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Network Methods and Design of Randomized Trials: Application to Investigation of COVID-19 Vaccination Boosters

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Abstract

Network science methods can be useful in design, monitoring, and analysis of randomized trials for control of spread of infections. Their usefulness arises from the role of statistical network models (SNMs) in molecular epidemiology and in study design. Computational models, such as agent-based models that propagate disease on simulated contact networks, can be used to investigate the properties of different study designs and analysis plans. Particularly valuable is the use of these methods to assess how magnitude and detectability of intervention effects depend on both individual-level and network-level characteristics of the enrolled populations. Such investigation also provides an important approach to assessing consequences of study data being incomplete or measured with error. To address these goals, we consider two SNMs: exponential random graph models, and the more flexible congruence class models. We focus first on an historical use of these methods in design and monitoring of a cluster randomized trial in Botswana to evaluate the effect of combination HIV prevention modalities compared to standard of care on HIV incidence. We then present a framework for the design of a study of booster vaccine effects on infection with, and forward transmission of, SARS-CoV-2 variants. Motivation for the study is driven in part by a guidance from the UK to base approval of booster vaccines with "strain changes" that target variants on results of neutralizing antibody tests and information about safety, but without requiring evidence of clinical efficacy. Using designs informed by our agent-based network models, we show it may be feasible to conduct a trial of novel SARS-CoV-2 vaccines in a single large campus to obtain useful information regarding vaccine efficacy against susceptibility and infectiousness. If needed, the sample size could be increased by extending the study to a small number of campuses. Novel network methods may be useful in developing pragmatic SARS-CoV-2 vaccine trials that can leverage existing infrastructure to reduce costs and hasten the development of results.

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Introduction

This paper discusses how new network methods can contribute to design, monitoring and analysis of studies that help in controlling infectious diseases—with applications to SARS-CoV-2 and HIV infections. Below we discuss how novel network methods were used in the design of the Botswana Combination HIV Prevention study (BCPP), and how they might be useful in design of studies of efficacy of novel COVID-19 vaccines on susceptibility (VE_S) and infectiousness (VE_I). This is unlikely to be resolved soon; as Borio et al. noted: "As with yearly influenza vaccines, an updated formulation targeted to the circulating [SARS-CoV-2] variants will likely be needed to maximize protection from infections and severe disease.".[1] To illustrate our ideas, we consider issues that would arise in designing a pragmatic trial of COVID-19 vaccine effects in a college campus setting. An institution with congregate living may be appropriate for such a trial, because a high proportion of transmissions might occur within the institution and because data needed to guide study design might be available.

Three questions arise with regard to development and implementation of novel vaccines: 1) when should currently available vaccines be replaced by others that target new variants?, 2) what variants should be targeted?, and 3) What categories of people at risk should receive the new vaccine (as initial vaccination or booster)? To help address such questions, extensive analyses of immune correlates protection from the mRNA-1273 SARS-CoV-2 Vaccine have been performed.[2] Their results suggest both that such correlates are likely to play a valuable role in formulating policy regarding implementation of SARS-CoV-2 vaccines against newer variants and that obtaining clinical evidence of these effects might aid in clarifying exactly what this role should be. As Gilbert et al. noted, the estimated percentage of vaccine effects mediated by immune correlates appears to compare favorably to those for influenza.[2]

Additional clinical studies might help in assessing the reliability of decisions based on immune correlates or other laboratory measures. For example, Kennedy-Shaffer et al. developed methods to estimate vaccine efficacy against infection via effects on viral load; such methods are unquestionably of value, but they require an assumption that vaccine affects per contact infectiousness only through viral load and other measured covariates—and that the functional form of relationship is known.[3] New studies would be useful for goals like: a) prediction of efficacy based on neutralization (and perhaps other laboratory) data, and–our focus in this paper– b) direct clinical validation of the public health benefit of variant-targeted vaccines developed on the basis of their ability to neutralize variants.

To ground our proposal in published research, we first note that there is a broad literature on design of studies intended to investigate VE_S and VE_I. Halloran et al. (2010) defined these quantities and provided several possible designs for estimating them. An important goal of such studies is to estimate the indirect effect of vaccination of the study participants on protecting the other household members.[4] The authors noted that

VE_I, can be estimated epidemiologically by computing the ratio of 1) the per-contact frequency of transmission from vaccinated people who become infected and 2) the per-contact transmission frequency from unvaccinated people who become infected. As they also noted, to evaluate VE_I generally requires knowledge of transmission events, which may be observable in settings such as households or partnerships in which contacts can be defined.[5] One of their proposals sets randomized designs in mini-communities (mini-cohorts of people in a small transmission unit exposed to an infectious case). For example, one might randomize household members in households of an exposed case —at the individual member or household level.[6] Another proposed approach is an augmented study design, in which individuals are recruited from households of randomized index subjects in a vaccine trial, whether or not the index subject becomes infected. Yang et al. (2009) proposed a Bayesian model for evaluating antiviral efficacy in household studies for a variety of possible endpoints related to susceptibility and infectiousness.[7] Determining the best design can be challenging because of the complexity of the transmission networks and of the ongoing evolution of viral variants; therefore, as we discuss below, evaluating the properties of different design choices will depend on proper simulation studies.

This paper is organized as follows. We first discuss how novel network methods are useful in development agent-based models, and provide an application related to the design of the Botswana Combination Prevention Project (BCPP), which evaluated the benefit of combination HIV prevention methods. We then illustrate the use of novel network methods that can aid in the design of studies evaluating COVID-19 vaccines. Our focus is on designing a pragmatic study on the University of California San Diego (UC San Diego) campus, making use of available data and models of SARS-CoV-2 transmission on campus. We provide a simulation study of a COVID-19 vaccine trial based on development of an agent-based model, and then discuss how implementing such a trial in practice would benefit from new methods for combining information across different sources to make inference about transmission networks. Finally we describe some alternative approaches to evaluation of vaccines, based on novel network methods.

