Immune boosting bridges leaky and polarized vaccination models

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Abstract

Two different epidemiological models of vaccination are commonly used in dynamical modeling studies. The leaky vaccination model assumes that all vaccinated individuals experience a reduced probability of infection. The polarized vaccination model assumes that some fraction of vaccinated individuals are completely protected, while the remaining fraction remains completely susceptible; this seemingly extreme assumption causes the polarized model to always predict lower final epidemic size than the leaky model under the same vaccine efficacy. However, the leaky model also makes an implicit, unrealistic assumption: vaccinated individuals who are exposed to infection but not infected remain just as susceptible as they were prior to exposure. To adddress this latter assumption, we introduce an immune boosting mechanism, through which partially susceptible individuals can gain protection without developing a transmissible infection. A model where such boosted individuals are perfectly protected predicts identical epidemic dynamics as

the polarized vaccination model, thereby bridging the differences between two models. We further develop a generalized vaccination model to explore how the assumptions of immunity affect epidemic dynamics and estimates of vaccine effectiveness.

Introduction

Vaccination plays a critical role in controlling infectious disease outbreaks by protecting against new infections and associated disease (Iwasaki and Omer, 2020). In particular, if a critical vaccination threshold is reached, the reproduction number (defined as the average number of secondary infections caused by an infected individual) is reduced to below 1, and epidemics can be prevented (Anderson and May, 1985). But reaching a critical vaccination threshold can be challenging, and vaccines often provide partial protection (Gandon et al., 2003; Anderson et al., 2020).

Partial protection provided by vaccination raises important questions about how vaccine efficacy (in clinical trials) and vaccine effectiveness (in populations) should be estimated. Traditionally, both efficacy and effectiveness have been estimated by comparing the (cumulative) proportion of vaccinated individuals infected in a given time frame to the same proportion among unvaccinated individuals (Farrington, 1993). However, this approach implicitly assumes a single exposure per individual, and otherwise gives biased estimates, requiring different estimators specifically tuned to a particular scenario (Halloran et al., 1991). Other researchers have suggested using measures based on incidence rates (i.e., the rate at which new infections or cases are generated) to estimating vaccine efficacy; these methods are also subject to several biases (Rinta-Kokko et al., 2009; Lipsitch and Kahn, 2021). Heterogeneity in mixing patterns, susceptible depletion, and immune waning further hamper our ability to estimate vaccine efficacy and effectiveness (Halloran et al., 1992; Lipsitch, 2019; Kahn et al., 2022).

Even if vaccine efficacy can be accurately estimated, there are additional challenges to translating these estimates to population-level predictions about epidemic dynamics. In particular, there are two disparate ways of modeling vaccines with partial protections: "leaky" and "all-or-nothing" vaccine (Smith et al., 1984), which yield different dynamics even when vaccine efficacy (defined here as proportion of people protected from their first challenge) is held constant. The leaky vaccination model assumes that vaccinated individuals experience a reduced force of infection (e.g., multiplied by a factor $1 - \mathrm{VE_L} < 1$, where $\mathrm{VE_L}$ represents (leaky) vaccine efficacy. The "all-or-nothing" vaccination model assumes that the proportion $\mathrm{VE_P}$ of vaccinated individuals are completely protected and the remaining proportion $1 - \mathrm{VE_P}$ of vaccinated individuals are completely susceptible, where $\mathrm{VE_P}$ represents (polarized) vaccine efficacy, so-called because this model is anal-

ogous to the "polarized" model of cross-immunity, in which infection from one strain gives complete or no protection against other strains (Gog and Grenfell, 2002; Gomes et al., 2014).

There is some empirical support for both leaky (Lind et al., 2023) and polarized vaccines (Langwig et al., 2017), and the two assumptions can have sharply different consequences for outbreak predictions. Specifically, when these two models are used with the same nominal vaccine efficacy $\mathrm{VE_L} = \mathrm{VE_P}$, they predict different epidemic dynamics, including the final size (Smith et al., 1984): for a high force of infection, almost all individuals eventually get infected in the leaky model, whereas many individuals are permanently protected in the polarized model. Modelers tend to rely on the leaky assumption, including throughout the SARS-CoV-2 pandemic (Dyson et al., 2021; Gozzi et al., 2021; Marziano et al., 2021; Matrajt et al., 2021; Park et al., 2022) with some exceptions (Bubar et al., 2021; Buckner et al., 2021). Various reasons have been given, but most likely is a combination of convenience and tradition.

Both models represent simplifications of reality. The leaky model in particular overlooks a potentially important mechanism: individuals in this model do not lose any susceptibility when (implicitly) exposed to a challenge that does not result in infection. In fact, vaccinated individuals who successfully fight off exposures can experience immune boosting, thus becoming less susceptible to future infections without becoming infectious or developing symptoms from the exposure (Lavine et al., 2011; Yang et al., 2020).

In this study, we compare different approaches to dynamical modeling of vaccination and immunity. First, we construct a model with leaky vaccination and boosting, and show that the transmission dynamics of this model can bridge from the dynamics of the standard leaky model (with no boosting) to those of the polarized model (with perfect boosting). Then, we construct a generalized vaccination model, which includes all three mechanisms, and explore its dynamics. Finally, we use our framework to compare measures of vaccine effectiveness.

