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The impact of past epidemics on future disease dynamics

Shweta Bansal [a,b,*], Lauren Ancel Meyers [c,d]

[a] Center for Infectious Disease Dynamics, The Pennsylvania State University, 208 Mueller Lab, University Park, PA 16802, United States
[b] Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA
[c] Section of Integrative Biology and Institute for Cellular and Molecular Biology, University of Texas at Austin, 1 University Station, C0930, Austin, TX 78712, USA
[d] Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA

HIGHLIGHTS

- We develop a contact network approach to study the spread of partially-immunizing infections.
- Such pathogens restructure the host contact network in a highly preferential manner.
- Leaky immunity confers greater herd immunity at moderate pathogen transmissibility than polarized immunity.
- Heterogeneous contact patterns increase the probability that a pathogen can re-invade the host population.

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ABSTRACT

Many pathogens spread primarily via direct contact between infected and susceptible hosts. Thus, the patterns of contacts or *contact network* of a population fundamentally shape the course of epidemics. While there is a robust and growing theory for the dynamics of single epidemics in networks, we know little about the impacts of network structure on long-term epidemic or endemic transmission. For seasonal diseases like influenza, pathogens repeatedly return to populations with complex and changing patterns of susceptibility and immunity acquired through prior infection. Here, we develop two mathematical approaches for modeling consecutive seasonal outbreaks of a partially-immunizing infection in a population with contact heterogeneity. Using methods from percolation theory we consider both *leaky immunity*, where all previously infected individuals gain partial immunity, and *polarized immunity*, where a fraction of previously infected individuals are fully immune. By restructuring the epidemiologically active portion of their host population, such diseases limit the potential of future outbreaks. We speculate that these dynamics can result in evolutionary pressure to increase infectiousness.

1. Introduction

Immunity acquired via infection gives an individual protection from subsequent infection by the same or similar pathogen for some period of time. For diseases such as measles, varicella (chickenpox), mumps and rubella, complete immunity lasts a lifetime. Therefore, an individual who has been infected by one of these pathogens, once recovered, cannot be reinfected, nor transmit the infection again. For other diseases, immunity wanes with time, leaving previously infected individuals only partially protected against reinfection (called *partial immunity*). This degradation of immunity may be caused by antigenic variation in the circulating pathogen or loss of antibodies over time. The transition from complete to partial immunity can happen over different timescales: over a few weeks as with norovirus and rotavirus (White et al., 2008), over months or a few years as with influenza (Hope-Simpson, 1992), or over many years as with pertussis (van Boven et al., 2000). Here, we present new methods for modeling the epidemiological consequences of partial immunity.

Although partial immunity is not well-understood, there is evidence that partial immunity functions in one of two ways: leaky or polarized. For a degree of partial immunity q, leaky partial immunity implies that each immunized individual reduces their chances of getting reinfected and infecting others by a proportion q, whereas polarized partial immunity implies that a fraction q of immunized individuals enjoy full protection from reinfection and the remaining $(1-q)$ fraction are completely susceptible. Leaky partial immunity is expected to be the more common of the two, and more consistent with our understanding

* Corresponding author at: Center for Infectious Disease Dynamics, The Pennsylvania State University, 208 Mueller Lab, University Park, PA 16802, United States.
E-mail address: shweta@sbansal.com (S. Bansal).

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of the immune system (Kaufmann et al., 2002). Polarized partial immunity is less common, but can occur if some individuals are unable to mount a lasting immune response to an otherwise fully immunizing disease. It has been observed, for example, in vaccine and animal studies for varicella, meningococcal infection (Chaves et al., 2007), and Hepatitis C (Bukh et al., 2008; Farci et al., 1992).

Partial immunity may impact the host in multiple ways, and have far-reaching implications for the transmission of a disease through a population. Specifically, it can decrease one or both of two fundamental epidemiological quantities: *infectivity*, the probability that an infected individual will infect a susceptible individual with whom he or she has contact; and *susceptibility*, the probability that a susceptible individual will be infected if exposed to disease via contact with an infected individual. In mathematical models, the probability of transmission (*transmissibility*) during a contact between an infected and susceptible individual is often represented as a product of the infectivity of the infected node and the susceptibility of the susceptible node. Partial immunity can limit transmissibility either by lowering the probability of reinfection or reducing the degree to which an infected individual sheds the pathogen. Both, for example, occur in the case of influenza (Shulman, 1970; Clements et al., 1986).

Mathematical modeling of infectious disease dynamics has been dominated by the Susceptible-Infected-Recovered (SIR) compartmental model (Kermack and McKendrick, 1927) which considers infectious disease transmission in a closed population of homogeneously-mixed individuals. Contact network epidemiology is a tractable and powerful mathematical approach that goes beyond homogeneous-mixing and explicitly captures the diverse patterns of interactions that underlie disease transmission (Barbour and Mollison, 1990; Watts and Strogatz, 1998; Pastor-Satorras and Vespignani, 2001; Meyers et al., 2005; Shirley and Rushton, 2005; Bansal et al., 2007). In this framework, the host population is represented by a network of individuals (each represented by a node) and the disease-causing contacts (represented by edges) between them (Fig. 2(a)). The number of contacts (edges) of a node is called its *degree*, and the distribution of degrees throughout the network fundamentally influences where and when a disease will spread (Meyers et al., 2005; Newman, 2002; Bansal et al., 2007). The traditional SIR model has been mapped to a bond percolation process on a contact network, in which individuals independently progress through S, I, and R stages if and when disease reaches their location in the network (Newman, 2002). The bond percolation threshold corresponds to the epidemic threshold, above which an epidemic outbreak is possible (i.e., one that infects a non-zero fraction of the population, in the limit of large populations); and the size of the percolating cluster (or giant component) above this transition corresponds to the size of the epidemic. The standard bond percolation model for disease spread through a network, however, assumes a completely naive population without immunity from prior epidemics (Newman, 2002).

Compartmental Susceptible-Infected-Recovered-Susceptible (SIRS) models extend the traditional homogeneous-mixing SIR model to consider the eventual loss of complete immunity acquired through infection (Hoppenstead and Waltman, 1971; Waltman, 1974; Grassly et al., 2005). Compartmental models of partially immunizing infections have been developed in the context of particular pathogens such as influenza (Recker et al., 2007; Levin et al., 2004; Nuno et al., 2008). These models include two strains of the circulating pathogen and are either history-based (that is, they assume leaky partial immunity) (Andreasen et al., 1997; Ballesteros et al., 2009) or status-based models (that is, they assume polarized immunity) (Gog and Swinton, 2002; Ballesteros et al., 2009). While these studies have provided valuable insights into the impacts of antigenic variation and immunity on epidemic dynamics, they are limited by the assumptions of homogeneous-mixing.

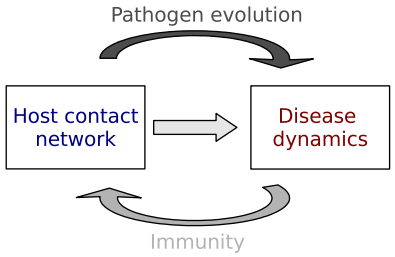

Fig. 1. A schematic of pathogen niche construction. Infection-acquired immunity and pathogen evolution shape the host population and future disease dynamics. Specifically, during an outbreak, infected individuals may acquire immunity to the circulating strain, thereby reshaping the epidemiological structure of the population for future outbreaks (medium gray arrow); the epidemiological structure of the population, in turn, directly constrains future outbreak dynamics (light gray arrow) and drives antigenic evolution of the pathogen (black arrow), thereby indirectly fueling the spread of disease to previously immunized individuals.

