

GLOBAL TASK FORCE ON CHOLERA CONTROL

CHOLERA VACCINES: A NEW PUBLIC HEALTH TOOL?

REPORT

**WHO MEETING, 10–11 DECEMBER 2002
GENEVA, SWITZERLAND**



**WORLD HEALTH ORGANIZATION
GENEVA**

CHOLERA VACCINES: A NEW PUBLIC HEALTH TOOL?

REPORT

WHO MEETING, 10–11 DECEMBER 2002
GENEVA, SWITZERLAND



WORLD HEALTH ORGANIZATION
GENEVA, 2004

© **World Health Organization, 2004**

All rights reserved

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

Contents

Summary	4
Introduction	5
1. Available vaccines: published data and evidence	6
1.1 Currently available vaccines and future perspectives	6
1.2 Summary of published data on mass vaccination and available evidence	6
1.3 Transfer of technology	7
2. Opportunities and limitations in vaccine use	8
2.1 Opportunities for vaccine use 2000–2002	8
2.2 Case studies/recent experiences	8
3. Need for additional public health tools for cholera control	9
3.1 Currently recommended control measures	9
3.2 Country-specific examples	10
3.3 Outbreak prediction and targeted interventions	11
4. Economic aspects of cholera outbreaks and of vaccine use	11
4.1 Economic aspects of cholera outbreaks	11
4.2 Economic aspects of vaccine use	11
4.3 Cost-effectiveness of vaccine use in endemic settings	12
4.4 Cost issues relating to safe water and sanitation	12
5. Decision-making process to guide the use of cholera vaccines	13
6. Working group sessions	13
7. Recommendations	14
References	15
Annex 1 — Agenda	17
Annex 2 — List of participants	19

Summary

The aim of the meeting *Cholera vaccines: a new public health tool?*, convened by WHO in Geneva in December 2002, was to consider the potential role that might be played by oral cholera vaccines in the prevention and control of cholera outbreaks and endemic disease, and to produce WHO recommendations on the use of such vaccines. This was a follow-up to the meeting on *Potential use of oral cholera vaccines in emergency situations*, held in Geneva on 12–13 May 1999, which had opened up the discussions on cholera vaccine use (1).

The meeting brought together more than 30 participants from cholera-prone countries, humanitarian organizations, United Nations agencies, scientific institutions, and WHO regional offices. (Participants are listed in Annex 2.) Manufacturers of cholera vaccines were invited to attend as observers on the first day only and were not present for sessions that dealt with developing guidelines for vaccine use.

The meeting was organized in five sessions addressing key aspects of cholera vaccine use as an additional public health tool. Recommendations were developed in working sessions related to: (1) vaccines per se, (2) vaccine use, and (3) epidemiological surveillance to facilitate effective cholera control programmes including vaccine use. Additionally it was recommended that WHO play an active role in supporting future development of cholera vaccine use.

Introduction

New oral cholera vaccines (OCV) have passed the stage of research and development, and some formulas are now commercially available. Thus far, these have been used principally by individual travellers from industrialized countries who risked being exposed to cholera while travelling in endemic areas. Recently, there has been renewed interest in using OCV as a public health intervention. It is felt that mass immunization, together with traditional control measures, could be an additional tool for cholera prevention and response to cholera outbreaks (2, 3), and meetings were convened by WHO in 1995 and 1999 to address this issue. The 1999 meeting led to recommendations for the use of cholera vaccines in some emergency situations; however, many questions were left unanswered (1).

OCV have already been used to prevent outbreaks of cholera in various settings. The experience gained from those interventions, while limited, can help to build an understanding of the best indications and the practical requirements for mass immunization with OCV. So far, however, since each of these situations has been unique, there are no precise definitions of high-risk settings, even in cholera-endemic countries, that would guide the decision to implement a vaccination campaign with OCV.

While it is recognized that most issues remain to be resolved, there is much demand for expert opinion on the use of OCV in mass immunization campaigns and for support to national initiatives. This meeting was convened to address these needs.

The aim of the meeting was to:

- study the role of vaccines in the prevention and control of cholera outbreaks and endemic disease and to produce WHO recommendations on the use of oral cholera vaccines;
- decide on further steps towards using oral cholera vaccines as a new public health tool in the light of existing constraints and limitations;
- agree on a framework for guidelines for the use of oral cholera vaccines in both emergency and endemic situations.

The specific objectives were to:

- review published data and available evidence on oral cholera vaccines;
- review recent use of oral cholera vaccines in public health;
- review opportunities for and limitations on vaccine use;
- review economic aspects of cholera outbreaks and of vaccine use;
- review the proposed decision-making process for the use of cholera vaccines;
- establish criteria for epidemic surveillance and evaluation of cholera vaccination campaigns;
- discuss further possible developments, including vaccine development, surveillance and outbreak prediction.

1. Available vaccines: published data and evidence

Safe and immunogenic OCV exist already The session aimed to clarify the following key concerns:

- What do we know about the different vaccines?
- How do the relevant studies on cholera vaccines in mass immunizations compare?
- What new vaccines are under development?

1.1 Currently available vaccines and future perspectives

Important progress has been made in cholera vaccine development. Three oral vaccines (two inactivated and one live attenuated) are currently available. One consists of killed whole-cell *Vibrio cholerae* O1 with purified recombinant B-subunit of cholera toxin (WC/rBS). After two doses, protection of 85–90% at 6 months in all age groups and of 62% at 1 year among adults has been demonstrated (4–6). Technology transfer has resulted in a variant of the WC/rBS vaccine containing no recombinant B-subunit (i.e. WC vaccine) being produced and tested in Viet Nam. A 66% protection 1 year after a two-dose vaccination was demonstrated in all age groups (7). The third vaccine consists of an attenuated, live, genetically modified *V. cholerae* O1 strain (CVD 103-HgR). Although 95% seroconversion and protection was demonstrated in volunteers in the USA (8), no convincing protection was achieved with this vaccine in a large field trial undertaken in Indonesia (see below).

