Cost–effectiveness of oral cholera vaccine in a stable refugee population at risk for epidemic cholera and in a population with endemic cholera

J. Murray,[1] D.A. McFarland,[2] & R.J. Waldman[3]

Recent large epidemics of cholera with high incidence and associated mortality among refugees have raised the question of whether oral cholera vaccines should be considered as an additional preventive measure in high-risk populations. The potential impact of oral cholera vaccines on populations prone to seasonal endemic cholera has also been questioned. This article reviews the potential cost–effectiveness of B-subunit, killed whole-cell (BS–WC) oral cholera vaccine in a stable refugee population and in a population with endemic cholera. In the population at risk for endemic cholera, mass vaccination with BS–WC vaccine is the least cost-effective intervention compared with the provision of safe drinking-water and sanitation or with treatment of the disease. In a refugee population at risk for epidemic disease, the cost–effectiveness of vaccination is similar to that of providing safe drinking-water and sanitation alone, though less cost-effective than treatment alone or treatment combined with the provision of water and sanitation. The implications of these data for public health decision-makers and programme managers are discussed. There is a need for better information on the feasibility and costs of administering oral cholera vaccine in refugee populations and populations with endemic cholera.

Introduction

The recent development of safe and reasonably effective oral cholera vaccines has made it possible to consider their use in situations where the risk of epidemic cholera is high. WHO has strongly discouraged the use of the previous cholera vaccines since they are largely ineffective and, when they confer protection, do so for a limited time. WHO and others have emphasized the need to use the limited resources available during epidemics on proven and effective control measures that reduce morbidity and mortality due to cholera and other diarrhoeal diseases (*1, 3*). Nevertheless, recent outbreaks of large cholera epidemics with high incidence and mortality among refugee populations have raised the question

of whether oral cholera vaccines should be considered as an additional preventive measure in high-risk populations (*4–9*). The potential impact of oral cholera vaccines on populations prone to endemic cholera has also been questioned.

This article reviews the potential cost–effectiveness of the B-subunit killed whole-cell (BS–WC) oral cholera vaccine in a refugee population and in a population with endemic cholera. We have made four general assumptions. First, we assume that in a population at risk for epidemic cholera, vaccine can never be used in isolation but may be considered in addition to the provision of safe drinking-water, sanitation, and appropriate treatment. Second, we assume that populations at risk of cholera can be vaccinated before the beginning of an outbreak. There are as yet no clear guidelines on how to predict the magnitude, timing, or severity of cholera outbreaks in high-risk populations. A recent WHO meeting (*10*) recommended that priority be given to research on predicting epidemics of cholera in these populations. Third, we assume that epidemic cholera is caused by the pandemic cholera strain *Vibrio cholerae* O1 biotype El Tor (*11*). Fourth, we have included acute watery diarrhoea (simple diarrhoea) in the analysis since it is almost invariably a major cause of morbidity and mortality in populations at risk for cholera. An analysis of the

[1] Technical Officer, BASICS (Basic Support for Institutionalizing Child Survival), 1600 Wilson Boulevard, Arlington, VA 22209, USA, and Research Associate, Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD, USA. Requests for reprints should be sent to this author at the former address.

[2] Associate Professor and Chair, Department of Health Policy and Management, Rollins School of Public Health, Emory University, Atlanta, GA, USA.

[3] Deputy Director for Technical Direction, BASICS, Arlington, VA, USA.

cost–effectiveness of interventions to prevent or control cholera should also consider their impact on other types of diarrhoea.

Methods

Baseline epidemiological assumptions

For both a refugee population and a population at risk for endemic cholera, we have assumed the following:

— the total population at risk is 100 000;
— a refugee population comprises displaced persons living in a single geographical area, dependent on outside assistance for the provision of all basic services, and with negligible in or out migration; this population is assumed to have little or no prior exposure to cholera;
— a population with endemic cholera comprises people living in a single geographical area with negligible migration and experiencing seasonal outbreaks of cholera;
— the period of observation is 1 year and all incidence and mortality rates are averaged over 1 year; and
— the age structure is characteristic of a population with a high total fertility rate, i.e. 20% <5 years, 30% 5–16 years, and 50% >16 years (12).

Pre-existing immunity. The refugee population is expected to have negligible pre-existing immunity to cholera. In the population with endemic cholera, 90% of those >5 years of age are protected because of acquired immunity and the entire population <5 years of age is unprotected (13, 14). In both populations simple diarrhoea may be caused by several different viral, bacterial, and parasitological agents (15–18).

Attack rates. In the refugee population, cholera incidence is assumed to be 8 cases per 1000 population per year. A wide range of cholera incidence has been reported in refugee populations (19–23) and rates are likely to vary considerably between populations depending on sanitation and hygiene, water quality and quantity, pre-existing immunity to cholera and other factors. The rate used is based on data from 17 reported outbreaks of cholera in 11 Mozambican refugee camps in Malawi between 1987 and 1994, with incidence ranging from 4 to 60 cases per 1000 population per year (10). Using these data, the overall average annual incidence per camp is estimated to be 8 per 1000 population. The cholera incidence used in this analysis is the same for each age group.

