An Investment Case for the Accelerated Introduction of Oral Cholera Vaccines

INTERNATIONAL VACCINE INSTITUTE

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Abbreviations and Acronyms

ADB   Asian Development Bank
ADIP   Accelerated Development and Introduction Plan
AIDS   Acquired Immune Deficiency Syndrome
CE   Cost-effective
CENCOBI   National Center for Control of Medico-Biological Products
CHOICE   WHO CHOosing Interventions that are Cost Effective
CHOVI   Cholera Vaccine Initiative
CFR   Case fatality rate
CIF   Customs, Insurance and Freight
COI   Cost of illness
DALY   Disability-adjusted life year
DHS   Demographic and Health Surveys
DOMI   Diseases of the Most Impoverished
DTP   Diphtheria, tetanus and pertussis vaccine
DVEF   Direct Vaccine Effectiveness
ELISA   Enzyme-linked Immunosorbent assay
EPI   Expanded Programme on Immunization
ETEC   Enterotoxigenic *Escherichia coli*
EU   European Union
FOB   Freight on board
GAVI   Global Alliance for Vaccines and Immunisation
GDP   Gross Domestic Product
GIDEON   Global Infectious Disease and Epidemiology Network
GIVS   Global Immunization Vision and Strategy
GMP   Good Manufacturing Practice
GNP   Gross National Product
HepB   Hepatitis B
Hib   *Haemophilus influenzae* type B
HIV   Human Immune Deficiency Virus
HPV   Human papillomavirus
ICDDR,B   International Centre for Diarrhoeal Disease Research, Bangladesh
ICG   International Coordinating Group
IFFIm   International Finance Facility for Immunisation
IFRC   International Federation of the Red Cross and Red Crescent
IHR   International Health Regulation
IV   Intravenous
IVEF   Indirect Vaccine Effectiveness
IVI   International Vaccine Institute
LPS   Lipopolysaccharide
MCV   Measles-containing vaccine
MMR   Measles, mumps and rubella vaccine
MOH   Ministry of Health
MOHFW   Ministry of Health and Family Welfare
MSF   Médecins Sans Frontières
NGO   Non-governmental organization
NIDs   National Immunization Days, India
NRA   National Regulatory Authority
NTPC   National Thermal Power Corporation, India
OEF   Oxford Economic Forecasting
OPV   Oral polio vaccine

ORS	Oral rehydration solution
ORT	Oral rehydration therapy
OVEF	Overall Vaccine Effectiveness
PAHO	Pan American Health Organization
PIRIs	Periodic Intensive Routine Immunizations
rBS	Recombinant B-subunit of cholera toxin
SAGE	WHO Strategic Advisory Group of Experts
SIA	Supplementary Immunization Activities
TFP	Total Factor Productivity
TT	Tetanus toxoid vaccine
TVEF	Total Vaccine Effectiveness
UN	United Nations
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
US	United States
VTI	Vaccine Technologies, Inc.
WC	Whole-cell (vaccine)
WC-rBS	Whole-cell recombinant B subunit (cholera vaccine)
WER	WHO Weekly Epidemiological Record
WHO	World Health Organization
WTO	World Trade Organization

Abbreviations of WHO Regions

AFR	WHO African Region
AMR	WHO Region of the Americas
EMR	WHO Eastern Mediterranean Region
EUR	WHO European Region
SEAR	WHO South-East Asia Region
WPR	WHO Western Pacific Region

Preface

New WHO recommendations regarding cholera vaccines

The World Health Organization issued a Position Paper on cholera vaccines in March 2010, in which it recommends that "cholera control be a priority in areas where the disease is endemic" and that control measures should include immunization with the currently available oral cholera vaccines, used in conjunction with traditional strategies, such as improvements in water and sanitation [WHO 2010]. WHO also recommended in the Position Paper that "pre-emptive vaccination be considered to prevent potential outbreaks or the spread of current outbreaks to new areas". Targeting vaccination to high-risk areas and population groups in cholera-endemic countries is recommended, as opposed to universal vaccination, since, in most countries, the disease is concentrated in certain areas (e.g., urban slums and rural areas with contaminated bodies of water). While recognizing that all age groups are vulnerable to the disease, the Position Paper recommends pre-school-aged and school-aged children as primary targets for cholera vaccination in endemic countries where resources are limited.

These recommendations were made in response to the growing frequency of large, often protracted cholera epidemics in Sub-Saharan Africa and Asia, including well-publicized outbreaks since 2000 in South Africa, Angola, Afghanistan and Ethiopia, Zimbabwe, and most recently, Haiti. The recommendations were also made in reaction to new data on the persistent problem of endemic cholera, including annual rates of laboratory-confirmed cholera from prospective population-based surveillance ranging from 0.5/1,000 to 4/1,000 in cities and slum areas of Africa and Asia, with infants and toddlers having rates as high as 9/1,000 [Deen et al., 2008].

A further impetus for the new WHO recommendations has been the licensure of a new oral cholera vaccine (Shanchol™) in India in 2009, which has since been pre-qualified by WHO. This vaccine, consisting of killed whole cells of *V. cholerae* O1 and O139, was developed specifically for use in endemic countries. This O1/O139 WC vaccine joins the only other oral cholera vaccine currently on the international market — the WC-rBS vaccine (Dukoral®), which was first licensed in 1991 and is also WHO pre-qualified. Dukoral® is used largely as a traveler's vaccine in developed countries, but mass vaccination campaigns using the vaccine in post-disaster situations and among endemic populations in Asia and Africa have been shown to be feasible (and where it was used in an endemic population in Mozambique, effective as well). While both Shanchol™ and Dukoral® are two-dose killed, whole-cell-based vaccines, the newer Shanchol™ has been shown to provide more sustained protection for at least three years). And because it lacks the cholera toxin component, this "WC only" vaccine does not require administration with a buffer or with water, making if more amenable to use under difficult field conditions in developing countries.

The WHO Strategic Advisory Group of Experts (SAGE), during its meeting in October 2009 at which it endorsed the new recommendations, stressed the need for an investment case for cholera vaccines to give the global health community, vaccine producers, and potential donors an idea of the potential demand for cholera vaccines – if provided through public sector immunization programs − what it would cost to meet this demand, what would be the global impact of vaccination on the disease, and whether it would be cost-effective. This investment case, funded by the Bill & Melinda Gates Foundation, has been designed to meet this request.

This report is intended for the international health community, vaccine manufacturers, prospective donor agencies, and policymakers from cholera-endemic countries.

A challenge to the global health community and an opportunity for vaccine producers

Developing a forecast of the demand for cholera vaccines provided through public sector programs in cholera-affected countries is especially critical to encourage existing producers to invest in increasing their cholera vaccine production capacity, as well as new manufacturers to acquire the technology to produce the vaccine. At present, the demand for oral cholera vaccines has been too uncertain for producers to invest in substantially increasing their production capacity beyond current low levels. This situation has created a "vicious circle" that has in the past delayed the introduction of new and under-utilized vaccines in developing countries, in which the uncertainty of demand leads to reluctance among suppliers to increase production, thus resulting in an inadequate supply and high prices. The challenge to the global health community is to turn this vicious cycle into a "virtuous cycle", in which a predictable and growing demand – facilitated by donor funding and technical support – leads current producers to increase their production capacity for the vaccine and possibly new producers to enter the market. This would result in the growth of global production capacity, in turn leading to predictable, lower prices (see figure). Financial and technical support from the GAVI Alliance and from several accelerated development and introduction plans (ADIPs) have helped create virtuous cycles for several newer vaccines in recent years, including hepatitis B, the pentavalent (DPT-HepB-Hib), and rotavirus vaccines.

The desired virtuous cycle of supply-demand for cholera vaccines
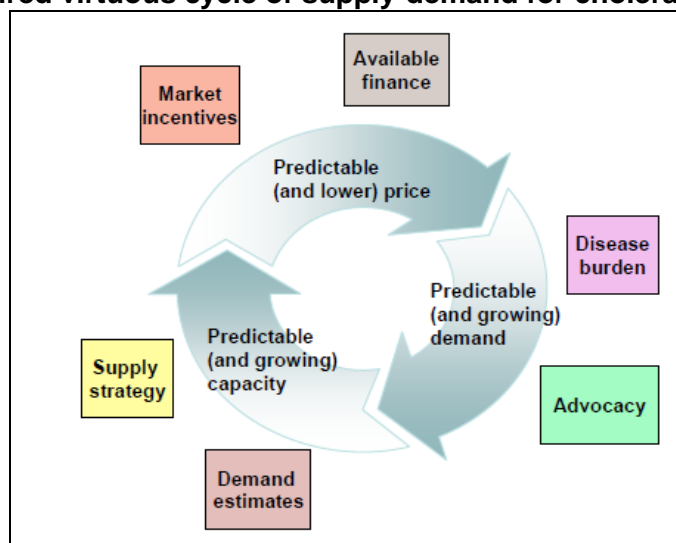
Source: [Milstein et al., 2007]

Purpose and challenges of this investment case

The purpose of this investment case is to provide a global evidence base for investing in oral cholera vaccines as part of a larger strategy that includes improvements to water, sanitation and hygiene.

With this investment case, we aim to answer the following questions:
- What is the global burden of cholera?
- What impact does the disease have on the larger economy?

- How should cholera vaccines be targeted for high-risk populations?
- Which countries are likely to adopt cholera vaccines and when?
- How should a cholera vaccine stockpile be used and how large should it be?
- For specific vaccination program options, how many cases will be averted and lives saved?
- How much will each of these vaccination program options cost and will they be cost-effective?
- How can a cholera vaccination program be financed?

The development of an investment case for cholera vaccines poses a number of challenges due in part to the nature of the disease, which may strike any area with inadequate or damaged water and sanitation infrastructure. As an example, much of the investment case was developed under the assumption that cholera has largely disappeared from the Western Hemisphere. However, this was prior to a large epidemic that erupted in Haiti in October 2010 and continued to the publication of this report. The Haiti epidemic is indicative of the constantly evolving threat of cholera.

The recent events in Haiti also demonstrate the difficulty in targeting cholera vaccines, since the incidence and severity of the disease can shift dramatically over a short time period. While many other vaccines are given universally (throughout a country), cholera vaccination would most likely be targeted only to high-risk groups, identified by age, socioeconomic status, and geography. The optimal targeting strategies are likely to vary from country to country and will depend on the specific epidemiology of the disease in each country. Therefore, this investment case presents four different vaccination scenarios or options for consideration that vary in scope of the target population (Large Target and Small Target) and by age group (all ages one and above vs. children 1-14 years old). These options provide upper and lower bounds of the potential costs and public health impact of cholera vaccination programs. Targeting at-risk populations will reduce the cost of the program, while protecting the populations at greatest risk. Additional disease burden data in each cholera-endemic country will greatly assist in targeting vaccination.

Contents of this investment case

This report provides a detailed estimate of the cholera disease burden (*Section 2.1.4* and *Appendix 1*), which had not been updated since the mid-1980s. Because of the macro-economic effects of cholera, the report also includes an estimate of the impact of cholera on national economies, based on an analysis of a cholera-endemic African country (*Section 2.2* and *Appendix 9*).

The revised estimates of cholera incidence and mortality form the basis for the forecast of cholera vaccine demand for the control of endemic cholera by year (*Section 4* and *Appendix 4*). Based on this forecast, the investment case proposes that cholera vaccination could be funded through two separate investments. "Investment 1" would be used for countries forecasted to introduce the vaccine between 2015 and 2017, and assuming success of this first investment, "Investment 2" would support countries introducing the vaccine between 2018 and 2020. The demand forecast and other analyses are conducted for the four vaccination program scenarios.

This study also provides an estimate of the needs for a vaccine stockpile that could be used for pre-emptive vaccination to prevent cholera outbreaks from occurring or from spreading (*Section 4.2* and *Appendix 5*). The stockpile would require a modest investment relative to the

cost of repeated campaigns in cholera endemic communities. Thus, the stockpile may be a gateway to more widespread use of oral cholera vaccines if it can be demonstrated that vaccination is logistically feasible at larger scales and the vaccine is effective in reducing cholera burden at the community level.

An analysis of the supply situation for oral cholera vaccines and future production needs required to both supply the stockpile and to meet the forecasted demand among endemic populations is also included (*Section 5.2*).

This investment case analyzes the impact of vaccination based on the demand forecast results for each vaccination program option up to 2030 – using a dynamic transmission model that takes into account both direct and indirect (herd) protection conferred by cholera vaccination (*Section 7* and *Appendix 8*). The cost and cost-effectiveness of each program option is also estimated (*Sections 6 and 9 and Appendices 7 and 10*). Lastly, the report explores the needs and options for financing cholera vaccination.

To both jumpstart the planning and implementation of cholera vaccination in potential "early adopter" countries, and to verify the results of the global investment case, country case studies of cholera vaccination have also been prepared for two potential early adopter countries – Bangladesh and Uganda. A summary of the findings for Bangladesh are presented in Appendix 11 and reports for each country study are forthcoming.

Table of Contents

Contents

Executive Summary

The Investment Objective

Although oral cholera vaccines have been available since the early 1990s, only one country to date – Vietnam – provides cholera vaccination in the public sector. The appearance onto the market in 2009 of a new lower-cost vaccine with longer, more sustained protection than the only other internationally-available vaccine, including in children under five, presents a new opportunity for the broader use of cholera vaccination to both curtail outbreaks and to significantly reduce the global burden of endemic cholera, as recommended by WHO in a Position Paper in 2010. Significant reductions in disease can be accomplished through geographically-targeted vaccination in a limited number of countries in sub-Saharan Africa and Asia, given the concentrated distribution of the disease. This is unlikely to occur, however, without financial support from donors.

The major objectives of investments in cholera vaccination are to:

- Support the introduction of cholera vaccine into cholera-endemic countries to control endemic disease and prevent or control outbreaks;

- Establish a global cholera vaccine stockpile for the prevention or control of cholera outbreaks; and

- Motivate industry to enter into or expand cholera vaccine production to meet the potential demand.

The Problem

Cholera is an acute, rapidly-dehydrating diarrheal disease transmitted through water or food contaminated with the bacterium, *Vibrio cholerae* O1 (or less frequently, O139), primarily in areas with poor access to safe drinking water and adequate sanitation. Rapid dehydration can lead to death within 24 hours in up to 50% of cases if not treated with intravenous or (for less severe cases) oral rehydration. With proper treatment, the case fatality rate may be reduced to much less than 1%. However, the poor and marginalized populations at greatest risk of cholera often lack ready access to adequate health care facilities, and the use of oral rehydration therapy (ORT) for children with diarrhea is inadequate and declining in many cholera-affected countries.

Cholera occurs both as endemic disease and in outbreaks, which can include large, explosive epidemics. Since the late 1990s, cholera epidemics have appeared in growing frequency, size and duration in Africa – including the 2008/09 epidemic in Zimbabwe, in Asia, and most recently in Haiti. Many outbreaks in the past decade have lasted up to a year or longer and are characterized by case fatality rates of 4% of higher. The severity of some of these outbreaks, including the Haiti epidemic, may be linked to the emergence of new, more virulent hybrid strains of *V. cholerae* O1 El Tor that produce the classical cholera toxin.

Also complicating treatment of cholera is the increase in and unpredictable patterns of resistance to antibiotics, which are used to reduce the duration of the illness and the fecal

excretion of cholera vibrios by infected individuals. There is also growing concern that global warming will increase the incidence of cholera by creating conditions, such as warmer water and salt water intrusion inland, that favor the growth of *V. cholerae*, and by increasing the frequency of floods, cyclones, and other extreme weather events.

A systematic analysis of the global burden of cholera, conducted as part of this investment case, estimates that there are, on average, three million cases of cholera requiring treatment and around 94,000 deaths each year, with 72% of cases and deaths occurring in children 14 years old and younger. The analysis identified 51 countries in sub-Saharan Africa and Asia where cholera is endemic – defined as where cases have been reported in at least three of the past five years – and 18 additional countries where cholera occurs sporadically. Twelve countries, including India, Bangladesh, Pakistan and nine African countries, account for more than 80% of the global burden, with India alone accounting for nearly 30%.

In addition to its impact on health, cholera is one of the few vaccine-preventable diseases that significantly affect countries' economies, particularly in such industries as tourism and food exports. An analysis conducted for this investment case by Oxford Economic Forecasting for Mozambique estimates that a large outbreak lasting nine months would result in a 2.1% decline in the country's Gross Domestic Product (GDP) in the year following the outbreak, and a 0.5% decline in the second year. These macro-economic costs are in addition to the direct costs of medical treatment, which are estimated to average US$8.50 -11.50 per episode for hospitalized and outpatient cases combined.

The Challenge: The control of cholera through targeted vaccination

The vaccines

Two safe and effective oral cholera vaccines are currently available internationally. The WC-rBS vaccine, produced by Crucell/SBL Vaccines and sold as Dukoral® since 1991, consists of killed whole cells of *V. cholerae* O1 and the B subunit of the cholera toxin. The vaccine is licensed for persons two years and older, and is given in two doses (three doses for 2-5 year olds), with an interval of one to six weeks. Because of the cholera toxin component, the vaccine requires co-administration with a relatively large volume of buffer solution (75 ml for children age 2-6 yrs. and 150 ml from age 6 yrs.) to neutralize gastric acid. In a clinical trial in Bangladesh the vaccine provided 85% protection for 4-6 months, 58% at two years following vaccination, dropping to 18% at three years. Cumulative efficacy over three years was 64% for all ages, but only 26% in children five years and younger. Revaccination is recommended after two years for persons six years and older, and every six months for 2-5 year olds due to rapid declines in protection in this age group. While mainly a traveler's vaccine used in industrialized countries, Dukoral® has been pre-qualified by WHO and used on a pilot basis in several African and Asian countries, both to preempt outbreaks in post-crisis situations and to control endemic disease. The most recent price paid by the public sector for the vaccine was around $5.25 per dose, although the producer has indicated its willingness to offer developing countries lower, more competitive prices for certain minimum quantities.

Another oral cholera vaccine, produced in Vietnam, was reformulated by the International Vaccine Institute in the mid-2000s in the aim of developing a lower-cost vaccine more amenable for use among cholera-endemic populations. This vaccine is also a two-dose killed whole cell vaccine, but it lacks the cholera toxin component, making it less expensive to produce and the use of a buffer unnecessary. It includes both O1 and O139 strains of *V. cholerae*. This modified "O1/O139 WC" vaccine has shown in an on-going trial in Kolkata, India,

sustained protection for at least three years, with a cumulative efficacy of 66% over three years. Protection in young children under five years of age was maintained for at least two years versus around six months for Dukoral®. Following technology transfer, the WC vaccine is being produced by Shantha Biotechnics of India, where it is marketed as Shanchol™, and in Vietnam by VaBiotech, under the name mORC-VAX®, and both vaccines were licensed in 2009 for persons one years and older. Shanchol™ was pre-qualified by WHO in 2011; pre-qualification of the Vietnamese vaccine must await a positive assessment of the country's national regulatory authority by WHO. Shantha has committed to a public sector price of $1.85 per dose for Shanchol™.

This investment case assumes use of the O1/O139 WC vaccine because of its improved performance in young children, improved logistics for administration in developing countries, and relatively easy access to its technology – facilitating its production by new manufacturers. While there are several live-attenuated cholera vaccines under development, these are unlikely to be available for at least five to ten more years and thus are not included in this investment case.

Strategies to control cholera through vaccination and forecasted demand

This investment case proposes both the introduction of cholera vaccination in high-risk areas of cholera-endemic countries to control endemic disease, and the establishment of a vaccine stockpile to prevent the occurrence or spread of cholera outbreaks in endemic and non-endemic countries. As recommended by WHO, cholera vaccination should be used in conjunction with – and not replace – other preventive and control measures, such as improvements in drinking water supply, sanitation and hygiene.

A global cholera vaccine stockpile would allow both endemic and non-endemic countries to vaccinate against cholera in emergency situations. The stockpile also may provide a gateway for endemic countries to use the vaccine before committing to repeated campaigns for high risk populations. Based on the experiences of the yellow fever and meningitis vaccine stockpiles, this investment case proposes establishing a pilot stockpile in 2012 of two million doses, enough to vaccinate nearly one million people. As demand is demonstrated, the stockpile could grow to five million and eventually to 10 million doses. This vaccine would target all persons one year old and above in affected areas

To estimate the potential demand for cholera vaccines to control endemic disease – assuming sufficient vaccine supply – a demand forecast was performed for 45 of the 51 endemic countries and 18 states in India with sufficient cholera incidence to make vaccination cost-effective. A semi-quantitative scoring system was developed to grade each country based on its cholera disease burden, immunization program capacity, history of adopting new vaccines, and experience with cholera vaccination and surveillance. The results from this scoring system in combination with qualitative insights about the likelihood of adoption in specific countries were used to project potential country adoption time frames. Thirty-three countries, including 12 Indian states, are forecasted to introduce cholera vaccination between 2015 and 2020, and are the focus of this investment case. Eleven "early adopters" are forecasted to introduce the vaccine during 2015-2017 while twenty-two would do so from 2018 to 2020. Twenty-six of these countries are in Sub-Saharan Africa, and five are in South Asia, including Bangladesh, India and Pakistan. The remaining two countries are in the WHO Eastern Mediterranean region (Pakistan and Iraq). The investment case proposes that cholera vaccine introduction be financed through two investments: Investment 1 for the 11 countries (including two Indian states) predicted to

adopt vaccination between 2015 and 2017, and Investment 2 for the 22 countries and 10 Indian states forecasted to introduce the vaccine from 2018 to 2020.

Because there is no standard strategy for targeting populations for preventive cholera vaccination within countries, estimates of the number of vaccine doses required for these 33 countries are made for four targeting strategies. These include a "Large Target" scenario in which urban slums and rural areas with poor access to improved water sources would be targeted, and a "Small Target" scenario targeting the highest risk sub-populations in these areas, equivalent to 50% of the Large Target population. For each of these scenarios, two age group options are presented: children 1-14 years old, and all persons one year and older. The size of the population targeted through these four options in the 33 countries ranges from 113 million to 637 million, the vast majority of whom would be the poor and marginalized populations. The forecast assumes that targeted vaccination would be rolled out in each country and Indian state over a three-year period and that revaccination would be required after three years.

The Large and Small Target populations are smaller than the total population at risk because we believed it was not feasible to provide the number of doses required to vaccinate all persons at risk. In addition, it was not possible to estimate separate incidence rates for the Small Target and the Large Target populations and thus the same rates were used for both populations, based on the global disease burden analysis. This may result in a conservative estimate of the impact and cost-effectiveness of the Small Target strategy if vaccination is only targeted to the highest risk (i.e., Small Target) groups, since their incidence rates may indeed be higher than the ones used in the analyses.

The demand forecast predicts that 9 million – 447 million persons would be vaccinated per year in the 11 Investment 1 countries by 2020, depending on the targeting strategy. This would require 19 million – 98 million doses each year. Extending the program to 22 more countries through Investment 2, beginning in 2018, would result in an additional 20 million – 87 million persons vaccinated per year by 2020, requiring 41-184 million additional doses annually.

Vaccine supply and pricing projections

Shantha's current production capacity of its Shanchol™ vaccine is two million doses per year. This could gradually increase to 25 - 30 million doses per year if an additional production facility dedicated to cholera vaccine production is built and validated. This analysis assumes the production capacity of Shanchol will increase to 30 million doses by 2015 and 40 million doses by 2016. The production capacity of VaBiotech – which plans to export its vaccine outside of Vietnam in the future – is around 10 million doses per year. Assuming the Vietnamese vaccine is pre-qualified by 2015, the total potential production capacity of pre-qualified O1/O139 WC vaccines will therefore be 30 million doses per year by 2015, increasing to 40 million doses in 2016. This will not be sufficient to meet the projected demand for vaccination in endemic countries, even for the smallest vaccination scenario, but would be sufficient to stock a global vaccine stockpile. Therefore, production capacity for the vaccine will have to be expanded, either by current producers building additional facilities, by new producers entering the market, or a combination of both. To address this supply constraint, the IVI has already transferred modified O1/O139 WC vaccine technology to Eubiologics, a Korean biotechnology company.

This investment case uses a price per dose of $1.85 for pre-qualified vaccine from 2012 to 2017, based on the current public sector price of Shanchol™. The analyses assume that the price will fall to $1.45 per dose in 2018 once demand starts to increase substantially, assuming additional manufacturers enter the market and manufacturing efficiency improves. Further price

declines may be limited due to the production process of the vaccine, which requires high concentrations of bacteria and long fermentation cycles.

Costs and financing needs

The estimated annual cost of the stockpile, including operational costs in the field, would be $5.5 million per year for a two-million dose stockpile and $23-27 million for a ten-million dose stockpile. The total cost of a cholera vaccine stockpile would be about $63 million for the period 2012-2017 during which the annual allocation of doses to the stockpile would increase from two million to 10 million. An additional $68 million would be required from 2018-2020, assuming that the size of the stockpile stays at 10 million doses. The proposed stockpile would be funded primarily by donors, who would cover the vaccine costs and 50% of the operational costs, with countries using the stockpile contributing the remaining 50%.

The estimated costs of the staggered introduction of oral cholera vaccine for controlling endemic disease into the 11 Investment 1 countries from 2015 to 2017 ranges from $107 million if only children are vaccinated in the Small Target areas to $585 million if all ages one and above are vaccinated in the Large Target areas. The costs of maintaining these programs in Investment 1 countries for the next three years (2018-2020) is higher because all of the countries would be fully operational over the period and due to population growth. Depending on the targeting option, an additional $129 million to $653 million would be required. The cost of introducing vaccination in 22 more countries through Investment 2 would range from $118 million to $528 million from 2018 to 2020.

Financing for cholera vaccination could come from several potential sources, including external partners and internal public and private sector sources. Due to uncertainty about whether and when the GAVI Alliance would support cholera vaccine introduction, other external sources of funding should be sought, including development banks, bilateral donors and regional donors (e.g., the EU) and could be part of broader economic development programs or efforts to mitigate the impact of climate change. Possible internal sources of financing include national health budgets, local governments, private industry (e.g., tourism and seafood industries), local NGOs, and health insurance.

Expected public health and economic impacts of the investment

To estimate the impact of cholera vaccination on endemic cholera incidence and mortality, a dynamic model of disease transmission was developed for preventive vaccination. The model incorporates estimates of herd protection of oral killed whole-cell-based cholera vaccines, based on data from the original trials of these vaccines in Bangladesh. Specifically, children-only vaccination programs are estimated to reduce the number of cases in the targeted areas by about 62% on average, while the all ages vaccination programs would reduce incidence in targeted populations by 75% on average. The impact on cholera incidence among the 45 countries with sufficient cholera burden to consider vaccination programs is shown in the figure.

If both Investments 1 and 2 are funded, the cumulative impact from 2015 to 2020 in the 33 target countries will be (depending on the targeting option):

- 1.1 – 2.9 million cholera cases prevented
- 34,800 – 86,500 lives saved

- 313,000 – 866,000 hospitalizations prevented
- Savings of $13 – 34 million in direct medical costs.

If both investments in vaccination continue through 2030 in these 33 countries, the cumulative impact from 2021 to 2030 is estimated to be:

- 6.5 – 15.7 million cholera cases prevented
- 225,000 – 547,000 lives saved
- 1.7 – 4.2 million hospitalizations prevented
- Savings of $73 – 180 million in direct medical costs.

Projected annual reduction in the number of cholera cases due to Investments 1 and 2
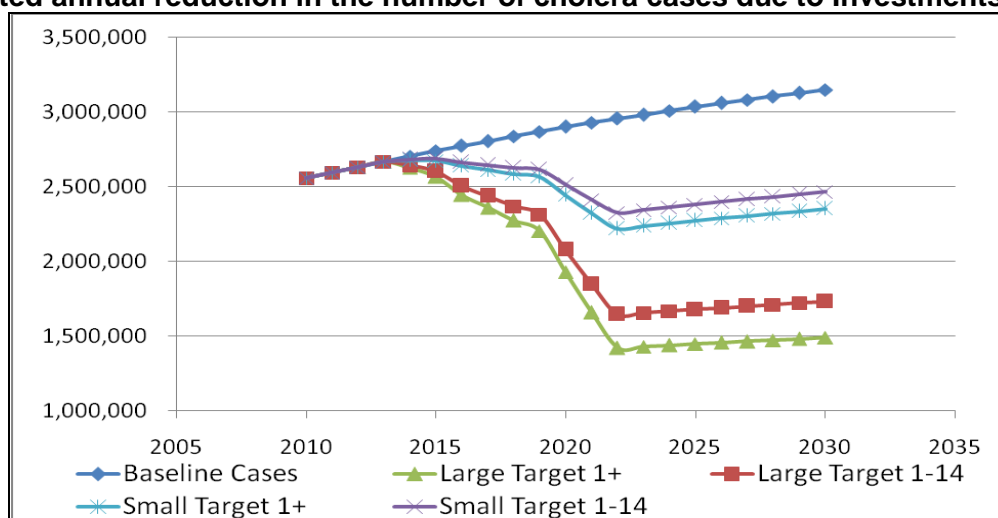
Additional vaccination benefits include:

- Continuing progress beyond Millennium Development Goal 4 (reducing childhood mortality) by preventing 118,000-272,000 deaths in children under five, most of which would occur after 2015;
- Contributing to meeting the GIVS objective of accelerating the introduction of new vaccines in developing countries;
- Reducing the negative impact of cholera on the economies of endemic and epidemic countries; and
- Reducing health inequities since cholera is a disease that disproportionately affects the poor and marginalized populations.

Cost-effectiveness of cholera vaccination

A cost-effectiveness analysis of cholera vaccination in the 33 target countries, predicted to introduce the vaccine for endemic disease during 2015-2020, was conducted as part of this investment case, using the estimates of impact, including herd protection effects. (No similar analysis was done for reactive vaccination with the stockpile given the lack of data on impact.) Using the WHO cost-effectiveness thresholds, vaccination of children or people of all ages one and above was found to be "very cost-effective" in all three WHO regions where these countries are located (AFR, SEAR and EMR). Depending on the region, the cost per disability-adjusted life year (DALY) averted was $151 - $383 for programs vaccinating children 1-14 years old and

$268 - $785 for programs vaccinating all ages – well below the weighted average GDP per capita of the target countries in each region (≈$1,000 - $1,200). Because incidence and mortality data were not available for sub-populations within countries, the same rates were assumed for the Small Target and Large Target areas and thus cost-effectiveness could be estimated only by target age group and WHO region. Since the incidence rates of the Small Target (highest risk) populations are likely to be higher than the ones used in the analyses, the impact and cost-effectiveness estimates may be conservative for the Small Target scenarios.

The greater cost-effectiveness of vaccinating children 1-14 years old compared to vaccinating all ages is due to both the higher incidence rates among children and the herd protection effects on adults from vaccinating children. The diminished efficiency of expanding vaccination from children to adults is demonstrated by the fact that the costs for the all-ages programs are about 240% greater than for the children-only programs, while only around 18% more cholera cases are prevented.

A sensitivity analysis, which used a wide range of estimates for four key variables – cholera incidence, case fatality rate, herd protection effects, and vaccination costs – found that the cost per DALY to vaccinate children continues to fall within the "very cost-effective" range, and falls within the "cost-effective" range for the all-ages option.

Constraints, probably of success and conclusions

Major constraints potentially affecting the success of this proposed investment in cholera vaccination include the lack of solid data on the cholera disease burden in most countries – impeding awareness of the disease among policymakers as well as the identification of high-risk areas and populations for targeting; the sense among some policymakers that vaccination will compete for financing and attention with longer-term improvements in water and sanitation; the need to organize mass vaccination campaigns to deliver the vaccine; and the current limited supply of oral cholera vaccines. However, policymakers in cholera-affected countries are showing growing interest in addressing the continued problem of endemic cholera and increasingly frequent and unpredictable epidemics, as shown by cholera vaccination demonstration projects currently underway or planned in several countries (including India, Bangladesh and Zanzibar). The donor community and vaccine producers – who must increase production capacity of cholera vaccines to meet the potential demand – will especially be critical to making the control of cholera through comprehension programs that include immunization a reality.

Conclusions

The development of lower cost oral cholera vaccines tailored for use in developing country settings provides an additional tool to combat both endemic and epidemic cholera, along with water and sanitation improvements and other traditional cholera control measures. A two-pronged approach for adding cholera vaccines to existing control strategies can help reduce the burden of the disease. To control endemic disease, vaccines should be targeted for high risk populations and age groups. For epidemic cholera, investment in a cholera vaccine stockpile would enable rapid responses to epidemics, such as those that have recently taken place in Haiti and Zimbabwe, as well as the prevention of potential outbreaks following floods and other emergency situations. The establishment of a cholera vaccine stockpile may catalyze expanded introduction of cholera vaccination since it will help ensure that vaccines are available and provide an incentive for countries to improve cholera surveillance. It will also provide valuable experience in deploying cholera vaccines prior to implementation of national programs.

If countries improve cholera surveillance, areas at high-risk of cholera can be accurately identified and vaccination will be more efficient. Vaccination campaigns limited to children one to 14 years of age are about twice as cost-effective as campaigns for all ages one year and older in endemic areas. Thus, limiting vaccination to children rather than persons of all ages would increase the cost-effectiveness of programs. However, vaccination during outbreaks should target all ages since incidence rates are higher and more uniform across age groups during epidemics.

Cholera vaccine introduction would contribute to maintaining progress for Millennium Development Goals 4 and 5 (reducing child and maternal mortality). It would also reduce the negative impact of cholera on the economies of countries with endemic or epidemic disease. Since cholera disproportionately affects the poorest communities of less developed countries, this intervention would also improve equity. However, due to the low economic status of affected communities, the adoption of cholera vaccines would require a concerted effort between at-risk countries, the donor community, and vaccine manufacturers.

Recommendations

Based on the results of this investment case, the following recommendations are made:

- A concerted advocacy and information dissemination effort should be conducted at the country, regional and global levels to communicate the value of vaccination using oral killed whole-cell based cholera vaccines in order to attract financing for the introduction of cholera vaccination in endemic countries. This effort should also stress the role of cholera prevention through immunization and water and sanitation improvements on improving equity for the impoverished and marginalized populations most at risk of cholera.

- Since vaccination programs for children ages 1-14 are considerably more cost-effective than vaccination of people of all ages, cholera-endemic countries should consider introducing currently available oral cholera vaccines to children in high-risk areas, combined with interventions to improve sanitation and water quality. However, reactive vaccination after an outbreak or flooding should target all ages over the age of one.

- Cholera surveillance should be established in endemic countries to inform policymakers of the magnitude of the disease in their country, to identify high-risk areas and populations, and to provide baseline data for measuring the impact of vaccination and other cholera control interventions.

- Financing should be sought for cholera vaccination demonstration projects in various endemic countries in Africa and Asia to inform decision-making about the use of cholera vaccines to reduce endemic disease. The demonstration projects can evaluate the feasibility and community acceptance of and demand for cholera vaccination and measure its impact (e.g., through case-control studies).

- A global cholera vaccine stockpile should be established to enable the rapid deployment of the vaccine for pre-emptive or reactive immunization in response to cholera outbreaks or natural disasters in cholera-endemic areas. The stockpile should start small (e.g., two million doses) and grow as its need and country demand is demonstrated.

- To minimize the risk to vaccine producers, the cholera vaccine stockpile should guarantee a minimum quantity of vaccine to be purchased annually. Any stock remaining at the end of the year can be used for preventive campaigns in endemic countries.

- Research should be conducted in conjunction with the use of the stockpile to determine the effectiveness of oral killed whole-cell cholera vaccines used reactively to prevent epidemics from spreading.

Part 1: The Proposed Investment

Section 1. Investment Objective

There are at present an estimated three million cases and around 94,000 deaths per year world-wide from both endemic and epidemic cholera, with children under five disproportionately affected. Increasingly large and prolonged cholera epidemics are taking their toll on national economies, health systems, and people's lives – both children and adults.

Despite the fact that oral cholera vaccines have been available since the early 1990s, only one country to date – Vietnam – provides cholera vaccination in the public sector (for high-risk populations). A new lower-cost vaccine with more sustained protection than the only other internationally-available vaccine came onto the market in 2009 and was pre-qualified by WHO in 2011. This new vaccine presents an opportunity for the broader use of cholera vaccination to both curtail outbreaks and to significantly reduce the global burden of endemic cholera. Significant reductions in disease can be accomplished through geographically-targeted vaccination in a limited number of countries in sub-Saharan Africa and Asia, given the concentrated distribution of the disease. The successful adoption and sustained use of cholera vaccines in these countries is unlikely, however, without financial support from donors.

Key objectives of the investment are to:

- Support the introduction of cholera vaccine into cholera-endemic countries to control endemic disease;

- Establish a global cholera vaccine stockpile for the prevention or control of cholera outbreaks; and

- Motivate industry to enter into or expand cholera vaccine production to meet the potential demand.

1.1   Two investments

This investment case proposes that cholera vaccination for the control of endemic disease be financed through two investments. Investment 1 would finance introduction of the vaccine in the first 11 countries forecasted to introduce cholera vaccination (between 2015 and 2017) (see *Section 4*). Assuming success with the implementation and impact of cholera vaccination in these initial countries, vaccination could be expanded to 22 more countries forecasted to introduce the vaccine from 2018 to 2020, through a second investment (Investment 2). Both investments continue up to 2020 for this investment case.

1.2   Expected benefits of the investments

Four options for targeting cholera vaccination within countries are presented in this investment case: two that vary by the scope of the target population (Large and Small Target) and two that vary by age group (1-14 year olds or all persons one and older). Taking the four options into account, it is estimated that over the period of 2015 to 2030, assuming vaccination continues to be financed, the impact of the two investments would be:

- 7.6 – 18.6 million cases of cholera prevented;

- 260,000 – 620,000 lives saved;
- Continuing progress toward Millennium Development Goal 4 (reducing childhood mortality) by preventing 118,000-272,000 deaths in children under five;
- 2.2 – 5.1 million hospitalizations averted; and
- Savings in medical costs of $140 million to $330 million.

Other benefits from the investment include:

- Contributing to meeting the GIVS objective of accelerating the introduction of new vaccines in developing countries;

- Reducing the negative impact of cholera on the economies of endemic and epidemic countries; and

- Reducing health inequities since cholera is a disease that disproportionately affects the poor and marginalized populations.

Section 2. Description of the Problem

2.1   The disease and its global burden

2.1.1   A description of cholera

Cholera is an acute, rapidly-dehydrating diarrheal disease caused by certain (toxigenic) serotypes of the bacterium, *Vibrio cholerae* (O1 and O139). The disease is spread through direct fecal-oral contamination or by ingesting contaminated water or food, including seafood from estuaries in the tropics or semi-tropics, where the pathogen resides. When humans – the only known vertebrate host of *V. cholerae* – ingest contaminated water or food, the bacteria multiplies rapidly in the intestine, making humans an amplifying host of the pathogen [Sack, 2006]. Contamination of the environment, including surface water, with the feces of these infected individuals further promotes the bacteria's growth and can lead to epidemics.

While only around 25% of persons infected with *V. cholerae* develop symptoms, 10-20% of those who do become symptomatic experience severe disease. Symptoms of severe cholera are profuse watery diarrhea and usually vomiting, leading to rapid dehydration. If untreated, the severe dehydration can lead to complications, such as renal failure, shock and pulmonary edema, resulting in death in more than 50% of cases, with most deaths occurring during the first day. For these reasons, WHO has called cholera "one of the most rapidly fatal infectious illnesses known" [WHO, 2001]. And unlike most other diarrheal diseases, cholera can be severe and even fatal in both adults and children.

Treatment of cholera consists mainly of rapid rehydration to replace lost fluids and electrolytes. Patients with mild or moderate dehydration can be treated with oral rehydration therapy (ORT), while severely dehydrated patients must be rehydrated rapidly with intra-venous (IV) fluids, followed by ORT once the patient is able to drink. WHO also recommends treatment with antibiotics for severe cases, since antibiotic therapy reduces by around 50% the volume of diarrhea, the duration of illness and time spent in the hospital, as well as the length of time the pathogen is excreted in the stool, thereby potentially reducing transmission of the infection to others [Sack et al., 2001]. During epidemics in poor countries, antibiotics to treat cholera can

actually save lives [Sack et al., 2001]. WHO recommends doxycycline or tetracycline for treating cholera, with erythromycin as an alternative in areas known to have strains resistant to these first-line drugs [WHO, 2005]. If patients have access to appropriate care for cholera, the case fatality rate should be 1% or less [WHO, 2007].

Cholera occurs both as endemic disease and in outbreaks, which can include large, explosive epidemics, as occurred in Zimbabwe in 2008/09 and Haiti from 2010 to the present. Countries where cholera is endemic often experience seasonal outbreaks each year.

Since 1817, there have been seven cholera pandemics. The first six were caused by the classical biotype of *V. cholerae* O1. We are now in the seventh pandemic, which began in 1961. This pandemic is caused by the second biotype of *V. cholerae* O1 – El Tor, which has replaced classical strains. While El Tor cholera has a lower rate of severe cases than the classical biotype, it persists longer in the environment and natural immunity through infection only provides 60-70% protection against subsequent infections, as compared to nearly 100% with the classical strain. New variant strains of El Tor that produce the classical cholera toxin have emerged in recent years in Asia and Africa, causing, many believe, a more clinically severe disease than the original El Tor strain (see *Section 2.1.3*).

The O139 serogroup of *V. cholerae* did not emerge until 1992 in India and Bangladesh. This serogroup now accounts for a small percent of clinical cases of cholera in Bangladesh (e.g., 2-9%) [Schwartz et al., 2006] and has not been found outside of Asia. There is no proven cross-protection between O1 and O139 serogroups.

2.1.2   *Risk factors and high-risk groups*

Risk factors for endemic cholera include the use of contaminated water for drinking and bathing and poor sanitation, as well as socio-demographic variables that are associated with poor water and sanitary conditions, such as poverty, low educational level, and high population density. Other risk factors found in recent studies include: having a household member with cholera [Sur et al., 2005]; eating contaminated food, especially seafood, that is undercooked or has stayed for several hours at ambient temperatures [Tauxe, 1998]; no previous exposure to the pathogen – placing young children particularly at risk; a lack or shortening of breastfeeding in infants; the reduced ability to produce gastric acid (hypochlorhydria); infection with *H. pylori* (which reduces stomach acid production); and having blood group O [Tauxe, 1998; Sack et al., 2004].

Floods are an important cause of cholera outbreaks in endemic countries like Bangladesh and parts of India, due to contamination of surface and well water. The risk of cholera epidemics is increased in an area where *V. cholerae* is circulating and there is a breakdown in water and sanitation systems resulting from natural disasters or man-made crises – as occurred in Zimbabwe in 2008/09. Rapid displacements of people into crowded areas such as refugee camps unable to suddenly handle their water and sanitary needs can further increase the risk of explosive outbreaks in cholera-endemic areas. The most common risk factors for cholera outbreaks reported to the ProMED disease reporting system were water source contamination, rainfall and flooding, and refugee settings [Griffith et al., 2006].

While cholera strikes all age groups, children under five years of age are normally at much greater risk of getting the disease in endemic areas than older children and adults, especially during non-epidemic periods. Prospective, laboratory-confirmed cholera surveillance conducted in the early 2000s by the Diseases of the Most Impoverished (DOMI) Program in four

sites (rural Matlab, Bangladesh; Beira, Mozambique; slum areas of Kolkata, India; and slums in North Jakarta, Indonesia) showed that the annual incidence rates for children less than five years old were two to four times higher than the rates found in the overall population (*Figure 1*). Annual rates of cholera incidence in these young children ranged from 2.0/1,000 to 8.8/1,000. Children 5-14 years of age had the next highest incidence rates in most locations. During epidemics, however, the risk is more evenly spread among age groups, and most cases are in adults.

