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Poor Vaccine Responders Mask the True Trend in Vaccine Effectiveness Against Progression to Severe Disease

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Abstract

Vaccines can reduce an individual's risk of infection and their risk of progression to severe disease given infection. The latter effect is less commonly estimated but is relevant for vaccine impact modeling and cost-effectiveness calculations. Using a motivating example from the COVID-19 literature, we note how vaccine effectiveness against progression to severe disease can appear to increase from below 0% to over 70% within 8 months. With true biological strengthening of this magnitude being unlikely, we use a mathematical modelling framework to identify parameter combinations where this phenomenon can occur. Fundamental features are an immunocompetent population with high initial protection against infection, contrasted with a vulnerable subpopulation with poor vaccine response against infection and progression. As a result, the earliest infections are among those with the weakest protection against severe disease. This work highlights methodological challenges in isolating a vaccine's effect on progression to severe disease after infection, and it signals the need for refined analytical methods to adjust for differences between the vaccinated infected and the unvaccinated infected populations.

Keywords

Vaccine waning; protection against infection; progression to severe disease

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Introduction

Many vaccines, including commonly used influenza and COVID-19 vaccines, provide stronger and more durable protection against severe disease than against infection or mild disease. Vaccines stimulate a complex adaptive immune response that includes cellular and humoral immunity at both systemic and mucosal levels [1]. Protection against infection may require local mucosal immunity (e.g., neutralizing IgA and IgG antibodies and resident T cells in the nasal cavity), whereas protection against severe disease may depend more on systemic immunity (e.g. memory CD8 T cells in lymphoid tissue and blood and circulating antibodies) [2,3]. Vaccine types may differ in the protection conferred against infection or mild disease. Intranasal or oral vaccines directly target the mucosal tissues and induce local antibodies, such as mucosal IgA, and T cells, which can function like a “first line of defense” for the immune system. In contrast, intramuscular vaccination primarily generates a systemic immune response, which may be slower to activate [4]. Instead of a “first line of defense,” a systemic response may function like a “second line of defense” which confers better protection against progression to severe disease after infection has been established.

In the framework of Halloran et al. [5], the direct effect of a vaccine for protecting an individual can be decomposed into (1) vaccine effectiveness to reduce susceptibility to infection, denoted VE_s , and (2) vaccine effectiveness to reduce progression to disease given infection, denoted VE_p . These two parts of the pathway combine to determine a vaccine’s effect on disease VE_{sp} , per the equation $(1 - VE_{sp}) = (1 - VE_s)(1 - VE_p)$. When $VE_p > 0$, the protection provided by a vaccine against severe disease is greater than the protection provided against infection alone (i.e., $VE_{sp} > VE_s$). Although the original framework uses infection and disease as the two steps, the logic of decomposing vaccine effects into a first endpoint and a conditional second endpoint can be generalized in many ways. For example, the first step could be disease with any symptoms, including mild symptoms, and the second endpoint could be severe disease, defined as requiring hospitalization [6]. For studies of inpatient populations, the first step could be hospitalization, and the second step could be admission to the intensive care unit or receipt of mechanical ventilation [7]. While the steps may vary across studies, the goal is to characterize the vaccine’s effectiveness in preventing progression to a more severe form of disease. Despite the presence of mild symptoms, for example, it quantifies how much a vaccine-induced second line of defense prevents severe symptoms requiring hospitalization.

The vaccine’s effect against progression to disease VE_p is a less commonly reported quantity than VE_{sp} or VE_s , although it has some notable uses. One use is in mathematical modeling of vaccine impact, as used to model COVID-19 vaccine prioritization strategies [8]. In these models, VE_s and VE_p must be parameterized separately as VE_s influences the vaccine’s ability to reduce transmission (i.e., indirect effects). Another use, as noted above, is in characterizing the vaccine-induced second line of defense, especially where this may be linked to markers of the immune system specific to preventing severe disease in an immune correlate analysis. For example, what is the role of the cellular immune response when antibody titers are insufficient to prevent SARS-CoV-2 infection [9]? Finally, VE_p plays a useful role in bridging VE_s and VE_{sp} . Because of their mathematical relationship,

knowledge of VE_{Sp} and VE_p can be used to infer VE_s , or knowledge of VE_s and VE_p can be used to infer VE_{Sp} . Studies that leverage multiple data sources to infer otherwise hard-to-estimate quantities are an interesting area of development in vaccine evaluation research.

A pattern observed for many COVID-19 vaccines is that of waning protection against infection (or any disease, even mild symptoms), but more durable protection against severe disease. Figure 1 shows an example from a 2021 study using surveillance data from North Carolina [10]. Although not directly reported, one can estimate protection against progression to severe COVID-19 requiring hospitalization conditional on having symptomatic COVID-19 using the previously noted mathematical relationship. Yet the implied pattern of VE_p over time raises questions about its interpretation. For protection against hospitalization to remain roughly steady over time while protection against symptomatic COVID-19 falls, vaccine protection against progression to severe COVID-19 *must appear to increase from below 0% to over 75% in 8 months*. It seems unlikely for such a large increase to represent a real strengthening of the immune system, thus meriting further investigation. Using mathematical modeling, we identify a potential mechanism where vaccine effectiveness against progression to severe disease appears to increase over time despite being constant in the model. We describe the challenges this presents for the interpretation of conditional vaccine effects.

Methods

To identify settings where VE_p appears to increase over time despite no true underlying increase, we structure a mathematical model defined by a limited number of subpopulations and parameters, with relative subpopulation sizes and baseline risk bounded to be realistic using COVID-19 as a model illness.

We modeled a population of 400,000 individuals, with 50% vaccinated. Our compartmental model includes four subpopulations: vulnerable (older adults, people with comorbidities, and others with reduced immune function) and immunocompetent, each divided into unvaccinated and vaccinated subgroups. Each subgroup is assigned a group number: Group 1 is vulnerable/unvaccinated, Group 2 is immunocompetent/unvaccinated, Group 3 is vulnerable/vaccinated, and Group 4 is immunocompetent/vaccinated. Group j 's daily risk of infection is governed by the baseline force-of-infection parameter $\gamma = 0.0056$ times multiplier α_j , as summarized in Table 1. Upon infection, a member of group j has risk of progressing to severe disease $k = 0.10$ times multiplier β_j .