Network Methods and Agent Based Models

Network methods can be useful in design, monitoring, and analysis of cluster randomized trials for control of spread of viral infections. This usefulness grows out of the role of statistical network models in molecular epidemiology and in design of cluster randomized trials. Agent-based models (ABMs)–simulations of actions and interactions among autonomous agents to assess their effects on entire systems–have been used to guide study design.[8] In our setting, the agents spread a virus through interactions, which collectively are referred to as a contact network; the propagation of the disease over a contact network is the focus of simulation. Such interactions include not only those among randomized participants in the study, but also those between these participants and people who are not enrolled in the study. Evaluation of vaccine efficacy against susceptibility will depend on consequences of interactions among randomized participants as well as between randomized participants and others.

Network methods based on models of propagation of virus on transmission networks are particularly useful in the evaluation of the impact of interference across randomized unit; interference occurs when the randomization status of one randomized unit impacts the outcome in a different randomized unit.[9] This is important because interference impacts power and interpretation of results. For example, the design of the Botswana Combination HIV Prevention Study (BCPP) was based on a simulation of interference across 30 villages randomized to intervention vs control.[8] We also consider a framework for studying the effect of booster COVID-19 vaccines in a university setting compared to a two-dose series, in order to investigate the feasibility of conducting pragmatic trials of the clinical effects of booster vaccines with "strain changes" selected on the basis of neutralizing antibody tests. As we describe below, development of such studies would require dealing with error in ascertainment of attribution of transmission events. In this regard, we discuss how this error might be accommodated in analyses by using new network methods applied to data on genetic distances between infection, geographic proximity, residence and other factors.

Use of an ABM in Study Design: Botswana Combination Prevention Project

The BCPP was a cluster randomized trial to compare a combined HIV prevention intervention to standard-of-care using a cluster randomized trial of 30 villages (clusters) in Botswana.[10] Wang et al. (2014) made use of an agent-based model (ABM) of HIV spread to aid in the design of this study.[8] To do so, the authors simulated the village-level impact of the intervention and investigated how network structure within and across randomized units (villages) affected power of the study. Much of this investigation focused on the impact on power of the proportion of partner pairs in which the two members resided in different villages assigned to different conditions, thereby resulting in spillover effects. The ABM described above was used to investigate this issue. Parameter values in the model were based on published results and information available from a pilot study in Mochudi, Botswana.[11,12,13,14,15,16]

In creating the ABM, the level of sexual mixing among the villages was highly relevant; increasing levels of mixing between intervention and standard-of-care communities would be expected to reduce the difference between them in cumulative incidence. Only a limited amount of information about such mixing was available, and it was known with considerably uncertainty. To address this concern, Wang et al. used a class of models that had been recently developed–congruence class models–which can accommodate uncertainty in network structure (e.g., number of relationships spanning across villages).[17] These models form a broad class that includes as special cases several common network models, such as the Erdős-Rényi-Gilbert model, stochastic block (SB) model and many exponential random graph models (ERGMs). A congruence class model is defined by (1) a network property or set of properties (such as degree distribution) and (2) a probability mass function on the congruence classes defined by values of the network property or properties. congruence class models do not impose any constraints on specifying the probability distribution associated with network properties included in a model. This flexibility allowed for the generation of networks for design of the BCPP study that are consistent with estimated level of mixing between pairs of communities as well as the uncertainty of these estimates.[8]

Using a simulation study based on the ABM based on a congruence class model, Wang et al. concluded that 15 clusters per arm and 500 member of a cohort in which incidence was measured would provide 95% power to detect the projected difference in cumulative HIV incidence between standard-of-care and intervention villages (3.93% and 2.34%) at the end of the third study year, assuming a coefficient of variation (standard deviation of cluster-specific incidence rates divided by their mean) of 0.25. At the end of the study, a total of 57 participants in the intervention group and 90 in the standard-care group acquired HIV infection (annualized HIV incidence, 0.59% and 0.92%, respectively). The HIV incidence ratio in the intervention group compared with the standard-care group was 0.69 ($p = 0.09$, by permutation test; 95% confidence interval [CI], 0.46 to 0.90 by pair-stratified Cox model).[10]

This ABM was also used during the course of the study to aid in decisions about study adaptations to changes in policy. In fact, while the trial was ongoing, the national treatment guidelines changed: the Botswana Ministry of Health recommended in 2016 that all HIV-positive patients, regardless of CD4 count or viral load levels, initiate antiretroviral therapy. This guideline change caused the standard care received in the control communities to become more similar to that in the intervention communities, raising concerns about a reduction in intervention effect that would adversely affect the study power. Based on a revision to the ABM that incorporated baseline and implementation process data collected during the study as well as the effect of treatment guideline changes, the study team revised the projected intervention effect. This effect and the incidence rate in the control arm were essential parameters in the conditional power analysis.[18] In addition, the agent-based model could be used to evaluate the impact of changes in study duration on power. The flexibility of the congruence class model-based ABM enabled the study team to guide decisions on how best to modify the study to adapt to changing conditions.

One useful feature of the congruence class model it allowed investigation of the impact of network features that the study team feared could impact power but about which nothing was known. Of particular concern was degree assortativity –the extent to which people with many partners have partners that do as well–that has been shown to impact the extent to which network structures are robust (i.e. remain relatively unaffected) to removal of high degree nodes.[19] The implication of this finding is that degree assortativity might potentially impact the total effect (indirect and direct) of treatment as prevention. congruence class models have the ability to vary levels of degree assortativity without modifying the marginal probability distribution of other network properties included in the model, such as degree distribution and mixing across communities. This feature permits isolation of the effect of degree assortativity on HIV incidence in each arm; and, hence, on the intervention effect. Figure 1 shows that the simulated incidence of HIV from the model does not vary based on degree assortativity, suggesting that accurate information about degree assortativity was not necessary for reasonably accurate estimates of power.

