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Interval estimates for epidemic thresholds in two-sex network models ☆

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Abstract

Epidemic thresholds in network models of heterogeneous populations characterized by highly right-skewed contact distributions can be very small. When the population is above the threshold, an epidemic is inevitable and conventional control measures to reduce the transmissibility of a pathogen will fail to eradicate it. We consider a two-sex network model for a sexually transmitted disease which assumes random mixing conditional on the degree distribution. We derive expressions for the basic reproductive number ($\mathscr{R}_0$) for one and heterogeneous two-population in terms of characteristics of the degree distributions and transmissibility. We calculate interval estimates for the epidemic thresholds for stochastic process models in three human populations based on representative surveys of sexual behavior (Uganda, Sweden, USA). For Uganda and Sweden, the epidemic threshold is greater than zero with high confidence. For the USA, the interval includes zero. We discuss the implications of these findings along with the limitations of epidemic models which assume random mixing.
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1. Introduction

Epidemic models exhibit critical behavior. When a population is below some critical threshold, a major outbreak of an infectious disease (i.e., an epidemic) cannot occur. Classically, epidemic thresholds were seen in terms of a critical number of susceptible hosts: a population with too few susceptible could not support an epidemic (Bailey, 1975). More modern treatments have focused on the threshold parameter $\mathscr{R}_0$, the basic reproduction number (Heesterbeek, 2002). $\mathscr{R}_0$ is defined as the expected number of secondary cases produced by a single (typical) index case in a completely susceptible population (Diekmann et al., 1990). In a deterministic model when $\mathscr{R}_0 > 1$, there will be an epidemic. The "epidemic threshold" occurs when $\mathscr{R}_0 = 1$. For a homogeneous, one-sex model of a directly transmitted pathogen and one disease state, $\mathscr{R}_0$ is given simply by the product of the transmissibility of the agent (τ), the average contact rate between susceptible and infected members of the population ($\bar{c}$), and the duration of infectiousness, which is the inverse of the removal rate, v when it is exponentially distributed ($\delta = v^{-1}$):

$$\mathscr{R}_0^{(U)} = \tau\bar{c}\delta, \tag{1}$$

where the superscript (U) indicates that $\mathscr{R}_0$ applies to a homogeneous (uniform) population. Thus, $\mathscr{R}_0$ is the product of the transmissibility of the agent given contact and the contact process. We say that an epidemic threshold exists if there is a level of transmissibility that produces $\mathscr{R}_0 \leqslant 1$. If an epidemic threshold exists we define the critical transmissibility to be the superium of transmissibilities that produces $\mathscr{R}_0 \leqslant 1$. The critical transmissibility can be expressed as a function of the contact structure. We provide specific definitions for particular models below.

This somewhat schematic definition of $\mathscr{R}_0$ enjoys the great advantage of easy interpretation. Public health campaigns designed to eliminate sexually transmitted infections (STIs) focus on one of three strategies suggested by (1): (a) reduce transmissibility (τ) through vaccines,

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barrier contraceptive use, or, in the case of non-curable viral infections, therapeutics which reduce viral load (e.g., HAART), (b) reduce the contact rate ($\bar{c}$) through education, or (c) increase the recovery rate (ν) through treatment of curable STIs. Some interventions combine strategies. For example, contact-tracing combines contact-reducing and recovery-rate increasing interventions (Janssen et al., 2001; Golden, 2002).

The definition of $\mathscr{R}_0$ in heterogeneous populations is somewhat more complex, though by discretizing "generations" of infections, its calculation is a simple extension of the homogeneous case (Diekmann et al., 1990; Diekmann and Heesterbeek, 2000). For many STIs with one disease state, heterogeneity is incorporated into models by way of a mixing matrix in which the population is stratified by sexual activity level and the matrix gives the activity-specific probability of interaction (Gupta et al., 1989; Anderson and Garnett, 2000).

For a population characterized by heterogeneous sexual activity, and in which there is random mixing linearly proportional to activity levels, Anderson et al. (1986) demonstrate that $\mathscr{R}_0$ becomes

$$\mathscr{R}_0^{(H)} = \mathscr{R}_0^{(U)}(1 + CV^2), \tag{2}$$

where CV is the coefficient of variation of sexual activity in the population (i.e., the standard deviation divided by the mean of the number of sexual partners). Clearly, populations characterized by large variance—and particularly large variance relative to the mean—will have higher reproduction numbers and thus, at lower levels of transmissibility attain the epidemic thresholds. One important class of models in which the variance in sexual activity level greatly exceeds the mean are the so-called "scale-free" models in which the frequency distribution of partnerships exhibits power-law behavior, and the theoretical variance is infinite (May and Lloyd, 2001; Liljeros et al., 2001; Dezső and Barabási, 2002).

Men's and women's sexual behavior differs systematically throughout the world as a function of cultural norms, gender-power relations, and social institutions regulating individual behavior. In Africa, home to the world's largest fraction of HIV sero-positive people, HIV is sexually transmitted primarily by contacts between men and women (WHO/UNAIDS, 2003). Two-sex models admit the possibility of an epidemic threshold not existing, even if the behavior of either of the sexes alone would yield a threshold (Newman, 2002b).

A second, related concern is that the partnership distributions' variance, while finite, could still be high enough to impede the effectiveness of transmissibility-based interventions. Since, for example, no vaccine is completely effective (Blower et al., 2001), a positive critical transmissibility could still pose a practical barrier to disease eradication if it were low enough.