Figure 1. Average annual incidence of culture-confirmed cholera per 1,000 population in four research sites
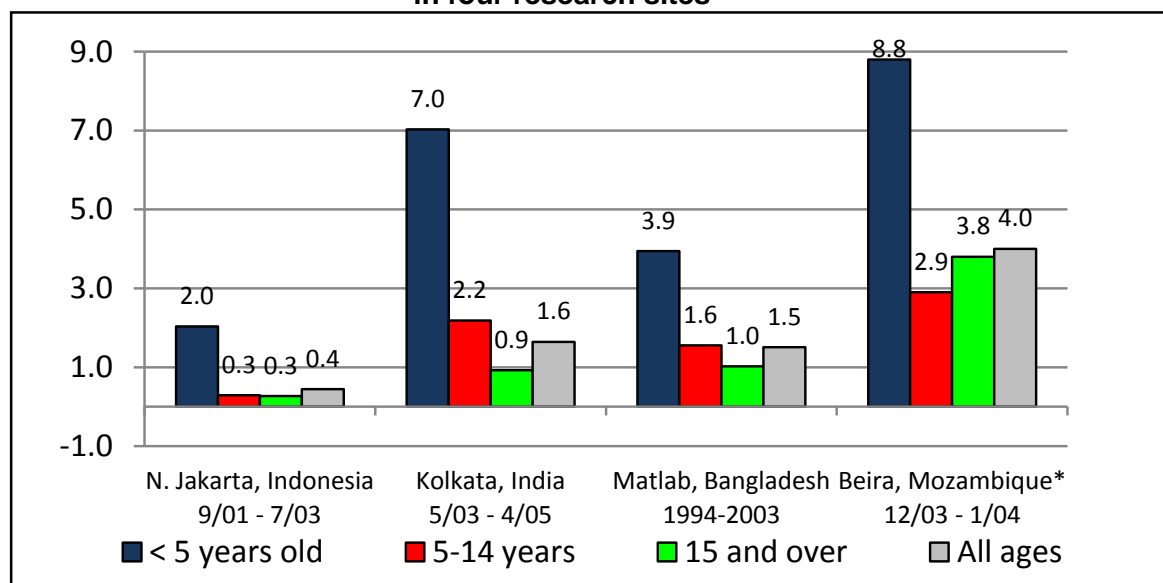
*Surveillance did not include pregnant women and children <2 years of age. Rates were corrected for direct protection from cholera vaccination. *Sources*: ICDDR,B (Matlab data); Diseases of the Most Impoverished Program [Deen et al., 2008].

2.1.3   Other recent cholera-related trends

Emergence of new, apparently more virulent strains of *V. cholerae* O1

Since the early 2000s, new variant strains of *V. cholerae* O1 have emerged and now predominate in South/Southeast Asia and parts of Africa. These strains are of the El Tor biotype, but produce the cholera toxin formerly produced only by classical strains. There is evidence from Bangladesh that these hybrid strains are more virulent and cause more severe disease than the original El Tor strains [WHO, 2008b; Siddique et al., 2009]. For example, while an average of 40% of cholera patients seen at two sentinel hospitals in Southern Bangladesh had severe diarrhea, this proportion increased to 70-79% in 2006 after the variant strain had completely replaced the original El Tor strain.

Antibiotic resistance

Also of concern is the increase and often fluctuating patterns of antibiotic resistant strains of *V. cholerae*, which can prolong the illness and complicate treatment. In addition to resistance to first-line drugs, such as tetracycline and erythromycin, which has existed for decades in India and elsewhere, multi-drug resistant strains that are resistant to four drugs at the same time – tetracycline, erythromycin, furazolidone, and trimethoprim-sulphamethoxazole

– have also emerged on the Indian sub-continent. Complicating treatment protocols is the fact that resistant strains can suddenly appear and then disappear as use of a drug declines. In recent years, reduced effectiveness of ciprofloxacin and other fluoroquinolones – used in areas where resistance to first-line antibiotics is common – has been seen in Bangladesh. Whereas a single 500 mg. dose of the drug was 94% effective in the 1990s in reducing symptoms and duration of the illness at the ICDDR,B Hospital in Dhaka, by 2005, a two-dose regimen was clinically successful in only 27% of adult cholera patients [Saha et al., 2006]. The continual pattern of antibiotic resistance to commonly-used therapies limits the effectiveness of treatment options for the disease and requires a constant search for new drugs that remain effective.

Potential impact of climate change on cholera incidence

Several of the effects of global warming may lead to increased incidence of cholera, according to climate scientists, biologists and cholera experts. Increases in the temperature of sea and surface water can lead to plankton blooms and increases in the growth of *V. cholera* [Lipp et al., 2002]. One 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 times [Huq et al., 2005]. The rise in sea levels predicted to result from global climate change will lead to greater salt water intrusion inland. This should favor the growth of *V. cholerae* in endemic countries, since brackish water appears to enhance the survival of the bacteria and the expression of cholera toxin [Lipp et al., 2002]. A study in Dhaka, Bangladesh found a correlation between increases in sea surface height in the Bay of Bengal – indicating sea water incursion inland – and increases in cholera cases at the ICDDR,B hospital [Lobitz et al., 2000].

Climate change is also expected to increase the frequency of extreme weather events, including floods, cyclones and droughts. Cholera outbreaks are a common occurrence during or following floods and cyclones in cholera-endemic countries such as Bangladesh, India and more recently, Pakistan, due to contamination of water supplies [Schwartz et al., 2006; Harris et al., 2008; Abramson et al., 2009]. Droughts are also believed to increase the risk of cholera, as they lead to a reduction in water usage (e.g., for washing food and hands) and a decrease in water quality. A study in Bangladesh showed that 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 [Hashizume et al., 2008]. Similarly, large outbreaks in Eastern Africa coincided with extreme rains from an especially strong El Nino/Southern Oscillation event [Griffith et al., 2006].

2.1.4   *A comprehensive analysis of the global cholera disease burden*

Background

The last systematic analysis of the global burden of cholera was performed nearly 25 years ago, when the Institute of Medicine estimated in 1986 an annual cholera incidence of six million cases and 120,000 deaths world-wide [Abramson et al., 2009]. This estimate was developed before the disease suddenly emerged in Latin America in the early 1990s and then virtually disappeared on the continent after 2000 (until the recent outbreak in Haiti), and before large epidemics were reported regularly from Africa. A systematic analysis to update the cholera disease burden was therefore performed as a critical part of this investment case, and forms the basis for the analyses of the demand forecast, impact, cost and cost-effectiveness of vaccination against cholera.

Methods

The methodology and detailed results of this disease burden analysis are presented in *Appendix 1*. In summary, cholera-endemic countries, as well as non-endemic countries that experience periodic outbreaks, were identified using four sources: the annual cholera reports in the WHO *Weekly Epidemiological Record*, postings from the ProMED disease reporting system, the Global Infectious Disease and Epidemiology Network (GIDEON) database, and published articles using PubMed. Following the WHO Position Paper, **cholera-endemic countries were defined as those where cases of cholera have been reported in at least three of the past five years** (ending in 2007 or 2008). The analysis identified 51cholera-endemic countries in Africa, Asia and the Middle East (*Figure 2*), and 18 additional (non-endemic) countries where cholera occurs sporadically, but which do not meet the definition of cholera-endemic. The list of these countries can be found in Tables 1 and 10 in *Appendix 1*. The analysis omitted the WHO Americas and European regions, from which, prior to the Haiti outbreak, only a small number of sporadic cases had been reported from non-travelers over the past decade.

Figure 2. The cholera-affected world by WHO region
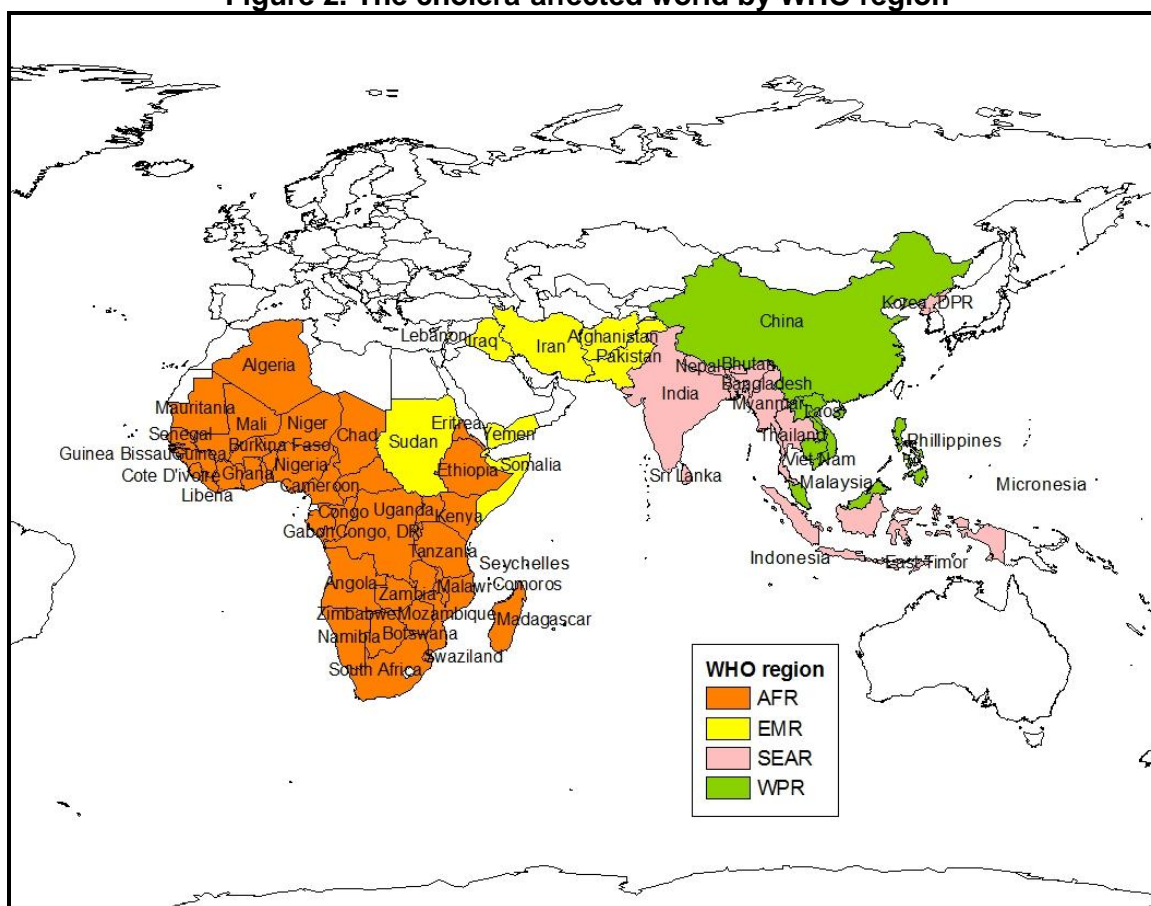
For the three largest countries with cholera – India, China and Indonesia – the analysis is limited to states or provinces that were identified as cholera-endemic, based on cholera reports in the past decade or so. Eighteen Indian states were identified as cholera-endemic (based on an analysis of epidemiological data from 1997 to 2006 in Kanungo et al. [2009]) (*Figure 3*). Five provinces in China and eight provinces or municipalities in Indonesia were also

identified as cholera-endemic and thus included in the disease burden analysis (see Table 16 in *Appendix 1*).

Figure 3. Cholera-endemic states in India
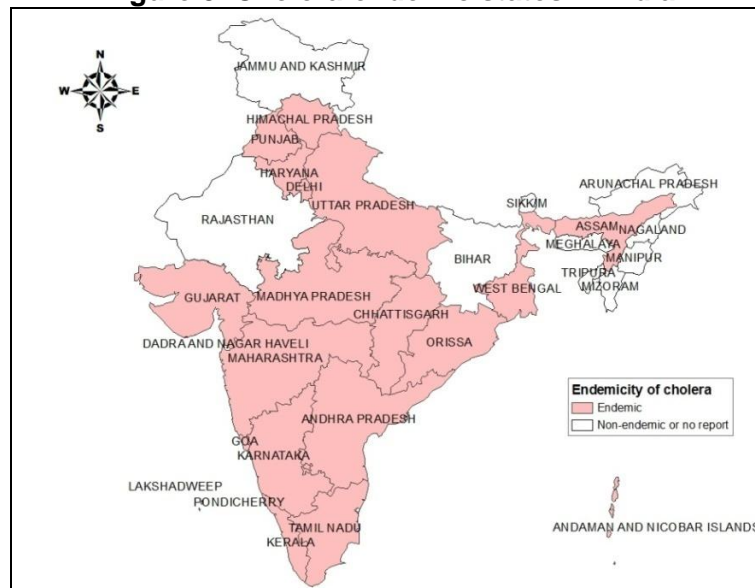
The analysis then estimated the size of the population in the 51 cholera-endemic countries that are most at risk of becoming infected with cholera, using U.N. data on the proportions of the population without access to improved sanitation as a proxy. This proportion in each country was multiplied by the country's population (or the population in cholera-endemic provinces or states in the case of India, China and Indonesia) to estimate the numbers of people at risk. The total population at risk for cholera in endemic countries was estimated at more than 1.4 billion people.

The annual number of cholera cases in endemic countries – defined as cases that seek treatment in a health facility, either as an inpatient or outpatient – was estimated using incidence rates from the prospective cholera surveillance studies conducted in Beira, Mozambique, Kolkata, India, and North Jakarta, Indonesia in the early 2000s by the DOMI Program. These rates were applied to countries that were in the same or neighboring regional sub-grouping (defined by WHO region and by level of mortality) as each of these three surveillance sites[1]. The incidence rates – ranging from 0.1/1,000 (in wealthier countries) to 4.0/1,000 – were then applied to *the population at risk for cholera in each country (i.e., those without improved sanitation)*. To be conservative, we assumed zero incidence of cholera for the populations not considered at risk. The number of cases in endemic countries is considered to be an average incidence, including both high incidence years with outbreaks, as well as low-incidence years.

The age distribution of cholera cases from the surveillance in Kolkata, India was used to estimate the incidence rates and number of cases for specific age groups among the at-risk

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[1] The WHO mortality strata range from A (low child and very low adult mortality) to E (high child and very high adult mortality). This produces sub-regions, such as AFRO-D, AFRO-E, EMRO-B and so forth. AFRO-E countries – those with the highest mortality rates – tend to be countries with high prevelance rates of HIV/AIDS, as compared to AFRO-D countries.

population in each of the 51 countries. The average age-specific annual incidence rates ranged from 7.3/1,000 (in infants) to 0.9/1,000 in adults (*Figure 4*).

Figure 4. Average age-specific incidence rates (per 1,000) among at-risk populations in cholera-endemic countries used for the disease burden analysis
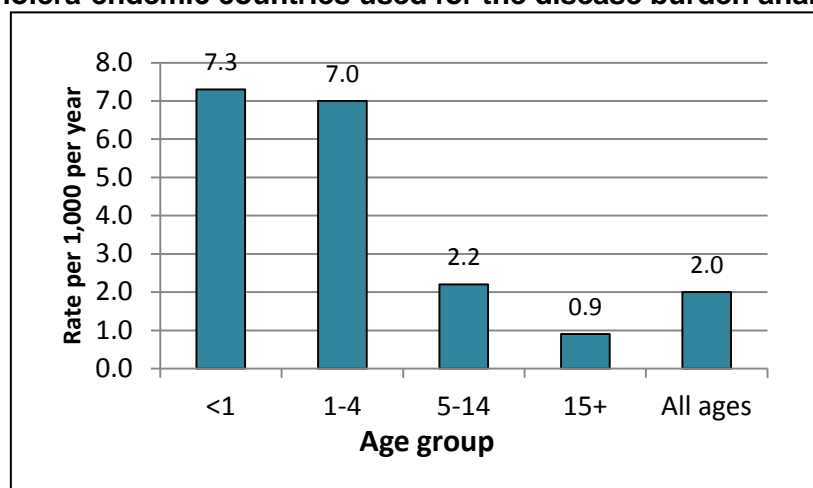
To estimate the number of annual deaths from cholera, we assigned average case fatality rates for each WHO region/mortality strata based on published case fatality rates (*Table 1*). These case fatality rates were then applied to the estimated number of cases in each country. These rates are likely to be conservative, since they are based on hospital-based data and community-based studies have shown that a portion of cholera cases die before reaching the hospital [Shikanga et al., 2009].

Table 1. Estimated cholera case fatality rates by WHO region/mortality strata

WHO region/ mortality strata	Case fatality (%)
AFR-D	3.8
AFR-E	3.8
EMR-B	1.3
EMR-D	3.2
SEAR-B	1.0
SEAR-D	3.0*
WPR-B	1.0
* CFR for Bangladesh is 1.5% based on the country case study.	

A separate analysis was conducted for Bangladesh, using country-specific data obtained from ICDDR,B for the country case study on cholera vaccination carried out as part of this global investment case (*Appendix 11*). The Bangladesh analysis assigned estimated incidence rates to different regions of the country, based on sentinel site surveillance conducted by ICDRR,B in six locations. It used a case fatality rate of 1.5%, based on local estimates.

Estimates of the number of cases in the 18 non-endemic countries were based on the average number of cases reported to WHO from these countries between 2000 and 2008. WHO estimates that reported cases represent only 5-10% of actual cholera cases [Gaffga et al., 2007]. We therefore applied a multiplier to the reported cases that assumes under-reporting of 90%.

Estimated global cholera burden and where it exists

An average of nearly three million cases of cholera seeking treatment in health facilities are estimated to occur each year (*Table 2*). As shown in *Figure 5*, nearly all cholera cases take place on two continents – Africa and Asia, with Sub-Saharan Africa and the Indian sub-continent accounting for the majority of cases.

Table 2. Estimated average number of cholera cases and deaths per year world-wide

WHO Region	No. countries		No. cases	Percent of total	No. deaths	Percent of total
	Endemic	Non-endemic				
AFR	34	8		49.8		58.8
EMR	6	2		7.1	6,575	7.0
SEAR	8	2	1,225,036	41.9	31,738	33.8
WPR	3	6		1.3	370	0.4
Total	**51**	**18**	**2,923,915**	**100**	**93,996**	**100.0**

About half of the cases and 59% of deaths occur in the AFR region. Another 42% occur in the Southeast Asia (SEAR) region – mainly India, Bangladesh and Nepal. Most cases in the Eastern Mediterranean region (EMR), 7% of the total disease burden or around 200,000 cases, occur in Pakistan, Sudan, Yemen, Afghanistan (considered non-endemic for cholera), Iraq and Somalia. The vast majority (97%) of cases and deaths take place in countries that meet the definition of cholera-endemic (*Figure 5*).

Figure 5. Estimates of annual cholera cases by WHO region and by cholera-endemic vs. non-endemic countries
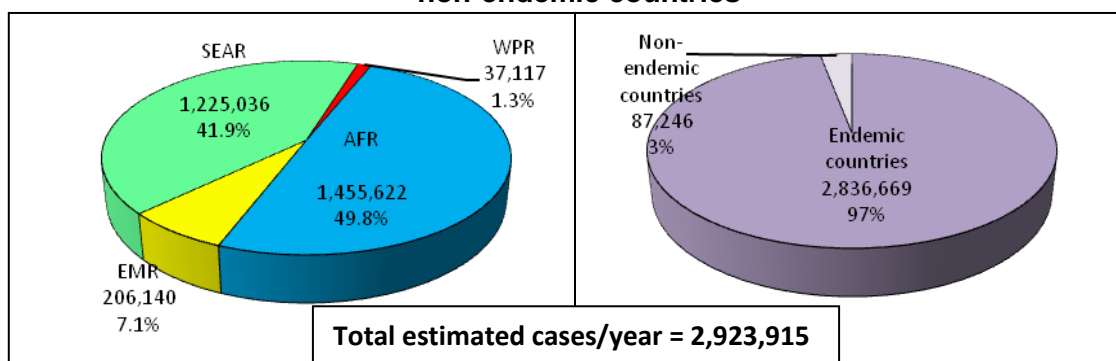
A map of cholera-endemic countries by their overall incidence rates (per the entire population) is shown in *Figure 6*. The countries with the highest incidence (≥2/1,000 for the total population) are mainly concentrated in a band of countries across Central Africa – from the Republic of Congo to Tanzania – and down the Eastern side of Africa from Ethiopia to Mozambique. Twelve countries – nine in Africa – account for more than 80% of the estimated global incidence and deaths (*Table 3*). The large numbers of cases in these 12 countries is due to their having incidence rates of at least 1/1,000 and, in many cases, the large size of their populations. India alone accounts for nearly 30% of the estimated global burden[2].

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[2] State-specific incidence rates were not estimated for India, due to a lack of data.

Figure 6. Geographical distribution of cholera incidence

Cholera incidence/1,000
- 🟥 >=2.0 per 1,000
- 🟥 1.0-2.0 per 1,000
- 🟨 0.5-1.0 per 1,000
- 🟩 <0.5 per 1,000
- ⬜ Non-endemic
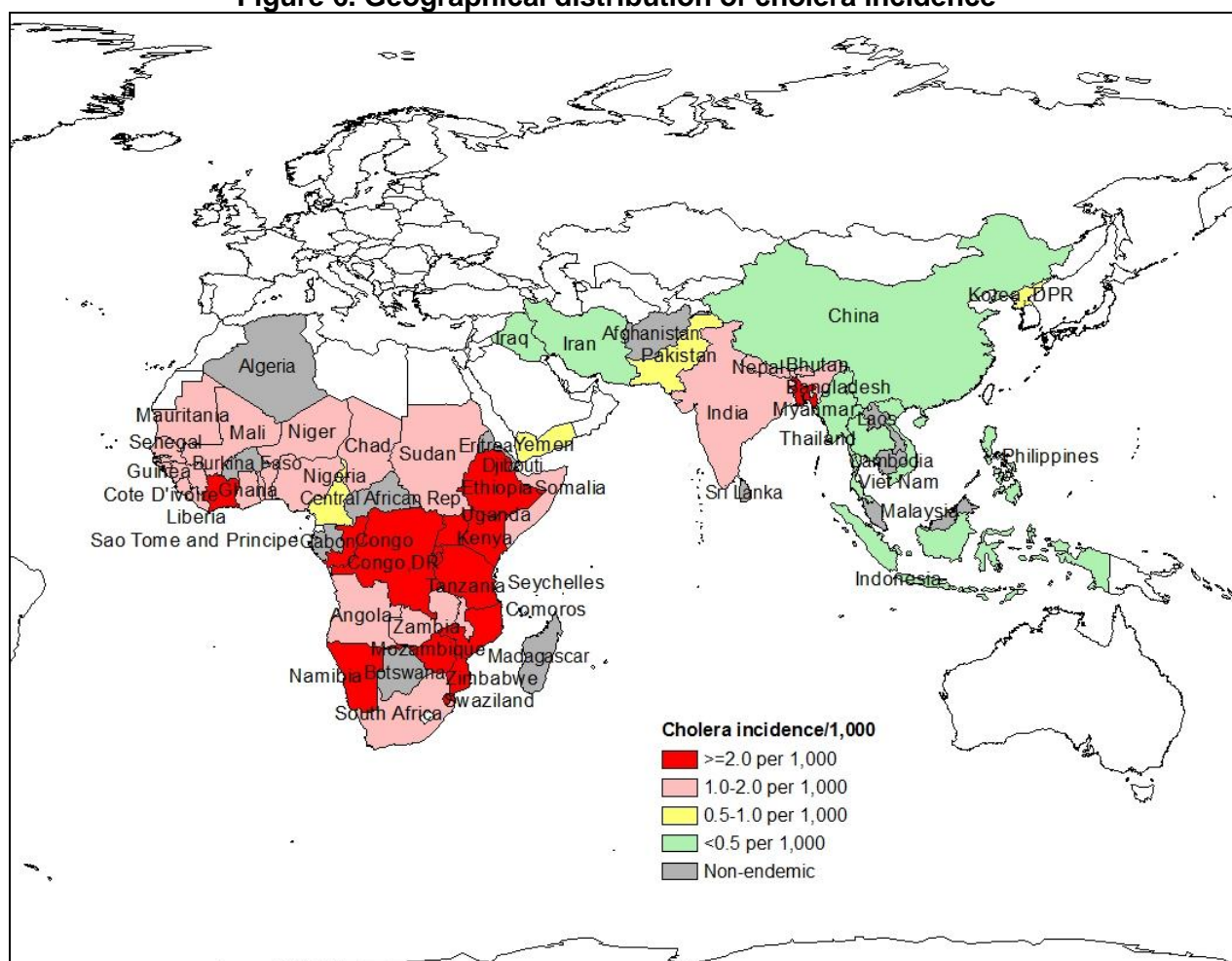
<u>Age groups most at risk</u>

Most cases and deaths (72%) are estimated to occur in children 14 years old and younger (*Figure 7*)[3]. The age group with the greatest number of cases (37%) is 1-4 year olds, followed by 5-14 year olds (25%). Infants account for 10% of cases. Children under the age of five years, while making up only around 12% of the total population in cholera-endemic countries, account for nearly half (47%) of the total cholera burden. However, it should be kept in mind that much of this burden is endemic disease, which disproportionately affects children. Cholera epidemics, on the other hand, cause disease more proportionally across all ages and, thus, the age breakdown for outbreaks would skew more towards adults and older children.

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[3] Since age-specific case fatality rates for cholera were not available, the same rates were used for all age groups within the same country grouping (WHO region + mortality strata). Thus, the breakdown by age group is the same for cases and deaths in this analysis.

Table 3. Countries with the greatest estimated number of cholera cases and deaths per year

Rank	Country	Cases			Deaths		
		Estimated no. /year	Percent of total	Cumulative percent of total	Estimated no./year	Percent of total	Cumulative percent of total
1	India	834,221	29.4%	29.4%	25,027	27.4%	27.4%
2	Bangladesh	303,975	10.7%	40.1%	4,560	5.0%	32.3%
3	Ethiopia	276,463	9.7%	49.9%	10,506	11.5%	43.8%
4	Nigeria	183,950	6.5%	56.4%	6,990	7.6%	51.5%
5	DR Congo	170,688	6.0%	62.4%	6,488	7.1%	58.6%
6	Pakistan	104,697	3.7%	66.1%	3,351	3.7%	62.2%
7	Tanzania	100,641	3.5%	69.6%	3,824	4.2%	66.4%
8	Uganda	85,865	3.0%	72.6%	3,263	3.6%	70.0%
9	Kenya	79,066	2.8%	75.4%	3,005	3.3%	73.2%
10	S. Africa	63,255	2.2%	77.7%	2,404	2.6%	75.9%
11	Mozambique	54,506	1.9%	79.6%	2,072	2.3%	78.1%
12	Ivory Coast	52,581	1.9%	81.4%	1,998	2.2%	80.3%
Total 12 countries		**2,309,908**	**81.4%**		**73,488**	**80.3%**	
Other endemic countries		526,761	18.6%	100.0%	18,002	19.7%	100.0%
Total in endemic countries		2,836,669	100.0%		91,490	100.0%	

Figure 7. Breakdown of cholera cases and deaths by age group in cholera endemic and non-endemic countries
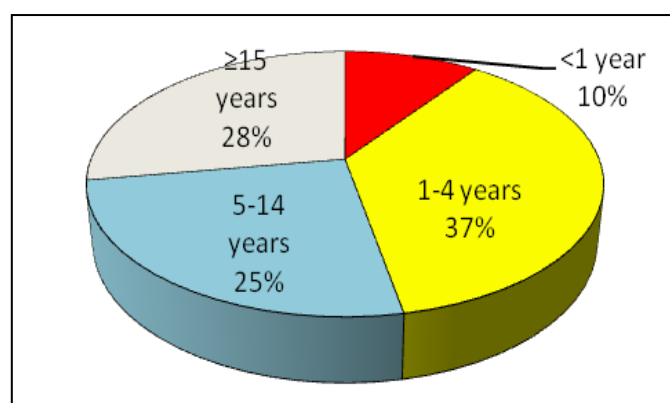
2.1.5 Cholera outbreaks

In areas where cholera is endemic, there are normally seasonal peaks or outbreaks once or twice a year. Since the late 1990s and especially in the 2000s, cholera epidemics reported to WHO or to ProMED have appeared in growing frequency, size and duration – both in endemic and non-endemic countries (*Figure 8*). The years 2006/2007 alone saw major widespread outbreaks in four African countries (Angola, Ethiopia, Sudan and Somalia), with reported cases totaling more than 225,000. Epidemics with at least 100,000 reported cases took place in the decade of the 2000s in four far-flung countries: Afghanistan, South Africa, India (West Bengal state), and Zimbabwe. The on-going cholera epidemic in Haiti that began in 2011

caused nearly 500,000 cases and 7,000 deaths up to January 2012. Since cholera cases are often under-reported or reported simply as acute watery diarrhea, the actual size of these epidemics was likely to be substantially higher.

Figure 8. Examples of major cholera outbreaks in the decade of the 2000s
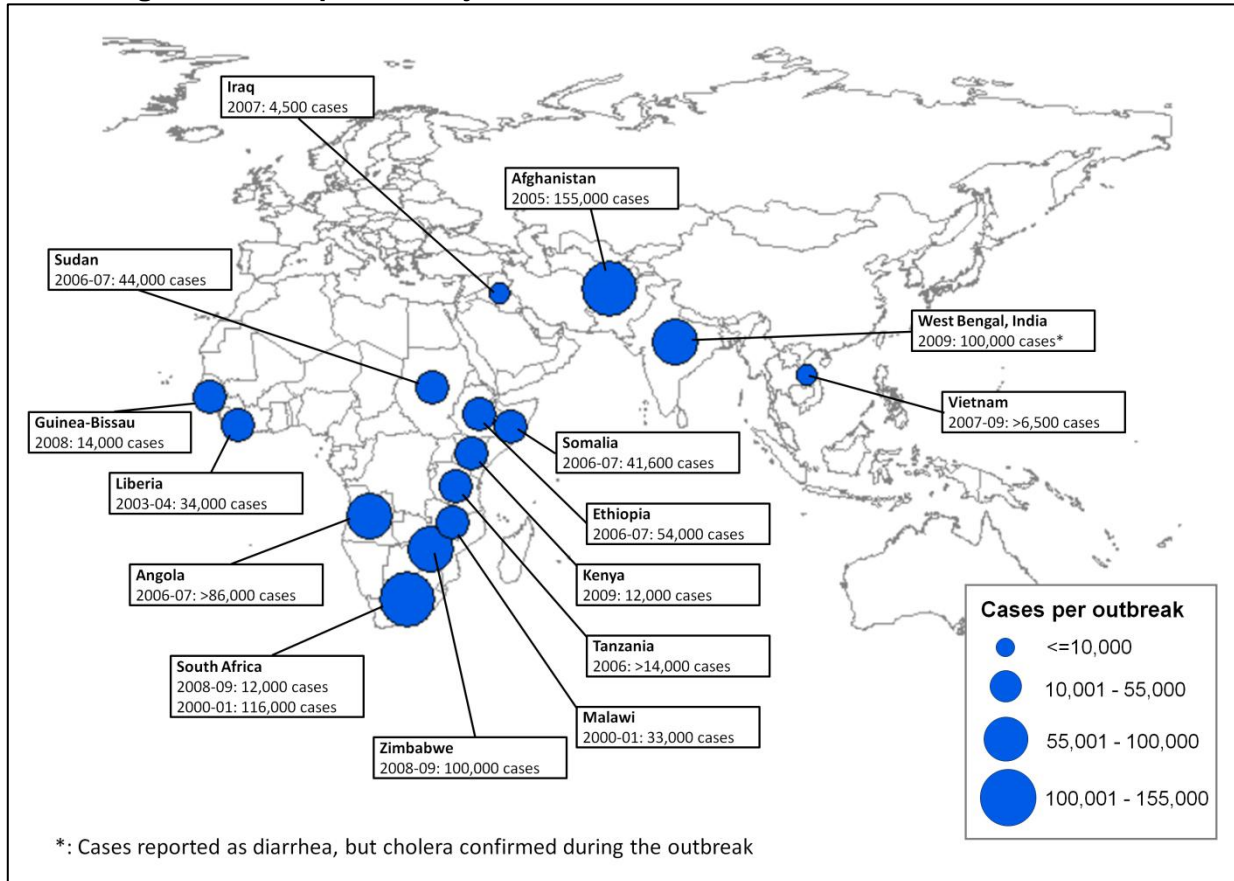
An analysis of cholera outbreaks reported through ProMED from 1995-2005 found 632 unique outbreaks – or more than 60 per year on average – the majority in Sub-Saharan Africa [Griffith et al., 2006]. The average outbreak affects more than 38,000 people and causes 1,555 deaths, with Africa accounting for 88% of the cases and deaths.

While cholera outbreaks have often swept through an area in a matter of weeks, many of the recent major epidemics have lasted within a country for eight months up to two years or longer – with the on-going Haiti epidemic and the 2008/09 epidemic in Zimbabwe (11 months) as prime examples. Major outbreaks, especially those in Africa, have been characterized by their reported high case fatality rates – often 4% or higher [Gaffga et al., 2007]. Reasons given for the rise in major, uncontrolled cholera outbreaks include deteriorating water and sanitation systems; the continual, often uncontrolled growth of urban slums with poor access to safe water and sanitation; poor or deteriorating health systems; and global climate change.

2.2 The economic burden of cholera

2.2.1 *Cost of cholera illness*

The average estimated total costs of cholera illness per year by WHO is shown in *Table 4*. These estimates, explained in detail in Appendix 10, assume that 75% of cases are mild enough to be treated on an out-patient basis, and 25% require hospitalization. The direct costs include medication, based on standard WHO treatment guidelines [WHO 2005], and the cost of care and hospitalization (based on standardized rates from WHO-CHOICE). Indirect costs are estimated from the average number of days lost from work by the patient or caretaker due to cholera, based on a multi-county study [Poulos et al., 2011]. The total average costs per case (direct and indirect) ranged from ≈$8-13 for outpatients and $46-78 for hospitalized cases, depending on the region. The average weighted cost of all cases (outpatients and inpatients) came to $17-27. These costs were then applied to the number of cases estimated in the disease burden analysis described above. The total estimated cost of illness per year is more than $57 million, of which 60% is for direct costs and 40% is for indirect costs. The cost of illness is highest in African countries, the region with the largest burden of disease, followed by the Southeast Asian region.

Table 4. Estimated cost of cholera illness per year by WHO regions, US$2010*

	AFR	EMR	SEAR	Total
Direct costs	$17,951,317	$2,172,754	$13,357,296	$34,073,050
Indirect costs	$11,795,641	$2,028,461	$8,806,306	$23,257,318
Total costs	**$29,746,958**	**$4,201,215**	**$22,163,602**	**$57,330,368**
*Based on average cost per case estimates of $24.30 - $26.50 for AFR, $20.10 for EMR and $16.80 for SEAR (see Appendix 10).				

2.2.2 *The macro-economic costs of cholera*

Impact of cholera outbreaks on the overall economy of cholera-affected countries

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 such industries as tourism and food exports. A cholera outbreak potentially affects both the supply and demand of goods and services in an economy.

On the demand side, international travel and tourism can decline dramatically in a country experiencing a cholera outbreak. This effect was seen in Peru during the country's large cholera epidemic in 1991. The demand for food produced in a country with cholera outbreaks can also decrease, especially seafood products often associated with cholera contamination.

Domestic and foreign investment can be affected as well. Companies may be less likely to invest in a country with regular cholera outbreaks due to periodic reductions in production and uncertainty around the length of the outbreaks. In addition, consumer spending may decline in a country if people are unwilling to travel to affected areas and/or stop eating food produced in these areas. They also may avoid crowded places, such as markets and restaurants, during an outbreak.

The supply of goods and services can be affected due to an outbreak's impact on the labor force, industry productivity, and costs of production. An outbreak could affect the labor

force if many workers are infected with cholera at the same time. Secondly, an industry's productivity could be reduced if transportation systems and other types of logistics are affected during an outbreak. For example, fewer drivers may be willing to travel to affected areas, which could lead to delayed delivery of resources used for manufacturing or production and to delays in the shipment of exports. The costs of producing goods may also increase, since reductions in transport and logistics could lead to higher prices for those services. In addition, market places may be shut down by the government or patronage may decrease.

Oxford Economic Forecasting modeled the impact of a cholera outbreak on the economy of Mozambique for this investment case. The assumptions of impact used in the analysis are based on assessments of Peru's cholera outbreak on its economy in the 1990's [Suarez and Bradford, 1993] and on an analysis of the impact of a European Union ban on fish imports from East African countries [Kimball et al., 2005] (described below). These assumptions include the following: 1) productivity would decrease by 1.8%; 2) travel and tourism would decrease by 72%; 3) food exports would decrease by 8%; 4) consumption would decline by 1%; and 5) investment would decline by 1.8%. Other assumptions and parameters used in the model are described in *Appendix 9*. These estimates must be qualified based on the fact that present-day Mozambique and 1990's Peru have substantially different economies. However, additional data for extrapolation do not exist.

The estimated impact of a nine-month long cholera outbreak on Mozambique's economy, summarized in *Table 5*, includes a 2.1% reduction in Gross Domestic Production (GDP) during the first year of the outbreak, corresponding to a loss of $245 million, and a reduction of 0.5% ($58 million) during the second year. There would also be a 0.7% increase in unemployment during the first year and a reduction in private consumption of an estimated $142 million over the course of two years (see *Appendix 9* for more details).

Table 5: Estimated macro-economic changes due to a cholera epidemic in Mozambique

Economic indicator	Year 1	Year 2
GDP (%)	-2.1%	-0.5%
GDP (US$ million)	-245	-58
GDP per capita (US$)	-5	-1
Private consumption	-1.2%	-0.3%
Private consumption (US$ million)	-114	-28
Consumer prices	0.2%	0.5%
Employment (%)	-0.7%	0.2%
Employment ('000s)	-56.3	-16.1

Impact on seafood exporting industries

A number of cholera-endemic countries are exporters of fish, shrimp and other seafood products; in some countries, including Bangladesh, the export of shrimp and other seafood has become a major industry. Since *V. cholerae,* including the pathogenic forms O1 and O139, live in shrimp and other crustaceans, many countries with endemic cholera are particularly prone to contamination of their shrimp and other seafood products. Vibrios can easily survive light cooking and then grow to an infectious dose if the food is held 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. 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.

In addition, more frequent detection of *V. cholera* O1 in estuary waters and a higher incidence rate among people in countries such as Bangladesh has been shown to be associated with increasing water surface temperatures (Suzita et. al. 2009). The risk of cholera contamination in exports of shrimp and other seafood products could therefore rise as a result of climate change.

Because seafood can be contaminated with pathogenic forms of *V. cholerae*, countries that import seafood carefully monitor the shipments to their countries, including conducting tests to detect contaminants. Importing countries have issued a series of import bans and detentions of seafood from cholera-endemic countries in the past two decades when contamination is found or when producers are not in compliance with food safety regulations[4]. A five-month ban imposed by the European Union on shrimp from Bangladesh in 1997 cost the industry an estimated $14.7 million [Cato and Lima dos Santos, 1998]. Another study found that the U.S. Food and Drug Administration had placed 68 import detentions on seafood products from Bangladesh just in the year 2001, due to sanitation and safety problems [Allshouse et al., 2003].

A further study assessed the impact of a European Union ban on fish imports following a cholera outbreak in the African countries of Mozambique, Kenya, Tanzania and Uganda in 1997 [Kimball et al., 2005]. The researchers paired data on fish exports from each African country to imports to a European country. The revenues from these exports were then compared with expected trade flows. The study estimated that the restrictions on fish exports resulted in losses of $332 million in the four countries for the four-year period of 1998-2002.

The risk of cholera contamination to the seafood industry is a compelling argument for vaccination against cholera for employees working in these industries, along with a program of regular laboratory testing of seafood products for contamination. There is also an argument to be made for vaccinating populations in the seafood-producing areas to prevent cholera outbreaks from occurring. The 2005 revision of the International Health Regulations, which no longer make official notifications of cholera to WHO compulsory, should help countries to admit they have the disease and to request assistance in improving surveillance and control, including immunization, without fearing trade restrictions [WHO, 2008a].

2.3 The challenge: how cholera can finally be controlled in cholera-affected countries

2.3.1 Current cholera prevention and treatment methods

Methods of preventing cholera

Like other diseases spread by the fecal-oral route, improvements in sanitation and access to clean water remain the mainstays of preventing both endemic cholera and cholera outbreaks. The most effective and long-term means of improving sanitation and water supplies is through the development of piped water, water treatment (i.e., chlorination systems), and piped sewerage systems. These systems led to the disappearance of cholera in the U.S. and Europe by the late 19th century. More recently, a comprehensive response to the re-emergence

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[4] E.g. the Hazard Analysis Critical Control point (HACCP) regulations.

of cholera in Mexico in the early 1990s involved large-scale water chlorination, latrine-building projects, improved waste disposal, laws banning the use of waste water to irrigate vegetables, and other interventions. This response was credited with effectively eliminating the disease in the country within six years [Gutierrez et al., 1998; Sepulveda et al., 2006] and similar efforts in other Latin American countries were instrumental in the disappearance of outbreaks on the continent by the year 2000.

Such efforts, however, require massive investments. It has been estimated that an investment of $37.5 billion international dollars will be required to meet the Millennium Development Goal of increasing the number of people with access to safe water by 50% by 2015 [Guerrant et al., 2003]. In sub-Saharan Africa, an estimated 45% of the population does not have access to safe water for drinking and 68% lack adequate sanitation [UNICEF/WHO, 2009]. Such large-scale programs are unlikely to reach these populations in Africa or the slums and poor rural areas of Asia in the foreseeable future.

As a low-cost, short- to medium-term alternative, a number of methods and products have been developed to improve the quality of water within the home (see *Appendix 2*). These "point-of-use" interventions include disinfecting water (through packaged chlorine solutions, solar disinfection, flocculants, filters, or a combination of methods), and the use of safe water storage vessels with narrow mouths or spigots, to prevent contamination by household members dipping their hands in water containers. Programs promoting these methods have been effective in parts of Africa and Asia in reducing overall diarrhea rates when introduced on a pilot basis, and, in a few studies, in reducing cholera incidence. However, the feasibility of scaling up these interventions nation-wide has not yet been demonstrated, nor has their long-term effectiveness, since they depend on behavioral change.

Other means of preventing cholera, besides improving water supplies and sanitation, include health education to promote hand washing with soap and safe food handling; promotion of exclusive breastfeeding for the first six months of life; strong disease surveillance; and the establishment and enforcement of basic sanitation laws for food industries, including food vendors (*Appendix 2*). All of these interventions are necessary components of a comprehensive strategy to prevent cholera and other diseases spread by the fecal-oral route.

The use of oral cholera vaccines through the public sector has only occurred in Vietnam, although a few pilot or demonstration projects have taken place. The use of these vaccines offers an additional prevention strategy that is becoming more feasible in cholera-endemic countries with the advent and licensure of a new lower-cost vaccine that was specifically developed for use in public health programs in endemic countries. As recommended by WHO, cholera vaccination should be used in conjunction with other preventive and control measures – not replace them.