A number of candidate vaccines are under development. An inactivated vaccine containing the O139 serogroup of *V. cholerae* is being developed in Sweden. Several live attenuated vaccines (including Peru 15, CVD 110, CVD 112) are also under development. Some have already been tested in volunteers and have shown a favourable safety and immunogenicity profile (9–11).

Currently some authors are considering an alternative approach, using conjugate cholera vaccines (12). Although this approach is still at the research stage, availability of conjugate cholera vaccines that provide long-term protective immunity would open prospects for other cholera control strategies.

1.2 Summary of published data on mass vaccination and available evidence

The number of published prospective field studies in which OCV have been used for mass immunization is limited. Killed vaccines were used in four trials and CVD 103-HgR in one. All published trials, which were considered to be of sound methodological quality, cover different combinations of epidemiological settings and populations at risk. Altogether, more than 172 000 individuals were included. The results (protective efficacy) were inconsistent overall, reflecting a lack of homogeneity among trials in terms of setting (endemic vs epidemic), target population, analytical methods, vaccine type, and vaccination regimen.

The most extensive field study with OCV was conducted in Bangladesh between 1985 and 1988; two different formulas of killed vaccines were used (4–6). Although results are highly relevant, the endemic setting of Bangladesh might have influenced favourable trends, in particular on long-term protection. Caution should therefore be exercised in extrapolating these results to purely epidemic situations, where no background immunity exists. In any case, the duration of protection afforded by current formulas does not seem to extend beyond 2 years – and probably less for children.

With killed vaccines, the widest variation in results is seen between studies in Bangladesh 1985–1988 and those in Peru 1993–1995 (13, 14). However, a number of relevant differences between the two may explain the discrepancy in the observed protective efficacy. The main lesson to be drawn is that, beyond the strict success of vaccine delivery to a population, numerous variables can influence the outcome of a vaccination campaign and its impact on public health.

The issue of the live CVD 103-HgR cholera vaccine in field trials is so far unsettled. In preclinical trials, protection of vaccinated volunteers challenged with a homologous (serogroup O1, classical) parental strain was total, starting after 8 days and lasting at least 4–6 months (15). Similarly, a protective efficacy of 91% against moderate or severe diarrhoea was observed in vaccinated volunteers challenged after 3 months with a heterologous (El Tor) strain (16). Contrasting with these excellent results, a single field trial carried out in Indonesia with a sample of 67 508 persons demonstrated no protective efficacy over 4 years (17). However, incidence of cholera in the test area was unexpectedly low so that it was impossible, at least during the first year, to reach statistical significance. More recently, a retrospective analysis of a mass vaccination campaign conducted in the Federated States of Micronesia suggested the protective efficacy of CVD 103-HgR vaccine when used in conjunction with standard control measures for the control of an ongoing outbreak (18).

With the spread of the AIDS pandemic, the use of OCV in mass immunization campaigns is likely to raise issues of safety and immunogenicity in HIV-infected individuals. Four published studies, only one of which considers immunogenicity, address this question (19–22). The limited conclusions that can be drawn at this point are the following:

- OCV are as safe in HIV-infected persons as in controls.
- Protective efficacy might be attenuated, particularly when CD4+ T-cells counts are below 500/ μ l.

The magnitude of the immune response to vaccination could be dependent on the level of environmental exposure to enteric pathogens, and differences in geographical or socio-economic contexts should be taken into account for future studies. More research on these topics is clearly needed.

1.3 Transfer of technology

The killed oral cholera vaccine is a good example of cooperation in technology transfer between developed and developing countries. After O1 WC/rBS and O1 WC vaccines exhibited similar protective efficacy in a cholera endemic area in Bangladesh (6), a transfer of technology of the O1 WC vaccine was conducted between the University of Gothenburg, Sweden, and the National Institute of Health and Epidemiology (NIHE) in Hanoi, Viet Nam, and an efficacy trial was carried out in Viet Nam (7).

In a second phase, a bivalent O1 + O139 serogroup WC vaccine was developed at NIHE, and an efficacy trial initiated in 1997 in Viet Nam. It was concluded that the vaccine was safe and elicited good immune response in all age groups (23); however, the clinical protection could not be evaluated because of the absence of cholera cases.

Ultimately, a transfer of technology was undertaken between NIHE in Hanoi on one side, and the Institute for Biological Products in Wuhan, China, and Biofarma in Bandung, Indonesia, on the other. This was made possible by the relatively simple technique of production of the WC vaccine and showed that this kind of technology transfer can be a solution to the production of cholera vaccine at low cost, still under conditions of good manufacturing practice. If successful, technology transfer will facilitate access to cholera vaccines for vulnerable populations in need, especially in cholera-endemic areas.

2. Opportunities and limitations in vaccine use

The presentation of various case studies aimed to identify the trigger mechanisms for considering mass vaccination. Although limited, the experience gained as a result of this intervention can build toward understanding the best indications and the practical requirements for mass immunization with OCV. The limitations in vaccine use should also be identified.

2.1 Opportunities for vaccine use 2000-2002

In Uganda in 1997, OCV were used to prevent outbreaks of cholera among a stable group of refugees (24). In 2000, the Federated States of Micronesia and the Republic of the Marshall Islands, which are exposed to ongoing outbreaks, decided upon mass campaigns in order to limit transmission of *V. cholerae* (*reactive strategy*). Viet Nam also vaccinated populations affected by flooding in the Mekong delta (*pre-emptive strategy*). In 2001, several opportunities for pre-emptive mass vaccination presented themselves, but the intervention was finally carried out in only one location – Mayotte Island – as a preventive measure against a cholera outbreak active in the Comoros archipelago. In 2002, three opportunities for vaccination arose (Goma volcano eruption, suburb in North Cameroon, refugees in Liberia), but no mass campaign was undertaken.

2.2 Case studies/recent experiences

The current strategy for the control of cholera outbreaks includes prevention measures (provision of safe water and soap, sanitation, excreta disposal, site planning), outbreak preparedness and response (cholera treatment centre, epidemiological surveillance, active case-finding), health education, and proper case management (rehydration therapy).

