

**The impact of contact structure on infectious disease control:
influenza and antiviral agents**

H. P. DUERR*¹, M. SCHWEHM¹, C. C. LEARY^{1,2}, S. J. DE VLAS³, M. EICHNER¹

¹ Dept. of Medical Biometry, University of Tübingen, Germany

² Dept. of Mathematics, State University of New York at Geneseo, USA

³ Dept. of Public Health, Erasmus MC, University Medical Center Rotterdam, The Netherlands

* Corresponding author:

Dr. Hans-Peter Duerr

Institut für Medizinische Biometrie, Westbahnhofstr. 55, D-72070 Tübingen

Phone: 07071/29 78259

Fax: 07071/29 5075

email: hans-peter.duerr@uni-tuebingen.de

www: <http://www.uni-tuebingen.de/modeling>

Running head: Influenza and network structure

1. SUMMARY

Planning adequate public health responses against emerging infectious diseases requires predictive tools to evaluate the impact of candidate intervention strategies. With current interest in pandemic influenza very high, modeling approaches have suggested antiviral treatment combined with targeted prophylaxis as an effective first-line intervention against an emerging influenza pandemic. To investigate how the effectiveness of such interventions depends on contact structure, we simulate the effects in networks with variable degree distributions. The infection attack rate can increase if the number of contacts per person is heterogeneous, implying the existence of high degree individuals who are potential super-spreaders. The effectiveness of a socially targeted intervention suffers from heterogeneous contact patterns and depends on whether infection is predominantly transmitted to close or casual contacts. Our findings imply that the various contact networks' degree distributions as well as the allocation of contagiousness between close and casual contacts should be examined to identify appropriate strategies of disease control measures.

Word count summary: 154

Keywords: Antiviral Agents, Community networks, Computer simulation, Disease outbreaks, Influenza, Super-spreader

2. INTRODUCTION

Understanding disease transmission and controlling disease outbreaks are primary public health objectives. The threat of emergent and re-emergent diseases, such as SARS and pandemic influenza, has made the research community and the general public more aware of the need for accurate and robust planning tools. Among these tools, individual-based computer simulations are important for allowing explicit consideration of contact structures in the population. Contact structures are the basis for the transmission of the infection, but they must be regarded as highly disease-specific and may remain unknown for many diseases. In these cases, model-based evaluations of competing intervention schemes must be subject to sensitivity analyses across varying networks.

With current interest in pandemic influenza very high, massive computer simulation models have been used to investigate optimal intervention strategies, and a promising intervention approach against emerging pandemic influenza is the distribution of antivirals based on geographic proximity and/or contact patterns [1,2]. Intervention strategies that rely on contact information are affected by the network structure and various investigations have shown that disease dynamics and intervention effectiveness depend on the type of the contact network (e.g. [3-11]).

Networks can be characterized by various measures, but epidemiological phenomena can often be sufficiently explained by the average degree [12], i.e. the average number of contacts per person. If, however, contacts in the population are highly dispersed, the infection dynamics may no longer be well characterized by the average degree [13]. Measures based on the variance and/or the skewness of the degree distribution [14] are then more appropriate, because they give more weight to the individuals who infect a disproportionately large numbers of other individuals. These so-called super-spreaders can introduce substantial stochasticity into the course of an epidemic [15], because their impact on the epidemic curve

strongly depends on when they are involved in transmission [16]. Scale-free networks, whose skewed degree distributions allow for the existence of highly connected individuals, are therefore potentially relevant for network epidemiology.

Scale-free networks show observed characteristics which cannot be reproduced by other types of networks [5,6,9,14,17]. Conclusions based on network studies, however, take place in a situation of uncertainty as they examine only a certain collection of networks. In infectious disease epidemiology, scale-free contact networks have to date been only described for sexual relationships [18,19]. The actual contact network involved in transmission of airborne diseases is difficult, perhaps impossible, to establish, but weakly skewed [2] or even normal degree distributions [20] have been suggested. Taken together, this means that networks generated by a preferential attachment scheme that can produce a range of degree distributions [21] might be candidates for studies in the field of network epidemiology.