Pastor-Satorras and Vespignani (2002) note that critical transmissibilities for "bounded scale-free" networks are higher than for homogeneous networks. While this result is not particularly novel in the context of mathematical epidemiology (cf. Hethcote and Yorke, 1984; Anderson et al., 1986; Gupta et al., 1989), it reinforces the need to examine quantitatively the effect of large degrees of behavioral heterogeneity on the epidemic thresholds of STIs.

The Anderson et al. (1986) result for heterogeneous $\mathscr{R}_0$ was derived for a compartmental model of infection dynamics and provides a clear intuition for why partnership distributions with power-law behavior can yield epidemics without critical behavior (see also May and Lloyd, 2001). Because of the discrete nature of sexual contact, models based on random graphs have become increasingly popular in the STI literature (Morris, 1997; Diekmann and Heesterbeek, 2000). It is not immediately clear that the result derived from a continuous-state compartmental model will directly apply to the discrete contact structure of a graph. Newman (2002b) has derived results for epidemic thresholds in graphs using probability-generating functions, which are a natural tool for dealing with discrete random variables such as the structure of random graphs. However, his treatment of the problem suffers from a somewhat unorthodox notation and terminology and thus obscures its deep links to standard theory in formal epidemiology. The key assumption employed by Newman (2002b) of random contact conditional on the degree distribution of the contact network means that his results are exactly analogous to the standard theory given, for example, in Anderson and May (1991) and Diekmann and Heesterbeek (2000).

The great majority of epidemic models that followed from the pioneering work of Anderson et al. (1986) are one-sex, either explicitly because they consider homosexual transmission dynamics (e.g., Gupta et al., 1989) or implicitly because they do not model the interaction of the sexes (Newman, 2002b).

In this paper, we consider models where individuals are represented as nodes in a network and edges represent heterosexual sexual contact. Disease spreads only through diffusion over the network of sexual contacts. We assume that the network is a realization of a stochastic process characterized by random mixing between individuals conditional on the individual activity levels (i.e., the nodal degrees) (Newman, 2002b). This assumption allows us to show the straightforward links between epidemic phenomena based on the next generation operator (e.g., Diekmann et al., 1990; Diekmann and Heesterbeek, 2000) and the percolation-theory results of Molloy and Reed (1995) and Newman (2002b). We focus on models for the population degree distributions in which the variance can greatly exceed the mean and estimate corresponding thresholds for two-sex epidemics in three population, Rakai district, Uganda, Sweden, and the United States.

In Section 2, we develop models for the sexual contact degree distribution. In Section 3, we derive the epidemic thresholds for these models within the random graph model of Newman (2002b) and show its relationship to

more standard theory in mathematical epidemiology (e.g., Diekmann and Heesterbeek, 2000). Section 3.4 gives methods for the estimation of the degree distribution models. Section 3.5 presents interval estimates for the epidemic thresholds and basic reproductive number. In Section 4 results are given for the degree distribution models, epidemic thresholds and basic reproductive number for the three populations. In Section 5, we discuss the epidemiological relevance of these results, and approaches to overcome the limitations of the models.

2. Models for degree distributions

Let $P(K=k)$ be the probability mass function of the number of partners within a well-defined period that a randomly chosen person in a population has had. We say $P(K=k)$ has *power-law behavior* with scaling exponent $\rho>1$ if there exist constants c_1, c_2, and M such that $0<c_1\leqslant P(K=k)k^{\rho}\leqslant c_2<\infty$ for $k>M$. Empirical distributions of the number of sex partners, both lifetime and over the past year, show a pronounced right-skew, with the great majority of people having few partners and some having many (Laumann et al., 1994; Lewin, 1996; Hubert et al., 1998; Aral, 1999; Youm and Laumann, 2002). This observation has led a number of authors to suggest that sexual partnership distributions have power-law behavior (Liljeros et al., 2001, 2003; Schneeberger et al., 2004). These authors do not consider the wide range of right-skewed distributions as plausible alternatives.

For $\rho\leqslant 3$, the variance of a distribution with power-law behavior is infinite. The Anderson et al. (1986) approximation for $\mathscr{R}_0$ therefore suggests that populations characterized by partnership distributions with power-law behavior and $\rho\leqslant 3$ will lack epidemic thresholds, since with infinite variance $\mathscr{R}_0^{(H)}>1$ for arbitrarily small transmissibility or duration of infectiousness. Note that an actual population will always have finite variance, and hence the extrapolation of mathematical models for the degree distributions that have infinite variance requires a careful assessment of the quality of the approximation provided by the model (Jones and Handcock, 2003; Handcock and Jones, 2004).

We focus on two competing stochastic mechanisms for the formation of sexual contact networks. The first is a variation on a preferential attachment process, such as those advocated by several recent authors (Barabási and Albert, 1999; Pastor-Satorras and Vespignani, 2001; Liljeros et al., 2001). The second process is a non-homogeneous Poisson model for partnership formation. The limiting distributions of both these mechanisms can be characterized by long tails. They have the additional benefit that they have the same number of parameters, facilitating comparison.

