

# Status of New Cholera Vaccines

The prospect of developing an effective cholera vaccine has improved in recent years, with increased understanding of the mucosal immune system that protects against enteric infections and the discovery that volunteers recovering from cholera were substantially protected against reinfection for several years. The ideal vaccine would be cheap, safe, easy to administer, and effective after a single dose, and would protect both nonimmune and immune persons against 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. Two new oral vaccines—the killed whole cell/B subunit (WC/B) formulation and the live mutant CVD 103 HgR—represent considerable progress toward these goals.

A cholera vaccine composed of killed whole bacteria is currently available commercially, but its use has been generally discouraged because it confers only modest and brief protection, does not prevent asymptomatic infection, and has only been tested in endemic settings where naturally acquired immunity was also present. Since two parenteral doses are required and protection develops only after several weeks, mass vaccination during an epidemic is impractical as well as potentially wasteful of resources that could be put into proven control measures. In the face of the current epidemic and in light of the recent development of new types of cholera vaccine, the status of these vaccines and WHO recommendations concerning their use were re-

viewed in a meeting that took place at PAHO Headquarters in Washington, D.C., on 3–4 May 1991.

## EVALUATION OF THE CANDIDATE VACCINES

### WC/B Vaccine

This vaccine consists of killed whole *V. cholerae* of both serotypes (Inaba and Ogawa) and both biotypes (classical and El Tor), together with purified B subunit, a harmless but immunogenic component of the cholera toxin. WC/B vaccine, as well as one consisting of the WC component alone, has been extensively tested in volunteers and in a large field trial in Bangladesh. These studies showed that the oral vaccine stimulated both local (intestinal) and serum antibody responses and had no side effects.

The Bangladesh trials found that the overall protection conferred by three doses of the WC/B vaccine was 85% during the first six months, decreased to 50–52% after three years, and was not appreciable during the fourth year. The WC vaccine was less protective at the outset (58%), but similar to WC/B after three years. Both vaccines provided less effective and briefer protection in children under five years of age than in older children or adults. It is theorized that natural immunity among older persons due to previous exposure may account for this discrepancy. Overall, the level of protection against El Tor cholera—the biotype implicated in the current epidemic in Latin America—was about 30% lower than against classical cholera.

The efficacy of the WC/B or WC oral vaccine has not been established in the sort of epidemic conditions prevalent in Latin America. Such conditions might

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Source: Pan American Health Organization, Health Situation and Trend Assessment Program and Research Coordination, "Final report: meeting on cholera vaccine, 3–4 May 1991," Washington, DC: PAHO; 1991 (unpublished document).

overwhelm vaccine-induced immunity. The protection rates found in the Bangladesh field trials are not a reliable prediction of these vaccines' efficacy in Latin America, where most persons are immunologically naive with respect to *V. cholerae*. In addition, these vaccines were less effective in persons with type O blood than in those with other blood types, and the proportion of persons in blood group O is about twice as great in Latin America as in Bangladesh. The meeting participants agreed that neither WC/B nor WC vaccine should be used for disease control in Latin America until vaccine efficacy could be determined under carefully controlled conditions.

#### *Further Studies*

Since the B subunit enhances short-term protection against cholera and also stimulates cross protection for several months against thermolabile enterotoxigenic *E. coli*, it was agreed that efforts should focus on development and evaluation of the WC/B vaccine. Further studies of the WC vaccine were not proposed.

Phase II trials are planned among adults in the United States and children in Chile and should be completed before the end of 1991. The trials are being organized by the U.S. Army, with advice on their design from external groups, including WHO.

Efficacy trials would ideally be carried out under epidemic circumstances, both in persons previously exposed to *V. cholerae* and those never exposed. However, this would require the ability to initiate a trial rapidly after a major outbreak begins, which might prove difficult. Another approach would be a trial in an area already extensively affected by cholera, which would yield data on vaccine efficacy among persons previously exposed to the El Tor biotype.

The precise immunization schedule to be used was not defined at the meeting, but at least two vaccine doses would be required. The shortest effective interval between doses should be explored during Phase II studies.

#### **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 the cholera toxin. The vaccine carries a slight risk of causing brief and mild diarrhea; however, most persons have no symptoms after immunization. It has not been evaluated in a field trial, but there have been extensive studies in volunteers in the United States, in whom a single dose of the vaccine was more immunogenic and protective than three doses of the WC/B vaccine (89%–100% protection against classical *V. cholerae* and 63%–64% protection against the El Tor biotype). Phase I trials have been carried out in Thai and Indonesian volunteers.

#### *Further Studies*

No efficacy trials have been conducted of the CVD 103 HgR live oral vaccine in cholera-endemic or epidemic areas, and it should not be used for disease control until such trials are 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. Such trials are planned for Chile, Costa Rica, and Peru, and are to be completed before the end of 1991. If these trials permit definition of a safe and reliably immunogenic dose, vaccine efficacy should then be determined in a cholera-endemic population, and efficacy or effectiveness in an epidemic setting.

## RECOMMENDATIONS

1. The available parenteral vaccines are not recommended in the present epidemic situation for the reasons noted earlier in this report.

2. Established WHO policy on cholera and diarrheal disease control should guide national efforts to control cholera in Latin America. These efforts should not be relaxed or deferred in anticipation that an effective vaccine will soon be available. Nevertheless, research to evaluate and develop such a vaccine should be accelerated.

3. The existing candidate vaccines should not be put into public health use

in Latin America at this time, since further information on their efficacy and effectiveness is required.

4. Efforts should be undertaken to improve the candidate vaccines, which would involve increasing their immunogenicity (e.g., with adjuvants), developing more practical one-dose formulations, and reducing production cost.

5. A joint mechanism must be established through which WHO/Geneva and PAHO can develop, review, and monitor cholera vaccine studies in the Americas. WHO/Geneva should continue overall coordination of global vaccine development.



### *Andean Health Emergency Program Against Cholera*

The Ministers of Health and the Directors of Social Security in the Andean Area, meeting on 21-22 April 1991 in Sucre, Bolivia, agreed to the formulation of an Andean Health Emergency Program Against Cholera (PAES-Cólera), which was later endorsed at the meeting of the Andean Presidential Council, held in Caracas, Venezuela, on 17-18 May. The Program has four components: environmental sanitation, care of patients, epidemiological surveillance, and social communication. It is to be carried out through two closely linked strategies: a short-term or emergency strategy, which requires mobilizing existing health care and sanitation resources, and a medium- and long-term strategy, which will seek to establish permanent control over the epidemic and make the needed improvements in the health sector as well as the water supply and sewerage sector.

Investments from both internal and external financing sources are necessary to avoid repetition of the current crisis. The short-term program proposal requires a minimum investment of approximately US\$270 million over three years. The World Bank estimates that within the next 10-12 years the Andean subregion will require investments valued at US\$17 billion in the water supply and sanitation sector to cover the 38 million additional inhabitants projected for the year 2000.

*Source:* Convenio Hipólito Unanue and Organización Panamericana de la Salud, Programa andino de emergencia en salud frente al cólera, Washington, D.C., May 1991 (mimeographed document).