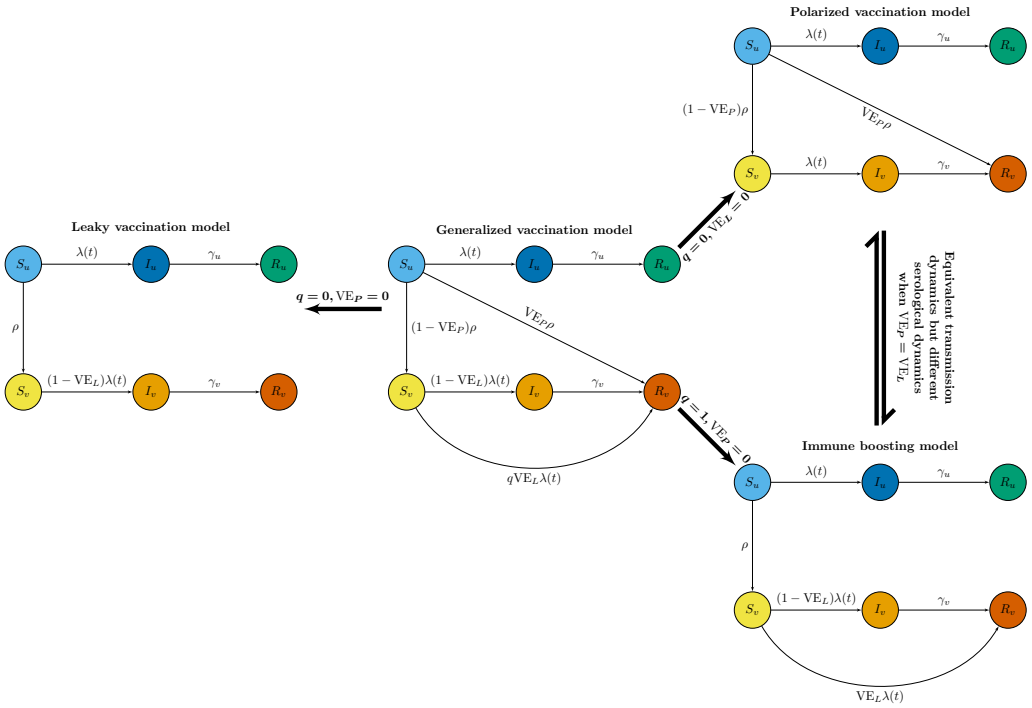

Figure 1: **A schematic diagram of four different vaccination models.** S represents susceptible individuals. I represents infected individuals. R represents recovered individuals. λ represents force of infection. ρ represents the rate of vaccination. p represents vaccine efficacy. γ represents recovery rate. θ represents the proportion of individuals that remain partially susceptible after vaccination. q represents the proportion of unsuccessful challenges that result in immune boosting. Subscripts u and v represents unvaccinated and vaccinated.

Mathematical models of vaccine-induced immunity

Throughout the paper, we assume that a population mixes homogeneously and that there is no loss of immunity (including indirectly through deaths and births); the latter assumption essentially corresponds to focusing on a single outbreak. We begin with a standard SIR model with a leaky vaccine, in which all vaccinated individuals experience a reduced probability of infection

by a factor of $1 - \mathrm{VE_L}$:

$$\frac{\mathrm{d}S_u}{\mathrm{d}t} = -\lambda(t)S_u - \rho S_u \tag{1}$$
$$\frac{\mathrm{d}I_u}{\mathrm{d}t} = \lambda(t)S_u - \gamma_u I_u \tag{2}$$
$$\frac{\mathrm{d}R_u}{\mathrm{d}t} = \gamma_u I_u \tag{3}$$
$$\frac{\mathrm{d}S_v}{\mathrm{d}t} = -(1 - \mathrm{VE_L})\lambda(t)S_v + \rho S_u \tag{4}$$
$$\frac{\mathrm{d}I_v}{\mathrm{d}t} = (1 - \mathrm{VE_L})\lambda(t)S_v - \gamma_v I_v \tag{5}$$
$$\frac{\mathrm{d}R_v}{\mathrm{d}t} = \gamma_v I_v \tag{6}$$

where subscripts u and v indicate the unvaccinated and vaccinated individuals; λ represents the baseline force of infection experienced by unvaccinated individuals; ρ represents vaccination rate; γ represents the recovery rate; and $\mathrm{VE_L}$ represents the vaccine efficacy, which also captures the amount of reduction in the probability of infection. This kind of model is sometimes called "history-based", since susceptibility of an individual depends only on their history of infections (or vaccination) (Gog and Grenfell, 2002; Gog and Swinton, 2002; Kucharski et al., 2016).

Conversely, the polarized vaccination model assumes that a proportion $\mathrm{VE_P}$ of vaccinated individuals become fully immune, whereas the remaining proportion $1 - \mathrm{VE_P}$ remain susceptible:

$$\frac{\mathrm{d}S_u}{\mathrm{d}t} = -\lambda(t)S_u - \rho S_u \tag{7}$$
$$\frac{\mathrm{d}I_u}{\mathrm{d}t} = \lambda(t)S_u - \gamma_u I_u \tag{8}$$
$$\frac{\mathrm{d}R_u}{\mathrm{d}t} = \gamma_u I_u \tag{9}$$
$$\frac{\mathrm{d}S_v}{\mathrm{d}t} = -\lambda(t)S_v + (1 - \mathrm{VE_P})\rho S_u \tag{10}$$
$$\frac{\mathrm{d}I_v}{\mathrm{d}t} = \lambda(t)S_v - \gamma_v I_v \tag{11}$$
$$\frac{\mathrm{d}R_v}{\mathrm{d}t} = \gamma_v I_v + \mathrm{VE_P}\rho S_u \tag{12}$$

This is the approach used in "status-based" models of cross immunity—such models keep track of immune statuses of individuals, rather than their histories (Gog and Grenfell, 2002; Gog and Swinton, 2002; Kucharski et al., 2016). For this model, the parameter $\mathrm{VE_P}$ is the measure of vaccine efficacy.

These two widely used models have important dynamical differences. For a given set of shared parameters, and the same value of vaccine efficacy, initial dynamics will be the same, but the permanent protection of individuals in the polarized model will always result in a lower final outbreak size than the leaky vaccination model. When both VE and the initial value of $\mathcal{R}$ are relatively high, this difference is large.

