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Cost-Effectiveness of New-Generation Oral Cholera Vaccines: A Multisite Analysis

Marc Jeuland, MSEE,[1] Joseph Cook, PhD,[2] Christine Poulos, PhD,[3] John Clemens, MD,[4] Dale Whittington, PhD,[1,5] DOMI Cholera Economics Study Group*

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]University of Washington, Seattle, WA, USA; [3]RTI International, Research Triangle Park, NC, USA; [4]International Vaccine Institute, Seoul, Korea; [5]Manchester Business School, Manchester, UK

ABSTRACT

Objectives: We evaluated the cost-effectiveness of a low-cost cholera vaccine licensed and used in Vietnam, using recently collected data from four developing countries where cholera is endemic. Our analysis incorporated new findings on vaccine herd protective effects.

Methods: Using data from Matlab, Bangladesh, Kolkata, India, North Jakarta, Indonesia, and Beira, Mozambique, we calculated the net public cost per disability-adjusted life year avoided for three immunization strategies: 1) school-based vaccination of children 5 to 14 years of age; 2) school-based vaccination of school children plus use of the schools to vaccinate children aged 1 to 4 years; and 3) community-based vaccination of persons aged 1 year and older.

Results: We determined cost-effectiveness when vaccine herd protection was or was not considered, and compared this with commonly accepted cutoffs of gross domestic product (GDP) per person to classify interventions as cost-effective or very-cost effective. Without including herd protective effects, deployment of this vaccine would be cost-effective only in school-based programs in Kolkata and Beira. In contrast, after considering vaccine herd protection, all three programs were judged very cost-effective in Kolkata and Beira. Because these cost-effectiveness calculations include herd protection, the results are dependent on assumed vaccination coverage rates.

Conclusions: Ignoring the indirect effects of cholera vaccination has led to underestimation of the cost-effectiveness of vaccination programs with oral cholera vaccines. Once these effects are included, use of the oral killed whole cell vaccine in programs to control endemic cholera meets the per capita GDP criterion in several developing country settings.

Keywords: Beira, cholera, cost-effectiveness, herd protection, Jakarta, Kolkata, Matlab, vaccines.

Introduction

Cholera is an infectious disease caused by exposure to the bacterium *Vibrio cholerae* O1 or O139, resulting in acute dehydration and sometimes death. In 2006, the World Health Organization (WHO) reported more than 236,000 cases worldwide and 6311 deaths, although these estimates are widely regarded as low due to underreporting [1]. The reemergence of cholera in parts of West Africa, and the continuing problem of cholera in East Africa and several parts of Asia have prompted increasing concern over vulnerability to infection of poor populations living in unsanitary conditions. Multilateral aid organizations such as the WHO have become interested in the potential of oral cholera vaccines for reducing such risks.

The conventional wisdom among public health experts is that prevention through improved sanitation and hygiene is the best method for controlling cholera. Unfortunately, this objective remains difficult to achieve in many locations, particularly in fast-expanding urban slums. Severe cholera is easily treatable with intravenous rehydration therapy if the patient is diagnosed promptly and has access to health care facilities, although recent cholera outbreaks in situations with inadequate health care have documented case fatality rates on the order of 20% and higher [2]. Another approach is to combine prevention and preparedness activities. This strategy might motivate more widespread use of newly developed oral cholera vaccines [3–10].

There are two internationally licensed oral cholera vaccines: the two-dose killed whole cell, recombinant B-subunit (WC/rBS) vaccine (Dukoral), produced by the Dutch company, Crucell (Leiden, The Netherlands); and the single-dose live attenuated CVD 103Hgr (Orochol), originally manufactured by Berna Biotech of Switzerland but no longer available. Both vaccines are used mainly by travelers from developed countries [3–8]. Field trials of WC/rBS vaccine in Bangladesh, Peru, and Mozambique indicated 80% protection for 6 months followed by declining effectiveness with time and a cumulative 50% protection for 3 years [4–6,8].

A modified version of the WC/rBS vaccine (containing only killed whole cells without the B subunit, also referred to as the WC vaccine) is produced in Vietnam and has been found to confer protection similar to WC/rBS [11]. Initial studies in Vietnam showed 66% effectiveness in the first year and 50% effectiveness over 3 to 5 years [9,10]. This vaccine has been modified to comply with WHO standards and is being evaluated in a large Phase III clinical trial in Kolkata, India [12]. It is anticipated that it will soon be manufactured by producers in India and other developing countries and will be available at a low price for public health programs in cholera-endemic countries.

Recent reanalyses of data from the Bangladesh trial have demonstrated that use of oral cholera vaccines conferred significant herd protection, through diminished risk of infection among nonvaccinees and enhanced protection of vaccinees who reside in

Address correspondence to: Marc Jeuland, Department of Environmental Sciences and Engineering, CB #7431, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. E-mail: jeuland@email.unc.edu
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*DOMI Cholera Economics Study Group: B. Maskery, MS, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; D. Lauria, PhD, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; J. Stewart, PhD, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; M. Lucas, MS, Ministry of Science and Technology, Maputo, Mozambique; Z. Islam, International Centre for Diarrheal Disease Research, Dhaka, Bangladesh; R. Malik, National Institute of Health Research and Development, Jakarta, Indonesia; M. Najib, National Institute of Health Research and Development, Jakarta, Indonesia; S. Chatterjee, National Institute of Cholera and Enteric Diseases, Kolkata, India.

vaccinated neighborhoods [13,14]. Such herd effects will increase the cost-effectiveness of vaccines.