The organization of a mass vaccination campaign with a cholera vaccine as an additional control measure is challenging:

- The logistics of such a campaign are onerous (shipment, cold chain, safe water).
- In an emergency situation, the initial, acute phase is often chaotic. Basic needs are not always covered, and there is frequently a lack of human and material resources.
- For reasons of security, infrastructure, remoteness, etc. it is not always possible to achieve access to the affected areas and to populations at risk.
- Negotiations with local authorities for vaccine acceptance and delivery can be long-winded because authorities are not familiar with the strategies for the use of OCV and the vaccine is usually not licensed in the country in question.
- It may be difficult to secure the commitment of political and administrative authorities, and of the community.
- Cholera outbreaks spread very rapidly in crowded and poor settings such as refugee camps and urban slums yet, for a two-dose vaccine, a minimum period of 4–5 weeks is needed to achieve protective efficacy in a community.

In conclusion, it is difficult to envisage the organization of mass vaccination with OCV in the acute phase of an emergency or where a cholera outbreak has already erupted, at least with the two-dose vaccine. However, mass cholera vaccination deserves more attention for specific indications, such as endemic situations with recurrent outbreaks or admission to refugee camps. In such contexts, a single-dose vaccine would be of potential interest. In any case, strong political commitment on the part of local authorities and extensive information for the population before the campaign are critical, as is the cost of the vaccine. Currently, at least one country (Viet Nam) is considering the introduction of a locally produced oral vaccine in the national expanded programme of immunization.

3. Need for additional public health tools for cholera control

This session addressed current recommended control measures, their strengths and their weaknesses. Key questions dealt with what would be required from an additional public health tool to make cholera control a success. How can available information on surveillance and knowledge of the local setting contribute to targeting interventions for preparedness in endemic and epidemic settings?

3.1 Currently recommended control measures

Efforts to control cholera began early in the nineteenth century, long before the organism responsible for the disease was recognized. Over the past four decades, however, improved understanding of the disease has led to the development of new approaches. Operational guidelines for cholera control, based on widely recommended control strategies, were prepared by WHO for use by its Member countries. Implementation of the guidelines was expected to reduce morbidity and mortality due to cholera.

Currently recommended measures for preventing and controlling cholera epidemics include ensuring safe drinking-water and safe food, improved sanitation, and proper case management. The importance of preparedness for cholera epidemics is also stressed. Preparedness can be achieved by training health staff at different levels in the clinical management of patients with acute diarrhoea, maintaining additional stocks of oral salts, intravenous fluids and antibiotics, and setting up surveillance and reporting mechanisms, as well as through health education for the community.

Outbreaks should be recognized by early warning systems to ensure timely response. This requires:

- identification of cholera patients using standard case definition;
- notification of appropriate authorities (national and international);
- mobilization of supplies, equipment, and other resources such as funds;
- maintenance of a buffer stock of supplies;
- activation of mobile intervention teams, particularly for remote areas where access to health facilities is difficult;
- setting up of emergency treatment centres.

Management of cholera patients includes appropriate rehydration therapy and proper use of antibiotics. Breastfeeding should not be interrupted. Laboratory methods are used to confirm outbreaks caused by *V. cholerae* O1 or O139 and to determine antibiotic sensitivity patterns.

The environmental management for control of cholera consists in:

- improving sanitation and sewage disposal;
- improving access to safe water;
- ensuring safe water storage;
- improving personal and domestic hygiene;
- improving food safety.

The eruption and persistence of cholera in Latin America, the proliferation of epidemics in recent years in Africa and among displaced populations, and the persistence of cholera in Asia raise questions of whether currently recommended control measures are adequate, universally applicable, and effective. New and additional strategies for the prevention and control of cholera are clearly needed.

3.2 Country-specific examples

West Bengal, India

Six of the seven cholera pandemics originated from West Bengal. Diarrhoeal diseases in general and cholera in particular (both O1 for 70% of cases and O139 for 30%) are endemic in this region and accounted for 1 million cases and 1103 deaths (of which more than 20% were due to cholera) in 2000. The cholera season runs from March to October, and epidemics occur frequently after natural disasters (floods, cyclones). Mass vaccination against cholera should ideally take place before the cholera season. However, the expected benefits of vaccination (cases reduced, deaths averted, hospitalization minimized) need to be balanced against the cost of the vaccine.

Assuming a cost per dose of US\$ 1 and two doses per person, the cost of the vaccine itself amounts to US\$ 160 million for the entire population of West Bengal (approximately 80 million). However, the total annual health budget of West Bengal is only US\$ 336 million. Considering only the populations living in the slums (10 million persons), the vaccine cost is still US\$ 20 million – to which infrastructural and human resource costs should be added.

Mass vaccination against cholera could be envisaged in West Bengal only if the vaccine is affordable (which could be achieved via technology transfer and local manufacture) and effective against both O1 and O139 serogroups.

Wajir district, Kenya

The district of Wajir is situated in north-eastern Kenya. The poor, rural population has the lowest health status in the country, and the area suffers recurrent droughts and floods as well as chronic insecurity. A cholera outbreak in 2001 persisted for 4 months and spread to four administrative divisions. Four hundred patients were treated at cholera treatment centres, and the average case-fatality rate was high (9%). This outbreak highlighted the lack of an effective epidemiological surveillance system and of skilled health staff. Epidemic preparedness and case management were poor. Community-based control strategies in general, and water and sanitation measures in particular, were considered to be of low priority.

In such a context, pre-emptive vaccination against cholera could be considered as a new public health tool provided that the vaccine would be available at low cost and easy to administer (with limited reliance on cold chain) and that the protection would be sufficiently long-lasting.

Mozambique

In Mozambique, only 35% of the population have access to potable water and 28% to adequate sanitation structures. Cities are surrounded by unorganized settlements and slums, where sanitation, drainage, and waste disposal are poorly controlled. The country experiences regular cholera outbreaks; the largest – in 1997/1998 – affected all provinces. The national strategy for rolling back cholera is based on both prevention (increasing water supply and sanitation coverage) and epidemic control measures, but it faces difficulties with intersectoral coordination as well as shortages of human and financial resources.

Mozambique currently spends US\$ 145 million a year for response alone. Mass vaccination against cholera would reduce the number of cases and of susceptible people, particularly in the most vulnerable groups. In turn, this would reduce the pressure of cholera outbreaks on the health system and on the communities.