Data and Study Design

UC San Diego COVID-19 Databases and ABM

We consider a study to evaluate efficacy of two different booster vaccines that makes use of the extensive infrastructure for COVID-19 monitoring which has been developed

at the University of California, San Diego. This infrastructure supports the collection of multiple different data types in real time. Currently existing databases contain the following information:

1. Testing and vaccination data
2. Residence location, class registration, athletic team participation (which provide information on potential contact network)
3. Contact tracing information
4. Wastewater testing at high resolution and frequency
5. Molecular sequencing of individuals and wastewater, both on campus and among the broader San Diego community
6. Isolation and quarantine location and status

Overlaying the above information regarding plausible contacts (e.g., common residence, classroom, or athletic team) on molecular sequencing trees permits ascertainment of types of contacts that are associated with transmission events. This effort is aided by a wastewater monitoring program that tests wastewater daily from about 340 buildings on campus. This high resolution and high frequency sampling combined with PCR testing is highly effective in providing early detection of infections– 85% of individual infections are detected earlier in the wastewater than in the individual test, even in the presence of weekly or biweekly asymptomatic testing.[20] Novel software allows for the resolution of multiple viral strains from wastewater.[21] Of particular importance for this investigation is the ability to detect emerging variants of concern days or weeks earlier compared to clinical samples as well as the presence of minor variants not detected in clinical samples. Phylogenetic analysis of wastewater and individual clinical samples revealed several small transmission clusters associated with campus residence, thereby facilitating containment by campus isolation protocols.[21] Hence, the extensive integrated data system provides data to inform agent-based modeling as well as to identify likely transmission events.

Goyal et al. (2021) made use of the information described above in developing an agent-based network model of SARS-CoV-2 transmission to assess the potential impact of strategies to reduce outbreaks at the UC San Diego.[22] They developed a SARS-CoV-2 transmission model that incorporates important features related to risk at UC San Diego, such as community composition (staff, faculty, and students on or off campus), campus residential configuration, and course registration. Details regarding the model are described in the above-referenced paper, but we summarize briefly here. The model includes 39,500 students (33,000 undergraduates and 6,500 graduates) who may live either on- or off-campus, as well as an estimated 18,900 faculty and staff expected to work on campus in Fall 2021. Each on-campus student is assigned a room in a UC San Diego residential hall. Based on status as undergraduate or graduate student, each student was assigned classes using UC San Diego's class registration or alternative instructional scenarios, developed in conjunction with UC San Diego administrative officials. Faculty were each assigned to teach one class. The model simulates an individual's progression through seven disease stages (from exposure to recovery). Transmissions among students, staff, and faculty occur through

interactions defined by the contact network. One limitation of the model is its failure to take into account uncertainty in estimates of network features. Such an accounting would be required to evaluate how such uncertainty impacts uncertainty in model-based projections of intervention effects. We note that approaches using congruence class models, such as that described in the Botswana agent based models above, could address this issue.

The model has been, and continues to be, used to guide policy–in particular regarding the UC San Diego “Return to Learn” COVID-19 mitigation strategy as well as similar efforts across University of California Campuses. Within UC San Diego, the modeling results are regularly presented to the Chancellor, Return To Learn Steering Committee, and University Cabinet. The model has been used to inform decisions surrounding asymptomatic testing frequency, vaccination recommendations, campus residential and non-residential building density, classroom modality and size limits, masking requirements, isolation and quarantine housing need, and the nature of the wastewater monitoring program itself. The results have also been presented to the University of California system-wide Return to Campus Workgroup to inform recommendations regarding asymptomatic testing frequency and vaccination.

UC San Diego booster study design

Our pragmatic study uses a design in which students are individually randomized; performance of alternative designs in which the unit of randomization is at the residential level (room, suite, floor) could also be investigated using the same ABM. Participants are randomized to standard of care, standard mRNA booster, or a hypothetical strain-changed booster. We use phylogenetic analyses of recent campus infections to identify:

1. Variants of Concern —variants that may result in altered vaccine efficacy.
2. Clusters of identical, or nearly identical, sequences - collections of sequences that differ by at most one nucleotide change from the earliest sequence in the cluster.

From all study participants, we collect information on vaccination history and clinical history. During the study period, we sequence all new infections among people who study or work on campus and assign each to an existing cluster (if such exists) and to a variant of concern. If a new infection presents with a genetic sequence that differs by more than one nucleotide change from any other sequence identified during the study, this sequence will serve as the “seed” for a new cluster. We monitor the growth of such clusters of people within each arm—as well among all students/employees on campus not in the study. All on campus are requested to test daily.

Primary Study Endpoints:

1. Infection with SARS-Cov-2 among randomized cohort.
2. Transmission event from randomized participant to others on campus (student, faculty or staff)—-whether in randomized cohort or not.

In practice, we would identify transmission pairs (with uncertainty) using the information from items 1–6 in the UC San Diego COVID-19 database. We use contact information as

well as viral genetic data and dates of testing to reduce the set of plausible transmission pairs. We note that because of the relatively slow rate of mutation of SARS-CoV-2 virus, viral genetic information alone may not be sufficient to identify transmission events. Genetic information can be very useful, however, in ruling out transmission events between pairs of people whose viral sequences have more than a single nucleotide change. Below we describe a method for using the totality of available data in analyses of vaccine efficacy. When there is more than one potential source partner for a given transmission, we propose weighting putative transmission pairs based on strength of evidence for that transmission event. For example, this type of analysis might place higher weight on same-sequence roommates infected a few days apart than to same-sequence pairs who only share classrooms. Such analyses might be used as part of the primary analysis itself, or be provided to an adjudication committee that reviews all available information to further reduce the set of plausible transmission pairs.