To better understand this gap, we consider an immune-boosting model. The leaky vaccination model implicitly assumes that vaccinated individuals who experience unsuccessful challenges (with probability $\mathrm{VE_L}$) remain susceptible; this is equivalent to assuming that vaccinated individuals are challenged with a lower force of infection $(1-\mathrm{VE_L})\lambda(t)$. However, in a homogeneously mixing population, we expect both vaccinated and unvaccinated individuals to be challenged with identical forces of infection λ. Therefore, the leaky vaccination model implicitly assumes that vaccinated individuals are unaffected by unsuccessful challenges, and thus have an *independent* probability $(1-\mathrm{VE_L})$ of infection for every challenge. The immune-boosting model, on the other hand, assumes that unsuccessful challenges elicit immune response, moving individuals from S_v to R_v compartment at rate $\mathrm{VE_L}\lambda(t)$ and thereby breaking the independence assumption of the leaky vaccine model:

$$\frac{\mathrm{d}S_u}{\mathrm{d}t} = -\lambda(t)S_u - \rho S_u \tag{13}$$

$$\frac{\mathrm{d}I_u}{\mathrm{d}t} = \lambda(t)S_u - \gamma_u I_u \tag{14}$$

$$\frac{\mathrm{d}R_u}{\mathrm{d}t} = \gamma_u I_u \tag{15}$$

$$\frac{\mathrm{d}S_v}{\mathrm{d}t} = -\lambda(t)S_v + \rho S_u \tag{16}$$

$$\frac{\mathrm{d}I_v}{\mathrm{d}t} = (1-\mathrm{VE_L})\lambda(t)S_v - \gamma_v I_v \tag{17}$$

$$\frac{\mathrm{d}R_v}{\mathrm{d}t} = \mathrm{VE_L}\lambda(t)S_v + \gamma_v I_v \tag{18}$$

In this model, both unvaccinated and vaccinated individuals are subject to identical forces of infection, which represent the per capita rate of challenges,

but the outcome of challenges differ.

The epidemiological dynamics (i.e., trajectories of I_u and I_v) predicted by the immune-boosting model (based on leaky vaccination) and the polarized vaccination model are identical: both models assume that individuals become vaccinated at rate ρ and move out of the S_v compartment at rate λ and only differ in when individuals get sorted based on the result of their next challenge. This equivalence allows us to bridge the difference between the leaky and polarized vaccination models. The equivalence holds regardless of infection characteristics of vaccinated individuals (i.e., the duration of their infection and their transmissibility).

Other studies have tried to characterize the differences between leaky and polarized vaccination models by considering a distribution of susceptibility (i.e., $1-$efficacy) among vaccinated individuals, where the susceptibility can vary anywhere between 0 and 1 with some probability distribution (Gomes et al., 2014). For example, the leaky assumption was previously modeled using a delta distribution (i.e., all individuals are equally susceptible), whereas the polarized assumption was previously modeled using a polarized distribution (i.e., some individuals have complete protection and others have no protection). While it is possible to bridge these two distributions using a continuous distributions, this approach also implicitly assumes that unsuccessful challenges remain just as susceptible. Instead, in Supplementary Materials, we show that under complete boosting, epidemic dynamics depend only on the mean (not the shape) of the susceptibility distribution.

Finally, we consider a generalized model that encompasses all three mechanisms above (dichotomous vaccine responses, partial protection, and im-

mune boosting):

$$\frac{\mathrm{d}S_u}{\mathrm{d}t} = -\lambda(t)S_u - \rho S_u \tag{19}$$

$$\frac{\mathrm{d}I_u}{\mathrm{d}t} = \lambda(t)S_u - \gamma_u I_u \tag{20}$$

$$\frac{\mathrm{d}R_u}{\mathrm{d}t} = \gamma_u I_u \tag{21}$$

$$\frac{\mathrm{d}S_v}{\mathrm{d}t} = -[1-(1-q)\mathrm{VE_L}]\lambda(t)S_v + (1-\mathrm{VE_P})\rho S_u \tag{22}$$

$$\frac{\mathrm{d}I_v}{\mathrm{d}t} = (1-\mathrm{VE_L})\lambda(t)S_v - \gamma_v I_v \tag{23}$$

$$\frac{\mathrm{d}R_v}{\mathrm{d}t} = \mathrm{VE_P}\rho S_u + q\mathrm{VE_L}\lambda(t)S_v + \gamma_v I_v \tag{24}$$

This model includes one new parameter, q, which represents the proportion of unsuccessful challenges that result in immune boosting. When $q = 0$ (i.e., in the absence of boosting), setting $\mathrm{VE_P} = 0$ gives us the leaky vaccination model. When $q = 1$ (i.e., in the presence of full boosting), setting $\mathrm{VE_P} = 0$ gives us the immune-boosting model, whereas setting $\mathrm{VE_L} = 0$ gives us the polarized vaccination model. The relationship between these four models are summarized in Fig. 1. The generalized vaccination model has a combined vaccine efficacy of $\mathrm{VE} = 1 - (1 - \mathrm{VE_L})(1 - \mathrm{VE_P})$. We later analyze the dynamics of the generalized vaccination model while keeping VE fixed.

Model simulations

We begin by comparing the dynamics of three individual models: leaky vaccination, polarized vaccination, and immune-boosting models. As an example, we consider a homogeneously mixing population. In this case, the force of infection is given by:

$$\lambda = \beta_u I_u + \beta_v I_v \tag{25}$$

For simplicity, we assume that, once infected, both unvaccinated and vaccinated individuals transmit at the same rate $\beta_u = \beta_v = 0.5$/day for an average of $1/\gamma = 5$ days. We also assume that $\phi = 0.5$ proportion of individuals are vaccinated at the beginning of an epidemic with 60% efficacy ($\mathrm{VE_P}$ or $\mathrm{VE_L} = 0.6$) and that vaccination does not continue during the outbreak ($\rho = 0$). For the leaky vaccination model and the immune-boosting

model, we set $S_v(0) = 1 - \phi$ and $R_v(0) = \phi$. For consistentency, we then set $S_v(0) = \phi(1 - \mathrm{VE_P})$ and $R_v(0) = \phi \mathrm{VE_P}$ as our initial condition for the polarized vaccination model.