3.3 Outbreak prediction and targeted interventions

The capacity to predict the occurrence, spread, and severity of cholera outbreaks remains limited. In an endemic context, outbreak episodes tend to occur at regular intervals and to be repetitive in well identified areas. This provides the opportunity for targeted interventions such as pre-emptive mass vaccinations. In an epidemic context, the occurrence and spread of cholera outbreaks are more difficult to predict, depending as they do on a multiplicity of factors (water and sanitation conditions, hygiene practices, access to and quality of health care, immunity, migration, etc.).

Better understanding of the specificity of each local situation is needed to determine strategies adapted to the epidemiological and sociological context. The performance of the surveillance system and the quality of data collection are critical for better preparedness and for implementation of outbreak control measures.

4. Economic aspects of cholera outbreaks and of vaccine use

The case study of Peru highlighted the costs related to cholera outbreaks and the strain on health care systems, public health structures, and households, as well as the impact on travel, tourism, and trade. Further presentations addressed economic aspects of vaccine use, including cost-effectiveness in endemic settings and the costs of providing sanitation and safe water.

4.1 Economic aspects of cholera outbreaks

The speed and strength of the outbreak in Peru in 1991 are evident from the numbers presented: a week after the first reported death in January 1991, public health authorities registered 543 cases and 20 deaths. Three months later Peru had 158 000 cases, with a case-fatality rate of around 7%. The year ended with 391 749 cases, 200 000 hospitalizations, and 2906 deaths in Peru alone, while the epidemic spread to the rest of Latin America. Conservative estimates put the direct costs of the outbreak at between US\$ 530 and 715 million just for Peru. The direct costs total US\$ 29 million for hospital/medical care and preventive care; the indirect costs include losses in productivity (absenteeism), loss of productive years of life as a consequence of premature deaths, tourism (down by US\$ 147.1 million), and exports (down by US\$ 27.7 million).

4.2 Economic aspects of vaccine use

Three studies evaluated the cost of a pre-emptive mass vaccination campaign with OCV (both killed and live attenuated vaccines) in endemic and epidemic situations (25–27). All studies compare the cost of vaccination with the cost of currently recommended control measures. For the killed two-dose vaccine, the cost saving threshold ranges from US\$ 0.16 to US\$ 0.38 per dose, depending on the strategy used for comparison (treatment alone or treatment + safe water/sanitation). For the CVD 103-HgR vaccine, the cost saving threshold was US\$ 1.81 per dose. The cost per fully immunized individual was found to be US\$ 0.53 in a stable refugee camp in Uganda (24) and US\$ 0.23 (with no international transport) in a non-emergency situation in Viet Nam (28).

4.3 Cost-effectiveness of vaccine use in endemic settings

Many nations continue to have a large burden of disease from endemic cholera – although this fact is often not reported by the countries and receives little attention. In Matlab, Bangladesh, the annual incidence rate of cholera ranges from 1 to 5 per 1000 population. Seasonal patterns vary by region but most seasons are predictable. In addition, cholera outbreaks occur at regular intervals, notably after flooding. Overall cholera cases account for 20% of admissions to Dhaka Hospital (at least 20 000 cases a year).

In the context of a developing country, successful OCV would need to be not only safe and effective, but also inexpensive and easy to deliver. The currently available OCV, although they address a major public health problem, remain expensive and are not convenient to use. In addition, the commitment from governments in developing countries is limited.

A cost-effectiveness model for cholera vaccination with oral vaccines was developed (29). The cost of the vaccine (including delivery) and the incidence of cholera were the most important variables in determining the cost-effectiveness of potential cholera vaccines. The efficacy of the vaccine was of less significance. The cost per death and per hospital admission averted declines with increasing incidence of cholera. However, even with a very inexpensive vaccine, vaccination became cost-effective only when incidence rates exceeded 1 per 1000. The model also showed that cost-effectiveness was highly dependent on the cost of the vaccine. At a cost of US\$ 0.40 per dose of vaccine, vaccination will cost less than US\$ 400 per death averted, which compares favourably with case management. On the other hand, two-dose vaccination at a cost of US\$ 3.00 per dose will cost more than US\$ 3000 per death averted, even with high incidence rates of cholera (D. Sack, unpublished data).

In conclusion, the cholera vaccine can be useful as a public health tool in endemic settings but:

- will need to be very inexpensive;
- must be easy to administer so that the costs of transport and delivery will not add excessively to the cost;
- will be cost-effective only for areas that have high rates of cholera;
- will not replace treatment facilities.

4.4 Cost issues relating to safe water and sanitation

A study that estimated the cost-effectiveness of selected interventions designed to improve access to safe water supplies, adequate sanitation and better hygiene was presented (30). Costs related to all resources required to put the interventions in place and maintain them and included investment costs and recurrent costs. Health benefits were presented in terms of healthy years gained. Non-health benefits were also estimated. The following were the main conclusions:

- Most of the interventions to improve access to safe water supply and adequate sanitation, taking into account only the health benefits for diarrhoeal diseases, are cost-effective.
- Disinfection at point of use was the most cost-effective intervention.

It is likely that interventions that targeted on key behaviours such as hand-washing would also provide high health yields and be highly cost-effective. While a regulated piped water supply is the ideal long-term aim, yielding the greatest overall health and other benefits, low-cost interventions have a great impact on health per unit of investment.

5. Decision-making process to guide the use of cholera vaccines

Authorities at ministerial level or at the headquarters of implementing organizations who are facing the decision to launch a vaccination campaign with OCV should consider the following issues and steps:

- background data;
- defined objectives of a mass immunization campaign;
- choice of vaccine formula;
- operational and economic aspects;
- ethical considerations;
- follow-up evaluation.

Although pure public health considerations are often paramount in the decision-making process, a range of other pressing issues (operational, economic, or purely political) can legitimately influence health authorities in their decisions. Ultimately, there will be some interplay between policy-makers (defining objectives), public health experts (assessing risks), and the market or potential donors (defining the costs of a campaign).

Once the decision has been taken to organize a mass immunization campaign, the target population, the geographical boundaries of the “population at risk”, and the best strategy/timing must be specified, taking into account safety, ethical, and operational constraints.

