Country Investment Case Study on Cholera Vaccination: Bangladesh
Acknowledgments

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<tr>
<td>AD</td>
<td>Auto-destruct</td>
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<tr>
<td>ADB</td>
<td>Asian Development Bank</td>
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<td>AEFI</td>
<td>Adverse events following immunization</td>
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<td>AFP</td>
<td>Acute flaccid paralysis</td>
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<tr>
<td>BCG</td>
<td>Bacille Calmette-Guerin vaccine</td>
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<tr>
<td>BRAC</td>
<td>Bangladesh Rural Advancement Committee</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control (U.S.)</td>
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<tr>
<td>CDD</td>
<td>Control of Diarrhoeal Disease (program)</td>
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<tr>
<td>CFR</td>
<td>Case fatality rate</td>
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<tr>
<td>cMYP</td>
<td>Comprehensive multi-year plan</td>
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<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
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<tr>
<td>DGHS</td>
<td>Directorate General of Health Services</td>
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<tr>
<td>DHS</td>
<td>Demographic and Health Survey</td>
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<tr>
<td>DIMO</td>
<td>District Immunization Medical Officer</td>
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<tr>
<td>DOMI</td>
<td>Diseases of the Most Impoverished Program</td>
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<tr>
<td>DPHE</td>
<td>Department of Public Health Engineering</td>
</tr>
<tr>
<td>DPT</td>
<td>Diphtheria, tetanus and pertussis vaccine</td>
</tr>
<tr>
<td>ECPP</td>
<td>Epidemic Control Preparedness Programme</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Program on Immunization</td>
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<tr>
<td>ESD</td>
<td>Essential services delivery</td>
</tr>
<tr>
<td>ETEC</td>
<td>Enterotoxigenic <em>E. coli</em></td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>FIC</td>
<td>Fully-immunized child(ren)</td>
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<td>FWA</td>
<td>Family Welfare Assistant</td>
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<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
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<tr>
<td>GDP</td>
<td>Gross domestic product</td>
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<tr>
<td>GEMS</td>
<td>Global Enterics Multi-Center Study</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>HA</td>
<td>Health Assistant</td>
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<tr>
<td>HACCP</td>
<td>Hazard Analysis Critical Control Point (regulations)</td>
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<tr>
<td>HiB</td>
<td><em>Haemophilus influenzae</em> type B</td>
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<tr>
<td>HNPSP</td>
<td>Health, Nutrition and Population Sector Programme</td>
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<tr>
<td>ICC</td>
<td>Inter-Agency Coordinating Committee</td>
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<tr>
<td>ICDDR,B</td>
<td>International Centre for Diarrhoeal Disease Research, Bangladesh</td>
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<tr>
<td>IEDCR</td>
<td>Institute of Epidemiology, Disease Control and Research</td>
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<tr>
<td>IPH</td>
<td>Institute of Public Health</td>
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<tr>
<td>ISS</td>
<td>Immunization service support</td>
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<td>IV</td>
<td>Intravenous</td>
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<td>IVI</td>
<td>International Vaccine Institute</td>
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<td>MOHFW</td>
<td>Ministry of Health and Family Welfare</td>
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<td>MOLGRDC</td>
<td>Ministry of Local Government, Rural Development and Cooperatives</td>
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<tr>
<td>NCIP</td>
<td>National Committee on Immunization Practice</td>
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<tr>
<td>NGO</td>
<td>Non-governmental organization</td>
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<tr>
<td>NID</td>
<td>National Immunization Day</td>
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<td>NNT</td>
<td>Neonatal tetanus</td>
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<td>NRA</td>
<td>National Regulatory Authority</td>
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<td>NRRT</td>
<td>National Rapid Response Team</td>
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<td>NWMP</td>
<td>National Water Management Plan</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>OPV</td>
<td>Oral polio vaccine</td>
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<tr>
<td>ORS</td>
<td>Oral rehydration salts</td>
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<tr>
<td>ORT</td>
<td>Oral rehydration therapy</td>
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<tr>
<td>PCDS</td>
<td>Priority Communicable Disease Surveillance</td>
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<tr>
<td>PHC</td>
<td>Primary health care</td>
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<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts</td>
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<tr>
<td>TT</td>
<td>Tetanus toxoid</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<tr>
<td>UNH</td>
<td>Upazila Health and Family Planning Officer</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>WC</td>
<td>Whole cell (vaccine)</td>
</tr>
<tr>
<td>WC-rBS</td>
<td>Whole-cell recombinant B subunit (cholera vaccine)</td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Executive Summary

Overview

This case study of cholera vaccination in Bangladesh is part of a global investment case for oral cholera vaccines conducted by the International Vaccine Institute (IVI), with funding from the Bill & Melinda Gates Foundation, and recommended by the World Health Organization’s Strategic Advisory Group of Experts (SAGE) in October 2009. Country case studies were prepared for Bangladesh and Uganda — two countries considered potential “early adopters” of cholera vaccination — to provide a local perspective to the global investment case. This case study should also provide a useful, evidence-based guide to policymakers in Bangladesh in making decisions about the use of oral cholera vaccines, as well as to the global health community in considering technical and financial support for cholera vaccine introduction. The study provides an estimate of the disease and economic burden of cholera each year in Bangladesh; assesses current cholera control measures; and estimates the cost, impact, and cost-effectiveness of cholera vaccination strategies that differ in size of the target areas and age groups and that are based on stated preferences of local policymakers. The study also assesses the feasibility of the national immunization program to successfully introduce cholera vaccination; and identifies the requirements to do so, including the financing needs, the likely challenges and constraints, and potential funding sources for a cholera vaccination program.

Methods

A five-person team from the International Vaccine Institute traveled to Bangladesh in December 2009 to collect information on the cholera disease burden and trends, the views of policymakers regarding cholera and cholera vaccination, the Expanded Program on Immunization (EPI), and other information needed to conduct the study. This information was supplemented by data from past research conducted by IVI on the cost-of-illness of cholera and the private demand for cholera vaccines conducted in Bangladesh, as well as data from published and unpublished reports and other literature. The analysis of impact of vaccination used a dynamic model of cholera transmission for South Asian countries, which incorporates the herd (indirect) protection of oral cholera vaccines among people not vaccinated, based on data from the original clinical trial of these vaccines conducted in Matlab in the mid-1980s, as well as direct protection among those vaccinated. Cost estimates and modeled impacts of vaccination were used to calculate the cost-effectiveness of alternative cholera vaccination strategies.

The burden of cholera disease in Bangladesh

Historically, the Ganges delta where Bangladesh and the state of West Bengal, India are located has been known as the “homeland of cholera” and the origin of six of the seven cholera pandemics in modern history. The disease remains endemic in most of the country, and epidemics commonly occur during or after floods, cyclones, and droughts. While there is no national surveillance system that can identify the total Bangladeshi cholera burden through laboratory diagnosis, an analysis conducted for this case study based on cholera sentinel site surveillance carried out by ICDDR,B over several years and based on experience in tracking cholera outbreaks through the joint government-ICDDR,B Epidemic Control Preparedness Programme, identified 28 out of the country’s 64 districts as at high risk for
cholera, with an estimated average annual incidence rate of 3/1,000. These districts make up 51% of the entire population. Another eight districts were identified as at medium risk (with estimated average incidence of 2/1,000), and the remaining 28 districts are considered at low (estimated at 1/1,000) or unknown risk. The analysis estimates that there are, on average, around 352,000 cases of cholera each year that seek care in a health facility — for a national annual incidence of 2.1/1,000. The disease causes an estimated 5,300 deaths per year, assuming a case fatality rate of 1.5%. The 28 “high-risk” districts account for nearly three-quarters (72%) of the national disease burden. Children under 15 years of age account for more than 60% of the cases and deaths, and children under age five have the highest rates of the disease — around 8/1,000 in the country as a whole and 11-12/1,000 in the high-risk districts.

According to policymakers and ICDDR,B scientists, cholera is becoming an increasingly urban disease in Bangladesh due to the growing slum populations and increasing strains on overburdened water and sewerage systems. There has been a dramatic rise in the estimated number of cholera cases coming to the ICDDR,B hospital in Dhaka since 2003, and large, flood-related epidemics in Dhaka have become more frequent in the past decade. There is also evidence that cholera in Bangladesh is becoming more clinically severe, and that climate change — resulting in increasing surface water temperatures, extremes in rainfall, and sea water incursion — will lead to an increase in cholera incidence, if preventive measures are not intensified. These trends have increased the awareness of and concern about cholera among government policymakers, leading to their approval of and collaboration with ICDDR,B on a feasibility study of oral cholera vaccination in the Mirpur section of Dhaka. This heightened concern among policymakers has also led to the country submitting a draft resolution calling for intensified global efforts to control cholera, including through mass vaccination campaigns, which was ratified by the World Health Assembly in 2011.

The economic burden and macro-economic impact of cholera

A cost-of-illness study conducted in Matlab in 2004/05 estimated that a hospitalized case of cholera costs, on average, $34 for children and $44 for adults (in 2010 dollars). Using these and other data, we estimate a weighted average of all cases — hospitalized and outpatient — of $16-21, assuming a hospitalization rate of 38%. These estimates include treatment costs incurred by both health facilities and patients, other out-of-pocket costs, and indirect costs of lost wages from work missed by patients or their caretakers. Applying these costs to the estimated average annual incidence of the disease, cholera costs the country around $6.3 million per year in treatment and other illness-related costs. These estimates do not include the costs of responding to the frequent cholera outbreaks that occur in the country.

Cholera is also one of the few vaccine-preventable diseases that can have a substantial impact on a country’s economy. While it is difficult to quantify the macro-economic impact of the disease in Bangladesh, there have been in the past 15 years a series of bans and import detentions from the European Union and the U.S. on shrimp from Bangladesh — the country’s second largest export product after garments. One ban imposed by the EU over a five-month period cost the shrimp industry almost $15 million in 1997 alone.
Current cholera control measures in Bangladesh

An estimated 22% of the rural population does not have access to safe drinking water, due largely to arsenic contamination of shallow tube wells, causing some people to revert back to using untreated surface water. Access to safe water in urban areas has been declining as the slum populations grow, water tables decline, and infrastructure deteriorates. Thus, only around one-half of Dhaka’s population is now estimated to have access to a safe, 24-hour water supply. In addition, only an estimated one-third of the rural population and 58% of the urban population have access to adequate sanitation facilities.

A number of large donor-supported projects are being implemented to meet the government’s goal of 100% of the population having access to safe water and adequate sanitation. These projects involve the construction of piped water systems and water treatment facilities in urban areas, arsenic mitigation (testing of tube wells and installing arsenic removal filters) in rural areas, and decentralized initiatives to build improved sanitation facilities. However, it will likely take many years before these goals are reached, during which time cholera is likely to remain a persistent problem. Cholera vaccination could therefore provide a short- to medium-term solution to control the disease in Bangladesh.

Laboratory-supported cholera surveillance, which will facilitate government decisions about whether and where to introduce cholera vaccination, is at present quite limited in Bangladesh, consisting mainly of on-going surveillance by ICDDR,B at its hospitals in Dhaka and Matlab. The government has, however, proven its ability to establish strong laboratory-confirmed surveillance for AFP/polio, influenza, nipah encephalitis, and other specific diseases, including through sentinel site surveillance. Cholera surveillance could be added to one of these programs, or earlier cholera surveillance programs conducted with ICDDR,B could be restarted. If cholera vaccination is introduced into the EPI, cholera surveillance would be added to the well-regarded, laboratory-supported EPI surveillance program to monitor incidence and detect outbreaks.

Concerning the treatment of cholera, oral rehydration solution (ORS) is readily available in government health clinics and hospitals, and IV fluid therapy is provided at health facilities at the upazila (sub-district) and higher levels for severely-dehydrated patients. However, many people, especially in rural areas, do not likely receive adequate or timely care for severe cholera, due to the population’s heavy reliance on unlicensed private practitioners and the lack of IV fluid therapy in government facilities below the upazila level. And while an impressive 85% of the population uses ORS or increased fluids for a child with diarrhea, only around 60% of children under five with diarrhea in rural areas were given ORS or other fluids according to one study — indicating the need to expand efforts to promote its use in rural parts of the country. Thus, there is a considerable need to further improve cholera treatment and the prevention of severe dehydration in Bangladesh.

How cholera vaccines could be used in Bangladesh

A killed whole-cell ("WC") oral cholera vaccine, modified by the International Vaccine Institute from a vaccine produced in Vietnam and transferred to Shantha Biotechnics of India, was licensed by the Indian government in 2009 and pre-qualified by WHO in 2011. This vaccine, Shanchol™, consisting of killed whole cells of V. cholerae O1 and O139, was developed specifically for use in endemic countries. It joins the only other oral cholera vaccine currently on the international market — the WC-rBS vaccine (Dukoral®), which is used
primarily as a travelers’ vaccine and has had a relatively high price to the public sector in the past. Shanchol™, which is given in two doses two weeks apart and is licensed for use in persons one year and older, has been found to be 66% protective for at least three years in an on-going clinical trial in Kolkata, India. Shantha has made plans to expand annual capacity from around 2-2.5 million doses at present to 10 million doses. Annual capacity could grow to 25-30 million doses with the construction of a dedicated cholera vaccine production facility.

The same modified WC vaccine is also now produced in Vietnam (as mORC-VAX), which the country hopes to sell on the international market in the future, once its national regulatory authority is approved by WHO. Another manufacturer, Eubiotics in South Korea, has received the production technology for the WC vaccine and has plans to build a larger scale production facility if it can secure funding. The WC vaccine could also be produced by other manufacturers in the future to create a sufficient and cost-competitive supply. The Government of Bangladesh has, in fact, expressed interest in having it produced or fill-finished locally in the private sector.

Bangladeshi policymakers interviewed for this case study were most interested in cholera vaccination that:

- is targeted to high-risk areas, such as urban slums;
- is phased in;
- is used to attack endemic disease as well as to prevent cholera outbreaks from occurring or spreading;
- targets all eligible ages (one year and above) if funding is available;
- piggybacks onto other immunization or health campaigns as much as possible; and
- combines vaccination with other cholera prevention measures, such as hand washing and breastfeeding promotion.

Challenges in implementing cholera vaccination in Bangladesh

Providing cholera vaccination through the public sector in Bangladesh will present a number of challenges, several due to the attributes of the vaccine. These challenges include:

- The fact that vaccination will be targeted to high-risk areas and populations and will not be provided throughout the country. This presents the challenge of identifying high-risk areas to target in the absence of a national cholera surveillance system;

- The fact that the currently available vaccines are not licensed for use in infants and that older children and even adults could be targeted for vaccination — making mass vaccination campaigns the most appropriate delivery strategy. Campaigns require considerable resources and effort to implement and can potentially interfere with routine immunization services. It will also be a challenge to achieve high vaccination coverage among older children and adults — especially men — if they are included in vaccination campaigns, since they have yet to be the target of immunization programs in Bangladesh.

- The fact that those most in need of the vaccine are usually the poorest and most marginalized populations in the country;

- The two-dose regimen of the vaccine and the need to revaccinate after three years;
- Determining if, when, and where to vaccinate following a natural disaster to pre-empt outbreaks; and
- Securing sustainable financing for cholera vaccination (discussed below).

**The ability of the EPI to successfully implement cholera vaccination**

The country’s EPI has the systems in place and experience to overcome many of these challenges, as evidenced by:

- A strong outreach delivery system, which constitutes the backbone of routine immunization services in rural areas;
- Strong centralized and decentralized management and supervision systems and structures for the EPI, including a vaccine procurement, storage, and distribution system separate from that of other pharmaceuticals and which serves both the public and private health sectors;
- High immunization coverage rates among children in 2009, including 75% of 12-month-olds being fully-immunized, 86% having received the third dose of DPT and hepatitis B vaccines, and 83% vaccinated against measles;
- Low drop-out rates for multi-dose vaccines (e.g., 2% between DPT1 and DPT3);
- The EPI’s ability to reach even the poorest communities, as shown by a difference in immunization coverage between the highest and lowest income quintiles of only around 6%.
- Experience in successfully implementing mass vaccination campaigns (polio, measles), including those targeting adults in specific high-risk areas (i.e., neonatal tetanus elimination campaigns). Ninety-five percent of children under five years of age were vaccinated with two doses of polio vaccine during the 2009 National Immunization Days; and
- The achievement of neonatal tetanus elimination in 2008 and a dramatic reduction in measles outbreaks.

There are also several regular campaigns that could provide an opportunity to efficiently incorporate cholera vaccines, including yearly National Immunization Days and semi-annual intensive campaigns to provide vitamin A supplements and deworming medicine.

**The projected impact, cost, and cost-effectiveness of cholera vaccination in Bangladesh**

Analyses were performed for two scenarios for targeting cholera vaccination — a Large Target scenario involving vaccination throughout the 28 high-risk districts identified as “high-risk” in the disease burden analysis, consisting of around half of the country’s population, and a Small Target scenario limited to urban slums and rural populations without safe water access in the high-risk districts, consisting of ≈18% of the population. Two age group options
were examined for each scenario: all ages one year and above, and children 1-14 years old only. Vaccination is assumed to begin in 2015.

The analyses assume use of the WC (Shanchol™) vaccine, which has a current public sector price of $1.85/dose. We assume that by 2018 the price of the WC vaccine will be reduced to $1.45 per dose as a result of increased production yield and efficiencies, as well as increased competition. This price is about halfway between the current public sector price of Shanchol™ and the private sector price of the Vietnamese vaccine ($1.00).

Vaccination would take place each year in one-third of targeted areas and would be repeated every three years (based on a three-year duration of protection of the vaccine). The analyses also assume coverage rates of 75% for 1-14 year olds and 50% for persons 15 and older, a vaccine efficacy rate of 70% for three years, and herd protection from the vaccine, using dynamic model estimates that were calibrated with clinical trial data from Matlab.

### Estimated cost, impact, and cost-effectiveness of four scenarios of cholera vaccination in Bangladesh, assuming use of the WC (Shanchol™) vaccine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Large Target (entire populations in high-risk districts)</th>
<th>Small Target (urban slums +selected rural populations in high-risk districts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number people vaccinated per year</td>
<td>6.1 million</td>
<td>15.8 million</td>
</tr>
<tr>
<td>Number doses required per year (2 doses + 5% wastage)</td>
<td>12.8 million</td>
<td>33.2 million</td>
</tr>
<tr>
<td>Annual vaccination costs (US$2010 $)^a</td>
<td>$28 - $33.4 million</td>
<td>$72.7 - $87.9 million</td>
</tr>
<tr>
<td>Cases prevented per year</td>
<td>154,000</td>
<td>194,000</td>
</tr>
<tr>
<td>Percent reduction in annual incidence</td>
<td>43%</td>
<td>54%</td>
</tr>
<tr>
<td>Cases averted from 2015-2030</td>
<td>2.4 million</td>
<td>3.1 million</td>
</tr>
<tr>
<td>Deaths averted from 2015-2030</td>
<td>36,000</td>
<td>46,000</td>
</tr>
<tr>
<td>Cost-effectiveness ratio (cost/DALY saved)^a</td>
<td>$387 - 419</td>
<td>$759 - 926</td>
</tr>
<tr>
<td>Degree of cost-effectiveness per WHO definition</td>
<td>Very cost-effective</td>
<td>Cost-effective</td>
</tr>
</tbody>
</table>

^a This range represents the expected cost per year at the current price of $1.85 per dose, as well as the expected long-term price of $1.45 per dose.

Under the Large Target scenario — vaccinating throughout the 28 high-risk districts — a program for children 1-14 years old would vaccinate around six million persons a year, cost around $28 - $33 million per year (with variation due to the change in price from $1.85 per dose in 2015-17 to $1.45 starting in 2018), and save $2.6 million per year in cost-of-illness. It would prevent 154,000 cases of cholera each year or a total of ≈2.4 million cases from 2015 to 2030. It would also prevent ≈36,000 deaths over this time period, reducing the national cholera incidence by 43%. This program would be “very cost-effective” (cost/DALY averted of $387 - $419), using the WHO definition of cost/DALY averted is less than or equal to the country’s gross domestic product (GDP) per capita ($641 in 2010).
Vaccinating all persons one year and older under the Large Target scenario would increase the numbers of persons vaccinated each year to almost 16 million, cost =-$73-$88 million per year, save $3.4 million in cost-of-illness, prevent 194,000 cases and 2,900 deaths each year — reducing cholera incidence by 54%. Over the 16-year period from 2015 to 2030, this program would prevent 3.1 million cases and 46,000 deaths. This option is less cost-effective than the children’s only program (with a cost/DALY averted of $759 - $926), but it would meet the WHO definition of “cost-effective” (cost/DALY averted is ≤3 times the GDP/capita).

Under the Small Target scenario — limited to urban slums and areas with poor access to safe water supplies in high-risk districts — a program for 1-14 year olds would vaccinate 2.1 million children per year, cost around $10 - $12 million, and save $900,000 in cost-of-illness. It would also reduce incidence by 54,000 cases per year or around 900,000 over 16 years — a 15% reduction in incidence overall. It would also be “very cost-effective”. Adding adults (15 and older) to this scenario would increase the numbers to be vaccinated each year to 5.5 million, increase the cost of the program to =$25.5-$31 million, but only prevent an additional 14,000 cases per year — or 68,000 per year total, for a 19% reduction in overall incidence. This Small Target program for all ages would be “cost-effective”, but not “very cost-effective”.

These results suggest that the greatest declines in incidence and the greatest efficiencies would be realized by vaccinating children in as many communities as possible within high-risk districts (i.e., the Large Target scenario), rather than limiting the geographic scope of the program in order to vaccinate both children and adults.

Financing for cholera vaccination

Adding cholera vaccination to the EPI would increase the total annual cost of the program by 10% for the children-only Small Target option, by 26-29% for either the children-only Large Target option or the all-ages Small Target option; and by 75% if all ages are vaccinated under the Large Target scenario. Depending on the program chosen, cholera vaccination is similarly priced and sometimes less expensive than other new vaccines, such as pneumococcal and rotavirus vaccines.

Financing for cholera vaccination could come from current sources of EPI funding, such as pooled funds from donors and the Government, the MOHFW’s revenue budget, or the GAVI Alliance, if it decides to support cholera vaccination. A number of alternative financing sources could also be possible, including private industry (e.g., seafood industry) and upcoming donor-supported projects to mitigate the impact of climate change in Bangladesh.
1. Introduction and Background

1.1 Background on cholera and cholera vaccines and rationale for the study

The momentum has been building for tackling the continual problem of cholera in parts of the world still affected by the disease, largely developing countries in Asia and Sub-Saharan Africa. The disease is a rapidly-dehydrating diarrheal illness spread by certain forms of the bacterium, *Vibrio cholerae*, through ingestion of contaminated water or food, primarily in areas with poor access to safe drinking water and adequate sanitation. Cholera can lead to death within 24 hours if not treated with intravenous or oral rehydration and has been described as “one of the most rapidly fatal infectious illnesses known” [WHO, 2001]. There is growing visibility of cholera in the past several years — due mostly to large epidemics that have received considerable media attention. These include the epidemic in Haiti that has killed more than 7,000 people since it began in October 2010, and Zimbabwe’s 11-month long epidemic in 2008/09 that caused 100,000 cases and killed more than 4,000 people. Cholera epidemics appear to be spreading to new, previously-unaffected countries (especially in Africa) and to be lasting longer. The decade of the 2000s witnessed a number of large epidemics in Africa and Asia — most notably in Angola, South Africa, Ethiopia, India (following cyclone Aila), and Afghanistan — often lasting many months. And while cholera epidemics tend to capture most of the attention, endemic cholera is still considered responsible for much of the global burden of the disease, which has been estimated at 3-5 million cases and 100,000 - 130,000 deaths per year [WHO, 2010]. Endemic cholera is especially prevalent on the Indian subcontinent, such as along the Bay of Bengal, as well as in other developing countries of Asia.

Oral rehydration therapy (ORT), along with IV rehydration, can reduce cholera case fatality from up to 50% without treatment to less than 1% with prompt and appropriate treatment. However, actual case fatality rates are likely to be higher than 1% in many areas, where people are not able to reach a health facility and receive adequate treatment in time. And even among patients who do reach a health facility, the reported case fatality in many countries in Africa remains high — 4% or more. There is also concern among some scientists about new strains of *V. cholerae* that have emerged in the past 15 or so years in both Asia and Africa. These strains are variants of the O1 El Tor biotype of cholera that has predominated world-wide since the 1960s, but they produce cholera toxin of the older, classical biotype and are believed by many experts to cause a more clinically severe disease than the original El Tor strains [Nair et.al., 2002; Ansarussaman et.al., 2007].

At the same time, there have been several advances in the development and use of oral cholera vaccines, which may be used as a complement to the traditional methods of controlling cholera that include improving water supplies and sanitation, health education (e.g., hand washing promotion), and treating cases with ORT before they become severe enough to require rehydration with IV fluids. A two-dose oral cholera vaccine, Dukoral®, has been available since the early 1990s. While it is mainly used as a travelers’ vaccine in developed countries, its use has been shown to be feasible in several instances both among endemic populations (in Beira, Mozambique and in Zanzibar) and in post-crisis situations (in Uganda, Darfur, Sudan, and Aceh, Indonesia following the tsunami). This killed whole-cell vaccine, which also contains part of the cholera toxin, provides ≈85% protection for four to six months and ≈60% protection two years following vaccination, with declining protection after two years. Protection was found to be shorter-lived in children less than six years of age. The
vaccine is licensed for use in persons two years and older, with revaccination recommended every two years in persons five years and older, and every six months for 2-5 year olds. Dukoral® must also be given with a buffer and clean water, which can pose logistical challenges in poor, remote areas, and has been relatively expensive for use in the public sector in developing countries (e.g., more than $5.00/dose).

A new cholera vaccine, developed specifically for use among endemic populations, was licensed in India in early 2009 and pre-qualified by WHO in 2011. The O1/O139 whole-cell (WC) vaccine, produced in India as Shanchol™, is also made up of killed whole cells of V. cholerae, but it lacks the cholera toxin component and thus does not require a buffer or water to administer. The vaccine has been shown in a large clinical trial in India to provide sustained protection for at least three years (66% overall), including in young children. The vaccine is licensed for use in persons one year and above.

In response to these new developments in the epidemiology of cholera and availability of a new vaccine, as well as to new evidence on the burden of the disease, its economic costs, and the effectiveness and value of vaccination, the World Health Organization issued a new Position Paper on cholera vaccines in early 2010 [WHO, 2010]. The Position Paper recommends that cholera be controlled in endemic areas through immunization using oral cholera vaccines in conjunction with other prevention and control strategies, and that preemptive vaccination also be considered to prevent outbreaks or their spread to new areas. The WHO Strategic Advisory Committee of Experts (SAGE), which made the recommendations during its meeting in October 2009, stressed the need for an “investment case” for cholera vaccines to provide WHO, donors, and the broader global health community with information on the potential demand for cholera vaccines, if provided through public sector immunization programs, the cost to meet this demand, the global impact of vaccination on the disease, and whether or not it would be cost-effective.

To meet this request, the International Vaccine Institute (IVI) has prepared an investment case for oral cholera vaccines with funding from the Bill & Melinda Gates Foundation. As part of this investment case, it was decided to conduct case studies in two countries — Bangladesh and Uganda — that were assessed as potential “early adopters” of cholera vaccination on the basis of several factors. These factors include having a recognized cholera problem in the country, expressed interest among government officials in exploring the idea of cholera vaccination, a strong national immunization program (an indicator of their ability to successfully introduce cholera vaccination), and political stability and lack of armed conflict, among other factors.

The country case studies may enable these countries to jumpstart the planning and implementation of cholera vaccine introduction. These country cases also go beyond the theoretical estimates of a global study to provide a greater sense of reality at the country level.

This case study was carried out with the close cooperation of the Bangladesh Ministry of Health and Family Welfare and the ICDRR,B.

1.2 Study objectives, components, and methods

The main objectives of this country case study of cholera vaccination are to:
1) Estimate the disease and economic burden of cholera in Bangladesh, including the average annual number of cases and deaths, the costs incurred by society from cholera illness, and the macro-economic impact of the disease, including major outbreaks;

2) Assist the Government of Bangladesh in making informed decisions about whether and how to introduce cholera vaccines as part of its cholera control programs by estimating the impact, cost, and cost-effectiveness of various cholera vaccination strategies;

3) Assess the feasibility of the country to successfully implement cholera vaccination and identify the needs of the immunization program, disease surveillance, and health system requirements to successfully implement the proposed vaccination strategies;

4) Identify potential constraints and challenges to the introduction of cholera vaccination in Bangladesh and how they can be addressed;

5) Identify the financing needs to implement a cholera vaccination program and possible financing options and funding sources; and

6) Ensure that the perspectives and requirements of national governments are represented in the global cholera vaccine investment case study.

This case study should provide a useful, evidence-based guide to policymakers in Bangladesh in making decisions about the use of oral cholera vaccines. It should also help guide the global health community and donors in considering technical and financial support for cholera control in Bangladesh that includes the use of oral cholera vaccines.

To collect information for this study, a five-person team from IVI, consisting of a medical epidemiologist and cholera expert, a health systems expert, a specialist in policy analysis for new vaccine introduction, and two health economists, visited Bangladesh over a 12-day period in November/December 2009. The team met with government officials, scientists, representatives from technical and donor agencies, clinicians, and others to collect information on:

- the cholera disease burden in Bangladesh;
- trends in incidence and high-risk groups;
- disease surveillance systems and cholera prevention and control activities in the country;
- policymakers’ views about the disease, its magnitude and priority among infectious diseases; and
- policymakers’ views on which cholera vaccination strategies would be preferable, what data would be required to inform government decisions, and how a cholera vaccination program could be financed.

Persons interviewed include senior officials from the Ministry of Health and Family Welfare, as well as persons responsible for the EPI program and for disease surveillance; local government officials responsible for primary health care and immunization services in urban areas; scientists and clinicians from the ICDDR,B, including several cholera experts; representatives from several international organizations supporting the country’s immunization program (WHO, UNICEF, World Bank); and representatives from the ministries
of education and fisheries. The team also made a field visit to an area of Dhaka where a feasibility study of cholera vaccination will take place and where they visited treatment and primary health care facilities. A complete list of persons interviewed can be found in Appendix 1.

Interviews were conducted mainly in small group meetings, and in some cases, with individuals. The interviews were semi-structured, using a question guide (shown in Appendix 2).

The team also collected data from the literature, from available published and unpublished reports, and from prior work that selected members had conducted in the country. A complete list of all references used for this study is given at the end of this report.

1.3 Background on Bangladesh

Bangladesh is a low-lying South Asian country with a population of over 164 million people that lies mainly within the broad delta of the Ganges and Brahmaputra rivers. Given its location, the country has often been the victim of devastating floods and cyclones. It is the most densely populated country in the world, with an estimated 1,102 people per square kilometer. While the country’s population growth has declined dramatically from a high of 2.68% per year in the early 1980s to 1.41 in 2008, with parallel declines in total fertility rate from 6.2 in 1981 to 2.34 in 2008, its population is still expected to reach more than 215 million by 2040. ¹ Bangladesh’s population is becoming increasingly urban; an estimated 27% (>42 million people) now live in cities — compared to 10% in 1975. This urbanization rate is expected to reach more than half of the population — around 116 million — by 2040.

Bangladesh has a gross domestic product (GDP) per capita of $641 (in 2010), placing it among the least developed countries in the world. Around 40% of the population lives below the poverty line, and an estimated 20% are considered extremely poor. ² Around 20% of the population does not have access to safe drinking water and 64% do not have improved sanitation. ³ An estimated 44% of the population over the age of 15 is still illiterate.

Despite these statistics, Bangladesh has been making steady economic and social gains in the past two decades, achieving economic growth rates of 4-5% per year since 2004. The percentage of the population living below the poverty line fell from 57% in 1991 to 40% today — a decline of 30%. The decline among those defined as extremely poor has been even greater — from 37% in 1983 to <20% today. ⁴ Literacy rates have also grown from an estimated 37% of the adult population in 1991 to 56% by 2007 (63% for males and 54% for females). Rates of net primary school enrollment (the percent of children of primary school age who are enrolled) have also increased — from <60% in 1991 to 91% in 2007 — and are actually higher for girls than for boys. However, still only around half (52%) of children who start first grade

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² Measured by caloric intake (WB integration report 2009).
⁴ Data sources for the poverty statistics are the Government of the People’s Republic of Bangladesh, 2008 and www.UN-BD.org Website. The data source for the education statistics is the Government of the People’s Republic of Bangladesh, 2008.
complete the fifth grade. These improvements have been reflected in the steady increase in Bangladesh’s score on the Human Development Index, from 0.35 in the mid-1970s to 0.417 in 1990 and to 0.543 in 2007, placing it among the medium-ranking countries on the index [UNDP 2010].

During this same period, Bangladesh has made impressive improvements in the health status of its population, in comparison to other nations in South Asia. Life expectancy at birth has climbed from 55 years in 1991 to 69 by 2010, with little differences between men and women. Infant mortality has declined by more than 60% since 1990, when it was 99/1,000 live births, to 38 in 2010, and mortality in children under five years of age has declined by two-thirds since 1990 — from 143/1,000 live births to 48/1,000 in 2010. Bangladesh is therefore on track to achieve the Millennium Development Goal of reducing the under-five mortality rate by two-thirds from 1990 to 2015.

