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Original Contribution

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

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Evidence from early observational studies suggested negative vaccine effectiveness (V_{Eff}) for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant. Since true V_{Eff} is unlikely to be negative, we explored how differences in contact among vaccinated persons (e.g., potentially from the implementation of vaccine mandates) could lead to observed negative V_{Eff}. Using a susceptible-exposed-infectious-recovered (SEIR) transmission model, we examined how vaccinated-contact heterogeneity, defined as an increase in the contact rate only between vaccinated individuals, interacted with 2 mechanisms of vaccine efficacy: vaccine efficacy against susceptibility (VE_S) and vaccine efficacy against infectiousness (VE_I), to produce underestimated and in some cases, negative measurements of V_{Eff}. We found that vaccinated-contact heterogeneity led to negative estimates when VE_I, and especially VE_S, were low. Moreover, we determined that when contact heterogeneity was very high, V_{Eff} could still be underestimated given relatively high vaccine efficacies (0.7), although its effect on V_{Eff} was strongly reduced. We also found that this contact heterogeneity mechanism generated a signature temporal pattern: The largest underestimates and negative measurements of V_{Eff} occurred during epidemic growth. Overall, our research illustrates how vaccinated-contact heterogeneity could have feasibly produced negative measurements during the Omicron period and highlights its general ability to bias observational studies of V_{Eff}.

bias; contact heterogeneity; COVID-19; SARS-CoV-2; transmission model; vaccine effectiveness; vaccine efficacy

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEIR, susceptible-exposed-infectious-recovered; SIR, susceptible-infectious-recovered; V_{Eff}, vaccine effectiveness; VE_S, vaccine efficacy against susceptibility; VE_I, vaccine efficacy against infectiousness.

Within 4 weeks of the emergence and in the context of rising cases of Omicron, population-based studies in Canada (1), Denmark (2), and the United Kingdom (3) had reported "negative vaccine effectiveness" against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Vaccine effectiveness (V_{Eff}) is calculated by comparing the rates of infection between vaccinated and unvaccinated individuals. Thus, an observed negative V_{Eff} measurement suggests that vaccinated individuals were acquiring infections at higher rates than unvaccinated individuals. One potential explanation for the increased infection was that the vaccine increased biological susceptibility, for example, if the virus had evolved to spread faster in vaccinated individuals (4). However, V_{Eff} measurements are calculated using observational data and thus subject to various biases, including but not limited to differences in testing/detection and exposures among vaccinated and unvaccinated populations (5). Differential exposures by vaccination status could stem from contact heterogeneity.

Contact heterogeneity refers to different levels of contact among and between population subgroups. Increased contact between vaccinated persons, potentially arising due to policies that restrict certain spaces to vaccinated individuals (e.g., vaccine mandates), is one type of contact heterogeneity (hereafter, vaccinated-contact heterogeneity). In this study, we tested: 1) whether vaccinated-contact

heterogeneity could lead to observed negative V_{Eff} measurements; 2) how this relationship is affected by 2 components of vaccine efficacy related to transmissibility: vaccine efficacy against susceptibility (VE_S) and vaccine efficacy against infectiousness (VE_I) (6); and, if negative measurements can be produced, 3) how this mechanism can be identified. As negative measurements of V_{Eff} are an example of an underestimate, we also explore how vaccinated-contact heterogeneity interacts with vaccine efficacies to influence the degree to which V_{Eff} is underestimated. We adopt both VE_S and VE_I as they are both part of a vaccine's benefit against transmission, with VE_S reflecting the reduced probability of vaccinated recipients acquiring infection and VE_I reflecting the reduced infectiousness of vaccinated individuals if a breakthrough infection occurs. We hypothesize that both vaccinated-contact heterogeneity and the levels of VE_S and VE_I contribute to producing measurements of negative V_{Eff}.

METHODS

To model the dynamics underlying measurements of V_{Eff}, we built a simple compartmental susceptible-exposed-infectious-recovered (SEIR) transmission dynamics model based on Shim and Galvani (7) that included vaccinated and unvaccinated individuals and assumed an all-or-nothing vaccine type ((8); Web Appendix 1 and Web Figure 1, available at https://doi.org/10.1093/aje/kwad055). We also created a complementary susceptible-infectious-recovered (SIR) transmission dynamics model to evaluate how the removal of a latency period (i.e., exposed state) affects measurements of V_{Eff} (Web Appendix 2). To explicitly account for potential contact differences, the transmission models contained both within-group contact rates for unvaccinated, c_{uu}, and vaccinated individuals, c_{vv}, as well as between-group contact rates for unvaccinated with vaccinated, c_{uv}, and vaccinated with unvaccinated, c_{vu}.