The growing body of evidence from oral cholera vaccine interventions can be analyzed to assess the cost-effectiveness of cholera immunization strategies in different locations around the world. A number of studies have previously examined the cost-effectiveness of prevention and treatment of cholera. The Disease Control Priorities (DCP) Project recently published a review of published evidence that ranks cholera immunization for infants with WC/rBS vaccine among the least cost-effective interventions targeting diarrheal disease, with cost-effectiveness ratios of US$1402 to US$8357 per disability-adjusted life year (DALY) averted [11]. The ratio for cholera vaccines was lowest in Sub-Saharan Africa, but still exceeded $1500. Consistent with these results, Murray et al. [15] found that the same vaccine was less cost-effective (about $3000/DALY averted) for preventing cholera in endemic situations than several other control strategies, including cholera disease treatment ($10–160/DALY averted) and water and sanitation improvements such as improved water supply plus latrine construction ($430/DALY averted). Murray et al. also emphasize that the cost-effectiveness results for cholera vaccination are highly sensitive to the cost of the vaccine.

The present research, coordinated by the International Vaccine Institute through the Diseases of the Most Impoverished (DOMI) Program, improves the economic assessment of oral cholera vaccine programs by more carefully measuring the demand for vaccines and the economic costs of illness in three countries in Asia (Bangladesh, India, Indonesia) and one in Africa (Mozambique). The study combines these economic factors with site-specific epidemiological information to conduct the first multicountry cost-effectiveness analyses (CEA) of cholera vaccination options. This study is also the first CEA to include cholera vaccine herd protection and the first to consider the low-cost vaccine that can be produced in Asia today.

Methods

Study Sites

Our study sites were locations where the DOMI prospective disease surveillance and economic studies took place. In Bangladesh, the study was conducted in Matlab (pop. 220,000), a seasonally flood-prone rural area 50 km southeast of Dhaka. Research on endemic cholera is well established through the International Center for Diarrheal Disease Research—Bangladesh (ICDDR–B). Our cost-effectiveness model assumed that the entire area (roughly 180 km^2) could be targeted by a cholera immunization effort. In India, we analyzed the effects of vaccinating residents of Tiljala and Narkeldanga (combined pop. 185,000), two densely populated slums in Kolkata with high cholera incidence. The surveillance studies took place in Narkeldanga, while the economic demand studies were conducted in Tiljala. In Indonesia, we examined programs in the surveillance areas of Tanjung Priok and Koja (combined pop. 161,000), high-incidence districts of North Jakarta. For Beira (pop. 550,000), a city in Mozambique confronted with seasonal flooding and endemic cholera, we analyzed city-wide vaccination programs.

Analytical Approach

Our cost-effectiveness model closely follows the approach described in the DCP Project and WHO's CHOICE project [11,16]. We assumed a one-time vaccination program in which the WC vaccine was administered orally in two doses distributed at two-week intervals. Health outcomes were calculated for the duration of the vaccine's efficacy.

Our model considered three different age groups: 1) young children, aged 1 to 4 (children below the age of 1 cannot be vaccinated); 2) school-aged children, 5 to 14 years; and 3) adults, ages 15 years and older. These cohorts corresponded to logical vaccination program options in the study locations: school-based programs focused on children ages 5 to 14 (Option 1); programs for all eligible children (ages 1 to 14) held at school-based vaccination outposts, with young children being brought in by parents or siblings (Option 2); and community-based vaccination programs for all age groups held in clinics or other outposts (Option 3). We assumed for simplicity that coverage rates among school-aged children in Options 1 and 2 would be similar to coverage rates in Option 3, although we recognize that school-based vaccination may allow for higher coverage in this age group than community-based vaccination. However, many of our sites may also have low rates of school attendance.

Unlike the WHO CHOICE approach, we took a public sector financial perspective. The numerator of the cost-effectiveness ratio is net public cost: total vaccination costs less publicly-borne costs of illness (COI) prevented by vaccination (discounted using a 3% real rate).

Vaccine manufacturing and delivery costs were assumed to be borne by the public sector (either government or donors), and we assumed that no user fees were collected from vaccine recipients. The alternative CHOICE methodology would also include private COI as a cost offset for the vaccination program, but we note that this approach does not account for the private costs of vaccination (travel and queuing), which in some locations could outweigh private COI savings (Jeuland M, Lucas M, Clemens J, Whittington D, unpubl. data). Cost-effectiveness results from a social perspective, which would include these two elements of private costs, are presented in the journal's online supplementary materials.

The Cost-Effectiveness Calculations

We first assessed the baseline burden of cholera disease in terms of cases, deaths, and DALYs for each of i age groups over the t years of the program in the four study sites. DALYs incorporate both reductions in morbidity (years of life lost to disability, YLD) and mortality (years of life lost, YLL). We used uniform age weights that applied the same value to an extra year of life regardless of the age of the recipient. We also used country-specific life expectancies (LE) from WHO life tables (available at: http://www.who.int/whosis/database/life_tables/life_tables.cfm) to calculate the number of life years saved for each age group and derived discounted life years saved using a 3% real discount rate. To calculate the DALYs avoided under different program options, we applied Equations 1–4:

$$YLD\ avoided_{i,t} = \{[(1 - CFR_i) \cdot Eff_t \cdot Cover_i \cdot N_i \cdot I_i] \cdot Length \cdot DALY\ weight\} \quad (1)$$

$$YLL\ avoided_{i,t} = \{[(CFR_i \cdot Eff_t \cdot Cover_i \cdot N_i \cdot I_i)/0.03] \cdot [1 - \exp(-0.03 \cdot LE_i)]\} \quad (2)$$

$$DALYs\ avoided_{i,t} = YLL_{i,t}\ avoided + YLD_{i,t}\ avoided \quad (3)$$

$$Total\ DALYs\ avoided_i = \sum_{t=0}^{Dur} (DALYs\ avoided_{i,t}) / (1 + 0.03)^t \quad (4)$$

where Eff_t is the effectiveness of the vaccine in year t, $Cover_i$ is the percentage of age group i that would be vaccinated if the vaccine were provided for free, CFR_i, I_i and N_i are the case fatality rate,

cholera incidence and number of people in age group *i*, *Length* is the disease's average duration, and *Dur* is the vaccine duration.

