Treatment and Vaccination Strategies to Control Cholera in Sub-Saharan Refugee Settings

A Cost-effectiveness Analysis

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Context.—There is significant controversy about how best to control cholera epidemics in refugee settings. Specifically, there is marked disagreement about whether to use oral cholera vaccines in these settings, despite the improved safety and effectiveness profiles of these vaccines.

Objective.—To determine the cost-effectiveness of alternative intervention strategies, including vaccination, to control cholera outbreaks in sub-Saharan refugee camps.

Design.—A cost-effectiveness analysis based on probabilities of cholera outcomes derived from epidemiologic data compiled for refugee settings in Malawi from 1987 through 1993; data for costs were obtained from a large relief agency that provides medical care in such settings.

Setting and Participants.—A hypothetical refugee camp with 50 000 persons in sub-Saharan Africa evaluated for a 2-year period.

Interventions.—We compared the costs and outcomes of alternative strategies in which appropriate rehydration therapy for cholera is introduced preemptively (at the establishment of a camp) or reactively (once an epidemic is recognized) and in which mass immunization with oral B subunit killed whole-cell (BS-WC) cholera vaccine is added to a rehydration program either preemptively or reactively.

Main Outcome Measures.—Cost per cholera case prevented and cost per cholera death averted.

Results.—In a situation with no available rehydration therapy suitable for the management of severe cholera, a strategy of preemptive therapy ($320 per death averted) costs less and is more effective than a strategy of reactive therapy ($586 per death averted). Adding vaccination to preemptive therapy is expensive: $1745 per additional death averted for preemptive vaccination and $3833 per additional death averted for reactive vaccination. However, if the cost of vaccine falls below $0.22 per dose, strategies combining vaccination and preemptive therapy become more cost-effective than therapy alone.

Conclusions.—Provision for managing cholera outbreaks at the inception of a refugee camp (preemptive therapy) is the most cost-effective strategy for controlling cholera outbreaks in sub-Saharan refugee settings. Should the price of BS-WC cholera vaccine fall below $0.22 per dose, however, supplementation of preemptive therapy with mass vaccination will become a cost-effective option.

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WORLDWIDE, crowded refugee camps with contaminated water sources and inadequate sanitation have been well described as foci for cholera outbreaks.[1-6] The rapidly growing number of refugees resulting from war, civil strife, famine, and natural disasters is expected only to add to the number who have already died as a consequence of such cholera epidemics. The provision of an adequate quantity of purified water and the establishment of suitable facilities for defecation pending appropriate sanitation systems are important measures to help prevent outbreaks of cholera in refugee settings. Appropriate case management with oral rehydration therapy, community outreach to improve case finding and access to treatment, and hospital management for severe cases can reduce the case-fatality ratio (CFR) in cholera epidemics from more than 50% to less than 1%.[4,7-12] In the last decade, however, the CFR in cholera outbreaks in refugee settings, even within the same country, has varied from less than 1% to as high as 25%. Such variation is in part a consequence of the disparate availability of resources needed to effectively manage such outbreaks.[12,13]

For editorial comment see p 552.

Clearly, more effective strategies to prevent cholera are needed. At present, use of additional interventions to assist in the control of cholera outbreaks in refugee settings is not recommended. Mass antibiotic chemoprophylaxis is considered ineffective and may be associated with the emergence of drug-resistant organisms.[4,14,15] In the past, injectable cholera vaccines have been rejected because of low efficacy and too short a duration of protection.[16] The recent availability of more efficacious oral cholera vaccines, such as the recombinant oral B subunit killed whole-cell (rBS-WC) vaccine, its nonrecombinant predecessor,[17-20] and the live attenuated CVD 103-HgR vaccine,[21,22] has led to renewed interest in vaccination to prevent outbreaks in situations with high cholera incidence, such as refugee populations.[23,24] However, controversy surrounds the cost-effectiveness of vaccination in such settings. To address this controversy, we report a cost-effectiveness analysis of several alternative intervention strategies, including vaccination, to control cholera outbreaks in sub-Saharan refugee settings.

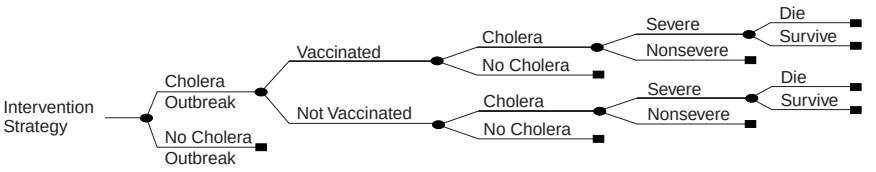

Figure 1.—Algorithm for possible outcomes following each of the intervention strategies in the cost-effectiveness model.

