vaccinated individuals where immunity has fully waned so that the relative susceptibility to infection is ε_0 (e.g. $\varepsilon_0 = 1$ describes a vaccine where immunity is eventually completely lost). For $j = 2, ..., n$, S_j describes vaccinated hosts that flow from S_{j+1}, where S_n consists of individuals that have been most recently vaccinated. Finally, I represents the infected class of hosts. All compartments sum to 1, so each class reflects a proportion of the population. We denote μ as the birth/death rate of the host, ν as the vaccination rate of the host population (i.e. we assume that vaccination occurs at random), ω as the waning rate of the immunity (i.e. $\frac{1}{\omega}$ is the average time to get from S_n to S_1), β as the transmission rate, and γ as the recovery rate. Furthermore, $\varepsilon(j)$ denotes the relative susceptibility of individuals in S_j, i.e. this represents the degree of waning that has occurred.

Thus, the function $\varepsilon(j)$ is the 'shape of waning immunity'. The model equations are therefore

$$\begin{aligned}
\frac{dS_0}{dt} &= \mu - (\mu+\nu)S_0 - \beta S_0 I,\\
\frac{dS_1}{dt} &= m\omega S_2 - (\mu+\nu)S_1 - \beta\varepsilon(1)S_1 I,\\
\frac{dS_i}{dt} &= m\omega S_{i+1} - (\mu+\nu+m\omega)S_i - \beta\varepsilon(i)S_i I \qquad (1<i<n),\\
\frac{dS_n}{dt} &= \gamma I + \nu\sum_{j=0}^{m} S_j - (\mu+m\omega)S_n,\\
\frac{dI}{dt} &= \beta S_0 I + \beta\sum_{j=1}^{m}\varepsilon(j)S_j I - (\mu+\gamma)I,
\end{aligned}$$

where $m = n - 1$.

In this paper, we examine the effect of the shape of waning immunity on potential pathogen invasion. Thus, we focus on the disease free equilibrium (P_0, where $I_0 = 0$), and the vaccination required so that it is stable. To obtain the disease-free equilibrium in our model, we set the model equations equal to zero (see S1 Appendix for detailed derivations), which gives

$$\begin{aligned}
S_0^* &= \frac{\mu}{\mu+\nu},\\
S_1^* &= \frac{\nu}{\mu+\nu}\left(\frac{m\omega}{\mu+\nu+m\omega}\right)^m,\\
S_i^* &= \left(\frac{m\omega}{\mu+\nu+m\omega}\right)^{n-i}\frac{\nu}{\mu+\nu+m\omega}, \qquad (1<i<n)\\
S_n^* &= \frac{\nu}{\mu+\nu+m\omega}.
\end{aligned}$$

In the absence of vaccination, the basic reproduction number is that of the classic SIR model, i.e.

$$\mathcal{R}_0 = \frac{\beta}{\mu+\gamma}.$$

With vaccination, i.e. $\nu > 0$, the control reproduction number $\mathcal{R}_C$ can be determined using the linearization of the $\frac{dI}{dt}$ equation at the disease-free equilibrium (see [39] for a generalized approach), i.e.,

$$\mathcal{R}_C = \frac{\partial}{\partial I}\frac{dI}{dt}\bigg|_{P_0} = \mathcal{R}_0\left(S_0^* + \sum_{j=1}^{m}\varepsilon(j)S_j^*\right). \tag{1}$$

Thus, when $\frac{1}{S_0^*+\sum_{i=1}^{m}\varepsilon(i)S_i^*}$ is less than $\mathcal{R}_0$, the pathogen can invade a population that is undergoing vaccination at rate ν, with the shape of immunity $\varepsilon(i)$ and rate of waning immunity ω. We denote the value of $\mathcal{R}_0$ required to invade a population being vaccinated under such a scheme to be $\mathcal{R}_{\text{inv}}$ or the "R invasion".

$$\frac{1}{S_0^* + \sum_{i=1}^{m}\varepsilon(i)S_i^*} = \mathcal{R}_{\text{inv}} \tag{2}$$

Thus, we can compute this quantity $\mathcal{R}_{\text{inv}}$ for any formulation of $\varepsilon(i)$. Clearly $\mathcal{R}_{\text{inv}}$ depends on the particular shape of waning. To illustrate a variety of cases, we use two different waning

schemes. Both of which facilitate the waning from fully immune individuals, $\varepsilon(n) = 0$, to fully waned individuals $\varepsilon(1) = \varepsilon_0$. The first is a simple exponential-like decelerating or accelerating function where more waning happens early or late in the waning period (Fig 1B), i.e.

$$\varepsilon(i) = \varepsilon_0 \left(\frac{n-i}{n-1} \right)^p. \tag{3}$$

The second scheme we use is a Hill-like function, to model 'threshold'-like waning (Fig 1C–1D), i.e.,

$$\varepsilon(i) = \varepsilon_0 \frac{(n-i)^p}{k^p + (n-i)^p} \left(\frac{k^p + (n-1)^p}{(n-1)^p} \right). \tag{4}$$

Note that the factor $\left(\frac{k^p + (n-1)^p}{(n-1)^p} \right)$ is so that $\varepsilon(1) = \varepsilon_0$. The results that follow hold for any particular choice of n, increasing n simply divides the population proportions into smaller slices but the beginning and endpoints of the waning process are still fixed.

