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Stochastic effects on endemic infection levels of disseminating versus local contacts

James S. Koopman [a,e,*], Stephen E. Chick [b,e], Carl P. Simon [c,e], Christopher S. Riolo [a], Geoffrey Jacquez [d]

[a] *Department of Epidemiology, University of Michigan, SPH-1, 109 Observatory Street, Ann Arbor, MI 48109-2029, USA*

[b] *Department of Industrial and Operations Engineering, University of Michigan, SPH-1, 109 Observatory Street, Ann Arbor, MI 48109-2029, USA*

[c] *Departments of Mathematics, Economics, and Public Policy, University of Michigan, SPH-1, 109 Observatory Street, Ann Arbor, MI 48109-2029, USA*

[d] *BioMedware Inc., Ann Arbor, MI 48104, USA*

[e] *Center for the Study of Complex Systems, University of Michigan, SPH-1, 109 Observatory Street, Ann Arbor, MI 48109-2029, USA*

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Abstract

The effects of two levels of mixing on endemic infection levels are shown to differ for identically conformed deterministic compartmental (DC) and stochastic compartmental (SC) models. Both DC and SC models give similar endemic levels when populations are large, immunity is short lived, and mixing is universal. But local transmissions and/or transient immunity decrease overall population infection levels in SC but not in DC models. DC models also fail to detect the greater effects of eliminating disseminating transmissions in comparison to eliminating local transmissions shown by SC models. These differences in model behavior arise because localities that encounter few infections from distant sites and that have stochastically low infection levels have decreased infection rates while localities with stochastically high levels of infection do not decrease the rate at which they lose infection. At the extreme this generates local stochastic die out with subsequent build up of susceptibility in SC but not DC models. This phenomenon should act upon all endemic infections that have changing geographic or social foci of infection. Neither standard epidemiological investigations nor sufficient-component cause models can capture these effects because they occur in the absence of differences between individuals.

* Corresponding author. Address: Department of Epidemiology, University of Michigan, SPH-1, 109 Observatory Street, Ann Arbor, MI 48109-2029, USA. Tel.: +1-734 763 5629; fax: +1-734 764 3192.

E-mail address: jkoopman@umich.edu (J.S. Koopman).

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1. Introduction

The network structure and the temporal patterns of contact between individuals through which infection spreads in a population are powerful determinants of infection levels in communities. Most analyses of the effects of contact patterns employ deterministic compartmental (DC) models, formulated using ordinary differential equations, to address the effects of varying contact patterns between individuals with different risk characteristics [1–26]. A quite separate type of contact pattern effect arises, however, in stochastic models where individuals mix at two levels, locally and at a distance. The potential for stochastic effects given multiple levels of mixing has long been discussed [27].

Stochastic models with discrete individuals having different risk characteristics are likely to exhibit both types of effect. Distinguishing these effects should help with both model design and model analysis. One way to separate them is to eliminate contact pattern effects due to risk characteristics by making all individuals identical. Watts has analyzed models where all individuals have the same risk factors but different levels of mixing exist [28,29]. But in these models, the individuals can differ in their relationships to all other individuals. Ball et al. have examined SIR models where all individuals not only have identical risk characteristics but have identical distributions of contacts as a function of distance from other individuals as well [30]. Analysis of their models provides mathematical insights into stochastic effects arising from two levels of mixing.

In order to further clarify the differences between these two different sources of contact pattern effects and in order to illustrate situations where these effects are likely to be of great importance, this paper examines models in which immunity is non-existent or short lived and in which all individuals have both identical risk factors and identical relationships to all other individuals. We show that DC models do not capture the effects of local versus disseminating transmissions. We demonstrate how important stochastic effects arising from two-level mixing can be for such endemic infections. And we analyze models that provide insights into the mechanism of stochastic effects from two levels of mixing.

The paper is organized as follows: Section 2 presents the epidemiological motivation for our analysis as well as the strategy we use to collapse spatial dimensions. Section 3 presents the simplest model where stochastic effects from two levels of mixing can alter infection levels. The stochastic compartmental (SC) version of this model is numerically solved to demonstrate the equilibrium distributions of time spent in different model states. Section 4 elaborates the model in two ways that increase stochastic spatial effects. We add identical groups to increase spatial distances and a transient immune state. We carry out simulation analyses to demonstrate the effects on mean equilibrium infection levels and to show the failure of DC models to capture these effects. Section 5 interprets the results and evaluates their impact on epidemiological analyses and on infection control decisions.

2. Motivation and strategy

Our work is motivated by decisions regarding the design of surveillance systems for gonorrhea, the choice of vaccine trial designs to detect vaccine effects on the transmission of non-typeable Haemophilus influenzae (NTHi), and the decision to institute expensive new water treatment processes to control endemic Cryptosporidium infection. We believe that the stochastic effects examined in this paper are important in all of these situations, as well as in any other situation where some localities are temporarily free of infection while infection remains endemically present in the larger population.

Rather than model any of the above infections in detail, we analyze highly abstract systems that highlight the mechanisms behind the phenomena of interest. Our models assume that every individual is identical with regard to susceptibility, contagiousness, contact rate, and location within the contact network. To make locations in the contact network identical, we make the contact structure symmetrical around each population segment or individual. We collapse all spatial dimensions defining contact patterns into two categories: 'local' and 'disseminating'. Local contacts are made only with nearby neighbors and disseminating contacts are made in locations where everyone is affected. Our models use simple and identical histories of infection and immunity for everyone. We first use an SIS model that represents the simplest situation that can capture the phenomenon on which we focus; later, we examine an SIRS model that can also describe some of the factors affecting the strength of that effect. We use two compartments for infection and immunity in our SIRS model because the work of Keeling and Grenfell [31] shows that the unrealistically long tails of simple exponential models affect the persistence of infection in a population.

3. A two-group SIS model

The simplest possible model with local and disseminating contacts is a two-group SIS model. Fig. 1 gives a graphical presentation of where mixing takes place between the two groups. The use of mixing sites here conforms to the preferred mixing formulation [1]. Preferred mixing is a special case of structured mixing [3]. Each group mixes at one site where they mix only with individuals from their own site and at a second site where they mix equally with members of both groups.

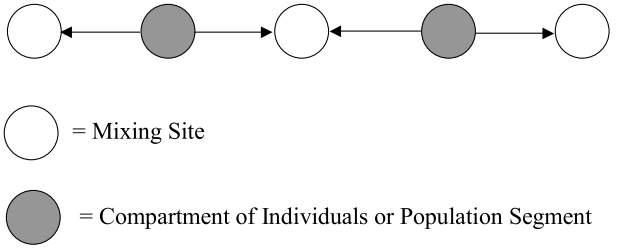

Fig. 1. Arrangement of groups and mixing sites examined in the SIS transmission system model.

3.1. The differential equation case

The differential equations for the model are

$$\begin{aligned}
\frac{dI_1}{dt} &= -\rho I_1 + c\beta S_1\left[f\frac{I_1}{N_1} + (1-f)\frac{I_1+I_2}{N_1+N_2}\right],\\
\frac{dI_2}{dt} &= -\rho I_2 + c\beta S_2\left[f\frac{I_2}{N_2} + (1-f)\frac{I_1+I_2}{N_1+N_2}\right],\\
S_1 &= N_1 - I_1,\\
S_2 &= N_2 - I_2,\\
N_1 &= N_2,
\end{aligned} \tag{1}$$

where I_i is the number of infected individuals in group i, S_i is the number of susceptible individuals in group i, N_i is the size of the population in group i, ρ is the recovery rate from infection, c is the rate at which individuals make contact, β is the probability of transmission given contact between an infected and susceptible individual, and f is the fraction of contacts reserved for one's own group. The first term in the square brackets in (1) is contact at the site reserved for a single group and the second term is contact at the common site where individuals from both groups are encountered. The basic reproduction number (R_0) in this deterministic model is identical for both groups and equals $c\beta/\rho$. The endemic level of infection for both groups is $1-(1/R_0)$. This equilibrium level does not change as one changes f, the fraction of contacts reserved for one's own group.

