Web Material

Testing Whether Higher Contact Among the Vaccinated Can Be a Mechanism for Observed Negative Vaccine Effectiveness

Korryn Bodner, Jesse Knight, Mackenzie A. Hamilton, and Sharmistha Mishra

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Web Appendix 1: SEIR transmission model

We used an $SEIR$ (susceptible, exposed, infectious, recovered) compartmental transmission dynamics model to perform our analyses (Web Figure 1). The model equations (coupled ordinary differential equations) are as follows:

$$\frac{dS_u}{dt} = -\beta S_u \left(c_{uu} \frac{I_u}{N_u} + (1 - VE_{\mathrm{I}}) c_{uv} \frac{I_v}{N_v} \right) \quad [1]$$

$$\frac{dE_u}{dt} = \beta S_u \left(c_{uu} \frac{I_u}{N_u} + (1 - VE_I) c_{uv} \frac{I_v}{N_v} \right) - E_u \mu$$

$$\frac{dI_u}{dt} = E_u \mu - I_u \gamma$$

$$\frac{dR_U}{dt} = I_u \gamma$$

$$\frac{dS_v}{dt} = -\beta S_v \left(c_{vu} \frac{I_u}{N_u} + (1 - VE_I) c_{vv} \frac{I_v}{N_v} \right)$$

$$\frac{dE_v}{dt} = \beta S_v \left(c_{vu} \frac{I_u}{N_u} + (1 - VE_{\mathrm{I}}) c_{vv} \frac{I_v}{N_v} \right) - E_v \mu$$

$$\frac{dI_v}{dt} = E_v \mu - I_v \gamma$$

$$\frac{dR_v}{dt} = I_v \gamma$$

where S_u, E_u, I_u, and R_u are the numbers of susceptible, exposed, infectious, and recovered unvaccinated individuals, respectively; S_v, E_v, I_v, and R_v are the corresponding numbers for vaccinated individuals; $N_u = S_u + E_u + I_u + R_u$ and $N_v = S_v + E_v + I_v + R_v$, which are the total numbers of unvaccinated and vaccinated individuals respectively; β is the probability of infection per contact; μ is the latency rate, γ is the recovery rate; VE_I is the vaccine efficacy against infectiousness; c_{uu} and c_{vv} are the within-group contact rates for unvaccinated and vaccinated individuals, respectively, and c_{uv} and

c_{vu} are the contact rates of unvaccinated with vaccinated and vaccinated with unvaccinated, respectively.

The initial conditions for vaccinated individuals included vaccine efficacy against susceptibility, VE_S, and were defined as:

$$S_v(t=0) = (1 - VE_S)N_v - \varepsilon,$$

$$E_v(t=0) = 0,$$

$$I_v(t=0) = \varepsilon,$$

$$R_v(t=0) = VE_S N_v$$

Whereas for unvaccinated individuals, our initial conditions were defined as:

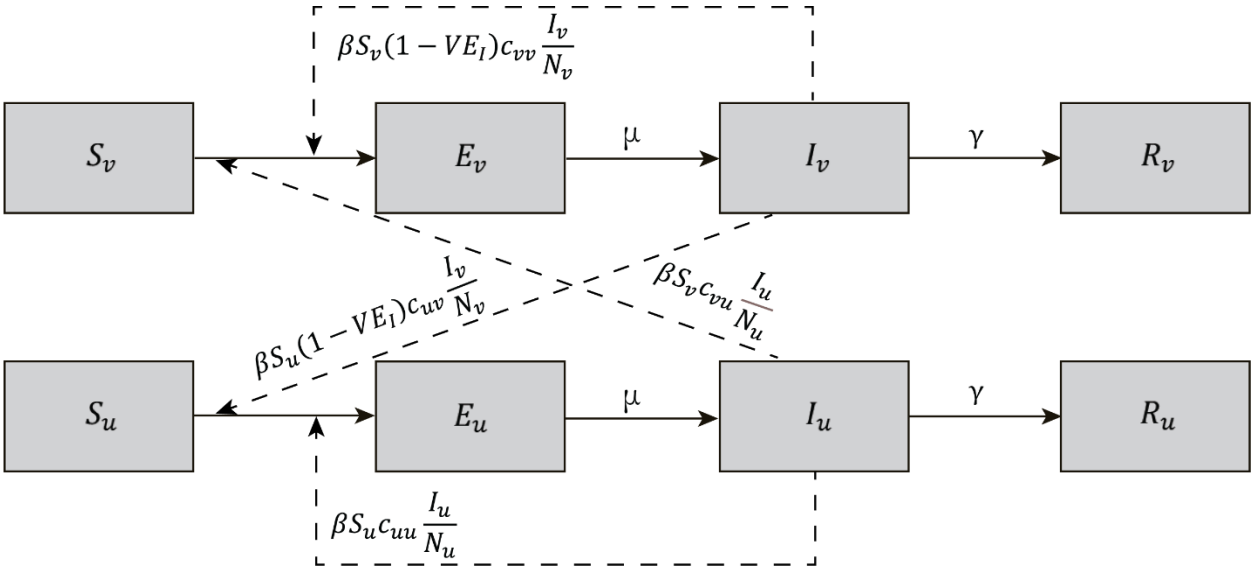
$$S_u(t=0) = N_u - \varepsilon,$$

$$E_u(t=0) = 0,$$

$$I_u(t=0) = \varepsilon,$$

$$R_u(t=0) = 0.$$

where $\varepsilon = 1$ was the number of infectious individuals introduced into each group at $t = 0$. The model was coded in R (version 4.1.2; (1)), and solved numerically using the *lsoda* function within the deSolve package (2).



Web Figure 1. A schematic of our $SEIR$ compartment model where S, E, I, and R represent the susceptible, exposed, infectious, and recovered individuals who are either vaccinated (v) or unvaccinated (u). Susceptible individuals become exposed via a transmission probability (β) based on their contact rates with either infectious vaccinated (c_{uv} or c_{vv}) or infectious unvaccinated individuals (c_{vu} or c_{uu}). Once exposed, all vaccinated and unvaccinated individuals become infectious at rate μ. Susceptible vaccinated and unvaccinated individuals have a reduced chance of infection when contacting an infectious vaccinated individual due to vaccine efficacy against infectiousness (VE_I). Protection due to vaccine efficacy against susceptibility (VE_S) is not included in the main equations but instead is included at the start of the simulation when a specified proportion of vaccinated individuals (defined by VE_S) is moved to the recovered (and thus immune) compartment. All individuals recover from infection at rate γ.

Web Appendix 2: SIR transmission model

In addition, we also built an SIR (susceptible, infectious, recovered) compartmental transmission dynamics model to assess how the removal of a latency period influences vaccine effectiveness measurements. The model equations (coupled ordinary differential equations) are as follows:

$$\frac{dS_u}{dt} = -\beta S_u \left(c_{uu} \frac{I_u}{N_u} + (1 - VE_{\mathrm{I}}) c_{uv} \frac{I_v}{N_v} \right) \quad [2]$$

$$\frac{dI_u}{dt} = \beta S_u \left(c_{uu} \frac{I_u}{N_u} + (1 - VE_I) c_{uv} \frac{I_v}{N_v} \right) - I_u \gamma$$