We fixed the Group 1 parameters $\alpha_1 = 1$ and $\beta_1 = 1$ and randomly sample $(\alpha_2, \alpha_3, \alpha_4, \beta_2, \beta_3, \beta_4)$ from the parameter space, each bounded between 0 and 1, to identify parameter combinations where the observed VE_p exhibits a large positive slope despite being modeled as constant. That preliminary analysis served as guidance for setting the default baseline parameters as shown in Table 1.

In our default setting, 7% of the population consists of vulnerable individuals, with 50% of both the vulnerable and immunocompetent individuals being vaccinated. The parameters

$\alpha_2 = \alpha_3 = 1$, indicating that vulnerable/unvaccinated and immunocompetent/unvaccinated individuals have the same risk of infection, and vaccination in the vulnerable group does not confer protection against infection. We relax this assumption in subsequent sensitivity analyses. In contrast, $\alpha_4 = 0.03$, which implies substantial protection against infection ($VE_s = 0.97$) in the immunocompetent, although we assume it wanes linearly from $\alpha_4 = 0.03$ to $\alpha_4 = 0.27$ in 6 months in corresponding Group 4, in line with estimated VE_s waning from data in Figure 1. We assume sterilizing immunity after infection, lasting for the 6-month study period.

In our default setting, $\beta_2 = 0.5$, so that the immunocompetent/unvaccinated have half the risk of progression to severe disease of the vulnerable/unvaccinated. Furthermore, $\beta_3 = 1$, implying that vaccination in the vulnerable group does not confer protection against progression to severe disease, an assumption that we subsequently relax. Finally, $\beta_4 = 0.03$, which implies substantial protection against progression to severe disease ($VE_p = 0.94$) in the immunocompetent. We assume this is constant during the study period.

One hundred simulations were run for each parameter set, and values were estimated over a 6-month period. These simulations are represented as thin grey lines in the corresponding figures (e.g., Figure 3A), with a thick line indicating the representative simulation closest to the averaged values across the six successive months. For each simulation, we summarize the count of infections in month t from group j ($n_{inf,j,t}$) and the count of severe cases in month t from group j ($n_{sev,j,t}$). Observed VE_p in month t (denoted $\widehat{VE}_{p,t}$) is estimated from one minus the fraction of vaccinated infections that are severe (Groups 3 and 4) over the fraction of unvaccinated infections that are severe (Groups 1 and 2), collapsing over vulnerability subgroup:

$$\widehat{VE}_{p,t} = 1 - \frac{\left(\frac{n_{sev,3,t} + n_{sev,4,t}}{n_{inf,3,t} + n_{inf,4,t}} \right)}{\left(\frac{n_{sev,1,t} + n_{sev,2,t}}{n_{inf,1,t} + n_{inf,2,t}} \right)}$$

To assess the effect of within-subgroup heterogeneity in vaccine-induced protection on the observed VE_p , we modeled α_3 , α_4 , β_3 , and β_4 as drawn from beta distributions rather than fixed. We created one beta distribution for each subgroup (vulnerable and immunocompetent) to draw our α_3 and α_4 values, respectively. Parameters β_3 and β_4 were either set equal to the assigned α parameter for each individual (in the case of correlated VE_s and VE_p) or independently drawn from the same beta distributions (for uncorrelated VE_s and VE_p). The waning of vaccine-induced protection against infection in vulnerable Group 3 was modeled by setting the daily rate of change in individual parameter α_3 as the difference between the mean of the corresponding Beta distribution, used to sample each individuals' parameter α_3 , and the value of α_3 , divided by 730 per day (reflecting a return to the unvaccinated level over two years in the baseline setting). If, after applying the daily change, the individual parameter α_3 reached a value of 1 or above, it was kept at 1. Similarly, the daily waning in the immunocompetent vaccinated group (Group 4) was modeled by adjusting each individuals's parameter α_4 . Each individual parameters β_3 and β_4 were kept constant,

indicating constant VE_p . All simulations were performed using R software version 4.2.1 (R Foundation, Vienna, Austria).

Results

Using our four-subgroup model, we identified parameter combinations where observed VE_p increases over time despite true VE_p remaining stable. Only a limited combination of parameters yielded results that closely resemble the experimental data in Figure 1, and these informed our default setting defined in Table 1, with results summarized in Figure 3. Observed VE_p is initially around zero before increasing to above 70%. Among early vaccine breakthrough infections (Groups 3 and 4), the vulnerable group (Group 3) is the majority of the breakthroughs, despite being only 7% of the total population. We note that initial observed VE_p can even be negative. This occurs because the early infections in the unvaccinated are spread across the vulnerable and immunocompetent population, while the early infections in the vaccinated are predominantly from the poorly protected vulnerable group. As VE_s wanes in the immunocompetent population, the immunocompetent population (Group 4) makes up a larger fraction of vaccine breakthrough infections. Given that the immunocompetent population is well-protected against progression to severe disease, observed VE_p increases. During the study, depletion of the susceptible population in the vulnerable/vaccinated (Group 3) also occurs, contributing to the changing balance over time.

In the previous example, VE_s wanes in the immunocompetent population, leading to more vaccine breakthroughs. We assessed whether a similar phenomenon could be observed with constant VE_s in the immunocompetent population. Figure 4 summarizes an example otherwise identical to that in Figure 3 except that VE_s is constant in the immunocompetent population ($\alpha_i = 0.03$ at all times). With constant VE_s in the immunocompetent population, VE_p can still appear to rise over time, yet the increase is attenuated compared to the previous waning VE_s scenario. We note faster depletion of the susceptible population in all subgroups except the vaccinated immunocompetent population (Group 4), so the vaccinated immunocompetent population represents a higher proportion of the vaccinated breakthrough infections as the study progresses. To further explore the impact of depletion of the susceptible population on our findings, we present variations of the default setting with two-fold higher and two-fold lower baseline force-of-infection in Supplemental Figure 1. We note that the observed value of VE_p at 6 months is slightly higher for the scenarios with higher force-of-infection, indicating the depletion of susceptibles phenomenon described above.