We will prove the statements of the last two sentences in the more general context of structured mixing [3]. Structured mixing was defined to model contacts made in a number of different social and geographic settings or 'activity groups'. Let f_{is} denote the fraction of subgroup is contacts that are made in setting s: $1 \leqslant i \leqslant v$, $1 \leqslant s \leqslant M$, $\sum_s f_{is} = 1$. We assume that the mixing within setting s is proportionate mixing, i.e., in setting s the fraction of contacts that a person in subpopulation i makes with individuals in subpopulation j is

$$\frac{f_{js}c_jN_j}{\sum f_{ps}c_pN_p},$$

where c_p is subgroup p's overall contact rate and N_p is the number of individuals in subgroup p. The transmission dynamics for the SIRS system structured mixing corresponding to Eq. (1) are given by system (A.1)–(A.3) in Appendix A.

Theorem 1. *Consider a population with subgroups that follow a structured mixing rule. Let f_{is} denote the fraction of individuals in subgroup i that interact in mixing site s. Suppose that the mixing in each mixing site is proportionate mixing. Suppose that the individuals have the same contact rate c and the same probability β of infection transmission given a contact. Then,*

1. *The basic reproduction number is $R_0 = c\beta D$ where $D = 1/\rho$ is the average length of an infection. If $R_0 \leqslant 1$, the no-disease equilibrium is globally asymptotically stable. If $R_0 > 1$, there is a unique endemic equilibrium and it is globally asymptotically stable.*
2. *If $R_0 > 1$, the fraction of infected individuals in each subgroup at the endemic equilibrium equals $1-(1/R_0)$.*

Notice that the results in Theorem 1 are independent of the f_{is}s, i.e. of the contact structure. Thus, this theorem is broader than the situation we have defined in the model examined in Eq. (1). The theorem is proven in Appendix A with specific reference to the SIRS model that will be examined later.

3.2. The stochastic compartmental model case

The analogous SC model has a similar structure, except that the number of infected individuals takes on discrete rather than continuous values [9,32,33]. A state of the SC model is described by the numbers (I_1, I_2) of infected individuals in group 1 and group 2. The flows between these states are depicted in Fig. 2. The labels on the arcs indicate the rate that a given transition will occur. In state (I_1, I_2), for example, a recovery in subgroup 1 occurs at rate ρI_1, and the rate that someone in

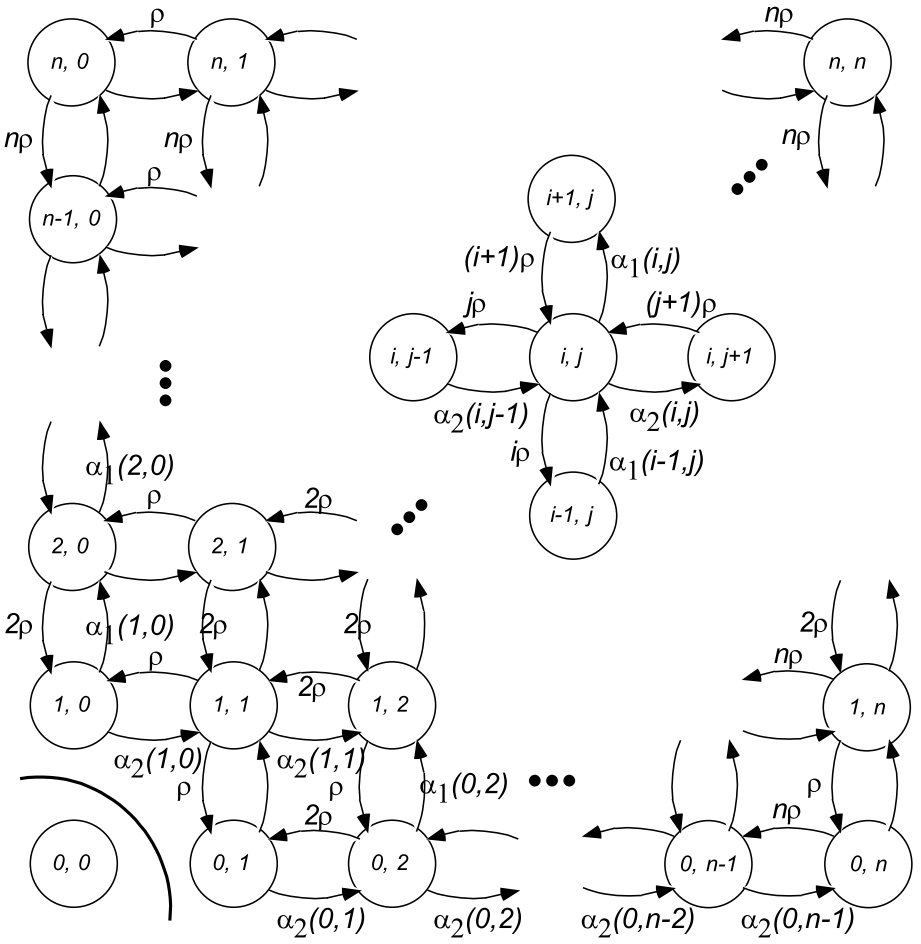

Fig. 2. Flows between states for the SIS SC model.

subpopulation 1 becomes infected is $\alpha_1(I_1, I_2)$. This latter rate is the sum of rates occurring at the two mixing sites. It is formulated as follows:

$$\alpha_1(I_1, I_2) = c\beta S_1 \left[f \frac{I_1}{N_1 - 1} + (1 - f) \frac{I_1 + I_2}{N_1 + N_2 - 1} \right],$$

where $N_1 = S_1 + I_1$ and $N_2 = S_2 + I_2$. The corresponding infection rate in the second subgroup is

$$\alpha_2(I_1, I_2) = c\beta S_2 \left[f \frac{I_2}{N_2 - 1} + (1 - f) \frac{I_1 + I_2}{N_1 + N_2 - 1} \right].$$

The model in Fig. 2 precludes the possibility that infection leaves the population by setting transitions from the (0,1) and (1,0) states to the (0,0) states to zero. Otherwise the (0,0) state would be an absorbing state representing the only stable equilibrium. Removing arcs to the absorbing state is one stochastic analog for studying endemic behavior. The other is the quasi-stationary model [34–36], which includes the arcs to the absorbing state but conditions on non-absorption. Although these two approaches can give somewhat different results if the populations are particularly small, the difference is small in comparison with the other differences explored in this paper, and is negligible in numerical experiments with $N_1 = N_2 = 100$ individuals. For a complete discussion, see Nåsell [35,36] and the references therein.

The endemic fraction for the SC model was determined in three steps:

(a) numerically determining the distribution of the number infected in each subpopulation by implementing the Chapman–Kolmogorov forward equations [37] in Berkeley Madonna [38] to describe the dynamics of the probability of being in each state,
(b) simulating until stationarity is reached, then
(c) computing the expected fraction of infected individuals, taking the expectation over the stationary distribution.

Results with $c = 2$, $\beta = 1$, $\rho = 1$ for different population sizes and different fractions reserved for their own group are presented in Table 1 and compared to the DC results (that always correspond to an infinite size population if individuals are considered to be indivisible). These results demonstrate that even in this situation, which minimizes the effects we wish to illustrate, the effects are important when population sizes are small or the fraction mixing locally is large.

