

The Impact of Past Epidemics on Future Disease Dynamics

Shweta Bansal^{*†‡} Lauren Ancel Meyers^{§¶}

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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 shapes 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 *perfect 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

^{*}Center for Infectious Disease Dynamics, The Pennsylvania State University, 208 Mueller Lab, University Park PA 16802

[†]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA

[‡]Corresponding Author: shweta@sbansal.com

[§]Section of Integrative Biology and Institute for Cellular and Molecular Biology, University of Texas at Austin, 1 University Station, C0930, Austin, TX 78712, USA

[¶]Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA

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 [41], over months or a few years as with influenza [20], or over many years as with pertussis [38]. 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 perfect. 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 perfect partial immunity implies that a fraction q of immunized individuals enjoy full protection from reinfection and the remaining $(1 - q)$ proportion are completely susceptible. Leaky partial immunity is expected to be the more common of the two, and more consistent with our understanding of the immune system [22]. Perfect 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 [12], and Hepatitis C [10, 15].

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 [36, 13].

Mathematical modeling of infectious disease dynamics has been dominated by the Susceptible-Infected-Recovered (SIR) compartmental model [23] which considers infectious disease transmission in a closed population of individuals who enjoy complete immunity following infection. The SIR model has been extended to Susceptible-Infected-Recovered-Susceptible (SIRS) dynamics to model the full loss of complete immunity after a temporary period of protection [21, 39], and has been applied successfully in several situations (e.g. [19]). Models of partially immunizing pathogens are less common, and have primarily been developed for particular pathogens, such as influenza [34, 24, 29]. They consider the impacts of antigenic variation and the resulting complex patterns of cross-immunity on epidemic dynamics, but are limited by the assumptions of homogeneous-mixing.

Contact network epidemiology is a tractable and powerful mathematical ap-

proach that goes beyond homogeneous-mixing and explicitly captures the diverse patterns of interactions that underlie disease transmission [5, 40, 31, 25, 35, 4]. 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 (Figure 1(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 [25, 27, 4]. 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 [27]. 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 [27].

In this paper, we extend the bond percolation framework to consider the impact of infection-acquired immunity on epidemiological dynamics. We model both perfect (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. The evolution of infectiousness, virulence and a pathogen’s antigenic characteristics are in part driven by the epidemiological environment. Although significant attention has been paid to the interaction between contact network structure and pathogen evolution and competition [8, 33, 37, 9, 28], we do not yet understand the inter-seasonal interactions via modification to the immunological structure of the host contact network. Feedback from an evolving organism to its own ecological and evolutionary environment is generally known as niche construction [30, 7]. Here, we use our models to explore a particular instance of niche construction: the impacts of prior epidemics on the future dynamics of the pathogen.

2 Methods: Incorporating Infection-Acquired Immunity into a Network Model

We present two mathematical approaches to modeling partial immunity. First, we model perfect partial immunity by completely removing a fraction of the individuals (their nodes and edges) who are infected during an epidemic (Figure 1(b)) from the network. Using the 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 percolation model. The underlying contact network topology remains intact, but nodes are classified either as partially immune or susceptible (Figure 1(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 model other effects of immunity.

Below, we use both models to consider dynamics in three network types: (a) Poisson, with degree distribution $p_k = e^{-\lambda}\lambda^k/k!$; (b) exponential, with degree distribution $p_k = (1 - e^{-\lambda})e^{-\lambda k}$; and (c) scale-free, with degree distribution $p_k = k^{-\gamma}/\zeta(\gamma)$, each with a mean degree of 10. All model predictions are verified using stochastic simulations which assume a simple percolation process with parameters to match the model.

2.1 Perfect Partial Immunity

Perfect partial immunity, sometimes known as “all-or-nothing” partial immunity or polarized 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 transmitting to others) 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 its edges) from the contact network and are no longer a part of the transmission process. The residual network, introduced in [16, 3] models this phenomenon. Previously, we characterized the residual network as the network made up of uninfected individuals and the edges connecting them, 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 chain of future epidemics. Now, we extend the description of the residual network to include not only uninfected nodes, but also nodes that were previously infected but have already 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.