In all simulations, we assumed 75% vaccination coverage. We explored 2 different contact scenarios: homogeneous contact, where vaccinated and unvaccinated individuals have equal contacts with random ("proportionate") mixing, and vaccinated heterogeneous contact where vaccinated individuals have increased within-group contact. In the homogenous contact scenario, we assumed 6 daily contacts per person, reflecting approximate contact rates from the United States and United Kingdom during the pandemic (9), and thus defined $c_{vv} = c_{uv} = 4.5$ and $c_{uu} = c_{vu} = 1.5$. In the vaccinated heterogeneous contact scenario, contacts between vaccinated were increased by 50% compared with the homogeneous contact scenario ($c_{vv} = 6.75$), with all other parameter values unchanged. We set the recovery rate to be 1/10 (10), the rate of progression from exposed to infectious (the reciprocal of the incubation period) to be 1/4 (11), and the probability of transmission to be 0.01, such that $R_0 = 6$ in a fully unvaccinated population with random mixing. Given the uncertainty surrounding vaccine efficacies, we focused our analyses on 2 different baseline values of VE_I and VE_S (0.1, 0.5) but also explored the dynamics of higher levels of vaccine efficacies (0.7, 0.9) to determine their effects on V_{Eff} measurements.

We conducted sensitivity analyses, varying VE_I and VE_S from 0.1 to 1 and increasing c_{vv} by 0% to 100% from the homogeneous contact scenario rates ($c_{vv} = 4.5$–9) to explore their effects on the production of observed negative V_{Eff}. To generalize beyond negative V_{Eff}, we also conducted additional sensitivity analyses exploring how different levels of vaccinated-contact heterogeneity and vaccine efficacies influence the maximum degree of V_{Eff} underestimation (i.e., the difference between the true V_{Eff} and the minimum measured V_{Eff} per scenario). In our sensitivity analyses, the analyses focused on the minimum V_{Eff} recorded to illustrate the maximum bias that would be observed in each given scenario. To start our simulations, we introduced 1 infected vaccinated and 1 infected unvaccinated individual into our population.

Following Haber (12), we measured $V_{Eff}(t)$ as $1 - relative\ risk(t)$ ($RR\,[t]$), with $RR(t)$ defined as:

$$RR(t) = \frac{\frac{CI_v(t)}{N_v}}{\frac{CI_u(t)}{N_u}}, \quad (1)$$

where $CI_v(t)$ and $CI_u(t)$ are the cumulative incidences for vaccinated and unvaccinated groups at time t, respectively, and N_v and N_u are the total numbers of vaccinated and unvaccinated individuals, respectively. As $CI_v(t)$ and $CI_u(t)$ are from the same simulated population that includes vaccinated and unvaccinated individuals, $V_{Eff}(t)$ should capture the direct effects of vaccination (i.e., VE_S) (6, 13). We also tracked how differences in the depletion of the proportion of susceptible vaccinated, $\frac{S_v(t)}{N_v}$, and unvaccinated, $\frac{S_u(t)}{N_u}$, interacted with VE_S to influence measurements of V_{Eff} over time.

RESULTS

Different contact patterns by vaccination status and levels of vaccine efficacies influenced the existence and degree of bias in measurements of V_{Eff}. First, scenarios of homogeneous contact according to vaccination status never led to underestimated or negative V_{Eff} and instead, after a short initial period (due to our initial conditions of equal vaccinated and unvaccinated cases), produced accurate measurements of V_{Eff} ($V_{Eff} = VE_S$). Second, scenarios of heterogeneous contact according to vaccination status consistently produced underestimated V_{Eff}, but resulted in negative V_{Eff} only in the context of lower vaccine efficacies ($VE_S = 0.1$, $VE_I = 0.1$, and $VE_S = 0.1$, $VE_I = 0.5$; Figure 1A). Third, while increased levels of vaccine efficacies reduced the effect of vaccinated-contact heterogeneity on V_{Eff} measurements, moderately high vaccine efficacies ($VE_S = VE_I = 0.7$) led to V_{Eff} underestimates when vaccinated-contact heterogeneity was high (100% higher contact; Figure 1A and Web Figure 2).

