Selected references

Epidemiology of cholera


In the most recent epidemic of cholera in Latin America, nearly a million cases were reported and almost 9000 people died between January 1991 and December 1993. The epidemic spread rapidly from country to country, affecting in three years all the countries of Latin America except Uruguay and the Caribbean. Case-control studies carried out in Peru showed a significant association between drinking water and risk of disease. Cholera was associated with the consumption of unwashed fruit and vegetables, with eating food from street vendors and with contaminated crabmeat transported in travellers' luggage. This article documents the spread of the epidemic and its routes of transmission and discusses whether the introduction of the epidemic to Peru and its subsequent spread throughout the continent could have been prevented.

PIP: Latin America's first cholera epidemic this century struck along the Peruvian coast in January 1991. Rapid and intense surveillance could not stop it from crossing Peru's borders. Public health interventions did keep the case fatality rate low (0.92%), however. Cholera first spread to Ecuador, then Colombia. By the end of 1993, all countries of Latin America except Uruguay and the Caribbean reported cholera cases. The greatest proportion of cholera cases and the highest incidence rate were in Peru (63.7% and 26.9/1000, respectively). Most cholera cases were reported in 1991 and were concentrated in Peru (82.3%). 45.5% of all cholera deaths occurred in 1991. Central America had the highest case fatality rates. The routes of transmission of *Vibrio cholerae* in this Latin America cholera epidemic included unwashed fruit and vegetables, contaminated food and ice from street vendors, contaminated drinking water, and contaminated crab meat transported in luggage. The source of the epidemic in Peru has not been identified. Peru had in place an extensive oral rehydration therapy program, an epidemic field investigation service, and laboratory resources. Most Latin American countries, particularly in rural areas and the outskirts of big cities, lack water supply and basic sanitation. Untreated waste water is discharged into rivers and the ocean. Inadequate sanitation facilities and the use of inadequately treated water are likely responsible for the spread of the cholera epidemic in Latin America.


Epidemics of cholera caused by *Vibrio cholerae* O1 occur regularly in Bangladesh, but until lately *V cholerae* non-O1 has been associated only with sporadic cases of diarrhoeal disease in many parts of the world, including Bangladesh. We describe a large epidemic of cholera-
like disease in Bangladesh that is due to a V cholerae non-O1. The epidemic began in December, 1992, in southern Bangladesh and spread throughout the country. By the end of March 107,297 cases of diarrhoea and 1473 deaths had been reported. The disease is indistinguishable from cholera in clinical features and response to treatment, but most of the cases are in adults, which suggests that the population has no previous immunological experience of the organism. At two centres 375 (40%) of 938 and 236 (48%) of 492 rectal swabs were positive for V cholerae non-O1, as were 5 of 54 surface water samples. 55 isolates of V cholerae non-O1 were studied in detail. They resembled El Tor vibrios in being resistant to polymyxin B and positive for agglutination of chicken erythrocytes. The strain did not belong to any of the 138 known V cholerae serogroups; so a new serogroup O139, with the suggested name Bengal, is proposed. All the isolates studied produced large amounts of an enterotoxin apparently identical to cholera toxin. This strain seems to have pandemic potential. It is important that other countries in southeast Asia are aware of the strain's potential to cause severe morbidity and mortality.


Since October 1992, > 150,000 cases of cholera have been reported from India and Bangladesh; the great majority of Vibrio cholerae isolates belong to the newly established serogroup O139. To better understand the interaction of genetic and epidemiologic factors responsible for their sudden appearance and rapid spread, representative toxigenic V. cholerae O139 isolates were molecularly characterized and compared with a set of toxigenic V. cholerae O1 and non-O1/non-O139 strains. DNA sequences of the cholera toxin B subunit gene and multilocus enzyme electrophoresis markers of V. cholerae O139 strains were identical to those of V. cholerae O1 isolates of the seventh pandemic. Two distinct ribotypes and four pulsed-field gel electrophoretic patterns were observed for O139 strains. V. cholerae O139 strains were very similar to V. cholerae O1 strains of the seventh pandemic but clearly different from the toxigenic V. cholerae strains of serogroups other than O1 and O139.