The substantial recent declines in deaths among children have been attributed to the delivery of more comprehensive, integrated maternal and child health services under the government’s Health, Nutrition and Population Sector Program (HNPS), including facility- and community-based Integrated Management of Childhood Illnesses (IMCI) [Government of Bangladesh, 2008]. They have also been attributed to steady increases in immunization coverage that have led to the elimination of neonatal tetanus, which used to be responsible for 21-56% of neonatal deaths [WHO, 2008], and to sharp declines in measles outbreaks — from 120 in 2005 to 34 in 2006 and 0 in 2007. Other likely factors are the relatively high use of ORT for children under five with diarrhea, which was estimated at 85% in the 2007 Demographic and Health Survey, and efforts to promote breastfeeding through a national Breastfeeding Campaign [Government of Bangladesh, 2008].

The three top causes of death in Bangladesh for all ages are pneumonia (14% of deaths), respiratory failure (7.5%), and diarrhea (6.26%) [WHO, 2005a]. According to a survey conducted in 2003, the top five causes of mortality in children under the age of five are neonatal and perinatal causes (e.g., birth asphyxia, birth injury, and premature birth) (48%), pneumonia (18%), measles and malnutrition as underlying causes (13%), injuries and drowning (8%), and diarrhea (6%). It is likely that measles has since declined as a cause of child mortality given the sharp increases in measles immunization coverage in the past decade (see Section 5). The importance of diarrhea as a cause of hospitalization is discussed in more detail in the following chapter.

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2. How serious a problem is cholera in Bangladesh?

2.1 Overview

Diarrheal diseases were the #1 cause of hospitalization at public facilities in 2008, accounting for more than 15% of all admissions. They were also the fifth leading cause of death among hospitalized children under the age of five [Government of Bangladesh, 2009]. From 1997 to 2001, diarrhea was the leading cause of all hospitalizations in five rural hospitals in different parts of the country [Siddique AK, unpublished data], and diarrheal disease due to *Vibrio cholerae* continues to be a major public health problem [Sack et al. 2003].

Historically, the Ganges delta located in Bangladesh and the neighboring Indian state of West Bengal has been known as the “homeland of cholera,” and six of the seven cholera pandemics in modern history are said to have originated there [Siddique et al., 1992]. While the current seventh pandemic — caused by the El Tor biotype of *V. cholerae* O1 El Tor — began in Indonesia in the early 1960s, the organism has thrived in Bangladesh and has become endemic in the country, where it resides in the estuaries along the Southern coast and in surface water inland. While the classical biotype disappeared in most locations in the 1990s, new strains of the disease have also emerged in Bangladesh in recent decades, including *V. cholerae* O139 in 1993, and a new strain of *V. cholerae* O1 El Tor that secretes the classical cholera toxin (discussed below).

Cholera in Bangladesh occurs both as endemic disease, with seasonal peaks before and after the monsoons, and in epidemics that often take place during or following the frequent floods, droughts, and cyclones that occur in the country.

2.2 Where does cholera exist in Bangladesh?

As in most developing countries, Bangladesh does not have a national surveillance system that can identify cholera through laboratory diagnosis. Much of what we know of the disease in Bangladesh and where it occurs comes largely from the ICDDR,B. The institute has conducted cholera-related research since 1960 and treats cholera patients both at its hospital in Dhaka and at its field station hospital in Matlab — a rural area Southeast of Dhaka where clinical trials of the first oral killed cholera vaccine to be licensed (Dukoral®) took place in the mid-1980s.

Cholera is both a rural and an urban disease in Bangladesh. It is associated with poor sanitation, contaminated water supplies — including surface water and shallow tube wells that are the main sources of drinking water in rural areas — as well as crowded living conditions, such as those found in the country’s urban slums.

2.2.1 Cholera in rural areas

From 1985 to 2008, laboratory-confirmed cholera was reported in outbreaks or found through surveillance in half (33 out of 64) of the country’s districts (see Figure 1). Long-term cholera surveillance conducted in Matlab found incidence rates that were as high as 3.5/1,000 in certain years in the 1990s, though rates have dipped below 1/1,000 since 2000. Laboratory-
confirmed cholera surveillance conducted in sentinel hospitals in four different, widely-dispersed areas of the country by ICDDR,B from 1997 to 2001 found the disease present in all four areas [Sack et al. 2003]. These include one area (Chaugachha) in the Western part of the country, where the disease had not been reported for the previous 10 years and which had been designated as the control area for the study. Among patients seeking health care with acute watery diarrhea for which a bacterial pathogen was identified, the percentage that tested positive for cholera was 20% in Mathbaria (where Matlab is located), 19% in Bakerganj and 11% in Chhatak, while the rate was 4% in Chaugachha (Table 1). Cholera was the cause of 14% of diarrheal cases in the four sites combined.

Figure 1. Districts with reported cholera cases from 1985 to 2008 (outbreaks or endemic disease)

Sources: Siddique et al. 1992; Siddique et al., 1994; Sack et al., 2003; Harris et al. 2008; Hashizume et al. 2008. Map courtesy of Dr. AK Siddique of ICDDR,B, who reviewed and supplemented it with unpublished data.
Table 1. Proportion of patients with acute watery diarrhea with laboratory-confirmed cholera in four rural hospitals in Bangladesh

<table>
<thead>
<tr>
<th></th>
<th>Matlab</th>
<th>Bakerganj</th>
<th>Chirak</th>
<th>Cheugachha</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>2,316</td>
<td>897</td>
<td>1,295</td>
<td>1,162</td>
<td>5,670</td>
</tr>
<tr>
<td>Patients with V. cholerae (O1 or O139)</td>
<td>460 (20%)</td>
<td>168 (19%)</td>
<td>139 (11%)</td>
<td>41 (4%)</td>
<td>808 (14%)</td>
</tr>
<tr>
<td>Patients &lt; 2 years of age</td>
<td>1,047 (45%)</td>
<td>259 (29%)</td>
<td>393 (30%)</td>
<td>467 (40%)</td>
<td>2,166 (38%)</td>
</tr>
</tbody>
</table>

Source: Sack et al. 2003.

2.2.2 Cholera in urban areas: evidence from Dhaka

Most of what is known about cholera in urban areas of Bangladesh is from Dhaka, where the ICDDR,B hospital — which primarily treats patients with diarrhea and is considered the premier hospital for diarrhea treatment in the city — has been conducting laboratory testing on 2% of all diarrheal patients since 1979. Based on this surveillance system, the hospital has treated an estimated 12,000 to 34,000 cases of cholera each year in the past 10 years (Figure 2). This does not capture all cholera cases seeking treatment in the city; ICDDR,B scientists estimate that around 80% of hospitalized cases of cholera and around 50% of less severe cases come to the ICDDR,B hospital [A.S.G. Faruque, personal communication]. However, these data do provide an indication of the magnitude and trends in cholera in Dhaka in recent years.

Figure 2. Estimated number of patients with cholera treated at the ICDDR,B hospital in Dhaka from 1999 to 2009, based on laboratory testing of 2% of diarrheal patients

Since 2003, there has been a dramatic rise in the estimated number of cholera cases coming to the hospital in Dhaka — from ∼12,000-18,000 cases per year in the early 2000s to more than 30,000 cases, except in 2008 (Figure 2). This increase is due to both a rise in the overall number of diarrheal patients coming to the hospital and to an increase in the proportion of patients with cholera. Amongst identified pathogens, cholera has been the #1 cause of diarrhea in patients in the 2% surveillance system in four of the last five years, overtaking rotavirus (Figure 3). While 16-20% of patients tested from 1999 to 2003 had stools positive for cholera, since 2004, cholera has accounted for up to 30% of patients tested.
ICDDR,B scientists attribute this sustained increase in cholera cases in Dhaka to flood-related outbreaks in some of these years (2004, 2007, 2009), to the continual uncontrolled growth of the population in Dhaka — especially in the slums, and to the growing strain of the rising slum population and crowded conditions on water and sanitation systems.

Figure 3. Distribution of diarrheal pathogens in patients under hospital surveillance at the ICDDR,B hospital in Dhaka, 1995-2008

Source: ASG Faruque, ICDDR,B

2.3 What age groups are most at risk of getting cholera in Bangladesh?

As in other cholera-endemic countries, cholera strikes all age groups in Bangladesh. However, young children are known to have the highest risk of getting the disease, especially during non-epidemic periods in endemic settings. Population-based, laboratory-confirmed surveillance conducted by ICDDR,B over a ten-year period (1994-2003) in Matlab shows that average incidence rates for cholera were more than four and a half times higher in children under one year of age (4.6/1,000), and nearly four times in children 1-4 years old (3.8/1,000) than in persons 15 and older (1/1,000) (Figure 4). In certain, high-incidence years, such as 1994, children under five years of age in Matlab had annual incidence rates as high as 9/1,000, compared to 3.5/1,000 in the overall population.

Data from the sentinel site surveillance in four rural areas of the country described in Section 2.2.1 above show a similar pattern (Figure 5 on the right). More than half of patients with diarrhea whose stool tested positive for *V. cholerae* (O1 or O139) at these hospitals were 10 years old or younger, and 37% were under the age of five. Adults 20 and older made up only 31% of cases. It could be however, that adults with cholera may be less likely to seek hospital care than children, especially less severe cases.

Even the youngest children — babies one month old or younger — are at risk for cholera. Recent data from ICDDR,B found that *V. cholerae* was the most common pathogen found in the stool of neonates hospitalized with diarrhea from 1991 to 2004. Of the 700 neonates whose stool tested positive for a bacterial pathogen, 277 (40%) had *V. cholerae* [Khan et.al., 2008]. According to clinicians at the hospital, the fact that infants, including
neonates, are getting infected with cholera in Dhaka is because many women are only breastfeeding partially and not exclusively for the first six months, due to their need to return to work soon after the baby is born.

**Figure 4. Average annual cholera incidence rates by age group from laboratory-confirmed, population-based surveillance in Matlab, 1994-2003**

![Chart showing average annual cholera incidence rates by age group](chart)

**Source:** ICDDR,B

**Figure 5. Age breakdown of laboratory-confirmed cases of cholera during epidemic and non-epidemic periods**

![Pie charts showing age breakdown of cholera cases](chart)

**Source:** Harris et al., 2008

*The 4 sites are Mathbaria (Matlab), Chaugachha, Bakerganj and Chhatlak. Source: Sack et al., 2003.

However, during cholera epidemics, especially following floods, attack rates appear to be more similar across all ages. Thus, the majority of cases are in adults, since they make up the largest segment of the population. For instance, during a major cholera outbreak in Dhaka in 2007 during severe flooding, two-thirds of cholera cases in the 2% surveillance system at ICDDR,B were 15 years old and older (Harris et al., 2008) (Figure 5 on the left). Only 17% were children less than five years old and 16% were 5-14 years old. When a new serogroup of the disease invades Bangladesh, as happened in 1993 with the emergence of *V. cholerae* O139 in the South, it also predominately strikes adults, presumably because of their lack of immunity to the new strain. Patients 15 years old and older accounted for 64% of cases.
treated in government hospitals who tested positive for the new strain of the disease and less than 3% were under the age of five [Siddique et al., 1994].

Additional data on the age distribution of cholera during outbreaks and non-outbreak periods are shown in Appendix 3.

As one would expect, people living in the same household as a person infected with cholera are also at greater risk of getting infected and of coming down with diarrhea. A recent study conducted in Dhaka by ICDDR,B showed that 73% of household contacts of patients hospitalized with cholera experience diarrhea — most shortly after the index case was hospitalized — and 21% had laboratory-confirmed cholera [Well et al., 2009].

2.4 The severity of cholera in Bangladesh and case fatality

There is a wide range of severity among cholera cases — from mild diarrhea to severe, rapidly-dehydrating disease. Scientists at ICDDR,B estimate that there are up to 1.2 million cases of cholera per year in Bangladesh, and that one in four (=300,000) are severe. Because of a lack of routine laboratory-confirmed cholera surveillance in the country and because many cases are treated at home (e.g., with ORS), it is difficult to verify these estimates.

However, there is evidence that the severity of clinical cases of cholera in Bangladesh is increasing, especially during outbreaks. During a major flood-related cholera epidemic in 2007, an estimated 75% of cholera patients coming to the ICRRD,B hospital were severely dehydrated and 78% required IV fluids — considerably higher than during previous outbreaks in 1998 and 2004 [Harris et al., 2008]. During a cholera outbreak in 2006 in the ICDDR,B cholera sentinel surveillance site of Bakerganj, 79% of patients with laboratory-confirmed cholera were severely dehydrated, compared to an average of 40% from 1998 to 2000 (Figure 6) [Siddique et al., 2009].

**Figure 6. Dehydration status of patients infected with V. cholerae O1 (El Tor) in Bakerganj, 1998-2001 and 2004-2006**

![Dehydration status chart](chart.png)

Source: Siddique et al. 2009

Some scientists attribute the increase in the severity of cholera cases to the emergence in Bangladesh of a new altered strain of V. cholerae O1 El Tor that secretes the classical cholera toxin — making it, they believe, more virulent [Nair et al. 2002]. Others believe that in Dhaka and other cities, this increased severity is due to the growth of the slums and increasing contamination and scarcity of water supplies.
The case fatality rate (CFR) of cholera in Bangladesh is unknown. During a large outbreak in the North in 1991, a CFR of 4% was estimated [Siddique et.al., 1992]. An outbreak in 1986 in Southern Bangladesh resulted in a CFR of 14% — before emergency treatment facilities were set up in the area and the rate was reduced to <1% [Siddique et.al., 1992]. Today, government officials and other experts believe that the case fatality rate from cholera is down significantly, due in large measure to the widespread use and easy availability of ORS in Bangladesh. It is known, however, that cholera-related deaths still occur because people delay seeking care due to their lower economic status or distance from health facilities. While the ICDDR,B hospital is able to save all cholera patients who are not co-infected with another disease or do not have a pre-existing condition, there are reports that during each flood-related outbreak in Dhaka, 35-50 people die on the way to the hospital, and 42 alone from the Mirpur section of Dhaka died en route during the 2007 epidemic [ICDRR,B 2010]. This led to the Government requesting the ICDDR,B to establish a satellite hospital/clinic in Mirpur, which opened the following year.

Since access to timely and appropriate treatment varies throughout the country, we use an estimated average CFR of 1.5% and a range of 1-2% for the disease burden and other analyses in this case study, based on expert opinion (see Section 2.7.4 below).

2.5 Cholera outbreaks in Bangladesh

Cholera outbreaks — ranging from seasonal peaks to epidemics that affect large parts of the country — are a frequent occurrence in Bangladesh. A study by the Epidemic Control Preparedness Programme of the Government of Bangladesh and ICDDR,B identified a series of cholera outbreaks from 1985 to 1991, affecting nearly 400 (=80%) of the country’s upazilas (subdistricts) and causing tens of thousands of cases and thousands of deaths [Siddique et.al.,1992]. The epidemic in 1988 alone, which took place during major flooding, caused nearly one million reported cases of diarrhea throughout the country. Based on testing of sample specimens, an estimated 39% of these cases were due to cholera, for a total of nearly 400,000 cases.

Major outbreaks have occurred in different parts of the country. An outbreak in 1991 spread throughout Northern Bangladesh over a three-month period, causing more than 200,000 reported cases of acute watery diarrhea — 57% of which were due to V. cholerae, according to laboratory testing — and more than 2,600 deaths [Siddique et al. 1992]. An outbreak caused by the new O139 biotype in 1993 spread to six districts in the South, causing 845 reported deaths before moving North [Siddique et al., 1994].

Many of the major cholera epidemics in recent years have taken place during or after large-scale floods, affecting up to 60% of the country, including Dhaka, for which we have the most data. These floods — and the outbreaks — have become more frequent in recent years. After a major outbreak in Dhaka during the floods in 1988, the next large-scale cholera outbreak in Dhaka wasn’t until major flooding occurred again in 1998 — ten years later. Subsequent flood-related outbreaks took place in Dhaka in 2004, 2007 and 2009 (Figure 7). While cases of rotavirus and enterotoxigenic E. coli (ETEC) also increased during these floods, cholera jumped from the third most frequently identified cause of diarrhea — well after rotavirus and after ETEC — to by far the most common cause, responsible for 33-40% of diarrheal cases coming to the ICDDR,B hospital (Figure 8) [Harris et.al., 2008]. During the floods in 2007 in Dhaka, an estimated 14,100 patients with cholera — 34% of all diarrheal
patients—visited the hospital over a nine-week period [Faruque, 2009]. Significantly more patients with cholera arrived at the hospital with severe dehydration than in non-flood periods [Harris et al., 2008].

Figure 7. Increasing frequency of flood-related cholera epidemics in Dhaka

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>2000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 8. Cases per month of cholera and other enteric pathogens among all patients (adults and children) seen at the ICDDR,B Dhaka Hospital in 2007

Note: all values are estimated based on surveillance data in 2% of total cases.
Source: Harris et al., 2008.

Besides major epidemics, seasonal outbreaks occur once or twice a year in many endemic areas, revolving around the monsoon season that runs from June to September. Peaks during the dry, pre-monsoon period (April-May) occur in some areas, such as Bakerganj in the South, while post-monsoon peaks are more pronounced in others (e.g., Mathbaria in the Middle Belt and Chhatak in the Northeast) [Sack et al., 2003].

2.6 Other recent cholera trends and patterns in Bangladesh

In addition to the increased frequency of flood-related cholera outbreaks in Dhaka and the increased severity of cases seeking treatment in the past few years, other recent trends that have been observed include the following:

- **Increasing urbanization of the disease.** While data on the relative incidence of the disease in rural vs. urban areas are not available, several government officials and ICDDR,B scientists believe that a shift in cholera incidence from rural to urban areas, such as Dhaka, is occurring, and that V. cholerae is becoming an important urban pathogen, especially in slum dwellers. Among the reasons for this shift that informants have given are improvements in sanitation and water supplies in some rural areas (e.g., tube well construction), while at the same time, urban populations continue to grow as a result of in-migration from rural areas. This unchecked growth and increased
crowding has placed increasing stress on water and sewerage systems — where sewerage and drinking water supplies can mix if water pressure cannot be maintained 24 hours per day. The urban population in Bangladesh is projected to increase from 40 million in 2006 to 116 million by 2040 — almost half of the total population (Figure 9), with much of this growth taking place in slum areas. Given the growing urbanization, as one ICDDR,B scientist pointed out, the number of cholera cases in urban areas will continue to grow, even if the incidence rates in slums remain the same.

**Figure 9. Projected urbanization of Bangladesh’s population**

![Urbanization of Bangladesh 1950-2040](image)

**Source:** World Urbanization Prospects: The 2007 Revision Population Database.

- **Increasing and unpredictable rates of antibiotic resistance.** While rehydration with IV fluids is the main treatment for severe cases of cholera, antibiotics are used to reduce the duration of the illness and the volume of diarrhea. Strains of *V. cholerae* resistant to multiple drugs at the same time — including tetracycline, erythromycin, furazolidone, and trimethoprim-sulphamethoxazole — were first detected in Bangladesh in 2004 [Faruque et al. 2007]. Within four to five months, nearly all cases with the Ogawa strain of *V. cholerae O1* seen at the ICDDR,B hospitals both in Dhaka and Matlab were resistant to all four antibiotics. Almost as suddenly, most cases in 2006 became sensitive again to tetracycline. *V. cholerae* strains have become less sensitive to ciprofloxacin — the main drug used by ICDDR,B in response to the rise in multi-drug resistant strains. Whereas a single dose of ciprofloxacin successfully reduced the symptoms and duration of the illness in the 1990s, by the early 2000s, it was no longer as effective, and the hospital switched to a single 500 mg dose of azithromycin as the main antibiotic therapy for cholera patients. The continual pattern of antibiotic resistance to commonly-used therapies limits the treatment options for the disease and requires a constant search for new drugs that will be effective.

- **Spread of the disease to new areas.** Cholera continues to appear suddenly in areas where the disease has been absent for decades. A recent example is in Pabna, in the East of the country, which experienced a ten-fold increase in diarrheal cases in
October 2009, and where 85% of tested specimens were found to be positive for *V. cholerae*. According to ICDDR,B experts, cholera had not been seen in Pabna for 30 years.

2.7 An estimate of the average number of cholera cases and deaths per year in Bangladesh

An estimation of the average annual cholera disease burden in Bangladesh was performed for this case study. The estimate can be used by policymakers in determining the importance of cholera in the country and the need to control it. The estimate is also used as the baseline of cholera incidence before any vaccination program is enacted, and thus is critical for the analyses of the impact and cost-effectiveness of cholera vaccination described in Section 7.

A cholera case for this analysis is defined as a case that receives treatment in a health facility — either on an inpatient or outpatient basis. This analysis was conducted in close consultation with ICDDR,B (Dr. A.K. Siddique) and based on data from sentinel site surveillance of cholera, conducted by ICDDR,B from 1997 to 2001 or later in five widely-separated areas of the country (Bakerganj, Begumganj, Chhatak, Mathbaria and Iswarganj) (of which all but Iswarganj are described in Sack et al., 2003). The steps involved in estimating the annual cholera disease burden and results are described below.

2.7.1 Mapping out the country by level of cholera risk

Based on experience in tracking cholera outbreaks through the joint Government of Bangladesh-ICDDR,B’s Epidemic Control Preparedness Programme and on the five-site sentinel surveillance, each of the country’s 64 districts was assigned to one of four cholera risk groups: high, medium, low, or unknown risk. The results are shown in Table 2 and Figure 10. According to this analysis, 28 (44%) of the country’s districts, consisting of 51% of the population, are at “high risk” for cholera. Eight districts (12% of the population) are considered at “medium risk,” and 14 districts (17% of the population) fall into the “low risk” category. Due to a lack of reports or surveillance, 14 districts in the Northwest corner of the country are in the “unknown risk” category.

<table>
<thead>
<tr>
<th>Districts by risk category</th>
<th>Districts</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>High</td>
<td>28</td>
<td>44%</td>
</tr>
<tr>
<td>Medium</td>
<td>8</td>
<td>12%</td>
</tr>
<tr>
<td>Low</td>
<td>14</td>
<td>22%</td>
</tr>
<tr>
<td>Unknown (no data)</td>
<td>14</td>
<td>22%</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>100%</td>
</tr>
</tbody>
</table>
Figure 10. Map of endemic cholera risk by district (provided by A.K. Siddique (ICDDR,B))
2.7.2 Estimating average annual incidence rates (by district category and age group)

An annual average incidence rate of cholera was then estimated for each district risk group (high, medium, etc.). The incidence rates are based on rates that were obtained in the ICDDR,B sentinel site surveillance in the five sites listed above (shown in Figure 10), after making assumptions about the catchment population for each sentinel hospital. The annual incidence rates in the five sites ranged from a high of 3.7/1,000 to a low of 1.2/1,000. These rates are averages that include both high- and low-incidence years, as well as outbreaks.

Based on these data, an average annual cholera incidence rate of 3/1,000 is assumed for the high-risk districts, 2/1,000 for the medium-risk districts, and 1/1,000 for the low-risk districts. The districts with unknown risk were assigned a rate of 1/1,000.

Age-specific incidence rates for each district risk category were then estimated for four age groups: <1 year, 1-4 years, 5-14 years, and 15 and older. To estimate these rates, we used the age distribution of cholera cases from the ICDDR,B sentinel site surveillance in four of the sites (all but Iswaranganj). The resulting distribution of cases by the four age groups is shown in Table 3.

### Table 3. Age breakdown of cholera cases used to estimate age-specific incidence rates (from sentinel site surveillance in four sites)*

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Percent of cholera cases</th>
<th>Cumulative percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>8.0%</td>
<td>8.0%</td>
</tr>
<tr>
<td>1-4</td>
<td>29.0%</td>
<td>37.0%</td>
</tr>
<tr>
<td>5-14</td>
<td>24.4%</td>
<td>61.4%</td>
</tr>
<tr>
<td>15 and older</td>
<td>38.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

*Sites are Bakerganj, Mathbaria, Chhatak, and Chaugachha (see Section 2.1 above and Sack et al. 2003).

We then applied this age distribution to the overall incidence rates estimated for each type of district (3/1,000 for high-risk, 2/1,000 for medium risk, etc.), in order to obtain age-specific annual incidence rates for each of the four district categories (Table 4). Children less than one year of age have the highest estimated cholera incidence rates, ranging from 4/1,000 to 12/1,000 and averaging 8.7/1,000 in the country as a whole. The next highest risk group is 1-4 year olds, with rates of 3.7-11/1,000 and 7.8/1,000 overall, followed by 5-14 year olds (with an average rate of 2.5/1,000). Adults have the lowest incidence rates, ranging from 0.6 - 1.7/1,000 and averaging 1.2/1,000. The estimated incidence for all ages in the country as a whole is 2.1/1,000 per year.

2.7.3 Calculating the average number of cholera cases per year

The age- and risk group-specific incidence rates described above were multiplied by the estimated number of people in each of these age and risk groups to obtain an estimate of the number of cases of cholera per year (Table 4). The estimated total average number of cases per year is around 352,000. Seventy-two percent of cases (around 253,000) occur in the 28 “high risk” districts that contain around half of the country’s population (Figure 11). Following the age breakdown shown in Table 3 above, around 216,000 (61%) of the annual number of cases occur in children 14 years old and younger.
### Table 4: Estimated annual cholera incidence rates, number of cases and death by district risk category and age group

<table>
<thead>
<tr>
<th>District risk category</th>
<th>Age group</th>
<th>Population</th>
<th>Annual incidence per 1,000</th>
<th>Annual cases</th>
<th>Annual deaths (best estimate using 1.5% CFR)</th>
<th>Annual deaths (range) (using 1-2% CFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&lt;1</td>
<td>1,670,499</td>
<td>12.1</td>
<td>20,000</td>
<td>300</td>
<td>200 - 400</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>6,692,295</td>
<td>11.0</td>
<td>73,000</td>
<td>1,100</td>
<td>700 - 1,500</td>
</tr>
<tr>
<td></td>
<td>5-14</td>
<td>17,710,265</td>
<td>3.5</td>
<td>62,000</td>
<td>900</td>
<td>600 - 1,200</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>58,387,318</td>
<td>1.7</td>
<td>98,000</td>
<td>1,500</td>
<td>1,000 - 2,000</td>
</tr>
<tr>
<td>All ages</td>
<td></td>
<td>84,461,377</td>
<td>3.0</td>
<td>253,000</td>
<td>3,800</td>
<td>2,500 - 5,100</td>
</tr>
<tr>
<td>Medium</td>
<td>&lt;1</td>
<td>375,133</td>
<td>8.1</td>
<td>3,000</td>
<td>45</td>
<td>30 - 60</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>1,503,070</td>
<td>7.3</td>
<td>11,000</td>
<td>170</td>
<td>110 - 220</td>
</tr>
<tr>
<td></td>
<td>5-14</td>
<td>3,977,080</td>
<td>2.3</td>
<td>9,300</td>
<td>140</td>
<td>90 - 190</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>13,111,664</td>
<td>1.1</td>
<td>14,600</td>
<td>220</td>
<td>150 - 290</td>
</tr>
<tr>
<td>All ages</td>
<td></td>
<td>18,966,947</td>
<td>2.0</td>
<td>38,000</td>
<td>600</td>
<td>400 - 800</td>
</tr>
<tr>
<td>Low or Unknown</td>
<td>&lt;1</td>
<td>1,206,368</td>
<td>4.0</td>
<td>4,900</td>
<td>70</td>
<td>50 - 100</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>4,833,634</td>
<td>3.7</td>
<td>18,000</td>
<td>270</td>
<td>180 - 360</td>
</tr>
<tr>
<td></td>
<td>5-14</td>
<td>12,789,655</td>
<td>1.2</td>
<td>15,000</td>
<td>230</td>
<td>150 - 300</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>42,165,018</td>
<td>0.6</td>
<td>23,000</td>
<td>350</td>
<td>230 - 460</td>
</tr>
<tr>
<td>All ages</td>
<td></td>
<td>60,994,676</td>
<td>1.0</td>
<td>61,000</td>
<td>900</td>
<td>600 - 1,200</td>
</tr>
<tr>
<td>All districts</td>
<td>&lt;1</td>
<td>3,252,001</td>
<td>8.7</td>
<td>28,000</td>
<td>400</td>
<td>280 - 560</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>13,029,999</td>
<td>7.8</td>
<td>102,000</td>
<td>1,500</td>
<td>1,000 - 2,000</td>
</tr>
<tr>
<td></td>
<td>5-14</td>
<td>34,477,000</td>
<td>2.5</td>
<td>86,000</td>
<td>1,300</td>
<td>900 - 1,700</td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>113,664,000</td>
<td>1.2</td>
<td>136,000</td>
<td>2,000</td>
<td>1,400 - 2,700</td>
</tr>
<tr>
<td>All ages</td>
<td></td>
<td>164,423,000</td>
<td>2.1</td>
<td>352,000</td>
<td>5,300</td>
<td>3,500 - 7,000</td>
</tr>
</tbody>
</table>

### Figure 11: Estimated breakdown of cholera cases and deaths by type of district

![Cholera Cases and Deaths by District Risk Category](image_url)
2.7.4 Estimated annual number of deaths from cholera

The estimated number of deaths from cholera each year in Bangladesh is around 5,300, with a range of 3,500 - 7,000. This estimate is based on the above analysis of the number of cases per year and an estimated case fatality rate of 1.5%, with a range of 1 to 2% (Table 4).

2.8 Climate change and its possible impact on cholera

Among the main effects of global climate change, which most scientists link to increased levels of fossil fuel use, are increases in the surface temperature of the oceans; a rise in sea levels and resulting seawater incursion inland; and increases in extreme weather events, such as cyclones, heavy rainfall, and droughts. Bangladesh was recently ranked as the country most affected by climate change in the world between 1990 and 2008, based on a climate risk index [Harmeling, 2009]. During this period, the country had the highest annual death toll from extreme weather events of all countries — mostly due to a devastating cyclone in 1991 — and annual losses of more than $2 billion due to weather events, equivalent to 1.8% of Gross Domestic Product per year.

A growing body of research is showing a direct link between the main manifestations of climate change, the growth of *Vibrio cholerae*, and increases in cholera incidence. *Vibrio cholerae*, including the forms that cause disease (biotypes O1 and O139), has been found to live in coastal waters, estuaries, and fresh water bodies in Bangladesh [Alam et al., 2006] and other tropical and semi-tropical countries. It has been called “a natural member of the aquatic microbial community” [Lipp et al., 2002, p. 759].

Zooplankton, such as microscopic copepods and other crustaceans, are a known reservoir for *V. cholerae*, and research in Bangladesh and elsewhere has shown that increases in the temperature of sea and fresh surface water can lead to plankton blooms and to increases in the growth of the bacteria [Lipp et al., 2002]. Such increases in the prevalence of vibrios enhance the risk of cholera outbreaks in areas where untreated water is used for drinking and household use [Mintz, 2009]. A study found that a 5°C rise in the water temperature of a lake in rural Bangladesh increased the risk of cholera cases appearing in the area by more than three-fold [Huq et al., 2005]. Another study in Dhaka also found a correlation between increases in the percent of diarrheal cases due to cholera at the ICDDR,B hospital and increases in the sea surface temperature in the Bay of Bengal, presumably due to plankton blooms [Lobitz et al., 2000].

Vibrios also grow especially well in brackish water, and there is evidence that “periodic intrusion of salt water appears to enhance survival” of vibrios and the expression of cholera toxin [Lipp et al., 2002]. The study in Dhaka, in fact, also found that increases in sea surface height — indicating sea water incursion inland — were also linked to increases in the cholera case load at the ICDDR,B hospital [Lobitz et al., 2000].

The amount of rainfall has been shown to be a factor in cholera incidence as well, including the seasonality of cholera pre- and post-monsoons. Both periods of heavy rainfall and lower than average rainfall in Dhaka were followed by increases in the estimated number of cholera cases at the ICDDR,B hospital in one study [Hashizume et al., 2008].

Given the evidence that increased surface water temperatures, rises in sea levels and extremes in rainfall amounts all enhance the risk of cholera, scientists and government health
officials in Bangladesh have expressed concern that cholera incidence and outbreaks could increase in the coming years due to global climate change. This increase could, however, be mitigated by stepped up improvements to water and sanitation systems and other preventive measures.

2.9 How Bangladeshi policymakers view cholera

2.9.1 Views about cholera incidence and its importance

During the IVI team’s country visit in December 2009, government officials and other opinion leaders were asked their views about the importance of cholera in Bangladesh, trends in its incidence, and causal factors. While those interviewed may not be representative of all key persons making or influencing health policy in Bangladesh, they did include several officials at the top of the MOHFW hierarchy, including the Health Minister, the State Minister of Health, the Health Secretary, the Director-General of Health Services, the Joint Secretary of Public Health, Joint Chief of Planning, and top officials in disease control. They also include current and former officials responsible for primary health care and immunization, but did not include officials who focused solely on diarrheal disease or cholera, who would likely be biased in singling out cholera as a major problem. Therefore, we believe that the views of those interviewed are indicative of the prevailing beliefs and opinions of government decision-makers and influential leaders in the area of health in the country.

Most government officials interviewed by the IVI team viewed cholera as a problem in Bangladesh, with some believing that incidence of the disease was increasing and that it now accounted for a greater proportion of severe diarrheal disease cases than in the recent past. Two senior health ministry officials described cholera as “re-emerging” in the country. Reasons given include the lack of safe water supplies in many areas — both rural and urban — with people in many rural areas continuing to rely on surface water for their drinking water supply or reverting back to surface water due to arsenic contamination of tube wells (“safe’ water is becoming unsafe.”) These officials also cited climate change as a factor, linking it to the spread of vibrios from coastal waters inland as a result of sea water incursion from rising sea levels.