2.1. Preferential attachment model

A mechanism that has been suggested for the formation of power-law sexual networks is preferential attachment (Albert and Barabási, 2000; Liljeros et al., 2001; Dezső and Barabási, 2002). This and related stochastic processes have a long history in applied statistics (Simon, 1955; Kendall, 1961; Irwin, 1963). Consider a population of r people in which (1) there is a constant probability p that the $(r+1)$st partnership in the population will be initiated from a randomly chosen person to a previously sexually inactive person, and (2) otherwise the probability that the $(r+1)$st partnership will be to a person with exactly k partners is proportional to $kf(k|r)$, where $f(k|r)$ is the frequency of nodes with exactly k connections out of the r total links in the population. The limiting degree distribution of those connected by this process as $r\to\infty$ is known as the Waring distribution (Irwin, 1963). The Yule distribution discussed by Simon (1955) and used by Jones and Handcock (2003) to model degree distributions is a special case of the Waring distribution with $p=(\rho-2)/(\rho-1)$.

The probability mass function (PMF) of the Waring distribution (Johnson et al., 1992) is

$$P(K=k|K>0) = \frac{(\rho-1)\Gamma(\rho+\rho_0)}{\Gamma(\rho_0+1)}\cdot\frac{\Gamma(k+\rho_0)}{\Gamma(k+\rho_0+\rho)},\quad \rho_0>-1, \tag{3}$$

where $\Gamma(\cdot)$ is the Gamma function and the mixing parameter ρ_0 is related to p via

$$p=\frac{\rho-2}{\rho+\rho_0-1}. \tag{4}$$

The Waring distribution has power-law behavior with scaling exponent ρ. The mean and variance of the Waring distribution are

$$\mathbb{E}(K|K>0)=\frac{1}{p},$$

$$\mathbb{V}(K|K>0)=\frac{(1-p)(\rho-1)}{p^2(\rho-3)}.$$

Thus, the expected value of the Waring distribution is simply the inverse of the probability of forming a tie to an individual lacking existing ties. Both the Waring and the Yule distributions have been re-discovered, apparently without awareness of their historical antecedents, by Levene et al. (2002) and Dorogovtsev et al. (2000), respectively, in the context of modeling growth of the Internet.

2.2. Non-homogeneous Poisson model

A reasonable alternative model to the preferential attachment mechanism is that people form partnerships according to a Poisson process. One possible behavioral mechanism that underlies this model is that people acquire new partners at a constant rate, λ. Clearly, the assumption that all people in the population are characterized by the same rate of partner acquisition is unreasonable. To include heterogeneity, we can model λ as a random draw from some population distribution $P(\lambda)$.

Here we model $P(\lambda)$ as a Gamma distribution with mean μ and standard deviation σ. Let $\lambda_i + 1$ be the expected number of partners for person i in the sub-population of those with at least one partner. The model can then be written

$$P(K = k|K>0, \lambda) = \frac{e^{-\lambda}\lambda^{k-1}}{\Gamma(k)}, \tag{5}$$

$$P(\lambda_i = \lambda) = \frac{e^{-\lambda/\eta_1}(\lambda/\eta_1)^{\eta_2-1}}{\eta_1\Gamma(\eta_2)}, \quad \lambda>0, \tag{6}$$

where $\eta = (\eta_1, \eta_2) = (\sigma^2/\mu, \mu^2/\sigma^2)$. The conditional distribution of K given $K>0$ is therefore negative binomial distribution shifted to $k = 1, 2, \ldots$. One interpretation of this distribution is that people are following a search for partners that satisfy a certain criterion and continue to acquire partners until they have η_2 such partners. Partners satisfy the criterion independently and each with probability p_c. This probability defines the scale parameter of the underlying heterogeneity distribution ($\eta_1 = (1-p_c)/p_c$). The mean and variance of the negative binomial in terms of the gamma mean-standard deviation parametrization are $\mathbb{E}(K|K>0) = \mu + \mu^2/\sigma^2$ and $\mathbb{V}(K|K>0) = (\sigma + \mu/\sigma)^2$. If the population heterogeneity distribution $P(\lambda)$ is right-skewed the partner distribution K will also be right-skewed. Thus, this model is one plausible alternative to the preferential attachment model that can have heavy tails, but does not have power-law behavior. As we shall see, this leads to different epidemic potentials for the two models even when their ability to describe the observed partnership distributions is similar.

3. Epidemic models on random graphs

The impact of the degree distribution on the spread of STDs on an arbitrarily defined contact structure has been studied by Newman (2002b), who gives both one-sex and two-sex results. Newman presents his results in terms of percolation theory. In what follows, we translate his formalism into a notation and terminology more familiar to epidemiologists.

3.1. $\mathscr{R}_0$ in a heterogeneous one-sex population

Suppose that the degree distribution of a population has PMF $P_\theta(K = k)$ where θ is the (possibly vector) parameter. For example, for the Waring model $\theta = (\rho, p)$ the scaling exponent and probability of recruiting a novice parameter. A fundamental characteristic of the distribution is the quantity we call the *concentration index*, $C(\theta)$, given by

$$C(\theta) = \frac{\mathbb{E}_\theta(K)}{\mathbb{E}_\theta(K^2) - \mathbb{E}_\theta(K)} = \frac{\mathbb{E}_\theta(K|K>0)}{\mathbb{E}_\theta(K^2|K>0) - \mathbb{E}_\theta(K|K>0)}, \tag{7}$$

where $\mathbb{E}_\theta(K)$ is the expectation of the random variable K with respect to the PMF $P_\theta(K = k)$. Higher values of $C(\theta) \geqslant 0$ indicate distributions that are more concentrated and a value of zero indicates a distribution with infinite variance.