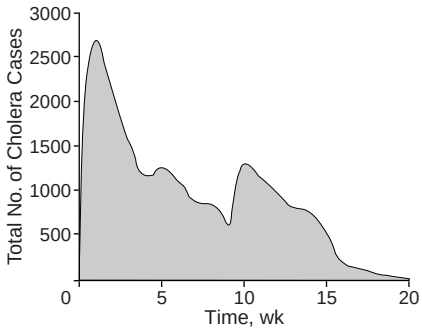

Figure 2.—Representative epidemic curve used in the base case analysis.

METHODS

Construction of the Model

Although not always attained, the provision of basic primary health care; safe, potable water; latrines; food; and oral rehydration solution is considered routine in all refugee settings. This baseline standard of care does not include any supplementary intervention to prevent or treat cholera. In our model, the following candidate intervention strategies have been compared with one another and also with the baseline standard of care: (1) preemptive treatment (PT), with the necessary staff and facilities to manage a cholera outbreak, including intravenous therapy for treatment of severe dehydration, set up at the inception of the camp (This is the strategy currently adopted and recommended by relief agencies, such as Médecins Sans Frontières [MSF].); (2) reactive treatment (RT), with the staff, facilities, and supplies to manage a cholera outbreak after the epidemic has been recognized; (3) PT combined with preemptive vaccination (PV), with vaccination conducted at inception of the refugee camp; (4) PT combined with reactive vaccination (RV), with the refugee camp vaccinated after the outbreak of cholera has been recognized; (5) RT combined with PV; and (6) RT combined with RV. The algorithm for the possible outcomes following each of the above intervention strategies is depicted in Figure 1. If an outbreak of cholera occurs, based on the attack rate, a certain proportion of the population will develop cholera. If a vaccination program is in effect, the fraction of the population developing cholera will also depend on vaccine coverage and the protective efficacy of the vaccine. The outcomes under analysis include severe and nonsevere cases of cholera and deaths from cholera. A severe case is defined as one requiring intravenous fluids for treatment.

Our cost-effectiveness analysis, in which the final indices of intervention performance are expressed as cost per case prevented and cost per death averted, was chosen over a cost-benefit analysis since estimation of the value of human life and other indirect costs, such as lost productivity, were beyond the scope of this research.

Data and Assumptions

Estimates for parameters and probabilities used in our base case analysis are based on unpublished, detailed epidemiologic information from 21 cholera outbreaks in Mozambican refugee camps in Malawi collected between 1987 and 1993 by MSF and Epicentre. Table 1 provides a summary of these estimates; those estimates for which data could not be obtained from these sources were derived from published studies or were provided by the authors.

Setting.—The setting chosen for this analysis is a hypothetical refugee camp with 50 000 persons situated in a cholera-endemic area of sub-Saharan Africa. The base year for analysis is 1995, and the analysis is based on the refugee camp being evaluated for a 2-year period, during which it is estimated that 20% of the camp population will be replaced as a consequence of migration.

Cholera Epidemic.—The probability of a cholera epidemic occurring during the 2-year time horizon is estimated to be 80%. For all refugee camps documented by MSF and Epicentre to have had a cholera outbreak, the median cumulative fraction of refugees who developed cholera during the first 2 years following the first cholera case in each camp was 3.65%. To derive other expected epidemiologic parameters, including week-specific attack rates, we overlaid the contours from the 21 epidemic curves for which detailed epidemiologic information was available and constructed a temporal distribution of the cumulative cases, representing the contribution of all 21 epidemics. To obtain a representative epidemic curve of approximately median duration and yet maintain the original cumulative attack rate, we added the week-specific attack rates for each 2-week period and applied this sum to a truncated 1-week period. In the resulting epidemic curve of 20 weeks' duration (Figure 2), 42% of the total cholera cases are expected to occur during the first 4 weeks, 55% during the first 6 weeks, 75% during the first 10 weeks, and 95% during the first 14 weeks.

