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Impact of oral cholera vaccines in cholera-endemic countries: A mathematical modeling study

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ABSTRACT

Background: Impact evaluation of vaccination programs is necessary for making decisions to introduce oral cholera vaccines (OCVs) in cholera-endemic countries.
Methods: We analyzed data to forecast the future global burden of cholera. We developed a mathematical model of cholera transmission in three countries as examples: Nigeria, Uganda, and Indonesia. After fitting the model, we evaluated the impact of OCVs delivered in four vaccination strategies varying by target age group and frequency of vaccination over the period of 2015–2030.
Results: Data suggest that the global annual incidence of cholera will increase from 3 046 238 in 2015 to 3 787 385 in 2030 with the highest burden in Asia and Africa where overall population size is large and the proportion of population with access to improved sanitation facilities is low. We estimate that OCV will reduce the cumulative incidence of cholera by half in Indonesia and >80% in Nigeria and Uganda when delivered to 1+ year olds every three years at a coverage rate of 50%, although cholera may persist through higher coverage rates (i.e., >90%). The proportion of person-to-person transmission compared to water-to-person transmission is positively correlated with higher vaccination impact in all three countries.
Conclusions: Periodic OCV vaccination every three or five years can significantly reduce the global burden of cholera although cholera may persist even with high OCV coverage. Vaccination impact will likely vary depending on local epidemiological conditions including age distribution of cases and relative contribution of different transmission routes.

1. Introduction

Cholera is a serious public health problem in developing countries. One recent study estimates there are 1.3–4.0 million cholera cases and 21 000–143 000 deaths per year [1]. As of 2012, there are 69 cholera-endemic countries with annual cholera incidences ranging from 10 to 2600 cases per 10 000 persons. In addition to being endemic to many countries, cholera can cause epidemics in populations with little or no natural immunity, often following natural disasters during which the quality of water and sanitation can be compromised. The cholera epidemic in Haiti following the catastrophic earthquake in 2010 provides a pertinent example, where 745 588 cases and 8972 deaths were reported to Ministry of Health as of 10 August 2015 [2].

Because the etiological agent, *Vibrio cholerae*, is transmitted via the fecal oral route, improving water, sanitation, and hygiene (WASH) is the cornerstone of a cholera control strategy [3]. However, improving WASH in low income countries requires sustained health effort and financial resources over many years, while oral cholera vaccines (OCVs) can produce an immediate impact for residents residing in endemic or epidemic areas [4–6]. Two OCVs that contain killed cholera *Vibrio* whole cells have been prequalified by WHO and are available for purchase by United Nations (UN) agencies [7]. WHO recommends periodic mass vaccination campaigns of OCVs targeted to preschool- and school-aged children in endemic areas with a pre-emptive and reactive vaccination strategies for epidemics [7].

However, OCVs have seldom been used for the control of cholera in either endemic or outbreak situations [3] and policy makers will likely require evidence of the feasibility and impact of vaccination programs before OCVs are widely used. Mass oral cholera vaccinations have been shown to be feasible in developing country settings including a Sudanese refugee camp in Uganda [8], South Sudan [9], during an outbreak in Guinea [10–12], and endemic

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areas in Haiti, Bangladesh, and India [5,13–16]. OCV vaccinations were shown to be successful at reducing cholera incidence during outbreak in Vietnam [17] and Zanzibar [18], and also in a cholera-endemic population in India [4,19,20], Bangladesh [5], and Haiti [6].

In addition, modeling studies have demonstrated hypothetical benefits of OCV vaccination in simulated epidemics in Haiti [13,21–23], Zimbabwe [24], and Bangladesh [25–27]. These studies provide insights into the impact of control measures in a relatively small area or over a short period. However, knowledge on the long-term impact of large-scale (e.g., national) vaccination programs would still be necessary to plan a large-scale introduction of the vaccine, which, for example, international organizations such as Gavi, the Vaccine Alliance can initiate. In this paper, we provide some possible estimates for the future global burden of cholera and the impact of OCV at the national level over the period of 2015–2030. We use mathematical models of cholera transmission to evaluate the impacts of OCV vaccination strategies in three example countries in Africa and Asia with high cholera burden. Vaccination strategies explored are similar to what Gavi explored in their vaccine investment strategy: vaccination of children aged 1–14 years or persons aged 1+ year and above every three or five years [28].

2. Methods

2.1. The current and future global burden of cholera

One study estimates cholera causes 1.3–4.0 million cases including 21 000–143 000 deaths per year as of 2012 [1]. The authors identified 69 cholera-endemic countries and categorized them into nine regions based on WHO region and mortality stratum: AFR-D, AFR-E, AMR-B, AMR-D, EMR-D, EUR-B, SEAR-B, SEAR-D, and WPR-B. They then estimated the cholera burden for each region.