Diekmann and Heesterbeek (2000) give the following expression for the basic reproduction number in a network:

$$\mathscr{R}_0 = \frac{\bar{\tau}}{\tau_c},$$

where $\bar{\tau}$ is the average integrated probability of transmission per random contact ("partnership") between an infected and susceptible individual and $\tau_c = C(\theta)$. The epidemiologically relevant contact rate in the graph is τ_c^{-1}. An epidemic will occur if $\mathscr{R}_0$ exceeds the threshold of 1. Expressed in terms of transmissibility, the epidemic threshold is $\bar{\tau} > \tau_c$. Hence, we refer to τ_c as the *epidemic threshold*. If an epidemic threshold exists, then τ_c is also the critical transmissibility. If the epidemic threshold does not exist τ_c can still be interpreted as the concentration index of the degree distribution of the graph. The notation highlights the dependence of this quantity and the critical transmissibility on the parameter, θ.

As an application, suppose that the degree distribution of a one-sex population follows the Waring model (3) with scaling exponent ρ and recruitment probability p. Then

$$C(\rho, p) = \frac{\mathbb{E}(K)}{\mathbb{E}(K^2) - \mathbb{E}(K)} = \begin{cases} \dfrac{p(\rho-3)}{2(1-p)(\rho-2)}, & \rho>3, \\ 0, & \rho \leqslant 3. \end{cases} \tag{8}$$

For the negative binomial model, the concentration index is most parsimoniously represented using the underlying gamma heterogeneity parameter η:

$$C(\eta) = \frac{\mathbb{E}(K)}{\mathbb{E}(K^2) - \mathbb{E}(K)} = \frac{1+\eta_1}{\eta_2(1-\eta_1)^2 - \eta_1^2}. \tag{9}$$

3.2. $\mathscr{R}_0$ in a heterogeneous two-sex population

For an epidemic in a heterogeneous population, the basic reproduction number is given by the spectral radius of the square matrix Θ (Diekmann and Heesterbeek, 2000). Θ is known as the next generation matrix, and its elements, θ_{ij} provide an accounting of the expected number of type i infections produced by a single type j infection in a completely susceptible population.

Consider a two-sex population where all disease transmission is heterosexual. Suppose that the degree distribution of the men and women in the population have PMFs with parameters θ_m and θ_f, respectively. We assume that the population follows the form of random mixing with respect to degree that satisfies the constraints on the degree distributions given in Newman (2002b). Let τ_{fm} denote the average integrated probability of transmission per partnership given contact between an infected male and susceptible female. The conditional integrated probability of females infecting males is τ_{mf}. The next generation

matrix is

$$\Theta = \begin{bmatrix} 0 & \tau_{fm}/C(\theta_f) \\ \tau_{mf}/C(\theta_m) & 0 \end{bmatrix}. \quad (10)$$

The basic reproduction number for this case is the dominant eigenvalue of Θ, given by

$$\mathscr{R}_0 = \frac{(\tau_{mf}\tau_{fm}))^{1/2}}{(C(\theta_m)C(\theta_f))^{1/2}} = \bar{\tau}/\tau_c, \quad (11)$$

where $\bar{\tau} = \sqrt{\tau_{fm}\tau_{mf}}$ is the geometric mean of transmissibility, and

$$\tau_c = [C(\theta_f)C(\theta_m)]^{1/2}. \quad (12)$$

For a fixed population structure, with sufficient statistics $C(\theta_f)$, $C(\theta_m)$, we can again call τ_c the *epidemic threshold*. If the epidemic threshold exists τ_c is also the critical transmissibility.

Newman (2002b) refers to the concentration index as the critical transmissibility (T_c), which it clearly is for the one-sex case. The concentration index notation, $C(\theta)$, makes specification of the epidemic thresholds in the two-sex case much more compact than Newman's original notation, which was in terms of probability-generating functions of the nodes and edges of the transmission graph.

3.3. Epidemic thresholds in heterogeneous population

Based on the common notation for the one- and two-sex populations it is simple to explore epidemic thresholds for their transmission models.

Assuming that the disease has mutually positive transmissibilities between men and women, Newman (2002b) effectively shows that an epidemic will occur with probability approaching one as the number of partnerships approaches infinity if τ_c is zero. That is, if either the female or the male degree distributions are characterized by infinite variance, there is no critical transmissibility which will keep $\mathscr{R}_0 \leqslant 1$. In this case there is no epidemic threshold and $\tau_c = 0$. Based on his results the probability of an epidemic approaches zero as the number of partnerships approaches infinity if

$$0 < \bar{\tau} \leqslant \tau_c. \quad (13)$$

In particular, this means that if $\tau_c > 1$ and the transmissibility is positive the probability of an epidemic approaches zero as the number of partnerships approaches infinity. The range of values of the population distributions that allow for a transition to an epidemic following random infection is defined by

$$0 < \tau_c < \bar{\tau}. \quad (14)$$

If both $C(\theta_f) > 0$ and $C(\theta_m) > 0$ so that $\tau_c > 0$, efforts to reduce transmissibility through medical or public health interventions have the potential for success. Examples of such interventions include vaccination, barrier contraceptive use, or therapeutics (e.g., anti-retroviral therapy).

For degree distributions with power-law behavior, such as the Waring, the probability of an epidemic approaches one as the number of partnerships approaches infinity if either ρ_m and ρ_f is less than or equal to 3. The probability of an epidemic approaches zero as the number of partnerships approaches infinity if $(\rho_m - 3)(\rho_f - 3) > 4(\rho_{0m} + 1)(\rho_{0f} + 1)$ regardless of the transmissibilities. The epidemic potential in the intermediate range will depend on the geometric mean of the transmissibilities $\bar{\tau}$ and the scaling parameters (θ_m, θ_f).