Simulation Study

To simulate the spread of SARS-CoV-2, we use the UC San Diego COVID-19 model described above.[22] The simulation uses the demographic characteristics of the UC San Diego population based on Fall 2021 data. This includes the number of students, staff, and faculty returning to campus as well as the number living in residential housing and taking in-person courses. Given the high rates of vaccination among the UC San Diego community (greater than 90%), we assumed–for the simulation–that all individuals were vaccinated, but none had received a booster. We simulated a three-arm randomized trial, where only the students (undergraduate and graduate) were assigned to the study arms; enrolling only students might make the study easier to implement in practice. Our simulation proceeds by randomizing allocation to Arm 1: standard of care (i.e., COVID-19 vaccination without booster), Arm 2: booster with current vaccine, and Arm 3: a hypothetical strain-change booster (modified based on the primary circulating COV). The trial was simulated for the duration of a UC San Diego academic session (80 days). We note that we do not model the important impact of waning vaccine efficacy during the trial. The precise impact of waning efficacy on power would depend on the exact timing of the vaccinations, the follow-up period, and the background incidence of SARS-CoV-2 infection. Estimates of vaccine efficacy would be averages over time and background incidence. Lower levels of incidence during time periods in which vaccine efficacy had been reduced would have less impact on power and on estimates of efficacy than if incidence was low when vaccine efficacy was highest.

Analytical Methods

A primary goal of our analyses is estimation of booster vaccine efficacy against susceptibility to infection, VE_S, which measures the direct preventive effect of the booster vaccine on the population of interest. An equally important goal is estimation of booster vaccine efficacy against infectiousness VE_I, defined as the reduction in onward transmission from an infected person who had received the booster compared to that from an infected person who had only the 2-dose vaccine regimen. We define these effects to be similar to those in Kahn et al. and Halloran et al, below.[23,4]

1. VE_S= 1- θ, where θ = the risk ratio of becoming infected with SARS-CoV-2 comparing the boosted arm to the 2-dose vaccine alone arm.
2. VE_I = 1- Φ, where Φ = the relative infectiousness of a boosted person compared to person on 2-dose regimen, both of whom become infected on study.

For each simulated experiment, we estimate θ from the observed number of infections at end of follow up and sample size in each arm. Φ is estimated by the ratio of the number of onward transmissions per infected person in the boosted arm to that quantity in 2-dose arm: [(# infected by booster recipients)/(# infected booster recipients)]/ [(# infected by 2-dose recipients)/(#infected 2-dose recipients)], where # refers to observed number. In the simulation, estimation of VE_I is based on our complete knowledge of the transmission network. Approaches to dealing with uncertainty in the ascertainment of transmission pairs as well as direction of transmission are discussed below.

Another quantity of interest–particularly for public health recommendations from such a trial–is the count of all of the infections attributed directly to a randomized participant (whether or not the infected person is a participant in the randomized study) plus 1 to include infection of that participant. We refer to this quantity as TN; it takes value 0 if the randomized participant was not infected. The booster effect on this quantity, $VE_{TN} = E(TN|Z = 1) - E(TN/Z = 0)$, where Z is an indicator of the randomized assignment. The endpoint can be interpreted as the number of infections directly prevented by boosted vaccination.

We can also use our model to simulate the effect of vaccinating all study participants with booster compared to providing no booster vaccination. This effect includes both direct and indirect effects of vaccination. Carnegie et al. (2014) demonstrated that, in special cases, analytical solutions could be found for estimating the causal estimand of interest–difference in outcome when treating all compared to treating no participants–using data from randomized trials.[24] Such solutions require models for the spread of a microbe as well as times to event (not considered here); Carnegie et al. considered a simple susceptible-infected (SI) model.[24] In the absence of such analytical solutions, our approach allows us to investigate the impact of different study designs and levels of vaccine efficacy on this important causal estimand through simulation. We could use this same approach to provide model-based projections of this causal estimand, using data from an actual study to parameterize the ABM.

Inference

We consider permutation tests (achieve through re-randomization) to test the null hypothesis of no booster effect on either susceptibility or infectiousness, that is, $VE_S = VE_I = 0$. The test statistic might be a weighted average of $\widehat{VE}_S$ and $\widehat{VE}_I$, the estimated VE_S and VE_I. The weights can depend on the public health questions of most interest. For example, if interest lies primarily in infectiousness, one might put weight of 1 on $\widehat{VE}_I$, which is most sensitive to departures of VE_I from 0. We note the standard re-randomization tests for the composite null hypothesis of $VE_I = 0$ (i.e., VE_S is left unspecified) in general would not be expected to control the nominal Type I error rates because of the difficulty of isolating the vaccine effect on infectiousness of the randomized index from its effect on susceptibility

(infected participants are a subset of all randomized participants). Nonetheless, we can use different test statistics to gain insight regarding vaccine effects.

We also consider another test statistic, which is the estimated booster effect on TN, $\widehat{VE}_{TN}$. Permutation tests based on $\widehat{VE}_{TN}$ will be sensitive to alternatives for which either VE_S or VE_I is not 0, because this test statistic captures between-arm differences in both infection and onward transmission.

Interpretation of results is enhanced by considering results of all tests jointly. If the permutation test based on $\widehat{VE}_I$ provides strong evidence to reject the null hypothesis but one based on $\widehat{VE}_S$ fails to reject, this would be suggestive of a booster effect on infectiousness rather than susceptibility. We note that the available vaccines could potentially be effective against severe disease caused by the Omicron variant, but less so against susceptibility; if prevention of severe disease were associated with shorter periods of infectiousness, this scenario may be plausible. For control of the pandemic, VE_{TN} may be of special interest, as it reflects all infections prevented by the vaccine that arose either through the infection of the randomized index or direct transmissions from the index after infection.

