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Intermittent treatment of severe influenza

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ABSTRACT

Severe, long-lasting influenza infections are often caused by new strains of the virus. The long duration of these infections leads to an increased opportunity for the emergence of drug resistant mutants. This is particularly problematic since for new strains there is often no vaccine, so drug treatment is the first line of defense. One strategy for trying to minimize drug resistance is to apply drugs periodically. During treatment phases the wild-type virus decreases, but resistant virus might increase; when there is no treatment, wild-type virus will hopefully out-compete the resistant virus, driving down the number of resistant virus. A stochastic model of severe influenza is combined with a model of drug resistance to simulate long-lasting infections and intermittent treatment with two types of antivirals: neuraminidase inhibitors, which block release of virions; and adamantanes, which block replication of virions. Each drug's ability to reduce emergence of drug resistant mutants is investigated. We find that cell regeneration is required for successful implementation of intermittent treatment and that the optimal cycling parameters change with regeneration rate.

1. Introduction

The influenza virus causes a potentially fatal illness that appears in both annual seasonal outbreaks and in occasional pandemics. While there are vaccines that can prevent infection, they must be re-formulated for every new strain (Jang and Seong, 2014; Soema et al., 2015), causing a delay in the availability of an adequate vaccine when a new strain of influenza arises. Unfortunately, influenza mutates rapidly (Drake, 1993), causing genetic drift of strains, and can also undergo re-assortment events (Qiao et al., 2014; Westgeest et al., 2014), creating entirely new strains. This means that vaccines are not a good first line of defense against new strains of influenza.

Influenza antivirals are typically effective against a wide variety of strains of influenza (Spanakis et al., 2014), making them a better choice for controlling spread of a new strain of influenza. Unfortunately, the rapid mutation rate of influenza also causes problems with the use of antivirals. Influenza resistance to antivirals arises through a single amino acid mutation (Abed et al., 2005; Baz et al., 2006; Bright et al., 2006; Gubareva et al., 2000), so resistance to antivirals can emerge quickly (Bright et al., 2006; Dharan et al., 2009; Zaraket et al., 2010). There are currently two classes of antivirals used for treatment of influenza. Adamantanes prevent uncoating of the virion after it has entered the cell by blocking the action of the M2 matrix protein (Abed et al., 2005). Unfortunately, resistance to adamantanes in circulating strains is already high (Bright et al., 2006; Dong et al., 2015), limiting its usefulness. Neuraminidase inhibitors prevent release of the virion from the cell by blocking the action of the neuraminidase surface protein (Abed et al., 2002; Gubareva et al., 2000). Most circulating strains are still sensitive to neuraminidase inhibitors (Spanakis et al., 2014), making them the antiviral of choice for pandemic stockpiles.

Given the rapid mutation rate of influenza and the limited number of antivirals available to treat influenza, it is important to investigate treatment strategies that might limit the emergence of resistance during the course of an infection. One strategy used in other infectious diseases is intermittent treatment (de Bree et al., 2017; Goujard et al., 2012). Intermittent treatment involves periodic switching between antiviral treatment and no treatment. If a drug resistant mutation arises during the treatment phase, its replication will not be suppressed by the antiviral, so the drug-resistant virus will multiply. Once treatment is stopped, however, any remaining wild-type virus can also freely multiply, and will hopefully out-compete the drug-resistant strain, driving down the number of drug-resistant virions. If the cycles of treatment and no treatment periods are correctly optimized, then both wild-type and drug-resistant virions can be eradicated (de Bree et al., 2017). Note that this strategy will only work consistently if the drug-resistant strain is less fit than the wild-type strain, which seems to be the

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case for at least some influenza drug-resistant mutations (Abed et al., 2016; Baek et al., 2015; Burnham et al., 2015; Butler et al., 2014; Paradis et al., 2015; Pascua et al., 2016).

While drug resistance can emerge during the course of a typical short duration seasonal infection (Dobrovolny and Beauchemin, 2017; Perelson et al., 2012), there is little time for it to be transmitted to other people. The bigger concern for transmission and spread of drug-resistant influenza is long-lasting, severe infections which allow for shedding of drug resistant influenza over several weeks or even months (Bruminhent et al., 2014; Eshaghi et al., 2014; Ghedin et al., 2012; Hurt et al., 2013). While severe influenza infections are long compared to seasonal infections, they are still much shorter than human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infections, which sometimes use intermittent treatment, and offer more limited choices for the length of the treatment on and treatment off periods.

In this paper, we study the emergence of drug resistance during severe infections by combining two models of within-host influenza, one which models severe infections (Dobrovolny et al., 2010) and one which models the emergence of drug resistance (Dobrovolny and Beauchemin, 2017). We apply intermittent treatment to the model via a switching function that either applies a constant drug treatment, or leaves the system untreated. We find that cell regeneration is critical for intermittent treatment to work and that when cell regeneration is fast enough, the periodicity of switching between treatment and no treatment phases does not affect the effectiveness of the treatment.

2. Methods

2.1. Modeling influenza infections

To capture the dynamics of severe influenza infections, the single cell population differential equation model with delayed viral production, as proposed in Baccam et al. (2006), was extended to a two target cell model in Dobrovolny et al. (2010). In terms of the nomenclature, we separated the two target cells into default (subscript d) and secondary (subscript s) cells with each containing a wild-type (subscript wt) and a mutant (subscript μ) subpopulation. In the model, the default cells represent the preferred target for human influenza, while the secondary population represents cells that can be infected by human influenza, but with more difficulty. The key parameters that control the differences between the two cell populations are the relative susceptibility to infection ($r_\beta \in \mathbb{R}^+$), the relative viral production rate ($r_p \in \mathbb{R}^+$) and the fraction of initial secondary target cells ($r_\mathrm{T} \in [0, 1]$). Initial allocation of a secondary cell population is a crucial step that makes our model capable of reproducing the dynamics of long-lasting influenza infections. Note that r_T only appears in the initial conditions and therefore does not explicitly appear in the system of differential equations.

