Cholera Vaccine Evaluation

In the light of the outbreak and spread of cholera in several countries in the Americas, the Pan American Health Organization convened a meeting of experts[1] to discuss recent developments and recommendations regarding cholera vaccines. The meeting took place on 3-4 May 1991 at Washington, D.C. The Final Report is presented below.

CHOLERA IN SOUTH AMERICA

The seventh pandemic of cholera reached the Americas in January 1991, when outbreaks of cholera were identified in four separate locations in Peru. By April, the disease had spread to Ecuador, Colombia, Brazil and Chile and some cases were documented in the United States. The rapid, relentless and unpredictable spread of disease raised the prospect that a much larger area of Latin America might soon be affected and that extraordinary preparedness and control measures were needed.

The measures recommended for epidemic control included setting up surveillance of disease, organizing effective treatment programs to prevent mortality, promotion of health education and other measures to ensure proper waste disposal, provision of safe water and food, investigation of the modes of transmission, and discouraging the use of mass chemoprophylaxis. While cholera vaccines are commercially available and have been offered by manufacturers to ministries of health in some of the countries affected, their use has been generally discouraged. Nevertheless, an effective vaccine would be a useful control measure when used in conjunction with the other activities described above. In the face of the current epidemic and in light of recent developments with new cholera vaccines, the status of this recommendation was reviewed.

BACKGROUND

1. Current recommendation for cholera vaccine

The current commercial cholera vaccine composed of killed whole bacteria given parenterally confers modest and brief protection, does not prevent asymptomatic infection, and has only been tested in endemic settings where naturally acquired immunity is also present. Since 1973, WHO has advised that the vaccine is ineffective for preventing the spread of cholera and has recommended that it not be required by countries as a condition of entry for persons arriving from an endemic area. Use of vaccination to prevent disease during an epidemic has also been discouraged because vaccine efficacy is low (about 30-60% protection), two doses are required and protection develops only after several weeks, mass vaccination requires resources that might otherwise be devoted to providing essential public health activities to control the epidemic and identify the modes of transmission, and vaccination can give the population a false sense of security, resulting in lessened efforts to implement other preventive measures.

2. Goals for a cholera vaccine

The prospect of developing an effective cholera vaccine has improved in recent years. This is based especially on a greatly improved understanding of the mucosal immune system that protects against enteric infections, and on evidence that volunteers recovering from cholera are substantially protected against reinfection for several years. The ideal vaccine would be cheap, safe, easy to administer, effective after a single dose, and would protect both nonimmune and immune persons from severe illness for a prolonged period, while possibly reducing the risk of asymptomatic infection. The vaccine would likely be given orally, to optimally stimulate enteric mucosal immunity. New oral vaccines, including the whole cell/B subunit formulation and the live mutant CVD 103 HgR represent considerable progress toward these goals.

3. Current status of candidate cholera vaccines

(a) *Killed whole cell/B subunit vaccine WC/B*

This candidate vaccine consists of killed *V. cholerae* of both serotypes (Inaba, Ogawa) and biotypes (classical, El Tor). To the WC component is added purified B subunit (B), a harmless but immunogenic component of cholera toxin. This vaccine, and WC component alone, have been extensively tested in volunteers and in a large field trial in Bangladesh. These studies showed that the vaccine, given orally, stimulates both local (intestinal) and serum antibody responses and has no side effects. The trial in Bangladesh, conducted

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in children and adult women from 1985 to 1988 showed the following:

(i) The combined WC/B vaccine or WC alone, given in three doses, performed equally well after three years of observation, giving 50-52% protection against cholera in all ages. During the fourth year of observation, neither vaccine afforded appreciable protection.

(ii) During the first 6 months after vaccination the WC/B vaccine gave 85% protection in all ages, whereas the WC vaccine gave 58% protection. The WC/B vaccine also gave significant protection against diarrhoea caused by enterotoxigenic *Escherichia coli* that produce LT toxin.

(iii) During the first 12 months both vaccines were much less protective in young children aged 37-60 months (16-18% protection) than in older children and adults (67-78% protection).

(iv) Protection in children aged 2-5 years averaged 24-47% during the first two years of followup, but then disappeared. In contrast, protection in older persons was sustained for three years, averaging 63-68%.

(v) Overall, the level of protection against El Tor cholera was about 30% lower than for classical cholera.

(vi) Protection by two doses of vaccine, although evaluated in a much smaller group, was equal to that evoked by three doses; one dose was much less effective.

These results are the most promising obtained to-date with any cholera vaccine, especially as regards duration of protection. The lower and relatively brief protection seen in young children is not explained, but may reflect an important contribution to immunity by natural exposure to *V. cholerae*, which occurs frequently in Bangladesh and leads to significant natural immunity among adults.

