We investigate the impact of contact structure clustering on the dynamics of multiple diseases interacting through coinfection of a single individual, two problems typically studied independently. We highlight how clustering, which is well known to hinder propagation of diseases, can actually speed up epidemic propagation in the context of synergistic coinfections if the strength of the coupling matches that of the clustering. We also show that such dynamics lead to a first-order transition in endemic states, where small changes in transmissibility of the diseases can lead to explosive outbreaks and regions where these explosive outbreaks can only happen on clustered networks. We develop a mean-field model of coinfection of two diseases following susceptible-infectious-susceptible dynamics, which is allowed to interact on a general class of modular networks. We also introduce a criterion based on tertiary infections that yields precise analytical estimates of when clustering will lead to faster propagation than nonclustered networks. Our results carry importance for epidemiology, mathematical modeling, and the propagation of interacting phenomena in general. We make a call for more detailed epidemiological data of interacting coinfections.

Individuals are at constant attack from infectious pathogens. Coinfection with two or more pathogens is common and can seriously alter the course of each infection from its own natural history. Infection with HIV increases susceptibility to many pathogens, especially tuberculosis, where coinfection worsens outcomes and increases transmission of both pathogens (1). Recent studies have examined epidemiological case counts to highlight the importance of upper respiratory infections (e.g., rhinovirus, influenza virus, respiratory syncytial virus [RSV]) and *Streptococcus pneumoniae* carriage leading to increased risk of pneumococcal pneumonia (2–5), although there are few dynamic transmission models of pneumococcus (PC) and other viral infections.

Models of disease transmission in structured populations have remained a main focus of network theory for over a decade as realistic descriptions of contact structures are necessary to understand how diseases are transmitted between individuals (6–11). Typically, specific structural properties (average degree, network size, clustering) are explored in isolation. It remains a strong (and potentially dangerous) assumption that results obtained with different models exploring distinct structural properties will give the same results when combined with other models exploring different properties. Disease transmission is a nonlinear problem with features of the propagation itself interacting in complex ways. In this paper, we focus on combining two much studied phenomena—realistic clustering of contact structure and the interaction of respiratory pathogens (influenza and PC pneumonia)—and show that a combination of these two phenomena leads to behavior that is unexpected given previous studies.

An impressive amount of research has focused on the impact of clustering on disease dynamics (12–19). Clustering is often simply described as the number of triangles (where the friend of my friend is also my friend) in a network, but usually also implies that links between nodes tend to be aggregated in well-connected groups. This aggregation tends to hinder the spread of the disease by keeping it within groups where links are more likely to connect to already infected (immune) nodes (18). Clustering plays an important role in Ebola virus transmission (20), respiratory infections (21, 22), and sexually transmitted infections (23, 24).

On the other hand, the interaction of two spreading agents has received a great amount of attention mostly due to the generality of such models (25, 26). These spreading agents can represent two different, but interacting, diseases (such as sexually transmitted infections) (26, 27); the propagation of awareness campaigns trying to stop the spread of an epidemic (25); or even the competition between a mutated strain of influenza and the original strain (10, 11, 28). These dynamics can by themselves exhibit complex behaviors; however, we will see here that they can be further influenced in equally complex ways by the structure imposed on the underlying network.

Here we describe a susceptible-infectious-susceptible (SIS) network model incorporating variable clustering strength and two interacting pathogens and provide a mean-field formalism to follow its dynamics. We find that synergistic coinfections can lead to faster disease spread on clustered networks than on an equivalent random network, contrary to previous studies considering single infections (18). We introduce a criterion based on tertiary infections (or two-step branching factor), which allows analytical prediction of whether a clustered or random network propagates infections most efficiently. Finally, we observe a first-order phase transition in epidemic final size, meaning that a microscopic change in transmissibility can lead to a macroscopic (and discontinuous) increase in disease prevalence. We also identify a dangerous parameter region where an infection would propagate

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**Significance**

Concurrent infection with multiple pathogens is an important factor for human disease. For example, rates of *Streptococcus pneumoniae* carriage (a leading cause of pneumonia) in children under five years can exceed 80%, and coinfection with other respiratory infections (e.g., influenza) can increase mortality drastically; despite this, examination of interacting coinfections on realistic human contact structures remains an understudied problem in epidemiology and network science. Here we show that clustering of contacts, which usually hinders disease spread, can speed up spread of both diseases by keeping synergistic infections together and that a microscopic change in transmission rates can cause a macroscopic change in expected epidemic size, such that clustered networks can sustain diseases that would otherwise die in random networks.

Author contributions: L.H.-D. and B.M.A. designed research, performed research, analyzed data, and wrote the paper. The authors declare no conflict of interest.

This article is a PNAS Direct Submission. Freely available online through the PNAS open access option.

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This article contains supporting information online at www.pnas.orglookup/suppl/doi:10.1073/pnas.1507820112/-/DCSupplemental.
rewiring is done by setting and numerically. The CS network will be compared with its interacting on these clustered networks.

It was shown how the clustering of links in groups slowed down model was studied in ref. 18. Using a mean-field description, it was exhibited as equal to the initial degree distribution of the CS (18).

We extend a recent description of propagation dynamics on a network structure and epidemic dynamics. The dynamics of a single disease on this community structure schematized as equal to the initial degree distribution of the CS (18).

Fig. 1. The effects of clustering on disease propagation (18). Schematization of the network topologies studied in this paper: we start with a random assignment of nodes to groups (Upper), from which we obtain a highly clustered network (Left) that can then be randomized for comparison (Right). The random network is obtained by randomly rewiring the clustered network, thereby preserving node degree. This rewiring allows the diseases to reach more nodes, but separates their paths of spread, lessening the effects of the synergism. In this cartoon, red and blue nodes correspond to individuals infected with a single disease, whereas purple nodes are cofected.

in a clustered network but not in a random network, indicating that movement of cofected individuals into new clustered networks of susceptible individuals could cause explosive outbreaks.