To model diseases in which transmission rates or risks differ between casual and close contacts (within-household contacts), the network structure must distinguish between these two groups [22,23]. For influenza, there is no consensus as to whether infection is predominantly transmitted via close or casual contacts, because it seems to depend on the strain involved, or at least be different for seasonal and pandemic influenza [22,24]. One would expect that the effectiveness of targeted interventions and prophylaxis schemes depends on how the overall basic reproduction number (R_0) is distributed between these two groups. Sensitivity analyses addressing this issue have so far not been performed.

The aim of this study is to investigate how the final size of an epidemic and the effectiveness of intervention depend upon network structure and the relative contagiousness of close and casual contacts, using a model of pandemic influenza and antiviral treatment combined with targeted prophylaxis. We explore these effects in networks which are based on preferential attachment, but allow for tunable degree distributions [21]. Dispersion of the degree

distribution is represented by its standard deviation (which is strongly determined by the degree of individuals with many contacts) and by the average clustering coefficient (describing to what extent people within neighborhoods are in contact with each other). Our results help to identify uncertainties of interventions in real social networks and emphasize the relevance of projects that investigate the structure of such networks.

3. METHODS

(a) Network

A simulated closed population of 10000 individuals was created and individuals in the population were assigned both close (household) contacts and casual (any other) contacts. For the close contacts, the population was partitioned into households whose sizes were chosen from a distribution of household sizes in Thailand, which has been regarded as a potential country of origin of pandemic influenza with detailed demographic data [2]. Everyone in a household was assumed to be in close contact with all other individuals in the household. The minimum, maximum and average household size is $H_{\min} = 1$, $H_{\max} = 10$ and $\bar{H} = 3.57$, respectively. The average number of close contacts in the network equals then

$\bar{D}_h = \sum_{i=H_{\min}}^{H_{\max}} (i-1)f_i = 3.13$, where N is the population size and f_i is the relative frequency of individuals who live in a household of size i .

The network for casual contacts was created using a generalization of the Barabási-Albert scale-free network generation algorithm (Barabási & Albert, 1999) in which a tuning distribution is used to alter the preferential attachment scheme, yielding degree distributions that can vary from that of the scale-free network [21]. In the classical preferential attachment procedure, the tuning distribution is uniform, yielding a degree distribution of the power law type which is represented by a straight line on log-log scale. The tuning distributions used for this investigation were beta distributions which allow for modifying the shape of the degree distribution in a flexible way, as illustrated in figure 1. The algorithm for the network of casual contacts starts with eight individuals who are connected as a ring, implying two casual contacts per individual (remaining contacts, see below). Network growth proceeds by subsequently adding new individuals who always establish four casual contacts to individuals of the existing network by the modified preferential attachment scheme. After the last

individual has been added, the remaining contacts for the initial ring of individuals were completed, using the modified preferential attachment scheme, too. The minimum degree of $D_{\min}=4$ results in those cases when an individual has only these four casual contacts and no close contacts. In order to test the sensitivity of our results to the initial ring configuration of individuals, networks were generated beginning with a complete graph on the initial individuals. Conclusions in this investigation do not depend on this initial configuration.

Figure 1 around here

Heterogeneity in the degree distributions of all contacts (close and casual) is represented by the standard deviation (SD). The above mentioned household structure of close contacts combined with a classic scale-free network of casual contacts yields degree distributions with $SD_{SF}\approx 10.8$. A degree distribution will be called underdispersed if $SD < SD_{SF}$ and overdispersed if $SD > SD_{SF}$. In general, the SD is highly influenced by outliers, given in this context by D_{\max} , the maximum degree of the degree distribution..

Networks with differing standard deviation and clustering were generated from 45 different parameter constellations, originating from nine different beta distributions (all parameter combinations of $\alpha \in \{1.0, 1.4, 2.0\}$ and $\beta \in \{0.7, 1.0, 1.2\}$) and 5 different clustering parameters ($c \in \{0, 0.25, 0.5, 0.75, 1.0\}$). The clustering parameter c is the probability that an individual chooses to connect randomly among the contact persons of his/her current contacts (triad formation step), instead of using the preferential attachment step. The algorithm produced degree distributions with values for the root skewness of $3.2 < SD < 17.2$, maximum degrees of $22 < D_{\max} < 960$ and average clustering coefficients between 0 and 0.5. With 100 simulation repetitions for epidemics with and without intervention, these variations result in $9 \cdot 5 \cdot 100 \cdot 2 = 9000$ total networks used for each of the three scenarios shown in figure 3.

