

Meeting report

Considerations around the introduction of a cholera vaccine in Bangladesh

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ABSTRACT

Cholera is an endemic and epidemic disease in Bangladesh. On 3 March 2013, a meeting on cholera and cholera vaccination in Bangladesh was convened by the Foundation Mérieux jointly with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B). The purpose of the meeting was to discuss the investment case for cholera vaccination as a complimentary control and prevention strategy. The performance of a new low cost oral cholera vaccine, Shanchol™, used in recent trials in Bangladesh, was also reviewed in the context of a potential large-scale public-sector vaccination program. Findings showed the oral vaccine to be highly cost-effective when targeting ages 1–14y, and cost-effective when targeting ages 1+y, in high-burden/high-risk districts. Other vaccination strategies targeting urban slums and rural areas without improved water were found to be cost-effective. Regardless of cost-effectiveness (value), the budget impact (affordability) will be an important determinant of which target population and vaccination strategy is selected. Most importantly, adequate vaccine supply for the proposed vaccination programs must be addressed in the context of global efforts to establish a cholera vaccine stockpile and supply other control and prevention efforts.

1. Introduction

A meeting on cholera and cholera vaccination was convened by the Foundation Mérieux in partnership with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) on 3 March 2013 in Dhaka, Bangladesh. After the successful completion of several cholera vaccine trials in the country, the purpose of the meeting was to discuss vaccination as a complimentary control and prevention strategy as Bangladesh takes steps to become the first country to use cholera vaccine in a large-scale public-sector program.

In Bangladesh, cholera is an endemic and epidemic disease where thousands are hospitalized daily during monsoon season, and where there is increasing awareness of the frequency and severity of outbreaks associated with floods and other natural disasters. While case fatality has fallen dramatically with timely access to oral or intravenous rehydration therapy, the recent availability of a new low-cost vaccine with longer, more sustained protection, Shanchol™ (Killed Bivalent (O1 and O139) Whole Cell Oral Cholera Vaccine, Shantha Biotechnics Limited [1]), presents the opportunity for vaccination as a complementary strategy to help reduce the national cholera burden. Shanchol™ was prequalified by the World Health Organization (WHO) in 2011 [2].

2. Bangladesh immunization program

Bangladesh has a high performing Expanded Program on Immunization (EPI) with 90 percent of districts achieving 90+ percent vaccination coverage with DTwP–HepB–Hib pentavalent vaccine [3]. The introduction of pneumococcal conjugate vaccine (PCV-13)

and rotavirus vaccine (Rota-2) is planned for the coming years. Bangladesh eliminated neonatal tetanus (NT) in 2008. Starting in 2006 Bangladesh implemented a highly successful measles reduction campaign and measles–rubella vaccine was introduced in 2012.

Bangladesh was declared polio free in August 2000. Imported polio was detected in 2006 when 18 polio cases were reported and confirmed [4]. Indigenous transmission of wild poliovirus has again been controlled since 2007. An intensive effort to eliminate polio from Bangladesh includes an emphasis on a high performing EPI, National Immunization Days (NIDs) and mop-up campaigns, and the establishment of a strong Acute Flaccid Paralysis (AFP) surveillance system [5].

3. Cholera prevention and control

Cholera is an acute diarrheal disease that can kill previously healthy patients within hours if left untreated by oral or intravenous rehydration therapy [6]. Most deaths are in patients that do not seek care or do not reach a treatment facility in a timely way. Cholera exists both as an endemic and epidemic disease, and the explosive pattern of outbreaks is attributed to a short incubation period of two hours to five days. The majority of cholera endemic countries is found in Asia and sub-Saharan Africa and report an overall case fatality rate of less than five percent [6]. However, in outbreak situations among the most vulnerable groups, the case fatality rate can be up to 50 percent [6]. Although likely a gross underestimate due to under reporting, the World Health Organization (WHO) estimates cholera is responsible for 100,000–130,000 deaths and 3–5 million cases every year, globally [6].

