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

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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, modelling 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.

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]).

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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 (S.D.) (which is strongly determined by the degree of individuals with many contacts) and by the average clustering coefficient (describing to what extent people within neighbourhoods 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.

METHODS

Network

A simulated closed population of 10 000 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 $\bar{H}=3{\cdot}57$ respectively. The average number of close contacts in the network then equals $\bar{D}_{\mathrm{h}}=\sum_{i=H_{\min}}^{H_{\max}}(i-1)f_i=3{\cdot}13$, where 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 [25] 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.

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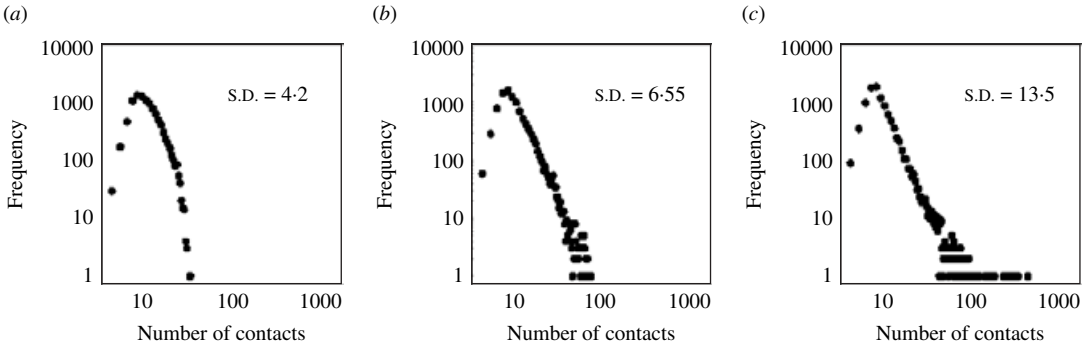

Fig. 1. Examples of degree distributions of different networks with increasing standard deviation (S.D.) in a population of 10 000 individuals. The unimodal structure in the low-degree region originates from close contacts within households. All networks have an average degree of 3·13 close and 8 casual contacts. The distributions were generated using the algorithm described in ref. [21] with no extra clustering ($c=0$) and beta tuning distributions with parameter values: (*a*) $\alpha=1{\cdot}4$, $\beta=0{\cdot}7$, (*b*) $\alpha=1{\cdot}4$, $\beta=1{\cdot}0$, (*c*) $\alpha=1{\cdot}0$, $\beta=1{\cdot}2$.

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.

Heterogeneity in the degree distributions of all contacts (close and casual) is represented by the S.D. The above-mentioned household structure of close contacts combined with a classic scale-free network of casual contacts yields degree distributions with $\text{S.D.}_{\text{SF}}\approx 10{\cdot}8$. A degree distribution will be called underdispersed if $\text{S.D.}<\text{S.D.}_{\text{SF}}$ and overdispersed if $\text{S.D.}>\text{S.D.}_{\text{SF}}$. In general, the S.D. is highly influenced by outliers, given in this context by $D_{\max}$, the maximum degree of the degree distribution.

Networks with differing S.D. and clustering were generated from 45 different parameter constellations, originating from nine different beta distributions [all parameter combinations of $\alpha\in(1{\cdot}0,\ 1{\cdot}4,\ 2{\cdot}0)$ and $\beta\in(0{\cdot}7,\ 1{\cdot}0,\ 1{\cdot}2)$] and five different clustering parameters [$c\in(0,\ 0{\cdot}25,\ 0{\cdot}5,\ 0{\cdot}75,\ 1{\cdot}0)$]. 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 $3{\cdot}2<\text{S.D.}<17{\cdot}2$, 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 $9\times5\times100\times2=9000$ total networks used for each of the four scenarios (see Table). Independent of the parameter settings, the network had an average of $\bar{D}_{\text{c}}=8$ casual contacts and $\bar{D}_{\text{h}}=3{\cdot}13$ close contacts yielding an average combined degree of $\bar{D}=11{\cdot}13$.

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 the Table. The parameter estimates described in the following paragraphs have been adopted from previous simulation studies [26, 27].