Means of treating the disease and preventing death

Since it became widely available in the 1970s and 1980s, the use of oral rehydration solution (ORS) is credited with saving countless lives by preventing severe dehydration due to cholera. Prior to the advent of ORS, intravenous (IV) fluids were the only means of treating dehydration. Since the availability of and access to adequate treatment with IV fluids were often limited, case-fatality rates of up to 20% were observed even in communities with good health facilities. With appropriate and timely use of ORS and IV rehydration, it is now estimated that case fatality due to cholera in patients arriving at a health facility should not exceed 1%.

16

Patients with severe dehydration require immediate IV fluid infusion until the severe dehydration is corrected and they are able to switch to ORS. Profuse vomiting that can occur with cholera can limit a patient's ability to take ORS. In addition, the use of ORS is still quite low and appears to be declining in many developing countries. Among 34 countries that have conducted Demographic and Health (DHS) surveys in both 2000 and 2005, declines in the use of ORS, recommended home fluids or other fluids to treat children with diarrhea were seen in 23 countries (68%) [Ram et al., 2008]. At present, only an estimated 32% of children under five years of age with diarrhea in developing countries receive ORS packets to treat their illness, and only 28% in Sub-Saharan Africa [UNICEF/WHO, 2009]. Clearly, much work is needed to expand the use of oral rehydration among households in developing countries and its promotion should be a key component of comprehensive cholera control programs.

2.3.2 Oral cholera vaccines

Two oral cholera vaccines are currently available and pre-qualified by WHO. Both consist of killed whole cells of *V. cholerae*[5], require two doses for protection, and have strong safety profiles. Detailed product profiles of both vaccines can be found in *Appendix 3.*

WC-rBS vaccine (Dukoral[®])

The WC-rBS vaccine, produced by Crucell/SBL Vaccines since 1991 and sold as Dukoral[®], consists of a mix of whole cells of Ogawa and Inaba strains of *V. cholerae* O1, along with the B (binding) subunit of the cholera toxin (see Table 1 in *Appendix 3* for the composition of the vaccine). The vaccine is licensed for persons two years and above and is given in two doses with an interval of one to six weeks (three doses for 2-5 year olds). Because of the B subunit, the vaccine requires administration with a buffer solution mixed with clean water at delivery sites.

In a large clinical trial in Matlab, Bangladesh in the mid-1980s, the vaccine provided 85% protection 4-6 months following vaccination, 62% at one year and 58% at two years – with a cumulative efficacy over three years of 64% in all ages, but only 26% in children five and under. Protection drops off to 18% at three years [Clemens et al., 1990] and thus revaccination is recommended every two years. Protection in children under the age of six years is 100% for the first 4-6 months, but declines quickly (38% at one year) and thus the license calls for children 2-5 years of age to be revaccinated every six months. A case-control study following a mass vaccination demonstration project in 2003/04 in Beira, Mozambique found that the vaccine was 84% effective in all eligible ages combined (two years and above) over a five-month period and 82% in 2-4 year olds [Lucas et al., 2005].

While Dukoral[®] is mainly used as a traveler's vaccine in developed countries, it has been pre-qualified by WHO and used on a demonstration or pilot basis in several post-crisis situations to preempt cholera outbreaks, including in refugee camps in Darfur, Sudan and Uganda and following the 2004 tsunami in Aceh, Indonesia. For the control of endemic cholera, in addition to the demonstration in Beira, Mozambique, the vaccine was provided to around 30,000 children and adults in Zanzibar in 2009 in a pilot project led by WHO and the Zanzibar Ministry of Health. All of these experiences have demonstrated that vaccination of both children and adults in developing countries with Dukoral[®] was feasible, although the need to mix the vaccine with a

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[5]A live attenuated single-dose vaccine (CVD 103-HgR) was licensed in the 1990s as a traveler's vaccine and produced by Berna Biotech (now Crucell), but is no longer being produced.

buffer solution, as well as its bulky packaging, can pose logistical challenges, especially under difficult field conditions.

Despite its availability on the international market for 19 years and recommendations by WHO in 2001 for the pre-emptive use of oral cholera vaccines for high-risk populations [WHO, 2001], Dukoral® has not been used by national immunization programs in any country to date. Among the reasons commonly cited are its relatively high cost (the most recent public sector price to WHO was $5.25 per dose); moderate levels of efficacy and length of protection, especially in young children; and the need for two doses with an interval of one or more weeks, complicating its use in emergency situations. Other reasons commonly cited are the unknown cholera disease burden in most countries, the preference among policymakers for water and sanitation improvements over vaccination, and the belief that vaccination would compete for funding and attention with these improvements. The producer has indicated its willingness to offer lower prices to developing countries for certain minimum quantities.

<u>O1/O139 whole-cell (WC) vaccine (Shanchol™ and mORC-Vax®)</u>

In the aim of making available an oral cholera vaccine especially appropriate for use in cholera-endemic countries, the IVI reformulated in the mid-2000s a "whole-cell only" oral cholera vaccine (without the B subunit) that contains O139 as well as O1 strains. This new bivalent vaccine is a modified version of a vaccine that had been produced in Vietnam since 1997 and that was based on a whole-cell only vaccine developed in Sweden and tested in Matlab in the same trial as the WC-rBS vaccine. Because they lack the cholera toxin component, whole-cell only vaccines can be produced at relatively lower cost and do not require a buffer or water to administer. The Vietnamese whole-cell only vaccine (ORC-VAX) had been given to more than 20 million persons between 1997 and 2008 in high-risk areas of Vietnam and following floods – making it the first oral cholera vaccine used broadly in a cholera-endemic country.

The Vietnamese vaccine was modified by the IVI to comply with WHO guidelines for the production of inactivated oral cholera vaccines and GMP requirements. This involved replacing a toxin-producing strain with two other strains and developing new ELISA assays to improve the consistency in antigen content and to verify the absence of cholera toxin (see Table 2 in Appendix 3). The modified vaccine also has twice the quantity of LPS antigen as Dukoral® of the original Vietnamese vaccine.

Following successful safety and immunogenicity trials of the modified vaccine in Vietnam and India, a Phase 3 trial of the vaccine among nearly 67,000 persons one year old and older was launched in 2006 in slum areas of Kolkata, India. The vaccine has been shown to provide 65% protection against culture-confirmed cholera at three years following vaccination and 66% over three years [Sur et al., 2009; 2011]. Protection is sustained for at least two years in children under five and for at least three years in older age groups. While the protection in year three appeared to decline for children under age five, the difference between this age group and others was not statistically significant. Disease surveillance for the trial is continuing for a total of five years following vaccination to determine if protection lasts longer than three years and after how many years revaccination is required.

The IVI and the Vietnamese producer, VaBiotech, transferred the technology for producing the vaccine to Shantha Biotechnics in India, and it was licensed by the Indian government in 2009 for persons one year and older. The license calls for two doses given at least 14 days apart for preventive use. The vaccine, sold as Shanchol™, was pre-qualified by

WHO in 2011. The producer is also developing streamlined packaging and a presentation suitable for mass vaccination campaigns in cholera-endemic countries. Safety and immunogenicity studies are currently underway to determine it the vaccine can be given to infants concomitantly with other EPI vaccines. An efficacy trial of a single dose of the vaccine and of a two-dose schedule with an interval of 28 days (instead of 14) is planned for 2012.

The same O1/O139 WC vaccine was also licensed in Vietnam in 2009 (as mORC-Vax[®]), to replace the original Vietnamese vaccine and will continue to be sold in the private sector as well as used by the EPI. VaBiotech plans to sell the vaccine on the international market and apply for WHO pre-qualification of the vaccine, once Vietnam's national regulatory receives a positive evaluation by WHO.

Since the O1/O139 WC vaccine is not patent-protected and its production technology has already been successfully transferred, other manufacturers can potentially acquire the technology and produce the vaccine, if they feel demand is sufficient to warrant the investment. See Section 5 for more information on the supply of oral cholera vaccines.

Herd effects of oral killed cholera vaccines

A re-analysis of data from the Matlab clinical trial of oral killed cholera vaccines revealed that both Dukoral[®] and a WC-only vaccine (the precursor to Shanchol[TM]) provided reduced cholera incidence among people not vaccinated as well as those vaccinated in a community [Ali et al., 2005]. The risk of getting cholera among placebo recipients in *baris* (clusters of households) with vaccination coverage rates of >51%[6] was not much higher than that of vaccinees in the same baris and was nearly five times lower than among placebo recipients in *baris* 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 *bari* than in a low coverage *bari* (*Figure 9*). The correlation between adult vaccination coverage and infant incidence was statistically significant [Ali et al., 2008]. The findings of herd protection have been recently reaffirmed during the clinical trial of Shanchol™ in Kolkata, India and during a demonstration project using Dukoral[®] in Zanzibar.

Figure 9. Cholera incidence rates among children too young to be vaccinated (<2 years) by level of vaccination coverage during the first year of follow-up in the Matlab clinical trials of two killed oral cholera vaccines
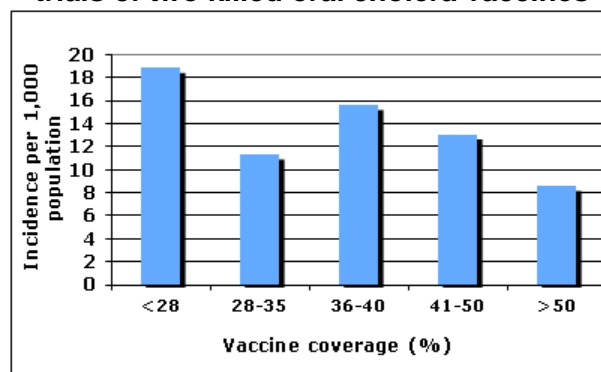
Source: [Ali et al., 2008]

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[6] 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).

The herd effects from oral cholera vaccines could substantially increase the impact of cholera vaccination beyond what the rates of direct protective efficacy would suggest. A model 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]. Estimates of herd protection based on the Matlab data are incorporated into the analyses of disease transmission and the impact and cost-effectiveness of oral cholera vaccination for this investment case (see *Section 7*).

Cholera vaccines in the pipeline

A number of cholera vaccines are in development throughout the world. The three most advanced candidates are all oral live attenuated mutants of *V. cholerae* O1 El Tor: 1) Peru 15 (developed at Harvard University and now owned by Vaccine Technologies, Inc. (VTI), 2) *V. cholerae* 638 (developed by Finlay Institute in Cuba), and 3) VA1.4 (developed in India). These new vaccines can potentially provide protection in a single dose, since live organisms could result in intestinal colonization, eliminating the need for repeat dosing. They also have the promise of longer-lasting protection than the currently-available killed whole-cell-based vaccines. These vaccine candidates may also be effective in infants, enabling their incorporation into routine infant immunization programs. The potential drawbacks of these vaccines include: 1) possible mutations of the attenuated strains in the environment, potentially rendering them virulent, 2) they require administration with a buffer, and 3) at present, all of them must be kept frozen. More information on these vaccines is shown in *Appendix 3*.

Each of the three most advanced vaccine candidates or their precursors have undergone safety and immunogenicity testing in humans in cholera-endemic countries, with positive results. Further Phase 2 trials are underway or are planned for each of these vaccines. Efficacy trials of all three vaccines are still likely several years away and thus, none are likely to be available on the market for at least five to ten more years.

Vaccine assumed for the analyses

The impact, cost and cost-effectiveness analyses in this investment case assume the use of the modified O1/O139 whole-cell (WC) vaccine. This vaccine was chosen for analysis because of its more sustained protection (especially in young children), lower age of effectiveness (one year old vs. two years), and improved adaptability for use in developing countries (i.e., no buffer and streamlined packaging) as compared to the WC-rBS (Dukoral®) vaccine. There is also the potential for the O1/O139 WC vaccine to be produced by more manufacturers over time – increasing the likelihood of sufficient production capacity to meet the forecasted demand and possibly further lowering the price, as new competitors enter the market. This does not preclude the use of Dukoral® in some countries, especially as the producer has offered competitive prices for public sector use.

None of the vaccines currently in development are included in this investment case, since the success and timing of their clinical development is at present too uncertain.

Section 3. Proposed strategies to control cholera through vaccination

3.1 Two-pronged approach towards cholera control

This investment case proposes a two-pronged approach towards the control of cholera through immunization:

1) Introduction of cholera vaccine into immunization programs in high-risk areas of cholera-endemic countries; and

2) Pre-emptive or reactive vaccination to prevent the occurrence or spread of cholera outbreaks both in endemic and non-endemic countries through the use of a global cholera vaccine stockpile.

3.2 Control of endemic cholera

3.2.1 Targeted beneficiaries

Population groups

We assume that in all countries, cholera vaccination will be targeted to areas considered at high risk for the disease, as opposed to being administered universally. High-risk areas can include those where cholera cases or outbreaks have taken place in the past, those identified by laboratory-based cholera surveillance, and absent such data, areas presumed to be at high risk, such as urban slums and low-income rural areas without safe water supplies or adequate sanitation. Countries may also choose to target vaccination for other marginalized populations assumed to be at high risk, such as refugees and internally-displaced persons. The vast majority of beneficiaries of cholera vaccination would therefore be the poor and marginalized groups in both urban and rural areas.

Target ages

The disease burden analysis estimated that nearly three-quarters (72%) of the annual cholera disease burden occurs in children 14 years and younger (see *Figure 7* above). Given this, many endemic countries may opt to target children 1-14 years old. Since the disease can strike all ages, some countries may opt instead to vaccinate all ages eligible to receive the vaccine, including adults. Ideally, sentinel site surveillance, if available, will be used to assist age targeting.

Other beneficiaries

Unlike several other vaccine-preventable diseases, cholera can have substantial macro-economic impacts in a country. As described in more detail in *Section 2.2.2* above, reports of cholera outbreaks can result in a sudden decline in tourists visiting the country and to a sharp reduction in exports of seafood and other food products and even outright bans. Even without outbreaks, the knowledge or suspicion that cholera exists in a country can suppress the growth of certain industries, such as tourism and food exporting businesses, and impact the economy as a whole. Therefore, other potential beneficiaries of a cholera vaccination program in endemic countries are tourism, food exporting and possibly other industries.

3.2.2 Vaccination delivery strategies and revaccination

The O1/O139 killed whole-cell vaccine is not currently licensed for use in infants and thus cannot be incorporated into the routine infant EPI schedule. Effectively controlling the disease will also require vaccinating primary and middle-school aged children, and potentially adults. For these two reasons, mass vaccination campaigns will be the most practical and effective means of delivering cholera vaccines to endemic populations, using schools, markets, and other appropriate community settings as vaccination points. Countries where EPI vaccines are routinely provided to children beyond the age of one year (e.g., a DPT booster at 18 months) could incorporate cholera vaccination into the routine schedule as a complementary strategy to the mass campaigns (for instance, to reach young children between campaigns). If studies underway in India show that the O1/O139 WC vaccine is efficacious in infants, the vaccine could be incorporated into the infant schedule, though mass vaccination for older ages will still be necessary, at least until endemic disease is reduced substantially in an area.

Data from the on-going Phase 3 trial in Kolkata indicate that the O1/O139 WC vaccine provides sustained protection for three years. Therefore, the analyses assume that revaccination will be required after three years and thus that mass vaccination campaigns will take place every three years. As data on the fourth and fifth year of follow-up become available from the trial, the recommended frequency of revaccination could be re-assessed.

3.3   Control of cholera outbreaks/epidemics

This investment case includes use of a global cholera vaccine stockpile. The stockpile analysis, described in *Section 4.2*, assumes that it would be used by both endemic and non-endemic countries to prevent outbreaks, such as following floods or cyclones, or to control currently occurring outbreaks from spreading to their country or to new areas within their country. Since outbreaks tend to strike all age groups, mass vaccination campaigns for outbreak control would cover all ages eligible for the vaccine.

Section 4. Target countries and demand forecast

4.1   Control of endemic cholera

4.1.1 Target countries

A demand forecast was conducted to determine which countries would introduce cholera vaccination to control endemic disease, and how many doses they would use each year over time. This analysis does not take vaccine production capacity into account, and thus assumes that supply will be able to meet the projected demand (see *Section 5*). The analysis, described in detail in *Appendix 4*, started with the 51 countries identified in the disease burden analysis as cholera-endemic (having reports of cholera in three of the past five years). Six countries where cholera vaccination was not found to be cost-effective due to relatively low incidence were eliminated from the analysis.[7]

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[7] These six countries are: China, Indonesia, Iran, Philippines, Thailand, and Vietnam.

For the remaining 45 countries, a scoring system was applied to determine which countries would introduce the vaccine by the year 2020, the last year of introduction included in this investment case. The scoring index includes four variables:

1) estimated cholera mortality rates (based on the IVI disease burden model described in *Section 2.2.1*, and on actual reports in the WHO *Weekly Epidemiological Record* and other sources);

2) the country's past history in introducing new vaccines (hepatitis B, Hib and pneumococcal conjugate) into their national immunization programs;

3) the country's coverage rates for measles-containing vaccine, as an indicator of the capacity and performance of its national immunization program; and

4) any past experience the country has had with cholera surveillance or vaccination, including demonstration projects or vaccine clinical trials.

The scores were then converted into predicted years of adoption of cholera vaccination. Two adjustments were made to the predicted adoption year: the time to adopt was delayed for countries prone to or experiencing political turmoil (e.g., DR Congo), and was accelerated for countries that are currently piloting cholera vaccination programs (e.g., Bangladesh and India) or that have expressed interest in introducing the vaccine (e.g., Uganda, Nigeria).The first year of introduction is assumed to be 2015 to allow sufficient time for Shantha to increase production capacity.

A total of 33 countries are predicted to introduce cholera vaccination to control endemic disease between 2015 and 2020 (see *Figures 10 and 11* below). The remaining 12 countries are projected to adopt cholera vaccination in 2021 or later, which is beyond the scope of this investment case.

Figure 10. Number of countries forecasted to adopt cholera vaccination from 2015 to 2020: cumulative and by year
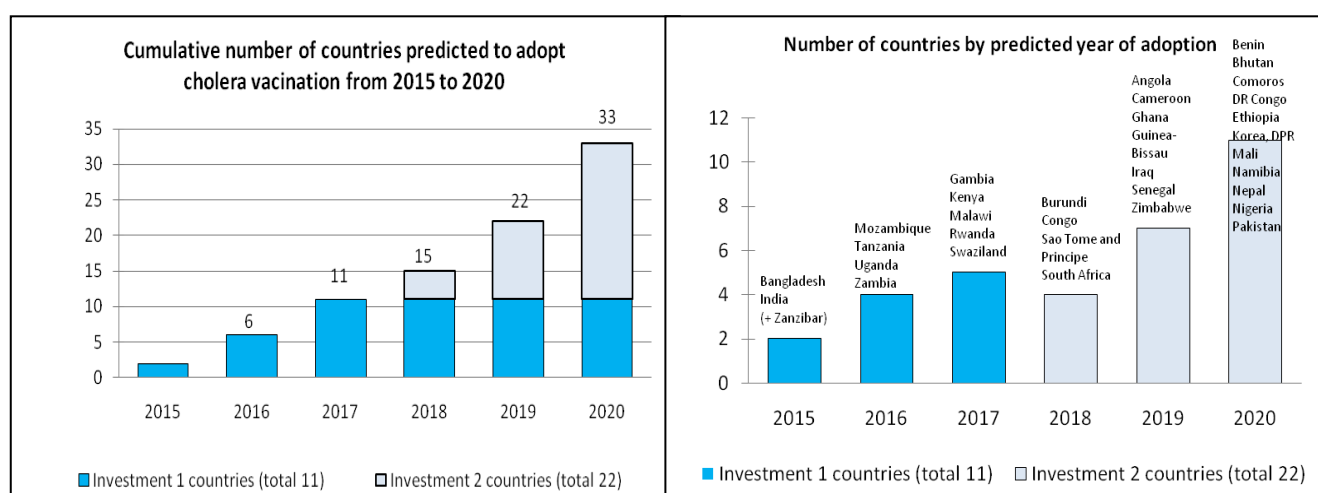
Note: India is predicted to introduce cholera vaccine by state, starting with two states in 2015 and continuing into Investment 2.

Figure 11. Map of the cholera-endemic world by predicted phase of cholera vaccine introduction
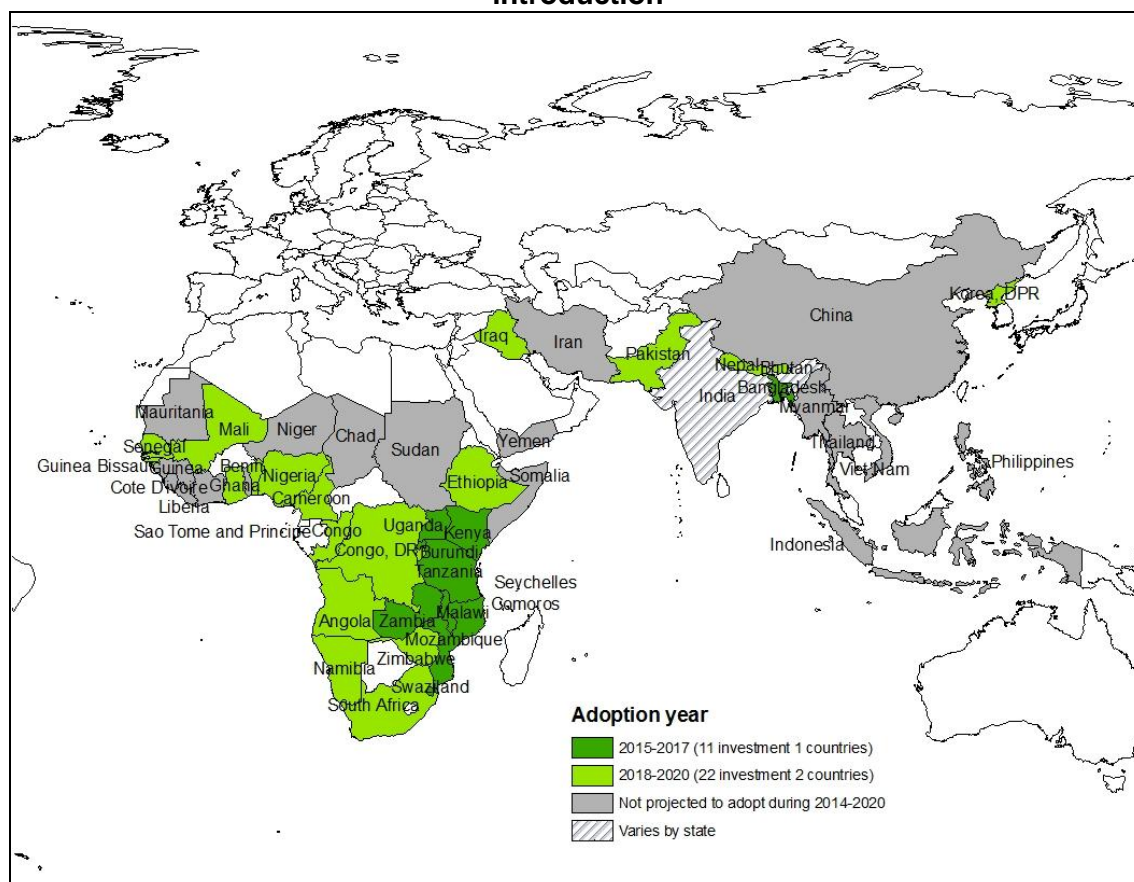
* Countries predicted to adopt cholera vaccination 2021 or later are beyond the scope of this investment case.

Eleven of these countries are forecasted to introduce the vaccine from 2015 to 2017 through what we are proposing as an initial investment ("Investment 1"). Investment 1 countries include the early adopting countries of Bangladesh, India (selected states), Uganda, Mozambique, Tanzania and Zambia – most of which have had experience with cholera vaccine demonstration projects or clinical trials, or have expressed interest in introducing the vaccine. Given its expressed interest in cholera vaccination and the vaccination demonstration project currently underway, the autonomous Tanzanian island of Zanzibar is predicted to introduce the vaccine a few years before the rest of Tanzania.

The remaining 22 countries are forecasted to adopt cholera vaccination between 2018 and 2020 through a second investment ("Investment 2").

Of the 33 countries included in this investment case, twenty-six (79%) are in the AFR region, five (15%) are in the Southeast Asian region, including India and Bangladesh, and two (Pakistan and Iraq) are in the Eastern Mediterranean region. Twenty-six (79%) of the countries are GAVI-eligible (as of 2010). Seven countries (21%), including Angola, S. Africa, and Iraq, either are not currently eligible or are graduating from GAVI support.

For India, which is assumed to introduce the vaccine one state at a time, all 18 of the country's 35 states and union territories identified in the disease burden analysis as cholera-endemic (based on were scored against two variables: average annual cholera incidence rates

(from the analysis in [Kanungo et al., 2009]) and measles vaccination coverage rates. Two states are forecasted to introduce cholera vaccination early on as part of Investment 1: West Bengal, where the efficacy trial of Shanchol™ is taking place, and Orissa, where a pilot introduction of the vaccine began in 2011. Ten more Indian states are forecasted to introduce cholera vaccination between 2018 and 2020 under Investment 2 (see *Figure 12*).

Figure 12. Forecasted phase of introduction of cholera vaccine in India, by state
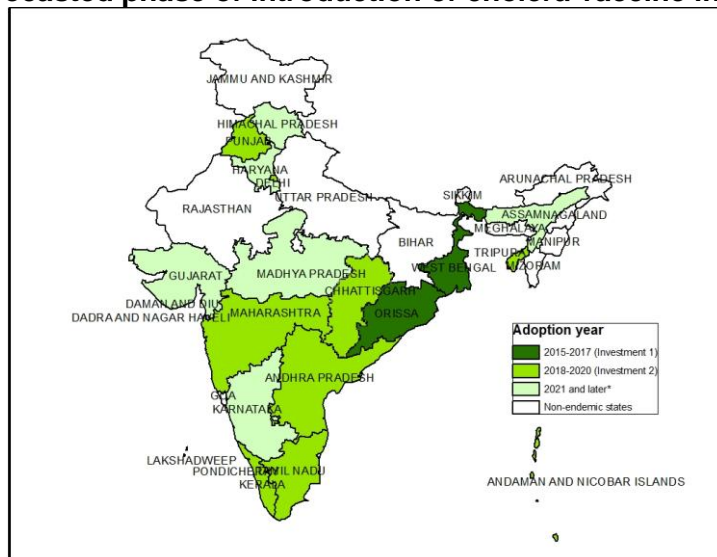
* Beyond the scope of this investment case

4.1.2 Predicted demand (number of vaccine doses)

The 2010 WHO Position Paper on cholera vaccines provides some guidance to countries for targeting cholera-endemic populations for cholera vaccination. It recommends targeting areas that have a recorded incidence of 1/1,000 population or more in at least three of the last five years, or, in the absence of incidence data, areas identified by public health officials as at high risk of cholera. WHO also recommends targeting children for vaccination, especially where resources are limited, although other high-risk groups (e.g., HIV+ individuals and pregnant women) and adults should be considered, as funding permits. Each country's approach for targeting at-risk populations for cholera vaccination and the target age group will depend to a large extent on available funding, as well as political and cultural factors.

Given these uncertainties, this investment case presents two scenarios for targeting populations for vaccination against endemic cholera (*Figure 13*). The "Large Target" scenario would target all persons living in urban slums and in rural areas with poor access to improved water sources. The "Small Target" scenario would target a sub-population of slum dwellers and rural residents without improved water supplies that would be considered at highest risk, and that consists of 50% of Large Target population. For each target scenario, we present two options for targeting age groups: children 1-14 years old, and all persons one year and above[8]. The population targeted for vaccination in the 33 target countries ranges from 113 million to 637 million, depending on the program option. In practice, different countries will choose different targeting options, including new ones not presented here. These scenarios, however, provide an estimate of the range of demand for cholera vaccine in endemic countries.

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[8] Assuming use of the WC O1/139 vaccine, which is licensed for use in persons one year and older.

Figure 13. Scenarios for targeting cholera vaccination in 33 cholera-endemic countries included in the investment case analyses
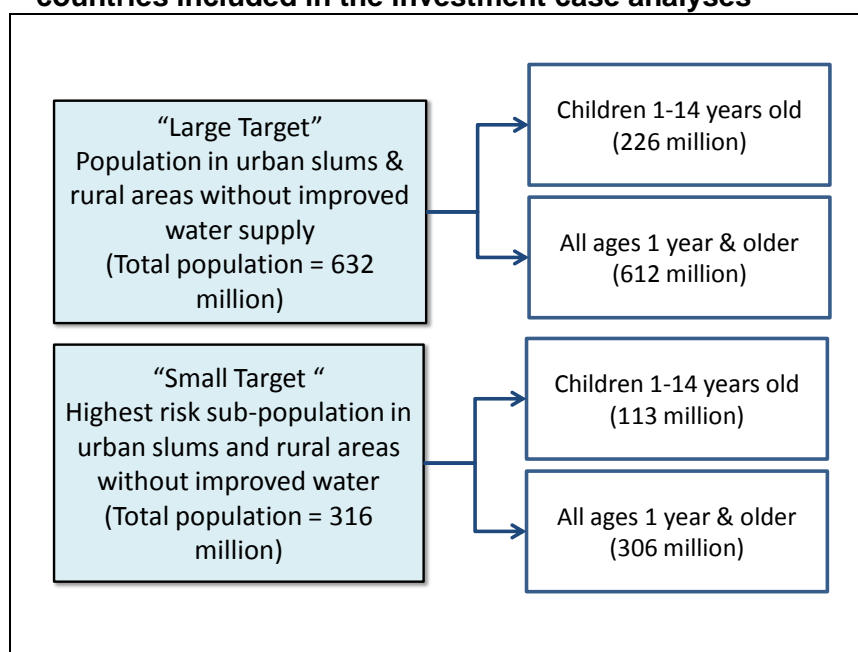
An analysis of predicted demand was performed to estimate the number of doses that would be used for each of the four program options in the 33 target countries, using software developed by Applied Strategies, Inc. (San Mateo, CA). The forecast estimates cholera vaccination coverage rates in each country, based on country-specific coverage rates for measles-containing vaccine, and assumes that cholera vaccine coverage would be 80% of the measles coverage rates among 1-14 year olds and 50% among persons 15 and older. The rate for measles vaccine is used because it is representative of vaccines that are administered at older ages (nine months or older). The resulting estimated cholera vaccine coverage rates range from 37% to 79% for 1-14 year olds and 23% to 50% for persons 15 and older. The analysis uses a vaccine wastage rate of 5%, assuming the vaccine is sold in single-dose vials. It also assumes that vaccination is phased in over three years in each country and that revaccination occurs after three years (see *Appendix 4* for more details on the assumptions and parameters used). The results are shown in *Figure 14*.

The Small Target program for children 1-14 years old (*Figure 14a*) would result in a demand of 18-21 million doses per year for Investment 1 countries from 2017 onward, and 41-44 million doses for Investment 2 countries from 2020 and after. In total, this program would require an annual total of 6-28 million doses for the first several years (2015-2019) and 60-65 million doses thereafter. If all ages are vaccinated (*Figure 14b*), Investment 1 countries would require 18-41 million doses per year for the first three years and 41-51 million doses from 2017 to 2030. Investment 2 countries would add another 4-20 million doses per year from 2018 to 2019, and 92-108 million doses per year after 2020, for a total of 135-159 million doses per year from 2020 to 2030.

Figure 14. Forecasted demand for cholera vaccine by program option and investment, 2015-2030 (million doses)

a. Small Target (highest at-risk populations): ages 1-14

b. Small Target: all ages 1+

c. Large Target, ages 1-14

d. Large Target, ages 1+
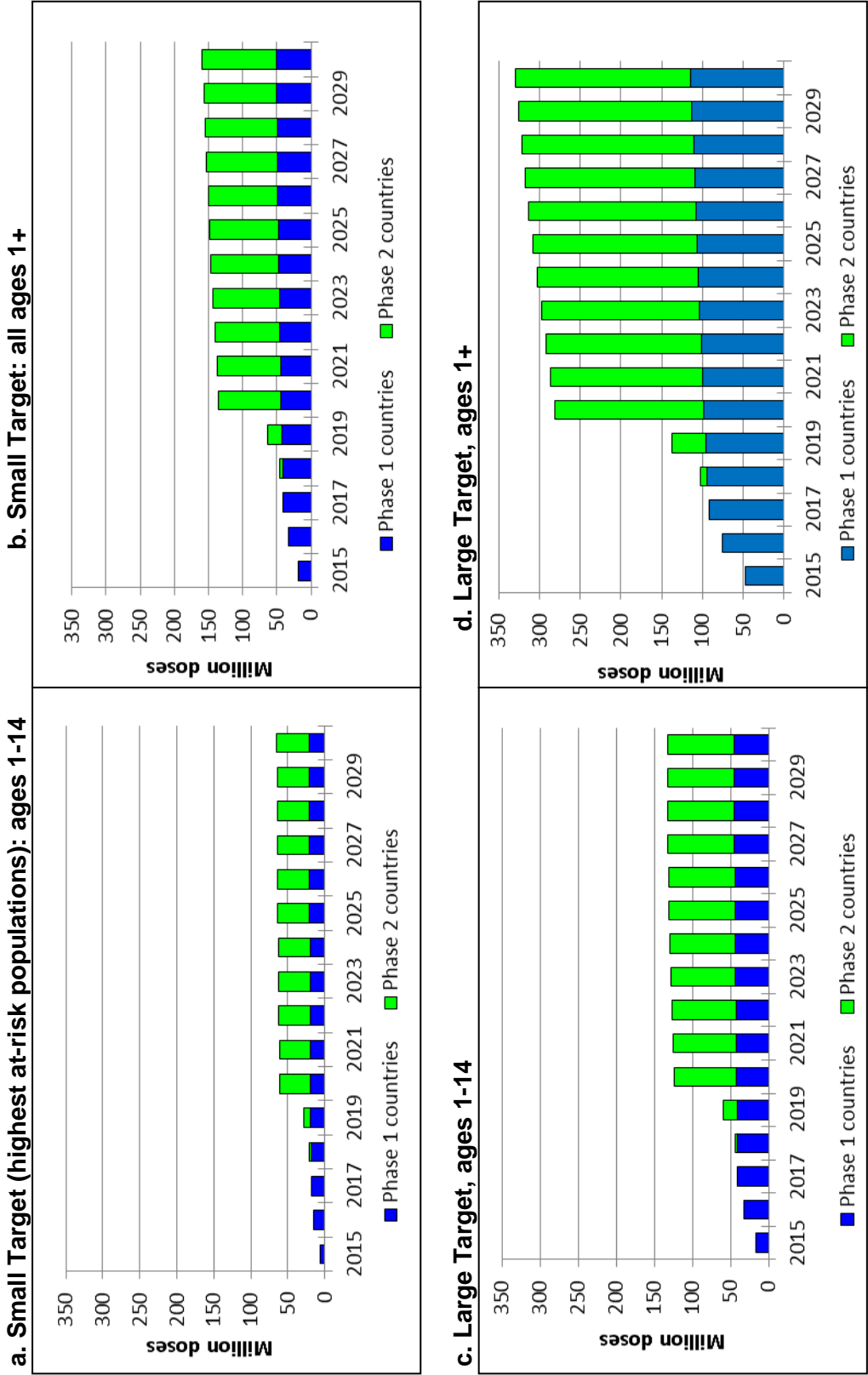
If all countries chose the Large Target strategy, the demand would essentially double. The program for 1-14 year olds in Investment 1 countries (*Figure 14c*) would require 17-32 million doses annually from 2015 to 2016, and 40-45 million doses per year from 2017 to 2030. The demand from Investment 2 countries would start at 3-18 million doses from 2018 to 2019, and then jump to 82-88 million doses per year from 2020 to 2030. The total requirements for both investments combined would therefore be 17-59 million doses per year from 2015 to 2019, and 124-133 million doses per year from 2020 to 2030 for the Large Target children-only scenario.

For the scenario in which all eligible ages are vaccinated in the Large Target areas (*Figure 14d*), the potential demand in the countries included in Investment 1 would start at 47 million doses in 2015 and grow to 92 million doses by 2017, as all 11 countries adopt the vaccine. The number of doses required for the Investment 1 countries would further increase incrementally to 114 million doses by 2030 as a result of population growth. Once countries under Investment 2 begin introducing cholera vaccination in 2018, the demand would rise by 41 million doses by 2019 and by 184 doses in 2020, when 11 countries are predicted to adopt the vaccine. Assuming both investments are funded, the total demand for the "all-ages, Large Target" scenario between 2020 and 2030 would be 281 million to 330 million doses.

In all scenarios, 65% of vaccine doses would be used in the AFR countries, 32% in SEAR (primarily Bangladesh and selected Indian states), and 3% in the two EMR countries (Pakistan and Iraq) (*Figure 15*). The great majority of the forecasted demand – 92% – would be used in countries that will remain GAVI-eligible after 2010. Detailed results of the demand forecast by age group, WHO region and GAVI eligibility can be found in *Appendix 4*.

Figure 15. Breakdown of demand (number of doses) for cholera vaccine for all scenarios by WHO region for the 33 target countries
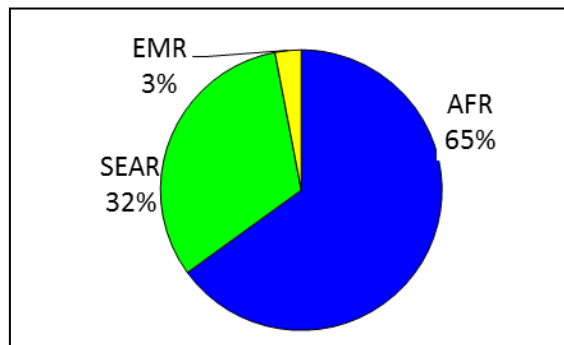
4.2   Control of cholera outbreaks: use of a cholera vaccine stockpile

4.2.1   Rationale for creation of a cholera vaccine stockpile

The WHO 2010 Position Paper on Cholera Vaccines recommends that "pre-emptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas" [WHO, 2010], p. 128]. The Position Paper also recommends that reactive vaccination "could be considered by local health authorities as an additional control measure, depending on the local infrastructure and following a thorough investigation of the current and historical epidemiological situation, and clear identification of geographical areas to be targeted." Decisions about the use of both pre-emptive and reactive

vaccination will be facilitated by the field testing and refinement of a decision-making and risk-assessment tool currently under development by WHO to guide health authorities on when to use cholera vaccine during crisis situations.

Based on recent experience responding to outbreaks of yellow fever and meningococcal meningitis, countries will be much more likely to conduct vaccination campaigns to prevent or control cholera outbreaks if there is a global cholera vaccine stockpile. It is likely that cholera vaccines would have been used to control the 2010-11 Haiti epidemic if a global stockpile existed. The stockpile will allow countries to rapidly acquire and use vaccine that is set aside each year for such emergencies. As described in *Section 2.3.2*, the feasibility of conducting successful mass vaccination campaigns using oral cholera vaccines during emergencies or in post-crisis situations has been demonstrated in several instances in the past 13 years. Modeling of the epidemics in Haiti and Zimbabwe also suggest that reactive vaccination, especially for populations identified as at high-risk of getting the disease during the outbreak, would have been highly cost-effective.

Establishment of a stockpile could also accelerate the use of the vaccine to control endemic disease in the same countries, provide an incentive for countries to improve cholera surveillance, and provide valuable experience in deploying cholera vaccines prior to their introduction of national programs.

4.2.2 How large should the stockpile be?

The number of people at risk for epidemic cholera each year can be estimated based on the number of cholera cases reported to WHO, ProMed and other sources, and the applying attack rates to determine the size of the population at risk. Using attack rates ranging from 3/1,000 to 10/1,000 based on estimates from recent outbreaks, between 13 million and 43 million people are estimated to be at risk of getting cholera during outbreaks in any particular year. However, this may be an over-estimate, since not all reported cases are likely to be the result of outbreaks. There are other factors, besides the number of people at risk, that will determine the demand for a cholera vaccine from a stockpile. These include the ability of a country to conduct mass vaccination campaigns, including during emergency situations, without interfering with other priority interventions, and the interest and political will among policymakers in using the vaccine.

Using the average ratio of vaccines distributed from the polysaccharide meningococcal vaccine stockpile to the reported number of meningitis cases in Africa over a three-year period yields an estimated demand of eight million doses of cholera vaccine per year for the African continent for outbreak prevention or control[9].

Based on the experiences of the yellow fever and meningitis vaccine stockpiles, this investment case proposes establishing a pilot stockpile in 2012 of two million doses, enough to vaccinate nearly one million people. The stockpile could begin in 2012 – a few years earlier than introduction of the vaccine for endemic disease control, since current production capacity is sufficient to supply this quantity. As demand is demonstrated, the stockpile could grow to five million and eventually to 10 million doses (*Figure 16*). As endemic countries roll out mass vaccination to control endemic disease, the need and demand for vaccine from the stockpile to prevent or control outbreaks may diminish over time. See *Appendix 5* for more details on the stockpile analysis.

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[9] After taking into account the two-dose regimen of cholera vaccine.

Figure 16. Projected number of doses of oral cholera vaccine used through a stockpile per year
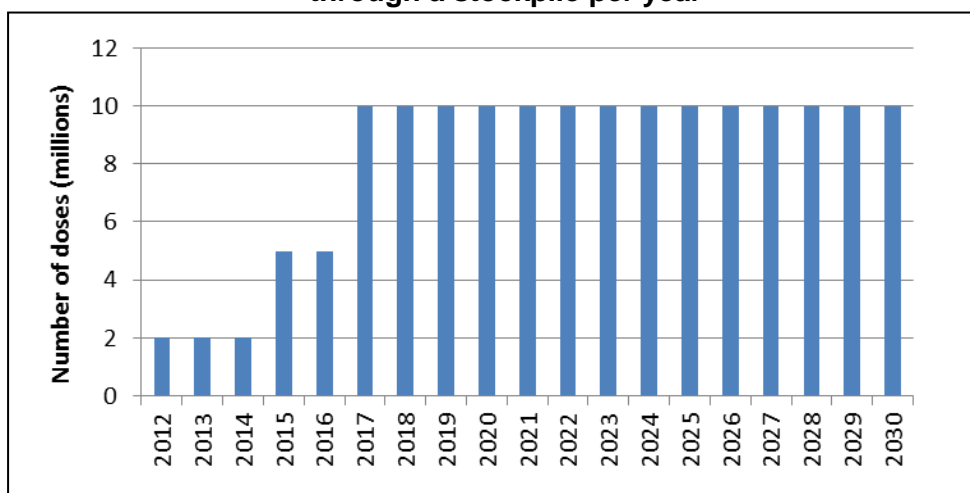
4.2.3 Management and operation of the cholera stockpile

The design and management of the proposed cholera vaccine stockpile can be informed by the experience of the yellow fever and meningitis vaccine stockpiles. Like these stockpiles, a central procurement agency, such as UNICEF, would establish contracts with one or more producers on an annual or longer basis, and the stockpile would be stored at the producer(s)' facilities. An International Coordinating Group (ICG), made up of UNICEF, WHO, and other relevant partners, would be responsible for making timely decisions in response to country requests for use of the stockpile, based on pre-established criteria. The ICG's secretariat could be located at WHO headquarters. As with the yellow fever vaccine stockpile, vaccine stock remaining at the end of the year could be used the following year for non-emergency use (e.g., as part of vaccine introduction in endemic countries), thus guaranteeing manufacturers a minimum demand each year and ensuring that unused vaccines would not be wasted. Therefore, the stockpile would be replenished in full at the beginning of each year.