Simulation Study Results

In our simulation study, we consider 3 different scenarios for booster vaccine efficacy: 1) $VE_S = 0$, $VE_I \neq 0$, 2) $VE_S \neq 0$, $VE_I = 0$, and 3) $VE_S \neq 0$, $VE_I \neq 0$. The study has 3 arms: a) standard of care, b) booster with currently available vaccine, c) booster targeting new variants. Each of the 3 scenarios is assumed to be represented in one the 3 possible pairwise comparisons. Scenario 1 corresponds to comparison of arms 2 and 1; scenario 2, to arms 3 and 2; scenario 3, to arms 3 and 1. To simulate clinical trials according to these assumptions, we set VE_S for the currently available booster (Arm 2) compared to standard of care (Arm 1) to be 0, and the VE_S for the booster targetting new variants (Arm 3) compared to the standard of care (Arm 1) to be 0.9; this results in VE_S comparing Arms 3 and 2 also having value 0.9. As our goal is illustration of our ideas rather than a final proposal of a specific study, these choices are somewhat arbitrary. The motivation for these particular choices is the magnitude of VE_S effects against the Wuhan variant observed in studies of licensed vaccines. The VE_I for the currently available booster compared to standard of care is set to 0.75, as is the VE_I for the new booster compared to standard of care; this results in the VE_I comparing Arms 3 and 2 having value 0. This choice reflects the concern that using vaccines to prevent onward transmission may be particularly challenging. We investigated four settings (denoted as $S1 - S4$). The first ($S1$) is a randomized comparison of the effects of interest for 5000 participants per arm. The remaining scenarios ($S2$-$S4$) simulate the effect of vaccinating all students in the UC San Diego campus community with one of the vaccine arms:

(S1) Randomized trial with 5,000 participants per arm.

(S2) All students receive standard of care (Arm 1).

(S3) All students receive currently available booster (Arm 2).

(S4) All students receive booster targetting new variants (Arm 3).

To assess our ability to estimate our primary effect measures (VE_S and VE_I), we conduct 10 replicates for the scenario $S1$. Figure 2 presents boxplot results of vaccine effect estimates for susceptibility of infection (VE_S) and infectiousness (VE_I) comparing Arms 2 to 1, Arms 3 to 1, and Arms 3 to 2. The dashed lines represent the values of VE_S (0 and 0.9) and VE_I (0 and 0.75) used in the simulations.

The mean difference in the estimates of VE_{TN} are −0.05 (range: −0.04 to −0.07), −0.13 (range: −0.11 to −0.16), and −0.09 (range: −0.07 to −0.09) for Arm 2 to Arm 1, Arm 3 to Arm 1, and Arm 3 to 2, respectively. As expected, the difference from zero was greatest for the estimate of VE_{TN} that compared Arms 3 to 1. The fact that the estimated VE_{TN} comparing Arms 3 to 2 is larger in magnitude than for that comparing Arms 2 to 1 suggests that the VE_{TN} depends more on VE_S than on VE_I in our simulation study; nonetheless, both VE_S and VE_I contribute to VE_{TN}. The large variability in VE_I comparing arms 3 and 2 arises from the large VE_S effect that reduces the number of infections and therefore transmissions in arm 3. In this type of setting, VE_{TN} may be particularly useful for evaluating the potential public health impact of vaccine effects.

Overall 6.1% of the entire simulated population is infected when the study enrolls 5,000 people per arm (Scenario $S1$) over an academic session of 80 days across the 10 simulations. When all students are given a booster, the percent infected is 2.9% ($S3$) for the currently available vaccine, and 0.8% ($S4$) for vaccine targetting new variants. The incidence of infection is considerably lower for either of these scenarios than for that in which no one receives a booster ($S2$)–which results in infection of over 9.3% of the population (see Figure 3).

We perform permutation tests in the scenario where each arm has 5000 participants by permuting the vaccine status of the study participants 1,000 times. We compared the simulated outcome values to each of the permutations to calculate p-values. This procedure was replicated 10 times on 10 different simulated datasets. We note that this randomization-based test procedure protects type I error control despite the dependence across outcomes that arises from the network-based simulation of epidemic spread. Wang and DeGruttola (2017) performed a simulation study of cluster randomized trials with correlated outcomes across randomized units, which showed protection of type I error control.[25]

The mean p-values across the 10 replicates using $\widehat{VE}_S$ as the test statistic were 0.001 for comparisons Arms 3 vs 1 and Arms 3 vs 2; for the comparison between Arms 2 vs 1 the mean p-value was 0.211. Using $\widehat{VE}_I$ as the test statistic, the mean p-values comparing Arms 2 vs 1 and Arms 3 vs 1 were 0.001 and 0.023, respectively; that comparing Arms 3 vs 2 was 0.095. The mean p-values based on $\widehat{VE}_{TN}$ comparing Arms 2 vs 1, Arms 3 vs 1, and Arms 3 vs 2 were 0.001. Because VE_{TN}–which assesses the reduction in the number of transmissions associated with each randomized index–includes the index as well as the count of the people who were infected by this index, it provides a summary measure that includes effects against susceptibility and infectiousness.

Combining Evidence to Accommodate Uncertainty in Transmission Networks

Estimation of VE_I and VE_{TN} based on a study like the one we describe requires the ability to identify the pair of individuals associated with each transmission event. In some cases, this is possible with near certainty; however, in many situations there is ambiguity about the event of occurrence of transmission and about which of the pair was the source of the virus. To deal with such uncertainty requires assessment of the probability of detecting transmission events as well as the accuracy of identifying the transmission partner pairs. Simulation studies can provide a basis for investigating the effect of varying strategies (e.g., increased testing) on this degree of accuracy as well for assessing the value of additional information to improve it. Such assessment requires integration of multiple sources of information, including the items listed as 1–6 in the UC San Diego COVID-19 Databases and ABM section. Wastewater testing may be particularly useful for identifying the potential number of un-diagnosed cases, which variants are circulating, and the timing of infections that occur before they are detected from individual-level tests. As we describe below, simulations using our ABM can be used to evaluate the extent to which the statistical analysis can generate reliable conclusions about VE, given errors in the classification of transmission events. Of particular interest is investigation of loss of efficiency and bias in estimation that arises from errors in inferring transmissions–and the extent to which combining across different sources of information can reduce such bias and improve efficiency.