Researchers have just begun to use network models to explore the dynamics of trans-seasonal cross-immunity. While there has been scant theoretical treatment of partially immunizing infections, network SIS models assume that individuals immediately and completely lose immunity at the time of recovery from infection (Pastor-Satorras and Vespignani, 2001; Eames and Keeling, 2002). Lattice and small world network models have also been used to study the relationship between population structure and pathogen evolution, and most concur that connectivity enhances the evolution of infectivity and virulence (Boots and Sasaki, 1999; Boots and Mealor, 2007; Read and Keeling, 2006, 2003; Haraguchi and Sasaki, 2000).

In this paper, we extend the bond percolation framework to incorporate infection-acquired immunity into a network model. We model both polarized (Section 2.1) and leaky (Section 2.2) partial immunity, and show that the two models are identical in the cases of no immunity or complete immunity, but make very different predictions for partial immunity. We then consider the impact of infection-acquired immunity in a heterogeneous and structured host population on both future epidemiological and evolutionary dynamics. The evolution of infectiousness, virulence and a pathogen's antigenic characteristics are in part driven by the epidemiological environment. Although the interactions between contact network structure and pathogen evolution and competition have been studied (Boots and Sasaki, 1999; Read and Keeling, 2003; van Baalen, 2002; Buckee et al., 2004; Nunes et al., 2006), we do not yet understand how prior outbreaks impact future disease dynamics by shaping the immunological structure of the underlying host contact network (Fig. 1). Feedback from an evolving organism to its own ecological and evolutionary environment is known as "niche construction" (Odling-Smee et al., 2003; Boni and Feldman, 2005); and here we use our new models to explore niche construction by immunizing pathogens. Our work captures the preferential impact of immunity on the highly connected portion of the population, and highlights the difference between waning immunity and replenishment of susceptibles due to births, two effects that cannot be distinguished in homogeneous-mixing models.

2. Methods: incorporating infection-acquired immunity into a network model

We present two mathematical approaches to modeling partial immunity. First, we model polarized partial immunity by

completely removing a fraction of the individuals (their nodes and edges) who are infected during an epidemic (Fig. 2(b)) from the network. Using the standard bond percolation model, we then derive epidemiological quantities for a subsequent outbreak in the immunized population. Second, we model leaky partial immunity using a new two-type bond percolation model. The underlying contact network topology remains intact, but nodes are classified either as partially immune or susceptible (Fig. 2(c)). In both models, we assume that both infectivity and susceptibility are reduced due to immunity, but the leaky partial immunity model can be easily adapted to consider other scenarios.

Below, we use both models to consider dynamics in three random networks of specified degree distributions: (a) Poisson, with degree distribution $p_k = e^{-\lambda}\lambda^k/k!$; (b) exponential, with degree distribution $p_k = (1-e^{\kappa})e^{-\kappa(k-1)}$; and (c) scale-free, with degree distribution $p_k = k^{-\gamma}/\zeta(\gamma)$, each with a mean degree of 10. Bond percolation is exact on infinite random graphs of the given structure, and all model predictions are verified using stochastic simulations which assume a simple percolation process with matching parameters on finite random graphs of the specified degree structure.

2.1. Polarized partial immunity

Polarized partial immunity, sometimes known as "all-or-nothing" partial immunity or perfect immunity, implies that for a partial immunity level $(1-\alpha)$, a fraction $(1-\alpha)$ of the infected population are fully immune to reinfection (and thus transmission) and the remaining proportion α are fully vulnerable to reinfection (and transmission to others thereafter.) In terms of a contact network, this means that a fraction of the previously infected nodes are now completely removed (along with their edges) from the contact network and are no longer a part of the transmission process. The residual network, introduced in Ferrari et al. (2006) and Newman (2005) models this phenomenon. Previously, we characterized the residual network as the network made up of uninfected individuals and the edges connecting them Ferrari et al. (2006), as we assumed that all infected individuals had gained full immunity to infection and thus could be fully removed (along with their edges) from the transmission chains of future epidemics. Here, we extend the description of the residual network to include not only uninfected nodes, but also nodes that were previously infected but have lost immunity. We apply bond percolation methods to this extended residual network to model the spread of a subsequent outbreak in a population that has already suffered an initial outbreak.

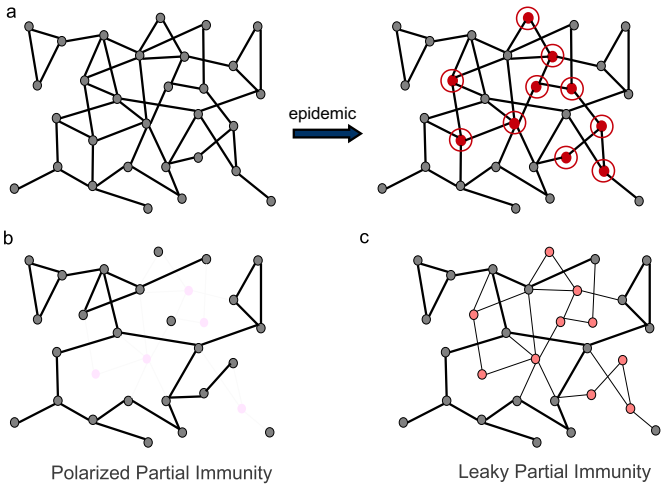

Fig. 2. Epidemiological contact networks. (a) Prior to an initial epidemic, all individuals are fully susceptible to disease (gray nodes). Then some individuals become infected during the epidemic (red nodes). (b) Polarized partial immunity (at 50%) means that half of the previously infected individuals are fully protected against reinfection, while the other half are fully susceptible again. (c) Leaky partial immunity (at 50%) means that all nodes remain in the network, but the edges leading to and/or from previously infected individuals are half as likely to transmit disease (illustrated here with the lighter edges.)

The simple Susceptible-Infectious-Recovered (SIR) bond percolation model allows us to derive fundamental epidemiological quantities. These quantities are simply based on the average transmissibility T of the pathogen (that is, the average probability that an infected node will transmit to a susceptible contact sometime during its infectious period) and the degree distribution of the host contact network, denoted $\{p(k)\}$ where $p(k)$ is the fraction of nodes with degree k. In particular, we can calculate the epidemic threshold (T_c) for a given network, above which a large-scale epidemic is possible; this is closely related to the traditional epidemiological quantity, R_0. We can also find the expected size of small outbreaks below this threshold and the expected size of an epidemic above the threshold (Newman, 2002). We will apply this method to calculate epidemic quantities for two consecutive seasons, and use subscripts 1 and 2 to denote initial and subsequent outbreak, respectively. Specifically, T_1 and T_2 denote the average transmissibilities of the pathogen in each season, respectively, and allow for evolution of infectiousness from one season to the next; $p_1(k)$ and $p_2(k)$ denote the fraction of susceptible nodes with k susceptible contacts prior to the first and second seasons, respectively; and u_1 and u_2 denote the fraction of contacts that remain uninfected following each outbreak (see Supplementary Information for calculation). We assume that all nodes are susceptible prior to the first season and that α is the proportion of infected individuals who have lost immunity following the first season.