To explore the sensitivity, we vary the parameter settings in Figure 5. In Figure 5, Panel A, we consider three additional VE_s waning speeds. Across all settings, observed VE_p increases over time, yet the dynamic range varies across settings. In Figure 5, Panel B, we vary the fraction of the population that is vulnerable. We observe the greatest dynamic range and largest rise in observed VE_p for the higher fractions studied. When a greater proportion of the population is vulnerable, the initial observed VE_p is lower, leading to a greater rise over time. In Figure 5, Panel C, we changed β_2 , governing the relative risk

of progression to severe disease given infection in the unvaccinated immunocompetent population compared to the unvaccinated vulnerable population. We find that this is another important parameter, with a negative initial observed VE_p when $\beta_2 = 0.1$ (unvaccinated immunocompetent population has one tenth the baseline risk of progression to severe disease of the unvaccinated vulnerable population). Thus, the rise in observed VE_p is greater when there is a wider difference in the baseline risk of progression to severe disease given infection between the vulnerability groups.

In Figure 5, Panel D, we varied α_4 , which governs the vaccine protection against infection in the immunocompetent. We demonstrate the importance of high VE_s (i.e., low α_4), at least initially, to observe a large rise in observed VE_p . Where initial VE_s is modest, the entire trajectory is flatter because there are more infections within the vaccinated immunocompetent population at all time points, including month one. In Figure 5, Panel E, we varied β_4 , which governs vaccine protection against progression to severe disease (as relative to β_2). We consider values of $\beta_4 = 0.25$ and 0.50 , implying immunocompetent population VE_p of 0.50 and 0 , respectively. This change affects both the starting and ending point of the trajectory, where the ending point is approximately the immunocompetent population VE_p . Finally, in Figure 5, Panel F, we considered settings where VE_p in the immunocompetent population wanes over time. This is modeled by β_4 approaching β_2 (risk in unvaccinated immunocompetent population) over time. We find that VE_p can appear to decline if VE_p wanes sufficiently fast, and then only after an initial rise. If underlying waning is slow, the entire trajectory can appear to rise.

Figure 6 summarizes results from simulations that include within-subgroup heterogeneity in VE_s and VE_p . In general, the observed rise occurs in VE_p when there is clear separation between the groups such that the vulnerable group has low VE_s and VE_p , while the immunocompetent group has high VE_s and VE_p . As the group means become more similar and the extent of overlap increases, the pattern lessens until the curve is nearly flat. The bimodal structure of the data with a latent subgroup induces a marginal correlation structure, but in additional simulations, we generate perfect within-subgroup correlation. We find that the added correlation slightly increases the dynamic range of the increase (see Supplemental Figure 2).

Finally, we explore the role of high initial VE_s in the immunocompetent group for our findings in Figure 7. In a setting where the vaccinated immunocompetent have high protection (α_4 and β_4 have mean 0.05) and the vaccinated vulnerable have some protection (α_3 and β_3 have mean 0.7) (Figure 7, Panel B), we note an increase in observed VE_p over time, though starting from a higher initial value (Figure 7, Panel E). In contrast, when we reverse the pattern so VE_s among the immunocompetent is lower (α_4 and β_4 have mean 0.3) and the vaccinated vulnerable have very little protection (α_3 and β_3 have mean 0.95) (Figure 7, Panel C), the observed VE_p curve is nearly flat (Figure 7, Panel F).

Discussion

We describe a phenomenon by which vaccine effectiveness against progression to severe disease given infection appears to increase over time as an artifact of population-level heterogeneity in vaccine protection. This work was motivated by observational studies of COVID-19 vaccines, where a similar pattern is implied by waning of protection against infection (or any disease) versus more durable protection against severe disease. To reproduce this phenomenon using a mathematical modeling framework, we found fundamental features to be an immunocompetent population that is at least initially well-protected against infection and progression to severe disease, contrasted with a poorly protected vulnerable subpopulation. The existence of these two subpopulations induces a correlation between VE_s and VE_p , such that individuals with low protection against infection also have low protection against progression to severe disease. This correlation is biologically sensible as a higher acquired level of overall immunity can translate to higher levels of both mucosal immunity (i.e., prevention of infection) and systemic immunity (i.e., progression to severe disease). As a result, the earliest vaccine breakthrough infections are predominantly those with the poorest protection, leading to a low initial estimate of VE_p . VE_p then appears to increase as more breakthrough infections occur in the well-protected immunocompetent population, either due to waning of protection against infection or depletion of the vulnerable vaccinated population [11].

Driving these results is the underlying challenge that VE_p is based on the post-vaccination outcome of infection, and the infected vaccinated are not directly comparable to the infected unvaccinated because some infections have been averted by the vaccine [11,12]. This fundamental issue of conditioning on a post-infection outcome has been recognized for comparing HIV viral load across vaccinated and unvaccinated cases in vaccine trials [13]. A related issue also appeared in studies of SARS-CoV-2 immune imprinting, as individuals who had a prior vaccine breakthrough infection may be more vulnerable in other regards [14]. A novel feature here is in the added dimension of time since vaccination. Waning VE_s and the differential acquisition of immunity across subgroups change the composition of the vaccine breakthrough infections, shifting the weighting of the population VE_p estimate from the vulnerable towards the immunocompetent.

Through a series of sensitivity analyses, we identified settings where this rise in observed VE_p was greatest. First, there is a high level of protection against infection (VE_s), even if short-lived (e.g., a temporary boost in neutralizing antibodies). The rise in observed VE_p is also greater when the size of the vulnerable group is increased. Nonetheless, we were able to observe a large rise even with only 7% of the population in this vulnerable subgroup. In practice, the proportion of the vulnerable population could be high if the study targets a more vulnerable population for enrollment, or if the vaccine generally does not work as well (i.e., greater proportion of non-responders). We balanced the proportion of the vulnerable across the vaccinated and unvaccinated groups, akin to a randomized trial, but the effect is greater when the percentage of vulnerable is higher in the vaccinated. In fact, we can entirely remove the unvaccinated, vulnerable group (Group 1) and still replicate this phenomenon.

The effect is greater when the difference in baseline risk of a severe outcome between the immunocompetent and the vulnerable group is greater.

Our analysis demonstrates the existence of this phenomenon but is not meant to be an exhaustive review of all possible scenarios. There may be other mechanisms that induce this pattern in observed VE_p , although we note that with our four-subpopulation structure, only the basic parameter combinations described yield results that closely resemble the experimental data. In practice, though, real-world data sets are highly heterogeneous, with more types of subpopulations and biases, and this variability may influence outcomes in a broad range of ways. Our simulations are intentionally simplified to focus on the driving features. For example, our core results adopt the strong assumption that the vaccine is ineffective for the vulnerable. We replicate the phenomenon after relaxing this assumption, but the pattern of increasing VE_p is most distinct when there is wide separation in vaccine protection between the vulnerable and the immunocompetent. Another simplifying assumption is that of sterilizing immunity after infection. For future work, an alternative approach would be to model infection-induced immunity against future infection (sometimes denoted IE_s) as waning over time but maintaining high infection-induced immunity against progression to severe disease (sometimes denoted IE_p) [15]. Yet, altering the force-of-infection in sensitivity analysis had little impact on the results, with the pattern observed even with attack rate <25% (Supplemental Figure 1A).