Fig. 2 compares epidemiological (A–C) and immune-status (D–F) trajectories predicted by the three models. As explained earlier, the leaky vaccination model predicts more infections among vaccinated individuals than the other two models, which predict identical incidence trajectories. The leaky vaccination model also predicts more among unvaccinated individuals because a larger outbreak among vaccinated individuals causes unvaccinated individuals to experience a greater forces of infection over time.

We further find that all three models predict different immune-status trajectories. (Fig. 2D–F). Here, we do not distinguish the sources of antibodies (whether derived from natural infections or vaccinations) and assume that individuals in R_u, S_v, and R_v compartments are seropositive (i.e., have antibodies against the infection), except in the case of polarized vaccination: in such case, we assume individuals in the S_v compartment are seronegative because they have not retained any immunity from the vaccination. The leaky vaccination model predicts the largest outbreak and therefore the highest levels of seroprevalence (89.7% by the end of the simulation). The immune-boosting model predicts lower seroprevalence (85.6%), reflecting the lower final size, while the polarized vaccination model predicts a still lower seroprevalence (79.9%) because of our assumption that people not protected by polarized vaccination are not seropositive.

We next use the generalized vaccination model to further investigate how the final size of the an epidemic among vaccinated individuals depends on assumptions about vaccine-derived immunity across a wide range of assumptions about the basic reproduction number $\mathcal{R}_0$ and vaccine efficacy VE (Fig. 3). In particular, we factor vaccine efficacy VE in terms of leaky vaccine efficacy $\mathrm{VE_L}$ and polarized vaccine efficacy $\mathrm{VE_P}$, and consider an intermediate case, in which $\mathrm{VE_L} = \mathrm{VE_P} = 1 - \sqrt{1 - \mathrm{VE}}$, as well as the extreme cases, in which case $\mathrm{VE_L} = \mathrm{VE}$ or $\mathrm{VE_P} = \mathrm{VE}$. First, when $\mathrm{VE_L} = \mathrm{VE}$, all vaccinated individuals have identical susceptibility; in this case, increasing the amount of boosting q reduces the final size as expected (see first column of Fig. 3). We observe biggest effects of boosting at intermediate vaccine efficacy, VE, and high basic reproduction number, $\mathcal{R}_0$ (see bottom left panel of Fig. 3). When vaccine efficacy is too low (or too high), then boosting has negligible effects because virtually everyone (or virtually no one) gets infected. As we increase $\mathcal{R}_0$, the leaky vaccination model predicts that all

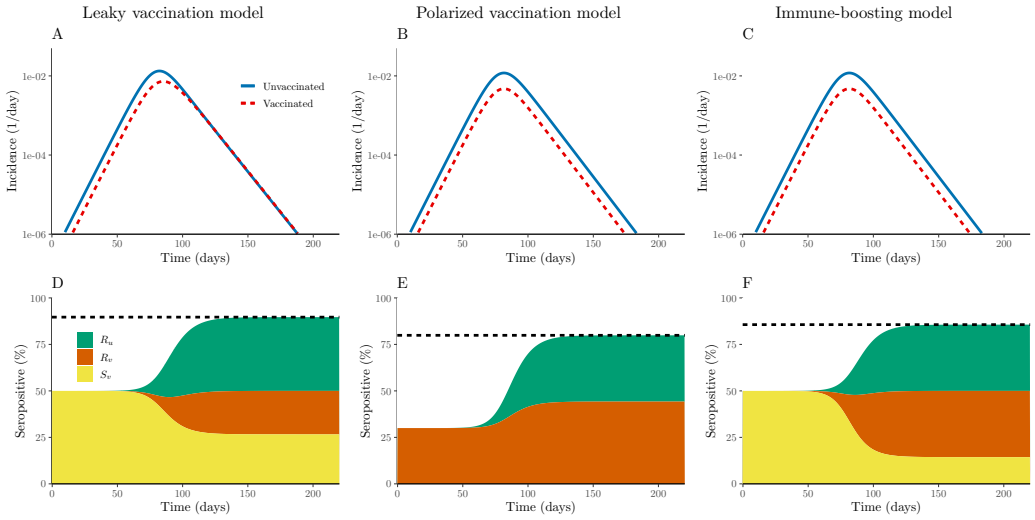

Figure 2: **Simulations of three different vaccination models.** (A–C) Incidence of infection among unvaccinated (blue solid) and vaccinated (red dashed) individuals. (D–F) Immune status over time (compartments R_u, S_v, and R_v). The S_v compartment is not included in the polarized vaccination model because it represents a set of individuals who have not retained any immunity from vaccination. Simulations are performed assuming $\beta_u = \beta_v = 0.5$/day for an average infectious periods of $1/\gamma = 5$ days. We also assume that $\phi = 0.5$ proportion of individuals are vaccinated at the beginning of an epidemic with 60% efficacy ($\mathrm{VE_P} = \mathrm{VE_L} = 0.6$) and that vaccination does not continue during the outbreak ($\rho = 0$).

vaccinated individuals will eventually get infected. On the other hand, the final size predicted by the immune-boosting model cannot be greater than $1-\mathrm{VE}$. As we increase $\mathrm{VE_P}$ (and decrease $\mathrm{VE_L}$ accordingly), the generalized vaccination model collapses to the polarized vaccination model, and the final size becomes insensitive to the boosting parameter q.