Network Structure and Epidemic Dynamics

We extend a recent description of propagation dynamics on a highly clustered network using overlapping community structure (18). This particular arrangement of nodes leads to the aggregation (or clustering) of nodes into well-connected groups, representing for example a person’s family or workplace. Every connection in this structure can be decomposed in terms of groups, where even single links between two individuals can be considered as a group of size two. Assuming that we know the distribution of group sizes (number of nodes per group) and of node memberships (number of groups per node), we can define a maximally random ensemble of clustered networks with a fixed community structure by randomly assigning nodes to groups (Fig. 1). Hence, the entire network structure is solely defined by two probability distributions, \( \{p_{ij}\} \) and \( \{g_{mn}\} \), respectively, which are the probabilities that a randomly selected group will contain \( n \) members (size \( n \)) or that a randomly selected individual will participate in \( m \) groups (\( m \) memberships).

The dynamics of a single disease on this community structure model was studied in ref. 18. Using a mean-field description, it was shown how the clustering of links in groups slowed down propagation as links are wasted on redundant (immune) connections instead of reaching new (susceptible) individuals. Expand propagation as links are wasted on redundant (immune) connections instead of reaching new (susceptible) individuals. Expand propagation as links are wasted on redundant (immune) connections instead of reaching new (susceptible) individuals.

The evolution of group states can be followed by a single, albeit more complicated, equation. This equation governs the rate of change in group state to another. For instance, the fraction of individuals infected by disease 1 and susceptible to disease 2 will change as

\[
\frac{d}{dt}[I_1S_2]_m = r_2[I_1I_2]_m - r_1[I_1S_2]_m + m\left(\beta_1B_{1SS}^1[I_1S_2]_m - \beta_2B_{1SS}^2[I_1S_2]_m\right),
\]

for cliques with one more individual in state \( [I_1I_2] \) which recovers from disease 1 \( \{i(j-1)(k+1)\}_m \rightarrow [jk]_m \). Notice that recoveries can increase the numbers \( i \) or \( j \) when one of the disease 2 infected individuals recovers from disease 2 or 1. Infection terms are similarly generalized, for example

\[
\beta_1(n - i - j + 1 - k)\{i(j-1)k\} + k\alpha + B_{1SS}^1[i(j-1)k]_m,
\]

for cliques with one less individual infected only with disease 2, such that the remaining \( [S_1S_2] \) individuals (in parentheses) can be

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( {g_{mn}} )</td>
<td>Distribution of groups per node (memberships)</td>
</tr>
<tr>
<td>( {p_{ij}} )</td>
<td>Distribution of nodes per group (sizes)</td>
</tr>
<tr>
<td>( \beta_{1(12)} )</td>
<td>Transmission rate of diseases 1 and 2, respectively</td>
</tr>
<tr>
<td>( r_{1(12)} )</td>
<td>Recovery rate of diseases 1 and 2, respectively</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>Factor of ( \beta ) in the presence of the other disease</td>
</tr>
</tbody>
</table>

Table 1. Description of parameters used in the model
Interactions observed for PC pneumonia and influenza, where estimates of increased acquisition of PC range from 2-fold to 100-fold (4, 30). Similarly, we use a very modular network where every node belongs to two cliques of size 10. These networks are chosen for two reasons: first, to avoid degree-degree correlations, where the effect of clustering will be the main structural effect (18); second, to feature a realistic local clustering coefficient (the ratio of triangles to pairs of links around a given node, here, $C \approx 0.47$) (31).

Fig. 2A presents the effects of clustering with noninteracting diseases and the same scenario in the presence of synergistically interacting diseases. We find that although clustering slows down the propagation of noninteracting diseases, it speeds up the propagation of synergistically interacting diseases. This result is important for network models of disease: random networks are considered worst case scenarios for the speed of disease propagation (18, 21), implying that models can justify working in a random network paradigm. However, this is clearly not always the case in the presence of interacting diseases with synergistic effect.

### Clustering Threshold

We are now interested in identifying a simple analytical criterion, as a function of the clustering coefficient $C$, and the disease interaction parameters $\alpha$, to determine when a clustered network structure is more efficient at synergistic disease transmission than a random structure. Because we are interested in the relative speed at which a pair of diseases move through a population, we can generalize the idea of the basic reproductive number $R_0$ and those that relaxed from the $[I_1I_2]$ state. This difference could potentially inform us on the cliques to which an individual belongs, some transitions being more likely to be found in the vicinity of coinfections, but this would break the Markovian behavior of the mean-field model and only appear to be relevant at high coupling strength beyond what we consider here (SI Appendix).

### Results

We validate our mean-field formalism with simulations of coinfections on highly clustered networks. We will focus on two diseases that can interact synergistically with their respective propagation, i.e., with $\alpha \geq 1$. Here, we focus on PC pneumonia with upper respiratory viral infections [e.g., influenza (3, 30) or RSV (5)]. As our baseline scenario, we use $\alpha = 4$; which, although strong, represents an interaction well within the range of interaction observed for PC pneumonia and influenza, where estimates of increased acquisition of PC range from 2-fold to 100-fold (4, 30).

Combining all possible recovery and infection terms yields the full equations as provided in SI Appendix. This new set of equations is coupled to the previous one through the mean-field of excess interactions $B_{UV}^{(e)}$ (interactions with outside groups)

$$B_{UV}^{(e)} = \left\{ \frac{\sum m(m - 1)[UV]_{lm}}{\sum [UV]_{lm}} \right\} B_{UV}^{(e)}.$$  

Finally, to close the model, we simply write the basic interaction mean-fields (average interaction within a given group) with the available information. For example, we find for disease 1

$$B_{SS}^{(1)} = \left\{ \frac{n(n - 1)}{\sum [jk]_{lm}} \right\} B_{SS}^{(1)},$$

$$B_{SS}^{(2)} = \left\{ \frac{n(n - 2)}{\sum [jk]_{lm}} \right\} B_{SS}^{(2)},$$

Intuitively, for $B_{SS}^{(1)}$, the susceptible individual is two times more likely to be part of a clique with two times more susceptible nodes: this is the $(n - i - j = k)$ factor. We then just average the infection terms of each possible clique, i.e., $n^2 [SS_{CS}^{(1)} + kSS_{CS}^{(1)}]$ over this biased distribution of cliques. Note that one interesting type of correlation is not taken into account: the difference between individuals in the $[I_1S_2]$ state that were infected from the $[S_1S_2]$ state and those that relaxed from the $[I_1I_2]$ state. This difference could potentially inform us on the cliques to which an individual belongs, some transitions being more likely to be found in the vicinity of coinfections, but this would break the Markovian behavior of the mean-field model and only appear to be relevant at high coupling strength beyond what we consider here (SI Appendix).
number, $R_0$ (32), to identify this clustering threshold. $R_0$ corresponds to the expected number of secondary infections caused by a single infected individual in an entirely susceptible population. The higher the $R_0$, in general, the faster a disease can spread. However, clustering is not taken into account for $R_0$, as it is a one-step branching factor: how many first neighbors will be infected during an individual’s infectious period. Clustering reflects how your neighbors might also be second neighbors, occurring on the second step of the branching process. We thus turn toward a generalized branching factor, $R_1$, equal to the number of tertiary infections caused by one coinfected individual (i.e., the number of second neighbors infected).