Next, we derive the degree distribution of the *residual network*, that is, the susceptible portion of the network following the initial outbreak. The probability that an individual of degree k will remain uninfected after the first epidemic is given by $\eta_1(k) = (1-T_1+T_1u_1)^k$ (Meyers et al., 2005 and Supplementary Information). For a randomly chosen individual in the network, this probability is $\eta_1 = \sum_k p_1(k)\eta_1(k)$. The nodes in the residual network (*residual nodes*) include the fraction η_1 of nodes that are not infected in the first season and the fraction $(1-\eta_1)\alpha$ of nodes that are infected but rapidly lose immunity, prior to the second outbreak. We refer to these as *uninfected* and *re-susceptible* nodes, respectively. The edges in the residual network (*residual edges*) include all edges in the original network that connect residual nodes to each other. The proportion of residual nodes with l residual edges just prior to the second outbreak is given by

$$p_2(l) = \frac{\sum_{k\geq l} p_1(k)(\eta_1(k)p_2(l|k,\text{uninfected}) + \alpha(1-\eta_1(k))p_2(l|k,\text{re-susceptible}))}{\sum_k p_1(k)(\eta_1(k) + \alpha(1-\eta_1(k)))} \quad (1)$$

where $p_2(l|k,\text{uninfected})$ and $p_2(l|k,\text{re-susceptible})$ are the probabilities that a residual node has l residual edges given that it originally had degree k and given that it is uninfected or re-susceptible, respectively, following the first season. The equations for these conditional probabilities explicitly consider the disease status of the residual node. For uninfected nodes, we know that none of the neighboring nodes transmitted disease to the focal node; for re-susceptible nodes, we know that one neighbor transmitted disease to the focal node and the focal node may have transmitted disease to some of its other neighbors. (Details provided in Supplementary Information.) Specifically, the probabilities that an uninfected or re-susceptible node

has l residual edges, given that it had k edges in the original network (prior to the first season), with $k \geq l$, are given by

$$p_2(l|k,\text{uninfected}) = \binom{k}{l}(u_1+(1-u_1)\alpha)^l((1-u_1)(1-\alpha))^{k-l}$$

$$p_2(l|k,\text{re-susceptible}) = \begin{cases} (1-\alpha)\tau^{(k-1)} & l=0 \\ \alpha\left(\binom{k-1}{l-1}\sigma^{(l-1)}\tau^{(k-1)-(l-1)}\right) & \\ \quad +(1-\alpha)\left(\binom{k-1}{l}\sigma^{l}\tau^{(k-1)-l}\right) & l\in[1,k-1] \\ \alpha\sigma^{(k-1)} & l=k \end{cases}$$

where, $\sigma=(u_1(1-T_1)(1-\alpha)+\alpha)$ and $\tau=((1-u_1+T_1u_1)(1-\alpha))$ are the probabilities that a random edge of a re-susceptible node (other than the edge connecting to the neighbor that originally infected the re-susceptible node) is residual or non-residual, respectively. $p_2(l|k,\text{re-susceptible})$ explicitly assumes that each re-susceptible node was infected by one of its neighbors during the initial epidemic. This transmitting neighbor was necessarily infected during the first epidemic, and subsequently lost immunity with probability α for the case $l=k$ or retained immunity with probability $(1-\alpha)$ for the case $l=0$. We note that $p_2(l|0,\text{re-susceptible})=0$, since nodes without contacts in the original network cannot be infected.

The residual degree distribution $\{p_2(l)\}$ thus reflects the epidemiologically active portion of the population following the initial epidemic. Although the residual network differs from the original contact network in degree distribution, component structure and other topological characteristics, it is still reasonable to model it as a semi-random graph using bond percolation methods (Newman, 2002), even if the original network is a non-random empirical network (see Supplementary Information).

Next, we use standard bond percolation techniques (Newman, 2002) to derive key epidemiological quantities for a subsequent outbreak. First we present an equation for the epidemic threshold, that is, the critical value of transmissibility above which a second epidemic is possible, given that previously infected individuals have polarized immunity. It is a function of the residual degree distribution $\{p_2(l)\}$, which incorporates the original network topology and the loss of immunity, α, and is given by

$$(T_2^c)_{polar} = \frac{\sum_l l p_2(l)}{\sum_l l(l-1)p_2(l)}.$$

If the second outbreak strain is below this threshold, then there are only small outbreaks, which, on average, have size

$$\langle s\rangle_{polar} = 1+\frac{T_2\sum_l l p_2(l)}{1-T_2/(T_2^c)_{polar}}.$$

Above the epidemic threshold, we may have large-scale epidemics with expected size

$$1-\sum_l p_2(l)u_2^l$$

where u_2 is the probability that a random edge in the residual network leads to a node which was uninfected in the second outbreak (see Supplementary Information). Thus the overall proportion of the population expected to become infected during a second epidemic, assuming polarized partial immunity at a level $(1-\alpha)$ is given by

$$(S_2)_{polar} = (\eta_1+\alpha(1-\eta_1))\left(1-\sum_l p_2(l)u_2^l\right)$$

where η_1 represents the size of the population which was uninfected in the first outbreak and $\alpha(1-\eta_1)$ is the proportion of the population that was infected in the previous outbreak but has lost immunity.

2.2. Leaky partial immunity

To model leaky partial immunity, we reduce the probabilities of reinfection and transmission for all nodes infected in the first epidemic. Rather than deleting nodes and attached edges entirely (as above), we introduce a two-type percolation approach in which the parameters of disease transmission depend on the epidemiological history of both nodes involved in any contact.

2.2.1. Two-type percolation

The standard bond percolation model of Newman (2002) assumes that, all nodes of a given degree k are homogeneous with respect to disease susceptibility and all edges are homogeneous (probabilities of transmission along edges are i.i.d. random variables with mean T). We extend the basic model to allow for two types of nodes, we call them A and B; and four types of edges, AA, AB, BA, BB, connecting all combinations of nodes. Allard et al. (2009) also discuss a general extension of this type. We use p_{ij} to denote the joint probability that a uniform random type A node has i edges leading to other type A nodes and j edges leading to type B nodes (where i the A-degree of the node and j the B-degree of the node). Similarly, q_{ij} denotes the joint probability of a type B node having an A-degree of i and a B-degree of j. The multivariate probability generating functions (PGFs) for these probability distributions are given by

$$f_A(x,y) = \sum p_{ij}x^iy^j$$

$$f_B(x,y) = \sum q_{ij}x^iy^j.$$

While f_A and f_B describe the distribution of degrees of randomly chosen A and B nodes, the degree of a node reached by following a randomly chosen edge is measured by the its excess degree (Newman, 2002). The PGFs for the A-excess degree and the B-excess degree of A and B nodes are given by

$$f_{AA}(x,y) = \frac{\sum i p_{ij}x^{i-1}y^j}{\sum i p_{ij}}, \quad f_{BA}(x,y) = \frac{\sum j p_{ij}x^iy^{j-1}}{\sum j p_{ij}}$$

$$f_{AB}(x,y) = \frac{\sum i q_{ij}x^{i-1}y^j}{\sum i q_{ij}}, \quad f_{BB}(x,y) = \frac{\sum j q_{ij}x^iy^{j-1}}{\sum j q_{ij}}$$

as illustrated in Fig. 3.

