Evaluating the effectiveness of antiviral treatment in models for influenza pandemic

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Abstract

We study the effectiveness of antiviral treatment in simple SEIR models, that are at the base of models used for influenza pandemic. The strategy is assessed in terms of the value of the reproductive ratio R_0.

We consider a general framework and analyse six different specific cases. The same antiviral strategy is simulated in all models, but they slightly differ in the compartmental structure. These differences correspond to different underlying assumptions concerning the timing of the intervention and the selection of individuals that receive treatment. It is shown that these details can have a strong influence on the predicted effectiveness of the strategy: for instance, with $R_0 = 1.8$ in absence

of treatment, different models predict that with treatment R_0 can become as low as 0.4, or as high as 1.3; still, in all models 70% of infected individuals are treated, and the infectiousness of treated individuals is reduced by 80%.

A particular assumption that can be included when modelling influenza is time-varying infectivity. We consider a specific model to verify if the predicted effectiveness of antiviral treatment is influenced by the inclusion of this assumption. We compare the results obtained with constant and variable infectivity, in relation also to the time of intervention.

It is likely that existing differences in the predictions of the effect of control measures depend on such modelling details. This finding stresses the need for carefully defining the structure of models, in order to obtain results useful for policy makers in pandemic planning.

Key words:

Antiviral treatment; influenza pandemic; infectious disease modelling; infection reproductive ratio

1 Introduction

The recent emergence of a highly pathogenic avian influenza virus and its subsequent transmission from infected poultry to humans has raised

concern about a future pandemic risk. An intensive preparedness planning is occurring in many countries and possible control measures are evaluated, often with the help of mathematical models. Since a pandemic vaccine is unlikely to be promptly available, other control measures have been considered to contain the pandemic in its earliest phases, while waiting for vaccine production and distribution. In this context, antiviral drugs are expected to play a major role both in prevention and in treatment (Balicer et al., 2004; Monto, 2003). They can be 70–90% effective as prophylaxis and shorten the duration of the infectious period by 1–1.5 days when used in treatment (Cooper et al., 2003; Monto, 2003; Longini et al., 2004; Hayden, 2001; Regoes and Bonhoeffer, 2006; World Health Organization, 2004).

Antiviral use has been widely investigated in mathematical modelling (Arino et al., 2006; Colizza et al., 2007; Cooper et al., 2006; Ferguson et al., 2005, 2006; Flahault et al., 2006; Gani et al., 2005; Germann et al., 2006; Longini et al., 2004, 2005; Wu et al., 2006). Some attention has been given also to the possible emergence of an antiviral-resistant influenza strain (Ferguson et al., 2003; Lipsitch et al., 2007; Regoes and Bonhoeffer, 2006), a real threat to the effectiveness of antiviral-based policies. But results of different studies are often in disagreement: if some authors draw positive conclusions about the possibility of slowing the spread of the infection and reduce the attack rate (Barnes et al., 2007; Colizza et al., 2007; Gani et al., 2005; Ger-

mann et al., 2006; Longini et al., 2004, 2005; Roberts et al., 2007), even in circumstances in which a resistant strain spreads widely (Lipsitch et al., 2007), others are more reluctant and suggest that a containment policy based on antivirals alone is unlikely to be successful (Ferguson et al., 2005, 2006; Flahault et al., 2006). These differences depend basically on the model considered and on the assumptions used in the model regarding the intervention.

Since many countries plan to rely on antivirals to face the pandemic during the early months and antivirals will probably be the only pharmaceutic intervention available in the initial phase, there is an evident need to clarify if and how the evaluation of antiviral efficacy is influenced by the model assumptions.

Instead of evaluating different strategies, we focus on one strategy and investigate its effectiveness in relation to the structure of the model, and its underlying assumptions. We consider the simplest scheme that can be considered to model influenza spread, i.e. a deterministic homogeneous SEIR (Susceptible - Exposed - Infectious - Removed) model. Alexander et al. (2008) have recently studied the optimal scheduling of antiviral treatment through the analysis of a homogeneous SEIR model with continuous age of infection. We extend the model in the direction of considering several different options about which infected individuals are treated and when; on the other hand, we subdivide the infectious period in discrete stages. We then anal-

yse quantitatively specific subcases of the general model; some of the cases correspond to models used in previous studies. Each case derives from the general model making precise assumptions on the time and way of intervention (in particular on the duration of infectivity before being testable and before the diagnosis), and therefore setting the pa- rameters of the general model appropriately. But this parameter choice gives rise to six models that, even if all deriving from one general model, have different structures corresponding to different modelling choices. Moreover, we always assume to treat the same fraction of infected, and to have the same efficacy of antivirals. All the models considered are easy to analyse mathematically, so that it is possible to quantify the effect of different modelling choices, whose relevance is usually disregarded to concentrate the attention on parameters uncertainties.

These models have all constant infectivity. Through the comparison to a model that includes time varying infectivity, we then investigate the effect of variable infectivity, and how it influences the evaluation of antivirals efficacy.

Many authors have investigated the effect of different antiviral-based interventions using rather complex models, including social and spatial structures, stochastic fluctuations and other factors. Even if a homogeneous model may be inappropriate to simulate a realistic influenza pandemic, it constitutes the basis of most models considered in

the literature. Its transparency allows to evaluate how the structure of the model influences the conclusions about the effectiveness of antiviral treatment. Complex models are definitely more realistic and suitable to simulate a pandemic, but they may obscure the role of underlying assumptions.