These views were not unanimous, however. One top health official felt that cholera was “not a major problem” and that incidence had declined, though he recognized that it still appeared following natural disasters such as Cyclone Aila.

2.9.2 Views about cholera-related mortality

Many officials believed that deaths due to acute watery diarrhea, including cholera, were “way down” as a result of the widespread use of oral rehydration therapy and that ORT had prevented “millions of child deaths” in Bangladesh, even if the number of cases was not decreasing. However, several, including some of these same officials, also believed that deaths from acute watery diarrhea were still occurring because of the continual problem of malnutrition among children and delays in people seeking health care, due to religious or cultural barriers or a lack of money. One MOHFW official, in fact, claimed that cholera was becoming “a killer disease”.

There was recognition among officials interviewed that the disease burden of cholera and where it is and is not a problem is poorly understood. Top officials therefore expressed
the need for improved surveillance, with the Director-General of Health Services suggesting a baseline survey involving sentinel site surveillance in different parts of the country to obtain a national picture of the disease.

2.9.3 How policymakers rank cholera among infectious disease priorities

To gauge where these policymakers and other persons interviewed placed cholera among their infectious disease priorities, they were asked to rank the top 10 infectious diseases based on their own personal views of their importance in Bangladesh, using a sheet listing 17 diseases (and an “other” category) (see the ranking sheet in Appendix 4). Fourteen persons completed the ranking sheet, including 10 officials from the MOHFW and the Dhaka City Corporation, two UNICEF representatives, and two representatives from professional associations. Some top officials, including the Minister of Health and the Director-General of Health Services, did not have time to complete the form.

Cholera was ranked among the top five infectious disease priorities by eight of the 14 respondents (57%), including six of the 10 government officials (60%) completing the sheet (Table 5). Using a scoring system in which a rank of “1” was converted to a score of 10, a rank of “2” was given a score of 9 and so on, up to “10” (score of 1), cholera received the third highest score, both among all respondents and among government officials only—coming after tuberculosis and pneumonia⁶ (Table 6). The disease scored higher than hepatitis (B or C) and other enteric infections, including rotavirus, “other diarrheal diseases (e.g., dysentery)” and typhoid fever.

<table>
<thead>
<tr>
<th>Type/origin of person interviewed</th>
<th>Frequency of responses by ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-2</td>
</tr>
<tr>
<td>MOHFW officials*</td>
<td>4</td>
</tr>
<tr>
<td>Dhaka city government official</td>
<td></td>
</tr>
<tr>
<td>Representatives from professional associations</td>
<td>1</td>
</tr>
<tr>
<td>UNICEF representatives</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
</tr>
</tbody>
</table>

⁶ Pneumonia included all bacterial causes of the disease, including Hib, pneumococcal disease, and meningococcal.

Besides the fact that not all policymakers interviewed completed this exercise, there could also have been a bias towards giving cholera a high rank, since those interviewed knew that the disease was the subject of the interviews. Nonetheless, these results, along with the findings from the policymaker interviews, suggest that the concern about and priority of cholera among health policymakers in Bangladesh has increased considerably since IVI conducted a survey in Bangladesh in 2001 of policymaker views about three enteric diseases: cholera, typhoid fever, and shigellosis [DeRoeck and Nyamete, 2001]. While there was a range of opinions expressed among government officials about the importance of cholera in 2001, most persons interviewed did not view it as a major health problem any longer in Bangladesh,
especially due to great declines in mortality as a result of the widespread use of ORT. The disease was then described as a “self-limiting disease”, “not alarming and not a concern”, “not as scary as it used to be”, and “well-managed”.

Table 6. Scores and rankings of infectious diseases among persons interviewed for the cholera vaccine country case study, Bangladesh

<table>
<thead>
<tr>
<th>Disease</th>
<th>Score for entire sample (n=14)</th>
<th>Disease ranking among all respondents</th>
<th>Score for government officials only (MOHFW, IEDCR, DCC) (n=10)</th>
<th>Disease ranking among government officials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>107</td>
<td>1</td>
<td>73</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>92</td>
<td>2</td>
<td>65</td>
<td>2</td>
</tr>
<tr>
<td>Cholera</td>
<td>83</td>
<td>3</td>
<td>61</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis (B,C)</td>
<td>72</td>
<td>4</td>
<td>45</td>
<td>4</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>68</td>
<td>5</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>58</td>
<td>6</td>
<td>44</td>
<td>5</td>
</tr>
<tr>
<td>Influenza</td>
<td>48</td>
<td>7</td>
<td>45</td>
<td>4</td>
</tr>
<tr>
<td>Meningitis</td>
<td>46</td>
<td>8</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>Other diarrheal diseases (e.g., dysentery)</td>
<td>46</td>
<td>8</td>
<td>42</td>
<td>6</td>
</tr>
<tr>
<td>Malaria</td>
<td>38</td>
<td>9</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>38</td>
<td>9</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>Dengue</td>
<td>36</td>
<td>10</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Filariasis</td>
<td>15</td>
<td>11</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Rubella</td>
<td>7</td>
<td>12</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Leprosy</td>
<td>5</td>
<td>13</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>HPV</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Rabies</td>
<td>2</td>
<td>15</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

The views expressed by policymakers during the 2009 visit by the investment case team reflect recent changes in the government’s public stance towards the disease. The Government still does not report cholera cases to WHO, due to a lack of laboratory confirmation of cases. However, since the new Health Minister assumed office in 2009, there is greater acceptance within the Government for scientists, the media and others to use the word “cholera”, whereas they could previously refer only to watery diarrhea. As discussed in Chapter 6, the Government of Bangladesh has also shown greater interest in cholera vaccination in recent years, having requested WHO twice (as a member of the WHO Executive Board) to add the topic of cholera vaccines to the agenda of the World Health Assembly. Bangladesh submitted a draft resolution in 2010 to the WHO Executive Board calling for intensified global efforts to control cholera, including through immunization. The resolution was considered and ratified by the World Health Assembly in 2011.

The MOH has also agreed to collaborate with ICDDR,B on a feasibility study of cholera vaccination in the Mirpur area of Dhaka using the Shanchol™ vaccine. These changes in government attitudes have been attributed to the large cholera outbreaks in Dhaka in 2007 following wide-scale flooding, increased media attention to cholera and acute watery diarrhea due to the increased frequency of outbreaks in Dhaka and elsewhere, and revisions
to the International Health Regulations in 2007 (which encourage countries to report cholera by calling for no trade sanctions against those that do).
3. The economic burden of cholera in Bangladesh: cost-of-illness and macro-economic impact

3.1 The cost-of-illness from cholera

3.1.1 Cost per case of cholera

According to a study conducted by the Diseases of the Most Impoverished (DOMI) Program in 2004-05 in the ICDDR,B hospital in Matlab, a hospitalized case of cholera costs society, on average, US $34 for children and $44 for adults (in 2010 dollars) [Poulos et.al. 2008]. These include the costs to the hospital for medical care and the direct “out-of-pocket” costs to patients and their families for drug charges, transportation to and from the hospital, lodging for family members, and so forth. They also include the indirect costs of lost wages resulting from the patient or family members missing work, and the loss in productivity from children missing school. Most of the difference in cost-of-illness between adults and children is, in fact, due to the higher indirect costs from adults in lost wages.

For this case study, we applied the cost estimates for hospitalized patients from Matlab to the country as a whole, since they are the only existing inpatient cost estimates for cholera patients in Bangladesh. Some of these costs, such as staff salaries and the use of azithromycin in place of older-generation antibiotics, may be higher at the ICDDR,B hospital in Matlab than in government hospitals and thus not representative of costs where most cholera patients are treated. However, other costs in Matlab may be lower due to higher quality treatment, which can result, for example, in fewer antibiotic resistant cases, shorter duration of illness, or fewer complications.

We estimate that a case of cholera treated on an outpatient basis costs, on average, $4.10 to $6.10 (in 2010 dollars) (Table 7). Because no outpatient cases were included in the Matlab study, these estimates are based on standard treatment regimens, standardized cost-per-visit estimates, and drug cost estimates from WHO, MSH, and other sources.

To estimate the weighted average cost of cholera cases — both hospitalized and outpatient — we used the hospitalization rate of 38% from a cholera study conducted in Kolkata, India [Poulos et al. 2008], since data on cholera hospitalization rates in Bangladesh are not available. We assume that the remaining 62% are treated on an outpatient basis and go home the same day. The average total cost-of-illness for cholera in Bangladesh is estimated to be around $16-21 per episode (in 2010 dollars), depending on the age of the patient.
Table 7. Estimated cost-of-illness per case of cholera in Bangladesh, US $2010

<table>
<thead>
<tr>
<th>Type of patient/cost</th>
<th>Age group</th>
<th>&lt;1</th>
<th>1-4</th>
<th>5-14</th>
<th>15+</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient (38%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct cost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.90</td>
<td>28.90</td>
<td>28.90</td>
<td>29.99</td>
<td>29.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect cost (e.g., lost wages)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.70</td>
<td>4.70</td>
<td>4.70</td>
<td>13.60</td>
<td>8.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33.60</td>
<td>33.60</td>
<td>33.60</td>
<td>43.60</td>
<td>38.20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Outpatient (62%)         |           |      |       |       |       |          |
| Direct cost              |           |      |       |       |       |          |
| 3.50                     | 3.80      | 4.60 | 4.00  | 4.00  |
| Indirect cost            |           |      |       |       |       |          |
| 1.10                     | 1.10      | 1.10 | 2.70  | 1.70  |
| Total                    |           |      |       |       |       |          |
| 4.10                     | 4.30      | 5.20 | 6.10  | 5.20  |

| All patients (weighted average cost) |          |      |       |       |       |          |
| Direct cost                   |           |      |       |       |       |          |
| 13.20                        | 13.30     | 13.80| 13.90 | 13.70 |
| Indirect cost                |           |      |       |       |       |          |
| 2.50                         | 2.50      | 2.50 | 6.80  | 4.40  |
| Total                        |           |      |       |       |       |          |
| $15.70                       | $15.80    | $16.30| $20.70| $18.10|


3.1.2 Annual cost of cholera

In looking at only cost-of-illness and not macro-economic costs, cholera costs on average more than $6.3 million to Bangladesh each year (Table 8). This estimate was derived by multiplying the estimated number of cases per year (for each age group) by the average cost-of-illness. This total includes $4.9 million in direct costs — to health facilities, patients, and families — and $1.4 million in indirect costs, such as lost wages. Children 14 and younger account for 56% of these costs, which is similar to their proportion of all estimated cases (61%).

Table 8. Estimated total cost of illness from cholera in Bangladesh per year, US $2010

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Annual no. cases</th>
<th>Direct cost-of-illness per case</th>
<th>Total direct cost-of-illness</th>
<th>Indirect Cost-of-illness per case</th>
<th>Total indirect cost-of-illness</th>
<th>Total cost-of-illness per case</th>
<th>Annual total COI (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>28,000</td>
<td>13</td>
<td>370,000</td>
<td>2.50</td>
<td>70,000</td>
<td>16</td>
<td>440,000</td>
</tr>
<tr>
<td>1-4</td>
<td>102,000</td>
<td>13</td>
<td>1,400,000</td>
<td>2.50</td>
<td>260,000</td>
<td>16</td>
<td>1,700,000</td>
</tr>
<tr>
<td>5-14</td>
<td>86,000</td>
<td>14</td>
<td>1,200,000</td>
<td>2.50</td>
<td>220,000</td>
<td>16</td>
<td>1,400,000</td>
</tr>
<tr>
<td>15+</td>
<td>136,000</td>
<td>14</td>
<td>1,900,000</td>
<td>6.80</td>
<td>900,000</td>
<td>21</td>
<td>2,800,000</td>
</tr>
<tr>
<td>All ages</td>
<td>352,000</td>
<td>$14</td>
<td>$4,870,000</td>
<td>$4.40</td>
<td>$1,450,000</td>
<td>$18</td>
<td>$6,340,000</td>
</tr>
</tbody>
</table>

These total cost-of-illness estimates are used in the cost-effectiveness analyses of vaccination to estimate the savings in treatment and other illness-related costs that will result from a reduction in the disease due to vaccination (see Section 7).
3.2 The macro-economic impact of cholera in Bangladesh: the case of the shrimp industry

Cholera is one of the few vaccine-preventable diseases that can have a significant impact on a country’s overall economy, particularly the effect that cholera outbreaks can have on suppressing such industries as tourism and food exporting. In this section, we focus on the impact that cholera has had and could continue to have on the Bangladesh shrimp industry, a major source of exports for Bangladesh.

3.2.1 Importance of the shrimp industry in Bangladesh

The shrimp industry in Bangladesh brings in approximately $250-330 million per year and employs over 600,000 people [Department of Fisheries, 2009]. The seafood industry is now the country’s second largest export industry after garments. It also accounts for 2.5% of the global production of shrimp.

Fish industries are located in areas of the country prone to both flooding and to cholera. Two areas in the South — the Chittagong-Cox’s Bazaar belt and Khulna, Shatkhira-Bagerhat belt — account for 95% of the total acreage of shrimp culture in the country [Battacharya et.al. 1999]. Production of shrimp by coastal aquaculture accounted for about 30% of annual shrimp production in 1999 [Battacharya et.al. 1999]. Aquaculture production is a 100% export-oriented activity, taking place in about 9,000 farms, while shrimp from fresh water is mostly destined for the domestic market.

The major buyers of the shrimp exported from Bangladesh are the U.S. (32% of exports), Japan (18%), Belgium (16%), and the U.K. (11%) [Battacharya et.al.1999].

3.2.2 The threat of shrimp contamination with V. cholerae

Since V. cholerae, including the pathogenic forms O1 and O139, live in shrimp and other crustaceans, these products are particularly prone to cholera contamination in Bangladesh, especially in the estuaries of the cholera-endemic Southern coast that act as reservoirs for the organism. Vibrios can easily survive light cooking and then grow to an infectious dose if the food is kept for several hours at ambient temperature. The risk of contamination is especially high during outbreaks, such as those following floods in which humans act as amplifying hosts to V. cholerae and their infected feces enter surface and sea water, further contaminating those water bodies and the animals that live in them.

In addition, as discussed in Section 2.8 above, more frequent detection of V. cholerae O1 in estuary waters and a higher incidence rate of cholera among people in Bangladesh has been shown to be associated with increasing water surface temperatures [Suzita et.al. 2009]. The risk of cholera contamination in shrimp exports could therefore rise as a result of climate change.

The disease can also be spread by people working in handling, transportation, processing, and storage of shrimp, if they are infected and do not follow hygienic behaviors.
3.2.3 The impact of cholera on shrimp exports

Because seafood is known to be easily contaminated, countries that import seafood carefully monitor the shipments to their countries, including conducting tests to detect contaminants. As a result of the regulations in importing countries, Bangladesh has a history of bans and import detentions on its shrimp and other seafood products. One of the most important events occurred in 1997 when the European Union placed a ban on shrimp imported from Bangladesh due to poor hygienic quality and non-compliance with Hazard Analysis Critical Control Point (HACCP) regulations. The estimated net cost of this ban, which lasted from August to December 1997, after considering shipments diverted to other countries, was $14.7 million to the Bangladesh frozen shrimp processing industry [Cato and Subasinge, 2003].

Other rejections of Bangladeshi seafood have occurred as well. In 1998, the EU specifically rejected a shipment of seafood from Bangladesh due to V. cholerae and other pathogens [FAO/WHO 2004]. One study found that the U.S. FDA had placed 68 import detentions on Bangladesh for adulteration of seafood products, such as sanitation and safety problems, during 2001 [Allshouse et al. 2004]. Most recently, in 2009, the EU imposed a ban on shrimp imports from Bangladesh due to contamination with the antibiotic nitrofurans [Daily Star 2009]. This ban was lifted in January 2010.

As a result of threats to shrimp and other fish exports by cholera and other pathogens, the EU is financing a project to help Bangladesh strengthen fish inspection and quality control. This project will be upgrading the country’s three existing Fish Inspection and Quality Control laboratories in Dhaka, Chittagong, and Khulna. This upgrade will include the purchase of new equipment to test shrimp and fish products for a variety of pathogens and other contaminants, and training of staff in operating the equipment and in hygienic practices.

Despite the new EU project, there remains a possibility that cholera could be transmitted to shrimp and other products during processing, shipping, and handling. Another ban on shrimp exports by the EU or more import detentions by the U.S. would be costly to the country.

The risk of cholera contamination to the shrimp industry is a compelling argument for cholera vaccination of employees and other workers associated with shrimp and other fishery industries, along with a program of regular laboratory testing of the products for contamination. There is also an argument to be made for vaccinating populations in shrimp-producing areas to prevent cholera outbreaks from occurring. It would be particularly appropriate since the government plans to begin reporting cholera cases and would not want to risk publicity about a cholera outbreak in a shrimp-producing area.
4. Current cholera control strategies and challenges

The main prevention and control measures for cholera, apart from vaccination, consist of the following:

- Efforts to provide safe drinking water and adequate sanitation to the population;
- Surveillance of acute watery diarrhea and cholera for early detection and response to cholera outbreaks and to identify high-risk areas for the control of endemic cholera;
- Health education and promotion of healthy behaviors to prevent the disease, such as exclusive breastfeeding for the first six months of life, hand washing with soap, and the use of oral rehydration solution (ORS) or recommended home fluids (RHF) to prevent severe dehydration and mortality from the disease; and
- Appropriate and timely treatment in health facilities at all levels, focusing on rehydration (ORS or IV fluid infusion for severe cases) and the use of effective antibiotics to reduce duration of the illness.

In this section, we summarize the efforts in Bangladesh — with a focus on water/sanitation improvements, cholera surveillance, and treatment — and discuss possible ways to improve diarrhea and cholera surveillance to inform the accelerated control of the disease.

4.1 Water and sanitation: current situation and efforts for improvement

4.1.1 Population access to safe water

According to a multi-cluster survey conducted by the Bangladesh Bureau of Statistics and UNICEF in 2006, most of the urban and rural populations of Bangladesh have access to sources of well or tap water: 97.1% of the rural population and 99.2% of the urban population [Pathey, 2007]. Although surface water supplies are ample in Bangladesh, the majorities of both urban and rural populations rely on groundwater because surface water would require treatment prior to consumption. Most of these people have access to shallow boreholes (or tube wells), though some of the urban population have access to piped water inside or outside of their homes. The wide-scale use of shallow tube wells has been made possible through large-scale water projects conducted by the government with the assistance of many donors as well as substantial private funding, and likely has reduced exposure to pathogens in the environment relative to accessing water from contaminated surface water sources.

In many areas, water from shallow tube wells has been found since the early 1990s to be contaminated with naturally-occurring arsenic [UNICEF, 2008a]. The DPHE works with UNICEF and other local partner institutions to test for arsenic concentrations and to mark tube wells as unsafe when arsenic concentrations exceed the national standard of 50 parts per billion. Of an estimated 8.6 million tube wells in the country, around 4.75 million have been tested. Of these, nearly 30% exceeded the standard. Among respondents to the multi-cluster survey cited above, 8% reported using water from marked, unsafe tube wells and another 38% reported that their tube wells had not yet been tested [Pathey, 2007]. Because
of arsenic contamination and falling water tables, many people are reportedly returning to the use of surface water for drinking and other uses, and the fraction of population with access to improved water sources in official statistics has been adjusted downward from 97% to 78% in rural areas [UN Statistics Division, 2009].

For the fraction of the population receiving piped water in urban areas, the quality of service has been declining due to constraints imposed by the rapidly increasing population — resulting from the rural-to-urban migration pattern — and declining water tables. According to an assessment by the Asian Development Bank (ADB), only half of Dhaka City inhabitants have access to safe water due to deteriorating infrastructure and illegal connections [ADB, 2007]. In addition, water service is intermittent, especially during the dry season from January through March. When service is interrupted, the distribution system may be contaminated by leaky sewer lines located adjacent to water supply lines. Groundwater is the primary source for the city’s water, but the water table has been falling, leading to additional shortages.

Improving the access to and quality of water and sanitation infrastructure is an important issue in Bangladesh. The Government’s Poverty Reduction Strategy Paper identifies water and sanitation activities as one of seven priority areas. A National Water Management Plan (NWMP) was adopted in 2004 to guide the country’s development of water resources. It established a goal that 100% of the urban population would have access to safe drinking water by 2010, with 75% having access to piped water within their homes. In rural areas, it also projected that 100% of the population would have access to safe water and to a means of mitigating arsenic (e.g., through the use of arsenic removal filters) by 2010. The plan further targeted 100% of the population having access to adequate sanitation facilities by 2010 for both rural and urban areas. However, these projections have not yet been met.

To address the problem in Dhaka, the Dhaka Water Supply and Sewerage Authority has received funding from the ADB and other development partners to make extensive repairs to the water conveyance system in order to minimize leakage and unaccounted for water and to construct surface water treatment plants to expand Dhaka’s water supply capacity. The goal of the project is to provide an uninterrupted water supply to 12 million Dhaka residents by 2013 [ADB, 2007].

4.1.2 Access to adequate sanitation

The multi-cluster survey [Pathey, 2007] found that only 32% of the rural population and 58% of the urban population had access to improved sanitation in 2006 [Pathey, 2007]. A number of initiatives are underway to improve access to adequate sanitation in the country. One is the Community Led Total Sanitation (CLTS), developed by WaterAid Bangladesh in 2000. This grassroots approach, cited in the National Water Management Plan, uses low cost materials and village peer pressure to increase population demand for sanitation facilities. Following a similar approach, the Department of Public Health Engineering and UNICEF are implementing the UK-funded Sanitation, Hygiene Education and Water Supply in Bangladesh (SHEWA-B) project to accelerate access to sanitation in the aim of meeting the Millennium Development Goal of reducing the proportion of the population without sustainable access to basic sanitation [UNICEF, 2008b]. The project set a goal to provide adequate sanitation for 30 million people between 2006 and 2009. The impact of this program will not be measurable until the results of the next round of the multi-cluster survey become available.
While the water and sanitation projects will have a positive impact on access to improved water and sanitation facilities, the improvements will probably take several years to implement. In the near to medium term, cholera is likely to remain a persistent problem for Bangladesh. In addition, the frequent floods can damage water and sanitation infrastructure, further delaying access to those in need. Thus, cholera vaccines could offer a short- to medium-term solution while continuing efforts to improve water and sanitation. As water and sanitation infrastructure is developed, the need for cholera vaccines will be reduced and should be continuously reassessed.

4.2 Disease surveillance in Bangladesh

4.2.1 Overview of infectious disease surveillance

Building a surveillance system for cholera with the ability to detect suspected cases in a timely manner and to diagnose them in the laboratory will greatly facilitate decisions about whether to introduce cholera vaccination, as well as the implementation and monitoring of a cholera vaccination program. Laboratory-confirmed surveillance will help the MOHFW to identify high-risk areas to target for the control of endemic cholera, and to detect and respond to cholera outbreaks early on. Cholera surveillance prior to and once a vaccination program is introduced will also be critical in evaluating the effectiveness and impact of the program.

As in most developing countries, there is at present no national surveillance of cholera that includes laboratory confirmation in Bangladesh. There are several disease surveillance systems or programs run by the MOHFW that include diarrhea — including acute watery diarrhea and bloody dysentery — but they are not capable of diagnosing cholera per se, since laboratory testing is usually not conducted (see Table 9). These systems are also managed by different agencies or departments of the ministry and are not always coordinated.

The Ministry’s main routine disease reporting system is a community-based survey conducted by Health Assistants who visit households each month to collect information about illnesses and deaths using a standard reporting form. These reports are compiled at the union level7 by Assistant Health Inspectors, and then at the upazila (sub-district) level by Upazila Health and Family Planning Officer (UNHPO). These upazila-level reports are sent simultaneously to the district Civil Surgeons and the national MOHFW (office of the Director of Primary Health Care under the Directorate General of Health Services (DGHS)), where they are compiled in a national “Control Room”. While these reports are normally sent on a monthly basis, surveillance activities are intensified during disease outbreaks, and reports for the disease in question are provided up the chain on a daily basis. The Upazila Health Complexes are now in the process of being equipped with computers so that their reports can be sent electronically to the Control Room. However, the quality of the data, as well as implementation of this surveillance system, is uneven, and the reports are not properly reviewed or validated [WHO/Bangladesh]. This system also does not include all major infectious diseases, such as malaria and tuberculosis, which are handled by control programs for these specific diseases.

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7 There are 3 wards per union. Bangladesh is divided administratively into six divisions, 64 districts, 482 upazilas, 4,500 unions, and 13,500 wards. Each district has a Civil Surgeon responsible for public health activities and reporting for the district.
<table>
<thead>
<tr>
<th>System/program</th>
<th>Responsible agency or department</th>
<th>Diseases covered</th>
<th>Includes laboratory diagnosis?</th>
<th>Location of surveillance</th>
<th>Frequency of reporting</th>
<th>Description and flow of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine (household level) disease surveillance</td>
<td>Primary Health Care Director, Directorate General of Health Services (DGHS), MOHFW</td>
<td>30 infectious and non-communicable diseases, including diarrhea (acute watery diarrhea and bloody dysentery)</td>
<td>No</td>
<td>Community-based (household visits)</td>
<td>Monthly (daily during disease outbreaks)</td>
<td>Data collected by health assistants during household visits, compiled by unions and upazilas (by UH&amp;FPOs) and submitted to district Civil Surgeons and the DGHS Control Room in the Ministry</td>
</tr>
<tr>
<td>Routine hospital disease reporting</td>
<td>Primary Health Care Director, DGHS, MOHFW</td>
<td>Range of infectious and non-communicable diseases</td>
<td>Most reports based on clinical diagnosis. Laboratory testing conducted in some hospitals for some diseases.</td>
<td>All public sector hospitals, from Upazila Health Complexes and above</td>
<td>Monthly</td>
<td>Reports compiled by UH&amp;FPOs and submitted to district Civil Surgeons and the DGHS Control Room</td>
</tr>
<tr>
<td>Priority Communicable Disease Surveillance (PCDS)</td>
<td>Institute of Epidemiology, Disease Control and Research (IEDCR)</td>
<td>9 priority diseases, including TB, malaria, encephalitis, leprosy, diarrheal disease</td>
<td>Most reports based on clinical diagnosis. Laboratory testing conducted in some hospitals for some diseases.</td>
<td>Community-based and hospital-based surveillance throughout the country</td>
<td>Weekly; daily during outbreaks</td>
<td>Community and hospital-based system established in 2004 to build early warning system for disease outbreaks. Data are compiled by UH&amp;FPOs and Civil Surgeons and submitted to IEDCR. System is now Web-based.</td>
</tr>
<tr>
<td>Sentinel site surveillance</td>
<td>IEDCR</td>
<td>16 diseases, including acute watery diarrhea and bloody dysentery</td>
<td>Most reports based on clinical diagnosis. Laboratory testing conducted in some hospitals for some diseases.</td>
<td>Selected hospitals in 1 upazila in 8 districts</td>
<td>Bi-weekly</td>
<td>Reports submitted to UH&amp;FPOs and Civil Surgeons in the participating districts and then to the IEDCR</td>
</tr>
<tr>
<td>Specialized surveillance programs</td>
<td>IEDCR</td>
<td>Influenza, Nipah, acute meningoencephalitis (JE, dengue, nipah), Salmonella (typhoid), others</td>
<td>Yes</td>
<td>Selected hospitals, including medical colleges</td>
<td>Bi-weekly to monthly, depending on the program</td>
<td>Sentinel hospital-based surveillance programs with laboratory testing. Influenza surveillance at 26 hospitals established with U.S. CDC and ICDDR,B support is considered a model for the country.</td>
</tr>
<tr>
<td>System/program</td>
<td>Responsible agency or department</td>
<td>Diseases covered</td>
<td>Includes laboratory diagnosis?</td>
<td>Location of surveillance</td>
<td>Frequency of reporting</td>
<td>Description and flow of data</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>-----------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Institutional disease</td>
<td>IEDCR</td>
<td>Priority diseases (same as for PCDS) and other infectious and non-communicable</td>
<td>Yes</td>
<td>8 large government Medical College</td>
<td>Monthly</td>
<td>Hospital directors are responsible for submitting reports to IEDCR</td>
</tr>
<tr>
<td>surveillance</td>
<td></td>
<td>diseases</td>
<td></td>
<td>hospitals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event-based surveillance</td>
<td>IEDCR</td>
<td>Outbreaks of any disease of public health importance, including acute watery</td>
<td>Yes (in collaboration with</td>
<td>Affected communities</td>
<td></td>
<td>Investigations conducted by National Rapid Response Team of IEDCR, based on reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diarrhea</td>
<td>medical colleges and some</td>
<td></td>
<td></td>
<td>of possible outbreaks from hospitals, Civil Surgeons and UH&amp;FPOs. For suspected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>district hospitals, ICDDR,B,</td>
<td></td>
<td></td>
<td>cholera outbreaks, IEDCR asks ICDDR,B for assistance in investigation and response.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>others)</td>
<td></td>
<td></td>
<td>The NRRT remains alert 24/7 and maintains a hotline for contact with Civil Surgeons.</td>
</tr>
<tr>
<td>Media surveillance</td>
<td>IEDCR</td>
<td>Outbreaks of any disease of public health importance, including acute watery</td>
<td>No</td>
<td>All over Bangladesh</td>
<td>Daily</td>
<td>An agency has been contracted to scan print and electronic media to provide a daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diarrhea</td>
<td></td>
<td></td>
<td></td>
<td>e-mail report to IEDCR</td>
</tr>
<tr>
<td>EPI surveillance system</td>
<td>EPI/Child Health and Limited</td>
<td>All diseases targeted by vaccines in the EPI schedule, except tuberculosis* (e.g.,</td>
<td>Yes, using Institute of</td>
<td>Community-based</td>
<td>Weekly/monthly,</td>
<td>Health Assistants during routine visits collect specimens among suspected cases and</td>
</tr>
<tr>
<td></td>
<td>Curative Care Program under</td>
<td>polio/AFP, measles, tetanus, hepatitis B, pertussis)</td>
<td>Institute of Public Health</td>
<td>depends on disease</td>
<td></td>
<td>sends them to IPH for testing. Supervision provided by district-level Surveillance</td>
</tr>
<tr>
<td></td>
<td>Primary Health Care Director,</td>
<td></td>
<td>(IPH) laboratories,</td>
<td></td>
<td></td>
<td>Medical Officers and others. If cholera vaccine were added to the EPI, cholera</td>
</tr>
<tr>
<td></td>
<td>DGHS</td>
<td></td>
<td>including national virology</td>
<td></td>
<td></td>
<td>surveillance would be added to this system.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>laboratory (for measles, polio, rubella)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Not including sentinel site surveillance conducted by specific disease control programs, such as TB, leprosy and HIV/AIDS.
Public sector hospitals — from the Upazila Health Complexes to district hospitals and above, also report disease and death information on a monthly basis, which makes its way up the chain to the district-level Civil Surgeons and the DGHS Control Room. These reports are based on clinical diagnosis and/or laboratory testing, depending on the disease and hospital. It is not clear what proportion of hospitals conduct laboratory testing for cholera on a routine basis, but apart from medical college hospitals, it is believed to be quite low.\(^8\)

In an effort to build an early warning system for infectious disease outbreaks, the Institute of Epidemiology, Disease Control and Research (IEDCR) — the country’s center for disease control — has developed a sentinel site, hospital-based Priority Communicable Disease Surveillance (PCDS) system, which tracks 13 priority diseases, including acute watery diarrhea, bloody dysentery, malaria, tuberculosis, leprosy, and others. This system — separate from the DGHS routine community-based and hospital-based reporting systems — involves weekly reports from the upazilas and districts to the IEDCR, which are now Web-based. Reports are based on clinical diagnosis, supported in some hospitals by laboratory testing.

Sentinel site surveillance, covering a range of diseases including diarrheal diseases and vaccine-preventable diseases, has also been on-going in eight districts (in one upazila each) through the IEDCR, as has Institutional Disease Surveillance in eight large government hospitals throughout the country. The MOHFW hopes to build upon this system to phase in sentinel site surveillance in all districts over a five-year period, with management by the IEDCR and support from WHO [WHO/Bangladesh].

The strongest disease surveillance systems in Bangladesh are laboratory-supported surveillance programs for specific diseases, often funded separately by external donors. These include specialized hospital-based surveillance programs each for influenza, nipah encephalitis, and acute meningo-encephalitis (Japanese encephalitis, nipah, and dengue). The recently-established influenza surveillance — developed by IEDCR in collaboration with ICDDR,B and with support from the U.S. CDC — involves laboratory-confirmed surveillance in a network of 12 tertiary hospitals and 14 district hospitals covering all six divisions. The system is supported by a newly-established national influenza reference laboratory at IEDCR, has been positively evaluated by WHO, and was instrumental in the development of a national influenza control policy. Vertical programs, such as tuberculosis control and leprosy control, also have separate, well-regarded sentinel site surveillance systems with laboratory support.

Among the most highly regarded surveillance systems in the country is the surveillance run by the EPI for diseases targeted by the program. The system includes surveillance of polio/AFP, measles, tetanus, and other vaccine-preventable diseases. Suspected cases are reported by community-based Health Assistants on a weekly basis, using an EPI-specific form, and submitted to the union, upazila, and district levels, with the district Civil Surgeons preparing a monthly report to the national EPI. Oversight is provided by Surveillance Medical Officers employed by the EPI and financially supported by WHO. Specimens from suspected cases are sent for testing to the Institute of Public Health (IPH) laboratories, which include the national polio/virology lab. Once a new vaccine is introduced into the EPI, surveillance for that disease is taken over by the EPI. This would be the case for cholera surveillance if the vaccine is added to the EPI.