So far, we have limited our discussions to vaccine efficacy, which we defined as the proportion of people protected from their first challenge. We distinguish this from vaccine *effectiveness*, which is measured empirically (Halloran et al., 2009). Here, we compare two ways of estimating vaccine effectiveness: using cumulative incidence or instantaneous hazard. Several factors can cause vaccine effectiveness to systematically differ from vaccine efficacy—in our case, the main reason is the fact that some vaccinated indi-

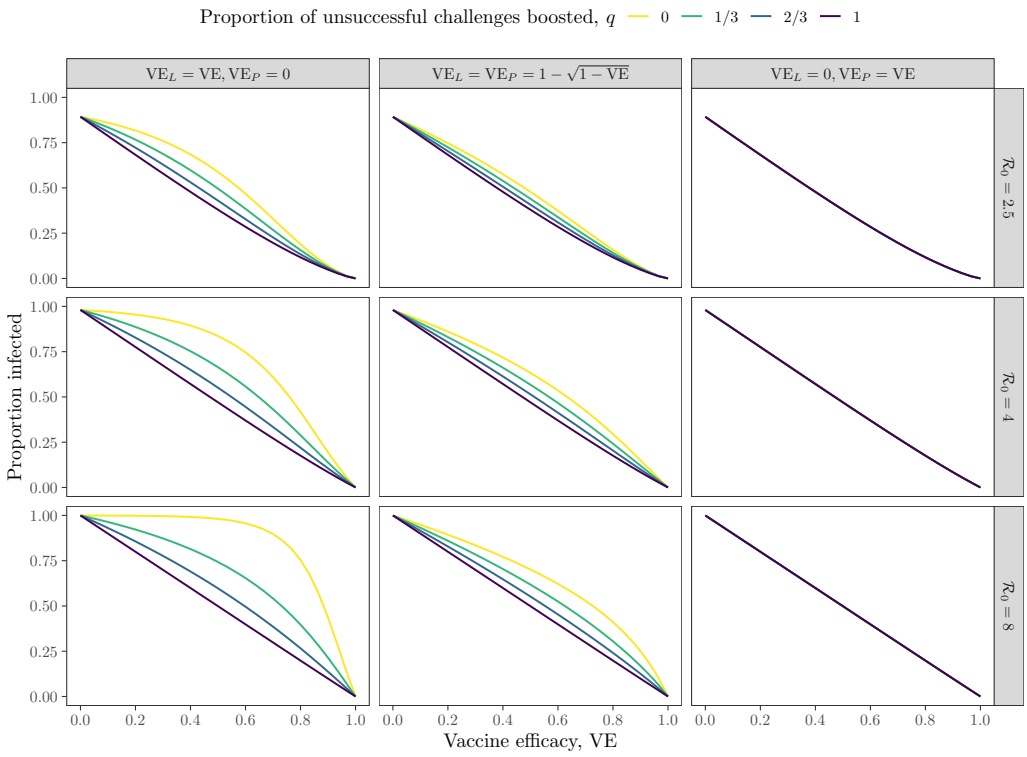

Figure 3: **Sensitivity of the final size of an outbreak among vaccinated individuals to assumptions about vaccine-derived immunity** Final size of an outbreak was calculated by simulating the generalized vaccination model for 220 days. All other parameters are the same as in Fig. 2.

viduals may be challenged multiple times.

Cumulative incidence refers to the cumulative proportion of infections among unvaccinated and vaccinated individuals; this is commonly used for measuring the vaccine effectiveness in real outbreaks (Farrington, 1993). Since we are modeling a single epidemic without a loss of immunity or multiple infections, we consider changes in total infections in a single outbreak. To do so, we add two additional compartments, which keep track of cumulative

incidence among unvaccinated C_u and vaccinated C_v individuals:

$$\frac{\mathrm{d}C_u}{\mathrm{d}t} = \lambda S_u \tag{26}$$

$$\frac{\mathrm{d}C_v}{\mathrm{d}t} = (1 - \mathrm{VE_L})\lambda S_v \tag{27}$$

Since we are neglecting vaccinations that occur during the outbreak ($\rho = 0$, the cumulative proportion of infections among vaccinated $p_v(t)$ and unvaccinated $p_u(t)$ individuals can be expressed as:

$$p_u(t) = C_u(t)/S_u(0) \tag{28}$$

$$p_v(t) = C_v(t)/S_v(0) \tag{29}$$

Then, the estimated vaccine effectiveness at time t is:

$$1 - \frac{p_v(t)}{p_u(t)}. \tag{30}$$

On the other hand, instantaneous hazard refers to the per-capita rate at which unvaccinated $h_u(t)$ and vaccinated $h_v(t)$ individuals get infected if they have not yet been infected yet. These quantities can be calculated by dividing the incidence of new infection by the number of uninfected individuals. The per-capita rate of infection $h_v(t)$ among vaccinated individuals in then given by:

$$h_v(t) = \frac{(1 - \mathrm{VE_L})\lambda(t)S_v(t)}{S_v(0) - C_v(t)}, \tag{31}$$

where $S_v(0) - C_v(t) \geq S_v(t)$ because vaccinated individuals can leave the $S_v(t)$ compartment via boosting; in other words, we are assuming that boosting is not observed, and that boosted individuals are neither counted as infected, nor removed from the denominator. The per-capita rate of infection $h_u(t)$ among unvaccinated individuals is straightforward:

$$h_u(t) = \frac{\lambda(t)S_u(t)}{S_u(t)} = \lambda(t). \tag{32}$$

Then, the estimated reduction in hazard at time t is:

$$1 - \frac{h_v(t)}{h_u(t)}. \tag{33}$$

We compare two estimates of vaccine effectiveness across a wide range of assumptions about vaccine-derived immunity in Fig. 4. We assume 60% efficacy (VE = 0.6) throughout, which represents the true value that we want to estimate. Under polarized vaccination ($VE_P = VE$, $VE_L = 0$), the cumulative-incidence reduction always gives correct answers throughout the epidemic—since the susceptible pool among unvaccinated and vaccinated individuals is depleted at the same rate λ, the ratios of their proportions of cumulative infections remain constant. Likewise, the cumulative-incidence reduction also gives correct answers under immune boosting ($q = 1$). However, when some challenges are not boosted ($q < 1$), using cumulative incidence underestimates the vaccine effectiveness beyond the exponential growth phase. This is because vaccinated individuals who have been exposed but are not boosted or infected still remain susceptible to future infections; larger final epidemic sizes predicted by these models (Fig. 3) then translate to a seemingly lower vaccine effectiveness.

