Abstract

Consider the causal effect that one individual’s treatment may have on another individual’s outcome when the outcome is contagious, with specific application to the effect of vaccination on an infectious disease outcome. The effect of one individual’s vaccination on another’s outcome can be decomposed into two different causal effects, called the “infectiousness” and “contagion” effects. We present identifying assumptions and estimation or testing procedures for infectiousness and contagion effects in two different settings: (1) using data sampled from independent groups of observations, and (2) using data collected from a single interdependent social network. The methods that we propose for social network data require fitting generalized linear models (GLMs). GLMs and other statistical models that require independence across subjects have been used widely to estimate causal effects in social network data, but, because the subjects in networks are presumably not independent, the use of such models is generally invalid, resulting in inference that is expected to be anticonservative. We introduce a way to ensure that GLM residuals are uncorrelated across subjects despite the fact that outcomes are non-independent. This simultaneously demonstrates the possibility of using GLMs and related statistical models for network data and highlights their limitations.

1 Introduction

We are concerned here with the effect that one individual’s treatment may have on another individual’s outcome, when the outcome is contagious. In the infectious disease literature, this is often called an indirect effect of treatment [Halloran and Struchiner, 1991], while the effect of an individual’s treatment on his own outcome is a direct effect. Indirect effects of infectious disease interventions are of significant importance for understanding infectious disease dynamics and for designing public health interventions. For example, the goal of many vaccination
programs is to achieve herd immunity, whereby a large enough subset of a population is vacci-

nated that even those individuals who remain unvaccinated are protected against infection. This is one type of indirect effect of a vaccination program; it has been extensively studied in the infectious disease literature (Anderson et al., 1985; Fine, 1993; John and Samuel, 2000; O’Brien and Dagan, 2003). Recently, interest has turned towards the identification and estimation of average individual-level indirect effects (Halloran and Struchiner, 1991, 1995; Halloran and Hudgens, 2012; VanderWeele and Tchetgen Tchetgen, 2011a; VanderWeele et al., 2012b; VanderWeele and Tchetgen Tchetgen, 2011b), such as the effect on a single member of a community of two different vaccination programs implemented on the rest of the community (Halloran and Struchiner, 1995).

VanderWeele et al. (2012b) demonstrated that the individual-level indirect effect of vaccination in communities of size two can be decomposed into two different effects, called the “infectiousness” and “contagion” effects. These two effects represent distinct causal pathways by which one person’s vaccination may affect another’s disease status. The contagion effect is the indirect effect that vaccinating one individual may have on another by preventing the vaccinated individual from getting the disease and thereby from passing it on. The infectiousness effect is the indirect effect that vaccination might have if, instead of preventing the vaccinated individual from getting the disease, it renders the disease less infectious, thereby reducing the probability that the vaccinated infected individual transmits the disease, even if infected.

VanderWeele et al. (2012b) only considered estimation of the infectiousness and contagion effects in a sample comprised of independent households of size two with one member of each household assumed to be homebound. The assumption that one individual is homebound and the assumption of independent households are restrictive, the latter because it requires that the households be sampled from distinct communities and geographic areas. Ogburn and VanderWeele (2013) considered the setting in which households are independent but both individuals may be exposed outside the household. Here, we relax the requirement of independent households of size two and provide extensions to independent groups of arbitrary size and to social networks.

Increasingly, data are available on the spread of contagious outcomes through social networks. This setting is considerably more complex than that considered in VanderWeele et al. (2012b), because the observed outcomes (e.g. disease status) are not independent of one another. There is a growing literature on the possibility of testing for the presence of different causal mechanisms using observational data from social networks and a consensus that more rigorous methods are needed.

An emerging body of work reports results from generalized linear models (GLMs) and, for longitudinal data, generalized estimating equations (GEEs) as estimates of peer effects, or the causal effect that one individual’s outcome may have on his or her social contacts’ outcomes (Ali and Dwyer, 2009; Cacioppo et al., 2009; Christakis and Fowler, 2007, 2008, 2013;
This work has come under criticism that can largely be summarized into two overarching themes. First, much of the criticism focuses on the ability to control for confounding when estimating peer effects, and specifically on the identifying assumptions that are required in order to tell the difference between the well known problem of homophily (the phenomenon by which individuals with similar traits are more likely to form social ties with one another) and peer influence (Cohen-Cole and Fletcher, 2008; Lyons, 2011; Noel and Nyhan, 2011; Shalizi and Thomas, 2011; VanderWeele, 2011). Homophily will not be an issue in many infectious disease settings, as many such illnesses, for example the seasonal flu, are unlikely to change the nature of social ties. Adequate control for confounding is still crucial, but we assume throughout that all potential confounders of the causal effects of interest are observed. This assumption should be assessed in any application of these methods and it may not hold in many real data settings; however, we do not focus on this assumption in the remainder of this paper.

The second class of criticisms addresses the use of statistical models for independent observations in this dependent data setting. Lyons (2011) and VanderWeele et al. (2012a) demonstrated the importance of ensuring that models are coherent when an observation can be both an outcome and a predictor (of social contacts’ outcomes); this is easily accomplished by using the observations at one time point as predictors and the observations at a subsequent time point as outcomes, a solution that was implemented in many of applications of GLMs and GEEs to social network data referenced above. More challenging is the fact that, when an analysis assumes independence but observations are in fact positively correlated, as we would expect them to be for contagious outcomes in a social network, the resulting standard errors and statistical inference will generally be anticonservative. In some cases, the assumption of independent outcomes may hold under the null hypothesis (VanderWeele et al., 2012a), but it is unknown whether tests that rely on this fact have any power to detect the presence of the causal effects of interest (Shalizi, 2012).

Our contribution to methodology for social network analysis is to adapt GLMs to ensure that the models can be correctly specified, with uncorrelated residuals, even when the outcome is contagious. We demonstrate the possibility of testing for the presence of contagion and infectiousness effects using social network data and generalized linear models (GLMs). We discuss the paradigmatic example of the effect of a vaccination on an infectious disease outcome, but effects like contagion and infectiousness are of interest in other settings as well. Our general approach to correctly specifying GLMs for a contagious outcome using network data could potentially be applied to any estimand for which GLMs are appropriate under independence. The tests that we propose have important limitations, most notably low power to detect effects unless networks are large and/or sparse. However, this work represents an important proof of concept in the ongoing endeavor to develop methods for valid inference using data collected from a single network. Furthermore, it clarifies the issues of model mis-
specification and invalid standard errors raised by previous proposals for using GMLs to assess peer effects using network data.

2 Social networks and contagion

Formally, a social network is a collection of individuals and the ties between them. The presence of a tie between two individuals indicates that the individuals share some kind of a relationship; what types of relationships are encoded by network ties depends on the context. For example, we might define a network tie to include familial relatedness, friendship, and shared place of work. Some types of relationships are mutual, for example familial relatedness and shared place of work. Others, like friendship, may go in only one direction: Tom may consider Sue to be his friend, while Sue does not consider Tom to be her friend. We will assume that all ties in our network are mutual or undirected, but the principles of our method extend to directed ties. A node whose characteristics we wish to explain is called an ego; nodes that share ties with the ego are its alters or contacts. If an ego’s outcome may be affected by his contacts’ outcomes, then we say that the outcome exhibits induction or contagion.

Social networks are crucial to understanding many features of infectious disease dynamics, and, increasingly, infectious disease researchers draw on social network data to refine their understanding of transmission patterns and treatment effects. For example, many mathematical models of infectious disease now incorporate social network structure, whereas they previously generally assumed uniform mixing among members of a community (Eubank et al., 2004; Klovdahl, 1985; Klovdahl et al., 1994; Keeling and Eames, 2005), and researchers collect data on sexual contact networks, since properties of these networks can inform strategies for controlling sexually transmitted diseases (Latora et al., 2006; Eames and Keeling, 2002, 2004).

It is desirable for a number of reasons to study infectiousness and contagion in the context of social networks rather than in independent communities. First, social network data may be easier to collect or to access than data on independent communities, as the latter setting requires sampling from a large number of different locations or contexts that are separated by time or space. Second, assessing whether traits can be transmitted from one individual to another through network ties is one of the central questions in the study of social networks; assessing infectiousness and contagion contributes further insight into this problem. Finally, social network data more realistically capture the true interdependencies of the individuals whom we can hope to treat with any public health intervention. Vaccine programs do not in general target distant, independent pairs of individuals; they target villages, cities, or communities in which individuals are interconnected and their outcomes correlated. Therefore, assessing the presence of vaccine effects in social network data may be more informative for real-world applications. The methods we present here represent a first step towards being able to estimate and perform inference about such effects using social network data.
Interventions to prevent infectious diseases generally operate in two ways. Some reduce the susceptibility of treated individuals to the disease, thereby preventing them from becoming infected. Examples of such interventions are vaccines for tetanus, hepatitis A and B, rabies, and measles (Keller and Stiehm, 2000). These vaccines have indirect effects that operate via contagion effects. Other interventions may reduce the likelihood that an infected individual passes on his infection to others. The malaria transmission-blocking vaccine is designed to prevent mosquitos from acquiring, and thereby from transmitting, malaria parasites upon biting infected individuals (Halloran and Struchiner, 1992). This vaccine has no protective effect for the vaccinated individual, but it renders vaccinated individuals less likely to transmit the disease. Therefore any indirect effect of the malaria transmission-blocking vaccine is due entirely to an infectiousness effect. Many interventions have indirect effects that operate via both contagion and infectiousness effects.

