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Constrained optimal control applied to vaccination for influenza

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ABSTRACT

The efficient time schedule and prioritization of vaccine supplies are important in mitigating impact of an influenza pandemic. In practice, there are restrictions associated with limited vaccination coverage and the maximum daily vaccine administration. We extend previous work on optimal control for influenza to reflect these realistic restrictions using mixed constraints on state and control variables. An optimal control problem is formulated with the aim of minimizing the number of infected individuals while considering intervention costs. Time-dependent vaccination is computed and analysed using a model incorporating heterogeneity in population structure under different settings of transmissibility levels, vaccine coverages, and time delays.

1. Introduction

An epidemic outbreak causes a crisis in public health accompanying social fear as well as a direct loss due to the disease. In developing a response plan to minimize socio-economic losses in disease outbreak, it is important to predict the transmission dynamics of an infectious disease, to compare the effects of different control strategies, and to design the best strategy. The World Health Organization(WHO) issued warning of pandemic influenza and encouraged to prepare countermeasures in 1999, but it did not draw much attention until the emergence of Severe Acute Respiratory Syndrome(SARS) in 2002–2003. Since the first SARS case was reported from Canton, China on December 2002, more than 31 countries worldwide reported 7956 confirmed cases including 666 fatal cases to the WHO by the end of 21 May, 2003. The SARS aroused great interest in the use of mathematical models to predict the course of the epidemic and to evaluate various management strategies [1]. This interest triggered studies for investigating the dynamics and control of infectious diseases and has been reinforced by the treatment of a pandemic including the influenza A(H1N1) 2009 [2].

Vaccination is the principal control measure for reducing the spread of many infectious diseases. The optimization of vaccination policies before their implementation is essential to better allocate resources and to minimize disease burdens. Recent advances have been made in optimizing vaccine distribution policies in specific settings [3–5]. Several studies have applied optimal control techniques to determine immunization strategies [6,7]. However, it is still complicated and controversial to address the best possible strategies because the dynamics of epidemics and the optimal use of vaccines depend on various factors including the structure of the population, vaccine availability, and transmissibility levels. In this context, we take into account of the size and heterogeneous dynamics of groups, different transmission levels, the total and daily maximum amount of vaccines available, and time delays in vaccine implementation.

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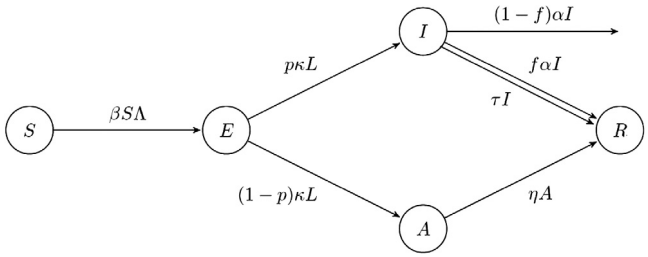

Fig. 1. Flow chart for the SEIAR model.

In this paper, we seek optimal time-dependent vaccination strategies within the vaccine availability. We begin by introducing a deterministic, compartmental model of influenza transmission incorporating the structure of the population with different dynamics. We then present the formulation of the optimal control problem to minimize the incidence while satisfying the constraints of the total and daily maximum amount of vaccines available. We use the penalty method to approximate this constrained optimization problem and derive an optimality system that characterizes the optimal control. Finally, we present the results of numerical simulations under various settings and conclude with a summary.

2. Mathematical models

The influenza model, SEIAR, is an extension of the standard SEIR model incorporating asymptomatic compartment [8]. In the SEIAR model, infected individuals in the exposed stage can either develop symptoms and move to an infective stage or develop no symptoms and move to an asymptomatic infective stage. This baseline model is modified to include control measures of vaccination and antiviral treatment. The nonlinear system of ODEs describing the influenza dynamics is given by

$$\begin{aligned} S'(t) &= -\beta S(t)\Lambda(t) - \psi\nu(t)S(t) \\ E'(t) &= \beta S(t)\Lambda(t) - \kappa E(t) \\ I'(t) &= p\kappa E(t) - \alpha I(t) - \tau I(t) \\ A'(t) &= (1-p)\kappa E(t) - \eta A(t) \\ R'(t) &= f\alpha I(t) + \tau I(t) + \eta A(t) + \psi\nu(t)S(t), \end{aligned} \tag{2.1}$$

with $\Lambda(t) = \epsilon E(t) + (1-q)I(t) + \delta A(t)$ and the initial conditions

$$S(0) = S_0, \qquad E(0) = E_0, \qquad I(0) = I_0, \qquad A(0) = A_0, \qquad R(0) = R_0.$$

Fig. 1 shows a flow diagram for model (2.1).

The model classifies individuals into five key compartments of susceptible (S), exposed (E), symptomatic infective (I), asymptomatic infective (A) and removed (R). The number of contact events sufficient for transmitting an infection is βN by mass action incidence, where N is the total population size. A fraction p of individuals in the exposed stage proceeds to the infective stage at the rate κ and the remainder goes to the asymptomatic infective stage also at the rate κ. Exposed individuals are assumed to reduce infectivity by a factor of ϵ, with $0 \le \epsilon \le 1$. The compartment E represents the latent stage when $\epsilon = 0$ and the initial asymptomatic and mildly infectious stage when $\epsilon > 0$. Infective members leave the compartment at the rate α with a fraction f recovering from the disease, whereas the rest dying of infection. On average infective individuals have their contact rate reduced by a factor of q. Asymptomatic members have their infectivity reduced by a factor of δ, with $0 \le \delta \le 1$, and progress to the removed compartment at the rate η. The time dependent control function $\nu(t)$ measures the rate at which susceptible individuals are vaccinated with vaccine efficacy ψ and the infective individuals are treated at the rate τ during the epidemic period.

In developing response plans for disease outbreaks, one seeks strategies that can minimize the incidence and/or disease related mortality while considering the cost of intervention strategies. The goal is to minimize the number of people who become infected at a minimal efforts of vaccination. Thus, the objective functional is given by

$$J(\nu) = \int_0^T PI(t) + Q\nu^2(t)dt.$$

In general, vaccination coverage and the maximum daily vaccine administration are limited during an epidemic. In our optimal control formulation, realistic restrictions associated with vaccination are incorporated using state variable inequality constraints. This can be stated

$$\begin{aligned} &0 \le \nu(t) \le 1 \\ &\nu(t)S(t) \le \nu_{max} \\ &\int_0^T \nu(t)S(t)dt \le \nu_{total}, \end{aligned} \tag{2.2}$$