As the calculation of $R_1$ depends on the scenario of interest, we consider the case of equivalent diseases ($\beta_1 = \beta_2 = \beta$ and $r_1 = r_2 = r$). See SI Appendix for a treatment of the general case. The first step is to calculate $R_0$ taking into account which neighbors receive disease 1, disease 2, or both. A coinfected individual can transmit both diseases in two ways: by transmitting both while recovered and transmitting the second. Summing the contribution of both possibilities gives the probability $T_2$ of transmitting both diseases

$$T_2 = \frac{2\alpha \beta}{2\alpha \beta + 2r} \left( \frac{\alpha \beta}{\alpha \beta + 2r} + \frac{r}{\alpha \beta + 2r + \alpha \beta + r} \right). \quad [5]$$

From this expression, it is straightforward to also write the probability $T_1$ of transmitting only one disease

$$T_1 = \frac{2\alpha \beta}{2\alpha \beta + 2r} \left( 1 - \frac{\alpha \beta}{\alpha \beta + 2r} - \frac{r}{\alpha \beta + 2r + \alpha \beta + r} \right) + \frac{2r}{2\alpha \beta + 2r + \beta + r}. \quad [6]$$

whose terms represent blocking the second transmission in $T_2$ or recovering before transmitting. We now want to calculate how many infections will be caused by each of these $z_1(T_1 + T_2)$ new infectious individuals ($z_1$ being the average excess degree).

The effect of this clustering coefficient is twofold: first, further infections are conditional on links not wasted with infected neighbors of the root node, and second, in the event of a single infection (probability $T_1$), the other disease can be received from these wasted links and boost the transmission rate for the non-wasted nodes. Considering that, on average, a node infected through the $T_1$ scenario, and now trying to infect a susceptible node, also has $n = (z_1 - 1) C (T_2 + T_1/2)$ neighbors already infected with the other disease, the probability of a coinfection occurring is thus $1 - (2r/(2r + \alpha \beta))^{\beta}$. This discrete probability can be converted to an effective continuous rate of coinfection through triangles (SI Appendix)

$$x = r \left[ \left( \frac{2r}{2r + \alpha \beta} \right)^{\beta} - \left( \frac{2r}{2r + \alpha \beta} \right)^n \right]. \quad [7]$$

With this in mind, we can write the probability of a tertiary infection caused by a secondary infection of only one disease

$$T_1 = [1 - C(T1 + T2)] \times \left[ \frac{\beta}{\beta + r + x + \beta + r + x} \left( \frac{2\alpha \beta}{2\alpha \beta + 2r + \beta + r} \right) \right] \quad [8]$$

which counts transmissions of a single or both diseases. The equivalent probability in the $T_2$ scenario is more straightforward if we neglect the probability of recovering and being reinfected (which is the standard way of calculating reproductive numbers). We thus write

$$T'_2 = \left[ 1 - C(T1 + T2) \right] \left[ \frac{2\alpha \beta}{2\alpha \beta + 2r + \beta + r} \right]. \quad [9]$$

Finally, $R_1$ is given by

$$R_1 = \gamma^2 \left( T_1 T'_1 + T_2 T'_2 \right), \quad [10]$$

and comparing $R_1$ obtained with a given $C$ or with $C = 0$ (ERN) will determine which network (clustered or not) spreads the diseases faster.

This approach is validated on Fig. 2B. Once again, we use networks constructed from cliques of size 10, such that clustering not only comes through the root node but also from other newly infected nodes. We also examine another clustered network, with the same degree distribution, but composed only of triangles, leading to a clustering coefficient around 0.06. We can see that our approach is able to give precise estimates of the coupling strength for which both clustered networks start spreading faster than their equivalent random networks.

Fig. 3 demonstrates this over a broad range of parameters. For realistic ranges of clustering and disease interaction, we find faster propagation on clustered networks than random. Of course, for very clustered networks (i.e., when $C \rightarrow 1$), there is no interaction parameters that can compensate the clustering. For intermediate values of $C$, the range of $\alpha$ leading to faster propagation on clustered networks gets narrower. For very strong clustering, the diseases end up using the same pathways and thus follow each other whether the network is clustered or not. Hence, we see a second switch in optimal network structure as we increase $\alpha$.

![Fig. 4. First-order phase transition and epidemic latent heat. (A) Emergence of an endemic steady state for a scenario where equivalent diseases are either noninteracting ($\alpha = 1$) or interacting ($\alpha = 4$) on the community structure (again, cliques of size 10) and its equivalent random network. Their transmission rates $\beta_1 = \beta_2$ are given as a fraction of the recovery rate $r_1 = r_2$. The shaded region highlights a parameter region where interacting diseases on CS networks can spread explosively, whereas they cannot on the ERN. (B) Time evolution of the interacting diseases at the value $\beta_1 = \beta_2 = 0.056$ (indicated with an arrow in A). The markers give the median state of the Monte Carlo simulations with error bars corresponding to the 75% interval, whereas the curves give the prediction of our mean-field formalism. Note that the epidemics die out on the ERN and not on the CS, despite the heavy stochasticity caused by the nearby discontinuity (as seen in A).](image-url)
First-Order Transitions and Outbreak Risk. We have thus far investigated the impacts of varying the coupling α between the two diseases. However, impact of clustering is expected to be stronger for more transmissible diseases (larger βi/ri). In fact, clustering should barely matter around the epidemic threshold where the endemic steady state goes to zero. One can understand this phenomenon by thinking of the probability that a triangle is actually explored by the diseases, which falls as the probability of transmission to the third power.

