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Intervention strategies for an influenza pandemic taking into account secondary bacterial infections

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ABSTRACT

Influenza infections often predispose individuals to consecutive bacterial infections. Both during seasonal and pandemic influenza outbreaks, morbidity and mortality due to secondary bacterial infections can be substantial. With the help of a mathematical model, we investigate the potential impact of such bacterial infections during an influenza pandemic, and we analyze how antiviral and antibacterial treatment or prophylaxis affect morbidity and mortality. We consider different scenarios for the spread of bacteria, the emergence of antiviral resistance, and different levels of severity for influenza infections (1918-like and 2009-like). We find that while antibacterial intervention strategies are unlikely to play an important role in reducing the overall number of cases, such interventions can lead to a significant reduction in mortality and in the number of bacterial infections. Antibacterial interventions become even more important if one considers the–very likely–scenario that during a pandemic outbreak, influenza strains resistant to antivirals emerge. Overall, our study suggests that pandemic preparedness plans should consider intervention strategies based on antibacterial treatment or prophylaxis through drugs or vaccines as part of the overall control strategy. A major caveat for our results is the lack of data that would allow precise estimation of many of the model parameters. As our results show, this leads to very large uncertainty in model outcomes. As we discuss, precise assessment of the impact of antibacterial strategies during an influenza pandemic will require the collection of further data to better estimate key parameters, especially those related to the bacterial infections and the impact of antibacterial intervention strategies.

Introduction

Infections with both seasonal and pandemic strains of influenza A virus can render hosts more susceptible to secondary bacterial infections, often resulting in significant morbidity and mortality (Bhat et al., 2005; Bonten and Prins, 2006; Brundage, 2006; Brundage and Shanks, 2008; Grabowska et al., 2006; Gupta et al., 2008; Hament et al., 1999; Maxwell et al., 1949; McCullers, 2006; Morens and Fauci, 2007; Morens et al., 2008; O'Brien et al., 2000; Stuart-Harris, 1979). The bacteria most common found in secondary infections are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Neisseria meningitides*, with others playing minor roles (Brundage and Shanks, 2008; Cartwright et al., 1991; Hageman et al., 2006; Hament et al., 1999; Hers et al., 1958; Jennings et al., 2008; Juven et al., 2000; Lim et al., 2001; Louria et al., 1959; Maxwell et al., 1949; McCullers, 2006; Morens et al., 2008; Shann et al., 1984; Stuart-Harris, 1959; Woodhead et al., 1987). Despite the general awareness of the importance of secondary bacterial infections, current studies that investigate containment or mitigation of a possible influenza pandemic do not consider such infections and the possible impact of antibacterial interventions (Ferguson et al., 2005; Ferguson et al., 2006; Germann et al., 2006; Halloran et al., 2008; Longini and Halloran, 2005; McCullers, 2008). Here, we model a pandemic influenza outbreak in the U.S. and explicitly consider secondary bacterial infections. We investigate how intervention strategies based on antiviral (AV) or antibacterial (AB) prophylaxis or treatment affect the number of influenza and bacteria cases and deaths. We study the impact of AV and AB control strategies in the context of both a severe and relatively mild pandemic, modeled after the 1918 and 2009 H1N1 outbreaks, respectively. For prophylaxis or treatment with antivirals, we consider the currently available neuraminidase inhibitors, i.e. oseltamivir and zanamivir (Moscona, 2005). (For a recent study that considers administration of multiple antivirals during an influenza pandemic, see Wu et al. (Wu et al., 2009)). For the antibacterial control strategies, we focus on prophylaxis in the form of vaccination against *Streptococcus pneumonia* (Klugman and Madhi, 2007; Madhi et al., 2004; Moberley et al., 2008), prophylactic administration of broad-spectrum antibacterial drugs (e.g. flouroquinolones, oxazolidinones or similar (Diekema and Jones, 2001; Zhanel et al., 2002)), or a

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mixture of the two. Antibacterial treatment is assumed to occur with the same type of broad-spectrum drugs.

We find that while antibacterial intervention strategies are unlikely to play an important role in reducing the overall number of cases, such interventions can lead to a significant reduction in mortality and in the number of bacterial infections. We show how antibacterial interventions become even more important if one considers the–very likely–scenario that during a pandemic outbreak, influenza strains resistant to antivirals emerge. The lack of precise estimation of many of the model parameters leads to rather large uncertainty in model outcomes. By performing a sensitivity analysis, we determine the parameters that have the most impact on the obtained results.

Mathematical models

The model without antiviral resistance

We use a compartmental, SIR-type model (Anderson and May, 1991; Hethcote, 2000) to study a pandemic outbreak in the U.S. Intervention strategies involve administration of antiviral (AV) drugs and antibacterial (AB) drugs or vaccines, either as prophylaxis or as treatment.

We assume that for a novel, pandemic strain, no immunity exists, the whole population is susceptible. A fraction f_p of the susceptibles, S, are assumed to receive AV prophylaxis. This prophylaxis has an efficacy of e_p. In case of failed prophylaxis, we follow Lipsitch et al. (Lipsitch et al., 2007) and assume that the a course of infection is comparable to an AV treated host. Since the literature suggests that during an influenza outbreak, initial influenza infection usually precedes bacterial infection, we ignore the possibility of primary bacterial infections, as well as the possibility of simultaneous infection of a susceptible host with influenza and bacteria (Brundage and Shanks, 2008; O'Brien et al., 2000).

Individuals who become infected with influenza are either untreated (u) or treated (t) with AV and prophylaxed (p) or not (n) with AB. We therefore have 4 compartments, labeled $I_{u,n}$, $I_{u,p}$, $I_{t,n}$, $I_{t,p}$. The first index refers to the treatment status with respect to AV, the second refers to the status of AB prophylaxis. The AB prophylaxed hosts have either received antibacterial (e.g. Streptococcal) vaccines or take antibacterial drugs in a prophylactic manner. We assume that all infected persons will become infectious cases. Influenza infected individuals can acquire secondary bacterial infections. One way this can happen is through dissemination of bacteria that existed as commensals in the host before the influenza infection. This can be modeled by assuming that a constant fraction of influenza infected acquire a bacterial infection. In the model, we assume that the influenza infecteds leave their compartments at rates $\nu_{i,j}$ (which is the inverse of the mean time of the influenza infection). A fraction, $d_{i,j}$ are assumed to die from the primary influenza infection. Another fraction, $c_{i,j}$, acquire secondary bacterial infections, and the majority $\nu_{i,j}(1-d_{i,j}-c_{i,j})$ recover. The values of these parameters depend on the status of AV treatment ($i=u$ or $i=t$) and AB prophylaxis ($j=p$ or $j=n$).

Additionally, it is possible that both influenza infected or bacteria infected hosts shed bacteria and that bacteria infected hosts still harbor some virus and spread the virus to susceptible hosts. We include transmission terms for all these possibilities in the force of infection terms (the λ's in the equations below). The indexes indicate the status of the infected host and the pathogen that is spread, e.g. "bi" stands for a bacteria infected host spreading influenza, "ib" stands for an influenza infected host spreading bacteria, etc.

Hosts infected with bacteria (and possibly also still virus) can receive either AV or AB treatment, neither, or both, giving four compartments which we label $B_{u,u}$, $B_{u,t}$, $B_{t,u}$, $B_{t,t}$. The first index refers to the treatment status with respect to AV, the second indicates AB treatment. In analogy to AV prophylaxis, we assume that influenza infected hosts that received AB prophylaxis but nevertheless acquired a bacterial infection will have a course of infection that resembles that of AB treated patients. Similarly, we assume that influenza infected hosts that received AV treatment will continue to receive this treatment after they become infected with bacteria. We assume that AV or AB treatment or prophylaxis levels are the same for the bacteria infected and the influenza infected. Hosts with bacterial infections leave their compartments at rates $\delta_{i,j}$. Some fraction ($\varepsilon_{i,j}$) die, most ($\delta_{i,j}(1-\varepsilon_{i,j})$) recover and are assumed to not further participate in the outbreak. Tables 1, 2 and 3 summarize the variables and parameters of the system, a flow diagram for the model is shown in Fig. 1, the model equations are given by