Table 1
Fraction of the population infected at endemic equilibrium for the ODE and SC models given different fractions of contacts that are made at local settings and different population sizes for the SC model

Size of each subgroup	Fraction of contacts made at local settings				
	0.0	0.25	0.50	0.75	0.90
DC (infinite size)	0.500	0.500	0.500	0.500	0.500
SC 10	0.460	0.458	0.451	0.432	0.391
SC 20	0.483	0.483	0.481	0.473	0.462
SC 50	0.495	0.494	0.493	0.492	0.490

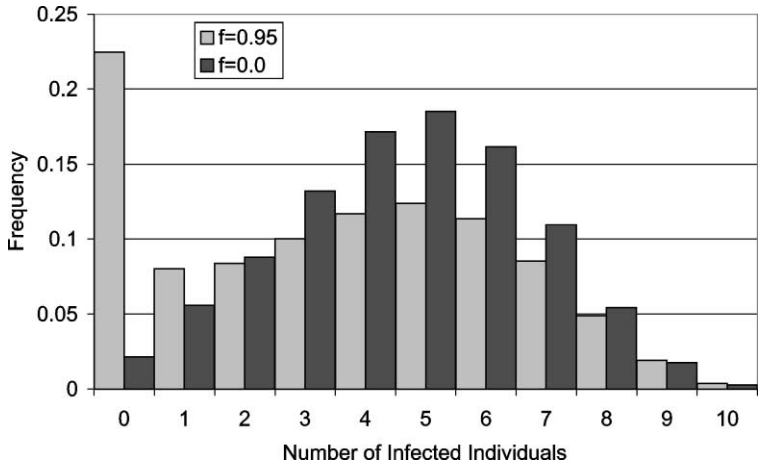

Fig. 3. Marginal distributions of infected individuals at endemic equilibrium for groups of size 10 in the two-group SIS model given no local mixing ($f = 0$) and 95% of mixing at local sites.

To help understand how this effect arises, we examine in Fig. 3 the marginal distributions for the number of infected individuals at endemic equilibrium for the identical and symmetric groups of size 10. We present these both given no local mixing and also with 95% of mixing occurring at the local site. Here we see that when there is no local mixing the distribution is unimodal, while given predominately local mixing there is a second peak at the zero level. The difference is due to the amount of time that the system can remain in the state in which no one is infected in one subgroup or the other. Given that all mixing takes place at the common site, susceptible individuals in a subgroup with no infected individuals come into contact with infected individuals in the other subgroup 20 times more frequently then in the case where only 5% of the mixing takes place in the common site. Therefore, at comparable infection levels in the population, the transition rates from $(0, I_2)$ to $(1, I_2)$ or from $(I_1, 0)$ to $(I_1, 1)$ are 20 times greater given no local mixing than given 95% local mixing. On the other hand, the transition rates from $(1, I_2)$ into $(0, I_2)$ or from $(I_1, 1)$ into $(I_1, 0)$ will be identical whether mixing is local or not because those flows only depend upon the transition rate from infected to susceptible, which in both cases equals ρ. To compensate for the differences in rates, the number of individuals in the $(0, I_2)$ or $(I_1, 0)$ states have to be 20 times higher in the case with 95% local mixing.

The same logic applies to the flows from $(1, I_1)$ into $(2, I_1)$ and from $(I_2, 1)$ into $(I_2, 2)$. The flows associated with a recovery will be equal under any mixing pattern. However, the flows associated with infection arising from local mixing will be lower than the corresponding flows arising from mixing at the common site. At the common site, there will be encounters with individuals in the other group, who on average have higher levels of infection.

At the other end of the scale where on average one group has an endemic prevalence higher than the mean, individuals in the high infection group are more likely to become infected as the fraction of local mixing increases. For, since the other group has a lower average prevalence of infection, mixing with that group increases the chance of encountering a susceptible instead of an infected individual. At the high end of the infection level in Fig. 3, the situation with 95% local

mixing has a higher frequency of states with high numbers of infection. That is due to the flow to even higher states increasing when contacts of susceptible individuals are mainly with the group that already has a high infection level. Given the stronger drive from high to higher and the weaker drive from low to higher in local mixing, the balance of infection frequency must lower the frequency of states that have the modal number of infected individuals.

4. A 100 group SIRS model

We now examine a slightly more complex model that allows us to demonstrate more clearly why local mixing decreases population infection rates and what conditions will enhance that effect. This model has 100 separate groups arranged in a circular pattern. Each group has local mixing not only in the site closest to them, but equally at the sites corresponding to their two nearest neighbors. There is also a central (disseminating) site where all groups can mix. The mixing structure is illustrated in Fig. 4 (with a smaller number of groups).

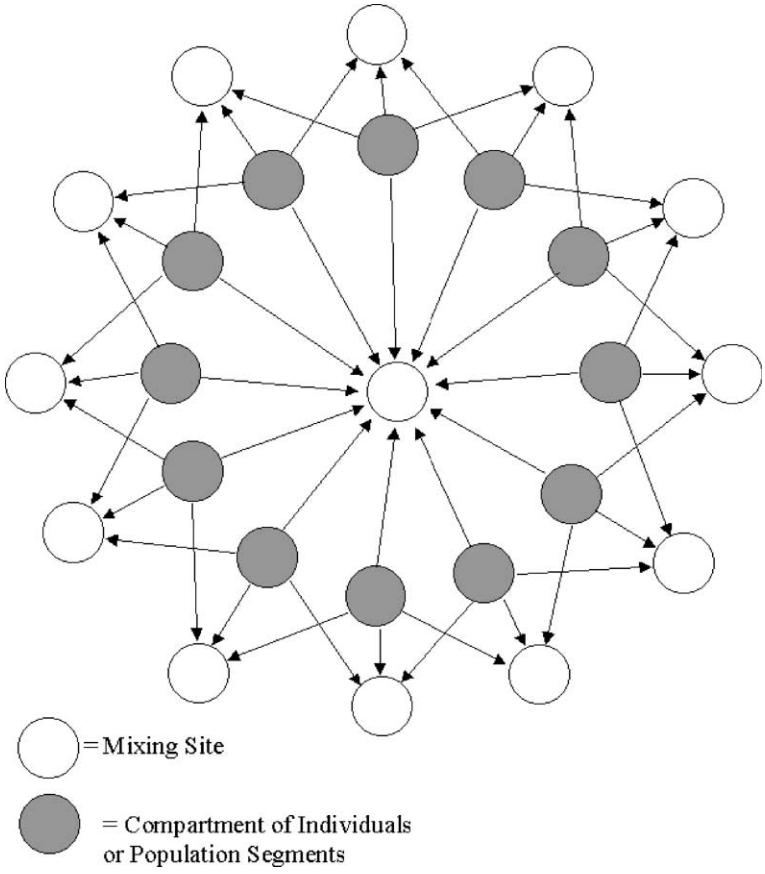

Fig. 4. Contact structure in the models with 100 groups and an SIRS pattern of infection.

We now include an additional state with complete immunity in the natural history of infection. We linked two sequential infection states and two sequential immune states so that the distributions of durations in each state had an Erlang distribution with shape parameter 2. We examined situations where the flow rates out of the immune state were equal to or twice as great as the flow rates out of the infected state.

4.1. The differential equation case

The differential equations for this system are presented in Appendix B. They were numerically solved using the Runge-Kutta 4 method on the Berkeley Madonna software [38].