The hazard reduction gives correct answers for the leaky vaccine model (when $q = 0$, $VE_L = VE$, and $VE_P = 0$) because the ratios of force of infection that unvaccinated and vaccinated individuals experience are always constant. However, the hazard reduction overestimates vaccine effectiveness in the presence of immune boosting: since boosted individuals have not yet been infected, the susceptible pool in the vaccinated group appears to be bigger than it really is, causing the per-capita rate of infection to seem smaller. Vaccine effectiveness is also overestimated for polarized vaccination for similar reasons.

We note that both estimates give correct answers during the exponential growth phase, regardless of underlying assumptions about immunity. More generally, we expect both estimates to give unbiased estimates as long as the depletion of susceptible pool is negligible among both vaccinated and unvaccinated individuals; in trial settings, where incidence is relatively low, this assumption may hold. But estimating vaccine effectiveness from real outbreaks is expected to be more difficult.

Discussion

Understanding the degree to which vaccination provides protection against infections is critical to predicting epidemic dynamics. The polarized model has been largely neglected in epidemiological modeling, in part due to its

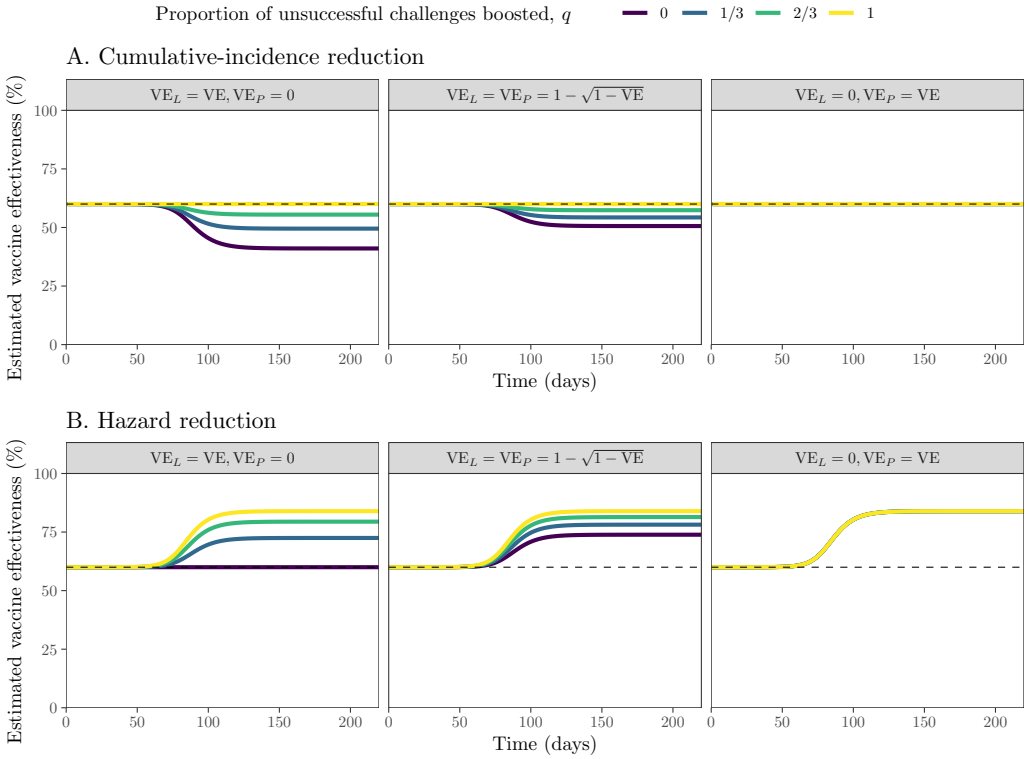

Figure 4: **Estimates of vaccine effectiveness using reduction in cumulative incidence (A) and hazard (B) over time.** Vaccine effectiveness was calculated by simulating the generalized vaccination model for 220 days. Colored lines represent the estimated vaccine effectiveness. Dashed lines represent the assumed vaccine efficacy. We assume $\mathcal{R}_0 = 2.5$ and a combined efficacy of VE $= 0.6$ throughout. All other parameters are the same as in Fig. 2.

apparently extreme assumption that a fraction of vaccinated individuals do not receive any protection. But the leaky vaccination model also makes an unrealistic assumption: that vaccinated individuals who are exposed to infections can still remain susceptible, independent of previous exposures. This assumption causes the leaky vaccination model to always predict a larger epidemic final size. This difference can be bridged with immune boosting. With boosting, vaccinated individuals can attain protection without developing a transmissible infection. In particular, the leaky model with perfect immune-

boosting model predicts identical epidemic dynamics to the polarized vaccination model because individuals in both cases are completely immune after surviving a single challenge.

Even though immune boosting and polarized vaccination models predict the same epidemic dynamics, they may have different immune-status dynamics. We investigate both aspects using a generalized vaccination model, which encompasses the mechanisms of all three models. The generalized vaccination model includes one additional parameter, which determines the amount of immune boosting. We use this model to show that the epidemic dynamics are most sensitive to the assumptions about vaccine-derived immunity at an intermediate vaccine efficacy.