Treatment Strategies.—Intravenous rehydration is the mainstay of treatment to prevent death in severe cholera cases. Oral rehydration solution is used for mild and moderate cases of dehydration. Doxycycline is administered to all patients and their close contacts. The time lag to recognize the epidemic and have the treatment centers operational is expected to be 1 week with PT. The time lag to institute treatment is expected to be 1 week longer with RT (ie, 2 weeks).

Vaccination Strategies.—Although several oral cholera vaccines are under development and evaluation, only vaccines containing killed whole cells have been evaluated in populations with endemic cholera. In these evaluations, BS-WC (including rBS-WC) was efficacious and devoid of any known adverse effects.[17-20] The protective efficacy of BS-WC against El Tor cholera in children younger than 5 years is estimated to be 80% in the first 6 months following vaccination and 0% thereafter. In those 5 years of age or older, BS-WC protection is estimated to be 80% in the first year following vaccination and 50% during the second year (J.D.C., unpublished data from a field trial in Bangladesh, 1985). In this analysis we assume that vaccination will be targeted to all age groups older than 12 months, that the vaccine will be administered in 2 doses separated by at least 2 weeks, and that vaccination will reduce the number of cholera cases in an epidemic but not the probability of whether a cholera epidemic occurs in the 2-year time horizon. Vaccine coverage is expected to be better with RV, with which there is an elevated perceived risk of disease by the refugees. With PV as the intervention, it is assumed that in-migrants over the 2-year time horizon would be vaccinated at the time of entry to the camp by existing health care providers.

Costs.—Table 1 includes cost estimates entailed in vaccination and treatment (in 1995 dollars) used in the base case analysis. Except for cost of vaccine, all estimates are based on actual costs incurred by MSF. Only direct costs are included in

the model. The treatment costs include the variable costs of drugs and treatment supplies (eg, doxycycline, oral rehydration solution, and Ringer lactate) and the fixed costs of freight, transportation, human resources, construction materials, and other equipment (eg, laboratory supplies, disinfectants, nursing material, stationery, lighting, tents, water pump, pipes, and water tank). The vaccination costs include the cost of vaccine, buffer, storage of vaccine in refrigerators, freight, vaccinators, supervisors, recorders, guards, vehicles, and other supplies (eg, vaccine carriers, cups, and vaccination cards). In the base case analysis we have discounted all direct costs but not outcomes occurring in the future to their net present value at a nominal rate of 10% per annum.[25]

Sensitivity Analyses.—Table 1 includes a plausible range for each of the variables we have elected to incorporate into 1-way sensitivity analyses. For an epidemic curve of 40 weeks' duration, we used the original temporal distribution of the cumulative cases representing the contribution of all 21 epidemics. To obtain a representative epidemic curve of 4 weeks' duration and yet maintain the original cumulative attack rate, we added the week-specific attack rates for each 10-week period and applied this sum to a truncated 1-week period.

Table 1.—Estimates Used in the Base Case Analysis and Plausible Ranges for Each Variable Incorporated Into the Sensitivity Analyses*

Variable	Estimate	Plausible Range
Population of refugee camp	50 000	20 000-100 000†
Proportion of population aged <5 y	0.20	0.15-0.25
Proportion of population replaced by migration	0.2†	0.05-0.5†
Probability of a cholera epidemic	0.8†	0.5-1.0†
Total attack rate for cholera epidemic	0.0365	0.004-0.08
Duration of epidemic, wk	20	4-40
Proportion of severe cholera cases	0.75	0.5-0.85†
Case-fatality ratio without/with "treatment" strategy‡	0.3/0.01	0.2-0.5/0.001-0.02
Time lag for treatment effect with PT/RT, wk	1/2†	0-3/1-4†
Vaccine coverage with PV/RV	0.7/0.8†	0.2-0.85/0.23-0.97†
Time lag for vaccine effect, wk§	6†	3-10†
Vaccine protective efficacy in those aged <5 y, 0-6/6-24 mo after vaccination	0.8/0.0‖	0.6-0.9/0.0-0.9†
Vaccine protective efficacy in those aged ≥5 y, 0-12/12-24 mo after vaccination	0.8/0.5‖	0.6-0.9/0.3-0.9†
Variable treatment costs, $/case¶	14	11.2-16.8†
Fixed PT/RT costs, thousands of $#		
300-900 cases	45/83	36-54/66-99†
901-1500 cases	75/131	60-105/90-157†
Cost of vaccine, $/dose	0.50**	0.05-1.00†
Cost of PV/RV program, thousands of $††	13/15	10-15/12-18†
Annual nominal discount rate for costs‡‡	0.10	0.00-0.20

