



**Proceedings of the
Policymakers' Meeting on the Introduction of
Cholera Vaccination
using New-Generation Oral Vaccines in India**

New Delhi, India

April 10, 2009

This meeting was supported by the Bill and Melinda Gates Foundation, and organized by the Department of Biotechnology, Indian Council of Medical Research, New Delhi, and the International Vaccine Institute, Korea.

Background

Cholera remains one of the most dreaded diseases afflicting mankind. In 2007, the World Health Organization (WHO) recorded 177,963 cholera cases and 4,031 deaths worldwide but these numbers are believed to be substantially underestimated due to surveillance limitations and countries' fear of trade and travel restrictions [1]. A review of cholera cases in India reported to WHO from 2003-2007 showed that the numbers were in the few thousands with a case fatality rate of < 1%. However, it is believed that the number of cholera cases and deaths occurring annually in India is much greater than the number reported. A literature review covering a four-year period from 2003 to 2006 found reported cholera outbreaks in 18 of the 35 States and Union Territories of India. Of these, 11 had cholera outbreaks reported for multiple years. These States and Territories are spread across India, showing that cholera is a country-wide cause of diarrheal illness.

While improved access to clean water and sanitation are the mainstays of cholera control, they require long-term investments, huge financial outlays, and sustained political commitment. Even though new-generation oral cholera vaccines (OCVs) have been available for more than two decades, and have been recommended by WHO for the control of endemic and epidemic cholera, they have not been extensively adopted by developing countries. Currently, the only WHO-prequalified OCV to date is the recombinant B-subunit killed whole-cell vaccine (rBS-WC), Dukoral® (Crucell/SBL). Dukoral® is internationally licensed for individuals two years and above, but is not licensed in India and is considered costly for routine use in public health settings. In addition, it requires at least two doses and needs to be co-administered with a relatively large volume of buffer solution. The other available OCV is the Vietnamese killed

whole cell-only vaccine. Following technology transfer from Swedish scientists, Vietnam produced a killed whole cell-only vaccine, which has been used in high-risk cholera areas in Vietnam. Licensed locally since 1997, this vaccine contains both *Vibrio cholerae* O1 and O139, and provides 50% protection for at least three years after vaccination. Because the vaccine does not require any buffer (making it easy to administer), is inexpensive, and relatively easy to produce, this vaccine was targeted by the International Vaccine Institute (IVI) for widespread international use.

However, the IVI found that for the vaccine to be purchased by UN agencies, the vaccine must be manufactured in a country with a WHO-approved National Regulatory Authority (NRA), and production must comply with WHO standards. Thus, the vaccine strains and production processes were modified by the IVI and the Vietnamese producer, and the manufacturing technology was transferred to Shantha Biotechnics in India, where the NRA, the Drugs Controller General of India, is WHO-approved. This modified vaccine has been shown to be safe and immunogenic in Phase II clinical trials in Vietnamese adults [2], and in Indian children and adults [3]. The Indian studies were conducted at the National Institute of Cholera and Enteric Diseases (NICED) in Kolkata, a constituent Institute of the Indian Council of Medical Research (ICMR) along with the IVI. It is now being evaluated in a placebo-controlled double-blinded randomized Phase III trial among >60,000 participants by NICED/IVI in Kolkata, and interim analyses have shown promising results for both safety and efficacy [4]. The vaccine was recently licensed in India, and it is expected that the Indian-manufactured cholera vaccine will be easily affordable. The results of the Phase III trial of this vaccine conducted by NICED/IVI in Kolkata will facilitate WHO-prequalification, which means that UN agencies can purchase the vaccine for use in the world's poorest countries.

Furthermore, recent findings from a reanalysis of the Bangladesh trial of killed OCVs (both BS-WC and WC only) by the IVI indicated that these vaccines provide herd protection against cholera among non-vaccinees [5], including those who were too young to be vaccinated [6], substantially increasing the public health impact of the WC-only OCV.