6. Working group sessions

The aim of the working group sessions was to develop recommendations relating to key issues in vaccine use. The different groups recommended a firm commitment to the use of OCV, particularly – but not exclusively – in endemic settings where better surveillance data on cholera are needed. The limitations of the two-dose vaccine in epidemic situations was highlighted and the need for safe and effective single-dose vaccines pointed out. A case-by-case situation analysis would always be required.

The participants underlined the need for a working group to concentrate on operational issues. A reference group for scientific support, advocacy, and coordination purposes should also be established. The need for a WHO secretariat to take the lead and facilitate the prerequisites (ethical clearance, regulatory approval, and registration) for the use of OCV was also pointed out. The participants were also concerned with the need for guidelines for OCV use in the field.

In a comprehensive discussion of further research needs, the following studies were considered to be top priorities:

- Phase III efficacy trial with CVD 103-HgR;
- safety of live vaccines among immunocompromised HIV-positive individuals and children under 2 years of age;
- role of the B subunit in the efficacy of killed vaccines;
- duration of the protective efficacy provided by OCV;
- feasibility studies in hyperendemic areas;
- economic impact of vaccine use.

The importance of technology transfer and the need for safeguards to ensure the availability of OCV at affordable prices were also clearly highlighted.

7. Recommendations

The recommendations that emerged from the meeting covered three major areas – vaccines per se, vaccine use, and epidemiological surveillance to facilitate effective cholera control programmes that include vaccine use.

Vaccines per se

- Available data indicate that the current OCV are safe and offer good protection for an acceptable period of time (12 and 24 months among children and adults, respectively).
- However, the need remains to obtain additional efficacy data on live OCV.
- O139 should be included in OCV: it is responsible for a significant proportion of cholera cases and there is major concern that it has the potential for becoming pandemic.

Vaccine use

- The use of OCV in certain endemic and epidemic situations is recommended (guidelines to be developed). Such use must be complementary to existing strategies for cholera control (safe water and sanitation, case management, etc.).
- Well designed demonstration projects in which OCV are used in endemic and epidemic situations should be implemented as soon as possible, preferably within the next 3 years, to provide information for use by global programmes. Each demonstration project should be evaluated by an independent group of experts.
- All partners in the Global Task Force on Cholera Control should assist countries in the timely implementation of these demonstration projects.

Epidemiological surveillance

- Surveillance systems for acute diarrhoea and cholera should be strengthened or, where no such systems exist, established. These surveillance systems are critical for assessing the true burden of disease, identifying the areas at highest risk, and detecting outbreaks of cholera at the earliest possible stage.
- All countries should develop accurate reporting mechanisms for cholera and information-sharing with the GTFC in order to facilitate effective cholera control programmes, including vaccination.

Additional recommendations

- WHO should develop draft guidelines for vaccine use.
- WHO should identify and follow up possible sites for demonstration projects and facilitate the preparation of project protocols.
- WHO should ensure regular meetings of a core group for review of demonstration projects and guidance.
- WHO should develop an information and advocacy strategy for regional offices, countries, and potential donors.
- WHO should help to identify likely sources of funds for implementation and follow-up.

References

1. *Potential use of oral cholera vaccines in emergency situations. Report of a meeting, Geneva, 12–13 May 1999.* Geneva, World Health Organisation, 1999 (CDS/CSR/EDC/99.4)
2. Cholera 2001. *Weekly Epidemiological Record*, 2002, 77:257–268.
3. Cholera vaccines. *Weekly Epidemiological Record*, 2001, 76:117–124.
4. Clemens JD et al. Field trial of oral cholera vaccines in Bangladesh. *Lancet*, 1986, 2:124–127.
5. 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.
6. Clemens JD et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. *Lancet*, 1990, 335:270–273.
7. Trach DD et al. Field trial of a locally produced killed oral cholera vaccine in Vietnam. *Lancet*, 1997, 349:231–235.
8. Kotloff KL et al. Safety and immunogenicity in North Americans of a single dose of live oral cholera vaccine CVD 103-HgR: results of a randomized, placebo-controlled, double-blind crossover trial. *Infection and Immunity*, 1992, 60:4430–4432.
9. Tacket CO et al. Safety and immunogenicity of live oral cholera vaccine candidate CVD 110, a delta ctxA delta zot delta ace derivative of El Tor Ogawa *Vibrio cholerae*. *Journal of Infectious Diseases*, 1993, 168:1536–1540.
10. Kenner JR et al. Peru-15, an improved live attenuated oral vaccine candidate for *Vibrio cholerae* O1. *Journal of Infectious Diseases*, 1995, 172:1126–1129.
11. Cohen MB et al. Randomized, controlled human challenge study of the safety, immunogenicity, and protective efficacy of a single dose of Peru-15, a live attenuated oral cholera vaccine. *Infection and Immunity*, 2002, 70:1965–1970.
12. Boutonnier A et al. Preparation, immunogenicity, and protective efficacy, in a murine model, of a conjugate vaccine composed of the polysaccharide moiety of the lipopolysaccharide of *Vibrio cholerae* O139 bound to tetanus toxin. *Infection and Immunity*, 2001, 69:3488–3493.
13. Sanchez JL et al. Protective efficacy of oral whole-cell/recombinant B subunit cholera vaccine in Peruvian military recruits. *Lancet*, 1994, 344:1273–1276.
14. Taylor DN et al. Two-year study of the protective efficacy of the oral whole cell plus recombinant B subunit cholera vaccine in Peru. *Journal of Infectious Diseases*, 2000, 181:1667–1673.
15. 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.
16. Tacket CO et al. Randomized, double-blind, placebo-controlled, multicentered trial of the efficacy of a single dose of live oral cholera vaccine CVD 103-HgR in preventing cholera following challenge with *Vibrio cholerae* O1 El Tor Inaba three months after vaccination. *Infection and Immunity*, 1999, 67:6341–6345.
17. Richie E et al. Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in north Jakarta, Indonesia, a cholera-endemic area. *Vaccine*, 2000, 18:2399–2410.
18. Calain P et al. Can oral cholera vaccination play a role in controlling a cholera outbreak? *Vaccine* (in press).
19. Eriksson K et al. Intestinal antibody responses to oral vaccination in HIV-infected individuals. *AIDS*, 1993, 7:1087–1091.