Our results may be useful when structuring more complex models, such as microsimulation models, and highlight the attention that should be paid to details of the model. Since the SEIR framework is always the skeleton of more complex models, the comparison between the results found with these models may help to understand the role of model assumptions in the evaluation of the efficacy of antiviral-based policies in pandemic containment.

2 Methods

In compartmental models with an SEIR structure the population is divided in four classes according to the disease state: susceptibles (S), that are all the individuals that can be infected, exposed (E), that are the individuals that have been infected but are not infectious yet and do not show symptoms, infectious (I), that is infected people that can transmit the infection, and immune or removed (R), that are all the individuals that have recovered or, in the worst cases, died. For influenza the mean latent and infectious period have been estimated to

approximately 1 (Ferguson et al., 2005) and 4 (Cauchemez et al., 2004; Hyman and LaForce, 2003; Longini et al., 2004; Mills et al., 2004) days respectively.

When modelling influenza many authors (Alexander et al., 2008; Arino et al., 2006; Chowell et al., 2007; Colizza et al., 2007; Ferguson et al., 2003; Nuno et al., 2007; Wu et al., 2006) divide the infectious period in phases to allow for asymptomatic stages, differences in infectivity or in symptoms severity. This allows also to structure treatment as administered at certain phases of infection. An alternative, which introduces an element of complexity into the model, would be to explicitly use the time-since-infection as a variable (Alexander et al., 2008; Brauer, 1995; Grais et al., 2003; Roberts et al., 2007).

We propose a model with a general structure in which the infectious period is divided in three phases. If no treatment is modelled, individuals progress through three infectious subclasses (I_1, I_2 and I_3) and finally recover. We assume that infected individuals, during the second infectious phase may be classified (with probability p) as individuals that can receive treatment and therefore enter class Y (individuals potentially selected for treatment) at the end of the period; individuals not classified for treatment enter the third infectious stage (class I_3). From class I_3 individuals recover spontaneously. Individuals in class Y (suitable for treatment) have the possibility to be treated, or may recover spontaneously, before actually receiving treatment. The

compartmental representation of the model is shown in Figure 1. Our model includes, we believe, a great variety of cases considered in the literature. Simpler models with fewer infectious stages can be obtained by formally setting equal to ∞ the exit rate from the missing stages.

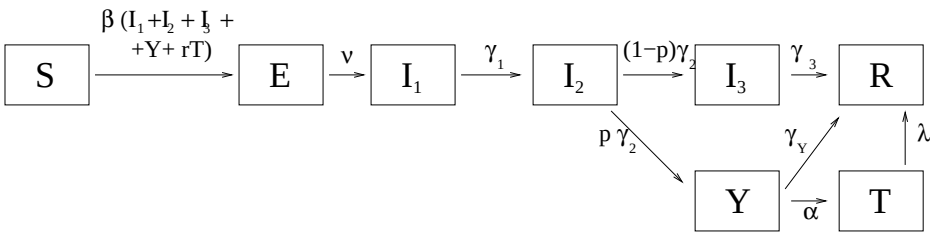

Figure 1: Compartmental representation of the general model considered. Individuals are divided in classes according to the disease state: S (susceptibles), E (exposed), I_1 (infectious during the first stage), I_2 (infectious during the second stage), I_3 (infectious during the third stage), Y (infectious that can receive treatment), T (treated), R (removed).

When simulating antiviral treatment of infected individuals we ignore preventive antiviral prophylaxis of their contacts, which is generally part of the recommended intervention strategies. Indeed in compartmental models, as the ones we are considering (Colizza et al., 2007; Gani et al., 2005; Germann et al., 2006; Longini et al., 2004, 2005), individual contacts are not defined so that such an intervention cannot be modelled exactly, although it can be approximated by an appropriate reduction of within-household transmission rates (Rizzo et al., 2008).

The classification between individuals that can receive treatment and those that cannot could depend on the severity of symptoms, or

could depend on behavioural or social features (geographical isolation, limited access to medical resources, tolerance of disease symptoms). We suppose in what follows that there is no difference in infectiousness between the two groups. Several authors (Colizza et al., 2007; Alexander et al., 2008) have assumed that individuals not selected for treatment are asymptomatic infectives and that they have a lower infectiousness; on the other hand, we stress the relevance of the potential presence of infectives that are as infectious as the others, but cannot be reached by treatment. Asymptomatic infectives with low infectivity add little to the reproduction ratio of the infection, so that ignoring them does not affect strongly the results.

The reproductive ratio of the model can be easily computed using the method of Diekmann and Heesterbeek (2000) and van den Driessche and Watmough (2002) and it is given by

$$R_0 = S_0\beta\left[\frac{1}{\gamma_1} + \frac{1}{\gamma_2} + (1-p)\frac{1}{\gamma_3} + p\left(\frac{1}{\alpha+\gamma_Y} + \frac{\alpha}{\alpha+\gamma_Y}\frac{r}{\lambda}\right)\right] \quad (1)$$

where S_0 is the fraction of individuals initially susceptible, r represents the reduction in the transmission due to treatment (corresponding to AVE_I in (Longini et al., 2004), 80% in the numerical example), β is the transmission rate, γ_1, γ_2, γ_3 and γ_Y are the exit rates from class I_1, I_2, I_3 and Y respectively, α is the treatment rate of selected individuals and λ is the recovery rate of treated individuals. We also assume that

antivirals shorten the infectious period of treated individuals (by 1 day in the numerical example).