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

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Table. *Parameter values used for the simulations (see Methods section)*

Population
Simulated population size: 10 000
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: $\beta_h = 0{\cdot}116$ and $\beta_c = 0{\cdot}058$ contacts per day, yielding an IAR of $\approx 50\,\%$
Scenario 2: $\beta_h = 0{\cdot}088$ and $\beta_c = 0{\cdot}044$ contacts per day, yielding an IAR of $\approx 30\,\%$
Scenario 3: $\beta_h = 0{\cdot}047$ and $\beta_c = 0{\cdot}094$ contacts per day, yielding an IAR of $\approx 50\,\%$
Scenario 4: $\beta_h = 0{\cdot}035$ and $\beta_c = 0{\cdot}070$ 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 %

CV, Coefficient of variation; IAR, infection attack rate. The 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.

the latent period, the length of which is assumed to be gamma distributed with mean $T_L = 1{\cdot}6$ 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 $T_I = 4{\cdot}1$ 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 asymptomatically, 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 1 day after the onset of symptoms, is continued for 5 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 10 days. Prophylaxis has a compliance of 80 % and reduces the susceptibility of an individual to 30 %.

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 $\sim 50\,\%$ or $\sim 30\,\%$ 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 ($\beta_h = 0{\cdot}5\beta_c$). This yields the following four scenarios:

(1) Transmission predominantly to close contacts, baseline IAR $\approx 50\,\%$ ($\beta_h = 0{\cdot}116$, $\beta_c = 0{\cdot}058$).
(2) Transmission predominantly to close contacts, baseline IAR $\approx 30\,\%$ ($\beta_h = 0{\cdot}088$, $\beta_c = 0{\cdot}044$).
(3) Transmission predominantly to casual contacts, baseline IAR $\approx 50\,\%$ ($\beta_h = 0{\cdot}047$, $\beta_c = 0{\cdot}094$).
(4) Transmission predominantly to casual contacts, baseline IAR $\approx 30\,\%$ ($\beta_h = 0{\cdot}035$, $\beta_c = 0{\cdot}070$).

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

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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,

$$S = \int_0^\infty m(1 - e^{-\beta\tau})\, Q(\tau)\, d\tau = m\left(1 - \left(\frac{1}{1 + \nu^2\beta\mu}\right)\right)^{1/\nu^2}.$$

(S is lower than the 'classical' R_0 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 $m_h = 3{\cdot}11$ close and $m_c = 8$ casual contacts on average, the four scenarios yield the following reproduction numbers:

(1) 50% IAR: $\beta_h = 0{\cdot}116$, $S_h = 1{\cdot}17$, $\beta_c = 0{\cdot}058$: $S_c = 1{\cdot}68$,
yielding $R_0 = 2{\cdot}85$.
(2) 30% IAR: $\beta_h = 0{\cdot}088$, $S_h = 0{\cdot}93$, $\beta_c = 0{\cdot}044$, $S_c = 1{\cdot}31$,
yielding $R_0 = 2{\cdot}24$.
(3) 50% IAR: $\beta_h = 0{\cdot}047$, $S_h = 0{\cdot}54$, $\beta_c = 0{\cdot}094$, $S_c = 2{\cdot}54$,
yielding $R_0 = 3{\cdot}08$.
(4) 30% IAR: $\beta_h = 0{\cdot}035$, $S_h = 0{\cdot}41$, $\beta_c = 0{\cdot}070$, $S_c = 1{\cdot}98$,
yielding $R_0 = 2{\cdot}39$.

RESULTS

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 ($\beta_h = 0{\cdot}088$, $\beta_c = 0{\cdot}044$, see Methods section and cf. Fig. 3*b*) the course of the epidemics as well as the IARs 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.

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 (Fig. 3*a*). With ten index cases in a population of 10 000 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 (Fig. 3*c*, *e*). Under intervention, epidemics with an IAR 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 (Fig. 3*c*) than by casual contacts (Fig. 3*e*). 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 (Fig. 3*c*) and from 80% to 20% in the casual-contact scenario (Fig. 3*e*) for weakly to highly dispersed degree distributions respectively.