As with the yellow fever stockpile, countries could be obliged to cover 50% of the operational costs of vaccination, with exceptions for hardship, and donors would cover the remaining 50%, as well as the cost of the vaccine. Middle-income countries could be required to reimburse the stockpile for vaccine costs once an emergency is over.

Section 5. Vaccine supply and pricing: current projections and future requirements to meet projected demand

5.1   Cholera vaccine producers and current and projected production capacity

There are currently three producers of oral cholera vaccines and production capacity is at present, quite limited. Crucell/SBL Vaccines is the sole producer of Dukoral® (WC-rBS) . The current production capacity of Dukoral® is about three million doses per year. However, the company can increase its production capacity, if there is a demonstrated demand for the vaccine.

The current production capacity for Shantha's O1/O139 (Shanchol™) vaccine is around two million doses in Shantha's existing production facility, which is shared with other vaccines. If the company builds a dedicated cholera vaccine production facility, production capacity could gradually increase to 25 - 30 million doses per year. For the supply analysis, we assume that the production capacity of Shanchol™ will increase to 20 million doses per year in 2015, and then to 30 million doses in 2016. The other producer of the modified O1/O139 WC vaccine, VaBiotech in Vietnam, has a production capacity of 10 million doses per year for its mORC-VAX® vaccine. Assuming that Vietnam's national regulatory authority is approved by WHO by 2013, we estimate that it will take two more years for the mORC-VAX® vaccine to be WHO pre-qualified (i.e., by 2015). The total projected supply of pre-qualified O1/O139 WC vaccine by 2015 is therefore 30 million doses per year, increasing to 40 million doses in 2016 (*Figure 17*)[10]. The IVI has also transferred the modified O1/O139 WC vaccine technology to Eubiologics, a Korean biotechnology company. Assuming Eubiologics can secure sufficient capital investment and proceed through development stages quickly, it could manufacture up to 25 million doses as early as 2015/16.

Figure 17. Projected production capacity for WHO pre-qualified* O1/O139 whole-cell only cholera vaccines under current plans
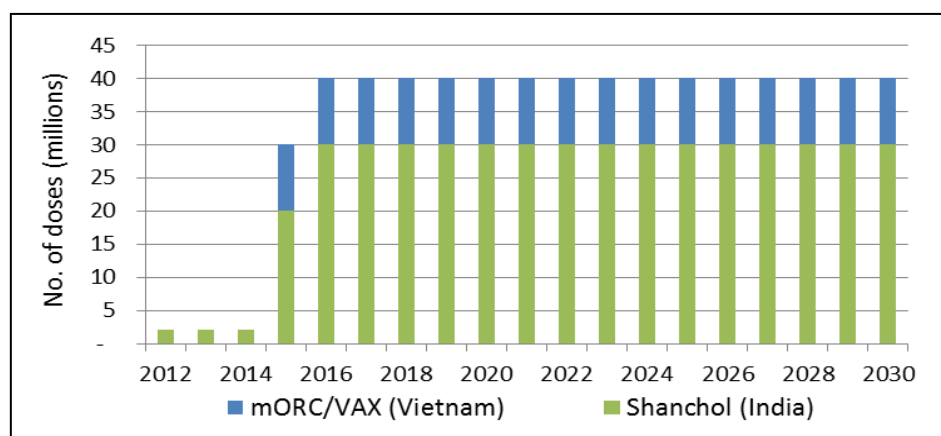
*Assuming mORC/VAX becomes WHO-prequalified in 2015

5.2   Supply requirements to meet projected global demand

This analysis estimates the expansion in capacity needed to meet the projected demand for cholera vaccine over time. This expansion can be achieved by current producers building additional cholera vaccine facilities or expanding capacity in their current facilities, by new producers entering the market, or through a combination of both. Since the O1/O139 WC vaccine is not patent-protected, it is very possible for new producers – likely emerging producers from developing countries – to acquire the technology and begin producing the vaccine, if they conclude that the vaccine demand and their return on investment would be sufficient.

The current production capacity of Shanchol™ is just sufficient to establish a two-million dose vaccine stockpile starting in 2012. The projected supply of O1/O139 WC vaccines

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[10] The supply of Dukoral® is not included in this analysis, since the investment case is based on the use of the modified O1/O139 WC only vaccine. However, Dukoral® could be used for endemic disease control or for the stockpile, increasing the global supply of oral cholera vaccines.

(Shanchol™ and mORC-Vax®) will also be sufficient if the stockpile grows to five million doses by 2015 and 10 million doses beginning in 2017. This takes into account only the global demand for public sector use and not private market sales (e.g., in India).

As shown in *Figures 18* and *19* and in *Table 6*, once the early adopter countries and two Indian states begin cholera vaccine introduction for the control of endemic disease in 2015, as projected in the demand forecast, the projected supply of 40 million doses will be sufficient to meet the demand (including the stockpile) through 2015 or 2016 for all but the largest introduction scenario (Large Target, all ages one and above). If all 33 countries in the demand forecast chose the Small Target option for 1-14 year olds (*Figure 18a*), there would be a projected shortfall, starting in 2020, of around 30 million doses per year. Assuming an average production capacity of 30 million doses per production facility, this would require that at least one additional facility be built and operational by 2020. If all 33 countries decided to vaccinate all persons one and older in the Small Target areas (*Figure 18b*), the gap between supply and demand would begin in 2016 and grow to 105 million doses per year by 2020, requiring the addition of four production facilities.

Figure 18. Supply vs. demand for O1/O139 WC cholera vaccines assuming all 33 countries adopt the Small Target option for endemic disease control and the creation of a vaccine stockpile for emergency use
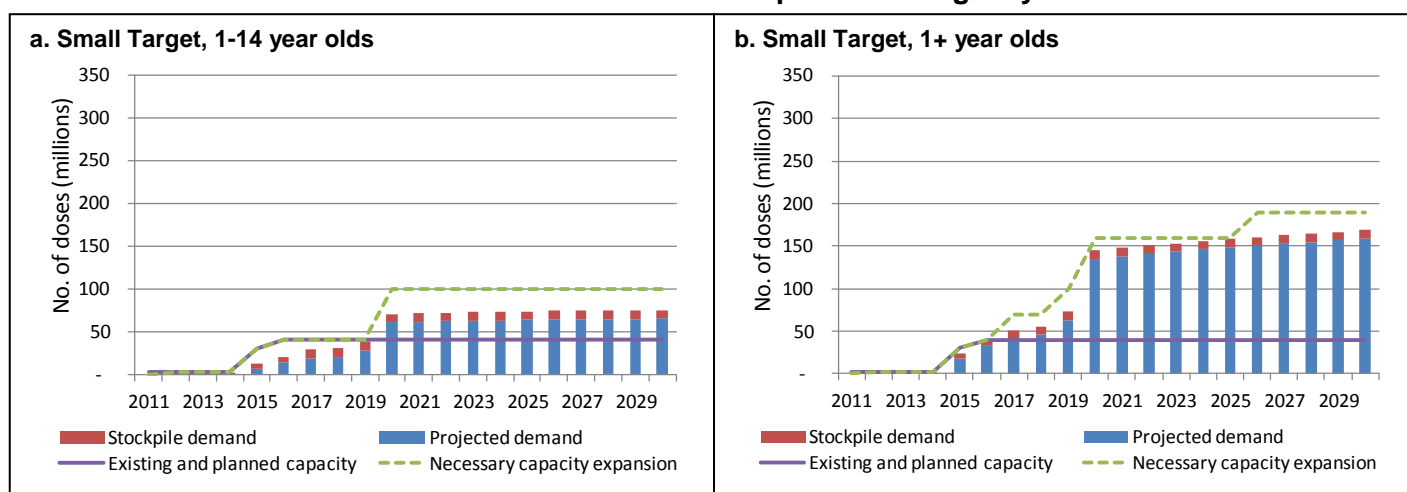
If all 33 countries chose to vaccinate only 1-14 year old children under the Large Target scenario *(Figure 19a)*, the gap between supply and demand would be around 94 -103 million doses per year between 2020-2030. This gap would require that four additional production facilities be built by 2020 (*Table 6*). The greatest gap between projected supply and demand – about 250 million doses per year in 2020 – would be realized if all 33 countries adopted the strategy of vaccinating all eligible ages in the Large Target areas (*Figure 19b*) – an unlikely scenario.

In summary, the production capacity from a dedicated Shanchol™ facility plus the existing mORC-Vax® capacity would be insufficient for even the smallest potential demand projection. However, entry by Eubiologics or another new manufacturer may fill the gap for the smallest projection. For all other scenarios, significant increases in production capacity would be required.

In reality, different countries will likely choose different vaccination strategies, including ones not included in this investment case, making it difficult to predict with much certainty the gap between vaccine supply and demand over time. However, as countries indicate interest in introducing cholera vaccine and make plans for doing so, and as donors indicate their interest in providing financial support, more precise forecasting can be conducted to guide both current and potentially new suppliers in making decisions on whether and how to meet the anticipated demand.

Figure 19. Supply vs. demand for O1/O139 WC cholera vaccines assuming all 33 countries adopt the Large Target option for endemic disease control and the creation of a vaccine stockpile for emergency use

a. Large Target, 1-14 year olds

b. Large Target, 1+ year olds
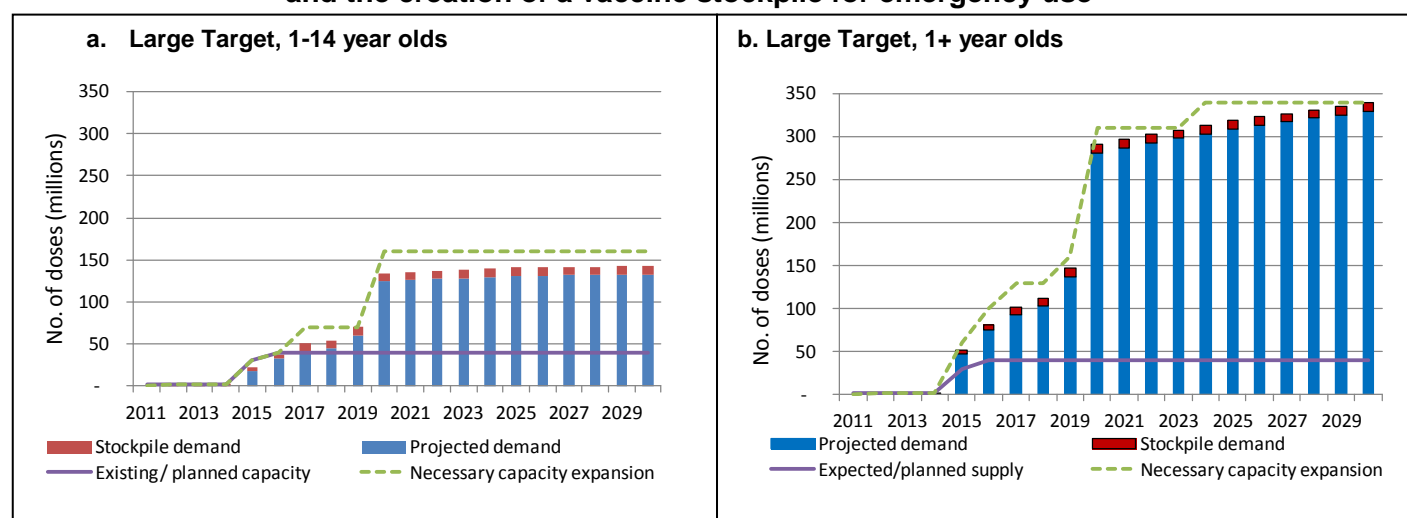
Table 6. Difference between currently projected supply and demand for WHO-prequalified O1/O139 whole-cell cholera vaccines and additional production facilities required to meet demand*

Year	Small Target scenarios				Large Target scenarios			
	1-14 year olds		1+ year olds		1-14 year olds		1+ year olds	
	No. doses (millions)	No. new facilities required**	No. doses (millions)	No. new facilities required**	No. doses (millions)	No. new facilities required**	No. doses (millions)	No. new facilities required**
2012	0	0	0	0	0	0	0	0
2014	0	0	0	0	0	0	0	0
2016	+21	0	2	0	3	0	-41	2
2018	+10	0	-16	1	-14	1	-72	1
2020	-30	1	-105	3	-94	3	-251	6
Total new facilities required by 2020		1		4		4		9

* Demand is based on the results of the demand forecast for the control of endemic cholera (see Section 4 and Appendix 4) and the establishment of a vaccine stockpile. The assumed size of the vaccine stockpile is 2 million doses from 2012 to 2014, 5 million doses from 2015 to 2016 and 10 million doses from 2017 to 2030. A "+" indicates a supply greater than projected demand, while a "-" indicates a supply less than demand.

** Assumes an average production capacity of 30 million doses per year per facility.

Section 6. Costs and financing needs

This section describes the costs and potential financing sources for the introduction of oral cholera vaccine with preventive campaigns, based on the results of the demand forecast presented in *Section 4*. Also, the cost of delivering cholera vaccines through the use of a global stockpile is discussed. As mentioned in the demand forecast, the analysis assumes that vaccination is phased in over three years in each country and that revaccination occurs after three years, based on the three year duration of protection demonstrated for Shanchol™ in the on-going clinical trial in Kolkata, India. Details on the analysis of costs are found in *Appendix 7*.

6.1   Cost of cholera vaccination

6.1.1   Assumed cost of vaccination per dose

The costs of introducing oral cholera vaccines in preventive campaigns consist of the cost of the vaccines, including vaccine wastage, and the operational cost of delivering the vaccines.

Projected vaccine prices

Relative to a number of other vaccines, the production of killed whole-cell-based cholera vaccines requires long fermentation cycles, because each dose requires a high concentration of each of five different strains of *V. cholerae*. Achieving economies of scale in production by increasing the yield is more limited than for several other vaccines because of the time per dose required to grow whole cell bacteria to the necessary cell densities. Therefore, it is unlikely that these vaccines will ever be available at prices as low as the basic EPI vaccines or the current hepatitis B vaccines. The current O1/O139 WC vaccine producers – Shantha and VaBiotech – are already based in developing countries, and thus the option of relocating production facilities to less expensive countries to save on production costs is not available.

Shantha has committed to a public sector price of $1.85 per dose for Shanchol™. The current price of the Vietnamese vaccine mORC-VAX® is $0.75 to the EPI program and $1.00 to the private sector. The prices of mORC-VAX® may have to increase to meet the production and quality control requirements for WHO pre-qualification. For this investment case, we assume an average public sector price per dose for O1/O139 WC vaccines of $1.85 from 2012 to 2017, and $1.45 from 2018 onward, as projected demand increases. This 21% reduction from the current public sector price of Shanchol™ is based on the assumption that there will be some increases in production efficiency and economies of scale, and potentially increased competition from new producers entering the market.

It is possible that the vaccine price could fall further with increased demand and additional efficiencies. We assume that the lowest possible price for a O1/O139 WC vaccine that meets the requirements of WHO pre-qualification is $1.00 per dose, which we use as the lower boundary in the sensitivity analyses. The upper boundary used in the analyses is $1.85, the current public sector price of Shanchol™. The assumed cost of insurance, customs and freight (CIF) is 15% of the vaccine price ($0.28 during the period of 2015-2017 and $0.22 from 2018 to 2020), for a total CIF price of $2.13 for the first period and $1.67 for the second period.

<u>Vaccine delivery costs</u>

The operational cost of delivering vaccines to the target populations includes logistics, social mobilization, training, monitoring and surveillance, and personnel costs. The operational cost per dose in this study is estimated at US$0.60 per dose, based on the WHO comprehensive Multi-Year Plans Guidelines for EPI vaccines [WHO 2006]. The sensitivity analysis includes a range of US$0.30 – $1.10, based on a range of cost estimates from studies of EPI vaccines and of oral cholera vaccination in different countries [Levin et al., 1999; Cavailler et al., 2006].

6.1.2 *Total estimated costs for endemic disease control (preventive campaigns)*

The estimated total costs of introducing oral cholera vaccine in the 11 Investment 1 countries (including two Indian states) during the period of 2015 to 2017 ranges from $107 million if only children are vaccinated in the Small Target (highest risk) areas to $585 million if all ages one and above are vaccinated in the Large Target areas (*Table 7*). The costs in Investment 1 countries for the next three-year period (2018-2020) increase slightly (ranging from $129 million to $653 million) due to population increases. The total costs of Investment 1 from 2015 to 2020 would therefore range from a low of $236 million for the children-only Small Target program to a high of $1.24 billion for the all-ages, Large Target program.

Table 7. Total estimated costs of introducing oral cholera vaccine for Investment 1 countries for the period of 2015 to 2020, by scenario, USD (2010) millions*

Population Target	Target age group	Population size (millions)	No. doses (millions)	Vaccine cost (millions)**	Vaccine delivery cost) (millions)	Total cost (millions)
2015-2017						
Small Target areas	1-14	19	39	$83	$24	$107
	1+	44	91	$195	$55	$250
Large Target areas	1-14	43	89	$190	$54	$244
	1+	102	215	$457	$129	$585
2018-2020						
Small Target	1-14	27	57	$95	$34	$129
	1+	61	128	$213	$77	$290
Large Target	1-14	59	124	$207	$75	$282
	1+	137	288	$480	$173	$653
Total 2015-2020						
Small Target	1-14	46	96	$178	$58	$236
	1+	104	219	$408	$132	$539
Large Target	1-14	102	214	$398	$128	$526
	1+	239	503	$937	$302	$1,238

* Includes two Indian states (Orissa and West Bengal) as well as the countries of Bangladesh, Mozambique, Tanzania, Zambia, Gambia, Kenya, Malawi, Rwanda and Swaziland.
** Vaccine price includes $1.85 for the FOB price and $0.28 for customs, insurance and freight charges, for a total CIF price of $2.13 per dose until 2017; and $1.45 for the FOB price and $0.22 for customs, insurance and freight charges, for a total CIF price of $1.67.

The estimated costs for Investment 2 are shown in *Table 8* for the time period of 2018 to 2020. The total costs range from $118 million for the Small Target program for children 1-14 years old to $528 million for the Large Target program for all ages. While Investment 2 includes 22 additional countries and 10 additional Indian states, most do not begin introduction until 2019

or 2020. Therefore, the full costs of implementation are realized over this three-year period only for the four countries and one Indian state forecasted to begin vaccine introduction in 2018. Eleven countries and five Indian states will not begin introduction until 2020 and thus, vaccination will have taken place in only one-third of the targeted areas in these countries by the end of this investment.

Table 8. Total estimated costs of cholera vaccination for Investment 2 countries for the period of 2018 to 2020 (Investment 2 countries) by scenario, USD (2010) millions*

Population Target	Target age group	Population size (millions)	No. doses (millions)	Vaccine cost (millions)**	Vaccine delivery costs (millions)	Total cost (millions)
Small Target	1-14	25	52	$87	$31	$118
	1+	55	116	$194	$70	$264
Large Target	1-14	49	104	$173	$62	$236
	1+	111	233	$388	$140	$528
* Includes 22 countries and 10 Indian states (see Section 4 and Appendix 4 for a list of countries and Indian states). * * Vaccine price includes $1.45 for the FOB price and $0.22 for shipping and handling, for a total CIF price of $1.67 per dose.						

If both investments are financed, the total costs from 2015 to 2020 would range from $354 million, if all 33 countries adopted the strategy of vaccinating children in the Small Target areas to $1.77 billion if all countries vaccinated all ages in the Large Target areas (*Table 9*). The total cost would be $762 - $803 million if all countries chose either the children only Large Target option or the all-ages Small Target option.

Table 9. Estimated cost of introducing oral cholera vaccine by investment from 2015-2020, US$ (2010) millions

Investment	Small Target		Large Target	
	Ages 1-14	Ages 1+	Ages 1-14	Ages 1+
Investment 1 countries:				
2015 - 2017	$107	$250	$244	$585
2018 - 2020	$129	$290	$282	$653
Total Investment 1 (2015 - 2020)	$236	$539	$526	$1,238
Investment 2 countries:				
2018 - 2020	$118	$264	$236	$528
Total Investment 1 and 2 from 2015 to 2020	$354	$803	$762	$1,766

Figure 20 shows the breakdown of the costs of the Small Target scenario for children 1-14 years of age by time period and by WHO region. Approximately half of the cost from 2015 to 2017 would be for vaccination in the Southeast Asian region, since Bangladesh and two Indian states – all with sizeable populations – are projected to introduce the vaccine during this period. The other half of the cost would occur in the nine African countries included in Investment 1. However, from 2018 to 2020, two-thirds of the costs will occur in the African region as 13 African countries, including Nigeria, are projected to adopt cholera vaccination. Two countries

from the Eastern Mediterranean region (Pakistan and Iraq) are also projected to introduce the vaccine during this period.

Figure 20. Total estimated cost of cholera vaccination for the Small Target scenario for 1-14 year olds by WHO region (US$ millions)
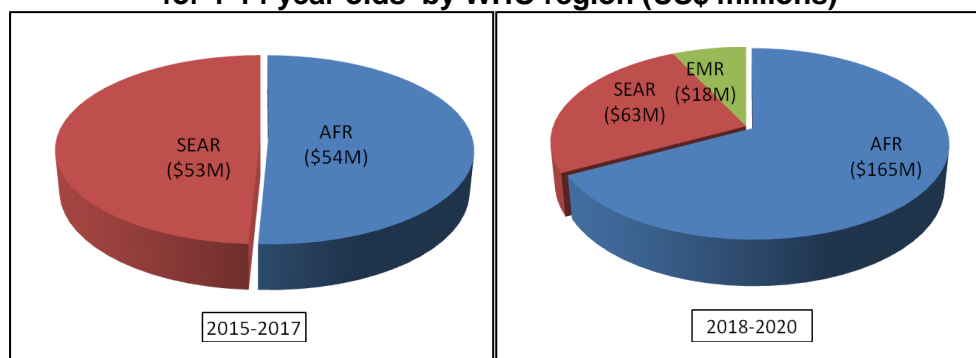
6.1.3. Total estimated costs of the vaccine stockpile

The total estimated cost for the stockpile is based on vaccine prices and delivery costs described above and the estimates of the size of the stockpile over time (see *Section 4.2*). As shown in *Figure 21*, the estimated cost of the stockpile, including the operational costs of delivering the vaccine in the field, would be $5.5 million per year for a two-million dose stockpile in 2012-2014, around $13.6 million per year for a five-million dose stockpile in 2015-16, and around $23-27 million per year for 10 million doses from 2017.

Figure 21. Projected costs of a cholera vaccine stockpile
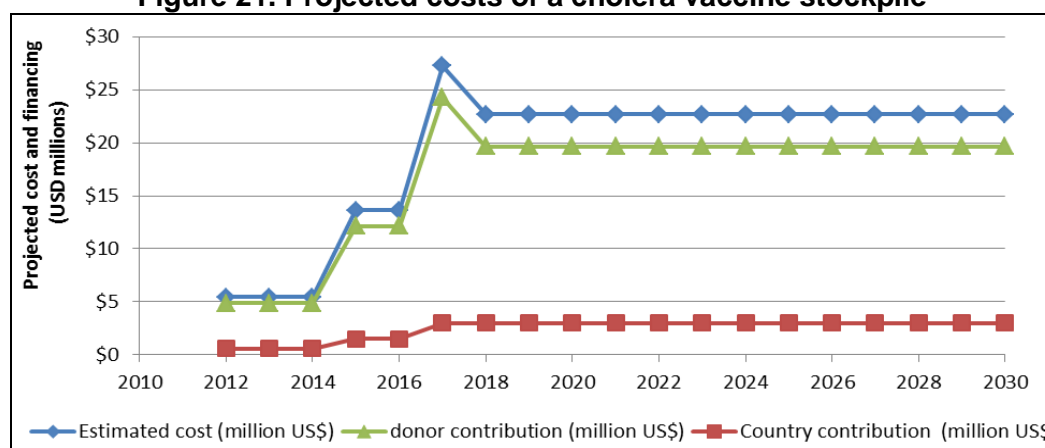
* Assumed vaccine price per dose is $1.85 from 2012 to 2017 and $1.45 beginning in 2018.

The total cost of a cholera vaccine stockpile would be about $71 million for the six year period of 2012-2017. An additional $68 million would be required from 2018 to 2020, assuming that the size of the stockpile stays at 10 million doses. The assumption used in the analysis is that the proposed stockpile would be funded primarily by donors, who would cover the purchasing costs as well as 50% of the operational costs. Countries that use vaccine doses from the stockpile would be expected to contribute the remaining 50% of operational costs.

6.2   Financing for cholera vaccination

Financing for cholera vaccination in endemic countries could come from several potential sources, including external partners and internal (government) sources (*Table 10*).

Table 10. Possible internal and external sources of financing for cholera vaccination

External	Internal
Bilateral Donors	National Government – MOH, other Ministries affected by cholera – e.g. Ministries of Fisheries and Agriculture
Development banks (e.g. World Bank)	Local governments(e.g., provinces, municipalities)
Regional donors (e.g. European Union)	Local NGOs and foundations
GAVI Alliance	Local Industries(e.g., restaurant/ hospitality, seafood, other food industries)
	Health insurance

6.2.1   Potential external sources of financing

One potential source of financing for low-income countries to introduce newer vaccines is the GAVI Alliance. However, due to the uncertainty about whether and when GAVI will begin providing support for cholera vaccine introduction, other sources of financing should be sought as well. Potential external sources of financing could be development banks, bilateral donors, and regional donors. Development banks could have an interest in financing or subsidizing cholera vaccination in their regions, especially given cholera's predominance among impoverished populations and the negative impact that it has on local economies. Financing for cholera vaccine could therefore be part of a larger economic development or health sector project.

Bilateral donors that are working to improve the conditions of vulnerable populations in developing countries may be interested in financing cholera vaccination, particularly if these groups live in flood-prone areas or are slow to adapt to behavior change to improve sanitation and hygiene.

Other multi-country donors such as the European Union are working in many countries to improve the technical capacity to process and produce foods for export. For example, the EU is financing a project to provide support to Bangladesh to strengthen inspection and quality control of seafood. A logical extension of this assistance would be financing for vaccination for the seafood workers and populations in surrounding communities.

In some countries, the priority of funding cholera vaccination could be related to the negative impact of climate change on the risk of cholera (discussed in *Section 2.1.3* above). Development banks, including the World Bank, are currently designing projects to mitigate the negative impact of climate change on the risk of cholera. As part of these projects, financing for cholera vaccination could be included.

6.2.2 Internal sources of financing

Governments usually provide funding for at least a proportion of the costs of introducing a new vaccine. They generally pay for the vaccine delivery (operational) costs and often a proportion of the cost of the vaccine as well. Health, finance, and planning ministries could advocate for funding from the health budget to introduce cholera vaccine in high-risk populations on the grounds that the control of outbreaks is costly both in terms of program manager time and expenses required to manage these events and treat infected persons. In addition, the economy in affected areas is often negatively impacted by these outbreaks. Other ministries may also have an interest in supporting the vaccination of at-risk populations because of cholera's potential impact on agriculture, fisheries and tourism.

Local governments may also be interested in introducing the vaccine if their populations are living in at-risk areas, and may be willing to pay for the vaccine or operational costs. For example, Delhi state in India has introduced and paid for hepatitis B, MMR, and typhoid Vi vaccines on its own. In addition, hepatitis B vaccine is also purchased in India by large state-owned companies, such as the power company, NTPC, for its employees and families [DeRoeck, 2001].

Private industry (e.g., seafood and tourism) also may perceive that cholera outbreaks have a negative impact on the demand for their goods and services. Thus, they may be interested in financing vaccination against cholera for their workers and/or populations living nearby. A further source of local funds could be local NGOs and foundations.

Consumers are often willing to pay for vaccines at subsidized prices, especially when they believe that they are at risk of contracting the disease. Some governments may be interested in introducing cholera vaccines at subsidized prices in their clinics so that the population can have access to them. Also, some vaccine producers may be willing to provide new vaccines to the public sector or to NGOs at discounted prices to increase utilization of their vaccine. For example, Indian producers, in concert with NGOs, ran big immunization camps in India to provide people hepatitis B vaccine at discounted prices.

Another potential source of financing is through health insurance, including national health insurance plans and private insurance (e.g., provided to workers).

6.2.3 Financing scenarios

Table 11 shows some potential scenarios for a mix of financing for cholera vaccination for children in Small Target areas in the first three years (2015-2017). Option 1 relies largely on internal sources of funding (central and local governments and local industries), which make up 60% of total financing. Option 2 is even more dependent on local sources, but on private sources more than public sources, with industries and consumers financing 50%. The third option is a scenario with more reliance on funding from external partners (80%).

Table 11. Possible financing scenarios for oral cholera vaccine during Phase 1, Small Target scenario, ages 1-14

Financing source	Option 1 Weighted towards local public and private sources		Option 2 Weighted towards local private sources		Option 3 Weighted towards external funding	
	%	Cost (millions)	%	Cost (millions)	%	Cost (millions)
National governments	25%	$27	15%	$16	10%	$11
Local governments	15%	$16	15%	$16	10%	$11
Local industries	20%	$22	25%	$27	0%	$0
Consumers	0%	$0	25%	$27	0%	$0
Development banks	0%	$0	20%	$22	50%	$54
Bilateral donors	40%	$43	0%	$0	30%	$32
Total	**100%**	**$107**	**100%**	**$107**	**100%**	**$107**

Part 2: Rationale for Investing

This part of the investment case examines the impact and cost-effectiveness of cholera vaccination for the control of endemic cholera, as well as potential constraints and probability of success. These analyses do not include the use of the projected cholera vaccine stockpile for emergencies, since there are no data available to estimate the potential impact of a cholera vaccine stockpile.

Section 7. Expected public health impact of oral cholera vaccines with preventive campaigns

In this section, the expected impact is shown for each investment with preventive vaccination from 2015 to 2020 in the 33 countries included in the investment case. Assuming these countries continue vaccination after 2020, we also show the cumulative impact from 2015 to 2030.

7.1. Assumptions used to estimate vaccination impact

Key assumptions used in estimating vaccination impact are shown in *Table 12* and described in detail in *Appendices 8 and 10.* The annual incidence and case fatality rates are taken from the analysis of the global burden of cholera described in *Section 2.1.4.* While it is expected that incidence rates would be higher for the Small Target (highest risk) population relative to the Large Target population, there are insufficient data to calculate an average relative difference in incidence rates, and therefore the same rates are assumed for both the Large and Small Target populations.

The populations targeted for vaccination are estimated from the demand forecast described in *Section 4.1.* As mentioned, the forecast assumed that the cholera vaccine coverage rate in each country would be 80% of the country's coverage rate for the first dose of measles vaccine for 1-14 year olds and 50% of the measles coverage rate for persons 15 and older (resulting cholera vaccination coverage estimates are 23% to 50% for 1-14 year olds and 37% to 79% for persons 15 and older).

The vaccine efficacy rate is based on the results over three years from the Phase 3 trial of the O1/O139 WC (Shanchol™) vaccine taking place in Kolkata, India. The estimates of herd protection are based on a deterministic dynamic model of disease transmission studies created for this investment case. The model was calibrated based on a re-analysis described in *Section 2.3.2.* of data from the original clinical trials of oral killed whole-cell based cholera vaccines in Matlab, Bangladesh, which provided evidence that cholera vaccination provides indirect protection to non-vaccinated members of the population as well as additional protection to those vaccinated [Ali et.al 2005]. The dynamic model also drew upon a stochastic model of cholera transmission that was developed for one cholera season within a community in Bangladesh, based on the Matlab data [Ali et al., 2005; Longini et al., 2007].

Based on assumed vaccination coverage rates, the model estimates that cholera vaccination for persons one year and older will provide 68-82% protection to the entire community (vaccinated and unvaccinated), depending on the region and age group (*Table 12*). Vaccinating 1-14 year olds is estimated to provide 57-74% protection. On average, programs

targeting children would reduce incidence in the targeted population by around 62%, while vaccinating all ages would result in a 75% reduction.

Table 12. Key assumptions used in vaccination impact estimates by WHO region

Parameter	Age Group or Time Period	AFR	SEAR	EMR
Annual incidence rate (per 1,000 population)	<1 1-4 5-14 15+	10.0 9.8 3.1 1.3	6.8 6.6 2.1 0.9	5.6 5.4 1.7 0.7
Case fatality rate		3.8%	2.5%*	3.2%
Direct vaccine efficacy rate (without herd protection) (all ages 1 and above)	70% over three years			
Overall protection of population (vaccinated and unvaccinated) with estimated herd effects:				
Vaccination of 1-14 years	<1 1-4 5-14 15+	61% 63% 65% 59%	57% 66% 66% 57%	67% 74% 74% 66%
Vaccination of 1+ year olds	<1 1-4 5-14 15+	68% 71% 74% 71%	74% 79% 79% 75%	77% 82% 82% 78%
Vaccine duration	3 years			
Frequency of revaccination	Every 3 years			
Vaccine coverage	For 1-14 years old: 80% of country-specific coverage rates for measles-containing vaccine For ≥15 year olds: 50% of coverage rates for measles-containing vaccine			

* The CFR for the Southeast Asian region is lower than in the disease burden analysis (Section 2 and Appendix 1), due to revisions made for Bangladesh, based on a separate analysis of cholera disease burden used in the Bangladesh country investment case study.

7.2   Impact of cholera vaccination on Investment 1 countries: 2015-2020

From 2015-2017 oral cholera vaccine would be introduced in 11 countries through Investment 1, based on the results of the demand forecast. Cumulatively from 2015 to 2020, this investment is estimated to have the following impact, with the range due to the four options for targeting vaccination within countries:

- 908,000 to 2.5 million cholera cases prevented
- 27,500 – 69,800 lives saved
- 263,000 – 751,000 hospitalizations averted
- Savings of $10.3 – 28.7 million in direct medical costs

Table 13 shows that for both the Small and Large Target scenarios, approximately half as many persons would be vaccinated under the 1-14 age option as for the all-ages option. However, the impact of cholera vaccination (in terms of cases averted, lives saved) would be increased by only 20-25% if administered to all ages rather than to children for both target

scenarios. This is because of the herd protection effect that lowers transmission of the disease among non-vaccinated persons (i.e., adults), if vaccination is limited to children.

Table 13. Impact of the investment in Investment I countries, 2015 to 2020, using transmission model with herd protection

Impact	Small Target		Large Target	
2015-2017:	**1-14**	**1+**	**1-14**	**1+**
No. vaccinated	18,682,000	43,570,000	42,616,000	102,197,000
No. cases averted	255,000	310,000	604,000	740,000
No. lives saved	6,900	8,300	15,300	18,400
No. hospitalizations prevented	78,000	96,000	192,000	237,000
Savings in direct medical costs, US$	$2,952,000	$3,603,000	$7,161,000	$8,794,000
2018-2020:				
No. vaccinated	27,000,000	60,807,000	59,168,000	137,119,000
No. cases averted	653,000	780,000	1,450,000	1,742,000
No. lives saved	20,600	24,300	43,400	51,400
No. hospitalizations prevented	185,000	223,000	425,000	514,000
Savings in direct medical costs, US$	$7,310,000	$8,759,000	$16,530,000	$19,931,000
Total 2015-2020:				
No. vaccinated	45,682,000	104,377,000	101,784,000	239,316,000
No. cases averted	908,000	1,090,000	2,054,000	2,482,000
No. lives saved	27,500	32,600	58,700	69,800
No. hospitalizations prevented	263,000	319,000	617,000	751,000
Savings in direct medical costs, US$	$10,262,000	$12,362,000	$23,691,000	$28,725,000

7.3   Impact of cholera vaccination on Investment 2 countries: 2018-2020

For Investment 2 countries, cholera vaccination would be introduced into twenty-two countries from 2018 to 2020. Cumulatively over this three-year period, this investment would:

- Prevent 200,000 – 460,000 cholera cases
- Save 7,300 – 16,700 lives
- Prevent 50,000 – 115,000 hospitalizations
- Save $ 2.3 million - $ 5.2 million in direct medical costs

The impact on Investment 2 countries in preventing morbidity and mortality is shown in *Table 14* by target and age group. The increase in impact from vaccinating adults as well as children would be even less in these countries (around 15%), as many of the Investment 2 countries have lower estimated incidence rates than the highly-endemic Investment 1 populations (dominated by Bangladesh and Indian states). This is because, according to the dynamic model of cholera transmission, the herd effects from vaccinating children only would be greater in higher-incidence than lower-incidence areas.

Table 14. Impact of the investment in Investment 2 countries, 2018-2020, using transmission model with herd protection

Impact	Small Target		Large Target	
	1-14	1+	1-14	1+
No. vaccinated	24,700,000	55,400,000	49,500,000	110,800,000
No. cases averted	200,000	230,000	401,000	460,000
No. lives saved	7,300	8,400	14,600	16,700
No. hospitalizations prevented	50,000	58,000	100,000	115,000
Savings in direct medical costs, US$	$2,299,000	$2,618,000	$4,598,000	$5,237,000

7.4   Impact of Investments 1 and 2 combined from 2015 to 2020

The total cumulative impact of both investments combined from 2015 to 2020 would be:

- 1.1 – 2.9 million cholera cases prevented
- 34,800 – 86,500 lives saved
- 313,000 – 866,000 hospitalizations prevented
- Savings of $13 – 34 million in direct medical costs.

The estimates by target scenario are shown in *Table 15*.

Table 15. Total cumulative impact of Investments 1 and 2 on burden of disease: 2015-2020, using transmission model with herd protection

Impact	Small Target		Large Target	
	1-14	1+	1-14	1+
No. vaccinated	70,406,000	159,770,000	151,243,000	350,147,000
No. cases averted	1,108,000	1,320,000	2,455,000	2,942,000
No. lives saved	34,800	41,000	73,300	86,500
No. hospitalizations prevented	313,000	377,000	717,000	866,000
Savings in direct medical costs, US$	$12,561,000	$14,980,000	$28,289,000	$33,962,000

7.5   Impact of investments 1 and 2 combined from 2015 to 2030

If cholera vaccination in the thirty-three countries is continued until 2030, its impact will increase substantially. By this time, all countries will have rolled out vaccination to all targeted areas and revaccination after three years will have taken place several times in all areas as well. The cumulative impact of Investments 1 and 2 combined from 2015 to 2030 will be:

- 7.6 – 18.6 million cases of cholera prevented;
- 260,000 – 620,000 lives saved;
- Continuing progress toward Millennium Development Goal 4 (reducing childhood mortality) by preventing 118,000-272,000 deaths in children under five;

- 2.0 – 5.1 million hospitalizations averted; and
- Savings in medical costs of $86 million to $212 million.

Table 16. Impact of the combined Investments 1 and 2 on burden of disease: 2015-2030, using transmission model with herd protection

Impact	Small Target		Large Target	
	1-14	1+	1-14	1+
No. vaccinated	371,727,000	869,188,000	770,922,000	1,824,148,000
No. cases averted	7,566,000	8,854,000	15,863,000	18,635,000
No. lives saved	259,600	301,500	530,200	617,000
No. hospitalizations prevented	2,002,000	2,354,000	4,282,000	5,059,000
Savings in direct medical costs, US$	$85,787,000	$100,067,000	$181,290,000	$212,414,000

Figure 22 shows the numbers of persons vaccinated each year through each investment and the cumulative number of lives saved from 2015 to 2030 for each of the four targeting scenarios. Since countries would phase in vaccination over three years, the number of persons vaccinated continues to increase until 2022. Similarly, the number of lives saved would rise rapidly until 2022 and then begin to plateau.

Figure 23 shows the cumulative number of cases and deaths averted from both investments over the period 2015-2030. Again, due to herd protection, there are only small differences in the numbers of cases and deaths averted between vaccination programs that target all ages greater than one year and those that target only children 1-14 years of age.

The overall reduction in annual cholera incidence projected to occur as a result of both Investments 1 and 2 is shown in *Figure 24* relative to the baseline situation in which none of the 45 countries with high cholera incidence use the vaccine. This assumes that there is no change in the overall cholera burden in the absence of vaccination. However, some countries may develop economically and/or improve water and sanitation infrastructure to reduce incidence independently of vaccination.

7.6   Other public health benefits of cholera vaccine introduction

The introduction of oral cholera vaccine will also have other public health benefits besides reductions in morbidity and mortality. It will reduce the size and frequency of costly outbreak responses, freeing up resources for other activities. It should also increase awareness amongst populations about cholera and how to prevent it, including the benefits of vaccination.