We report commonly used thresholds for cost-effective interventions. These thresholds compare net public cost per DALY to per capita income in the countries of interest (obtained from the International Monetary Fund's World Economic Outlook, April 2007). A "very cost-effective" intervention has a cost-effectiveness ratio less than per capita GDP; a "cost-effective" intervention has a ratio less than three times per capita GDP. Falling below these thresholds, however, indicates nothing about the cost-effectiveness of cholera vaccination in comparison to other types of health interventions. Financial resources for health are extremely limited in settings such as these study sites, and other health interventions that also pass these thresholds may have more attractive ratios.

Base-Case and Sensitivity Analysis

The first step in our cost-effectiveness analysis was to calculate the cost-effectiveness ratios of the three program options for the "base-case" set of parameter values presented in Table 1. We did these calculations twice. First, we used the standard vaccine effectiveness commonly cited in the literature. Then, we developed a mathematical relationship to account for herd protection which relates "overall" effectiveness to coverage rates in the population, as described below. All other parameters were kept the same.

Next, we investigated the impact of uncertainty in model parameters on cost-effectiveness outcomes. We systematically varied individual parameters over the uncertainty ranges listed in Table 1 while keeping all other parameters at their base case values. We then constructed tornado diagrams to see which ones contributed the most to uncertainty in model outcomes. In the interest of space, we do not present the tornado diagrams for all sites, but rather consolidate these results into one table.

Herd Protection Assumptions

In their recent article detailing the benefits of herd protective effects of killed oral cholera vaccines in Matlab, Bangladesh, Ali et al. showed that cholera incidence in placebo recipients in the year following vaccination was highly dependent on vaccine coverage rates in their neighborhoods [13]. They also found that the cholera incidence in vaccine recipients varied inversely with vaccine coverage. Longini et al. [14] used these data to construct epidemiological models predicting vaccine effectiveness as a function of vaccine coverage.

To illustrate the implications of these findings, we conducted two parallel sets of CEAs, in which all parameters were kept the same except for vaccine effectiveness. We assumed that the population in each location is static and that baseline incidence is constant over the three years of the intervention. Calculations in the first analysis ignored herd protection effects. Protection afforded by the vaccine was assumed to be 60% for the first two

Table 1 Description of sites and model parameters, with uncertainty ranges in brackets*

Parameters	Matlab, Bangladesh	Kolkata, India†	N. Jakarta, Indonesia	Beira, Mozambique
Site-specific parameters				
Population	220,000	185,000	161,000	550,000
Description	Rural	2 poor urban slums	2 poor urban districts	Citywide, urban and semiurban
Age of surveillance	All ages	All ages	All ages	All ages ≥ 1 years
Dates of surveillance	1994–2003	May '03–Apr '05	Aug '01–Jul '03	Dec '03–Jan '04‡
High cost-effectiveness threshold: GDP/capita§ (2007 US$)	486	871	1,812	382
Incidence (cases/1,000)				
<1 years	4.6 [2.3–9.2]	7.2 [3.6–14.3]	4.0 [2.0–8.0]	N/A
1–4 years	3.8 [1.9–7.5]	7.0 [3.5–14.0]	1.5 [0.8–3.1]	8.8¶ [4.4–17.6]
5–14 years	1.6 [0.8–3.1]	2.2 [1.1–4.4]	0.3 [0.1–0.6]	2.9 [1.4–5.7]
15+ years	1.0 [0.5–2.1]	0.9 [0.5–1.8]	0.3 [0.1–0.5]	3.8 [1.9–7.7]
Public COI (2007 US$)				
Overall	19 [10–38]	18 [9–36]	25 [13–52]	28 [14–56]
1–4 years	20 [10–40]	15 [8–30]	26 [13–52]	26 [13–52]
5–14 years	20 [10–40]	15 [8–30]	26 [13–52]	26 [13–52]
15+ years	18 [9–36]	20 [10–40]	24 [12–48]	30 [15–60]
Vaccine delivery cost (2007 US$/dose)	0.5 [0.3–2.5]	0.5 [0.3–2.5]	1.0 [0.6–5.0]	0.5 [0.3–2.5]
Vaccine purchase price (2007 US$/dose)	0.6 [0.4–0.8]	0.6 [0.4–0.8]	0.6 [0.4–0.8]	0.6 [0.4–0.8]
Percent coverage if vaccine is free (%)				
1–4 years	64 [48–88]	74 [60–85]	52 [39–60]	53 [40–86]
5–14 years	55 [41–89]	55 [40–63]	38 [29–44]	59 [44–65]
15+ years	34 [26–53]	56 [40–62]	24 [18–26]	61 [46–67]
Parameters assumed to be the same across sites				
Effectiveness of vaccine				
No herd protection	0.6** [0.5–0.7]			
Overall protection	Varies††			
Duration of vaccine (years)	3 [2–4]			
Length of illness (days)	4 [2–8]			
DALY weight	0.105 [0.08–0.27]			
Case fatality rate (%)	1 [0.5–3]			
Discount rate (%)	3			
Campaign coverage (%)	80 [60–100]			

*Base case value shown, with uncertainty range in brackets.
†Only the neighborhoods of Tiljala and Narkeldanga are included.
‡Surveillance conducted during a case-control study of vaccination effectiveness held in Beira.
§From country statistics on GDP per capita (IMF, World Economic Outlook Database, 2008).
¶Only 2 to 4 year olds.
**Overall effectiveness beyond the second year is assumed to be 17% less than in years 1 and 2, equivalent to a base case reduction from 60 to 50%.
††In the base case, overall vaccine effectiveness varies depending on coverage level, as shown in Figure 1. For the sensitivity analysis, the vaccine protection effect is assumed to range from no reduction in overall effectiveness to a 33% reduction in all years. This parameter is referred to as *Herd Extent* in Table 5.