Independent of the parameter settings, the network had an average of $\bar{D}_c = 8$ casual contacts and $\bar{D}_h = 3.13$ close contacts yielding an average combined degree of $\bar{D} = 11.13$.

(b) Individual-Based Simulation

The contact network is the basis for a stochastic individual-based simulation of an influenza epidemic. Each network node represents an individual and each edge represents a potential contact along which the infection can spread. Individuals have discrete internal states describing the states of infection, symptoms and treatment. State changes of the individuals are executed in chronological order, using parameters as listed in Table 1. The parameter estimates described in the following paragraphs have been adopted from previous simulation studies [25,26].

The *infection states* are 'susceptible', 'exposed', 'infectious' and 'removed', following the notation of classic SEIR models. Initially all individuals except the index cases are susceptible. Infection is introduced into the population by 10 randomly chosen index cases on day zero. Newly infected individuals enter the latent period, the length of which is assumed to be gamma distributed with mean $T_L=1.6$ days and a coefficient of variation of $CV_L=35\%$. Individuals in the latent period are not yet infectious and show no symptoms. In the subsequent infectious period (gamma distributed with mean $T_I=4.1$ days and $CV_I=23\%$), individuals infect contacts with rate β (see next section). Loss of immunity is neglected, as only epidemic (and no endemic) scenarios are investigated.

The *symptom states* are 'asymptomatic', 'symptomatic' and 'immune' or 'dead'. Symptoms, which are a prerequisite for diagnosis and treatment (see below), appear at the beginning of the infectious period. For influenza we assume that a fraction of $1-F_s=33\%$ of infections proceed asymptotically, and that these individuals are only half as infectious as symptomatic cases ($r=50\%$). We assume that about $F_w=73\%$ of infected and symptomatic

cases stay at home, having contact with family members only. The other 27 % of symptomatic cases continue circulating and transmitting the infection to their casual contacts. The symptomatic state ends with the infectious period, after which individuals no longer contribute to transmission as they are either immune or dead.

The *treatment states* are 'no treatment', 'prophylaxis' and 'treatment'. The intervention scheme is based on antiviral treatment of cases and prophylaxis of their close contacts. Treatment is restricted to the 67 % of infected individuals who show symptoms and we assume a compliance rate of 80 %. Treatment starts one day after the onset of symptoms, is continued for five days and reduces infectiousness by 62 %. Prophylaxis of close contacts (i.e., household members) begins simultaneously with the treatment of the symptomatic family member, but lasts for a period of ten days. Prophylaxis has a compliance of 80 % and reduces the susceptibility of an individual to 30 %.

(c) *Transmission rates and infection attack rates*

Transmission rates were chosen so that baseline epidemics in networks with the highest variance and without intervention cause an infection attack rate (**IAR**) of either approximately 50 % or approximately 30 % of the population. Since the distribution of R_0 between close and casual contacts is not known, we address by sensitivity analyses two hypotheses: the rate of transmission to close contacts (index h) is either twice the rate of transmission to casual contacts (index c) ($\beta_h=2 \beta_c$) or vice versa ($\beta_h=0.5 \beta_c$). This yields the following four scenarios:

1. Transmission predominantly to close contacts, baseline IAR \approx 50 % ($\beta_h=0.116$, $\beta_c=0.058$)
2. Transmission predominantly to close contacts, baseline IAR \approx 30 % ($\beta_h=0.088$, $\beta_c=0.044$)
3. Transmission predominantly to casual contacts, baseline IAR \approx 50 % ($\beta_h=0.047$, $\beta_c=0.094$)
4. Transmission predominantly to casual contacts, baseline IAR \approx 30 % ($\beta_h=0.035$, $\beta_c=0.070$)

Within each scenario, contact rates are kept constant and thus, changes in the IAR are attributable to network structure.