    Incidence of cholera in the population with endemic disease is estimated from data from similar populations, i.e. 3, 1.5 and 0.3 cases per 1000 population per year for those aged <5, 5–16 and >16 years, respectively (24–28). The incidence of simple diarrhoea for both populations is derived from community-based data, i.e. 2600 and 200 cases per 1000 population per year for those aged <5 and ≥5 years, respectively (15, 29).

Mortality. In the absence of treatment, cholera case–fatality ratios have been shown to be high; a ratio of 20% for all age groups has been reported (19–22, 29–32). Case-fatality ratios for simple diarrhoea in the absence of treatment are estimated at 0.7% for those aged <5 years and 0.14% for those aged ≥5 years (these assume that 70% of all patients with severe simple diarrhoea will die if not treated). These data apply to both the stable refugee population and the population with endemic cholera.

Risk of severity. For patients with cholera, 20% are at high risk of severe dehydration and death. For those with simple diarrhoea, 1% aged <5 years and 0.2% aged ≥5 years are at high risk of severe dehydration and death. For the present analysis, it is assumed that 50% of all severe cases can be managed effectively as outpatients by the use of oral rehydration therapy and that the remainder will require admission to hospital, intravenous fluid replacement, and treatment with antibiotics.

Access to services. The entire refugee population is assumed to have access either to hospital or to outpatient services, since resources and personnel will have been effectively mobilized to supply the population. In the population with endemic cholera, access to inpatient treatment services is assumed to be 50% and access to outpatient services 80%.

Assumptions for public health interventions

Treatment. In 90% of cases, treatment for cholera is outpatient oral rehydration therapy; the remaining 10% will require inpatient treatment with intravenous fluid therapy and antibiotics. Effective treatment for simple diarrhoea is oral rehydration therapy in 99.5% of cases and inpatient treatment in the remainder. With treatment, cholera mortality is expected to fall from 20% to 1% of all cases for all age groups (22, 31–34). Mortality from simple diarrhoea is expected to be reduced by 50% through use of oral rehydration therapy to 0.35% and 0.07% per year among those aged <5 years and ≥5 years, respectively.

Water and sanitation. The provision of an adequate supply of safe drinking-water and adequate sanita-

tion is expected to reduce cholera incidence by 40% and that of simple diarrhoea by 27%. These figures are based on a number of community-based studies (35–37). The impact of these interventions is the same in both refugee populations and populations with endemic cholera.

Vaccine. The analysis was conducted using data on the BS–WC oral cholera vaccine, which has been demonstrated to be well tolerated and to have a relatively long-lasting effect in field trials in Bangladesh (38, 39). This vaccine can be given in two oral doses 7–14 days apart, with protection beginning 7 days after the second dose. Since a population may be exposed to cholera at any time during the 12-month period of observation following vaccination, effectiveness is averaged over the year using data from the field trial in Bangladesh (39). The BS–WC vaccine provides protection against both the classical and El Tor cholera biotypes, and protection against the El Tor biotype alone is estimated from field trial data. Overall vaccine effectiveness at 1 year was 50% for children aged 2–5 years and 70% for persons ≥5 years. The entire population (adults and children) is assumed to be eligible for vaccination and all vaccine is delivered at least 7 days before the onset of the outbreak. Although levels of pre-existing immunity in the adult population from an endemic area are likely to be high, all adults will need to receive the vaccine since there is no practical method for determining immunity before an outbreak.

   In the refugee population, vaccination coverage during the 1-year period of observation was 80% for all age groups. Coverage in the endemic population was 80% for children <5 years and 50% for persons ≥5 years of age. Effectiveness of vaccination in the stable refugee population at 1 year was 40% (0.5 × 0.8) for children <5 years and 56% (0.7 × 0.8) for persons ≥5 years of age. Effectiveness in populations with endemic cholera at 1 year was 40% (0.5 × 0.8) for children <5 years and 35% (0.7 × 0.5) for persons ≥5 years of age. A 10% loss factor was added to vaccine cost calculations. It was assumed that BS–WC vaccine can be safely administered to the entire population of adults and children.

Assumptions for costing public health interventions

Only direct health sector costs are included in the analysis, including direct costs regardless of the source of funds. Costs to the patient, such as time lost from work, transportation costs and out-of-pocket expenses, are not included in the cost analysis. While these costs are often significant, they have not been routinely measured in studies costing public health

interventions, with the result that reliable figures are not available. The cost analysis is therefore aimed at public health decision-makers responsible for re-source allocation, rather than heads of households. Costs are calculated over a 1-year period, as are capital costs for interventions. Water and sanitation infrastructure costs are included, although they are not usually attributable directly to the health sector alone. All costs are given in US$ at 1990 values.