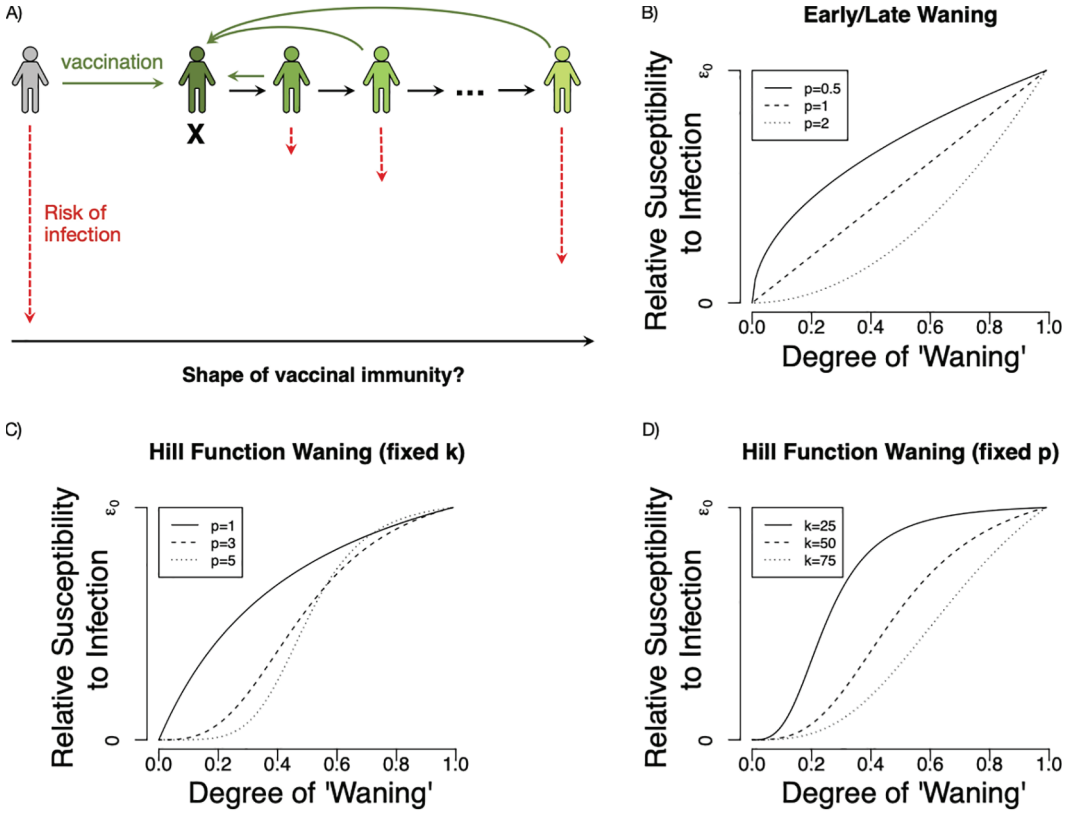

Fig 1. (A) Illustrative schematic of population vaccination and immunity waning process. (B-D) depict possible variation in the ε_0, which is the relative susceptibility to infection in individuals with fully-waned vaccinal immunity. Note that, here, the "degree of 'waning'" is a measure of the number of compartments away from complete immunity, i.e. a degree of 'waning' of 0 is when individuals are still in the S_n compartment, whereas a degree of 'waning' of 1 is when individuals are in the S_1 compartment. In all three of these panels (and beyond), $n = 100$. (B) Accelerating/decelerating waning when $p = 0.5, 1, 2$. (C) Hill-like function for fixed $k = 50$ and $p = 1, 3, 5$. (D) Hill-like function fixed for $p = 3$ and $k = 25, 50, 75$.

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Results and discussion

We begin by visualizing $\mathcal{R}_{\text{inv}}$ over a variety of vaccination rates, waning rates, and over various waning schemes. In Fig 2, we illustrate the dependence of $\mathcal{R}_{\text{inv}}$ on the duration of immunity and vaccination rate. For a particular parameter pair, we see that changing the waning scheme can dramatically alter the protection of a population. For example, a comparison of the early and late waning schemes (Fig 2, comparing the top row and bottom row respectively) for the same vaccination rate and duration of immunity, reveals that the $\mathcal{R}_{\text{inv}}$ can be more than four times greater if waning happens later. This is a massive difference, and has important implications for population level pathogen prevention.

So far, we have assumed that the shape of waning immunity is exponential-like, and thus is either concave-up or concave-down. In reality, waning is likely more complex, with changes in concavity in the relative susceptibility to infection. To explore this, we use a Hill-like function to describe the shape of waning immunity. In Fig 3, we plot $\mathcal{R}_{\text{inv}}$ (as in Fig 2), but we now vary the two waning shape parameters of the Hill-like function. In particular, we find that as p increases there is some increase in $\mathcal{R}_{\text{inv}}$. However, the fold change in $\mathcal{R}_{\text{inv}}$ for a particular change in p for a particular combination of ν and ω is larger if the relative susceptibility after waning (ε_0) is changed. This is due in part to each form of the Hill-like waning function ultimately waning to ε_0 regardless of shape, so fully waned individuals are still contributing to population level protection more if ε_0 is smaller. As such, these two parameters combine to explain the protection experienced by the population. In Fig 3B, we adjust k instead, showing it can also have a significant impact on the resulting $\mathcal{R}_{\text{inv}}$. As expected, we find that when individuals lose their immunity earlier in the waning period (when k is smaller), the population is overall more susceptible, and thus the $\mathcal{R}_{\text{inv}}$ is lower. (Note that this is akin to our findings in Fig 2).