$$\frac{dR_U}{dt} = I_u \gamma$$

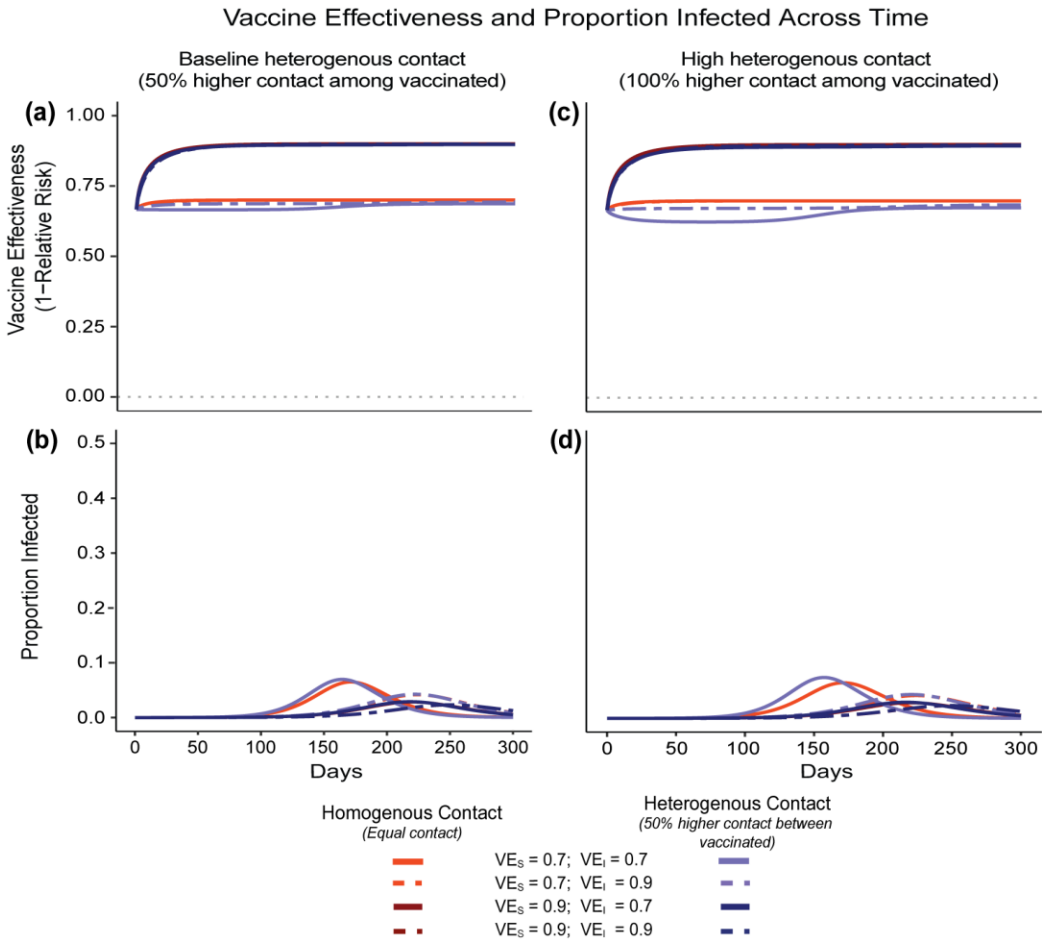
$$\frac{dS_v}{dt} = -\beta S_v \left(c_{vu} \frac{I_u}{N_u} + (1 - VE_I) c_{vv} \frac{I_v}{N_v} \right)$$

$$\frac{dI_v}{dt} = \beta S_v \left(c_{vu} \frac{I_u}{N_u} + (1 - VE_{\mathrm{I}}) c_{vv} \frac{I_v}{N_v} \right) - I_v \gamma$$

$$\frac{dR_v}{dt} = I_v \gamma$$

where S_u, I_u, and R_u are the numbers of susceptible, infectious, and recovered unvaccinated individuals, respectively; S_v, I_v, and R_v are the corresponding numbers for vaccinated individuals; $N_u = S_u + I_u + R_u$ and $N_v = S_v + I_v + R_v$, which are the total numbers of unvaccinated and vaccinated individuals respectively. Definitions and values of the parameters and initial conditions are the same as those defined in Web Appendix 1 (without using the exposed condition). The model was coded in R (version 4.1.2; (1)), and solved numerically using the *lsoda* function within the deSolve package (2).

Additional SEIR transmission dynamics model results: high vaccine efficacies



Web Figure 2. Vaccine effectiveness and the proportion infected over time comparing homogeneous contact scenarios with two heterogeneous contact scenarios (baseline and high) using an $SEIR$ transmission dynamics model. Homogeneous contact rates (equal contacts among vaccinated and unvaccinated individuals) and heterogenous contact rates (vaccinated have higher and more contact with vaccinated individuals) interact with vaccine efficacy against susceptibility (VE_S) and vaccine efficacy against infectiousness (VE_I) to influence measurements of vaccine effectiveness over time (a and c) and the proportion of infected (exposed or infectious) individuals over time (b and d). Baseline levels of heterogeneous contact (50% higher contact between vaccinated; a and b) and high levels of heterogenous contact (100% higher contact between vaccinated; c and d) both result in underestimated vaccine

effectiveness when vaccine efficacies are moderately high (0.7) with the effect more pronounced in the high heterogeneous contact scenario. For both levels of heterogeneous contact, underestimates disappear once VE_S is very high (0.9), which also coincides with only a small proportion of the population becoming infected.