Consistent with Theorem 1, we find that the DC model generates a prevalence of infection at equilibrium equal to $1 - 1/R_0$, independent of the values of f. In this case as before, $R_0 = c\beta/\rho$ is identical for all subgroups because they all have identical parameter values.

From a public health point of view, it is important to know whether interventions should concentrate on the local sites or on the disseminating site. In particular, we consider the decision to reduce to zero the transmission probabilities of contacts made at either local sites or at common sites in order to assess whether there is a greater effect from eliminating transmission from an equal number of contacts made at the different sites. Theorem 2 states that in the deterministic DC model, it makes no difference whether one intervenes in the local neighborhoods or at the common site. Its proof is presented in Appendix A.

Theorem 2. *Consider again populations where subpopulations follow a structured mixing rule. Let f_{is} denote the fraction of individuals in subgroup i that interact in mixing site s. Suppose that the mixing in each mixing site is proportionate mixing. Suppose that the individuals have the same contact rate c and the same probability β of infection transmission given a contact. Now suppose that there are two types of mixing sites, A_1 and A_2 – those A_1, as in Theorem 1, in which the probability of infection transmission given a contact is a positive constant β and others (A_2) for which $\beta = 0$, i.e. no transmission occurs. Let $f_i = \sum_{s \in A_2} f_{is}$ be the fraction of contacts made by individuals in subgroup i in a mixing site where no transmission occurs. If $f_i = f$ independently of i, then the conclusions of Theorem 1 are true if one replaces R_0 by $R_0(1 - f)$. In particular, the basic reproduction number and endemic levels are not aected by the choice of mixing sites for eliminating transmission.*

4.2. The stochastic compartmental model case

For the corresponding SC model, we put 12 individuals in each of 100 subgroups. Susceptible individuals change from the susceptible state to the infectious state upon effective contact with infected individuals. The duration of time in the infectious state before becoming immune has an Erlang distribution with a shape parameter of two and a mean of two time units. In the deterministic model, this is handled by linking two stages of infection. In a similar fashion, we modeled movement from the immune stage back to the susceptible stage by a distribution of durations again having an Erlang distribution with a shape parameter of two. We varied the mean in different experiments. All prevalence values presented represent the prevalence of combined infectious and immune states. This abstractly corresponds to 'seroprevalence' under the assumption that seropositivity begins when infection begins and ends when immunity ends.

The dimensionality associated with 100 subgroups makes exact solutions a computational challenge; so we used stochastic simulations to estimate endemic infection levels. We simulated the SC models using the GERMS [9,10] software. We note two caveats of the use of that software. First, GERMS gives duration to contacts but we made the durations so short that they were effectively instantaneous, consistent with the DC assumptions. We set the durations to 10^{-6} time units and the rate of infection transmission during a contact to 9×10^6 per time unit. These settings make each contact a very brief event that transmits infection nearly 100% of the time – consistent with our choice of $\beta = 1$ in the simulations reported above. Second, since GERMS does not prevent infection from leaving the system, there are some simulation runs in which infection leaves the system. The fact that the absorbing state is reached for a particular set of parameters is interesting in its own right. Low transmission rates and high durations of the immune state increase the probability of reaching the no-infection absorbing state. For runs where the absorbing state was not reached, the average infection level is a good approximation for the mean endemic level for the stochastic system for both stochastic models (the one that eliminates transitions to the absorbing state or the quasi-stationary distribution that conditions on non-absorption).

4.2.1. Varying the fraction of contacts made centrally or locally

The first set of SC experiments illustrates how an increasing frequency of local contacts leads to significant stochastic effects not captured by the ODE model. The contact rate was set at 0.8 per time unit. The duration of infection and the duration of immunity were both set at two time units. In the deterministic model a transmission probability of $\beta = 1$ results in a basic reproduction number (R_0) for all individuals of 1.6. In the deterministic model, Theorem 2 states that it makes no difference if these are made locally or at the disseminating site. In the stochastic model, however, as Ball et al. [30] have shown, the effective R_0 has local and global components that do not simply sum up as in the deterministic model case even though all individuals are identical. The fraction of contacts made in the disseminating site was progressively decreased from 100% to 0% in 10% decrements. Two SC simulations with separate random number seeds were conducted for 460 time units at each setting and endemic infection fractions were examined from 60 to 460 time units. Except in some cases in which infection died out globally from the population, the endemic infection level was reached well before the 60th time unit. The mean infection levels across the 400 time units for both simulations are presented in Fig. 5. The maximum difference in means for the two runs was 0.014, and most means were much closer.

As Theorem 1 asserts, changing these mixing site proportions has no effect in the deterministic model. The fraction of the population that is susceptible at equilibrium is $1/R_0$ in all our experiments no matter what fraction of contacts are made at different sites. There is little difference between the deterministic and stochastic models when mixing occurred only at the central disseminating site. (See Jacquez and Simon [34], who rely on Kurtz [39], for the proof of this result.) However, as the fraction of contacts made in local settings is increased, there is a considerable divergence between the deterministic and stochastic model.

Fig. 6 illustrates the effects of setting the transmission probability to zero in 10% of contacts, i.e., the effects of intervening locally or globally. There, we see that the deterministic model gives the same result not only for any frequency of local versus disseminating contacts, but also when the 10% elimination of transmission comes during local or during disseminating contacts. On the other hand, eliminating transmission from disseminating contacts reduces transmission more than

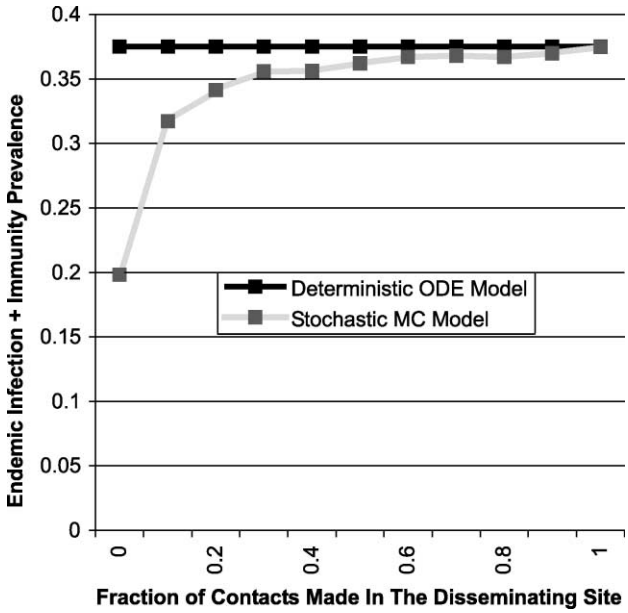

Fig. 5. Comparison of endemic prevalence of infection plus immunity for deterministic and stochastic models where the fraction of contacts made in the central disseminating site is varied.