The availability of an inexpensive, safe, and effective vaccine that is easy to produce and to administer will greatly facilitate the expanded role of vaccines in the control of cholera.

Therefore, on April 10, 2009, a policymakers' meeting was convened in New Delhi, India by the Department of Biotechnology, ICMR, and the IVI to discuss the introduction of cholera vaccination in India using the IVI-modified OCV. Representatives from 14 different organizations and agencies attended the meeting (please see Appendix).

Overview of presentations

Introductory speeches were made by Dr. V.M. Katoch (Secretary & Director General, ICMR), Mr. Samar Ghosh (State Health Secretary, Ministry of Health & Family Welfare, West Bengal), Dr. Bindu Dey (Advisor, Department of Biotechnology), Dr. John D. Clemens (Director General, IVI), and Dr. J.P. Narain (Director of Department of Communicable Diseases, SEARO/WHO).

Acknowledgements were made to the Department of Biotechnology, Government of India, NICED, Bill & Melinda Gates Foundation, IVI, and ICMR for their support.

Dr. Dilip Mahalanabis described the trends and issues in vaccination against enteric diseases, with a particular focus on cholera. Cholera vaccines that are currently available or under development include: the oral whole-cell (WC) killed vaccine with B subunit (Dukoral®), the reformulated oral WC killed vaccine (developed in Vietnam), live oral CVD, Peru-15, and VA

1.3/1.4 (a Phase II trial has shown it to be immunogenic). While there is the promise of new vaccines in the pipeline, cholera still faces the problem of gross under-reporting by developing countries due to limited surveillance systems and disease stigma.

Dr. G.B. Nair characterized the disease burden of cholera in India, using data from the Government of India, WHO, and a surveillance study in Kolkata. The evidence indicates that cholera is on the rise in India; it is endemic with seasonal outbreaks; and it affects all age groups, especially the very young, which contradicts previous beliefs that cholera is not a major problem in infants. Studies also show that the distribution of *V. cholerae* O1 biotype El Tor is nationwide, while *V. cholerae* O139 is only found in several states. Furthermore, India faces a high prevalence of outbreaks nationwide, and current outbreaks have a longer duration compared to outbreaks in the past. The rapid spread of cholera across India may be due to high transmission and high rate of mutations of *V. cholerae*. The rapid evolution of *V. cholerae* is believed to be responsible for the development and emergence of more virulent hybrid and altered strains, such as the classical toxin-producing El Tor strain.

Dr. N.K. Ganguly described existing tools for the control of cholera in India. Long-term interventions (improved water safety, sanitation, and hygiene) are essential but challenges to implementation exist (e.g., limited resources and difficulties in applying knowledge into practice). Therefore, vaccines are a good short- to medium-term solution to control cholera. However, vaccination and improvements in water safety, sanitation and hygiene should be considered together as a comprehensive package for the control of cholera. Cholera needs to be recast as a global public health problem. Recent research has shown that *Vibrio cholerae* is a complex pathogen with a plastic genome and complex ecology. Thus, global warming and

globalization may lead to an increase in cholera cases worldwide, not just in developing countries.

Dr. John D. Clemens presented the interim analysis results from a Phase III trial of the IVI-reformulated oral killed WC cholera vaccine in Kolkata and described how the vaccine was developed. The vaccine was originally produced in Vietnam as a low-cost alternative to Dukoral® following technology transfer from Swedish scientists. Containing killed whole *V. cholerae* O1 and O139 cells without the B subunit, this vaccine was licensed by VaBiotech (Vietnamese producer). Studies showed that this vaccine had no major side effects and provided 50% protection for three to five years. However, the vaccine had several limitations, among which production was not compliant with the current Good Manufacturing Process (cGMP); inadequate standardization of antigens, which was not compliant with WHO regulations for production of killed OCV; and Vietnam's NRA was not WHO-approved. The IVI determined that internationalization of the vaccine may only proceed if the vaccine was modified to comply with cGMP and WHO standards for manufacturing, and if vaccine production was in a country with a WHO-approved NRA. Thus, the vaccine was modified, resulting in an oral cholera vaccine with increased *V. cholerae* O1 content and more El Tor strains, and complied with international standards for vaccine manufacturing. The production technology was transferred to Shantha Biotechnics in India, which had a WHO-approved NRA. Phase II studies among adults in SonLa, Vietnam, and among adults and children in Kolkata, India showed that the modified OCV is highly immunogenic and safe. A double-blind, randomized clinical Phase III trial is currently being conducted in Kolkata by NICED/IVI to assess protection of a two-dose regimen. Interim analysis results show that vaccination coverage rates were relatively high (64% for the first dose and 62% for the second dose), no major side effects were reported, and protection was