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\(^8\) According to ICDDR,B informants.
When a possible disease outbreak is detected by a hospital, UHF&FPO, Civil Surgeon, or others involved in disease surveillance, it is the responsibility of the IEDCR to conduct an investigation by mobilizing a National Rapid Response Team (NRRT) made of experts from the agency. This team is assisted on the ground by an 11-member response team in each of the 64 districts and a five-member team at the upazila level, which have all received training from IEDCR. In the case of a potential cholera outbreak, the IEDCR requests the assistance of ICDDR,B to test specimens to confirm cholera and to help with the response. From 2006 to 2009, the IEDCR investigated three confirmed cholera outbreaks.

### 4.2.2 Cholera surveillance in Bangladesh

As mentioned above, surveillance of cholera is not routinely conducted by the Government, due to the lack of systematic laboratory testing in government facilities for the disease. Most laboratory testing for cholera is conducted by medical college hospitals, private hospitals, and ICDDR,B. However, the Government (i.e., IEDCR) does conduct laboratory-based surveillance during cholera outbreaks, often in collaboration with ICDDR,B. In addition, from 1985 to 1991, the Government and ICDDR,B collaborated on the Epidemic Control Preparedness Programme (ECPP) to detect and respond to diarrheal disease epidemics. The program, which operated in much of the country (=400 rural upazilas), employed physicians to investigate epidemics of acute watery diarrhea detected through the routine household-based surveillance system, and to collect stool specimens for testing at ICDDR,B. This program found *V. cholerae* to be the most common enteric pathogen isolated during a series of diarrhea outbreaks during these years, accounting for 40% of identified isolates [Siddique, 1992]. Despite the fact that it was the only government-supported systemic cholera surveillance backed by reliable laboratory testing, the program was scaled back once donor-support ended.

At present, long-term, laboratory-confirmed surveillance of cholera and other diarrheal diseases is being conducted by ICDDR,B in several areas of Dhaka and a few other locations (Table 10). These studies include the 2% sampling of all diarrheal patients coming to the ICDDR,B hospital in Dhaka, in which stool samples are tested for six enteric diseases, including cholera (as described in Section 2 above). The ICDDR,B routinely sends weekly reports from this surveillance to the MOHFW, thus providing the Government with the first alert for outbreaks of cholera and other diarrheal diseases in Dhaka. As part of the cholera vaccine demonstration project taking place in the Mirpur area of Dhaka (described in Section 6.2), every third diarrheal patient from Mirpur who comes to the main ICDDR,B hospital has a stool sample tested for *V. cholerae* and other enteric pathogens. Laboratory-confirmed surveillance for cholera and other diarrheal diseases is also taking place in Mirzapur in Central Bangladesh among children less than five years old hospitalized with diarrhea at one hospital as part of the multi-country Global Enterics Multi-Center Study (GEMS) of the main pathogenic causes of diarrhea in young children. Community-based surveillance of diarrheal, febrile, and respiratory infections is also on-going in the Kamalapur area of Dhaka. And finally, the ICDDR,B field hospital in Matlab continues to conduct hospital-based surveillance of cholera and other diarrheal diseases, as it has for nearly 50 years.

As described in Section 2 above, ICDDR,B conducted sentinel site cholera surveillance in Upazila Health Complexes in five different rural parts of the country in the late 1990s and early 2000s, upon which the analysis of the cholera disease burden presented in this report is based. The Government of Bangladesh has expressed interest in working with ICDDR,B to expand laboratory-supported cholera disease surveillance, and discussions between the two are currently on-going.
Table 10. Current diarrheal disease surveillance by ICDDR,B that includes cholera laboratory diagnosis

<table>
<thead>
<tr>
<th>Study (dates)</th>
<th>Location</th>
<th>Description</th>
<th>Catchment population</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% systematic sampling of diarrheal patients (since 1979)</td>
<td>ICDDR,B hospital in Dhaka</td>
<td>Stool specimen from every 50th patient presenting with diarrhea is tested for 6 enteric pathogens, including <em>V. cholerae</em>, <em>Shigella</em>, ETEC, rotavirus</td>
<td>Most of Dhaka, especially low-income areas</td>
</tr>
<tr>
<td>On-going hospital-based cholera surveillance (since 1963)</td>
<td>Matlab</td>
<td>Testing of in- and outpatients with diarrhea at ICDDR,B field hospital</td>
<td>200,000</td>
</tr>
<tr>
<td>Global Enterics Multi-Center Study (GEMS) (since December 2006)</td>
<td>Mirzapur, central Bangladesh</td>
<td>Study of pathogenic causes of moderate to severe hospitalized cases of diarrhea in children &lt;5 years at the Kumudini Hospital, Tangail</td>
<td>240,000</td>
</tr>
<tr>
<td>Targeted cholera surveillance as part of oral cholera vaccination demonstration project (2009-2013)</td>
<td>Mirpur, Dhaka and ICDDR,B hospital</td>
<td>Stool specimens and additional demographic and other data is collected from every third patient with diarrhea coming to ICDDR,B hospital</td>
<td>240,000</td>
</tr>
<tr>
<td>Infectious disease surveillance</td>
<td>Kamalapur, Dhaka</td>
<td>Community-based surveillance of respiratory, diarrheal, and febrile illnesses</td>
<td>200,000</td>
</tr>
</tbody>
</table>

4.2.3 Possible means of improving cholera surveillance in Bangladesh

Most policymakers and experts in Bangladesh interviewed for this case study believed that enhanced laboratory-based surveillance of cholera would be critical to inform decisions by the Government to introduce cholera vaccination — and, if such a program is approved — to identify areas to target for vaccination. Many felt that cholera surveillance would best be implemented through collaboration between IEDCR and ICDDR,B.

To create efficiencies and reduce costs, cholera surveillance could be added to other laboratory-based surveillance programs currently operating in the country, or prior cholera surveillance activities could be resuscitated. Possibilities for laboratory-based cholera surveillance suggested by informants and IVI team members include the following:

- Add cholera to the AFP/polio surveillance system run by the EPI, given the national reach and strength of this system and the fact that both diseases require stool specimens for testing;
- Conduct sentinel site surveillance for cholera by adding the disease to the twenty-six-hospital influenza surveillance program established by IEDCR;
- Establish a diarrheal disease sentinel surveillance system in five different areas of the country, similar to the surveillance based at Upazila Health Complexes conducted by ICDDR,B in rural areas in the late 1990s and early 2000s;
Reactivate the Epidemic Control Preparedness Programme (ECPP) with strong government cooperation. While this surveillance system investigated diarrheal disease outbreaks, as opposed to conducting long-term surveillance, it would both help the government to respond rapidly and systematically to cholera outbreaks and would help identify high-risk areas for targeting vaccination.

4.3 Control and treatment of acute watery diarrhea and cholera in Bangladesh

The Control of Diarrhoeal Disease (CDD) Programme has been in place in the MOHFW since 1979. The program, under the Director, Primary Health Care (PHC), initiated integrated disease control measures with uniform national guidelines for all levels of the public service delivery system with strong behavior change communication. Oral rehydration treatment (ORT) corners with designated beds were established in all public hospitals from the upazila to the national level. As a result, diarrheal disease management and its preventive measures have been very much in practice throughout the country. The CDD now operates under the Essential Services Delivery (ESD) program.

Severe cases of cholera in rural areas requiring IV fluids and hospitalization must seek treatment at Upazila Health Complexes or higher-level government facilities (e.g., district hospitals), since diarrheal cases are placed in isolation wards. Antibiotics, such as tetracycline, ciprofloxacin, and amoxicillin are also available and given to suspected cholera patients. However, due to the increasing incidence of multi-drug resistant cholera, effective drug therapy may not be available at government health facilities in all areas. Oral rehydration solution is readily available in all government health clinics and hospitals for mildly to moderately dehydrated patients, as well as for severely dehydrated patients following effective treatment with IV fluids.

Nonetheless, a study conducted in 2003/04 of health care utilization for children under five with diarrhea of at least two days duration, consisting of a representative sample of households throughout the country, revealed that 30-40% of cases received no care outside of the home and the great majority of those who did seek care used unlicensed private practitioners, drug sellers, and homeopaths [Larson 2006]. Only 6% of rural and slum households sought care in the public sector. The likelihood of these unlicensed private practitioners providing appropriate care for cholera patients is much less than among public sector providers or licensed private practitioners.

Bangladesh, where ORT was developed, has been among the most successful countries in promoting the use of ORS at the household level. During large-scale educational campaigns conducted by the Government of Bangladesh, BRAC, and other NGOs in the 1980s, families were taught during home visits how to prepare and use ORS. ORS packages are inexpensive and readily available in corner shops throughout the country. The 2007 Demographic and Health Survey for Bangladesh shows that 85% of households use ORS, recommended home fluids, or increased fluids for childhood cases of diarrhea [NIPORT 2009]. The proportion of children receiving ORS in slum areas of city corporations (Dhaka and Chittagong) was an impressive 71%. However, there are still significant discrepancies in ORS use between rural and urban dwellers, with 49% of children under five with diarrhea living in rural areas receiving ORS, compared to =60-80% of children in urban areas [Larson 2006]. The proportion in rural areas increased to =60% when other dehydration fluids are included.
Providing access to all Bangladeshis with adequate care for cholera and the prevention of severe dehydration will therefore require the increased household use of ORS in rural areas, the increased use by the population of public sector health facilities for the treatment of diarrheal diseases, and increased access to public facilities with the capacity to provide high-quality treatment for severe cholera. This includes appropriate and timely IV fluid infusion and the administration of effective antibiotics.
5. The National Expanded Program on Immunization (EPI) in Bangladesh: would it have the capacity to successfully implement cholera vaccination?

5.1 Introduction

5.1.1 Structure of the immunization program

Bangladesh launched its national EPI in 1979, which since the beginning, has been run as a vertical program. The program is actually operated under two different systems — one for rural areas managed by the Ministry of Health and Family Welfare (MOHFW), and an NGO-based system for urban areas overseen since 1999 by the Ministry of Local Government, Rural Development and Cooperatives (MOLGRDC) (Figure 12). The program — considered among the strongest programs run by the MOHFW in the country — receives substantial technical support from the World Health Organization (WHO) and UNICEF. It also received financial support from donors through both a pooled funding mechanism managed by the World Bank, and project-specific, non-pooled funding from a large number of multi-lateral and bilateral donor agencies (see Section 8 for more information on EPI financing).

**Figure 12. EPI service delivery system in Bangladesh**

Routine immunization services in rural areas are provided through district hospitals and health centers, Upazila (sub-district) Health Complexes, and union-level clinics, as well as at EPI outreach sites, through which the majority of immunizations in rural areas are provided. The program focuses on outreach services as a mainstay of immunization delivery in rural areas, which is quite unique among national immunization programs. A system of eight outreach sites per ward — each serving a population of around 1,000 people and consisting of schools, marketplaces, and other community settings — was established in the 1980s to deliver immunization services through monthly outreach sessions. These services are provided by two types of government-paid, community-based health paraprofessionals: Health Assistants (HAs), who provide a range of basic health services (e.g., diarrheal disease control, malaria control, management of common illnesses, nutrition advice), and Family Welfare Assistants (FWAs), women who mainly deliver family planning services. These health workers are assisted by a cadre of volunteers from NGOs and the community who mobilize women to bring their children to immunization sessions and raise awareness about immunization in their communities.

For the urban population, routine immunizations are provided on a daily basis at fixed health clinics run by local NGOs. These clinics also provide outreach services anywhere from twice a week to once a month, depending on need. The city corporations (e.g., Dhaka City Corporation) and municipalities contract out the delivery of services in the Essential Services Delivery (ESD) package — including immunization, reproductive health services, communicable disease control, and other primary health care services — to NGOs through an open bidding process. Dhaka City Corporation, for instance, has contracts with eight NGOs through which 89 primary health care centers and family welfare centers provide these services in all of the city’s 10 zones.

This system of urban NGO-run clinics is supported by several international donor projects. These include the Urban Primary Health Care Project, funded by a consortium led by the Asian Development Bank (ADB), and two USAID-funded programs: the Urban Family Health Project and the NGO Service Delivery Program. The latter runs 318 “Smiling Sun” clinics in both urban and rural areas, as well as 8,500 satellite clinics [World Bank 2009]. Oversight for this system is provided by the MOLGRDC, which must approve all contracts between city corporations or municipalities and NGOs. The Ministry of Health and Family Welfare, however, sets national immunization policy and guidelines that the NGOs must follow, and provides training, all EPI vaccines, and cold chain equipment and management to the NGO-run clinics.

5.1.2 Vaccines included in the EPI

There are currently four vaccines in the infant schedule against eight diseases: BCG, the pentavalent DPT-hepatitis B-phaemophilus influenza type B (Hib) vaccine (since mid-2009), oral polio vaccine, and measles (Table 11). In addition, tetanus toxoid (TT) is given to all women of child-bearing age (15-49 years) using a five-dose schedule, as part of the national program to eliminate maternal and neonatal tetanus.

The Program is applying for support from the GAVI Alliance for the introduction of pneumococcal conjugate vaccine and rotavirus vaccine. The EPI also has plans to introduce a

9 Bangladesh is divided administratively into six divisions, 64 districts, 482 upazilas, 4,500 unions and 13,500 wards. For immunization service delivery, the wards are further subdivided into sub-blocks (8 per ward).
second dose of measles vaccine into the immunization schedule for children (age not determined yet). Other vaccines mentioned by government officials during the Cholera Investment Case study team’s visit that have been discussed for possible introduction into the EPI in the future are rubella (e.g., measles-rubella) and typhoid vaccines.

In the rest of this section, we discuss the attributes, experience and performance of the EPI, as they relate to the Program’s ability to introduce and provide cholera vaccination and to address the special challenges that this vaccination program will pose. These challenges include:

- the two-dose regimen of the vaccine, with an interval of two weeks between doses\(^{10}\);
- the fact that the vaccine cannot be administered before the age of one year and that older children and even adults may be targeted for vaccination; and
- the need to revaccinate after three to five years.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Targeted Disease(s)</th>
<th>Number doses</th>
<th>Age/population given</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Tuberculosis</td>
<td>1</td>
<td>At birth</td>
</tr>
<tr>
<td>Oral polio vaccine (OPV)</td>
<td>Polio</td>
<td>4</td>
<td>6, 10, 14 weeks, 9 months (with measles)</td>
</tr>
<tr>
<td>DPT-hepB-Hib*</td>
<td>Diphtheria, pertussis, tetanus, hepatitis B, <em>haemophilus</em> influenza type b (hib)</td>
<td>3</td>
<td>6, 10, 14 weeks</td>
</tr>
<tr>
<td>Measles</td>
<td>Measles</td>
<td>1</td>
<td>9 months</td>
</tr>
<tr>
<td>Tetanus toxoid (TT)</td>
<td>Tetanus</td>
<td>5</td>
<td>Women 15-49 years old</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td></td>
<td>Interval between doses</td>
</tr>
<tr>
<td></td>
<td>1(^{st})</td>
<td></td>
<td>- 4 weeks</td>
</tr>
<tr>
<td></td>
<td>2(^{nd})</td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>3(^{rd})</td>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td>4(^{th})</td>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td>5(^{th})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\) Nationwide since July 2009.

\(^{**}\) Pregnant women receive the dose for which they are eligible at the time of pregnancy.

### 5.2 Key aspects of Bangladesh’s EPI as they relate to the feasibility and capacity to successfully introduce cholera vaccine

#### 5.2.1 Strong vertical management and infrastructure of the Program

The EPI is one of several programs of the Essential Services Delivery (ESD) package — along with treatment for acute respiratory infections (ARI), the control of diarrheal diseases and other programs managed by the Child Health and Limited Curative Care Program of the MOHFW. However, it is managed as a vertical program, with staff positions from the national to the upazila level dedicated 100% to EPI; vaccine procurement, transport, and storage systems separate from other MOHFW programs; and program-specific supervision, monitoring, and surveillance systems. This vertical structure has enabled strong management and

\(^{10}\) Assuming use of the modified O1/O139 whole-cell ("WC") vaccine licensed in India as Shanchol™.
adequate infrastructure without the EPI having to compete for resources with other health programs. It has also facilitated substantial funding from donors — making the EPI a “relatively resource rich program”, with considerable funding earmarked specifically for immunization [World Bank 2009, p. 29]. The Program is, in fact, the “largest, best funded and most successful of the child health sub-programs” [World Bank 2009, p. 28] and given its importance, it is managed by the Child Health Program Manager himself, with strong oversight from the Line Director of the ESD/Director of Primary Health Care.

To ensure the priority of the EPI, the Bangladesh Government, with donor support, has created a series of EPI-specific posts from the division to the upazila level. These include Divisional Coordinators (with WHO support), and at the district-level, Surveillance Medical Officers (WHO-funded), EPI Supervisors, District Immunization Medical Officers (supported with GAVI funding), and cold chain technicians. EPI-specific positions at the upazila-level are EPI technicians, EPI managers, and vaccine porters, who deliver vaccines from the upazilas to outreach sites. And while the field workers that actually provide vaccinations — the Health Assistants and Family Welfare Assistants — provide a range of primary health care services, they receive per diems and allowances to attend EPI trainings, which take place at regular intervals.

Supervision, monitoring and evaluation are also conducted separately from other health programs. The EPI has its own Management Information System, covering surveillance of vaccine-preventable diseases, immunization coverage, and surveillance of Adverse Events Following Immunization (AEFI). Supervision in each district is provided by the Civil Surgeons, EPI Supervisors, District Immunization Medical Officers, Surveillance Medical Officers, as well as the upazila-level Managers and EPI technicians. The EPI supervision, surveillance, monitoring, and evaluation systems are, in fact, “regarded as one of the most successful of all programs in the health sector” [World Bank 2009, p. 33].

As in many developing countries, Bangladesh’s system of procuring, storing, and distributing vaccines for the public sector is also separate from the logistics and supply chain management of other medicines and health and family planning commodities. All vaccines are procured by UNICEF and stored in a network of cold rooms managed by the EPI at the central and district levels and at each Upazila Health Complex, which is responsible for cold storage and distribution of vaccines to the unions and wards. This system is also considered more reliable than other logistics systems of the MOHFW [World Bank 2009].

To ensure high performance of the immunization program in urban areas, the EPI procures all vaccines in the EPI schedule for the NGO-run clinics, providing them for free. The Program delivers the vaccines to ward-level cold rooms, which are managed by the city corporations and NGOs, and from which the vaccines are distributed to all the NGO-run clinics in the ward. All of the refrigerators and other cold chain equipment used in urban areas have also been provided by the EPI. In addition to providing training to the NGO health workers, including training in the use of a newly-introduced vaccine, the EPI receives immunization monthly reports from all of the city corporations and municipalities.

5.2.2 A focus on outreach delivery of immunization

Community-based Health Assistants and Family Welfare Assistants provide routine EPI during monthly sessions at around 108,000 outreach sites throughout the country. These health workers also conduct home visits to register newborns and women who have reached
the age of 15 into the EPI registration book and to provide information about immunization and the EPI outreach sessions.

This system of outreach has been considered by many to be a key factor in the Program’s relatively strong performance and its ability to reach even poor and marginalized populations. The existence of this system also strengthens the country’s ability to effectively deliver a cholera vaccine. Since the currently available cholera vaccines cannot be given to infants and since a broad age range of children and even adults could be included in a cholera vaccination program, community-based vaccination campaigns using such outreach sites will likely be the most appropriate and convenient means of delivering the vaccine.

It should be noted, however, that the Government plans on shifting the delivery of primary health care services in rural areas from this outreach approach to fixed health facilities over the next 10 years by revitalizing Community Clinics that will provide one-stop health and family planning services. These clinics — each of which are to serve a population of ~6,000 and be no more than a 30-minute walk from anyone’s home — were initiated in the late 1990s and early 2000s, but many were later abandoned. The community clinics will each be staffed by three people: a Health Assistant, a Family Welfare Assistant, and a Community Health Worker — a new position for which the Government has created 13,500 openings throughout the country. The establishment of Community Clinics is being supported in 13 low-performing districts by the GAVI Health System Strengthening (HSS) Program [MoHPFW 2008]. It is planned that over time, routine EPI will be delivered from the Community Clinics, with a gradual reduction in home visits and outreach services, except in remote areas.

5.2.3 A “campaign culture” and experience

The Bangladesh EPI has extensive experience in conducting vaccination campaigns and has built a strong “campaign culture”, to quote one key informant. This experience will facilitate the delivery of cholera vaccines, and certain campaigns, including the following, could in fact serve as vehicles to add cholera vaccination:

- **National Immunization Days (NIDs) for the eradication of polio.** The EPI has conducted 18 NIDs from 1995 to 2010. These campaigns provide more than 40 million doses of oral polio vaccine (OPV) to children 0-59 months old throughout the country in a single day, with a second round to provide a second dose four or five weeks later. The NIDs involve the participation of all 50,000 or so Health Assistants and Family Welfare Assistants, and a cadre of around 650,000 volunteers from many sectors, including teachers, soldiers, police, and scouts. The EPI has established around 140,000 vaccination sites for the NIDs, during which children also receive vitamin A supplements and deworming medicine. During several days following the NID, volunteers conduct house-to-house mop-up campaigns to identify and vaccinate children who were missed. Since there are two rounds for each NID, these campaigns could also be used to provide the two-dose oral cholera vaccine in high-risk areas, which could target young children (aged 1-5) only or older children as well. While the interval between doses stated in the leaflet of the Shanchol™ vaccine is 14 days, a study to test the immunogenicity of the vaccine when the two doses are given 28 days

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11 As of May 2012, approximately 11,000 community clinics have been built.
12 Many of which are the same as the EPI routine outreach sites.
apart — around the same interval as the two rounds of each NID — is taking place in Kolkata, India.

- **Measles vaccination campaigns.** To meet the country’s goal of reducing measles mortality by half from 1999 to 2006, the EPI conducted a nationwide measles catch-up vaccination campaign in 2005-06, through which 35 million children nine months to ten years old were vaccinated over a three-week period. The campaign used schools as vaccination points during the first week, while the routine EPI outreach sites and fixed sites were used during the second and third weeks, in conjunction with the regular monthly EPI sessions, so as not to disrupt the delivery of routine EPI services. A follow-up measles campaign took place over two weeks in January 2010 for all children nine months to five years of age, using the regular EPI outreach sites to provide the vaccine along with other routine EPI vaccinations.

- **Neonatal tetanus elimination campaigns.** In addition to routine vaccination of women 15-49 years of age with five doses of TT, the EPI has conducted vaccination campaigns since 1995 for women in selected areas to ensure that they receive all five doses. The campaigns have targeted high-risk, low-coverage upazilas and unions within different districts. Three campaigns — in 1995, 1999-2001, and 2006 — have taken place, each targeting 2.6 to 3.5 million women [MOHFW 2007]. As discussed below, WHO validated the elimination of neonatal tetanus in Bangladesh in 2008, which was likely achieved through a combination of routine TT immunization and the NNT campaigns. Since TT is the only vaccine given by the public sector in Bangladesh to adults, the lessons learned from this program on how to reach adults could be very relevant to a cholera vaccination program that could include adults. Experience of the NNT campaigns in targeting only high-risk upazilas and unions is also relevant for a cholera immunization program that is limited to high-risk populations, such as those without access to safe water supplies.

- **Periodic intensive campaigns to provide vitamin A supplements and antihelminths.** These campaigns, which provide deworming medicine to children six months to ten years of age and vitamin A supplements to children under five, are another possible model or vehicle for cholera vaccination. The campaigns take place on a Saturday every six months throughout the country at routine EPI outreach sites and schools.

5.2.4 **Bangladesh’s experience in introducing new vaccines into the EPI**

In recent years, the EPI has introduced two new vaccines into the infant immunization schedule, both with support from the GAVI Alliance. Hepatitis B was introduced in a phased manner over three years from 2003 to 2005, as a separate (monovalent) vaccine given with DPT. The Government later decided to introduce Hib vaccine following a Hib disease burden study, by replacing the DPT and hepatitis B vaccines with the pentavalent DPT-hepatitis B-Hib vaccine. This occurred first in a pilot project in one district in January 2009 and then nationwide six months later.

Through these two vaccine introductions, the Government has established systems and procedures for the introduction of a new vaccine into the EPI. These include cascade training of health workers on the use of the new vaccine; the development or revision of guidelines for its use; revisions to immunization cards and EPI registration forms; and increasing the cold
storage capacity to accommodate the new vaccine, based on an analysis of additional volume needs.

Since hepatitis B vaccine was introduced, the rates of fully immunized children (FIC) by 12 months of age has increased (from 56% in 2003 to 71% in 2006), according to the Coverage Evaluation Survey [Bangladesh EPI 2009] (Figure 5-2). Therefore, it appears that the introduction of this vaccine did not negatively impact the delivery of other EPI vaccines or the program in general. However, the hepatitis B vaccine was incorporated into the existing infant immunization schedule and the pentavalent actually replaced two existing vaccines, and thus the introduction of these vaccines did not require a change in schedule or special efforts to deliver them. The situation for cholera vaccination would be substantially different, since it would involve vaccinating children beyond infancy and perhaps adults in mass immunization campaigns.

5.2.5 The establishment of a formal structure for decision-making for the introduction of new vaccines and other EPI program improvements

The MOHFW established the National Committee on Immunization Practice (NCIP) in 2008 to institute a systematic, evidence-based process for making policy decisions about the introduction of new vaccines and other changes in the EPI. The Committee consists of Bangladeshi government officials with expertise in pediatrics, public health, and other relevant fields, and is chaired by the Health Secretary. The NCIP is supported by a permanent Technical Sub-Committee, made up of experts from WHO and UNICEF, pediatricians, EPI program managers, and the line Director of ESD. This sub-committee makes recommendations to the NCIP, based on an analysis of existing data. The EPI must now obtain approval from the Committee before submitting an application to the GAVI Alliance to support the introduction of a new vaccine or other program changes.

The NCIP, which meets on an as-needed basis, approved the introduction of Hib (pentavalent) vaccine into the EPI in 2008 and is in the process of developing a national vaccination policy document.

The NCIP and the national vaccination policy should help facilitate decisions about the introduction of cholera vaccination in the future, based on solid evidence from the oral cholera vaccine feasibility study taking place in the Mirpur area of Dhaka, as well as from current and future disease surveillance studies, disease burden estimates, and economic and other analyses from this country case study and future research.

5.2.6 The immunization program’s performance

According to the Comprehensive Multi-Year Plan (cMYP) for 2008-10 for the Bangladesh immunization program, “immunization has been one of Bangladesh’s greatest public health success stories. The program has prevented an estimated 2 million deaths from 1987 to 2000 and continues to prevent approximately 200,000 deaths per year” [MOHFW 2007, p.8]. The EPI’s accomplishments — in reducing deaths from measles and neonatal tetanus for example — have likely made an important contribution to the country’s achievement in reducing mortality in children <5 years of age by two-thirds since 1990.

The Bangladesh Coverage Evaluation survey conducted in 2009 estimated that immunization coverage at the age of 12 months ranged from 99% for BCG vaccine to 83% for
measles (Table 12) [Bangladesh EPI 2009]. Coverage for the third dose of DPT — a common measure of a country’s EPI performance and which now includes the third dose of hepatitis B — was 86% at 12 months of age. The survey also found that 95% of children under the age of five received OPV during both rounds of the NIDs in 2009. The percentage of children who received all vaccines in the infant schedule (fully immunized children or FIC) by 12 months was estimated to be 75%. The survey also found that 95% of women with children 1-11 months of age had had at least two doses of tetanus toxoid vaccine, while coverage for all five TT doses drops to 34% of these women.

Table 12. Rates of valid vaccination coverage, Bangladesh Coverage Evaluation Survey, 2009*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>National</th>
<th>Urban</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among children 12 months of age*:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td>99%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>OPV3</td>
<td>93%</td>
<td>92%</td>
<td>93%</td>
</tr>
<tr>
<td>DPT3</td>
<td>86%</td>
<td>86%</td>
<td>85%</td>
</tr>
<tr>
<td>Hepatitis B3</td>
<td>86%</td>
<td>86%</td>
<td>85%</td>
</tr>
<tr>
<td>Measles</td>
<td>83%</td>
<td>82%</td>
<td>83%</td>
</tr>
<tr>
<td>Fully Immunized Child (FIC)</td>
<td>75%</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>• Male</td>
<td>76%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>• Female</td>
<td>75%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>• Highest income quintile</td>
<td>72.3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>• Lowest income quintile</td>
<td>78.7%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Among mothers with children 1-11 months of age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT2</td>
<td>95%</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>TT3</td>
<td>81%</td>
<td>81%</td>
<td>81%</td>
</tr>
<tr>
<td>TT5</td>
<td>34%</td>
<td>34%</td>
<td>34%</td>
</tr>
</tbody>
</table>

* Valid coverage means that the vaccination was given before a child’s first birthday. Coverage information is based on vaccination card data and history taken from mothers. Source: Bangladesh EPI 2009.

The EPI has made great strides in increasing immunization coverage in the past seven years (Figure 13). While FIC rates remained steady — at ~51-54% in the late 1990s and early 2000s — they have increased 44% from 52% in 2001 to 75% in 2009. Part of these gains has been due to a sharp reduction in dropout rates between early and late vaccine doses. The dropout rates in 2009 were only 2% between DPT1 and DPT3 and 7% between DPT1 and measles vaccination (see Appendix 5). Nine years ago, these dropout rates were 15% and 25%, respectively. This progress led the GAVI Alliance to give Bangladesh an award in 2009 for Best Immunization Performance for a large country.

There are little or no differences in immunization coverage rates between rural and urban areas — with identical FIC rates of 75% — nor between boys and girls (Table 12). This indicates that the provision of immunization through NGOs in urban areas is equally as good as the government-run EPI services in rural areas. A key measure of equity — the difference in coverage rates between the wealthiest 20% of the population (highest income quintile) and the poorest 20% — was 6.4% (78.7% vs. 72.3%), which is considered quite small. Since 2006, the EPI, with help from UNICEF and the GAVI Alliance, has supported 15 low-performing districts to increase vaccination coverage using the Reach Every District (RED) Strategy. This support includes additional funding for transport and logistics, help with preparing micro-plans, and the development of a tally sheet to identify specific children to target for each session and to track them to ensure completion of all doses. The FIC rate by 12 months of age
in these 15 districts rose from an average of 52% in 2005 to 74% in 2009. By 2009, only four of the districts had FIC rates below 70% and none were below 60%. The EPI has also made progress in reaching un-immunized children — those never vaccinated or who dropped out — through the LAUNCH Project initiated in 2008 in 23 districts with low DPT3 coverage rates.

**Figure 13. Trends in national valid vaccination coverage by 12 months of age among 12-23 month old children**

![Chart showing vaccination coverage trends](chart.png)

*Source: Bangladesh EPI 2009.*

### 5.2.7 Impact of the EPI's performance on disease

The impact of both improving routine immunization rates and implementing supplemental immunization campaigns for polio, measles, and neonatal tetanus includes the following:

- The last indigenous case of polio was found in 2000 [MOHFW 2007], and the last imported case was in 2006;

- Measles outbreaks and cases have declined sharply since 2000, when there were an estimated 18,000 measles-related deaths in children. No outbreaks of laboratory-confirmed measles were detected in 2007 and 2008, and only two took place in 2009. These numbers compare to 68 outbreaks in 2004,120 in 2005 (causing 10,146 reported cases), and 34 in 2006.

- According to a former top EPI official, diphtheria and pertussis have virtually disappeared in Bangladesh;

- The elimination of neonatal tetanus has been achieved (defined as an incidence of <1/1,000 live births), according to a joint MOHFW-WHO-UNICEF study conducted in 2008 [WHO 2008]. An estimated 93% of newborns in 2009 were protected at birth against tetanus, based on coverage rates of TT2 among pregnant women, with little difference between urban and rural women.
5.2.8 Implications for cholera vaccination

These results from the 2009 coverage survey indicate that:

1) The EPI has been successful in reaching marginalized and low-income populations and in significantly closing the gap in coverage between high- and low-income children and between urban and rural populations. It is also making significant progress in ensuring high coverage in all districts throughout the country. Since cholera primarily strikes the poor, this suggests that the Program could effectively reach the populations most in need of cholera vaccination;

2) The Program has proven its ability in recent years to achieve high coverage rates and low drop-out rates for vaccines with multiple doses, including the three-dose DPT and hepatitis B vaccines. While the two-dose oral cholera vaccines would not be given during routine immunization sessions to most recipients, unlike DPT and hepatitis B, the EPI has also shown its ability to achieve high coverage of oral polio vaccination for the two-round NIDs, albeit with strong participation from all sectors of society;

3) The EPI has been able to reach the adult population with a multi-dose vaccine — having achieved coverage rates of 95% nationwide for TT2 among women with young children, and 81% for TT3 (which is given six months after TT2).