The model can be viewed as an age of infection epidemic model and analyzed using the approach of the Kermack-McKendrick model proposed in (Brauer, 2005). The analysis shows that R_0 is a threshold value: if $R_0 \leq 1$, starting from any initial state S_0, only a few new infections will occur, without a major epidemic; if $R_0 > 1$, starting from a large enough susceptible fraction S_0, a major epidemic will occur; during the outbreak the number of susceptibles can only decrease and, when the epidemic dies off, will finally settle to an equilibrium value, that depends on the value of R_0. The larger R_0, the smaller is the number of individuals that escapes the infection (Diekmann and Heesterbeek, 2000).

It seems therefore adequate to judge the efficacy of antiviral treatment through the resulting reduction of R_0, as computed from (1). An antiviral treatment is generally measured by the reduction in infectivity (r), the reduction of the period of infectivity (that will be parametrised later), and by the fraction P of the infected that are treated. A standard computation shows that this is given by

$$P = p\,\frac{\alpha}{\alpha + \gamma_Y} \tag{2}$$

It is however clear from (1) that P, r and the length of the period

of infectivity of treated individuals are not sufficient to obtain R_0. In order to understand better which are the factors leading to larger or smaller reductions of R_0, we have considered several submodels, most of which have been chosen by other authors to investigate the effect of antivirals. The compartmental representation of each model is shown in Fig. 2.

Although the formulae given above apply to the general model, all the cases we will consider in detail belong to one of two model structures: either p is equal to 1, so that all infected individuals enter the class Y and can be selected for treatment; or γ_Y is equal to 0, so that all individuals entering class Y (those potentially selected for treatment) are actually treated. It will be seen later that choosing one structure or the other changes substantially the estimate of the efficacy of antiviral treatment.

In the first model all individuals are potentially treatable: when they leave the latent class they go directly to class Y, the only infectious class. From then on, they either enter the class of treated individuals (at rate α) or recover (at rate γ_Y). This is a special case of the general model and may be obtained letting γ_1 and γ_2 go to infinity and setting $p = 1$. According to (2) the overall probability of being treated is given by $\alpha/(\alpha + \gamma_Y)$. A model with this structure has been previously used by Flahault et al. (2006) to simulate antiviral treatment of cases.

In the second model we assume that, as the individuals leave the

latent class, they are immediately classified either (with probability p) as individuals that will be treated (subgroup Y) or (with probability $1-p$) not (subgroup I_3). Individuals in subgroup Y will enter the group of treated individuals at rate α, while those in subgroup I_3 will recover at rate γ_3. This model may be obtained letting γ_1 and γ_2 go to infinity and setting $\gamma_Y = 0$ in the general model. This model has the same structure as the models proposed by Alexander et al. (2008) and Chowell et al. (2006), even if in their models only a fraction of individuals selected for treatment are actually treated (that is $\gamma_Y \neq 0$), and individuals in class I_3 are considered as asymptomatic with reduced infectivity.

Influenza is characterised by a short incubation period, a high attack rate and a lack of disease specific symptoms (Balicer et al., 2004). All these epidemiological characteristics can impose difficulties in identifying cases promptly when they enter the infectious class and may cause a delay in treatment. This aspect has been considered in several studies (Ferguson et al., 2005, 2006; Germann et al., 2006; Longini et al., 2005), in which intervention has been postponed to the second or third day after symptoms onset. Therefore all the following models include a delay in treatment, assuming that some time is needed to identify cases and organise treatment. This period might be considered also as an infectious but asymptomatic stage.

In the third model we assume that at the end of this phase, in-

fectious individuals are either identified and treated or they enter the class I_3 and will not be treated. A similar model has been proposed by Gani et al. (2005), and Ferguson et al. (2003) have introduced an analogous mild asymptomatic infection stage in their model. The model is obtained letting γ_1 and α go to infinity.

Models 4 and 5 integrate the presence of the first phase of unrecognised infection with the treatment scheme used in Models 1 and 2, respectively. In Model 4, after a first infectious phase, all individuals are potentially treatable (class Y). Then they either enter the treated class (at rate α) or recover (at rate γ_Y). To obtain this model we have set $p = 1$ and let γ_2 go to infinity in the general model. In Model 5, after a first infectious phase, individuals are assigned either to subgroup I_3, or to subgroup Y. Individuals in subgroup Y will enter the group of treated individuals at rate α, while those in subgroup I_3 will recover at rate γ_3. This is obtained letting γ_2 go to infinity and setting $\gamma_Y = 0$. A model with this structure has been considered by Wu et al. (2006) (with hospitalised instead of treated individuals) to include an initial asymptomatic phase of the infectious period, while similar infectious stages, but in a more complex model, have been proposed by Nuno et al. (2007).