3.4. Estimating the degree distribution

Much of the empirical work on characterizing the degree distribution of samples from a variety of physical, biological, and social networks is based on regression concepts, in which the scaling parameter is estimated from the regression of the apparently linear region of the plot of the logarithm of the survival function $P(K \geqslant k)$ against $\log(k)$. OLS regression is not an appropriate inferential tool for this problem as the data violate a variety of assumptions linear regression (Jones and Handcock, 2003). Furthermore, the apparent linearity of the tail can be a spurious visual illusion owing to the cumulative nature of the log-survival plot. In order to move away from ad hoc curve fits, Handcock and Jones (2004) advocate the specification of stochastic process models for network formation. Such stochastic models are amenable to empirical verification and allow estimation of model parameters using maximum likelihood.

We estimated the Waring and negative binomial parameters for three populations: (1) Rakai District, Uganda (Wawer, 1992), (2) Sweden (Lewin, 1996), (3) USA (Laumann et al., 1994). Descriptions of these data sets are given in Handcock and Jones (2004). We adapt the model to allow for the possibility that the tail behavior (i.e., $k > 1$) of the degree distribution may differ fundamentally from the majority of the observations for which $k = 0$ or 1 (May and Lloyd, 2001). We generalized the models to allow separate parameters to fit the probabilities of lower degrees. The parametric model is fit only to values $K \geqslant k_{\min} > 0$, and we use likelihood-based model selection procedures (e.g., Burnham and Anderson, 2002) to choose the best fitting model. Specifically, we used a corrected Akaike Information Criterion (AIC_c) (Simonoff and Tsai, 1999). Full details of the fitting procedure can be found elsewhere (Jones and Handcock, 2003; Handcock and Jones, 2004).

3.5. Confidence intervals for epidemic thresholds and $\mathscr{R}_0$

Uncertainty in the network model parameters, θ will produce uncertainty in the concentration index and, hence, the epidemic threshold of the population. To assess this uncertainty quantitatively, we constructed 95% bootstrap confidence intervals for $C(\theta)$ (Efron and Tibshirani, 1993). For each population of n individuals, the observed values

of individual partner counts were re-sampled with replacement to produce 5000 samples of size n and $C(\theta)$ for each replicate sample was calculated. Intervals for the epidemic threshold were then based on these and Eq. (12). Intervals for $\mathscr{R}_0$ were computed using Eqs. (12) and (11), conditional on a level for $\bar{\tau}$.

4. Results

4.1. Degree models

The results for the Waring model MLE fits are presented in Table 1. For both men's and women's networks from all three populations $\rho > 3$, indicating finite variance. Nonetheless, the parameter values for the USA yield quite low values of $C(\theta)$.

The results for the negative binomial model MLE fits are presented in Table 2. For all samples but the American women, the negative binomial model fits better than the Waring, as indicated by the AIC_c values. Fig. 1 plots the inferred distribution of the Poisson parameter λ for the three populations. As expected, all three populations show a great deal of right-skew. The heterogeneity in propensity to have additional partners is very similar for men and women and for the Western countries. In Uganda, women are much less likely to form additional partners than the men.

4.2. Confidence intervals for epidemic thresholds

We estimated 95% confidence intervals of the epidemic threshold level (Eq. (12)) for each population using each of the four combinations of underlying degree models (e.g., male Waring, female Waring, etc.). The confidence intervals for the Waring and negative binomial models are compared in Fig. 2. The intervals for the negative binomial model tend to be higher than those of the Waring for the Sweden and the USA. In Uganda, the epidemic threshold is much higher and more uncertain than the two countries in the developed world. As the epidemic threshold is above one for Uganda, the model predicts that an epidemic cannot occur there no matter the transmissibility. Fig. 3 plots the confidence intervals for the best fitting models. For Uganda, the model predicts that an epidemic cannot occur regardless of the transmissibility. It is clear that this is not consistent with reality as Rakai is home to a mature AIDS epidemic. The current estimate of HIV/AIDS prevalence in Rakai is 16%, a generalized epidemic by any definition. If the random mixing model is roughly correct an epidemic would not be possible. This disjunction between the epidemiology in Rakai and the model predictions is clearly problematic and will be taken up in the Discussion (Section 5).

For Sweden, all models yield bounds on the epidemic threshold which do not overlap with zero, so a critical transmissibility exists below which an epidemic will not

Table 1
Parameter estimates for the Waring model

Country	Sex	AIC_c	$k_{\min}$	ρ	p	$C(\theta)$
Uganda	Women	1061.3	1	8.68	0.94	7.64
	Men	1576.2	2	4.58	0.83	0.97
Sweden	Women	2143.9	2	4.45	0.49	0.75
	Men	3025.0	2	6.53	0.61	1.56
USA	Women	3208.7	1	3.11	0.77	0.17
	Men	3247.8	2	4.47	0.45	0.24

AIC_c is the corrected Akaike Information Criterion for the best fitting Waring model, $k_{\min}$ is the lower cutoff degree, ρ is the scaling exponent, p is the probability of forming a tie to an individual lacking partners, and $C(\theta)$ is the concentration index for the parameter values.