5.3 Remaining challenges and areas for improvement

Despite the impressive gains made by the national EPI in recent years, there are a number of challenges faced by the Program that could negatively affect its performance if not addressed. These include:

- **Personnel shortages.** Due to retirements and attrition in recent years, there were 10,000 vacant positions for Health Assistants and Family Welfare Assistants (out of around 50,000 posts) as of December 2009. The Government is currently recruiting to fill all of these positions. Doctors and nurses are also in short supply; while there should be nine public sector doctors in each upazila, the current average is only three or four. The MOHFW also plans to recruit 4,500 doctors, as well as 4,000 nurses to reduce this gap;

- **Cold chain capacity.** The cold chain capacity at the central and local levels was recently doubled to accommodate the needs of the single-dose pentavalent vaccine. However, capacity will need to be further increased considerably if other new vaccines, including cholera and vaccines with high storage requirements, such as pneumococcal conjugate and rotavirus vaccines, are introduced into the EPI;

- **High vaccine wastage rates.** Current estimated vaccine wastage rates in Bangladesh are quite high: 84% for BCG, 70% for measles, and 35% for TT. Since the pentavalent vaccine — which comes in single-dose vials — replaced DPT (in 10-dose vials), wastage for this vaccine has declined from 45% to 6%, according to WHO informants. Wastage

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of the cholera WC vaccine should be low since it is also presented in single-dose vials and will be administered mainly through mass vaccination campaigns, which normally result in considerably less wastage than routine EPI sessions;

- **Financing and sustainability.** As discussed in detail in Section 8, more than half of the cost of Bangladesh's immunization program, including all vaccine costs, are financed by donors, both through pooled funds and non-pooled funding sources such as GAVI, USAID, UNICEF, WHO, and the Japanese government. If donor interest in cholera vaccination is low or if donor funding is insufficient to cover the costs of a cholera control program in a country as large as Bangladesh, the country may need to tap national government or other local sources to implement the program and ensure its sustainability.
6. How could cholera vaccines be used in Bangladesh?

6.1 The currently available oral cholera vaccines

Two oral cholera vaccines are currently available for use internationally (see Table 13). Both consist of a mix of different strains of killed whole cells of *V. cholerae* and both have strong safety profiles.

6.1.1 The WC-rBS vaccine (Dukoral®)

The WC-rBS vaccine, marketed as Dukoral® and first licensed in 1991, contains killed cells of *V. cholerae* O1 (both classical and El Tor), as well as a recombinant B subunit of the cholera toxin. The vaccine is licensed for persons two years and older and is given in two doses, usually one or two weeks apart (with three doses six months apart for 2-5 year olds). The vaccine was found in a large clinical trial conducted in Matlab, Bangladesh in the mid-1980s among children of both sexes aged 2-15 and women 15 and older to provide 85% protection 4-6 months following vaccination, 62% at one year, and 58% at two years [van Loon et.al. 1996]. Protection dropped off to 18% at three years and thus revaccination is recommended every two years. Protection in children under the age of six years was 100% for the first 4-6 months, but declined quickly (to 38% at one year) and thus the license calls for children 2-5 years of age to be revaccinated every six months. The cumulative efficacy of the vaccine over three years was found to be 64% in all ages, but only 26% in children aged two to five years [Clemens et.al. 1990].

While Dukoral® is mainly used as a travelers’ vaccine in developed countries, it has been pre-qualified by WHO and used on a demonstration or pilot basis in several post-crisis situations (in refugee camps in Darfur, Sudan, and Uganda and post-tsunami in Aceh, Indonesia), and in a cholera-endemic population in Mozambique. These experiences demonstrated that vaccination of both children and adults in developing countries with Dukoral® was feasible, although the need to mix the vaccine with a buffer and water, as well as its bulky packaging, can pose logistical challenges in the field. The vaccine is produced in Sweden by Crucell/SBL Vaccines. While the vaccine sells for up to $20 or more per dose in the private market in developed and developing countries, the price is volume-dependent, and the company has indicated it would offer competitive prices to the public sector for firm annual orders meeting a certain minimum volume.

6.1.2 The modified WC O1/O139 vaccine (Shanchol™)

A killed whole-cell vaccine without the cholera toxin component has been produced in Vietnam since 1997, following technology transfer from Sweden. This “whole-cell only” or “WC” vaccine also includes a strain of the *V. cholerae* serogroup, O139, which first emerged in Bangladesh and India in the early 1990s, making it a bivalent (O1/O139) vaccine. Because it lacks the B subunit of the cholera toxin, it can be produced at relatively lower cost and does not require a buffer or water to administer. More than 20 million doses of the Vietnamese

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14 A third vaccine – an oral live attenuated single-dose vaccine (CVD 103-HgR) was licensed as a travelers’ vaccine in the early 1990s (as Orochol® or Mutachol®), but is no longer being produced.
15 According to the package insert, the two doses of Dukoral can be given 1-6 weeks apart.
vaccine have been administered in Vietnam in high-risk areas and following floods — thus making it the first oral cholera vaccine used broadly in a cholera-endemic country.

Table 13. Profile of the currently available oral cholera vaccines

<table>
<thead>
<tr>
<th>Feature/Characteristic</th>
<th>WC-rBS</th>
<th>Modified WC bivalent (O1/O139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Dukoral®</td>
<td>Shanchol™ (India)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mORC-VAX (Vietnam)</td>
</tr>
<tr>
<td>Producer</td>
<td>Crucell/SBL Vaccines</td>
<td>Shantha Biotechnics (India)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VaBiotech (Vietnam)</td>
</tr>
<tr>
<td>Year first licensed</td>
<td>1991</td>
<td>2009</td>
</tr>
<tr>
<td>WHO pre-qualified?</td>
<td>Yes</td>
<td>Shanchol pre-qualified in 2011.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mORC-VAX not pre-qualified.</td>
</tr>
<tr>
<td>Vaccine type/composition</td>
<td>Killed <em>V. cholerae</em> O1 whole cells (Inaba and Ogawa, classical and El Tor) + recombinant cholera toxin B subunit</td>
<td>Killed <em>V. cholerae</em> O1 whole cells (Inaba and Ogawa, classical and El Tor) + O139</td>
</tr>
<tr>
<td>Lowest age approved for</td>
<td>2 years old</td>
<td>1 year old</td>
</tr>
<tr>
<td>license</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of doses and</td>
<td>2 doses 1-6 weeks apart (3 doses for children 2-5 year olds)</td>
<td>2 doses 14 days apart</td>
</tr>
<tr>
<td>schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation and presentation</td>
<td>Liquid vaccine suspension in single-dose or two-dose vials + bicarbonate buffer in effervescent granules in sachet. Two vials/sachets per box.</td>
<td>Liquid vaccine in single-dose vials. Plans underway to develop single-dose squeeze tube containers.</td>
</tr>
<tr>
<td>Requires buffer?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Water requirements</td>
<td>Vaccine and buffer are mixed in 150 ml of water (chlorinated or not) for persons &gt;5 years old (75 ml for 2-5 year olds).</td>
<td>No water is required.</td>
</tr>
<tr>
<td>Safety/tolerability</td>
<td>High, including in HIV+ individuals</td>
<td>High; safety in HIV+ individuals not yet known but is presumed</td>
</tr>
<tr>
<td>Efficacy rates in cholera-affected</td>
<td>1985 trial results in Bangladesh: 64% over 3 years (cumulative)(26% in 2-5 year olds)</td>
<td>2006-2011 trial results in Kolkata, India: 77% at 2 years following vaccination and 65% at 3 years; 66% over 3 years (cumulative)</td>
</tr>
<tr>
<td>countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of sustained protection</td>
<td>2 years in persons &gt;5 years old</td>
<td>At least 3 years in children and adults*</td>
</tr>
<tr>
<td></td>
<td>6 months in children ≤5 years of age</td>
<td></td>
</tr>
<tr>
<td>Confers herd protection?</td>
<td>Yes</td>
<td>Very likely (based on reanalysis of data on the WC vaccine from the original Matlab clinical trials)</td>
</tr>
<tr>
<td>Cold chain requirements</td>
<td>License requires 2-8°C, but remains stable for 1 month at 37°C</td>
<td>License requires 2-8°C. Stability tests at ambient temperatures being studied.</td>
</tr>
<tr>
<td>Shelf life</td>
<td>3 years</td>
<td>2 years on the label. Stability testing indicates that the shelf life could be extended to 3 years.</td>
</tr>
<tr>
<td>Price to the public sector</td>
<td>Will depend on production volume. Company is willing to offer competitive prices for a certain minimum annual volume.</td>
<td>Shantha's current price is $1.85/dose. Price of mORC-VAX to the EPI program in Vietnam is $0.75/dose.</td>
</tr>
</tbody>
</table>

*The clinical trial of the vaccine in Kolkata, India is continuing for five years following vaccination (until 2011). Thus data on the vaccine’s duration of protection at four and five years will be available in the future.
The Vietnamese vaccine was modified by the International Vaccine Institute (IVI) in an effort to make available internationally a low-cost oral cholera vaccine that is more amenable for use in cholera-endemic countries. The vaccine was modified by replacing certain strains, doubling the quantity of antigen (LPS), and developing new quality control assays — all in order to meet both Good Manufacturing Practice (GMP) requirements and WHO guidelines for the production of inactivated oral cholera vaccines (see Appendix 6 for a comparison of the composition of Dukoral®, the original and modified WC vaccines).

The modified WC vaccine requires two doses given two weeks apart. A Phase III trial of the vaccine among nearly 67,000 children (one year and older) and adults in slum areas of Kolkata, India has shown that it provides 77% protection at two years following vaccination, 65% at three years, and 66% cumulatively over three years against culture-confirmed cholera [Sur et al., 2009; Sur et al., 2011]. Protection has thus far been shown to be sustained over three years, including among 1-4 year olds, and thus revaccination is currently indicated after three years. The interval between initial and subsequent vaccinations may be extended if data from on-going surveillance in the trial site shows that it continues to provide sufficient protection after three years.

IVI, in partnership with the Vietnamese producer VaBiotech, transferred the technology for producing the vaccine to Shantha Biotechnics in India. The new vaccine, marketed as Shanchol™, was licensed by the Indian government in 2009 for persons one year and older and was pre-qualified by WHO in September 2011. With a grant from the Bill & Melinda Gates Foundation, the vaccine will be evaluated using an alternative schedule of 28 days between doses, and as a single-dose vaccine. The 28-day schedule, if proven effective, would allow its use during the two rounds of the NIDs (usually 4-5 weeks apart), while a single dose would facilitate vaccination in outbreak situations.

Shantha has committed to making the vaccine available globally and is offering the vaccine to the public sector for $1.85 per dose. Over time, the price may decline as a result of increased demand, future improvements in production efficiency and economies of scale, and increased competition. The current production capacity for Shanchol™ in its present facility is 2-2.5 million doses per year. However, the company intends to build a dedicated facility for producing the vaccine, if demand is sufficient. The dedicated facility could produce 10 million doses of Shanchol™ per year initially, with a potential maximum capacity over time of 25-30 million doses. Based on these assumptions, we use for this investment case an estimated (pre-shipping) price of $1.85 per dose, from 2015 to 2017 and $1.45 beginning in 2018. This estimated long-term price is about halfway between the current public sector price of Shanchol™ ($1.85) and the price of the modified vaccine sold on the private market in Vietnam ($1.00).

The producer also plans to package the vaccine in single-dose squeeze tubes to increase its ease of use in developing countries, including in mass vaccination campaigns.

In order to create a sufficient, cost-competitive supply, IVI has transferred the technology for the WC vaccine to Eubiotics, a Korean biotechnology company. Assuming Eubiotics can secure sufficient capital investment and proceed through development stages quickly, it could manufacture up to 25 million doses as early as 2015/16. In addition, IVI has transferred the production procedures and quality control assays to VaBiotech for the modified WC vaccine, which was licensed in Vietnam in 2009 as mORC-VAX. VaBiotech expects
to place the vaccine on the international market and have it pre-qualified by WHO once the country's NRA has been positively assessed by WHO.

6.1.3 Indirect (herd) protection from killed oral cholera vaccines

Killed whole-cell-based oral cholera vaccines have been shown to provide herd protection — that is, to protect people in a community where vaccination has taken place who themselves were not vaccinated. A re-analysis of data from the Matlab clinical trial revealed that both Dukoral® and a WC-only vaccine (the precursor to Shanchol™) provided nearly as much protection to people not vaccinated as to those vaccinated in a community, if just more than half of the targeted population received the vaccine16 [Ali et al. 2005]. The risk of getting cholera was 1.47/1,000 among placebo recipients in bars with vaccination coverage rates for the targeted population of >51%, compared to 1.27/1,000 among those vaccinated in the same bars, and 7/1,000 among placebo recipients in bars with low vaccination coverage (<28%).

Children under the age of two years (who were too young to be vaccinated) were less than half as likely to get cholera if they lived in a high vaccination coverage bar than in a low coverage one (Figure 14) [Ali et al. 2008]. Preliminary analysis of the Kolkata trial of Shanchol™ also shows herd protection in this urban slum population. The herd effects from oral cholera vaccines could substantially increase the impact of cholera vaccination beyond what their rates of direct protective efficacy would suggest. A modeling of cholera transmission in Matlab, based on the above data, predicts that vaccinating 50% of a population will reduce cholera incidence for the first six months following vaccination by 93% in the community as a result of both direct and herd protection [Longini et al., 2007]. The estimates of herd protection from the Matlab data are figured into the analyses of the impact and cost-effectiveness of oral cholera vaccination for this case study (see Section 7).

Figure 14. Cholera incidence rates among children too young to be vaccinated (<2 years old) by level of vaccination coverage of the bar during the first year of follow-up in the Matlab clinical trial of two killed oral cholera vaccines*

*The level of coverage is that among the targeted population of children 2-15 years old and women 15 and older. Source: Ali 2008

The population that was targeted for vaccination in the trial consisted of children 2-15 years old and women 15 and over (no adult males).
6.2 Interest among policymakers and stakeholders in Bangladesh in the use of oral cholera vaccines

6.2.1 Recent indications of government interest in cholera prevention

The Government of Bangladesh has recently shown considerable interest in controlling acute watery diarrhea and cholera, and in exploring the use of oral cholera vaccines as part of these control efforts. According to those interviewed during the case study team’s visit, this interest in cholera prevention and in the possible use of oral cholera vaccines is a result of the continued incidence of acute watery diarrhea; reported outbreaks of cholera in new areas not considered cholera-endemic (including Pabna in the Western part of the country); and the increased frequency of large outbreaks following floods in Dhaka. Further fueling this interest are perceived worsening trends in disease incidence due to climate change and to growth of urban slums, placing stress on already inadequate water and sewerage systems (discussed above in Section 2).

Recent indications of the Government’s interest in preventing cholera, including through vaccination, include the following:

- Since Bangladesh became a member of the Executive Board of WHO in 2008, it twice requested that the topic of cholera vaccines be included in the agenda of the World Health Assembly. As a result, the WHA discussed the issue during its 2011 meeting and passed a resolution, which, among other things, urges member states to “undertake planning for and give consideration to the administration of vaccines, where appropriate, in conjunction with other recommended prevention and control methods and not as a substitute for such methods.”\(^{17}\) The resolution also requests WHO to coordinate with funding agencies on possible support for cholera vaccine introduction in low-income countries; to support further research on safe, efficacious, and affordable cholera vaccines; to promote transfer of relevant vaccine manufacturing technologies to countries at risk for cholera; and to develop practical evidence-based policy guidelines on the appropriate and cost-effective use of oral cholera vaccines in low-income countries.

- The Ministry of Health and Family Welfare requested ICDDR,B to open up a diarrhea clinic/hospital in the large, low-income Mirpur section of Dhaka in 2008 in response to reports that more than 20% of diarrhea cases presenting at the ICDDR,B hospital were coming from this area. The satellite clinic was opened in April 2009.

- The Government of Bangladesh approved and is fully collaborating with ICDDR,B on a large feasibility study of cholera vaccination in the Mirpur section of Dhaka. The study, funded by the Bill & Melinda Gates Foundation, is evaluating the feasibility and effectiveness of cholera vaccination (using Shancho\(^{TM}\)) — both alone and in combination with the promotion of hand washing and safe water treatment interventions\(^{18}\) — in comparison with a control group. The feasibility study involves

\(^{17}\) The resolution can be found at [http://www.who.int/cholera/technical/resolution/en/index.html](http://www.who.int/cholera/technical/resolution/en/index.html).

\(^{18}\) Consists of a comprehensive behavior change communications program targeted to households, shopkeepers, and schools to promote hand washing with soap, the use of point-of-use water treatment products (disinfectants and water filters), and the establishment of hand washing stations that dispense water and hold soap in people’s homes.
240,000 people, with a target of 160,000 persons one year old and above receiving the vaccine. Vaccination took place in 2011, with an estimated coverage rate of 88% (personal communication by A. Cravio). Government policymakers have been closely involved in the planning and implementation of the study, and many serve on various advisory and steering committees for the project. These include the Health Ministry and Secretary of the MOHFW, who chairs the project’s overall Advisory Committee.

Several government officials interviewed during the case study team’s visit expressed interest in preventing the disease and not just preventing deaths or “providing medicine”. Some also made the point that ORS could not be used to treat severely dehydrated patients. The team found keen interest among government officials in the Mirpur feasibility study to determine the efficacy of the Shanchol™ vaccine and hygiene/safe water interventions, as well as the vaccine’s safety. The Government views the study as critical to decisions about whether to introduce cholera vaccination into the EPI and see it as a possible first step in a phased introduction of the vaccine. The Director-General of Health Services declared that, since safe water has not yet been provided to the entire population, the Mirpur study could make an important contribution to reducing endemic cholera in Bangladesh.

6.2.2 Interest in local vaccine production

A key driver of the Government’s interest in exploring cholera vaccination is the recent appearance onto the market of a lower cost oral cholera vaccine (Shanchol™) and the possibility of it being produced locally in Bangladesh. During the case study team’s visit, several health policymakers, including the Health Minister, mentioned the anticipated local production of the new killed, whole-cell cholera vaccine, which they assume will cost less to the Government than imported vaccines.

The Government has shown keen interest in the local production of vaccines and has sought assistance from WHO to upgrade its national regulatory authority (NRA) to enable it to regulate locally-produced vaccines in order to meet the requirements for WHO pre-qualification. This will require building capacity in conducting Good Manufacturing Practice (GMP) inspections of production facilities, in conducting clinical trials, and in laboratory testing of vaccines. The Government has upgraded its NRA, the Directorate of Drug Administration, to a higher administrative level (Directorate General); is increasing its staff from 220 to 370; and is developing new laboratories, with on-going technical assistance from WHO and financial support from bilateral aid agencies.

One private sector pharmaceutical manufacturer, INCEPTA, has decided to invest in vaccine production. The company has become the country’s second largest drug producer in just 10 years, and now exports to 74 countries, including many in the EU. INCEPTA plans to start with the fill-finish of bulk vaccines purchased from producers in other countries and is currently constructing a fill-finish facility in a building that will be dedicated to vaccine production. It has expressed interest specifically in fill-finishing and later producing cholera vaccine. The company plans on meeting GMP requirements in order to be able to export vaccines and is interested in having its vaccines WHO pre-qualified as well as approved by the European and U.S. regulatory authorities. It envisions a domestic market for its vaccines to include both the private market and the Government.
6.2.3 Interest in an integrated approach towards cholera control

Most MOHFW officials interviewed were favorable to the idea of cholera vaccination, or at least to the study taking place in Mirpur. However, non-health sector officials and some persons from partner organizations believed that cholera should be controlled mainly through improvements in water and sanitation, not through vaccination. According to these informants, many health facilities and schools do not have adequate sanitation or clean drinking water, and the government will be open to criticism if they provide cholera vaccines in these settings without addressing this problem. Among health officials who saw a potential role for cholera vaccines, several favored an integrated approach that includes water and sanitation improvements, the promotion of exclusive breastfeeding for the first six months of life, the promotion of hand washing, as well as vaccination. As the Director-General of Health Services stated, “vaccines should not be the only answer”. This interest in a comprehensive approach to cholera prevention is reflected in the design of the Mirpur feasibility study, which is evaluating behavioral change communications as well as cholera vaccination.

6.3 Evidence of private demand for cholera vaccines in the local population

The impact of vaccination depends on the public acceptance and willingness to receive vaccines. If a cholera vaccine program is launched, estimating what proportion of the targeted population would be vaccinated is important to determine whether the program would be successful and to plan the logistics and financing for the program. The predicted demand is also a key variable in estimating the impact and cost-effectiveness of vaccination.

A study of the private demand and willingness-to-pay for modern cholera vaccines was conducted in Matlab in 2005 by the Diseases of the Most Impoverished (DOMI) Program, using a contingent valuation methodology [Islam et al., 2008]. Respondents from nearly 600 randomly-selected households were informed about cholera and cholera vaccines, received an explanation about a vaccine that is 50% effective for three years, and were tested on their understanding. They were then asked how many vaccines they would purchase for their household and for whom at one of six randomly-assigned prices ranging from Tk. 10-600 (US $0.15 - $8.90). A statistical model was used to evaluate the effect of household characteristics and price on demand for the vaccine. The model predicts that people were considerably more likely to have their children vaccinated than themselves or other adults in the household at any price. Demand for the vaccine was strongly influenced by its price, the household’s income, the respondents’ perceived risk of cholera, and the perceived severity of the disease.

Figure 15 shows the “raw” and modeled household demand for cholera vaccine given to children and adults as a function of price. For the lowest price presented to respondents (Tk. 10), the raw data indicate that coverage may reach 75% for children age 1-14 years and 55% for adults age 15 and greater. Assuming that vaccines are provided free of charge, actual coverage rates may be greater if the proposed Tk. 10 is perceived as a barrier for some respondents. In contrast, coverage may be reduced if people are unaware of or unable to participate in scheduled campaigns. However, the public awareness for polio vaccination campaigns is sufficient to achieve coverage rates of 95% for children under five. Based on the DOMI findings and the EPI’s recent coverage track record, the assumed coverage rates for cholera vaccination used in these analyses described in Section 7 are 75% for children 1-14 years of age and 50% for persons 15 and older.
6.4 Views on how to implement cholera vaccination in Bangladesh

The case study team solicited the views of government officials, ICDDR,B scientists, and other informants to develop program options and strategies for cholera vaccination to analyze for this study.

6.4.1 Two-pronged approach toward cholera control

Most persons interviewed envisioned a two-pronged strategy, which would attack endemic disease and try to control outbreaks preemptively during droughts or following floods or cyclones. One prominent cholera expert saw the need for a national stockpile of oral cholera vaccine for preemptive outbreak control, in addition to regular vaccine procurement for endemic disease control.

6.4.2 Geographic targeting to control endemic disease

The vast majority of government officials and ICDDR,B scientists felt that universal vaccination against cholera (i.e., throughout the country) was not necessary and that targeted vaccination in high-risk areas would be sufficient to control endemic disease in Bangladesh. Most informants would target urban areas as well as selected rural areas, with some mentioning the southern coastal belt, in part because of the importance of the shrimp industry in that area. Some policymakers and scientists felt that high-risk areas could be identified by selecting urban slums and rural areas with poor water supply or sanitation. Others, including the Director-General for Health Services, believed it was necessary to conduct sentinel site surveillance in several areas to obtain a national picture of cholera incidence before deciding where and how to target a cholera vaccination program.

Several persons interviewed suggested a phased approach towards vaccine introduction, starting with urban slum areas in Dhaka, then moving to slums of other cities and to high-risk rural areas. The EPI program would be able to target vaccination down to the union or even the ward level, as it has done for the neonatal tetanus elimination program.
based on union- or ward-specific data on neonatal deaths, neonatal tetanus cases, and TT coverage. Wards or unions could be targeted for cholera vaccination using data population access to clean water or adequate sanitation, or based on reports of acute watery diarrhea.

6.4.3 Ages to target for cholera vaccination

Most government officials and scientists recommended vaccinating all eligible ages, that is one year old and above, assuming use of the WC (Shanchol™) vaccine. Reasons given were that cholera strikes all ages, with adults often passing it on to their children who tend to dehydrate more quickly, and that the majority of cases that require hospitalization (e.g., at the ICDDR,B hospital in Dhaka) are in older children and adults. If funding was not sufficient to cover all ages, some policymakers suggested targeting “vulnerable ages” such as children under five or under 10 years of age. However, all recommended that vaccination to prevent outbreaks following natural disasters would require vaccinating the entire population in the affected areas.

6.4.4 Suggested strategies for delivering cholera vaccination

Currently available oral cholera vaccines are not licensed for use in infants (the minimum age for Shanchol™ is 12 months old). Thus, the vaccine could only be incorporated into the EPI schedule in Bangladesh if the schedule, which currently ends with measles vaccination at nine months of age, is revised. The vaccine is currently being evaluated in a study in India in infants nine months old when co-administered with measles vaccine. If the vaccine proves to induce immune responses at this age, it could possibly be provided to infants through the routine EPI program at nine months with measles vaccine. However, since these children would need to be revaccinated after three or possibly more years, and since older children and even adults would likely be targeted for cholera vaccination in Bangladesh, mass vaccination campaigns were viewed as the most appropriate and efficient means of delivering the vaccine beyond infancy.

Cholera vaccination campaigns were seen as highly feasible in Bangladesh, given the EPI program’s considerable experience with NIDs, nation-wide measles vaccination catch-up and follow-up campaigns, and other supplemental immunization activities. Since the vaccine is administered orally, the vast infrastructure of volunteers used to provide oral polio vaccine during the NIDs could be utilized for cholera vaccination campaigns. The campaigns could take place both at NID delivery sites and outreach sites used for the monthly routine immunization sessions in rural areas. For maximum efficiency and to save costs, cholera vaccination could be piggybacked onto other national campaigns in targeted areas. These include the annual NIDs and the biannual campaigns to deliver vitamin A and deworming medicine. Both of these campaigns target children under the age of five, and thus older children and possibly adults would have to be informed and encouraged to attend as well to receive the cholera vaccine.

School-based vaccination campaigns for cholera are also considered highly feasible. Schools are already being used as delivery points for the NIDs and were used throughout the country for the measles catch-up campaigns for children up to the age of 10. The Ministry of Education has a representative on the country’s Inter-Agency Coordination Committee (ICC) and thus collaboration between the health and education ministries for immunization already exists. One challenge for school-based cholera vaccination, however, would be to reach non-enrolled children, who account for around half of all children by 5th grade.
6.5 Proposed cholera vaccination strategies to analyze

Based on the above views of policymakers and scientists, this study analyzes the cost, impact, and cost-effectiveness of two options for targeting the population geographically to control endemic cholera and two age group options. The “Large Target” option will involve vaccinating entire districts identified in the disease burden analysis (Chapter 2) as “high-risk” for cholera — consisting of 28 of the country’s 64 districts and comprising around half of the population. The “Small Target” option would limit vaccination to slum populations in urban areas, as well as to rural populations in the high risk districts, without access to a safe drinking water supply. This option would cover around 35% of the population in high-risk districts and 18% of the entire population of the country.

For each option, the analyses include: a) all ages eligible to receive the vaccine (one year and above assuming use of the Shanchol™ vaccine) and b) children 1-14 years of age only. The results of the cost, impact, and cost-effectiveness analyses for each of these options are found in Section 7.

6.6 Main challenges to implementing cholera vaccination in Bangladesh

The country case study team identified and discussed with policymakers the following challenges that cholera vaccination would pose and ways to address them (the challenge of the cost and financing of the program is discussed in Sections 7 and 8):

- **Identifying areas at high risk for endemic cholera.** Determining which areas to target for cholera vaccination should ideally be based on laboratory-confirmed surveillance. Given the current lack of laboratory infrastructure in the public health sector, it would be difficult to conduct laboratory-based surveillance, such as through sentinel sites in each suspected high-risk district. A targeting strategy that selects areas below the district level, such as upazilas, unions, or wards, poses even more of a challenge in identifying these areas. One possible strategy is to set up sentinel site surveillance in five or six different parts of the country — or one in each of the country’s six divisions — and to make judgments about which districts in each area to target, based on the surveillance data and knowledge of living conditions in the districts. Until laboratory-confirmed cholera surveillance can be established in Bangladesh, targeted areas for vaccination could be selected solely on the basis of living conditions, such as slum areas and rural areas with poor access to clean water or adequate sanitation. Even with this approach, however, policymakers would want to monitor the incidence of cholera and acute watery diarrhea in areas targeted for vaccination both prior to and following vaccination in order to evaluate the impact of vaccination.

- **Providing vaccination following a natural disaster and determining if, when, and where to vaccinate preemptively.** Once a flood or cyclone occurs, the affected area is often inaccessible for several days and once the population is reached, the top priorities are usually providing water, food, shelter, and other critical needs. Providing cholera vaccine at the same time would pose challenges, especially since the current licenses of oral cholera vaccines require that a cold chain be maintained. The fact that the vaccines are oral, however, would facilitate their use during such emergencies. The need for two doses given two weeks apart could also pose challenges in these situations. Studies underway of the effectiveness of a single dose
of the Shanchol™ vaccine, as well as of an alternate schedule for the two-dose regimen involving a month between doses, could lead to changes in the recommended dosage or schedule in emergency situations. Officials would also need to decide whether areas in or near the disaster zone are at significant risk for cholera.

- **How to achieve high coverage with cholera vaccination, especially if older children and adults are targeted.** The EPI has proven its ability to achieve high immunization coverage of infants and is making significant progress in improving coverage in all of the nation’s districts. The Program has also been able to achieve high coverage of women 15-49 years of age with tetanus toxoid (TT) vaccination through a combination of routine immunization and campaigns in selected areas. No immunization program has yet taken place in the country that targets older children (other than girls for TT) or adult males, as may be the case for cholera vaccination. The challenge of reaching the majority of children beyond the 4th or 5th grade who are no longer in school may be especially difficult. The EPI would need to conduct intensive and effective communications activities to draw these non-traditional groups for immunization, taking advantage of the country’s high population coverage with TV, radio, and cell phone use. The Government has contracts with cell phone companies to send SMS messages to their subscribers with public announcements, which has been used to announce NIDs.

- **Logistical challenges of implementing mass vaccination campaigns.** Vaccination campaigns require substantial planning, mobilization of sufficient numbers of qualified personnel and volunteers, procurement and delivery of vaccines and supplies, and other logistical needs. The Bangladesh Government has demonstrated its ability to successfully plan and implement mass vaccination campaigns, including 18 NIDs, drawing upon different sectors of the government and society. However, mass cholera vaccination campaigns that target all persons one year and older in selected areas, could — depending on the scope of vaccination geographically — involve much larger numbers of vaccinees than prior vaccination campaigns, thereby substantially increasing the logistical needs and challenges. Nonetheless, the fact that the EPI has been able to conduct NIDS throughout the country in a single day — providing 40 million doses of OPV in two rounds and achieving 95% coverage — as well as its successful neonatal tetanus campaigns targeting 15-49 year old women, suggests that it could meet these challenges.

Campaigns can also negatively impact routine immunization services, since the same personnel and outreach workers are involved in both. To avoid this problem, cholera vaccination campaigns could be designed like the measles catch-up campaigns, in which measles vaccine was provided for one week in schools and then for two weeks at routine EPI outreach sites, in conjunction with regular EPI sessions, to avoid disrupting the provision of routine immunizations.

- **The need to revaccinate against cholera periodically.** There is now evidence that the WC vaccine provides sustained protection for at least three years and perhaps longer. People will need to be revaccinated once immunity subsides. This could be every three years or less frequently (e.g., every five years), depending on the results of continued follow-up in the clinical trial of the vaccine in Kolkata.
7. What would be the impact, cost, and cost-effectiveness of cholera vaccination in Bangladesh?

To assist policymakers in deciding whether to introduce cholera vaccination and what type of program to design, this study has estimated the projected costs and benefits of cholera vaccination for the four program scenarios described in Section 6 (see Figure 16 below). The benefits include the estimated number of cases and deaths that will be prevented as a result of vaccination, as well as the cost savings (e.g., in treatment costs and lost wages). The costs of a vaccination program include both the cost of the vaccine and the costs of delivering the vaccine, including salary, transport, storage, and other costs. We also examine the cost-effectiveness — in terms of cost per case or death prevented — of each of the four program options, and define the results in terms of cost per DALY (disability-adjusted life year) using the WHO definitions of cost-effectiveness.

These analyses assume that Bangladesh would use the WC (Shanchol™) vaccine because of its lower cost, longer protection (especially in young children), and improved adaptability for use in developing countries (no buffer, streamlined packaging), as compared to the WC-rBS (Dukoral®) vaccine. In addition, government officials and one local pharmaceutical company (INCEPTA) have expressed interest in local production of the vaccine (see Section 6.2.2 above). The assumption is that the vaccine would either be purchased from Shantha, or a local producer would fill-finish bulk vaccine from Shantha and perhaps eventually produce it on its own.

7.1 Cholera vaccination scenarios and expected uptake of the vaccine

As described in Section 6.5, the Large Target option would target entire districts identified in the disease burden analysis as high-risk for cholera. These 28 districts contain around half of the country’s population (~84.5 million). The Small Target option selects areas within these 28 high-risk districts, including slum areas of cities and rural areas (e.g., unions, wards, or upazilas), where the population does not have access to safe drinking water. These areas in the Small Target option contain around 18% of the country’s population or around 29.6 million people. For each of these options, the government could decide to target children 1-14 years of age or all ages one and above, including adults. Thus, the target population would vary from around 8.5 million for children 1-14 years old in the Small Target areas to nearly 83 million people if all ages (one and above) are targeted in all 28 high-risk districts (Large Target) (Figure 16).

For all of these scenarios, vaccination is assumed to take place through community-based mass vaccination campaigns. These scenarios address the control of endemic cholera and do not include preemptive or reactive vaccination to halt or limit cholera outbreaks.

For each scenario, the program is assumed to be rolled out over a three-year period, beginning in 2015. By phasing in the vaccination program, strains on cold chain facilities and human resources should be reduced. Thus, vaccination would take place each year in around one-third of the targeted areas. We also assume that vaccine protection lasts three years, and that revaccination takes place in each target area every three years. Therefore, populations
vaccinated in 2015 would be revaccinated in 2018, those vaccinated in 2016 would be revaccinated in 2019, and so forth. If the results of on-going surveillance for the clinical trial of Shanchol™ in Kolkata show that protection lasts four or five years, the interval between vaccinations could be extended accordingly.