Condensed Proceedings

seen in all targeted age groups (68% protective efficacy among individuals aged 1 year and older).

The IVI also assessed the impact of herd protection by reanalyzing data from the 1985 field trial of killed OCVs in Matlab, Bangladesh. Non-vaccinees and vaccinees were both protected if they resided in highly vaccinated neighborhoods. Modeling of the combined direct and herd protection from killed OCVs predicted near-extinction of cholera with population coverage rates as low as 50%. In summary, the IVI-modified cholera vaccine is safe, easy to administer, protective in all age groups, complies with WHO requirements, confers greater protection against El Tor strains, and has a major public health impact due to effects of direct and herd protection.

Dr. Dipika Sur presented results of cost-effectiveness modeling studies for the modified oral killed WC cholera vaccine to assess its affordability and cost-effectiveness for use in India. A one-time vaccination program in which the WC vaccine was administered orally in two doses at a two-week interval was assumed. The duration of vaccine protection was assumed at three years, and the vaccine was assumed to provide 68% direct protection for the first two years. Costs were measured from the public perspective. Official WHO thresholds for cost-effective interventions were used, which compare net public cost per DALY to per capita income of the country (GDP). A “very cost-effective” threshold in India is less than Rs 35,972 (cost/DALY avoided is less than 3 times the GDP/capita) and a “cost-effective” threshold is less than Rs 107,917 (cost/DALY avoided is less than the GDP/capita). The net public cost per DALY avoided was calculated for three different program options: a school-based program targeting 5-14 years old children (Rs 16,107), a school-based program targeting 1-14 years old children (Rs 15,359), and a community-based program targeting 1 year and above (Rs 34,898). All three

programs were found to be very cost-effective, falling below GDP thresholds. The second option was the most cost-effective out of the three options. The results were robust, supporting the introduction of the modified licensed cholera vaccine in India.

Overview of discussions

Discussions focused on gaps in cholera disease burden knowledge in India, and on the introduction of cholera vaccines into India's public health system. The major issues are insufficient surveillance data from different areas of the country, and underreporting by local governments. Good surveillance data is needed, and in order to generate such data, more funding is needed to establish surveillance systems. Suggestions to address the issues included conducting district-wide analyses to identify "hot spots" in India; and linking local surveillance to the government through the Infectious Diseases Surveillance Network of the Ministry of Health. Stronger efforts should also be made to translate research into applied public health tools.

As the modified whole-cell oral cholera vaccine is safe, effective, and cost-effective, the NTAGI should consider recommending the introduction of the vaccine into public health programs targeted to appropriate populations in India. The new vaccine may be considered in outbreaks, and the IVI is pursuing a study to address this. It was agreed that initial vaccine introduction should be made in endemic settings, starting with the states of West Bengal or Orissa, and it should proceed in a step-by-step fashion with gradual replication of vaccination programs in other areas. The progress of pilot introductions will be evaluated, and based on experiences, broader policy/expansion to new areas will be considered. Follow-up meetings were suggested to ensure that the agenda will move forward. Finally, it was reiterated that even though vaccination

is a key intervention, it should be considered with long-term interventions (e.g., improvements in water safety, sanitation and hygiene) as part of a comprehensive package of public health tools to control cholera in India.