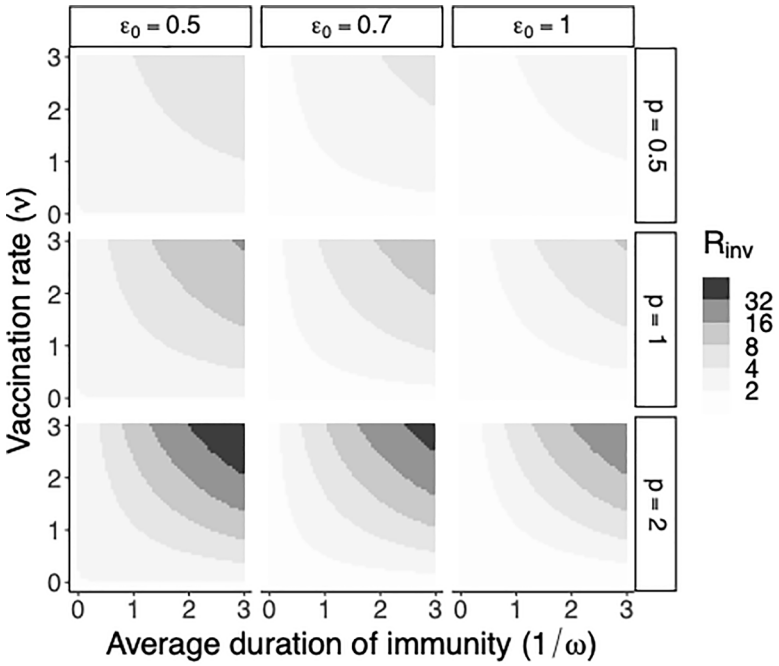

Fig 2. $\mathcal{R}_{\text{inv}}$ calculated for the combination of duration of immunity, vaccination rate, immunity remaining after waning, and the shape parameter of the early/late waning function (Eq 3). Here we fix $\mu = 0.02$.

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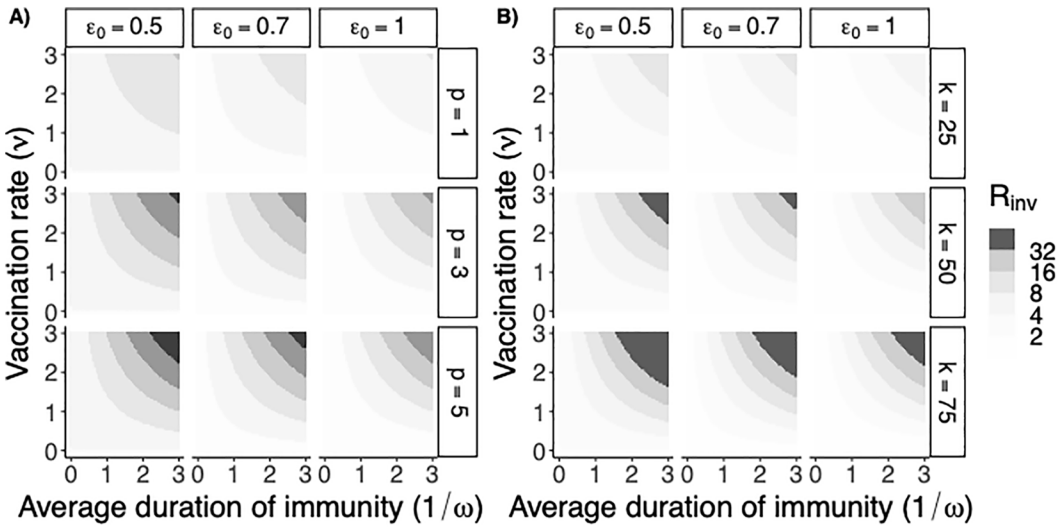

Fig 3. $\mathcal{R}_{inv}$ calculated for the combination of duration of immunity, vaccination rate, immunity remaining after waning, and the shape parameter of the waning function. In A) we fix $k = 50$, in B) $p = 3$. Similar to Fig 2, here we fix $\mu = 0.02$. In panels (A) and (B), we focus on varying p and k, respectively.

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In both situations that we have examined, it is clear that ε_0 and the shape of vaccinal waning can have a major effect on the resulting values of $\mathcal{R}_{inv}$. Importantly, as more immunity is preserved after the waning period (i.e., as ε_0 is decreased), the potential for progressively larger $\mathcal{R}_{inv}$ values becomes possible. Additionally, waning curves that preserve immunity early in the waning process provide higher levels of population protection. Therefore, our results illustrate the importance of including both the shape of waning and this endpoint level of immunity in epidemiological models. In particular, such granularity enables more precise predictions about the $\mathcal{R}_{inv}$ for a particular population. Furthermore, increases in vaccination rates can alleviate pessimistic outcomes. Thus, quantifying the shape of waning vaccinal immunity is paramount, especially for emerging broadly-protective vaccines.

In Fig 4, we illustrate the fold change in $\mathcal{R}_{inv}$ for a particular shape parameter and relative susceptibility after waning for both shape functions. These changes are with respect to a baseline assumption about the shape of the waning function, where $\varepsilon_0 = 1$ and $p = 1$ (e.g. simple linear waning all the way to fully susceptible, see Fig 1B) for the simple accelerating/decelerating waning function or $\varepsilon_0 = 1$, $p = 5$, and $k = 50$ (e.g. a parameter set where p and k both can exert control over the shape of the curve, see Fig 1C and 1D) for the Hill-like function type waning.