Table 1 around here

(d) Basic reproduction number R_0

We assume that the time until infection is exponentially distributed with mean $1/\beta$ and density $P(t) = \beta e^{-\beta t}$, and the probability that a contact is infected by time t is

$\int_0^t P(\tau) d\tau = 1 - e^{-\beta t}$. The expected number of persons who are infected by time t if m persons

are in contact with the case is then $S^* = m(1 - e^{-\beta t})$. All m contact persons are infected if the case is contagious forever. Since this is not true, S^* must be weighted with the probability that a case is infectious by time t , and we assume the infectious period to be gamma distributed

with mean μ and coefficient of variation ν , thus $Q(t) = \frac{e^{-t/\mu\nu^2} t^{1/\nu^2 - 1} (1/\mu\nu^2)^{1/\nu^2}}{\Gamma(1/\nu^2)}$. Weighting S^*

with $Q(t)$ yields the expected number of secondary infections,

$$S = \int_0^{\infty} m(1 - e^{-\beta\tau}) Q(\tau) d\tau = m \left(1 - \left(\frac{1}{1 + \nu^2 \beta \mu} \right) \right)^{1/\nu^2}. \quad (S \text{ is lower than the "classical" } R_0 \text{ which}$$

does not adequately consider the infectious period, leading to a situation where repeated infections of the same individual are possible and consequently, the spread of the disease is overestimated [23]).

A model with close and casual contacts involves the two contact rates β_h and β_c , and m_h close and m_c casual contacts. Correspondingly, the expected numbers of secondary infections can be calculated as S_h and S_c , and a proxy for the basic reproduction number is their sum, i.e.

$R_0 = S_h + S_c$. With $m_h=3.11$ close and $m_c=8$ casual contacts on average, the four scenarios yield the following reproduction numbers:

1. 50% IAR: $\beta_h=0.116$: $S_h = 1.17$, $\beta_c=0.058$: $S_c = 1.68$, yielding $R_0 = 2.85$
2. 30% IAR: $\beta_h=0.088$: $S_h = 0.93$, $\beta_c=0.044$: $S_c = 1.31$, yielding $R_0 = 2.24$
3. 50% IAR: $\beta_h=0.047$: $S_h = 0.54$, $\beta_c=0.094$: $S_c = 2.54$, yielding $R_0 = 3.08$
4. 30% IAR: $\beta_h=0.035$: $S_h = 0.41$, $\beta_c=0.070$: $S_c = 1.98$, yielding $R_0 = 2.39$

4. RESULTS

(a) *Epidemic curves*

Figure 2 shows examples of simulated epidemics in networks with high (a) and low (b) dispersion of the degree distribution. Although transmission is driven by the same transmission rates in both networks ($\beta_h=0.088$, $\beta_c=0.044$, see Methods and cf. figure 3b) the course of the epidemics as well as the infection attack rates differ considerably. Epidemics in networks with high variance pervade the population more quickly with more individuals infected compared to epidemics in networks with lower variance. More specific comments are given in the next two paragraphs.

Figure 2 around here

(b) *Highly contagious influenza strains*

For highly contagious influenza strains, the size of the epidemic does not depend on heterogeneity in the degree distribution if no intervention is performed (figure 3a). With ten index cases in a population of 10000 people, major epidemics occur in more than 99 % of simulations, independent of whether infection is predominantly transmitted via close or casual contacts. On the other hand, intervention effectiveness does depend on heterogeneity in the degree distribution and is more efficient in networks with low variance than with high variance (figure 3c and e). Under intervention, epidemics with an infection attack rate of 20-30 % still occur in highly heterogeneous networks, but they become increasingly rare as the variance decreases. As the proposed intervention is directed more towards close contacts, it is more efficient if transmission is predominantly driven by them (figure 3c) than by casual contacts (figure 3e). Using a threshold of 500 cases (5 % of the study population) to define successful containment, the probability of intervention success decreases from 100 to 40 % in the close contact scenario (figure 3c) and from 80 to 20 % in the casual contact scenario (figure 3e) for weakly to highly dispersed degree distributions, respectively.