*Unless otherwise indicated, all data were provided by Médecins Sans Frontières and Epicentre, Paris, France. PT indicates preemptive therapy; RT, reactive therapy; PV, preemptive vaccination; and RV, reactive vaccination.
†Estimated by the authors.
‡See the Centers for Disease Control and Prevention,[4] Mandara and Mhalu,[7] Carpenter,[8] Tauxe and Blake,[9] Tauxe et al,[10] Mahalanabis et al,[11] and Swerdlow et al.[12]
§Time to recognize the epidemic, to vaccinate the population, and for the population to react to the vaccine.
‖Unpublished data from a field trial of oral cholera vaccination in Bangladesh (J.D.C.).
¶Includes the costs of drugs and treatment supplies.
#Includes the costs of infrastructure, transportation, and human resources.
**Estimated by J. Holmgren, MD, PhD, Gothenburg University, Gothenburg, Sweden; written communication; May 29, 1997.
††Includes the costs of supplies, transportation, and human resources (excludes the cost of vaccine).
‡‡See Weinstein.[25]

RESULTS

Base Case Analysis

The results of the base case analysis are summarized in Table 2. Relative to the standard of no supplemental rehydration therapy, a strategy of PT is expected to prevent 270 cholera deaths at a cost of $86 293 ($320 per death prevented), whereas an RT strategy is expected to cost more, $136 482, to prevent fewer (233) cholera deaths ($586 per death prevented).

If vaccination is to be incorporated into a treatment strategy, strategies combining a vaccination intervention with RT are expected to prevent no further cholera cases, prevent fewer cholera deaths, and cost more than the same vaccination intervention combined with PT. Again, relative to the standard, a strategy of PT plus PV is expected to cost $209 per case prevented and $442 per death averted, whereas a strategy of PT plus RV is expected to cost $360 per case prevented and $529 per death averted. The estimated incremental cost of adding a vaccination campaign to PT is $71 per case prevented and $1745 per extra death averted for PV, compared with $155 per case prevented and $3833 per extra death averted for RV.

Table 2.—Summary of the Base Case Analysis*

	Intervention Strategy						
	Standard	PT	RT	PT and PV	RT and PV	PT and RV	RT and RV
Severe cases	1095	1095	1095	627	627	779	779
Nonsevere cases	365	365	365	209	209	260	260
Total cases	1460	1460	1460	836	836	1039	1039
Cholera deaths	329	59	96	34	55	42	93
Vaccination costs, $	0	0	0	79 491	79 491	70 464	70 464
Treatment costs, $	0	86 293	136 482	50 834	85 085	80 977	131 167
Total cost, $	0	86 293	136 482	130 325	164 576	151 441	201 631
Cost/case prevented, $†	. . .	. . .	. . .	209	264	360	479
Cost/death prevented, $†	. . .	320	586	442	601	529	855
Incremental cost/case prevented, $‡	. . .	. . .	. . .	71	45	155	155
Incremental cost/death prevented, $‡	. . .	. . .	. . .	1745	686	3833	20 669

*Abbreviations are expanded in the first footnote to Table 1.
†Compared with the standard strategy.
‡Incremental cost compared with the corresponding treatment strategy alone.

Sensitivity Analyses

At extreme values in the 1-way sensitivity analyses, strategies that incorporated RT were found to be less effective and to cost more than corresponding strategies that incorporated PT. For strategies incorporating vaccination, the indices of cost-effectiveness were found to be most sensitive to the epidemic attack rate, vaccine coverage, cost of vaccine, vaccine protective efficacy in those 5 years of age or older, epidemic duration, time lag for vaccine effect, and time lag for treatment effect. For the extreme values of each of these variables, the incremental cost per case prevented and cost per extra death averted of adding either PV or RV to PT are presented in Table 3. Other than the results shown in Table 3, we did not find any significant impact on the results of our base case analysis during sensitivity analyses for all the other variables listed in Table 1.