$$
\begin{aligned}
\lambda_{ii} &= \beta_{u,n}I_{u,n} + \beta_{u,p}I_{u,p} + \beta_{t,n}I_{t,n} + \beta_{t,p}I_{t,p}\\
\lambda_{bi} &= \alpha_{u,u}B_{u,u} + \alpha_{u,t}B_{u,t} + \alpha_{t,u}B_{t,u} + \alpha_{t,t}B_{t,t}\\
\lambda_1 &= \lambda_{ii} + \lambda_{bi}\\
\lambda_{bb} &= \gamma_{u,u}B_{u,u} + \gamma_{u,t}B_{u,t} + \gamma_{t,u}B_{t,u} + \gamma_{t,t}B_{t,t}\\
\lambda_{ib} &= \kappa_{u,n}I_{u,n} + \kappa_{u,p}I_{u,p} + \kappa_{t,n}I_{t,n} + \kappa_{t,p}I_{t,p}\\
\lambda_2 &= \lambda_{bb} + \lambda_{ib}\\
\dot{S} &= -\lambda_1(1-e_pf_p)S\\
\dot{I}_{u,n} &= (1-g_p)(1-f_t)(1-f_p)\lambda_1 S - \nu_{u,n}I_{u,n} - k_{u,n}\lambda_2 I_{u,n}\\
\dot{I}_{u,p} &= g_p(1-f_t)(1-f_p)\lambda_1 S - \nu_{u,p}I_{u,p} - k_{u,p}\lambda_2 I_{u,p}\\
\dot{I}_{t,n} &= (1-g_p)(f_t(1-f_p) + f_p(1-e_p))\lambda_1 S - \nu_{t,n}I_{t,n} - k_{t,n}\lambda_2 I_{t,n}\\
\dot{I}_{t,p} &= g_p(f_t(1-f_p) + f_p(1-e_p))\lambda_1 S - \nu_{t,p}I_{t,p} - k_{t,p}\lambda_2 I_{t,p}\\
\dot{B}_{u,u} &= (1-f_t)(1-g_t)(\nu_{u,n}c_{u,n} + k_{u,n}\lambda_2)I_{u,n} - \delta_{u,u}B_{u,u}\\
\dot{B}_{u,t} &= (1-f_t)g_t(\nu_{u,n}c_{u,n} + k_{u,n}\lambda_2)I_{u,n}\\
&\quad + (1-f_t)(\nu_{u,p}c_{u,p} + k_{u,p}\lambda_2)I_{u,p} - \delta_{u,t}B_{u,t}\\
\dot{B}_{t,u} &= f_t(1-g_t)(\nu_{u,n}c_{u,n} + k_{u,n}\lambda_2)I_{u,n}\\
&\quad + (1-g_t)(\nu_{t,n}c_{t,n} + k_{t,n}\lambda_2)I_{t,n} - \delta_{t,u}B_{t,u}\\
\dot{B}_{t,t} &= f_tg_t(\nu_{u,n}c_{u,n} + k_{u,n}\lambda_2)I_{u,n} + f_t(\nu_{u,p}c_{u,p} + k_{u,p}\lambda_2)I_{u,p}\\
&\quad + g_t(\nu_{t,n}c_{t,n} + k_{t,n}\lambda_2)I_{t,n} + (\nu_{t,p}c_{t,p} + k_{t,p}\lambda_2)I_{t,p} - \delta_{t,t}B_{t,t}
\end{aligned}
$$

The model with antiviral resistance

We only consider a single pandemic outbreak in our study. Since bacteria generally have longer generation times and lower mutation rates compared to influenza virus, it is reasonable to assume that an AB that is effective against a particular bacteria strain at the beginning of the pandemic will be effective throughout the outbreak. We therefore only model the potential of resistance generation by the virus against the AV. Resistance arises during AV treatment. A small fraction, μ, of hosts infected with drug sensitive influenza who receive AV treatment cause secondary infections with the resistant strain (Handel et al., 2007a; Handel et al., 2009). We assume that this fraction is the same for AV treated hosts infected with influenza or bacteria (the latter can still

Table 1
Variables for the model. AB = antibacterial, AV = antiviral.

Symbol	Meaning
S	Susceptible hosts
$I_{u,n}$	AV untreated, AB non-prophylaxed influenza infected host
$I_{u,p}$	AV untreated, AB prophylaxed influenza infected host
$I_{t,n}$	AV treated, AB non-prophylaxed influenza infected host
$I_{t,p}$	AV treated, AB prophylaxed influenza infected host
$B_{u,u}$	AV untreated, AB untreated bacteria infected hosts
$B_{u,t}$	AV untreated, AB treated bacteria infected hosts
$B_{t,u}$	AV treated, AB untreated bacteria infected hosts
$B_{t,t}$	AV treated, AB treated bacteria infected hosts

Table 2
Parameters of the model other than transmission parameters (which are given separately in Table 3).

Symbol	Meaning	Value/range	Assumptions/references
N_0	Population size	3×10^8	U.S. population
e_p	Efficacy of AV prophylaxis	0.8	Based on Refs. (Yang et al., 2006; Halloran et al., 2007)
$\nu_{u,n}$	Clearance rate (1/mean duration of infection) of influenza infected hosts: AV untreated, AB non-prophylaxed	1/4.8	Based on Ref. (Carrat et al., 2008)
$\nu_{u,p}$	AV untreated, AB prophylaxed	$\nu_{u,n}$	AB prophylaxis does not alter duration of influenza infection (Louria et al., 1959; Maeda et al., 1999; Carrat et al., 2004)
$\nu_{t,n}$	AV treated, AB non-prophylaxed	1/3.4	Reduction of infectious period by ≈30% (Hayden et al., 1999; Treanor et al., 2000; Whitley et al., 2001; Aoki et al., 2003)
$\nu_{t,p}$	AV treated, AB prophylaxed	$\nu_{t,n}$	AB prophylaxis does not alter duration of influenza infection
$\delta_{u,u}$	Clearance rate (1/mean duration of infection) of bacteria infected hosts: AV untreated, AB untreated	1/5–1/15	based on (Brundage and Shanks, 2008; Klugman et al., 2009)
$\delta_{u,t}$	AV untreated, AB treated	(1.5–2) $\delta_{u,u}$	AB treatment leads to faster recovery (Kaiser et al., 1996; Kaiser et al., 2001)
$\delta_{t,u}$	AV treated, AB untreated	(1–1.25) $\delta_{u,u}$	AV treatment leads to somewhat faster recovery (McCullers, 2004)
$\delta_{t,t}$	AV treated, AB treated	(1.75–2)$\delta_{u,u}$	Combined AB and AV treatment are synergistic
$c_{u,n}$	Fraction of influenza infected hosts who become bacteria infected: AV untreated, AB non-prophylaxed	0.05–0.2	Based on Refs. (Kaiser et al., 2000; Kaiser et al., 2003; Brundage, 2006)
$c_{u,p}$	AV untreated, AB prophylaxed	(0.25–0.75) $c_{u,n}$	AB prophylaxis lowers the probability of bacterial infection (Madhi et al., 2004; Moberley et al., 2008)
$c_{t,n}$	AV treated, AB non-prophylaxed	(0.75–1) $c_{u,n}$	AV treatment lowers the probability of bacterial infection (Kaiser et al., 2000; Kaiser et al., 2003; Whitley et al., 2001; Cole et al., 2002)
$c_{t,p}$	AV treated, AB prophylaxed	(0.1–0.5) $c_{u,n}$	Combined AV treatment and AB prophylaxis are synergistic
$d_{u,n}$	Fraction of influenza infected hosts who die: AV untreated, AB non-prophylaxed	$(1–5)\times10^{-3}$	≈1% −5% deaths for 1918-like, most deaths due to bacterial infections (Soper, 1918; Mills et al., 2004; Brundage, 2006; Bonten and Prins, 2006; Brundage and Shanks, 2008; Morens et al., 2008); ≈0.1% −0.5% deaths for 2009-like, few deaths due to bacterial infections (Fraser et al., 2009; for Disease Control, C., Prevention, 2009; Jamieson et al., 2009; Garske et al., 2009)
$d_{u,p}$	AV untreated, AB prophylaxed	$d_{u,n}$	AB prophylaxis does not affect death due to virus (Louria et al., 1959; Maeda et al., 1999; Carrat et al., 2004)
$d_{t,n}$	AV treated, AB non-prophylaxed	(0.25–0.75) $d_{u,n}$	AV treatment reduces mortality
$d_{t,p}$	AV treated, AB prophylaxed	$d_{t,n}$	AB prophylaxis does not affect death due to virus
$\varepsilon_{u,u}$	Fraction of bacteria infected hosts who die: AV untreated, AB untreated, 1918-like	$(1–2.5)\times10^{-1}$	≈1% −5% deaths for 1918-like, most deaths due to bacterial infections (Soper, 1918; Mills et al., 2004; Brundage, 2006; Bonten and Prins, 2006; Brundage and Shanks, 2008; Morens et al., 2008)
	2009-like	$(1–2.5)\times10^{-3}$	≈0.1% −0.5% deaths for 2009-like, few deaths due to bacterial infections (Fraser et al., 2009; for Disease Control, C., Prevention, 2009; Jamieson et al., 2009; Garske et al., 2009)
$\varepsilon_{u,t}$	AV untreated, AB treated	(0.1–0.5) $\varepsilon_{u,u}$	AB treatment reduces death due to bacterial infection (Louria et al., 1959)
$\varepsilon_{t,u}$	AV treated, AB untreated	(0.5–1) $\varepsilon_{u,u}$	AV treatment reduces death due to bacterial infection (McCullers, 2004; McCullers and Bartmess, 2003)
$\varepsilon_{t,t}$	AV treated, AB treated	(0.01–0.2) $\varepsilon_{u,u}$	Combined AB and AV treatment are synergistic (McCullers, 2004)
f_p	Fraction of uninfecteds receiving AV prophylaxis	0–1	Varied for different scenarios
f_t	Fraction of influenza infecteds receiving AV treatment	0–1	Varied for different scenarios
g_p	Fraction of influenza infecteds receiving AB prophylaxis	0–1	Varied for different scenarios
g_t	Fraction of co-infecteds receiving AB treatment	0–1	Varied for different scenarios