Existing methods for assessing causal effects using network data are limited. Some recent proposals give methods for assessing indirect effects when treatment can be randomized (Airoldi et al., 2013; Aronow and Samii, 2012; Bowers et al., 2013; Rosenbaum, 2007), but these methods are of limited use in observational settings or for teasing apart specific types of indirect effects like the infectiousness and contagion effects. Much of the extant literature relies on GLMs and GEEs, despite the fact that the key assumption of independent outcomes across subjects is unlikely to hold in social network settings (Lyons, 2011). In this paper, we introduce a way to ensure that GLM residuals are uncorrelated across subjects despite the fact that outcomes are non-independent; this facilitates the use of GLMs to assess infectiousness and contagion effects in social network contexts. We demonstrate through simulations that our methods do have some power to detect the presence of contagion and infectiousness effects; however, in order to ensure that residuals are uncorrelated, we make several adaptations to naive GLMs; unfortunately these can result in low power. The applications that we discuss in this paper do not require the use of GEEs to account for within-subject dependence over time, but the general principles that we use to adapt GLMs to the network setting apply to GEEs as well.

3 Infectiousness and contagion in independent groups of size 2

3.1 Notation and assumptions

Consider $K$ households comprised of two individuals each and separated by space or time such that an infectious disease cannot be transmitted between individuals in different households. Borrowing terminology from the social network literature, we will refer to one individual as the alter, denoted $a$, and the other as the ego, denoted $e$. For now we assume that in each household the ego is unvaccinated, and that all vaccination occurs before the start of follow-up.
Contagion and infectiousness effects are analogous to causal mediation effects of the alter’s vaccination on the ego’s outcome, mediated by the alter’s disease status (VanderWeele et al., 2012b). We formally define these effects in the next section after first introducing key notation and identifying assumptions.

For individual \(i\) in household \(k\), let \(Y_{ik}^t\) be the outcome at time \(t\) and \(C_{ik}\) be a vector of covariates. Let \(V_{ak}\) be an indicator of vaccination for the alter in household \(k\). Below we omit the subscript \(k\) when context allows. Define \(Y_{ik}^t(v)\) to be the counterfactual outcome we would have observed for individual \(i\) in household \(k\) at time \(t\), if, possibly contrary to fact, the alter had received treatment \(v\). Let \(M_k\) be a variable that lies on a causal pathway from \(V_{ak}\) to \(Y_{ek}^t\). Let \(Y_{ek}^t(v, m)\) be the counterfactual outcome for the ego at time \(t\) that we would have observed if \(V_{ak}\) had been set to \(v\) and \(M_k\) to \(m\). Throughout we make the consistency assumptions that \(M_k(v) = M_k\) when \(V_{ak} = v\), that \(Y_{ek}^t(v, m) = Y_{ek}(v)\) when \(V_k = v\) and \(M_k = m\), and that \(Y_{ek}(v, M_k(v)) = Y_{ek}(v)\). Let \(Y_{ek}^t(v, M_k(v'))\) be the counterfactual disease status for the ego in household \(k\) that we would have observed at time \(t\) if \(V_{ak}\) had been set to \(v\) and \(M_k\) to its counterfactual value under \(V_{ak} = v\). To ensure that this counterfactual is well-defined, we assume that it is hypothetically possible to intervene on the mediator without intervening on \(V_{ak}\). Let \(C_k = (C_{ak}, C_{ek})\). In order to identify functionals of nested counterfactuals like \(Y_{ek}^t(v, M(v'))\) we require the following four assumptions (Pearl, 2001):

\[
Y_{ek}^t(v, m) \perp V_a \mid C, \tag{1}
\]

\[
Y_{ek}^t(v, m) \perp M \mid V_a, C, \tag{2}
\]

\[
M(v) \perp V_a \mid C, \tag{3}
\]

and

\[
Y_{ek}^t(v, m) \perp M(v') \mid C \tag{4}
\]

where \(A \perp B \mid C\) denotes that \(A\) is independent of \(B\) conditional on \(C\). Assumptions (1), (2), and (3) correspond to the absence of unmeasured confounders for the effects of the exposure on the outcome (\(V_a\) on \(Y_{ek}^t\)), of the mediator on the outcome (\(M\) on \(Y_{ek}^t\)), and of the exposure on the mediator (\(V_a\) on \(M\)), respectively. Assumption (4) requires that no confounder of the effect of \(M\) on \(Y_{ek}^t\) is affected by \(V_a\). Discussion of these assumptions in the context of mediation analysis can be found in Pearl (2001). Discussion and extension of these assumptions to settings with interference or spillover effects can be found in Ogburn and VanderWeele (2013), including discussion of how to determine which covariates must be included in \(C\).
3.2 Previous methodology for decomposing the indirect effect into infectiousness and contagion effects

3.2.1 Identification

VanderWeele et al. (2012b) described the decomposition of indirect effects into contagion and infectiousness effects in communities of size two. They assumed that the outcome can only occur once for each individual during the follow-up period. This is a reasonable assumption for many infectious disease outcomes, for example for the common flu with a follow-up period consisting of a single flu season. They further assumed that in each pair the ego cannot be exposed to the disease except by the alter, as might be the case if the ego were homebound. Let $t_f$ be the time of the end of follow-up and $Y_{fke}$ be an indicator of whether the ego in household $k$ has had the disease by the end of follow-up. VanderWeele et al. (2012b) defined the population average indirect effect of vaccination on the ego as $E\left[Y_{fke}(1) - Y_{fke}(0)\right]$, or the expected difference in the counterfactual disease status of the ego at end of follow-up when the alter is vaccinated compared to when the alter is not vaccinated. When the ego is homebound, the indicator $Y_{fke}$ of whether the ego in household $k$ has had the disease by the end of follow-up is, equivalently, an indicator of whether the ego was infected by the alter in household $k$. In order to generalize the discussion of vaccine effects to settings in which the ego can be infected from outside the home, the outcome $Y_{fke}$ should be defined more precisely as the indicator of whether the ego was sick after the alter. Specifically, let $Y_{fke} = I(\text{alter was sick at time } T < t_f \text{ and ego was sick at time } S, T < S \leq t_f)$.

The contagion effect is the protective effect that treating one individual has on another’s disease status by preventing the treated individual from getting the disease and thereby from transmitting it. Let $T_k$ be the time of the first case of the disease in household $k$. This is akin to the effect of one individual’s treatment on another’s disease status as mediated by the first individual’s disease status. For the purposes of the analysis below, we define a disease case to begin when an individual becomes infectious. If infectiousness does not coincide with the appearance of disease symptoms then we may not observe the timing of disease cases directly, but we could infer the time based on when symptoms appear and on known disease dynamics. For example, an individual with the flu will generally be infectious one day before he is symptomatic (Earn et al., 2002). Therefore, if flu is the disease under study we would classify an individual as having the disease beginning one day before he reported having flu symptoms. We assume throughout that there are no asymptomatic carriers of the disease. If neither individual in household $k$ is ever sick then we define $T_k$ to be the end of follow-up. Now $Y_{Tk}$ is an indicator of whether the alter is sick at time $T_k$, i.e. an indicator of whether the alter is the first individual in the group to get sick; if neither individual gets sick then it will be 0. Let $T_k(v)$ be the time at which the first infection in household $k$ would have occurred if the alter had, possibly contrary to fact, had vaccine status $v$. Let $Y_{Tk(v)}(v)$
be the counterfactual disease status of the alter at time $T_k(v)$ had he had vaccine status $v$. Let $Y_{ek}^{ij} = I(\text{individual } e_k \text{ became infectious after time } T_k \text{ and on or before time } t_f)$. The contagion effect is given by a contrast in counterfactuals of the form $Y_{e}^{ij} (v, Y_{a}^{T(v')}(v'))$ where, unlike in the mediation framework we described in Section 3.1, the variable $Y_{a}^{T(v')}$ that plays the role of mediator may be a different random variable in the two terms in the contrast. Specifically, the population average contagion effect is $E \left[ Y_{e}^{ij} \left(0, Y_{a}^{T(1)}(1)\right) \right] - E \left[ Y_{e}^{ij} \left(0, Y_{a}^{T(0)}(0)\right) \right]$, and $Y_{a}^{T(0)}$ and $Y_{a}^{T(1)}$ will be different random variables whenever $T(0) \neq T(1)$. This contrast is the difference in expected counterfactual outcomes for the ego when the vaccine status of the alter is held constant at 0 but his infection status is set to that under vaccination in the first term and to that under no vaccination in the second term of the contrast. It captures the effect that vaccination might have had on the disease status of the ego by preventing the alter from contracting the disease. The nested counterfactuals are well-defined because we can imagine intervening on $Y_{ka}^{T_k}$ without intervening on $V_{ka}$, for example by administering immune boosters to prevent the alter from being infected or by exposing the alter to a high dose of flu virus in a laboratory setting to cause infection.