As models 4 and 5 correspond respectively to models 1 and 2, Model 6 is comparable to Model 3. After the phase I_1, individuals enter class I_2 during which they are either identified and treated or they enter the

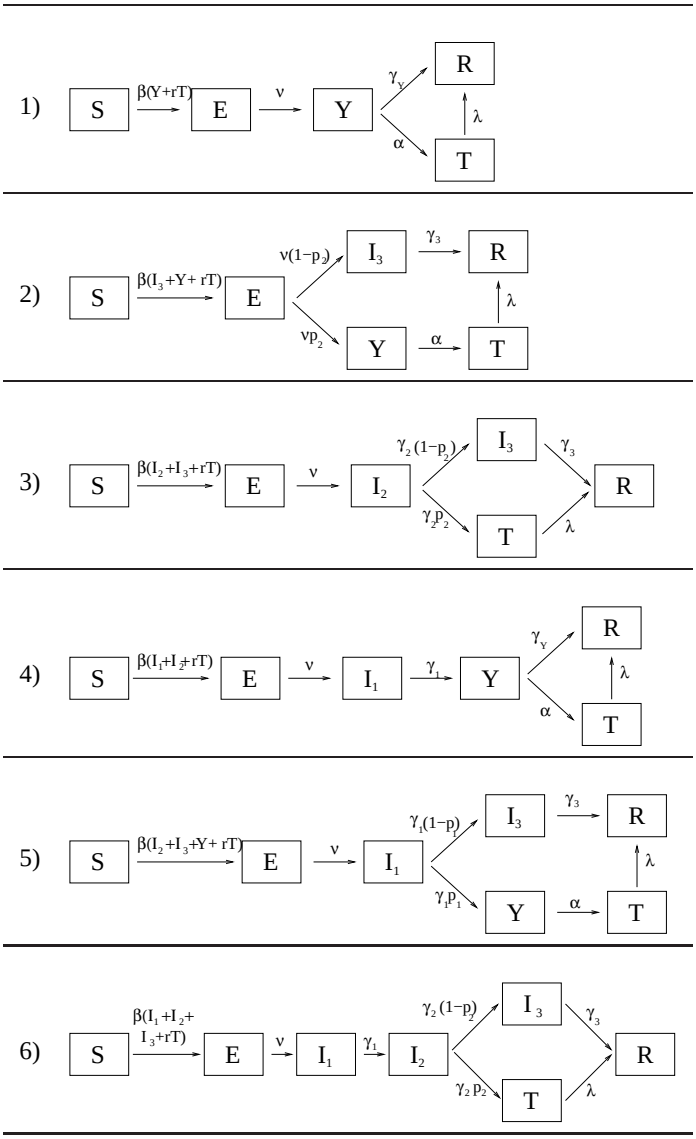

Figure 2: Compartmental representation of the six models considered. Individuals are divided in classes according to the disease state: S (susceptibles), E (exposed), I_1, I_2, I_3 (infectious in different stages), Y (selected for treatment), T (treated), R (removed). The transmission rate β is assumed to be constant.

third stage of the infectious period and then recover. This model is obtained from the general model letting α go to infinity.

For each model we have computed the average infectious period T_I in absence of intervention, the average infectious period T_{AV} for a treated individual and the average infectious period T_{noAV} for a non-treated individual. We will use their mathematical expressions, given in Table 1, for parameter calibration. The reproductive ratio R_0 is computed directly from (1), using the assumptions on the parameters made for each model.

#	$\mathbf{T}_I$	$\mathbf{T}_{AV}$	$\mathbf{T}_{noAV}$	$\mathbf{R}_0/\beta S_0$
1)	$\frac{1}{\gamma_Y}$	$\frac{1}{\alpha+\gamma_Y}+\frac{1}{\lambda}$	$\frac{1}{\alpha+\gamma_Y}$	$\frac{1}{\alpha+\gamma_Y}+\frac{\alpha}{\alpha+\gamma_Y}\frac{r}{\lambda}$
2)	$\frac{1}{\gamma_3}$	$\frac{1}{\alpha}+\frac{1}{\lambda}$	$\frac{1}{\gamma_3}$	$(1-p)\frac{1}{\gamma_3}+p\left(\frac{1}{\alpha}+\frac{r}{\lambda}\right)$
3)	$\frac{1}{\gamma_2}+\frac{1}{\gamma_3}$	$\frac{1}{\gamma_2}+\frac{1}{\lambda}$	$\frac{1}{\gamma_2}+\frac{1}{\gamma_3}$	$\frac{1}{\gamma_2}+(1-p)\frac{1}{\gamma_3}+p\frac{r}{\lambda}$
4)	$\frac{1}{\gamma_1}+\frac{1}{\gamma_Y}$	$\frac{1}{\gamma_1}+\frac{1}{\gamma_Y+\alpha}+\frac{1}{\lambda}$	$\frac{1}{\gamma_1}+\frac{1}{\gamma_Y+\alpha}$	$\frac{1}{\gamma_1}+\frac{1}{\alpha+\gamma_Y}+\frac{\alpha}{\alpha+\gamma_Y}\frac{r}{\lambda}$
5)	$\frac{1}{\gamma_1}+\frac{1}{\gamma_3}$	$\frac{1}{\gamma_1}+\frac{1}{\alpha}+\frac{1}{\lambda}$	$\frac{1}{\gamma_1}+\frac{1}{\gamma_3}$	$\frac{1}{\gamma_1}+(1-p)\frac{1}{\gamma_3}+p\left(\frac{1}{\alpha}+\frac{r}{\lambda}\right)$
6)	$\frac{1}{\gamma_1}+\frac{1}{\gamma_2}+\frac{1}{\gamma_3}$	$\frac{1}{\gamma_1}+\frac{1}{\gamma_2}+\frac{1}{\lambda}$	$\frac{1}{\gamma_1}+\frac{1}{\gamma_2}+\frac{1}{\gamma_3}$	$\frac{1}{\gamma_1}+\frac{1}{\gamma_2}+(1-p)\frac{1}{\gamma_3}+p\frac{r}{\lambda}$