This standard assumption is not always justified, however. Fig. 4 presents endemic steady states for clustered and random networks over a range of transmission rates βi with and without coinfection synergism. We find two major results: One, clustering can lower the epidemic threshold; and two, strong synergy between diseases modifies the dynamics and leads to a first-order discontinuous transition. Typically, first-order phase transitions are the result of a build-up of latent heat, here corresponding to an epidemic potential. Just before the discontinuity both diseases are waiting for the other to prime the outbreak, which is similar to other recent observations of first-order transitions in disease spread requiring pathogen mutation (11) or multiple exposures (33).

Coupling these two surprising results, we see that for a critical range of parameters, a microscopic increase in transmissibility can cause a macroscopic difference in the expected epidemic size on a clustered network but not on an otherwise equivalent random network. This conclusion is confirmed in the shaded region of Fig. 4A: the diseases spread to around 90% of nodes in the clustered network, whereas the outbreak is unnoticeable in the random network.

In the context of diseases that spread heavily in daycares and schools, this means that a small difference in the clustering of contacts could translate to a difference between no outbreak and a complete contagion for interacting pathogens such as influenza and PC pneumonia.

Discussion
Here we demonstrated that synergistic coinfections, such as pneumonia caused by S. pneumoniae and influenza, may actually spread faster and farther on clustered networks than on random networks. This result is similar to the recent observation that behaviors or opinions can propagate more rapidly in clustered social networks than in their random equivalent due to social reinforcement (34, 35). Our model thus suggests that we could also expect to see faster transmission on clustered networks in the context of diseases requiring multiple exposures before infection, which can also lead to discontinuous phase transitions (33).

We identified a threshold above which a clustered network structure will enhance the spread of synergistic coinfections. Finally, we demonstrated a first-order phase transition in final epidemic size and identified regions where coinfected individuals can start large outbreaks on clustered networks where they wouldn’t on random networks. Our results provided here have clear implications for understanding transmission dynamics of interacting diseases on realistic contact networks and for network-based modeling of infectious disease transmission.

Understanding how diseases interact within host and between hosts in populations with realistic contact structure is of key importance to epidemiologists working to limit the transmission of diseases in these populations. Pneumococcal carriage rates in children under five years old interacting in highly clustered communities (daycares and households) can exceed 80% (36), and influenza infections are common. According to our results, transplanting a child coinfected with PC and influenza into a new clustered setting with susceptible hosts could result in an unexpectedly large outbreak. Similar outbreaks of sexually transmitted diseases could occur if individuals coinfected with syphilis and HIV (27), for example, entered into a clustered network of susceptible individuals, such as prostitution networks (24).

Our results are of importance to the field of epidemic modeling in general. Common practice is to run epidemic dynamics on random networks or mass action models, as these are considered worst case scenarios for transmission. We showed that network clustering facilitates synergistically interacting diseases because tight clustering keeps the diseases together. Our clustering threshold can be used by modelers to test whether they should be considering random or clustered network dynamics when trying to identify pessimistic transmission scenarios.

Our study has implications for epidemiology, mathematical modeling, and for the understanding the propagation of interacting phenomena in general. However, as illustrated by the problems encountered in trying to identify ranges of realistic parameters (Fig. 3), there is a dire need for data in the context of interacting epidemics. Not only is it hard to estimate realistic contact network properties, but one would also need to be able to estimate the transmissibility of a pathogen in both the absence and presence of other possible interacting diseases. Therefore, although this work is a step forward in terms of theory, it should also be taken as a call for better data.

ACKNOWLEDGMENTS. This work was supported by the Santa Fe Institute, the James S. McDonnell Foundation Postdoctoral fellowship (L.-H.-D.), and the Santa Fe Institute Omidyar Postdoctoral fellowship (B.M.A.).
Supplemental Information for
“Complex dynamics of synergistic coinfections on realistically clustered networks”

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I. NETWORK STRUCTURES

A. Community structure

The network structure employed here can be fully decomposed only in terms of groups, where even single links between two individuals can be considered as a group of size two. Assuming that we fix the distribution of group sizes (number of nodes per group) and of node memberships (number of groups per node), we can define a maximally random ensemble of clustered networks with a fixed community structure by randomly assigning nodes to group (see Supplementary Figure 1). Hence, the entire network structure is solely defined by two probability distributions \( \{p_n\} \) and \( \{g_m\} \) generated by the following probability generating functions (PGFs):

\[
P_0(z) = \sum_{n=0}^{\infty} p_n z^n ,
\]

\[
G_0(z) = \sum_{m=0}^{\infty} g_m z^m ,
\]

which are simply built from the probabilities \( p_n \) and \( g_m \) that a randomly selected individual will participate in \( n \) groups or that a randomly selected group will contain \( m \) members. Similar functions can be defined to generate the probabilities that a random group of a random individual is shared by \( n - 1 \) other participants or that a random individual in a random group participates in \( m - 1 \) other groups. We simply note that these quantities are proportional to \( np_n \) or \( mg_m \) and thus find our second set of PGFs:

\[
P_1(z) = \frac{\sum_n np_n z^{n-1}}{\sum_n np_n} = \frac{P_0'(z)}{P_0'(1)} = \nu^{-1} P_0'(z) ,
\]

\[
G_1(z) = \frac{\sum_m mg_m z^{m-1}}{\sum_m mg_m} = \frac{G_0'(z)}{G_0'(1)} = \mu^{-1} G_0'(z)
\]

where \( \nu \) and \( \mu \) are respectively the mean numbers of individuals per clique and cliques per individual used to normalize the distributions. Note that the mean of a distributed quantity is simply given by the derivative of the corresponding PGF evaluated at unity.

B. Equivalent random networks (ERN)

In order to highlight the effects of community structure (CS) versus random networks (RN), both topologies are studied analytically and numerically. The CS network will be compared with its equivalent random network (ERN): a network with exactly

Supplementary Figure 1. Schematization of the particular topology and dynamics studied in this paper. An open mark represents a susceptible individual; a shaded one, an infectious (infected with one of two diseases, or both); and a black one, a group (or clique). The topology is constructed by allowing individuals to belong to a given number of cliques where they can be linked to other participants (solid lines). Note that in the formalism, the cliques are differentiable by their exact population and state, while the precise connections between them remain unspecified and they are simply linked to a mean-field. Although the average connections of individuals in a given state are also known.
the same degree distribution, but with randomly connected nodes. Note that on our general model of community structure, the PGF for the degree distribution is simply generated by:

$$G_0 [P_1 (z)] .$$

(5)

The mapping of a CS to describe an ERN following this particular degree distribution is simple matter. We set $P_0^{ERN}(z) = z^2$ so that all groups are of size two (i.e. regular links) and then set $G_0^{ERN}(x) = G_0 [P_1 (z)]$ to fix the membership distribution as equal to the initial degree distribution of the CS network.