Vaccinated-contact heterogeneity caused measurements of V_{Eff} to vary across time. In the heterogeneous contact scenarios, the highest underestimates, and the measurements of negative V_{Eff}, occurred only during periods of epidemic growth (Figure 1A–B). For the scenarios where negative

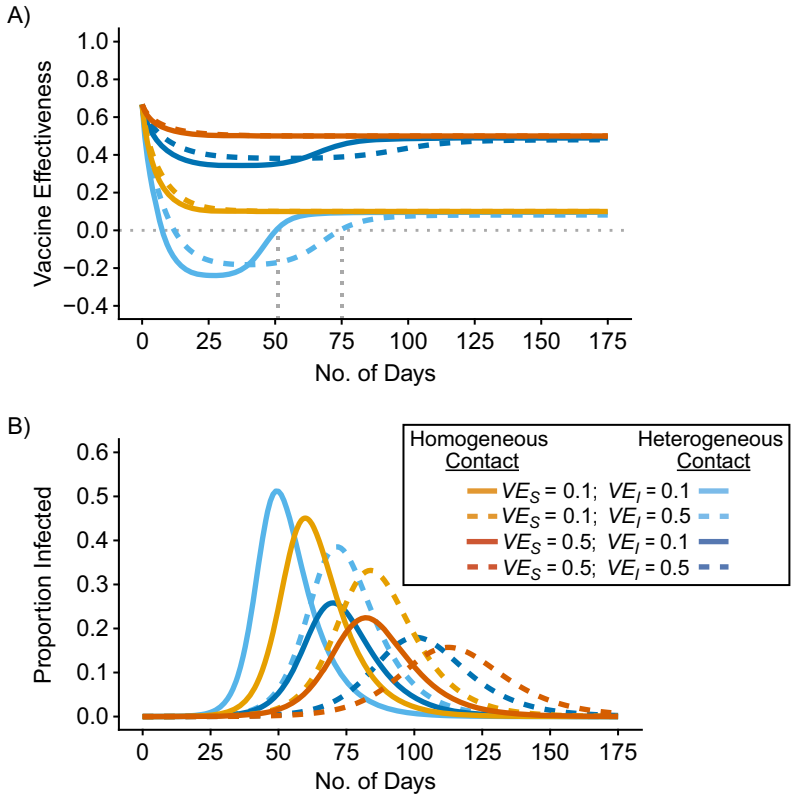

Figure 1. Simulation results illustrating how vaccine effectiveness (1 – relative risk) and infection dynamics are influenced by contact patterns and vaccine efficacies. Homogeneous contact rates (equal contacts among vaccinated and unvaccinated individuals) and heterogeneous contact rates (vaccinated have higher contact between vaccinated) 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 the proportion of infected (exposed or infectious) individuals over time (B). Measurements of negative vaccine effectiveness became positive once the proportion of susceptible unvaccinated individuals became lower than the proportion of susceptible vaccinated individuals combined with the level of VE_S (gray vertical lines; Web Appendix 3). Note that here the heterogeneous contact scenarios assume 50% higher contact between vaccinated individuals compared with the homogenous contact scenarios.

V_{Eff} was produced, V_{Eff} became positive only once the proportion of susceptible unvaccinated was lower than the combined proportion of susceptible vaccinated with the proportion immune due to vaccination (i.e., the level of VE_S; Web Figure 3 in Web Appendix 3). Both SEIR and SIR transmission dynamics models produced largely consistent infection and V_{Eff} dynamics. The main influence of the latency period was on the timing of the negative V_{Eff} periods: SIR models with heterogeneous contact scenarios resulted in consistently earlier V_{Eff} crossovers from negative to positive compared with the SEIR models that accounted for a 4-day incubation period (day 25 vs. 51 for $VE_S = VE_I = 0.1$; day 41 vs. 75 for $VE_S = 0.1$ and $VE_I = 0.5$; Figure 1 and Web Figure 4).

In the sensitivity analyses, we found that the maximum negative V_{Eff} recorded for a given scenario was moderately influenced by VE_I, and it was strongly influenced by the levels of VE_S and the contact between vaccinated individuals (Figure 2). For example, when VE_S was less than 0.15 and c_{vv} was 100% higher than the homogeneous contact scenario, V_{Eff} was strongly negative (less than −0.5). VE_I was less influential on negative V_{Eff}, but high levels of VE_I (>0.9), could still help prevent negative V_{Eff} even at low VE_S (0.1). As the production of negative V_{Eff} is a more extreme example of an underestimate, VE_S, VE_I, and the amount of contact between vaccinated individuals also influenced the degree to which V_{Eff} was underestimated. In general, increasing contact between vaccinated individuals led to larger underestimates, especially when paired with lower VE_I and, especially, VE_S (e.g., $VE_S = VE_I = 0.1$, maximum underestimate = 0.7; Web Figure 5). Vaccine efficacies strongly mediated the effect of this heterogeneous contact, with moderate levels of VE_S and VE_I resulting in smaller underestimates (e.g., $VE_S = VE_I = 0.7$, maximum underestimate = 0.07) and very high levels of VE_S (0.9) resulting in accurate V_{Eff} measurements (even with 100% higher contact; Web Figure 5).