Figure 22. Annual number of persons vaccinated and cumulative deaths prevented from 2015 to 2030 (Investment 1 and 2)

a. Small Target, 1-14 year olds

b. Small Target, all ages 1+

c. Large Target, 1-14 year olds

d. Large Target, all ages 1+
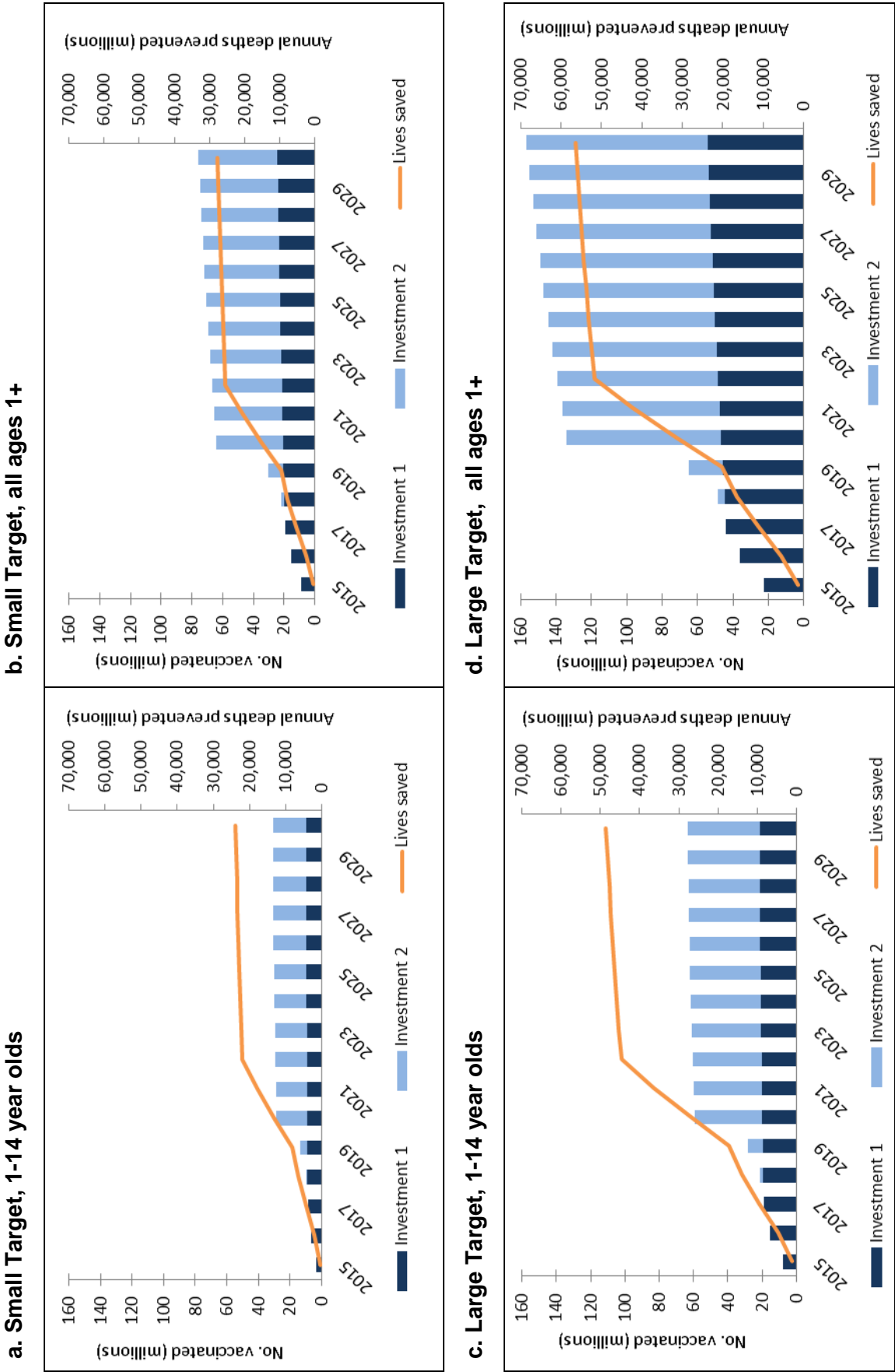
Figure 23. Cumulative cases and deaths averted through cholera vaccination, Investments 1 and 2 from 2015 to 2030

a. Small Target, 1-14 year olds
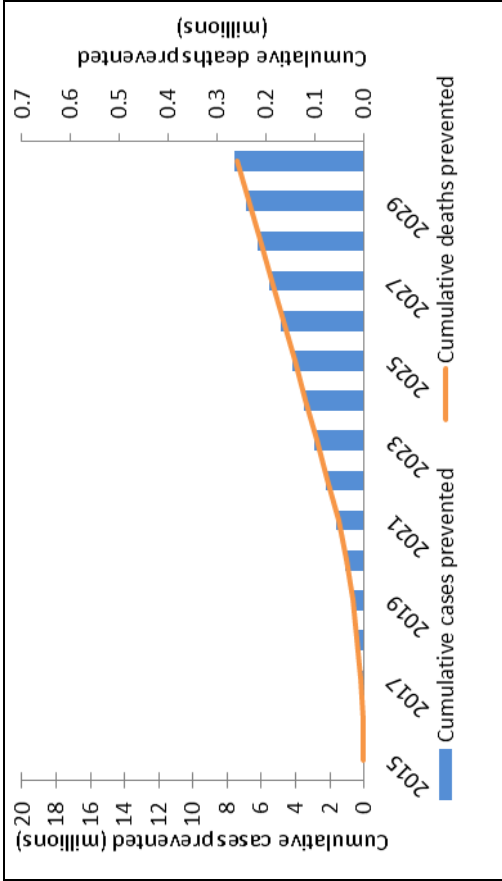
b. Small Target, all ages 1+
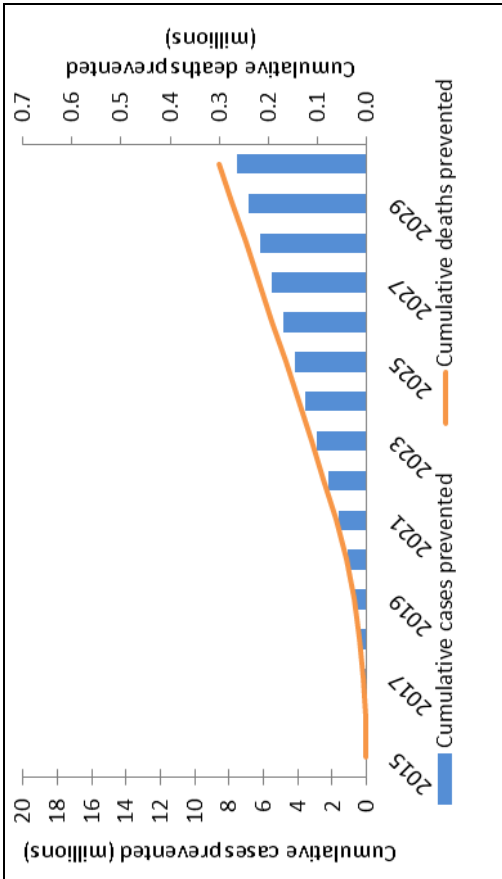
c. Large Target, 1-14 year olds
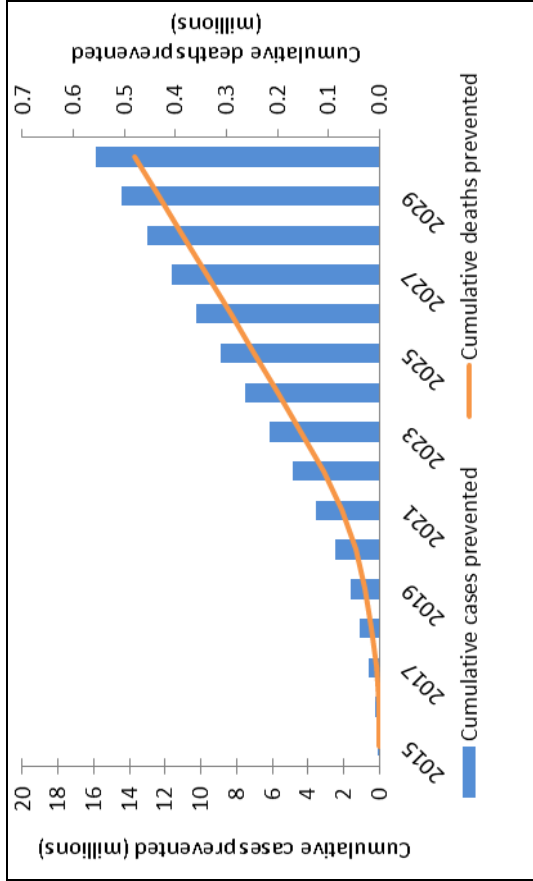
d. Large Target, all ages 1+
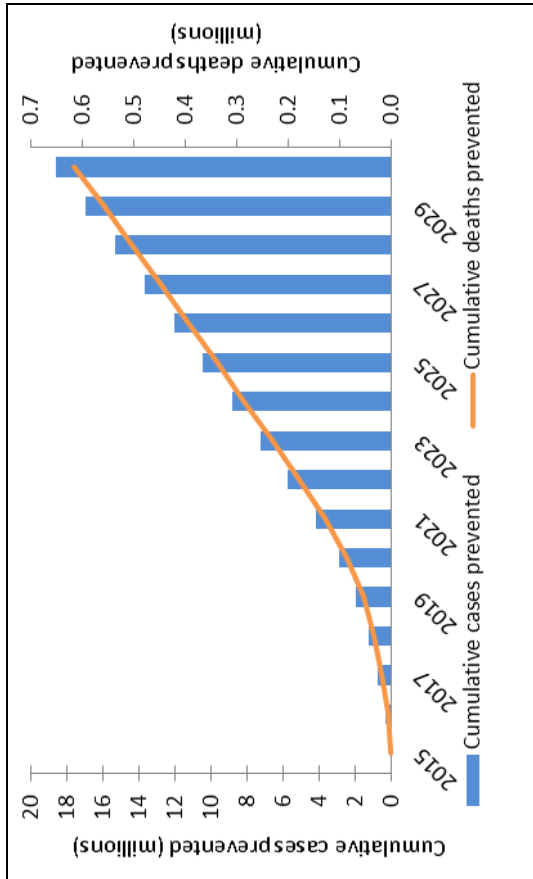
Figure 24. Projected annual reduction in the number of cholera cases due to Investments 1 and 2
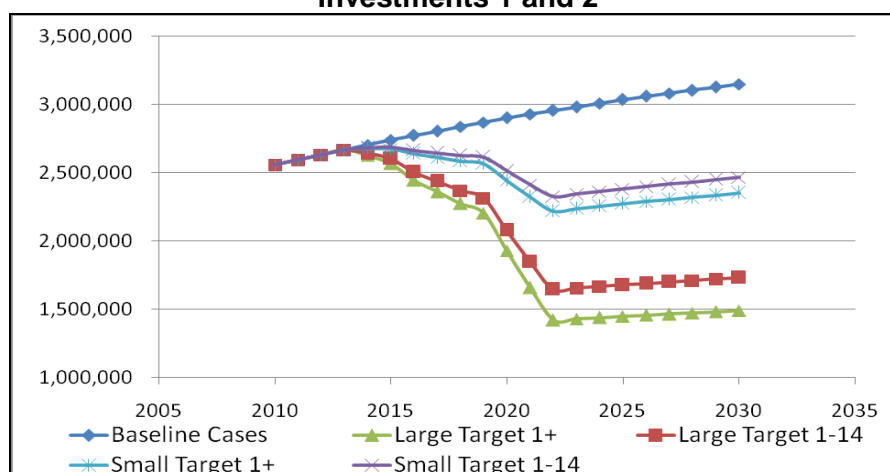
Section 8. Economic analysis

8.1 Cost-effectiveness analysis

A cost-effectiveness study of introducing oral cholera vaccine was conducted by the IVI as part of this investment case for each of the four vaccination targeting scenarios presented. The main measure used is the cost per disability-adjusted life year (DALY) averted as a result of vaccination. This cost-effectiveness ratio is calculated by dividing the net costs of providing oral cholera vaccine through preventive campaigns (the costs of campaigns minus the cost of illness) by the number of DALYs averted.

The cost effectiveness of using vaccines from the stockpile reactively is not estimated due to a lack of data. When stockpile doses are used preemptively in endemic populations, the cost effectiveness should be similar to the estimates for preventive use in endemic areas.

Estimates of cost savings from vaccination were derived by estimating the cholera cost-of-illness, as described above in *Section 2.2.1*. The analysis estimates impact of cholera vaccination with herd protection effects taken into account as described in *Section 7.* The impact of cholera vaccination without herd protection is shown in the sensitivity analysis. As described above, the assumed vaccine price is $1.85 per dose, plus 15% for shipping and handling, for a total of $2.13 per dose during 2015-2017 and $1.45 per dose plus 15% for a total of $1.67 from 2018 onwards. Thus, the weighted average cost of vaccination for the 2015-2020 period is $1.62 plus 15 for a total of $1.86 per dose. Other assumptions and parameters used in the cost-effectiveness analysis are summarized in more detail in *Appendix 10*.

Because available data do not differentiate between cholera incidence and case fatality rates among different sub-populations, the same rates in each country are assumed for the Small Target areas as for the Large Target areas. Since all other parameters in the model are also the same for these two targeting scenarios, the cost-effectiveness results do not differ by Large and Small Target programs, and thus are shown only by target age group and WHO region.

The cumulative cost of targeted cholera vaccination of children 1-14 years old in the 33 countries included in this investment case from 2015 to 2030 would be $151 - $383 per

DALY averted, depending on the WHO region (*Figure 25*). Vaccinating all ages one year and above would cost $267 - $785 per DALY averted. The net cost per death prevented are estimated to be ≈$4,800 - $12,000 if only children 1-14 are vaccinated, and $8,500 - $23,900 if all eligible ages are vaccinated.

These results were then compared to the weighted average Gross Domestic Production (GDP) per capita of the countries included in the analysis, by region, which were ≈$1,000 - $1,200. Using the thresholds established by the 2002 *World Health Report*, interventions with a cost/DALY averted of less than the GDP per capita are considered "very cost-effective", while those with a cost/DALY averted of less than three times the per capita GDP are considered "cost-effective". ***Both programs that target 1-14 year olds and those that include all ages one and above would therefore be "very cost-effective" in all three WHO regions where the target countries are located***.

The introduction of oral cholera vaccine would be the most cost-effective in the African region as compared to other regions, due to the higher estimated cholera incidence and case fatality rates in this region. The greater cost-effectiveness of vaccinating children 1-14 years old compared to vaccinating all ages is due to both the higher incidence rates among children and the herd protection impact of the vaccination program. The diminished efficiency of expanding vaccination from children to adults is demonstrated by the fact that the costs for the all-ages programs are about 240% greater than for the children-only programs, while only about 18% more cholera cases are prevented.

Figure 25. Cost of cholera vaccination per DALY averted by target age group and WHO region, 2015-2030, with herd effects taken into account
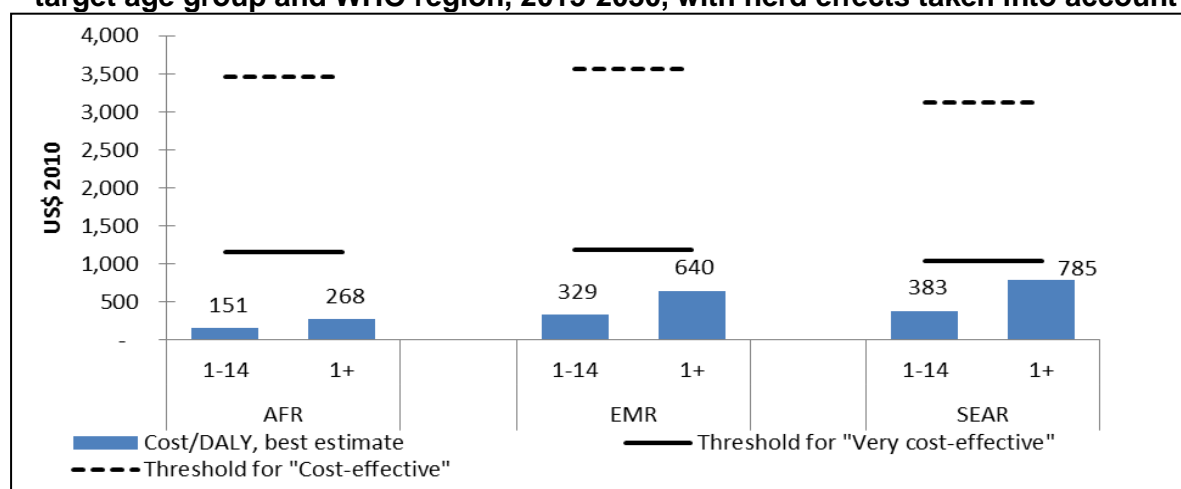
Note: Threshold for "Very cost-effective" is the weighted average GDP amongst the countries included in the investment case.

When the herd effects of cholera vaccination are not included in the analysis, the cost-effectiveness ratios are somewhat higher (see *Figure 1 in Appendix 10*). However, vaccinating children only is still found to be "very cost-effective" in all three WHO regions, as is vaccinating all ages one and above in the African region. In the other regions, vaccination of all ages one and above is cost-effective.

8.2 Sensitivity Analysis

In the sensitivity analysis, the impact of changes in assumptions for the key variables on cost-effectiveness is evaluated. Key drivers of the cost-effectiveness analysis are estimates of cholera incidence, the case fatality rate, herd protection effects, and vaccination costs. As can be seen in *Table 17*, even if the four variables are varied by a wide range, the

cost per DALY for children continues to fall within the "very cost-effective" range and, for the all-age option, it falls within the "cost-effective" range.

Table 17. Results of sensitivity analyses: Cost of cholera vaccination per DALY averted with varying values for key variables (US$)

Parameter	Base Case Value	Range	Cost per DALY averted					
			AFR		EMR		SEAR	
			1-14	1+	1-14	1-14	1+	1-14
Cholera Incidence	Varies by country	50-150% of base	95 - 317	173 – 550	213 - 673	420 – 1,295	265 - 671	549 – 1,362
Case Fatality Rate	Varies by country/region	1-5%	115 - 572	203 – 1,002	210 – 1,048	409 – 2,040	198 - 987	406 – 2,022
Herd protection	With herd protection	With and without herd protection	151 - 324	268 – 540	328 - 732	639 – 1,315	383 - 694	785 – 1,348
Vaccination cost: price + delivery	$2.46 ($1.86 + $0.60)	$1.45-$3.23	83 - 203	152 – 356	186 - 436	370 - 844	218 - 508	464 - 1057
Baseline estimates			151	264	328	639	383	785

8.3   Equity impact

The introduction of oral cholera vaccines is a good intervention for reducing health inequities since cholera strikes mainly the poorest and most marginalized populations with little access to clean water, adequate sanitation and decent health services. These populations, which tend to live in urban slums and poor rural areas, would be the very targets of cholera vaccination.

Because populations at-risk for cholera have limited access to health services, persons infected with cholera are less likely to receive treatment in a timely fashion. The people most likely to die from cholera are those who do not reach a health facility in time, either because of distance, inability to pay, or social taboos [Sack et al., 2006]. In Bangladesh, a study found a reduction of more than 30% in overall mortality among women receiving oral cholera vaccines during the year following the Matlab cholera vaccine trial [Clemens et al., 1988]. The reduction in mortality was found only in adult females, presumably because the women vaccinated against cholera were conservative Muslim women who were less likely to travel to seek health care. Similarly, in Dhaka City, the majority of persons who die from cholera are women since many do not seek care until it is too late (personal communication, ASG Faruque, ICDDR,B).

Many countries have proven their ability to reach even the very poor and persons with restrictive mobility with vaccination since these services can be provided through campaigns and mobile services in hard-to-reach areas without routine health services. As a result, access to immunization services tends to be higher and more equitable than access to health care services as a whole, especially curative care. Therefore, the poor are be more likely to be reached with a cholera vaccine than to obtain timely, high-quality care for cholera.

Improvements in water and sanitation are also targeted at low-income populations and reduce inequities, but usually require a longer period to implement. The introduction of vaccines will prevent cholera cases over the short and medium term until improvements in water and sanitation are made.

Section 9. Constraints and probability of success

9.1 Political, social and cultural constraints

9.1.1 Denial of the problem and lack of awareness among policymakers

A key hindrance to the control of cholera has been the reluctance of governments to admit its existence in their countries, due to fears of economic repercussions, such as bans on food exports and declines in tourism. As a result, WHO reports represent only an estimated 5-10% of actual clinical cases, and some of the most highly-endemic countries report few or no cases each year. This official denial in some countries, coupled with the lack of solid data on the cholera disease burden in nearly all countries, has often resulted in a low awareness of the persistent problem of cholera among political leaders and policymakers. This low awareness is especially true regarding endemic cholera, which, unlike epidemic cholera, does not get reported in the media and does not lead to a large international response.

However, attitudes among policymakers regarding cholera have begun to change and political will has increased to both recognize and address it as a problem. One key reason is the growing frequency of large, protracted, often uncontrolled cholera epidemics in the last decade or so (see *Figure 8* above), such as the Zimbabwe epidemic and the on-going epidemic in Haiti. These large-scale outbreaks have received considerable attention in the international and local media and have alarmed neighboring countries fearing spread of the outbreaks across their borders. With increased and diverse means of communications in the digital age, it is also increasingly difficult for governments to hide cholera outbreaks from the media and the public.

9.1.2 Competition between vaccination and other cholera control measures

At both global and national levels, policymakers have often viewed cholera vaccination as competing with other traditional means of controlling the disease, such as improving water quality and access to adequate sanitation and behavioral change (e.g., hand washing) [DeRoeck et al., 2005]. These measures are seen as means of controlling the disease permanently, as opposed to the shorter team and incomplete protection conferred by vaccination. However, with the occurrence of more frequent and longer-lasting cholera epidemics – sometimes causing thousands of deaths – there is growing interest among policymakers in endemic countries in vaccination as a potentially critical tool in controlling the disease in the short- to medium-term. In Bangladesh, for example, where the government has not reported cholera cases to WHO since the early 1990s, the government is a full partner in a pilot project in Dhaka to prevent the disease through a combination of vaccination (using Shanchol™), safe water treatment interventions, and the promotion of hand washing. A number of African governments have also indicated interest in cholera vaccination, including Zanzibar, where a vaccination demonstration project is currently taking place.

In addition, as recommended by WHO, cholera vaccination should be combined with other control measures, such as the distribution of point-of-use water treatment supplies and health education messages. Experts have argued that combining vaccination with water and sanitation interventions will, in fact, create synergies that will accelerate reduction in the disease (e.g., by reducing vibrios in the environment) [Sack, 2006].

9.1.3 Managing expectations and the need for effective communications

Since cholera is only one cause of acute watery diarrhea, and since cholera vaccines are not 100% effective, it will be critical that cholera vaccination is not sold to the public and to health workers as a way to eliminate severe diarrhea altogether and that cases of acute watery diarrhea not be seen as "vaccine failures". In fact in some countries, such as Bangladesh, the word for diarrhea and cholera are the same. Training of health workers and public education activities must therefore provide accurate information that puts cholera vaccination in the proper context as one of several tools to control severe diarrheal disease.

9.1.4 The challenge in reaching older children and adults, including men

Infants and young children are the main targets for most vaccines provided through national immunization programs in developing countries, and many countries have been able to achieve high immunization coverage among this age group. They have less experience with immunization programs that also target older children and adults. Achieving high coverage with cholera vaccine among these older age groups may present a challenge in many cholera-endemic countries, since vaccines are often viewed by the population as something given to children. This challenge has been manifested in the relatively low rates of tetanus toxoid vaccine coverage for women of reproductive age in many countries as compared to coverage of infant vaccines. Reaching older boys and adult men, who are rarely targets for immunization, will especially be a challenge and will require effective, targeted communication strategies and messages.

However, in recent years, countries have gained experience in immunizing older children through second-dose measles campaigns, many achieving high coverage. In addition, other new vaccines that countries are introducing also have expanded or older age targets, such as HPV (for pre-adolescent girls) and meningococcal conjugate vaccine, which is being targeted for people age 1-29 years old in mass vaccination campaigns in Africa. Strategies that countries devise for these vaccination programs to reach older age groups can benefit cholera vaccination programs and vice versa. High coverage can also be achieved by combining cholera vaccination with these vaccines or other health interventions in mass campaigns.

Schools are a logical venue for immunizing older children. However, the challenge will be in reaching children who are not in school, especially older children who have dropped out after a few years of primary school (assuming vaccination targets children up to 14 years old). This will require setting up other community-based vaccination points besides schools, as well as encouraging non-enrolled children through communications campaigns to come to schools for the vaccination.

9.2 Epidemiological and environmental constraints

9.2.1 Limited data on cholera incidence and epidemiology

Most countries lack solid information on their cholera disease burden, due to generally weak disease surveillance systems; the fact that cholera may not be distinguishable from other causes of acute watery diarrhea, especially in young children; and the lack of laboratory diagnosis capabilities in many areas. Epidemiological evidence of cholera is critical to the development of effective cholera control programs in two key respects. First, national policymakers and donors may require solid, laboratory-confirmed information on the magnitude of the disease in their country before investing in the introduction of cholera vaccine. Second, in nearly all countries, cholera vaccination will be limited to areas at high risk of the disease, which are best identified through laboratory-confirmed surveillance data. Setting up laboratory-supported surveillance, such as sentinel

site surveillance, will therefore be a critical component of cholera vaccination programs – both to identify areas to target and to document the impact of vaccination and other control measures.

9.2.2 The existence of vibrios in the environment

The fact that vibrios can live in water, including estuaries, lakes, and even wells also complicates control of the disease. While it will be impossible to completely eradicate vibrios from the environment, it will be possible through vaccination, improved sanitation and other control measures to prevent their transmission and ability to cause outbreaks.

9.2.3 The unpredictability of cholera outbreaks and limited capacity for risk assessment

History has shown that it is often difficult to predict where and when a cholera outbreak will strike. This unpredictability makes it difficult for health decision-makers to decide whether, when and where to vaccinate either preemptively – such as following floods or to thwart outbreaks in neighboring countries from crossing the border – or reactively, once an outbreak has begun. The field-testing and further refinement of risk assessment/decision-making tools, under development by WHO, should therefore be an integral component of a global cholera vaccine stockpile.

9.3 Technical constraints

The two main technical constraints of killed whole-cell based oral cholera vaccines are the two-dose regimen separated by two weeks (in the case of the O1/O139 WC vaccine), and the fact that immunity wanes after three (or perhaps more) years, requiring revaccination. For the control of endemic disease, a two-dose regimen does not present an insurmountable problem, as EPI programs handle a number of multi-dose vaccines and a number of countries have reduced dropout rates between doses significantly in recent years. The two-dose regimen poses a greater challenge when the vaccine is used in crisis or post-crisis situations. If the O1/O139 WC vaccine is found to confer protection in a single dose in an upcoming clinical trial, this will improve the vaccine's attractiveness among policymakers for use in emergency situations. An alternative schedule of the vaccine – with an interval of 28 days between the two doses – is also being evaluated, which, if proven efficacious, would facilitate its use in conjunction with the polio vaccination campaigns (e.g., National Immunization Days (NIDs)), which are held in two rounds normally four to five weeks apart.

Based on data from the on-going trial of Shanchol™ in Kolkata, India, the vaccine provides protection for at least three years. The need to revaccinate the population every three years increases the cost and logistical challenges of cholera vaccination programs. The interval between doses could be extended, however, if protection is found to be sustained after four or even five years in the Kolkata trial. The original WC vaccine produced in Vietnam was found to protect up to five years [Thiem et al., 2006].

Oral killed cholera vaccines are fairly heat stable and thus cold chain requirements are no more stringent than other vaccines (2-8ºC). Stability tests are taking place to determine if Shanchol™ can be stored at ambient temperatures for an extended period. Shantha also has plans to develop streamlined packaging for the vaccine (currently in single-dose vials) destined for public sector programs in order to reduce its storage volume requirements.

9.4 Programmatic and institutional constraints

9.4.1 The need for delivery of the vaccine through mass campaigns

Since cholera vaccines are not currently licensed for use in infants and since older children and perhaps even adults will be targeted, mass vaccination campaigns will be the most appropriate means of delivering the vaccine. Cholera vaccine is quite amenable to delivery through mass campaigns, since it is an oral vaccine and can be administered by volunteers and non-health workers. However, mass vaccination campaigns require considerable financial and human resources and can sometimes negatively impact the delivery of routine immunization services. One way to reduce these extra requirements is to piggyback cholera vaccination onto other vaccination or health campaigns as much as possible, such as NIDs, measles catch-up or follow-up campaigns, Periodic Intensive Routine Immunization (PIRIs), and Child Health Days or Weeks. Social mobilization for such combined campaigns would need to ensure that all target ages are drawn to the campaigns and not just young children.

9.4.2 Funding constraints

Securing sufficient funding to pay for the vaccine presents a formidable challenge to the introduction of cholera vaccine in endemic countries, many of which are among the world's poorest nations. Accelerated introduction in multiple countries, as envisioned in this investment case, will be most feasible if the GAVI Alliance or other large donor decides to support cholera vaccination in a major way. However, because of the macro-economic impact of cholera, as well as the fear that major outbreaks can cause, the possible sources of funding for cholera vaccination is likely to be greater than for other new vaccines. As discussed in *Section 6.2* above, entities that could be motivated to finance cholera vaccination as an economic as well as a health intervention include regional development banks, international and local NGOs, local industries (seafood, tourism), as well as the national and local governments in the countries themselves. Securing sufficient funds for the vaccine stockpile and for vaccine introduction in endemic countries will require intensive advocacy to the global health community, technical agencies, donor organizations, private industries, and national and local governments.

9.4.3 Competing vaccine priorities

Many of the countries identified in this investment case as cholera-endemic are also considering introducing other new or under-utilized vaccines, such as rotavirus, pneumococcal, meningitis A conjugate, and HPV vaccines, several with GAVI support. Each new vaccine introduction requires training of health workers, the establishment of surveillance for the target disease, additional cold storage space, changes in immunization forms, as well as additional financial resources. Efforts should therefore be encouraged to assist countries in weighing their infectious disease control priorities, including cholera vaccination, through impact and cost-effectiveness analyses, such as those promoted by PAHO's ProVAC Initiative.

In addition, during complex emergencies, such as floods, the provision of cholera vaccine through use of the stockpile will likely have to share resources with other priority interventions, such as providing water, food and shelter.

9.5 Limited vaccine supply

At present, there is one WHO-prequalified manufacturer (Shantha) for O1/O139 WC vaccines, one other manufacturer that is not WHO-prequalified (VaBiotech), and a third

manufacturer to whom O1/O139 WC vaccine technology has been transferred (Eubiologics). However, the current supply of oral cholera vaccines is extremely limited. Under current plans, the total projected global supply of O1/O139 WC vaccines will only meet the projected demand under the smallest vaccination scenario (vaccination of 1-14 year olds in Small Target areas) through 2020. The control of cholera through immunization, as envisioned in this investment case, cannot therefore be realized without an expansion in the global production capacity of the vaccine, either by current producers expanding their capacity or by new manufacturers entering the market, or a combination of both.

Vaccine producers will not invest in either expanding or launching cholera vaccine production without an estimate of the potential demand. Projecting demand for cholera vaccines is more complicated than for universal infant vaccines, since it is not certain which targeting strategies different countries will choose. However, as some early adopter countries show serious interest in the vaccine and begin making plans and as donors indicate their interest in supporting them, a more precise demand forecast will be possible. Advocacy and lobbying of vaccine producers by countries, the global health community and donors to take an increased interest in cholera vaccine production will also be critical.

9.6   Critical risks

A summary of the main critical risks and how to minimize them is shown in Table 18.

Table 18. Critical risks of investing in cholera vaccination

Risk	Risk Rating	Risk Minimization
Limited information on cholera incidence and epidemiology results in limited knowledge of magnitude of the disease and difficulty in targeting at-risk areas	High, but modifiable	Support improved cholera surveillance in endemic countries
Countries and donors not knowledgeable about value of cholera vaccination	Variable and dependent on level of advocacy for vaccines in country	Conduct continuous advocacy on the value of cholera vaccination at global, regional and national levels
Insufficient supply of vaccine	Moderate, dependent on planning and speed of adoption of vaccine	Strengthen demand forecasting as well as supply chain. Transfer technology of O1/O139 WC vaccine to willing emerging producers.
Countries unable to sustain vaccine financing	Variable by country	Support efforts to increase overall health and immunization spending; lobby for GAVI and other donors to support introduction of vaccine.
Difficulty in reaching older children and adults (if targeted) through vaccination campaigns	Low to moderate and varies by country	Social mobilization campaigns need to emphasize age groups to be vaccinated and stress the importance of all target ages participating in vaccination campaigns.

Section 10. Conclusions and recommendations

The recent cholera outbreak in Haiti demonstrates that the scourge of cholera continues to threaten the lives as well as the economic and political security of disadvantaged populations. The development of lower cost oral cholera vaccines provides an additional tool to combat both endemic and epidemic cholera. However, the spatial and temporal heterogeneity of cholera incidence complicates the identification of appropriate

cholera vaccination strategies. This investment case examined a two-pronged approach for deployment of cholera vaccines: 1) targeting of high risk populations in cholera-endemic countries and 2) investment in a cholera vaccine stockpile to enable rapid response to large cholera outbreaks.

Introduction of cholera vaccines in conjunction with ongoing efforts to improve water, sanitation, across cholera-endemic populations would substantially reduce the estimated three million cases of cholera and 94,000 deaths that occur each year. Thirty-three countries in Sub-Saharan Africa and South Asia, including 12 Indian states, are forecasted to introduce cholera vaccination between 2015 and 2020, and are the focus of this investment case. In addition, a proposed global cholera vaccine stockpile would provide up to an additional 10 million doses per year for both endemic and non-endemic countries to vaccinate against cholera to mitigate or prevent outbreaks. This stockpile would have an annual cost of $23 million, but could play an important role in preventing or curtailing large epidemics.

Vaccination campaigns limited to children only are about twice as cost-effective as all-age campaigns in high risk areas. This is because of herd protection effects and because of higher incidence rates among children than adults in endemic areas. The all-ages programs would cost about 2.3 times more to cover adults in addition to children, but only avert about 18% more cases. Countries may therefore want to consider targeting children in high-risk areas rather than persons of all ages. On the other hand, vaccination during outbreaks should target all ages since incidence rates tend to be more uniform across age groups during epidemics.

The importance of good surveillance cannot be over-emphasized to ensure that high-risk areas are accurately identified and that vaccination will be effectively used. Thus, endemic countries should add cholera to their existing surveillance programs if possible or otherwise implement a separate surveillance program, if required.

The current production capacity for cholera vaccine is limited and not expected to increase until 2015. Current planned capacity will not be sufficient to both supply a global stockpile and meet the projected demand for vaccination to control endemic disease, even for the smallest vaccination scenario. Therefore, production capacity for the vaccine will have to be expanded, either by current producers building additional facilities, by new producers entering the market, or a combination of both. While production capacity will not be sufficient to meet the projected demand for endemic disease control, it would be sufficient to stock a global vaccine stockpile. Thus, the creation of a global vaccine reserve may be considered an initial strategy to accelerate the achievement of all of the goals laid out in this investment case.

Cholera vaccine introduction would contribute to maintaining progress for Millennium Development Goals 4 and 5 (reducing child and maternal mortality). It would also reduce the negative impact of cholera on the economies of endemic and epidemic countries. Since cholera disproportionately affects the poorest communities of less developed countries, this intervention would also improve equity. However, due to the low economic status of affected communities, the adoption of cholera vaccines would require a concerted effort between at-risk countries, the donor community, and vaccine manufacturers.

Recommendations

Based on the results of this investment case, the following recommendations are made:

- A concerted advocacy and information dissemination effort should be conducted at the country, regional and global levels to communicate the results of the investment case analyses and the value of vaccination using oral killed whole-cell based cholera vaccines in order to attract financing for the introduction of cholera vaccination in endemic countries. This effort should also stress the role of cholera prevention through immunization and water and sanitation improvements on improving equity for the impoverished and marginalized populations most at risk of cholera.

- Since vaccination of children ages 1-14 are considerably more cost-effective than vaccination of people of all ages, cholera-endemic countries should consider introducing currently available oral cholera vaccines to children in high-risk areas, combined with interventions to improve sanitation and water quality. However, reactive vaccination after an outbreak or flooding should target all ages over the age of one.

- Cholera surveillance should be established in endemic countries to inform policymakers of the magnitude of the disease in their country, to identify high-risk areas and populations, and to provide baseline data for measuring the impact of vaccination and other cholera control interventions.

- Financing should be sought for cholera vaccination demonstration projects in various endemic countries in Africa and Asia to inform decision-making about the use of cholera vaccines to reduce endemic disease. The demonstration projects can evaluate the feasibility and community acceptance of and demand for cholera vaccination and measure its impact (e.g., through case-control studies).

- A global cholera vaccine stockpile should be established to enable the rapid deployment of the vaccine for pre-emptive or reactive immunization in response to cholera outbreaks or natural disasters in cholera-endemic areas. The stockpile should start small (e.g., two million doses) and grow as its need and country demand is demonstrated.

- To minimize the risk to vaccine producers, the cholera vaccine stockpile should guarantee a minimum quantity of vaccine to be purchased annually. Any stock remaining at the end of the year can be used for preventive campaigns in endemic countries.

- Research should be conducted in conjunction with the use of the stockpile to determine the effectiveness of oral killed whole-cell cholera vaccines used reactively to prevent epidemics from spreading.

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Appendices

Appendix 1.
Estimation of the global burden of cholera: methods and results

1. Introduction

There are few reports that provide a detailed epidemiology of cholera and most experts agree that the ones that do exist substantially underestimate the true incidence of the disease. As a result, a detailed estimation of cholera disease burden was conducted as part of this cholera vaccine investment case. This analysis estimates the average annual number of cholera cases and deaths, by age group and WHO region, both in cholera-endemic countries and in countries affected by cholera but not considered endemic. A case of cholera is defined for this analysis as a case in which the person seeks health care either in the public or private sector.

In summary, the analysis identified cholera-endemic countries from reports of cholera to WHO and other sources, and estimated the population at risk of cholera in each country using data on the proportions of the population without access to adequate sanitation. We then applied site-specific incidence rates from laboratory-confirmed prospective cholera surveillance conducted in the early-mid 2000s in several sites in Asia and Africa to the at-risk populations in the identified cholera-endemic countries. That is, the incidence rate from each study site was applied to all countries in the same WHO sub-region (stratified by mortality levels) as the study site. This yielded the average number of cholera cases per year. Sub-region specific case fatality rates – based on a review of the literature – were then applied to the estimated number of cases in each country to obtain an estimate of annual deaths. An estimate of cholera cases and deaths in non-endemic countries (where cholera occurs, but less regularly) was also calculated, based on reports of outbreaks.

This appendix describes in detail the step-by-step methodology used for this analysis, as well as the results.

2. Identifying countries with cholera and classifying them by cholera-endemic and non-endemic

The method used for selecting countries to include in this analysis is shown in Figure 1. To determine which countries to include in the analysis, we used reports from 2003 to 2008 from the annual cholera reports to WHO published in the *Weekly Epidemiological Record (WER)*. These were supplemented with published articles using the PubMed database, ProMED postings, Global Infectious Disease and Epidemiology Network (GIDEON) database, and other sources (literature and/or posted on a website).

Countries with mostly imported cases or very few non-imported cases (i.e., transmission was not sustained) were considered as not having a cholera problem and were eliminated from the analysis. These include all of North America, Central and South America, Europe, Australia and New Zealand. Of the 35 countries in the Americas (AMR), only Brazil and Paraguay have reported non-imported cholera cases in the last nine years (up to 2008), and only during one year each. Of the 52 countries in the WHO EUR region, only three non-imported cases from Poland, Ukraine, and Russia have been reported since 2005.

Figure 1. Process used for identifying countries affected by cholera
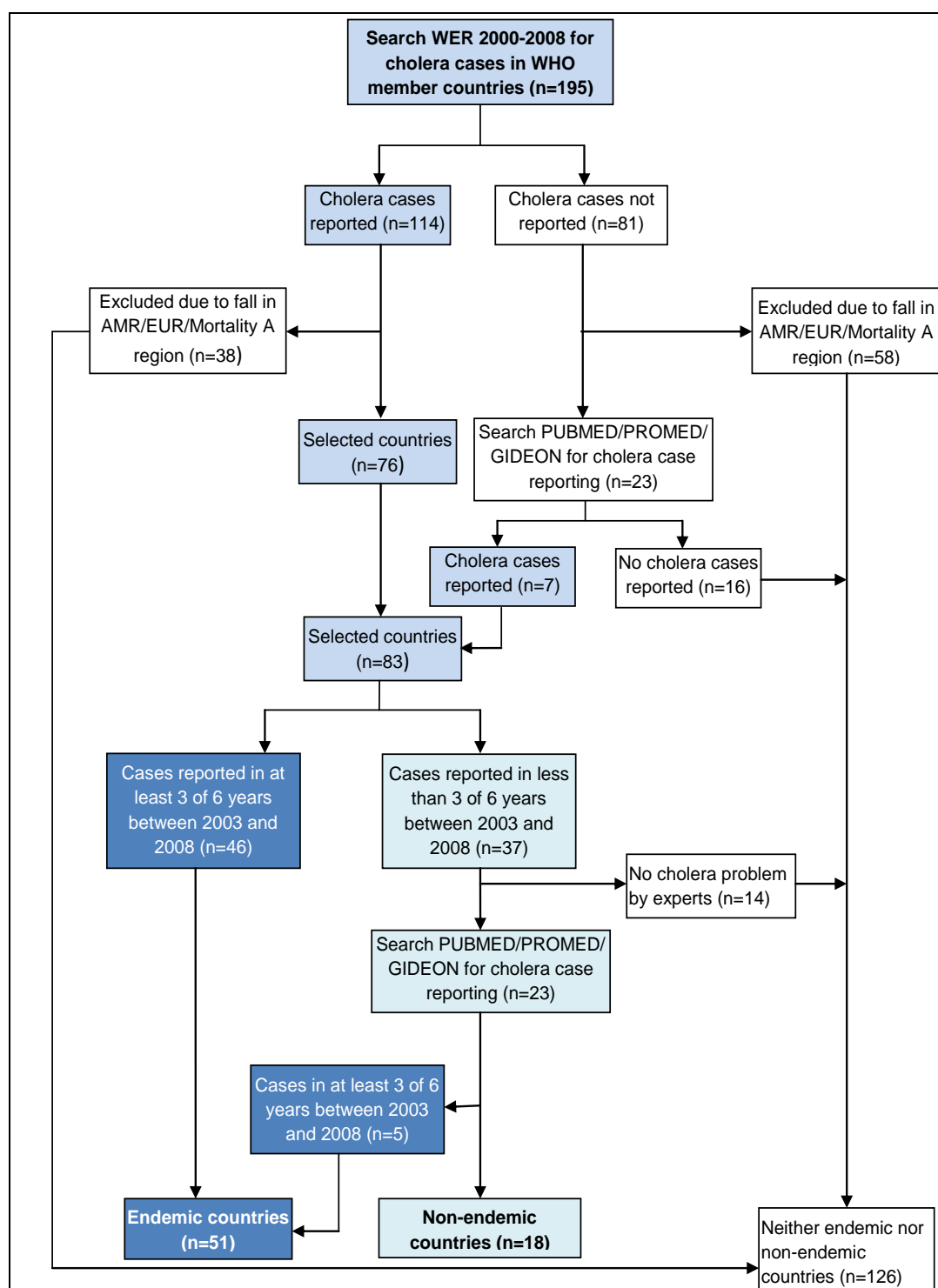
This left 69 countries in four WHO regions (AFR, SEAR, EMR, WPR) that had reported cases of non-imported cholera between 2003 to 2008. Countries were defined as cholera-endemic if there were reports of cholera cases in at least three of the past six years from 2003 to 2008. Countries that did not meet this criterion, but which had reported cholera cases in at least one year between 2000 and 2008 from the same data sources listed above were classified as non-endemic for cholera. Of the 69 cholera-affected countries identified in this analysis, 51 were classified as cholera-endemic (see Figure 2 and Table 1) and 18 countries were classified as non-endemic (listed in Section 5 below). The reported incidence

and mortality data used for this analysis by year and source for all 69 countries are shown in Table 15 at the end of this appendix.

**Table 1. Countries identified in the analysis as cholera-endemic,
by WHO region and mortality stratum (51 countries)**

Country	WHO region and mortality stratum	Country	WHO region and mortality stratum
Angola	AFR-D	Mauritania	AFR-D
Bangladesh	SEAR-D	Mozambique	AFR-E
Benin	AFR-D	Myanmar	SEAR-D
Bhutan	SEAR-D	Namibia	AFR-E
Burundi	AFR-E	Nepal	SEAR-D
Cameroon	AFR-D	Niger	AFR-D
Chad	AFR-D	Nigeria	AFR-D
China	WPR-B	Pakistan	EMR-D
Comoros	AFR-D	Philippines	WPR-B
Republic of Congo	AFR-E	Rwanda	AFR-E
DR Congo	AFR-E	Sao Tome and Principe	AFR-D
Côte d'Ivoire	AFR-E	Senegal	AFR-D
Ethiopia	AFR-E	Sierra Leone	AFR-D
Gambia	AFR-D	Somalia	EMR-D
Ghana	AFR-D	South Africa	AFR-E
Guinea	AFR-D	Sudan	EMR-D
Guinea-Bissau	AFR-D	Swaziland	AFR-E
India	SEAR-D	Tanzania, United Republic of	AFR-E
Indonesia	SEAR-B	Thailand	SEAR-B
Iran (Islamic Republic of)	EMR-B	Togo	AFR-D
Iraq	EMR-D	Uganda	AFR-E
Kenya	AFR-E	Viet Nam	WPR-B
Korea (DPR)	SEAR-D	Yemen	EMR-D
Liberia	AFR-D	Zambia	AFR-E
Malawi	AFR-E	Zimbabwe	AFR-E
Mali	AFR-D		

3. Further classifying countries to estimate cholera incidence and case fatality rates

Countries were also classified using the WHO sub-region mortality strata in order to assign cholera incidence and case fatality rates to them (see below) [1]. In this classification, countries with low child mortality and very low adult mortality are in stratum A; countries with low child and adult mortality are in stratum B; those with low child and high adult mortality are in stratum C; countries with high child and high adult mortality are in stratum D; and those with high child mortality and very high adult mortality are in stratum E. All countries in the E stratum are in the WHO African region and are mainly distinguished from AFR-E countries by their higher rates of HIV/AIDS.