II. THE MODEL

We study the dynamics of two interacting Susceptible-Infectious-Susceptible (SIS) diseases. Meaning that at any given time, each individual is either susceptible or infectious in regards to each disease. Without interaction with the other disease, an infectious individual would infect its susceptible neighbors at a rate $\beta_i$ and recover at a rate $r_s$.

To keep track of both diseases simultaneously, we distinguish nodes by their state $[XY]\_m$ where $m$ is their membership number, $X \in \{S_1, I_1\}$ corresponds to the first disease and $Y \in \{S_2, I_2\}$ to the second.

Similarly, we will distinguish groups by their size $n$ and the states of the nodes they contain; i.e., $[ijkl]_n$, where $i$ is the number of $[I_1S_2]$, $j$ is the number of $[S_1I_2]$ and $k$ is the number of $[I_1I_2]$ such that $n-i-j-k$ yields the number of $[S_1S_2]$. Keeping track of the number of nodes with both diseases is important considering we are interested in the effect of co-infection.

Let us now distinguish each possible infection by the state $[XY]$ of the infector and the state $[UV]$ of the infectee. If $[XY] = [II]$ or $[UV] \in \{[IS],[SI]\}$, than a factor $\alpha$ modifies the basic transmission rates $\beta_i$. For example, an $[I_1I_2]$ individual will transmit the first disease to $[S_1S_2]$ or $[S_1I_2]$ individuals at a rate $\alpha \beta_1$.

A. Mean-field description

With this in mind, a mean-field description of the time evolution can be written in the spirit of existing formalisms. Leaving out all explicit mention of time dependencies as all variables and mean-fields vary in time, the population density within each node state evolves as

$$\frac{d}{dt} [S_1S_2]_m = r_1 [I_1S_2]_m + r_2 [S_1I_2]_m - m (\beta_1 B_{SS}^{(1)} + \beta_2 B_{SS}^{(2)}) [S_1S_2]_m$$

(6)

$$\frac{d}{dt} [I_1S_2]_m = r_2 [I_1I_2]_m - r_1 [I_1S_2]_m + m (\beta_1 B_{SS}^{(1)} [S_1S_2]_m - \beta_2 B_{IS}^{(2)} [I_1S_2]_m)$$

(7)

$$\frac{d}{dt} [S_1I_2]_m = r_1 [I_1I_2]_m - r_2 [S_1I_2]_m + m (\beta_2 B_{SS}^{(2)} [S_1S_2]_m - \beta_1 B_{SI}^{(1)} [S_1I_2]_m)$$

(8)

$$\frac{d}{dt} [I_1I_2]_m = -(r_1 + r_2) [I_1I_2]_m + m (\beta_1 B_{SI}^{(1)} [S_1I_2]_m + \beta_2 B_{IS}^{(2)} [I_1S_2]_m)$$

(9)

where the $B_{ij}^{(k)}$ mean-field of interactions (i.e. the average interaction on disease $i$ per membership for a node in state $[UV]$). Notice that in the equations, the first row of terms are the recovery events, and the second the infection events. The challenge in correctly writing the equation is thus solely to correctly identify to which state each event transfers some population density. Conservation of total population density (i.e. the sum over all states remains equal to one) is easily verified as the sum of Eqs. (6) to (9) is zero.
Here, there are two ways by which we can follow an equivalent methodology. First, we can infect a fraction of cliques. The typical initial conditions used in disease models imply infecting a random, but very small, fraction of the population. Notice that creating a clique implies either removing an individual implies either removing a $i$ or $j$, through their infection with disease 2 or 1 respectively; just as recoveries can create $i$ or $j$ individuals when a $k$ recovers from disease 2 or 1.

Finally, to close the model, we simply write the interaction mean-fields (average interaction within a given group) with the available information:

$$ \frac{d}{dt} [ijk]_n = (i+1) r_1 [(i+1) jk]_n + (j+1) r_2 [i (j+1) k]_n + (k+1) \left\{ r_1 [i (j-1) (k+1)]_n + r_2 [(i-1) j (k+1)]_n \right\} $$

$$ - (ir_1 + jr_2 + kr_1 + kr_2) [ijk]_n + \beta_1 (n-i-1-j-k) \left\{ (i-1) + k\alpha + \tilde{B}_{SS}^{(1)} \right\} [i(j-1)k]_n $$

$$ - \beta_1 (n-i-j-k) \left\{ i + k\alpha + \tilde{B}_{SS}^{(1)} \right\} [ijk]_n + \beta_2 (n-i-j+1-k) \left\{ (j-1) + k\alpha + \tilde{B}_{SS}^{(2)} \right\} [i(j-1)k]_n $$

$$ - \beta_2 (n-i-j-k) \left\{ j + k\alpha + \tilde{B}_{SS}^{(2)} \right\} [ijk]_n + \beta_2 (i+1) \left\{ j\alpha + (k-1)\alpha + \tilde{B}_{SI}^{(2)} \right\} [(i+1) j (k-1)]_n $$

$$ - \beta_1 j \left\{ i\alpha + k\alpha + \tilde{B}_{SI}^{(1)} \right\} [ijk]_n $$

where this set of equations is coupled to the previous one through the mean-field of excess interactions $\tilde{B}_{UV}^{(x)}$ (interactions with outside groups), i.e.

$$ \tilde{B}_{UV}^{(x)} = \left( \frac{\sum_{m} m(m-1)[UV]_m}{\sum_{m} m[UV]_m} \right) B_{UV}^{(x)}. $$

The first four terms of Eq. (10) are those corresponding to recoveries; positive for those corresponding to cliques relaxing into $[ijk]_n$ and negative for those where $[ijk]_n$ relaxes into less infected state. The other terms represent each possible infection event. Notice that creating a $k$ individual implies either removing a $i$ or $j$, through their infection with disease 2 or 1 respectively; just as recoveries can create $i$ or $j$ individuals when a $k$ recovers from disease 2 or 1.