These findings illustrate challenges in interpreting VE_p in both randomized trials and observational studies, and they provide a reason to approach such analyses cautiously. First, estimating VE_p from the earliest breakthrough infections can give a very biased picture of VE_p for the broader population. Second, increases in VE_p over time may reflect a change in the composition of infected individuals rather than a true strengthening of protection against progression to severe disease. To detect this potential bias in real-world studies, investigators can pay close attention to the composition of vaccinated cases over time. Where this issue may be present, earliest vaccinated cases will be highly skewed towards the vulnerable but will shift over time.

Despite the limitations of VE_p , the quantity has an important role for vaccine impact modeling, as well as for comparing the performance of vaccines with different mechanisms of action (e.g., intranasal and intramuscular). For COVID-19 vaccines, there is great interest in being able to characterize the role of T cells, their durability, and their impact on protection against severe disease [16,17]. Thus, better analytic strategies for quantifying protection against progression to severe disease are needed. In our analysis, we did not adjust for subpopulation (vulnerable versus immunocompetent). With covariates on immune status, subgroup-specific estimates can be generated, as in a study of VE_p for the Ad26.COV2.S (Johnson & Johnson) COVID-19 vaccine to prevent progression to highly severe disease among hospitalized adults [7]. This study found that immunocompetent adults had higher protection against hospitalization and against progression to severe disease than immunocompromised adults. In the absence of data on immune status, measurable covariates (e.g. age, pre-existing conditions) can be used to form subgroups. Standardization could be applied to adjust for differences in population composition over time. Finally,

causal inference methods like principal stratification can be used [12], imposing defined assumptions on who would be infected with or without vaccination to yield an interpretable estimate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of competing interest

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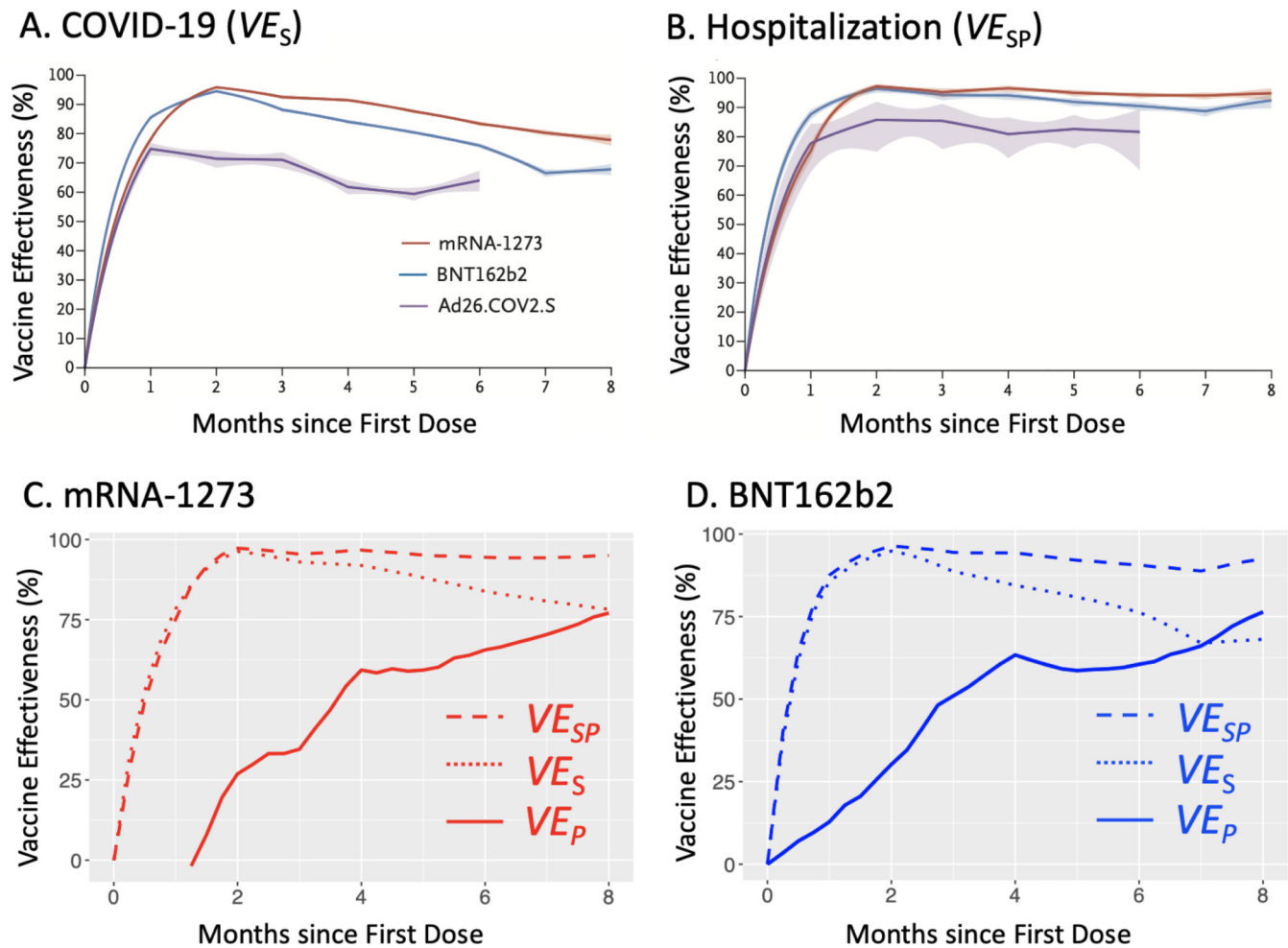


FIGURE 1. The vaccine effectiveness of vaccines against Covid-19.