The population average infectiousness effect is $E \left[ Y_{e}^{ij} \left(1, Y_{a}^{T(1)}(1)\right) \right] - E \left[ Y_{e}^{ij} \left(0, Y_{a}^{T(1)}(1)\right) \right]$. This is akin to the effect of one individual’s treatment on another’s disease status, not mediated through the first individual’s disease status. This effect operates if treatment renders cases of disease among treated individuals less likely to be transmitted. Suppose that the alter in group $k$ would get the flu first if vaccinated. That is, $Y_{ak}^{T_k(1)}(1) = 1$. Then the infectiousness effect is the difference in counterfactual outcomes for the ego comparing the scenario in which the alter is vaccinated and infected first with the scenario in which the alter is unvaccinated and infected first. If the alter in group $k$ would not get the flu first under vaccination, then the infectiousness effect for group $k$ is null.

By the consistency assumption we made in Section 3.1 above, $E \left[ Y_{e}^{ij} \left(1, Y_{a}^{T(1)}(1)\right) \right] = E \left[ Y_{e}^{ij} \left(1\right) \right]$ and $E \left[ Y_{e}^{ij} \left(0, Y_{a}^{T(0)}(0)\right) \right] = E \left[ Y_{e}^{ij} \left(0\right) \right]$. The indirect effect of the vaccination of the alter on the ego decomposes into the sum of the contagion and infectiousness effects as follows:

$$
E \left[ Y_{e}^{ij} \left(1\right) \right] - E \left[ Y_{e}^{ij} \left(0\right) \right] = E \left[ Y_{e}^{ij} \left(1, Y_{a}^{T(1)}(1)\right) \right] - E \left[ Y_{e}^{ij} \left(0, Y_{a}^{T(0)}(0)\right) \right] \\
= E \left[ Y_{e}^{ij} \left(1, Y_{a}^{T(1)}(1)\right) \right] - E \left[ Y_{e}^{ij} \left(0, Y_{a}^{T(1)}(1)\right) \right] + E \left[ Y_{e}^{ij} \left(0, Y_{a}^{T(1)}(1)\right) \right] - E \left[ Y_{e}^{ij} \left(0, Y_{a}^{T(0)}(0)\right) \right]
$$

The assumptions made by VanderWeele et al. (2012b) allow for the identification of the infectiousness and contagion effects even if disease status is only observed at the end of follow-up. Because the ego cannot be infected except by the alter, $Y_{ak}^{T_k} = 0$ if and only if neither individual is observed to get sick and $Y_{ak}^{T_k} = 1$ if and only if $Y_{ak}^{T_f} = 1$. Therefore $Y_{ak}^{T_f}$ can be
substituted for $Y_{T_k}$ in the expressions above.

Ogburn and VanderWeele (2013) gave identifying assumptions for the infectiousness and contagion effects in groups of size two when the time of infections is observed. They did not assume that only one member of each pair is exposed from outside of the group; instead they assumed that the probability of the ego contracting the disease within a fixed follow-up interval if exposed at time $t$ is constant in $t$. This ensures that the time of the first infection $T$ is not a confounder of the mediator-outcome relationship, which would constitute a violation of assumption (4) because $T$ is affected by $V_a$. Suppose that the two members of each pair are distinguishable from one another, for example parent-child pairs. We select one of the two to be the alter (e.g. the parent) and the other is the ego (the child). Alternatively, if the individuals are exchangeable, that is, if we have no reason to think that the indirect effect and its components will be different for one than for the other, then we can randomly choose which subject is the alter and which is the ego. Ogburn and VanderWeele (2013) defined the indicator $Y_{T+s}$ of whether the ego is sick after time $T$ and by time $T+s$ to be the outcome, where $s$ is a constant that allows $T$ to determine a new end of follow-up. This ensures that $T$ does not confound the mediator-outcome relationship. The constant $s$ should be chosen to be the sum of the infectious period ($f$) and the incubation period ($b$) of the disease under study. The infectious period is the length of time during which an infected individual is infectious, and the incubation period is the length of time between being infected and becoming infectious. If the alter becomes infectious at time $T$, then he can infect the ego until time $T+f$. If infected at time $T+f$, the ego will become infectious at time $T+k+f+b = T_k+s$. Therefore if the alter infects the ego, the ego must be infectious by time $T_k+s$. We assume throughout that the time to efficacy of vaccine is immediate and that the infectious and incubation periods are constant across individuals.

Let $Y^T_{T_k}(v')+(v, Y^T_{ak}(v'))(v')$ be the counterfactual outcome we would have observed for the ego in group $k$ at time $T_k(v')+s$ if the alter’s vaccine status were set to $v$ and the alter’s disease status at time $T_k(v')$ were set to its counterfactual under vaccine status $v'$. The average contagion effect in this setting is given by $E[Y^T_{T_k}(v')+s (0, Y^T_{a}(1))]-E[Y^T_{T_k}(v')+s (0, Y^T_{a}(0))]$ and the average infectiousness effect by $E[Y^T_{T_k}(v')+s (1, Y^T_{a}(1))]-E[Y^T_{T_k}(v')+s (0, Y^T_{a}(1))].$ The sum of these two effects is the average indirect effect $E[Y^T_{T_k}(v'+s (1)]-E[Y^T_{T_k}(v'+s (0)].$ Although the disease status of the ego is measured $s$ days after the first infection instead of at the end of follow-up, this indirect effect still captures any effect that the alter’s vaccination status can have on the ego’s disease status, because after time $T+s$ any change in the disease status of the ego cannot be caused by $V_a$.

So far we have described all effects on the difference scale, but everything we have written applies equally to effects on the ratio and odds ratio scales. On the ratio and odds ratio scales the indirect effect of vaccination decomposes into a product of the contagion and in-
fectiousness effects. On the ratio scale, the average indirect effect of $V_a$ on the disease status of the ego is $E \left[ Y_e^{T(1)+s}(1) \right] / E \left[ Y_e^{T(0)+s}(0) \right]$, which is a product of the average infectiousness effect, $E \left[ Y_e^{T(1)+s}(1, Y_a^{T(1)}(1)) \right] / E \left[ Y_e^{T(1)+s}(0, Y_a^{T(1)}(1)) \right]$, and the average contagion effect, $E \left[ Y_e^{T(1)+s}(0, Y_a^{T(0)}(1)) \right] / E \left[ Y_e^{T(0)+s}(0, Y_a^{T(0)}(0)) \right]$. On the odds ratio scale for a binary outcome the decomposition is

$$ \frac{E \left[ Y_e^{T(1)+s}(1) \right] \left(1 - E \left[ Y_e^{T(0)+s}(0) \right]\right)}{E \left[ Y_e^{T(0)+s}(0) \right] \left(1 - E \left[ Y_e^{T(1)+s}(1) \right] \right)} \times \frac{E \left[ Y_e^{T(1)+s}(1, Y_a^{T(1)}(1)) \right] \left(1 - E \left[ Y_e^{T(1)+s}(0, Y_a^{T(1)}(1)) \right] \right)}{E \left[ Y_e^{T(1)+s}(0, Y_a^{T(1)}(1)) \right] \left(1 - E \left[ Y_e^{T(1)+s}(1, Y_a^{T(1)}(1)) \right] \right)} \times \frac{E \left[ Y_e^{T(1)+s}(0, Y_a^{T(0)}(1)) \right] \left(1 - E \left[ Y_e^{T(0)+s}(0, Y_a^{T(0)}(0)) \right] \right)}{E \left[ Y_e^{T(0)+s}(0, Y_a^{T(0)}(0)) \right] \left(1 - E \left[ Y_e^{T(1)+s}(0, Y_a^{T(1)}(1)) \right] \right)}$$

where the first line is the indirect effect, the second line is the infectiousness effect, and the third line is the contagion effect.