Having formalized the structure of the contact network in PGFs, we can now derive the distributions for the number of infected edges, which are edges over which disease has been successfully transmitted. We assume that for each edge type (XY),

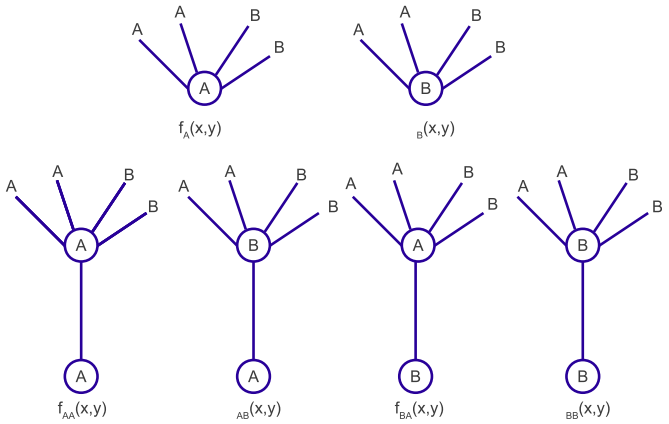

Fig. 3. The probability generating functions give the numbers of A and B contacts for each type of vertex (top). The four excess degree distributions give the numbers of each type of contact for a vertex chosen by following a uniform random edge (bottom).

transmission probabilities are i.i.d. random variables with averages denoted T_{XY}, and that these values can vary among the four edge types. Then the PGFs for the number of infected ("occupied") edges emanating from a node of type A and B are, respectively

$$f_A(x,y;T_{AA},T_{AB}) = f_A((1+(x-1)T_{AA}),(1+(y-1)T_{AB}))$$

$$f_B(x,y;T_{BA},T_{BB}) = f_B((1+(x-1)T_{BA}),(1+(y-1)T_{BB})).$$

Each of these generating functions was derived following the arguments outlined in Newman (2002) for the simple bond percolation SIR model. We can similarly derive the PGFs for the number of infected excess edges emanating from a node of type A (B), at which we arrived by following a uniform random edge from a node of type A (B):

$$f_{AA}(x,y;T_{AA},T_{AB}) = f_{AA}((1+(x-1)T_{AA}),(1+(y-1)T_{AB}))$$

$$f_{BA}(x,y;T_{AA},T_{AB}) = f_{BA}((1+(x-1)T_{AA}),(1+(y-1)T_{AB}))$$

$$f_{AB}(x,y;T_{BA},T_{BB}) = f_{AB}((1+(x-1)T_{BA}),(1+(y-1)T_{BB}))$$

$$f_{BB}(x,y;T_{BA},T_{BB}) = f_{BB}((1+(x-1)T_{BA}),(1+(y-1)T_{BB})).$$

The PGFs for outbreak sizes starting from a node of type A or B, respectively, are then given by

$$F_A(x,y;T_{AA},T_{AB}) = xf_A(F_{AA}(x,y;\{T\}),F_{AB}(x,y;\{T\});T_{AA},T_{AB})$$

$$F_B(x,y;T_{BA},T_{BB}) = yf_B(F_{BA}(x,y;\{T\}),F_{BB}(x,y;\{T\});T_{BA},T_{BB})$$

where F_{AA} and F_{BA} are the PGFs for the outbreak size distribution starting from an (infected) node of type A which has been reached by following an edge from another (infected) node of type A or B, respectively. Similarly, F_{AB} and F_{BB} are the PGFs for the outbreak size distribution starting from an (infected) node of type B which has been reached by following an edge from another (infected) node of type A or B, respectively. These PGFs are as follows:

$$F_{AA}(x,y;\{T\}) = xf_{AA}(F_{AA}(x,y;\{T\}),F_{AB}(x,y;\{T\});T_{AA},T_{AB})$$

$$F_{BA}(x,y;\{T\}) = xf_{BA}(F_{BA}(x,y;\{T\}),F_{BB}(x,y;\{T\});T_{AA},T_{AB})$$

$$F_{AB}(x,y;\{T\}) = yf_{AB}(F_{BA}(x,y;\{T\}),F_{BB}(x,y;\{T\});T_{BA},T_{BB})$$

$$F_{BB}(x,y;\{T\}) = yf_{BB}(F_{BA}(x,y;\{T\}),F_{BB}(x,y;\{T\});T_{BA},T_{BB})$$

Again following the method of Newman (2002), we can derive the expected size of a small outbreak and the epidemic threshold (given in the Supplementary Information). The expected numbers of A and B nodes infected in a small outbreak are found by taking partial derivatives of the PGF for the outbreak size distribution

$$\langle s\rangle_A = \left.\frac{\partial F_A}{\partial x}\right|_{x=1,y=1} + \left.\frac{\partial F_B}{\partial x}\right|_{x=1,y=1}$$

$$\langle s\rangle_B = \left.\frac{\partial F_A}{\partial y}\right|_{x=1,y=1} + \left.\frac{\partial F_B}{\partial y}\right|_{x=1,y=1}.$$

Finally, we can find the size of a large-scale epidemic among A nodes and among B nodes as:

$$\begin{aligned} S_A(T_{AA},T_{AB}) &= 1-F_A(1,1;T_{AA},T_{AB}) \\ &= 1-\sum p_{ij}(1+(a-1)T_{AA})^i(1+(c-1)T_{AB})^j \end{aligned} \quad (2)$$

$$\begin{aligned} S_B(T_{BA},T_{BB}) &= 1-F_BB(1,1;T_{BA},T_{BB}) \\ &= 1-\sum q_{ij}(1+(b-1)T_{BA})^i(1+(d-1)T_{BB})^j \end{aligned} \quad (3)$$

where $a = F_{AA}(1,1;\{T\})$, $b = F_{BA}(1,1;\{T\})$, $c = F_{AB}(1,1;\{T\})$, $d = F_{BB}(1,1;\{T\})$. The probability of a large-scale epidemic can be derived similarly. The numerical values for the size and probability of an outbreak will be equal if $T_{AB} = T_{BA}$. Further details are provided in the Supplementary Information.

This two-type percolation model provides a general framework for modeling pathogens with variable transmissibility and host populations with immunological heterogeneity.

2.2.2. Modeling leaky immunity with two-type percolation

We now apply the two-type percolation method to model leaky partial immunity. In this model, type A nodes represent individuals who were not infected in the initial epidemic and thus have no prior immunity, and type B nodes represent those who were infected and maintain partial immunity (at a level $1-\alpha$). (Note that α gives the fraction of immunity lost in both models.) Here, we assume that prior immunity causes equivalent reductions in both infectivity and susceptibility (α), but the approach can be extended easily to include more complex models of immunity. Specifically, during the subsequent epidemic, type A individuals (previously uninfected) have a susceptibility of one and an infectivity of T_2, while type B individuals (previously infected) have a susceptibility of α and an infectivity of $T_2\alpha$. Correspondingly, $T_{AA} = T_2$, $T_{AB} = T_2\alpha$, $T_{BA} = T_2\alpha$, and $T_{BB} = T_2\alpha^2$.