Finally, assumptions about vaccine-derived immunity also have important implications for estimating vaccine effectiveness. Vaccine effectiveness can be estimated based either on cumulative incidence or on hazard rates. Cumulative-incidence-based effectiveness estimates reflect efficacy for polarized vaccination and complete-boosting models, whereas hazard-based estimates reflect efficacy for the leaky vaccination model. Neither method reflects efficacy for intermediate cases. These differences are driven by different assumptions about what happens when individuals are challenged more than once; thus both methods reflect efficacy when the cumulative hazard of infection is low. Conversely, interpretation of effectiveness estimates when a large fraction of unvaccinated individuals have been infected depends on (usually unknown) details of immune dynamics.

We rely above on a simplifying assumption that natural infections (as well as polarized vaccination and immune boosting) provide permanent protection against future infections. In practice, both infection- and vaccine-derived immunity wane over time for many pathogens (Heffernan and Keeling, 2009; Lewnard and Grad, 2018; Pérez-Alós et al., 2022). When immunity wanes, polarized vaccination and immune-boosting models may not necessarily predict identical dynamics. In particular, individuals who gain complete protection through polarized immunity may immediately enter the R_v compartment upon vaccination, whereas those who gain complete protection through immune boosting take longer to enter the R_v compartment because they need to be exposed to infections. These differences can translate to shorter delays between reinfection events for the polarized immunity model, which in turn can lead to dynamical differences at the population level.

There are also other complexities that need to be considered. For example, individuals who are boosted after vaccination can have different immu-

nity profiles compared to those who attained strong protection from vaccination alone. These individuals also likely have different immunity profiles from those who have been infected but never been vaccinated. These differences can also cause polarized vaccination and immune-boosting models to behave differently. Despite these limitations, immune boosting, which is often neglected in epidemic models of vaccination, is still expected to be an important mechanism for understanding dynamics of many pathogens.

We have provided a unifying framework for understanding the impact of vaccination on the spread of infectious disease. The specifics of how vaccination translates into immunization defines the population burden of infection via its effect on the epidemic final size. Yet discussion of how the two extreme models commonly used (leaky and polarized) are related has been lacking. By making this link, we both illustrate the spectrum of trajectories expected for a range of configurations, and illuminate the effects of these assumptions on medium-term vaccine effectiveness.

Supplementary Text

Here, we show that, in the presence of immune boosting, epidemic dynamics are independent of the shape of the susceptibility distribution (depending only on mean susceptibility). To do so, we assume that a vaccinated individual's susceptibility $0 \leq p \leq 1$ (i.e., probability of infection given challenge) follows some distribution $f(p)$:

$$\frac{\mathrm{d}S_u}{\mathrm{d}t} = -\lambda(t)S_u - \rho S_u \tag{34}$$

$$\frac{\mathrm{d}I_u}{\mathrm{d}t} = \lambda(t)S_u - \gamma_u I_u \tag{35}$$

$$\frac{\mathrm{d}R_u}{\mathrm{d}t} = \gamma_u I_u \tag{36}$$

$$\frac{\partial S_v(p)}{\partial t} = -\lambda(t)S_v(p) + f(p)\rho S_u \tag{37}$$

$$\frac{\partial I_v(p)}{\partial t} = p\lambda(t)S_v(p) - \gamma_v I_v(p) \tag{38}$$

$$\frac{\mathrm{d}R_v}{\mathrm{d}t} = \int_0^1 \left[(1-p)\lambda(t)S_v(p) + \gamma_v I_v(p)\right]\,\mathrm{d}p \tag{39}$$

Due to immune boosting, $S_v(p)$ is always depleted at a per-capita rate of $\lambda(t)$ regardless of the values of p, meaning that the (normalized) distribution of $S_v(p)$ will always follow $f(p)$. To obtain the dynamics of total prevalence $I_v = \int I_v(p)\,\mathrm{d}p$, we can integrate $\partial I_v(p)/\partial t$ across p:

$$\frac{\mathrm{d}I_v}{\mathrm{d}t} = \int_0^1 \left[\frac{\partial I_v(p)}{\partial t}\right]\,\mathrm{d}p \tag{40}$$

$$= \int_0^1 \left[p\lambda(t)S_v(p) - \gamma_v I_v(p)\right]\,\mathrm{d}p \tag{41}$$

$$= \int_0^1 \left[pf(p)\lambda(t)S_v - \gamma_v I_v(p)\right]\,\mathrm{d}p \tag{42}$$

$$= \bar{p}\lambda(t)S_v - \gamma_v I_v, \tag{43}$$

where $\bar{p}$ represents the mean of the distribution $f(p)$, and $S_v = \int S_v(p)\,\mathrm{d}p$ represents the proportion of total susceptible, vaccinated individuals. Therefore, the dynamics of total prevalence I_v depends only on the mean susceptibility $\bar{p}$ and not on the shape of the distribution $f(p)$ under immune boosting.

References

Anderson, R. M. and R. M. May (1985). Vaccination and herd immunity to infectious diseases. *Nature 318*(6044), 323–329.

Anderson, R. M., C. Vegvari, J. Truscott, and B. S. Collyer (2020). Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. *The Lancet 396*(10263), 1614–1616.

Bubar, K. M., K. Reinholt, S. M. Kissler, M. Lipsitch, S. Cobey, Y. H. Grad, and D. B. Larremore (2021). Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. *Science 371*(6532), 916–921.

Buckner, J. H., G. Chowell, and M. R. Springborn (2021). Dynamic prioritization of COVID-19 vaccines when social distancing is limited for essential workers. *Proceedings of the National Academy of Sciences 118*(16), e2025786118.

Dyson, L., E. M. Hill, S. Moore, J. Curran-Sebastian, M. J. Tildesley, K. A. Lythgoe, T. House, L. Pellis, and M. J. Keeling (2021). Possible future waves of SARS-CoV-2 infection generated by variants of concern with a range of characteristics. *Nature communications 12*(1), 1–13.

Farrington, C. (1993). Estimation of vaccine effectiveness using the screening method. *International journal of epidemiology 22*(4), 742–746.