The simple Susceptible-Infectious-Recovered (SIR) bond percolation model allows us to derive fundamental epidemiological quantities 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 [27]. This assumes that the probabilities of transmission from infected nodes to susceptible nodes are *iid* random variables. We can then calculate the epidemic threshold for a given network (T_c), above which a large scale epidemic is possible; this is closely related to the traditional epidemiological quantity, R_0 . We can also find the probability and expected size of an epidemic above that threshold as well as the probability that an individual at the end of a randomly chosen edge (contact) does not become infected during an epidemic (u) [27]. 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 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 the each outbreak.

The probability that an individual of degree k will remain uninfected after the first epidemic can be calculated as $(1 - T_1 + T_1 u_1)^k$ [25]. We denote this probability $\eta_1(k)$. We next derive the degree distribution of the epidemiologically active portion of the network following the initial outbreak. This includes both nodes that were not infected and nodes that were infected and subsequently lost immunity, as well as all edges connecting them. The fraction of *active* nodes with k *active* edges just prior to the second outbreak is given by

$$p_2(k) = \frac{p_2^{uninfected}(k) + \alpha p_2^{infected}(k)}{\sum_j p_1(j) \eta_1(j) + \alpha \sum_j p_1(j) (1 - \eta_1(j))} \quad (1)$$

where $p_2^{uninfected}(k)$ and $p_2^{infected}(k)$ are the fractions of susceptible nodes with k susceptible neighbors among previously uninfected and infected nodes, respectively and α is the proportion of infected individuals who have lost immunity prior to the second outbreak. The denominator of Equation 4 gives the proportion of the network that is susceptible prior to the second outbreak, where the first term considers previously uninfected nodes, and the second term gives the proportion α of previously infected nodes.

The probability that a node in the residual network has k remaining edges (i.e. edges that connect them to other susceptible nodes), given that it had κ edges in the initial network is the following:

$$p_2(k|k_{init} = \kappa) = \binom{\kappa}{k} (u_1 + (1 - u_1)\alpha)^\kappa ((1 - u_1)(1 - \alpha))^{\kappa - k}$$

For every node in the residual network, remaining edges include (a) those that lead to nodes that were uninfected in the previous epidemic (which occurs with probability u_1 [3]) and (b) those that lead to nodes that were infected but have lost immunity (which occurs with probability $(1 - u_1)\alpha$). Then the degree distribution prior to season two can thus be rewritten as,

$$p_2(k) = \frac{\sum_{\kappa \geq k} p_1(\kappa) \eta_1(\kappa) p_2(k|k_{init} = \kappa) + \alpha \sum_{\kappa \geq k} p_1(\kappa) (1 - \eta_1(\kappa)) p_2(k|k_{init} = \kappa)}{\sum_j p_1(j) \eta_1(j) + \alpha \sum_j p_1(j) (1 - \eta_1(j))}$$

We provide the full derivation of this equation in the Supplementary Information.

The residual degree distribution $\{p_2(k)\}$ 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 (as shown in [3]) and thus apply bond percolation methods [27]. Additionally, we show in Supplementary Information that both immunity models also perform well on non-random realistic or empirical

networks. We next derive epidemiological quantities that predict the fate of a subsequent outbreak through the residual network.

The probability generating function (PGF) for the second season degree distribution in terms of the PGF for the initial degree distribution, $\Gamma_1(x)$ is given by

$$\Gamma_2(x) = \frac{\Gamma_1(r(x(1-s) + s)) + \alpha\Gamma_1((1-r)(x(1-s) + s))}{\Gamma_1(r) + \alpha(1 - \Gamma_1(r))}.$$

where $r = (1 - T_1 + T_1 u_1)$ is the probability that disease was not transmitted along a uniform random edge in the first epidemic; and $s = (1 - u_1)(1 - \alpha)$ is the probability that a node at the end of a uniform random edge was infected gained full immunity.