Table 2
Parameter estimates for the negative binomial model

Country	Sex	AIC_c	$k_{\min}$	t_e	p_c	μ	σ	$C(\theta)$
Uganda	Women	1058.3	2	0.27	0.19	0.22	0.96	6.60
	Men	1574.4	4	3.58	0.52	1.72	1.26	0.82
Sweden	Women	2142.9	1	0.38	0.36	0.24	0.65	2.31
	Men	3024.3	1	0.66	0.25	0.49	1.23	1.21
USA	Women	3210.0	4	2.86	0.15	2.42	3.68	1.88
	Men	3204.3	1	0.78	0.26	0.58	1.30	0.93

AIC_c is the corrected Akaike Information Criterion for the best fitting negative binomial model, $k_{\min}$ is the lower cutoff degree, t_e is the expected stopping time of the negative binomial, p_c is the probability a person satisfies the criterion, μ is the mean of the underlying gamma distribution, σ is the standard deviation of the gamma distribution, and $C(\theta)$ is the concentration index for the parameter values. To aid interpretation of the model we have included the alternative parametrization: t_e is the expected stopping time of the negative binomial, and p_c is the probability a person satisfies the criterion.

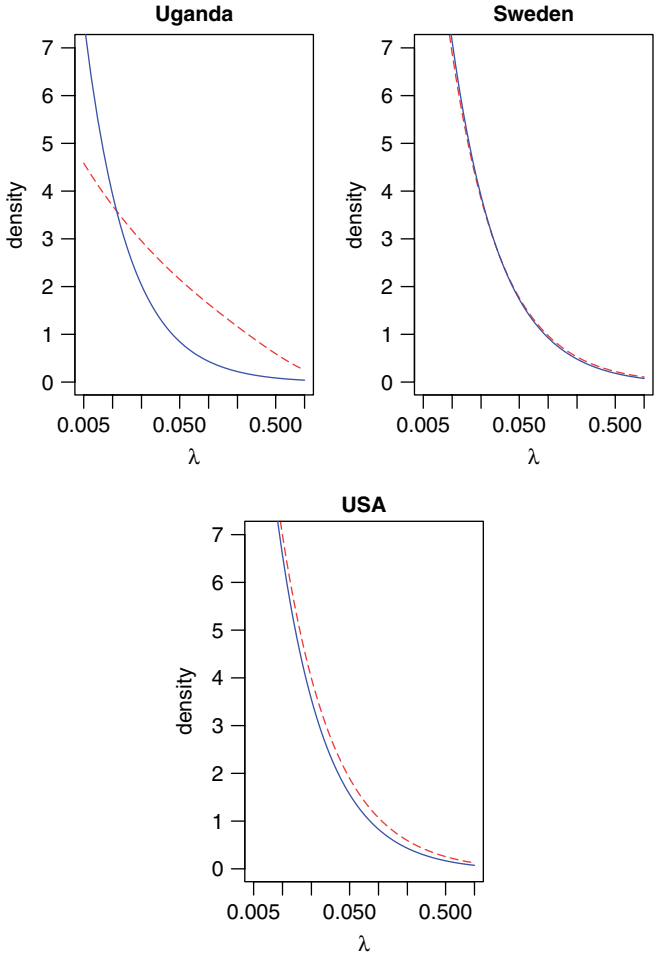

Fig. 1. Gamma heterogeneity in the rate of partner acquisition in the three populations. Women are solid blue lines, men are dashed red lines.

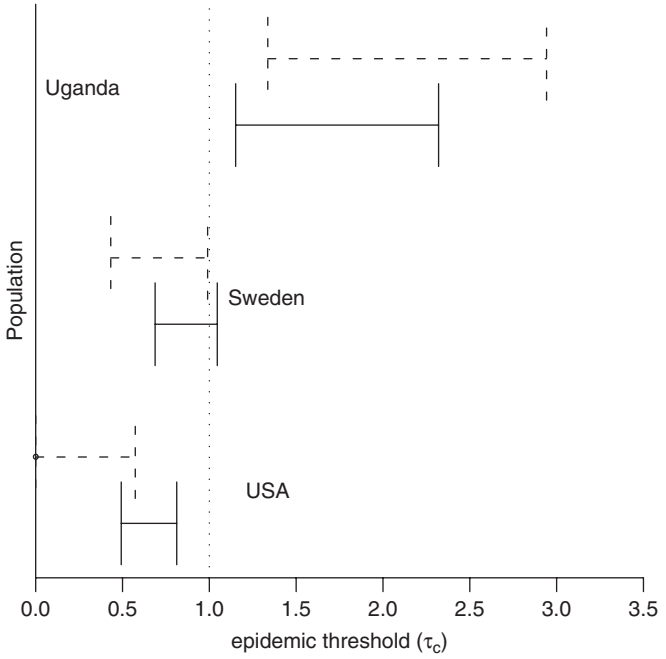

Fig. 2. Comparison of the 95% bootstrap confidence intervals for the epidemic threshold given by the negative binomial model (solid lines) and the Waring model (dashed lines) for each population.