Web Appendix 3: Derivation of the relationship between vaccine effectiveness, the proportion of susceptible individuals and vaccine efficacy against susceptibility

Following Haber (3), we define vaccine effectiveness over time, $V_{Eff}(t)$ as follows:

$$V_{Eff}(t) = 1 - RR(t) \qquad [3]$$

with

$$RR(t) = \frac{\frac{CI_v(t)}{N_v}}{\frac{CI_u(t)}{N_u}} \qquad [4]$$

where $CI_v(t)$ and $CI_u(t)$ are the cumulative incidences for vaccinated and unvaccinated groups at time *t,* respectively. Given equations 3 and 4:

$$V_{Eff}(t) \geq 0 \text{ when } \frac{CI_v(t)}{N_v} \leq \frac{CI_u(t)}{N_u} \qquad [5]$$

and

$$V_{Eff}(t) < 0 \text{ when } \frac{CI_v(t)}{N_v} > \frac{CI_u(t)}{N_u} \qquad [6]$$

We define $CI_v(t)$ and $CI_u(t)$ as:

$$CI_v(t) = E_v(t) + I_v(t) + \widehat{R_v}(t)\,, \qquad [7]$$

$$CI_U(t) = E_u(t) + I_u(t) + R_u(t)$$

where $\widehat{R_v}(t)$ is the number of individuals at time *t* who have recovered from infection and thus does not include those immune from vaccination (i.e. does not include $VE_S N_v$). Let $N_V = S_v(t) + E_v(t) + I_v(t) + \widehat{R_v}(t) + VE_S N_v$ and $N_U = S_u(t) + E_u(t) + I_{U(t)} + R_u(t)$ with N_v and N_u defined as constant over time given no mortality exists in the system. Using equations 7 and these definitions, we can rearrange equation 5 as:

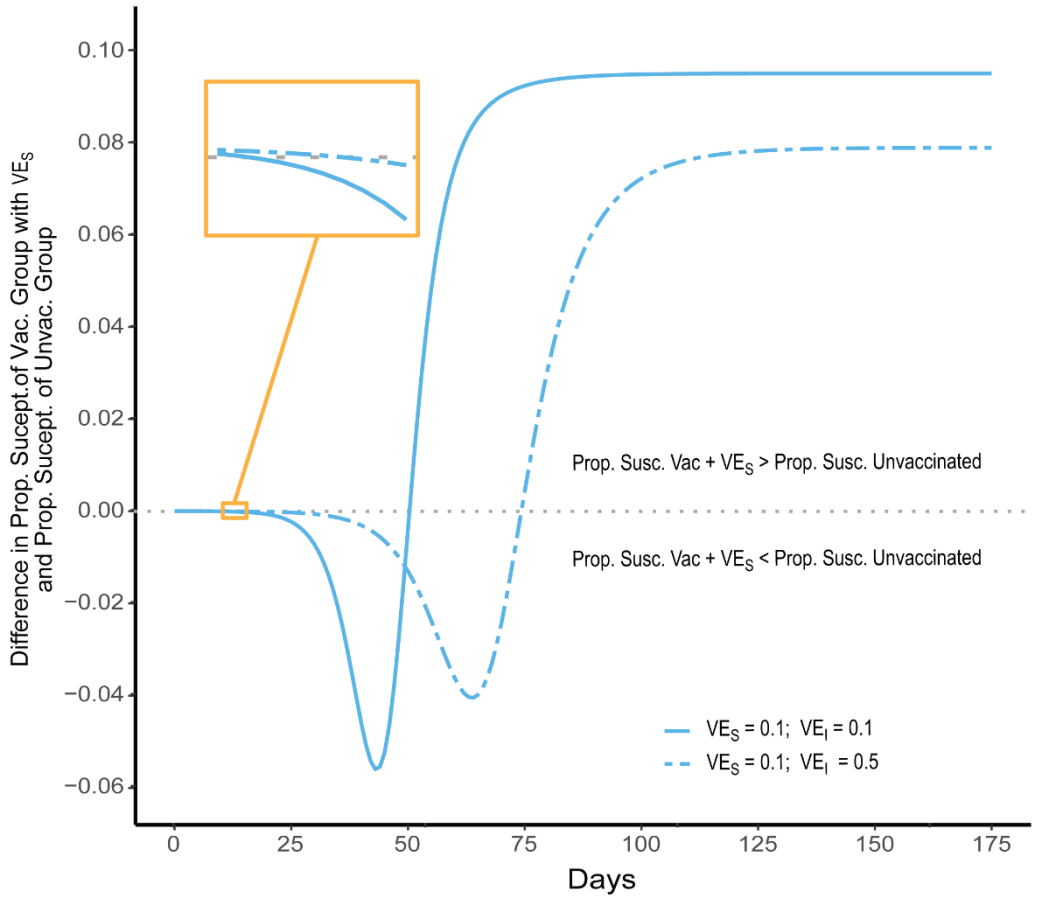
$$\frac{N_V - S_v(t) - VE_S N_v}{N_v} \leq \frac{N_u - S_u(t)}{N_u} \qquad [8]$$

