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Emergence and spread of drug resistant influenza: A two-population game theoretical model

Kamal Jnawali [a, *], Bryce Morsky [a], Keith Poore [a], Chris T. Bauch [b]

[a] Department of Mathematics and Statistics, University of Guelph, 50 Stone Road East, Guelph, Ontario, N1G 2W1, Canada
[b] Department of Applied Mathematics, University of Waterloo, 200 University Avenue West, Waterloo, Ontario, N2L 3G1, Canada

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ABSTRACT

Background: The potential for emergence of antiviral drug resistance during influenza pandemics has raised great concern for public health. Widespread use of antiviral drugs is a significant factor in producing resistant strains. Recent studies show that some influenza viruses may gain antiviral drug resistance without a fitness penalty. This creates the possibility of strategic interaction between populations considering antiviral drug use strategies.

Methods: To explain why, we develop and analyze a classical 2-player game theoretical model where each player chooses from a range of possible rates of antiviral drug use, and payoffs are derived as a function of final size of epidemic with the regular and mutant strain. Final sizes are derived from a stochastic compartmental epidemic model that captures transmission within each population and between populations, and the stochastic emergence of antiviral drug resistance. High treatment levels not only increase the spread of the resistant strain in the subject population but also affect the other population by increasing the density of the resistant strain infectious individuals due to travel between populations.

Results: We found two Nash equilibria where both populations treat at a high rate, or both treat at a low rate. Hence the game theoretical analysis predicts that populations will not choose different treatment strategies than other populations, under these assumptions. The populations may choose to cooperate by maintaining a low treatment rate that does not increase the incidence of mutant strain infections or cause case importations to the other population. Alternatively, if one population is treating at a high rate, this will generate a large number of mutant infections that spread to the other population, in turn incentivizing that population to also treat at a high rate. The prediction of two separate Nash equilibria is robust to the mutation rate and the effectiveness of the drug in preventing transmission, but it is sensitive to the volume of travel between the two populations.

Conclusions: Model-based evaluations of antiviral influenza drug use during a pandemic usually consider populations in isolation from one another, but our results show that strategic interactions could strongly influence a population's choice of antiviral drug use policy. Furthermore, the high treatment rate Nash equilibrium has the potential to become socially suboptimal (i.e. non-Pareto optimal) under model assumptions that might apply under other conditions. Because of the need for players to coordinate their actions, we

List of abbreviations: *L*, treat at a low rate; *H*, treat at a high rate; *NE*, Nash equilibria; *ODE*, Ordinary differential equation.

* Corresponding author.
E-mail addresses: kjnawali@uoguelph.ca (K. Jnawali), bmorsky@uoguelph.ca (B. Morsky), kpoore@uoguelph.ca (K. Poore), cbauch@uwaterloo.ca (C.T. Bauch).

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conclude that communication and coordination between jurisdictions during influenza pandemics is a priority, especially for influenza strains that do not evolve a fitness penalty under antiviral drug resistance.

1. Introduction

Case importation is the primary means by which horizontally transmitted infectious diseases of humans can move between populations. For instance, the 2009 pandemic influenza A (pH1N1) viral strain originated in Mexico, but quickly spread to other countries through international travel (World Health Organizationet al, 2009). pH1N1 spread as much in 6 weeks as other influenza strains spread in six months (World Health Organization (WHO)et al., 2009). After an imported case of pH1N1 was identified in Germany on 27 April 2009 (only a month after the virus was identified in Mexico City) the global transmission of pH1N1 appeared to be on the horizon (Novel influenza A (H1N1) Investigation Team et al 2009).