Ranges for some parameter values can be obtained directly from the listed references, for other parameters the listed references were merely used to guide our estimates for a parameter range. If we could not find any references that could be used to guide our estimates, we guessed a range. Units for rates are (1/day), other parameter are dimensionless.

harbor some virus, as described in the previous section). For a resistant strain, AV treatment or prophylaxis has no impact but AB prophylaxis or treatment can make a difference. Our model therefore needs to be extended by four classes, influenza infecteds with resistant virus who receive AB prophylaxis, $I_{r,p}$, resistant influenza infecteds who do not receive AB prophylaxis, $I_{r,n}$, bacteria infecteds with resistant virus receiving AB treatment, $B_{r,t}$ and untreated bacteria infecteds harboring resistant virus, $B_{r,u}$. Table 4 lists the parameters for the resistant compartments, the equations of the model including resistance are

$$
\begin{aligned}
\lambda_{ii} &= \beta_{u,n}I_{u,n} + \beta_{u,p}I_{u,p} + (1-\mu)\beta_{t,n}I_{t,n} + (1-\mu)\beta_{t,p}I_{t,p}\\
\lambda_{bi} &= \alpha_{u,u}B_{u,u} + \alpha_{u,t}B_{u,t} + (1-\mu)\alpha_{t,u}B_{t,u} + (1-\mu)\alpha_{t,t}B_{t,t}\\
\lambda_1 &= \lambda_{ii} + \lambda_{bi}\\
\lambda_{bb} &= \gamma_{u,u}B_{u,u} + \gamma_{u,t}B_{u,t} + \gamma_{t,u}B_{t,u} + \gamma_{t,t}B_{t,t}\\
\lambda_{ib} &= \kappa_{u,n}I_{u,n} + \kappa_{u,p}I_{u,p} + \kappa_{t,n}I_{t,n} + \kappa_{t,p}I_{t,p}\\
\lambda_2 &= \lambda_{bb} + \lambda_{ib}\\
\lambda_r &= \mu(\beta_{t,n}I_{t,n} + \beta_{t,p}I_{t,p} + \alpha_{t,u}B_{t,u} + \alpha_{t,t}B_{t,t}) + \beta_{r,n}I_{r,n} + \beta_{r,p}I_{r,p}\\
&\quad + \alpha_{r,u}B_{r,u} + \alpha_{r,t}B_{r,t}\\
\dot{S} &= -\lambda_1(1-e_pf_p)S - \lambda_rS
\end{aligned}
$$

$$
\begin{aligned}
\dot{I}_{u,n} &= (1-g_p)(1-f_t)(1-f_p)\lambda_1S - \nu_{u,n}I_{u,n} - k_{u,n}\lambda_2I_{u,n}\\
\dot{I}_{u,p} &= g_p(1-f_t)(1-f_p)\lambda_1S - \nu_{u,p}I_{u,p} - k_{u,p}\lambda_2I_{u,p}\\
\dot{I}_{t,n} &= (1-g_p)(f_t(1-f_p) + f_p(1-e_p))\lambda_1S - \nu_{t,n}I_{t,n} - k_{t,n}\lambda_2I_{t,n}\\
\dot{I}_{t,p} &= g_p(f_t(1-f_p) + f_p(1-e_p))\lambda_1S - \nu_{t,p}I_{t,p} - k_{t,p}\lambda_2I_{t,p}\\
\dot{I}_{r,n} &= (1-g_p)\lambda_rS - \nu_{r,n}I_{r,n} - k_{r,n}\lambda_2I_{r,n}\\
\dot{I}_{r,p} &= g_p\lambda_rS - \nu_{r,p}I_{r,p} - k_{r,p}\lambda_2I_{r,p}\\
\dot{B}_{u,u} &= (1-f_t)(1-g_t)(\nu_{u,n}c_{u,n} + k_{u,n}\lambda_2)I_{u,n} - \delta_{u,u}B_{u,u}\\
\dot{B}_{u,t} &= (1-f_t)g_t(\nu_{u,n}c_{u,n} + k_{u,n}\lambda_2)I_{u,n}\\
&\quad + (1-f_t)(\nu_{u,p}c_{u,p} + k_{u,p}\lambda_2)I_{u,p} - \delta_{u,t}B_{u,t}\\
\dot{B}_{t,u} &= f_t(1-g_t)(\nu_{u,n}c_{u,n} + k_{u,n}\lambda_2)I_{u,n}\\
&\quad + (1-g_t)(\nu_{t,n}c_{t,n} + k_{t,n}\lambda_2)I_{t,n} - \delta_{t,u}B_{t,u}\\
\dot{B}_{t,t} &= f_tg_t(\nu_{u,n}c_{u,n} + k_{u,n}\lambda_2)I_{u,n} + f_t(\nu_{u,p}c_{u,p} + k_{u,p}\lambda_2)I_{u,p}\\
&\quad + g_t(\nu_{t,n}c_{t,n} + k_{t,n}\lambda_2)I_{t,n} + (\nu_{t,p}c_{t,p} + k_{t,p}\lambda_2)I_{t,p} - \delta_{t,t}B_{t,t}\\
\dot{B}_{r,u} &= (1-g_t)(\nu_{r,n}c_{r,n} + k_{r,n}\lambda_2)I_{r,n} - \delta_{r,u}B_{r,u}\\
\dot{B}_{r,t} &= g_t(\nu_{r,n}c_{r,n} + k_{r,n}\lambda_2)I_{r,n} + (\nu_{r,p}c_{r,p} + k_{r,p}\lambda_2)I_{r,p} - \delta_{r,t}B_{r,t}
\end{aligned}
$$

Table 3
Parameters governing the transmission processes of bacteria or influenza from the different classes of infected hosts.

