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An age-structured model for cholera control with vaccination[☆]

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A R T I C L E I N F O

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A B S T R A C T

We formulate an age-structured cholera model with four partial differential equations describing the transmission dynamics of human hosts and one ordinary differential equation representing the bacterial evolution in the environment. We conduct rigorous analysis on the trivial (disease-free) and non-trivial (endemic) equilibria of the system, and establish their existence, uniqueness, and stability where possible. Meanwhile, we perform an optimal control study for the age-structured model and seek effective vaccination strategies that best balance the outcome of vaccination in reducing cholera infection and the associated costs. Our modeling, analysis and simulation emphasize the complex interplay among the environmental pathogen, the human hosts with explicit age structure, and the age-dependent vaccination as a disease control measure.

1. Introduction

Although regarded as one of the oldest known diseases, cholera remains a serious public health burden in those regions where poverty and poor sanitation are prevalent. The causing agent for cholera is the bacterium *Vibrio cholerae*, which is typically transmitted to human hosts through ingesting contaminated water and food [31]. The main symptom of cholera infection is profuse watery diarrhea that can lead to dehydration, drop in blood pressure, kidney failure, and possible death within days if not promptly treated. In recent years, a number of cholera outbreaks have taken place in Africa, South Asia, and South America, with annually 3–5 million cases of infection estimated by the World Health Organization (WHO) [41].

Current intervention methods for cholera include antibiotics, rehydration therapy, vaccination, and water sanitation. Antibiotic treatment for cholera is credited for saving a large number of lives, though the administration of antibiotics can quickly lead to bacterial resistance [26]. Oral rehydration using salt water, while unable to prevent cholera infection, is extremely effective for preventing death. Water sanitation, as well as improvement of infrastructure for water and hygiene, are ultimately the most useful means to combat cholera, but such control measures could be highly expensive, time consuming, and may not be available in an emergency setting of cholera outbreak. Vaccination has long been regarded as a cost-effective approach for cholera prevention, and has recently renewed interest for use in the course of a cholera epidemic [22]. In particular, WHO conditionally recommended the deployment of cholera vaccines in cholera emergency settings [43]. In Haiti, cholera vaccines were used with success during the recent cholera outbreak after a major earthquake in 2010 [33].

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There are, however, many important questions that remain to be answered in the design of control strategies against cholera [18]. For example, what would be the most effective means to reduce the morbidity and mortality, and what would be the optimal balance between the effects and costs of the control measures? In particular, recent studies [25,31] have shown that the susceptibility, disease risk and severity, and transmission of cholera among human hosts vary significantly by ages. As an example, it has been observed that while young children and some older people are most vulnerable to cholera, newborns seem to be protected against the infection from maternally derived immunity and the antibodies in breast milk [17]. Consequently, a concern of public health administration is whether age-based vaccination protocols can effectively reduce the infection and slow the spread of cholera, while limiting the costs of the control. To address the issue, we need a deep understanding of cholera dynamics, especially the details of age-structured transmission pattern.

Mathematical modeling, analysis, and simulation for infectious diseases have long provided useful insight toward better understanding of disease mechanisms and more effective prevention and control of disease outbreaks. Particularly, a large number of mathematical studies have been devoted to cholera (see, e.g., [2,5,8,9,14,20,23,28–30,36–40]). Among these, however, very few are concerned with age-structured dynamics of cholera. Alexanderian et al. proposed a model to investigate the impact of ages on the spread of cholera epidemics [1]. Brauer et al. analyzed an age-of-infection cholera model which includes both the infection age of human hosts and the biological age of pathogen [4]. Recently, Fister et al. formulated an age-structured model [15] that incorporates the effect of vaccination, with a distinction between symptomatic and asymptomatic infections among human hosts. Despite these efforts, detailed analysis of age-structured cholera dynamics has not been conducted, partly due to the complexity of the mathematical models.