20. Lewis DJM et al. Immune response following oral administration of cholera toxin B subunit to HIV-1 infected UK and Kenyan subjects. *AIDS*, 1994, 8:779–785.
21. Ortigao de Sampaio MB et al. Increase in plasma viral load after oral cholera immunization of HIV-infected subjects. *AIDS*, 1998, 12:F145–F150.
22. Perry RT et al. A single dose of live oral cholera vaccine CVD 103-HgR is safe and immunogenic in HIV-infected and HIV-uninfected adults in Mali. *Bulletin of the World Health Organization*, 1998, 76:63–71.
23. Trach DD et al. Investigations into the safety and immunogenicity of a killed oral cholera vaccine developed in Viet Nam. *Bulletin of the World Health Organization*, 2002, 80:2–8.
24. Legros D et al; Mass vaccination with a two-dose oral cholera vaccine in a refugee camp. *Bulletin of the World Health Organization*, 1999, 77:837–842.
25. Temporado Cookson S et al. A cost-benefit analysis of programmatic use of CVD 103-HgR live oral cholera vaccine in a high-risk population. *International Journal of Epidemiology*, 1997, 26:212–219.
26. Murray J, McFarland DA, Waldman RJ. Cost-effectiveness of oral cholera vaccine in a stable refugee population at risk for epidemic cholera and in a population with endemic cholera. *Bulletin of the World Health Organization*, 1998, 76:343–352.
27. Naficy A et al. Treatment and vaccination strategies to control cholera in sub-saharan refugee settings: a cost-effectiveness analysis. *Journal of the American Medical Association*, 1998, 279:521–525.
28. Naficy A et al. Cost of immunization with a locally produced, oral cholera vaccine in Viet Nam. *Vaccine*, 2001, 19:3720–3725.
29. Sack DA, Freij L, Holmgren J. Prospects for public health benefits in developing countries from new vaccines against enteric infections. *Journal of Infectious Diseases*, 1991, 163:503–506
30. Haller L, Bartram J. Estimating the costs and health benefits of water and sanitation interventions. (Submitted for publication)

Annex 1 – Agenda

10 DECEMBER DAY 1

08:30	Registration	
09:00	Welcome address and opening remarks	Dr Z. Hallaj
09:15	Introduction	Dr C-L. Chaignat

Session 1 Available vaccines: published data and evidence

09:30	Currently available vaccines and future perspectives	Dr D. Steele
09:40	Summary of published data on mass vaccination and available evidence	Dr P. Calain
10:10	South–south transfer of technology	Dr D. Trach
10:20	Discussion	Dr B. Ivanoff

Session 2 Opportunities and limitations in vaccine use

11:15	Case studies/recent experiences: • Complex emergencies • Federated States of Micronesia • Cameroon	Dr D. Legros Dr P. Calain Dr K. Hammadi/ Dr E. Le Saout
11:45	Opportunities for vaccine use 2000–2002	Dr C-L. Chaignat
11:50	Discussion and lessons learnt	

Session 3 Need for additional public health tools for cholera surveillance and control

14:00	Currently recommended control measures	Dr K. Siddique
14:10	Country-specific examples: • West Bengal, India • Kenya, Wajir district • Mozambique	Dr S. Bhattacharya Dr L. Doull Dr A. Barretto
14:40	Outbreak prediction and targeted interventions	Dr S. Briand
15:00	Discussions and lessons learnt	

Session 4 Economical aspects of cholera outbreaks and of vaccine use

16:00	Economic aspect of cholera outbreaks	Dr U. Panisset
16:10	Economic aspects of vaccine use	Dr C-L. Chaignat Dr P. Calain
16:20	Cost-effectiveness of vaccine use in endemic settings	Dr D. Sack Dr K. Siddique
16:30	Cost issues relating to safe water and sanitation	Dr J. Bartram
16:40	Discussion and lessons learnt	
17:15	Summary of the day	

11 DECEMBER DAY 2

Session 5 Decision-making process to guide the use of cholera vaccines (plenary)

- 8:30 – 9:30 Review of specific aspects of the working document:
• Decision-making process and its components Dr P. Calain
• Logistic aspects of a campaign

Working Group Sessions

Aim: to develop recommendations with regard to key issues in vaccine use
Three groups working in parallel reporting back to plenary

Session 6 Develop criteria to decide on vaccine use in mass immunizations

- 9:30 Working session
11:30 Report to plenary
12:00 Discussion and recommendations

Session 7 Discuss operational issues and suggest further steps to guide vaccine use in mass immunizations

- 14:00 Working session
16:00 Report to plenary
16:30 Discussion and recommendations
17:00 Summary of meeting
17:30 Closing remarks

Annex 2 – List of participants

Humanitarian organizations and United Nations agencies

EPICENTRE

Dr Dominique Legros, EPICENTRE, 8 rue Sabin, 75011 Paris, France
Tel. +33 1 4 21 2929; Fax: +33 1 4 21 2803; E-mail: dlegros@epicentre.msf.org

International Committee of the Red Cross

Dr Eric Burnier, International Committee of the Red Cross, Avenue de la Paix 19, 1202 Geneva, Switzerland
Tel. +41 22 734 6001; E-mail: eburnier@icrc.org

International Federation of Red Cross and Red Crescent Societies

Dr Bernard Morinière, Senior Medical Epidemiologist, International Federation of Red Cross and Red Crescent Societies, 17 Chemin des Crêts, Petit-Saconnex, 1211 Geneva 19, Switzerland
Tel. +41 22 730 4222; Fax: +41 22 733 0395; E-mail: bermejo@ifrc.org

Medical Emergency Relief International

Ms Linda Doull, Health Director, Medical Emergency Relief International, 5–13 Trinity Street, Borough, London SE1 1DB, England
Tel. +44 020 7378 4847; Fax: +44 207 378 4899; E-mail: linda.doull@merlin.org.uk