### 3.2.2 Estimation

The contagion and infectiousness effects are analogous to the natural indirect and direct effects, respectively, of the effect of $V_a$ on $Y_e^{T+s}$ with $Y_a^T$ as the mediator. Natural indirect and direct effects have been written about extensively in the causal inference and mediation literature (see e.g. Pearl, 2001; Robins and Greenland, 1992; Robins and Richardson, 2010) and it is well-known how to estimate them in a variety of settings (Imai et al., 2010; Valeri and VanderWeele, 2013). This setting differs from those considered by other authors because the outcome $Y_e^{T+s}$ is, by definition, equal to 0 whenever $Y_a^T$ is equal to 0; therefore one must be careful to ensure that any model specified for $E \left[ Y_e^{T+s} \mid V_a, Y_a^T, C \right]$ is consistent with this restriction. VanderWeele et al. (2012b) describe how to estimate the contagion and infectiousness effects on the ratio scale in households of size two when one individual is homebound, but the procedure they present overlooks this restriction and therefore the models they suggest may fail to converge.

We describe a procedure for estimating the contagion and infectiousness effects that is appropriate for the setting considered in VanderWeele et al. (2012b) and for the setting in which neither individual is assumed to be homebound. We describe estimation of the effects on the difference and ratio scales. Estimation of effects on the odds ratio scale is also possible. Suppose that assumptions (1) through (4) hold for the effect of $V_a$ on $Y_e^{T+s}$ with $Y_a^T$ as the
mediator and covariates \( C \), and that the following two models are correctly specified:

\[
\begin{align*}
\log \left\{ \mathbb{E} \left[ Y_a^{T+s} \mid V_a, Y_a^{T} = 1, C \right] \right\} &= \gamma_0 + \gamma_1 V_a + \gamma_2 C \\
\text{logit} \left\{ \mathbb{E} \left[ Y_a^{T} \mid V_a, C \right] \right\} &= \eta_0 + \eta_1 V_a + \eta_2 C.
\end{align*}
\]

If the outcome is rare then (5) can be replaced with a logistic model. The contagion effect conditional on covariates \( C = c \) on the difference scale is given by

\[
E \left[ Y_e^{T(1)+s}(0, Y_a^{T(1)}(1)) \mid c \right] - E \left[ Y_e^{T(1)+s}(0, Y_a^{T(1)}(0)) \mid c \right] \\
= 0 + E \left[ Y_a^{T+s} \mid V_a = 0, Y_a^{T} = 1, c \right] \left\{ E \left[ Y_a^{T} \mid V_a = 1, c \right] - E \left[ Y_a^{T} \mid V_a = 0, c \right] \right\} \\
= e^{\gamma_0+\gamma_2} \frac{\frac{e^{\eta_0+\eta_1 V_a+\eta_2 c}}{1 + e^{\eta_0+\eta_1 V_a+\eta_2 c}}}{\frac{1}{1 + e^{\eta_0+\eta_1 V_a+\eta_2 c}}},
\]

and the infectiousness effect conditional on covariates \( C = c \) is given by

\[
E \left[ Y_e^{T(1)+s}(1, Y_a^{T(1)}(1)) \mid c \right] - E \left[ Y_e^{T(1)+s}(0, Y_a^{T(1)}(1)) \mid c \right] \\
= 0 + E \left[ Y_a^{T+s} \mid V_a = 1, c \right] \left\{ E \left[ Y_e^{T+s} \mid V_a = 1, Y_a^{T} = 1, c \right] - E \left[ Y_e^{T+s} \mid V_a = 0, Y_a^{T} = 1, c \right] \right\} \\
= \frac{e^{\eta_0+\eta_1 V_a+\eta_2 c}}{1 + e^{\eta_0+\eta_1 V_a+\eta_2 c}} \left( e^{\gamma_0+\gamma_1 V_a+\gamma_2 c} - e^{\gamma_0+\gamma_2} \right).
\]

The contagion and infectiousness effects can be estimated by fitting models (5) and (6) and plugging the parameter estimates into the expressions above. The standard errors for these estimates can be bootstrapped or derived using the delta method (similar to those derived in Valeri and VanderWeele, 2013 for the natural direct and indirect effects). Alternatively, a Monte Carlo based approach similar to Imai et al. (2010) can be used for estimation of the effects and their standard errors. Software packages like SAS and SPSS mediation macros (Valeri and VanderWeele, 2013) or the R mediation package (Imai et al., 2010) cannot be used in this setting because instead of (5), which models the conditional expectation of the \( Y_a^{T+s} \) only in the \( Y_a^{T} = 1 \) stratum, these packages require fitting a model for \( E \left[ Y_e^{T+s} \mid V_a, Y_a^{T}, C \right] \).

If the ego can also be vaccinated then \( V_e \) must be included in \( C \). If \( V_a \) interacts with \( V_e \) or with any other covariates, these interactions can be incorporated into the models and pose no difficulty for estimation. To test whether there is a contagion effect, we can simply test whether \( 1 = 0 \). To test whether there is an infectiousness effect we can simply test whether \( 1 = 0 \).

Using the parameters of models (5) and (6) we can also estimate the contagion and infectiousness effects on the ratio scale. The contagion effect conditional on \( C = c \) is given
by
\[
E[Y_e^{T(1)+s}(0,Y_a^{T(1)}(1)) | c] = \frac{0 + E[Y_e^{T+s} | V_a = 0, Y_a^{T} = 1, c] E[Y_a^{T} | V_a = 1, c]}{0 + E[Y_e^{T+s} | V_a = 0, Y_a^{T} = 1, c] E[Y_a^{T} | V_a = 0, c]}
\]
\[
= \frac{E[Y_a^{T} | V_a = 1, c]}{E[Y_a^{T} | V_a = 0, c]}
\]
\[
= \frac{e_{\eta} + e_{\eta_0+\eta_1+\eta_2}c}{1 + e_{\eta_0+\eta_1+\eta_2}c}
\]

(7)

and the infectiousness effect is given by
\[
E[Y_e^{T(1)+s}(1,Y_a^{T(1)}(1)) | c] = \frac{0 + E[Y_e^{T+s} | V_a = 1, Y_a^{T} = 1, c] E[Y_a^{T} | V_a = 1, c]}{0 + E[Y_e^{T+s} | V_a = 0, Y_a^{T} = 1, c] E[Y_a^{T} | V_a = 1, c]}
\]
\[
= \frac{E[Y_a^{T+s} | V_a = 1, Y_a^{T} = 1, c]}{E[Y_a^{T+s} | V_a = 0, Y_a^{T} = 1, c]}
\]
\[
= e_{\eta_1}.
\]

(8)

Under the restriction that $Y_e^{T+s} = 0$ whenever $Y_a^{T} = 0$, the contagion effect on the ratio scale is simply a measure of the effect of the alter’s vaccination on the alter’s outcome. It is mathematically undefined if $E[Y_e^{T+s} | V_a = 0, Y_a^{T} = 1, c] = 0$, that is, if the ego’s outcome has no effect on the alter’s outcome, but it is natural to define it to be equal to the null value of 1 in this case. The infectiousness effect on the ratio scale is simply a measure of the effect of the alter’s vaccination on the ego’s outcome among pairs in which the alter is sick first, that is, in the $Y_a^{T} = 1$ stratum.

4 Infectiousness and contagion in groups of more than two

Although allowing both individuals in a household to be infected from outside the household generalizes the results of VanderWeele et al. (2012b), it still requires the strong assumption, inherent in the identifying assumptions described in Section 3, that the alter and ego do not share any potentially infectious contacts. If both of the individuals in a given household could be infected from outside the household by the same mutual friend, then that friend’s disease status would be a confounder of the mediator-outcome relationship; if unobserved, it would constitute a violation of assumption (2). We can relax the assumption of no mutual contacts outside of the household by collecting data on any such contacts and controlling for them as covariates in our estimating procedure.

In this section, we consider identification and estimation of the contagion and infectiousness
effects when independent groups of individuals are sampled. We assume that each group includes a pair of individuals who furnish the exposure, mediator, and outcome variables, plus all mutual and potentially infectious contacts of the pair. Several types of sampling procedures could give rise to this data structure. For example, one possibility would be to sample workplaces and randomly select two individuals to play the role of the alter and ego; another would be to sample household pairs first, ascertain the identities of potential mutual contacts outside of the home, and include all such contacts in the data collection moving forward. The sampling procedure does not affect the identification or estimation results described below.