$$1 - \frac{S_v(t)}{N_v} - VE_S \leq 1 - \frac{S_u(t)}{N_u}$$

$$\frac{S_v(t)}{N_v} + VE_S \geq \frac{S_u(t)}{N_u}$$

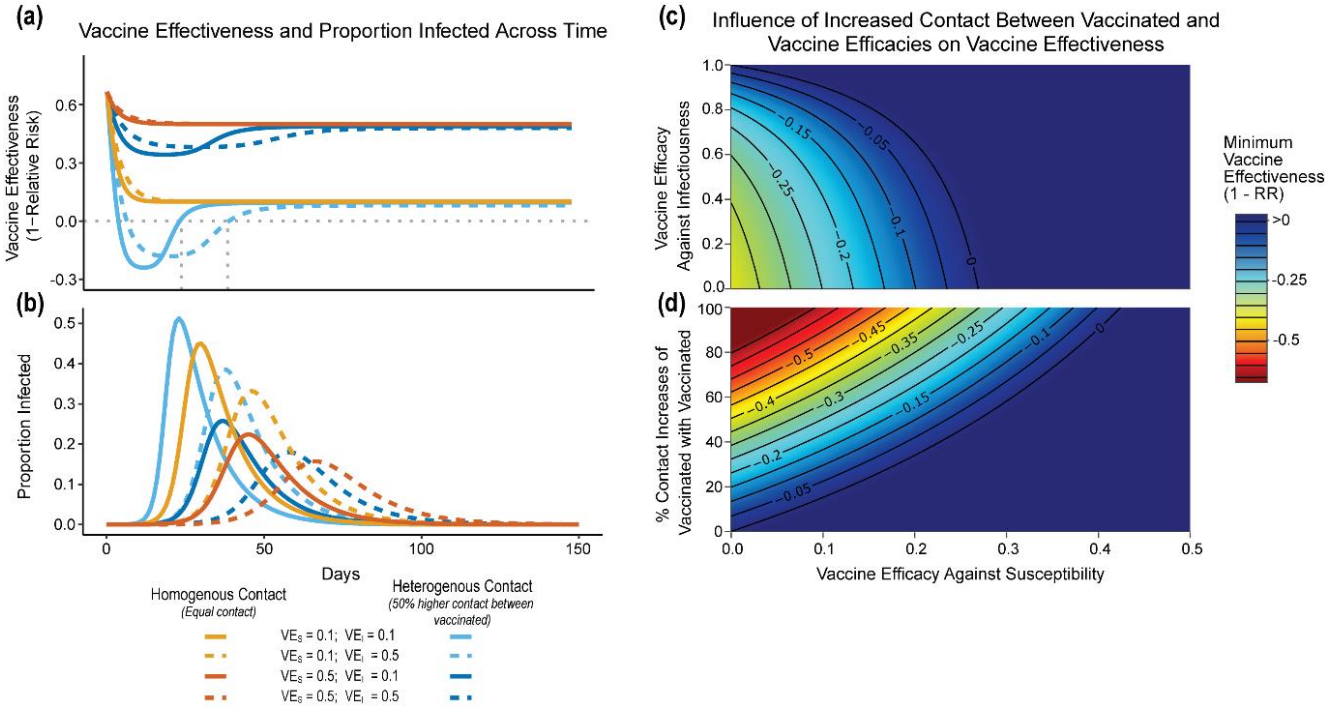
Here we find that $V_{Eff}(t)$ becomes non-negative only when the proportion of susceptible unvaccinated, $\frac{S_u(t)}{N_u}$, is less than the combined proportion of susceptible vaccinated, $\frac{S_v(t)}{N_v}$, and those vaccinated and immune (VE_S). Similarly, using equations 7 and the inequality of equation 6, we find that V_{Eff} is negative when $\frac{S_u(t)}{N_u}$ is greater than the combined proportion of $\frac{S_v(t)}{N_v}$ with VE_S. Note that these relationships also hold assuming no latency period (i.e. for SIR model dynamics).