Bacteriology/pathogenesis


Isogenic mutant strains of V. cholerae O1 lacking elements of a genetic regulon controlled by toxR and implicated in virulence were tested in volunteers. A deletion mutation in ctxA, the gene encoding the A subunit of cholera toxin, markedly attenuated disease symptoms without affecting intestinal colonization. Deletion of toxR, the gene encoding the cholera toxin-positive regulatory protein resulted in a diminution in colonizing capacity. A deletion mutation in tcpA, encoding the major subunit of the toxin coregulated pilus (regulated by toxR), abolished the colonizing capacity of this strain. These results show for the first time the role of a specific pilus structure in colonization of the human intestine by V. cholerae O1 and exemplify the significance of a genetic regulon in pathogenesis.
Cholera vaccines

Killed oral vaccine


Mucosal and systemic immune responses to a new oral cholera vaccine, consisting of the B subunit plus killed vibrios, were studied in Bangladeshi volunteers and compared with those to clinical cholera. A single peroral dose of vaccine induced a local IgA antitoxin response in intestinal-lavage fluid of seven of eight vaccinees; the response closely mimicked that of patients convalescing from cholera, and evidence of the induction of local immunologic memory was found as well. Two peroral doses were needed for stimulation of an intestinal IgA immune response to the lipopolysaccharide of Vibrio cholerae that was comparable to the response obtained after clinical cholera. This response to peroral immunization was considerably stronger than that to parenteral vaccination, although the intramuscular route gave rise to the strongest IgG antitoxin and antilipopolysaccharide responses in serum. The results suggest that B subunit-whole cell vaccine, when given in at least two oral doses, may be a good candidate for use in cholera prophylaxis.


The B subunit (BS) of cholera toxin and that of the heat-labile enterotoxin (LT) of enterotoxigenic Escherichia coli (ETEC) are antigenically similar. We therefore assessed whether a combined cholera toxin BS/whole-cell (BS-WC) oral vaccine against cholera conferred cross-protection against LT-producing ETEC (LT-ETEC) diarrhea in a randomized, double-blind field trial among rural Bangladeshi children and women. The 24,770 persons who ingested two or more doses of BS-WC vaccine were compared with 24,842 controls who took two or more doses of killed whole-cell (WC) oral cholera vaccine. Sixty-seven percent fewer episodes of LT-ETEC diarrhea were noted in the BS-WC group than in the WC group during short-term (three-month) follow-up (P less than .01), but no reduction was evident during the ensuing nine months. Short-term protection was particularly notable against LT-ETEC diarrhea causing life-threatening dehydration (protective efficacy, 86%; P less than .05).


Because of demonstrable cross-reactivity of cellular antigens contained in B subunit-killed whole-cell (BS-WC) and killed whole-cell-only (WC) oral cholera vaccines with antigens of various non-cholera species of the family Vibrionaceae (NCV), the protection conferred by
the vaccines against diarrhoea associated with NCV was evaluated during a randomized, double-blind field trial in Bangladesh. Children aged 2-15 years and women aged greater than 15 years (62,285 in number) received three doses of BS-WC vaccine, WC-only vaccine, or a placebo consisting of Escherichia coli K12 strain (K12). During 1 year of follow-up, the incidence of treated episodes of diarrhoea associated with non-cholera vibrios known to be enteric pathogens (non-01 Vibrio cholerae, V. fluvialis, V. parahaemolyticus, V. mimicus) in the placebo group was low (1.9 cases per 10,000 recipients) and identical to that for the two vaccine groups combined. The incidence (per 10,000 recipients) of treated diarrhoeal episodes associated with Aeromonas species was considerably higher, but nearly identical in the three groups (26.1 cases for BS-WC, 26.0 cases for WC; 25.9 cases for K12). Pleisiomonas shigelloides was not isolated from any participant. It is concluded that NCV other than Aeromonas were rarely isolated from diarrhoeal patients in our study population and that killed oral vaccines which were effective against cholera exhibited no detectable cross-protection against diarrhoea associated with NCV organisms.