This allows us to derive the epidemic threshold for the subsequent outbreak, that is, the critical value of transmissibility above which a second epidemic is possible, given that some previously infected individuals have perfect immunity. It is a function of the original network topology (via the PGF $\Gamma_1(x)$) and the loss of immunity, α , and is given by

$$(T_{2c})_{perfect} = \frac{\Gamma_2'(1)}{\Gamma_2''(1)} = \frac{\Gamma_1'(r)r(1-s) + \alpha\Gamma_1'(1-r)(1-r)(1-s)}{\Gamma_1''(r)r^2(1-s)^2 + \alpha\Gamma_1''(1-r)(1-r)^2(1-s)^2}$$

where $\Gamma_1'(r), \Gamma_1'(1-r)$ are the average degrees among previously uninfected nodes and infected nodes, respectively. If the second strain is above this epidemic threshold, then the following equation gives the expected fraction of the residual population infected during the resulting epidemic

$$S_2 = 1 - \Gamma_2(u_2)$$

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 fraction expected to become infected during a second epidemic, assuming perfect partial immunity at a level $(1 - \alpha)$ is given by

$$(S_2)_{perfect} = S_2 \left(\sum_k p_1(k)\eta_1(k) + \alpha \left(1 - \sum_k p_1(k)\eta_1(k) \right) \right)$$

where $\sum p_k \eta_k$ represents the size of the population which was uninfected in the previous outbreak and $\alpha(1 - \sum p_k \eta_k)$ 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 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 [27] 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. (A similar model was recently introduced in [1].) 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

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

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

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 [27]. The PGFs for the A -excess degree and the B -excess degree of A and B nodes are given by

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

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

as illustrated in Figure 2.

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), 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 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 [27] 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):

$$\begin{aligned} f_{AA}(x, y; T_{AA}, T_{AB}) &= f_{AA}((1 + (x - 1)T_{AA}), (1 + (y - 1)T_{AB})) \\ f_{BA}(x, y; T_{AA}, T_{AB}) &= f_{BA}((1 + (x - 1)T_{AA}), (1 + (y - 1)T_{AB})) \\ f_{AB}(x, y; T_{BA}, T_{BB}) &= f_{AB}((1 + (x - 1)T_{BA}), (1 + (y - 1)T_{BB})) \\ f_{BB}(x, y; T_{BA}, T_{BB}) &= f_{BB}((1 + (x - 1)T_{BA}), (1 + (y - 1)T_{BB})) \end{aligned}$$

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

$$\begin{aligned} F_A(x, y; T_{AA}, T_{AB}) &= x f_A(F_{AA}(x, y; \{T\}), F_{AB}(x, y; \{T\}); T_{AA}, T_{AB}) \\ F_B(x, y; T_{BA}, T_{BB}) &= y f_B(F_{BA}(x, y; \{T\}), F_{BB}(x, y; \{T\}); T_{BA}, T_{BB}) \end{aligned}$$

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

$$\begin{aligned} F_{AA}(x, y; \{T\}) &= x f_{AA}(F_{AA}(x, y; \{T\}), F_{AB}(x, y; \{T\}); T_{AA}, T_{AB}) \\ F_{BA}(x, y; \{T\}) &= x f_{BA}(F_{BA}(x, y; \{T\}), F_{BB}(x, y; \{T\}); T_{AA}, T_{AB}) \\ F_{AB}(x, y; \{T\}) &= y f_{AB}(F_{BA}(x, y; \{T\}), F_{BB}(x, y; \{T\}); T_{BA}, T_{BB}) \\ F_{BB}(x, y; \{T\}) &= y f_{BB}(F_{BA}(x, y; \{T\}), F_{BB}(x, y; \{T\}); T_{BA}, T_{BB}) \end{aligned}$$

Again following the method of [27], 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:

$$\begin{aligned} \langle s \rangle_A &= \frac{\partial F_A}{\partial x} \Big|_{x=1, y=1} + \frac{\partial F_B}{\partial x} \Big|_{x=1, y=1} \\ \langle s \rangle_B &= \frac{\partial F_A}{\partial y} \Big|_{x=1, y=1} + \frac{\partial F_B}{\partial y} \Big|_{x=1, y=1} \end{aligned}$$

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

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

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

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 equal sized 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 type *A* and type *B* nodes depend on the course of the initial epidemic, and are given by

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

$$q_{ij} = p_1(i+j)(1-\eta_1(i+j)) \binom{i+j}{i} u_1^i (1-u_1)^j$$

respectively, where i is the *A*-degree and j is the *B*-degree. Further explanation can be found in Supplementary Information.