Table 1: Results found analysing Models 1 to 6 (#). T_I, T_{AV} and T_{noAV} are, respectively, the average infectious period in absence of intervention, of treated and untreated individuals with intervention. R_0 is the reproductive ratio of the model, found from (1), as βS_0 times the expression reported in the last column; β is the transmission rate of untreated individuals and S_0 is the initial fraction of susceptible individuals; other parameters can be seen in Fig. 2

3 Numerical results

Parameter calibration

In order to compare the values for R_0 found in different models, that include different parameters, it is necessary to properly calibrate the parameters. We have estimated the values of the parameters to investigate the effect of intervention on the value of R_0 and how this effect vary when we consider different models.

First of all, we require that, in absence of antiviral treatment, the mean infectious period has to be the same (4 days) in all models. This implies the condition $T_I = 4$, where T_I is the mean infectious period in absence of treatment and is given, for each model, in Table 1.

Secondly, the probability of receiving treatment, computed using (2) is the same ($P = 0.7$) in all models. In Models 1 and 4 this probability is given by $\alpha/(\alpha + \gamma_Y)$, and thus determines the value of α, while in Models 2, 3 and 5 it is represented by p and so we are free to set α. In Models 1 and 2 individuals receive treatment, on average, $1/\alpha$ days after leaving class E; therefore in Model 2 we have kept α as in Model 1. Analogously in Model 5 we have taken it as in Model 4 (individuals receive treatment, on average, $1/\alpha$ days after leaving class I_1).

In Model 3 we assume individuals have the possibility to be treated one day after becoming infectious. This could be due, for example, to

a first asymptomatic phase. Therefore we set $1/\gamma_2 = 1$. Then from the relation $1/\gamma_2 + 1/\gamma_3 = 4$ we can estimate γ_3.

In Models 4 to 6 we have introduced a 1 day delay in treatment administration, which gives $1/\gamma_1 = 1$. Using the assumption of a 4 days natural infectious period, we can estimate γ_Y and γ_3.

As for the effect of antivirals, we assume that the infectiousness is reduced by 80% by antivirals, hence $r = 0.2$.

Finally, we need to establish the value of λ, reflecting the shortening of the infectiousness period of treated individuals. A commonly used assumption (see for example Colizza et al., 2007) is that the infectious period of treated individuals T_{AV} is 1 day shorter than T_{noAV}, the infectious period of untreated individuals. However, Table 1 shows that, for Models 1 and 4, $T_{AV} > T_{noAV}$; hence, it is not possible to require $T_{AV} = T_{noAV} - 1$. In other words, the time spent in the infectious class by a treated individual is on average longer than the infectious time of an individual that does not receive treatment. Nevertheless, if $1/\lambda = 1/\gamma_Y$, that is if treatment has no effect on the duration of the infectious period, on average the individuals will stay in the infectious class $1/\gamma_Y$ days, as one would expect; however, those being treated stay there longer than the average, while those not being treated less than the average. This apparently bizarre fact comes from the assumption that being treated and recovering are two competing risks; hence, individuals that receive treatment are those that naturally would have

a longer infectious period.

To overcome this problem, we choose to assume, following Colizza et al. (2007), $T_{AV} = T_I - 1$, which allows us to find λ. For Models 2, 3, 5, and 6, since $T_{noAV} = T_I$, this makes no difference, and we can see from Table 1 that this relation can be used to obtain λ as long as $1/\gamma_3 - 1/\alpha > 1$ (for Models 2 and 5) or $1/\gamma_3 > 1$ (for Models 3 and 6). Similarly, for Models 1 and 4, provided that $1/\gamma_Y - 1/(\alpha + \gamma_Y) > 1$,the relation $T_{AV} = T_I - 1$ allows us to find λ.

In Models 1 and 4 we actually treat individuals with an infectious period longer than the average T_I, so the assumption $T_{AV} = T_I - 1$ may be too optimistic. Another possibility would be to consider T^*_{AV}, defined as the infectious period of treated individuals when treatment has no effect (i.e. $\lambda = \gamma_Y$) and to require $T_{AV} = T^*_{AV} - 1$, which corresponds to $1/\lambda = 1/\gamma_Y - 1$. Results do not differ significantly; the highest variation is found with Model 1: if we assume a reproductive ratio of 1.8 in absence of treatment, we obtain $R_0 = 0.65$ with the hypothesis $T_{AV} = T_I - 1$ and $R_0 = 0.74$ with the hypothesis $T_{AV} = T^*_{AV} - 1$. Therefore we present only the results obtained with the first hypothesis.

The parameter values used are given in Table 2.