Outpatient oral rehydration therapy

The cost of treating a child with simple diarrhoea on an outpatient basis ranges from US$ 1.30 to US$ 9.13 (40–43, D.A. McFarland & D.L. Krunshaar, unpublished data, 1992). The midpoint of the range, US$ 4.67, has been used to estimate the cost of outpatient treatment for patients with cholera and simple diarrhoea in both populations (41). Costs include oral rehydration salts, personnel, supplies, and facility costs such as maintenance and annual depreciation.

Inpatient treatment

Inpatient costs include those for intravenous therapy, drugs, personnel, supplies, laboratory tests, and facilities. An estimate from Lesotho (US$ 46.82) has been used because it is the most comprehensive cost analysis available of hospital treatment in a developing country (41). This cost estimate includes the costs of personnel, facilities and drugs, including intravenous therapy. It is an upper estimate since it includes costs for permanent facilities, whereas in stable refugee settings less permanent inpatient facilities may be constructed. The inpatient cost of treating individuals who are severely dehydrated is the same whether the condition is caused by cholera or diarrhoea.

Water and sanitation

Stable refugee population. The costs of water and sanitation programmes vary widely and depend on local rainfall, availability of water sources, topography, geography, geology, population density, pumping requirements and many other factors (44). The Water and Sanitation for Health Project has collected country-level data for estimates of urban and rural water and sanitation projects (45). Annual costs were based on a 10% discount over 20 years. Median annual costs, inclusive of construction and maintenance, for water and sanitation facilities consisting of stand pipes and pit latrines are approximately US$ 9.50 and US$ 2.50, respectively, or about US$ 12.00 per capita per year, which is the value

used in the analysis. This cost is expected to be incurred whether or not cholera is present, in order to provide safe drinking-water and sanitation. For the present analysis, therefore, the entire cost of providing safe drinking-water and sanitation is borne as an intervention to prevent simple diarrhoea. It is likely that the provision of drinking-water and sanitation will have many benefits over and above the prevention of diarrhoea and cholera, and therefore that these costs ascribed to simple diarrhoea in this analysis are an overestimate. In addition to infrastructure costs, we estimate a cost of US$ 5.00 per year for public hygiene programmes (R. Varley, personal communication, 1996). The total annual cost per capita of providing safe drinking-water and sanitation is therefore US$ 17.00.

An intervention specific for cholera is bucket chlorination, which is estimated to cost US$ 16.00 per day for every 30 000 people (L. Roberts, personal communication, 1995). If buckets are chlorinated for 3 months during an epidemic, the expected cost per person is US$ 0.048. This is the only water-specific cost attributed to cholera.

Population with endemic cholera. A deep-well water system has been used for the analysis in endemic populations. The per capita cost of constructing and maintaining a deep well is approximately US$ 12.00 (*45*). The estimated per capita cost of a pit latrine is US$ 2.50 (*44, 45*) and public hygiene costs of US$ 5.00 per capita per year are estimated. The total annual cost per capita for water and sanitation programmes is US$ 19.50. Since water and sanitation will be provided whether or not cholera is present, the entire cost of providing water and sanitation is allocated to simple diarrhoea. The costs of a cholera-specific intervention are the same as those for refugee populations.

Oral cholera vaccine

Stable refugee population. The cost of the oral BS–WC cholera vaccine purchased in bulk is currently US$ 1.50 per dose (*10*). The entire population of children and adults is eligible for this vaccine and should receive two doses at least 7 days apart for maximum effectiveness. Thus the per capita cost of vaccine is US$ 3.00. The cost of a kit for delivering oral vaccine to 5000 people was calculated from UNICEF product information sheets for 1993–94 to be US$ 1500, i.e. a per capita cost of US$ 0.30. This kit contains a small generator, cold box, vaccine carriers, cold packs, thermometers, cups and spoons, and record cards.

The other major cost of administering cholera vaccine in stable refugee populations is that of personnel. In such populations it is expected that vaccine administration will most closely resemble a campaign strategy. Shepard (*46*) estimated the cost per contact (excluding vaccine and other supply costs) of administering one dose of measles vaccine using a campaign strategy to be US$ 1.48. Using these data, the personnel cost per capita for cholera vaccination is US$ 2.96, since two doses of vaccine need to be given. This is an upper estimate because personnel costs for an oral vaccine would be less than those for administering parenteral vaccines requiring the use of needles and syringes.

Thus the total cost per capita of administering two doses of cholera vaccine in a stable refugee population is US$ 6.26, i.e. US$ 300 for vaccine, US$ 0.30 for nonpersonnel costs, and US$ 2.96 for personnel costs.

Population with endemic cholera. Vaccines are delivered using a fixed-site or facility-based strategy according to the Expanded Programme on Immunization (EPI) model. The annual per capita cost of cholera vaccine remains US$ 3.00. In the absence of data on immunization costs for adults, the nonvaccine cost estimate for children is applied to both children and adults. This assumes that no additional personnel will be required to expand coverage to adults (i.e. that existing facilities are adequately staffed), and that no additional costs are incurred for health education or social mobilization. The nonvaccine cost per fully immunized child using a fixed-site strategy is US$ 10.02 (*47*). All nonvaccine costs will be divided equally among the immunizations routinely given in an EPI programme (three doses of diphtheria–pertussis–tetanus (DPT), three doses of oral poliovirus vaccine (OPV), and one dose of measles vaccine) and the two doses of cholera vaccine — a total of nine doses. Thus the annual per capita nonvaccine cost per dose is US$ 1.11 and the total annual per capita cost of cholera immunization in an endemic population is US$ 5.22, i.e. US$ 3.00 for vaccine and US$ 2.22 for all other costs, including personnel.