DISCUSSION

Our results demonstrated how vaccinated-contact heterogeneity, defined as higher contact levels between

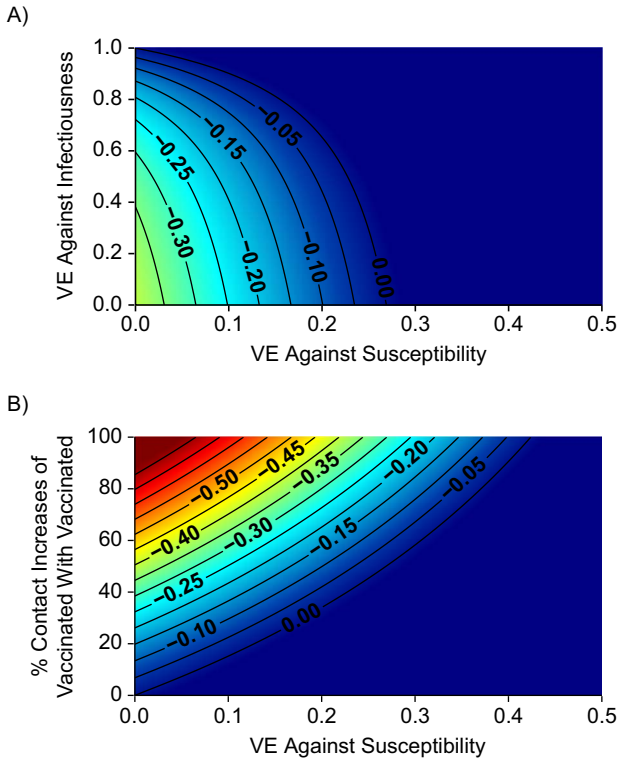

Figure 2. Simulation results illustrating the sensitivity of negative vaccine effectiveness (V_{Eff}) measurements to vaccine efficacy (VE) against infectiousness (VE_I), vaccine efficacy against susceptibility (VE_S), and the degree of higher contact between vaccinated individuals. The existence and degree of observed negative V_{Eff}, measured using the relative risk, was influenced by VE_I (A), the % increase in contact between vaccinated individuals (i.e., vaccinated-contact heterogeneity bias) (B), and VE_S (A and B). Colors indicate the maximum negative V_{Eff} measurement (the minimum V_{Eff}) observed for a given simulation with >0 indicating a nonnegative measurement. Similar patterns also emerge when measuring the effect of VE_I, VE_S, and the vaccinated-contact heterogeneity bias on V_{Eff} underestimates (Web Figure 5).

vaccinated individuals, could lead to observed measurements of negative V_{Eff}. We also identified how these heterogeneous contact patterns could produce underestimated V_{Eff} when the degree of contact heterogeneity was lower and/or when vaccine efficacies were higher. Thus, we illustrate different plausible scenarios where vaccines can be perceived to be either less beneficial or even harmful despite providing benefits to a population (vaccine efficacies of >0).

Vaccinated-contact heterogeneity can negatively bias measurements of V_{Eff}. In general, a negative measurement of V_{Eff} will be observed only when the underestimate (i.e., the degree of downward bias) is larger than the true vaccine benefit. When vaccinated-contact heterogeneity was present, different levels of bias in V_{Eff} were produced depending on the levels of vaccine efficacies (Figure 2; Web Figure 5), with this bias disappearing when vaccine efficacies were high (e.g., Web Figure 2). As both vaccine efficacies, through their influence on epidemic dynamics, mediate the effect and temporal pattern of the contact heterogeneity bias (Figure 1), observing negative measurements requires the underlying vaccine efficacies to be lower—in particular, lower VE_S. As V_{Eff} against Omicron has been found to be consistently lower compared with those recorded for other variants (e.g., Tseng et al. (14)), higher vaccine efficacies and their ability to mediate the effects of vaccinated-contact heterogeneity could explain how this bias could be present before Omicron despite the absence of prior negative measurements.