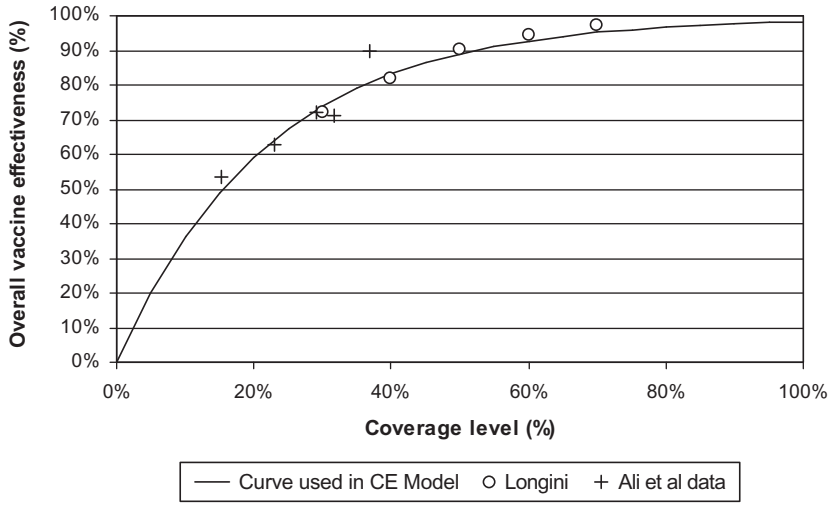

Figure 1 Model of overall cholera vaccine effectiveness as a function of vaccination coverage rate in year 1 in herd protection scenario and comparison with results from epidemiological studies [13,14]. The results shown from Longini et al. [14] assume vaccine effectiveness against susceptibility is 60% and efficacy against infectiousness is 50%. Estimates for effectiveness in year 3 were adjusted down by 17% to represent the vaccine's waning protection in time.

years following vaccination, declining to 50% effectiveness in the third year, consistent with evidence from the Vietnamese field trial [9]. The second analysis shows how ratios change when herd protection effects are incorporated. We specified two simple relationships for effectiveness—"total protection" for the vaccinated, and "indirect protection" for the unvaccinated as a function of population coverage based on data from Ali et al. using the approach outlined in the supporting information for Cook et al. [17]. This analysis yields predictions for "overall" protection (protection in the entire population) that are consistent with the models described in Longini et al. [14], as shown in Figure 1. We modeled third year overall effectiveness with herd protection declining by the same percentage (17%) as in the first analysis. We allowed the duration of the protection to vary from 2 to 4 years, with 3 years in the base case.

Other Model Parameters

The site-specific and general parameters for the cost-effectiveness model are shown in Table 1 for both the base case and the ranges for sensitivity analyses.

Incidence. The epidemiological data came from prospective population-based surveillance conducted by the DOMI program in three sites (Kolkata, N. Jakarta and Beira) and from long-term surveillance conducted by the ICDDR,B in Matlab, Bangladesh [18]. These incidence rates may underestimate the true incidence of cholera because they are based on passive surveillance studies. As a result, we test the sensitivity of the cost-effectiveness ratios to a wide range of incidence rates, spanning from half of the field-measured rates to two times those rates.

Case fatality rates (CFRs). Because our study sites had health care systems prepared to handle cholera cases, CFRs were low. The WHO reports CFRs for our countries ranging from 0.1% in India in 2004 to 1.1 and 1.4% in Mozambique and Indonesia, respectively, in 2005 [1,19] (Bangladesh did not report to the WHO in 2004 and 2005). Though high CFRs—20% or higher—have been observed in recent cholera outbreaks in situations with inadequate health care [2,15], we believe that 1 percent CFRs are probably reasonable, and use it for the base case. Our uncertainty range goes from 0.5 to 3% in all four study sites.

DALY weights. Because there are no published DALY weights specific to cholera, we adopted the 0.105 standard applicable for diarrheal disease during the period of illness [20]. This 0.105 weight that we use may understate the pain and suffering that cholera patients endure, but the short duration of the disease means that the morbidity burden has little effect on cost-effectiveness ratios. Our uncertainty range goes from 0.08 (dengue fever) to 0.27 (diseases such as malaria, Japanese encephalitis, and acute upper respiratory infections).We assumed that the average patient was sick for 4 days (range 2–8 days), with no long-term health effects for recovered patients, as treatment with intravenous rehydration therapy leads to quick recovery.

Cost of illness. The DOMI project included studies to estimate the public cost of illness (COI) associated with cholera cases in the four study locations (Poulos C, Riewpaiboon A, Stewart JF, et al., unpubl. data). Following the approach of the DCP [11], these COI estimates were not adjusted for purchasing power parity. These data have not been published, so some additional explanation is warranted. Table 2 (from Poulos et al.) presents a summary of the information that was collected in the COI studies.

The studies used standardized household surveys—administered to culture-confirmed patients at 7 and 14 days after the laboratory confirmation—to collect information on private COI. For adult cases, the patient was interviewed; for children, an adult in the household identified as familiar with the episode and household finances was interviewed. The questionnaires included questions for determining direct and indirect costs. Direct costs included the costs of medical treatment, transportation, food, lodging, and other special items. The indirect costs included 1) lost wages due to lost work time by the patients, their caregivers, and their substitutes, and 2) productivity losses due to forgone non-market activities such as school, housework, and childcare. The monetary value of nonmarket activities was estimated from the subject's age and the type of activity displaced [20].