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
γ_1 (d^{-1})	$+\infty$	$+\infty$	$+\infty$	1	1	1
γ_2 (d^{-1})	$+\infty$	$+\infty$	1	$+\infty$	$+\infty$	1
γ_3 (d^{-1})	0.25	0.25	0.33	0.33	0.33	0.5
γ_Y (d^{-1})	0.25	0	0	0.33	0	0
α (d^{-1})	0.58	0.58	$+\infty$	0.77	0.77	$+\infty$
λ (d^{-1})	0.56	0.78	0.5	0.91	1.4	1
p	1	0.7	0.7	1	0.7	0.7
r	0.2	0.2	0.2	0.2	0.2	0.2
R_0^i/R_0^{noAV}	0.36	0.65	0.55	0.51	0.73	0.69

Table 2: Parameters values of the models. λ has been calibrated requiring $T_{AV} = T_I - 1$. The last row shows the effectiveness of antiviral treatment measured as the reduction in the reproductive ratio R_0. R_0^{noAV} represents the reproductive ratio of general model without intervention (that is with $p = 0$, while R_0^i is the reproductive ratio of Model i.

Reduction of R_0

The general model without intervention is characterised by an average infectious period $1/\gamma = 1/\gamma_1 + 1/\gamma_2 + 1/\gamma_3$, the sum of the average duration of each infectious phase. Its reproductive ratio is given by $R_0 = \beta S_0/\gamma$ (that is (1) with $p = 0$), where β is the transmission rate and S_0 the initial fraction of susceptible individuals. R_0 is a key epidemiological parameter (Diekmann and Heesterbeek, 2000) and it is often used to assess the effectiveness of control measures. A strategy able to lower the reproductive ratio is generally considered successful, in particular if it reduces R_0 to a value below 1. In fact, if $R_0 < 1$, the number of infections will, on average, decline and the epidemic will quickly get extinct.

Using the parameters values given in Table 2, we have evaluated

the effectiveness of the same intervention strategy when implemented in different ways, as described by the models considered. We have computed the ratio between the R_0 of the model without intervention and the reproductive ratio of the model with intervention for each of the models investigated. This ratio tells how much the reproductive ratio is reduced under antiviral treatment. Results are given in Table 2 and show how the reduction is very sensitive to the assumptions made when modelling the intervention. In Models 1 and 2 individuals have the same probability of receiving treatment and, on average, they are treated after 1.7 days in both models. But in Model 1 the intervention seems to be much more effective. With an hypothetical R_0 of 1.8, a value commonly used to simulate a future pandemic (Ferguson et al., 2005), using Model 1 we would conclude that antivirals are able to contain the pandemic, reducing the value of R_0 below 1. The same conclusion is not reached using Model 2.

As expected, the introduction of a delay in antivirals administration reduces significantly the effectiveness of the control measure. This can be observed comparing Model 1, 2 and 3 with Models 4, 5 and 6, which are their respective refinements. Assuming hypothetically $R_0 = 1.8$, antiviral treatment would reduce it to 0.65, 1.17 and 0.99 if simulated with Model 1, 2 or 3 and to 0.9, 1.3 and 1.24 with Model 4, 5 or 6, where a one day delay has been included.

We have assumed a treatment delay of one day, but some authors

(Ferguson et al., 2005) have considered a delay of two days. To investigate the effect of a longer delay we can compare, for example, Model 3 and Model 6. With a one day delay (Model 3) we have $R_0 = 2.2\beta S_0$. A two days delay (Model 6) gives $R_0 = 2.76\beta S_0$. As expected, a longer delay in antivirals administration reduces significantly the effectiveness of the intervention.

4 A comparison between constant and varying infectivity

Isselbacher et al. (1994) have observed the natural course of influenza and have reported its clinical characteristics in an otherwise healthy 28-years-old male. According to them, the virus shed is maximal 2 days after the onset of illness and then decreases and reaches a minimum on day 5. Taking these results into consideration, it is reasonable to assume that the infectivity of an individual varies in time, determining a variability in the transmission rate. To assess the importance of considering different levels of infectivity, we have designed a specific model that allows us to compare the results obtained assuming constant or varying infectivity. The model follows basically the structure of Model 6, but we assume that treated individuals follow an infection path similar to the untreated ones, with two phases characterised by different infectivity. Although other model structures are certainly possible,

this allows us to understand the interaction of treatment timing with variable infectivity.

Precisely, we make the following assumptions: without treatment, after the latent period individuals go through three infectious stages, each characterised by a specific infectivity and then recover. According to the results of Isselbacher et al. (1994), we assume a first low-infectivity stage lasting $1/\gamma_1 = 1$ day, followed by a second stage with high infectivity lasting $1/\gamma_2 = 2$ days and by a third stage again with low infectivity lasting $1/\gamma_3 = 1$ day. Varying infectivity is translated in non-constant transmission rates. According to the results of Isselbacher et al. (1994), we have assumed $\beta_1 = \beta_3 = 3/5\beta_2$, thus representing lower infectivity during the first and third stage. β_1, β_2 and β_3 are the transmission rates during the three infectious stages respectively. Infected individuals can receive treatment at the end of the first stage (with probability p_1), thus entering class T_2 or after the second stage (with probability p_2), entering class T_3. The transmission rate of treated individuals is reduced by a factor r, as in previous models, and therefore it will be equal to $r\beta_2$ in class T_2 and to $r\beta_3$ in class T_3. We further assume that individuals stay in class T_2 1.5 days before advancing to class T_3, while individuals treated after the end of the second infectious stage recover after 0.5 days. The compartmental representation of the model is given in Figure 3.