(c) *Moderately contagious influenza strains*

For moderately contagious influenza strains, the size of the epidemic depends on heterogeneity in the degree distribution even when no interventions are performed (figure 3b). The average number of infections increases from ~1000 when the variance is low to ~3000 when the standard deviation is high. The variability in the size of the epidemics is inversely related to the dispersion in the degree distribution, as indicated by the coefficient of variation which decreases from 100 % for epidemics resulting from weakly heterogeneous degree distributions to 40 % for epidemics resulting from highly heterogeneous degree distributions. Both effects - the increasing size and the decreasing variability of the epidemics - make the distinction between small outbreaks and vast epidemics more pronounced as the variance

increases. The probability of an epidemic increases from 50 to 85 % for weakly to highly heterogeneous degree distributions, respectively. For moderately contagious influenza strains, the proposed intervention efficiently controls epidemics in networks with low variance (figure 3d, f). For networks with higher variance, however, the probability of successful containment decreases to 80 % (figure 3d) and to 50 % (figure 3f), depending on whether the infection is predominantly transmitted to close or casual contacts.

Figure 3 around here

5. DISCUSSION

Investigating characteristics of a hypothetical influenza epidemic and the effects of intervention under different networks shows that the infection attack rate of an epidemic and the effectiveness of intervention can depend on dispersion in the degree distribution of the number of contacts and the distribution of transmission rates between close and casual contacts. With parameters specifically adjusted to influenza and targeted distribution of antivirals, we have followed a parameter-rich and realistic modelling approach, using networks which are produced by a modified preferential attachment step as a possible representation of contact structures in the population.

Degree distributions with high variance or the occurrence of high-degree individuals can be associated with an accelerated course of the epidemic [14] (see also figure 2) and with an increased infection attack rate (figure 3b). The effect on the increased infection attack rate is limited if the infectious agent is highly contagious, i.e. if infection is efficiently transmitted from the outset, producing a self-exhausting infection process that cannot be further propagated by contact patterns (figure 3a). We conclude that heterogeneous degree distributions increase the infection attack rate of epidemics which are produced by moderately effective transmission - and that is the situation when intervention is applied (figures 3c-f). Contact patterns will influence intervention success less, if intervention is targeted geographically [1,2], rather than socially, as assumed in this investigation.

Apart from measures of dispersion and clustering in the degree distribution, additional network characteristics influence the epidemiological outcome of an epidemic [9,12]. The type of network [3,16] and the population size [5] have an effect on the probability of an epidemic occurring and/or the final size of the epidemic. For the networks studied here in the case of an influenza epidemic, we have found that clustering is a negligible factor with respect to epidemiological outcomes (results not shown). However other studies have shown that

clustering can influence the size of the epidemic [27], indicating that epidemiological outcomes can be highly network-specific. For a more generalized approach describing the effects of close and casual contact patterns on the epidemics, see [23].

The maximum degree in our networks largely determines the variance of the degree distribution and the relationship for the networks used in this investigation is $\text{Var} = 10.5 + 0.33 D_{\max}$ with $r^2 = 0.93$. Thus, epidemiological outcomes may be explained largely by the influence of only one individual in the network, the individual with the highest degree. To date it is not clear to what extent this effect is restricted to networks which are built on the basis of preferential attachment. Extending the present conclusions to a wider class of networks would be an important advance for infectious disease studies.

Word count main text: 3050

ACKNOWLEDGEMENTS

The authors like to thank Dr. H. Nishiura for providing helpful comments on this manuscript. This work has been supported by EU projects SARScontrol (FP6 STREP; contract no. 003824) (HPD) and INFTRANS (FP6 STREP; contract no. 513715) (CCL, MS)), the National Science Foundation (NSF 0436298) (CCL), the MODELREL project, funded by DG SANCO (no. 2003206—SI 2378802) (MS, ME), and by the German Ministry of Health (MS, ME). The work was done partially while the author was visiting the Institute for Mathematical Sciences, National University of Singapore in 2005. The visit was supported by the Institute.