We can again here see the importance of understanding how waning happens in an individual. The change in $\mathcal{R}_{inv}$ across the range of even this modest set of choices can be more than double, or even result in a decrease in the $\mathcal{R}_{inv}$ for a given choice compared to the baseline. When we look specifically at threshold type waning, we see that the relative susceptibility after waning (ε_0) exerts much more control over this change than p. But when we allow k to vary we can see a very large range of outcomes for $\mathcal{R}_{inv}$.

It is worth noting that differences in population immunity may simply be driven by differences in the total immunity generated by a vaccine, represented by the area under the waning curve. In Fig 5 we show the population level susceptibility for two different waning curves with identical areas under them (Fig 5A). We then compute the difference between the resulting community susceptibility in Fig 5B. From this it is clear that the linear waning

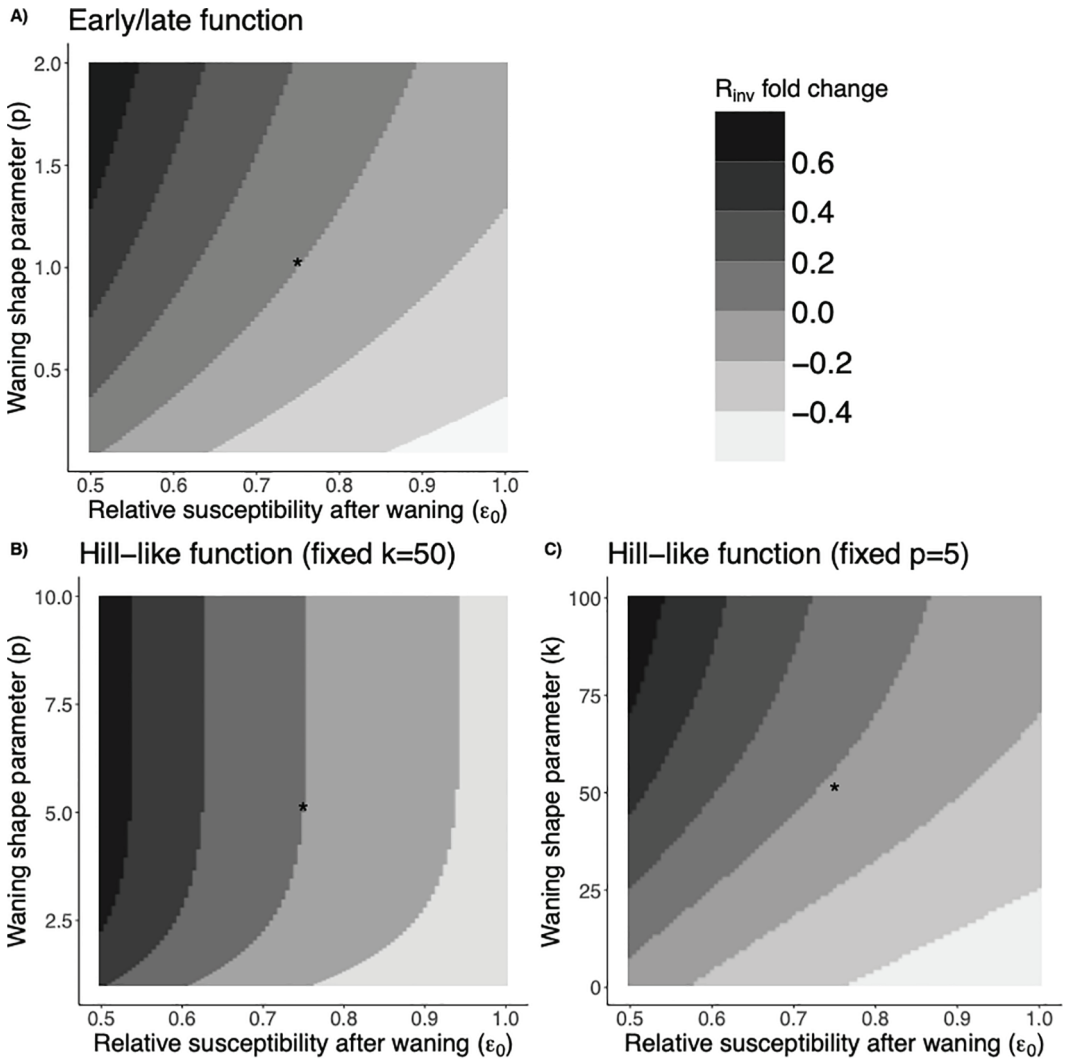

Fig 4. Shows the $\mathcal{R}_{inv}$ fold change with respect to a baseline waning shape where $\varepsilon_0 = 0.75$ for the (A) accelerating/decelerating waning function where the baseline is $p = 1$, or the (B) Hill-like function for fixed $k = 50$ or for (C) fixed $p = 3$ where the baseline is $k = 50$ and $p = 5$. In each plot $\mathcal{R}_{inv}$ fold change is calculated with respect to the baseline in the center of the plot marked with a star. The other model parameters are held constant at $\mu = 0.02$, $\omega = 1$, and $\nu = 1$.

