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Dynamics and Optimal Control of a Size-Structured Influenza Model Linking Within-Host and Between-Host

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Dedicated to Prof. Ma Zhien on the occasion of his 90th birthday, with deep gratitude for his contributions to research and for his encouragement to the younger generation.

Abstract. Multi-scale models improve the prediction of key epidemic factors and disease prevalence by capturing the interaction between individual immune responses and the spread of diseases among the population, helping to implement targeted control strategies for disease management. In this paper, we develop a novel size-structured influenza model based on the nested rules, aiming to explore how the replication of influenza virus affects its transmission at a population level. We calculate the basic reproduction numbers separately at the individual and population levels and rigorously prove the conditions under which the feasible equilibrium exists and is stable. Then, by evaluating the effectiveness of four measures consisting of individual antiviral treatment and population vaccination, we can determine an optimal treatment to minimize both the influenza cases and the total expenditure on influenza prevention. Numerical results reveal the complex interactions between the two interventions and the progression of the epidemic.

AMS subject classifications: 92D30, 92D25
Key words: Multi-scale influenza model, size-structure, optimal control, cost-effectiveness.

1 Introduction

Influenza is a kind of respiratory infectious disease. According to the different core protein types of the virus, it is classified into four types (A, B, C, and D). Among these, influenza A viruses (IAVs) transmit through droplets and aerosols, adhering to the ep-

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ithelial cells of an individual's respiratory tract, proliferating and causing influenza. This can lead to pneumonia and potentially trigger other complications in patients [7]. During the 1918-1919 influenza pandemic, approximately a third of people were infected, which resulted in an estimated 100 million deaths worldwide [38]. To date, more than 15 million cases of respiratory tract infectious have been reported, resulting in approximately 200,000 hospitalizations attributed to IAVs [27]. Since the three globally well-known influenza pandemics in the 20th century, influenza has remained a major threat to global public health and economic development, despite the advances in medicine [20, 24, 35].

Within a host, the immune response is vital for limiting IAV propagation and mitigating the impact of influenza. Actually, IAV infection is usually self-limited due to the interaction between IAV replication and adaptive immunity [40]. The hemagglutinin (HA) of IAVs binds to receptors on the surface of a host cell, promoting endocytosis and the fusion of the virion with epithelial cells [34]. This process activates the host immune response and eliminates the infected epithelial cells. At the beginning of infection, the host immune system initiates an innate immune response. Natural killer cells (NK) and type I interferon (IFN)-I help resist viral invasion by promoting phagocytosis and clearance of IAV [2, 43]. Meanwhile, adaptive immune response is stimulated accordingly. $CD8^+$T cells (CTLs) initiate immune effects by recognizing and binding to viral antigens. Activated CTLs proliferate and differentiate into effector cells, which are capable of eliminating infected cells and clearing IAVs by releasing cytotoxic substances [37]. In the initial phase of infection with IAV in humans and animals, the viral load typically increases sharply within the first 1-2 days and subsequently reaches a peak. Although the severity of the illness may not be directly linked to the level of the virus loads or particular immune factors [14], a higher viral load can still impact how the disease evolves [5]. Comprehending the relationships among viral load, immune response, and progression of disease are significant for predicting health conditions of patients and implementing corresponding measures [30].

During an infectious process, when the virus invades the human body, there occurs an interaction between the evolution of the virus within a host and the dynamics of transmission among individuals. The immune-pathogen interactions within an individual are investigated by the within-host model, while disease transmission and strategies for its control are addressed by the between-host model. To build a bridge between the two scales, Gilchrist and Sasaki were the first to propose the multi-scale models, which have since been widely applied in the dynamic analysis of various chronic diseases [13], such as HIV [11], Cholera [29], Influenza [17, 28] and others [16, 21]. The main linking mechanism for within-host to between-host model is transmission rate, while the linking mechanisms for between-host to within-host model are pathogen loads and growth rates [8]. For parasitic infection models, the coupled models can help to determine critical conditions that lead to a rise in parasite within a host and provide strategic guidance for disease prevention and control [6]. Under such circumstances where predators are present or there is a competition among populations, the probable characteristics of diseases and their main roles in the dynamics of predator-prey were studied in [3]. The relationship