A more detailed explanation appears in the Supplementary Material S0. These estimates are much higher than the number of cases reported to WHO, which varies from 190 130 to 589 854 by year from 2008 to 2012 [29–33]. WHO acknowledges that many cholera cases are not recorded because of limited surveillance and fear of trade and travel sanctions [34]. We therefore base the current global burden of cholera on these estimates.

To estimate the future burden, we assumed per capita cholera incidence will be stable in cholera-endemic countries. However, cholera incidence at the country level will change as do the population size and the proportion of population with access to improved sanitation facilities, without which people will be at risk of cholera in cholera-endemic countries. We estimated the proportion of the population at risk of cholera after 2015 by fitting a saturating exponential function to the data on the population with access to improved sanitation facilities (see Supplementary Material S1 for details) [35]. By multiplying these estimated proportions with the UN projected population size (medium variant) [36], we calculated the expected size of the population at risk of cholera. We then calculated burden of cholera by multiplying the expected size of the population at risk of cholera with incidence per capita per year estimates, as is done in the previous study [1].

2.2. The mathematical model of cholera transmission

The model tracks the size of the population uniquely characterized by a combination of infection status (i.e., susceptible, exposed, infectious, or recovered) and age (<1, 1–4, 5–14, or 15+ year olds). The model also tracks the concentration of vibrio cholera in the water to simulate the transmission via vibrio cholera in the water in addition to person-to-person transmission.

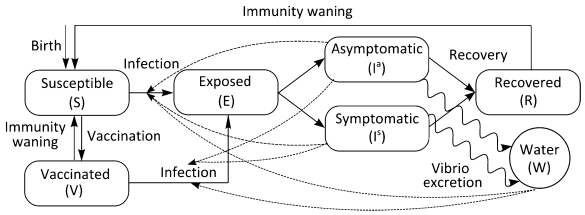

Fig. 1. Schematic for the flow of people across disease and vaccination status. Newly infected people undergo exposed (not infectious) and either asymptomatic or symptomatic states, and then recover. Susceptible people may receive vaccine and are partially protected from infection. Vaccine-induced and naturally acquired immunities decay over time. Death occurs in each subpopulation, but is omitted in the figure for simplicity. Susceptible or vaccinated individuals may be infected by infectious (symptomatic or asymptomatic) individuals or through vibrio in the water (shown as dashed lines).

Fig. 1 shows a schematic of the model, omitting age groups for simplicity. The model is formulated by a system of ordinary differential equations (see Supplementary Material S2), with parameters shown in Table 1. The rate of new infections by person-to-person transmission is determined by the product of the size of the susceptible population, the proportion of the infectious population, and transmission rate per unit time, β^I. Rate of new infections via water-to-person route is determined according to Holling type II functional response with another transmission rate parameter, β^W [37]. Transmission rates can have seasonality, which is modeled using a sine function (see Supplementary Material S2). Infected people acquire temporary immunity after recovery, as do vaccine recipients after receiving two doses of OCVs.

We assess dynamics of cholera transmission and the impact of vaccination programs under a broad range of parameter values to address their uncertainties (Table 1). Using Latin hypercube sampling, we generated 200 samples, which we assume is large enough to cover the parameter space adequately, for each of 10 parameters related to natural history of infection (δ, η, ε, γ, and ω) and the biology of the vibrio cholera (μ^B, σ, κ, ϕ, and τ), where parameter values are based on previous studies and our best guesses [20,25,26,30,38–43]. In addition, we set the ratio r of the person-to-person (β^I) to water-to-person (β^W) transmission rate at 100 000 as baseline. This is loosely based on the previous study, where parameter estimates imply the ratio is about 200 000 [26]. However, values of β^W and β^I will likely be unidentifiable from real data that always comes with noise [44]. We examine the ratio of β^I to β^W over a broad range (10–10^6). Our preliminary exploration of the model also showed that we can fit the model to data with either β^I or β^W alone using most parameters sets, and if we try to estimate both parameters simultaneously, the model is usually stuck in local minima, which limits our chance to explore different combinations of β^I and β^W. We implemented a system of differential equations in Java and integrated it using the 4th order Runge–Kutta method.

2.3. Model calibration

We simulate cholera transmission for three example countries with high, medium, and low cholera burden: Nigeria in AFR-D, Uganda in AFR-E, and Indonesia in SEAR-B. We calculated age-specific death rates by country from life expectancy at age 0, 1, 5, and 15 (see Supplementary Material S3), and then adjusted birth rates to match the size of the simulated population with the expected size of the population at risk of cholera. Then we calibrated the model again by adjusting four parameters, β^W (or β^I), χ_2, χ_3, and χ_4 such that the difference between the model and the data in incidence and age distribution of cholera cases is minimized (see Supplementary Material S3) [45–48]. Hereafter, we mention only β^W instead of "β^W (or β^I)" for simplicity, but β^I is also varied

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