In Web Figure 3 (below), we illustrate that the inequality of equation 5 was not maintained in our vaccinated contact heterogeneity scenarios and that the two inequality changes that occurred in each scenario defined the period of negative V_{Eff} measurements.



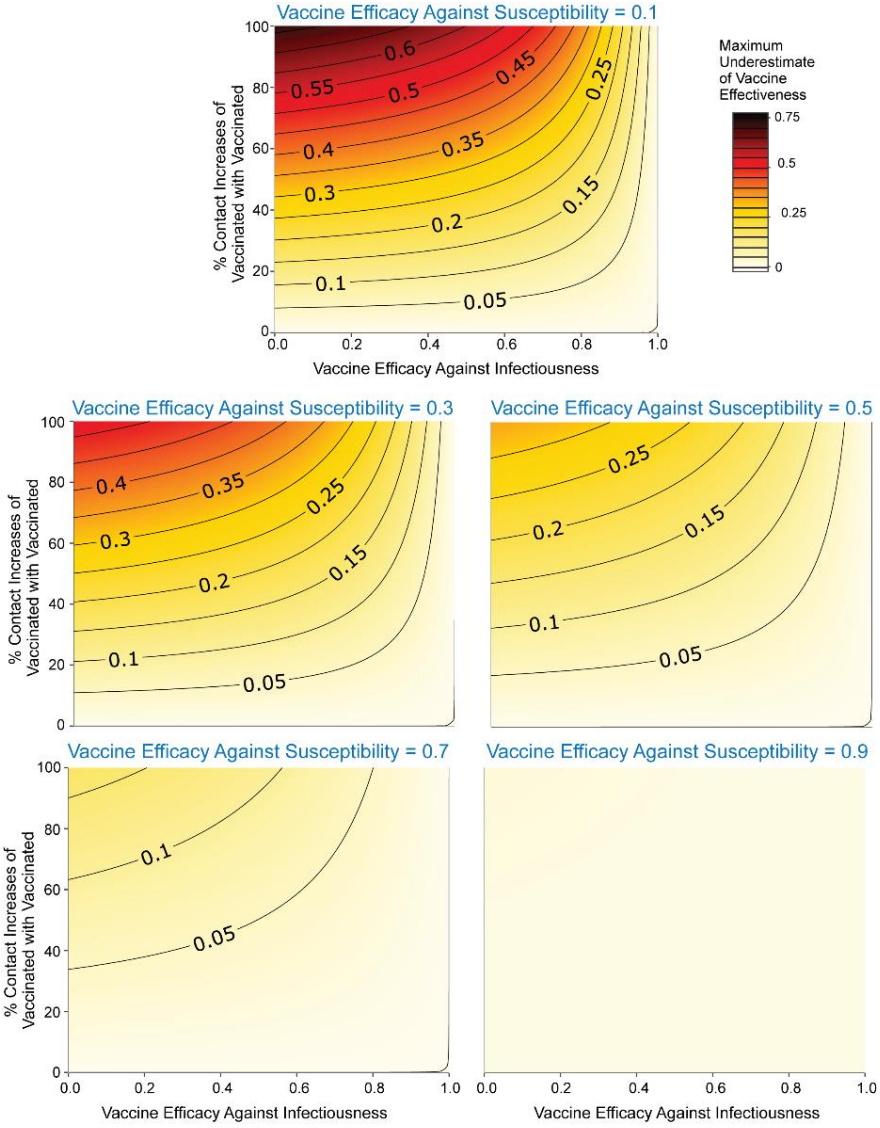
Web Figure 3: A measure of the differences between the proportion of vaccinated susceptibles (Prop. Susc. Vac) and the proportion of unvaccinated susceptibles (Prop. Susc. Unvac.) accounting for vaccine efficacy against susceptibility (VE_S) over time. After an initial period, both vaccinated heterogeneous scenarios (VE_S = VE_I = 0.1 [solid line]; VE_S =0.1 and VE_I = 0.5 [dashed line]) have a higher proportion of susceptible unvaccinated individuals compared to the combined proportion of susceptible vaccinated and immune vaccinated individuals (VE_S). This relationship remains until day 51 (VE_S =0.1 and VE_I =0.1) and 75 (VE_S =0.1 and VE_I = 0.5) when this inequality flips with the timing of these crossovers corresponding to when vaccine effectiveness switches from negative to positive. Note that higher levels of VE_I (0.5) resulted in a longer period of observed negative measurements due to VE_I benefiting both vaccinated and unvaccinated individuals and thus slowing the speed of the epidemic (see Figure 1 in the main text).