Médecins Sans Frontières

Dr Elizabeth Le Saout, Médecins Sans Frontières, rue du Lac 12, Case postale 6090, 1211 Geneva 6, Switzerland
Tel. +41 22 849 8484; Fax: +41 22 849 8488; E-mail: Elisabeth.LESAOUT@geneva.msf.org

Ms Karima Hammadi, Médecins Sans Frontières, rue du Lac 12, Case postale 6090, 1211 Geneva 6, Switzerland
Tel. +41 22 849 8484; Fax: +41 22 849 8488; E-mail: Karima.Hammadi@geneva.msf.org

Swiss Humanitarian Aid

Dr Flavio Del Ponte, Swiss Humanitarian Aid Unit, Freiburgstrasse 13, 3003 Bern, Switzerland
Tel. +41 31 322 3124; Fax: +41 31 324 1694; E-mail: flavio.delponte@deza.admin.ch

Dr J.P. Stamm, Swiss Humanitarian Aid Unit, Freiburgstrasse 13, 3003 Bern, Switzerland
Tel. +41 31 322 3124; Fax: +41 31 324 1694; E-mail: jpstamm@iprolink.ch

United Nations Children's Fund

Dr A. Paganini, Senior Health Advisor, Health Programme Division, United Nations Children's Fund, UNICEF House, 3 United Nations Plaza, New York, NY 10017, USA
Tel. +1 212 8246 338; Fax: +1 212 824 6460; E-mail: apaganini@unicef.org

United Nations High Commissioner for Refugees

*Dr Serge Malé, Health and Community Development Section, United Nations High Commissioner for Refugees, rue de Montbrillant 94, 1202 Geneva 2, Switzerland
Tel. +41 22 739 8407; Fax: +41 22 739 7377; E-mail: male@unhcr.ch

Ms Kate Burns, United Nations High Commissioner for Refugees, rue de Montbrillant 94, 1202 Geneva 2, Switzerland
Tel. +41 22 739 8003; Fax: +41 22 739 7371

Scientific institutions

Aga Khan University

Dr Zulfiqar Ahmed Bhutta, Paediatrics and Child Health, The Aga Khan University, P.O. Box 3500, Stadium Road, Karachi 74800, Pakistan (*Chairman*)
Tel. +92 21 493 0051 ext. 4721; Fax: +92 21 493 4294; E-mail: zulfiqar.bhutta@aku.edu

Centers for Disease Control and Prevention

Dr Roger Glass, Rotavirus Laboratory, Division of Viral Diseases, Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA
Tel. +1 404 639 3577; Fax: 404 639 3645; E-mail: rig2@cdc.gov

Dr Eric Mintz, Diarrheal Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA - Tel. +1 404 639 3461; Fax: +1 404 639 2205; E-mail: rig2@cdc.gov

International Centre for Diarrhoeal Disease Research, Bangladesh

*Dr David Sack, Director, International Centre for Diarrhoeal Disease Research, Bangladesh, GPO Box 128, Dhaka 1000, Bangladesh
Tel. +880 2 882 3031; Fax: +880 2 882 6050; E-mail: dsack@icddr.org

Dr A.K. Siddique, Epidemic Control Preparedness Programme, International Centre for Diarrhoeal Disease Research, Bangladesh, GPO Box 128, Dhaka 1000, Bangladesh
Tel. +880 2 882 3031; Fax: +880 2 882 6050; E-mail: siddique@icddr.org

Indian Council of Medical Research

*Dr N.K. Ganguly, Director-General, Indian Council of Medical Research, Ansari Nagar, Post Box 4911, New Delhi 110 029, India
Tel. +91 11 651 7204; Mobile: +91 98 111 8457; Fax: +91 11 686 8662/651 1547;
E-mail: gangulynk@icmr.delhi.nic.in

Dr Sujit Bhattacharya, Director, National Institute of Cholera and Enteric Diseases, Indian Council of Medical Research, P-33 CIT Road, Scheme XM, Beliaghata, P.O. Box 177, Calcutta 7000 010, India
Tel. +91 33 350 1176; Fax: +91 33 350 5066; E-mail: bsujit@vsnl.net

Institut Pasteur

Dr Jean-Michel Fournier, Chef de l'Unité du Cholera et des Vibrions, 25-28 Rue du Docteur Roux, Cedex 15, 75724 Paris, France
Tel. +33 145 688220; Fax: +33 145 688223; E-mail: fournier@pasteur.fr

International Vaccine Institute

*Dr John Clemens, Director, International Vaccine Institute, Seoul National University Campus, Shillim Dong, Kwanak-Ku, PO Box 14, Seoul 151-600, Republic of Korea
E-mail: jclemens@ivi.int

Dr Bernard Ivanoff, DOMI Programme, International Vaccine Institute, Résidence les Ronsiers, 36B Route de Saint Cergue, 1260 Nyon, Switzerland
E-mail: bivan@bluewin.ch

Instituto de Investigación Nutricional

*Dr Claudio Lanata, Instituto de Investigación Nutricional, Av. La Molina 865, Lima 12, Peru
Tel. +51 1349 6023; Fax: +51 1349 6025; E-mail: clanata@iin.sld.pe

National Institute of Hygiene and Technology

Dr Dang Duc Trach, Director, National Programme of Immunization, National Institute of Hygiene and Epidemiology, 1 Yersin Street, Hanoi 10 000, Viet Nam
Tel. +84 4 972 29 89; Fax: +84 4 821 26 60; E-mail: trach@fpt.vn

University of Gothenburg

Dr Jan Holmgren, University of Gothenburg, Department of Medical Microbiology and Immunology, Box 435, 40530, Gothenburg, Sweden
Tel. +46 31 342 4911; Fax: +46 31 82 0160; E-mail: Jan.Holmgren@microbio.gu.se

University of Maryland

*Dr Myron Levine, University of Maryland School of Medicine, 685 W. Baltimore Street, HSF 480, Baltimore, MD 21201, USA
Tel. +1 410 706 7588; Fax: +1 410 706 6205; E-mail: mlevine@medicine.umaryland.edu