Using the quantities derived above, we can model epidemics that leave varying levels of individual-level partial immunity. Using equations 7 and 8, for example, we can solve for the size of the epidemic in a second epidemic with (individual-level) leaky partial immunity, $(1 - \alpha)$:

$$(S_2)_{leaky} = \left(\sum_k p_1(k)\eta_1(k) \right) S_A(T_2, T_2\alpha) + \left(1 - \sum_k p_1(k)\eta_1(k) \right) S_B(T_2\alpha, T_2\alpha^2).$$

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 residual network model probabilistically removes nodes and edges corresponding to the fraction (α) of infected nodes expected to lose immunity entirely. The two-type percolation 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 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.

In Figure 3, we compare the predicted sizes of a second epidemic for both the perfect 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 (Figure 3(a)), the two models simplify to the standard bond percolation model on the original network, and thus make identical predictions. Assuming full immunity (Figure 3(c)), the perfect 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 deactivating 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 (Figure 3(b)). At $\alpha = 0.5$, leaky immunity confers greater herd immunity than perfect 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, leaky immunity goes a long way towards protecting all previously infected hosts whereas perfect immunity protects only a fraction of these hosts; when it is more highly contagious, however, leaky immunity is insufficient to protect hosts with large numbers of contacts whereas perfect immunity is not diminished. 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 $\alpha \rightarrow 0$. (We elaborate further on these results in the Supplementary Information.)

We explore intermediate levels of immunity further in Figure 4, 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 perfect 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.

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; and if it is more transmissible than the original strain, then it may have the potential to reach previously unexposed individuals.

Figure 5 indicates the minimum transmissibility required for the new strain to cause an epidemic (that is, its critical transmissibility T_{2c}), 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 Figure 5). Generally the homogeneous Poisson network is less vulnerable to re-invasion than the heterogeneous scale-free network. The blue curves in figure 5 show combinations of T_1 and α where the epidemic threshold for the new strain equals the transmissibility of the original strain ($T_{2c} = T_1$) 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 invade and above which the strain can 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 the new strain can only invade if it is more contagious than the original strain ($T_2 > T_1$). Below this point, the network topology and preexisting immunity create a selective environment that excludes the original strain and favors more transmissible variants. The perfect immunity model yields similar results (Supplementary Information.)

Some epidemiologists have speculated that there are 'trade-offs' between virulence and infectiousness, implying that more infectious pathogens will necessarily be more virulent [2, 14, 11, 17]. If true, figure 5 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 naïve host populations [18].

4 Discussion & Conclusion

In this work, we have considered the impact of pathogen spread on future outbreaks of the same or similar pathogen and on pathogen invasion and evolution. We have compared two standard models for immunity, perfect and leaky, and found that the extent of herd immunity varies with the pathogen transmissibility and the degree and nature of immunity. Leaky immunity appears to confer greater herd immunity at moderate levels of pathogen infectiousness for all levels of partial immunity, whereas perfect immunity is more effective at higher transmissibilities.

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 perfect 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) [32]. These results thus suggest that contact reductions will be more effective than a comparable degree of transmission reductions at higher levels of pathogen infectiousness.

The evolution of new antigenic characteristics in a pathogen that escape prior immunity and the evolution of higher transmissibility both depend on genetic variation. Thus, the more infections there are in the first season, the greater the opportunity for evolutionary change [6]. 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 [26, 38].

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 yet allow for replenishment or depletion of susceptibles due to births and deaths.

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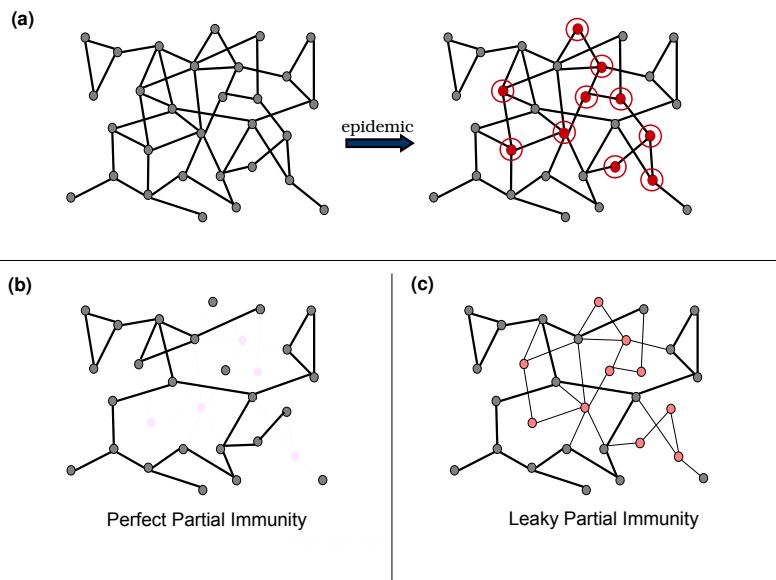