6. REFERENCES

1. Ferguson NM, *et al.* Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 2005; 437: 209-214.
2. Longini IM, Jr., *et al.* Containing pandemic influenza at the source. *Science* 2005; 309: 1083-1087.
3. Barthelemy M, *et al.* Dynamical patterns of epidemic outbreaks in complex heterogeneous networks. *Journal of Theoretical Biology* 2005; 235: 275-288.
4. Dezso Z, Barabasi AL. Halting viruses in scale-free networks. *Physical review. E, Statistical, nonlinear, and soft matter physics* 2002; 65: 055103.
5. May RM, Lloyd AL. Infection dynamics on scale-free networks. *Physical review. E, Statistical, nonlinear, and soft matter physics* 2001; 64: 066112.
6. Pastor-Satorras R, Vespignani A. Epidemic spreading in scale-free networks. *Physical Review Letters* 2001; 86: 3200-3203.
7. Pastor-Satorras R, Vespignani A. Epidemic dynamics in finite size scale-free networks. *Physical review. E, Statistical, nonlinear, and soft matter physics* 2002; 65: 035108.
8. Meyers LA, Newman ME, Pourbohloul B. Predicting epidemics on directed contact networks. *Journal of Theoretical Biology* 2005: Epub ahead of print.
9. Shirley MDF, Rushton SP. The impacts of network topology on disease spread. *Ecological Complexity* 2005; 2: 287-299.
10. Eubank S, *et al.* Modelling disease outbreaks in realistic urban social networks. *Nature* 2004; 429: 180-184.
11. Pourbohloul B, *et al.* Modeling control strategies of respiratory pathogens. *Emerging Infectious Diseases* 2005; 11: 1249-1256.
12. Christley RM, *et al.* Infection in social networks: using network analysis to identify high-risk individuals. *American Journal of Epidemiology* 2005; 162: 1024-1031.
13. Lloyd-Smith JO, *et al.* Superspreading and the effect of individual variation on disease emergence. *Nature* 2005; 438: 355-359.
14. Barthelemy M, *et al.* Velocity and hierarchical spread of epidemic outbreaks in scale-free networks. *Physical Review Letters* 2004; 92: 178701.
15. Li Y, *et al.* Predicting super spreading events during the 2003 severe acute respiratory syndrome epidemics in Hong Kong and Singapore. *American Journal of Epidemiology* 2004; 160: 719-728.

16. Meyers LA, *et al.* Network theory and SARS: predicting outbreak diversity. *Journal of Theoretical Biology* 2005; 232: 71-81.
17. Volchenkov D, Volchenkova L, Blanchard P. Epidemic spreading in a variety of scale free networks. *Physical review. E, Statistical, nonlinear, and soft matter physics* 2002; 66: 046137.
18. Schneeberger A, *et al.* Scale-free networks and sexually transmitted diseases: a description of observed patterns of sexual contacts in Britain and Zimbabwe. *Sexually transmitted diseases* 2004; 31: 380-387.
19. Liljeros F, *et al.* The web of human sexual contacts. *Nature* 2001; 411: 907-908.
20. Edmunds WJ, O'Callaghan CJ, Nokes DJ. Who mixes with whom? A method to determine the contact patterns of adults that may lead to the spread of airborne infections. *Proceedings of the Royal Society of London. Series B* 1997; 264: 949-957.
21. Leary CC, *et al.* Tuning degree distributions of scale-free networks. *Physical review. E, Statistical, nonlinear, and soft matter physics* 2006; submitted.
22. Longini IM, Jr., *et al.* Estimating household and community transmission parameters for influenza. *American Journal of Epidemiology* 1982; 115: 736-751.
23. Ball F, Neal P. A general model for stochastic SIR epidemics with two levels of mixing. *Mathematical Biosciences* 2002; 180: 73-102.
24. Cauchemez S, *et al.* A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. *Statistics in Medicine* 2004; 23: 3469-3487.
25. Elveback LR, *et al.* An influenza simulation model for immunization studies. *American Journal of Epidemiology* 1976; 103: 152-165.
26. Longini IM, Jr., *et al.* Containing pandemic influenza with antiviral agents. *American Journal of Epidemiology* 2004; 159: 623-633.
27. Newman ME. Properties of highly clustered networks. *Physical review. E, Statistical, nonlinear, and soft matter physics* 2003; 68: 026121.

