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Emergence of drug resistance: implications for antiviral control of pandemic influenza

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Given the danger of an unprecedented spread of the highly pathogenic avian influenza strain H5N1 in humans, and great challenges to the development of an effective influenza vaccine, antiviral drugs will probably play a pivotal role in combating a novel pandemic strain. A critical limitation to the use of these drugs is the evolution of highly transmissible drug-resistant viral mutants. Here, we develop a mathematical model to evaluate the potential impact of an antiviral treatment strategy on the emergence of drug resistance and containment of a pandemic. The results show that elimination of the wild-type strain depends crucially on both the early onset of treatment in indexed cases and population-level treatment. Given the probable delay of 0.5–1 day in seeking healthcare and therefore initiating therapy, the findings indicate that a single strategy of antiviral treatment will be unsuccessful at controlling the spread of disease if the reproduction number of the wild-type strain (R_0^s) exceeds 1.4. We demonstrate the possible occurrence of a self-sustaining epidemic of resistant strain, in terms of its transmission fitness relative to the wild-type, and the reproduction number R_0^s. Considering reproduction numbers estimated for the past three pandemics, the findings suggest that an uncontrollable pandemic is likely to occur if resistant viruses with relative transmission fitness above 0.4 emerge. While an antiviral strategy is crucial for containing a pandemic, its effectiveness depends critically on timely and strategic use of drugs.

Keywords: influenza pandemic; antiviral therapy; drug resistance; delay epidemic models

1. INTRODUCTION

The threat of an impending influenza pandemic, possibly through mutation of the present deadly avian strain H5N1, has galvanized global efforts to understand the potential benefits and limitations of mitigation strategies. Previous modelling studies have considered pharmaceutical and non-pharmaceutical interventions (Ferguson *et al.* 2003, 2005, 2006; Longini *et al.* 2004, 2005; Gani *et al.* 2005; Germann *et al.* 2006) and rationalized the use of antiviral drugs as the first-line defence against a new pandemic strain. The effects of these drugs are twofold: (i) they reduce the infectivity and duration of infectiousness by inhibiting virus replication and (ii) reduce susceptibility; these will in turn decelerate the spread of infection in the population to afford time for development of new vaccine candidates.

There are two groups of antiviral drugs available for treatment and prophylaxis of influenza: M2 inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). Despite the effectiveness of these drugs in reducing influenza-related morbidity and mortality, the emergence of drug resistance poses a critical limitation on their application. Incidence of viral resistance to M2 inhibitors has been associated with an increasing rate in seasonal influenza, possibly through widespread or indiscriminate use of the drugs (Bright *et al.* 2005). Neuraminidase inhibitors are less prone to selecting for resistant mutations (Moscona 2005; Regoes & Bonhoeffer 2006), and therefore offer a better option for pandemic preparedness. However, recent emergence of oseltamivir resistance has raised concerns about our strengths in facing an influenza pandemic (Kiso *et al.* 2004; de Jong *et al.* 2005; Moscona 2005; Regoes & Bonhoeffer 2006).

The strategy of antiviral therapy raises a number of public health concerns regarding the optimal use of drugs

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