REVIEW O e Acce

A e e f a e a ca de f f e a A fec a ce c e: e ea ed a d c a e ge a ead

C AA B [1*†], A [2†]

budding, which takes place only at the apical surface membrane of infected cells [13], can be detected 5–6 hours post-infection (hpi), and is maximal 7–8 hpi (see Table 1). The period between successful infection of the cell and the productive release of viral progeny is often called the "eclipse phase". Just as it did upon cell entry, the HA on the surface of the virions will again bind the sialic acid receptors. The virus neuraminidase (NA) is responsible for cleaving the sialic acid receptors on the surface of the cells to allow the newly-produced influenza virions to break free of the cell that has produced it and go on to infect other cells. Successive cycles of cell infection quickly result in an exponential growth of viral titer, which peaks around 2–3 days post-infection (dpi). The infection typically resolves in 3–5 dpi, and virus can typically be isolated between 1–7 dpi [7]. In a primary infection with influenza, pathogen-specific antibodies (Abs) and $CD8^+$ cytotoxic T lymphocytes (CTL) are first observed around 5 dpi, peaking around 7 dpi, whereas in a secondary infection Abs and CTLs can respond as early as 3 dpi [14]. Cellular regeneration of the epithelium begins 5–7 dpi but complete resolution can take up to one month [15]. Figure 1 illustrates the kinetic of the course of an influenza infection within a host.

Several aspects of influenza infections are still unresolved. For instance, the contributions of strain-specific cell tropism, pre-existing immunity, and host genetic factors in shaping the virulence and transmissibility of a particular influenza strain are not well understood [16,17]. There is much to be learned about how a strain's genotype shapes complex phenotypes such as virulence and transmissibility. Most of these unresolved aspects will require a quantitative analysis of the key players and of

importance of the models to public health and promising directions for additional modeling studies.

Mathematical models of influenza infection and drug action

Overview of the models

The most basic models considered to capture the dynamics of influenza infections, both in vivo and in vitro, consist of sets of ordinary differential equations (ODEs), namely

$$\text{No latent phase}\quad \begin{aligned}\frac{dT}{dt} &= -\beta TV\\ \frac{dI}{dt} &= \beta TV - \delta I\\ \frac{dV}{dt} &= pI - cV\end{aligned} \qquad (1)$$

$$\text{or with a latent phase}\quad \begin{aligned}\frac{dT}{dt} &= -\beta TV\\ \frac{dE}{dt} &= \beta TV - kE\\ \frac{dI}{dt} &= kE - \delta I\\ \frac{dV}{dt} &= pI - cV\end{aligned} \qquad (2)$$

These models describe the dynamics of susceptible target cells, T, which become infected at rate β by the free virions, V. In model (1), the newly infected cells, I, immediately begin to produce virus, whereas in model (2), newly infected cells first undergo a latent or eclipse phase, E, before they become infectious, I, after an average time $1/k$

peaks around 2–3 dpi, before decaying exponentially. Target cells are consumed rapidly, with the population of infected cells peaking around the same time as viral titer.

Because this type of model does not explicitly incorporate an immune response (IR), it is said to be target-cell limited, i.e. the virus load reaches its peak and subsequently declines once most cells have been infected and few susceptible cells remain. More accurately, the peak is reached when $\beta TV \approx \delta I$. The target-cell limited nature of the models is clearly illustrated in Figure 2 where most target cells have been depleted by 54 hpi, around the time of viral titer peak. This almost complete depletion of target cells needs to be understood in the context of susceptibility: Cells susceptible to the virus and able to produce progeny virions as described by the model do not necessarily directly correspond to all epithelial cells in the respiratory tract. Indeed, it is not well known

fully resolved. We will return to this point later when we discuss models which incorporate an IR.

To our knowledge, the first mathematical model proposed to describe the within-host dynamics of an influenza infection was introduced by Larson et al. in 1976

onto target cells, and incorporates a fixed delay of 4.5 h between cell infection and the start of viral production, instead of an explicit eclipse phase as in model (2). The model in [42] provides a good fit to HA titer data. From their study, the authors conclude that viral yield in these systems can be most effectively maximized by increasing the total number of susceptible cells, upregulating viral production rate, and delaying the apoptosis of infected cells. In a follow-up study, Sidorenko et al. developed a

fit the data well. It is still possible, and quite likely, that

and the half-life of virions. Other parameters that have been estimated from some models include the average

constant over time [98] and mathematical models have incorporated this using a time-varying infectivity for vir-

were able to use a combination of data and simple models to estimate the duration of infectiousness and other quantities. Liao et al. [129] reanalyzed the same dataset and used it to estimate the re

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