The initial amount of wild-type virus (V_wt) and mutant virus (V_μ) proceed to infect primary target cells (T_d) at rate β and secondary target cells (T_s) at rate $r_\beta\beta$. Once infected, cells migrate into their eclipse phase (E), where they are producing viral proteins and RNA, but not yet releasing new virus, and then turn into productively infected cells I at rates τ_E^{-1} and τ_I^{-1}, respectively. There are four distinct types of cells: any combination of default or secondary with wild-type or mutant are possible. Once primary (secondary) target cells have reached their productive stage, they will produce virus at rate p ($r_p p$) while slowly dying off at rate c. When target cells die they accumulate as D, from which they may regenerate back to available target cells T at rate ℓ.

An infection is medicated with drugs of two types. Drugs based on adamantanes prevent the virus from infecting available target cells and the drug's efficacy on wild-type and mutant strains is controlled via parameters m_wt and m_μ. Neuraminidase inhibitor based drugs (NAI) do not prevent cell infection but prevent production of new virions. The drug's efficacy is controlled by the parameters n_wt and n_μ. All efficacies assume values between 0 and 1 and represent the relative reduction in infection rate (for adamantanes) or production rate (for NAIs) caused by the antiviral. We make the assumption that the efficacy remains constant during treatment, even though antivirals are taken as pills which causes a time-varying drug concentration. Recent work has shown that the assumption of constant drug efficacy adequately approximates time-varying drugs (Palmer et al., 2017).

We additionally would like to allow the mutation of each virus entity from its wild-type into a drug-resistant strain (and vice versa). In the model, this is incorporated via the choice of mutation rate μ_nt that fixes the probability with which either virus type will mutate. A number of different mutations have been reported for adamantanes (Abed et al., 2005; Bright et al., 2006; Hay, 1996; Hayden, 1996) and NAIs (Baz et al., 2006; Gubareva et al., 2000), but in our model we restrict ourselves to the most common type of mutation (S31N in the M2 protein for amantadines and H275Y in the N1 protein for the NAI-based drug oseltamivir) and assume that they occur at the average mutation rate of influenza A, namely $\mu_\mathrm{nt} = 7.3 \times 10^{-5}$ per nucleotide per replication (Drake, 1993).

The model resulting from these contemplations is a system comprised of 14 differential equations. These can be compacted by means of an index j that assumes a wildtype or mutant stance,

$$\dot{\boldsymbol{T}} = \begin{pmatrix} \dot{T}_\mathrm{d} \\ \dot{T}_\mathrm{s} \end{pmatrix} = -\left(\beta_\mathrm{wt} V_\mathrm{wt} + \beta_\mu V_\mu\right) \begin{pmatrix} 1 & 0 \\ 0 & r_\beta \end{pmatrix} \boldsymbol{T} + \ell \boldsymbol{D} \tag{1a}$$

$$\dot{\boldsymbol{E}}_j = \begin{pmatrix} \dot{E}^j_\mathrm{d} \\ \dot{E}^j_\mathrm{s} \end{pmatrix} = (1 - m_j)\beta_j V_j \begin{pmatrix} 1 & 0 \\ 0 & r_\beta \end{pmatrix} \boldsymbol{T} - \tau_E^{-1} \boldsymbol{E}_j \tag{1b}$$

$$\dot{\boldsymbol{I}}_j = \begin{pmatrix} \dot{I}^j_\mathrm{d} \\ \dot{I}^j_\mathrm{s} \end{pmatrix} = \tau_E^{-1} \boldsymbol{E}_j - \tau_I^{-1} \boldsymbol{I}_j \tag{1c}$$

$$\dot{V}_j = (1 - n_j) p_j \begin{pmatrix} 1 - \mu_\mathrm{nt} \\ r_p - r_p \mu_\mathrm{nt} \\ \mu_\mathrm{nt} \\ r_p \mu_\mathrm{nt} \end{pmatrix} \cdot \begin{pmatrix} \boldsymbol{I}_\mathrm{wt} \\ \boldsymbol{I}_\mu \end{pmatrix} - c V_j \tag{1d}$$

$$\dot{\boldsymbol{D}} = \begin{pmatrix} \dot{D}_\mathrm{d} \\ \dot{D}_\mathrm{s} \end{pmatrix} = \tau^{-1}\left(\boldsymbol{I}_\mathrm{wt} + \boldsymbol{I}_\mu\right) - \ell \boldsymbol{D}. \tag{1e}$$

The different compartments of the model and their interactions are shown in Fig. 1. In the absence of cell regeneration, this is a target cell limited model where the infection terminates when all target cells have been infected. This does not equate to death of the patient however, since not all cells in the respiratory tract are target cells for influenza (Chan et al., 2013; Hui et al., 2017). We include cell regeneration as proportional to the number of dead cells which represents stimulation of reproduction by cell death (Beers and Morrisey, 2011). Since the two target cells of the model represent two different types of cells, we assume that death of default cells stimulates regeneration of default cells and death of secondary cells stimulates regeneration of secondary cells.

All of the differential equations that describe our model are fully deterministic and can be solved by choice of a stable integration method. In doing so, the observables will assume non-discrete values (along the positive real axis), which is a behavior that we would like to restrict, due to the discrete nature of the underlying cell model. ODEs produce the mean-field dynamics and are not representative of the course of the infection in a single patient. Some patients will clear the wild-type virus before a drug resistant mutant appears and not have any infection at all. In other patients,