TABLE 1

Population

Simulated population size: 10000

Introduction of infection by 10 index cases, randomly chosen from the population

Infection

Duration of latent period: gamma distributed with mean 1.6 days and CV =35%

Duration of infectious period: gamma distributed with mean 4.1 days and CV =23%

Immunity: no loss of immunity

Fraction of infections that are asymptomatic: $1-F_s = 33\%$

Contagiousness

Scenario 1: $\beta_h = 0.116$ and $\beta_c = 0.058$ contacts per day, yielding an IAR of $\approx 50\%$

Scenario 2: $\beta_h = 0.088$ and $\beta_c = 0.044$ contacts per day, yielding an IAR of $\approx 30\%$

Scenario 3: $\beta_h = 0.047$ and $\beta_c = 0.094$ contacts per day, yielding an IAR of $\approx 50\%$

Scenario 4: $\beta_h = 0.035$ and $\beta_c = 0.070$ contacts per day, yielding an IAR of $\approx 30\%$

Reduction of infectiousness of asymptomatic cases: $r = 50\%$

Fraction of circulating cases among symptomatic cases: $1-F_w = 27\%$

Antiviral treatment of cases

Duration: 5 days

Delay: 1 day after onset of symptoms

Compliance: 80 %

Infectiousness under treatment is reduced by 62 %

Antiviral prophylaxis of close contacts

Duration: 10 days

Delay: 1 day after onset of symptoms of a family member

Compliance: 80 %

Susceptibility under prophylaxis is reduced by 70 %

Table 1: Parameter values used for the simulations (see Methods). The infection attack rate (IAR) is determined by the contact rate β and is the overall percentage of the population that is infected during the course of the epidemic. CV: Coefficient of variation.

Legends:

Figure 1: Examples of degree distributions of different networks with increasing standard deviation (SD) in a population of 10000 individuals. The unimodal structure in the low-degree region originates from close contacts within households. All networks have an average degree of 3.13 close and 8 casual contacts. The distributions were generated using the algorithm described in [21] with no extra clustering ($c=0$) and beta tuning distributions with parameter values: **(a)**: $\alpha=1.4$, $\beta=0.7$, **(b)**: $\alpha=1.4$, $\beta=1.0$, **(c)**: $\alpha=1.0$, $\beta=1.2$.

Figure 2: Examples of simulated epidemics in populations with different network structures. Each graph gives three realizations resulting from the degree distribution shown in the inset. The degree distribution is fixed for the three realizations, respectively, but epidemiological factors (e.g. the time of infection of high-degree individuals or the duration of their infectious period) are subject to random variation given the parameters listed in table 1. Infection attack rates (IARs) of the epidemics are shown in the legend. The six epidemics are a subset of the scenario in figure 3b. **(a)**: Epidemics in a highly heterogeneous network (SD=13.5) with a maximum degree of $D_{\max}=479$ contacts. **(b)**: Epidemics in a network with lower standard deviation (SD=4.2) with $D_{\max}=33$ contacts.

Figure 3: Distributions of the sizes of outbreaks and epidemics occurring under different networks and transmission modes. Left column: Highly contagious influenza strain causing an infection attack rate of $\sim 50\%$. Right column: Moderately contagious influenza strain causing an infection attack rate of up to $\sim 30\%$. Epidemic outcomes under no intervention (a,b).

Effects of intervention are shown dependent on whether infection is predominantly transmitted to close (c,d) or casual (e,f) contacts. Bars have a width of 100 cases. For each graph, 4500 simulations were performed.