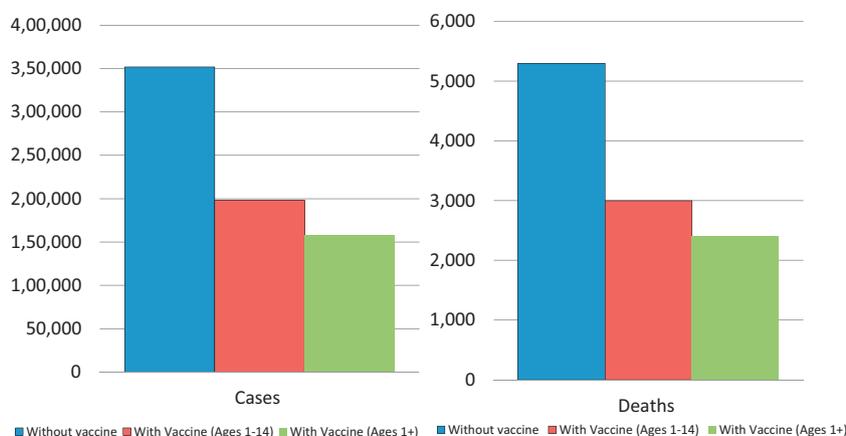


Fig. 1. (A, B) Estimated annual impact of cholera vaccination, ages 1–14 and 1+ in high-burden/high-risk districts, Bangladesh.

Over the last several years one hallmark of the global cholera burden is increased awareness of major cholera outbreaks. WHO currently recommends oral cholera vaccines for complementary use in endemic areas as well as areas at risk of outbreaks, including preemptive use in humanitarian emergencies [6]. Following the 2010 cholera outbreak in Haiti the World Health Assembly passed a resolution for WHO to develop updated and practical guidelines on the use of oral cholera vaccines in conjunction with other control strategies [7,8]. In 2011 WHO convened a working group to advise the creation of a vaccine stockpile specifically intended for outbreak response [9].

4. Cholera in Bangladesh

Endemic and epidemic cholera is a major public health problem in Bangladesh [10,11] and the entire national population (155 m people) is presumed to be at risk of disease [12]. There is no accurate data on the number of cholera cases and deaths in the country. Estimates suggest an incidence of approximately 450,000 cases per year [12]. During 2009, >2 million acute watery diarrhea cases were registered but the proportion that were cholera is unknown [13]. One study estimates that 22 percent of acute watery diarrhea may be cholera [14]. Multidrug-resistant [13] and El Tor strains of cholera have recently emerged in Bangladesh [15]. Multidrug-resistant and El Tor cholera are associated with more severe outcomes, longer hospital stays, and higher case fatality rates. Rapid urbanization is likely contributing to an increase in the rates of cholera in the country [16,17].

5. Findings

Throughout the course of the meeting, presentations highlighted the high performing EPI, the achievements and successes of accelerated disease control efforts and new vaccine introductions following the Bangladesh National Implementation Plan, cholera burden and cholera control and prevention policy, using models to evaluate vaccination strategies for epidemic and endemic cholera control, as well as the Bangladesh investment case for cholera vaccine and updates on cholera vaccine pilot projects in Bangladesh.

Cholera control and prevention strategies that do not include vaccination are well established and mostly effective, yet cholera remains poorly controlled in both endemic and epidemic contexts. Research findings presented by ICDDR, B reveal that new lower cost oral cholera vaccines can be a complementary tool to combat both endemic and epidemic cholera when coupled with access to safe

water, basic sanitation, good hygiene practices, and rehydration therapy and clinical treatment.

Major findings included:

Disease burden and economic burden: Cholera is an endemic and epidemic disease in Bangladesh with approximately 350,000 cases and 5300 deaths attributed to cholera annually [18]. It is also becoming an increasingly urban disease due to growing peri-urban slum populations and overburdened water and sanitation systems. ICDDR, B cholera surveillance indicates 28 of Bangladesh's 64 districts are considered to be "high-burden" or "high-risk" for cholera [18]. Over half of the country's population resides in these high-burden/high-risk districts. Cholera cost-of-illness in Bangladesh is estimated to be US\$6.3 million per year [18].