The joint degree distributions for a randomly chosen uninfected (type A) and infected (type B) node connecting to i uninfected and j infected nodes are respectively given by

$$p_{ij} = \frac{p_1(i+j)\eta_1(i+j)\binom{i+j}{i}(u_1)^i(1-u_1)^j}{\sum_k p_1(k)\eta_1(k)}$$

$$q_{ij} = \frac{p_1(i+j)(1-\eta_1(i+j))\binom{i+j-1}{i}(u_1(1-T_1))^i((1-u_1)+u_1T_1)^{j-1}}{\sum_k p_1(k)(1-\eta_1(k))}.$$

p_{ij} describes the probability of an uninfected node of original degree $(i+j)$ having i uninfected neighbors and j infected neighbors. The probability of a node being uninfected and having original degree $(i+j)$ is calculated as $\eta_1(i+j)p_1(i+j)$. Such an uninfected node would have i uninfected neighbors (with probability u_1) and j infected neighbors (with probability $(1-u_1)$). Similarly, q_{ij} describes the probability of an infected node of original degree $(i+j)$ having i uninfected neighbors and j infected neighbors. The probability of a node being infected and having original degree $(i+j)$ is calculated as $(1-\eta_1(i+j))p_1(i+j)$. Such an infected node would have i uninfected neighbors (with probability $u_1(1-T_1)$); $j-1$ infected neighbors who were either (a) infected by another source (with probability $(1-u_1)$), or (b) infected by the node in question (with probability u_1T_1); and one additional infected neighbor who infected the node in question. We note that $q_{i0} = 0$ because an infected node must have at least one infected neighbor.

Using the quantities derived above, we can model epidemics that leave varying levels of individual-level partial immunity. Using Eqs. (2) and (3), for example, we can solve for the size of the epidemic in a second epidemic with (individual-level) leaky partial immunity, $(1-\alpha)$

$$(S_2)_{leaky} = (\eta_1)S_A(T_2,T_2\alpha)+(1-\eta_1)S_B(T_2\alpha,T_2\alpha^2).$$

We derive the epidemic threshold, $(T_2^c)_{leaky}$, and the average size of small outbreaks, $\langle s\rangle_{leaky}$, for the leaky immunity model in the Supplementary Information.

2.3. Comparison to homogeneous-mixing models with immunity

We compare our network model to homogeneous-mixing mean-field (compartmental) models with polarized and leaky immunity. Compartmental SIR dynamics are given by

$$dS/dt = -\frac{\langle k\rangle\beta SI}{N}$$

$$dI/dt = \frac{\langle k \rangle \beta SI}{N} - \gamma I$$

where β is the transmission rate, γ is the recovery rate, $\langle k \rangle$ gives the mean degree of the population, $S(0) = S_0 - 1$, $I(0) = 1$ and $\Sigma = N - S(\infty)$ gives the final epidemic size for a population of size N.

To model polarized immunity at a level α, we use these equations for two consecutive seasons. First, an initial epidemic occurs in a naive population ($S_0 = N$) with $\beta = \beta_1$, resulting in a final epidemic size Σ; then a second epidemic occurs with $S_0 = (N - \Sigma) + \alpha\Sigma$, $I(0) = 1$, and $\beta = \beta_2$.

To model leaky immunity at a level α, we use these equations to model the first seasons. As with polarized immunity, the initial epidemic occurs in a naive population ($S_0 = N$) with $\beta = \beta_1$, resulting in an epidemic of size Σ. However, prior to the second season, we split the population into two subpopulations: previously uninfected and previously infected individuals. The SIR dynamics during a second epidemic in the two subpopulations is then given by

$$dS_i/dt = -\left(\sum B_{ij} I_j\right) S_i/N$$

$$dI_i/dt = \left(\sum B_{ij} S_j\right) I_i/N - \gamma I_i$$

for $i = 1,2$ corresponding to the previously uninfected and previously infected populations, respectively, $S_1(0) = N - \Sigma$, $S_2(0) = \Sigma$ and

$$B = \langle k \rangle \beta_2 \begin{bmatrix} 1 & \alpha \\ \alpha & \alpha^2 \end{bmatrix}$$

describing the reduction in susceptibility and infectivity due to leaky immunity for each pair of interactions.

When comparing these models to our network-based models, we let $\beta = T\gamma/(1-T)$ where T is the pathogen transmissibility.

3. Results

3.1. Impact of one epidemic on the next

We have introduced two distinct mathematical approaches for modeling the epidemiological consequences of naturally acquired immunity. The polarized immunity model probabilistically removes nodes and edges corresponding to the fraction (α) of infected nodes expected to lose immunity entirely. The leaky immunity model tracks the epidemiological history of all individuals and reduces the infectivity and susceptibility of all previously infected nodes by a fraction (α). By adjusting α, both models can explore the entire range of immunity from none to complete. At $\alpha = 1$, these model the absence or complete loss of immunity and thus would apply when the second season strain is entirely antigenically distinct from the prior strain. At $\alpha = 0$, these model full immunity or no loss of prior immunity and might apply when a secondary epidemic is caused by the same or very similar pathogen as caused the first epidemic. Values of α between 0 and 1 represent partial immunity to the second pathogen, with the level of protection increasing as α approaches 0. Note that the total susceptibility and total transmissibility over the entire network is equal in the two immunity models (see Supplementary Information).

In Fig. 4, we compare the predicted sizes of a second epidemic for both the polarized and leaky models against simulations for a Poisson, exponential and scale-free random network (of the same mean degree) and under the conditions of no prior immunity ($\alpha = 1$), partial immunity ($\alpha = 0.5$), and full immunity ($\alpha = 0$) for values of transmissibility between 0 and 0.5. There is a strong congruence between our analytical calculations and their corresponding simulations. Assuming no immunity (Fig. 4(a)), the two models simplify to the standard bond percolation model on the original network, and thus make identical predictions. Assuming full immunity (Fig. 4(c)), the polarized immunity model removes all previously infected nodes (and the corresponding edges) before the second outbreak; and the leaky immunity model sets transmissibility along all edges leading from and to previously infected nodes to zero, thus de-activating those nodes entirely. Consequently, the models also converge at this extreme. The two models are, however, fundamentally different for any level of intermediate partial immunity between ($0 < \alpha < 1$) as they assume different models of immunological protection. At $\alpha = 0.5$ (Fig. 4(b)), leaky immunity confers greater herd immunity than polarized immunity at low values of transmissibility, while the reverse is true for more infectious pathogens. The makeup of the previously infected population is identical in both models and biased towards high degree individuals. When the pathogen is only mildly contagious, partial protection may be sufficient to prevent infection for most hosts. Thus, leaky immunity (where all previously infected hosts have some immunity) may yield a

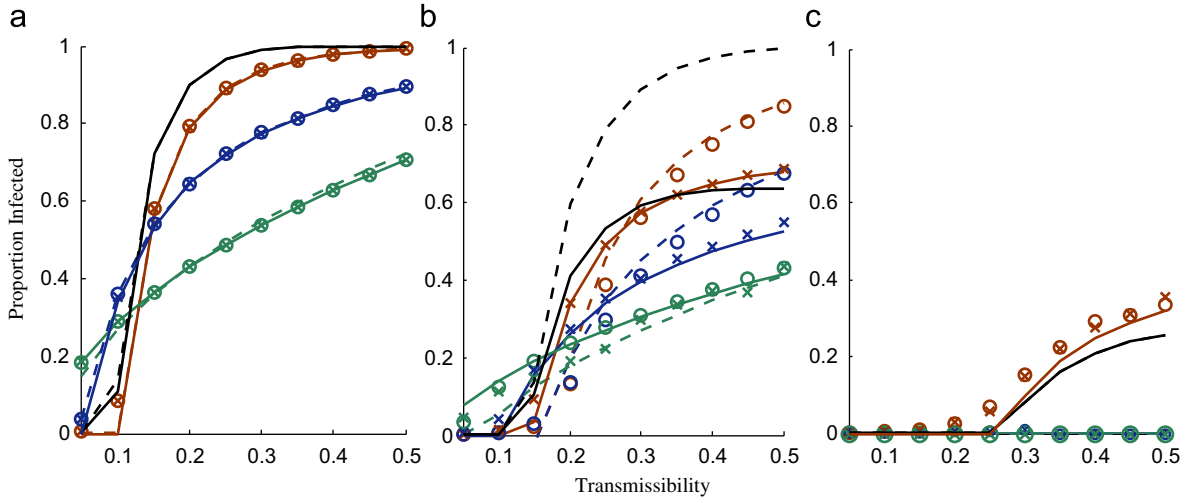

Fig. 4. Expected size of a second epidemic as infectiousness increases. We compare the predictions of our mathematical models for polarized (solid line) and leaky (dashed line) immunity to corresponding numerical simulations (crosses and circles indicate polarized and leaky immunity, respectively). Calculations are for three types of networks: mean field (black); and Poisson (red), exponential (blue), and power law (green) networks with mean degree 10, for three levels of immunity: (a) no immunity ($\alpha = 1$), (b) partial immunity ($\alpha = 0.5$), and (c) full immunity ($\alpha = 0$), and for a range of second strain transmissibility values (T_2) along each x-axis (assuming $T_1 = 0.15$ in all cases).