Symbol	Meaning	Value/range	Assumptions/references
$k_{u,n}$	Susceptibility of influenza infecteds to bacterial infections: AV untreated, AB non-prophylaxed	1	Arbitrary choice
$k_{u,p}$	AV untreated, AB prophylaxed	$(0.25–0.75)k_{u,n}$	AB prophylaxis lowers susceptibility to bacterial infection (Madhi et al., 2004; Moberley et al., 2008)
$k_{t,n}$	AV treated, AB non-prophylaxed	$(0.75–1)k_{u,n}$	AV treatment lowers susceptibility to bacterial infection (Kaiser et al., 2000; Kaiser et al., 2003; Whitley et al., 2001; Cole et al., 2002)
$k_{t,p}$	AV treated, AB prophylaxed	$(0.1–0.5)k_{u,n}$	combined AV treatment and AB prophylaxis are synergistic
$\beta_{u,n}$	Influenza transmission rate of an influenza infected hosts: AV untreated, AB non-prophylaxed	$R_0 \frac{\nu_{u,n}}{N_0}$	$R_0 = 1.8$-2.2 for 1918-like outbreak (Mills et al., 2004; Viboud et al., 2006), $R_0 = 1.4$-1.8 for 2009-like outbreak (Yang et al., 2009; Fraser et al., 2009; Pourbohloul et al., 2009)
$\beta_{u,p}$	AV untreated, AB prophylaxed	$\beta_{u,n}$	AB prophylaxis does not affect influenza transmission
$\beta_{t,n}$	AV treated, AB non-prophylaxed	$0.5\ \beta_{u,n}$	based on (Yang et al., 2006; Halloran et al., 2007), adjusted upwards since we also explicitly consider a reduction in infectious period
$\beta_{t,p}$	AV treated, AB prophylaxed	$\beta_{t,n}$	AB prophylaxis does not affect influenza transmission
$\alpha_{u,u}$	Influenza transmission rate of a bacteria infected host: AV untreated, AB untreated	$(0-2)\frac{\delta_{u,u}}{N_0}$	can vary between non-shedders and spreading as well as influenza infecteds (Louria et al., 1959; Young et al., 1972; Maxwell et al., 1949; Okamoto et al., 2003)
$\alpha_{u,t}$	AV untreated, AB treated	$(0.5–1)\ \alpha_{u,u}$	AB treatment reduces symptoms and therefore influenza transmission (Stuart-Harris, 1959)
$\alpha_{t,u}$	AV treated, AB untreated	$0.5\ \alpha_{u,u}$	same reduction as for influenza infected host (Yang et al., 2006; Halloran et al., 2007)
$\alpha_{t,t}$	AV treated, AB treated	$(0.25–0.5)\ \alpha_{u,u}$	combined AB and AV treatment are synergistic
$\kappa_{u,n}$	Bacteria transmission rate of an influenza infected hosts: AV untreated, AB non-prophylaxed	$(0-4)\frac{\nu_{u,n}}{n_0}$	no direct estimates are available, but influenza infection might lead to increased bacteria spread (Brimblecombe et al., 1958; Brundage, 2006; Sheretz et al., 1996; Bassetti et al., 2005; Brundage and Shanks, 2008)
$\kappa_{u,p}$	AV untreated, AB prophylaxed	$(0.2–0.6)\ \kappa_{u,n}$	AB prophylaxis reduces bacterial load and therefore bacteria transmission
$\kappa_{t,n}$	AV treated, AB non-prophylaxed	$(0.7–1)\ \kappa_{u,n}$	AV treatment reduces symptoms and therefore bacteria transmission
$\kappa_{t,p}$	AV treated, AB prophylaxed	$(0.1–0.3)\ \kappa_{u,n}$	combined AB prophylaxis and AV treatment are synergistic
$\gamma_{u,u}$	Bacteria transmission rate of a bacteria infected host: AV untreated, AB untreated	$(0-4)\frac{\delta_{u,n}}{n_0}$	no direct estimates available, but see e.g. (Kajita et al., 2007; Hoti et al., 2009)
$\gamma_{u,t}$	AV untreated, AB treated	$(0.2–0.6)\ \gamma_{u,u}$	AB treatment reduces bacterial load and symptoms and therefore bacteria transmission
$\gamma_{t,u}$	AV treated, AB untreated	$(0.7–1)\ \gamma_{u,u}$	AV treatment reduces symptoms and therefore bacteria transmission
$\gamma_{t,t}$	AV treated, AB treated	$(0.1–0.3)\ \gamma_{u,u}$	combined AB and AV treatment are synergistic

Model implementation

The set of deterministic ordinary differential equations described above was implemented in Matlab R2007a (The Mathworks). The code is available from the authors. For each of the different scenarios described in the results section, we simulated 10 000 pandemic outbreaks with different values for the model parameters. Parameter sampling was performed using Latin Hypercube Sampling (LHS) (Blower and Dowlatabadi, 1994), we assumed uniform distributions of the parameters in the ranges given in Tables 2–4. To assess the influence of different parameters on the results, we performed sensitivity analyses (Hoare et al., 2008; Marino et al., 2008). Both the Latin Hypercube sampling and sensitivity analysis were performed using SaSAT (Hoare et al., 2008). Unless otherwise stated, we assume that intervention starts after 500 influenza cases have occurred.

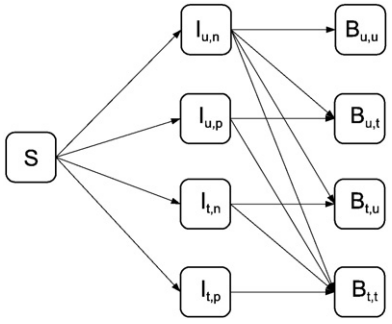

Fig. 1. Flow diagram for the basic model. See Table 1 for definition of the variables and the text for more details.

Results

We use the mathematical model to investigate how different levels of AV and AB prophylaxis or treatment affect the number of influenza and bacteria infected cases, the peak number of cases, and the number of deaths during an influenza pandemic in the U.S. We start with a model in which only commensal bacteria that colonized a host before influenza infection cause secondary bacterial infections. Next, we consider a scenario where both influenza and bacteria infected hosts can spread bacteria or virus. We then investigate how the emergence or pre-existence of AV resistant influenza changes the effect of the different intervention strategies. We further show how differences in the delay time before control starts affect the results, and how results change for a less severe pandemic. Lastly, we perform a sensitivity analysis to determine which parameters have the most impact on the outcomes.

The impact of antiviral and antibiotic intervention strategies in the absence of bacteria transmission

Commensal bacteria are likely to be an important source for secondary bacterial infections. We therefore start out with a model in which influenza infected hosts can develop secondary bacterial infections through the invasion of commensal bacteria that already reside in the host, but neither influenza nor bacteria infected hosts are assumed to spread bacteria ($\alpha_{i,j} = \kappa_{i,j} = \gamma_{i,j} = 0$).

Fig. 2 shows the time course of 100 simulated infections for the baseline scenario with no AV or AB intervention strategies. The chosen values for R_0 and death rates (see Tables 2 and 3) lead to a total fraction of infecteds of $\approx$70–90%. This number is solely dictated by the range of R_0 values we used. Data from most influenza outbreaks suggests that the fraction of infecteds is lower than what would be

Table 4
Additional model parameters for the AV resistant influenza strain.

Symbol	Meaning	Value/range	Assumptions/references
$\nu_{r,n}$	Clearance rate of influenza infected hosts: AV resistant, AB non-prophylaxed	$\nu_{u,n}$	Same as for drug sensitive strain
$\nu_{r,p}$	AV resistant, AB prophylaxed	$\nu_{r,n}$	AB prophylaxis does not alter duration of influenza infection (Louria et al., 1959; Maeda et al., 1999; Carrat et al., 2004)
$\nu_{r,u}$	Clearance rate of bacteria infected hosts: AV resistant, AB untreated	$\delta_{u,u}$	Same as for drug sensitive strain
$\nu_{r,t}$	AV resistant, AB treated	$\delta_{u,t}$	Same as for drug sensitive strain
$c_{r,n}$	Fraction of influenza infected hosts who become bacteria infected: AV resistant, AB non-prophylaxed	$c_{u,n}$	Same as for drug sensitive strain
$\nu_{r,p}$	AV untreated, AB prophylaxed	$c_{u,p}$	Same as for drug sensitive strain
$d_{r,n}$	Fraction of influenza infected hosts who die: AV resistant, AB non-prophylaxed	$d_{u,n}$	Same as for drug sensitive strain
$d_{r,p}$	AV resistant, AB prophylaxed	$d_{u,p}$	Same as for drug sensitive strain
$\varepsilon_{r,u}$	Fraction of bacteria infected hosts that die: AV resistant, AB untreated	$\varepsilon_{u,u}$	Same as for drug sensitive strain
$\varepsilon_{r,t}$	AV resistant, AB treated	$\varepsilon_{u,t}$	Same as for drug sensitive strain
$k_{r,n}$	Susceptibility of influenza infecteds to bacterial Infections: AV resistant, AB non-prophylaxed	$k_{u,n}$	Same as for drug sensitive strain
$k_{r,p}$	AV resistant, AB prophylaxed	$k_{u,p}$	Same as for drug sensitive strain
$\beta_{r,n}$	Influenza infection rates of influenza infecteds: resistant, AB non-prophylaxed	$(0.75–1)\ \beta_{u,n}$	Fitness cost of resistance between 25% and 0% (Herlocher et al., 2004; Yen et al., 2005)
$\beta_{r,p}$	resistant, AB prophylaxed	$\beta_{r,n}$	AB prophylaxis does not affect influenza transmission
$\alpha_{r,u}$	Influenza infection rates of bacteria infected host: AV resistant, AB untreated	$(0.75–1)\ \alpha_{u,u}$	Fitness cost of resistance between 25% and 0% (Herlocher et al., 2004; Yen et al., 2005)
$\alpha_{r,t}$	AV resistant, AB treated	$(0.5–1)\ \alpha_{r,u}$	AB treatment reduces symptoms and therefore influenza shedding (Stuart-Harris, 1959)
μ	Resistance generation	10^{-3}	Conservative value based on estimates in (Handel et al., 2007a)

For most of the parameters we assumed that the drug resistant strain differs little from the drug sensitive strain.

expected solely based on the value of R_0. The discrepancy is likely due to both the fact that we assume that every infection is symptomatic and the fact that our model assumes a homogeneous population. The percentage of deaths goes up to $\approx$5%. This represents a rather severe outbreak with deaths similar to those seen in the 1918 pandemic. We use this setting as a "worst case" scenario. We will discuss a situation that is more like the 2009 pandemic below.