The protective efficacy (PE) of B subunit killed whole-cell (BS-WC) and killed whole-cell-only (WC) oral cholera vaccines was assessed in a randomised double-blind field trial among children aged 2-15 years and women over 15 years in rural Bangladesh. Among the 62 285 subjects who received three doses of BS-WC, WC, or Escherichia coli K12 strain placebo, cumulative PE at 3 years of follow-up was 50% for BS-WC and 52% for WC. PE was similar against severe and non-severe cholera, but was significantly lower in children who were vaccinated at 2-5 years (26% for BS-WC; 23% for WC) than in older persons (63% for BS-WC; 68% for WC). Among persons vaccinated at 2-5 years, protection at 4-6 months of follow-up was similar to that for older persons, but rapidly waned thereafter and was not evident during the third year of follow-up. In contrast, persons vaccinated at older ages were protected even in the third year of follow-up (PE 40% for BS-WC; 62% for WC). PE was substantially higher against classical cholera (58% for BS-WC; 60% for WC) than against El Tor cholera (39% and 40%).


BACKGROUND: Several studies have shown that orally administered killed cholera vaccines are safe and protective in populations at risk of cholera in developing countries. However, these vaccines have not been adopted for use in developing countries because of their expense and limited efficacy in young children. We have tested an inexpensive, killed whole-cell cholera vaccine developed and produced in Vietnam. METHODS: The efficacy of the vaccine was assessed in a large-scale, open field trial in people at least 1 year old residing in 22,653 households in the central coastal city of Hue. Alternate households were assigned vaccine (67,395 people; two doses per person) or no vaccine (67,058 people). Surveillance for cholera was conducted in all Ministry of Health facilities serving this population. Analysis was by intention to treat. FINDINGS: During an outbreak of El Tor cholera 8-10 months after vaccination, 37 cases of cholera requiring inpatient care occurred among age-eligible people
allocated to the vaccine group, and 92 cases among age-eligible people allocated to the no-vaccine group (protective impact 60% [95% CI 40-73]). Among the 51,975 people who received the complete two-dose vaccine regimen, the protective efficacy was 66% (46-79): in this subset, the protective efficacy was similar for children aged 1-5 years (68%) and for older people (66%). INTERPRETATION: These findings suggest that oral killed whole-cell vaccines can confer substantial protection against El Tor cholera in young children, who are at highest risk of cholera in endemic settings. An inexpensive, locally produced, and effective oral cholera vaccine may be within reach of the limited health-care budgets of poor countries with endemic cholera, if our findings can be replicated in a randomised double-blind trial.

PIP: Vibrio cholera 01, El Tor biotype, entered Vietnam in 1964 and during 1990-94 an average of 3240 cases were reported annually with a case-fatality rate of about 1%. The efficacy of an inexpensive, killed whole-cell cholera vaccine developed in Vietnam was assessed in a large-scale, open field trial in the city of Hue. The vaccine contained V. cholera 01 constituents: heat-killed V. cholera Inaba, heat-killed V. cholera Ogawa, and formalin-killed V. cholera Inaba. All 134,453 residents, aged 1 year or older, of 22,653 households in 19 communes were eligible to take part in the trial. Alternate households were assigned vaccine (67,395 people; 77% received 2 doses per person) or no vaccine (67,058 people serving as controls) during December 1992 and January 1993 by 80 vaccination teams. Following the vaccination no cases of cholera were detected until late August 1993. Between August 20 and October 4, 1993, there were 129 cases of cholera requiring inpatient care among age-eligible participants. The isolates were 01 serogroup and Ogawa serotype. There were 37 cases of cholera in the vaccine group and 92 cases in the control group. The risk of cholera was 0.5/1000 and 1.4/1000, respectively. The protective impact was 60% (95% confidence interval [CI] 40-73; p 0.001). Among 51,975 recipients of 2 vaccine doses the protective efficacy was 66% (CI 46-79; p 0.001). The protective efficacy was similar for children 1-5 years old (68%) and for older people (66%). The protective efficacy was somewhat higher among the vaccinated living in homes with unclean water sources (74% vs. 62%). The protective efficacy was also higher against severe than against non-severe cholera (76% vs. 58%). Oral killed whole-cell vaccines can protect against El Tor type cholera in children who are highest risk. The government has lately added a killed V. cholera 0139 strain to the existing formulation. Phase 2 tests of safety are under way, and a large-scale, randomized, double-blind field trial will start in 1997.