To measure public costs of illness, data from health facilities providing treatment were obtained first (from facilities serving the disease burden study) to produce estimates of the average costs of the following: a day's hospitalization, clinic visit, and medicines and diagnostic tests. This information was combined with data on payments to health facilities from the sample of patients who were visited during the household surveys (for medicines, tests, or other direct costs). The portion of the total cost of treatment that was borne by the public sector was calculated as the provider cost of treatment minus any fees received from patients for their treatment. Though public treatment cost

Table 2 Components of *ex post* private and public costs of illness

Component	Private costs	Public costs
Direct Costs	Treatment—including: Diagnostic tests Medicine Examination Bed charges* Transportation Nonmedical items—including foods and beverages used to aid treatment Lodging and meals for other persons† Other payments	Publicly borne costs of: An outpatient visit in a public clinic A day of hospitalization in a public hospital The medicines received by the patient in the treatment of the disease The diagnostic tests used for patients with the disease.
Indirect Costs	Patient's lost income/production Substitute laborers' net lost income/production‡ Caretakers' lost income/production Other persons' lost income/production	Not applicable

*These were most often persons who accompanied the patient when they sought treatment.
†If there is an overnight stay.
‡This is "net" because substitute laborers result in a net increase or decrease in lost productivity. On the one hand, they can increase losses if they are not able to perform their own work. On the other hand, they reduce losses when they replace patients' lost labor. This item is equal to (substitute laborers' own lost income/production) + (substitute laborers' contributions to income/production by doing patients' work).

studies in each country were not identical because of differences in the health care systems, availability of data, and the design of the DOMI projects in each country, similar components were measured to maximize comparability of findings (Poulos C, Riewpaiboon A, Stewart JF, et al., unpubl. data).

It should be noted that the public cost studies in Matlab, Kolkata and Beira only collected complete data for hospitalized patients, though hospitalization rates in Matlab and Beira were nearly 100%. In Kolkata, where the hospitalization rate was 51%, public COI estimates may be overestimated.

Coverage. DOMI studies estimated private demand for cholera vaccines; these were used to predict coverage levels for different ages given the provision of a free vaccine [21–23]. Our estimates of vaccine coverage were adjusted to account for the effect of giving respondents time to think about their demand for vaccines. Several of these studies of private demand for cholera and typhoid vaccines have found that respondents given the opportunity to consider a vaccine scenario overnight express more certainty about their responses and lower willingness to pay. Coverage rates predicted by these studies varied from 24% among adults in North Jakarta to 74% among young children in Kolkata, but were typically between 50% and 60% (Table 1). For sensitivity analysis, we allowed these estimates to range from a 25% decrease in coverage from these base coverage levels to the unadjusted ("no time-to-think") demand estimates (which were 10–30% higher depending on the site and age group). We also assumed that 80% of people would be informed of the vaccination effort in each site (range 60–100%).

Cost of vaccination. The social cost of a cholera vaccination program is composed of three main components: 1) the cost of acquiring vaccines from the manufacturer; 2) the cost of delivering and administering the vaccine to the target population; and 3) the time and pecuniary costs incurred by household members to travel to the vaccination outpost and to wait to receive the vaccine. None of the three cost components is known with certainty. They depend on a number of factors for which there is little information in the published vaccine cost literature. For cost estimates in the present analysis, we relied on a recent review and analysis of this literature by D. Lauria and J. Stewart (unpubl. ms.) and on data collected during other vaccine demonstration projects (for typhoid) in several DOMI study sites, the cholera vaccine demonstration project in Beira, Mozambique, and the Phase III clinical trial of the WC vaccine in Kolkata.

We assumed a vaccine cost, including shipping and wastage, of US$0.60 per dose in the base case, in all sites (range US$0.4–0.8), derived from the estimated production costs of the Vietnamese vaccine [24]. We use the same base case acquisition cost for all sites, because the cost of customs, freight and insurance are within the overall margin of error.

We followed a commonly used convention in the cost-effectiveness literature (see Sinha et al. [25] for a recent example) and assumed that delivery costs are captured in a constant marginal cost per vaccinated individual rather than including fixed (i.e., set up) costs. This implies constant returns to scale in vaccination. We assumed that the marginal delivery cost per dose is the same for a school-based program (Options 1 and 2) as for a community-based vaccination program (Option 3). For the sites in Bangladesh, India, and Mozambique, we used Lauria and Stewart's estimate of US$0.50 per dose for delivery costs in the low-income countries. For Indonesia, we used Lauria and Stewart's estimate of US$1.0 per dose for middle-income countries.

In the sensitivity analyses, we based the uncertainty ranges on the 16 studies for low-income countries reviewed by Lauria and Stewart. The 12.5% to 87.5% confidence interval (obtained by dropping the two highest and two lowest delivery cost estimates) is US$0.3–US$2.5 per dose, which we use as the lower and upper bounds in the sensitivity analysis. Because their study only included 6 middle-income countries and because costs are assumed to be twice as high in middle income countries, we derived the uncertainty range for Indonesia by doubling the range described above for low-income countries, or US$0.6–US$5.0 per dose.

Results

Base-Case Analysis

Table 3 presents results for the three program options when herd protection is ignored. Consistent with conventional wisdom, no programs are very cost-effective using the commonly cited threshold of per capita GDP. The ratios are best for programs that reach the youngest children because the disease mostly affects the young in these sites (see Table 1).

When vaccine herd protection is incorporated, this picture changes (Table 4). Depending on the program, the predicted

