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Optimized oral cholera vaccine distribution strategies to minimize disease incidence: A mixed integer programming model and analysis of a Bangladesh scenario

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ABSTRACT

In addition to improved sanitation, hygiene, and better access to safe water, oral cholera vaccines can help to control the spread of cholera in the short term. However, there is currently no systematic method for determining the best allocation of oral cholera vaccines to minimize disease incidence in a population where the disease is endemic and resources are limited. We present a mathematical model for optimally allocating vaccines in a region under varying levels of demographic and incidence data availability. The model addresses the questions of *where, when, and how many doses of vaccines* to send. Considering vaccine efficacies (which may vary based on age and the number of years since vaccination), we analyze distribution strategies which allocate vaccines over multiple years. Results indicate that, given appropriate surveillance data, targeting age groups and regions with the highest disease incidence should be the first priority, followed by other groups primarily in order of disease incidence, as this approach is the most life-saving and cost-effective. A lack of detailed incidence data results in distribution strategies which are not cost-effective and can lead to thousands more deaths from the disease. The mathematical model allows for what-if analysis for various vaccine distribution strategies by providing the ability to easily vary parameters such as numbers and sizes of regions and age groups, risk levels, vaccine price, vaccine efficacy, production capacity and budget.

1. Introduction

According to the World Health Organization (WHO), there are approximately 1.4–4.3 million cases of cholera globally per year, leading to 28,000–142,000 deaths [1]. Caused by consumption of *Vibrio cholerae* contaminated food and water, cholera is an acute infection of the intestines which can lead to severe dehydration and death without prompt treatment [2]. Improved water, sanitation and hygiene (WASH) strategies provide a long-term solution in areas where the disease is highly prevalent. However, the necessary infrastructure developments to achieve this are costly and time-consuming [3], and the impact of such improvements may not be immediate in areas where poor sanitation practices are longstanding and culturally acceptable [4]. WASH strategies alone may be insufficient during outbreaks [5]. Vaccination with an oral cholera vaccine (OCV) can help control the spread of a cholera outbreak in the short term, while investments continue into infrastructure and WASH strategies [3].

Researchers have analyzed the impact of vaccination on cholera outbreaks in various countries/regions including Micronesia [6], Zimbabwe [7], Haiti [8], Bangladesh [9], and Guinea [10]. A cholera vaccination program could significantly reduce disease burden and be cost effective [11]. Instituting a mass vaccination campaign requires significant planning and investment, but researchers have found OCV mass vaccination campaigns to be feasible in Mozambique [12,13], Bangladesh [14], Haiti [15,16] and India [17]. Other studies have estimated disease incidence and the impact of long-term vaccination interventions [18]. A global OCV stockpile of 10 million doses by 2017 could support such vaccination campaigns in response to cholera outbreaks [19]. The GAVI vaccine alliance has committed financial resources with the goal of increasing the stockpile to 20 million doses by 2020 [20].

The country of Bangladesh is taking steps to become the first country to incorporate a cholera vaccine into a large-scale public-sector vaccination program [21]. Previous research on

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Table 1
The 2009 population and base incidence rate for cholera in Bangladesh by age group and region [28].

	Age group	Initial population	Base incidence rate
High risk regions	1–4 years	6,693,295	0.0110
	5–14 years	17,710,265	0.0035
	>15 years	58,387,318	0.0017
Medium risk regions	1–4 years	1,503,070	0.0073
	5–14 years	3,977,080	0.0023
	>15 years	13,111,664	0.0011
Low risk regions	1–4 years	4,833,634	0.0037
	5–14 years	12,789,655	0.0012
	>15 years	42,165,018	0.0006

Bangladesh has investigated the cost of illness from cholera [22,23] the cost–effectiveness of OCV vaccination [24–26], and the cost–effectiveness of different strategies for mass vaccination [27–29].

Whether during an outbreak or in a population where the disease is endemic, the goal of a vaccination campaign is to reduce the impact of a disease by minimizing the number of cases and deaths that occur. However, there is currently no systematic method for determining the best OCV distribution strategy under limited resources. Previous research that attempted to answer the questions of where, when, and in what amounts to send vaccines considered a time horizon of 6 months or less [30,31], did not differentiate target populations by age, and assumed that vaccine efficacies remain the same during the three years following vaccination. We present a mathematical model which provides an efficient and effective method for projecting the best OCV distribution strategy to minimize cases (and deaths) over a multi-year period while considering target populations differentiated by age and vaccine efficacies up to five years.