Accuracy of estimating not only individual transmission events, but also the entire transmission networks, can be aided by making use of the totality of such information. Achieving this goal requires a principled method to integrate multiple data sources. There have been important statistical developments that can aid in such efforts; for example, methods for estimating covariate effects on hazards of infectious contact using phylogenies, epidemiological data, and knowledge about the contact network.[26] Such methods work can be used to estimate VE. While complete knowledge of the contact network is rarely feasible, the shape of a phylogeny has been show to strongly depend on the contact network structure.[27] Inference about contact network structure from epidemiological data has also been described (e.g., times of infection).[28,29,30] Although these approaches focus on contact networks, they nonetheless apply to transmission networks as well. In either case, the Bayesian inference approach uses a Markov chain Monte Carlo (MCMC) algorithm, which makes it possible to sample networks from their posterior distribution. The most recent published work is based on the family of ERGMs, which provides more flexibility than previous approaches by allowing the inclusion of covariate information (such as place of residence).[31] Recently novel methods were developed to for estimation of ERGM parameters from ego-centric data obtained in surveys of risk behavior.[32,33] In order to integrate information from such surveys into analyses that use viral sequence and epidemiological data, however, the estimates from Krivitsky et al. (2022) need to be incorporated as prior information in the MCMC algorithm proposed by Groendyke et al. (2012).[30] We know of no available methods for doing so. Furthermore, as mentioned by Groendyke et al., there are computational limitations of the approach that restrict estimation

of properties for contact networks to dyadic independent properties, thereby precluding exploration of dyadic dependent network properties, i.e., dependency across edges (dyads) between pairs of nodes.[30] Dyadic dependent properties include degree distribution and clustering, which have been identified as essential for understanding infectious disease transmission dynamics.[34]

To develop an approach that can integrate the multiple data sources as well as investigate dyadic dependent network properties, we propose use of congruence class models. By calculating the relative probability of transmission based on the sample from the posterior distribution of the congruence class model model, we can estimate the relative probabilities of transmission by each possible source partner for each plausible transmission pair–that is, the probability of a given directed edge representing the source of infection of a given participant. We can use these probabilities to marginalize estimates of VE_I over all plausible transmission pairs (see Montezeri et al., 2020).[35] Such a method is essential for efficient use of resources to estimate VE_I. Current approaches can rely on a committee to evaluate which transmission pairs are and are not valid. But in fact each decision can affect subsequent decisions, because of the nature of transmission networks. Furthermore, transmission pairs known with certainty are included in analyses in the same way as those that remain speculative–again reducing efficiency of estimation and causing variance estimates to be too optimistic.

Alternative Approaches to Vaccine Assessment

One alternative approach to estimating booster vaccine effects is based on pairwise analyses of transmission event across the entire study population; this approach might be particularly valuable if study participants (randomized or otherwise) resided in relatively closed communities like those in a university. In a two arm study of, say, strain-changed booster (arm 1) compared to other booster (arm 2), one would estimate 4 parameters describing 4 types of transmissions: A infects A; A infects B; B infects A; B infects B. This analysis would be straightforward if all of the transmissions were known without error. In the more plausible case of ascertainment with error, one might use the approach described in the section above on combining evidence for modeling the entire observed transmission network. This approach identifies collections of plausible networks that are consistent with available data. The method would proceed by estimating transmission parameters of interest for each network in the collection. (The transmissions associated with a given minor variant would consist of network components–sets of nodes that have no links to any other such sets). By modeling the entire network using Bayesian methods of Goyal and DeGruttola,[22] we can estimate a posterior probability for each network in the collection. As described above, this permits estimation of posterior means (and associated credible intervals) of the transmission parameters of interest by marginalizing over the set of posterior probabilities for each network. Testing hypotheses regarding these parameters–for example that onward transmission from participants in Arm 1 is different from that for those in Arm 2–can be achieved through use of permutation tests.

We note that information about transmission networks estimated at universities across the US and elsewhere could serve as prior distributions for such analyses and thereby provide

insights that are not available from analyses performed only at the pairwise level. In this regard, we can use the totality of such evidence to aid in ascertaining plausibility of the properties of entire networks–not simply plausibility of pairwise transmissions. For example, if networks tended to be assortative (i.e. infected people who transmit to many others tend to infect those who go on to do so as well) then priors for assortative networks (e.g. those with a structure that supports superspreadering) could be selected to reflect this property. Furthermore, the information from the network observed in the study could provide additional evidence in support of a given network property. Another advantage of the approach we describe is the ability to handle settings for which there is no local information to distinguish among plausible sets of transmission pairs. Consider, for example, a setting in which two people infected with viruses with identical genetic sequences attend a gathering at which larger numbers of people become infected with the same variant. From data obtained from this group alone, there is no way to distinguish among the large sets of plausible transmission pairs. Our proposed approaches above might either spread the posterior probability mass approximately equally among such pairs– and thereby accommodate this uncertainty in the inference on the treatment effect–or make use of the totality of information regarding individual characteristics and network structures (mixing patterns) to distribute the probability mass in some other way.

In addition to marginalizing across sets of plausible networks to estimate transmission network properties related to HIV and Ebola transmission, Montezeri et al. (2020) also discussed relationships between phylogenies and transmission networks.[35] In their setting, as in ours, one source of uncertainty is the time order in which people were infected with the pathogen under study. An interesting parallel between phylogenetic and transmission networks is that likelihoods for the former can also be based on probabilities of directed edges between pairs of nodes (genetic sequences). These probabilities characterize features of evolution such as the occurrence of different types of transitions and transversions. Further investigation of ways to combine across genetic and other sources of individual and network-level information could improve our ability to make use of data collected in studies such as the one we propose.

Discussion

This paper investigates pragmatic designs of trials of strain-changed and other vaccine boosters in a university setting. (We note that a novel vaccine could be modified in some other way.) Our main focus was to demonstrate how novel network methods can aid in design, monitoring and analysis of studies. Perhaps most original is the idea of using congruence class models in analyses of impact of vaccine on infectiousness. This approach allows for marginalization across collections of plausible transmission networks–not just over sets of pairs–by allowing for estimation of the posterior probability of each network. Doing so may not only make more efficient use of the available data, but also provide more reliable estimates of variance of estimated vaccine effects. Therefore, it might not only reduce bias (if there is some systematic bias in adjudication of transmission events) but also provide more realistic evaluation of uncertainty.