Next, we investigate how different intervention strategies (IS) based on AV or AB treatment or prophylaxis reduce the number of total and bacterial cases, the peak number of cases, and the number of deaths compared to the baseline scenario without interventions (Fig. 3). We find that AV treatment (IS1) reduces the number of both influenza and secondary bacterial infections and the mortality by $\approx$25%, while the peak number of cases is reduced by about 50%. If AV prophylaxis is added (IS2), the reduction in cases and the reduction in mortality increases. As expected, AB treatment added to AV treatment (IS3) does not lead to an additional reduction in influenza or bacteria cases compared to IS1, but does much better in reducing death compared to IS1 and IS2. AB prophylaxis in addition to AV treatment (IS4) also does not reduce influenza cases or the peak total cases, but prevents additional bacteria cases—the type of cases that are most likely to be hospitalized. Reduction of mortality is somewhat lower for IS4 than is achieved by IS3. Combining AB prophylaxis and treatment on top of AV treatment (IS5) leads to a reduction in mortality that is

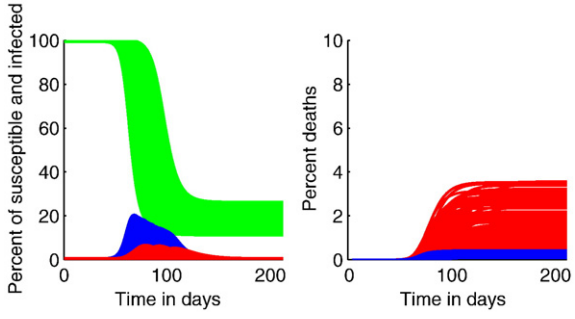

Fig. 2. Time course of 100 simulated infections. Left: Susceptibles (green), Influenza infected (blue) and Bacteria infected (red), expressed as percent of the total population. Right: total deaths due to influenza (blue) and bacteria (red) infections, expressed as percent of the total population.

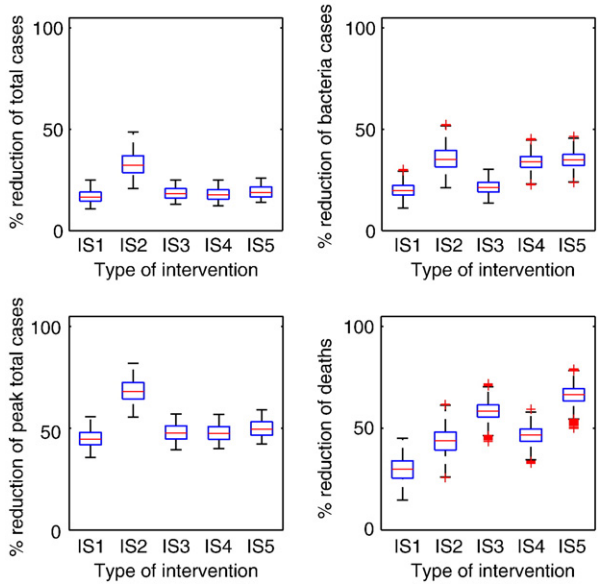

Fig. 3. Reduction in cases and deaths for different AV and AB intervention strategies. Shown is the percent reduction compared to a no intervention situation. Boxplots show results from 10 000 simulations for different parameter values as described in the methods section. We assume that only influenza virus can be transmitted between hosts, bacterial infections occur at a fixed rate, caused by commensal bacteria. The different intervention strategies (IS) are: 30% AV treatment (IS1), 30% AV treatment and 15% AV prophylaxis (IS2), 30% AV treatment and 60% AB treatment (IS3), 30% AV treatment and 30% AB prophylaxis (IS4), 30% AV treatment and 60% AB treatment and 30% AB prophylaxis (IS5). Note that the percentages for the different intervention strategies are based on different baselines: 15% of AV prophylaxis means 15% of all susceptibles receive prophylaxis, 30% of AV treatment means 30% of influenza infected receive AV treatment, 60% of AB treatment means 60% of bacteria infected receive treatment, and so on. This is the reason why we choose different percentages for the different strategies—it is more feasible to administer AB treatment to a larger fraction of bacteria infected, simply because the overall number is lower.

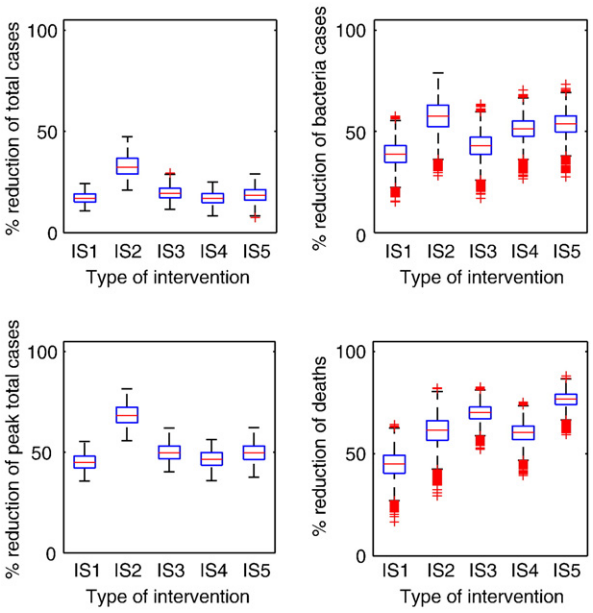

Fig. 4. Reduction in cases and deaths in the presence of pathogen spread. Both influenza and bacteria infected hosts can transmit virus or bacteria. The different intervention strategies are the same as described in Fig. 3.

similar to IS3. Overall, adding AB control strategies does little to reduce the total number of cases but is effective in reducing mortality.

The impact of antiviral and antibiotic intervention strategies in the presence of bacteria transmission

It is possible that hosts with an influenza infection who are carriers of commensal bacteria start to spread those bacteria (Bassetti et al., 2005; Brundage, 2006; Brundage and Shanks, 2008; Sheretz et al., 1996). Further, bacteria infected hosts might also spread bacteria. Additionally, while some evidence seems to suggest that hosts infected with bacteria do not simultaneously have high viral titers (Louria et al., 1959; Young et al., 1972), in at least some situations, virus was reported to be found together with bacteria (Louria et al., 1959; Maxwell et al., 1949), or bacterial infection increased viral load in animal models (Okamoto et al., 2003). It is therefore also possible that bacteria infected hosts still harbor and spread influenza. We now investigate such a situation where both influenza and bacteria infected hosts can spread both pathogens. Fig. 4 shows the reduction in cases and mortality for the same five intervention strategies as considered in Fig. 3. Overall, the results are similar to those seen in Fig. 3; the reduction in bacteria cases and mortality increases somewhat. We also investigated situations where only influenza infecteds transmit both pathogens or influenza infecteds transmit both pathogens but bacteria infecteds only transmit bacteria. The results for such scenarios are very similar to Figs. 3 and 4 (not shown).

The impact of antiviral and antibiotic intervention strategies taking into account antiviral drug resistance

Previous studies have suggested that during a large outbreak and extensive AV use, the emergence of resistance to anti-influenza drugs, such as the neuraminidase inhibitors, is likely (Alexander et al., 2007; Brockmann et al., 2008; Handel et al., 2009; Lipsitch et al., 2007; Regoes and Bonhoeffer, 2006). Indeed, the first few cases of drug resistance for the 2009 H1N1 strain have already been reported (2009). Here, we consider how emergence or pre-existence of AV drug resistance impacts the usefulness of AV or AB intervention strategies. While AB resistance is certainly a serious problem (Dancer, 2004; Levy and Marshall, 2004; Lipsitch, 2001; Livermore, 2005; Memoli et al., 2008), the relatively short timescale of an influenza pandemic makes it probable that AB drugs that are effective at the beginning of the pandemic outbreak remain effective for the duration of the outbreak. We therefore assume that bacteria remain sensitive throughout the outbreak to the drugs being used for AB control and only consider AV resistance. In one scenario, we assume that AV resistance does not pre-exist but emerges during the pandemic. Alternatively, it might be possible that by the time a pandemic influenza virus reaches the U.S., a certain fraction of the infected hosts already harbor an influenza strain that is resistant to AV drugs. We therefore also consider a scenario where an influenza strain resistant to the AV drugs already exists at a low frequency at the beginning of the pandemic.