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function causes more susceptibility in the community compared to the step-wise waning, due to more loss of immunity earlier in the waning process. Since individuals are re-vaccinated randomly, delaying waning means that individuals have more immunity before they become revaccinated on average. The magnitude of this effect increases as individuals become vaccinated more frequently (such that they are less likely to wane into the regime where the step-wise waning results in them being more susceptible), and if the duration of vaccine derived immunity is long.

The shape of the waning process clearly has large implications for the population level dynamics, as the same exact vaccination rate and duration of immunity we can generate populations with $\mathcal{R}_0$ up to four times another population's $\mathcal{R}_0$. The only difference between these two populations being the waning process. In particular, the amount of immunity that is lost early in the waning period and the relative susceptibility after waning (ε_0) matter significantly

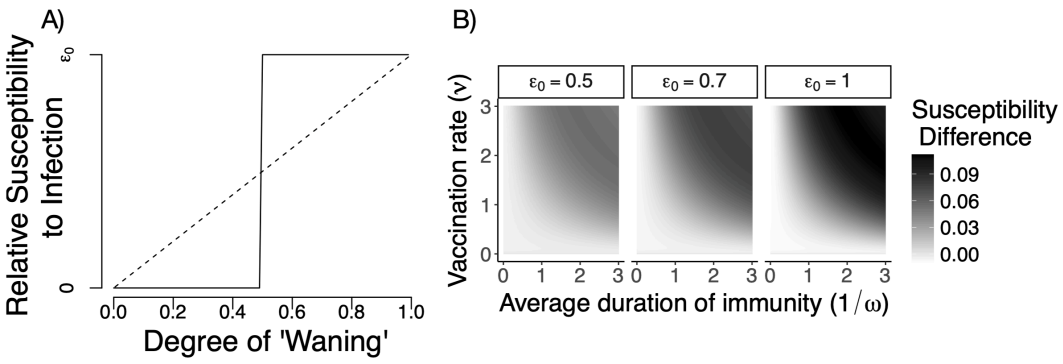

Fig 5. Different waning functions with the same area under the curve can have different population susceptibility. A) Shows two different waning functions with the same area under the curve. B) Shows the difference in population susceptibility between the linear case and the step-wise case, for a range of vaccination parameters. The shading indicates the amount of increased susceptibility in the linear waning case due to additional early waning.

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to population level susceptibility. As more immunity is preserved later into and after the waning period, a population is comparatively much more protected. This improved protection is true for multiple forms of waning functions, showing that what matters is the host susceptibility rather than any particular functional form.

Caveats and future work

To examine the effect of the shape of waning vaccinal immunity on community immunity, our modelling framework has many simplifying assumptions, and we have omitted other important characteristic. Furthemore, and perhaps most importantly, we have ignored epidemiological dynamics and focused on community immunity. However, in the absence of such protection, pathogen invasion would be possible, and it would be particularly salient to explore the resulting medium- and long-term dynamics in our model. Classical work has shown that sustained epidemiological oscillations can occur if there are more than two fully immune compartments in an SIRS-like model [40]. Thus, our model may also exhibit such periodicity, and investigating this possibility would be important to guide vaccination policies for ongoing epidemics.

Second, our model assumes that individuals are vaccinated randomly. However, non-random vaccination, e.g., vaccinating individuals who have gone the longest without receiving a vaccination, could cause increases in $\mathcal{R}_{\text{inv}}$. Furthermore, heterogeneities in vaccine uptake, or in age structure [41] or transmission [42,43], could also affect $\mathcal{R}_{\text{inv}}$. For example, May and Anderson [44] examined the effect of heterogeneities in space on optimal vaccination. Furthermore, both the duration and the shape of waning vaccinal immunity may themselves be age-dependent. Thus, the interplay of these factors with the shape of waning vaccinal immunity are important areas for future research.

Third, we have focused on transmission-blocking immunity, but clinical severity of infections as vaccinal immunity wanes may be epidemiologically important, and may crucially shape policy. Relatedly, we have ignored the economics of vaccination in our model. However, these will likely hinge on clinical severity, and can affect decision-making regarding vaccine development and deployment [22,45]. Thus, extending our model to include clinical immunity in addition to economic considerations would be fruitful avenues to explore.

Our model does not consider the stochastic dynamics of epidemics, which are likely to be particularly important in low case counts and elimination settings. It would be useful to develop a stochastic extension of our model to understand how larger and more frequent outbreaks may occur in populations near $R_{inv} = 1$. Further extensions could also incorporate additional factors for disease control [46], including socio-epidemiological factors including individual decision making [47,48].

Additionally, social dynamics and adherence to (pharmaceutical or nonpharmaceutical) interventions can influence pathogen dynamics, and vice-versa (see e.g. [47,49,50]). Furthermore, vaccine hesitancy and refusal may shape population susceptibility [51,52]. For example, the synergistic effects of multiple family members being vaccinated together or social groups refusing vaccines can be important factors for pathogen control via community immunity.

Finally, while social dynamics could potentially complicate vaccination strategies, our model could also be adapted to incorporate other biological features, such as maternal immunity or explicit vaccinal cross-immunity. For example, maternal antibodies present in infants could be key for elimination of certain pathogens, and these wane over time [53]. Additionally, our framework could be adapted to examine strain-specific cross-protection, which is key for understanding how UIVs may be employed [21–26].