Future directions

Consensus was reached on the efficacy, safety, and feasible use of the modified whole-cell oral cholera vaccine. For the next step forward, the group recommends that the National Technical Advisory Group on Immunization (NTAGI) should consider the introduction of the vaccine into public health programs targeted to appropriate populations in India. Pilot vaccination programs will be initiated in select highly endemic areas such as known areas in West Bengal or Orissa. The pilot programs will be monitored and evaluated, and further expansion to other areas, as well as wider policy changes, will be made based on the pilot programs. Logistical and operational issues will need to be defined, and follow-up meetings should occur to ensure that the agenda will move forward. Underreporting was recognized as an issue, as well as the need for establishment of a national surveillance system in order to generate more disease burden data. Consequently, a proposal was submitted by NICED requesting for funding from the ICMR. The proposal aims to identify the different etiologic agents of diarrhea from give ICMR centers in India.

Participants in the meeting were:

From India: Bindu Dey, Megha Khatri, Department of Biotechnology, Ministry of Science and Technology, New Delhi; V M Katoch, Indian Council for Medical Research, New Delhi; Anuja Krishnan, Institute of Molecular Medicine, New Delhi; Sunil D Khaparde, Ministry of Health and Family Welfare, New Delhi; Samar Ghosh, Ministry of Health and Family Welfare, West

Bengal; Sanjay M Mehandale, National AIDS Research Institute, Pune; Mihir Bhattacharya, Amit Ghosh, G B Nair, Dipika Sur, National Institute of Cholera and Enteric Diseases, Kolkata; Nirmal K. Ganguly, Sanjukta Sen Gupta, National Institute of Immunology, New Delhi; Varaprasad Reddy, Mandeep Singh Dhingra, , Shantha Biotechnics Limited, Hyderabad; Dilip Mahalanabis, Society for Applied Studies, Kolkata; Satish Kumar Gupta, United Nations Children's Fund, New Delhi; Jai P Narain, Sujit K. Bhattacharya, Paul P Francis, Arun Thapa, World Health Organization, New Delhi.

From International Vaccine Institute, Seoul, Republic of Korea: John D Clemens, Deborah Gene Hong, Eunyong Kim, Jayoung Kim, Anna Lena Lopez, Karima Saleh.

From Bill and Melinda Gates Foundation, Seattle, US: Jan M Agosti, K J Singh.

Acknowledgements to Deborah Hong for her part in drafting the proceedings.

References:

- [1] Cholera, 2007. *Wkly Epidemiol Rec* 2008 Aug 1;83(31):269-83.
- [2] Anh DD, Canh do G, Lopez AL, Thiem VD, Long PT, Son NH, et al. Safety and immunogenicity of a reformulated Vietnamese bivalent killed, whole-cell, oral cholera vaccine in adults. *Vaccine* 2007 Jan 22;25(6):1149-55.
- [3] Mahalanabis D, Lopez AL, Sur D, Deen J, Manna B, Kanungo S, et al. A randomized, placebo-controlled trial of the bivalent killed, whole-cell, oral cholera vaccine in adults and children in a cholera endemic area in Kolkata, India. *PLoS ONE* 2008;3(6):e2323.
- [4] Sur D, Lopez AL, Kanungo S, Paisley AM, Manna B, Ali M, et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-

randomised, double-blind, placebo-controlled trial. *Lancet* 2009; DOI:10.1016/S0140-6736(09)61297-6.

[5] Ali M, Emch M, von Seidlein L, Yunus M, Sack DA, Rao M, et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. *Lancet* 2005 Jul 2-8;366(9479):44-9.

[6] Ali M, Emch M, Yunus M, Sack D, Lopez AL, Holmgren J, et al. Vaccine Protection of Bangladeshi infants and young children against cholera: implications for vaccine deployment and person-to-person transmission. *Pediatr Infect Dis J* 2008 Jan;27(1):33-7.