Figure 1: Epidemiological contact networks. (a) Prior to an initial epidemic, all individuals are fully susceptible to disease (gray nodes). Then some individuals become infected during the epidemic (red nodes). (b) Perfect partial immunity (at 50%) means that half of the previously infected individuals 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.)

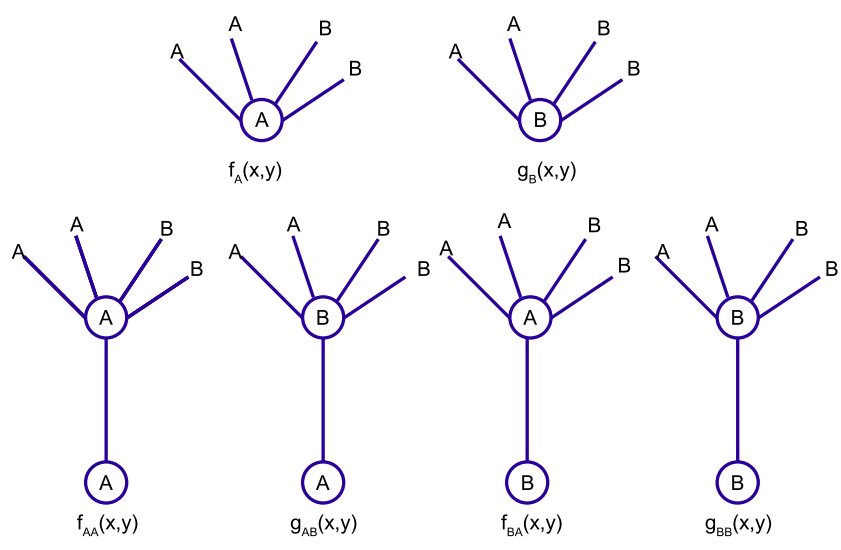


Figure 2: The probability generating functions give the numbers of A and B contacts for each type of vertex (top). The four excess degree distributions give the numbers of each type of contact for a vertex chosen by following a uniform random edge (bottom).

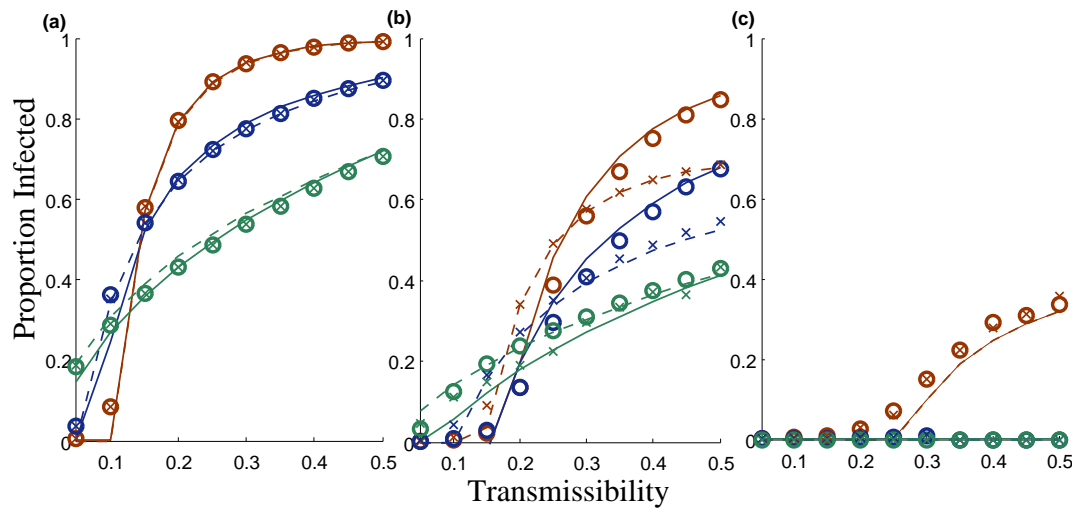


Figure 3: Expected size of a second epidemic as infectiousness increases. We compare the predictions of our mathematical models for perfect (dashed line) and leaky (solid line) immunity to corresponding numerical simulations (crosses and circles indicate perfect and leaky immunity, respectively). Calculations are for three types of networks: Poisson (red), exponential (blue), and power law (green) 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).