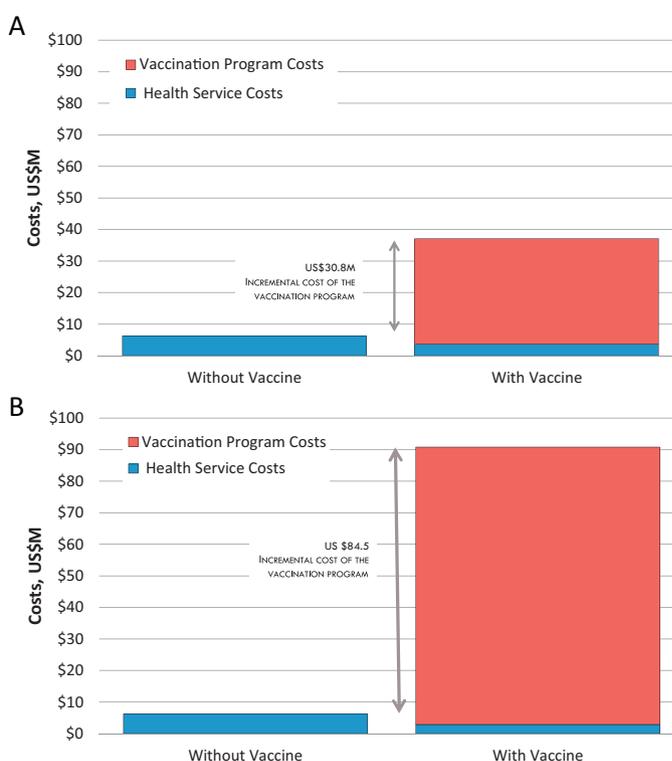


Fig. 2. (A) Health service and minimum program costs for cholera vaccination, ages 1–14 in high-burden/high-risk districts, Bangladesh (in million USD). (B) Health service and minimum program costs for cholera vaccination, ages 1+ in high-burden/high-risk districts, Bangladesh (in million USD)

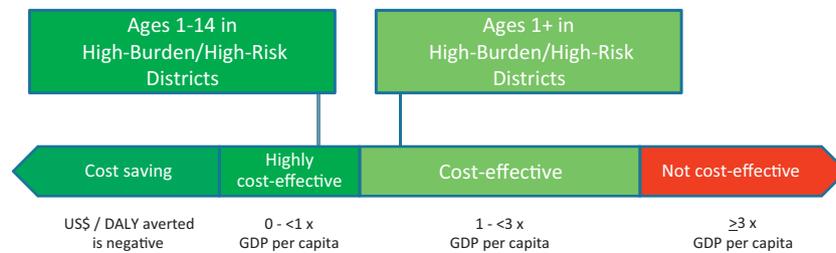


Fig. 3. Cost-effectiveness of cholera vaccination, ages 1–14 and 1+ in high-burden/high-risk districts, Bangladesh

Vaccine efficacy and impact: A two-dose regimen administered to residents one year or older in India showed Shanchol™ to have 66 percent efficacy for at least three years, with significant herd immunity conferred [19]. Shanchol™ is easy to administer as it does not require the administration of a buffer solution.

Depending upon the strategy, it is estimated that vaccination could prevent between 68,000 and 194,000 cases of cholera in Bangladesh annually [18]. Modeling has shown that vaccinating 50–70 percent of the population may stop outbreaks in endemic areas such as Bangladesh [20].

Economic analysis: Analysis of vaccination impact in cholera endemic areas of Bangladesh by the International Vaccine Institute (IVI) [15] has demonstrated that using Shanchol™ (assumptions: revaccination every 3 years; 70% efficacy; vaccine coverage in year of introduction: 75% children 1–14y, 50% adults 15+y):

- vaccination programs targeting 1–14y in high-burden/high-risk districts have the potential, on an average, to reduce the number of cases and deaths by 43 percent while vaccination programs targeting 1+y have the potential to reduce the number of cases and deaths by 54 percent (Fig. 1A and B).
- while vaccination programs will reduce cost-of-illness expenditures, the estimated incremental cost of a vaccination program in 28 high-burden/high-risk districts can be substantial (Fig. 2A and B). Targeting 1–14y represents up to a 35 percent increase in the national EPI budget and targeting 1+y represents up to a 91% increase in the national EPI budget.
- cholera vaccination is highly cost-effective when targeting ages 1–14y, and cost-effective when targeting ages 1+y, in high-burden/high-risk districts (Fig. 3; for terminology and definitions, see: WHO. CHOosing Interventions that are Cost Effective (WHO-CHOICE) [21]). Other vaccination strategies targeting urban slums and rural areas without improved water were found to be cost-effective.