Let \( k \) index the \( k \)th group, \( k = 1, ..., K \). Let \( Y_{ik}^t \) be an indicator of whether individual \( i \) in group \( k \) has had the disease by day \( t \). As in Section 3, we define a case of the disease to begin when the individual becomes infectious and let \( s = f + b \) be the sum of the infectious and incubation periods for the disease. We assume that vaccination occurs before the start of follow-up. Given a non-rare outcome like the flu and time measured in discrete intervals like days, it is likely that we would observe multiple individuals to get sick on the same day. We therefore do not make the assumption, made in Section 3, that no two individuals can be observed to get sick at the same time. For group \( k \), let \( e_k \) index the ego, whose flu status we wish to study, and let \( a_k \) index the alter, whose vaccination status may or may not have an effect on the ego’s disease status. We index the other individuals in group \( k \) by \( 1, 2, ..., n_k \). Let \( T_k \) be the time of the first infection in the \( k \)th alter-ego pair. As in Section 3, the ego furnishes the outcome, \( Y_{e_k}^{T_k+s} \). The alter furnishes the treatment, vaccine status \( V_{a_k} \), and the mediator, indicator of first infection \( Y_{a_k}^{T_k} \). When context allows, we omit the subscript \( k \).

The definition of the mediator needs to be modified slightly to reflect the fact that the alter and the ego could get sick at the same time: let \( Y_{a_k}^T \) be an indicator of whether the alter was sick and the ego healthy at time \( T \). Let \( Y_{e_k}^{T+s} \) be an indicator of whether the ego got sick between time \( T + b \), which is the first time at which the alter could have infected the ego, and time \( T + s \), which is the last time at which the alter could have infected the ego. This definition preserves the interpretation of \( Y_{a_k}^T \) as an indicator that the alter was sick before the ego; if the ego and the alter simultaneously fell ill on day \( T \) then \( Y_{a_k}^T \) will be 0, which is desirable because the ego cannot have caught the disease from the alter if they both fell ill on the same day. It also preserves the restriction, discussed in Section 3, that \( Y_{e_k}^{T+s} \) is equal to 0 whenever \( Y_{a_k}^T \) is.

\[
Y_{e_k}^{T(v')+s} \left(v, Y_{a_k}^{T(v')(v')}\right)
\]

is the counterfactual flu status of the ego at time \( T(v') + s \) had the alter’s vaccine status been set to \( v \) and his flu status at time \( T(v') \) set to its counterfactual value under vaccine status \( v' \), where \( T(v') \) is the time at which the first infection in the alter-ego pair would have occurred if \( V_{a_k} \) had been set to \( v' \). The effects of interest are the average
contagion effect

\[ Con = \frac{E \left[ Y_e^{T(1)+s} (0, Y_a^{T(1)} (1)) \right]}{E \left[ Y_e^{T(0)+s} (0, Y_a^{T(0)} (0)) \right]} \] (9)

and the average infectiousness effect

\[ Inf = \frac{E \left[ Y_e^{T(1)+s} (1, Y_a^{T(1)} (1)) \right]}{E \left[ Y_e^{T(1)+s} (0, Y_a^{T(1)} (1)) \right]} \], (10)

where the expectations are taken over all ego-alter pairs.

In order to identify the effects defined in (9) and (10), we must measure and control for all confounders of the relationships between \( Y_e^{T+s} \) and \( Y_a^T \), and in particular the potential mutual infectious contacts of the alter and ego. To motivate our procedure for controlling for these confounding contacts, consider the simple case of a group of size three, comprised of a child (ego), a parent (alter), and a grandparent. In the event that the grandparent contracted the flu first and transmitted it to both the child and the parent, the grandparent’s flu status would clearly be a confounder of the mediator-outcome relationship. But the grandparent’s entire disease trajectory is not a potential confounder; in particular anything that happens to the grandparent after time \( T \), that is after the first infection in the parent-child pair, occurs after the mediator and cannot possibly confound the mediator-outcome relationship. In this simple, three-person group, it suffices to control for an indicator of whether the grandparent has been sick by time \( T - b \), where \( T \) is the time of the first infection between the parent and child, and \( T - b \) is the latest time at which the grandparent could have been the cause of an infection at time \( T \).

In practice, we will likely have to sample groups of size greater than three in order to control for confounding by potential mutually infectious contacts. It is generally sufficient to control for a summary measure of the infections occurring before \( T - b \) in each group. If each infectious contact of an individual has an independent probability of transmitting the disease to the individual, then the sum \( \sum_{i=1}^{n_k} Y_{ki}^{T-b} \) of indicators of whether each mutual contact has been sick by time \( T - b \) suffices to control for confounding by potential mutual infectious contacts. Under a different transmission model, the proportion \( \sum_{i=1}^{n_k} Y_{ki}^{T-b} / n_k \) of contacts who were sick by time \( T - b \) could be the operative summary measure. If some of the mutual contacts may have been vaccinated, then separate summary measures (sum or proportion sick by time \( T - b \)) should be included for vaccinated and for unvaccinated contacts. In what follows we will assume that the sum is an adequate summary measure.
4.1 Alternative sampling schemes

Alter-centric sampling can also be used to collect data on variables that suffice to identify the contagion and infectiousness effects. Instead of sampling an alter-ego pair and all of their mutual contacts, we can sample an individual to serve as the alter and all of his potentially infectious contacts. The ego is randomly selected from among the alter’s contacts. Conditional on the number of the alter’s contacts who have been infectious by day $T - b$, $Y_a^T$ is independent of the number of mutual contacts who were sick by time $T - b$. The number of mutual contacts is no longer a confounder of the relationship between $Y_a^T$ and $Y_e^{T+s}$ and there is no need to ascertain the identity or disease status of the mutual contacts. However, the number of potentially infectious contacts of a single person can be vast, and it may be easier to identify mutual contacts of a pair of individuals than all contacts of any one individual.

5 Infectiousness and contagion in social networks

So far, we have assumed that our observations, comprised of groups of individuals, were independent of one another. This assumption will, in general, be violated when the alter-ego pairs are sampled from a single community or social network. We introduce some new notation for this context after briefly describing the example that will serve as the basis for our exposition and later for our simulations and data analysis. Consider tracking the seasonal flu in the student population of a college at which all students live in dorms on campus. Each student is a node in the network. We define a tie to exist between two nodes if the individuals regularly interact with one another in a way that could facilitate transmission of the flu. For example, if two individuals are roommates, eat together in the dining hall, or are close friends, then their nodes share a tie. We observe each individual’s flu status every day over the course of the flu season, which lasts for 100 days.

The contagion and infectiousness effects $Con$ and $Inf$, defined in Section 4, are not estimable from social network data using the methods that we propose below. Instead we can define new contagion and infectiousness effects such that hypothesis tests based on the new effects are valid and consistent tests of the hypotheses that $Con$ and $Inf$ are null. We give assumptions under which the new estimands are estimable from network data using GLMs and we demonstrate that tests of the hypotheses for the new estimands are valid and consistent for $Con$ and $Inf$.

5.1 Assumptions

Along with assumptions [1] - [4], we make several additional assumptions that facilitate inference using social network data. Define $A_i = \{j : i$ and $j$ share a tie$\}$ to be the collection
of indices for individual \( i \)'s contacts. We assume that

\[
Y^t_i \perp Y^r_j \bigg| \left\{ \sum_{m \in A_i : V_m = v} Y^t_{m-b}, v = 0, 1 \right\}, \text{ for all } j \notin A_i \text{ and } r \leq t. \tag{11}
\]

The set in the conditioning event includes the number of vaccinated contacts of individual \( i \) who were sick on or before day \( t-b \) and the number of unvaccinated contacts of individual \( i \) who were sick on or before day \( t-b \). This assumption says that the outcome of individual \( i \) at time \( t \) is independent of all past outcomes for non-contacts of \( i \), conditional on a summary measure of the flu history of the contacts of \( i \). In other words, contacts act as a causal barrier between two nodes who do not themselves share a tie. If two individuals, \( i \) and \( j \), do not share a tie, then they can have no effect on one another’s disease status that is not through their contacts’ disease statuses. Because \( t-b \) is the latest time at which a disease transmission could affect \( Y^t_i \), we do not need to condition on the contacts’ outcomes past that time. This assumption implies that the total number of vaccinated and unvaccinated contacts of individual \( i \) who have been sick by day \( t-b \) are a sufficient summary measure of the complete history of all of \( i \)'s contacts. It could easily be modified so that the probability of being infected at any given time depends on a different summary measure, for example on the proportion of alters who were infectious at or before time \( t-b \).

We also assume that

\[
Y^t_i \perp V_j \bigg| \left\{ \sum_{m \in A_i : V_m = v} Y^t_{m-b}, v = 0, 1 \right\}, \text{ for all } j \notin A_i \tag{12}
\]

and that, for any covariate \( C \) that is required for (11) through (14) to hold,

\[
Y^t_i \perp C_j \bigg| \left\{ \sum_{m \in A_i : V_m = v} Y^t_{m-b}, v = 0, 1 \right\}, \text{ for all } j \notin A_i. \tag{13}
\]

These assumptions state that any effect of the covariates (including vaccination) of nodes without ties to \( i \) on \( i \)'s disease status would again have to be mediated by the disease statuses of \( i \)'s contacts. Assumption (12) implies that the infectiousness effect is not transitive: whether individual \( j \) caught the flu from a vaccinated or unvaccinated person has no influence on whether individual \( j \) transmits the flu.