Irrespective of whether PV or RV was added to PT, the only situation in which

Table 3.—Estimates of Incremental Costs per Case Prevented and per Extra Death Prevented of Adding PV or RV to PT for the Extreme Values of the Most Sensitive Assumptions Incorporated Into 1-Way Sensitivity Analyses*

Variable	Incremental Cost/ Case Prevented, $†		Incremental Cost/ Death Prevented, $†	
	PT and PV	PT and RV	PT and PV	PT and RV
Base case	71	155	1745	3833
Epidemic total attack rate				
0.08	14	43	339	1057
0.004	1149	1516	28 442	37 520
Vaccine coverage				
0.85	56	125	1382	3102
0.20	433	574	10 715	14 198
Cost of vaccine/dose				
$0.05	−22†	40	−549†	995
$1.00	174	282	4295	6986
Vaccine protective efficacy in those aged ≥5 y‡				
90%/90%	51	136	1270	3372
60%/30%	162	211	4005	5215
Duration of epidemic				
40 wk	70	58	3380	2939
4 wk	74	70 464§	649	70 464§
Time lag for vaccine effect¶				
3 wk	70	58	1738	1392
10 wk	72	287	1775	7100
Time lag for PT effect				
3 wk	71	155	836	1835
0 wk	71	155	9413	20 669

*Abbreviations are expanded in the first footnote to Table 1.
†Incremental cost compared with the corresponding treatment strategy alone. Negative values reflect a savings as opposed to an incremental cost.
‡First year/second year after vaccination.
§Extra cost of vaccination with no effectiveness.
¶Time to recognize the epidemic, to vaccinate the population, and for the population to respond to the vaccine.

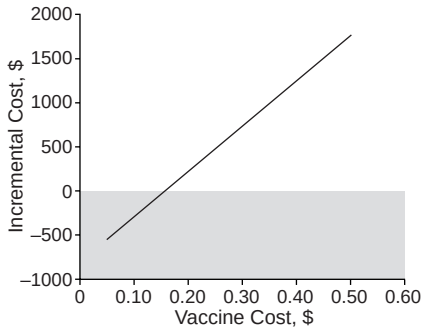

Figure 3.—Incremental cost per death prevented of adding preemptive vaccination to preemptive treatment as a function of vaccine cost in cents.

vaccination incorporated into a treatment strategy was found to be inherently more cost-effective than the treatment strategy alone was when the cost of vaccine fell sufficiently. In terms of cost per death prevented, PT plus PV becomes more cost-effective than PT when the cost per dose of vaccine falls to $0.22 or less. Moreover, as shown in Figure 3, if the cost of vaccine falls below $0.16 per dose, the incremental cost of adding PV to PT falls below 0, and the combined strategy is expected both to cost less and to prevent more deaths than treatment alone.

Our base case analysis found PT plus PV to be more cost-effective than PT plus RV. This finding persisted during sensitivity analyses (Table 3), except for 2 situations in which PT plus RV was marginally more cost-effective than PT plus PV. First, if the time lag for vaccine effect (time to recognize the epidemic, to vaccinate the population, and for the population to respond to the vaccine) was reduced to 3 weeks, the incremental cost per case prevented fell to $58 for adding RV to PT, compared with $70 for adding PV to PT, and the incremental cost per extra death prevented fell to $1392 for adding RV to PT, compared with $1738 for adding PV to PT. Second, if the epidemic duration was prolonged to 40 weeks, the incremental cost per case prevented fell to $58 for adding RV to PT, compared with $70 for adding PV to PT, and the incremental cost per extra death prevented fell to $2939 for adding RV to PT, compared with $3380 for adding PV to PT. In contrast, for any epidemic of less than 6 weeks' duration, a strategy employing RV is expected to incorporate the extra cost of vaccination ($70 464) with no cases prevented and no extra deaths averted.

COMMENT

In any chosen strategy, PT, the intervention currently recommended by MSF, would be preferred over RT, since irrespective of whether a vaccination intervention is adopted or not, strategies that incorporate PT are expected to cost less and to be more effective than corresponding strategies that incorporate RT. These observations persisted throughout the sensitivity analyses.

If vaccination were to be incorporated into an intervention strategy, PT plus PV, the strategy found to be more cost-effective in the base case analysis, would be preferred over PT plus RV. During sensitivity analyses, PT plus PV remained more cost-effective than PT plus RV except when the duration of the cholera epidemic was prolonged to 40 weeks or when the time lag for vaccine effect was reduced to 3 weeks. Since the duration of a cholera epidemic cannot be predicted, the only practical situation in which PT plus RV could be considered a more cost-effective option would be when the time lag for vaccine effect was expected to be 3 weeks or less. In such a situation, the marginally superior cost-effectiveness of PT plus RV should be weighed against the possibility that the concurrent treatment of cases and use of reactive vaccination might disrupt both activities, a disruption we did not account for in our analyses.