Finally, to close the model, we simply write the interaction mean-fields (average interaction within a given group) with the available information:

$$ B_{SS}^{(1)} = \frac{\sum_{[ijk]} (n-i-j-k) (i + k\alpha) [ijk]_n}{\sum_{[ijk]} (n-i-j-k) [ijk]_n} $$

$$ B_{SI}^{(1)} = \frac{\sum_{[ijk]} j (i\alpha + k\alpha) [ijk]_n}{\sum_{[ijk]} i [ijk]_n} $$

$$ B_{SS}^{(2)} = \frac{\sum_{[ijk]} (n-i-j-k) (j + k\alpha) [ijk]_n}{\sum_{[ijk]} (n-i-j-k) [ijk]_n} $$

$$ B_{SI}^{(2)} = \frac{\sum_{[ijk]} i (j\alpha + k\alpha) [ijk]_n}{\sum_{[ijk]} i [ijk]_n} $$

These expressions are easily understood with the following logic. For instance with the case of $B_{SS}^{(1)}$, the susceptible individual is two times more likely to be part of a clique with two times more susceptible nodes, which is what the $(n-i-j-k)$ factor takes into account. We then just average the infection terms of each possible clique, e.g. $i + k\alpha$, over this biased distribution of cliques.

### B. Initial conditions

The typical initial conditions used in disease models imply infecting a random, but very small, fraction $I(0)$ of the population. Here, there are two ways by which we can follow an equivalent methodology. First, we can infect a fraction $I_1(0)$ of the population with the first disease, and independently infect a fraction $I_2(0)$ with the second disease. This leads to the following initial conditions for the node states:

$$ [SS]_{m(0)} = (1 - I_1(0)) (1 - I_2(0)) g_m $$

$$ [IS]_{m(0)} = I_1(0) (1 - I_2(0)) g_m $$

$$ [SI]_{m(0)} = (1 - I_1(0)) I_2(0) g_m $$

$$ [II]_{m(0)} = I_1(0) I_2(0) g_m $$
and initial conditions following a multinomial process for the clique states:

\[
[ijk]_n(0) = \frac{n!}{(n-i-j-k)!i!j!k!} [I_1(0)I_2(0)]^k \times [(1 - I_1(0)) I_2(0)]^i [I_1(0) (1 - I_2(0))]^s \times [(1 - I_1(0)) (1 - I_2(0))]^{n-i-j-k}.
\]

These initial conditions could model the introduction of two unrelated, but interacting, diseases at the exact same time within a population. However, one of the initial motivation is the modeling of diseases which are directly related. For instance, we can consider the case of two strains of influenza where one is a mutation of the first. In these cases, where the two interacting diseases share similar points of entry, we can more directly model the initial conditions by infecting a fraction \(I(0)\) of the population with both diseases. We thus write, for individuals,

\[
[SS]_m(0) = (1 - I(0)) g_m
\]

\[
[IS]_m(0) = [SI]_m(0) = 0
\]

\[
[II]_m(0) = I(0) g_m
\]

and for cliques,

\[
[ijk]_n(0) = \frac{n!}{k! (n-k)!} (1 - I(0))^{n-k} I(0)^k.
\]

C. Monte Carlo simulations

To perform MC simulations of the model, we have generated networks with the structure presented in Section I via the following numerical algorithm:

i. generate a sequence \(\{m_i\}\) of length \(N\) subjected to distribution \(\{g_m\}\);

ii. generate a sequence \(\{n_j\}\) subjected to distribution \(\{p_n\}\) until \(\sum_j n_j = \sum_i m_i\);

iii. for each \(i\), produce \(m_i\) individuals tagged as \(i\);

iv. for each \(j\), produce \(n_j\) groups tagged as \(j\);

v. randomly assign each individual to a group;

vi. for each \(i\), link \(i\) with every \(i'\) (with \(i' \neq j\)) assigned to its \(n_j\) groups.

The final ensemble of links presents a topology as shown in Supplementary Figure 1 with a degree distribution generated by Eq. (5). For every generated network, a fraction \(I(0)\) of individuals are randomly infected and the SIS dynamics is simulated in discrete time using time steps \(\Delta t\) (we choose \(\Delta t\) such that all \(\beta_i\Delta t\) and \(r_i\Delta t\) are lesser than \(10^{-3}\)):

i. at each \(\Delta t\), every susceptible neighbor of every infectious individual is infected with probability \(\Delta t\) times the corresponding transmission rate;

ii. at each \(\Delta t\) every infectious individual recovers with probability \(\Delta t\) times the corresponding recovery rate.

III. MEAN-FIELD ERROR AND MARKOVIAN APPROXIMATION

In the main text, we mention correlations between node states and the cliques in which they are found: e.g., a node relaxing from \([I_1I_2]\) to \([S_1I_2]\) is more likely to be found in a clique with both diseases than a clique with only the second disease, even if they both have the same amount of \([S_1I_2]\) nodes. Including these correlations would mean keeping track of the recent history of node states, therefore breaking the Markov property within the mean-field model. Since this has strong implications for the modeling, our first step is to ignore these correlations through a Markovian approximation.

Obviously, since these correlations are not present if the diseases do not interact, we expect that the stronger the interaction parameter \(\alpha\), the stronger the ignored correlations should be. We here investigate where our mean-field model breaks down. Supplementary Figure 2 shows how the mean-field formalism still works relatively well at the maximal coupling strength considered in the main text. However, we also see that the clustered version of the formalism (with cliques bigger than size two) is more prone to error and eventually fails at higher coupling strength.
IV. DETAILS OF THE BRANCHING FACTOR ANALYSIS

The main text introduces a two-step reproductive number around a node with both diseases. In SIS dynamics, reproductive numbers are typically calculated during one infectious period and thus ignore events implicating infectious individuals recovering and getting re-infected. In the main text, we calculated the number of individuals infected during a first step around our root node (keeping track of their states) and the number infected during a second step around these nodes (regardless of their state). Let us explain the logic used in both of these steps.