(b) *Live oral vaccine, CVD-103 HgR*

This candidate vaccine consists of live *V. cholerae* that have been genetically manipulated to delete the gene encoding the A subunit of cholera toxin. A mercury resistance marker has also been inserted in the bacteria. The vaccine has a very small risk of causing brief and mild diarrhoea when fed to volunteers; however, most persons have no symptoms after immunization. The vaccine has not been evaluated in a field trial, but there have been extensive studies in volunteers. In the USA these have shown that:

(i) A single dose of vaccine ($5x10^8$ cfu) was more immunogenic and protective in American volunteers than three doses of WC/B vaccine:

- 92% had a 4-fold or greater vibriocidal antibody response;

- there was 89-100% protection against challenge with classical *V. cholerae*;

- there was 63-64% protection against challenge with El Tor *V. cholerae*, and,

- overall, there was 83% protection against "severe" diarrhoea (1 litre or more of stool).

(ii) In Thai and Indonesian volunteers Phase I trials have shown that:

- Seroconversion for vibriocidal antibody was much better in university students (63-92%) than military recruits (20-39%), and

- Seroconversion in Indonesian children aged 5-9 years was only 16% following a dose of 5×10^8 cfu, but incrased to 79-86% after doses of 5×10^9 or 1×10^{10} cfu.

EVALUATION AND USE OF AVAILABLE CHOLERA VACCINES

1. Public health use of vaccines for control of the epidemic in Latin America

This would include the use of vaccines to protect individuals from illness (especially serious disease) and, possibly control the spread of cholera.

a) *Parental cholera vaccine.* This is considered in the section on background.

b) *Candidate oral cholera vaccines.*

Whole cell/B subunit or whole cell oral vaccines. The efficacy of these vaccines has not been established for the sort of epidemic conditions prevalent in Latin America.

Although the vaccines might show efficacy equal to or greater than that seen in Bangladesh, there are several reasons why efficacy might be lower. These include:

(i) All illness in Latin America is caused by the El Tor biotype of *V. cholerae*, whereas in Bangladesh 60-70% was due to the classical biotype; in Bangladesh the level of protection evoked by the vaccines was about one-third less *versus* El Tor disease than against disease caused by classical strains.

(ii) Most persons at risk in Latin America are immunologically naive with respect of *V. cholerae*. It is possible that vaccine efficacy in Bangladesh was

enhanced in persons already partially immunized by natural exposure to *V. cholerae*.

(iii) Immunization in Latin America would likely be under epidemic conditions, or the threat of an epidemic. Conditions prevailing during an epidemic might overwhelm vaccine induced immunity, thus reducing its apparent efficacy.

(iv) These vaccines were less effective in persons with blood group O, than in those with other blood groups. The proportion of persons with O blood group is about twice as great in Latin America as in Bangladesh.

Additionally, it was noted that available WC/B vaccine would likely contain B subunit made of recombinant bacteria and therefore was a "new" vaccine. For this reason, Phase II studies, and possibly efficacy trials, should be completed before the vaccine is used for disease control.

It was agreed that neither WC nor WC/B vaccine should be used for disease control in Latin America until vaccine efficacy could be determined under carefully controlled conditions.

CVD 103 HgR live oral vaccine. There have been no efficacy trials of this vaccine either in cholera endemic or epidemic areas. This vaccine should not be used for disease control until such trials have been done. These trials should be preceded by Phase II studies in adults and children that clearly establish a safe and immunogenic dose of the vaccine.

2. Evaluation of candidate cholera vaccines

(a) *Objectives and general considerations*

These apply to all candidate vaccines now being considered for human trials: WC, WC/B, and CVD 103 HgR. The major objectives are to determine short term (e.g., 6 months) vaccine efficacy for preventing serious, life-threatening illness. Additional important objectives are to define vaccine efficacy in both young children and adults, to determine the duration of vaccine efficacy, and to determine the effect of vaccination on the occurence of asymptomatic infection.

These objectives will require carefully designed trials to determine vaccine efficacy or effectiveness. In either case, the trials would probably need to be randomized, controlled and preferrably double blind. Based on logistical considerations, randomization may either be on an individual basis or using clusters. It will be particularly difficult to plan and conduct such trials with a minimum of delay, especially given the political and social pressures related to vaccine evaluation during a cholera epidemic. Nevertheless, the general objective should be to institute one or more trials, if possible, late in 1991, when the next summer season begins and an increase in cholera cases is likely.

It is recognized that a successful trial would create a large demand for the vaccine. At a minimum, vaccine should be provided free for trial participants in the control groups. Efforts should also be made, in collaboration with the vaccine manufacturer, to maximize vaccine availability for the host country and the Region. However, this may take some time.

(b) *WC and WC/B vaccines*

In view of the substantial reduction already achieved in the cost of B subunit and the optimistic prospects for further substantial decreases, this component of the vaccine no longer accounts for the majority of the cost for WC/B vaccine. As B subunit enhances short term protection against cholera, and also stimulates cross protection for LT-ETEC lasting several months, it was agreed to focus further efforts only on development and evaluation of WC/B vaccine. Further studies with WC vaccine would not be proposed.

Studies required for WC/B vaccine in Latin America include:

(i) ***Phase II trials.*** These are planned first to be done in North American adults and then in children in Chile. The trials can begin when vaccine is available (July-August 1991) and should be completed before the end of 1991. The trials are being organized by the U.S. Army. The advice of external groups, including WHO, is sought with regard to the design of these trials.