If vaccines are not immediately available during an influenza pandemic, antiviral drugs are one of the most effective ways to reduce the health burden of infections (Ferguson et al., 2005). There are four types of antiviral drugs available to treat influenza: oseltamivir, zanamivir, amantadine and rimantadine (Ortiz et al., 2008). However, some factors delay the onset of treatment, and emergence and transmission of antiviral drug viruses may reduce the efficacy of treatment (Handel, Longini, & Antia, 2009). M_2 inhibitors such as amantadine and rimantadine work only against influenza A. In contrast, neuraminidase inhibitors such as zanamivir and oseltamivir are effective against both influenza A and influenza B (Winquist et al., 1999). Neuraminidase inhibitors block the function of the viral neuraminidase protein enzyme that prevents the discharge of viruses from the infected host cell and precludes new host cells from getting infected. The development of oseltamivir resistance is minimal if it is used at recommended doses for treatment (Aoki, Boivin, & Roberts, 2006). However, high rates of resistance are possible: 18% prevalence of resistance to oseltamivir has been observed among treated children in Japan (Kiso, Mitamura, Sakai-Tagawa, Shiraishi, Kawakami, Kimura, Hayden, Sugaya, & Kawaoka, 2004). Also, in 2008, a high level of emergence and spread of oseltamivir resistance viruses was observed in Europe (Meijer et al., 2009).

A number of mathematical models (primarily, ordinary differential equation models) have explored the potential impact of the emergence of drug resistant influenza and its spread during an outbreak (Moghadas, BowmanRöst, & Wu, 2008; Regoes & Bonhoeffer, 2006; Stilianakis, Perelson, & Hayden, 1998). This research has provided useful insights into the emergence and spread of drug-resistant influenza. These models predict that the final size of a pandemic can be reduced by applying an adaptive antiviral strategy with properly timed increases in drug usage, and that chemoprophylaxis of susceptible individuals is one of the best ways to reduce the force of infection of an epidemic and keep the emergence of drug resistant viruses low (Lee, Chowell, & Castillo-Chávez, 2010). A recent study (Chao, Bloom, Kochin, Antia, & Longini, 2012) presents a stochastic model of influenza. A stochastic model is a tool for assessing the impact of noise on a dynamical systems' trajectories, and generates probability distributions of possible outcomes by allowing random variation in one or more inputs over time. The importance of recognizing stochasticity relates to the fact that some characteristics of the spread of infectious diseases can depend on random events. In a small population especially, stochasticity is expected to play a significant role in epidemic dynamics, especially when the number of infected hosts is low and epidemic fade-out is likely to happen (Isham, 2004).

Most previous models on the emergence of antiviral drug resistance focus on dynamics in a single population in isolation from other populations, however, there are conditions under which decisions about antiviral drug use in one population can affect other populations, which calls for the use of tools like game theory. Game theory is the study of decision-making where players make choices that affect the outcomes (payoffs) for other players—the formalization of strategic interactions in a group (Osborne, 2004). The Prisoner's Dilemma, for instance, is a two player game in which each player can choose between two strategies, either cooperate or defect. Each player earns a high payoff r when both cooperate, but if only one of them cooperates, the one who defects will gain a very high payoff t while the cooperator will get a very low payoff s. If both defect, both receive moderate payoff u (where $t > r > u > s$). It can be shown that both players would be better off if they cooperated (since $r > u$) but what actually happens is that both players, if thinking strategically, will defect (since $t > r$). As a result, a situation where both players defect is the Nash equilibrium—the expected outcome of the game. This game captures the clash between individually optimal versus socially optimal actions. In the case of antiviral drug use during a pandemic, there may be strategic aspects of antiviral drug use decisions of multiple populations connected through travel. For instance, consider two populations connected through travel, where a decision-maker in each population must decide how antiviral drugs will be distributed in their population. Under certain epidemiological circumstances, it may make sense for the two populations to cooperate (in the sense of the Prisoner's Dilemma) with one another by both treating their infected individuals at a low level and thereby avoiding emergence of drug resistance. However, one population may defect by adopting a higher treatment level, thereby increasing the chance that a drug resistant strain is created and spread to the other population. The incentive for this strategy is the reduction in the final size of the epidemic. However, defection is available to both populations, and thus both have the incentive to defect by treating at a high level. If a drug resistant influenza strain is as transmissible as the non-