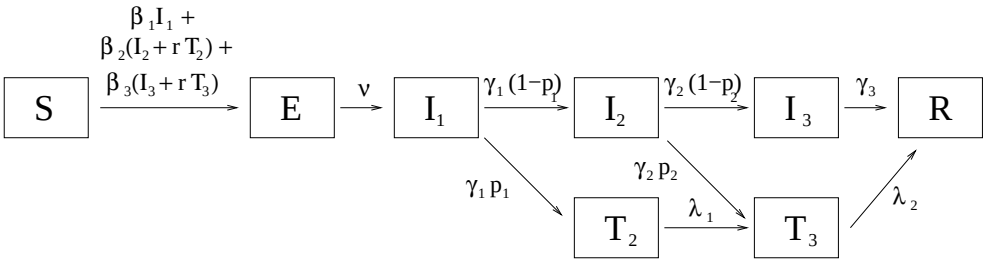

Figure 3: Compartmental representation of the model considered to include varying infectivity. Individuals are divided in classes according to the disease state: S (susceptibles), E (exposed), I_1, I_2, I_3 (infectious in different stages), T_2 (treated at the end of the first infectious stage), T_3 (treated at the end of the second infectious stage), R (removed).

The reproductive ratio of the model is given by

$$\begin{aligned} R_0 &= S_0 \left[\beta_1 \frac{1}{\gamma_1} + \beta_2 \left((1-p_1)\frac{1}{\gamma_2} + p_1 \frac{r}{\lambda_1}\right) + \right. \\ &+ \left. \beta_3 \Big((1-p_1)\,(1-p_2)\,\frac{1}{\gamma_3} + p_1 \frac{r}{\lambda_2} + (1-p_1) p_2 \frac{r}{\lambda_2}\Big)\right] \qquad (3) \end{aligned}$$

where λ_1 and λ_2 are the recovery rates of treated individuals.

The probability of receiving treatment in the model considered is given by $P = p_1 + (1-p_1)\,p_2$ and we have set it equal to 0.7, coherently with the previous numerical examples. Defining $Q = \frac{p_1}{P}$ as the proportion of individuals treated after the first infectious phase, we have investigated the dependence of the effect of antiviral treatment on the timing of intervention. Namely, varying Q between 0 and 1 we change from a scenario where all the treated individuals receive prophylaxis after the second infectious stage (very late) to a scenario where treatment is administered to all selected individuals after the first infectious

stage (that is two days in advance). Further, for a given Q, we can compare results obtained with varying and constant infectivity, obtained setting $\beta_1 = \beta_2 = \beta_3$.

Figure 4 shows that introducing variable infectivity can influence the results, although to a limited extent quantitatively, and makes the time of intervention even more crucial in the evaluation of the effectiveness of antiviral treatment. As expected, the higher the proportion of individuals treated after the first phase, the more effective the intervention is, both with variable and with constant infectivity. For example, with varying infectivity, assuming $R_0 = 1.8$ in absence of treatment we obtain $R_0 = 0.92$ if we treat all the selected individuals after the first phase ($Q = 1$) and $R_0 = 1.6$ if we treat all the selected individuals two days later ($Q = 0$). From $Q = 0$ to $Q = 1$ R_0 decreases linearly. In case of constant infectivity the results are analogous, but R_0 varies only from 0.97 to 1.51.

5 Conclusions

We have considered different models for an epidemic with antiviral treatment. All models have an SEIR structure and derive from the same general model. We have shown that details in the model assumptions can strongly influence the evaluation of antiviral treatment as a containment measure for pandemic influenza. It must be remarked

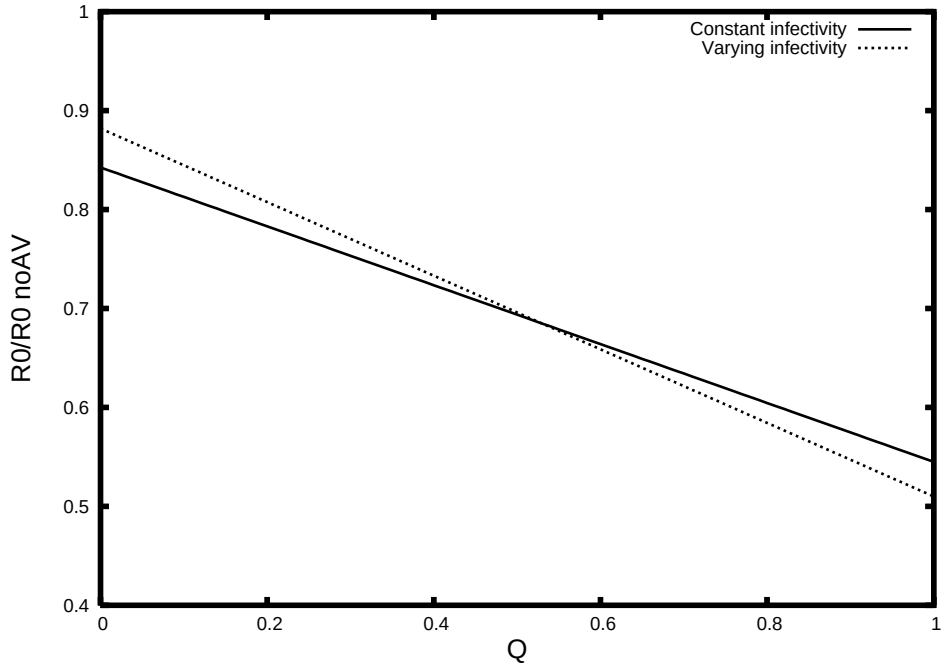

Figure 4: Relative effectiveness of antiviral treatment, computed as the ratio between the reproductive rate with intervention (model in Figure 3) and the reproductive rate of the plain SEIR model. In the model individuals may be treated at the end of the first or second infectious phase. Q represents the proportion of treated individuals that receive prophylaxis after the first phase. The graph shows results for varying and constant (i.e. $\beta_1 = \beta_2 = \beta_3 = \beta_T = \beta$) infectivity.