Net costs

The net cost of an intervention is the total cost of the intervention minus the treatment costs of the cases averted by the intervention.

Outcome measures

Baseline epidemiological assumptions are applied to the standard populations in order to generate the expected morbidity and mortality levels for cholera and simple diarrhoea. The key interventions are then

added (oral cholera vaccination, water supply and sanitation, treatment, and combinations of these) in order to calculate the morbidity and mortality that would be averted.

For each relevant intervention, the net costs per case and per death averted for both cholera and simple diarrhoea are calculated for each population.

Disability-adjusted life years

Not all interventions have an impact on both cases and deaths, nor is it possible directly to compare the net cost per case averted with the net cost per death averted. To overcome this limitation, disability-adjusted life years (DALYs) (48), which combine the effects of mortality and morbidity, are used.

For the purposes of this analysis, we constructed a spreadsheet and calculated the burden of disease in DALYs attributable to cholera and simple diarrhoea in the two populations. The formula used in the spreadsheet was based on the DALY formula developed by Murray & Lopez (49).

Each cholera episode lasts 3 days and has a disability weighting of 0.92, i.e. a patient needs assistance with activities of daily living such as eating, personal hygiene and toilet use (49). To calculate the total number of DALYs in a population of 100 000, an average age for contracting cholera of 25–29 years is used for the refugee population and of 1–4 years for the endemic population. The same age ranges are used for cholera deaths. The standard life expectancies used in the analysis are those reported by Murray & Lopez (49).

An episode of simple diarrhoea lasts 3 days and has a disability weighting of 0.60, i.e. ability to perform recreational, educational, procreational, and occupational activities is limited (49). In both

populations, an average age of onset of 1–4 years is used for cases of and deaths from simple diarrhoea.

Results

Results are presented for both a refugee population at risk of epidemic cholera and for a population with endemic cholera. Costs per case, deaths, and DALYs averted are calculated for each intervention, based on assumptions costs, morbidity, and mortality. Tables 1 and 2 summarize the combined results for each intervention in the two settings. The relative differences between the various interventions and combinations of interventions are more important than their cost in US dollars, which will vary with local circumstances.

In a population with endemic cholera, the net costs per DALY averted are considerably higher since incidence is lower and access to health care facilities is also assumed to be lower. In this population, the highest cost per DALY averted (US$ 2973) is that for cholera vaccination followed by the provision of safe drinking-water and sanitation (US$ 433). The lowest cost per DALY averted is realized by inpatient treatment (US$ 7). The most cost-effective combination of interventions is water and sanitation plus treatment (US$ 327). Combining vaccination with the provision of water and sanitation substantially improves the relative cost–effectiveness of vaccination alone though this combination remains relatively cost–ineffective.

In a stable refugee population, the net costs per DALY averted are much lower since attack rates are higher and access to health care facilities is assumed to be 100%. In this population, costs per DALY averted for vaccination (US$ 269) and the provision

Table 1: **Costs per disability-adjusted life year (DALY) averted, by intervention type, for cholera and simple diarrhoea combined in a population at risk for endemic cholera**

Intervention	Net cost (US$)	Cholera cases averted (n)	Simple diarrhoea cases averted (n)	Cholera deaths averted (n)	Simple diarrhoea deaths averted (n)	DALYs averted (n)	Net cost per DALY averted (US$)
Vaccine	573 845	40	0	8	0	193	2973
Drinking-water and sanitation	1 954 800	43	18 360	9	104	4 133	433
Outpatient treatment	317 107	0	0	8	78	2 023	157
Inpatient treatment	9 551	0	0	6	49	1 294	7
Drinking-water and sanitation + vaccine	2 529 000	67	18 360	14	104	4 253	556
Drinking-water and sanitation + treatment	2 281 458	43	18 360	15	196	6 439	327

Table 2: **Costs per disability-adjusted life year (DALY) averted, by intervention type, for cholera and simple diarrhoea combined in a stable refugee population at risk for epidemic cholera**

Intervention	Net cost (US$)	Cholera cases averted (n)	Simple diarrhoea cases averted (n)	Cholera deaths averted (n)	Simple diarrhoea deaths averted (n)	DALYs averted (n)	Net cost per DALY averted (US$)
Vaccine	688 600	422	0	85	0	2 562	269
Drinking-water and sanitation	1 704 800	320	18 360	64	104	5 846	276
Outpatient treatment	320 021	0	0	79	97	4 416	72
Inpatient treatment	12 782	0	0	79	97	4 416	3
Drinking-water and sanitation + vaccine	2 393 400	573	18 360	114	104	7 356	313
Drinking-water and sanitation + treatment	2 075 973	320	18 360	158	244	11 679	170

of safe drinking-water and sanitation (US$ 276) are essentially the same. The lowest cost per DALY averted is realized by inpatient treatment alone (US$ 3). Combining the provision of water and sanitation with treatment is the most cost-effective combination of interventions (US$ 170). The net cost per DALY averted for the provision of water and sanitation and vaccination combined is slightly higher than the cost of each intervention separately.