The main objectives of this paper are to improve our present knowledge in cholera dynamics related to age structures, to mathematically clarify the concern in the design of age-based vaccination protocols, and to explore optimal vaccination strategies for cholera. To that end, we propose an age-structured cholera model that consists of four partial differential equations (PDEs) and one ordinary differential equation (ODE). We then conduct rigorous analysis on the equilibria of the system, including both trivial (disease-free) and non-trivial (endemic) equilibria, and establish their existence, uniqueness, and stability wherever possible. We next perform an optimal control study for the age-structured model and seek an optimal balance between the outcome of vaccination and the associated costs.

The remainder of this paper is organized as follows. In Section 2, we present our age-structured model as a mixed PDE–ODE system, with necessary notations and assumptions. In Section 3, we conduct a careful analysis for the disease-free (or, infection-free) equilibrium, and prove its existence, uniqueness, and local and global stabilities. Furthermore, we establish the existence and uniqueness of the endemic equilibrium. In Section 4, we construct and analyze an age-based optimal control model in terms of vaccination. We conduct extensive numerical simulations for the optimal vaccination solutions under different scenarios. Finally, we conclude the paper with some discussion in Section 5.

2. Formulation of the model

As a start, we develop a PDE–ODE coupled system to describe the age-dependent cholera dynamics. We assume that the total human population is divided into four classes: susceptible, infected, vaccinated, and recovered. Let $S(t, a), I(t, a), V(t, a), R(t, a)$ denote, respectively, the age-densities of the susceptible, infected, vaccinated, and recovered parts of the human population, where a denotes age and time t denotes time. Let $B(t)$ be the concentration of vibrios in the contaminated environment at time t. We employ a saturation incidence [9,32] in the form of $\beta(a)\frac{B(t)}{B(t)+\kappa}$ to model the force of infection from the environment, where κ is the half saturation concentration of environmental vibrio.

Transmission of cholera usually stems from the waterborne bacteria *Vibrio cholerae*, and therefore the infection occurs as a result of an effective contact between a susceptible individual and the pathogenic vibrios, reflected by the contact rate $\beta(a)$. It is well known that improvements in water supply, sanitation, food safety and community awareness of disease risks are the best means of preventing cholera. In addition, WHO [41] has suggested that oral cholera vaccines with demonstrated safety and effectiveness have recently become available. The deployment of cholera vaccines, through immunizing populations at higher risk of infection, provides an effective tool to complement those traditional measures against cholera outbreaks. Thus, we further assume that susceptible individuals are vaccinated at an age-specific rate $\psi(a)$, with a vaccine efficacy $1-\sigma$ (where $\sigma \in (0, 1]$). Infected individuals are treated and subsequently enter the recovered class at a rate $\gamma(a)$. $\mu(a)$ is the natural mortality rate of human population. Infected individuals contribute to vibrios in the aquatic environment at an age-dependent rate $\alpha(a)$ and vibrios have a reduction rate μ_b, which includes the natural death and other means of the removal of the pathogen in the environment. Since the case fatality rates for cholera generally are very low (at or below 1%) [42], we assume that the cholera-induced mortality can be neglected in this study. All these parameters take positive values. The variables, parameters and their biological interpretations are given in Table 1 and a flow diagram of the model is depicted in Fig. 1.

Based on these assumptions, the dynamics of the disease transmission are described by the following equations:

$$\frac{\partial S(t,a)}{\partial t} + \frac{\partial S(t,a)}{\partial a} = -\beta(a)\frac{B(t)}{B(t)+\kappa}S(t,a) - (\psi(a)+\mu(a))S(t,a),$$
$$\frac{\partial I(t,a)}{\partial t} + \frac{\partial I(t,a)}{\partial a} = \beta(a)\frac{B(t)}{B(t)+\kappa}(S(t,a)+\sigma V(t,a)) - (\gamma(a)+\mu(a))I(t,a),$$