We first consider a single link between an infectious node and a susceptible node. The transmission probability $p_1$ can be calculated as follows. First suppose that the infectious node remains infectious for a period $T$ of time, than the probability $\rho(T)$ that it will infect its neighbour is given by

$$\rho(T) = 1 - \lim_{\delta t \to 0} (1 - \beta \delta t)^{T/\delta t} = 1 - e^{-\beta T}.$$  \hfill (16)

Second, the cumulative distribution for the length of the period of infectiousness $T$ can be written as:

$$F(T) = 1 - \lim_{\delta t \to 0} (1 - r \delta t)^{T/\delta t} = 1 - e^{-r T}.$$  \hfill (17)

By differentiating $F(T)$, one obtains the probability distribution for $T$:

$$f(T) = \frac{dF(T)}{dT} = re^{-r T},$$  \hfill (18)

which is easily proved to be normalized. Finally, from $f(T)$ and $\rho(T)$, the total probability of infection can be calculated as follows:

$$p_1 = \int_0^\infty \rho(T)f(T) dT = \frac{\beta}{\beta + r}.$$  \hfill (19)

Meaning if two events occur at rate $a$ and $b$, we know $a$ occurs before $b$ with probability $a/(a + b)$. This logic alone allowed us to calculate the number of infected first neighbours.

The second step is more complicated. In this step, we consider separately nodes that were infected with a single or both diseases in the first step. The latter scenario is simpler, these nodes behave like the root node, but have their effective excess degree, which should be $z_1$ reduced to $z_1[1 - C(T1 + T2)];$ removing the faction of neighbors that were shared by the root node and are already infected (negative impact of clustering). The first scenario, where the node is only infectious with one disease, needs to consider the possibility that these shared neighbors have the other disease and infect the node of interest, boosting its transmissibility (positive impact of clustering).

Consider Supplementary Figure 3, we are focusing on the relations between node $i$ and its susceptible neighbors, which on average would be $z_1[1 - C(T1 + T2)]$ nodes (here one). We also know that of its other neighbors, a number $(z_1 -$
Supplementary Figure 3. The positive impact of clustering is to keep diseases together. Here, node $i$ and $j$ were infected with only one disease (red and blue disease respectively) by the root node, reducing node $i$’s chances of infecting the susceptible node. However, because of the triangle, node $i$ gets a second chance at co-infection through nodes $j$ and $k$ (not the root node which was dealt with in the first step). This would boost its transmissibility and chances of infecting its susceptible neighbor. We want to map this scenario to a simpler case where node $i$ tries to infect its neighbors, but also gets the second disease at a constant infection rate $x$ through a mean field of $j$ and $k$.

1) $[1 - C(T1/2 + T2)]$ (here two, $j$ and $k$) are infected with the disease that node $i$ does not have. We thus calculate the probability $p_2$ that node $j$ infects node $i$ with the other disease before node $i$ recovers. Using the same logic as before, a transmission rate $\alpha\beta$, and noting $T_1$ and $T_2$ the time before either of them recovers from the relevant disease, we get

$$p_2 = \int_0^\infty f(T_1) \left[ \int_0^{T_1} f(T_2)\rho(T_2)dT_2 + \int_{T_1}^\infty f(T_2)\rho(T_1)dT_2 \right] dT_1 = \frac{\alpha\beta}{\alpha\beta + 2r}$$

(20)

which is consistent with our previous logic. To account for the $n = (z_1 - 1) [1 - C(T1/2 + T2)]$ neighbors which could co-infect node $i$, we can write the total probability as

$$1 - (1 - p_2)^n.$$  

(21)

We now want to map this probability to a mean-field continuous rate of coinfection. Say that we know the value $x$ of this rate, the probability that this rate infects node $i$ before it recovers would simply be $x/(x + r)$. Assuming an equality between both point of views, we can determine that the value of $x$ is

$$x = r \left[ \left( \frac{2r}{2r + \alpha\beta} \right)^{-n} - \left( \frac{2r}{2r + \alpha\beta} \right)^n \right].$$

(22)

This rate of coinfection on first neighbors with only a single disease allowed us to calculate the second step of our two-step reproductive number as shown in the main text.

V. COMPLETE BRANCHING FACTOR ANALYSIS

We start with a single node infected with both diseases. For the first step of our criterion, we need to distinguish the probability of transmitting disease 1 only, disease 2 only, or both diseases. The latter scenario can occur in one of two ways: either by transmitting both while co-infected; or transmitting a first one then recovering from it before transmitting the second one. Summing the two events yields the probability $T_{11}$ of a co-infected transmitting both diseases to a given first neighbor, i.e.,

$$T_{11} = \frac{\alpha\beta_1}{\alpha\beta_1 + \alpha\beta_2 + r_1 + r_2} \left[ \frac{\alpha\beta_2}{\alpha\beta_1 + \alpha\beta_2 + r_1 + r_2} + \frac{r_1}{\alpha\beta_2 + r_1 + r_2} \left( \frac{\alpha\beta_1}{\alpha\beta_2 + r_2} \right) \right]$$

$$+ \frac{\alpha\beta_2}{\alpha\beta_1 + \alpha\beta_2 + r_1 + r_2} \left[ \frac{\alpha\beta_1}{\alpha\beta_1 + \alpha\beta_2 + r_1 + r_2} + \frac{r_2}{\alpha\beta_1 + r_1 + r_2} \left( \frac{\alpha\beta_1}{\alpha\beta_1 + r_1} \right) \right].$$

(23)

Similarly, a co-infected can transmit only the first disease in one of two ways, either by infecting while co-infected then recovering before the second transmission occurs; or by recovering from the second disease then transmitting the first one. Again, summing these events gives the probability $T_{1S}$ of a co-infected transmitting only the first disease. The same logic applies to the probability $T_{S1}$ of transmitting only the second disease. We can thus write
\[ T_{IS} = \frac{\alpha \beta_1}{\alpha \beta_1 + \alpha \beta_2 + r_1 + r_2} \left[ 1 - \frac{\alpha \beta_2}{\alpha \beta_2 + r_1 + r_2} - \frac{r_1}{\alpha \beta_2 + r_1 + r_2} \left( \frac{\alpha \beta_2}{\alpha \beta_2 + r_2} \right) \right] + \frac{r_2}{\alpha \beta_1 + \alpha \beta_2 + r_1 + r_2} \left( \frac{\beta_1}{\beta_1 + r_1} \right), \] 
\[ T_{SI} = \frac{\alpha \beta_2}{\alpha \beta_1 + \alpha \beta_2 + r_1 + r_2} \left[ 1 - \frac{\alpha \beta_1}{\alpha \beta_1 + r_1 + r_2} - \frac{r_2}{\alpha \beta_1 + r_1 + r_2} \left( \frac{\alpha \beta_1}{\alpha \beta_1 + r_1} \right) \right] + \frac{r_1}{\alpha \beta_1 + \alpha \beta_2 + r_1 + r_2} \left( \frac{\beta_2}{\beta_2 + r_2} \right). \] 
\[ (24) \quad (25) \]

We now know that a single co-infected individual will on average cause \( z_1 T_{II} \) co-infections, \( z_1 T_{IS} \) infections from the first disease, and \( z_1 T_{SI} \) from the second, in its first neighborhood. We call those secondary infections. Our two-step branching process then looks at the number of tertiary infections, i.e. the number of infections in the second neighborhood, regardless of which disease is actually being transmitted.