Sensitivity analysis

A sensitivity analysis was performed for vaccination costs and effectiveness. Costs per DALY averted for a range of vaccine costs are summarized in Table 3. In Viet Nam, the cost of producing killed WC oral cholera vaccine without the B subunit has been estimated to be US$ 0.05–0.10 per dose (2). In a refugee population at risk for epidemic cholera, reducing the vaccine cost to US$ 0.05 per dose would make the use of vaccine alone more cost-effective than the provision of water and sanitation and treatment

Table 3: **Sensitivity analysis of cost per disability-adjusted life year (DALY) averted, by cost of BS–WC oral cholera vaccine, in a stable refugee population and in a population at risk for endemic cholera**

Cost of two doses of vaccine (US$)	Intervention cost per DALY averted (US$)	
	Stable refugee population	Endemic population
3.00	269	2 973
1.50	204	2 120
0.75	172	1 693
0.50	161	1 550
0.10	144	1 322

combined. The cost per DALY averted for vaccination alone equals that for the provision of water and sanitation and treatment combined when the vaccine cost reaches approximately US$ 0.38 per dose. In a population with endemic cholera, reducing the cost per dose of vaccine does not improve its relative cost-effectiveness.

Costs per DALY averted for different measures of vaccination effectiveness, using current vaccine costs, are summarized in Table 4. The effectiveness of vaccination may be changed either by increasing coverage with existing vaccines or improving the effectiveness of the vaccine. In a refugee population at risk for epidemic cholera, the effectiveness of vaccination would need to reach 80% in those aged <5 years and 90% in those aged ≥5 years in order to compete in cost–effectiveness with the provision of water and sanitation and treatment combined. In a population with endemic disease, vaccination would remain the least cost-effective intervention even if its effectiveness could be increased to 80% and 75% in those aged <5 and ≥5 years, respectively.

Discussion

Stable refugee population

In a stable refugee population at risk for epidemic disease, BS–WC oral cholera vaccine is as cost-effective as the provision of safe drinking-water and sanitation alone, while remaining less so than treatment alone. Lowering the cost of the vaccine to ≤US$ 0.38 per dose at current estimates of vaccination effectiveness would make vaccination as cost-effective as combining the provision of water and sanitation and treatment. Vaccination is more likely to be a viable option in this population since it is

Table 4: **Sensitivity analysis of costs per disability-adjusted life year (DALY) averted by effectiveness of vaccination with BS–WC oral cholera vaccine in a stable refugee population and in a population at risk for endemic cholera**

Stable refugee population			Endemic population		
Age group (years)	Effectiveness of vaccination (%)	Intervention cost per DALY averted (US$)	Age group (years)	Effectiveness of vaccination (%)	Intervention cost per DALY averted (US$)
<5	40	269	<5	40	2973
≥5	56		≥5	35	
<5	50	246	<5	50	2383
≥5	60		≥5	45	
<5	60	209	<5	60	1987
≥5	70		≥5	55	
<5	70	184	<5	70	1699
≥5	80		≥5	65	
<5	80	162	<5	80	1400
≥5	90		≥5	75	

more cost-effective and since additional resources may be available.

There are two important considerations for public health decision-makers who need to decide on strategies for managing epidemic cholera and other diarrhoeal diseases. The first is the likely effectiveness of vaccination in the target population. The effectiveness of vaccination against the El Tor biotype at 1 year has been estimated from data obtained in field trials in Bangladesh, averaged over a 12-month period. In reality, effectiveness varies with the timing of the epidemic, being considerably higher than the 1-year average if the epidemic closely follows vaccination, and becoming progressively lower with time between vaccination and the onset of the epidemic. Effectiveness will be further reduced if cholera breaks out before vaccination has been completed. There is a need for better data on the epidemiological and environmental predictors of the timing of cholera outbreaks in these settings. There is no field trial evidence that the effectiveness at 1 year of the BS–WC vaccine currently licensed for use against the El Tor biotype is higher than that estimated in the present analysis. In studies on volunteers, the CVD 103HgR oral live attenuated vaccine exhibited short-term effectiveness against the El Tor biotype of around 65% (50, 51) and can be given in a one-dose schedule, although there are as yet no reliable long-term field trial data available.