Figure 2. Countries classified as cholera-endemic in the analysis, by WHO region
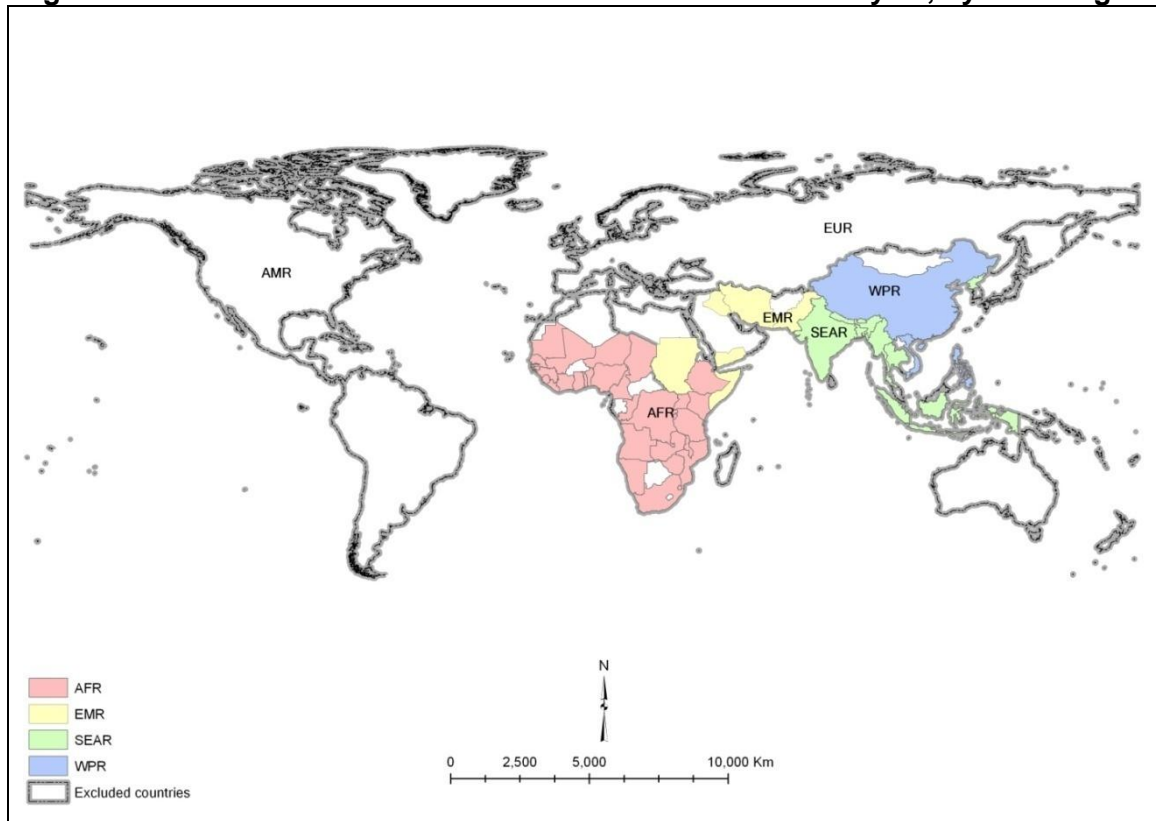
4.   Estimating the cholera disease burden in endemic countries

Estimating the population at risk for cholera

To estimate the population at risk of cholera in the 51 endemic countries, we started with population data from the United Nations Development Program (UNDP) for 2005 [2]. For the three largest countries, we chose only states and provinces that had reported cholera (from 2000 to 2007 for China and Indonesia) and from 1997 to 2006 for India (see Table 16 at the end of this appendix for a list of cholera-endemic provinces and states in China, India and Indonesia). The total population in the 51 countries (including only cholera-endemic states or provinces in China, India and Indonesia) is around 2.6 billion people.

It is unlikely that the entire populations of cholera-endemic countries are at risk for cholera. Risk may be correlated with the geography and climate of the land or the socio-economic status of the people. To estimate the population at risk by country, we used estimates of the percentages of the population in each country that had access to improved sanitation, based on the WHO's data from year 2008 [3]. The proportion of the population *lacking access* to improved sanitation was assumed to be the population at risk. The at-risk population by country was calculated by multiplying the country's population (or the population in the cholera-endemic provinces or states in India, Indonesia and China) by the percentage lacking access to improved sanitation.

The total at-risk population in cholera-endemic countries is estimated at more than 1.4 billion people (Table 2). The WHO mortality sub-region, SEAR-D, which includes India and Bangladesh, accounts for 48% (695 million) of the world's entire population at risk for

cholera, followed by the AFR-E and AFR-D sub-regions. The estimated at-risk population for each of the 51 endemic countries and how these figures were derived is shown in Table 17.

Table 2. The estimated population at risk of cholera in 51 cholera-endemic countries, by age group and WHO mortality strata sub-region, based on 2005 population data

WHO region and mortality stratum	<1	1-4	5-14	15+	Total
AFR-D	7,263,193	26,196,367	52,535,547	110,467,584	196,462,691
AFR-E	9,249,952	33,633,859	68,074,583	143,647,847	254,606,241
EMR-B	222,056	803,894	2,282,964	8,508,636	11,817,550
EMR-D	3,433,940	12,983,900	27,601,692	70,440,358	114,459,890
SEAR-B	977,969	3,856,737	9,109,637	36,499,215	50,443,558
SEAR-D	15,809,789	61,822,667	154,103,298	463,096,836	694,832,590
WPR-B	1,935,598	7,695,605	20,779,707	90,119,874	120,530,784
Total	**38,892,497**	**146,993,029**	**334,487,428**	**922,780,350**	**1,443,153,304**

Estimating cholera incidence rates

There are very few estimates of age-specific cholera incidence available in the literature. Prospective laboratory-confirmed surveillance of cholera conducted in the mid-2000s by the Diseases of the Most Impoverished (DOMI) Program [4] yielded age-specific cholera incidence rates in Kolkata, India; North Jakarta, Indonesia and Beira, Mozambique (see Table 3).

Table 3. Average annual incidence rates of cholera by age group in three sites where laboratory-confirmed prospective cholera surveillance was conducted through the DOMI Program

Age group	Kolkata, India (May 2003-Apr 2005)			Jakarta, Indonesia (Aug 2001-Jul 2003)			Beira, Mozambique (2003-2004)		
	Popl.	Cases	Rate/ 1000/yr	Popl.	Cases	Rate/ 1000/yr	Popl.	Cases	Rate/ 1000/yr[‡]
<1y	698	10	7.16	3,121	25	4.01	-	-	-
1-4y	3,782	53	7.01	12,620	39	1.55	1,686*	9	8.8
5-14y	11,440	50	2.19	29,093	17	0.29	17,861[†]	38	3.5
15y+	42,143	78	0.93	115,423	62	0.27			
Total	**58,063**	**191**	**1.64**	**160,257**	**143**	**0.45**	**19,547**	**47**	**4.0**

[*] age group 2-<5 years
[†] age group ≥ 5 years
[‡] Rates were corrected for direct protection from cholera vaccination, as this surveillance took place during a cholera vaccine demonstration project.

Source: [4]

Given the lack of country-specific data, we assumed that the overall incidence rates observed from these studies were representative of the at-risk populations of the WHO sub-regions, based on perceived similarities in cholera risk between the DOMI sites and the at-risk populations of the sub-region as a whole. We therefore applied the overall incidence rates found at each DOMI site to the at-risk populations in other countries in the corresponding WHO sub-region. These assumed incidence rates by WHO mortality strata sub-region are shown in Table 4. To be conservative, we assumed zero incidence for the population considered not to be at risk (i.e. the population with access to improved sanitation).

Thus, in the WHO Southeast Asian region (SEAR), the North Jakarta incidence rate was applied to the assumed at-risk populations in Indonesia and other countries in SEAR-B with endemic cholera. The Kolkata incidence rate was applied to India and other countries in

SEAR-D with endemic cholera, as well as to the EMR-D sub-region, which includes Pakistan, Somalia and other countries thought to experience significant cholera burden.

Table 4. Assumed annual cholera incidence rates in at-risk populations (without access to clean water supplies) used in the analysis and source of information by WHO region and mortality stratum

WHO region and mortality stratum	Annual incidence rate/1000*	Source of information
AFR-D	2.00	Beira, Mozambique and WER data
AFR-E	4.00	Beira, Mozambique data
EMR-B	0.10	Assumption-based
EMR-D	1.64	Kolkata data
SEAR-B	0.45	Jakarta data
SEAR-D	1.64	Kolkata data
WPR-B	0.10	Assumption-based
* Incidence rate in at-risk (not entire) population only.		

The one Southeast Asian country where the Kolkata rate was not applied was Bangladesh. Instead, we used the estimated cholera incidence rate derived from an analysis performed as part of the country case study of cholera vaccination that was conducted as a supplement to this global investment case (see separate Bangladesh country case study report).

For the African region (AFR), the Beira, Mozambique incidence rate was applied to the at-risk populations of cholera-endemic countries in AFR-E. In the absence of representative data for AFR-D, we compared the mean and median estimates of cholera incidence reported in the WER for AFR-D and AFR-E countries from 2000-2008. This comparison is possible because most of the countries in the AFR appear to report cases to WHO on an annual basis, unlike some other WHO regions. The average and median number of cases reported in endemic AFR-E countries is about 1.5 times greater than those reported in endemic AFR-D countries. In order to be conservative, we assumed that the incidence rate in AFR-D countries would be about 50% of the incidence rates observed for Beira. In the absence of data for countries in WPR-B or EMR-B, we assumed that incidence rates for at-risk populations would be low, about 0.1 cases per 1,000 persons (Table 4).

Estimating age-specific cholera incidence in endemic countries

After determining the overall cholera incidence rates in the at-risk populations for each of the 51 endemic countries, as described above, we then estimated age-specific incidence rates for each of the seven WHO sub-regions included in the analysis. To do so, we used the age-specific cholera incidence rates obtained from the DOMI study in Kolkata, India to determine the proportion of cases in each age group. This proportional distribution was then applied to the overall incidence rates in each sub-region to come up with age-specific incidence rates for each sub-region. The formulas used for these calculations are shown in the box below.

Using this methodology, we estimate that, on average, there are around 2.8 million cases of cholera that require health care each year in the 51 cholera-endemic countries (Table 5). The average annual incidence rate among the at-risk populations (not the entire populations) is 2.0 per 1,000 (ranging from 0.10-4.0). As shown in Table 6, the African region of WHO accounts for half of the total incidence, with the Southeast Asian region, including India and Bangladesh, accounting for another 43%. A map of countries by cholera incidence rates (per country population) is shown in Figure 3.

Incidence is greatest in children less than five years old, who account for more than 1.3 million cases or 46% of the total estimated annual incidence (Table 5). Age-specific incidence rates by WHO region are shown in Figure 4. The estimated number of cases by country and age group is shown in Table 18 at the end of this appendix.

Formulas for calculating age-specific cholera incidence in endemic countries

The number of expected cholera cases for the j th age group of the i th country is:

$$C_{ij} = P_{ij} \times IRe_{ij}$$

P_{ij} is the population of the j th age group of the i th country ; IRe_{ij} is the estimated incidence rate of the j th age group of the i th country.

The parameter, IRe_{ij} is computed as:

$$IRe_{ij} = IRk_j \times \hat{\theta}_i$$

Where, IRk_j is the incidence rate of Kolkata at j th age group. The estimated coefficient for country i, $\hat{\theta}_i$, was obtained using the least squares method that minimized the square of difference between observed and estimated incidence rate, as follows:

$$\hat{\theta}_i = \underset{\theta_i}{\mathrm{argmin}} \left(\sum_{i=1}^{k} P_i \times IRa_i - \sum_{i=1}^{k}\sum_{j=1}^{4} P_{ij} \times IRk_j \times \theta_i \right)^2$$

Table 5. Estimated average annual number of cholera cases in endemic countries by age group and WHO region and mortality stratum, 2005

WHO region and mortality stratum	<1	1-4	5-14	15+	Total	Rate/1,000 in at-risk population
AFR-D	45,062	159,118	99,714	89,035	392,929	2.0
AFR-E	115,374	410,737	259,704	232,709	1,018,524	4.0
EMR-B	93	330	292	459	1,174	0.1
EMR-D	19,099	70,711	46,951	50,858	187,619	1.6
SEAR-B	1,806	6,973	5,147	8,760	22,686	0.4
SEAR-D	100,408	379,474	305,771	416,029	1,201,682	1.7
WPR-B	846	3,287	2,785	5,137	12,055	0.1
TOTAL	**282,688**	**1,030,630**	**720,364**	**802,987**	**2,836,669**	**2.0**
Rate/1,000*	**7.3**	**7.0**	**2.2**	**0.9**	**2.0**	

*The denominator is at-risk population for all countries except Bangladesh, where the entire population is considered at risk of cholera.

Figure 3. Geographical distribution of cholera incidence
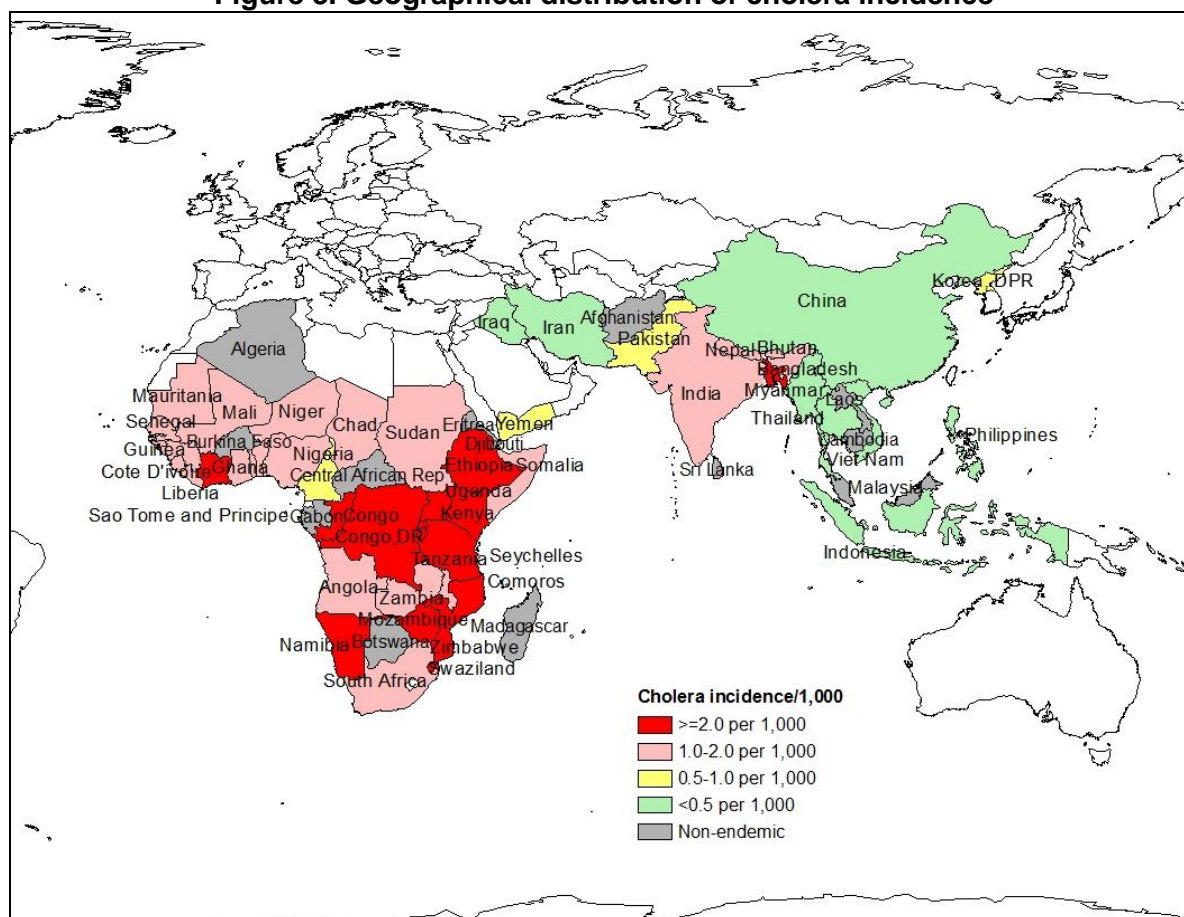
Table 6. Estimated average annual number and percent of cholera cases in endemic countries by WHO region

WHO region	No. countries	No. cholera cases	Percent of total
AFR	34	1,411,453	49.8%
EMR	6	188,793	6.7%
SEAR	8	1,224,368	43.1%
WPR	3	12,055	0.4%
Total	**51**	**2,836,669**	**100.0%**

Figure 4. Age-specific incidence rates of cholera by WHO region in cholera-endemic countries, 2005
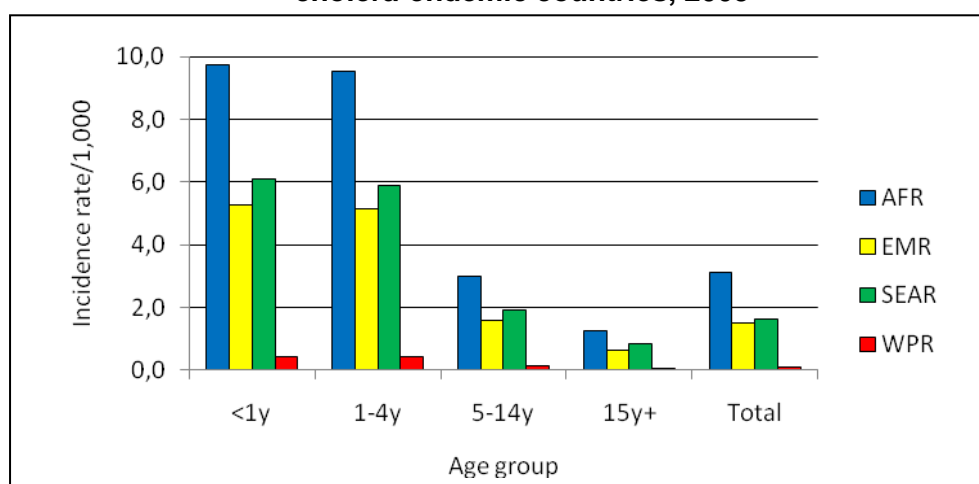
Estimating the number of cholera deaths in endemic countries

Reported case fatality rates of cholera from the literature are shown in Table 7. Based on these data, we calculated variance weighted average cholera case fatality rates by the WHO sub-regions [25]. We used the same cholera case fatality rates in AFR-D and AFR-E sub-regions, because the available data for AFR-D countries are older and we presumed that cholera case fatality rates for the AFR-D and AFR-E sub-regions are more or less similar. Cholera mortality estimates are not available for any of the cholera-endemic countries of SEAR-B and WPR-B sub-regions. We assumed lower case fatality rates (1.0%), because we believe that appropriate health care is more accessible in those countries. The resulting estimated case fatality rates by WHO sub-region are shown in Table 8.

Table 7. Summary of cholera case fatality rates reported in the literature

Year/Date	Country	WHO sub-region	Cholera cases	Deaths	CFR*	Variance (var.)	Weight (1/var.)	Source
Oct 1994-Jan 1995	Guinea-Bissau	AFR-D	1,169	43	3.68	0.30	3.30	[5]
Jan 1996-Dec 1996	Nigeria	AFR-D	1,384	92	6.65	0.45	2.23	[6]
Jun 1997- Mar 1998	Kenya	AFR-E	14,275	547	3.83	0.03	38.74	[7]
Nov 2003-Feb 2004	Zambia	AFR-E	4,343	154	3.55	0.08	12.70	[8]
Aug 1990-Dec 1990	Malawi	AFR-E	1,931	68	3.52	0.18	5.68	[9]
August, 2005	Iran	EMR-B	560	7	1.28	0.20	4.96	[10]
October 15, 2008	Iraq	EMR-D	500	8	1.60	0.31	3.18	[11]
July 24, 1994	Yemen	EMR-D	150	17	11.33	6.70	0.15	[12]
February 5, 2007	Somali	EMR-D	110	15	13.64	10.71	0.09	[13]
April 21, 2006	Sudan	EMR-D	5369	180	3.35	0.06	16.57	[14]
Sep 1991-Nov 1991	Bangladesh	SEAR-D	210,265-235,810	8,410-9,432	4.00	0.00	580.86	[15]
2002-2006	India	SEAR-D	164,100	705	0.31	0.00	207.11	[16-24]
* Case fatality rate (%)								

Table 8. Estimated cholera case fatality rates byWHO sub-region

WHO sub-region	Case fatality (%)
AFR-D	3.8
AFR-E	3.8
EMR-B	1.3
EMR-D	3.2
SEAR-B	1.0
SEAR-D	3.0
WPR-B	1.0

These case fatality rates were then applied to the estimated annual of cholera cases shown in Table 5 to obtain the average annual number of deaths, as shown in Table 9. We estimated that cholera kills about 91,000 people annually in endemic countries, corresponding to a rate of 6.3 deaths per 100,000 people at-risk. The mortality rates varied from 0.1 deaths per 100,000 persons at-risk in EMR-B and WPR-B countries to 15.2 deaths per 100,000 in AFR-E countries. Children under five years of age account for 48% of the

estimated cholera deaths (about the same as the proportion of cases, since the same case fatality rates were used across ages within a particular sub-region), and they experience much higher mortality rates than other ages.

Table 9. Estimated average annual number of cholera deaths in endemic countries by age group and WHO sub-region, 2005

WHO sub-region	<1	1-4	5-14	15+	Total	Rate/ 100,000*
AFR-D	1,712	6,045	3,788	3,383	14,928	7.6
AFR-E	4,384	15,610	9,868	8,842	38,704	15.2
EMR-B	1	4	4	6	15	0.1
EMR-D	612	2,263	1,503	1,627	6,005	5.2
SEAR-B	18	70	52	88	228	0.5
SEAR-D	2,647	10,062	8,056	10,725	31,490	4.5
WPR-B	8	32	28	52	120	0.1
TOTAL	**9,382**	**34,086**	**23,299**	**24,723**	**91,490**	**6.3**
Rate/100,000*	24.1	23.2	7.0	2.7	6.3	
*The denominator is the population at-risk for cholera for all countries except Bangladesh, where the entire population is considered at risk.						

The estimated number of cases by country and age group is shown in Table 19 at the end of this appendix.

5.   Estimating the cholera disease burden in non-endemic countries

The 18 countries that had reported cholera in at least one year between 2000 and 2008, but did not meet the definition of cholera-endemic (reported cases in three of the last five years), are shown in Table 10. These 18 countries represent 175 million people (in 2005) – 78 million (45%) of whom are at risk of cholera, using the same definition based on the proportion of people in each country without access to improved sanitation [3].

Estimating cholera incidence in non-endemic countries

The estimated number of cholera cases in non-endemic countries was based on the reported numbers of cases identified from a compilation of the WER, PROMED, GIDEON, and PubMed databases for the period of 2000 to 2008 (shown by country in Table 15). The average number of cases per year was estimated by adding together all cases identified from 2000-2008 and dividing the total by nine years. Since WHO estimates that the WER reports only 5-10% of total cholera cases seeking health care, we assume that the numbers of reported cases represent only 10% of all cholera cases in non-endemic countries. The average annual number of cases from 2000-2008 was therefore divided by 10% to obtain estimates of the cholera burden in non-endemic countries. Since age-specific distributions are not available from *WER* data, we again used age-specific incidence rates from prospective surveillance in Kolkata, India to estimate the proportionate distribution of cases among different age groups by WHO mortality sub-region.

We estimated about 87,000 cases of cholera in non-endemic countries per year, on average, or 1.1 cases per 1,000 people at risk (Table 11). Four countries alone –Afghanistan, Burkina Faso, Cambodia, and Madagascar – account for 85% (74,271) of estimated annual incidence. Children under five years of age make up 50.5% of cases.

Table 10. Non-endemic countries (that do not meet the definition of cholera-endemic but which reported cholera between 2000 and 2008) (n=18)

Country	WHO sub-region	Total population in 2005	Estimated population at risk of cholera (2005)
Afghanistan	EMR -D	29,863,000	20,904,101
Algeria	AFR -D	32,854,000	1,971,240
Botswana	AFR -E	1,765,000	935,451
Burkina Faso	AFR -D	13,228,000	11,508,360
Cambodia	WPR -B	14,071,000	10,131,120
Central African Republic	AFR -E	4,038,000	2,786,221
Djibouti	EMR -D	793,000	261,690
Eritrea	AFR -E	4,401,000	4,180,951
Federated States of Micronesia	WPR -B	110,000	82,501
Fiji	WPR -B	848,000	245,920
Gabon	AFR -D	1,384,000	885,760
Lao People's Democratic Republic	WPR -B	5,924,000	3,080,480
Madagascar	AFR -D	18,606,000	16,373,280
Malaysia	WPR -B	25,347,000	1,520,820
Marshall Islands	WPR -B	62,000	11,780
Seychelles	AFR -D	81,000	81,000
Sri Lanka	SEAR-B	20,743,000	2,904,020
Timor-Leste	SEAR-D	947,000	558,731
Total		**175,065,000**	**78,423,426**

Table 11. Estimated average annual number of cholera cases in non-endemic countries by age group and WHO sub-region and mortality stratum, 2005

Country	WHO sub-region	<1	1-4	5-14	15+	Total	Rate / 1,000
Afghanistan	EMR -D	2,044	7,208	4,415	3,490	17,157	0.8
Algeria	AFR -D	175	649	516	803	2,143	1.1
Botswana	AFR -E	4	18	13	16	51	0.1
Burkina Faso	AFR -D	2,144	7,156	4,262	3,567	17,129	1.5
Cambodia	WPR -B	1,631	5,976	4,347	4,851	16,805	1.7
Central African Republic	AFR -E	18	69	44	42	173	0.1
Djibouti	EMR -D	20	75	44	51	190	0.7
Eritrea	AFR -E	31	112	66	62	271	0.1
Federated States of Micronesia	WPR -B	13	56	35	39	143	1.7
Fiji	WPR -B	32	122	98	125	377	1.5
Gabon	AFR -D	112	425	252	330	1,119	1.3
Lao PDR	WPR -B	585	2,095	1,318	1,428	5,426	1.8
Madagascar	AFR -D	2,563	9,314	6,040	5,263	23,180	1.4
Malaysia	WPR -B	190	754	551	798	2,293	1.5
Marshall Islands	WPR -B	2	6	4	6	18	1.5
Seychelles	AFR -D	13	48	7	35	103	1.3
Sri Lanka	SEAR-B	1	3	2	4	10	0.0
Timor-Leste	SEAR-D	96	267	156	139	658	1.2
Total		**9,674**	**34,353**	**22,170**	**21,049**	**87,246**	**1.1**

Estimating cholera deaths in non-endemic countries

The expected annual number of cholera deaths in non-endemic countries was calculated by multiplying the estimated case fatality rates for each WHO sub-region shown in Table 8 by the estimated number of cases shown in Table 11. The age distribution of deaths again depends on the distribution of age-specific incidence because the same case fatality rate for all age groups is assumed within a particular sub-region. In total, we estimate about 2,500 cholera deaths per year in non-endemic countries, corresponding to an annual mortality rate of about 3.2 per 100,000 population (Table 12).

Table 12. Estimated annual deaths from cholera in non-endemic countries by age group and WHO sub-region and mortality stratum, 2005

Country	WHO sub Region	<1	1-4	5-14	15+	Total	Rate/ 100,000
Afghanistan	EMR -D	65	231	141	112	549	2.6
Algeria	AFR -D	7	25	20	31	83	4.2
Botswana	AFR -E	0	1	0	1	2	0.2
Burkina Faso	AFR -D	81	272	162	136	651	5.7
Cambodia	WPR -B	16	60	43	49	168	1.7
Central African Republic	AFR -E	1	3	2	2	8	0.3
Djibouti	EMR -D	1	2	1	2	6	2.3
Eritrea	AFR -E	1	4	3	2	10	0.2
Federated States of Micronesia	WPR -B	0	1	0	0	1	1.2
Fiji	WPR -B	0	1	1	1	3	1.2
Gabon	AFR -D	4	16	10	13	43	4.9
Lao People's Democratic Republic	WPR -B	6	21	13	14	54	1.8
Madagascar	AFR -D	97	354	230	200	881	5.4
Malaysia	WPR -B	2	8	6	8	24	1.6
Marshall Islands	WPR -B	0	0	0	0	0	0.0
Seychelles	AFR -D	0	2	0	1	3	3.7
Sri Lanka	SEAR-B	0	0	0	0	0	0.0
Timor-Leste	SEAR-D	3	8	5	4	20	3.6
Total		**284**	**1,009**	**637**	**576**	**2,506**	**3.2**

6. The total cholera disease burden

The estimated average numbers of cases and deaths combined in endemic and non-endemic countries are shown in Tables 13 and 14, respectively. In all, the analysis estimates more than 2.9 million cholera cases and nearly 94,000 deaths per year, on average. Cases in non-endemic countries account for only an estimated 3% of the total (Figure 5). The breakdown of the total burden by WHO region is similar to the breakdown of endemic disease (Table 6), with half of the cases in the African region, 42% in the Southeast Asian region, and 7% in the Eastern Mediterranean.

Table 13. Estimated total average number of cholera cases in endemic and non-endemic countries per year

WHO region	Endemic countries		Non-endemic countries		Total cases	Percent of total
	No. countries	No. cases	No. countries	No. cases		
AFR	34	1,411,453	8	44,169	1,455,622	49.8
EMR	6	188,793	2	17,347	206,140	7.1
SEAR	8	1,224,368	2	668	1,225,036	41.9
WPR	3	12,055	6	25,062	37,117	1.3
Total	**51**	**2,836,669**	**18**	**87,246**	**2,923,915**	**100.1**

Table 14. Estimated total average number of cholera deaths in endemic and non-endemic countries per year

WHO region	Endemic countries		Non-endemic countries		Total deaths	Percent of total
	No. countries	No. deaths	No. countries	No. deaths		
AFR	34	53,632	8	1,681	55,313	58.8
EMR	6	6,020	2	555	6,575	7.0
SEAR	8	31,718	2	20	31,738	33.8
WPR	3	120	6	250	370	0.4
Total	**51**	**91,490**	**18**	**2,506**	**93,996**	**100.0**

Figure 5. Estimates annual cholera cases by WHO region and by cholera-endemic vs. non-endemic countries
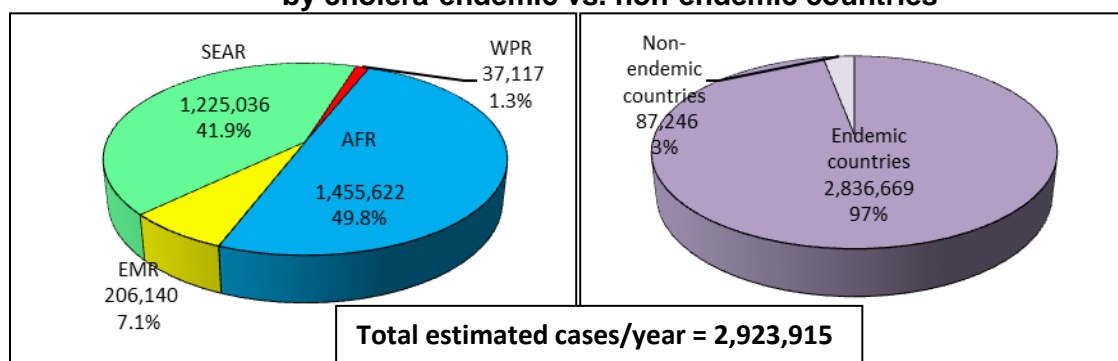
7.   Conclusions

We have estimated the global burden of cholera in endemic and non-endemic countries in a systematic way despite the limitations in the available literature. Most of our data are derived from estimates from the literature, including frequency of cholera incidence, populations at risk, age-specific cholera incidence rates, and case fatality rates. We present a conservative estimate on the burden of cholera and find that the estimated cholera-attributable deaths are very close to what has been often quoted in the literature (100,000 – 130,000 per year) [26].

Additional tables

Table 15. Reported cholera cases by country based on WER, PUBMED, PROMED, AND GIDEON, 2000-2008

Reported Cholera cases from 2000 to 2008(Black: WER, Blue: PUBMED, Red: PROMED, Green: GIDEON, Purple: Others)

Country	WHO Region-Mortality Stratum	Year 2000 Cases	Year 2000 Death	Year 2001 Cases	Year 2001 Death	Year 2002 Cases	Year 2002 Death	Year 2003 Cases	Year 2003 Death	Year 2004 Cases	Year 2004 Death	Year 2005 Cases	Year 2005 Death	Year 2006 Cases	Year 2006 Death	Year 2007 Cases	Year 2007 Death	Year 2008 Cases	Year 2008 Death
Afghanistan	EMR-D	4,330	198	4,499	114		3	41	7			33						4,384	22
Algeria	AFR-D				1														
Angola	AFR-D													67,257	2,722	18,422	513	10,511	243
Bangladesh	SEAR-D	92		42		30,000		79		>3780		197		334		282			
Benin	AFR-D	468	11	3,943	71	270	13	434	11	642	9	749	11	91	1			985	5
Bhutan	SEAR-D							29		27		29		38		5			
Botswana	AFR-E																	8	1
Burkina Faso	AFR-D	617	14	477	7			1				1,050	16						
Burundi	AFR-E	1,021	16	1,003	20	577	8	432	18	819	14	1,309	18	886	7	365	2	234	4
Cambodia	WPR-B									57	1								
Cameroon	AFR-D	123	29	259	7	66	8	207	36	8,005	137	2,847	110	922	35	10	1		
Central African Republic	AFR-E									320	48								
Chad	AFR-D			5,244	226			55	7	5,531	272	90	14	1,668	71				
China	WPR-B	1,834	1	140				223	1	244	1	980	4	161	2	168		174	
Comoros	AFR-D	3,297	91	226	4	1,567	46	56								1,555	29	4	4
Congo	AFR-E	9	2											175	10	7,785	133	156	
Congo, Democratic Republic of	AFR-E	14,995	941	5,728	195	31,658	1,979	27,272	989	7,665	228	13,430	244	20,642	426	28,269	600	30,150	548
Côte d'Ivoire	AFR-E			5,912	305	4,188	143	1,034	50	105	9	39	6	414	15	8	1	7	1
Djibouti	EMR-D	1,828	32											123	11	372	25		
Eritrea	AFR-E															119	9	1	
Ethiopia	AFR-E									16				54,070	575	24,121	272	3,862	23
Fiji	WPR-B									1									
Gabon	AFR-D					6		629										2	

76

Reported Cholera cases from 2000 to 2008 (Black: WER, Blue: PUBMED, Red: PROMED, Green: GIDEON, Purple: Others)

Country	WHO Region-Mortality Stratum	Year 2000		Year 2001		Year 2002		Year 2003		Year 2004		Year 2005		Year 2006		Year 2007		Year 2008	
		Cases	Death	Cases	Death	Cases	Death	Cases	Death	Cases	Death	Cases	Death	Cases	Death	Cases	Death	Cases	Death
Gambia	AFR-D											214	13			12	1	1	
Ghana	AFR-D	3,331	74	5,487	160	3,614	65	204	4	407	6	3,166	51	3,357	107	179	18	1,223	25
Guinea	AFR-D	517	36	392	22	61	11	6	1	1,516	117	3,821	107	3,242	219	8,546	311	513	32
Guinea-Bissau	AFR-D				6	842	6	290	2	155	3	25,111	399	37		153	8	14,323	225
India	SEAR-D	3,807	18	4,081	6	3,455	10	2,893	2	4,695	7	3,155	6	1,939	3	2,635	3	2,680	1
Indonesia	SEAR-B										40	1,338	19					1,007	27
Iran (Islamic Republic of)	EMR-B			105	1	118		96	1	94	1	1,133	11			19		72	4
Iraq	EMR-D	532	4			718		187		35						4,696	24	925	11
Kenya	AFR-E	1,157	78	1,001	55	291	10			870	15	816	21	870	11	1,206	67	3,091	113
Korea, Democratic People's Republic of	SEAR-D			162	1	4			1		1	16			5	7			
Lao People's Democratic Republic	WPR-B	12,440	520	2,941	5	2,042	5									169	3	201	3
Liberia	AFR-D	365	10	1,062	413	1,115		34,740	38	2,786	4	3,823	18	4,929	17	3,063	7	1,236	3
Madagascar	AFR-D	29,083	1,693	7,219		27		5											
Malawi	AFR-E	2,391	56	2,395	42	32,618	911	2,736	34	675	4	1,105	11	4,148	55	475	5	831	26
Malaysia	WPR-B	124	1	557	11					16				237	2				
Mali	AFR-D			67	9	18	2	1,455	119	2,839	205	1,178	76	7				153	5
Marshall Islands	WPR-B	300	6																
Mauritania	AFR-D					80		34	8			4,132	70	25		3			
Micronesia (Federated States of)	WPR-B	3,452	20																
Mozambique	AFR-E	17,647	253	8,794	102	24,375	342	13,758	102	20,080	110	2,226	24	6,306	29	2,622	22	9,087	102
Myanmar	SEAR-D										4	337	19					45	1
Namibia	AFR-E														5	14		3,496	38
Nepal	SEAR-D										46				4	16,162	>200		
Niger	AFR-D	211	38	194	16	236	12	292	11	2,178	57	553	55	1,232	81	24	2	972	70
Nigeria	AFR-D	2,799	43	2,199	104	5,429	154	1,933	87	3,186	185	4,477	174	2,028	127	1,661	48	5,410	247

Reported Cholera cases from 2000 to 2008 (Black: WER, Blue: PUBMED, Red: PROMED, Green: GIDEON, Purple: Others)

Country	WHO Region-Mortality Stratum	Year 2008 Cases	Year 2008 Death	Year 2007 Cases	Year 2007 Death	Year 2006 Cases	Year 2006 Death	Year 2005 Cases	Year 2005 Death	Year 2004 Cases	Year 2004 Death	Year 2003 Cases	Year 2003 Death	Year 2002 Cases	Year 2002 Death	Year 2001 Cases	Year 2001 Death	Year 2000 Cases	Year 2000 Death
Pakistan	EMR-D									17		39	4	30		Year 2000~2001: 689 cases			
Philippines	WPR-B		3			66	1	139	2	533	2		3			174		213	6
Rwanda	AFR-E	23		1,453	21	405	21	89	21	586		12				157	2	1,235	8
Sao Tome and Principe	AFR-D	119	4	90		926	9	1,966	33										
Senegal	AFR-D	1,283	20	3,984	24	365	10	31,719	458	1,227	10								
Seychelles	AFR-D			178	1	1													
Sierra Leone	AFR-D	62		2,219	84	2,560	99		6	513			42						
Somalia	EMR-D	1,281	16	41,643	1,182					4,490	26	11,020	56	2,775	159	1,821	124	7,496	563
South Africa	AFR-E	3,907	22					3,503	28	2,767	35	3,901	35	10,004	45	106,151	232	19,667	68
Sri Lanka	SEAR-B													9		1		2	
Sudan	EMR-D	17,241	118	13,731	500	30,662	1,011												
Swaziland	AFR-E	1		65		18		64		1,075	16	32	16	134	13	5,612	2	141	16
Tanzania, United Republic of	AFR-E	2,911	88	1,609	65	14,297	254	2,945	94	10,319	272	710	32	11,920	297	1,300	52	4,637	156
Thailand	SEAR-B	436	3	1,428	7	35	7												
Timor-Leste	SEAR-D													30	2	561	6		6
Togo	AFR-D	397	3	65	1	1,159	25	1,320	15	1,080	33	384	28	257	14	2,696	132	338	23
Uganda	AFR-E	3,726	120	276	3	5,194	106	4,924	98	3,380	91	4,377	129	2,274	133	247	4	1,595	107
Viet Nam	WPR-B	853		1,946			14				1								
Yemen	EMR-D		16	40		77													
Zambia	AFR-E	2,061	39	2,286	35	5,360	183	1,503	7	12,149	373	1,049	29	339	12	3,109	165	2,283	156
Zimbabwe	AFR-E	60,055	2,928	65	4	789	61	516	26	119	9	1,009	35	3,125	192	650	14	1,675	96

References of records from PROMED, PUBMED, and GIDEON are available under request.

**Table 16. Cholera-endemic areas of China, India
and Indonesia included in the disease burden analysis**

Province/State	Population
China (5 provinces):	
Guandong	94,490,000
Zhejiang	50,600,000
Shanghai	18,580,000
Fujian	35,810,000
Hainan	8,450,300
Total	**207,930,300**
Indonesia (8 provinces/cities):	
West Java	35,729,537
Irian Jaya	651,958
Sumatra	43,309,707
Jakarta	8,389,443
Banten	8,098,780
Tangerang	1,487,000
Bogor	866,034
Maluku	1,205,539
Total	**99,737,998**
India (18 states):	
Andhra Pradesh	80,712,000
Assam	28,665,000
Chhattisgarh	22,594,000
Gujarat	54,979,000
Haryana	23,314,000
Himachal Pradesh	6,455,000
Karnataka	56,258,000
Kerala	33,265,000
Madhya Pradesh	66,390,000
Maharashtra	104,804,000
Orissa	38,887,000
Punjab	26,059,000
Tamil Nadu	65,135,000
Tripura	3,407,000
West Bengal	85,216,000
Andaman & Nicobar Island	419,000
Chandigarh	1,103,000
Delhi	16,021,000
Total	**713,683,000**

Sources: ProMED reports (available at www.promed.org) for China and Indonesia; Kunungo et.al. 2010 (for India); ProMED reports and Agtini et.al. 2005 (for Indonesia).