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 (Fig. 3*b*). The average number of infections increases from ~1000 when the variance is low to ~3000 when the S.D. is high. The variability in the size of the epidemics is inversely related to the dispersion in the degree distribution, as indicated by

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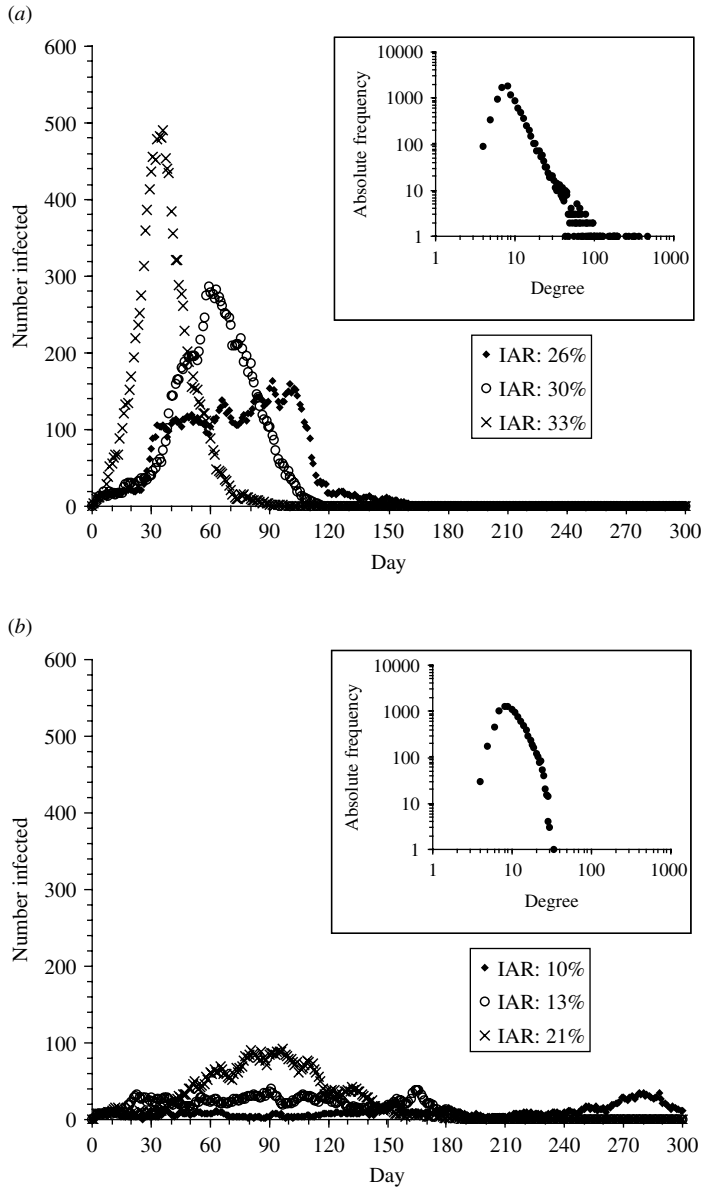

Fig. 2. Examples of simulated epidemics in populations with different network structures. Each graph gives three realizations resulting from the degree distribution shown in the inset. The degree distribution is fixed for the three realizations respectively, but epidemiological factors (e.g. the time of infection of high-degree individuals or the duration of their infectious period) are subject to random variation given the parameters listed in the Table. Infection attack rates (IARs) of the epidemics are shown in the key. The six epidemics are a subset of the scenario in Figure 3*b*. (*a*) Epidemics in a highly heterogeneous network (S.D. = 13·5) with a maximum degree of $D_{max} = 479$ contacts. (*b*) Epidemics in a network with lower standard deviation (S.D. = 4·2) with $D_{max} = 33$ contacts.

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 (Fig. 3*d*,*f*). For networks with higher variance, however, the probability of successful containment decreases to 80% (Fig. 3*d*) and to 50% (Fig. 3*f*), depending on whether the infection is predominantly transmitted to close or casual contacts.