Panel A shows estimates of vaccine effectiveness in reducing the risks of symptomatic Covid-19. **Panel B** shows estimates of vaccine effectiveness in reducing hospitalization due to severe Covid-19 (adapted from Lin et al., NEJM 2022). **Panel C** and **Panel D** show estimated VE_P defined as the likelihood of not being hospitalized when infected with Covid-19, for the mRNA-1273 and BNT162b2 vaccines, respectively. Corresponding data for VE_S and VE_{SP} were digitized from (A) and (B) and VE_P was calculated as $1-(1-VE_{SP})/(1-VE_S)$. An increase in estimated VE_P over time is observed for both vaccines, which raises questions about the current methodology from a biological perspective. The data were digitized using WebPlotDigitizer (<https://automeris.io/>).

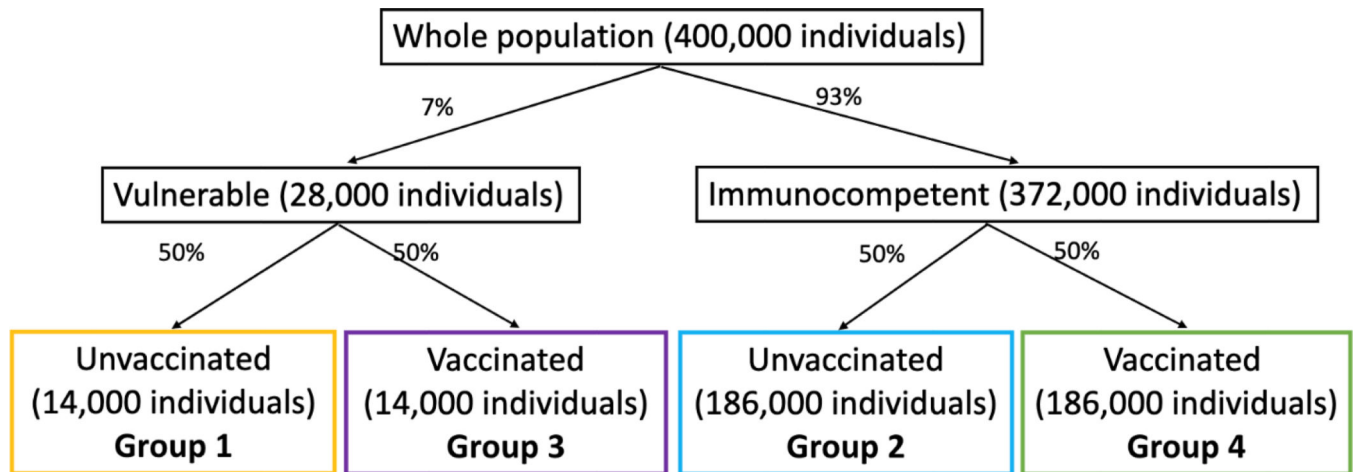
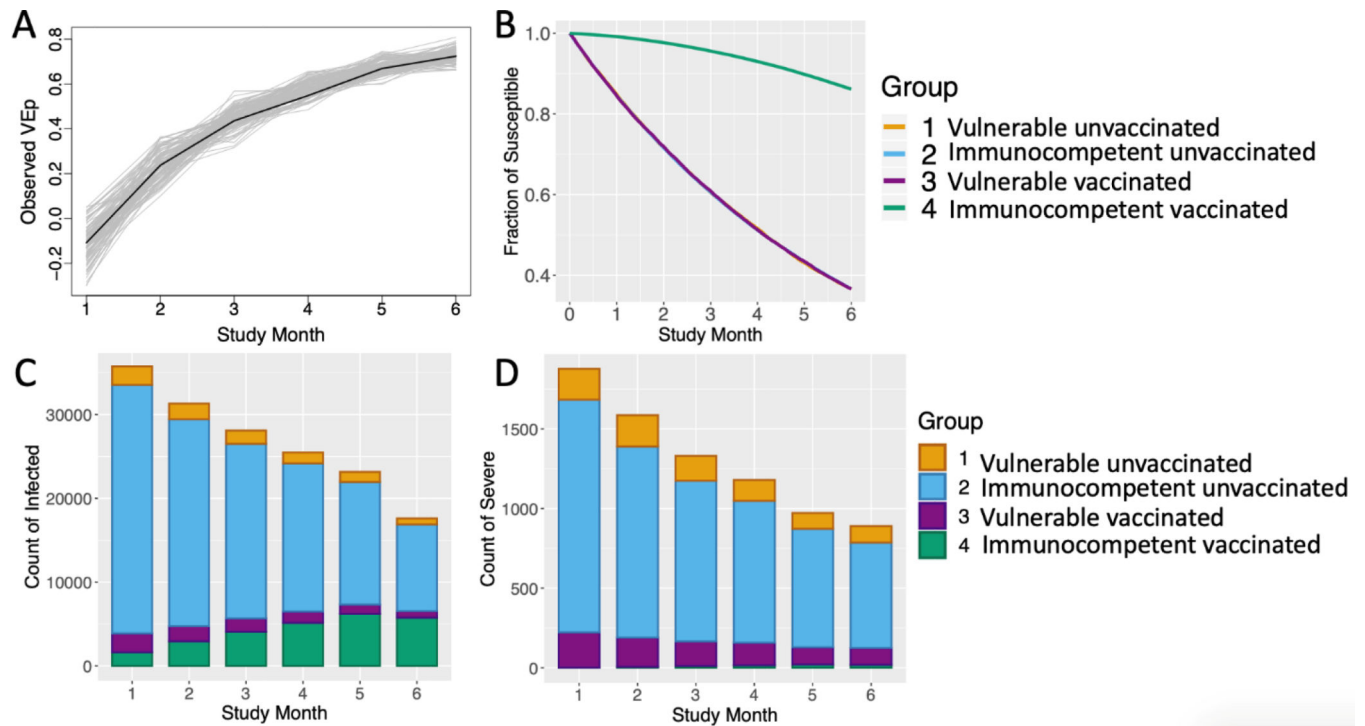
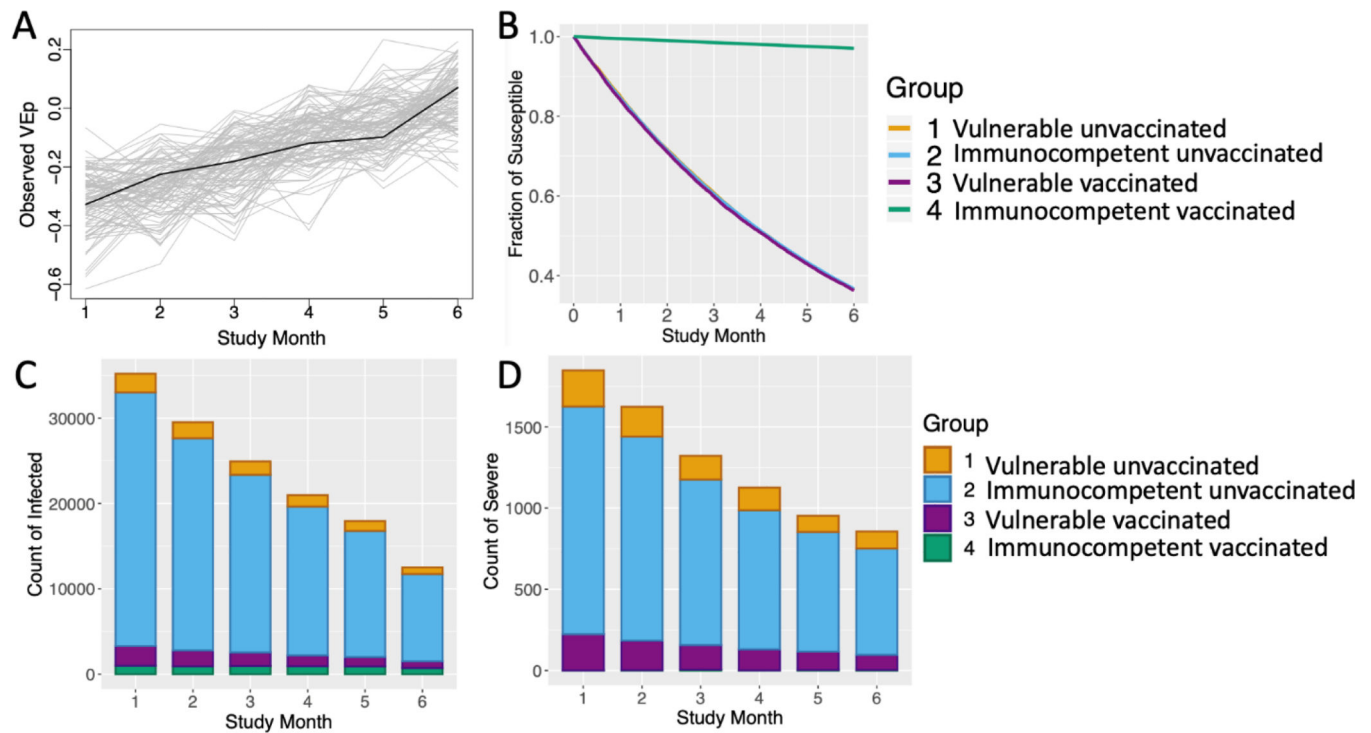