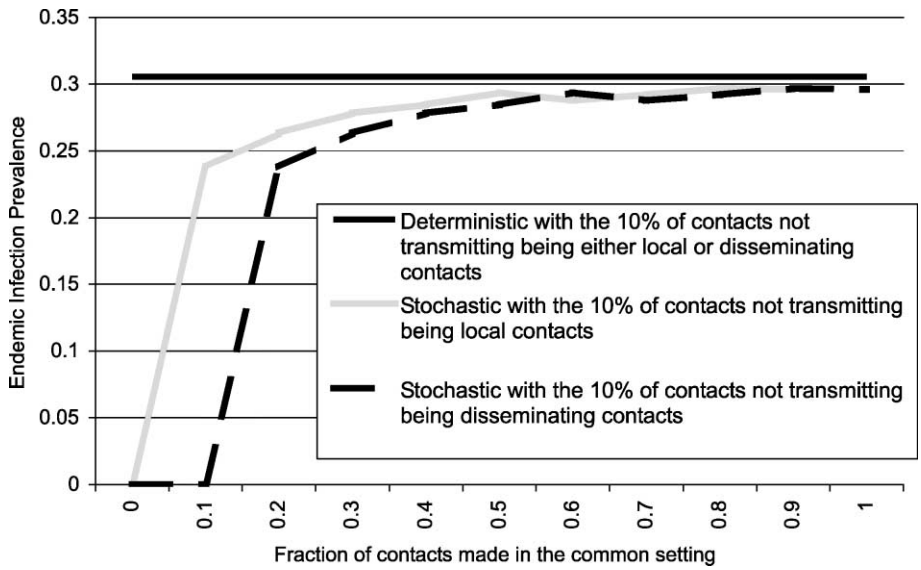

Fig. 6. Comparison of endemic prevalence of infection plus immunity for deterministic and stochastic models where 10% of contacts do not transmit as a function of whether it is local or disseminating contacts that do not transmit.

eliminating transmission from local contacts when the fraction of disseminating contacts is relatively small.

4.2.2. Varying the basic reproduction number

We conducted a second set of experiments to show how the level of transmission influences the stochastic effects we have just demonstrated. In these experiments, we examined the fraction of contacts that were disseminating contacts at only two values, 100% and 0%. We varied the contact rates from 0.55 to 4. The corresponding range of basic reproduction numbers covered varied from 1.1 to 8. In addition to presenting the mean endemic prevalence, we also present the maximum and minimum endemic prevalence. Fig. 7 presents the results when all mixing is at the common site. Note that there is little difference between the stochastic and deterministic mean until transmission dies out in the entire population – at R_0 values of 1.2 and 1.1. When infection dies out, we do not present the stochastic mean. Even at these values of R_0, however, infection circulated for a considerable time before dying out and the maximum prevalence levels are above the deterministic levels. Also, note from Fig. 7 that the range of endemic prevalence increases considerably as the R_0 approaches 1. This increase occurs because when infection reaches low levels by chance, it takes some time for infection to build up again. The previous model analyzed clearly demonstrated why this is the case. During the slow recovery from stochastically low levels of infection, the fraction of the population that is susceptible builds up, thus creating the potential for a new high peak of infection once the level of infection starts to take off. This, in turn, lowers the level of susceptibility generating the potential for another plunge in prevalence that can sustain cycles in stochastic models that damp out in deterministic models [47]. Of course, if the infection level goes to zero, the endemic level thereafter is zero.

Fig. 8 describes the corresponding situation in which all contact is local. Here we see that the stochastic mean endemic levels of the combined infectious and immune periods deviate substantially from the deterministic levels – even at quite high R_0 values. We also see that, when all mixing is local, the range of endemic prevalence values increases more rapidly as R_0 is lowered than when all mixing is at a central site. This is again due to the stochastic forces generating cycles

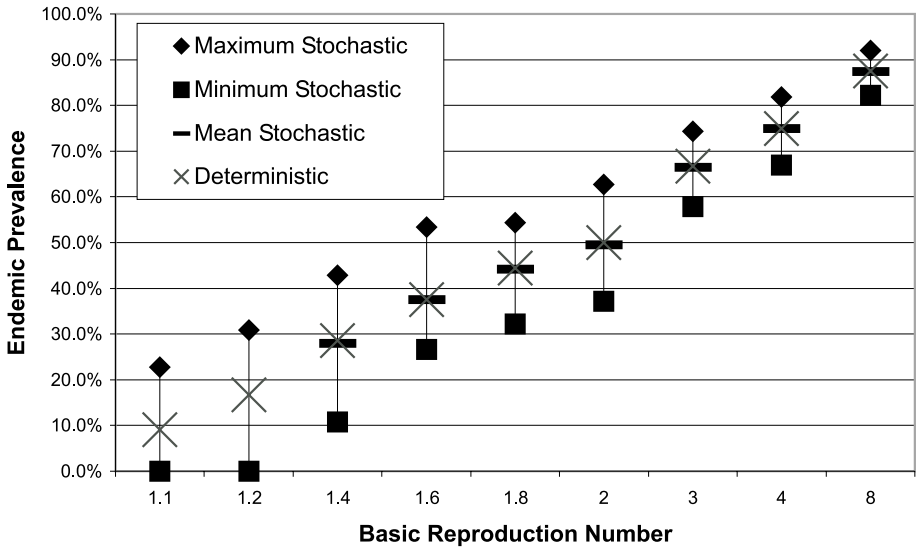

Fig. 7. Comparison of endemic prevalence of infection plus immunity for deterministic and stochastic models in a homogeneous population mixing completely randomly.

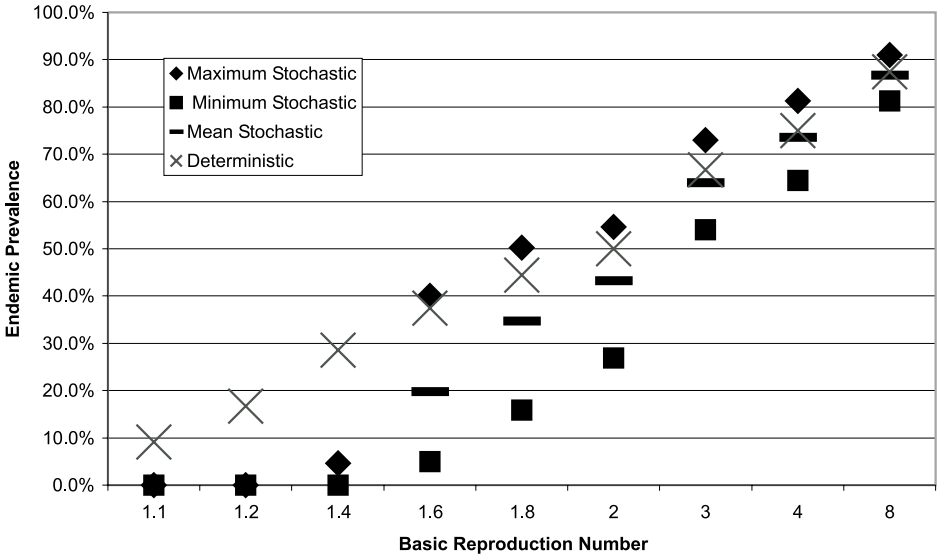

Fig. 8. Comparison of endemic prevalence of infection plus immunity for deterministic and stochastic models in a homogeneous population where mixing only occurs at local sites.

discussed earlier. Localities that encounter few infections from distant sites and that have stochastically low infection levels have decreased infection rates while localities with stochastically high levels of infection do not decrease the rate at which they lose infection. This allows for build up of susceptibility levels that can amplify the next cycle. This amplified cyclic behavior causes infection to die out from the entire population at much higher R_0 values when transmission is local.

4.2.3. Varying the duration of immunity

We have chosen values for the duration of immunity that would be unrealistically short for many infections. Otherwise, given longer durations of immunity and our simulation population size of 1200, infection dies out from the entire population too readily. The duration of immunity has a very strong influence on the stochastic die out of local transmission and thus on the stochastic effects of local versus disseminating transmissions. To illustrate this effect, we cut the duration of immunity in half. The results are shown in Fig. 9, where we see that duration of immunity does not affect endemic seroprevalence in deterministic models but the stochastic effects are roughly proportionate to the duration of immunity.