In vaccine studies, the choice of the null hypothesis is often that VE_S is less than or equal to some lower bound, below which the vaccine would not be considered as appropriate for use in practice. Such tests for VE_S can be easily performed using parametric models, but permutation tests would be more challenging in this setting and require additional assumptions (Rabideau and Wang 2021).[36] In addition, isolating the effect of VE_I would require causal modeling to adjust for the fact that it is only measurable on the subset enrolled participants who become infected. To illustrate this point, consider a setting in which participants with high exposure to SARS-CoV-2 are less protected by booster compared to those with low exposure. Consider also the case where infected people with high exposure are more likely to transmit. In this setting, estimators of VE_I that condition of infection of the index could be biased because of the proportion of infected people at high risk of transmission would tend to be greater in the boosted than non-boosted groups. Our proposed metric VE_{TN}, which assesses the effect of vaccines in blocking infections and direct transmissions that follow from it, is measurable on all randomized subjects. It might be useful for assessing the potential of a vaccine to control spread of the virus under study. Other approaches for settings in which a large number of people will have value 0 for outcomes, include the “chop-lump” tests that assign a score of 0 for uninfected individuals and disease severity score that is greater than 0 for the infected individuals. An equal number of zeros is removed from both groups, and the test is conducted on the on the remaining scores, which are mostly greater than zero.[37] We note that it would be useful to conduct further investigation of different inference methods, including consideration of type I error control, power, and empirical coverage of confidence intervals. Such investigation might also include additional simulation studies in a variety of settings.

The college setting for many sites chosen by the NIH-funded CoVPN 3006 study offers advantages described above with regard to identifying contacts and engaging entire communities. Our proposed trial framework shares some of these features but would ideally build on already existing infrastructure for testing (including for wastewater testing), information about contact networks, and genetic sequencing. We also believe that appropriate use of modern network methods could improve precision and efficiency of analyses.

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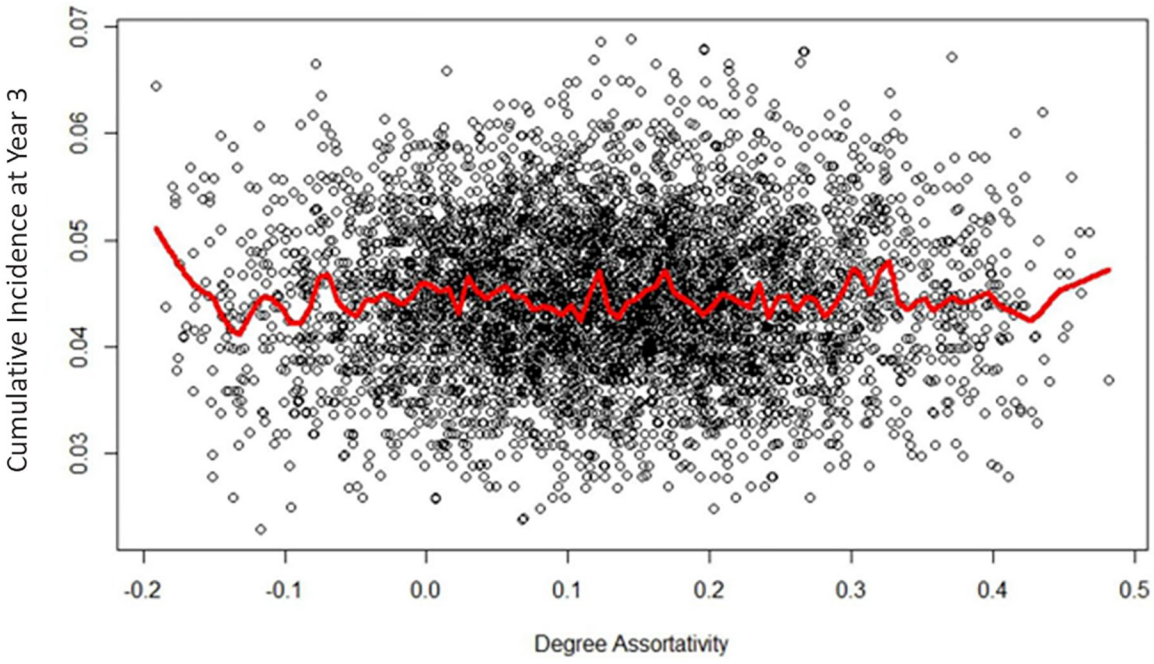