Word count Legends: 310

FIGURE 1

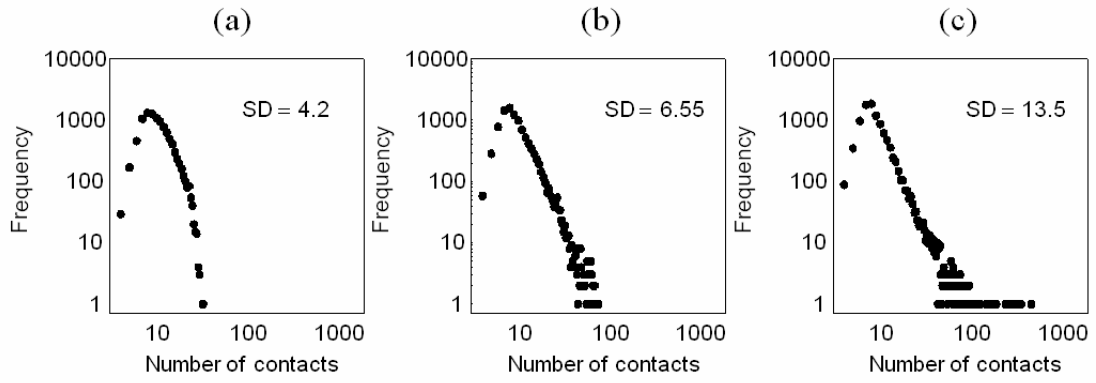


FIGURE 2

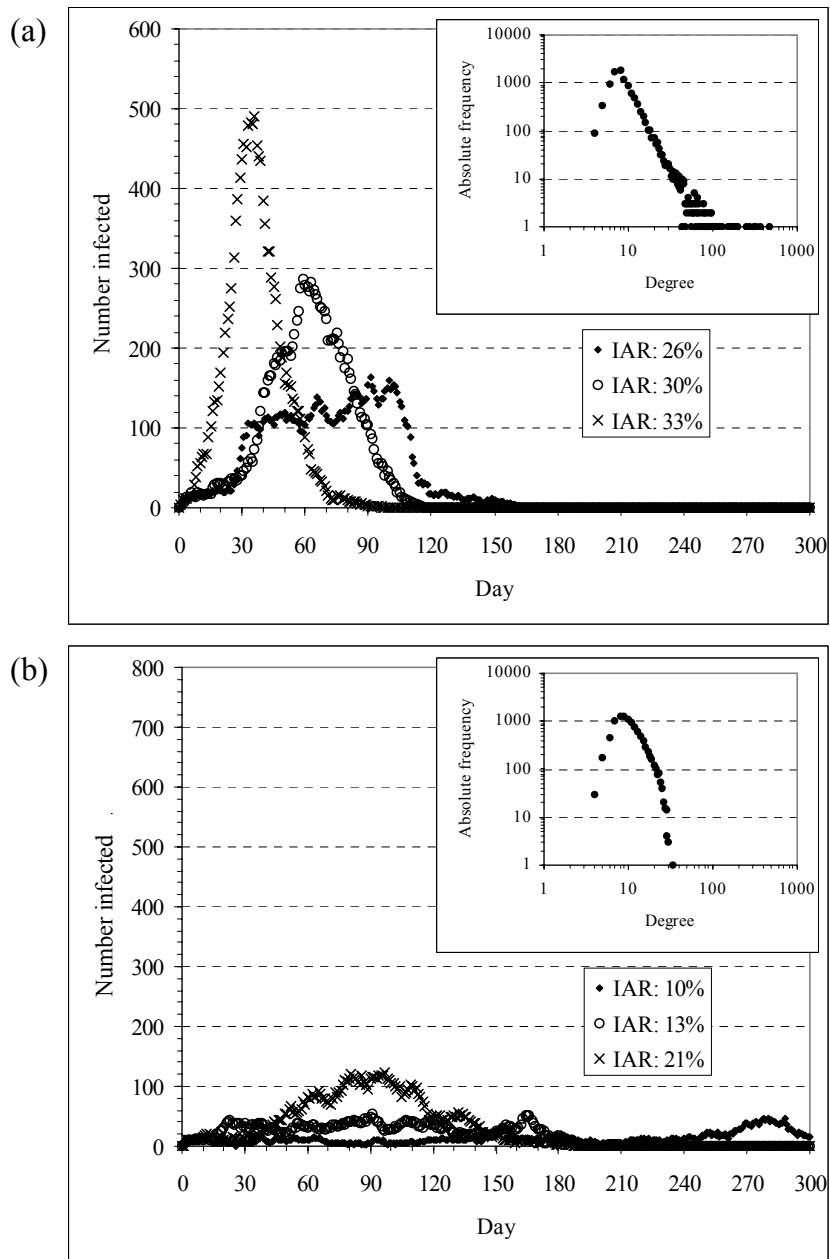


FIGURE 3