Fig. 5 shows results for the same situation as shown in Fig. 4, but now with the inclusion of AV resistant virus. Not unexpectedly, the AV

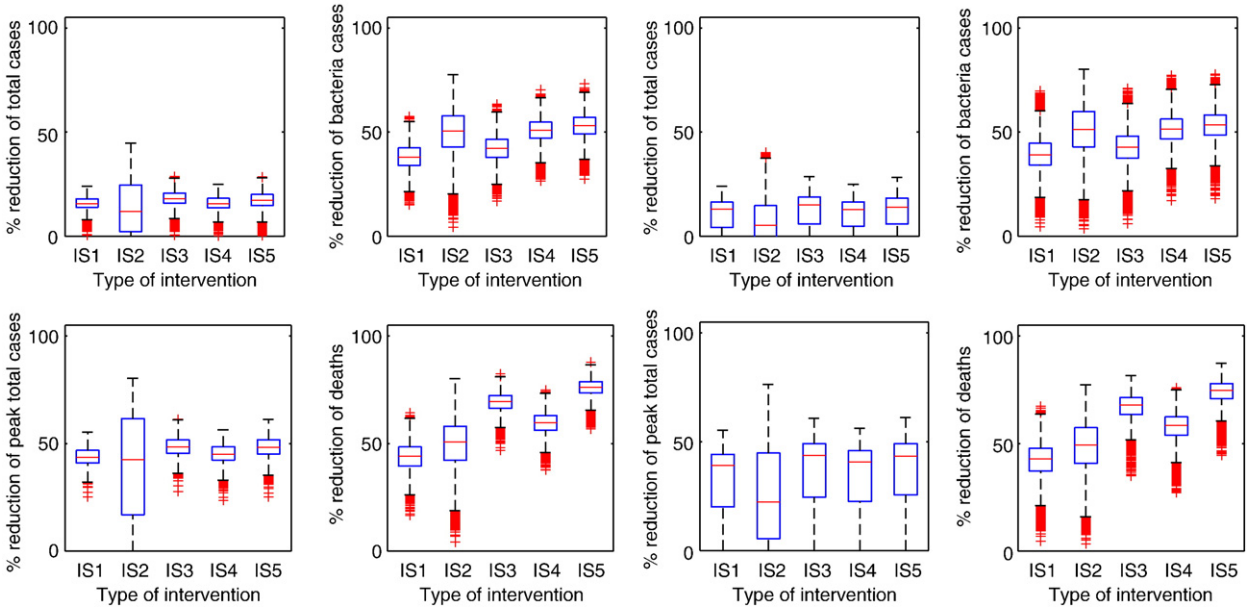

Fig. 5. Reduction in cases and deaths for different levels of antiviral and antibiotic treatment. Left: Resistant virus is assumed to emerge during the pandemic. Right: Resistant virus is present at a 10% level at the start of the outbreak. Both influenza and bacteria infected hosts can transmit virus or bacteria. The different intervention strategies are the same as described in Fig. 3.

control strategies perform worse in the presence of resistance. This is most noticeable for AV prophylaxis. The reason for this is that AV prophylaxis reduces the fitness of the drug sensitive strain enough for the resistant strain to quickly emerge and to cause a strong and uncontrolled "second wave" (Eichner et al., 2009; Handel et al., 2007b; Handel et al., 2009; Lipsitch et al., 2007; Moghadas et al., 2008). In contrast, the different AB strategies are little affected and IS3-IS5 are still able to prevent a significant amount of mortality, similar to the levels for the situation without resistant virus present.

Varying the start of intervention

So far, we assumed that intervention starts after 500 infected cases have occurred. This assumes that the time it takes to determine that an outbreak is occurring and the logistics to get the intervention measures implemented is rather short. With regard to the 2009 pandemic, rapid intervention on a global scale is certainly not possible anymore—though it might still be possible for localized outbreaks. In any case, it is worth investigating how changes in the time lag before intervention start affect the results. In Fig. 6, we consider scenarios where intervention starts later, after either 1% or 10% of the population have already been infected. The 1% scenario leads to results that are almost identical to the rapid intervention scenario (compare Fig. 6 left with Fig. 4), while the effectiveness of control is reduced for the 10% scenario. Overall, and somewhat encouragingly, these results suggest that some delay in implementing the control strategies is tolerable and does not impact their effectiveness too much. However, we want to point out that the actual biological transmission process is stochastic, and that a stochastic model favors early intervention more heavily, as we discussed previously (Handel et al., 2009).

The impact of intervention strategies on a less severe pandemic

So far we assumed a situation where the influenza virus has a relatively high R_0 and the percentage of deaths is comparable to the severe 1918 outbreak. Given the currently ongoing 2009 H1N1 pandemic with its lower R_0 and mortality that seems not much higher than seasonal strains (for Disease Control, C., Prevention, 2009; Fraser et al., 2009; Jamieson et al., 2009; Yang et al., 2009), we decided to investigate the impact of the various control strategies in such a situation. We consider scenarios with both absence and presence of AV resistance. As Fig. 7 shows, the different control strategies have an increased impact with regard to reduction of cases (compare Fig. 7 left with Fig. 4 and Fig. 7 right with Fig. 5 left). For this scenario, the AB based control strategies, IS3-IS5, show little improvement over IS1, even for the reduction in mortality. This is not too surprising since we assumed for the 2009-like scenario both a lower R_0 and that most deaths are *not* due to secondary bacterial infections (see Tables 2 and 3)—hence the obvious reduction in importance of AB strategies. Drug resistance emergence has again the expected effect, namely lowering the impact of AV strategies.

Sensitivity analysis

Our model contains many parameters that are not very well known. We therefore performed a large number of simulations for different values of the parameters. In this section, we describe results from a sensitivity analysis that helps to understand the impact of different parameters on the results presented in the previous sections. We focused on the scenario with transmission of bacteria and virus and no drug resistance, i.e. the scenario shown in Fig. 4. We computed partial rank correlation coefficients (PRCC) (Hoare et al., 2008; Marino et al., 2008) for the different outcomes (reduction of total, bacteria and peak cases and reduction of deaths) and the different intervention strategies.

Table 5 summarizes the results for the most influential parameters for a given output and IS. As can be seen, the influenza transmission parameter $\beta_{u,n}$ has by far the largest impact on the results, mainly because it drives the overall outbreak dynamics. (Note that the parameters $\beta_{u,p}$, $\beta_{t,n}$ and $\beta_{t,p}$ are not included in the sensitivity analysis since these are fixed once $\beta_{u,n}$ has taken on a specific value). Most other parameters are found to be very important for some results but not others. Among the parameters that are often important are those describing the transmission process ($\alpha_{i,j}$, $\kappa_{i,j}$, $\gamma_{i,j}$) and the fraction of influenza infecteds that acquire bacterial infections through commensal mechanism ($c_{i,j}$). Not surprisingly, the parameters specifying the fraction of bacteria hosts that die ($\varepsilon_{i,j}$) strongly impact the results for mortality. The importance of some parameters depends strongly on the IS. For instance the rate of influenza