Table 3 Key vaccination program outcomes without herd protection effects

Parameters	Matlab, Bangladesh	Kolkata, India	N. Jakarta, Indonesia	Beira, Mozambique
Option 1: School-based program targeting school children (5–14 years)				
Number vaccinations	21,296	16,036	14,421	65,938
Cases avoided over 3 years	56	60	7	322
% Reduction in cases	5	6	3	5
Deaths avoided over 3 years	1	1	0	3
DALYs avoided over 3 years	15	16	2	78
Public COI avoided	$1,083	$873	$181	$8,125
Total program costs	$46,851	$35,279	$46,146	$145,064
Average cost per vaccinee	$2.2	$2.2	$3.2	$2.2
Net public cost (Total program costs—Public COI avoided)	$45,768	$34,405	$45,965	$136,939
Net public cost per case avoided	$813	$578	$6,418	$426
Net public cost per death avoided	$81,265	$57,768	$641,825	$42,555
Net public cost per DALY avoided	$2,999	$2,125	$23,415	$1,748
Option 2: School-based program targeting all 1–14 year olds				
Number vaccinations	34,475	23,702	19,712	89,282
Cases avoided over 3 years	141	151	21	672
% Reduction in cases	14	16	10	10
Deaths avoided over 3 years	1	2	0	7
DALYs avoided over 3 years	39	42	6	166
Public COI avoided	$2,708	$2,212	$532	$16,956
Total program costs	$75,845	$52,145	$63,077	$196,420
Average cost per vaccinee	$2.2	$2.2	$3.2	$2.2
Net public cost	$73,137	$49,932	$62,545	$179,464
Net public cost per case avoided	$519	$331	$2,970	$267
Net public cost per death avoided	$51,929	$33,097	$297,008	$26,725
Net public cost per DALY avoided	$1,886	$1,199	$10,632	$1,081
Option 3: Community-based program (all persons 1 year and older)				
Number vaccinations	72,653	82,796	38,473	257,595
Cases avoided over 3 years	207	244	30	1,772
% Reduction in cases	20	25	14	26
Deaths avoided over 3 years	2	2	0	18
DALYs avoided over 3 years	54	63	8	383
Public COI avoided	$3,884	$4,017	$735	$48,907
Total program costs	$159,836	$182,150	$123,112	$566,710
Average cost per vaccinee	$2.2	$2.2	$3.2	$2.2
Net public cost	$155,952	$178,133	$122,378	$517,802
Net public cost per case avoided	$752	$731	$4,131	$292
Net public cost per death avoided	$75,208	$73,071	$413,111	$29,223
Net public cost per DALY avoided	$2,897	$2,836	$15,576	$1,353
GDP Thresholds (for reference)				
Cost-effective (3 × GDP/cap)	$1,458	$2,613	$5,436	$1,146
Very cost-effective (GDP/cap)	$486	$871	$1,812	$382

number of cases avoided increases by a factor of 3 to 10 over the estimates that ignore herd effects. The largest reduction in disease burden is in Beira, with 2615, 3393, and 5692 cases of cholera avoided for Options 1, 2, and 3, respectively, when accounting for herd protection, in comparison with 322, 672, and 1772 cases without. In Kolkata, the cases avoided for Option 3 increase threefold, from 244 to 779. Though the GDP per capita cutoffs are somewhat arbitrary, all three programs in Beira and Kolkata are considered very cost-effective. In Matlab, Option 1 is very cost-effective, and the other two options are cost-effective. The ratios are higher in North Jakarta due to the higher assumed cost of vaccination and lower cholera incidence, but higher per capita GDP in Indonesia makes results for all three programs cost-effective.

Uncertainty Analysis

Sensitivity analysis reveals that five model parameters have a large influence on the ratios in these different sites: the cost of vaccination, incidence, the CFR, the vaccine's duration, and the extent of herd protection (Table 5). Parameters such as the public COI, DALY weight, duration of illness, and coverage rates are relatively less important. The cost per fully vaccinated person contributes the most to uncertainty in ratios in all sites, for all program options. Figure 2 facilitates the comparison of sensitivity to cost across sites. It also shows the consequences of ignoring vaccine herd protection: there is little chance that any program would be considered very cost-effective even under the optimistic assumptions about the cost per fully vaccinated person if herd protection is ignored. In addition, ignoring herd protection effects could lead to choosing less cost-effective programs. For example, in Beira, one might mistakenly favor community-based mass vaccination over vaccination of school children.

Discussion

Several observations emerge from this analysis. First, even vaccination programs that include only school children proved sufficient to provide substantial reductions in the overall burden of cholera through herd protection. For example, in Beira, where a program targeted at school children delivers about 66,000 vaccines for a population coverage rate of 12%, the overall protection rate was 38% (Fig. 1). As a result of indirect protection, it has been found that the number of cases avoided is over eight times than when herd protection is not included in the analysis. Importantly, infants who are too young to be safely vaccinated receive some protection [26]. These cost-effectiveness results with herd protection are dependent on the coverage rate that is assumed because vaccine efficacy is a function of coverage rates.

Table 4 Key vaccination program outcomes with herd protection effects*

Parameters	Matlab, Bangladesh	Kolkata, India	N. Jakarta, Indonesia	Beira, Mozambique
Option 1: School-based program targeting school children (5–14 years)				
Number vaccinations	21,296	16,036	14,421	65,938
Cases avoided over 3 years	341	301	65	2,615
% Reduction in cases	33	31	30	38
Deaths avoided over 3 years	3	3	1	26
DALYs avoided over 3 years	87	78	17	576
Public COI avoided	$6,360	$4,875	$1,604	$71,254
Net public cost	$40,491	$30,404	$44,542	$73,810
Net public cost per case avoided	$119	$101	$687	$28
Net public cost per death avoided	$11,877	$10,106	$68,703	$2,823
Net public cost per DALY avoided	$463	$390	$2,616	$128
Option 2: School-based program targeting all 1–14 year olds				
Number vaccinations	34,475	23,702	19,712	89,282
Cases avoided over 3 years	517	448	91	3,393
% Reduction in cases	50	47	42	49
Deaths avoided over 3 years	5	4	1	34
DALYs avoided over 3 years	133	117	24	751
Public COI avoided	$9,651	$7,201	$2,243	$92,244
Net public cost	$66,194	$44,944	$60,835	$104,176
Net public cost per case avoided	$128	$100	$672	$31
Net public cost per death avoided	$12,810	$10,041	$67,202	$3,071
Net public cost per DALY avoided	$497	$384	$2,542	$139
Option 3: Community-based program (all persons 1 year and older)				
Number vaccinations	72,653	82,796	38,473	257,595
Cases avoided over 3 years	749	779	135	5,692
% Reduction in cases	73	81	62	82
Deaths avoided over 3 years	7	8	1	57
DALYs avoided over 3 years	191	200	35	1241
Public COI avoided	$13,927	$12,836	$3,322	$156,188
Net public cost	$145,909	$169,314	$119,790	$410,522
Net public cost per case avoided	$195	$217	$891	$72
Net public cost per death avoided	$19,471	$21,744	$89,052	$7,212
Net public cost per DALY avoided	$764	$845	$3,400	$331
GDP Thresholds (for reference)				
Cost-effective (3 × GDP/cap)	$1,458	$2,613	$5,436	$1,146
Very cost-effective (GDP/cap)	$486	$871	$1,812	$382

*Note that the total program costs, and average cost per immunized person are the same as those reported in Table 2.