that, although the compartmental structure of some models considered may appear unusual, they are all quite natural and suitable to simulate the intervention; some have indeed been used in previous studies.

As discussed in Section 2, there is an implicit difference between Models 1 and 4, on one side, and Models 2, 3, 5 and 6 on the other: in Model 1 (and 4) the individuals that do not get treatment are those who recover faster than they can be targeted for treatment; this has

the consequence, already discussed, that the average infection period of untreated individuals is shorter than the average infectious period in the absence of intervention. In Model 2 (and 3, 5 and 6) it is assumed that infectives can be in principle distinguished between those that will be treated and those that will be not; the average infection period of untreated individuals (as well as their infectivity) is exactly the same as the average infectious period in absence of interventions.

From the results shown in Table 2 it can be seen that there is indeed a corresponding difference in the reduction of R_0 because of antiviral treatment between the two groups of models. This can also be seen in the formula for R_0: in Models 1 and 4 the probability of receiving treatment is given by $P = \frac{\alpha}{\alpha+\gamma_Y}$ and the mathematical expression of R_0 can be rewritten as $R_0 = \beta S_0 \left((1-P)\frac{1}{\gamma_Y} + P\frac{r}{\lambda}\right)$ ($+\beta S_0 \frac{1}{\gamma_1}$ in Model 4). In Models 2 and 5 $P = p$ and $R_0 = \beta S_0 \left((1-P)\frac{1}{\gamma_3} + P(\frac{1}{\alpha} + \frac{r}{\lambda})\right)$ ($+\beta S_0 \frac{1}{\gamma_1}$ in Model 5). Considering that $\gamma_Y = \gamma_3$ in Models 1 and 4, we can see that the difference between them is in the term $\frac{P\beta S_0}{\alpha}$, the force of infection of treated individuals during the period before treatment starts. In other words, the value of R_0 in Models 1 and 4 looks as if we were ignoring the fact that treated individuals are infectious before receiving treatment.

These results show that the question of who is treated is decisive: it is very different if treated individuals are those, for one reason or another, outside the reach of the health system, if they are asymptomatic

with low infectivity, or those that recover faster. These assumptions are often implicitly included into the structure of the model, that should therefore be chosen carefully.

A second factor strongly affecting the effectiveness of intervention is the timing of treatment. This can be seen by comparing Models 1, 2 and 3, on one side, with Models 4, 5 and 6, that are analogous, except that a first infectious period is added, where no treatment is possible. Clearly, the inclusion of a time delay in drug administration reduces significantly its impact on the dynamics of the epidemic.

Time varying infectivity makes timing of intervention even more crucial. In fact, if infectivity is lower in the first and last stage of the infectious period, and higher in the middle stage, a late intervention is even less effective than in the case of constant infectivity: at the end of the middle stage, an individual will have already infected almost all the individuals it would eventually infect. On the other hand, missing treatment in the first infectious stage is less crucial, since few individuals would be infected anyway during that stage. This can be seen from Fig. 4 that shows the effectiveness of intervention as a function of the proportion Q of individuals treated after the first stage: there exists a threshold value Q_t (in the numerical example $Q_t \approx 0.53$) such that if $Q < Q_t$ the intervention is more effective if infectivity is constant than if it is variable (most individuals treated after the second stage), while it is less effective if $Q > Q_t$ (most individuals treated after the first

stage).

Our study shows that, when studying the effectiveness of anti-viral treatment, much attention should be paid to the assumptions (often implicit) about the timing of intervention and the individuals that get treatment: even if the same intervention is apparently being modelled, different models can lead to different conclusions. The detailed structure of the model is very relevant and should be carefully evaluated and specified when assessing the importance of the results.

Although the models considered are all SEIR-type models for a homogeneous population, the results immediately translate to more complex SEIR models used to simulate an influenza pandemic. In fact, R_0 for an epidemic in a metapopulation is strongly influenced by the value of R_0 in each population in isolation (Diekmann and Heesterbeek, 2000), and may even be the same under some special choices of the contact matrix (Colizza et al., 2007). Individual-based models (Ferguson et al., 2005) are more flexible, and can incorporate detailed assumptions about the timing of infectiousness and antiviral use, as well as allowing for antiviral prophylaxis of case contacts. Still, the results of this paper stress the need of making consistent and realistic choices when building any kind of model, and especially of making them transparent. Different results on the evaluation of containment strategies may depend on hidden assumptions in the model structure. Hence, the structure of models has to be carefully defined, in order

to obtain results that can be useful for policy makers in pandemic planning.

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Short title

Antiviral treatment effectiveness

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