Every year since its introduction in 1991, there have been epidemics of cholera in Lima, Peru. Vaccination is one approach to the control of cholera. A pilot study was conducted to assess the safety and immunogenicity of a whole cell plus recombinant B subunit (WC/rBS) cholera vaccine in Lima, Peru. Five hundred and forty-one volunteers aged 2-65 years received two doses two weeks apart of WC/rBS vaccine or Escherichia coli K12 placebo administered in bicarbonate buffered water. Symptoms were monitored on all subjects and blood was collected from 102 persons before the first dose and two weeks after the second dose. Mild post-vaccination gastrointestinal symptoms were reported with equal frequency for both the vaccine and placebo recipients. Among 51 vaccines, 49% had a twofold or greater increase in serum vibriocidal titers (GMT = 78; range < 1:10 to 1:5120); and 92% and 82% developed a twofold or greater serum anti-cholera toxin IgG and IgA response, respectively. Persons with
elevated prevaccination vibriocidal titers had a decreased response to the WC/rBS. Age and blood group did not affect the immune response. The WC/rBS vaccine was safe and immunogenic in a group of native Peruvians.

Live oral vaccine


Attenuated Vibrio cholerae oral vaccine CVD 103-HgR was well tolerated by 324 Thai soldiers and civilians. Most received a single 5 x 10(8) cfu dose, while 40 each received one or two 5 x 10(9) cfu doses. Vibriocidal antibody (the best correlate of immunity) seroconversion was lower in soldiers than civilians (P less than .001). Increasing the vaccine dose to 5 x 10(9) cfu raised the geometric mean titer (P less than .001). A second 5 x 10(9) cfu dose one week later did not notably increase seroconversions. Likelihood of seroconversion was inversely correlated with baseline vibriocidal titer (P less than .001). CVD 103-HgR caused seroconversion in most subjects with baseline titers less than or equal to 1:40, including 100% of civilians after one 5 x 10(8) cfu dose, 79% of soldiers after one 5 x 10(9) cfu dose, and 45% of soldiers after one 5 x 10(8) cfu dose. In persons with elevated baseline titers, vibriocidal antibody seroconversion is not a sensitive measure of whether vaccine has boosted intestinal immunity; for such subjects, other measurements must be used. Study regimens in endemic areas should use a single 5 x 10(9) cfu dose.