2. Methods

We developed a mixed integer programming model (OCV-MIP) for determining the optimal distribution of OCVs to minimize cases (and deaths). A mixed integer programming model is a system of equations and inequalities containing an objective function and constraints [32]. We apply this model to Bangladesh and compare distribution strategies resulting from different levels of demographic information under fixed or varying vaccine efficacies by age group and year. We determine the optimal allocation of vaccines to minimize the number of cases of cholera over an eight year period, and compare the numbers of expected cases avoided for each strategy given varying levels of vaccine supply. We consider vaccine allocations which allow for partial vaccination in an extended model and analyze the impact of single dose efficacy assumptions.

We perform a cost–effectiveness analysis and determine the vaccine price thresholds where each strategy becomes cost-effective. We consider varying case fatality rates, and also investigate the benefits of investing for fewer than eight years. Finally, we examine the cost–effectiveness of a more targeted approach to vaccination.

2.1. Case study: Bangladesh

The Bangladesh parameters used in our analysis are provided by the International Vaccine Institute based on observed data from a 2009 study [28] (Table 1). These include initial population size and cholera incidence by age group and region. Regions are divided into high risk, medium risk, and low risk, with age groups of 1–4 years, 5–14 years, and 15+ years. We do not consider children younger than age 1 in our analysis because they are not eligible for vaccination, though this group has the highest disease incidence with approximately 28,000 cases annually. Thanks to herd immunity, vaccinating others might decrease the incidence rate and deaths for this age group as well, but this possibility is not included in the calculations. As reported in Table 1, the highest incidence rates occur among younger populations. We assume a birth rate of 20/1000 and death rate of 6/1000 [33,34] (see 8-year population growth projection in Appendix).

2.2. Oral cholera vaccine – Shanchol

We consider the OCV Shanchol, which was prequalified by the WHO in 2011 [35] and is approved for all age groups older than 1 year old. Multiple studies have investigated the efficacy of two doses of Shanchol [36–39]. Bhattacharya et al. [40] estimate a 65% cumulative protective efficacy over 5 years from two doses of Shanchol, and we use this estimate in our initial analysis. The authors also report protective efficacies over 5 years by age group and year since vaccination. We analyze the impact of these reported efficacies on the recommended vaccine allocation (results provided in Appendix).

Shanchol is easier to administer than Dukoral (the other licensed and commercially available OCV) as it does not require a buffer solution and provides a greater protective efficacy especially for children younger than 5 years [19,38]. Shanchol costs $1.85 vs. $5.25 per dose for Dukoral [41]. A mass vaccination campaign in Bangladesh with the OCV Shanchol was completed in 2011, with high coverage and acceptance and few adverse events [42]. Other trials have shown that the vaccine is safe and immunogenic [43,44], with greater immunogenicity in children ages 1–17 than for adults [45] though this does not necessarily translate into increased protective efficacy for this group.

3. Mixed integer programming model

In creating a mathematical model (OCV-MIP) for determining the best OCV distribution strategy, the goal is to determine the number of persons in each age group and region to vaccinate each year. We initially assume that each vaccinated person receives two doses in the same year, and at the beginning of the respective year implying that 1st year vaccine efficacies are valid the entire year. We assume that vaccinated persons are not vaccinated again within five years. The total cost per vaccinated person is assumed to be $4 ($2/dose). $2 per dose assumes $1.45 vaccine cost (2018 estimate [28]), a cost of $.25 for customs, insurance and freight (CIF) and $.30 for delivery. The case fatality rate was estimated as 1.5% based on a 2009 study in Bangladesh [28], but could be much lower thanks to improving healthcare infrastructure. We test a range of case fatality rates (from 0.5% to 1.5%). We initially assume a fixed vaccine protective efficacy of 65% each year following vaccination, up to five years, and 0% vaccine efficacy in all subsequent years [40], and then we investigate the impact of varying efficacies by age and year since vaccination (results provided in Appendix). The complete model formulation of OCV-MIP can be found in Appendix.

4. Results

4.1. Allocation strategies

We used OCV-MIP to compare distribution strategies resulting from considering groups differentiated by (i) age, (ii) region, and (iii) age and region. As a baseline for comparison, we estimate the number of potential cases if there is no vaccine intervention. The number of cases avoided over an eight year period by the different vaccination strategies is reported in Fig. 1 (we assume that in the

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