Table 17. Population at risk of cholera in endemic countries, by country (2005 population)

Country	WHO region-mortality stratum	Total population	% population lacking access to improved sanitation	Population at risk
Afghanistan	EMR-D	29,863,000	70	20,904,101
Algeria	AFR-D	32,854,000	6	1,971,240
Angola	AFR-D	15,941,000	50	7,970,500
Bangladesh	SEAR-D	141,822,000	100	141,822,000
Benin	AFR-D	8,439,000	70	5,907,300
Bhutan	SEAR-D	2,163,000	48	1,038,240
Botswana	AFR-E	1,765,000	53	935,451
Burkina Faso	AFR-D	13,228,000	87	11,508,360
Burundi	AFR-E	7,548,000	59	4,453,320
Cambodia	WPR-B	14,071,000	72	10,131,120
Cameroon	AFR-D	16,322,000	49	7,997,780
Central African Republic	AFR-E	4,038,000	69	2,786,221
Chad	AFR-D	9,749,000	91	8,871,590
China	WPR-B	207,930,300 (Cholera-affected Provinces)	35	72,775,604
Comoros	AFR-D	798,000	65	518,700
Congo	AFR-E	3,999,000	80	3,199,200
Côte d'Ivoire	AFR-E	18,154,000	76	13,797,040
Democratic People's Republic of Korea	SEAR-D	22,488,000	41	9,220,080
Democratic Republic of the Congo	AFR-E	57,549,000	69	39,708,810
Djibouti	EMR-D	793,000	33	261,690
Eritrea	AFR-E	4,401,000	95	4,180,951
Ethiopia	AFR-E	77,431,000	89	68,913,590
Federated States of Micronesia	WPR-B	110,000	75	82,501
Fiji	WPR-B	848,000	29	245,920
Gabon	AFR-D	1,384,000	64	885,760
Gambia	AFR-D	1,517,000	48	728,160
Ghana	AFR-D	22,113,000	90	19,901,700
Guinea	AFR-D	9,402,000	81	7,615,620
Guinea-Bissau	AFR-D	1,586,000	67	1,062,620
India	SEAR-D	713,683,000 (Cholera-affected States)	72	513,851,760
Indonesia	SEAR-B	99,737,998 (Cholera-affected Provinces)	48	47,874,238
Iraq	EMR-D	28,807,000	24	6,913,680
Islamic Republic of Iran	EMR-B	69,515,000	17	11,817,550
Kenya	AFR-E	34,256,000	58	19,868,480
Lao People's Democratic Republic	WPR-B	5,924,000	52	3,080,480
Liberia	AFR-D	3,283,000	68	2,232,440
Madagascar	AFR-D	18,606,000	88	16,373,280
Malawi	AFR-E	12,884,000	40	5,153,600

Country	WHO region-mortality stratum	Total population	% population lacking access to improved sanitation	Population at risk
Malaysia	WPR-B	25,347,000	6	1,520,820
Mali	AFR-D	13,518,000	55	7,434,900
Marshall Islands	WPR-B	62,000	19	11,780
Mauritania	AFR-D	3,069,000	76	2,332,440
Mozambique	AFR-E	19,792,000	69	13,656,480
Myanmar	SEAR-D	50,519,000	18	9,093,420
Namibia	AFR-E	2,031,000	65	1,320,150
Nepal	SEAR-D	27,133,000	73	19,807,090
Niger	AFR-D	13,957,000	93	12,980,010
Nigeria	AFR-D	131,530,000	70	92,071,000
Pakistan	EMR-D	157,935,000	42	66,332,700
Philippines	WPR-B	83,054,000	22	18,271,880
Rwanda	AFR-E	9,038,000	77	6,959,261
Sao Tome and Principe	AFR-D	157,000	76	119,320
Senegal	AFR-D	11,658,000	72	8,393,760
Seychelles	AFR-D	81,000	100	81,000
Sierra Leone	AFR-D	5,525,000	89	4,917,251
Somalia	EMR-D	8,228,000	77	6,335,560
South Africa	AFR-E	47,432,000	41	19,447,120
Sri Lanka	SEAR-B	20,743,000	14	2,904,020
Sudan	EMR-D	36,233,000	65	23,551,450
Swaziland	AFR-E	1,032,000	50	516,000
Thailand	SEAR-B	64,233,000	4	2,569,320
Timor-Leste	SEAR-D	947,000	59	558,731
Togo	AFR-D	6,145,000	88	5,407,600
Uganda	AFR-E	28,816,000	67	19,306,720
United Republic of Tanzania	AFR-E	38,329,000	67	25,680,430
Viet Nam	WPR-B	84,238,000	35	29,483,300
Yemen	EMR-D	20,975,000	54	11,326,500
Zambia	AFR-E	11,668,000	48	5,600,640
Zimbabwe	AFR-E	13,010,000	54	7,025,400
Total		**2,476,372,298**		**1,443,153,304**

Table 18. Estimated number of cholera cases in endemic countries by age group and by country, 2005

Country	WHO sub-region	<1	1-4	5-14	15+	Total	Rate/ 1,000*
Angola	AFR-D	2,013	7,061	4,137	3,469	16,680	2.1
Bangladesh	SEAR-D	24,316	88,114	74,471	117,074	303,975	2.1
Benin	AFR-D	1,377	4,779	3,019	2,666	11,841	2.0
Bhutan	SEAR-D	178	680	364	569	1,791	1.7
Burundi	AFR-E	2,262	7,339	4,661	3,968	18,230	4.1
Cameroon	AFR-D	1,563	5,771	3,942	3,803	15,079	1.9
Chad	AFR-D	2,329	8,039	4,521	3,861	18,750	2.1
China	WPR-B	409	1,596	1,422	3,277	6,704	0.1
Comoros	AFR-D	107	397	257	242	1,003	1.9
Republic of Congo	AFR-E	1,623	5,738	2,837	3,006	13,204	4.1
Côte d'Ivoire	AFR-E	5,560	20,293	13,541	13,187	52,581	3.8
Korea, DPR	SEAR-D	833	3,475	2,859	5,648	12,815	1.4
Democratic Republic of the Congo	AFR-E	21,536	73,364	41,694	34,094	170,688	4.3
Ethiopia	AFR-E	30,702	111,918	71,325	62,518	276,463	4.0
Gambia	AFR-D	140	537	356	346	1,379	1.9
Ghana	AFR-D	3,554	13,478	9,433	9,785	36,250	1.8
Guinea	AFR-D	1,754	6,105	3,771	3,499	15,129	2.0
Guinea-Bissau	AFR-D	288	980	574	445	2,287	2.2
India	SEAR-D	70,708	270,259	215,764	277,490	834,221	1.6
Indonesia	SEAR-B	1,733	6,682	4,955	8,273	21,643	0.5
Iraq	EMR-D	1,172	4,501	3,057	2,945	11,675	1.7
Islamic Republic of Iran	EMR-B	93	330	292	459	1,174	0.1
Kenya	AFR-E	9,068	31,750	19,901	18,347	79,066	4.0
Liberia	AFR-D	594	2,025	1,177	954	4,750	2.1
Malawi	AFR-E	2,550	8,934	5,670	4,425	21,579	4.2
Mali	AFR-D	1,985	6,749	4,057	3,116	15,907	2.1
Mauritania	AFR-D	548	1,892	1,012	1,128	4,580	2.0
Mozambique	AFR-E	5,987	21,869	14,261	12,389	54,506	4.0
Myanmar	SEAR-D	1,008	4,105	3,069	5,350	13,532	1.5
Namibia	AFR-E	433	1,703	1,249	1,326	4,711	3.6
Nepal	SEAR-D	3,365	12,841	9,244	9,898	35,348	1.8
Niger	AFR-D	3,678	12,504	6,793	5,440	28,415	2.2
Nigeria	AFR-D	21,016	74,057	47,320	41,557	183,950	2.0
Pakistan	EMR-D	10,269	38,242	25,535	30,651	104,697	1.6
Philippines	WPR-B	189	742	591	667	2,189	0.1
Rwanda	AFR-E	3,177	10,995	7,010	6,426	27,608	4.0
Sao Tome and Principe	AFR-D	22	85	60	57	224	1.9
Senegal	AFR-D	1,744	6,361	4,170	3,924	16,199	1.9
Sierra Leone	AFR-D	1,162	4,041	2,395	2,259	9,857	2.0
Somalia	EMR-D	1,359	4,884	2,801	2,562	11,606	1.8

Country	WHO sub-region	<1	1-4	5-14	15+	Total	Rate/ 1,000*
South Africa	AFR-E	5,229	21,032	15,571	21,423	63,255	3.3
Swaziland	AFR-E	161	673	508	510	1,852	3.6
Thailand	SEAR-B	73	291	192	487	1,043	0.4
Togo	AFR-D	1,188	4,257	2,720	2,484	10,649	2.0
Uganda	AFR-E	11,299	37,784	20,831	15,951	85,865	4.4
United Republic of Tanzania	AFR-E	10,872	38,816	27,656	23,297	100,641	3.9
Viet Nam	WPR-B	248	949	772	1,193	3,162	0.1
Yemen	EMR-D	2,345	8,491	5,301	4,498	20,635	1.8
Zambia	AFR-E	2,538	9,303	6,146	4,899	22,886	4.1
Zimbabwe	AFR-E	2,377	9,226	6,843	6,943	25,389	3.6
Total		**282,688**	**1,030,630**	**720,364**	**802,987**	**2,836,669**	**2.0**

*The denominator is at-risk population for all countries except Bangladesh, where the entire population is considered at risk of cholera.

Table 19. Estimated number of cholera deaths by age group and by country, 2005

Country	WHO sub-region	<1	1-4	5-14	15+	Total	Rate / 100,000*
Angola	AFR-D	76	268	157	132	633	7.9
Bangladesh	SEAR-D	365	1,322	1,117	1,756	4,560	3.2
Benin	AFR-D	52	182	115	101	450	7.6
Bhutan	SEAR-D	5	20	11	17	53	5.1
Burundi	AFR-E	86	279	177	151	693	15.6
Cameroon	AFR-D	59	219	150	145	573	7.2
Chad	AFR-D	89	305	172	147	713	8.0
China	WPR-B	4	16	14	33	67	0.1
Comoros	AFR-D	4	15	10	9	38	7.3
Congo	AFR-E	62	218	108	114	502	15.7
Côte d'Ivoire	AFR-E	211	771	515	501	1,998	14.5
Democratic People's Republic of Korea	SEAR-D	25	104	86	169	384	4.2
Democratic Republic of the Congo	AFR-E	818	2,788	1,584	1,296	6,486	16.3
Ethiopia	AFR-E	1,167	4,253	2,710	2,376	10,506	15.2
Gambia	AFR-D	5	20	14	13	52	7.1
Ghana	AFR-D	135	512	358	372	1,377	6.9
Guinea	AFR-D	67	232	143	133	575	7.6
Guinea-Bissau	AFR-D	11	37	22	17	87	8.2
India	SEAR-D	2,121	8,108	6,473	8,325	25,027	4.9
Indonesia	SEAR-B	17	67	50	83	217	0.5
Iraq	EMR-D	38	144	98	94	374	5.4
Islamic Republic of Iran	EMR-B	1	4	4	6	15	0.1
Kenya	AFR-E	345	1,207	756	697	3,005	15.1
Liberia	AFR-D	23	77	45	36	181	8.1
Malawi	AFR-E	97	339	215	168	819	15.9
Mali	AFR-D	75	256	154	118	603	8.1

Country	WHO sub-region	<1	1-4	5-14	15+	Total	Rate / 100,000*
Mauritania	AFR-D	21	72	38	43	174	7.5
Mozambique	AFR-E	228	831	542	471	2,072	15.2
Myanmar	SEAR-D	30	123	92	161	406	4.5
Namibia	AFR-E	16	65	47	50	178	13.5
Nepal	SEAR-D	101	385	277	297	1,060	5.4
Niger	AFR-D	140	475	258	207	1,080	8.3
Nigeria	AFR-D	799	2,814	1,798	1,579	6,990	7.6
Pakistan	EMR-D	329	1,224	817	981	3,351	5.1
Philippines	WPR-B	2	7	6	7	22	0.1
Rwanda	AFR-E	121	418	266	244	1,049	15.1
Sao Tome and Principe	AFR-D	1	3	2	2	8	6.7
Senegal	AFR-D	66	242	158	149	615	7.3
Sierra Leone	AFR-D	44	154	91	86	375	7.6
Somalia	EMR-D	43	156	90	82	371	5.9
South Africa	AFR-E	199	799	592	814	2,404	12.4
Sudan	EMR-D	127	467	328	326	1,248	5.3
Swaziland	AFR-E	6	26	19	19	70	13.6
Thailand	SEARB	1	3	2	5	11	0.4
Togo	AFR-D	45	162	103	94	404	7.5
Uganda	AFR-E	429	1,436	792	606	3,263	16.9
United Republic of Tanzania	AFR-E	413	1,475	1,051	885	3,824	14.9
Viet Nam	WPR-B	2	9	8	12	31	0.1
Yemen	EMR-D	75	272	170	144	661	5.8
Zambia	AFR-E	96	354	234	186	870	15.5
Zimbabwe	AFR-E	90	351	260	264	965	13.7
Total		9,382	34,086	23,299	24,723	91,490	6.3

*The denominator is the population at-risk for cholera for all countries except Bangladesh, where the entire population is considered at risk.

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Appendix 2.
Cholera prevention and control measures

- ❖ **Provision of clean water and safe water storage**:
  - Piped water systems
  - Treatment (chlorination at the municipal level)
  - Point of use household interventions:
    - Filtration with cloths (e.g., saris) placed over water collection pots (where vibrio-bearing copepods proliferate in water), ceramic filtration
    - Chlorine solutions
    - Boiling water
    - Solar or heat disinfection using clear bottles
    - Flocculant disinfectants
    - Provision of improved water storage containers (e.g., with narrow mouths or spigots)

- ❖ **Improvements in sanitation and waste disposal**:
  - Construction of sewerage systems
  - Latrine construction

- ❖ **Appropriate case management:**
  - Rapid and appropriate rehydration with oral rehydration salts (ORS) or IV fluids
  - Antibiotic therapy for severe cases

- ❖ **Health education**:
  - Promotion of hand washing with soap
  - Promotion of safe preparation and storage of food
  - Promotion of breastfeeding
  - Promotion of domestic and personal hygiene
  - Awareness campaigns during outbreaks to encourage people with symptoms to seek immediate health care

- ❖ **Improvements in food safety**:
  - Enactment of food safety laws for restaurants, food vendors and food processing factories
  - Banning of unsafe agricultural practices (e.g., use of residual or sewerage water to irrigate crops)

- ❖ **Strengthening of disease surveillance/reporting and early warning systems**:
  - Strengthening of disease and environmental surveillance
  - Establishment or strengthening of diagnostic laboratories
  - Establishment of an alert and response mechanism (e.g., during outbreaks)

- ❖ **Vaccination using oral cholera vaccines**
  - Routine or pre-emptive vaccination in endemic areas (including refugees or internally displaced persons in endemic areas)
  - Reactive vaccination in some emergency situations

Appendix 3. Profiles of the current cholera vaccines and vaccines under development

Currently available vaccines:

Feature/Characteristic	WC-rBS	Modified WC bivalent (O1/O139)
Commercial name	Dukoral®	Shanchol™ (India) mORC-VAX (Vietnam)
Producer	Crucell/SBL Vaccines	Shantha Biotechnics (India) VaBiotech (Vietnam)
Year first licensed	1991	2009
Vaccine type/composition	Killed *V. cholerae* O1 whole cells (Inaba and Ogawa, classical and El Tor) + recombinant cholera toxin B subunit	Killed *V. cholerae* O1 whole cells (Inaba and Ogawa, classical and El Tor) + O139
Route of administration	Oral	Oral
Lowest age approved for license	2 years old	1 year old
Number of doses and schedule	2 doses given 7-14 days apart (3 doses for children 2-5 years old)	2 doses given 14 days apart
Formulation and presentation	Liquid vaccine suspension in single-dose or two-dose vials + bicarbonate buffer in effervescent granules in sachet. Two vials/sachets per box	Liquid vaccine in single-dose vials. Plans underway to reduce packaging and modify presentation for Shanchol™ to facilitate its use for mass campaigns in developing countries.
Requires buffer?	Yes	No
Water requirements	Vaccine and buffer are mixed in 150 ml of water (chlorinated or not) for persons >5 years old (75 ml for 2-5 year olds).	No water is required.
Safety/tolerability	High, including in HIV+ individuals	High; safety in HIV+ individuals not yet known but presumed
Time of earliest onset of protection after full vaccination	1 week	Unknown (likely to be 1 week, given similar composition as Dukoral)
Efficacy rates in cholera-affected countries	1985 trial results in Bangladesh: 58% at 2 years of follow-up 18% at 3 years of follow-up	2006-2011 trial results in Kolkata, India: 65% at 3 years of follow-up and 66% over 3 years (cumulative)
Duration of sustained protection	2 years in persons >5 years old 6 months in children ≤5 years of age	At least 3 years in persons 5 years and older; 2 years in children 1-4*
Confers herd protection?	Yes	Very likely (based on reanalysis of data on the WC vaccine from the original Matlab clinical trials)
Cold chain requirements	License requires 2-8°C, but remains stable for 1 month at 37°C	License requires 2-8°C. Stability tests at ambient temperatures being conducted.
Storage volume	39 L per 1,000 doses	25 L per 1,000 doses**

Feature/Characteristic	WC-rBS	Modified WC bivalent (O1/O139)
requirements		
Shelf life	3 years	2 years on the label. Stability testing indicates that the shelf life could be extended to three years.
Price to the public sector	Will depend on production volume. Company is willing to offer competitive prices for a certain minimum annual volume.	Shantha's current price is $1.85/dose. Price of mORC-VAX to the EPI program in Vietnam is ≈$0.75/dose. Prices of vaccine available internationally could be reduced over time with increased production experience/ efficiencies and increased competition.
WHO pre-qualified?	Yes	Yes (since 2011)

* The clinical trial of the vaccine in Kolkata, India is continuing for five years following vaccination (till 2011). Thus data on the vaccine's duration of protection at four and five years will be available in the future.
** Calculation assumes that the vaccine boxes are removed from Thermocol shippers for cold storage.

Composition of killed whole-cell based oral cholera vaccines:

Element/Strain	WC-rBS (Dukoral®)	Original Vietnamese WC vaccine (ORCVax®)	Modified WC vaccine (Shanchol™)
O1 strains:			
▪ El Tor Inaba (Phil 6973), formalin-killed	2.5×10^{10} cells	5×10^{10} cells	600 EU LPS
▪ Classical Ogawa (Cairo 50), heat-killed	2.5×10^{10} cells	2.5×10^{10} cells	300 EU LPS
▪ Classical Ogawa (Cairo 50), formalin-killed	2.5×10^{10} cells	---	300 EU LPS
▪ Classical Inaba (569B), formalin-killed	---	2.5×10^{10} cells	---
▪ Classical Inaba (Cairo 48), heat-killed	2.5×10^{10} cells	---	300 EU LPS
O139 (4260B), formalin-killed	---	5×10^{10} cells	600 EU LPS
Recombinant cholera toxin B subunit	1 mg	---	---

Most advanced cholera vaccine candidates:

Characteristic	Peru-15	*V. cholerae* 638	VA1.4
Developer	Harvard University	Finlay Institute, Cuba	3 Indian government research laboratories
Producer	VTI, U.S. and China	Finlay Institute, Cuba	Shantha Biotechnics, Hyderabad, India (contract manufacturer)
Vaccine type/composition	Live attenuated O1 El Tor Inaba (C6709) with deletion of entire cholera toxin genetic element and engineered to be non-motile and non-recombinational	Live attenuated O1 El Tor Ogawa (C7258) with deletion of entire cholera toxin genetic element (CTXΦ) and modification of the *hapA* gene	Live attenuated non-toxigenic O1 El Tor Inaba strain (devoid of CTX prophage)
Route of administration	Oral	Oral	Oral
Number of doses	One	One	One
Formulation	Lyophilized	Lyophilized	Lyophilized
Need for buffer?	Yes	Yes	Yes
Target ages	All ages, including infants Potentially (Phase II studies in infants underway)	All ages, including infants	All ages, including infants
Cold chain requirements	Must be kept frozen at -20°C	Must be kept frozen at -20°C (can be kept for 3 months at 2-8°C)	Must be kept frozen at -20°C
Status of development and human testing	Phase I/II trials in adults, toddlers and infants (9	Series of Phase II and challenge studies in	Phase I/II study in adult men in Kolkata, India

Characteristic	Peru-15	*V. cholerae* 638	VA1.4
	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.	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.	completed for VA1.3 vaccine in 2004. Phase I/II studies of new version (VA1.4) being planned in Kolkata.
Safety results	No significant differences in rates of side effects between vaccine and placebo recipients. Mild symptoms in 3% of children and 5% of adults vaccinated.	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.	Mild adverse events in 3/186 vaccinees (1.6%)
Vibriocidal seroconversion rates ($\geq$4-fold rise in titers from baseline)	Adults – 75% 2-5 year olds – 84% 9-23 month olds – 70%	100% in Havana; 97% in Maputo	57%
Will producer apply for WHO pre-qualification?	Yes, if Phase III clinical trial results are positive.	Yes, if clinical trial results are positive. Vaccine was developed especially for use in cholera-endemic countries in Africa.	Likely, if results of clinical trial are positive.

Appendix 4. Methods and assumptions for the global demand forecast of cholera vaccines for use in endemic countries

1. Overview

In this investment case, the projections of the costs, impact and cost-effectiveness of cholera vaccine to control endemic disease are based on the results of a strategic demand forecast conducted for this investment case. The forecast estimates the year a country will introduce cholera vaccination, the numbers of people that will be vaccinated, and the number of doses that will be required (including wastage) each year and over time, based on the data and assumptions used in the analysis. This appendix describes the modeling method, data sources, key assumptions and detailed results of the demand forecast. The demand forecast for a global vaccine stockpile is presented separately in Appendix 5.

This forecast projects the "potential demand" for cholera vaccine, and does not adjust for the supply of vaccine, as currently projected (see Appendix 6). Since cholera vaccination will be targeted to specific cholera-endemic countries and to high-risk populations within countries, it is important to predict which countries will introduce the vaccine, when they would introduce it, as well as the size of the population to be targeted for cholera vaccination. By estimating the potential demand, this analysis should assist manufacturers in making decisions about whether to produce cholera vaccine and what production capacity is required.

In addition to the demand forecast for the use of cholera vaccine to control endemic disease, this investment case includes the use of a vaccine stockpile (with a maximum quantity of 10 million doses per year) to prevent or control outbreaks in both cholera-endemic and non-endemic countries. The stockpile analysis is found in Appendix 5.

2. Selection of target countries and forecasting year of introduction of cholera vaccination

Scoring system and variables included

To determine which countries would introduce cholera vaccination to control endemic disease, the analysis started with the 51 countries identified in the disease burden analysis as cholera-endemic (having reports of cholera in three of the past five years). Six countries (China, Indonesia, Iran, Philippines, Thailand and Vietnam) in which cholera vaccination was not found to be cost-effective, due to relatively low incidence and mortality, were assumed not to introduce the vaccine and thus eliminated from the demand forecast (see Section 8 and Appendix 10). For the remaining 45 countries, a semi-quantitative scoring system was used to predict the year each country would adopt cholera vaccination. The scoring system, in which the lower the score, the sooner the country will introduce cholera vaccine, uses the following four variables:

- **Disease burden**: It is assumed that countries with a high cholera disease burden will introduce cholera vaccination sooner than other countries, all other things being equal. Disease burden is measured for this index in terms of cholera mortality rates. Two mortality estimates were calculated. The first was based on the incidence derived from the IVI cholera disease burden analysis described in Appendix 1. The second mortality estimate was one based on the number of cases reported in the WHO *Weekly Epidemiological Record* (WER), PubMed and Gideon combined (shown in Table 15 of Appendix 1). This number was then

divided by a correction factor of 10% since WHO estimates that only around 5-10% of cholera cases are reported (WHO 2009d). The incidence numbers compiled in the *WER* and other sources are reported data only and thus may be more indicative of a country's surveillance system or willingness to address cholera than the incidence rates derived from the IVI model. The reported incidence figures also vary more than the modeled incidence. For both sets of incidence rates, the cholera mortality rate was calculated using population figures for the entire country and the case fatality rates that were standardized by WHO mortality stratum in the disease burden analysis (which ranged from 1% to 3.8%) (see Table 8 of Appendix 1). The two mortality rates were then converted to scores in quintiles, with the highest mortality rates assigned a score of zero and the lowest rates a score of 1 (see Table 1 below). The two scores were averaged to obtain the disease burden score.

- **Past history with the introduction of new and under-utilized vaccines into national immunization programs**: We assume that cholera-endemic countries that were early adopters of Hib, Hepatits B, or pneumococcal vaccines will adopt cholera vaccines sooner than countries that have not introduced these vaccines quickly. For Hepatitis B and Hib vaccines, countries are assigned scores between 1 and 5, with early adopters receiving lower scores and late adopters higher scores. The years of adoption are grouped into blocks of 3-4 years, and thus countries that adopted these vaccines in the first 3-4 years amongst all developing countries received a score of 1, countries that adopt in the second three years received a score of 2, and continuing to the latest adopters who received a score of 5. The years of adoption of new vaccines are taken from a database maintained by UNICEF and WHO showing estimated coverage rates for each of these vaccines by year [WHO, 2009]. For the pneumococcal conjugate vaccine, countries that have either submitted an application to GAVI or have already adopted the vaccine received a low score of 1, while the remaining countries receive no score[11] (i.e. their scores depend only on Hib and Hepatitis B adoption). For countries that have not applied for GAVI support for the pneumococcal conjugate vaccine, only the scores for hepatitis B and Hib vaccines were used. The average score for the three vaccines were used to generate a composite vaccine adoption history of between 0 and 1. Details on the adoption history by country (developed by Applied Strategies) are shown in Table 7 at the end of this appendix.

- **Performance and capacity of the national immunization program**: Studies have shown that countries with higher immunization coverage rates for the basic EPI vaccines adopt new vaccines significantly earlier than countries with lower coverage rates. For example, the speed of introducing Hib and hepatitis B vaccines was significantly correlated with coverage rates for the third dose of DPT vaccine [Miller and Flanders, 2000; Rossi et al., 2007]. While past investment cases have used DPT3 coverage rates as a proxy for the capacity of a country's EPI, we have chosen the coverage rates for measles-containing vaccine (MCV), such as measles or measles-mumps-rubella (MMR), since these vaccines are given at a slightly older age (beginning at nine months) compared to DPT, and since the cholera vaccine is not licensed for children under one year of age. Countries with MCV coverage rates of less than 50% were assigned a score of 1 and those with coverage rates greater than 90% were given a score of 0.

- **Experience with laboratory-confirmed cholera surveillance or cholera vaccination**: Research has shown that countries that have conducted disease burden studies for a particular vaccine-preventable disease or had prior experience with the vaccine in question,

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[11] The sources for this information was the GAVI website:
http://www.gavialliance.org/performance/country_results/index.php

such as through a clinical trial, demonstration project or extensive use in the private sector, are more likely to be early adopters of the vaccine (see Wenger et. al. 2000 about Hib vaccine introduction). We therefore included a score for country experience with (or plans for) cholera surveillance projects, cholera vaccine clinical trials or demonstration projects. Countries with experience in laboratory-confirmed cholera surveillance (e.g., Indonesia) received a score of 0.67. Those that have participated in or are planning a cholera vaccine demonstration project, but haven't conducted surveillance (such as Zambia, where Epicentre is planning a cholera vaccine demonstration project) received a score of 0.33. Countries with experience or plans both for cholera surveillance and use of the vaccine through either a clinical trial or demonstration project (e.g., India, Bangladesh, Mozambique) were assigned a score of zero. Cholera vaccination programs undertaken in refugee camps were not included in this analysis because these are typically executed by NGOs with little government interaction.

Table 1. Scoring countries for cholera vaccine adoption

Score	Disease burden		Vaccine adoption history	Immunization program capacity	Cholera surveillance and/or vaccination experience	Total score	Year of adoption
	Annual mortality rate per 100,000 based on IVI disease burden model	Annual mortality rate per 100,000 based on WER, ProMED and published reports	Total score for introduction of Hib, Hepatitis B, and pneumococcal conjugate vaccines*	Reported MCV** coverage rate	DP-Demonstration Project, CT-Clinical Trial, S- Surveillance		
1	<2.3	<0.4	≥5	<50%	No experience = 1	< 1.5	2016
0.75	2.3 - 5.4	0.4 - 3.4	4 - 5	50% - 65%	S = 0.67	1.5 - 2.0	2017
0.50	5.4 - 7.6	3.5 - 6.3	3 - 4	65% -80%	CT or DP only = .33	2.0 - 2.25	2018
0.25	7.6 - 14	6.4 - 28	2 - 3	80% - 90%	Both CT/DP and S = 0	2.25 - 2.5	2019
0	≥14	≥28	<2	≥90%		2.5 - 2.75	2020
						2.75 or more	2021 or beyond

* See explanation of how vaccine adoption history was scored above in the text. Score for pneumococcal conjugate vaccine introduction is based on whether or not the country applied to GAVI for support for the introduction of this vaccine.
** MCV = measles-containing vaccine (measles, measles-rubella or measles-mumps-rubella (MMR)

The scores were totaled and converted to year of adoption shown in Table 1 in the right-hand columns, with the lower the score, the earlier the predicted year of vaccine introduction.

Adjustments were made to the predicted time to adopt vaccination for several countries. The time to adopt was delayed for countries prone to or experiencing political turmoil, such as the Democratic Republic of the Congo and Zimbabwe. On the other hand, the time to adopt was accelerated for two countries – Bangladesh and India – that are currently piloting or planning cholera vaccination programs. Bangladesh has begun a feasibility study of cholera vaccination in a large, low-income section of Dhaka, using Shanchol™ vaccine either imported directly from India or purchased in bulk and fill-finished by a local private sector drug manufacturer. In India, a Phase 3 trial of Shanchol™ is continuing in Kolkata in West Bengal state, and a pilot vaccine introduction project using the same vaccine is being planned in the state of Orissa. In both countries, the predicted year of vaccine introduction is 2015 – the earliest year that any country

is assumed to introduce the vaccine. This year was chosen for two reasons. First, manufacturing capacity at Shantha will not be expanded beyond the current capacity of 2 -2.5 million doses per year until 2015 when a dedicated cholera vaccine production facility at Shantha is expected to come on line. Second, the GAVI Alliance may decide to support the introduction of cholera vaccine, which will accelerate its introduction, but will not be considering the support of any additional vaccines until 2013.

The time to adopt was also accelerated for three countries that have expressed interest in introducing the vaccine. These are: 1) Uganda, where numerous government officials expressed interest in using cholera vaccines during a country case study visit to the country by the IVI investment case team; 2) Nigeria, which has expressed interest in acquiring a limited supply of Shanchol™ to protect health workers during the cholera outbreaks of 2010; and 3) Nepal, which has shown its willingness to introduce other vaccines for targeted use in high-risk areas (i.e., Japanese encephalitis vaccine).

Scoring Indian states

Cholera vaccine is expected to be introduced in certain states in India where the disease is considered endemic, and not throughout the country, following the model of Japanese encephalitis vaccine use. Therefore, a scoring system was applied to eighteen states where an extensive literature review identified cholera through reports of outbreaks or through laboratory-confirmed surveillance between 1997 and 2006 [Kanungo et. al. 2010]. The scoring uses two variables: 1) average annual cholera incidence rates (based on the Kanungo analysis) and 2) measles vaccination coverage rates, as a proxy for the performance and capability of the state immunization program. It is assumed that states with a greater cholera disease burden and higher coverage rates for measles vaccine would introduce cholera vaccine earlier than other states. The conversion of these variables into scores is shown in Table 2.

Table 2. Scoring states in India for cholera vaccine adoption

Score	Disease burden	Immunization program capacity
	Average annual cases per 100,000 persons*	Reported measles vaccine coverage rate
1	<0.1	< 50%
0.75	0.1 -0.3	50% - 65%
0.50	0.3 -1	65% - 80%
0.25	1 -10	80% - 90%
0	≥10	> 90%

* Based on an analysis of disease outbreaks and laboratory-confirmed surveillance between 1997 and 2006 (see Kanungo et. al. 2010)

Total score	Year of adoption
0.25	2018
0.50	2019
0.75	2020
≥ 1.0	2021

Results

The scores and predicted year of cholera vaccine introduction for the 45 cholera-endemic countries included in this analysis are shown in Table 3. The years of adoption are grouped into three time periods: the years 2015 to 2017, the years 2018 to 2020 and 2021 to 2023. This investment case includes only the 33 countries that are predicted to introduce cholera vaccination by the year 2020, though the impact and cost of vaccination are analyzed in this investment case up to 2030.

Eleven countries are predicted to introduce the vaccine from 2015 to 2017, which we propose would be financed through an initial investment ("Investment 1"). The earliest adopters, such as Bangladesh, Mozambique, India and Tanzania, have a demonstrated cholera burden, a strong immunization program, and have already undertaken or planned cholera surveillance and/or clinical trials and demonstration projects. It should be noted that while the mainland of Tanzania is predicted to introduce the vaccine starting in 2016, the island of Zanzibar – where a cholera vaccine demonstration project headed by WHO is currently in progress, using Dukoral® – is forecasted to introduce the vaccine in 2015. This is based on the expressed interest of the island's health ministry, as a result of continual cholera outbreaks and fears of their impact on the island's main industry, tourism.

Another 22 countries – primarily in Africa – are forecasted to introduce the vaccine by 2020.

The results for the states of India are shown in Table 4. The demand forecast predicts that Orissa and West Bengal will be the first adopters – introducing the vaccine in 2015, based on their current experience field testing or piloting the Shanchol™ vaccine. These two states would therefore be part of Investment 1. Ten additional states are predicted to introduce the vaccine during Investment 2 (between 2018 and 2020). Six states are forecasted to adopt cholera vaccination beyond 2020 and are therefore not included in the demand forecast.

A list of the countries and Indian states by WHO region, year and phase of adoption, and GAVI eligibility is shown in Table 6 at the end of this appendix.

While the countries in Investment 1 and 2 are considered to be the most likely adopters, there is some uncertainty, especially concerning the time frame for adoption. Some countries may make large improvements in water and sanitation over the next ten years, reducing their cholera risk and thus the need for cholera vaccination. However, it is difficult to predict at this time in which countries this will occur.

3.   Forecasting demand (number of doses used per year)

Selecting populations for targeted vaccination

The demand forecast defines populations at risk of cholera in two ways:

1) For rural populations: the percent of the population that does not have access to a safe water supply (using data from the UN Population Division[12]); and

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[12] The portion of the population lacking access to safe water was used as a proxy for the population at risk of cholera instead of those lacking adequate sanitation, as used in the disease burden analysis in Appendix 1. This is because the population lacking improved sanitation is very large and it is assumed that cholera vaccination programs would have to target smaller populations. It is also likely that populations lacking access to safe water also lack adequate sanitation, and thus are assumed to be at greatest risk of cholera.

Table 3. Scoring results and predicted year and phase of adoption of cholera vaccine for 45 cholera-endemic countries

Country	Disease Burden			Vaccine Adoption History		Immunization program capacity/performance		Early Experience with cholera surveillance or vaccination		Total score	Projected Year of adoption	Years to add or subtract from algorithm	Year of adoption	Invest-ment
	Annual mortality rate (estimated deaths per 100,000 based on IVI model)	Mortality rate (estimated deaths from 2000-2008 per 100,000 from WER and other sources)	Score (average of both estimates)	HepB, Hib, Pneumo Conjugate Adoption Score	Total Score	Measles-containing vaccine coverage (%) projection for 2008-2009	Score	DP-Demonstration Project, CT-Clinical Trial, S-Surveillance, N-none	Score					
GAVI-eligible countries														
Bangladesh	5.13	1.14	0.75	5.0	1.00	89	0.25	CT&S	0.00	2.00	2018	-3	2015	1
India***	4.89	0.17	0.875	4.5	0.75	70	0.50	CT&S	0.00	2.13	2018	-3	2015	1
Uganda	16.90	5.68	0.25	3.0	0.50	68	0.50	N	1.00	2.25	2019	-3	2016	1
Tanzania	14.89	8.33	0.125	4.5	0.75	88	0.25	DP&S	0.00	1.13	2016	0	2016	1
Mozambique	15.17	32.43	0.00	4.5	0.75	77	0.50	DP&S	0.00	1.25	2016	0	2016	1
Zambia	15.53	22.72	0.125	4.0	0.75	85	0.25	DP	0.33	1.46	2016	0	2016	1
Gambia	7.14	1.32	0.625	1.3	0.00	91	0.00	N	1.00	1.63	2017	0	2017	1
Kenya	15.12	1.98	0.375	2.3	0.25	90	0.00	N	1.00	1.63	2017	0	2017	1
Rwanda	15.07	2.40	0.375	2.3	0.25	92	0.00	N	1.00	1.63	2017	0	2017	1
Malawi	15.89	38.81	0.00	3.0	0.50	88	0.25	N	1.00	1.75	2017	0	2017	1
Burundi	15.56	6.30	0.25	3.5	0.50	84	0.25	N	1.00	2.00	2018	0	2018	2
Sao Tome and Principe	6.70	109.73	0.25	4.5	0.75	93	0.00	N	1.00	2.00	2018	0	2018	2
Zimbabwe	13.74	40.87	0.125	3.0	0.50	66	0.50	N	1.00	2.13	2018	+1	2019	2
Ghana	6.92	4.45	0.50	3.0	0.50	86	0.25	N	1.00	2.25	2019	0	2019	2
Guinea-Bissau	8.19	162.56	0.125	4.5	0.75	76	0.50	N	1.00	2.38	2019	0	2019	2
Cameroon	7.16	6.57	0.375	3.7	0.50	80	0.50	N	1.00	2.38	2019	0	2019	2
Senegal	7.33	19.41	0.375	3.5	0.50	77	0.50	N	1.00	2.38	2019	0	2019	2
Mali	8.11	3.25	0.50	3.0	0.50	68	0.50	N	1.00	2.50	2020	0	2020	2
Congo, DR	16.33	16.49	0.125	3.7	0.50	67	0.50	N	1.00	2.13	2018	+2	2020	2
Comoros	7.33	54.59	0.25	4.5	0.75	76	0.50	N	1.00	2.50	2020	0	2020	2

Country	Disease Burden			Vaccine Adoption History		Immunization program capacity/performance		Early Experience with cholera surveillance or vaccination		Total score	Projected Year of adoption	Years to add or subtract from algorithm	Year of adoption	Invest ment
	Annual mortality rate (estimated deaths per 100,000 based on IVI model)	Mortality rate (estimated deaths from 2000-2008 per 100,000 from WER and other sources)	Score (average of both estimates)	HepB, Hib, Pneumo Conjugate Adoption Score	Total Score	Measles-containing vaccine coverage (%) projection for 2008-2009	Score	DP-Demonstra-tion Project, CT- Clinical Trial, S- Surveillance, N - none	Score					
Ethiopia	15.25	5.03	0.25	4.5	0.75	74	0.50	N	1.00	2.50	2020	0	2020	2
Korea, DPR	4.19	0.07	0.875	4.5	0.75	98	0.00	N	1.00	2.63	2020	0	2020	2
Benin	7.62	5.42	0.375	3.5	0.50	61	0.75	N	1.00	2.63	2020	0	2020	2
Nigeria	7.59	3.85	0.375	4.5	0.75	62	0.75	N	1.00	2.88	2021	-1	2020	2
Nepal	5.37	2.73	0.75	5.0	1.00	79	0.50	N	1.00	3.25	2023	-3	2020	2
Togo	7.47	6.01	0.50	4.5	0.75	77	0.50	N	1.00	2.75	2021	0	2021	*
Liberia	8.11	100.46	0.125	4.5	0.75	64	0.75	N	1.00	2.63	2021	+1	2021	*
Yemen	5.84	0.02	0.75	2.3	0.25	62	0.75	N	1.00	2.75	2021	0	2021	*
Niger	8.32	1.92	0.50	4.5	0.75	80	0.50	N	1.00	2.75	2021	0	2021	*
Guinea	7.55	10.32	0.375	4.5	0.75	64	0.75	N	1.00	2.88	2021	0	2021	*
Côte d'Ivoire	14.48	3.58	0.25	4.5	0.75	63	0.75	N	1.00	2.75	2021	0	2021	*
Pakistan	5.05	0.01	0.875	4.0	0.75	85	0.25	N	1.00	2.88	2021	0	2021	*
Sierra Leone	7.63	4.60	0.375	4.5	0.75	60	0.75	N	1.00	2.88	2021	0	2021	*
Chad	8.04	5.99	0.375	4.5	0.75	23	1.00	N	1.00	3.13	2022	0	2022	*
Mauritania	7.46	7.74	0.375	5.0	1.00	65	0.75	N	1.00	3.13	2022	0	2022	*
Myanmar	4.48	0.14	0.875	5.0	1.00	82	0.25	N	1.00	3.13	2022	0	2022	*
Somalia	5.86	39.58	0.25	5.0	1.00	24	1.00	N	1.00	3.25	2023	0	2023	*
Non GAVI-eligible countries														
Swaziland	14.00	57.91	0.00	4.0	0.75	95	0.00	N	1.00	1.75	2017	0	2017	1
Rep. of Congo	15.69	12.43	0.125	3.7	0.50	79	0.50	N	1.00	2.13	2018	0	2018	2
South Africa	12.00	32.55	0.125	2.0	0.25	62	0.75	N	1.00	2.13	2018	0	2018	2
Angola	7.94	50.95	0.125	4.5	0.75	79	0.50	N	1.00	2.38	2019	0	2019	2

Country	Disease Burden			Vaccine Adoption History		Immunization program capacity/performance		Early Experience with cholera surveillance or vaccination		Total score	Projected Year of adoption	Years to add or subtract from algorithm	Year of adoption	Investment
	Annual mortality rate (estimated deaths per 100,000 based on IVI model)	Mortality rate (estimated deaths from 2000-2008 per 100,000 from WER and other sources)	Score (average of both estimates)	HepB, Hib, Pneumo Conjugate Adoption Score	Total Score	Measles-containing vaccine coverage rate (%) projection for 2008-2009	Score	DP-Demonstration Project, CT- Clinical Trial, S- Surveillance, N - none	Score					
Iraq	5.00	3.65	0.625	2.3	0.25	69	0.50	N	1.00	2.38	2019	0	2019	2
Bhutan	5.10	0.41	0.75	4.0	0.75	99	0.00	N	1.00	2.50	2020	0	2020	2
Namibia	14.00	11.23	0.125	5.0	1.00	73	0.50	N	1.00	2.63	2020	0	2020	2
Sudan	5.30	9.30	0.50	4.0	0.75	79	0.50	N	1.00	2.75	2021	+1	2022	*

* Beyond the scope of this investment.
** For India, vaccine introduction is assumed to be state-by-state (see Table 4 below).

Table 4. Scoring results and predicted year and phase of adoption of cholera vaccine for the states of India

Country	Population (x 10⁶)	Cholera disease burden					Immunization program capacity		Total score	Year of adoption	Investment
		Data from literature review of cholera outbreaks [a]			Average annual incidence from outbreak data (cases per 100,000)	Score	Measles-containing vaccine coverage rate (%) [b]	Score			
		No. of outbreaks	Cases	Deaths							
Orissa	39	13	102,778	86	26	0	79	0.5	0.5	2015	1
West Bengal	85	16	60,458	353	7.3	0.25	88	0.25	0.5	2015	1
Delhi	16	4	4,859	-	3.7	0.25	92	0	0.25	2018	2
Chhattisgarh	1.1	3	7,715	46	70	0	74	0.5	0.5	2019	2
Tripura	3.4	1	6,261	43	18	0	71	0.5	0.5	2019	2
Andaman & Nicobar Island	0.4	2	20,478	6	510	0	70	0.5	0.5	2019	2
Kerala	33	6	1,463	-	0.45	0.5	97	0	0.5	2019	2
Andra Pradesh	81	2	3,618	-	0.45	0.5	82	0.25	0.75	2020	2
Maharashtra	105	6	1,077	-	0.13	0.75	99	0	0.75	2020	2
Tamil Nadu	65	2	213	2	0.16	0.75	99	0	0.75	2020	2
Chandigarh	1.1	3	430	-	3.9	0.25	70	0.5	0.75	2020	2
Punjab	26	1	19	-	0.14	0.75	92	0	0.75	2020	2
Assam	1.2	2	11,069	266	92	0	45	1	1	2021	*
Haryana	23	2	207	-	0.12	0.75	89	0.25	1	2021	*
Himachal Pradesh	6.5	1	4	-	0.006	1	99	0	1	2021	*
Gujarat	55	1	809	-	0.15	0.75	78	0.5	1.25	2021	*
Karnataka	56	3	360	-	0.065	1	85	0.25	1.25	2021	*
Madhya Pradesh	66	3	220	20	0.033	1	73	0.5	1.5	2021	*

[a] Data from Kanungo et.al. (2009
[b] Data from Wolfson et.al. (2007)
* Beyond the scope of this investment

2) For populations, the percent of the population living in urban slums.