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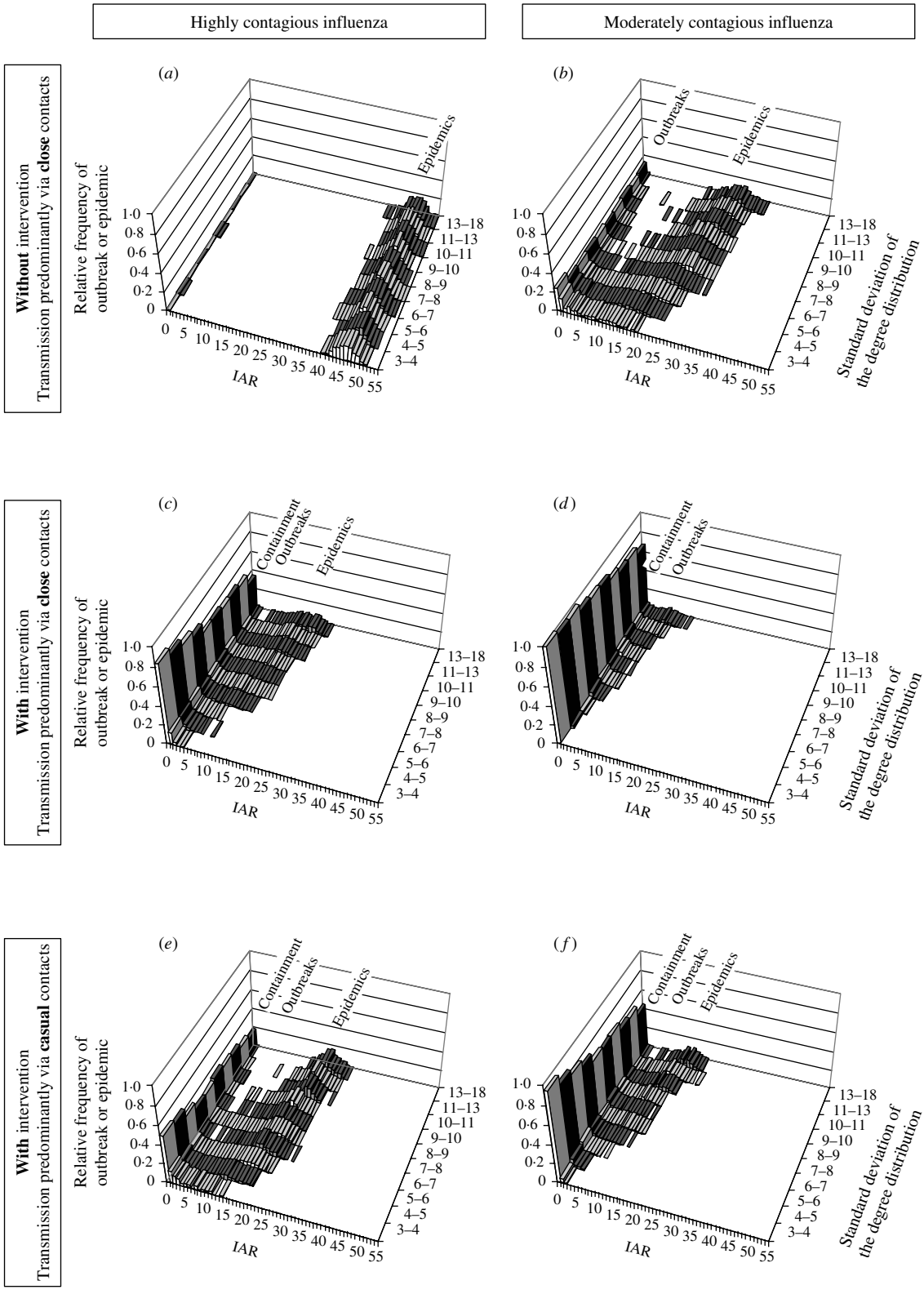

Fig. 3. Distributions of the sizes of outbreaks and epidemics occurring under different networks and transmission modes. Left panels: Highly contagious influenza strain causing an infection attack rate (IAR) of ~50%. Right panels: Moderately contagious influenza strain causing an IAR of up to ~30%. Epidemic 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 panel, 4500 simulations were performed.

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DISCUSSION

Investigating characteristics of a hypothetical influenza epidemic and the effects of intervention under different networks shows that the IAR 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 Fig. 2) and with an increased IAR (Fig. 3*b*). The effect on the increased IAR 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 (Fig. 3*a*). We conclude that heterogeneous degree distributions increase the IAR of epidemics which are produced by moderately effective transmission – and that is the situation when intervention is applied (Fig. 3*c–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 [28], 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 ref. [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 $\mathrm{Var} = 10{\cdot}5 + 0{\cdot}33\ D_{\max}$ with $r^2 = 0{\cdot}93$. 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.

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DECLARATION OF INTEREST

None.

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