Figure 16. Options for targeting cholera vaccination used in the analyses

```
"Large Target"  
(High Risk districts)  
(51% of population)  

- Children 1-14 years old  
  (24,403,560)  
- All ages 1 year and older  
  (82,790,878)

"Small Target"  
(Urban slums + rural areas in High Risk districts without improved water)  
(18% of population)  

- Children 1-14 years old  
  (8,541,246)  
- All ages 1 year and older  
  (28,975,807)
```

The analyses assume that 75% of children 1-14 years and 50% of adults (15 and older) in target areas would be vaccinated in a cholera vaccination program managed by the national EPI. These projected coverage rates are based on a survey of market demand for cholera vaccines conducted in Matlab in 2005 (see Section 6.3) and on coverage rates achieved by the EPI for other vaccines in recent years.

The expected numbers of people to be vaccinated each year and over a three-year period are shown in Table 14. Targeting 1-14 year olds in selected areas of high-risk districts (Small Target) would involve vaccinating around 2.1 million children each year or 6.4 million over three years—around 4% of the country’s total population. At the other extreme, if the program targets all eligible ages throughout the 28 high-risk districts (Large Target), nearly 16 million people would be vaccinated each year or more than 47 million over three years (29% of the total population). The expected numbers of people vaccinated would be similar for the children-only program in the Large Target areas as the program for all ages in the Small Target areas: around five and a half to six million per year or 16-18 million over three years.
Table 14. Expected numbers of persons vaccinated against cholera

<table>
<thead>
<tr>
<th>Target option/ age group</th>
<th>Target population (2010 estimate)</th>
<th>Assumed vaccination coverage rates</th>
<th>Estimated no. vaccinated over 3 years</th>
<th>Estimated no. vaccinated each year</th>
<th>Percent of total national population vaccinated over 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Target 1-14</td>
<td>24,403,560</td>
<td>75%</td>
<td>18,303,000</td>
<td>6,100,000</td>
<td>11.1%</td>
</tr>
<tr>
<td>1+</td>
<td>82,790,878</td>
<td>75% for 1-14 years old; 50% for 15+</td>
<td>47,496,000</td>
<td>15,800,000</td>
<td>28.9%</td>
</tr>
<tr>
<td>Small Target 1-14</td>
<td>8,541,246</td>
<td>75%</td>
<td>6,406,000</td>
<td>2,100,000</td>
<td>3.9%</td>
</tr>
<tr>
<td>1+</td>
<td>28,76,807</td>
<td>75% for 1-14 years old; 50% for 15+</td>
<td>16,624,000</td>
<td>5,500,000</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

7.2 Estimated cost of cholera vaccination in Bangladesh

The estimated cost per year of each of the four program options are shown in Table 15. These estimates assume the following:

- A price of the WC vaccine to the public sector of $1.85 per dose from 2015 to 2017, based on the current public sector price of Shanchol™. As described above in Section 6.1, the projected price is assumed to decline to $1.45 by 2018, based on assumed improvements in production efficiencies and increased competition from other vaccine producers. To this base price, we add 15% to cover customs, insurance, and shipping (CIF), resulting in an effective vaccine procurement cost of $2.13 from 2015 to 2017, and $1.67 beginning in 2018.

- A cost of $0.52/dose for all costs incurred in delivering the vaccine in mass campaigns. This estimate is based on the estimated vaccine delivery cost for the follow-up measles vaccination campaigns conducted in Bangladesh in 2010. This estimate is likely conservative since cholera vaccine is given orally while measles vaccine is injected. Oral vaccines should cost less to deliver, since no injection supplies are required, more vaccinations can be administered over a given period of time, and volunteers can provide the vaccine, reducing labor costs. In the sensitivity analyses, the delivery costs are varied from $0.30 - $1.00 per dose.\(^{19}\)

- The total cost of vaccination, including the vaccine, shipping costs, and delivery/operational costs, is therefore $2.65 ($2.13 CIF vaccine price and $0.52 per dose for delivery costs) from 2015-2017 and $2.19 ($1.67 CIF vaccine price and $0.52 per dose for delivery costs) starting in 2018.

- A vaccine wastage rate of 5%, assuming the vaccine continues to be sold in single-dose containers.

\(^{19}\) The low end of the range is based on the cost of delivering oral polio vaccine in Bangladesh in 1999 [Levin et al., 1999] and the high end is slightly less than the cost of delivering Dukoral® in a 2005 demonstration project conducted in Beira, Mozambique.
The Large Target program would cost $28 - $33 million if 1-14 year olds are vaccinated, and $73 - $88 million if adults are included. The costs of the Small Target programs would be about 65% less: $10 - $12 million for the children-only option and $25 - $31 million if all ages are included. The range of prices reflects the decline in the projected price of the vaccine from the initial $1.85 per dose to $1.45 per dose.

Table 15. Estimated costs per year of cholera vaccination, by program option (US$ 2010)

<table>
<thead>
<tr>
<th>Population target</th>
<th>Age group</th>
<th>Estimated no. people vaccinated</th>
<th>No. doses required (2 doses + 5% wastage)</th>
<th>Vaccination cost/dose*</th>
<th>Annual vaccination cost, 2010 US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Target</td>
<td>1-14</td>
<td>6.1 million</td>
<td>12.8 million</td>
<td>$2.19 - 2.65</td>
<td>28 – 33.4 million</td>
</tr>
<tr>
<td></td>
<td>1+</td>
<td>15.8 million</td>
<td>33.2 million</td>
<td></td>
<td>72.7 – 87.9 million</td>
</tr>
<tr>
<td>Small Target</td>
<td>1-14</td>
<td>2.1 million</td>
<td>4.5 million</td>
<td>$2.19 - 2.65</td>
<td>9.8 – 11.9 million</td>
</tr>
<tr>
<td></td>
<td>1+</td>
<td>5.5 million</td>
<td>11.6 million</td>
<td></td>
<td>25.5 – 30.7 million</td>
</tr>
</tbody>
</table>

* See explanation in the text for the projected vaccine costs and delivery/operations costs.

7.3 The public health impact of cholera vaccination: estimates of cases and deaths prevented and cost savings

7.3.1 Cases prevented and lives saved

Vaccine effectiveness rates incorporating herd effects

To estimate the impact of cholera vaccination, we calculated the number of expected cholera cases and deaths — both with and without vaccination — with the difference being the number of cases and deaths prevented as a result of the vaccination program. To do so, we assume an efficacy rate of the WC vaccine of 70% over three years, based on the results of the clinical trials of the vaccine in Kolkata (See Section 6). A dynamic model of cholera transmission was developed for certain countries in South and Southeast Asia, including Bangladesh and India. The model takes into account both the direct protection from being vaccinated and the indirect (herd) protection among people who have not been vaccinated but who live in a community where vaccination has taken place. These herd effects — which increase as vaccination coverage rates rise — are based on an analysis of herd protection following the clinical trials of killed oral cholera vaccines in Matlab, described in Section 6.1.3 above.

Assuming that 75% of children 1-14 years old and 50% of people 15 and older are vaccinated in a target area, the combined effects of direct and indirect protection conferred by the vaccine will result in a 76% reduction in disease over three years in the area if the vaccination covers all ages, and a 59% reduction if the program is limited to 1-14 year olds (Figure 17). The reduction is assumed to occur only in places where vaccination takes place, with incidence remaining unchanged in non-vaccinated areas. Importantly, children less than one year old, who are too young to receive the vaccine but who have the highest cholera incidence rates of all age groups, would be 73% less at risk of getting cholera if the vaccination program includes children and adults, and 56% less at risk if the program is
limited to 1-14 year old children. Clearly, the larger the range of ages vaccinated in a community, the greater the overall reduction in disease as a result of both direct and herd protection.

**Figure 17. Effectiveness of WC oral cholera vaccine over 3 years in areas targeted for vaccination, taking direct and indirect (herd) protection into account**

<table>
<thead>
<tr>
<th>Reduction in cholera incidence</th>
<th>Vaccinating children aged 1-14 years</th>
<th>Vaccinating people aged 1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>56%</td>
<td>73%</td>
</tr>
<tr>
<td>1-14 years old</td>
<td>65%</td>
<td>78%</td>
</tr>
<tr>
<td>15+ years old</td>
<td>59%</td>
<td>74%</td>
</tr>
<tr>
<td>Total population</td>
<td>76%</td>
<td>76%</td>
</tr>
</tbody>
</table>

*Assumes vaccination coverage rate of 75% for 1-14 year olds and 50% for persons 15 years old and older.

**Annual number of cases and deaths prevented**

From these estimates of overall vaccine protection, and using the incidence rates for high-risk districts from the disease burden analysis (shown in the box below), we estimate that the Large Target option will prevent around 150,000 cases and about 2,300 deaths per year — a 43% reduction in the total national disease burden — if children 1-14 years old are vaccinated (*Table 16* and *Figure 18*). If adults are included in the Large Target program, it will prevent more than 190,000 cases and nearly 3,000 deaths — a reduction in the national burden of 54%. The Small Target option would prevent around one-third as many cases and deaths: 54,000 cases and 800 deaths for the children-only program, and 68,000 cases and 1,000 deaths if adults are included. This translates into a 15% reduction in annual cases and deaths nation-wide for the children-only program and 19% for the program that includes adults.

<table>
<thead>
<tr>
<th>Assumed cholera incidence rates used for the impact and cost-effectiveness analyses (for high-risk districts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>&lt;1</td>
</tr>
<tr>
<td>1-4</td>
</tr>
<tr>
<td>5-14</td>
</tr>
<tr>
<td>15+</td>
</tr>
<tr>
<td>Overall</td>
</tr>
</tbody>
</table>
Table 16. Estimated annual impact of cholera vaccination on national disease burden, by program option

<table>
<thead>
<tr>
<th>Age</th>
<th>Large Target</th>
<th>Small Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-14</td>
<td>1+</td>
</tr>
<tr>
<td>Number vaccinated per year</td>
<td>6.1 million</td>
<td>15.8 million</td>
</tr>
<tr>
<td>Cases prevented</td>
<td>154,000</td>
<td>194,000</td>
</tr>
<tr>
<td>Lives saved total</td>
<td>2,300</td>
<td>2,900</td>
</tr>
<tr>
<td>DALY saved, total</td>
<td>73,000</td>
<td>92,000</td>
</tr>
</tbody>
</table>

Figure 18. Annual number of persons to be vaccinated and estimated reduction in the national incidence from cholera

Number of cases and deaths prevented from 2015 to 2030

The cumulative number of cases and deaths prevented through vaccination is shown in Figure 19 for each of the four proposed program options. The Small Target program for children 1-14 years of age would prevent about 850,000 cases and 13,000 deaths over the period from 2015 to 2030, while the Small Target program for all ages greater than one year would prevent about 1.1 million cases and 16,000 deaths. If the Large Target option is chosen and only children age 1-14 are vaccinated, the number of cases prevented would increase to 2.4 million, with about 37,000 averted deaths. If all ages greater than one year old are vaccinated, the program would prevent 3.1 million cases and 46,000 deaths over this 16 year timeframe. These findings suggest that if programs are expanded to include adults as well as children, the number of cases and deaths prevented does not increase markedly (only by around 29%). On the other hand, there are large differences in the number of cases and deaths prevented between Small Target and Large Target programs (an increase of more than 180%).
Figure 19. Cumulative Impact of cholera vaccination, 2015-2030*

![Graphs showing cumulative impact of cholera vaccination for different age groups and target sizes.](image)

*Impact estimates take herd protection into account.
Figure 20 shows the trends in cholera incidence over time if no new cholera control program is implemented ("baseline") and if the various cholera vaccination program options are introduced. The increase in the number of cases if no vaccination or other new control measures are implemented is due to the increase in the population over time. This figure further shows that expanding from the Small Target to Large Target programs has a much greater impact than expanding from the children-only programs to the programs covering all ages one year and older.

Figure 20. Projected number of cholera cases from 2010 to 2030 in Bangladesh without vaccination and with vaccination, by program scenario

7.3.2 Savings in cost-of-illness from cholera vaccination

The savings in cost-of-illness from cholera as a result of vaccination total $900,000 to $3.4 million per year, depending on the vaccination program (Table 17). The direct savings in cost-of-illness – for medical treatment (incurred both by health facilities and patients), transportation, and other out-of-pocket costs – vary between $2.0 to $2.6 million for the Large Target programs, and between $700,000 and $900,000 for the Small Target programs. These savings are approximately equivalent to 4-8% of the expected annual cost of the cholera vaccine program. The savings in indirect cost-of-illness, such as lost wages due to the patient or caregiver missing work, vary from $200,000 to $300,000 for the Small Target programs and from $600,000 to $800,000 for the Large Target programs.

7.4 Comparing cost to impact: is cholera vaccination cost-effective in Bangladesh?

Comparing the cost of the different vaccine program scenarios to their impact on reducing disease, the scenario with the greatest impact – vaccinating all persons one year and older throughout the 26 high-risk districts (Large Target) – would reduce incidence nation-wide by more than half (54%), but would cost an estimated $88 million per year at the current price of $1.85, and $73 million per year at the expected long-term price of $1.45
At the other end, the Small Target program for children 1-14 years old would cost around $10-12 million a year but would reduce the national disease burden by only 15%. A Large Target program that involves children only would cost around the same as the Small Target program that includes all ages ($28 - $34 million vs. $26 - $32 million). However, the impact of the children-only Large Target program would be more than twice that of the Small Target all-ages program—a reduction in cholera incidence nationwide of 43% vs. 19%. This suggests that it would be more efficient to vaccinate children in as many communities as possible within high-risk districts, rather than limiting the geographic scope of the program in order to vaccinate both children and adults.

Table 17. Estimated annual savings in cholera cost-of-illness with cholera vaccination programs (US$2010)*

<table>
<thead>
<tr>
<th></th>
<th>Large Target</th>
<th>Small Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-14</td>
<td>1+</td>
</tr>
<tr>
<td>Direct cost savings</td>
<td>2,000,000</td>
<td>2,600,000</td>
</tr>
<tr>
<td>Indirect cost savings</td>
<td>600,000</td>
<td>800,000</td>
</tr>
<tr>
<td>Total costs</td>
<td>2,600,000</td>
<td>3,400,000</td>
</tr>
</tbody>
</table>

* Based on age-specific cost estimates, ranging from $16-21 per case (see Table 7 in Section 3.1.1). Costs include those incurred by both the government and individuals.

Figure 21. Annual cholera vaccination program costs (US $2010) and estimated reduction in the national incidence from cholera

Measures of cost-effectiveness, such as cost per case, death, or disability-adjusted-life-year (DALY) prevented are another means of determining the value of an intervention and comparing different program options. These measures are derived by dividing the net cost of the vaccination program by its impact. The net cost is the total cost of the program minus the savings in cost-of-illness (both direct and indirect). The key assumptions used for the cost-effectiveness analyses are shown in the box below, while a detailed list of assumptions is available in Appendix 7. A description of the technical details for the cost-effectiveness analysis is included as Appendix 8.
The children-only programs — both for the Large and Small Target options — would cost an estimated $170 - $200 for each case prevented (depending on the vaccine price), while the programs that include all ages would cost more than double ($360 - 440) (Table 18). Vaccinating 1-14-year-olds would cost $11,000 - $14,000 for every cholera death prevented compared to nearly $24,000 - $29,000 if all ages are vaccinated.

Table 18. Estimates of cost-effectiveness for cholera vaccination by target option and age group, US $2010

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Large Target</th>
<th>Small Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-14</td>
<td>1+</td>
</tr>
<tr>
<td>Cost per case prevented</td>
<td>170 - 200</td>
<td>360 - 440</td>
</tr>
<tr>
<td>Cost per death prevented</td>
<td>11,000 - 14,000</td>
<td>24,000 - 29,000</td>
</tr>
<tr>
<td>Cost per DALY averted</td>
<td>350 - 390</td>
<td>760 - 930</td>
</tr>
</tbody>
</table>

The results for each age option are the same whether the entire high-risk districts (Large Target) or just selected communities in these same districts (Small Target) are targeted for vaccination. This is because we used the same incidence rates (for high-risk districts), vaccination program costs, and other variables for both the Large and Small Target options, since estimates for these variables below the district level were not available. In reality, incidence rates are likely to be higher in the slums and in rural areas with poor water supplies selected for the Small Target option than in the high-risk districts as a whole. If this is true, the cost-effectiveness of the Small Target programs will be better than the Large Target programs.

The cost per DALY averted is a measure commonly used to compare the cost-effectiveness of different health interventions and to evaluate cost-effectiveness against criteria established by WHO. Vaccination saves DALYs by reducing both morbidity (years of life lost to disability) and deaths (years of life lost). Most of the gains in DALYs from cholera vaccination (shown in Table 18 above) are due to the reduction in deaths, and not in morbidity, since the illness is of short duration and does not usually lead to long-term disability. More information on DALYs and how they were estimated can be found in Appendix 8.

According to WHO, a program is “very cost-effective” if its costs per DALY averted is less than or equal to the average Gross Domestic Product (GDP) per capita, which is $641 in Bangladesh in 2010. A program is “cost-effective” if the cost per DALY averted is less than or equal to three times the GDP per capita, or $1,923. Depending on the assumed vaccine price, the cost per DALY averted through vaccination is $350 - $430 for the children-only programs.
and $760 - $930 for the vaccination programs that include adults (Figure 22). Thus, the children-only programs are very cost-effective, and the programs that include all ages meet the definition of “cost-effective”, but not “very cost-effective”. While the children-only programs — for the Small and Large Target scenarios — are both very cost-effective, the Large Target program for children would reduce the total number of cholera cases much more than the Small Target program (43% vs. 15%). This again suggests that if financing is available, vaccinating all 1-14 year olds throughout the 28 high-risk districts, as called for in the Large Target scenario, appears to be the most efficient and cost-effective program option for reducing the national cholera disease burden.

Figure 22. Cost-effectiveness ratios of the cholera vaccination program options against WHO cost-effectiveness thresholds

![Cost-effectiveness ratios of the cholera vaccination program options against WHO cost-effectiveness thresholds](image)

7.5 Sensitivity analyses

Since several of the key variables used in the cost-effectiveness analyses are estimates, including the case fatality rate, incidence rates, and vaccination costs, sensitivity analyses were performed that vary the assumptions, using a range of values, in order to determine their impact on the cost-effective results (Table 19). For the sensitivity analysis, the base case uses a pre-shipping vaccine price of $1.65 or $1.90 procurement cost with consideration of insurance and transport costs, which is the midpoint between the current price of $1.85 and the expected long-term price of $1.45. The children-only programs (both Large and Small Target) would still be “very cost-effective” if the maximum values are assumed for case fatality rate (2%), CIF vaccine price ($2.13/dose), and vaccine delivery costs ($1.15/dose). Vaccinating children would no longer be “very cost-effective” if the cholera incidence rates are half of what was assumed (resulting in a cost/DALY averted of $810), or if there is no herd protection from the vaccine ($720/DALY averted). While a duration of protection greater than three years further reduces the cost per DALY averted, the vaccine is already very cost-effective at the established duration of three years.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case</th>
<th>Uncertainty range</th>
<th>Cost/death prevented</th>
<th>Cost/DALY prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual incidence per 1,000</td>
<td>Varies by age group</td>
<td>50% - 150% of base case</td>
<td>$7,800 - $26,000</td>
<td>$250 - $810</td>
</tr>
<tr>
<td>Cholera case fatality rate (%)</td>
<td>1.50%</td>
<td>1.0%-2.0%</td>
<td>$9,200 - $18,000</td>
<td>$290 - $580</td>
</tr>
<tr>
<td>Vaccine price (CIF)</td>
<td>$1.90</td>
<td>$1.15-$2.13</td>
<td>$8,100 - $13,500</td>
<td>$260 - $430</td>
</tr>
<tr>
<td>Vaccine delivery costs (US$ 2010)</td>
<td>$0.52</td>
<td>$0.30-$1.00</td>
<td>$11,000 - $15,000</td>
<td>$350 - $470</td>
</tr>
<tr>
<td>Herd protection</td>
<td>Yes</td>
<td>No</td>
<td>$12,000 - $28,000</td>
<td>$390 - $790</td>
</tr>
<tr>
<td>Duration of vaccine protection (years)</td>
<td>3</td>
<td>3 - 5</td>
<td>$6,900 - $12,000</td>
<td>$230 - $390</td>
</tr>
<tr>
<td>Base case pre-shipping vaccine price of US$1.65 + 15% CIF = US$1.90</td>
<td></td>
<td></td>
<td>$12,000</td>
<td>$390</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case</th>
<th>Uncertainty range</th>
<th>Cost/death prevented</th>
<th>Cost/DALY prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual incidence per 1,000</td>
<td>Varies by age group</td>
<td>50% - 150% of base case</td>
<td>$17,000 - $54,000</td>
<td>$550 - $1,700</td>
</tr>
<tr>
<td>Cholera case fatality rate (%)</td>
<td>1.50%</td>
<td>1.0%-2.0%</td>
<td>$20,000 - $40,000</td>
<td>$630 - $1,300</td>
</tr>
<tr>
<td>Vaccine price (US$ 2010)</td>
<td>$1.90</td>
<td>$1.15-$2.13</td>
<td>$18,000 - $29,000</td>
<td>$680 - $930</td>
</tr>
<tr>
<td>Vaccine delivery costs (US$ 2010)</td>
<td>$0.52</td>
<td>$0.30-$1.00</td>
<td>$24,000 - $32,000</td>
<td>$760 - $1,000</td>
</tr>
<tr>
<td>Herd protection</td>
<td>Yes</td>
<td>No</td>
<td>$26,000 - $50,000</td>
<td>$840 - $1,600</td>
</tr>
<tr>
<td>Duration of vaccine protection (years)</td>
<td>3</td>
<td>3 - 5</td>
<td>$15,000 - $23,900</td>
<td>$510 - $840</td>
</tr>
<tr>
<td>Base case pre-shipping vaccine price of US$1.65 + 15% CIF = US$1.90</td>
<td></td>
<td></td>
<td>$26,000</td>
<td>$840</td>
</tr>
</tbody>
</table>

The programs in which all persons one year and older are vaccinated would change from “cost-effective” to “very cost-effective” if cholera incidence, case fatality rate, or duration of vaccine protection are greater than the assumptions used in the base case, or if vaccine prices or delivery costs are lower than expected. Vaccinating all ages would still be cost-effective, even if the maximum value of each of these variables is assumed, when varied one at a time. We can therefore conclude that all of the scenarios presented in this case study for cholera vaccination are likely to be either very cost effective or cost-effective, using the WHO definitions.
8. How can cholera vaccination be paid for: financing needs and sustainability

8.1 Sources of immunization financing in Bangladesh

Bangladesh’s 2009 Public Expenditure and Institutional Review found that while expenditures on health are low compared to those of other countries in the region, the value obtained from these expenditures is relatively high [World Bank, 2009]. That is, health outcomes are better in Bangladesh than in countries that spend similar amounts. In particular, the Expanded Program on Immunization (EPI) has been very effective and has few disparities in its immunization rates between different socio-economic classes (as discussed in Section 5), despite the fact that resource allocation in the health sector is not considered to favor the poor.

Part of the reason that the EPI in Bangladesh has been so effective is that it has been considered a priority program by the Government. It has therefore received high levels of funding from the government and its development partners. Funding for the EPI in Bangladesh flows through three sources:

1) The Revenue Budget, which is entirely financed by the Government and which pays for MOHFW staff salaries and routine recurrent expenditures (e.g. transport and maintenance) (see Table 20). It also funds long-term training, operational costs of central and regional warehouses, the MOHFW integrated information system, and co-financing of GAVI-supported vaccines.

2) The Development Budget from pooled funds from the Health, Nutrition and Population Sector Program (HNPS), the Government’s sector-wide program that focuses on integrated maternal and child health services to help it reach the health-related Millennium Development Goals. The HNPS pooled funds consists of funding from external donors (=75%) and the Government (=25%). The development budget finances the basic EPI vaccines and injection supplies, short-term training for health assistants (HAS) and family welfare assistants (FWAs), and other program costs associated with integrated services, such as health education and promotion.

3) Funds from individual donor agencies, such as the GAVI Alliance, WHO, UNICEF, and CIDA, that are earmarked specifically for immunization services. The GAVI Alliance provides different types of support to the EPI through three programs: 1) support for the introduction of new vaccines, including the pentavalent DPT-hepB-Hib vaccine and soon the pneumococcal conjugate vaccine, 2) funds for additional vaccinators and contractual District Immunization Medical Officers (DIMOs) through Immunization Service Support (ISS), and 3) Health System Strengthening Support (HSS) to expand the network of community clinics (CCs) in the country. WHO finances divisional and district surveillance officers. Earmarked funds from development partners also pay for supplementary immunization activities, such as polio NIDs and measles vaccination campaigns, short-term training, supervision of warehouses, surveillance, and cold chain equipment.
In urban areas, the funding for immunization operational costs is part of a broader package of essential health services financed by development partners. The Asian Development Bank (ADB) provides funding to city corporations and municipalities to contract out to NGOs and the private sector for service delivery, including immunization. In addition, the U.S. Agency for International Development (USAID) supports service delivery programs in urban areas through a network of NGOs that manage “Smiling Sun” clinics. Their contracts specify that the NGOs must provide all services included in the MOHFW’s Essential Services Package, including immunization.

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>MOHFW revenue budget (Government-funded)</th>
<th>Development budget (HNPSN pooled funding*)</th>
<th>Earmarked donor funds (e.g. GAVI, USAID, ADB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff salaries</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional vaccinators/district immunization medical officers in rural areas</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Older vaccines and injection supplies</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New vaccines</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(co-financing for GAVI vaccines)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine recurrent costs for rural areas</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Supplementary Immunization Activities (polio NIDs, measles campaigns, etc.)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Staff salaries and recurrent costs of urban immunization program</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cold chain equipment and maintenance</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Information systems, monitoring and evaluation</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Disease surveillance</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Combination of partner and Government funds

As shown in Figure 23, the largest source of financing for the EPI in 2010 is GAVI, which provides 45% of the total EPI expenditures, followed by the MOHFW, which contributes 43%. Other sources of financing include HNPSN pooled funds (9%), WHO (2%), USAID (1%), ADB (1%), and other (1%).
8.2 Costs of the EPI

Table 21 shows the estimated resource needs of the immunization program during the years 2006-2010, using data from Bangladesh's 2008-2010 comprehensive Multi-Year Plan for the Immunization Program [MOHFW,2007], which were modified to include the introduction of pentavalent vaccine in 2009. These costs show what is required for the program, regardless of who paid for the various expenditures. The costs of the EPI doubled in one year from around $57 million in 2008 to more than $115 million in 2009, with the introduction of the pentavalent vaccine, and then reduced to about $97 million in 2010. With the addition of this vaccine, the procurement of vaccines and related supplies (e.g., auto-destruct disposable syringes) now make up the largest share of the total costs of the EPI — 47% to 51% in 2009 and 2010. Until the new vaccine was introduced, service delivery costs, paid largely by the Government, were the largest single program expenditure.


<table>
<thead>
<tr>
<th>Cost Component</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>Total 2006-2010</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines &amp; Injection supplies</td>
<td>32,081,000</td>
<td>25,367,000</td>
<td>19,321,000</td>
<td>74,155,000</td>
<td>56,925,000</td>
<td>207,849,000</td>
<td>51.0%</td>
</tr>
<tr>
<td>Service delivery</td>
<td>37,989,000</td>
<td>37,924,000</td>
<td>36,626,000</td>
<td>40,088,000</td>
<td>38,096,000</td>
<td>190,723,000</td>
<td>46.8%</td>
</tr>
<tr>
<td>Advocacy and communication</td>
<td>306,000</td>
<td>312,000</td>
<td>53,000</td>
<td>54,000</td>
<td>55,000</td>
<td>790,000</td>
<td>0.19%</td>
</tr>
<tr>
<td>Monitoring and disease surveillance</td>
<td>1,305,000</td>
<td>1,363,000</td>
<td>1,465,000</td>
<td>1,553,000</td>
<td>1,547,000</td>
<td>7,353,000</td>
<td>1.8%</td>
</tr>
<tr>
<td>Program management</td>
<td>110,000</td>
<td>113,000</td>
<td>115,000</td>
<td>117,000</td>
<td>119,000</td>
<td>574,000</td>
<td>0.14%</td>
</tr>
<tr>
<td>Total</td>
<td>71,793,000</td>
<td>65,098,000</td>
<td>57,351,000</td>
<td>115,067,000</td>
<td>96,843,000</td>
<td>407,282,000</td>
<td>99.9%</td>
</tr>
</tbody>
</table>

Source: cHVP for 2006-2010
8.3 How much would cholera vaccination add to the costs of the EPI?

If cholera vaccination were to be introduced in Bangladesh, it is important to know how much this intervention will add to the total costs of the EPI program. Table 22 shows the annual costs of introducing cholera vaccine in relation to the overall EPI resource requirements, assuming use of the WC (Shanchol™) vaccine. As seen in Chapter 7, the Large Target scenario, in which cholera vaccination would take place throughout the 28 districts identified in Section 2 as “high-risk” for cholera, would cost around $73 - 88 million per year for the program that includes all ages one year and above, and around $28 - 34 million a year if only children 1-14 years old are vaccinated. This Large Target scenario would increase the Bangladeshi EPI resource requirements by 75 - 91% for the program that includes all ages one and above, and by 29 - 35% if the program is limited to children 1-14 years of age.

**Table 22. Annual budget requirements for cholera vaccination using Shanchol™ in Bangladesh for different immunization program options***

<table>
<thead>
<tr>
<th></th>
<th>Large Target (28 entire high-risk districts)</th>
<th>Small Target (Urban slums and rural areas with unimproved water sources in high-risk districts)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ages 1+</td>
<td>1-14 year olds</td>
</tr>
<tr>
<td>Total costs of vaccination</td>
<td>$73 - $88 million</td>
<td>$28 - $34 million</td>
</tr>
<tr>
<td>Total EPI budget in 2010</td>
<td>$96.8 million</td>
<td>$96.8 million</td>
</tr>
<tr>
<td>% change in resource requirements of the EPI</td>
<td>75 - 91%</td>
<td>29 - 35%</td>
</tr>
</tbody>
</table>

* Cost includes price of vaccine per dose (ranging from $1.45 - $1.85), 15% for customs, insurance and freight (for CIF price of $1.67 - $2.13) and $0.52/dose for delivery/operational costs (see Chapter 7 for details on the projected costs).

If the Small Target option is selected, it would increase the total costs of the EPI on average by 26 - 33% if all eligible ages are included, and by 10 - 12% if the program targeted children 1-14 years of age only.

Table 23 compares the annual cost and cold chain storage requirements for the two currently available oral cholera vaccines, Shanchol™ and Dukoral®, for the Large Target scenarios. The estimated price for Dukoral® is $5.25 per dose (before shipping costs), based on the most recent negotiated price with WHO for the vaccine. At this price, the projected costs of vaccination using Dukoral® would be approximately three times as high as vaccination with Shanchol™. It should be noted that the price of $5.25/dose was for a small quantity of vaccine and that Crucell/SBL Vaccines has indicated it would be willing to lower its price further given sufficient demand; thus the actual public sector price could be smaller. Dukoral® would also have higher cold chain requirements since its vaccine volume, including secondary packaging, is 36% larger than that of Shanchol™.

Table 24 compares the annual resource and cold chain storage requirements of introducing cholera vaccine throughout the 28 high-risk districts (Large Target option) with the requirements of introducing pneumococcal and rotavirus vaccines into the infant EPI schedule in 2010. These vaccines were selected for comparison because Bangladesh policymakers indicated their interest in introducing these vaccines into its routine program.
The vaccines would be delivered using different vaccination strategies — cholera vaccines through periodic campaigns for children and possibly for adults, and pneumococcal and rotavirus vaccines for infants through the routine immunization program. This comparison includes the full price of the vaccines, regardless of who is paying for them. While the Government of Bangladesh will co-finance only a small percent of the actual vaccine cost for the pneumococcal and rotavirus vaccines provided through the GAVI Alliance ($0.20/dose), the full cost is given here, since the Government will be expected to pay the entire cost of the vaccines once GAVI support ends.

Table 23. Comparison of the annual cost of cholera vaccination and storage requirements for the Large Target programs with Shanchol™ and Dukoral® vaccines

<table>
<thead>
<tr>
<th></th>
<th>Shanchol™</th>
<th>Dukoral®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ages 1+</td>
<td>1-14 years</td>
</tr>
<tr>
<td>Estimated price to the public sector per dose (including 15% for customs, insurance, and freight)*</td>
<td>$1.67 - 2.13</td>
<td>$1.67 - 2.13</td>
</tr>
<tr>
<td>Vaccine delivery/operational cost</td>
<td>$0.52</td>
<td>$0.52</td>
</tr>
<tr>
<td>Total vaccination cost per dose</td>
<td>$2.19 - 2.65</td>
<td>$2.19 - 2.65</td>
</tr>
<tr>
<td>Vaccine volume per dose/cold chain requirements for 2 doses</td>
<td>25.5 cm³/51 cm³</td>
<td>25.5 cm³/51 cm³</td>
</tr>
<tr>
<td>Estimated number of people to be vaccinated per year**</td>
<td>15.8 million</td>
<td>6.1 million</td>
</tr>
<tr>
<td>Total no. doses required per year (2 doses +5% wastage)</td>
<td>33.2 million</td>
<td>12.8 million</td>
</tr>
<tr>
<td>Total costs</td>
<td>$73 - 88 million</td>
<td>$28 - 34 million</td>
</tr>
<tr>
<td>Percent change in total costs of immunization program</td>
<td>75 - 91%</td>
<td>29 - 35%</td>
</tr>
</tbody>
</table>

* Assumed base prices per dose are: $1.45 for cholera vaccine and $5.25 for Dukoral. Fifteen percent has been added to these prices for customs, insurance, and freight costs.
** Assuming coverage rate of 75% for children 1-14 years and 50% for 15 year olds and older (see Table 14 in Section 7.1).