Gandon, S., M. Mackinnon, S. Nee, and A. Read (2003). Imperfect vaccination: some epidemiological and evolutionary consequences. *Proceedings of the Royal Society of London. Series B: Biological Sciences 270*(1520), 1129–1136.

Gog, J. and J. Swinton (2002). A status-based approach to multiple strain dynamics. *Journal of mathematical biology 44*(2), 169–184.

Gog, J. R. and B. T. Grenfell (2002). Dynamics and selection of many-strain pathogens. *Proceedings of the National Academy of Sciences 99*(26), 17209–17214.

Gomes, M. G. M., M. Lipsitch, A. R. Wargo, G. Kurath, C. Rebelo, G. F. Medley, and A. Coutinho (2014). A missing dimension in measures of vaccination impacts. *PLoS pathogens 10*(3), e1003849.

Gozzi, N., P. Bajardi, and N. Perra (2021). The importance of non-pharmaceutical interventions during the COVID-19 vaccine rollout. *PLoS computational biology 17*(9), e1009346.

Halloran, M., I. Longini, and C. Struchiner (2009). *Design and Analysis of Vaccine Studies*. Statistics for Biology and Health. Springer New York.

Halloran, M. E., M. Haber, and I. M. Longini Jr (1992). Interpretation and estimation of vaccine efficacy under heterogeneity. *American Journal of Epidemiology 136*(3), 328–343.

Halloran, M. E., M. Haber, I. M. Longini Jr, and C. J. Struchiner (1991). Direct and indirect effects in vaccine efficacy and effectiveness. *American journal of epidemiology 133*(4), 323–331.

Heffernan, J. and M. Keeling (2009). Implications of vaccination and waning immunity. *Proceedings of the Royal Society B: Biological Sciences 276*(1664), 2071–2080.

Iwasaki, A. and S. B. Omer (2020). Why and how vaccines work. *Cell 183*(2), 290–295.

Kahn, R., S. J. Schrag, J. R. Verani, and M. Lipsitch (2022). Identifying and alleviating bias due to differential depletion of susceptible people in postmarketing evaluations of covid-19 vaccines. *American journal of epidemiology 191*(5), 800–811.

Kucharski, A. J., V. Andreasen, and J. R. Gog (2016). Capturing the dynamics of pathogens with many strains. *Journal of mathematical biology 72*(1), 1–24.

Langwig, K. E., A. R. Wargo, D. R. Jones, J. R. Viss, B. J. Rutan, N. A. Egan, P. Sá-Guimarães, M. S. Kim, G. Kurath, M. G. M. Gomes, et al. (2017). Vaccine effects on heterogeneity in susceptibility and implications for population health management. *mbio 8*(6), 10–1128.

Lavine, J. S., A. A. King, and O. N. Bjørnstad (2011). Natural immune boosting in pertussis dynamics and the potential for long-term vaccine failure. *Proceedings of the National Academy of Sciences 108*(17), 7259–7264.

Lewnard, J. A. and Y. H. Grad (2018). Vaccine waning and mumps re-emergence in the United States. *Science translational medicine 10*(433), eaao5945.

Lind, M. L., M. Dorion, A. J. Houde, M. Lansing, S. Lapidus, R. Thomas, I. Yildirim, S. B. Omer, W. L. Schulz, J. R. Andrews, et al. (2023). Evidence of leaky protection following COVID-19 vaccination and SARS-CoV-2 infection in an incarcerated population. *Nature communications 14*(1), 5055.

Lipsitch, M. (2019). Challenges of vaccine effectiveness and waning studies. *Clinical Infectious Diseases 68*(10), 1631–1633.

Lipsitch, M. and R. Kahn (2021). Interpreting vaccine efficacy trial results for infection and transmission. *Vaccine 39*(30), 4082–4088.

Marziano, V., G. Guzzetta, A. Mammone, F. Riccardo, P. Poletti, F. Trentini, M. Manica, A. Siddu, A. Bella, P. Stefanelli, P. Pezzotti, M. Ajelli, S. Brusaferro, G. Rezza, and S. Merler (2021). The effect of COVID-19 vaccination in Italy and perspectives for living with the virus. *Nature Communications 12*(1), 7272.

Matrajt, L., J. Eaton, T. Leung, and E. R. Brown (2021). Vaccine optimization for COVID-19: Who to vaccinate first? *Science Advances 7*(6), eabf1374.

Park, S. W., J. Dushoff, B. Grenfell, and J. S. Weitz (2022). Intermediate levels of asymptomatic transmission can lead to the highest levels of epidemic fatalities. *medRxiv*.

Pérez-Alós, L., J. J. A. Armenteros, J. R. Madsen, C. B. Hansen, I. Jarlhelt, S. R. Hamm, L. D. Heftdal, M. M. Pries-Heje, D. L. Møller, K. Fogh, R. B. Hasselbalch, A. Rosbjerg, S. Brunak, E. Sørensen, M. A. H. Larsen, S. R. Ostrowski, R. Frikke-Schmidt, R. Bayarri-Olmos, L. M. Hilsted, K. K. Iversen, H. Bundgaard, S. D. Nielsen, and P. Garred (2022). Modeling of waning immunity after SARS-CoV-2 vaccination and influencing factors. *Nature Communications 13*(1), 1614.

Rinta-Kokko, H., R. Dagan, N. Givon-Lavi, and K. Auranen (2009). Estimation of vaccine efficacy against acquisition of pneumococcal carriage. *Vaccine 27*(29), 3831–3837.

Smith, P., L. Rodrigues, and P. Fine (1984). Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies. *International journal of epidemiology 13*(1), 87–93.

Yang, L., B. T. Grenfell, and M. J. Mina (2020). Waning immunity and re-emergence of measles and mumps in the vaccine era. *Current opinion in virology 40*, 48–54.