greater number of protected hosts than polarized immunity (where a fraction of previously infected hosts have full immunity). When the pathogen is more highly contagious, however, the reverse may be true, that is, leaky immunity may leave many more previously infected hosts insufficiently protected than polarized immunity. We find further that network heterogeneity acts consistently across different levels of immunity. The Poisson network has the most homogeneous degree distribution followed by the exponential network and finally the scale-free network with considerable heterogeneity. Holding mean degree constant, variance in degree increases the vulnerability of the population (allowing epidemics to occur at lower rates of transmissibility), yet generally reduces the ultimate size of epidemics when they occur. At high levels of immunity, the susceptible network at the start of the second season becomes more sparse and homogeneous. Thus the impact of network variance on the second epidemic diminishes as immunity increases, that is, as $\alpha \to 0$. (We elaborate further on these results in the Supplementary Information.)

We explore intermediate levels of immunity further in Fig. 5, and again find reasonable agreement between our analytic predictions and simulations. As expected, increasing levels of immunity (from left to right) decrease the epidemic potential of a second outbreak. At these intermediate values of transmissibility ($T_1 = 0.15$ and $T_2 = 0.3$), leaky immunity tends to confer lower herd immunity than polarized immunity, except at extremely high levels of immunity. The level of immunity at which the predicted epidemic sizes for two immunity models cross represents the point at which leaky partial immunity for all prior cases effectively protects more individuals than the complete removal of a fraction of those cases. This transition point occurs at a higher level of immunity in the exponential network than the Poisson network, and never occurs in the scale-free network, perhaps because the immunized individuals in the more heterogeneous networks tend to have anomalously high numbers of contacts thus limiting the efficacy of partial protection.

Figs. 4 (black curves) and 5(a) also show predictions of the mean-field models of polarized and leaky immunity. For full immunity ($\alpha = 0$) and no immunity ($\alpha = 1$) the two homogeneous-mixing models make identical predictions: at $\alpha = 1$, both models reduce to $S_0 = N$ and a homogeneous transmission rate β; and at $\alpha = 0$, both models reduce to one population of size $S_0 = N - \Sigma$ and transmission rate β. However, at an intermediate level of immunity ($\alpha = 0.5$), the mass action models predict that polarized immunity consistently provides more herd protection than leaky immunity (in contrast to the network model prediction of a threshold above which polarized immunity provides greater protection than leaky immunity and below which the reverse is true). A similar discrepancy between the models occurs in Fig. 5: in the mass action model (Fig. 5(a)), polarized immunity consistently offers more population-level protection than leaky immunity over all levels of immunity for a fixed intermediate value of transmissibility ($T_2 = 0.3$). The early (low immunity and low transmissibility) advantage of leaky immunity in the network model stems from the preferential infection and resulting immunization of the highest degree (most connected) individuals. In the compartmental model, all individuals have identical contact rates and thus leaky immunity loses this advantage and the reduced effective population size under polarized immunity model always gives a lower final epidemic size. As discussed in Bansal et al. (2007), the compartmental model is equivalent to a network model in which all individuals have identical degree. Of the three networks considered here, it is most similar to although not identical to the relatively homogeneous Poisson network model, as seen in Figs. 4 and 5.

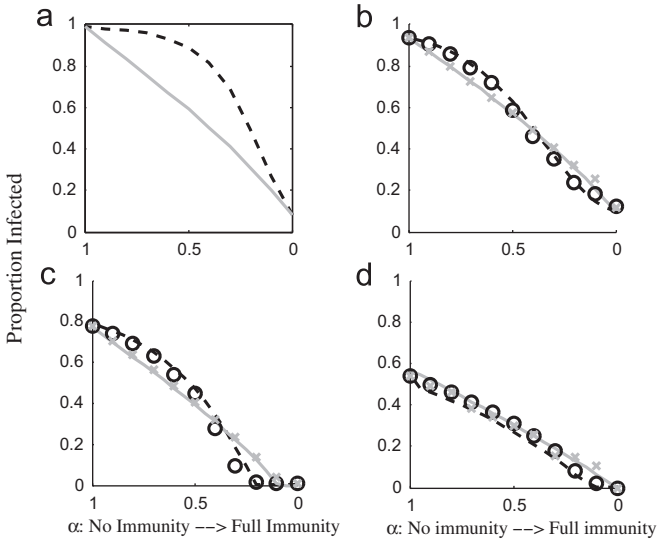

Fig. 5. Expected size of a second epidemic as immunity increases. We compare predictions of the polarized immunity model (gray solid lines), leaky immunity model (black dash lines) and simulations for each model (gray cross and black circle markers, respectively). Calculations and simulations are for networks with (a) mean-field (b) Poisson, (c) exponential, and (d) scale-free degree distributions with mean degree of 10, at transmissibilities $T_1 = 0.15$ and $T_2 = 0.3$.

3.2. Pathogen re-invasion and immune escape

When a pathogen enters a population that has experienced a prior outbreak, its success will depend on the extent and pattern of naturally-acquired immunity in the host population. The new pathogen may not be able to invade unless it is significantly different from the original strain. If it is antigenically distinct from the prior strain, then prior immunity may be irrelevant; if it is more transmissible than the original strain, then it may have the potential to reach previously unexposed individuals.

Fig. 6 indicates the minimum transmissibility required for the new strain to cause an epidemic (that is, its critical transmissibility T_{2_c}), as a function of the transmissibility of the original strain (T_1) and the level of leaky immunity (α). The leakier the immunity (high α) and the lower the infectiousness of the original strain (low T_1), the more vulnerable the population to a second epidemic (light coloration in Fig. 6). Generally the homogeneous Poisson network is less vulnerable to re-invasion than the heterogeneous scale-free network. The blue curves in Fig. 6 show combinations of T_1 and α where the epidemic threshold for the new strain equals the transmissibility of the original strain ($T_{2_c} = T_1$, see Supplementary Information) and have two complementary interpretations. First, if we assume that the new strain is exactly as transmissible as the original strain ($T = T_2 = T_1$), then the curves indicate the critical level of cross-immunity ($\alpha_c(T)$) below which the strain can never re-invade and above which the strain can re-invade with some probability that increases with α. This threshold indicates the extent of antigenic evolution (or intrinsic decay in immune response) required for a second epidemic to occur. The more heterogeneous the contact patterns (scale-free versus Poisson network), the lower the amount of immune escape required for a pathogen of the same transmissibility to re-invade. Second, if we assume a fixed level of immune decay (α), then the curves indicate the critical initial transmissibility (T_1) above which it is possible for the original strain or a similarly infectious variant to invade. Below this transmission rate, the network topology and preexisting immunity prevent the re-emergence of the pathogen and only permit epidemics of more transmissible variants. The polarized immunity model yields similar results (Supplementary Information).