FIGURE 2. Schematic of Study Design.

We modeled a population of 400,000 individuals, with 7% classified as vulnerable and 9% as immunocompetent. Half of each group is vaccinated, resulting in four groups: Vulnerable, unvaccinated (Group 1, orange box); Immunocompetent, unvaccinated (Group 2, blue box); Vulnerable, vaccinated (Group 3, purple box), and Immunocompetent, vaccinated (Group 4, green box). Consistent group colors are used throughout the figures for clarity and comparison.

**FIGURE 3.**

Simulation results for default scenario with waning VE_s . Individuals were classified by group, where Group 1 (orange) is vulnerable/unvaccinated, Group 2 (blue) is immunocompetent/unvaccinated, Group 3 (purple) is vulnerable/vaccinated, and Group 4 (green) is immunocompetent/vaccinated. **Panel A** plots observed VE_p in the entire study population over the 6-month study period. **Panel B** plots fraction susceptible in four groups over the 6-month study period, with Groups 1, 2, and 3 following the same curve. **Panel C** shows the count of infected by study month, with colors indicating the group. **Panel D** is as Panel C but for the count of severe disease.

**FIGURE 4.**

Simulation results for scenario with constant VE_S . Individuals were classified by group, where Group 1 (orange) is vulnerable/unvaccinated, Group 2 (blue) is immunocompetent/unvaccinated, Group 3 (purple) is vulnerable/vaccinated, and Group 4 (green) is immunocompetent/vaccinated. **Panel A** plots observed VE_p in the entire study population over the 6-month study period. **Panel B** plots fraction susceptible in four groups over the 6-month study period, with Groups 1, 2, and 3 following the same curve. **Panel C** shows the count of infected by study month, with colors indicating the group. **Panel D** is as Panel C but for the count of severe disease.