The costs of introducing cholera vaccine using the Large Target option if children age 1-14 years are vaccinated with Shanchol™ are intermediate between the cost to introduce rotavirus and pneumococcal vaccines. The costs of introducing Shanchol™ for the Large Target, all ages 1+ program, are similar to the cost of introducing pneumococcal vaccine at the $7.00 per dose price, about double the cost compared to the long-term pneumococcal vaccine price of $3.50, and about four times greater than the cost of introducing rotavirus vaccine. If Shanchol™ is given only in urban slums and rural areas without improved water (Small Target option), the costs of cholera vaccination would be lower. The Small Target option, if vaccination is limited to children, would be less costly than introducing rotavirus vaccine (not shown).

The additional cold chain requirements per fully vaccinated individual are lower for the cholera than the pneumococcal vaccine due to the smaller vaccine volume and number of doses required. The cold chain requirements of Shanchol™ are approximately half those of pneumococcal vaccine, but are higher than those of Rotarix® vaccine.
Table 24. Comparison of cost and cold chain requirements of Shanchol™ cholera vaccine with pneumococcal and rotavirus vaccines

<table>
<thead>
<tr>
<th></th>
<th>Shanchol™ cholera vaccine throughout high-risk districts (Large Target)</th>
<th>Pneumococcal Vaccine (7-valent)</th>
<th>Rotavirus (2-dose Rotarix®) vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target population</td>
<td>All ages 1+</td>
<td>1-14 years</td>
<td>infants</td>
</tr>
<tr>
<td>Cost per dose (with 15% added for shipping, insurance, handling)*</td>
<td>$1.67 - 2.13</td>
<td>$1.67 - 2.13</td>
<td>$4.03 - 8.05</td>
</tr>
<tr>
<td>Delivery cost</td>
<td>$0.52</td>
<td>$0.52</td>
<td>$0.80</td>
</tr>
<tr>
<td>Vaccination cost per dose</td>
<td>$2.19 - 2.65</td>
<td>$2.19 - 2.65</td>
<td>$4.83 - 8.85</td>
</tr>
<tr>
<td>Vaccine volume/cold chain requirements per person</td>
<td>25.5 cm³/51 cm³</td>
<td>25.5 cm³/51 cm³</td>
<td>55.9 cm³/ 168 cm³</td>
</tr>
<tr>
<td>Total cold chain requirements (cm³)</td>
<td>697,345,539</td>
<td>274,715,096</td>
<td>582,196,328</td>
</tr>
<tr>
<td>Number of doses</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Target population</td>
<td>82,800,000</td>
<td>24,400,000</td>
<td>3,252,000</td>
</tr>
<tr>
<td>Coverage rate for complete series</td>
<td>75% for 1-14, 50% for 15+</td>
<td>75%</td>
<td>85%</td>
</tr>
<tr>
<td>Wastage rate</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Total no. doses required</td>
<td>33.2 million</td>
<td>12.8 million</td>
<td>8.7 million</td>
</tr>
<tr>
<td>Total costs of vaccination</td>
<td>$73 - 88 million</td>
<td>$28 - 34 million</td>
<td>$42 - 77 million</td>
</tr>
<tr>
<td>AD syringes**</td>
<td>NA</td>
<td>NA</td>
<td>$748,200</td>
</tr>
<tr>
<td>Total cost of vaccine and supplies</td>
<td>$73 - 88 million</td>
<td>$28 - 34 million</td>
<td>$43 - 78 million</td>
</tr>
<tr>
<td>Percent change in total costs of immunization program</td>
<td>75 - 91%</td>
<td>29 - 35%</td>
<td>44 - 80%</td>
</tr>
</tbody>
</table>

* Assumed based prices per dose are $1.45 - 1.85 for cholera vaccine, $2.50 for rotavirus vaccine and $3.50 - 7.00 for pneumococcal vaccine. Fifteen percent has been added to these prices for shipping and handling.
** Estimated unit price of AD syringes = $0.086.

8.4 Potential sources of financing for cholera vaccination

There are several potential sources of financing for oral cholera vaccination: 1) traditional sources, such as the MOHFW budget, HNPSF pooled funds and the GAVI Alliance; 2) global warming/climate change funding; and 3) local non-government sources, such as local industries affected by cholera.

8.4.1 Traditional sources of financing

Bangladeshi policymakers stated that, if the pilot introduction of cholera vaccination in Mirpur in Dhaka City is successful, their preferred source of financing would be GAVI support. However, they understood that GAVI funding may not be available and that they might have to seek other sources of financing for the vaccine.

The MOHFW could be expected to pay for the operational costs associated with introducing the vaccine, such as transport and health personnel costs, since it already pays
for these for other vaccines. This contribution from the Revenue Budget would cover approximately 25% of the costs of introducing cholera vaccine.

Another potential source of financing is pooled funds from the Development Budget. If policymakers and program managers make the case for the relevance and importance of providing cholera vaccine to the MOHFW and to donors, there could potentially be funding to purchase the vaccine. It will be important to plan to incorporate this resource requirement into their regular health planning and budgeting process, such as developing the comprehensive multi-year plan (cMYP) and the next phase of the HNPSP.

8.4.2 Climate change funding

Another possible source of funding for oral cholera vaccine is through external funds for climate change-related projects in the country. As described above in Section 2.8, research suggests that the incidence of cholera is likely to increase with flooding and/or droughts in cholera-prone areas that occur with climate variability.

Since Bangladesh has been designated as a country likely to be severely impacted by climate change, several development partners and the Government are developing a Climate Change Trust Fund to be managed by the Government to mitigate the impact of climate change in the country. Given the link between climate change and cholera incidence, potential funding could be solicited from the trust fund for the introduction of cholera vaccination.

8.4.3 Local non-government sources of financing

Industries that are adversely affected by cholera outbreaks could potentially be interested in paying for cholera vaccination in the localities in which they work. For example, the seafood and restaurant industries have a vested interest in ensuring that their workers and surrounding communities do not have cholera and may therefore be willing to defray some of the costs of cholera vaccination in these communities.

8.5 Financial sustainability of the program

Assuming that the cholera vaccination feasibility study that is taking place in the Mirpur section of Dhaka is successful and leads to a government decision to introduce cholera vaccination in the public sector, and assuming the program is funded with donor funding such as GAVI or climate change project funding, the country should develop a plan to gradually take over the financing of the vaccine to improve its financial sustainability. It is also possible that the incidence of cholera can be reduced through other interventions such as improved sanitation and the provision of safe water. In that way, the use of oral cholera vaccines could be gradually phased out in Bangladesh.
9. Summary and conclusions

9.1 The burden of cholera in Bangladesh

Disease burden

- Cholera remains endemic in most of Bangladesh and the disease burden from both endemic cholera and cholera outbreaks is substantial. Both rural populations and urban dwellers, especially those living in the ever-growing slums of Dhaka and other major cities, are at risk for the disease.

- An analysis of cholera incidence based on long-term sentinel site surveillance in several areas of the country estimates that there are around 350,000 cases of cholera that seek health care on average each year and around 5,000 deaths, for a nation-wide incidence rate of 2.1/1,000 per year.

- More than half of the country’s population lives in the 28 districts that the analysis identifies as “high risk” for cholera (with an average annual incidence of 3.0/1,000). These districts account for 72% of the estimated cholera disease burden in the country.

- Children under the age of five years suffer the highest incidence rates — around 8/1,000 on average per year for the country as a whole and up to 11-12/1,000 in the high-risk districts.

Trends in cholera epidemiology

- Cholera is becoming an increasingly urban disease in Bangladesh. Based on data from the ICDDR,B hospital, cholera incidence appears to be increasing in Dhaka since 2004 and large, flood-related epidemics have become more frequent in the city, with major outbreaks in 2004, 2007, and 2009.

- There is also evidence that the disease is becoming more clinically severe, especially during outbreaks, with up to 70-80% of patients presenting at health facilities severely dehydrated and requiring immediate IV fluid infusion. Some scientists attribute this to a new altered strain of V. cholerae — a strain of the O1 El Tor biotype, but with the more virulent classical cholera toxin — that has emerged in Bangladesh in the past decade.

- A growing body of research shows a link between climate change and increases in cholera incidence, as a result of increasing surface water temperatures, sea water incursion (potentially leading to migration of vibrios inland), and extremes in rainfall amounts (both droughts and heavy rainfall). This link, and the fact that Bangladesh has been ranked as the country most affected by climate change in the past decade, is causing concern among scientists and government officials that the future could see more frequent large-scale outbreaks of the disease.

Concern about the disease among policymakers
9.2 The economic burden of cholera

Cost-of-illness

- The cost-of-illness of cholera in Bangladesh is estimated at about $6.3 million per year on average, including both costs to the Government for treating patients and costs incurred by patients and their families (e.g., out-of-pocket medical expenses, transports, lost wages from missed work). This estimate does not take macro-economic costs into account.

The macro-economic impact of cholera

- Unlike many other vaccine-preventable diseases, cholera, especially when it occurs in outbreaks, has a well-recognized impact on the overall economy of a country.

- The shrimp industry in Bangladesh is especially affected by the disease. In the past 15 years, there have been a number of bans by the EU of shrimp exports from Bangladesh and import detentions on seafood by the U.S. One five-month ban by the EU in 1997 alone cost the shrimp processing industry nearly $15 million. As a result, the Ministry of Fisheries & Livestock, with EU funding, is upgrading its three existing Fish Inspection and Quality Control laboratories to be able to test shrimp for *V. cholerae* and other bacteria.

- Vaccination of shrimp industry employees and populations in shrimp-producing areas is another means of controlling cholera contamination of shrimp that should be considered.

9.3 Cholera prevention and control measures in Bangladesh

Water and sanitation improvements

- Nearly one quarter of the rural population of Bangladesh does not have access to improved water sources, largely as a result of arsenic contamination of shallow tube wells. Only around one-half of the population of Dhaka has access to a safe and consistent water supply due to growth in slum populations, an overburdened infrastructure, and dwindling ground water supplies.

- Less than one-third of the rural population and less than 60% of the urban population have access to adequate sanitation facilities.

- The Government has a goal to provide access to safe drinking water and adequate sanitation to 100% of the population. A number of donor-supported projects are underway to provide piped water and water treatment facilities in urban areas, to mitigate arsenic in rural areas (e.g., by identifying contaminated tube wells and
providing arsenic removal filters), and to provide tens of millions more people with improved sanitation.

- Reaching these goals will take a number of years, during which cholera is likely to remain a persistent problem. Cholera vaccination could therefore provide a short- to medium-term solution to control the disease in Bangladesh.

**Disease surveillance**

- Government disease reporting systems and programs track acute watery diarrhea, but do not systematically confirm cholera through laboratory testing. The only laboratory-supported surveillance of cholera at present is conducted by ICDDR,B through a number of long-term and time-limited programs in Dhaka and a few rural areas.

- The detection and response to cholera outbreaks also need to be strengthened.

- The Government of Bangladesh has proven its ability to establish strong laboratory-supported sentinel site surveillance for selected diseases, including influenza. To inform decisions about whether and where to introduce cholera vaccination, sentinel site surveillance for cholera could be established in different parts of Bangladesh, perhaps by piggybacking to an existing sentinel site surveillance program, or by resurrecting earlier cholera surveillance programs in collaboration with ICDDR,B.

- If cholera vaccine is added to the EPI for use in high-risk areas, cholera surveillance would be handled by the EPI surveillance program, which includes laboratory testing at the Institute of Public Health and is considered among the strongest disease surveillance systems in the country.

**Cholera control and treatment**

- Diarrheal disease management in public sector health facilities has been very much in practice throughout the country since the 1980s, with the development of national treatment guidelines, the establishment of oral rehydration treatment (ORT) corners with designated beds in all public hospitals from the upazila to the national level, and the availability of IV rehydration therapy at the upazila and higher levels. As a result, oral rehydration solution is readily available in all government health clinics and hospitals for mildly to moderately dehydrated patients, as well as for severely dehydrated patients following effective treatment with IV fluids.

- The ICDDR,B hospital is a major treatment center for diarrhea and cholera patients in Dhaka, treating approximately 12,000 to 34,000 cases of cholera each year.

- Despite great efforts to improve the treatment of cholera in government health facilities, many people, especially in rural areas, do not likely receive adequate care, especially for severe cases. This is due to the population’s heavy reliance on unlicensed private practitioners or drug sellers and to the lack of facilities that can adequately treat severe dehydration (with IV fluids) in remote areas (e.g., below the level of Upazila Health Complexes).
Policymakers in Bangladesh credit ORT with saving the lives of many people with acute watery diarrhea, including cholera, and the country has a high level of usage of ORS, recommended home fluids, or increased fluids for children with diarrhea (85% of households). However, only around half of children under five years of age with diarrhea in rural areas are given ORS, indicating the need to expand efforts to promote its use in rural parts of the country.

9.4 The EPI’s capacity to successfully implement cholera vaccination

Bangladesh’s Expanded Programme on Immunization (EPI) is well-experienced and skilled to implement cholera vaccination successfully in accordance with the requirements of the vaccine and the disease.

The Program’s capabilities relevant to cholera vaccination — which at present cannot be administered to infants and which may target older children and even adults— include the following:

- The proven ability to achieve high immunization coverage and to reach even the poorest communities, which are likely the most affected by cholera. This is demonstrated by the small difference in immunization coverage rates between the highest and the lowest income quintiles, and by progress in reaching areas with low coverage rates through the Reach Every District (RED) strategy;

- The existence of a strong outreach system, which forms the backbone of the EPI delivery system in rural areas. The system consists of more than 100,000 outreach posts through which routine EPI sessions are given monthly throughout the country by a cadre of health auxiliary workers. The existence of this system avoids the need to establish a new system for community-based cholera vaccination campaigns or new vaccination sites;

- Extensive experience with mass vaccination and health campaigns, including 18 NIDs, national measles vaccination catch-up and follow-up campaigns, and twice-yearly campaigns to provide vitamin A and deworming medicine to children nation-wide. The country has an infrastructure in place for vaccination campaigns, including NID sites, a cadre of volunteers, and strong social mobilization capacity (including widespread media and cell phone coverage for SMS messaging);

- A strong urban NGO-run immunization program, which has achieved coverage rates similar to those of the government-run rural-based system, and which is reportedly used by all but the very wealthy;

- A strong record in reducing drop-out rates for EPI vaccines (down to 2% for the first to the third dose of DPT), thus indicating that high coverage with the two-dose oral cholera vaccine could be achieved;

- Experience using schools as vaccination points for the NIDs and measles catch-up campaigns, in collaboration between the ministries of health and education. This is relevant since schools may be an appropriate vehicle for cholera vaccination for school-aged children;
• Proven ability to be able to reach adults with vaccination — both through routine immunization and geographically-targeted campaigns — as shown by the EPI’s success in eliminating neonatal tetanus through vaccination of women, as well as children.

9.5 How cholera vaccines could be used in Bangladesh

- Interest among health policymakers in Bangladesh to control cholera, including through vaccination, has increased considerably in recent years, prompted by recent large-scale flood-related outbreaks, the apparent spread of the disease to new areas, and evidence from ICDDR,B of increased incidence and severity of the disease. The appearance onto the market of a lower-cost vaccine (Shanchol™), developed specifically for use in developing countries, has contributed to this interest.

- This interest has been manifested by the Government’s collaboration on a cholera vaccine feasibility study that began in 2010 in a large low-income area of Dhaka, and by its submission to the WHO Executive Board of a draft resolution calling for an intensified global response to cholera, including the use of oral cholera vaccines, which was ratified by the World Health Assembly in 2011.

- The possibility of local production of the WC vaccine by private manufacturers has also piqued government interest in exploring cholera vaccination in the country.

- Strategies for cholera vaccination that policymakers interviewed for this study were most interested in include: 1) geographically targeting cholera vaccination to high-risk areas and not throughout the country; 2) phasing in vaccination, starting with the slums of Dhaka; 3) vaccinating all ages, including adults, but focusing on children if funds are limited; 4) piggybacking cholera vaccination with other immunization or health campaigns as much as possible (e.g., NIDs, semi-annual vitamin A/deworming campaigns); 5) combining cholera vaccination with other measures, such as hand washing promotion, improvements in water and sanitation, and breastfeeding promotion, for an integrated approach towards cholera prevention and control; and 6) vaccinating preemptively to prevent the spread of outbreaks, which would target all ages in the vicinity of an outbreak.

9.6 Challenges to implementing cholera vaccination in Bangladesh

- Ideally, areas to be targeted for cholera vaccination should be identified through laboratory-based surveillance. Until such a system is established, areas can be targeted for vaccination based on living conditions (e.g., slums) and epidemiological data and analyses, such as the disease burden analysis presented in this report and routine diarrheal disease statistics.

- There are challenges during cholera outbreaks in deciding if, when, and where to vaccinate preemptively to halt the spread of the disease. In addition, vaccination following cyclones or floods poses logistical challenges, especially when critical needs such as food, water, and shelter must also be provided.

- If the Government decides to vaccinate all ages in targeted areas, achieving high coverage among older children and adults (especially men) may prove challenging,
since the national immunization program has thus far been limited to young children and women. It will especially be important to vaccinate adults to control or prevent outbreaks.

- Securing financing for a cholera vaccination program will also be challenging, especially if the GAVI Alliance decides not to support the introduction of cholera vaccines (see Financing below).

9.7 The projected impact, cost, and cost-effectiveness of cholera vaccination in Bangladesh

- The study analyzed two scenarios for targeting cholera vaccination geographically: one involving vaccinating throughout the 28 high-risk districts identified in the disease burden analysis (Large Target scenario), consisting of around half of the population; and one limiting the program to urban slums and rural populations without access to an improved water supply (Small Target), comprising around 35% of the population in the high-risk districts and 18% of the nation’s population. Two age group options were examined for each scenario — all ages one year and above, and children age 1-14 years old only.

- The analyses assume use of the WC (Shanchol™) vaccine, which is currently sold at a public sector price of $1.85/dose. We further assume that economies of scale may reduce the long-term price to $1.45/dose ($1.67 with shipping and handling factored in). Vaccination would take place each year in one-third of targeted areas and would be repeated every three years (based on a duration of protection of three years). The analyses also assume coverage rates of 75% for 1-14 year olds and 50% for persons 15 and older, a vaccine efficacy rate of 70% for three years, and herd protection from the vaccine using dynamic model estimates that were calibrated with data from a re-analysis of the results of the original clinical trial of oral killed cholera vaccines in Matlab.

- Under the Large Target scenario — vaccinating throughout 28 high-risk districts — a program for children 1-14 years old would vaccinate around six million persons a year, cost around $28 - 34 million per year (depending on vaccine price), save $2.6 million per year in cost-of-illness, prevent 154,000 cases each year (=2.4 million from 2015 to 2030), and =36,000 deaths over this time period, reducing the national cholera incidence by 43%. This program would be “very cost-effective” (cost/DALY averted of $350 - $430), using the WHO definition of cost/DALY averted is less than the country’s GDP per capita. Vaccinating all persons one year and older under the Large Target scenario would increase the numbers of persons vaccinated each year to just under 16 million, cost around $73 - $88 million per year, save $3.4 million in cost-of-illness, prevent 194,000 cases and 2,900 deaths each year — reducing cholera incidence by 54%. Over the 16-year period from 2015 to 2030, this program would prevent 3.1 million cases and 46,000 deaths. This option is less cost-effective than the children’s only program (with a cost/DALY averted of $760 - $930), but would meet the WHO definition of “cost-effective” (cost/DALY averted is ≤3 times the GDP/capita).

- Under the Small Target scenario — limited to urban slums and areas with poor access to safe water supplies in high-risk districts — a program for 1-14 year olds would vaccinate 2.1 million children per year, cost around $10 - $12 million, and save
$900,000 a year in cost-of-illness. It would also reduce incidence by 54,000 cases per year or around 850,000 over 16 years — a 15% reduction in incidence overall, and would also be “very cost-effective”. Adding adults (15 and older) to this scenario would increase the numbers to be vaccinated each year to 5.5 million, increase the cost of the program to $26 - 32 million, and prevent an additional 14,000 cases per year — or 68,000 per year total, for a 19% reduction in overall incidence. This Small Target program for all ages would be “cost-effective”, but not “very cost-effective”.

- These results suggest that the greatest declines in incidence and the greatest efficiencies would be realized by vaccinating children in as many communities as possible within high-risk districts (i.e., the Large Target scenario), rather than limiting the geographic scope of the program in order to vaccinate both children and adults.

9.8 Financing of cholera vaccination

- The financing requirements for the EPI in 2010 are around $97 million per year. Implementing cholera vaccination through the EPI would increase the total costs of the program by 10-12% for the children’s-only Small Target option; by 26-34% for either the children’s only Large Target option or the all-ages Small Target option; and by 75-91% if all ages are vaccinated under the Large Target scenario.

- Financing for cholera vaccination could come from current funding sources of the EPI, which include: a) pooled funds from donors and the Government through the World Bank-managed HNPSP Program (which currently pays for all vaccines except the GAVI-supported pentavalent); b) the MOHFW’s Revenue Budget, which covers operational expenses of the EPI; and c) the GAVI Alliance, which is financing health service strengthening and the pentavalent vaccine, if GAVI decides to include cholera vaccine in its portfolio.

- Alternative sources of financing that could be considered for cholera vaccination include funding from donor-supported projects to mitigate the impact of climate change (currently under development), and private industry, such as the seafood industry.
References


Government of Bangladesh, Department of Fisheries Brochure, 2009.


Harmeling W. Global climate risk index 2010: who is most vulnerable? Weather-related loss events since 1990 and how Copenhagen needs to respond. GermanWatch Briefing Paper, Bonn, Germany, December 2009.


Appendices

1. Contact list for the Bangladesh country case study team visit, December 1-11, 2009

2. Question guide for the Bangladesh country case study on cholera vaccination

3. Additional information on cholera disease burden in Bangladesh

4. Sheet for ranking perceived importance of infectious diseases given to informants

5. Additional information on the EPI in Bangladesh

6. Additional information on cholera vaccines

7. Key assumptions and parameters used in the analyses by age group

8. Technical details for cost-effectiveness analysis
Appendix 1. Contact list for the Bangladesh country case study visit, December 1-11, 2009

Ministry of Health & Family Welfare
Prof. A.F.M. Ruhal Haque, Minister, Ministry of Health & Family Welfare
Dr. Mozibur Rahman Fakir, State Minister
Mr. Shaikh Altarf Ali, Secretary
Prof. Shah Monir Hossain, Director General of Health Services
Dr. Syed Umar Khuyam, Joint Secretary (Public Health & WHO)
Dr. Mahamadur Rahman, Director, Institute of Epidemiology, Disease Control and Research (IEDCR)
Dr. Baranda Nath Mandol, Director, Primary Health Care and Line Director, Essential Services Delivery
Dr. A. B. M. Jahangir Alam, ex-Director, Primary Health Care and Line Director, Essential Services Delivery
Dr. Abdul Lalil Mandol, Program Manager, EPI
Dr. Narendra Nath Dewri, Civil Surgeon, Dhaka
Dr. Mia Belayet Hossain, Director, Disease Control
Brigadier General Dr. Md. Ismail Hossain, Director General of Drug Administration
Khandaker Sagir Ahmed, Superintendent of Drugs
Md. Abdul Mannan, Joint Chief, Planning
Dr. Nasreen Khan, Medical Officer, Management Information Systems

Ministry of Local Government, Rural Development and Cooperatives
Dr. Prasanta Bhusan Barua, Joint Secretary (Development)

Dhaka City Corporation
Brigadier General (Dr.) Md. Showkat Ali, Chief Health Officer
Dr. Md. Nurul Islam, Deputy Chief Health Officer

Ministry of Education
Nurul Hoque Mazumder, Chief, Planning

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Dr. Md. Shahadat Hossain, Head, Longer Stay Unit
Dr. Md. Anowar Hossain, Head, Clinical Laboratory Services
Dr. Hubert Endtz, Director, Laboratory Sciences Division
Dr. Pradip Kumar Bardhan, Head, Special Care Unit
Dr. Ziaul Islam, Associate Scientist, Health Systems & Economics Unit
Dr. Firdausi Qadri, Senior Scientist, Immunology
Dr. Peter Kim Streatfield, Head, Population Programme and Head, Health and Demographic Surveillance Unit, Public Health Sciences Division
Dr. Iqbal Ansary Khan
Dr. Md. Sirajul Islam, Head, Environmental Microbiology, Laboratory Sciences Division
Dr. Zahid Hayat Mahmud, Associate Scientist, Environmental Microbiology Laboratory
Dr. A. K. Siddique, Consultant Epidemiologist
Dr. Md. Jasim Uddin, Associate Scientist, Health Systems and Infectious Diseases
Dr. ASG Faruque, Scientist, Clinical Sciences Division
Dr. Mohuil Chowdhury, Senior Research Investigator, Immunology Unit, Laboratory Sciences Division

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World Bank
Tania Dmytraczenko, Senior Health Economist

UNICEF
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Dr. Jucy Merina Adhikari, Immunization Officer, Health and Nutrition Section

Bangladesh Perinatal Society
Prof. T A Chowdhury, Member of the Board of Trustees

Bangladesh Pharmaceutical Association
Mr. Abdul Muktadir, Secretary General and Managing Director, Incepta Pharmaceuticals Ltd.

NGOs
Dr. S. M. Mohiuddin Kamal, Executive Director, Radda, MCH-FP Centre
Appendix 2. Question guide for the Bangladesh country case study on cholera vaccination

A. Questions for MOH officials and policymakers

Perceptions/views regarding cholera:

- Does the MOH have an official list of priority diseases?
- If so, is acute watery diarrhea or cholera on the list and where does it rank?
- In your personal view, where does cholera rank as a priority in Bangladesh? (fill out the ranking sheet please.)
- Is the priority or attitude towards cholera within the government changing and if so, how (e.g., since the last policymaker survey in 2001)?
- Ask about reporting cholera to WHO and if that will be happening now (and when) and why the policy is changing. Is it because of the new IHRs (International Health Regulations) that went into effect in 2007?\(^{20}\)
- Does the disease reporting system differentiate cholera from other causes of acute watery diarrhea (AWD)?
- Do you know the approximate disease burden (e.g., incidence rate or number of cases annually) of cholera in Bangladesh? What data do you have? (breakdown by region or province?) What’s the average case fatality rate (CFR)?
- Is cholera everywhere in the country or in certain areas only?
- Is the disease burden mainly from endemic (continual) disease or from seasonal or periodic outbreaks or both? If both, which pattern is responsible for the most of the disease burden, in your view or based on the available data?

Current diarrheal/cholera control measures and programs (facts and views):

- Can you describe the current prevention and control programs (in more detail for certain people, less for top policymakers):
  - Prevention:
    - Water and sanitation improvements, including point-of-use (POU) programs
    - Zinc supplementation
    - Health education, other
  - Treatment:

\(^{20}\) Claire-Lise Chaingnat reported at the Annecy meeting that Bangladesh will start reporting cholera to WHO next year, apparently.
• ICMI or case management
• ORS: ask about use in Bangladesh, how prevalent, types of ORT used (home-made solutions vs. ORS packets, rice-based solutions, etc) and changes in ORS use over time
• IV rehydration treatment in the urban and rural areas: how available and adequate is it, especially in peripheral areas?
• Zinc supplements for treatment
• Antibiotic use and antibiotic resistance trends and patterns

- What are your views on the adequacy of each of these measures, both in rural and urban areas, especially for the control of cholera?

**Views about vaccination against cholera:**

- Review the current cholera vaccines with them (using the cholera vaccine factsheet) and ask their opinions about them.

- Would the government (MOHFW) be interested in vaccination against cholera as an additional cholera control measure? Why/why not?

- If so, ask about vaccination strategies they think would be appropriate for Bangladesh (e.g., geographic targeting vs. universal vaccination; age groups to target; mass campaigns vs. routine vaccination, etc. - see list under EPI program interviews, but go into less detail).

- Is there a strong health NGO presence in the country that may be interested in deploying vaccines? Can private doctors or clinics play a role in vaccination?

- How would you integrate cholera vaccination into the current immunization program (e.g., part of EPI as routine to 2-5 year olds, school-based vaccination, etc.)

**Decision-making process for new vaccines and centers of influence:**

- What is the current process for decision-making regarding the introduction of new vaccines?

- How are demands for the introduction of improvement in the diagnosis and treatment of communicable diseases balanced with the demands for non-communicable diseases (NCD’s)? Is there an explicit mechanism for decision making?

- Is there an overall health strategy which deals with NCD’s and communicable diseases which refers to such mechanism?

- Ask about the new technical vaccine advisory group: its name, whether it’s functioning. Have they made any major recommendations to the EPI yet (which ones?) and its influence/clout in policy decisions.

- Who are other key players and centers of influence regarding vaccination policy? Do you think the Min. of Econ & Trade would play a role in the decision process, i.e. would he be interested and push for it?
What criteria would be critical to them in deciding about the use of an oral cholera vaccine (in terms of safety, efficacy, minimum age of use, number of doses, maximum cost, donor funding, cold chain and storage requirements, etc.)?

(Review tables on vaccine fact sheet with them): Do the current vaccines meet your requirements or the criteria of the government? How/how not?

What types of data are important/less important now in informing decisions regarding new vaccines in Bangladesh, e.g.:
- Disease burden data: need country-wide estimates or would site-specific data from high-risk areas be sufficient? Are there sufficient data now in Bangladesh to make a decision? Need breakdown of data in wealth categories?
- Vaccine efficacy or field effectiveness (e.g., from other countries)?
- Local data on vaccine safety, immune response in local population, feasibility, and population acceptance/demand (which ones)?
- Estimates of impact and cost-effectiveness/cost savings?
- Resource use, other than finance, e.g. health staff, management, transport, cold chain requirements?

What local studies would be required before a cholera vaccine could be introduced into the public sector in Bangladesh? Ask about the vaccine demonstration project that’s being planned in Dhaka with ICDDR,B and whether this will be sufficient.

Would a local champion be required to get a cholera vaccine included in the EPI program and would such a person exist in Bangladesh?

Ask about the process for the decision to introduce pentavalent vaccine, if time and depending on the person interviews.

Are cholera vaccines available in your country? (Directorate of Drug Administration or NDRA)

Does your country have pricing control regulations on drugs/vaccines? (specify whether mean taxes or other types of regulations)

Does your country impose import taxes and custom duties on vaccines or drugs?

Does your government have regulations about price markups and/or maximum price levels for vaccines or drugs?

**Health systems aspects**

- Has the country actually received support for the implementation of its 2008 proposal to GAVI for the strengthening of its health system, started to implement this and evaluated its impact on vaccination and immunization rates?
- Any immunization related support from other development partners or technical agencies?
Does measurement of effectiveness of health education take place, especially as regards infectious disease prevention and vaccine awareness among the target population?

What would be the greatest barriers or constraints to the public sector introduction and use of cholera vaccines and how could they be overcome? E.g.:

- The vaccines can’t be given until the age of 1 or 2 years old (depending on the vaccine): how would you reach children 1-15 years old?
- Has school-based vaccination ever been done in Bangladesh (e.g., measles SIAs)? (Ask specifically about the switch from TT to Td using school-based vaccination as planned in the cMYP)
- How would you reach adults?
- How would you reach the poorer categories of the population?
- How feasible are community-based campaigns in Bangladesh for vaccines other than polio?
- Financial resources?
- Human resources?
- Leadership & management capacity?
- Communication infrastructure (media etc)?
- Decentralization (potentially impeding priority setting, management capacity, and funding)?
- Budget volatility (impact of international financial crisis)?
- Regulatory capacity and requirements?
- Vaccine quality surveillance and control
- Health management information system capacity (personnel number & skills; hardware and connectivity)?
- Coordination among development partners?
- Procurement regulation?
- Transport infrastructure?
- Climate and regular blocking of transport routes?
- Political strife
- Vertical program (no integration of vaccination in mainstream health care)?
- Cultural/religious factors?
- Regulation and commitment of private health sector?

B. More detailed questions to ask surveillance officials (in addition to questions above regarding cholera disease and control measures)

- Ask about diarrheal disease surveillance:
  - Is there a diarrheal disease surveillance system in the country? Describe the surveillance system and its effectiveness (timely, complete, and reliable reporting system)?
  - Are standard operating procedures available for bacterial disease surveillance including reagents and equipment?
  - Routine reporting system (ask to see forms used)
  - Any sentinel site surveillance (e.g., continuation of ICDDR,B work in 4 rural areas)?
- Which types of facilities perform lab tests to identify etiology of diarrheal diseases? Ask about the distribution of labs. What percent of cases are tested, in their estimation?

- Does a mechanism for quality control of labs exist? (is there a national reference lab?)

- Is there a system of outbreak investigation for infectious diseases? For diarrheal diseases specifically? Ask them to describe (e.g., who gets reports and how, who investigates, type of investigation done, control measures they take, etc.). Ask them to describe a recent outbreak investigation.

- Try to gather as much available data on cholera/AWD as possible from routine reporting system and any studies.