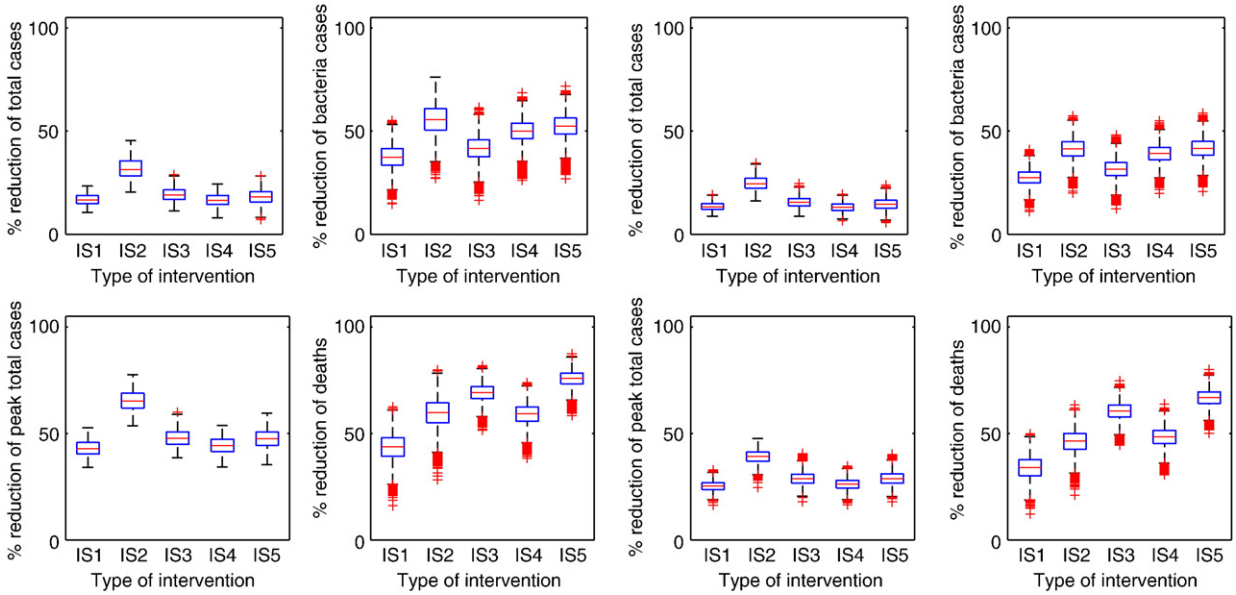

Fig. 6. Reduction in cases and deaths as the start of intervention changes. Control starts after 1% (left) or 10% (right) of the population have already been infected. Both influenza and bacteria infected hosts can transmit virus or bacteria. The different intervention strategies are the same as described in Fig. 3.

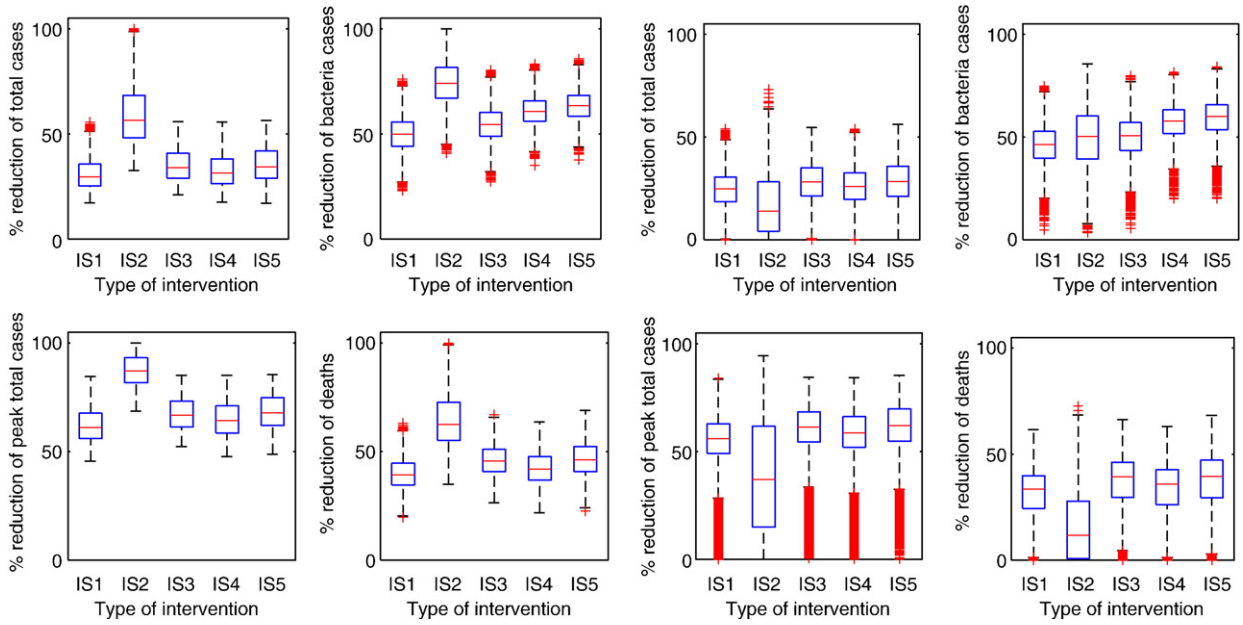

Fig. 7. Reduction in cases and deaths for a mild pandemic. Both influenza and bacteria infected hosts can transmit virus or bacteria. The different intervention strategies are the same as described in Fig. 3. Left: no antiviral resistance. Right: resistance is assumed to emerge during the pandemic.

transmission by bacteria infected hosts receiving AB treatment ($\alpha_{u,t}$) has a strong impact for IS3 and IS5 but not other IS. This is again not surprising, since IS3 and IS5 are the two intervention strategies that include AB treatment.

We also looked at the PRCC for other scenarios, specifically the scenario with antiviral resistance present (Fig. 5 right) and the 2009-like scenario (Fig. 7 left). We do not show the PRCC tables for those scenarios since they add little further insight, but briefly mention the main findings: As one might expect, for the situation with antiviral resistance present, the parameter describing transmission of the resistance strain, $\beta_{r,n}$ becomes very important, analogous to the importance of $\beta_{u,n}$ in the absence of resistance. Similarly, the parameter describing transmission of the resistant influenza strain by bacteria infected hosts ($\alpha_{r,u}$) becomes important in most scenarios. For the mild, 2009-like pandemic, the most notable change is that for the reduction in mortality, the parameters $d_{i,j}$ describing death due to influenza infections increase in importance, while the parameters $\varepsilon_{i,j}$ describing bacteria-induced mortality are of reduced importance. This finding is expected since for the 2009-like scenario, most deaths are assumed to be due to primary influenza infections. For the other outcomes (reduction in total or peak cases) the importance of the parameters differs only in minor ways from the results shown in Table 5.

For PRCC to be meaningful, the results need to depend monotonically on the parameters. We checked this by investigating scatterplots for the most influential parameters from Table 5. We found monotonicity in all instances. Fig. 8 shows example scatterplots for four different parameters. Other parameters lead to similar results (not shown).

Table 5
Partial rank correlation coefficients for the scenario shown in Fig. 4, i.e. transmission of both virus and bacteria.

Parameter	Intervention strategy				
	IS1	IS2	IS3	IS4	IS5
Reduction of total cases					
$\beta_{u,n}$	−0.96 (1)	−0.96 (1)	−0.95 (1)	−0.95 (1)	−0.93 (1)
$c_{u,n}$	−0.15 (3)	−0.18 (2)	−0.01 (19)	−0.02 (15)	0.04 (12)
$\alpha_{u,u}$	−0.11 (5)	−0.16 (3)	0.29 (3)	0.13 (3)	0.28 (2)
$\alpha_{u,t}$	0.002 (29)	−0.006 (18)	−0.33 (2)	−0.08 (10)	−0.23 (3)
$\delta_{t,u}$	0.22 (2)	0.15 (4)	0.06 (11)	0.11 (4)	0.02 (17)
$k_{u,p}$	−0.007 (19)	−0.001 (29)	−0.02 (15)	0.27 (2)	0.18 (4)
Reduction of bacteria cases					
$\beta_{u,n}$	−0.65 (1)	−0.73 (1)	−0.64 (1)	−0.58 (1)	−0.56 (1)
$c_{u,p}$	−0.01 (13)	−0.02 (14)	−0.02 (19)	−0.51 (2)	−0.48 (2)
$c_{t,n}$	−0.42 (2)	−0.33 (2)	−0.37 (2)	−0.30 (3)	−0.27 (3)
$\kappa_{u,n}$	0.16 (3)	0.14 (3)	0.16 (4)	0.13 (6)	0.12 (8)
$\gamma_{u,u}$	0.15 (4)	0.11 (7)	0.16 (3)	0.12 (7)	0.13 (7)
Reduction of peak cases					
$\beta_{u,n}$	−0.97 (1)	−0.97 (1)	−0.97 (1)	−0.97 (1)	−0.96 (1)
$c_{u,p}$	$<10^{-3}$ (32)	−0.005 (23)	0.002 (30)	−0.30 (3)	−0.23 (5)
$c_{t,n}$	−0.32 (3)	−0.19 (3)	−0.22 (6)	−0.20 (6)	−0.12 (11)
$\alpha_{u,u}$	−0.11 (6)	−0.17 (4)	0.32 (3)	0.15 (9)	0.33 (2)
$\alpha_{u,t}$	−0.01 (17)	−0.01 (15)	−0.42 (2)	−0.12 (11)	−0.32 (3)
$k_{u,p}$	−0.006 (23)	$<10^{-3}$ (31)	−0.02 (17)	0.32 (2)	0.23 (7)
$\delta_{t,u}$	0.48 (2)	0.27 (2)	0.16 (9)	0.28 (4)	0.08 (13)
Reduction of deaths					
$\beta_{u,n}$	−0.56 (3)	−0.70 (2)	−0.47 (4)	−0.48 (3)	−0.38 (5)
$\varepsilon_{u,u}$	0.79 (2)	0.66 (3)	0.81 (1)	0.76 (2)	0.78 (1)
$\varepsilon_{u,t}$	0.01 (18)	0.004 (25)	−0.78 (2)	−0.23 (5)	−0.77 (2)
$\varepsilon_{t,u}$	−0.86 (1)	−0.74 (1)	−0.67 (3)	−0.79 (1)	−0.54 (3)

Shown are the value (rank) of all coefficients that are among the three most influential for at least one intervention strategy.