Figure 1.
Simulated Cumulative HIV Incidence at Year 3 by Degree Assortativity

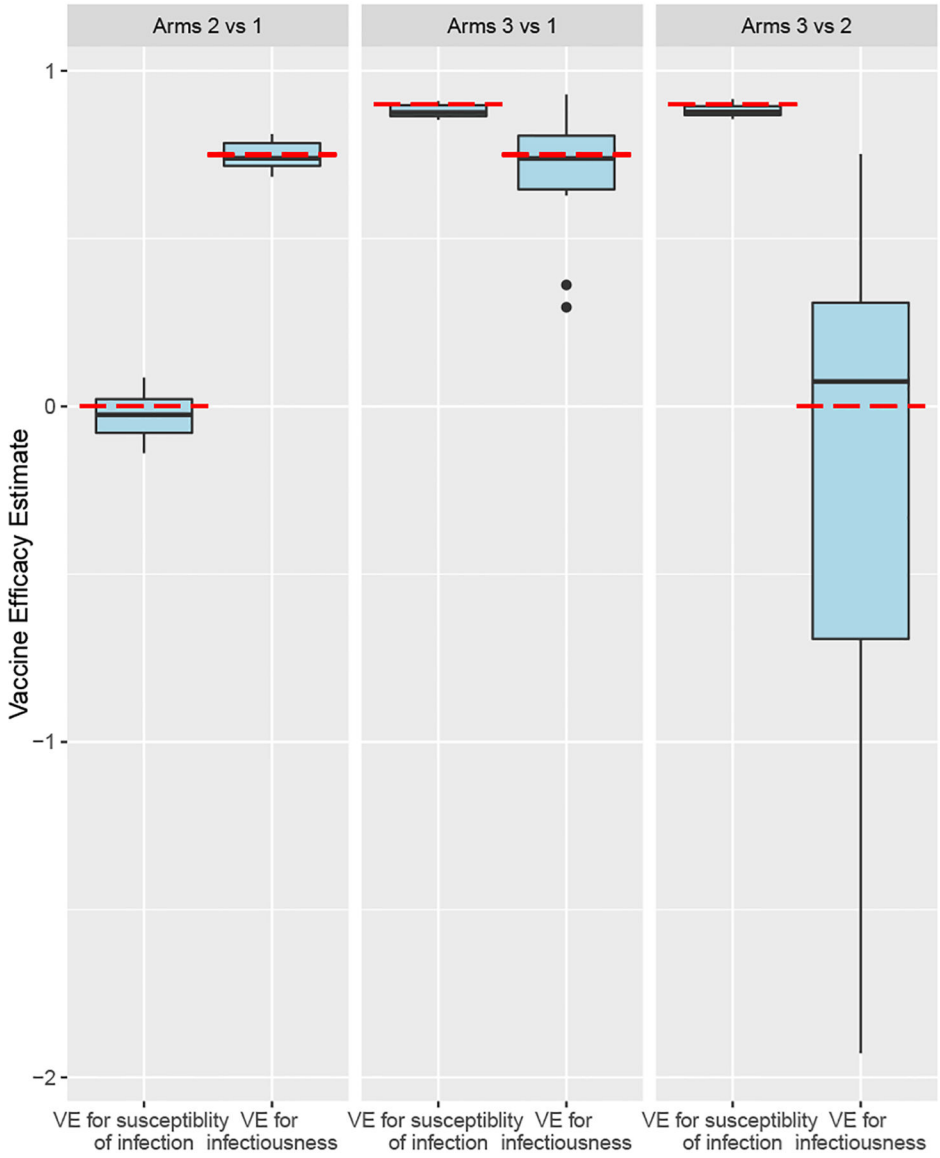

Figure 2.

Vaccine efficacy for susceptibility to infection (VE_S) and infectiousness (VE_I) of Arm 2 to Arm 1, Arm 3 to Arm 1, and Arm 3 to 2; the dashed lines are the values of VE_S (0, 0.9, and 0.9) and VE_I (0.75, 0.75, and 0) used in the simulations of S1.

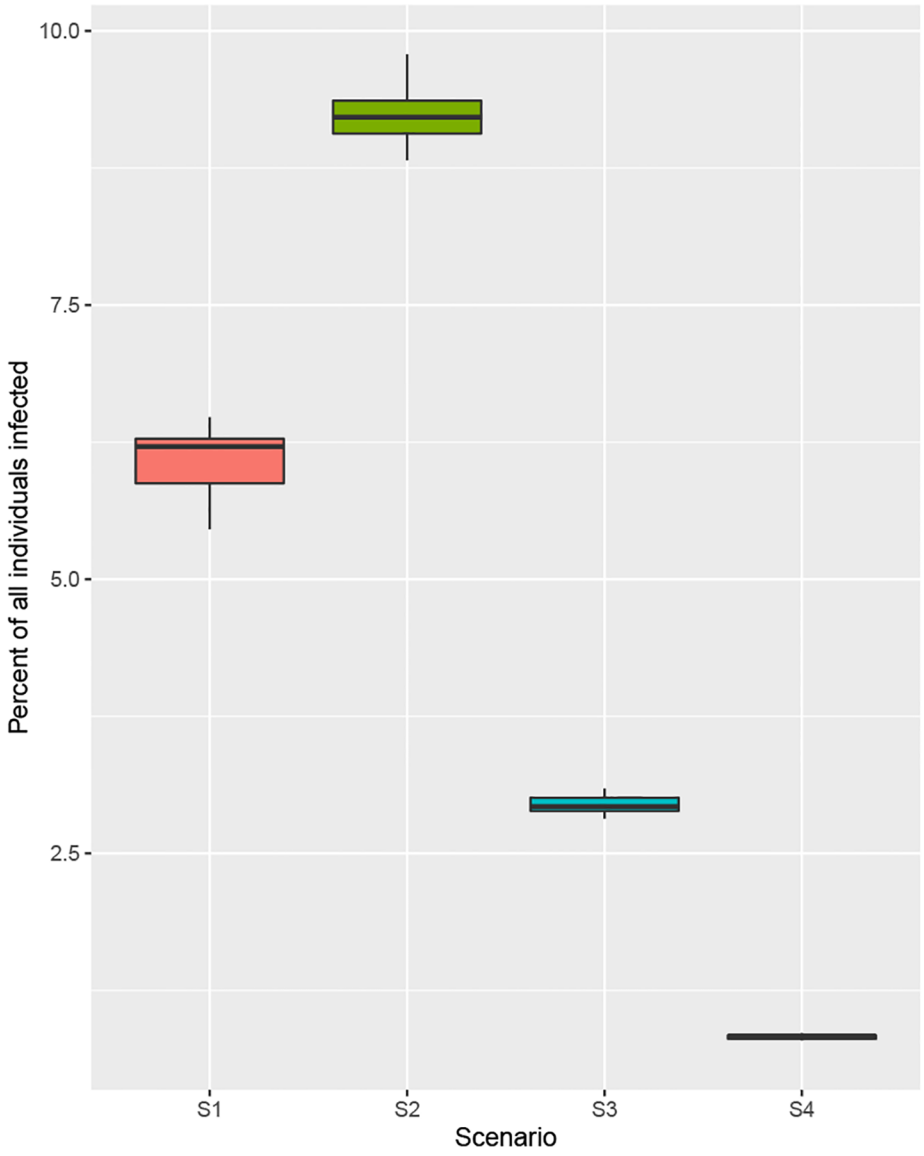

Figure 3.
Percent of individuals infected for each of the scenarios (S1-S4) over an academic session of 80 days.