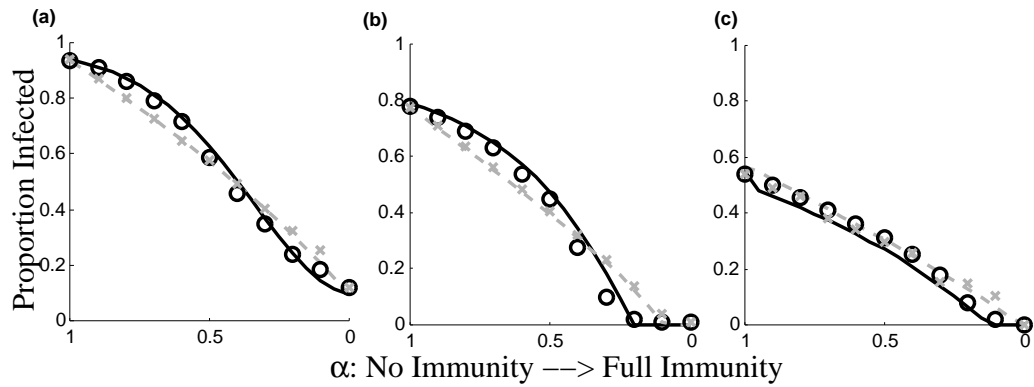


Figure 4: Expected size of a second epidemic as immunity increases. We compare predictions of the perfect immunity model (gray dashed lines), leaky immunity model (black solid lines) and simulations for each model (gray cross and black circle markers, respectively). Calculations and simulations are for networks with (a) Poisson, (b) exponential, and (c) scale-free degree distributions with mean degree 10, at transmissibilities $T_1 = 0.15$ and $T_2 = 0.3$.

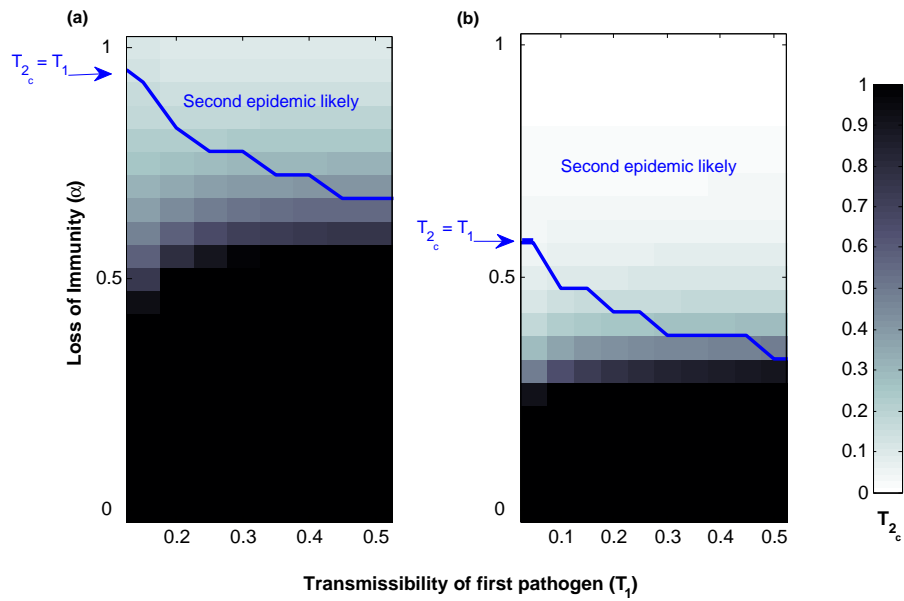


Figure 5: Epidemic threshold (T_{2c}) in the second season. The colors indicate the level of transmissibility required for the second strain to invade the population (cause an epidemic), assuming leaky partial immunity for (a) a Poisson-distributed network and (b) a scale-free network, each with mean 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 $T_{2c} = T_1$; above the line $T_{2c} < T_1$, and invasion by the original pathogen is possible.