Second, as shown in Figure 1, the rate of increase of overall vaccine protection decreases as a function of coverage; i.e., the marginal effect of increased herd protection decreases as coverage increases. As a result, effective targeting can keep program costs low while still conferring significant protection to the population as a whole. When herd protection is ignored, programs targeting the highest incidence age group (children aged 1–4) are clearly the most cost-effective (Table 3). However, if herd protection is incorporated in the analysis, in all four sites, the cost-effectiveness of programs targeting school children (ages 5–14) is similar to that of programs targeting all eligible children (ages 1–14), despite the differences in incidence among age groups

Table 5 Effect of individual parameters on cost-effectiveness ratios (2007US$ per DALY avoided), ranked in order of significance to variation in results*

	Most important		Second		Third		Fourth		Fifth	
	Parameter	Low–High	Parameter	Low–High	Parameter	Low–High	Parameter	Low–High	Parameter	Low–High
Matlab, Bangladesh										
Program Option 1	Cost	259–1,525	Incidence	186–989	CFR	151–905	Duration	338–666	Herd extent	424–673
Program Option 2	Cost	281–1,627	Incidence	203–1,057	CFR	163–973	Duration	365–713	Herd extent	456–721
Program Option 3	Cost	450–2,429	Incidence	336–1,592	CFR	252–1,506	Duration	574–1,086	Herd extent	708–1,097
Kolkata, India										
Program Option 1	Cost	211–1,280	Incidence	150–828	CFR	125–750	Duration	278–555	Herd extent	350–561
Program Option 2	Cost	209–1,263	Incidence	148–817	CFR	124–740	Duration	275–548	Herd extent	346–554
Program Option 3	Cost	499–2,649	CFR	277–1,657	Incidence	375–1,740	Duration	634–1,190	Herd extent	780–1,203
N. Jakarta, Indonesia										
Program Option 1	Cost	1,587–9,717	CFR	869–5,195	Incidence	1,248–5,313	Duration	2,018–3,676	Herd extent	2,452–3,713
Program Option 2	Cost	1,541–9,449	CFR	844–5,048	Incidence	1,211–5,165	Duration	1,960–3,573	Herd extent	2,383–3,609
Program Option 3	Cost	2,078–12,560	CFR	1,131–6,761	Incidence	1,641–6,882	Duration	2,633–4,772	Herd extent	3,193–4,819
Beira, Mozambique										
Program Option 1	Cost	12–607	Incidence	(–22)–356	CFR	35–207	Duration	49–203	Herd extent	90–207
Program Option 2	Cost	19–637	Incidence	(–16)–376	CFR	38–228	Duration	58–218	Herd extent	100–221
Program Option 3	Cost	140–1,219	Incidence	77–762	CFR	102–610	Duration	207–487	Herd extent	280–493

*Assumes herd protection; Program Option 1 targets only school-aged children (5–14.9); Option 2 also includes young children (1–4.9); Option 3 is a mass program targeting all ages; reported uncertainty ranges correspond to parameter ranges specified in Table 1.

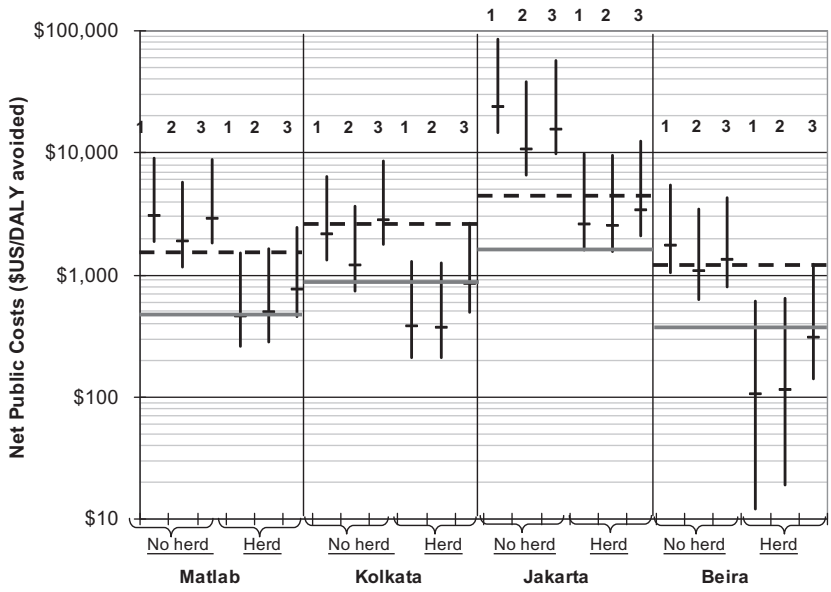

Figure 2 The influence of the cost of vaccination on cost-effectiveness ratios (log scale). Thick gray lines indicate the "very cost-effective" threshold; dotted black lines the "cost-effective" threshold. Program options (1, 2, and 3) are labeled above the ranges. Ranges ignoring herd protection are displayed to the left; those incorporating these effects are to the right. The lower bound of the range is associated with the low cost shown in Table 1; the upper bound is the high cost.

(Table 4). This is because a proportionally larger share of herd protection benefits is captured by the smaller program that only includes school children. For example, in Kolkata, expanding the program to include 1 to 4 year olds as well as 5 to 14 year olds leads to a 16% increase in reduction of the disease burden, but the ratio hardly changes. In general, the most cost-effective options would be programs designed to target eligible young children (1–4 years old) and other vulnerable populations while still achieving sufficient overall coverage to capture herd protection benefits.