Embedded in assumptions (11)-(13) is the assumption that all ties are equivalent and all non-ties are equivalent with respect to transmission of the outcome. This is likely to be a simplification of reality. It can be relaxed (see Section 5.3), but we make it now for heuristic purposes. It rules out the possibility that some types of ties, like roommates, are more likely to facilitate disease transmission than others, like friends who live in different dorms. It allows
an individual to come into contact with and possibly infect (or be infected by) people with
whom he does not share a tie, but it entails that he will come into contact with any individual
in the network who is not his contact with equal probability. This rules out, for example, the
possibility that an individual is more likely to be infected by the friends of his friends than by
a distant node on the network.

We also make the no-unmeasured-confounding assumption that, if there exists a person
with whom two individuals in the network interact regularly, then that person is also in the
network (with ties to both individuals). In some settings it may be possible to satisfy this
condition, e.g. in full sociometric studies conducted de novo, or in studies of online data.

5.2 Estimation and hypothesis testing

Consider the following strategy for estimating a new contagion and new infectiousness effect,
defined below:

1. Randomly select from the network \(K\) pairs of nodes such that the two nodes in each
   pair share a tie, but, for each pair, neither node nor any of their contacts has a tie to a
   node in any other pair or to the contacts of any member of any other pair. The number
   of possible such pairs will depend on the network size and topology. In the next section,
   we discuss methods for sampling these pairs. Randomly select one member of each pair
to be the ego and one to be the alter.

2. Index the pairs by \(k\), and let \(e_k\) index the ego and \(a_k\) the alter in the \(k^{th}\) pair. For
   the \(k^{th}\) pair, define a group, also indexed by \(k\), that includes nodes \(a_k, e_k, A_{e_k},\) and
   \(A_{a_k}\). That is, it includes the alter-ego pair and all nodes with ties to either the alter or
   the ego. Due to the way we selected pairs, none of the members of group \(k\) can belong
to any other group. Below, we suppress the index \(k\) when context allows. As in the
sections above, \(T_k\) is the time of the first infection in the pair \((a_k, e_k)\). Let \(C_k\) be a
collection of covariates for group \(k\), where the variables included in \(C\) are precisely those
required for assumptions \(\mathcal{H}\) through \(\mathcal{H}_4\) to hold for outcome \(Y_e^{T(1)+b}\), mediator \(Y_d^{T(1)}\),
and treatment \(V_a\). Note that \(V_e\) should be included in \(C\) as it is likely to be a confounder
of the mediator - outcome relationship. The number of mutual contacts of the alter and
ego who were sick by time \(T - b\) must also be included.

3. Let \(U_{e_k}^{T_k+f}\) and \(L_{e_k}^{T_k+f}\) be the number of unvaccinated and vaccinated nodes, respectively,
with ties to \(e_k\) who were sick by time \(T_k + f\). Define \(U_{a_k}^{T_k-b}\) and \(L_{a_k}^{T_k-b}\) similarly as the
number of unvaccinated and vaccinated nodes, respectively, with ties to \(a_k\) who were sick
by time \(T_k - b\). Recall that \(f\) is the infectiousness period and \(b\) the incubation period,
declared in Section 3.2.1.
4. Estimate an average modified contagion effect

\[ Con^* = \frac{E \left[ Y_e^{T(1)+s} (0, Y_a^{T(1)}(1)) \mid U_a^{T-b}, L_a^{T-b}, U_e^{T+f}, L_e^{T+f}, C \right]}{E \left[ Y_e^{T(0)+b} (0, Y_a^{T(0)}(0)) \mid U_a^{T-b}, L_a^{T-b}, U_e^{T+f}, L_e^{T+f}, C \right]} \]

and an average modified infectiousness effect

\[ Inf^* = \frac{E \left[ Y_e^{T(1)+s} (1, Y_a^{T(1)}(1)) \mid U_a^{T-b}, L_a^{T-b}, U_e^{T+f}, L_e^{T+f}, C \right]}{E \left[ Y_e^{T(1)+s} (0, Y_a^{T(1)}(1)) \mid U_a^{T-b}, L_a^{T-b}, U_e^{T+f}, L_e^{T+f}, C \right]} \]

and their standard errors.

Through Step 2, the procedure we described is nearly identical to the proposal in Section 4, the only difference being that groups are extracted from a network in Step 1 rather than being independently ascertained. Consideration for this sampling scheme becomes crucial when we estimate the parameters of GLMs like (5) and (6). The standard errors derived from these GLMs are consistent only if the residuals across groups are uncorrelated. The residuals are indeed uncorrelated for independent groups, but, in the network setting, they generally are not. However, the set of additional covariates introduced in Step 3 essentially blocks the flow of information between groups. Conditional on these additional covariates, the residuals are uncorrelated, even in the network setting (see next section for proof). Roughly, because \( U_{T_k}^{T} + f \) and \( L_{T_k}^{T} + f \) summarize the disease statuses of the ego’s contacts \( b \) days before the outcome \( Y_{e_k}^{T(1)+s} \) is assessed, conditioning on them ensures that the outcomes are uncorrelated across groups. Because \( U_{a_k}^{T-b} \) and \( L_{a_k}^{T-b} \) summarize the disease statuses of the alter’s contacts \( b \) days before the mediator \( Y_{a_k}^{T(1)} \) is assessed, conditioning on them ensures that mediators are uncorrelated across groups.

The effects defined in Step 4 differ from Con and Inf only in the conditioning set, but this changes slightly the causal effect being estimated. Conditioning on \( U_{T_k}^{T-b} \) and \( L_{T_k}^{T-b} \) is just like conditioning on an extra pair of confounders: these variables occur before the mediator and are independent of the treatment; therefore they can be considered to be pre-treatment covariates. On the other hand, \( U_{e_k}^{T+f} \) and \( L_{e_k}^{T+f} \) occur after the mediator and lie on a possible pathway from the mediator to the outcome. Conditioning on these variables has the effect of biasing \( Con^* \) and \( Inf^* \) towards the null relative to Con and Inf, because it blocks the path from \( Y_a^{T} \) to \( Y_e^{T+s} \) that operates when the alter infects a friend of the ego, who then infects the ego. However, conditioning on these variables leaves the direct path from \( Y_a^{T} \) to \( Y_e^{T+s} \) open, and this path operates whenever the alter infects the ego directly. Therefore, whenever Con and Inf are non-null so are \( Inf^* \) and \( Con^* \). Hypothesis tests using \( Con^* \) and \( Inf^* \) are conservative and consistent for hypothesis tests for Con and Inf. Similarly, tests that \( Con^* \) and \( Inf^* \) are less than the null value or are greater than the null value are also valid and
consistent for the analogous tests for Con and Inf, respectively.

5.2.1 Justification for the use of GLMs

Suppose that the models

\[ g(E \left[ Y_{ek}^{Tk+s} \mid V_{ak}, Y_{ak}^{Tk} = 1, U_{a}^{T-b}, L_{a}^{T-b}, U_{e}^{T+f}, L_{e}^{T+f}, C_k \right]) \]  

\[ = \beta_0 + \beta_1 V_{ak} + \beta_2 U_{a}^{T-b} + \beta_3 L_{a}^{T-b} + \beta_4 U_{e}^{T+f} + \beta_5 L_{e}^{T+f} + \beta_6 C_k \]  

(14)

and

\[ m(E \left[ Y_{ak}^{Tk} \mid V_{ak}, U_{a}^{T-b}, L_{a}^{T-b}, U_{e}^{T+f}, L_{e}^{T+f}, C_k \right]) \]  

\[ = \alpha_0 + \alpha_1 V_{ak} + \alpha_2 U_{a}^{Tk-b} + \alpha_3 L_{a}^{Tk-b} + \alpha_4 U_{e}^{Tk+f} + \alpha_5 L_{e}^{Tk+f} + \alpha_6 C_k \]  

(15)

are correctly specified for \( g() \), \( m() \) known link functions. For the effect on the ratio scale with a binary common outcome like the flu we would specify \( g() \) to be the log link and \( m() \) the logit link, like we did in Sections 3 and 4. We have only to prove that the residuals from model (14) are uncorrelated with one another and that the residuals from model (15) are uncorrelated with one another (Breslow, 1996; Gill, 2001).