- Is the risk of cholera similar throughout the country or are there high-risk and lower-risk areas? Where are they?

- Is the disease burden mainly from endemic (continual) disease or from seasonal or periodic outbreaks or both? If both, which pattern is most responsible for the disease burden, in your view or from the data?

- Ask about antibiotic resistance: prevalence, trends, and who will know more about this.

- How can cholera surveillance be improved in their opinion? Ask about:
  - Type of surveillance: sentinel sites vs. strengthening routine disease reporting
  - Outcome to measure: syndromic, clinical diagnosis, or lab-confirmed disease?
  - If sentinel surveillance, where would you set up sites?
  - What surveillance could you do to measure impact of vaccination?
  - Is there a plan to improve diarrheal disease surveillance and what does that look like, including implementation & financing?
  - What organizations/institutes should do any enhanced surveillance and how could it be funded?

C. Questions for EPI policymakers and staff (EPI manager, Line Director for ESP, etc.)

Update on the EPI Program:

- Ask about the major goals and objectives of the EPI at present (get current EPI plan if one exists). What are the top priorities of the program?

- Major programs and efforts: ask about progress to date, low- and high-performing areas, efforts to improve, and priorities for initiatives, such as:
  - measles elimination
  - RED (Reach Every District)
  - immunization program strengthening (e.g., with GAVI ISS money)
  - Hib/pentavalent introduction
  - health services strengthening (HSS) with GAVI or other support
  - other initiatives.
Current coverage and equity: reaching all areas and all wealth categories?
Are vital statistics reliable as basis for the calculation of coverage rates?
Current coverage: adherence to vaccination schedules and timeliness of vaccinations?
  o % of FIC’s at 1 year of age and at later ages?
Quality control mechanisms?
Constraints for implementation of programs and reasons for missing set targets?

History of the introduction of pentavalent vaccine (with Hib):
  o How was the decision made: New vaccine advisory committee involved? What factors led to the decision? What data were critical to the decision? Who were the key decision-makers?
  o When was it introduced?
  o How long did the decision process take? (related to availability of GAVI financing)
  o Was Hib introduction phased in or done all at once? How long did it take to cover the target population and what immunization rate is achieved?
  o If phased in, how were the first areas chosen (based on EPI performance and local capacity?)?
  o What hurdles did the program meet? (Distinguish between program related factors and general health system issues.)

Ask about their plans and goals for the EPI for the next five years or so:
  o Any other vaccines they want to introduce?
  o Other changes/improvements to the program (e.g., in infant EPI schedule, booster doses after infancy, increasing coverage especially among the poor etc.)?

Any experience with school-based vaccination in Bangladesh (e.g., measles SIAs)? If so, get information on which vaccines, when, where, etc.

Would you anticipate that a program that also targeted older children (besides infants) would be more expensive than traditional vaccination? Would it be less expensive to provide vaccinations through schools?

Any experience with mass vaccination campaigns apart from polio NIDs (or SNIDs)? For what vaccines?

Decision-making and the new immunization technical advisory group: Ask about:
  o how the group is functioning;
  o number of members and the composition;
  o the importance of their recommendations in setting policy and whether all new EPI initiatives must first be recommended by the committee;
  o process they use for making a recommendation, including data requirements.

**EPI cost and financing questions:**

Has your country estimated the cost of EPI vaccine delivery for routine and campaigns (only for routine or also for campaigns and other delivery strategies)?
Do you know the per capita cost for service delivery (excluding vaccine and syringe costs)? If so, what is it?
- per capita cost in $................. for routine
- per capita cost in $................. for campaigns
- per capita cost in $................. for polio campaigns

What’s the current EPI budget? Breakdown by line item (% vaccines). Breakdown of vaccine budget by vaccine

If EPI was considering introducing a new vaccine, is there a calculation on cost of introducing new vaccine (re # people targeted, # of doses required, wastage rate assumption, price estimate, cold chain requirements etc.)?

What funding strategies would be considered: (GAVI, Other donor financing? User fees? Ministry of Health funds? Other?)

Does your country receive non-GAVI financial assistance to cover the cost of NIP vaccines?

What is the vaccine wastage rate for polio in your country?

Has your country taken steps to reduce vaccine wastage rates?

Does the EPI department participate in the medium-term planning and budgeting exercise/annual budget and planning exercise with the MOH?

Do provincial/district health officers participate in the annual budget and planning exercise for the EPI program with the national EPI office?

What percentage of the government health budget is allocated to the immunization program?

**Data needs for introducing a new vaccine:**

What data does the MOH or advisory committee now require before a new vaccine can be introduced through the EPI? Probe:
- Require local disease burden estimates? What type of data is sufficient (e.g., routine reports vs. prospective population-based studies vs. data from sentinel site surveillance)?
- Need estimate of mortality or case fatality rates?
- Require local data on safety and immunogenicity?
- Data requirements re vaccine efficacy and effectiveness (data from the literature and from other countries sufficient? Need at least regional data?)
- Cost-effectiveness or other economic analyses?
- On-going studies to determine the impact on disease, hospitalization rates, etc.?

Ask about data requirements for Hib introduction and how the impact of Hib vaccination is being measured, if at all (if not already asked above).
Views regarding cholera vaccination in Bangladesh:

- Ask about major strategies to prevent and control cholera (see questions for MOHFW officials above).
- How adequate are these measures in their opinion?
- Do you think there’s a role for a cholera vaccine in Bangladesh? Why/why not?
- What criteria or conditions would a cholera vaccine need to meet before it would be approved for introduction into the EPI, in terms of:
  - Number of doses for primary immunization
  - Safety: would study being done in Dhaka with IDCCR,B be sufficient?
  - Minimum acceptable efficacy rate
  - Minimum age at which the vaccine can be administered
  - Minimum acceptable duration of protection and frequency of booster doses
  - Minimum heat stability/cold chain requirements
  - Maximum cost per series
  - Liquid vs. lyophized?
  - Must be funded through GAVI or another donor?
- Review with them key information about cholera vaccines (currently available and ones under development), using the vaccine factsheet. Do the currently available vaccines meet your requirements? How/how not for each vaccine?
- What specific studies, if any, beyond the demonstration being conducted by IDCCR,B do you think would be required for Shanchol or Dukoral, in order for the MOHFW to make a decision about their introduction? (e.g.,:
  - Study of feasibility, e.g., through a demonstration project, since the vaccination could require mass campaigns and involve older children and adults?
  - Study of demand for the vaccine since older children and adults may be targeted?
  - Other?

Possible cholera vaccination strategies appropriate for Bangladesh:

- Would their primary interest for using cholera vaccines be to control endemic cholera, control/prevent outbreaks, or both?
- Would they target all areas of the country for vaccination or certain areas only? If the latter, how would they define and identify high-risk areas?
- Would they likely phase in vaccination by area?
- What ages and other high-risk groups would they target? Children only? Pregnant women? Other adults?
- Vaccination delivery strategies: would they suggest routine or mass campaigns; school- or community-based campaigns, etc.?

- What types of social mobilization activities would have to be conducted to promote cholera vaccination? Does the capacity for such activities exist?

- What groups would be involved in the delivery of the vaccine? Would NGOs or the private sector have a possible role? Which NGOs?

- How often would they revaccinate, given health system capacity and cost considerations?

- Ask about idea of combining vaccination with other prevention/control measures - which ones? How?

- How could the vaccination be financed? Would they consider it if GAVI doesn’t support cholera vaccination? Could the government add the financial requirements to their EPI budget? Alternative or complementary sources of funding (e.g., donor funding, NGO assistance, financing from fishermen’s cooperatives or other such organizations)?

**Possible financing strategies for cholera vaccination:**

- Once the OCV is available, would the government encourage the private sector to provide cholera vaccines?

- Would the government encourage the private sector to participate (as public-private partnership) within the public sector programs in providing cholera vaccines?

- Would the government consider charging users for cholera vaccines in the public sector?

- Would you consider giving cholera vaccines to the private sector and asking them not to charge for delivering the vaccines?

- Is the cholera vaccine available at the private pharmacies? (check at pharmacies first and determine which one is available)

- **GAVI related questions:**
  - Has a request to GAVI ever been refused or been in need of further clarification? If so, for what reasons?
  - How long does it take on average to prepare a GAVI request and to get a decision, respectively the funds transferred to Bangladesh accounts?
  - Examine GAVI applications to report the number of GAVI financed vaccines incorporated into the national vaccination schedule. (lit review)

- (Provide table comparing Dukoral and Shanchol vaccine characteristics). Assuming external financial assistance is NOT available, which cholera vaccine would your country most likely procure for vaccination program?
Assuming external financial assistance is available and that the copay is US$0.10, which cholera vaccine would your country most likely procure for vaccination program?

Would your country be willing to purchase cholera vaccines from a producer stockpile in the event of a severe outbreak WITHOUT financial assistance?

Which cholera vaccine is your country most likely to procure for an outbreak control program?

Would your country be willing to deliver cholera vaccines in the event of a severe outbreak if a cholera vaccine stockpile were available at a subsidized price?

If no, would you consider implementing an outbreak control if vaccines are provided for free and delivery costs are partially subsidized?

Requirements and challenges for cholera vaccine introduction and how they can be addressed:

How would the EPI have to prepare for cholera vaccine introduction in terms of:

- Training needs: need to prepare guidelines or other written documents? What type of training would be required, how long would it take (ask about training for pentavalent introduction);

- Cold chain, transport, and storage needs: could current transport and cold chain capacity handle this vaccine:
  - Have you faced any vaccine shortages or interruptions in supply?
  - How do you distribute vaccines throughout the country?
  - Have you faced any vaccine shortages due to distribution problems?
  - Have you faced any problems with stock management?

- Implementing mass campaigns:
  - Could they build upon experience with polio campaigns or SIAs for measles, MNT, others?
  - How would they achieve high coverage among older children and adults of all wealth categories?
  - Ask about their MNT program and TT coverage rates among women, and any lessons learned that can be applied to cholera vaccination.

- School-based vaccination:
  - Would this be feasible? Would it present a big challenge? (any gender issues?)
  - Has it been done before (e.g., for measles)?
  - Is there an existing agreement between the health and education ministries for school-based health activities? Would such an agreement be needed for cholera vaccination?
  - How would children not in school be reached?

- Regulatory requirements: (how long and what is required to get a new vaccine licensed? If it’s licensed first in the private sector, are there additional requirements for public sector use?)
• **Procurement:** what procurement method would be used and how long would procurement take? (e.g. via UNICEF?)

**D. Questions for Dhaka City Corporation:**

• Ask about their immunization program, cities they cover, coverage rates and progress, pentavalent introduction, etc.

• Would cholera vaccination be popular in the cities?

• What ages could realistically be reached? Have they done any adult vaccination programs (e.g., MNT)? How successful have they been and what coverage rates have been achieved?

• How would they go about delivering an oral cholera vaccine (e.g., mass campaigns?) and what venues would be good?

• Would they expect to get the vaccine from the government or try to get a donor such as the Asian Development Bank to finance the vaccine?

• What types of public awareness campaigns and messages would they use to draw people to get vaccinated? What media would they use?

• Can private health care providers play a role, including the for-profit ones? If so, which?

• What other interventions/materials should accompany the vaccination (e.g., health education talks or materials; POU supplies such as chlorine tablets and safe water storage containers (could sell?)?  

• What challenges do they foresee for the introduction of a new vaccine?

**E. NGOs and professional associations:**

• Bangladesh Pediatric Association and  
  o Involvement in immunization policy development and implementation?  
  o View on health system factors, influencing vaccine adoption and uptake by target population?

• Bangladesh Pharmaceutical Association (dependent of their eventual role in distribution)  
  o Involvement in immunization policy development and implementation?  
  o View on health systems factors?  
  o Distribution issues

• Local charities or not for profit NGO’s involved in health services delivery  
  o Involvement in diarrheal disease control and in vaccination?  
  o Health systems issues?
F. NGOs that treat cholera including ICDDR,B, CARE, and others. These may also be presented to public treatment facilities.

- Where are cholera patients most likely to go for treatment? (self care/home? public clinic/hospital facilities? private clinic/hospital facilities? pharmacy? traditional healers? other?)

- What percentage of cholera patients are likely to go for treatment at a public health facility?

- What percentage of cholera patients are likely to go for treatment at a private health facility?

- In your opinion, do cholera patients (acute watery diarrhea) go to clinics for treatment?

- What is the source of this information about health-seeking practices? (community surveillance system? sentinel sites? periodic surveys (e.g. demographic health survey)? public sector clinical reporting system? public and private clinical reporting system? ad hoc or unknown?)

- Are children under 5 suffering from cholera, more or less likely to go to clinics, as compared to those above 15-years old?

- In your opinion, do cholera patients (acute watery diarrhea) get hospitalized for treatment?

- What % of cholera patients do you estimate are hospitalized for treatment?

- What is the source of this information about hospitalization? (community surveillance system? sentinel sites? periodic surveys (e.g. demographic health survey)? public sector clinical reporting system? public and private clinical reporting system? ad hoc or unknown?)

- What is the average hospital stay (number of days) per cholera patient?

- Are children under 5 suffering from cholera more likely to be hospitalized as compared to those above 15-years old?

- At what price is ORS available in the public/private facilities (clinics/hospitals)?

- What are the average prices of IV's at public/private health centers and hospitals?

- What is the average price of drugs (to control acute watery diarrhea) at public/private facilities?

- What is the average price of a hospital bed day at public/private hospitals or health centers?
- What are the user fees at public/private clinics for outpatient treatment of acute watery diarrhea?

- What are the average costs for diagnostic tests for acute watery diarrhea?

- What are the average travel times for acute watery diarrhea patients in urban areas and rural areas?

G. UNICEF, WHO, the World Bank and other donors involved in immunization

Lot of the same questions about performance of the current EPI program, feasible strategies for cholera vaccination, EPI program and health system challenges, financing possibilities, etc.

H. Various ministries (including fisheries, economics, agriculture, and tourism)

- Do you think that cholera outbreaks have an effect on the economy in your country?

- If so, how has your economy been affected by cholera outbreaks?

- Have exports of any commodities such as fish been affected by cholera outbreaks? (see tables below)

  **Potential Exports affected by Cholera Outbreaks:**

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- Have trade embargoes ever been placed on fish products or other products from your countries due to cholera?

- Has tourism in your country been affected by cholera outbreaks?

- Do you think that the productivity of the labor force has been affected by cholera outbreaks?

- Do you think that if Bangladesh begins to report its cases of cholera annually to WHO that the economy will be affected?

- Do you think that a cholera vaccine would make a difference to your country’s economic growth?

- Do you think that there could be private sector support for financing of the vaccine for workers in industries affected by cholera?
Appendix 3. Additional information on cholera disease burden in Bangladesh

Table A3.1. Cholera in Bangladesh from published articles, 1985 to 2008

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*Data from [Harris, 2008 #196]; [Hashizume, 2008 #234]; [Sack, 2003 #207]; Siddique, 1992 #225; Siddique, 1994 #222*
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<td>3807</td>
<td>1684</td>
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<td>&lt;2 yrs</td>
<td>16%</td>
<td>&lt;15 yrs</td>
<td>50%</td>
<td>0-4 yrs</td>
<td>8%</td>
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<td>8%</td>
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<td>2 to 4 yrs</td>
<td>21%</td>
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<td>1-2 yrs</td>
<td>8.5%</td>
<td>2 to 4 yrs</td>
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<td>5 to 10 yrs</td>
<td>17%</td>
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<td>3-4 yrs</td>
<td>14.0%</td>
<td>5 to 14 yrs</td>
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<td>10 to 20 yrs</td>
<td>15%</td>
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<td>5-9 yrs</td>
<td>23.1%</td>
<td>5 to 14 yrs</td>
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<td>20 to 60 yrs</td>
<td>27%</td>
<td>15 to 29 yrs</td>
<td>15 to 39 yrs</td>
<td>30.5%</td>
<td>15+ yrs</td>
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<td>60+ yrs</td>
<td>5%</td>
<td>30+ yrs</td>
<td>40+ yrs</td>
<td>10.3%</td>
<td>15+ yrs</td>
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*a* Age distribution from routine surveillance  
*b* Age distribution during outbreaks from 1985-1992 due to *V. cholerae* O1  
*c* Age distribution during outbreak in 1993 due to *V. cholerae* O139  
*d* Age distribution during the 2007 post-flood outbreak due to *V. cholerae* O1
Appendix 4. Sheet for ranking perceived importance of infectious diseases given to informants

Please put a number next to the disease to show how you would rank them in order of importance as a disease that needs to be controlled in your country. Number 1 would be your greatest priority, #2 your second, etc. Just rank the top 10. Thank you very much!

___  HIV/AIDS
___  Malaria
___  Pneumonia (caused by Hib, pneumoccocal disease, meningococcal disease, etc.)
___  Meningitis (caused by Hib, pneumoccocal disease, meningococcal disease, etc.)
___  Tuberculosis
___  Rotavirus diarrhea
___  Cholera
___  Other diarrheal diseases (e.g., dysentery)
___  Japanese encephalitis
___  Dengue fever
___  Typhoid fever
___  Hepatitis (specific which types): ________________________________
___  Influenza (pandemic or seasonal)
___  Rabies
___  HPV (cervical cancer)
___  Leprosy
___  Filariasis
___  Other (please specify): ________________________________
Appendix 5. Additional information on the EPI in Bangladesh

Trends in national vaccination dropout rates for DPT1-DPT3 and DPT1- measles among 12-23 month old children from 1992 to 2009

Source: Coverage Evaluation Survey 2009
Appendix 6. Additional information on cholera vaccines

Composition of killed whole-cell based oral cholera vaccines:

<table>
<thead>
<tr>
<th>Element/Strain</th>
<th>WC-rBS (Dukoral®)</th>
<th>Original Vietnamese WC vaccine (ORCVax®)</th>
<th>Modified WC vaccine (Shanchol™)</th>
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<tr>
<td>O1 strains:</td>
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<tr>
<td>• El Tor Inaba (Phil 6973), formalin-killed</td>
<td>2.5 x 10^{10} cells</td>
<td>5 x 10^{10} cells</td>
<td>600 EU LPS</td>
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<tr>
<td>• Classical Ogawa (Cairo 50), heat-killed</td>
<td>2.5 x 10^{10} cells</td>
<td>2.5 x 10^{10} cells</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>• Classical Ogawa (Cairo 50), formalin-killed</td>
<td>2.5 x 10^{10} cells</td>
<td>---</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>• Classical Inaba (569B), formalin-killed</td>
<td>---</td>
<td>2.5 x 10^{10} cells</td>
<td>---</td>
</tr>
<tr>
<td>• Classical Inaba (Cairo 48), heat-killed</td>
<td>2.5 x 10^{10} cells</td>
<td>---</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>O139 (4260B), formalin-killed</td>
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<td>5 x 10^{10} cells</td>
<td>600 EU LPS</td>
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<tr>
<td>Recombinant cholera toxin B subunit</td>
<td>1 mg</td>
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Most advanced cholera vaccine candidates:

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<th>Characteristic</th>
<th>Peru-15</th>
<th>V. cholerae 638</th>
<th>VA1.4</th>
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<tbody>
<tr>
<td>Developer</td>
<td>Harvard University</td>
<td>Finlay Institute, Cuba</td>
<td>3 Indian government research laboratories</td>
</tr>
<tr>
<td>Producer</td>
<td>VTI, U.S. and China</td>
<td>Finlay Institute, Cuba</td>
<td>Shantha Biotechnics, Hyderabad, India (contract manufacturer)</td>
</tr>
<tr>
<td>Vaccine type/composition</td>
<td>Live attenuated O1 El Tor Inaba (C6709) with deletion of entire cholera toxin genetic element and engineered to be non-motile and non-recombinational</td>
<td>Live attenuated O1 El Tor Ogawa (C7258) with deletion of entire cholera toxin genetic element (CTXΦ) and modification of the hapa gene</td>
<td>Live attenuated non-toxigenic O1 El Tor Inaba strain (devoid of CTX prophage)</td>
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<tr>
<td>Route of administration</td>
<td>Oral</td>
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<td>Number of doses</td>
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<td>Formulation</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
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<tr>
<td>Need for buffer?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Characteristic</td>
<td>Peru-15</td>
<td>V. cholerae 638</td>
<td>VA1.4</td>
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<td><strong>Target ages</strong></td>
<td>All ages, including infants Potentially (Phase II studies in infants underway)</td>
<td>All ages, including infants</td>
<td>All ages, including infants</td>
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<tr>
<td><strong>Cold chain requirements</strong></td>
<td>Must be kept frozen at -20°C</td>
<td>Must be kept frozen at -20°C (can be kept for 3 months at 2-8°C)</td>
<td>Must be kept frozen at -20°C</td>
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<tr>
<td><strong>Status of development and human testing</strong></td>
<td>Phase I/II trials in adults, toddlers, and infants (9 months old) completed in Bangladesh in 2005. Studies underway in 9-12 month-olds when co-administered with measles vaccine in Bangladesh and India and in HIV+ adults in Thailand.</td>
<td>Series of Phase II and challenge studies in adults completed in Cuba. Phase I/II study completed in 2007 in adults in Mozambique. Vaccine will next be tested in children in Phase I/II studies in endemic countries.</td>
<td>Phase I/II study in adult men in Kolkata, India completed for VA1.3 vaccine in 2004. Phase I/II studies of new version (VA1.4) being planned in Kolkata.</td>
</tr>
<tr>
<td><strong>Safety results</strong></td>
<td>No significant differences in rates of side effects between vaccine and placebo recipients. Mild symptoms in 3% of children and 5% of adults vaccinated.</td>
<td>No significant differences in side effects between vaccine and placebo recipients in Mozambique. In Cuba, 75% of vaccinees vs. 18% of placebo recipients had mild adverse events.</td>
<td>Mild adverse events in 3/186 vaccinees (1.6%)</td>
</tr>
<tr>
<td><strong>Vibriocidal seroconversion rates</strong></td>
<td>Adults - 75% 2-5 year olds - 84% 9-23 month olds - 70%</td>
<td>100% in Havana; 97% in Maputo</td>
<td>57%</td>
</tr>
<tr>
<td><strong>Will producer apply for WHO pre-qualification?</strong></td>
<td>Yes, if Phase III clinical trial results are positive.</td>
<td>Yes, if clinical trial results are positive. Vaccine was developed especially for use in cholera-endemic countries in Africa.</td>
<td>Likely, if results of clinical trial are positive.</td>
</tr>
</tbody>
</table>
## Appendix 7: Key assumptions and parameters used in the analyses by age group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age group</th>
<th>&lt;1</th>
<th>1-4</th>
<th>5-14</th>
<th>≥15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual cholera incidence rates (per 1,000) (high-risk areas)</td>
<td></td>
<td>12.1</td>
<td>11.0</td>
<td>3.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Cholera case fatality rate</td>
<td></td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Assumed cholera vaccination coverage rates</td>
<td>NA</td>
<td>75%</td>
<td>75%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Vaccine efficacy (direct protection)</td>
<td>NA</td>
<td>70%</td>
<td>70%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Overall protection of community (with herd effects)*:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vaccination of 1-14 year olds</td>
<td></td>
<td>56%</td>
<td>65%</td>
<td>56%</td>
<td>59%</td>
</tr>
<tr>
<td>- Vaccination of 1+ year olds</td>
<td></td>
<td>73%</td>
<td>78%</td>
<td>74%</td>
<td>76%</td>
</tr>
<tr>
<td>Duration of vaccine protection and frequency of revaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 years</td>
</tr>
<tr>
<td>Vaccine wastage rate†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Vaccine delivery cost per dose, 2010 US$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$0.52</td>
</tr>
<tr>
<td>Cost-of-illness (direct and indirect) (2008 US$)</td>
<td></td>
<td>$15.70</td>
<td>$15.80</td>
<td>$16.30</td>
<td>$20.70</td>
</tr>
<tr>
<td>Duration of illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 days</td>
</tr>
<tr>
<td>DALY weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.105</td>
</tr>
<tr>
<td>Discount rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3%</td>
</tr>
</tbody>
</table>
Appendix 8. Technical details for cost-effectiveness analysis

Explanation of how DALY estimates were derived

The financial cost estimates do not account for the mortality and pain and suffering caused by cholera. Disability adjusted life years (DALY) calculations are standardized to account for these losses and are estimated based on the duration of disease, the case fatality rate, and the expected number of life years remaining for those who die. The number of DALYs lost to cholera are estimated using standard discounting and age weighting following Fox-Rushby and Hanson (2001 #76).

According to the indirect COI surveys, the average duration of cholera symptoms was about 3.5 days; estimates for adults and children were similar. This duration estimate is slightly less than estimates for other countries in the multi-site cholera COI study, which included Kolkata, India, N. Jakarta, Indonesia, and Beira, Mozambique {Poulos, 2008 #1}. We use a slightly higher duration estimate of 5 days because it is likely that the duration is greater for those who do not have access to treatment from ICDDR, B. There is no cholera-specific DALY weight. In the place of a cholera-specific estimate, the DALY weight for all-cause diarrhea is used instead, 0.105 {Mathers, 2005 #57}. This is likely to be an underestimate for severe cholera. The remaining life expectancy by age group is summarized in Table A.8.1 based on standard life tables from WHO.

The average number of DALYs per case varies by age group depending on the remaining life expectancy {WHO, 2006 #58}. The total number of DALYs incorporate both reductions in morbidity (years of life lost to disability, YLD) and mortality (years of life lost, YLL). The numbers of life years saved for each age group are discounted using a 3% real discount rate. The numbers of disability life years lost are equal to the duration of disease multiplied by the DALY weight. The number of discounted life years are calculated from the case fatality rate multiplied by the discounted number of years lost.

\[ YLD_{i} = f(\sum N_{i} \cdot I_{i} \cdot (1 - CFR_{i}) \cdot (1 - w^{DALY})) \]  

\[ YLL_{i} = f(\sum N_{i} \cdot I_{i} \cdot CFR_{i} \cdot \left(1 - e^{-d \cdot LE_{i}}\right)) \]

where \( CFR_{i} \) is the case fatality rate, \( l \) is the disease's average duration, \( d \) is the discount rate and \( N_{i}, I_{i}, \) and \( LE_{i} \) are the population, incidence, and the remaining life expectancy by age group. The function \( f() \) is the standard age weighting function described in Fox-Rushby and Hanson (2001).
Table A.8.1 Parameters used to estimate DALYs

<table>
<thead>
<tr>
<th>Age</th>
<th>0-1</th>
<th>1-4</th>
<th>5-14</th>
<th>15+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case duration, days</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>DALY weight</td>
<td></td>
<td></td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>DALY discount rate</td>
<td></td>
<td></td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Life expectancy, year</td>
<td>81</td>
<td>79</td>
<td>72</td>
<td>46</td>
</tr>
</tbody>
</table>

The total number of DALYs lost are summarized by age and risk group as shown in Table A.8.2, assuming a case fatality rate of 1.5%. While the indirect COI per case is greatest for adults, the number of DALYs lost per case is greatest for children because their expected remaining life years are greater than for adults. In total, about 171,000 DALYs are lost every year in Bangladesh. The numbers of YLL are more than a thousand times greater than YLD across all age groups, indicating that mortality is much more important than morbidity in DALY calculations.

Table A.8.2 Annual estimate of DALYs lost to cholera

<table>
<thead>
<tr>
<th>District type</th>
<th>Age group</th>
<th>YLD</th>
<th>YLL</th>
<th>DALY (best estimate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>All</td>
<td>470</td>
<td>170,219</td>
<td>170,694</td>
</tr>
<tr>
<td>0-1</td>
<td>3</td>
<td>14,184</td>
<td>14,187</td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>64</td>
<td>54,395</td>
<td>54,459</td>
<td></td>
</tr>
<tr>
<td>5-14</td>
<td>136</td>
<td>48,619</td>
<td>48,755</td>
<td></td>
</tr>
<tr>
<td>15+</td>
<td>272</td>
<td>53,021</td>
<td>53,293</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>All</td>
<td>340</td>
<td>122,422</td>
<td>122,763</td>
</tr>
<tr>
<td>0-1</td>
<td>2</td>
<td>10,201</td>
<td>10,203</td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>46</td>
<td>39,121</td>
<td>39,167</td>
<td></td>
</tr>
<tr>
<td>5-14</td>
<td>98</td>
<td>34,967</td>
<td>35,065</td>
<td></td>
</tr>
<tr>
<td>15+</td>
<td>195</td>
<td>38,133</td>
<td>38,328</td>
<td></td>
</tr>
<tr>
<td>Mid-High Risk</td>
<td>All</td>
<td>51</td>
<td>18,328</td>
<td>18,379</td>
</tr>
<tr>
<td>0-1</td>
<td>0</td>
<td>1,527</td>
<td>1,527</td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>7</td>
<td>5,857</td>
<td>5,864</td>
<td></td>
</tr>
<tr>
<td>5-14</td>
<td>15</td>
<td>5,235</td>
<td>5,250</td>
<td></td>
</tr>
<tr>
<td>15+</td>
<td>29</td>
<td>5,709</td>
<td>5,738</td>
<td></td>
</tr>
<tr>
<td>Low Risk (Low and No Data)</td>
<td>All</td>
<td>28</td>
<td>29,469</td>
<td>29,552</td>
</tr>
<tr>
<td>0-1</td>
<td>1</td>
<td>2,456</td>
<td>2,457</td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>11</td>
<td>9,417</td>
<td>9,428</td>
<td></td>
</tr>
<tr>
<td>5-14</td>
<td>24</td>
<td>8,417</td>
<td>8,441</td>
<td></td>
</tr>
<tr>
<td>15+</td>
<td>47</td>
<td>9,179</td>
<td>9,226</td>
<td></td>
</tr>
</tbody>
</table>

Cost-effectiveness methodology

An economic analysis of vaccination programs requires a careful accounting of the costs and benefits of vaccination. The costs of a vaccination program include both the price paid to
vaccine suppliers as well as the program implementation costs to pay salaries, transport and store vaccines, and to administer the program. The benefits of vaccination include both improvements in health based on averted illnesses as well as reduced cholera treatment costs. In order to compare cholera vaccination with other potential health investments, cost-effectiveness metrics may be used. These include the cost per case averted, the cost per death averted, or the cost per DALY averted [Jeuland, 2009 #50; Cook, 2008 #70]. Following Jeuland et al. [2010 #67], an important parameter in this calculation is the effectiveness of the vaccination program over time $\text{Eff}_i$:

$$\frac{\Delta \text{Total Cost}}{\Delta \text{DALYs averted}} = \frac{\sum_i N_i \cdot \text{Cov}_i \cdot c - \text{COI}^{\text{averted}}}{\sum_{t=1}^{\text{Dur}} \sum_i f\left((\text{YLL averted}_{i,t} + \text{YLD averted}_{i,t})\right)/(1 + d)^{t-1}}$$

$$\sum_{t=1}^{\text{Dur}} \sum_i \text{Eff}_{i,t} \cdot N_i \cdot I_i \cdot f\left((\text{CFR}_i \cdot (1 - e^{-d \cdot \text{LE}_i})/d + (1 - \text{CFR}_i) \cdot (1 - \text{w}^{\text{DALY}}))\right)/(1 + d)^{t-1},$$

where $\text{YLD averted}_{i,t}$ and $\text{YLL averted}_{i,t}$ are the years of life in disability averted and the years of life lost averted in age group $i$ and year $t$ due to vaccination. $\text{Eff}_{i,t}$ is the effectiveness of the vaccine for group $i$ in year $t$, $\text{LE}_i$, $\text{CFR}_i$, $I_i$ and $N_i$ are the life expectancy, case fatality rate, cholera incidence and number of people in age group $i$, $I_i$ is the average duration of the disease, $\text{Dur}$ is the duration of vaccine effectiveness, $\text{w}^{\text{DALY}}$ is the DALY weight ascribed to cholera, and $d$ is the discount rate. The function $f()$ refers to the standard age-weighting function shown in Fox-Rushby and Hanson (2001). The parameter $c$ is the cost of the vaccine per fully-immunized person, and $\text{COI}^{\text{averted}}$ is the cost of illness averted, which is equal to:

$$\text{COI}^{\text{pub avoided}} = \sum_{t=1}^{\text{Dur}} \sum_i \text{Eff}_{i,t} \cdot N_i \cdot I_i \cdot \text{COI}^{\text{pub}}/(1 + d)^{t-1},$$

where $\text{COI}^{\text{pub}}$ is the public cost of illness per case of cholera in age group $i$. The cost per DALY is calculated from the government perspective (i.e. the net cost of vaccination is the sum of purchase and delivery costs less the projected public COI savings due to vaccination).

Indirect or herd protection effects of cholera vaccination are well documented based on the 1985 oral cholera vaccine trial in Matlab (Ali et al. 2005; Longini et al. 2007). As part of the global investment case for cholera vaccination, a dynamic model of cholera vaccination was undertaken. This model estimates the impact of vaccination to indirectly reduce the spread of cholera within populations by reducing the probability of encountering a cholera-infected individual and reducing the excretion of cholera into public-accessed water sources. The estimation of herd protection depends on both the number of people in each population group as well as group-specific coverage rates. The parameter, $\text{Eff}_{i,t,v}$ is calculated from

$$\text{Eff}_i = \text{Eff}(N_1, ..., N_v, \text{Cov}_1, ..., \text{Cov}_N),$$

where $\text{COV}_i$ is the coverage rate for group $i$.

In summation, the cost-effectiveness of a vaccination program depends on the number of people vaccinated, incidence and case fatality rates, the duration of protection, the public cost per case treated, and the duration and severity of illness.


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