Vaccine supply: A remaining challenge is the provision of an adequate vaccine supply. Current worldwide production capacity of Shanchol™ is two million doses per year [18]. This will need to be scaled up to 13–33 million doses per year for high-burden/high-risk districts in Bangladesh alone [18] and global needs will be much higher, raising the issue of how a limited supply of vaccine will be distributed.

Dynamic modeling: Modeling is used to evaluate vaccination and other intervention strategies. High quality surveillance data reflecting the epidemiology of disease is used in the models. Health care utilization and hospitalization data is also critical. When used together in a model, this data together with vaccine efficacy and program coverage data inform which are the most efficient control and prevention efforts. Efforts should be made to further support and develop surveillance and health care utilization data and their use in dynamic modeling.

Integrated control and prevention strategies: Policymakers are showing growing interest in the implementation of cholera vaccination programs as a complement to rehydration therapy and water, sanitation and hygiene (WaSH) interventions.

6. Conclusion

Cholera is an endemic and epidemic disease in Bangladesh and the entire national population (155 m people) is presumed to be at risk of disease. Though with timely access to clinical services oral and intravenous rehydration therapies can successfully reduce the case fatality rate to less than one percent, not all affected populations have this access and the prevention of cholera remains a high priority.

The findings of this meeting indicate that the use of oral cholera vaccine as a complimentary control and prevention strategy can substantially reduce cholera burden in Bangladesh. Economic analyses of various vaccination strategies show targeting ages 1–14y in high-burden/high-risk districts is highly cost-effective. Other vaccination strategies are cost-effective. Regardless of cost-effectiveness (value), the budget impact (affordability) of the proposed vaccination program will be an important element in the decision-making process and determinant of which target population and vaccination strategy is selected.

Most importantly, as production is limited, adequate vaccine supply for the proposed vaccination programs must be addressed in the context of global efforts to establish a cholera vaccine stockpile and supply other control and prevention efforts.

Bangladesh has a high performing EPI program and has made significant advances with NT elimination, measles mortality reduction, polio elimination and new vaccine introductions. Meeting participants supported the need for discussions on the introduction of oral cholera vaccine in Bangladesh.

Presenters and moderators:

- Dr. Mohammad Ali, International Vaccine Institute, Korea;
- Dr. Tajul Islam A. Bari, EPI Program Manager, Bangladesh;
- Dr. Adwoa Bentsi-Enchill, WHO, Switzerland;
- Dr. Dennis Chao, Fred Hutchinson Cancer Research Center, USA;
- Dr. John D. Clemens, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B), Dhaka, Bangladesh;
- Dr. Vittal Mogasale, International Vaccine Institute, Korea;
- Dr. Christopher B. Nelson, Sabin Vaccine Institute, USA;
- Dr. Firdausi Qadri, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B), Dhaka, Bangladesh;
- Dr. A. K. Siddique, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B), Dhaka, Bangladesh;
- Dr. Mesbah Uddin, Bangladesh Pediatric Association, Bangladesh;
- Dr. Thomas F. Wierzbza, International Vaccine Institute, Korea.