Despite considerable experience with single-dose, live, oral cholera vaccine CVD 103-HgR in Asia, Europe, and the Americas, the vaccine had not been evaluated in sub-Saharan Africa or on individuals infected with human immunodeficiency virus (HIV). We therefore conducted a randomized, placebo-controlled, double-blind, cross-over clinical trial in 38 HIV-seropositive (without clinical acquired immunodeficiency syndrome (AIDS)) and 387 HIV-seronegative adults in Mali to assess its safety and immunogenicity. Adverse reactions (fever, diarrhoea and vomiting) were observed with similar frequency among vaccine and placebo recipients. The vaccine strain was not isolated from the coprocultures of any subject. The baseline geometric mean titre (GMT) of serum vibriocidal antibody was significantly lower in HIV-seropositives (1:23) than in HIV-seronegatives (1:65) (P = 0.002). Significant rises in vibriocidal antibody were observed in 71% of HIV-seronegatives and 58% of HIV-seropositives after one 5 x 10(8) cfu dose, and 45% of soldiers after one 5 x 10(8) cfu dose. In persons with elevated baseline titers, vibriocidal antibody seroconversion is not a sensitive measure of whether vaccine has boosted intestinal immunity; for such subjects, other measurements must be used. Study regimens in endemic areas should use a single 5 x 10(9) cfu dose.
of this single-dose, oral cholera vaccine in high-risk populations such as refugees in sub-Saharan Africa.

PIP: In response to the 1994 cholera outbreak that swept through Rwandan refugee camps near Goma, Zaire, in 1994, the World Health Organization explored the immunogenicity of a new generation of single-dose, live oral cholera vaccines. One such vaccine, CVD 103-HgR, has been evaluated in Asia, Europe, and the Americas, but not in sub-Saharan Africa or in individuals infected with HIV. Therefore, the present study evaluated the safety and immunogenicity of this new vaccine in a randomized, placebo-controlled, double-blind, crossover clinical trial in Mali. Enrolled were 38 HIV-positive individuals without full-blown AIDS and 387 HIV-negative adults. Adverse reactions (fever, diarrhea, and vomiting) occurred with equal frequency in vaccine and placebo recipients. The vaccine strain was not isolated from the coprocultures of any subject. The baseline geometric mean titre (GMT) of serum vibriocidal antibody was significantly lower in HIV-positive subjects (1:23) than HIV-negatives (1:65). Significant rises in vibriocidal antibody were observed in 71% of HIV-seronegatives and 58% of HIV-positives and in 40% of HIV-positives with CD4 counts below 500/mcl. After immunization, the peak vibriocidal GMT in HIV-negative subjects was 1:584 compared with 1:124 in HIV-positive subjects. In HIV-positives with a CD4 count below 500/mcl, the peak vibriocidal GMT was 1:40. Although serologic responses were significantly attenuated among HIV-positive subjects, especially those with CD4 counts below 500/mcl, CVD 103-HgR was safe in HIV-infected Malian adults. Further evaluations of this single-dose oral cholera vaccine are recommended in high-risk populations such as refugees in sub-Saharan Africa.


A randomized, double-blind, placebo controlled trial was conducted in 50 healthy Swiss adults to assess the safety and immunogenicity of the live oral attenuated cholera vaccine candidate strain Vibrio cholerae CVD 103-HgR (classical, Inaba). A single dose of 5 x 10(8) viable CVD 103-HgR organisms, administered in a buffered liquid formulation, was well tolerated as compared with individuals who received an equivalent amount of heat-killed Escherichia coli K-12 placebo. Eighty-eight percent of subjects receiving CVD 103-HgR mounted a significant (greater than fourfold) rise in Inaba vibriocidal titre while 68% did so for the heterologous Ogawa serotype. The magnitude of the vibriocidal antibody response (as measured by peak geometric mean titre and by fold-rise in titre over baseline) was greater for the homologous Inaba serotype. Nineteen out of 25 volunteers (76%) responded with a significant (p less than 0.05) rise in serum antitoxin levels. No vaccinee who received the E. coli K-12 placebo mounted a significant rise in either vibriocidal or antitoxin antibody levels. These results corroborate the safety and immunogenicity of CVD 103-HgR in healthy adult volunteers.

We conducted a double-blind, placebo-controlled, randomized crossover study to evaluate the safety and immunogenicity of a single $5 \times 10^8$-CFU dose of live oral recombinant cholera vaccine CVD 103-HgR in 94 North American adults. The vaccine was well tolerated without associated adverse reactions. Despite minimal fecal excretion of vaccine, 97% of subjects exhibited serum vibriocidal antibody and 72% had antitoxin responses.