Conclusion

In the midst of the current circulation of H5N1 in cattle, the general pandemic risk of influenza viruses has been underlined. In parallel, current circulation of SARS-CoV-2, and the continued emergence of new variants, highlights the importance of community immunity. To prevent pathogen invasion, such protection hinges on the characteristics of vaccinal immunity, which include duration, strength (i.e. relative susceptibility after waning is complete), and how vaccinal immunity is lost. In this paper, we developed a modeling framework to investigate the interplay between the shape of waning vaccinal immunity with buffered susceptibility. For general vaccination and waning schemes, we analytically computed the $\mathcal{R}_0$ pathogens would require for successful invasion. We then examined multiple potential waning functions, and we showed that the relative susceptibility of a fully-waned host is a crucial determinant of invasion potential. Furthermore, we illustrated that a simple change regarding how much immunity wanes early after infection versus later in the waning period could result in more than four times the population-level protection.

Overall, our work highlights the importance of a potential Global Immunological Observatory [54–56] and large cohort studies [57] to determine the trajectory of waning and the relative susceptibility of infection of fully-waned individuals for a number of emerging and circulating pathogens, which echoes Saad-Roy, Wagner et al. [4]. Furthermore, these data would be particularly relevant in the context of the development and deployment of pan-coronavirus/pan-sarbecovirus vaccines, in addition to broadly-protective influenza vaccines, and could inform policy on repeat vaccinations.

Supporting information

S1 File. Contains the code needed to generate the figures found in the main text.
(R)

S1 Appendix. Contains the detailed derivation of the disease-free equilibrium of our model.
(PDF)

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Supervision: Mike Boots, Chadi M. Saad-Roy.

Visualization: Graham Richard Northrup.

Writing – original draft: Graham Richard Northrup.

Writing – review & editing: Graham Richard Northrup, Mike Boots, Chadi M. Saad-Roy.

References

1. Koelle K, Martin MA, Antia R, Lopman B, Dean NE. The changing epidemiology of SARS-CoV-2. Science. 2022;375(6585):1116–21. https://doi.org/10.1126/science.abm4915 PMID: 35271324
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533–4. https://doi.org/10.1016/S1473-3099(20)30120-1 PMID: 32087114
3. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science. 2020;368(6493):860–8. https://doi.org/10.1126/science.abb5793 PMID: 32291278
4. Saad-Roy CM, Wagner CE, Baker RE, Morris SE, Farrar J, Graham AL, et al. Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years. Science. 2020;370(6518):811–8. https://doi.org/10.1126/science.abd7343 PMID: 32958581
5. Weitz JS, Beckett SJ, Coenen AR, Demory D, Dominguez-Mirazo M, Dushoff J, et al. Modeling shield immunity to reduce COVID-19 epidemic spread. Nat Med. 2020;26(6):849–54. https://doi.org/10.1038/s41591-020-0895-3 PMID: 32382154
6. Lucia-Sanz A, Magalie A, Rodriguez-Gonzalez R, Leung C-Y, Weitz JS. Modeling shield immunity to reduce COVID-19 transmission in long-term care facilities. Ann Epidemiol. 2023;77:44–52. https://doi.org/10.1016/j.annepidem.2022.10.013 PMID: 36356685
7. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603–15. https://doi.org/10.1056/NEJMoa2034577 PMID: 33301246
8. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403–16. https://doi.org/10.1056/NEJMoa2035389 PMID: 33378609
9. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99–111. https://doi.org/10.1016/S0140-6736(20)32661-1 PMID: 33306989
10. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford, UK: Oxford University Press; 1991.
11. Anderson RM, Vegvari C, Truscott J, Collyer BS. Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. Lancet. 2020;396(10263):1614–6. https://doi.org/10.1016/S0140-6736(20)32318-7 PMID: 33159850
12. Saad-Roy CM, Levin SA, Metcalf CJE, Grenfell BT. Trajectory of individual immunity and vaccination required for SARS-CoV-2 community immunity: a conceptual investigation. J R Soc Interface. 2021;18(175):20200683. https://doi.org/10.1098/rsif.2020.0683 PMID: 33530857
13. Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021;385(19):1761–73. https://doi.org/10.1056/NEJMoa2110345 PMID: 34525277