In a clustered network, there is overlap between the second neighborhood and the first, such that neighbors of the original co-infection can be infected during the second step of the process if they were not already. Let us consider one of the \( z_1 T_{IS} \) first neighbors infected only with the first disease. We already know that in its own neighbors, a number \((z_1 - 1)C (T_{II} + T_{IS})\) of them are already infected with the same disease. This is the negative impact of clustering on the dynamics. However, a number \((z_1 - 1)C (T_{II} + T_{SI})\) are infected with the other disease, such that they could transmit it to the node of interest and affect its transmissibility. This is a potentially positive impact of clustering depending on the nature of the coupling between diseases.

Still considering the same first neighbor infected with the first disease, we want to know the rate at which it is co-infected by one of the \((z_1 - 1)C (T_{II} + T_{SI})\) neighbors infected with the second disease. Assume that we know the value \( x_1 \) of that rate, then the probability of co-infection before recovery would simply be \( x_1 / (x_1 + r_1) \). Since we can also write that probability as every node involved recovering before co-infection, we can require the following equality:

\[ \frac{x_1}{x_1 + r_1} = \left( \frac{r_1 + r_2}{\alpha \beta_2 + r_1 + r_2} \right)^{(z_1-1)CT_{SI}} \left( \frac{r_1 + r_2}{\alpha \beta_2 + r_1 + r_2} \right)^{(z_1-1)CT_{II}}. \] 
\[ (26) \]

The same logic obviously applies for co-infection involving a node only infected with the second disease. We can solve for the effective rates of co-infection through clustering, i.e. \( x_1 \) and \( x_2 \), and obtain

\[ x_1 = r_1 \left( \frac{r_1 + r_2}{\alpha \beta_2 + r_1 + r_2} \right)^{(z_1-1)CT_{SI}} \left( \frac{r_1 + r_2}{\alpha \beta_2 + r_1 + r_2} \right)^{(z_1-1)CT_{II}} \]
\[ - \left( \frac{r_1 + r_2}{\alpha \beta_2 + r_1 + r_2} \right)^{(z_1-1)CT_{II}} \left( \frac{r_1 + r_2}{\alpha \beta_2 + r_1 + r_2} \right)^{(z_1-1)CT_{SI}} \],
\[ (27) \]

\[ x_2 = r_2 \left( \frac{r_1 + r_2}{\alpha \beta_1 + r_1 + r_2} \right)^{(z_1-1)CT_{IS}} \left( \frac{r_2 + r_1}{\alpha \beta_1 + r_1 + r_2} \right)^{(z_1-1)CT_{II}} \]
\[ - \left( \frac{r_2 + r_1}{\alpha \beta_1 + r_1 + r_2} \right)^{(z_1-1)CT_{II}} \left( \frac{r_2 + r_1}{\alpha \beta_1 + r_1 + r_2} \right)^{(z_1-1)CT_{IS}} \].
\[ (28) \]

With these effective rates, we can write the probabilities of a tertiary infection from a node only infected with one of the two diseases, respectively \( T'_{IS} \) and \( T'_{SI} \), as

\[ T'_{IS} = [1 - C (T_{IS} + T_{SI} + T_{II})] \left[ \frac{\beta_1}{\beta_1 + r_1 + x_1} + \frac{x_1}{\beta_1 + r_1 + x_1} (T_{IS} + T_{SI} + T_{II}) \right] \] 
\[ (29) \]
\[ T'_{SI} = [1 - C (T_{IS} + T_{SI} + T_{II})] \left[ \frac{\beta_2}{\beta_2 + r_2 + x_2} + \frac{x_2}{\beta_2 + r_2 + x_2} (T_{IS} + T_{SI} + T_{II}) \right] \] 
\[ (30) \]

whose terms are, respectively, the probability of directly passing a disease before co-infection, or of passing at least one of the diseases after co-infection. More directly, we can write the probability of a tertiary infection, regardless of which disease is passed, from an individual who received both diseases from the original co-infected:
Supplementary Figure 4. Monte Carlo simulations of the dynamics of Figure 3 in the main text with $C = 0.47$ and $\alpha = 20$. This is a slightly over-coupled case where the diseases initially spread faster on the ERN than on the CS. This slight difference is captured by our criterion.

\[ T_{II} = [1 - C (T_{IS} + T_{SI} + T_{II})] (T_{IS} + T_{SI} + T_{II}) \]  

From all of these, we write the number of tertiary infections caused by an original co-infected individual as

\[ R_1 = z_1^2 (T_{IS} T_{IS} + T_{SI} T_{SI} + T_{II} T_{II}) \]  

VI. OVER-COUPLED DISEASES

Like the standard reproductive number, our two-step branching factor criterion is an approximation of the first steps of a disease. However, one scenario being faster at first does not imply that it is necessarily faster in the long run. Meaning that the question which structure spreads diseases most efficiently is not always well-defined. A good example of that is found in the case of over-coupled disease, i.e., diseases where the coupling factor $\alpha$ is so strong that the ERN spreads more efficiently than the CS even if the opposite was through for some $\alpha' < \alpha$. For instance, on Figure 3 in the main text, this scenario is found for $\alpha > 10$ in the case of networks with $C \approx 0.47$.

One particular example of this dynamics is demonstrated in Supplementary Figure 4. The criterion is right in the sense that the initial steps of the diseases spread slightly more quickly on the ERN than on the CS, but the CS also rapidly catches up. This illustrates how, like the basic reproductive numbers on which it is based, our approach only captures the difference in both dynamics at an early time.