The second important consideration for decision-makers is the logistics of achieving an acceptable level of vaccination coverage in these populations. It may be difficult to vaccinate refugee populations before the onset of a cholera outbreak, since there are no clear criteria for predicting a chol-

era outbreak and because of the problem of vaccinating large populations quickly. Médecins sans Frontières has reported immunizing 1500 persons a day in a crowded but organized setting (10), although there is no experience of administering a liquid oral vaccine in 40–150-ml doses in these conditions. In addition, any vaccination campaign would have to allow an interval of at least 7 days between doses to induce a full antibody response. The timing and speed of vaccination in these populations will be critical to the effectiveness of the strategy. Rapid mass vaccination strategies are likely to require considerable resources, since teams have to be mobilized, vaccine has to be procured and delivered, and vaccinees have to be organized to receive two doses of vaccine. There is a risk that mass vaccination campaigns will take personnel and resources away from other interventions that have been demonstrated to be more cost-effective (although mass measles vaccination campaigns are routinely conducted, they usually target only the population <5 years with a single dose). These other interventions will prevent and treat diarrhoea from any cause, including the cholera 0139 serogroup.

Endemic population

In populations at risk for endemic cholera, mass vaccination with BS–WC oral cholera vaccine is less cost-effective than the provision of safe drinking-water and sanitation or treatment. Currently available oral cholera vaccine should therefore not be considered part of the routine vaccination schedule in countries with seasonal endemic disease.

Vaccination is less cost-effective in this population because access to health facilities is poorer than that in an organized refugee setting, and because it is considerably harder to achieve high levels of coverage using facility-based services. Even the best vaccination programmes in stable non-displaced populations rarely achieve greater than 80% coverage of infants aged <12 months. A programme to administer mass cholera vaccine would have to achieve a high coverage in children aged <5 years every year with a two-dose schedule. The adult population would be even harder to reach. A campaign to raise awareness of the need for two doses of cholera vaccine would add substantially to vaccine delivery costs and in a population at risk for endemic disease mass campaign strategies are unlikely to be sustainable.

The need for further information

Analyses of this type can be useful for public health decision-makers. Although the estimated costs will vary considerably with local circumstances, their relative proportions will remain constant. Further information is needed on predictors of both the timing and character of cholera outbreaks, strategies, and costs for conducting mass vaccination campaigns with a two-dose vaccine in high-risk populations, and the potential impact of vaccination on the course of an outbreak if vaccination begins after the onset of the disease. In addition, there are currently no data on the impact of vaccination with BS–WC vaccine on individuals with human immunodeficiency virus (HIV) infection or severe malnutrition, and use of the vaccine in populations with a high prevalence of these conditions should be carefully considered. Long-term vaccine effectiveness trials (52) are required for the BS–WC and WC vaccines and the CVD 103HgR live attenuated vaccine. Such trials should include a costing component that calculates costs for all intervention strategies in a real-life setting. Ultimately the relative cost–effectiveness of an oral cholera vaccine will depend not only on its safety, effectiveness, and duration of protection against the El Tor biotype, but also on the feasibility of administering it to high-risk populations.

Résumé

Rentabilité du vaccin anticholérique oral dans une population stable de réfugiés exposée au risque de choléra épidémique et dans une population où le choléra est endémique

La mise au point récente de vaccins anticholériques oraux sûrs et raisonnablement efficaces a permis d'envisager leur utilisation dans des endroits où le risque de choléra épidémique est élevé. L'OMS a fortement déconseillé l'emploi des vaccins anticholériques précédemment disponibles, car leur efficacité est faible et leur durée de protection limitée. A la suite d'importantes épidémies de choléra qui se sont produites récemment dans des populations de réfugiés et qui ont entraîné une incidence et une mortalité élevées, on s'est posé la question de savoir si les vaccins anticholériques oraux pouvaient être considérés comme une mesure de prévention supplémentaire dans les populations à haut risque. On s'est aussi interrogé sur l'impact potentiel de ces vaccins sur les populations exposées au choléra endémique saisonnier.

Le présent article examine la rentabilité potentielle du vaccin anticholérique oral tué de sous-unité B, préparé à partir de germes entiers (BS-WC), dans une population stable de réfugiés et dans une population où le choléra est endémique. Nous avons formulé quatre hypothèses générales. Premièrement, nous avons considéré que, dans une population exposée au risque de choléra épidémique, le vaccin ne peut jamais être utilisé isolément, mais peut s'accompagner d'autres mesures (approvisionnement en eau de boisson saine, assainissement et traitement approprié). Deuxièmement, nous avons supposé qu'il est possible de vacciner des populations exposées au risque de choléra avant le début d'une flambée. Troisièmement, nous avons supposé que le choléra épidémique est causé par la souche de choléra pandémique *Vibrio cholerae* O1 biotype El Tor. Quatrièmement, nous avons inclus dans l'étude la diarrhée aqueuse aiguë (diarrhée simple), car elle est presque toujours une cause majeure de morbidité et de mortalité dans les populations exposées au risque de choléra. Une analyse de la rentabilité des interventions visant à prévenir ou combattre le choléra doit aussi envisager leur impact sur d'autres types de diarrhée.