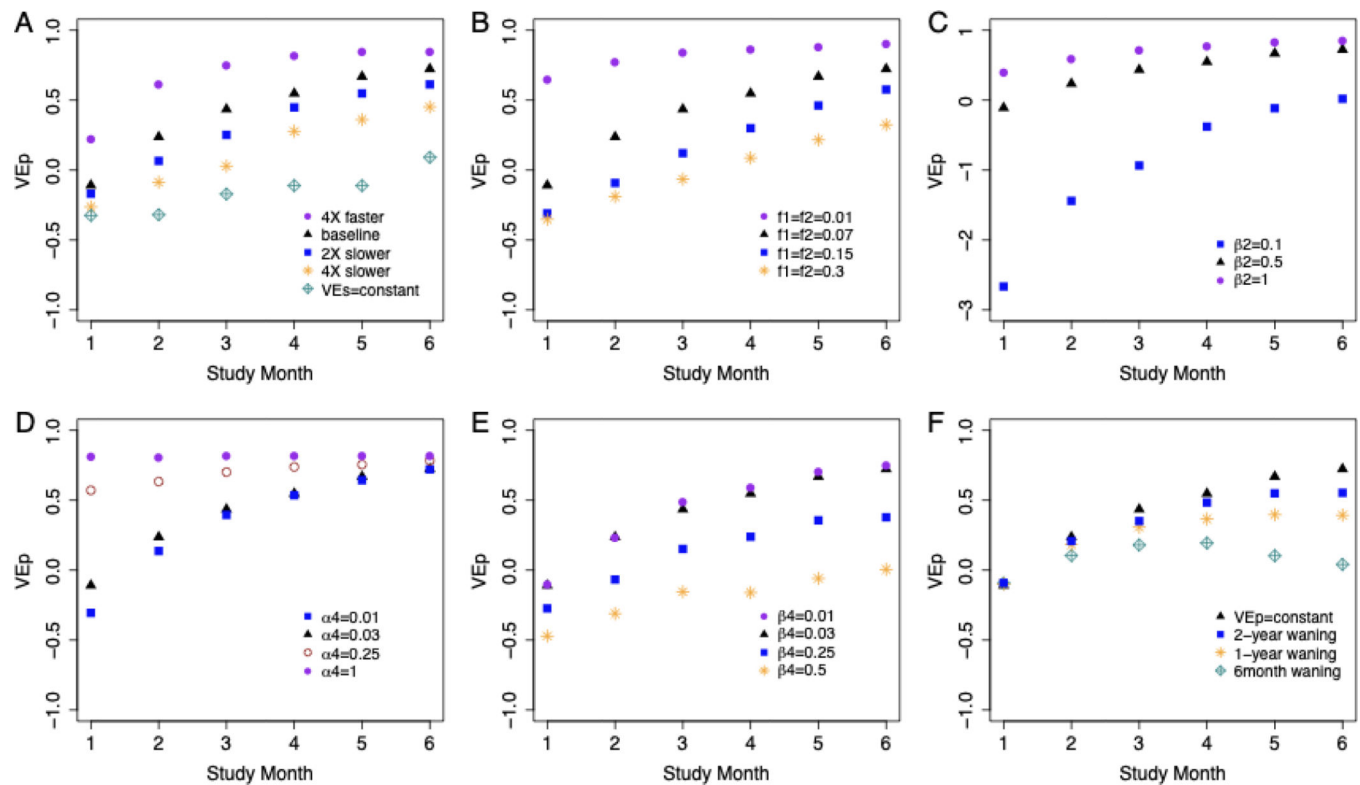


Figure 5.

Parameter sensitivity analysis and its effect on observed VE_p . For each panel and condition, 100 simulations are run, and the plotted/representative curve is the one closest to the average over to the 100 simulations (see Supplemental Figure). Baseline parameters: $\alpha_2 = \alpha_3 = 1$; $\alpha_4 = 0.03$ initially, linearly waning to $\alpha_4 = \alpha_2$ in 730 days; $\beta_2 = 0.05$; $\beta_3 = 1$; $\beta_4 = 0.03$.

Panel A illustrates the role of different extent of waning of vaccine effectiveness for susceptibility (VE_s). **Panel B** describes the impact of the fraction of the vulnerable population. **Panel C** shows the effect of changing the baseline progression to severe disease in unvaccinated group 2, which represents the majority of the unvaccinated population. **Panel D** changes the level of protection against infection, described by parameter α_4 , in Group 4 (vaccinated immunocompetent population). **Panel E** illustrates the effect of different levels of protection against disease progression in responders (parameter β_4). **Panel F** compares cases of no waning in progression to severe disease in vaccinated group 4 with its waning from $\beta_4 = 0.03$ to its baseline level equal to $\beta_2 = 0.5$ during different time periods (6 months, 9 months, and 1 year). Black triangles indicate the baseline model parameters.

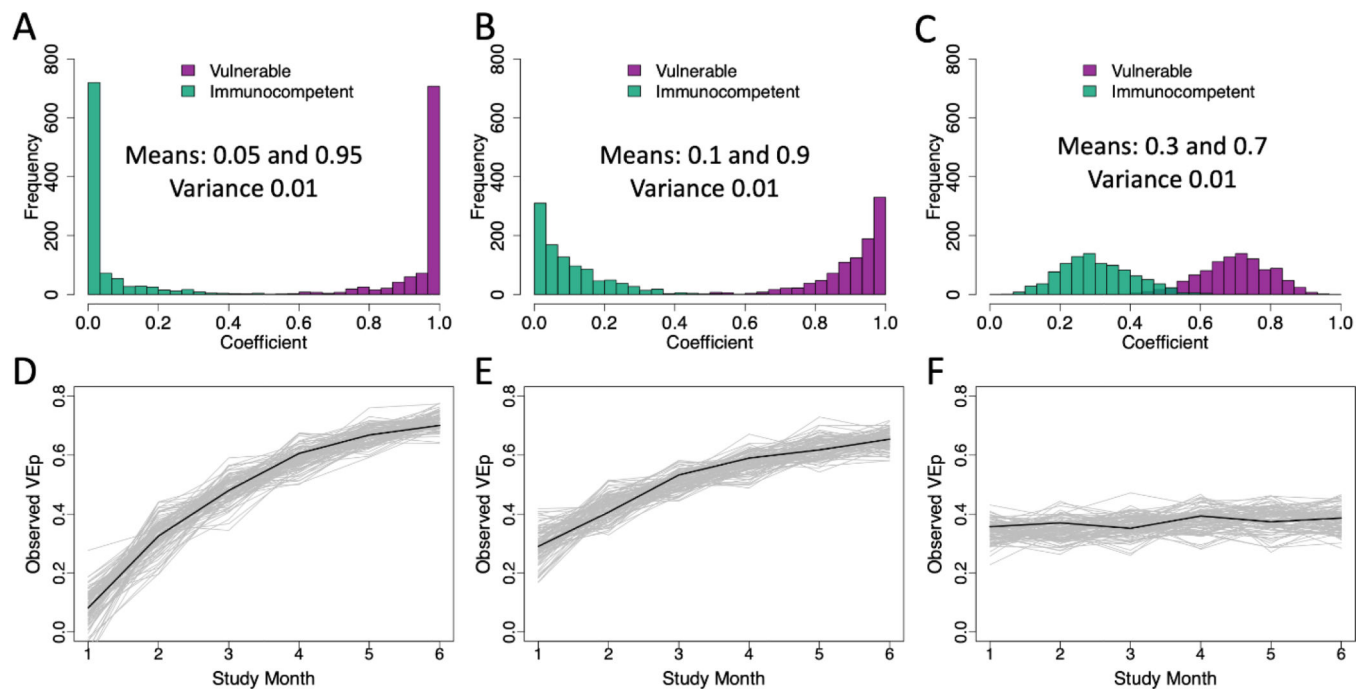


Figure 6. Simulation results from a sensitivity analysis that integrates within-subgroup heterogeneity in VE_s and VE_p .