Discussion

We studied AV and AB intervention strategies using a mathematical model that explicitly included bacterial infection and potential bacteria transmission. Overall, we find that AB intervention strategies do not lead to significant reduction in the total number of cases–even for the situation where bacteria infected hosts can transmit both virus and bacteria. However, AB control measures help to reduce the number of bacterial infections–which are more likely in need of medical attention or hospitalization. Additionally, AB treatment or prophylaxis can significantly reduce mortality. This is achieved by specifically targeting bacteria infected hosts that have a high risk of mortality—a different mechanism than the reduction of deaths through prevention of total cases that AV prophylaxis can bring about.

Not unexpectedly, the role of AB intervention becomes especially important if we consider the possibility that resistance renders AV drugs useless, which could occur early in the infection, for instance if

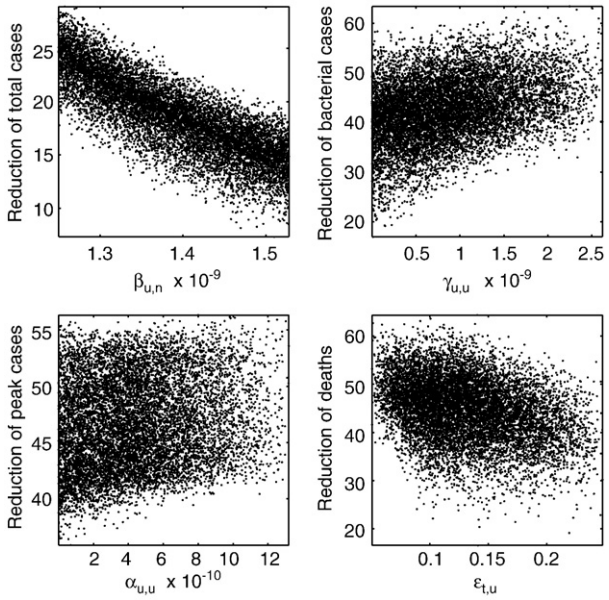

Fig. 8. Scatterplots for four of the parameters shown in Table 5. Top left: reduction of total cases for IS5 as function of $\beta_{u,n}$ (PRCC = −0.93). Top right: reduction of bacterial cases for IS3 as function of $\gamma_{u,u}$ (PRCC = 0.16). Bottom left: reduction of peak cases for IS4 as function of $\alpha_{u,u}$ (PRCC = 0.33). Bottom right: reduction of deaths for IS2 as function of $\varepsilon_{t,u}$ (PRCC = -0.74). All *y*-axes values are in percent.

initial containment strategies generate a resistant strain that can spread easily. Obviously, if a significant fraction of the bacteria were resistant to the AB intervention, this would diminish their effectiveness. For instance if half of the population harbored bacteria that were resistant to the administered drugs, it would in effect represent an intervention strategy with the level of AB treatment or prophylaxis reduced by half (if the latter is based on drugs, not vaccines). However, while AB resistance is a serious issue, it is reasonable to assume that any AB drug that has been found effective against bacteria at the beginning of a pandemic outbreak will remain effective for the comparably short duration of the outbreak. Future studies might want to focus on the potential impact of AB resistance. As expected, we find that if mortality due to bacterial infections is low (a 2009-like scenario), the impact of AB control strategies is reduced.

As is the case with any mathematical model, ours include a number of simplifying assumptions. The main assumption inherent in the model formulation is the homogeneity of the population. Hosts are categorized by their infection status but not further. More detailed models could take into account different age classes, possible spatial structure, and other details. Further, we ignored asymptomatic infections, we assumed that hosts always need to be infected with influenza before they can harbor a bacterial infection, and we ignored mixed drug sensitive and drug resistant virus infections. Also inherent in the model formulation is the assumption that infectious periods are exponentially distributed. It is known that relaxing this assumption can sometimes change results (Lloyd, 2001; Wearing et al., 2005). Our model uncertainty came from sampling of parameters, we ignored the inherently stochastic nature of the transmission process. While this is likely justified for the dynamics of the drug sensitive virus, the resistant strain might require stochastic treatment (Handel et al., 2009; Handel et al., 2006). For bacterial infections, it is not clear how important stochastic effects might be, but experimental data suggest that secondary bacterial infections often occur in heterogeneous clusters (Brundage, 2006; Brundage and Shanks, 2008).

Clearly, our model is only the first step towards more detailed models that could be used to study the dynamics of co-infection (Ferguson et al., 2005; Ferguson et al., 2006; (Germann et al., 2006; Halloran et al., 2008; Longini et al., 2005). However, it seems currently not very useful to try and implement a more complicated model. This is because many of the parameters even for our relatively simple model are poorly known. While we used reports from the existing literature to estimate parameters, often the reported data are so vague that our estimates are mostly educated guesses. A more complicated model would simply exacerbate the problem of unknown parameter values. As our sensitivity analysis shows, some of the poorly known parameters affect the results by a lot. While the transmission rate of influenza ($\beta_{u,n}$) is usually relatively well known, this is not the case for the transmission rates of bacteria ($\kappa_{u,u}$, $\gamma_{u,n}$), where solid data is essentially non-existent. As Table 5 shows, both of these parameters are among the most influential for some scenarios. Other parameters, such as the effect of AB treatment on the potential for influenza transmission ($\alpha_{u,t}$) or the fraction of influenza infected hosts that develop secondary bacterial infections under the various intervention strategies ($c_{i,j}$) also strongly influence the results and are equally poorly known. Lastly, the most important parameters with regard to reduction in mortality is the rate of death of bacteria infected hosts ($\varepsilon_{u,u}$), and the impact of AB and AV treatment on that rate ($\varepsilon_{u,t}$, $\varepsilon_{t,u}$). Especially the latter two are very poorly studied. For instance our reading of Ref. (Louria et al., 1959) suggests to us that antimicrobial therapy was successful in preventing deaths due to bacterial infections, while others have interpreted the same (sparse) data as suggesting that antibacterial drugs have no or little effect (Nicholson, 1998). The need for better data is obvious. Hopefully, one good that will come out of the current 2009 pandemic outbreak will be the availability of additional data, such that models can be further refined and used as predictive tools. This is important since even with a currently ongoing pandemic, we already know that a new one will arise at some point in the future—and the next pandemic strain one might well be less benign than the 2009 pandemic strain.

In summary, we have built and analyzed what seems to be the first model that explicitly considers bacterial infections and the use of both antiviral and antibacterial intervention strategies during an influenza pandemic. We find that while antibacterial intervention strategies are unlikely to play an important role in reducing the overall number of cases, such interventions can lead to a significant reduction in mortality and in the number of bacterial infections. We consider our study a first step towards exploring the role of antiviral and antibacterial control strategies in preventing cases and deaths during an influenza pandemic. While the lack of precision in our results precludes precise predictions based on our model, the qualitative findings are robust for the different scenarios we investigate. Our study therefore lends further support to previous suggestions that pandemic preparedness plans should not only include AV and non-pharmacological intervention strategies, but also include intervention strategies based on AB treatment or prophylaxis–in the form of both drugs and vaccines–as part of the overall influenza control strategy (Bonten and Prins, 2006; Brundage, 2006; Brundage and Shanks, 2008; McCullers, 2008; Morens et al., 2008).

Acknowledgments

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