Du point de vue de la réduction de la morbidité et de la mortalité par choléra et diarrhée simple, la rentabilité du vaccin BS-WC est comparée à celle des autres mesures (approvisionnement en eau de boisson saine, assainissement et traitement de la maladie). Des hypothèses fondamentales concernant la situation épidémiologique et le coût des interventions sont formulées et les résultats sont résumés en termes d'années de vie corrigées de l'incapacité (DALY). Une analyse de sensibilité est présentée pour comparer les différents rapports coût/efficacité de la vaccination.

L'étude montre clairement que, dans une population exposée au risque de choléra endémique, la vaccination de masse au moyen du vaccin BS-WC, comparée avec l'approvisionnement en eau de boisson, l'assainissement et le traitement, est l'intervention qui présente le rapport coût/efficacité le moins satisfaisant. Dans une population de réfugiés exposée à l'épidémie, la rentabilité de la vaccination est proche de celle de l'approvisionnement en eau de boisson et de l'assainissement, mais elle reste inférieure à celle du traitement seul ou du traitement associé à l'approvisionnement en eau et à l'assainissement. L'importance de ces données pour les responsables de la santé publique et les administrateurs de programme est examinée. Il faut disposer d'une meilleure information sur la faisabilité et les coûts de l'administration du vaccin anticholérique oral dans les populations de réfugiés et dans les populations où le choléra est endémique.

References

1. **Clemens J, Spriggs D, Sack D.** Public health considerations for the use of cholera vaccines in cholera control programs. In: Wachsmuth IK, Blake PA, Olsvik O, eds. Vibrio cholerae and cholera: molecular to global perspectives. Washington, DC, American Society for Microbiology, 1994: 425–440.
2. **Trach DD et al.** Field trial of locally produced, killed, oral cholera vaccine in Vietnam. Lancet, 1997, 349: 231–235.
3. Guidelines for cholera control. Geneva, World Health Organization, 1993.
4. **Sack RB.** Prospects for control of cholera with oral vaccines. Journal of diarrhoeal diseases research, 1992, 10: 1–3.
5. **Mekalanos J, Sadoff J.** Cholera vaccines: fighting an ancient scourge. Science, 1994, 265: 1387–1389.
6. **Sack D.** Cholera control. Lancet, 1994, 344: 616–617.
7. **Pierce NF et al.** Cholera treatment. Lancet, 1994, 334: 1022.
8. **Blok L, Sondorp E.** Cholera treatment. Lancet, 1994, 334: 1022–1023.
9. **Steffen R.** New cholera vaccines — for whom? Lancet, 1994, 334: 1241–1242.
10. The potential role of new cholera vaccines in the prevention and control of cholera outbreaks during acute emergencies. Report of a meeting, Geneva, 13–14 February, 1995. Geneva, World Health Organization, 1995 (unpublished document CDR/GPV/95.1; available on request from Division of Diarrhoeal and Acute Respiratory Disease Control, World Health Organization, 1211 Geneva 27, Switzerland).
11. **World Health Organization.** Cholera in 1993. Weekly epidemiological record, 1994, 69(28): 205–212.
12. **United Nations Children's Fund.** The state of the world's children 1994. New York, Oxford University Press, 1994.
13. **Levine M et al.** Duration of infection-derived immunity to cholera. Journal of infectious diseases, 1981, 143: 818–820.
14. **Glass R et al.** Endemic cholera in rural Bangladesh, 1966–1980. American journal of epidemiology, 1982, 116: 959–970.
15. **Bern C et al.** The magnitude of the global problem of diarrhoeal disease: a ten-year update. Bulletin of the World Health Organization, 1992, 70: 705–714.
16. **Claeson M, Merson M.** Global progress in the control of diarrheal diseases. Pediatric infectious disease journal, 1990, 9: 345–355.
17. **Black R et al.** Incidence and severity of rotavirus and Escherichia coli in diarrhoea in rural Bangladesh. Lancet, 1981, 1: 141–143.
18. **Stewien K et al.** Viral, bacterial and parasitic pathogens associated with severe diarrhoea in the city of São Paulo, Brazil. Journal of diarrhoeal diseases research, 1993, 11: 148–152.
19. **Mulholland K.** Cholera in Sudan: an account of an epidemic in a refugee camp in eastern Sudan, May–June 1985. Disasters, 1985, 9: 247–258.
20. **Moren A et al.** Practical field epidemiology to investigate a cholera outbreak in a Mozambican refugee camp in Malawi, 1988. Journal of tropical medical hygiene, 1991, 94: 1–7.
21. **Siddique A et al.** Cholera epidemic and natural disasters; where is the link. Tropical and geographical medicine, 1989, 41: 377–382.
22. **Goma Epidemiology Group.** Public health impact of Rwandan refugee crisis: what happened in Goma, Zaire, in July, 1994? Lancet, 1995, 345: 339–398.
23. **Martines J et al.** Diarrheal diseases. In: Jamison DT et al., eds. Disease control priorities in developing countries. New York, Oxford University Press, 1993: 91–116.
24. **Mosley WH, Bart KJ, Sommer A.** An epidemiological assessment of cholera control programs in rural East Pakistan. International journal of epidemiology, 1972, 1: 5–11.