Beyond testing vaccinated-contact heterogeneity feasibility as a mechanism of bias, we also identified a temporal signature in V_{Eff} measurements that indicates when this mechanism could be the cause of observed negative V_{Eff}.The only major effect of including/excluding a latency period was the specific timing when negative V_{Eff} were found. These similarities in temporal signature patterns are due to both SEIR and SIR models generating similar epidemic curves, with the differences in the timing of observed negative values attributable to the stretch factor applied to SEIR epidemic curves that arises due to the added incubation period (15). In the context of vaccinated-contact heterogeneity, negative measurements for both models only occurred during epidemic growth when the proportion of susceptible unvaccinated was higher than the proportion of susceptible vaccinated (mediated by VE_S; Web Figure 3). In each of the empirical studies, the negative V_{Eff} measurements coincided with Omicron's epidemic growth stage (1–3). If measurements of V_{Eff} are consistently updated and found to change direction later in an epidemic, this would suggest the negative measurement may have been the result of vaccinated-contact heterogeneity. Similarly, if in the future, positive but low measurements of V_{Eff} become notably higher following the peak of an epidemic, it could signal that vaccinated-contact heterogeneity might be causing V_{Eff} to be underestimated.

Vaccinated-contact heterogeneity is one possible cause of negative V_{Eff}, but other biases, such as selection bias via testing access or health-seeking behavior (5), as well as higher immunity among unvaccinated from prior infection could also potentially cause observed negative measurements. Moreover, our analysis focused on an all-or-nothing vaccine type for simplicity, but a leaky vaccine type (16) could impart a different temporal pattern for the vaccinated-contact heterogeneity bias. Additionally, assuming a leaky vaccine type may also result in a different mediating effect of vaccine efficacies on the vaccinated-contact heterogeneity bias, as in this scenario, all vaccinated individuals could potentially become infected given enough exposures. Important next steps for researchers will include exploring other potential biases that may lead to negative V_{Eff} and including how assumptions surrounding leaky versus all-or-nothing vaccine type may influence V_{Eff} measurements over time.

Although our study was designed to explain potential mechanisms, and not to specify which values of VE_S, VE_I, and contact differences most likely caused observed negative measurements, the findings have important implications for the conduct and interpretation of observational studies measuring V_{Eff}. When conducting observational studies, researchers should attempt to address vaccinated-contact

heterogeneity when measuring V_{Eff} or at a minimum acknowledge its potential existence and consequences. While differences in exposure risk according to vaccination status have long been recognized as an important source of bias (17); identifying and addressing these differences is and will remain challenging (18). Contact surveys (e.g., POLYMOD (19); B.C. Mix COVID-19 Survey (20)) are an important tool to help identify differences in contact patterns across segments of the population. These types of surveys can be used to address vaccinated-contact heterogeneity specifically by not only recording survey respondents' numbers of contacts per day but also their vaccination status and the vaccination status of their primary contacts. When paired with mathematical transmission models, which can also be used to estimate vaccine efficacies and effectiveness (7), differences in contact patterns across vaccinated and unvaccinated groups could be explicitly accounted for, thereby eliminating these biases from the estimates. If it is not possible to assess whether vaccinated-contact heterogeneity is present, then reports and public communication should ensure that the interpretation of V_{Eff}, particularly if it is negative or low, includes the possibility of this bias.

Failing to acknowledge vaccinated-contact heterogeneity and other biases that cause observed negative V_{Eff} can have implications for the management of coronavirus disease 2019 (COVID-19) infection. Specifically, biases that produce apparent negative V_{Eff} can amplify vaccine mistrust (21) as well as affect vaccine benefit/risk assessments, resulting in less recognition of vaccines as a valid control measure. Hence, in the worst-case-scenario, these biases could inadvertently lead to overall higher COVID-19 transmission and a greater potential for epidemic outbreaks.

Here we have highlighted one possible pathway for V_{Eff} to be underestimated and even appear negative when vaccines are beneficial. Moreover, we have also outlined how vaccinated-contact heterogeneity can be mediated by both VE_S and VE_I and how its presence can be identified via a key temporal signature. Overall, our findings not only illustrate a potential mechanism for negative V_{Eff} measurements found for the Omicron variant, but also provide a potential explanation for observed negative V_{Eff} in future studies.

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R code to perform all simulations and analyses is available on Github (https://github.com/kbbodner/contact_and_NegVE.git).

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Conflict of interest: none declared.

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