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References

- [1] Shantha Biotechnics. Shanchol domestic package insert – India; 2011. Available from: <http://www.shanthabiotech.com/files/Shanchol%20Domestic%20Pack%20insert.pdf> [accessed 11.11.13].
- [2] World Health Organization. Immunization standards – inactivated oral cholera. Available from: http://www.who.int/immunization_standards/vaccine_quality/pq_250.cholera.1dose.shantha/en/index.html [accessed 11.11.13].
- [3] World Health Organization. WHO vaccine-preventable diseases: monitoring system. Available from: http://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=BGD&commit=OK [accessed 26.08.13].
- [4] World Health Organization. Polio eradication in Bangladesh. *NewsL Reg Off South-East Asia* 2007;(August):15.
- [5] Koehlmoos TP, Harbandu S, Khan IA, Uddin J. Impact of measles eradication activities on routine immunization services and health systems in Bangladesh. *International Centre for Diarrhoeal Disease Research, Bangladesh, ICDDR, B working paper no. 173*; 2010.
- [6] World Health Organization. Cholera vaccines: WHO position paper. *Wkly Epidemiol Rec* 2010;85(13):117–28. Available from: <http://www.who.int/wer/2010/wer8513.pdf> [accessed 18.10.13].
- [7] World Health Organization Sixty-fourth World Health Assembly. Cholera: mechanisms for control and prevention: report by the Secretariat. *World Health Organization report number: A64/18*; 17 March 2011. Available from: <http://apps.who.int/iris/bitstream/10665/33611/A64.18-en.pdf> [accessed 18.10.13].
- [8] World Health Organization Sixty-fourth World Health Assembly. Resolutions, decisions and annexes. *World Health Organization report number: WHA64/2011/REC/1*; 2011. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA64-REC1/A64.REC1-en.pdf [accessed 18.10.13].
- [9] World Health Organization. WHO Technical Working Group on creation of an oral cholera vaccine stockpile, WHO/HSE/PEP/2012.2; 2012. Available from: http://www.who.int/cholera/publications/oral_cholera_vaccine/en/ [accessed 18.10.13].
- [10] Siddique AK, Zaman K, Baqui AH, Akram K, Mutsuddy P. Cholera epidemics in Bangladesh: 1985–1991. *J Diarrhoeal Dis Res* 1992;10(June (2)):79–86 [accessed 18.12.13].
- [11] Sack RB, Siddique AK, Longini Jr IM, Nizam A, Yunus M. A 4-year study of the epidemiology of *Vibrio cholerae* in four rural areas of Bangladesh. *J Infect Dis* 2003;187(January (1)):96–101. Available from: <http://jid.oxfordjournals.org/content/187/1/96.full.pdf> [accessed 18.12.13].
- [12] Ali M, You YA, Kim YE, Sah B, Masker B. The global burden of cholera. *Bull World Health Organ* 2012;90(3):209–18. <http://dx.doi.org/10.2471/BLT.11.093427> [accessed 17.12.13].
- [13] World Health Organization. Cholera, 2009. *Wkly Epidemiol Rec* 2010;85(31):293–308. Available from: <http://www.who.int/wer/2010/wer8531.pdf> [accessed 18.10.13].
- [14] ICDDR, B. The 2001 cholera outbreak in Kishorganj. *Health Sci Bull* 2011;9(3):15–22. Available from: <http://www.icddr.org/what-we-do/publications/cat.view/52-publications/10042-icddr-periodicals/10048-health-and-science-bulletin-bangla-and-english/12672-vol-9-no-3-english-2011-12674-the-2011-cholera-outbreak-in-kishorganj>
- [15] Siddique AK, Nair GB, Alam M, Sack A, Huq A. El Tor cholera with severe disease: a new threat to Asia and beyond. *Epidemiol Infect* 2010;138(3):347–52 [accessed 18.12.13].
- [16] Chowdhury F, Rahman MA, Begum YA, Khan AI, Faruque ASG. Impact of rapid urbanization on the rates of infection by *Vibrio cholerae* O1 and enterotoxigenic *Escherichia coli* in Dhaka, Bangladesh. *PLOS Negl Trop Dis* 2011;5(4):1–8. <http://dx.doi.org/10.1371/journal.pntd.0000999> [accessed 17.12.13].
- [17] Harris A, Chowdhury F, Begum Y, Khan AI, Faruque ASG. Shifting prevalence of major diarrheal pathogens in patients seeking hospital care during floods in 1998 and 2007 in Dhaka, Bangladesh. *Am J Trop Med Hyg* 2008;79(5):708–14. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2749297/> [accessed 17.12.13].
- [18] International Vaccine Institute. Country investment case study on cholera vaccination: Bangladesh. Seoul, South Korea: International Vaccine Institute; 2012. Available from: <http://www.ivi.int/web/www/04.03> [accessed 18.10.13].
- [19] Sur D, Kanungo S, Sah B, Manna B, Ali M. Efficacy of a low-cost, inactivated whole-cell oral cholera vaccine: results from 3 years of follow-up of a randomized, controlled trial. *PLOS Negl Trop Dis* 2011;5(10):1289. <http://dx.doi.org/10.1371/journal.pntd.0001289> [accessed 17.12.13].
- [20] Longini Jr IM, Nizam A, Ali M, Yunus M, Shenvi N, Clemens J. Controlling endemic cholera with oral vaccines. *PLOS Med* 2007;4(11):336. <http://dx.doi.org/10.1371/journal.pmed.0040336> [accessed 17.12.13].
- [21] World Health Organization. CHOosing interventional that are cost effective (WHO-CHOICE) – cost effectiveness thresholds. Available from: http://www.who.int/choice/costs/CER_thresholds/en/index.html

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