Result 1 Let \( Res_{ak} = Y_{ak}^{Tk} - m^{-1} \left( \alpha_0 + \alpha_1 V_{ak} + \alpha_2 U_{a}^{Tk-b} + \alpha_3 L_{a}^{Tk-b} + \alpha_4 U_{e}^{Tk+f} + \alpha_5 L_{e}^{Tk+f} + \alpha_6 C_k \right) \).

Then \( Res_{ak} \) and \( Res_{ah} \) are uncorrelated.

Proof Without loss of generality assume that \( T_k > T_h \). Under correct specification of (15),

\[ E[Res_{ak}] = E[Res_{ah}] = 0. \]  

Therefore \( Cov(Res_{ak}, Res_{ah}) = E[Res_{ak}Res_{ah}] \). Letting \( S_k \) denote the set of variables \( \{V_{ak}, U_{a}^{Tk-b}, L_{a}^{Tk-b}, U_{e}^{Tk+f}, L_{e}^{Tk+f}, C_k\} \), we have

\[ E[Res_{ak}Res_{ah}] \]

\[ = E[E[Res_{ak}Res_{ah} \mid S_k, S_h]] \]

\[ = E[E \left[ \left\{ Y_{ak}^{Tk} - E \left[ Y_{ak}^{Tk} \mid S_k \right] \right\} \left\{ Y_{ah}^{Tk} - E \left[ Y_{ah}^{Tk} \mid S_h \right] \right\} \mid S_k, S_h \right]] \]

\[ = E \left[ E \left[ Y_{ak}^{Tk} - E \left[ Y_{ak}^{Tk} \mid S_k \right] \mid S_k, S_h \right] \times E \left[ Y_{ah}^{Tk} - E \left[ Y_{ah}^{Tk} \mid S_h \right] \mid S_k, S_h \right] \right] \]

\[ = E \left[ E \left[ Y_{ak}^{Tk} \mid S_k, S_h \right] - E \left[ Y_{ak}^{Tk} \mid S_k \right] \right] \times E \left[ Y_{ah}^{Tk} \mid S_h \right] \times E \left[ Y_{ah}^{Tk} \mid S_h \right] \]

\[ = E \left[ E \left[ Y_{ak}^{Tk} \mid S_k \right] - E \left[ Y_{ak}^{Tk} \mid S_k \right] \right] \times E \left[ Y_{ah}^{Tk} \mid S_h \right] \times E \left[ Y_{ah}^{Tk} \mid S_h \right] \]

\[ = 0. \]

The second equality follows from the correct specification of (15). The third equality holds because, by assumptions (11), (12), and (13), \( Y_{ak}^{Tk} \perp Y_{ah}^{Tk} \mid S_k, S_h \). The fifth inequality holds because \( Y_{ak}^{Tk} \perp S_h \mid S_k \), again by assumptions (11), (12), and (13).
Result 2 Let \( R_{\text{e}k} = Y_{\text{e}k}^{T_k+s} - g^{-1} \left( \beta_0 + \beta_1 V_{\text{a}k} + \beta_2 U_{\text{a}k}^{T_k-b} + \beta_3 U_{\text{e}k}^{T_k+f} + \beta_4 L_{\text{a}k}^{T_k-b} + \beta_5 L_{\text{e}k}^{T_k+f} + \beta_6 C_k \right) \).

Then \( R_{\text{a}k} \) and \( R_{\text{a}h} \) are uncorrelated.

The proof of Result 2 is very similar to the proof of Result 1 and we therefore omit it. It relies on the fact that, conditional on the fact that \( T + f = T + s - b \) and therefore conditioning on \( U_{\text{a}k}^{T_k+f} \) and \( L_{\text{e}k}^{T_k+f} \) satisfies the conditions of assumptions (11), (12), and (13) and renders \( Y_{\text{e}k}^{T_k+s} \) independent of outcomes, vaccines, and covariates for other groups.

5.2.2 Implementation

Step 1 is the most difficult to implement. One could enumerate all possible ways of partitioning the network into non-overlapping groups comprised of a pair of nodes and all of their contacts, associate the partitions with a discrete uniform distribution, and randomly sample one realization of the uniform distribution. Steps 2 and 3 of the testing procedure are perfunctory. If we define \( C^* = \left( U_{\text{a}}^{T-b}, L_{\text{a}}^{T-b}, U_{\text{e}}^{T+f}, L_{\text{e}}^{T+f}, C \right) \) to be a new collection of covariates then step 4 proceeds as in Sections 3 and 4. Interactions between components of \( C^* \) and the other predictors in the model can easily be accommodated. To test the hypotheses that \( \text{Con} \) and \( \text{Inf} \) are null, we estimate 95% confidence intervals for the modified contagion and infectiousness estimands (\( \text{Con}^* \) and \( \text{Inf}^* \)) based on the estimates and standard errors calculated in Step 4. We reject the hypothesis that \( \text{Con} \) is null if our confidence interval for the estimand in \( \text{Con}^* \) does not include the null value and we reject the hypothesis that \( \text{Inf} \) is null if our confidence interval for the estimand in \( \text{Inf}^* \) does not include the null value.

5.3 Relaxing some assumptions

We assumed throughout that vaccination occurs before the start of follow-up, but this is not necessary for our methods. If vaccination can occur during follow-up, define \( V_t^i \) to be an indicator of having been vaccinated by time \( t \). Assume that the effect of vaccination, including any infectiousness effect, is immediate. If an individual becomes infectious on day \( T \), he would have been infected on day \( T-b \). If he was vaccinated by time \( T-b \), then the vaccine would have been in full effect at the time of infection. Then \( V_{\text{a}}^{T-b} \) can replace \( V_{\text{a}} \) as the “treatment” in the contagion, infectiousness, and indirect effects. We similarly redefine the summary measures for vaccinated and unvaccinated contacts of the alter and ego that appear in assumptions (11) through (13) and that are included in \( C \). Include \( V_{\text{e}}^{T-b} \) in the set of confounders because the mediator occurs at time \( T \) and therefore the ego’s vaccination status at time \( T-b \) suffices to control for any confounding.

We assumed throughout that the infectious and incubation periods (\( f \) and \( b \)) are constant across individuals. These assumptions, along with the assumption that the effect of vaccination is immediate, could be relaxed if the determinants of time to efficacy of vaccine, length of infectious period, and length of incubation period were observed covariates. In this case we
could, for example, infer effective time of vaccination, incubation period, and infectious period for each individual based on their covariates.

We assumed in Section 5.2 that the probability of disease transmission between two connected nodes does not depend on the type of tie. This assumption can be avoided with the addition of several covariates to models (14) and (15): we would condition on the type of tie that exists between the alter and the ego, and also include separate $U$ and $L$ terms for each type of tie. We also assumed in Section 5.2 that an individual will come into contact with any individual in the network who is not his contact with equal probability. This can be relaxed by expanding the $k$ groups we define in Step 1 of the estimation procedure to include nodes within several degrees of separation from the alter and ego.

6 Simulations

6.1 Independent groups

We ran simulations for three different sample sizes, $K = 200$, $K = 500$, and $K = 1000$ independent groups. Each group comprised an alter, an ego, and $n_k$ mutual contacts. First we generated $K$ contact group sizes $n_k$ by sampling from a Poisson distribution with mean $\lambda = 3$. Next, we assigned vaccination statuses to each individual in each group, including the alters and egos, with probability $0.4$. We simulated the behavior of each group during a flu epidemic over 100 days. For the purposes of the simulation, we assumed that each member of a group had contact with all other members of the same group. Each day, an uninfected member of a group had a baseline probability of $p_o$ of being infected from outside of the group, a baseline probability of $p_u$ of being infected by any infectious, unvaccinated member of the same group and a baseline probability of $p_v$ of being infected by any infectious, vaccinated member of the same group. If vaccinated, an individual’s probability of being infected by any source was multiplied by $\delta \leq 1$. If infected on day $t$, an individual was infectious from day $t + 1$ through day $t + 4$ and incapable of being infected or transmitting infection from day $t + 5$ until the end of follow-up. This corresponds to an incubation period of $b = 1$ and an infectious period of $f = 3$, and it mimics the flu, for which the incubation period is between one and three days and the infectious period is between three and six days (Earn et al., 2002).