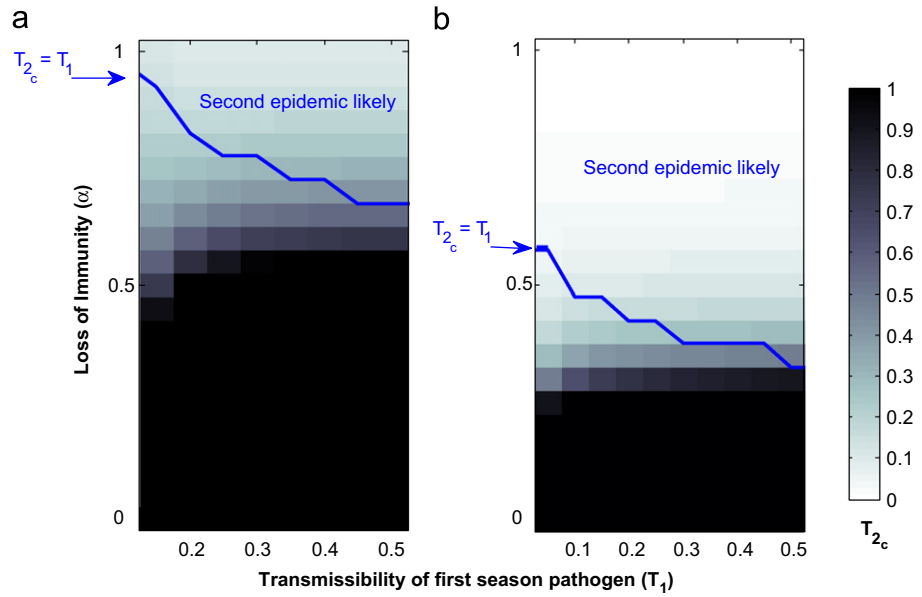

Fig. 6. Epidemic threshold (T_{2_c}) in the second season. The colors indicate the level of transmissibility required for the second strain to invade the population (cause an epidemic), assuming leaky partial immunity for (a) a Poisson-distributed network and (b) a scale-free network, each with mean degree of 10. The *x*-axis gives the first season transmissibility (T_1) and *y*-axis gives the loss of immunity (α). The blue line denotes $T_{2_c} = T_1$; above the line $T_{2_c} < T_1$, and re-invasion by the original pathogen is possible.

A well-known hypothesis in the theory of pathogen evolution is that increases in virulence correlate positively with increases in transmissibility (Anderson and May, 1982; Ewald, 1987; Bull, 1994; Frank, 1996). If true, Fig. 6 suggests that naturally acquired immunity, by opening niches for more infectious variants, may indirectly lead to the evolution of greater virulence. This is consistent with a previous study showing that host populations with high levels of immunity maintain more virulent pathogens than naive host populations (Gandon et al., 2001). In addition, Fig. 6 also suggests that more homogeneous host contact patterns (i.e. small variability in numbers of contacts) enhance the evolution of more virulent pathogens. This complements the results of Boots and Sasaki (1999) and other studies that have shown that global connectivity in spatially structured host populations fosters the evolution of pathogen virulence.

4. Discussion and conclusion

In this work, we have considered the impact of infectious disease outbreaks on the future spread and evolution of the pathogen. We have compared two standard models for immunity, polarized and leaky, and found that the extent of herd immunity varies with the pathogen transmissibility and the degree and nature of immunity. Leaky immunity is expected to confer greater herd immunity at moderate levels of pathogen infectiousness across all levels of partial immunity, whereas polarized immunity is expected to be more effected at higher transmissibilities.

The evolution of new antigenic characteristics that escape prior immunity in a pathogen and the evolution of higher transmissibility in a pathogen both depend on genetic variation. Thus, the more infections there are in the first season, the greater the opportunity for evolutionary change (Boni et al., 2004). This poses a trade-off for the pathogen: a large initial epidemic may generate variation that fuels evolution yet wipes out the susceptible pool for the subsequent season; while a small initial outbreak leaves a large fraction of the network susceptible to future transmission yet may fail to generate sufficient antigenic or other variation for future adaptation. We have shown that the trade-off between generating immunity via infections and escaping immunity via antigenic drift will depend not only on the size of the susceptible population, but also on its connectivity. Although we have focused primarily on the role of antigenic drift, these models also apply to loss of immunity through decay in immunological memory, as occurs following pertussis and measles infections (Mossong and Muller, 2003; van Boven et al., 2000).

Our work suggests that contact heterogeneity can have far-reaching impacts on disease dynamics and evolution. Our models reveal that pathogens restructure their host population networks in a highly preferential manner, that does not resemble an unbiased random process. Thus, in contrast to the predictions of mean-field models (Grenfell et al., 2002; Broutin et al., 2010), our analyses suggest that the replenishment of susceptibles through waning immunity differs fundamentally from the introduction of susceptibles through births.

This analysis also has implications for public health intervention strategies. Contact-reducing interventions (e.g., patient quarantine and social distancing) and vaccination often result in complete removal of a fraction of individuals from the network (akin to polarized immunity), whereas transmission-reducing interventions (e.g., face-masks and other hygienic precautions) typically reduce transmissibility along edges leading to and from a fraction of individuals (akin to leaky immunity) (Pourbohloul et al., 2005). These results thus suggest that contact reductions will be more effective than a comparable degree of transmission reductions at higher levels of pathogen infectiousness.

Much epidemiological work, particularly the analysis of intervention strategies, ignores the immunological history of the host population. Thus our effort to incorporate host immune history into a flexible individual-based network model will potentially advance our understanding of the epidemiological and evolutionary dynamics of partially immunizing infections such as influenza, pertussis, or rotavirus. However, these provide just an initial step in this direction, as the models consider only two consecutive seasons and do not take into account longer-term interactions or changes in the structure of the contact network between seasons.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.radphyschem.2011.02.020.