Oral vaccines offer great promise as public-health measures to prevent disease in less-developed countries. CVD 103-HgR, a genetically engineered, attenuated, Vibrio cholerae O1 strain has proved effective in industrialised countries. We have assessed the safety, immunogenicity, and excretion of this live cholera vaccine in children in north Jakarta, Indonesia. 412 children aged 5-9 years received single doses of $5 \times 10^6$, $5 \times 10^7$, $5 \times 10^8$, $5 \times 10^9$, or $1 \times 10^{10}$ colony forming units (CFU) of CVD 103-HgR or placebo ($5 \times 10^8$ inactivated Escherichia coli K-12) with buffer. All doses were well tolerated. The $5 \times 10^8$ CFU dose, which is highly immunogenic in subjects in industrialised countries (greater than 90% seroconversion), elicited seroconversions of vibriocidal antibody in only 16% of Indonesian children. By contrast, a single $5 \times 10^9$ CFU dose of vaccine resulted in high rates (75% and 87%) of seroconversion with two different batches of vaccine. A batch prepared with a centrifugation step gave significantly higher geometric mean titres (16-fold increase over baseline) than did a batch in which there was a filtration step between fermentation and lyophilisation (10-fold increase over baseline). At a $5 \times 10^9$ CFU dose, CVD 103-HgR is well tolerated and highly immunogenic in Indonesian children and should therefore be further investigated for use as a one-dose live oral cholera vaccine in developing countries.

PIP: In February-March 1990, health workers administered a single dose of the oral cholera CVD 103 HgR vaccine with $5 \times 100$ million colony forming units (CFU), $5 \times 10$ million CFU, or $5 \times 1$ million CFU or of a placebo to 274 5-9 year old children in a village within the catchment area of the Infectious Diseases Hospital in North Jakarta, Indonesia. In September-October 1990, they gave a dose of the same vaccine containing either $5 \times 1$ billion CFU or $1 \times 10$ billion CFU from 1 of 2 different batches or a placebo ($5 \times 100$ million inactivated Escherichia coli K 12) to 140 5-9 year old children. 70 children also received an extra dose of buffer. They conducted these trials to examine the safety, immunogenicity, and excretion of this live cholera vaccine. The higher dose genetically engineered oral cholera vaccine ($5 \times 1$ billion CFU) resulted in higher seroconversion rates than the $5 \times 100$ million CFU vaccine which has 90% seroconversion rates among North American and European children (16% vs. 75-87% for 2 different batches). The centrifuged prepared vaccine resulted in significantly greater geometric mean titers (16-fold rise over baseline) than did the filtered prepared vaccine (10-fold rise over baseline) ($p=.001$). The extra buffer did not improve immunogenicity of CVD 10 HgR in these children. None of the 124 children who took the $5 \times 1$ billion or $1 \times 10$ billion CFU dose excreted the attenuated strain of Vibrio cholerae O1. Thus this recombinant vaccine strain would unlikely enter the environment or be transmitted to others. The frequency of adverse reactions was basically the same for the vaccine and the placebo. These results showed that the Indonesian children tolerated a single $5 \times 1$ billion dose of CVD 103 HgR well and induced considerable immunogenicity. Future studies using the same dose in 2-4 year old children are planned.

The genes encoding the A (toxic) subunit of cholera toxin were deleted from pathogenic Vibrio cholerae O1 strain 569B by recombinant techniques, leaving intact production of immunogenic, non-toxic B subunit. The resultant strain, CVD 103, evaluated for safety, immunogenicity, and efficacy as a live oral vaccine, was highly attenuated and elicited strong antibacterial and antitoxic immune responses; a single dose significantly protected volunteers against challenge with pathogenic V cholerae O1 of either serotype or biotype. A further derivative, CVD 103-HgR, which has an Hg++-resistance gene to differentiate it from wild-type vibrios, was also well-tolerated, immunogenic, and protective; moreover, faecal excretion of this derivative was significantly lower than that of CVD 103, which should minimise environmental spread of the vaccine. CVD 103-HgR is a candidate for expanded clinical trials in endemic areas.