Note that shortening the duration of immunity in DC models does not change either the R_0 of infection or the relationship of that R_0 to the endemic prevalence of combined infection and immunity. It does, however, change the endemic level of infection since when immunity lasts half as long as infectiousness, two thirds of the combined infection plus immunity level is in the infection state, while at a ratio of 1 to 1 only half of the combined infection plus immunity is in the infection state. The effect of duration of immunity arises because stochastic forces generating the mean differences between DC and SC models which were discussed earlier are amplified by longer periods of low infection.

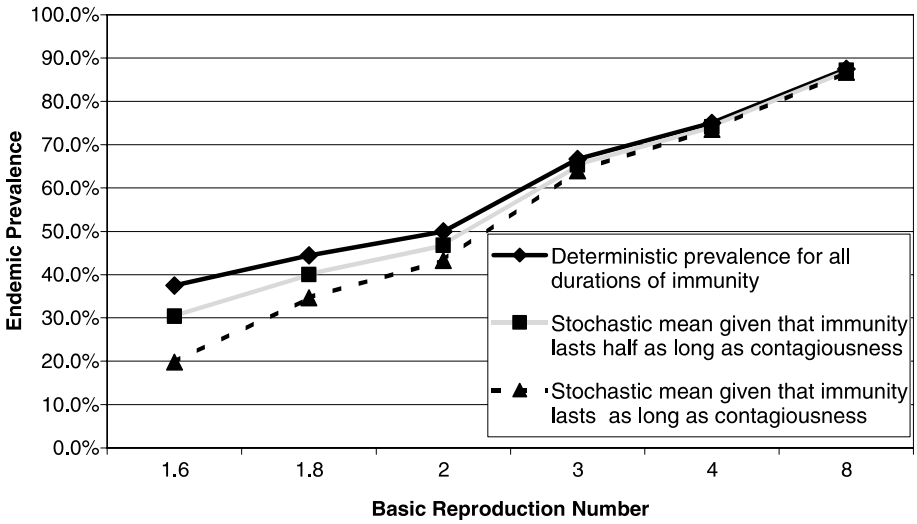

Fig. 9. The effect of the duration of immunity on the endemic prevalence of combined infection and immunity given stochastic and deterministic models with varying ratios of the durations of contagious infection and immunity.

5. Discussion and implications

We have examined stochastic effects on endemic infection levels arising from two levels of contact and have demonstrated that these effects cause transmissions made in central disseminating sites to increase endemic population infection levels more than transmissions made in local settings. By isolating stochastic effects arising due to two levels of contact from other contact pattern effects in the context of endemic transmission, we can scrutinize the mechanisms behind these stochastic effects. The universality of these mechanisms indicates that they are likely to be important in almost all endemic infection situations.

Stochastic effects related to small population size have been discussed and analyzed for some time [27,40]. In the context of geographic spread of infection, Bartlett [27] long ago alluded to the likely action of the mechanism behind the stochastic effects that we have examined. More recently, metapopulation analyses have emphasized how contact structure in space affects transmission dynamics [41]. Mollison [42,43] presents a deep analysis of the effects of spatial contact pattern and rates of spatial dispersion in stochastic models. Metapopulation effects and spatial dispersion rates are certainly affected by the phenomenon of stochastic effects from two levels of contact that we have examined. Likewise, family structure effects on transmission dynamics [30,44] are influenced by the phenomena we have presented. What we have done is to isolate that phenomenon from other contact pattern effects in transmission dynamics such as contact patterns within and between risk groups.

An elegant analysis of local and global contact effects by Ball et al. [30] also isolates the phenomenon of stochastic effects given two levels of contact. It does so in the context of epidemic takeoff in SIR models, in contrast to our focus on the endemic level in SIS ands SIRS models.

The analysis by Ball et al. [30] of basic reproduction number formulations that reflect threshold phenomena seems directly applicable to the endemic infection situation we have analyzed.

However, the endemic situation we have analyzed is likely to be more important than the SIR epidemic situation both because the endemic situation has a stochastic effect that the epidemic situation lacks and because the endemic phenomenon have such wide implications for public health.

With regard to mechanisms, the phenomenon of increasing levels of susceptibility in local areas that can sustain transmission but are stochastically free of infection is not relevant to the epidemic situation. In the endemic situation infection sweeps through an area and then the immunity levels generated by infection are lost due to waning, births, or immigration. Infection is stochastically lost from local areas when infection sweeps through because the local reproduction number falls near or below one. In the epidemic situation there is no time for reemerging susceptibility to act.

With regard to public health importance, the underlying mechanism of reseeding infection in areas free of infection due to stochastic effects but capable of sustained transmission is quite likely acting in every *endemic* situation. That can be seen by the fact that for almost any endemic infection there is some scale of geographic and social analysis where the presence of infection fluctuates between different units of the endemically infected population.

Comparing endemic and epidemic situations can cause one's perception of the implications of stochastic effects in models with two levels of transmission to shift between amplifications due to local transmissions and amplifications due to the global or disseminating transmissions. In the SIR work on this phenomenon [30] and in related analyses of the effects of families on transmission dynamics [44], family transmissions are treated as amplifying the effects of community transmissions. The way to get such amplification seems to be to increase local transmission. However, in our presentation the disseminating transmissions play an increasingly amplifying role as the frequency with which transmission dies out locally increases. We are viewing the same phenomenon as has been examined for SIR infections. But whereas the analyses of Ball et al. [30] lead them to conclude that one should focus interventions so that they cover local transmission units evenly, our analysis leads us to conclude that intervention should be focused on interrupting global or disseminating transmissions. This difference is illusory. In real world situations where this phenomenon occurs, and it occurs almost everywhere, one must conduct a system analysis to see whether a focus on local or global transmission control is indicated.

We also focus on the failure of deterministic models to capture these effects in a way that enhances the importance of the findings of Ball et al. [30]. This failure is hard to notice because deterministic models do capture strong effects of contact patterns. In fact, these strong effects of contact patterns have been a major theme recently in the analysis of models based upon differential equations [1–26,46]. Many modelers feel that differential equation models can provide the basic insights needed to consider the effects of transmission dynamics while discrete individual models are a compromise that one must make in order to realistically model real world situations where decisions must be made with enough detail to capture all factors that should influence the decision. By confining our analysis to situations in which all individuals are identical with regard both to individual characteristics and network relationships, we isolated the effects we wished to demonstrate from the contact pattern effects that are captured by differential equation models. We have shown that DC models fail to capture a widespread phenomenon that significantly affects the efficiency of focusing interventions on local or on disseminating transmissions.

Another way to think about the failure of deterministic models to capture two-level mixing effects is to realize that in deterministic models, all contacts reach out to an essentially infinite

distance. The differential equation assumption of either infinite population size or divisible humans means that no contacts are more local or disseminating than any other contacts. Local transmissions, however, generate local correlations between immunity levels that slow transmission.

Part of the locality effects that we have illustrated can be captured in differential equation models that incorporate the correlations just mentioned [47–49]. Such correlation models provide a needed link between compartmental models and network models. Network models by their very nature incorporate local mixing except in the extreme of random graphs. The correlation structure that arises is a function of network structure.

We demonstrated that the stochastic effects that differentiate local and disseminating transmissions increase as the duration of immunity increases. The effect of immunity as a determinant of local stochastic fade out has been noted previously [31]. How this effect should influence the targeting of control efforts, however, has not been noted. Longer immune periods do not change the fraction of the population that is susceptible. They do, however, decrease the ratio of infectious to immune individuals in a population. Thus, longer immune periods make it more likely that infection will die out locally. Given the small population sizes we examined, the same conditions that promote local die out of infection promote global die out of infection. Global die out of infection given long immunity periods constrained our analysis to situations where immunity lasted no longer than infectiousness. But it seems safe to conclude by extrapolation and by analogy to previous work [31] that when durations of immunity are longer, stochastic effects will further increase the influence of disseminating transmissions. Some infections, like Cryptosporidium infections and NTHi, will have periods of immunity considerably longer than their periods of infectiousness. Others, like gonorrhea, may have such narrow and transient immunity that it can be ignored.