References

Allard, A., Noel, P., Dube, L., Pourbohloul, B., 2009. Heterogeneous bond percolation on multitype networks with an application to epidemic dynamics. Phys. Rev. E 79 (3), 036113.
Anderson, R.M., May, R.M., 1982. Coevolution of hosts and parasites. Parasitology 85, 411–426.
Andreasen, V., Lin, J., Levin, S.A., 1997. The dynamics of cocirculating influenza strains conferring partial cross-immunity. J. Math. Biol. 35, 825–842.
Ballesteros, S., Vergu, E., Cazelles, B., 2009. Influenza A gradual and epochal evolution: insights from simple models. PLoS One 4 (10), e7426.
Bansal, S., Grenfell, B., Meyers, L.A., 2007. When individual behavior matters: homogeneous and network models in epidemiology. J. R. Soc. Interface 4 (16).
Barbour, A., Mollison, D., 1990. Epidemics and random graphs. In: Stochastic Processes in Epidemic Theory. Springer. pp. 86–89.
Boni, M.F., Gog, J.R., Andreasen, V., Christiansen, F.B., 2004. Influenza drift and epidemic size: the race between generating and escaping immunity. Theor. Popul. Biol. 65 (2 March), 179–191.
Boni, M.F., Feldman, M.W., 2005. Evolution of antibiotic resistance by human and bacterial niche construction. Evolution 59 (3).
Boots, M., Mealor, M., 2007. Local interactions select for lower pathogen infectivity. Science 315, 1284–1286.
Boots, M., Sasaki, A., 1999. Small worlds and the evolution of virulence. Proc. Biol. Sci. 266, 1933–1938.
van Boven, M., de Melker, H.E., Schellekens, J.F., Kretzschmar, M., 2000. Waning immunity and subclinical infection in an epidemic model: implications for pertussis in the Netherlands. Math. Biosci. 164, 161–182.
Broutin, H., Viboud, C., Grenfell, B.T., Miller, M.A., Rohani, P., 2010. Impact of vaccination and birth rate on the epidemiology of pertussis: a comparative study in 64 countries. Proc. Biol. Sci. 277, 3239–3245, http://dx.doi.org/10.1098/rspb.2010.0994.
Buckee, C.O., Koelle, K., Mustard, M.J., Gupta, S., 2004. The effects of host contact network structure on pathogen diversity and strain structure. Proc. Natl. Acad. Sci. 101 (29), 10839–10844.
Bukh, J., Thimme, R., Meunier, J., Faulk, K., Spangenberg, H.C., Chang, K., Satterfield, W., Chisari, F.V., Purcell, R.H., 2008. Previously infected chimpanzees are not consistently protected against reinfection or persistent infection after reexposure to the identical hepatitis c virus strain. J. Virol. 82, 8183–8195.
Bull, J., 1994. Virulence. Evolution 48, 1423–1435.
Chaves, S., Gargiullo, P., Zhang, J., Civen, R., Guris, D., et al., 2007. Loss of vaccine-induced immunity to varicella over time. N. Engl. J. Med. 356, 1121–1129.
Clements, M.L., Betts, R.F., Tierney, E.L., Murphy, B.R., 1986. Serum and nasal wash antibodies associated with resistance to experimental challenge with influenza a wild-type virus. J. Clin. Microbiol. 24, 157–160.
Eames, K.T.D., Keeling, M.J., 2002. Modeling dynamic and network heterogeneities in the spread of sexually transmitted diseases. Proc. Natl. Acad. Sci. 99, 13330–13335.
Ewald, P.W., 1987. Transmission modes and evolution of the parasitism–mutualism continuum. Ann. NY Acad. Sci. 503, 295–306.
Farci, P., Alter, H.J., Govindarajan, S., Wong, D.C., Engle, R., Lesniewski, R.R., Mushahwar, I.K., Desai, S.M., Miller, R.H., Ogata, N., Purcell, R.H., 1992. Lack of protective immunity against reinfection with Hepatitis C virus. Science 258 (October), 135–140.
Ferrari, M., Bansal, S., Meyers, L.A., Bjornstad, O., 2006. Network frailty and the geometry of herd immunity. Proc. Biol. Sci. 273, 2743–2748.
Frank, S.A., 1996. Models of parasite virulence. Q. Rev. Biol. 71, 37–78.
Gandon, S., Mackinnon, M., Nee, S., Read, A.F., 2001. Imperfect vaccines and the evolution of pathogen virulence. Nature 414, 751–756.
Gog, J.R., Swinton, J., 2002. A status-based approach to multiple strain dynamics. J. Math. Biol. 44, 169–184.
Grassly, N.C., Fraser, C., Garnett, G.P., 2005. Host immunity and synchronized epidemics of syphilis across the United States. Nature 433, 417–421.
Grenfell, B.T., Bjornstad, O.N., Finkenstadt, B., 2002. Dynamics of measles epidemics: scaling noise, determinism and predictability with the TSIR model. Ecol. Mono. 72, 185–202.
Haraguchi, Y., Sasaki, A., 2000. Evolution of parasite virulence and transmission rate in a spatially structured population. J. Theor. Biol. 203, 85–96.
Hope-Simpson, R.E., 1992. The Transmission of Epidemic Influenza. Plenum Press, New York.
Hoppenstead, F., Waltman, P., 1971. A problem in the theory of epidemics II. Math. Biosci. 12, 133–145.
Kaufmann, S., Sher, A., Ahmed, R., 2002. Immunology of Infectious Diseases. ASM Press.
Kermack, W.O., McKendrick, A.G., 1927. A contribution to the mathematical theory of epidemics. Proc. R. Soc. A 115, 700–721.
Levin, S., Dushoff, J., Plotkin, J., 2004. Evolution and persistence of influenza A and other diseases. Math. Biosci. 188, 17–28.
Meyers, L.A., Pourbohloul, B., Newman, M.E.J., Skowronski, D.M., Brunham, R.C., 2005. Network theory and SARS: predicting outbreak diversity. J. Theor. Biol. 232, 71–81.
Mossong, J., Muller, C.P., 2003. Modelling measles re-emergence as a result of waning of immunity in vaccinated populations. Vaccine 21, 4597–4603.
Newman, M.E.J., 2002. Spread of epidemic disease on networks. Phys. Rev. E 66 (016128).
Newman, M.E.J., 2005. Threshold effects for two pathogens spreading on a network. Phys. Rev. Lett. 95 (108701).
Nunes, A., Telo da Gama, M.M., Gomes, M.G.M., 2006. Localized contacts between hosts reduce pathogen diversity. J. Theor. Biol. 241, 477–487.
Nuno, M., Castillo-Chavez, C., Feng, Z., Martcheva, M., 2008. Mathematical models of influenza: the role of cross-immunity, quarantine and age-structure. In: Lecture Notes in Mathematics. Springer, Berlin. pp. 349–364.
Odling-Smee, F.J., Laland, K.N., Feldman, M.W., 2003. Niche construction: The neglected process in evolution. In: Monographs in Population Biology, vol. 37. Princeton University Press.
Pastor-Satorras, R., Vespignani, A., 2001. Epidemic dynamics and endemic states in complex networks. Phys. Rev. E 63 (066117).
Pourbohloul, B., Meyers, L.A., Skowronski, D.M., Krajden, M., Patrick, D.M., 2005. Modeling control strategies of respiratory pathogens. Emerg. Infect. Dis. 11, 1249–1256.
Read, J., Keeling, M.J., 2003. Disease evolution on networks: the role of contact structure. Proc. R. Soc. B 270, 699–708.
Read, J.M., Keeling, M.J., 2006. Disease evolution across a range of spatio-temporal scales. J. Popul. Biol. 70, 201–213.
Recker, M., Pybus, O., Nee, S., Gupta, S., 2007. The generation of influenza outbreaks by a network of host immune responses against a limited set of antigenic types. Proc. Natl. Acad. Sci. 104, 7711–7716.
Shirley, M.D.F., Rushton, S.P., 2005. The impacts of network topology on disease spread. Ecol. Complex 2, 287–299.
Shulman, J.L., 1970. Effects of immunity on transmission of influenza: experimental studies. Progr. Med. Virol. 12, 128–216.
van Baalen, M., 2002. Contact networks and the evolution of virulence. In: Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management. Cambridge University Press, Cambridge.
Waltman, P., 1974. Deterministic threshold models in the theory of epidemics. In: Lecture Notes in Biomathematics, vol. 1.
Watts, D., Strogatz, S.H., 1998. Collective dynamics of small world networks. Nature 393 (441).
White, L., Buttery, J., Cooper, B., Nokes, D., Medley, G., 2008. Rotavirus within day care centres in Oxfordshire, UK: characterization of partial immunity. J. R. Soc. Interface 5, 1481–1490.