To provide optimum protection against classical and El Tor biotypes of Vibrio cholerae O1, a single-dose, oral cholera vaccine was developed by combining two live, attenuated vaccine strains, CVD 103-HgR (classical, Inaba) and CVD 111 (El Tor, Ogawa). The vaccines were formulated in a double-chamber sachet; one chamber contained lyophilized bacteria, and the other contained buffer. In the first study, 23 U.S. adult volunteers received CVD 103-HgR at 10(8) CFU plus CVD 111 at 10(8), 10(7), or 10(6) CFU, CVD 111 alone at 10(7) CFU, or placebo. In the second study, 275 Peruvian adults were randomized to receive CVD 103-HgR at 10(9) CFU plus CVD 111 at 10(9) or 10(8) CFU, CVD 111 alone at 10(9) CFU, CVD 103-HgR alone at 10(9) CFU, or placebo. Three of 15 U.S. volunteers who received CVD 111 at 10(7) CFU developed mild diarrhea, compared to none of 4 who received CVD 111 at 10(6) CFU and 1 of 4 who received placebo. Twelve (63%) of 19 vaccine recipients shed the El Tor vaccine strain. All but one volunteer developed significant Ogawa and Inaba vibriocidal antibody titers. Volunteers who received CVD 111 at 10(7) CFU had geometric mean Ogawa titers four to five times higher than those of volunteers who received the lower dose. In the second study, all dosage regimens were well tolerated in Peruvians. About 20% of volunteers who received CVD 111 at the high dose excreted the El Tor organism, compared to 7% in the low-dose group. CVD 111 was detected in the stools of two placebo recipients, neither of whom had symptoms or seroconverted. In all vaccine groups, 69 to 76% developed fourfold rises in Inaba vibriocidal antibodies. Among those who received the bivalent vaccine, 53 to 75% also developed significant rises in Ogawa vibriocidal antibodies. We conclude that it is feasible to produce a single-dose, oral bivalent vaccine that is safe and immunogenic against both biotypes (El Tor and classical) and both serotypes (Inaba and Ogawa) of cholera for populations in both developed and developing parts of the world.
Cost-effectiveness analyses


BACKGROUND: Cholera spread to Latin America in 1991; subsequently, cholera vaccination was considered as an interim intervention until long-term solutions involving improved water supplies and sanitation could be introduced. Three successive summer cholera outbreaks in northern Argentina and the licensing of the new single-dose oral cholera vaccine, CVD 103-HgR, raised questions of the cost and benefit of using this new vaccine.

METHODS: This study explored the potential benefits to the Argentine Ministry of Health of treatment costs averted, versus the costs of vaccination with CVD 103-HgR in the relatively confined population of northern Argentina affected by the cholera outbreaks. Water supplies and sanitation in this area are poor but a credible infrastructure for vaccine delivery exists.

RESULTS: In our cost-benefit model of a 3-year period (1992-1994) with an annual incidence of 2.5 case-patients per 1000 population and assumptions of vaccine efficacy of 75% and coverage of 75%, vaccination of targeted high risk groups would prevent 1265 cases. CONCLUSION: Assuming a cost of US$602 per treated case and of US$1.50 per dose of vaccine, the total discounted savings from use of vaccine in the targeted groups would be US$132,100. The projected savings would be altered less by vaccine coverage (range 75-90%) or efficacy (60-85%) changes than by disease incidence changes. Our analysis underestimated the true costs of cholera in Argentina because we included only medical expenditures; Indirect losses to trade and tourism had the greatest economic impact. However, vaccination with CVD 103-HgR was still cost-beneficial in the base case.


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 50000 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.

Unpublished WHO documents on cholera vaccines/immunization