Country representatives**Chad**

Dr Daugla D. Moto, Swiss Tropical Institute (ITS-CSSI/T), B.P. 972 N'Djaména, Chad
Tel. +235 52 30 74; Fax: +235 52 37 22; E-mail: cssiitsn@intned.td

Ghana

*Dr Samuel O. Sackey, Head, Disease Control Unit, Ministry of Health, P.O. Box M.44, Accra, Ghana
E-mail: dcumoh@africaonline.com.gh

Mexico

*Dr Jaime Sepulveda Amor, Director-General, Instituto Nacional de Salud Pública, Av. Universidad 655, Col. Santa Maria Ahuacatitlan, 62508 Cuernavaca, Morelos, Mexico
Tel. +52 2 73 112097/175734; Fax: +52 2 73 112472; E-mail: jsepulveda@insp3.insp.mx

Mozambique

*Dr Avertino Barreto, Department of Epidemiology and Endemics, Ministry of Health, P.O. Box 264, Maputo, Mozambique
Tel. +258 1 421 305; Fax: + 258-1-431 305; E-mail: avertino@dusdee.imoz.com
Dr Marcelino Lucas, Department of Environment, Ministry of Health, Maputo, Mozambique
(*Rapporteur*)

Pakistan

Dr Faizullah Kakar, WHO Medical Officer/Epidemiologist, Early Warning System Project, National Institute of Health, Chak Shazad Road, Islamabad, Pakistan (*Rapporteur*)
Tel. +92 51 2400 22 108/2417 43; Fax: +92 51 2240430; Email: kakar@comsats.net.pk

Philippines

Dr Mario Baquilod, Chief, Center for Infectious Diseases, Department of Health, San Lazaro Compound, Sta Cruz 2, Marikina City 1807, Philippines
Tel. +632 743 8301, local 2350; Fax: +632 711 6808; E-mail: mbaquilod@hotmail.com

South Africa

Dr H. Chabalala, Deputy Director, Emerging and Re-emerging Infectious Diseases, National Health Department, Room 1409, Hallmark Building, Pretoria, South Africa
Tel. +27 12 312 0995; E-mail: ChabaH@health.gov.za

United Republic of Tanzania

*Dr Deo Mtasiwa, DUHP, P.O. Box 633 20 Dar-es-Salaam, United Republic of Tanzania
Email: duhp@twiga.com

Vaccine manufacturers (*observers*)

SBL Vaccines/Powderject

Dr Nils Carlin, European Medical Affairs, SPL Vaccines, SE-105 21 Stockholm, Sweden
Tel. +46 8 735 10 000; Fax: +46 8 83 41 74; E-mail: nils.carlin@powderject.com

Mr Bjorn Sjostrand, Director, SBL Vaccines, SE-105 21 Stockholm, Sweden
Tel. +46 8 735 10 000; Fax: +46 827304; E-mail: bjorn.sjostrand@powderject.com

Aventis

Mr Michael Attlan, International Tender, Aventis Pasteur, SA, 2 Ave Pont Pasteur, 69367 Lyon
Cedex 07, France
Tel. +33 4 37 37 7075; E-mail: Michael.Attlan@aventis.com

Berna Biotech

Dr Jean François Viret, Head of Research Department, Berna Biotech Ltd, Rehhagstrasse 79,
CH-3018, Bern, Switzerland
Tel. +41 31 980 6363; Fax: +41 31 980 67 85; E-mail: jf.viret@bernabiotech.com

Dr Guido Dietrich, Berna Biotech Ltd, Rehhagstrasse 79, CH-3018, Bern, Switzerland
Tel. +41 31 980 6363; Fax: +41 31 980 67 85; E-mail: Guido.Dietrich@bernabiotech.com

Secretariat

WHO regional offices

AFRO

*Dr Paul Lusamba, Regional Advisor, Communicable Disease Surveillance and Response
Tel. +263 4 746 000/011/070; Fax: +263 4 746 867/127; E-mail: lusambap@whoafr.org

AMRO

*Dr Marlo Libel, Regional Adviser, Communicable Diseases, Division of Disease Prevention and
Control
Tel. +1 202 974 3259; Fax: +1 202 974-3129; E-mail: libelmar@paho.org

Dr Ulysses Panisset, Regional Adviser on Research for Health and Development Research
Coordination
Tel. + 1 202 974 3586; Fax: +1 202 974-3129; E-mail: panisseu@paho.org

EMRO

Dr Zuhair S. Hallaj, Director, Communicable Disease Control
Tel. +203 483 0090; Fax: +202 276 5414; E-mail: hallajz@emro.who.int

EURO

*Dr Bernardus Ganter, Regional Adviser, Communicable Disease Surveillance and Response
Tel. +45 3917 1398; Fax: +45 3917 1851; E-mail: bga@who.dk

SEARO

*Dr M.V.H. Gunaratne, Regional Adviser, Communicable Disease Surveillance and Response
Tel. +91 11 331 7804-23; Fax: +91 11 337 8438; E-mail: gunaratnem@whosea.org

WPRO

*Dr Hitoshi Oshitani, Regional Adviser, Communicable Disease Surveillance and Response
Tel. +632 528 9730; Fax: +632 521 1036; E-mail: oshitanih@wpro.who.int

WHO headquarters

*Dr Teresa Aguado, HTP/VAB
Dr J.K. Bartram, PHE/WSH
Dr Sylvie Briand, CDS/CSR/NCS
Dr Philippe Calain, CDS/CSR/NCS
Dr Claire-Lise Chaignat, CDS/CSR/NCS
Dr Alessandro Colombo, EHP/EHA
Dr Maire Connolly, CDS/CPE
*Dr N. Dellepiane, HTP/VAB
*Dr Olivier Fontaine, FCH/CAH
*Dr Alya Jaafar Dabbagh, HTP/VAB
*Dr Marie-Paule Kieny, HTP/VAB
Dr Frédérique Marodon, CDS/CSR/NCS
Dr Duncan Steele, HTP/VAB
Dr Tessa Tantorres, GPE/EQC
*Dr Eugenio Villar Montesinos, FCH/RHR

Secretaries

Ms Geraldine Griffin, CDS/CSR/NCS
Ms Pam Hindle, CDS/CSR/NCS

* Unable to attend