5.1. Epidemiological data and stochastic effects from two levels of contact

Our analysis of a model with completely identical individuals demonstrates the insufficiency of standard epidemiological methods that seek causes of disease by comparing disease rates as a function of individual characteristics. In a situation where there are absolutely no differences between individuals, there are no comparisons for standard epidemiological methods to make. This demonstrates the intrinsic impossibility of the sufficient-component cause model [45] to capture transmission system effects even when individuals are classified by the characteristics of the individuals to whom they are exposed.

Most epidemiologists with responsibility for controlling infection transmission in their jurisdictions never undertake analyses of the population dynamics of transmission. They simply compare infection levels across groups to identify risk factors. Thus they are unlikely to generate any data that can reflect upon the phenomenon we have examined.

Most transmission system theorists likewise fail to consider field measurements that could determine whether real world situations are most consistent with stochastic or deterministic models. One outstanding exception to this is the work of Keeling and Grenfell [50] on measles infection patterns over space and time in Great Britain. They found that observed patterns could not be explained by deterministic models but were quite consistent with stochastic models. Another exception is the work of Rohani et al. [51]. These analyses, however, depend upon time and space patterns from surveillance data gathered uniformly over large areas for very long periods of

time. If we are dependent upon such data to advance a science of infection transmission system analysis, progress will be extremely slow.

A promising new source of data whose utility deserves exploration with stochastic models is genetic distances between pairs of infectious agents isolated from individuals with known contact points in the transmission system. Such genetic distances are best determined from nucleotide sequences that are becoming more readily available. Because the number of transmissions to most recent common ancestors will differ for specified pair types given different models, such measurements might provide a basis for estimating transmission model parameters.

5.2. Examples requiring analysis of stochastic effects from two levels of contact

We have illustrated stochastic phenomena that can significantly alter one's assessment of whether to focus on one kind of transmission or another. Such phenomena are likely to be important whenever an endemic infection is not uniformly present in different subgroups but hops around among them or at least leaves some subgroups free of infection for periods of time that cover several infectious periods. We discuss three cases that are foci of our research.

5.2.1. Cryptosporidium

The relative importance of waterborne versus direct transmission of Cryptosporidium is a key factor in decisions about water treatment regulations costing billions of dollars. Two different types of studies are being used to assess the contribution of water contamination to endemic Cryptosporidium levels. Community level studies are comparing the endemic infection levels in communities with groundwater supplies to levels in communities with the more common surface water sources. Groundwater is unlikely to be contaminated with Cryptosporidia, while surface water is likely to be contaminated. In one such ecological comparison, the groundwater community had an endemic prevalence of antibodies to Cryptosporidium of approximately 10% while the surface water community had a level closer to 30% [52]. Studies of this type would be quite expensive if they were to include a sufficient number of communities to give reasonable confidence intervals for their estimates. Consequently, a second type of study may be more influential. Infection levels are being studied in families that receive either a truly effective home water filter or a placebo water filter. Results are not yet available from these studies. The analysis presented here, however, indicates that this type of study will miss most of the benefits that can be expected from community water purification systems. A small attributable fraction of waterborne transmission in this type of study could make a large difference at the population level because the waterborne transmissions will be highly disseminating and will reseed infection in subgroups in the population where infection is repeatedly dying out.

5.2.2. Gonorrhea

Gonorrhea has been traditionally thought of as an infection without immunity. However, it appears that gonorrhea induces some immunity to specific strains and that some of the appearance of lack of immunity in many studies derives from a failure to distinguish different strains [53,54]. This possibility has implications for interpreting analyses of models of gonorrhea transmission. Garnett et al. found that deterministic ODE models of gonorrhea transmission fail to reproduce the balance between core and non-core population infection rates [55]. They found a

smaller ratio of infection in non-core groups compared to core groups in their models than was observed in field data. They discount the role of immunity in generating this disparity and speculate that the disparity was due to failure of their models to capture contact pattern effects. The important contact pattern effects could be those that can be captured with deterministic models or those that we have demonstrated here. If they are those we have demonstrated, non-core transmission rates will be higher than rates that are consistent with deterministic models.

5.2.3. Non-typeable Haemophilus influenzae

The common bacteria NTHi is found only in humans. It frequently colonizes the nasopharynx and causes otitis media, sinusitis, and bronchitis, resulting in more than a billion dollars in direct medical care costs each year. Medical treatment of otitis media has more than doubled in recent decades. Children in daycare have two to three times the risk of otitis as children not in daycare. Vaccines are being developed for NTHi and it is hoped that the vaccine trials to be conducted will be able to detect the effects of vaccination on transmission that were such a surprise for Haemophilus influenzae type B. We are investigating the utility of using daycare centers as the unit of randomization in trials so that transmission effects can be perceived. To that end we have constructed a DC model of the NTHi transmission system and found that infection levels in one daycare center are unlikely to affect infection levels in other daycare centers. Our deterministic models, however, might have underestimated the disseminating effect of daycare transmissions because they do not take into account stochastic effects from two levels of transmission. Like Cryptosporidium, NTHi is likely to induce only short-term immunity, at least in children, because that is the nature of the mucosal immunity that attacks colonizing bacteria. Thus the chances are good for waning of immunity in local settings when infection dies out. This, together with the observation of fluctuating levels of infection in daycare centers, indicates that the stochastic effects from two levels of contact are probably important.

The spread of NTHi in family (local) settings and daycare (disseminating) settings is a good vehicle with which to compare the benefits of local versus global intervention. The conclusions about local interventions in [30] do not apply in this case because this is an SIRS endemic situation, not an SIR epidemic. Intuitively, daycare interventions would seem to have a higher chance of success than household interventions, partly because the close and multifaceted interactions within families make successful intervention there so difficult.

Some of the differences between our approach and that of [30] arise because Ball et al. focuses on intervention via vaccination. However, the fact that vaccination is directed at individuals rather than at behaviors of individuals in [30] implies that vaccination cannot distinguish between local and global transmission. This paper focuses on broader mechanisms of intervention, such as hygiene in families and in daycare centers in NTHi intervention and water purification systems in households and in cities in Cryptosporidium interventions.

5.3. Implications for conducting transmission system analyses

Our findings indicate that to analyze the effects of local or disseminating transmissions stochastic models are needed. That does not mean that DC models should have no role in such an analysis. Because DC models are more readily analyzed than SC models, they could be profitably used to explore many aspects of a transmission system. But such analyses should only be con-

sidered as preliminary and they should be extended through the construction and analysis of corresponding stochastic models.

The theoretical basis for the transition from DC to SC models is being solidified. In many situations, including the models described here and elsewhere [9,10,32,33], the DC models can be derived as large-population limits of SC models. For example, Kurtz [39] and Benaim and Hirsch [56] have shown that many stochastic models converge to the corresponding deterministic model as the population size goes to infinity. Thus, a logical approach to transmission system analysis would be to begin with DC models. When sufficient progress is made with this model form, then one could transform the deterministic models to SC models and assess the extent to which small compartment sizes and stochastic effects change model behavior.