At the onset of a cholera epidemic, the sooner the treatment centers can be made fully operational, the smaller the expected number of deaths. With PT, if this time lag is reduced to less than 1 week, the expected incremental cost per extra death prevented of adding a vaccination campaign will become greater. In such a situation, the major impact of vaccination is expected to be the reduction of cholera cases.

Should the cost of vaccine fall from the current estimate of $0.50 to below $0.16 per dose, a combined strategy of PV plus PT would both prevent more deaths and be less costly than PT alone. This cost saving (or negative incremental cost) of adding PV to PT occurs when the money saved in treatment costs (due to the fewer cases requiring treatment following vaccination) is greater than the cost of the vaccination program itself.

Several assumptions in our model have worked to diminish the predicted cost-effectiveness of strategies incorporating vaccination compared with treatment alone. We assumed a CFR of 1% in the presence of treatment strategies. The median CFR in the 21 epidemics reviewed by MSF and Epicentre was 1.6%. Unless relief agencies with comparable expertise in managing cholera cases respond to a given epidemic, it is unlikely that the CFR will be as low. Furthermore, because of inadequate data, additional expected benefits from vaccination, such as induction of herd immunity and other manifestations of reduced transmission, cross-protection against diarrhea from enterotoxigenic *Escheri-*

chia coli, and protection of vaccinated out-migrants against cholera, have not been included in our analysis.[26,27]

On the other hand, there are also potential adverse effects of a vaccination campaign that we have not addressed. A vaccination campaign against cholera may interfere with other essential public health measures being instituted in the refugee camp concurrently. These public health measures include the provision of potable water, sanitation, and basic primary health care (eg, treatment of other illnesses, such as malaria; vaccination of children against measles; and attention to appropriate nutrition). In addition, following a vaccination campaign, vaccinated individuals may be lulled into a false sense of security and may not pursue other preventive measures, thereby putting themselves at an increased risk of infection by pathogens transmitted via feces.

It is important not to generalize the results of this analysis to all conceivable refugee settings. The refugee camps incorporated into our analyses could be considered as relatively established, and they provided what we have referred to as a baseline standard of care. In certain catastrophic situations, as illustrated by the massive epidemic of cholera early in the Goma, Zaire, refugee crisis of 1994,[5] there may be no adequate health infrastructure, food, or potable water. While such devastating conditions last, it is implausible that any supplementary vaccination program to prevent cholera can be implemented.

Cholera epidemics continue to occur in refugee settings despite current efforts to implement nonvaccine prevention strategies. Unless changes are made to these current strategies or additional nonvaccine prevention strategies are employed, it is reasonable to expect continued outbreaks of cholera in refugee settings. In our analyses, we have not evaluated the potential effectiveness and costs of nonvaccine prevention strategies beyond those currently employed on a routine basis.[28] Dedicating personnel to ensure that no lapses occur in chlorination of the central water supply or improving water handling and point-of-use chlorination are examples of such strategies.[29]

We chose the BS-WC (including rBS-WC) cholera vaccine for this analysis, since it is the only oral cholera vaccine to have been evaluated in populations with endemic cholera. Once published data regarding the clinical performance of the live attenuated CVD 103-HgR vaccine in a cholera-endemic setting become available, our model can be adapted to incorporate this vaccine into the analysis.

The ability to produce rBS-WC vaccine or a comparably safe and efficacious vaccine at a low cost (approaching $0.22 per dose) should be considered a major priority in vaccine development. It is foreseeable that economies of scale in the production of the rBS-WC vaccine could result in a lower cost per dose. Furthermore, it is reassuring that a developing country such as Vietnam is reported to be producing a killed oral cholera vaccine below this cost threshold.[30] Effectiveness studies of such vaccines are needed to determine whether they can be used in a cost-effective way to prevent cholera epidemics in refugee settings. These effectiveness studies could also serve to address collectively many of the aforementioned limitations of this analysis.

Our sensitivity analyses have also revealed that the cost-effectiveness of vaccination is significantly diminished as vaccine coverage falls. Therefore, if vaccination is to be incorporated into an intervention strategy, all possible measures that are known to improve vaccine coverage should be undertaken. Active support provided by refugee community health workers has been shown to be associated with high immunization coverage in refugee camps in Somalia.[31] Further research into factors that may improve vaccine acceptance by refugees appears warranted.

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