25. **Mosley WH, Khan M.** Cholera epidemiology — some environmental aspects. *Progress in water technology*, 1979, **11**: 309–316.

26. **McCormack WM et al.** Endemic cholera in rural East Pakistan. *American journal of epidemiology*, 1969, **89**: 393–404.

27. **de Zoysa I, Feachem R.** Interventions for the control of diarrhoeal diseases among young children: rotavirus and cholera immunization. *Bulletin of the World Health Organization*, 1985, **63**: 569–583.

28. **Mosley WH et al.** Report of the 1966–67 cholera vaccine trial in rural East Pakistan. *Bulletin of the World Health Organization*, 1972, **47**: 229–238.

29. **Snyder D, Merson M.** The magnitude of the global problem for acute diarrhoeal disease: a review of active surveillance data. *Bulletin of the World Health Organization*, 1982, **60**: 605–613.

30. **Tauxe R et al.** Epidemic cholera in Mali: high mortality and multiple routes of transmission in a famine area. *Epidemiological information*, 1988, **100**: 279–289.

31. **Siddique A et al.** Cholera epidemics in Bangladesh: 1985–1991. *Journal of diarrhoeal diseases research*, 1992, **10**: 79–86.

32. **Mahalanabis D et al.** The use of Ringer's lactate in the treatment of children with cholera and acute non-cholera diarrhoea. *Bulletin of the World Health Organization*, 1972, **46**: 311–319.

33. **Glass RI, Black RE.** The epidemiology of cholera. In: Barua D, Greenough WB, eds. *Cholera*. New York, Plenum, 1992: 129–154.

34. **Baqui AH, Yunus M, Zaman K.** Community operated treatment centers prevented many cholera deaths. *Journal of diarrhoeal diseases research*, 1984, **2**: 92–98.

35. **Esrey SA, Feachem RG, Hughes JM.** Interventions for the control of diarrhoeal diseases among young children: improving water supplies and excreta disposal facilities. *Bulletin of the World Health Organization*, 1985, **63**: 757–772.

36. **Esrey SA et al.** Effects of improved water supply and sanitation on ascariasis, diarrhoea, dracunculiasis, hookworm infection, schistosomiasis and trachoma. *Bulletin of the World Health Organization*, 1991, **69**: 609–621.

37. **Esrey SA, Habicht JP.** Epidemiologic evidence for health benefits from improved water and sanitation in developing countries. *Epidemiologic reviews*, 1986, **8**: 117–126.

38. **Clemens JD et al.** Field trial of oral cholera vaccines in Bangladesh: results of one year of follow-up. *Journal of infectious diseases*, 1988, **158**: 60–69.

39. **Clemens JD et al.** Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. *Lancet*, 1990, **335**: 270–273.

40. **Phillips M, Kumato-Rodríguez J, Mota-Hernández F.** Costs of treating diarrhoea in a children's hospital in Mexico City. *Bulletin of the World Health Organization*, 1989, **67**: 273–280.

41. **Diarrhoeal Diseases Control Programme.** Cost-effectiveness analysis of oral rehydration therapy. *Weekly epidemiological record*, 1990, **65**(36): 275–279.

42. **Lerman SJ, Shepard DS, Cash RA.** Treatment of diarrhoea in Indonesian children: what it costs and who pays for it. *Lancet*, 1985, 2: 651–654.

43. **Bennett S.** The immunisation and diarrhoea control programmes: a unit cost study. *Lesotho epidemiological bulletin*, 1989, **4**: 15–20.

44. **Okun DA.** The value of water supply and sanitation in development: an assessment. *American journal of public health*, 1988, **78**: 1463–1467.

45. **Okun DA.** *The value of water supply and sanitation in development: an assessment of health-related interventions*. Washington, DC, U.S. Agency for International Development, 1987 (Technical Report No. 43, Water and Sanitation for Health Project).

46. **Shepard DS.** Economic analysis of investment priorities for measles control. *Journal of infectious diseases*, 1994, **170**(Suppl. 1): S56–S62.

47. **Brenzel L.** *The costs of EPI.* Washington, DC, U.S. Agency for International Development, 1990.

48. **World Bank.** *World development report 1993: investing in health.* New York, Oxford University Press, 1993.

49. **Murray CJL, Lopez AD, eds.** *Global comparative assessments in the health sector: disease burden, expenditures and intervention packages.* Geneva, World Health Organization, 1994.

50. **Tacket CO et al.** Onset and duration of protective immunity in challenged volunteers after vaccination with live oral cholera vaccine CVD 103-HgR. *Journal of infectious diseases*, 1992, **166**: 837–841.

51. **Levine MM et al.** Safety, immunogenicity and efficacy of recombinant live oral cholera vaccine CVD 103 and CVD 103-HgR. *Lancet*, 1988, 2: 467–470.

52. **Clemens J et al.** Evaluating new vaccines for developing countries. *Journal of the American Medical Association*, 1996, **275**: 390–396.