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Appendix A. Proofs of Theorems 1 and 2 in Section 4.1

Theorem 2 relates to an SIRS system with vital dynamics and Theorem 1 relates an SIS system. We deal with the more complex SIRS system first as the simpler system falls out of that readily. Recall that we are working with structured mixing in which the population is divided into n subgroups. Contacts are made in M mixing sites or 'activity settings'. A fraction f_{is} of subgroup is contacts are made in mixing site s. This proof is for the general case of an SIRS model with births and deaths occurring at rate μ, recovery from infection and acquisition of immunity occurring at rate κ, and loss of immunity occurring at rate ϖ, the susceptible individuals in subgroup i are denoted by X_i, the infectious individuals by Y_i and the immune individuals by Z_i. The mixing at each site is proportionate mixing. The contact rate c_i and the probability of transmission during a contact, β_i, are both independent of i. Note, this proof is made for a more general case than the second model. It allows the transmission probability to vary according to the susceptibility level of the subgroup to whom transmission is directed. The dynamics of transmission are given by

$$X' = -c_i X_i \sum_s f_{is} \frac{\sum_j f_{js} c_j \beta_j Y_j}{\sum_j f_{js} c_j N_j} - \mu X_i + \mu N_i + \varpi Z_i, \tag{A.1}$$

$$Y' = +c_i X_i \sum_s f_{is} \frac{\sum_j f_{js} c_j \beta_j Y_j}{\sum_j f_{js} c_j N_j} - \mu Y_i - \kappa Y_i, \tag{A.2}$$

$$Z' = \kappa Y_i - \mu Z_i - \varpi Z_i. \tag{A.3}$$

See Eqs. (11) and (12) in [57]. As described in Eqs. (13)–(15) and (33)–(35) of [57], the function $V = \sum_i \beta_i c_i D Y_i$, where D is the average length of infection $1/(\mu + \kappa)$, works well as a Liapunov function for this system. The derivative V' of V along orbits of this system is

$$V' = \sum_i \beta_i c_i D Y_i',$$

$$V' = \sum_i (R_i - 1)\beta_i c_i Y_i,$$

after some rearranging (Eqs. (33)–(35) of [53]), where

$$R_i = \sum_s f_{is}\beta_i \left(\frac{\sum_j c_j^2 D f_{js} X_j}{\sum_j c_j^2 f_{js} N_j} \right). \tag{A.4}$$

Since $X_j \leqslant N_j$ and by assumption $c_j = c$, $\beta_j = \beta$ for all j

$$R_i = c\beta D \sum_s f_{is} \left(\frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} \right) \leqslant c\beta D \equiv R_0. \tag{A.5}$$

If $R_0 \leqslant 1$, $V' < 0$ by (A.4) and V is decreasing on all orbits to $V = 0$, the no-disease equilibrium $Y_i = 0$ for all i and this equilibrium is globally asymptotically stable.

If $R_0 > 1$, one computes by substitutions into (A.1)–(A.3) that

$$\frac{X_j}{N_j} = \frac{1}{R_0}, \quad \frac{Y_j}{N_j} = \left(1 - \frac{1}{R_0}\right), \quad \frac{Z_j}{N_j} = \left(1 - \frac{1}{R_0}\right) \frac{\kappa}{\mu + \kappa + \varpi}, \tag{A.6}$$

a zero of system (A.1)–(A.3). By [58], it is the only endemic equilibrium of this system and is locally asymptotically stable.

In an SIS model with no Z_i class, the same proof works. The endemic equilibrium ((A.6) with $\kappa = 0$) is globally asymptotically stable [59] when $R_0 > 1$.

We now modify the proof of Theorem 1 to prove Theorem 2. Suppose now that the probability β_{js} of transmission given a contact depends on the subgroup j of the infected individual and on the activity group s. In this case, R_i in (A.4) can be written as

$$R_i \equiv \sum f_{is}\beta_{is} \frac{\sum_j c_j^2 D f_{js} X_j}{\sum_j c_j D f_{js} N_j}. \tag{A.7}$$

We assume, as in the statement of Theorem 2, that $c_j = c$ for all j, that $\beta_{is} = 0$ for $s \in \mathrm{A}_2$ and all i, that $\beta_{is} = \beta$ for all $s \in \mathrm{A}_1$ and all I, and that $\sum_{s\in A_2} f_{is} = f$ independent of i. Then

$$\begin{aligned} R_i &= cD \sum_{s\in A_1} f_{is}\beta_{is} \frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} + cD \sum_{s\in A_2} f_{is}\beta_{is} \frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} = cD\beta \sum_{s\in A_1} f_{is} \frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} \\ &\leqslant cD\beta \sum_{s\in A_1} f_{is} \cdot 1 \quad \text{since } x_j \leqslant N_j \\ &= cD\beta(1 - f) \quad \text{since } \sum_{s\notin A_1} f_{is} = f \text{ for each } i. \end{aligned}$$

As before, if $cD\beta(1 - f) < 1$, $R_i - 1 < 0$ for all i and $V' < 0$, i.e., the no-disease equilibrium is globally asymptotically stable. If $cD\beta(1 - f) > 1$, then for $X_j(0)$ near N_j, R_i will be >1 for all i, $V' > 0$, and the infection spreads.

One replaces R_0 by $R_0(1-f)$ in the expressions in (A.6) to specify the endemic equilibrium in this situation.

Appendix B. Differential equations for the 100 subgroup model

σ the flow rate out of each of the two immune stages
δ the flow rate out of each of the two infected stages
ρ the fraction of contacts made at the central disseminating site
ε the effective contact rate (the rate of making contact with anyone times the transmission probability per contact)
υ the fraction of contacts not made at the central disseminating site that are made in the neighboring two local mixing sites
S_i the fraction of susceptible individuals in local group i $(i:1\ldots100)$
I_{ji} the fraction of infected individuals in local group i $(I=1\ldots100)$ at stage j of infection $(j=1,2)$; the infectious and immune stages were modeled with two compartments each
R_{ji} the fraction of immune individuals in local group i $(i:1\ldots100)$ at stage j of immunity
L_i fraction of individuals at the local mixing site i that are infected
C fraction of individuals at the central common mixing site that are infected

$$
\begin{aligned}
&\mathrm{d}S_i/\mathrm{d}t = \sigma R_{i2} - S_i\varepsilon\{(1-\rho)\upsilon(L_{i-1}+L_{i+1}) + (1-\rho)(1-2\upsilon)L_i + \rho C\},\\
&\mathrm{d}I_{1i}/\mathrm{d}t = S_i\varepsilon\{(1-\rho)\upsilon(L_{i-1}+L_{i+1}) + (1-\rho)(1-2\upsilon)L_i + \rho C\} - \delta I_{1i},\\
&\mathrm{d}I_{2i}/\mathrm{d}t = \delta I_{1i} - \delta I_{2i},\\
&\mathrm{d}R_{1i}/\mathrm{d}t = \delta I_{2i} - \sigma R_{1i},\\
&\mathrm{d}R_{2i}/\mathrm{d}t = \sigma R_{1i} - \sigma R_{i2},
\end{aligned}
$$

$$
C = \frac{\sum_i \sum_j I_{ij}}{\sum_i \sum_j I_{ij} + R_{ij} + \sum_i S_i},
$$

$$
L_i = \frac{(1-\rho)\upsilon\left(\sum_j I_{ji-1} + I_{ji+1}\right) + (1-2\rho)\sum_j I_{ji}}{(1-\rho)\upsilon\left\{\left(\sum_j I_{ji-1} + I_{ji+1} + R_{ji-1} + R_{ji+1}\right) + S_{i-1} + S_{i+1}\right\} + (1-2\rho)\upsilon\left(S_i + \sum_j I_{ji} + R_{ji}\right)},
$$

where calculated values of $i=0$ are transformed to $i=100$ and calculated values of $i=101$ are transformed to 1.

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