In all simulations, we fixed $p_o = 0.01$. We specified two different simulation settings for the parameters $\delta$, $p_v$, and $p_u$, one setting corresponding to the null of no infectiousness or contagion effects ($\delta = 1; p_v = p_u = 0.4$) and one setting corresponding to the presence of protective contagion and infectiousness effects ($\delta = 0.1; p_v = 0.5, p_u = 0.05$). We simulated 500 epidemics each under of the two scenarios, and for each simulation we estimated the infectiousness and contagion effects as follows: Among the subset of groups with $Y_a^T = 1$ and using a log-linear link function, we regressed $Y_e^{T+s}$ on $V_a$ and on the set of potential
Table 1: Simulation results for independent groups

| Number of groups | Infectiousness (SE) | Coverage | Contagion (SE) | Coverage |
|------------------|---------------------|----------|----------------|----------|
| K = 200          | 1.014 (0.138)       | 94%      | 1.016 (0.202)  | 94%      |
| K = 500          | 1.001 (0.082)       | 92.2%    | 0.997 (0.117)  | 93.6%    |
| K = 1000         | 0.997 (0.057)       | 95%      | 1.001 (0.083)  | 94%      |

| Number of groups | Infectiousness (SE) | Power   | Contagion (SE) | Power   |
|------------------|---------------------|---------|----------------|---------|
| K = 200          | 0.453 (1.160)       | 49%     | 0.258 (0.079)  | 100%    |
| K = 500          | 0.443 (0.154)       | 86%     | 0.255 (0.049)  | 100%    |
| K = 1000         | 0.445 (0.107)       | 100%    | 0.258 (0.034)  | 100%    |

Confounders comprised by the ego’s vaccination status, the sum $U_{Ta}^{T-b}$ of unvaccinated mutual contacts who were infectious at time $T-b$, and the sum $L_{Ta}^{T-b}$ of vaccinated mutual contacts who were infectious at time $T-b$. We regressed $Y_{Ta}^T$ on the same covariates using a logistic link function. The contagion and infectiousness effects are identified by the expressions given in (7) and (8), evaluated at the sample mean value of the covariates $U_{Ta}^{T-b}$ and $L_{Ta}^{T-b}$. We bootstrapped the standard errors with 500 bootstrap replications.

The results are given in Table 1. For each simulation setting, that is, for each sample size ($K$) and for both the null hypothesis and the alternative hypothesis, we present the mean point estimates for the infectiousness and contagion effects on the ratio scale, the mean bootstrap standard error estimator, and the percent coverage of the 95% confidence interval based on the 2.5th and 97.5th bootstrap quantiles. For simulations under the null hypothesis, we report coverage and for simulations under the alternative we report power, given by 100% minus the percent coverage. The point estimates are stable across sample sizes and the coverage of the basic bootstrap confidence interval is close to 95% under the null for all $K$. The power under the alternative is 100% for the contagion effect, but for the infectiousness effect power is low (49%) when $K = 200$.

6.2 Social network data

The procedure proposed in Section 5.2 for hypothesis testing using social network data suffers from low power. In part this is because $Con^*$ and $Inf^*$ are biased towards the null relative to $Con$ and $Inf$, but the primary reason for the loss of power is the extraction of conditionally independent pairs of nodes from the network. As the simulation illustrates, this results in a dramatic reduction in the sample size used for analysis. Because infectious outcomes sampled from nodes in a network are dependent, the effective sample size for inference about such outcomes will always be smaller than the observed number of nodes, and how much more infor-
information about the parameters of interest is available depends on the specific setting. Important areas for future research include determining the effective sample size when observations are sampled from a network and are therefore dependent, and developing methods that make use of all available information.

We ran simulations for three different network sizes: 12000 nodes, 10000 nodes, and 8000 nodes. We simulated a network of 10000 nodes as follows: first, we simulated 2000 independent groups of 5 nodes, with each group being fully connected (i.e. there are ties between each pair of nodes in the group of 5). For each node we then added a tie to each out-of-group node with probability 0.0001. Because ties are undirected (if node $i$ is tied to node $j$, then by definition node $j$ is tied node $i$), this results in approximately 2 expected out-of-group ties per node. To simulate networks of size 12000 and 8000, we simulated 2400 and 1600 independent groups, respectively, and scaled the probability of an out-of-group tie to maintain an expected value of approximately 2 for each node. This network structure could represent a sample of families living in a city, where individuals are fully connected to the members of their family and occasionally connected to members of other families. After running step 1 of the procedure outlined in Section 5.2, we were left with $K = 707$ alter-ego pairs for the network of size 12000, $K = 581$ for the network of size 10000, and $K = 466$ for the network of size 8000.

On each of these three fixed networks, we simulated 200 epidemics under the null of no infectiousness or contagion effect and 200 epidemics under the alternative. For each simulation, we assigned vaccination statuses to each individual in the network with probability 0.5. We then simulated the behavior of each group during a flu epidemic over 100 days. An uninfected node had a probability of $p_o = 0.01$ of being infected from outside of the network on day 1 and there were no outside infections thereafter. Under the alternative, on each day an uninfected node had a baseline probability of $p_a = 0.5$ of being infected by any infectious, unvaccinated contact and group and a baseline probability of $p_v = 0.01$ of being infected by any infectious, vaccinated contact. If vaccinated, an individual’s probability of being infected by any source was multiplied by $\delta = 0.2$. Under the null, on each day an uninfected node had a probability of $p_u = p_v = 0.5$ of being infected by any infectious contact (that is, node with which it shared a tie). To ensure that the contagion effect was null, we specified that $\delta = 1$, that is, that vaccination had no protective effect against contracting the flu. In both settings, if infected on day $t$ an individual was infectious from day $t + 1$ through day $t + 4$ and incapable of being infected or transmitting infection from day $t + 5$ until the end of follow-up.

For each simulation, we estimated the infectiousness and contagion effects following the procedure described in Section 5.2. We evaluated these effects at the sample mean value of the covariates $U_a^{T-b}$, $I_a^{T-b}$, $U_e^{T+f}$ and $L_e^{T+f}$. We bootstrapped the standard errors with 1000 bootstrap replications. The results are given in Table 2. For each simulation setting, that is for each network size and for both the null hypothesis and the alternative hypothesis, we present the mean point estimates for the infectiousness and contagion effects on the ratio
Table 2: Simulation results for network data

| Network size | Infectiousness (SE) | Coverage | Contagion (SE) | Coverage |
|--------------|---------------------|----------|---------------|----------|
| 8000 nodes   | 0.996 (0.001)       | 100%     | 1.205 (1.657) | 96%      |
| 10000 nodes  | 1.000 (0.001)       | 100%     | 1.183 (1.183) | 94%      |
| 12000 nodes  | 1.001 (0.001)       | 100%     | 1.166 (0.)    | 94%      |

| Network size | Infectiousness (SE) | Power  | Contagion (SE) | Power |
|--------------|---------------------|--------|---------------|-------|
| 8000 nodes   | 0.650 (0.259)       | 45%    | 0.168 (0.017) | 99%   |
| 10000 nodes  | 0.616 (0.072)       | 53%    | 0.164 (0.013) | 100%  |
| 12000 nodes  | 0.609 (0.054)       | 63%    | 0.164 (0.010) | 100%  |

scale, the mean bootstrap standard error estimator, and the percent coverage of the 95% confidence interval based on the 2.5th and 97.5th bootstrap quantiles. For simulations under the alternative hypothesis we calculated the power, given by 100% minus the percent coverage. For the 8000- and 10000-node networks, there were 6 and 1 simulations, respectively, out of 200, for which the GLMs used to estimate the parameters involved in the contagion and infectiousness effects did not converge due to empty strata of the predictors. We omit these simulations from the results in Table 2, but note that in a extreme cases convergence could be an issue in addition to power.

The point estimates are stable across network sizes and the coverage of the basic bootstrap confidence interval is close to or above 95% under the null for all network sizes. The power under the alternative is close to 100% for the contagion effect for all network sizes, but for the infectiousness effect power is low: 45% for the network of size 8000, increasing to 63% for the network of size 12000.

One concern that has been raised about previous uses of statistical models like GLMs and GEEs for network data is the possibility that the models lack any power to reject the null hypothesis when the alternative is true (Shalizi, 2012). This is a concern because the models are inherently misspecified under the alternative hypothesis, even if they are correctly specified under the null hypothesis. Because the methods we propose here can be correctly specified under both the null and the alternative hypotheses, they can be powered to reject the null hypothesis when the infectiousness or contagion effect is present.

7 Discussion

We proposed methods for consistently estimating contagion and infectiousness effects in independent groups of arbitrary size; these methods are easy to implement and perform well
in simulations. We extended our methodology to groups sampled from social network data, providing a theoretically justified method for using GLMs to analyze network data. Note that the principles we applied to GLMs can be applied to GEEs as well, resulting in correctly specified GEEs for network data. The principles that justify our use of GLMs to estimate the contagion and infectiousness effects are easily extended to any estimand for which GLMs would be a desirable modeling tool. However, our network data methods require a large amount of data and are not appropriate for small or dense networks. On the one hand this highlights the fact that dependence among observations in networks reduces effective sample size and necessitates larger samples; on the other hand methods should be developed that can harness more information from the data and increase the power to detect contagion, infectiousness, and other causal effects.

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