(ii) ***Efficacy/effectiveness trials.*** The major need is for a trial to define vaccine efficacy under epidemic circumstances both in persons previously exposed to *V. cholerae* and those never exposed. This might require the ability to initiate a trial rapidly after a major outbreak begins. It is recognized that this would be difficult to achieve, but it should be attempted. The most appropriate approach was not agreed, but needs to be carefully explored and planned, possibly preparing for a trial in more than one site. WC/B vaccine (up to 300,000-400,000 doses) may be available for such a trial (or trials) from the U.S. Army. Alternatively, it could be produced by Swedish Bacteriological Laboratories (and possibly Pasteur-Merieux) by the end of 1991. Release of vaccine by the U.S. Army requires approval by the Surgeon General, U.S. Public Health Service.

A trial with WC/B vaccine could also be considered in an area already extensively affected by cholera. This would yield data on vaccine efficacy in persons previously exposed only to the El Tor biotype, which is different from the situation in Bangladesh, where exposure to classical *V. cholerae* is common.

These trials, or separate trials, should also be designed to evaluate the effect of the vaccine on asymptomatic infection.

The precise immunization schedule to be used was not defined, although at least two doses would be required. The shortest effective interval between doses should be explored during Phase II studies. The role of a booster immunization, e.g., at 6 months, in sustaining protection should also be considered.

(c) *CVD 103 HgR vaccine*

Further Phase II trials are required before efficacy or effectiveness trials of this vaccine can be planned. Phase II trials, in both adults and children, are planned for Chile, Peru and Costa Rica, to be completed before the end of 1991. If these define a safe and reliably immunogenic vaccine dose, vaccine efficacy should then be determined in a cholera-endemic population, and efficacy or effectiveness in an epidemic setting, as described above for WC/B vaccine.

FURTHER DEVELOPMENT OF CANDIDATE CHOLERA VACCINES

Efforts should be encouraged to "improve" both the WC/B and live oral cholera vaccines, based on results of the studies described above. Some agreed approaches included:

1. WC/B vaccine

The WC component should be modified to include a greater proportion (at least 50%) of El Tor strains. It should also contain maximum amounts of TCP antigen. Further efforts should be made to reduce vaccine cost, both with regard to B subunit and the WC component. The vaccine should be produced in a more convenient galenic formulation, presumably a lyophylized powder that would be reconstituted with buffer salts in water before use.

Longer term improvement of the vaccine should include efforts to develop a one-dose formulation, possibly by the use of microspheres that incorporate vaccine components, are taken up by M cells overlying Peyer's patches, and "deliver" the vaccine components to the mucosal immune system slowly or in a phased manner over several days or weeks. Approaches to improve the immunogenicity of WC/B with adjuvants should also be explored.

2. Live oral vaccine

Approaches to improve the immunogenicity of live oral vaccines should be pursued. These could include the use of other vaccine strains, e.g., CVD 110 (an El Tor strain that is negative for ZOT), CVD 103 HgR2, a strain with 10-fold greater colonizing capacity than CVD 103 HgR, and other live, genetically manipulated strains.

RECOMMENDATIONS

1. Established WHO policy on cholera and diarrhoeal disease control should guide national efforts to control cholera in Latin America. These efforts should not be relaxed or deferred in anticipation that they would soon be substantially modified by the availability of an effective vaccine. Nevertheless, research to evaluate and develop an effective vaccine should be accelerated to the greatest extent possible.
2. Existing WHO recommendations concerning parenteral cholera vaccine were confirmed; namely, it is recommended that it should not be used for control of cholera.
3. It is recommended that existing candidate vaccines (WC, WC/B and CVD 103 HgR) should not be put to public health use in Latin America at this time. Further information is required on the efficacy and effectiveness of WC/B and CVD 103 HgR before such recommendations can be made.
4. No further evaluation of oral WC vaccine is recommended.
5. Phase II studies should be conducted to define the most immunogenic dose of CVD 103 HgR vaccine in children and adults. If acceptable results are obtained, an efficacy trial should be done in an endemic area, and an efficacy or effectiveness trial in an epidemic area.
6. Phase II studies of WC/B vaccine (based on recombinant B subunit) should be done in adults and children. If acceptable results are obtained, an efficacy or effectiveness trial should be done in an epidemic area.
7. Trials with all candidate vaccines should seek to determine the extent of protection in adults and children, to define protection in persons previously exposed to *V. cholerae* and those never exposed, to define the duration of protection, and to evaluate protection against asymptomatic infection.
8. Efforts should be undertaken to improve existing candidate vaccines. This involves improving their immunogenicity, developing practical galenic formulations, and reducing production cost.
9. Decisions need to be made about a joint mechanism for WHO/HQ and PAHO to develop, review and monitor cholera vaccine studies in the Americas. It is recommended that WHO/HQ continue overall coordination of global vaccine development.

(*Source*: Research Coordination Unit and Health Situation and Trend Assessment Program, PAHO.)