For vaccinated individuals, the distributions of α_3 and α_4 are modeled by two beta distributions. The three columns correspond to settings with different group-specific mean values. Coefficients characterizing VE_s and VE_p were drawn from the corresponding beta distributions for vulnerable and immunocompetent vaccinated individuals. **Panel A:** Histogram of 1,000 draws for vulnerable individuals (Beta(3.5625, 0.1875); mean = 0.05, variance = 0.01) and immunocompetent individuals (Beta(0.1875, 3.5625); mean = 0.95, variance = 0.01). **Panel B:** Vulnerable individuals follow Beta(7.2, 0.8) (mean = 0.9, variance = 0.01), and immunocompetent individuals follow Beta(0.8, 7.2) (mean = 0.3, variance = 0.01). **Panel C:** Vulnerable individuals follow Beta(14, 7) (mean = 0.7, variance = 0.01), and immunocompetent individuals follow Beta(7, 14) (mean = 0.3, variance = 0.01). The coefficients for VE_s and VE_p are uncorrelated for each individual. Supplemental figure 2 shows how the correlation between coefficients characterizing VE_s and VE_p for each individual affects the observed VE_p .

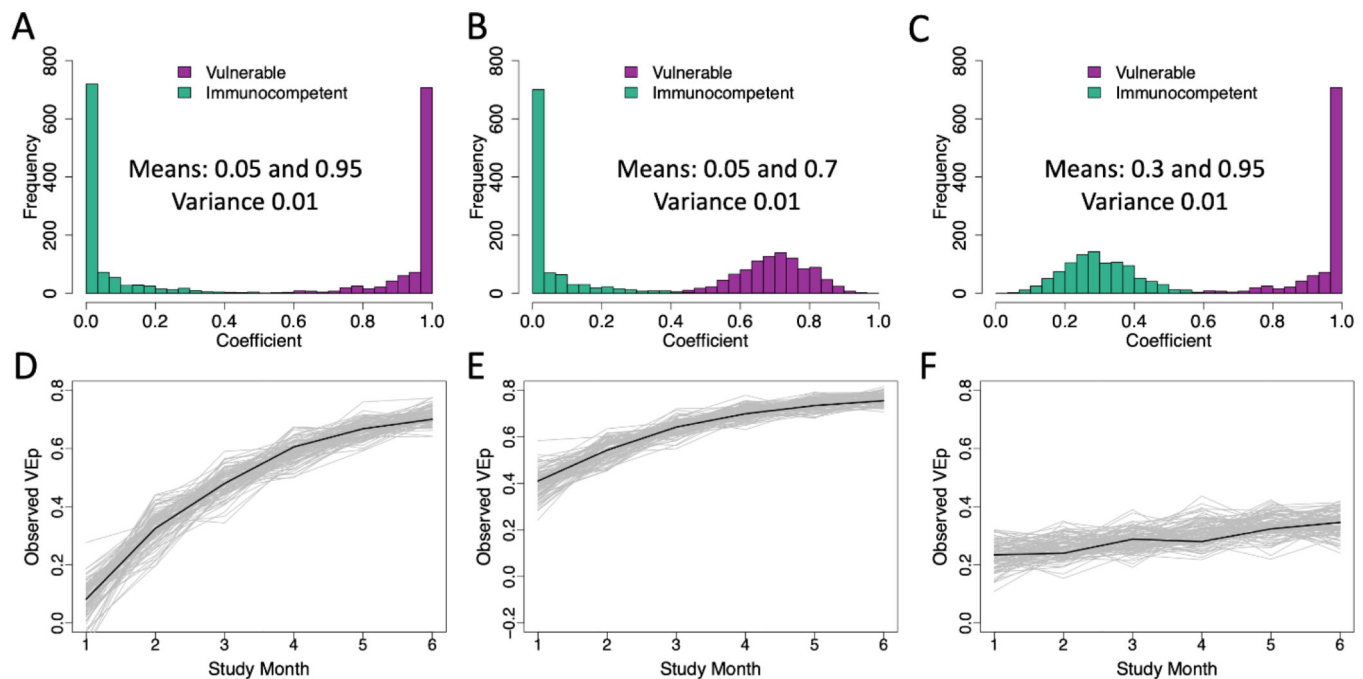


Figure 7. Effect of high vaccine-induced protection in immunocompetent group and low vaccine-induced protection in vulnerable group on observed VE_p .

Panels A-C display histograms of 1,000 draws for coefficients α and β for vulnerable and immunocompromised individuals. **Panel A:** Coefficients α_3 and β_3 for vulnerable/vaccinated are drawn from $\text{Beta}(3.5625, 0.1875)$, and α_4 and β_4 for immunocompetent/vaccinated from $\text{Beta}(0.1875, 3.5625)$. **Panel B:** Coefficients α_3 and β_3 are drawn from $\text{Beta}(14, 7)$, while α_4 and β_4 follow $\text{Beta}(0.1875, 3.5625)$. **Panel C:** Coefficients α_3 and β_3 are drawn from $\text{Beta}(3.5625, 0.1875)$, and α_4 and β_4 from $\text{Beta}(7, 14)$. **Panels D-F** present model results for the observed VE_p over a six-month period, corresponding to uncorrelated α and β coefficients drawn as described in **Panels A-C**.

TABLE 1.

Summary of model parameters and default values. Parameters are labeled by group number, where Group 1 is vulnerable/unvaccinated, Group 2 is immunocompetent/unvaccinated, Group 3 is vulnerable/vaccinated, and Group 4 is immunocompetent/vaccinated. Members of group j are exposed to force-of-infection $\alpha_j \gamma$ where α_j is the multiplier of daily risk of infection, and $\gamma = 0.0056$ is the baseline value. The α_j parameters imply subgroup-specific VE_S values; the default setting assumes no protection against infection in the vulnerable, and high initial protection in the immunocompetent. Given infection, members of group j have probability of progressing to severe disease of $\beta_j k$, where β_j is the multiplier of risk of progression, and $k = 0.10$ is the default value. The β_j parameters imply subgroup-specific VE_P values; the default setting assumes no protection in the vulnerable subgroup and high protection in the immunocompetent.

	Unvaccinated		Vaccinated		Vaccine effect	
Population	Multiplier of daily risk of infection	Multiplier of risk of progression given infection	Multiplier of daily risk of infection	Multiplier of risk of progression given infection	Subgroup VE_S	Subgroup VE_P
Vulnerable	α_1	β_1	α_3	β_3	$1 - \alpha_3/\alpha_1$	$1 - \beta_3/\beta_1$
<i>Default setting</i>	1	1	1	1	0	0
Immunocompetent	α_2	β_2	α_4	β_4	$1 - \alpha_4/\alpha_2$	$1 - \beta_4/\beta_2$
<i>Default setting</i>	1	0.5	0.03	0.03	0.97	0.94