14. Ferdinands JM, Fry AM, Reynolds S, Petrie J, Flannery B, Jackson ML, et al. Intraseason waning of influenza vaccine protection: Evidence from the US Influenza Vaccine Effectiveness Network, 2011-12 through 2014-15. Clin Infect Dis. 2017;64(5):544–50. https://doi.org/10.1093/cid/ciw816 PMID: 28039340
15. Zelner J, Petrie JG, Trangucci R, Martin ET, Monto AS. Effects of Sequential Influenza A(H1N1)pdm09 Vaccination on Antibody Waning. J Infect Dis. 2019;220(1):12–9. https://doi.org/10.1093/infdis/jiz055 PMID: 30722022
16. Petrie JG, Ohmit SE, Johnson E, Truscon R, Monto AS. Persistence of Antibodies to Influenza Hemagglutinin and Neuraminidase Following One or Two Years of Influenza Vaccination. J Infect Dis. 2015;212(12):1914–22. https://doi.org/10.1093/infdis/jiv313 PMID: 26014800
17. Mao T, Israelow B, Peña-Hernández MA, Suberi A, Zhou L, Luyten S, et al. Unadjuvanted intranasal spike vaccine elicits protective mucosal immunity against sarbecoviruses. Science. 2022;378(6622):eabo2523. https://doi.org/10.1126/science.abo2523 PMID: 36302057
18. Park Y-J, De Marco A, Starr TN, Liu Z, Pinto D, Walls AC, et al. Antibody-mediated broad sarbecovirus neutralization through ACE2 molecular mimicry. Science. 2022;375(6579):449–54. https://doi.org/10.1126/science.abm8143 PMID: 34990214
19. Bartsch SM, O'Shea KJ, John DC, Strych U, Bottazzi ME, Martinez MF, et al. The potential epidemiologic, clinical, and economic value of a universal coronavirus vaccine: a modelling study. EClinicalMedicine. 2024;68:102369. https://doi.org/10.1016/j.eclinm.2023.102369 PMID: 38545093
20. Cankat S, Demael MU, Swadling L. In search of a pan-coronavirus vaccine: next-generation vaccine design and immune mechanisms. Cell Mol Immunol. 2024;21(2):103–18. https://doi.org/10.1038/s41423-023-01116-8 PMID: 38148330
21. Saad-Roy CM, McDermott AB, Grenfell BT. Dynamic Perspectives on the Search for a Universal Influenza Vaccine. J Infect Dis. 2019;219(Suppl_1):S46–56. https://doi.org/10.1093/infdis/jiz044 PMID: 30715467
22. Arinaminpathy N, Saad-Roy CM, Yang Q, Ahmad I, Yadav P, Grenfell B. A global system for the next generation of vaccines. Science. 2022;376(6592):462–4. https://doi.org/10.1126/science.abm8894 PMID: 35482858
23. Andrews SF, Graham BS, Mascola JR, McDermott AB. Is It Possible to Develop a "Universal" Influenza Virus Vaccine? Immunogenetic Considerations Underlying B-Cell Biology in the Development of a Pan-Subtype Influenza A Vaccine Targeting the Hemagglutinin Stem. Cold Spring Harb Perspect Biol. 2018;10(7):a029413. https://doi.org/10.1101/cshperspect.a029413 PMID: 28663207
24. Andrews SF, Joyce MG, Chambers MJ, Gillespie RA, Kanekiyo M, Leung K, et al. Preferential induction of cross-group influenza A hemagglutinin stem-specific memory B cells after H7N9 immunization in humans. Sci Immunol. 2017;2(13):eaan2676. https://doi.org/10.1126/sciimmunol.aan2676 PMID: 28783708
25. Pica N, Palese P. Toward a universal influenza virus vaccine: prospects and challenges. Annu Rev Med. 2013;64:189–202. https://doi.org/10.1146/annurev-med-120611-145115 PMID: 23327522
26. Arinaminpathy N, Riley S, Barclay WS, Saad-Roy C, Grenfell B. Population implications of the deployment of novel universal vaccines against epidemic and pandemic influenza. Journal of The Royal Society Interface. 2020;17(164):20190879.
27. Khurana S, King LR, Manischewitz J, Posadas O, Mishra AK, Liu D, et al. Licensed H5N1 vaccines generate cross-neutralizing antibodies against highly pathogenic H5N1 clade 2.3.4.4b influenza virus. Nat Med. 2024;30(10):2771–6. https://doi.org/10.1038/s41591-024-03189-y PMID: 39013430
28. Bailey NT. The mathematical theory of infectious diseases and its applications. 2nd ed. 1975.
29. Saad-Roy CM, Morris SE, Boots M, Baker RE, Lewis BL, Farrar J, et al. Impact of waning immunity against SARS-CoV-2 severity exacerbated by vaccine hesitancy. PLoS Comput Biol. 2024;20(8):e1012211. https://doi.org/10.1371/journal.pcbi.1012211 PMID: 39102402
30. Morris SE, Pitzer VE, Viboud C, Metcalf CJE, Bjørnstad ON, Grenfell BT. Demographic buffering: titrating the effects of birth rate and imperfect immunity on epidemic dynamics. J R Soc Interface. 2015;12(104):20141245. https://doi.org/10.1098/rsif.2014.1245 PMID: 25589567
31. Saad-Roy CM, Morris SE, Metcalf CJE, Mina MJ, Baker RE, Farrar J, et al. Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes. Science. 2021;372(6540):363–70. https://doi.org/10.1126/science.abg8663 PMID: 33688062
32. Wagner CE, Saad-Roy CM, Morris SE, Baker RE, Mina MJ, Farrar J, et al. Vaccine nationalism and the dynamics and control of SARS-CoV-2. Science. 2021;373(6562):eabj7364. https://doi.org/10.1126/science.abj7364 PMID: 34404735
33. Saad-Roy CM, Morris SE, Baker RE, Farrar J, Graham AL, Levin SA, et al. Medium-term scenarios of COVID-19 as a function of immune uncertainties and chronic disease. J R Soc Interface. 2023;20(205):20230247. https://doi.org/10.1098/rsif.2023.0247 PMID: 37643641