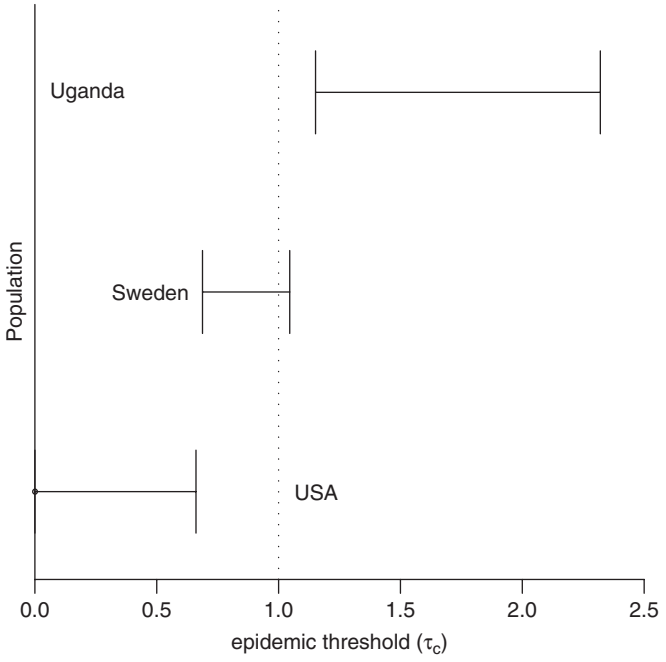

Fig. 3. 95% bootstrap confidence intervals for the epidemic threshold given by the best fitting model in each population.

occur. The confidence interval includes one, so it is possible that a critical transmissibility exists above which an epidemic must occur. In the USA, the confidence interval for the best fitting negative binomial-Waring model includes zero but does not include one. The test of the hypothesis that the threshold is zero against the alternative that it is positive has p-value $= 0.69$. Hence, the model predicts that there is a transmissibility above which the USA is certain to have an epidemic, and that this transmissibility may be zero.

4.3. Confidence intervals for $\mathscr{R}_0$

In this section we compute confidence intervals for $\mathscr{R}_0$. We do this conditional on an integrated transmissibility. Gray et al. (2001) estimate the probability of HIV transmission per coital act for the same population represented in our sample from the Rakai district, Uganda. They did not find a significant difference between τ_{fm} and τ_{mf}. To calculate a maximally conservative estimate, we can use the upper quintile of their estimate per act ($\gamma = 0.0015$), multiplied by both the mean number of coital acts reported per month, and the number of months over which the local network data were collected (i.e., 12). This yields an estimate of $\tau_{mf} = \tau_{fm} = 0.162$ so $\bar{\tau} = 0.162$.

Fig. 4 presents 95% confidence intervals for $\mathscr{R}_0$ for each population conditional on this value of $\bar{\tau}$. For comparability we have used the conservative Rakai value of $\bar{\tau}$ for Sweden and USA. The interval for Uganda is quite

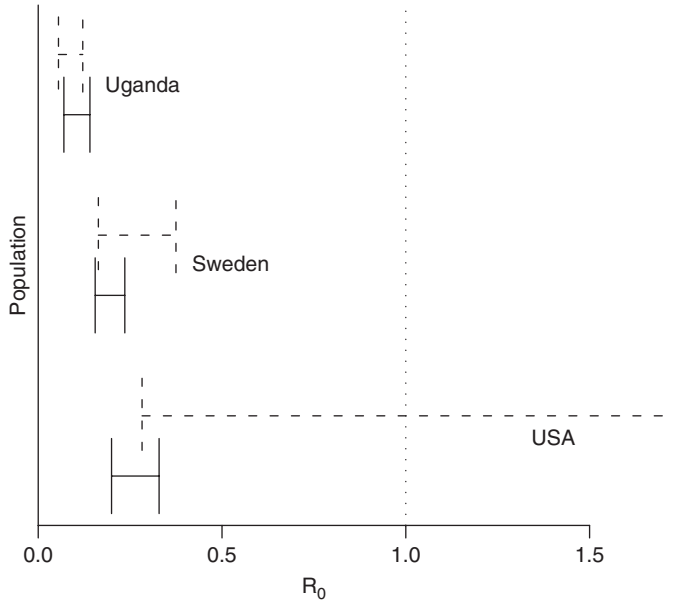

Fig. 4. Comparison of the 95% bootstrap confidence intervals for $\mathscr{R}_0$ given by the negative binomial model (solid lines) and the Waring model (dashed lines) for each population.

low—indeed as we have seen it will be below the epidemic threshold of one for all values of $\bar{\tau}$. For Sweden the estimates of $\mathscr{R}_0$ are about one-quarter of those required to ensure an epidemic. Thus, regardless of transmissibility there is negligible probability of an epidemic. Thus, both models correctly predict that there is not a general epidemic in Sweden.

For the United States, the confidence interval for the negative binomial model predicts an $\mathscr{R}_0$ comparable to that for Sweden and a negligible probability of an epidemic. The scale-free Waring model indicates only that we can be 95% confident that $\mathscr{R}_0$ is above 0.27. As we have seen, it predicts that an epidemic may be possible in the USA for any positive transmissibility. Based on the MLEs for the scaling parameters of the Waring model, the MLE of $\mathscr{R}_0$ for the USA is 0.81 (Eqs. (12), (11), and (8)). This indicates that the United States is possibly below, but quite near the epidemic threshold.

5. Discussion

Using a graph-theoretic, two-sex epidemic model, we are able to calculate confidence bounds for epidemic thresholds and reproductive numbers in three populations. Our results indicate that there is very high probability that two of the populations, Uganda and Sweden, are characterized by non-zero epidemic thresholds. Confidence intervals for the epidemic threshold in the USA include the zero value (i.e., the epidemic threshold may not be positive). The best fitting model suggests that there could be no epidemic threshold in the United States. However, alternative non-scale-free models close to it in terms of model fit indicate the presence of an epidemic threshold.