Third, community-based vaccination programs that include adults are shown to be generally less cost-effective than interventions targeted at all eligible children. The reasons for the lower cost-effectiveness of adult interventions differ depending on whether the herd protection effect is incorporated into the analysis. If herd protection is ignored, the lower incidence among adults would suggest better prospects from designing programs aimed at children. If herd protection is taken into account, going from small programs targeting only school children to somewhat larger programs for all eligible children provides direct and herd protection benefits that are comparable to added vaccination costs. However, moving from child-only programs to vaccinating both children and adults requires expenses that rise faster than do the additional protective benefits of vaccination. The diminishing health returns from vaccinating additional people are a direct consequence of the diminishing marginal effect of herd protection, shown in Figure 1.

Fourth, the cost-effectiveness and disease burden reduction of cholera vaccination vary substantially across the sites studied. The ratios for Beira are on par with some of the more cost-effective health interventions considered in the Disease Control Priorities Project ($100 or less). Next in line, Kolkata and Matlab have similar ratios ($350–$500), but the relative value of these programs depends on somewhat arbitrary thresholds for cost-effectiveness (higher in Kolkata owing to higher per capita GDP). North Jakarta has relatively low cholera incidence, and ratios there are much higher. This variation emphasizes the importance of using detailed site-specific data for disease incidence, mortality rates and other population-specific parameters in the cost-effectiveness analysis, and suggests that caution should be used in extrapolating the cost-effectiveness ratios from these specific sites to locations in other parts of the world. An additional difficulty with generalizing the results from these sites is the substantial uncertainty associated with the effect of herd protection in different locations. The only existing empirical study of this effect comes from Matlab, Bangladesh.

Two particular limitations of our use of this herd protection data from Bangladesh should be noted. First, herd protection depends on location-specific conditions, such as the local disease epidemiology and transmission. Because we did not have detailed information about how such factors might influence herd protection against cholera, we applied the herd effects observed in Bangladesh to our analyses of all study sites. Second, published data and models of the herd protection only correspond to the first year following vaccination, whereas cholera immunizations are generally thought to offer three-year protection, during which time the direct effectiveness of the vaccine wanes. Data from the Bangladesh trial do reveal that vaccine herd protective effects were undiminished through two years of follow-up [M. Ali, personal communication]. For year 3, we diminished the vaccine herd protective effects by 17% to correspond with observed decreases in direct effectiveness.

Cost-effectiveness ratios can provide a useful starting point for comparing the relative value of using public monies for cholera vaccination rather than other health interventions. The financial realities facing resource-deprived health systems in developing countries make it impossible to carry out all potentially "very cost-effective" interventions. The DCP Project reports ratios of $7 and $68 per DALY avoided for scaled-up Expanded Program on Immunization (EPI) programs and BCG vaccine against tuberculosis, respectively; these interventions thus appear more attractive than cholera vaccination [11]. However, the DCP's ratio of $296 for concurrent Hib and Hepatitis B vaccination is higher than our ratio for cholera vaccine programs for children in Beira. A number of other vaccines included in the DCP's report (e.g., Hib alone, hepatitis alone) also have less attractive ratios than many of the cholera programs analyzed in this article, although these vaccines may also show herd protection effects. Incorporating these effects could improve the cost-effectiveness of these vaccines as well.

Policymakers are especially interested in comparing the cost-effectiveness of cholera vaccination programs with water and sanitation interventions [11,15]. When herd protection is incorporated into the cost-effectiveness calculations, the results presented in this article suggest that in several locations (e.g., Beira, Kolkata, and Matlab) cholera vaccination of children is likely to compare favorably with the cost-effectiveness of water and sanitation interventions. However, cost-effectiveness ratios using health outcomes are not the only basis for choosing between cholera vaccination and water and sanitation interventions. Other factors in the decision include the nonhealth benefits obtained from water and sanitation interventions, feasibility of implementation, longevity of the interventions, and financing constraints [27,28]. Many water and sanitation interventions provide protection against a range of diseases, and offer substantial time savings and aesthetic lifestyle benefits to households. Cholera vaccination, however, only provides benefits in the form of reduced cost of illness and reduced mortality risk from a single disease [28]. The benefits from water and sanitation interventions also last longer than the 3 years of protection offered by cholera vaccines. On the other hand, water and sanitation interventions are much more capital intensive than cholera vaccination programs, and are therefore more difficult to finance [28]. Finally, it may be difficult in crowded urban areas to find effective low-cost water and sanitation interventions that deliver health and time savings benefits [27]. In such cases, cholera vaccination may provide health improvements until the construction of new housing and until associated water and sanitation infrastructure is financially feasible.

In addition to cost-effectiveness analysis, decision makers should at least undertake a full economic cost-benefit analysis (CBA) before making decisions concerning cholera vaccination. CBA would give a more complete picture of whether programs should be implemented from a social perspective. The best programs might pass a CBA test and appear very cost-effective, but some programs may be very cost-effective and fail a CBA test, or vice versa. CEA makes an implicit assumption that every DALY should be treated equally, which fails to account for heterogeneity in risk preferences, vulnerability to disease, and demand for improved health. Besides including public COI savings, economic CBA would incorporate private costs of vaccination and benefits such as private COI savings, increased productivity and wages from not missing work and private willingness to pay (WTP) for avoided risks of death from disease and pain and suffering [29,30]. Where WTP for cholera protection among some members of the population is high, the importance of vaccine herd protection effects would argue for at least making vaccines available at cost in pharmacies or health clinics, since the population as a whole would benefit from increased indirect protection.

In summary, our cost-effectiveness calculations that incorporate herd protection show that oral cholera vaccination of children is more cost-effective than previously thought. Unlike the results for cholera vaccines summarized in the DCP [11], we show that cholera vaccination may in fact be cost-effective once vaccine herd protection effects are taken into account, and given the use of a cheaper alternative to the Dukoral™ vaccine. Though the relationships between coverage, targeting, and protection in different types of settings call for further study, the results presented here show that vaccinating children against cholera should be strongly considered as a public health intervention in Beira, Matlab, and Kolkata.

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