34. Reluga TC, Medlock J, Perelson AS. Backward bifurcations and multiple equilibria in epidemic models with structured immunity. J Theor Biol. 2008;252(1):155–65. https://doi.org/10.1016/j.jtbi.2008.01.014 PMID: 18325538
35. Heffernan JM, Keeling MJ. Implications of vaccination and waning immunity. Proc Biol Sci. 2009;276(1664):2071–80. https://doi.org/10.1098/rspb.2009.0057 PMID: 19324753
36. Hogan AB, Wu SL, Doohan P, Watson OJ, Winskill P, Charles G, et al. The value of vaccine booster doses to mitigate the global impact of the Omicron SARS-CoV-2 variant. medRxiv. 2022;2022.
37. El Khalifi M, Britton T. Extending susceptible-infectious-recovered-susceptible epidemics to allow for gradual waning of immunity. J R Soc Interface. 2023;20(206):20230042. https://doi.org/10.1098/rsif.2023.0042 PMID: 37700711
38. El Khalifi M, Britton T. SIRS epidemics with individual heterogeneity of immunity waning. J Theor Biol. 2024;587:111815. https://doi.org/10.1016/j.jtbi.2024.111815 PMID: 38614211
39. van den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math Biosci. 2002;180:29–48. https://doi.org/10.1016/s0025-5564(02)00108-6 PMID: 12387915
40. Hethcote HW, Stech HW, Van Den Driessche P. Nonlinear oscillations in epidemic models. SIAM J Appl Math. 1981;40(1):1–9. https://doi.org/10.1137/0140001
41. Lavine JS, Bjornstad ON, Antia R. Immunological characteristics govern the transition of COVID-19 to endemicity. Science. 2021;371(6530):741–5. https://doi.org/10.1126/science.abe6522 PMID: 33436525
42. Laxminarayan R, Wahl B, Dudala SR, Gopal K, Mohan B C, Neelima S, et al. Epidemiology and transmission dynamics of COVID-19 in two Indian states. Science. 2020;370(6517):691–7. https://doi.org/10.1126/science.abd7672 PMID: 33154136
43. Althouse BM, Wenger EA, Miller JC, Scarpino SV, Allard A, Hébert-Dufresne L. Stochasticity and heterogeneity in the transmission dynamics of SARS-CoV-2. arXiv preprint 2020. https://doi.org/10.48550/arXiv.2005.13689
44. May RM, Anderson RM. Spatial heterogeneity and the design of immunization programs. Mathematical Biosciences. 1984;72(1):83–111. https://doi.org/10.1016/0025-5564(84)90063-4
45. Klepac P, Laxminarayan R, Grenfell BT. Synthesizing epidemiological and economic optima for control of immunizing infections. Proc Natl Acad Sci U S A. 2011;108(34):14366–70. https://doi.org/10.1073/pnas.1101694108 PMID: 21825129
46. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci U S A. 2004;101(16):6146–51. https://doi.org/10.1073/pnas.0307506101 PMID: 15071187
47. Bauch CT, Earn DJD. Vaccination and the theory of games. Proc Natl Acad Sci U S A. 2004;101(36):13391–4. https://doi.org/10.1073/pnas.0403823101 PMID: 15329411
48. Bauch CT. Imitation dynamics predict vaccinating behaviour. Proc Biol Sci. 2005;272(1573):1669–75. https://doi.org/10.1098/rspb.2005.3153 PMID: 16087421
49. Traulsen A, Levin SA, Saad-Roy CM. Individual costs and societal benefits of interventions during the COVID-19 pandemic. Proc Natl Acad Sci U S A. 2023;120(24):e2303546120. https://doi.org/10.1073/pnas.2303546120 PMID: 37285394
50. Saad-Roy CM, Traulsen A. Dynamics in a behavioral-epidemiological model for individual adherence to a nonpharmaceutical intervention. Proc Natl Acad Sci U S A. 2023;120(44):e2311584120. https://doi.org/10.1073/pnas.2311584120 PMID: 37889930
51. Wagner CE, Prentice JA, Saad-Roy CM, Yang L, Grenfell BT, Levin SA. Economic and behavioral influencers of vaccination and antimicrobial use. Frontiers in Public Health. 2020;8:6141113.
52. Dubé E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J. Vaccine hesitancy: an overview. Hum Vaccin Immunother. 2013;9(8):1763–73. https://doi.org/10.4161/hv.24657 PMID: 23584253
53. Guerra FM, Crowcroft NS, Friedman L, Deeks SL, Halperin SA, Severini A, et al. Waning of measles maternal antibody in infants in measles elimination settings - a systematic literature review. Vaccine. 2018;36(10):1248–55. https://doi.org/10.1016/j.vaccine.2018.01.002 PMID: 29398276
54. Metcalf CJE, Farrar J, Cutts FT, Basta NE, Graham AL, Lessler J, et al. Use of serological surveys to generate key insights into the changing global landscape of infectious disease. Lancet. 2016;388(10045):728–30. https://doi.org/10.1016/S0140-6736(16)30164-7 PMID: 27059886
55. Metcalf CJE, Mina MJ, Winter AK, Grenfell BT. Opportunities and challenges of a World Serum Bank - Authors' reply. Lancet. 2017;389(10066):252. https://doi.org/10.1016/S0140-6736(17)30054-5 PMID: 28118913

56. Mina MJ, Metcalf CJE, McDermott AB, Douek DC, Farrar J, Grenfell BT. A Global Immunological Observatory to meet a time of pandemics. Elife. 2020;9:e58989. https://doi.org/10.7554/eLife.58989 PMID: 32510329

57. Saad-Roy CM, Metcalf CJE, Grenfell BT. Immuno-epidemiology and the predictability of viral evolution. Science. 2022;376(6598):1161–2. https://doi.org/10.1126/science.abn9410 PMID: 35679395