The models predict no epidemic in Uganda, despite Rakai having one of the most mature HIV/AIDS epidemics in the world. Four points may help to explain this apparent paradox. First, Rakai is characterized by a declining epidemic (Stoneburner and Low-Beer, 2004) and our finding that an epidemic cannot occur regardless of transmissibility may simply reflect the contracting epidemic. This seems somewhat unlikely however, since the HIV/AIDS prevalence is still 16%, higher than most other regions in the world. A second possibility which is closely related to the first is that there is potential censoring of highest-activity people due to premature mortality. The inclusion of more highly active individuals would have made the contact pattern less concentrated, making an epidemic more likely. A third intriguing possibility is that epidemiological assumptions underlying the HIV/AIDS epidemic in Africa are incorrect. Specifically, some recent research has suggested that the role of heterosexual transmission of HIV in Africa has been greatly overestimated and that a large fraction of HIV is attributable to contaminated needles (Brewer et al., 2003; Gisselquist and Potterat, 2003). The parenteral amplification hypothesis is interesting, but seems to have failed some critical empirical tests (Walker et al., 2003; Lopman et al., 2005). Finally, the epidemic model may simply fail to capture the actual risk structure of Rakai.

While the two-sex graph-theoretic formalism employed in this paper potentially increases the realism of models of STI dynamics, it still contains a major weakness which ultimately limits its utility. Specifically, it assumes random mixing conditional on degree. We suspect that this is the primary reason for the failure of the model to correctly predict the epidemic situation in Rakai. For compartmental epidemic models structured by activity class, departures from random mixing can either slow (if mixing is disassortative) or accelerate (if mixing is assortative) epidemic growth (Morris, 1991; Marschner, 1992; Garnett and Anderson, 1996). In either case, models with heterogeneous activity will yield lower equilibrium prevalence (Anderson and May, 1991). This point is made clear by the final-size equation given by Anderson and May (1991, p. 272) under heterogeneity:

$$I_\infty = 1 - (1 + \Lambda)^{-1/CV^2}, \tag{15}$$

where I_∞ is the overall fraction of the host population ever infected, Λ is an integrated measure of the force of infection over the course of the epidemic, and CV is the coefficient of variation of sexual activity in the population—see (2). Clearly, as $CV \to \infty$, $I \to 0$, a point recently re-emphasized by May and Lloyd (2001). This observation suggests that policy recommendations that emerge from recent discussions of "scale-free" networks (Liljeros et al., 2001) should be viewed with a strong degree of skepticism.

Newman (2002a) notes that correlations in the connectivity of nodes in a network can reduce epidemic

thresholds. The extent of assortative mixing by degree in sexual networks is an open empirical question in epidemiology. While Newman (2002a) notes the implications of such correlations for epidemic processes on social networks, the social network data he analyzes come from various professional collaboration networks (e.g., scientific co-authoring, business board membership, movie co-starring) and not from epidemiologically relevant network samples. There is no reason to believe that the structure of a sexual contact network resembles the collaboration network of mathematics papers. We suggest that sex and mathematics, while both potentially "social," are rather different activities.

Empirical work in epidemiology indicates that some networks show assortativeness by degree, some do not (Stoner et al., 2000), while some show it weakly (Garnett et al., 1996; Barlow et al., 1997). Degree-based correlations based on standard local network sampling procedures (Morris, 1997) are subject to considerable error. Respondents typically have accurate knowledge of their partners' behavior when they believe their partners have other partners (i.e., high specificity). However, respondents appear to be much worse judges of their partners' behavior when they report that their partners do not have other partners (i.e., low sensitivity) (Stoner et al., 2003). Unbiased estimates of assortative mixing by degree are further complicated by the fact that when sampling networks, a random sample of graph nodes does not yield a random sample of the graph's edges, and for STIs, the clear unit of epidemiological analysis is the partnership.

The answer to the question of degree-based correlations depends on the availability of quality data on the structure of the network that is not present in most sexual history surveys. Such surveys typically only ask questions about the number of sex partners. However, the information necessary for evaluating degree-based correlations is available from link-tracing designs and related adaptive designs (Goodman, 1961; Thompson and Seber, 1996). These observations emphasize the need for partner enrollment studies (e.g., Johnson et al., 2003) to facilitate improved inference on the contact structures which support STI epidemics.

In contrast with the recent network research suggesting that properties of sexual networks may facilitate STI spread and persistence—effectively lowering epidemic thresholds—the spatially motivated work of Sander et al. (2002) suggests that social networks can actually impede the spread of an STI. Whether or not the spatial lattice metaphor applies in any way to human intimate contacts, the point that *localization effects*, by partitioning sexual networks, could slow the spread of an STI (Keeling, 1999). The localization effects could be, literally, geographic or they could be social. For example, Laumann et al. (1994) report effective structural zeros in the NHSLS mixing-by-race matrix. African-American women are exceptionally unlikely to have white male partners, making direct transmission between these compartments rare.

A large body of research suggests that human sexual relations, like other forms of social interaction, are anything but random (e.g., Morris, 1991; Laumann et al., 1994; Youm and Laumann, 2002; McPherson et al., 2001). Modeling epidemics on contact structures which reflect, for example, differential homophily by age and race, and low levels of transitivity is a challenging task. Nonetheless, strong statements regarding optimal control and eradication strategies must be predicated on the best models for the system in question.

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