Web Figure 4: SIR transmission dynamics model results



Vaccine effectiveness and infection dynamics produced by an SIR model are shown to be influenced by contact heterogeneity and vaccine efficacies. Homogeneous contact rates (equal contacts among vaccinated and unvaccinated individuals) and heterogenous contact rates (vaccinated have more contacts with vaccinated individuals) interact with vaccine efficacy against susceptibility (VE_S) and vaccine efficacy against infectiousness (VE_I) to influence (a) measurements of vaccine effectiveness over time and (b) the proportion of infected individuals over time. Negative vaccine effectiveness becomes positive once the proportion of susceptible unvaccinated individuals became lower than the proportion of susceptible vaccinated individuals combined with the level of VE_S (grey vertical lines; Web Appendix 2). The minimum vaccine effectiveness was sensitive to (c) VE_I, (d) the % increase in contact between vaccinated individuals (d), and (c and d) VE_S. Note that colours in (c) and (d) indicate the maximum negative vaccine effectiveness (or the minimum vaccine effectiveness) observed for a given simulation with >0 indicating a non-negative measurement.

Web Figure 5: Sensitivity analyses for SEIR transmission dynamics model exploring the degree of underestimation of vaccine effectiveness



Sensitivity of the vaccine effectiveness (V_{Eff}) maximum underestimate to the level of vaccine efficacy against infectiousness (VE_I) and to the degree of contact between vaccinated individuals across five levels of vaccine efficacy against susceptibility (VE_S; 0.1, 0.3, 0.5, 0.7 and 0.9). The maximum underestimate of V_{Eff} (i.e. the minimum V_{Eff} measurement over time subtracted from the true vaccine effectiveness [i.e. the level of VE_S]) was driven by the % increase in contact between vaccinated

individuals (i.e. vaccinated contact heterogeneity bias) and was strongly mediated by the level of VE_S and to a lesser extent, by the level of VE_I. Note that contour plots were generated using $SEIR$ models initiated with 3 unvaccinated and 1 vaccinated infectious individual(s) to prevent initial conditions from producing the largest V_{Eff} underestimate (initial conditions change the starting value of V_{Eff} but overall dynamics and V_{Eff} underestimates due to vaccinated contact heterogeneity are not affected).

References

1. R Core Team. R: A language and environment for statistical computing. 2021;(https://www.r-project.org/)

2. Soetaert K, Petzoldt T, Setzer RW. Solving Differential Equations in R: Package deSolve. *J. Stat. Softw.* 2010;33(9).

3. Michael Haber. Estimation of the direct and indirect effects of vaccination. *Stat. Med.* 1999;18:2101–2109.