Using these definitions, there are an estimated 789 million people at risk of cholera in the 51 countries identified as cholera-endemic in the disease burden analysis (see Appendix 1). Of these, 632 million people live in the 33 countries forecasted to introduce cholera vaccination by 2020 and are therefore included in this investment case. See Table 8 at the end of this appendix for data on population access to clean water by country that were used for this analysis.

Most countries are assumed to target cholera vaccination to specific high-risk areas and populations, as opposed to providing the vaccine universally, to limit the costs of this intervention. These countries may use different approaches to identifying the at-risk population to target. Thus, this investment case presents two scenarios for targeting populations for cholera vaccination (Figure 1). In the Large Target scenario, all persons living in urban slums and in rural areas with poor access to improved water sources would be targeted for vaccination. The Small Target scenario would limit vaccination to 50% of urban slum dwellers and 50% of rural residents without access to improved water supply, based on the assumption that some sub-populations would be at significantly greater risk than others. For each target scenario, we present two options for targeting age groups: children 1-14 years old, and all persons one year and above (assuming use of the WC O1/O139 vaccine. The population targeted for vaccination in the 33 target countries would therefore range from 233 million to 637 million in the Large Target areas, and 113 to 306 million in the Small Target areas, depending on the age group selected.

Figure 1. Scenarios for targeting cholera vaccination in 33 cholera-endemic countries included in the investment case analyses
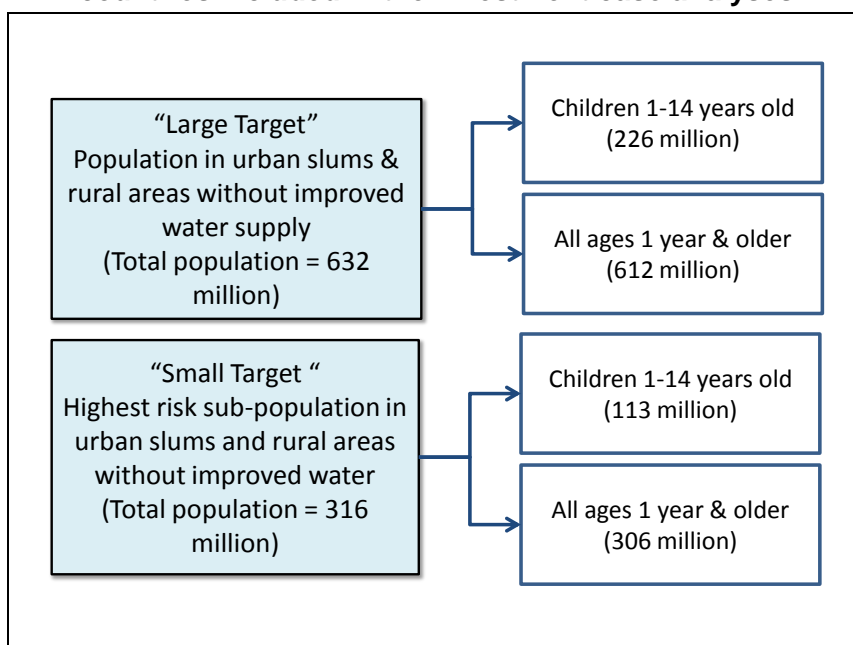
Model for demand forecasting and variables and assumptions used

To forecast the number of doses to be used by year for the 33 countries and 12 Indian states predicted to introduce cholera vaccination in Investment1 or 2 (2014-2020), we used a

software package developed by Applied Strategies of San Mateo, CA and adopted for cholera vaccine. The model is pre-populated with basic data for developing countries for each year from 2009 to 2050. The pre-populated data include birth and population data (from the UN population database), coverage rates for measles-containing vaccine, DPT, school attendance rates, WHO regions, GAVI eligibility and other data.

The demand forecast uses the following variables and assumptions:

- **Cholera vaccination coverage rates:** The model uses country-specific coverage rates for measles-containing vaccine (MCV) (e.g., measles or measles-mumps-rubella) as the basis for predicting coverage rates for cholera vaccination. Measles coverage was viewed as a better proxy for cholera vaccination than DPT coverage (which has been used for several vaccine investment cases). This is because measles vaccine is given at an older age (nine months) than DPT, and the WC O1/O139 cholera vaccine assumed for these analyses cannot be used under the age of one year. The assumed coverage rates for cholera vaccination used in the analyses are 80% of the MCV coverage rates for children 1-14 years old, and 50% of the MCV coverage rates for persons 15 and older. We assume a lower coverage rate for adults, since experience with TT and other vaccines have shown that they are more difficult to reach than infants and children and since they may perceive that they have a lower risk of cholera than children.

- **Number of doses and wastage rate:** The model assumes two doses would be given to each individual. The assumed vaccine wastage rate is 5%, based on the use of single-dose containers, such as vials or blow-filled seal containers, and on the assumption that the vaccines will be delivered via campaigns, which normally result in less wastage than routine vaccination sessions.

- **Rollout of vaccination and frequency of revaccination:** Vaccination is each country is assumed to be phased in over a three-year period, with one-third of the target population reached each year. Revaccination is assumed to take place every three years, based on current data from the Kolkata efficacy trial of the WC O1/139 (Shanchol™) vaccine. This assumption may need to be revised in the future, if the vaccine is shown in the on-going trial in Kolkata to provide protection for more than three years.

Results

By investment

The forecasted demand by investment for the four targets and age group options is shown in Figure 2. Assuming both investments are funded, the Large Target approach would require 281 to 330 million doses per year once it ramps up, or a total over 16 years of 3.8 billion doses, if all eligible ages are included. In contrast, limiting the target ages to children 1-14 years old would reduce the annual need to between 124 and 133 million doses once Investment 2 countries ramp up, for a total over the 16-year period from 2014 to 2030 of 1.6 billion doses. The Small Target scenarios cut these figures in half, since they target only half of the assumed at-risk population. Vaccinating all eligible ages in the Small Target areas would therefore consume 135 to159 million doses per year, once Investment 2 countries enter the picture, or a total of 1.8 billion doses from 2015 to 2030. Vaccinating only children 1-14 years old would require an annual maximum of 65 million doses or a total of 780 million doses over the 16-year period.

<u>By age</u>

Figure 3 shows the estimated demand (based on MCV coverage rates) by two age groups (1-14 and 15 and older) for the Large and Small Target scenarios. For both scenarios, around 42% of vaccine doses would be given to children and 58% to persons 15 and older.

Figure 3. Forecasted demand for cholera vaccine under the Large and Small Target
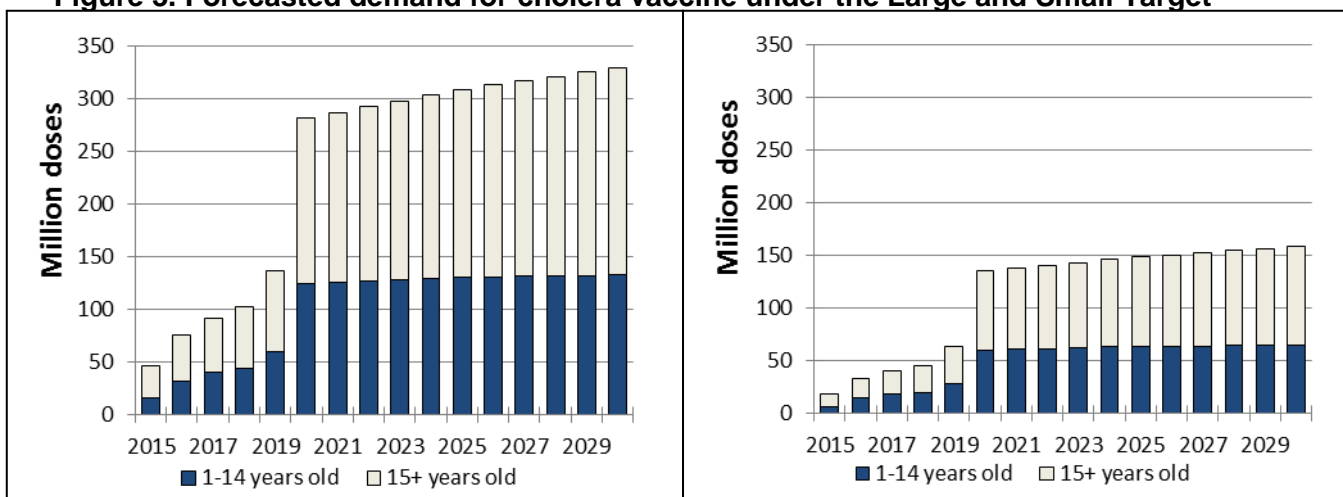
<u>By WHO region</u>

As shown in Figure 4, 65% of the total number of doses would be used in the African region, regardless of program option. Thirty-two percent would be used in the Southeast Asian region (with India and Bangladesh the largest users by far), and 3% in the Eastern Mediterranean region (Pakistan and Iraq).

<u>By GAVI eligibility</u>

The vast majority of vaccine doses (92%) would be used in the 26 of the 33 countries included in the investment case that are GAVI-eligible, as shown in Table 5.

Figure 2. Forecasted demand for cholera vaccine by program option and investment, 2015-2030 (million doses)

a. Large Target (urban slums and rural populations without safe water), all ages 1 year and older

b. Large Target, 1-14 years old

c. Small Target (50% of at-risk populations), all ages 1 year and older

d. Small Target,1-14 years old
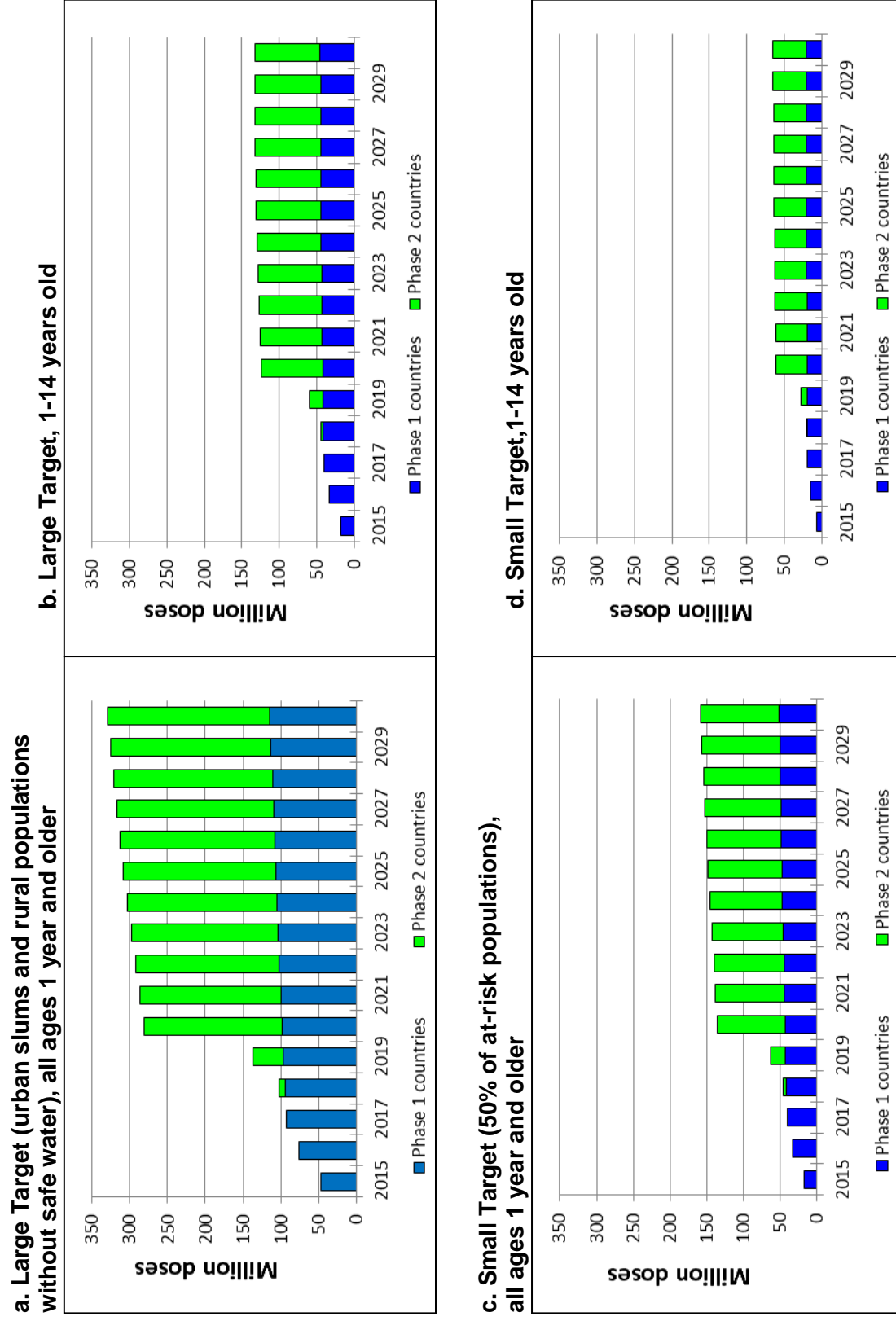
Figure 4. Forecasted demand for cholera vaccine by WHO region

a. Large Target, all ages 1 year and older

b. Large Target, 1-14 years old

c. Small Target, all ages 1 year and older

d. Small Target, 1-14 years old
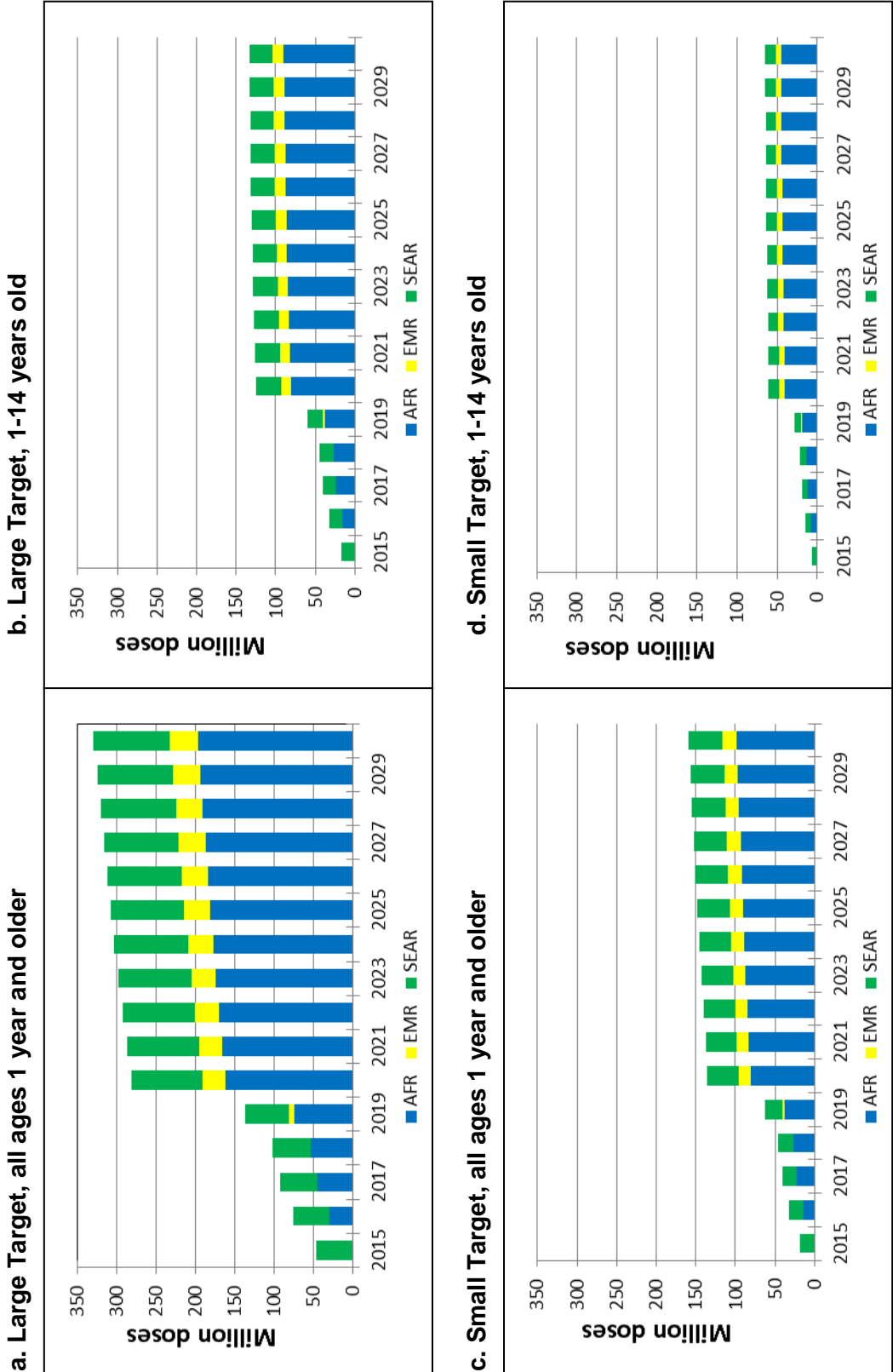
Table 5. Forecasted demand (number of doses) for cholera vaccine by investment and GAVI eligibility of countries, 2015-2030

Investment/GAVI eligibility of countries	Large Target		Small Target	
	1-14 years old	1+ year & older	1-14 years old	1+ year & older
Investment 1:				
GAVI-eligible	651,089,794	1,571,019,873	296,840,256	695,972,881
Non-GAVI-eligible	1,506,292	3,389,968	753,146	1,694,984
Total Investment 1	**652,596,086**	**1,574,409,841**	**297,593,402**	**697,667,865**
Investment 2:				
GAVI-eligible	845,121,202	1,977,822,428	422,425,195	988,387,411
Non-GAVI-eligible	121,217,991	278,478,977	60,608,996	139,239,488
Total Investment 2	**966,339,193**	**2,256,301,405**	**483,034,191**	**1,127,626,899**
Investments 1 and 2:				
GAVI-eligible	1,496,210,996	3,548,842,301	719,265,452	1,684,360,292
Non-GAVI-eligible	122,724,283	281,868,945	61,362,142	140,934,473
Total Investments 1 + 2	**1,618,935,279**	**3,830,711,246**	**780,627,593**	**1,825,294,765**

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Additional tables

**Table 6. Cholera-endemic countries by year of predicted
cholera vaccine adoption, investment and GAVI eligibility**

WHO region	Country/Indian state	Projected year of adoption	Phase of introduction (investment)	GAVI-eligible?
AFR	Angola	2019	2	N
AFR	Benin	2020	2	Y
AFR	Burundi	2018	2	Y
AFR	Cameroon	2019	2	Y
AFR	Comoros	2020	2	Y
AFR	Congo	2018	2	N
AFR	Congo, DR	2020	2	Y
AFR	Ethiopia	2020	2	Y
AFR	Gambia	2017	1	Y
AFR	Ghana	2019	2	Y
AFR	Guinea-Bissau	2019	2	Y
AFR	Kenya	2017	1	Y
AFR	Malawi	2017	1	Y
AFR	Mali	2020	2	Y
AFR	Mozambique	2016	1	Y
AFR	Namibia	2020	2	N
AFR	Nigeria	2020	2	Y
AFR	Rwanda	2017	1	Y
AFR	São Tomé and Príncipe	2018	2	Y
AFR	Senegal	2019	2	Y
AFR	South Africa	2018	2	N
AFR	Swaziland	2017	1	N
AFR	Tanzania	2016	1	Y
AFR	Uganda	2016	1	Y
AFR	Zambia	2016	1	Y
AFR	Zimbabwe	2019	2	Y
EMR	Iraq	2019	2	N
EMR	Pakistan	2020	2	Y
SEAR	Bangladesh	2015	1	Y
SEAR	Bhutan	2020	2	N
SEAR	Korea, DPR	2020	2	Y
SEAR	Nepal	2020	2	Y

WHO region	Country/Indian state	Projected year of adoption	Phase of introduction (investment)	GAVI-eligible?
Indian states (n=12)				
SEAR	West Bengal	2015	1	Y
SEAR	Orissa	2015	1	Y
SEAR	Delhi	2018	2	Y
SEAR	Tripura	2019	2	Y
SEAR	Kerala	2019	2	Y
SEAR	Chhattisgarh	2019	2	Y
SEAR	Andaman and Nicobar Islands	2019	2	Y
SEAR	Tamil Nadu	2020	2	Y
SEAR	Punjab	2020	2	Y
SEAR	Maharashtra	2020	2	Y
SEAR	Chandigarh	2020	2	Y
SEAR	Andhra Pradesh	2020	2	Y

Table 7. Vaccine adoption history scores by country (from Applied Strategies)

Country	Hepatitis B Year of Adoption	Score	Country	Hib Year of Adoption	Score	Country	Pneumo Conjugate Vaccine Expected Year of Adoption*	Score	Country	Total Adoption Score (Average of All Available Scores)
Papua New Guinea	1989	1	Gambia	1997	1	Guyana	2008	1	Cuba	1.0
Cuba	1990	1	Cuba	1999	1	Nicaragua	2008	1	Gambia	1.3
Solomon Islands	1991	1	Nicaragua	1999	1	Gambia	2009	1	Nicaragua	1.7
Mongolia	1991	1	Honduras	1999	1	Honduras	2009	1	Honduras	1.7
Zimbabwe	1994	2	Bolivia	2000	2	Rwanda	2009	1	Guyana	2.3
Moldova	1995	2	Guyana	2001	2	Cameroon	2010	1	Rwanda	2.3
Gambia	1995	2	Kenya	2001	2	Central African Republic	2010	1	Kenya	2.3
Kiribati	1995	2	Ghana	2002	2	Congo	2010	1	Yemen	2.3
Bhutan	1997	3	Malawi	2002	2	Kenya	2010	1	Bolivia	2.5
Nicaragua	1999	3	Rwanda	2002	2	Mali	2010	1	Mongolia	2.5
Yemen	1999	3	Uganda	2002	2	Yemen	2010	1	Papua New Guinea	2.5
Armenia	1999	3	Burundi	2004	3	Congo, Dem. Rep.	2010	1	Solomon Islands	2.5
Bolivia	2000	3	Zambia	2004	3	Afghanistan	NA		Ghana	3.0
Honduras	2000	3	Benin	2005	3	Angola	NA		Malawi	3.0
Uzbekistan	2001	4	Senegal	2005	3	Armenia	NA		Uganda	3.0
Kyrgyzstan	2001	4	Yemen	2005	3	Azerbaijan	NA		Mali	3.0
Georgia	2001	4	Angola	2006	4	Bangladesh	NA		Kiribati	3.0
Guyana	2001	4	Burkina Faso	2006	4	Benin	NA		Moldova	3.0
Azerbaijan	2001	4	Ukraine	2006	4	Bhutan	NA		Zimbabwe	3.0
Kenya	2001	4	Mali	2007	4	Bolivia	NA		Central African Republic	3.3

Country	Hepatitis B Year of Adoption	Score	Country	Hib Year of Adoption	Score	Country	Pneumo Conjugate Vaccine Expected Year of Adoption*	Score	Country	Total Adoption Score (Average of All Available Scores)
Mozambique	2001	4	Djibouti	2007	4	Burkina Faso	NA		Benin	3.5
Ghana	2002	4	Ethiopia	2007	4	Burundi	NA		Burundi	3.5
Madagascar	2002	4	Sierra Leone	2007	4	Cambodia	NA		Senegal	3.5
Mali	2002	4	Mongolia	2008	4	Chad	NA		Cameroon	3.7
Pakistan	2002	4	Eritrea	2008	4	Comoros	NA		Congo	3.7
Benin	2002	4	Sri Lanka	2008	4	Côte d'Ivoire	NA		Armenia	4.0
Eritrea	2002	4	Central African Republic	2008	4	Cuba	NA		Bhutan	4.0
India	2002	4	Chad	2008	4	Korea, DPR	NA		Eritrea	4.0
Malawi	2002	4	Guinea	2008	4	Djibouti	NA		Madagascar	4.0
Rwanda	2002	4	Guinea-Bissau	2008	4	Eritrea	NA		Pakistan	4.0
Tajikistan	2002	4	Kiribati	2008	4	Ethiopia	NA		Tajikistan	4.0
Uganda	2002	4	Lesotho	2008	4	Georgia	NA		Ukraine	4.0
Tanzania	2002	4	Liberia	2008	4	Ghana	NA		Zambia	4.0
Indonesia	2003	4	Madagascar	2008	4	Guinea	NA		Lesotho	4.0
Ukraine	2003	4	Moldova	2008	4	Guinea-Bissau	NA		Sudan	4.0
Côte d'Ivoire	2003	4	Niger	2008	4	Haiti	NA		Angola	4.5
Sao Tome and Principe	2003	4	Pakistan	2008	4	India	NA		Azerbaijan	4.5
Viet Nam	2003	4	Papua New Guinea	2008	4	Indonesia	NA		Burkina Faso	4.5
Lesotho	2003	4	Solomon Islands	2008	4	Kiribati	NA		India	4.5
Comoros	2003	4	Sudan	2008	4	Kyrgyzstan	NA		Kyrgyzstan	4.5
Lao People's Democratic Republic	2004	4	Tajikistan	2008	4	Lao People's Democratic Republic	NA		Mozambique	4.5

Country	Hepatitis B Year of Adoption	Score	Country	Hib Year of Adoption	Score	Country	Pneumo Conjugate Vaccine Expected Year of Adoption*	Score	Country	Total Adoption Score (Average of All Available Scores)
Nigeria	2004	4	Togo	2008	4	Lesotho	NA		Tanzania	4.5
Burundi	2004	4	Zimbabwe	2008	4	Liberia	NA		Uzbekistan	4.5
Senegal	2004	4	Cameroon	2009	5	Madagascar	NA		Comoros	4.5
Sudan	2004	4	Comoros	2009	5	Malawi	NA		Côte d'Ivoire	4.5
Korea, DPR	2004	4	Congo	2009	5	Mauritania	NA		Djibouti	4.5
Nepal	2005	5	Côte d'Ivoire	2009	5	Mongolia	NA		Ethiopia	4.5
Bangladesh	2005	5	Afghanistan	2009	5	Mozambique	NA		Georgia	4.5
Myanmar	2005	5	Azerbaijan	2009	5	Myanmar	NA		Guinea	4.5
Cameroon	2005	5	Bangladesh	2009	5	Nepal	NA		Indonesia	4.5
Sri Lanka	2005	5	Bhutan	2009	5	Niger	NA		Lao People's Democratic Republic	4.5
Zambia	2005	5	Congo, Dem. Rep.	2009	5	Nigeria	NA		Nigeria	4.5
Mauritania	2005	5	India	2009	5	Pakistan	NA		Sao Tome and Principe	4.5
Cambodia	2006	5	Kyrgyzstan	2009	5	Papua New Guinea	NA		Sierra Leone	4.5
Afghanistan	2006	5	Lao People's Democratic Republic	2009	5	Moldova	NA		Sri Lanka	4.5
Angola	2006	5	Mauritania	2009	5	Sao Tome and Principe	NA		Viet Nam	4.5
Burkina Faso	2006	5	Mozambique	2009	5	Senegal	NA		Chad	4.5
Guinea	2006	5	Nepal	2009	5	Sierra Leone	NA		Korea, DPR	4.5
Congo	2007	5	Sao Tome and Principe	2009	5	Solomon Islands	NA		Guinea-Bissau	4.5
Congo, Dem. Rep.	2007	5	Tanzania	2009	5	Somalia	NA		Liberia	4.5
Timor-Leste	2007	5	Uzbekistan	2009	5	Sri Lanka	NA		Niger	4.5
Sierra Leone	2007	5	Viet Nam	2009	5	Sudan	NA		Togo	4.5

Country	Hepatitis B Year of Adoption	Score	Country	Hib Year of Adoption	Score	Country	Pneumo Conjugate Vaccine Expected Year of Adoption*	Score	Country	Total Adoption Score (Average of All Available Scores)
Djibouti	2007	5	Armenia	2009	5	Tajikistan	NA		Congo, Dem. Rep.	3.7
Ethiopia	2007	5	Nigeria	2009	5	Timor-Leste	NA		Afghanistan	5.0
Central African Republic	2008	5	Cambodia	2010	5	Togo	NA		Bangladesh	5.0
Chad	2008	5	Georgia	2010	5	Uganda	NA		Mauritania	5.0
Guinea-Bissau	2008	5	Haiti	NA	5	Ukraine	NA		Myanmar	5.0
Niger	2008	5	Indonesia	NA	5	Tanzania	NA		Nepal	5.0
Togo	2008	5	Myanmar	NA	5	Uzbekistan	NA		Cambodia	5.0
Liberia	2008	5	Korea, DPR	NA	5	Viet Nam	NA		Haiti	5.0
Somalia	NA	5	Timor-Leste	NA	5	Zambia	NA		Somalia	5.0
Haiti	NA	5	Somalia	NA	5	Zimbabwe	NA		Timor-Leste	5.0

* Based on the country's application to GAVI for support for pneumococcal conjugate vaccine introduction (see explanation in text above).

Table 8. Summary of population averages for cholera risk factors for the 33 countries included in the demand forecast

WHO Region	Country	Total population at risk, 2010	Percent without access to improved sanitation	Urban fraction of population	Percent of urban population that are in slums	Percent of population that is rural	Percent of rural population without access to improved water	Overall percent of population that is either urban slum or rural without access to improved water
GAVI-eligible								
AFR	Benin	6,448,219	70	41	72	59	43	55
AFR	Burundi	5,026,129	59	10	64	90	30	34
AFR	Cameroon	9,779,592	49	57	47	43	53	50
AFR	Comoros	449,378	65	28	69	72	19	33
AFR	Congo, DR	46,800,972	69	34	76	66	71	73
AFR	Ethiopia	75,628,289	89	17	82	83	69	71
AFR	Gambia	840,351	48	56	45	44	19	34
AFR	Ghana	21,899,480	90	50	45	50	29	37
AFR	Guinea	8,362,242	81	34	46	66	41	43
AFR	Guinea-Bissau	1,103,745	67	30	83	70	53	62
AFR	Kenya	23,700,482	58	22	55	78	51	52
AFR	Liberia	2,789,202	68	60	56	40	48	53
AFR	Malawi	6,276,714	40	19	66	81	28	35
AFR	Mali	7,327,707	55	32	66	68	52	56
AFR	Mauritania	2,557,913	76	41	94	59	46	66
AFR	Mozambique	16,149,912	69	37	80	63	74	76
AFR	Nigeria	110,781,242	70	48	66	52	70	68
AFR	Rwanda	5,344,150	52	18	72	82	39	45
AFR	Sao Tome and Principe	125,702	76	61	71	39	17	50
AFR	Senegal	9,259,716	72	42	38	58	35	36
AFR	Tanzania	30,176,514	67	26	66	74	54	57
AFR	Uganda	22,643,629	67	13	67	87	40	43
AFR	Zambia	6,363,489	48	35	57	65	59	58
AFR	Zimbabwe	6,827,782	54	37	18	63	28	24

WHO Region	Country	Total population at risk, 2010	Percent without access to improved sanitation	Urban fraction of population	Percent of urban population that are in slums	Percent of population that is rural	Percent of rural population without access to improved water	Overall percent of population that is either urban slum or rural without access to improved water
EMR	Pakistan	77,596,386	42	36	48	64	13	25
SEAR	Bangladesh**	164,425,491	64	27	71	73	22	35
SEAR	India[†]	756,132,480	72	30	35	70	14	20
SEAR	Korea, DPR	9,836,188	41	63	NA	37	0	NA
SEAR	Nepal	21,792,458	73	17	61	83	12	20
Non GAVI-eligible								
AFR	Angola	9,496,354	50	57	87	43	61	75
AFR	Republic of Congo	3,006,942	80	61	53	20	65	58
AFR	Namibia	1,437,824	65	37	34	60	10	19
AFR	South Africa	20,701,887	41	61	29	40	18	24
AFR	Swaziland	600,952	50	25	20	69	49	42
EMR	Iraq	7,552,008	24	67	53	22	44	50
SEAR	Bhutan	340,072	48	34	44	88	21	29

[†] States and territories of India included = Andhra Pradesh, Assam, Goa, Gujarat, Haryana, Himachal Pradesh, Karnatka, Kerala, Madhya Pradesh, Maharastra, Orissa, Punjab, Tamil Nadu, Uttar Pradesh, West Bengal, Andaman & Nicobar Island, Chandigarh, and Delhi
** Due to persistent flooding, it is assumed that the entire population of Bangladesh is at risk for cholera.

Appendix 5. Proposed use and design of a cholera vaccine stockpile

1.   Overview

Global stockpiles have been built since the late 1990s for vaccines against meningococcal meningitis and yellow fever – two diseases that can cause explosive epidemics. Countries have used these stockpiles to vaccinate in response to outbreaks in their country or in surrounding countries. Both the meningitis and yellow fever vaccine stockpiles have proved to be popular with developing countries. More than 40 million doses of meningitis vaccine were delivered through a stockpile of meningococcal vaccine from 1997 (when it began) to 2008, as were 52 million doses of yellow fever vaccine from the establishment of a stockpile in 2001 to 2008 [Costa 2009]. Both vaccine stockpiles have grown several fold since they began.

According to WHO, the objectives of establishing global vaccine stockpiles are to: 1) ensure rapid access to vaccines for countries experiencing epidemics, 2) promote the optimal use of vaccines, 3) promote the use of vaccines of assured quality and safe injection practices, and 4) coordinate international efforts to respond to epidemics [Costa 2009].

This appendix discusses prior use of oral cholera vaccines in emergency or post-emergency situations, appropriate uses of a cholera vaccine stockpile, the projected size and cost of a stockpile, and how it should be managed and operated, based on experiences with the meningoccocal and yellow fever vaccine stockpiles.

2.   Recommendations concerning the establishment of a cholera vaccine stockpile and past use of oral cholera vaccines to pre-empt or control cholera outbreaks

The World Health Organization recommended the establishment of a two-million dose cholera vaccine stockpile in 1999 for pre-emptive use in high-risk populations before a cholera outbreak has occurred, based on the model of the polysaccharide meningococcal vaccine stockpile established a few years earlier [WHO 1999]. The cholera vaccine stockpile has never been established. According to WHO, this was due to the lack of guidelines for the use of oral cholera vaccines, the lack of a tool to assess the risk of cholera and to predict where it will spread, the relatively high cost of the main cholera vaccine available at the time (the WC-rBS vaccine, Dukoral®), and limitations found with the use of Dukoral® in some crisis or post-emergency situations [Chaignat and Monti 2007].

An added complication was the fact that cholera vaccination was recommended for pre-emptive use only and not for use reactively once a cholera outbreak had already begun. The yellow fever and meningococcal vaccine stockpiles, on the other hand, were designed mainly for use in response to outbreaks. Reactive vaccination with oral cholera vaccines was considered limited for several reasons, including:

- The perceived short duration of cholera outbreaks (e.g., 3-4 weeks) in a specific location, making it difficult to organize and implement vaccination campaigns in time before the outbreak has naturally moved on;

- The two-dose regimen of the WC-rBS vaccine with at least a one week interval between doses, further limiting the speed in which full vaccination can be completed;

- In the case of Dukoral®, the need to administer the vaccine mixed with a buffer solution and potable water, requiring a large volume of potable water at the vaccination sites; and

- The need to focus on other urgent health needs during outbreaks, including setting up make-shift cholera treatment facilities and isolation wards, as well as providing clean water and sanitation, making the organizing of mass vaccination campaigns challenging.

While no cholera vaccine stockpile has yet been established, mass cholera vaccination campaigns have been implemented in a number of instances, including both in post-crisis situations to prevent outbreaks from occurring, and during ongoing cholera outbreaks (Table 1). Several of these campaigns were demonstration projects in response to recommendations made during WHO meetings since the late 1990s and in the 2001 WHO Position Paper on cholera vaccines. The Position Paper recommended the use of oral cholera vaccines in "certain endemic and epidemic situations" to complement the provision of safe, water, sanitation, case management and other cholera control strategies [WHO 2001; WHO 2002; WHO 2006]. These demonstration projects included the pre-emptive use of Dukoral® in three post-crisis situations – in a refugee camp of South Sudanese in Uganda, in two refugee camps in Darfur in 2004, and in Aceh, Indonesia following the tsunami in 2005.

Table 1. Past use of oral cholera vaccines in emergency or post-crisis situations

Location (year)	Situation/ population	Pre-emptive/ reactive	Vaccine	Number of doses	Source
Vietnam (1997-Present)	High-risk populations	Both (e.g., following floods, in areas in and surrounding cholera outbreaks, pre-emptively among high-risk populations)	ORC-VAX (locally-produced killed WC vaccine)	>20 million	[Khiem et al., 2003; DeRoeck and Jodar, 2004]
Northern Uganda (1997)	Sudanese refugees in six stable refugee settlements	Pre-emptive	Dukoral® (2-dose WC-rBS)	63,220	[Naficy et al., 1998]
Mayotte Island (French island at Southeastern part of Comoros) (2000)	Local population	Pre-emptive (during cholera outbreak on other islands of Comoros)	Dukoral®	93,000	[Olsson and Parment, 2006], WHO 2002
Pohnpei, Micronesia (2000/01)	Population in Pohnpei and surrounding islands	Reactive (in response to outbreak in Pohnpei)	Orochol® (live single-dose CDV 103-HgR)	48,000	[Calain et al., 2004]
Darfur, Sudan 2004	Internally-displaced persons in two camps	Pre-emptive	Dukoral®	103,000	[Chaignat and Monti, 2007]
Aceh, Indonesia 2005	Internally-displaced persons following the tsunami	Pre-emptive	Dukoral®	137,000	[WHO Global Task Force on Cholera Control, 2006]

In all three experiments, cholera vaccination was found to be feasible, although logistical issues resulting from the crises (e.g., the destruction of roads in Aceh) and due to the vaccine

(bulky packaging, the need to administer with a buffer and clean water) created challenges and increased the cost of the campaigns. While no outbreaks occurred in these populations following the vaccination campaigns, no systematic studies of their effectiveness were conducted. However, a cholera outbreak occurred in the area of the refugee camps in Northern Uganda the year following the vaccination campaigns. While 28 cases occurred in the 29 camps where no vaccination had taken place (attack rate of 0.04%), no cases took place in the six vaccinated camps, and 330 cases took place in the non-refugee population where water and sanitation conditions were considerably worse (attack rate of 0.59%) [WHO 1999; Dorlencourt 1999]. While this suggests that the vaccination campaigns were effective, caution must be taken, given the non-randomized, non-blinded nature of the study. No cholera outbreaks took place in Aceh, however, the area was not known to be endemic for cholera before the tsunami and was therefore probably not a good choice for pre-emptive vaccination.

Cholera vaccination, using the single-dose live Orochol® vaccine, was conducted reactively in Pohnpei, Micronesia and surrounding islands in 2000/01 in response to an outbreak on the island [Calain 2004]. The vaccination was shown in a retrospective case-control study to be 79% effective, although the study was not randomized or controlled. Production of Orochol® vaccine was suspended by the manufacturer in the mid-2000s for business reasons.

The most extensive use of oral cholera vaccines both to pre-emptive outbreaks and reactively against currently occurring ones has been in Vietnam, where more than 20 million doses of the locally-produced two-dose killed whole-cell vaccine have been administered since 1997. Vaccination has taken place pre-emptively during and following floods, and on a regular basis among high-risk populations. The vaccine has also been used on several occasions during outbreaks, including high-incidence communities of Hanoi during a cholera outbreak in 2008, in which at least 100,000 doses were administered [Anh et al., 2011]. The Vietnamese program is able to mobilize quickly because of: 1) local production and ready access to the vaccine, 2) a strong cholera outbreak surveillance system, and 3) a developed infrastructure of volunteers who can assist in implementing vaccination campaigns.

In 2010, WHO, in a new Position Paper on cholera vaccines, again recommended the pre-emptive use of cholera vaccines "to prevent potential outbreaks or the spread of current outbreaks to new areas" [WHO 2010, p. 128]. However, it also recommended that local health authorities consider reactive vaccination if circumstances are conducive for it (i.e., adequate local infrastructure) and "following a thorough investigation of the current and historical epidemiological situation, and clear identification of geographical areas to be targeted" [WHO 2010, p. 128]. One reason for the new consideration of reactive vaccination – despite the two-dose regimen of killed whole-cell based – is the recent occurrence of long-lasting cholera epidemics (e.g., 11 months in Zimbabwe in 2008/09 and 15 months in Angola in 2006/07), and evidence that outbreaks can last several months even in a single area (see Table 2 and Figures 4-6 at the end of this appendix). For example, new cases of cholera were still occurring in Harare – the epicenter of the outbreak – nine months after it began [WHO/Zimbabwe 2009]. As of March 2011, Haiti's epidemic has lasted more than five months. This changes the equation on whether vaccination can be conducted in time to halt an outbreak.

In addition, immunological studies suggest that the modified WC O1-O139 vaccine (Shanchol™) induces an immune response after a single dose [Kanungo 2009] and a single-dose regimen of the vaccine will soon be tested in a Phase 3 efficacy trial. If proven effective after one dose, there will very likely be increased interest among policymakers in using the WC O1-O139 vaccine for reactive vaccination during outbreaks.

Table 2. Duration of recent cholera outbreaks in specific areas

Location	Year(s)	Duration	Source
Lusaka, Zambia	2003/04	27 weeks	Sasaki et. al. 2008
Pohnpei, FSM	2000/01	9 months	Calain et. al. 2004
Kahuna refugee camp, Kenya	2005	3 months	Shultz et.al. 2009
Harare, Zimbabwe	2008/09	> 9 months	WHO/Zimbabwe 2009
Uganda (various areas)	2003-2010	Range of 4-27 weeks	Uganda MOH

3.   Suggested strategies for use of a cholera vaccine stockpile

In accordance with the WHO 2010 recommendations, a cholera vaccine stockpile could be used by countries pre-emptively to prevent outbreaks in high-risk situations, such as following or during floods in cholera-endemic areas. It could also be used to prevent an outbreak in one country from spreading across the border or to other regions within the same country that are known to have cholera or have conditions conducive to the spread of the disease.

The stockpile could also be utilized for reactive vaccination (i.e., in the same areas where an outbreak is taking place), under certain conditions. Deciding whether to conduct reactive vaccination is trickier, since a review of recent outbreaks show that their duration in a certain geographic area can vary considerably – from as little as three to four weeks to as long as 10 months or more. In Uganda, for example, of a non-random sample of 14 cholera outbreaks that occurred between 2003-2010, the duration of these outbreaks ranged from four to 27 weeks, with three (21%) lasting less than two months and the other 11 (79%) lasting between two and six months (Uganda MOH 2010, personal communication) (see Figure 6 at the end of this appendix). While vaccination could have likely averted many cases in Lusaka, Zambia and Harare, Zimbabwe, it would have had little effect in other areas where the disease has passed through quickly. According to Dr. Godfrey Bwire of the Uganda Ministry of Health, it should be sufficient to vaccinate the population of sub-counties within districts to arrest the spread of disease once cholera has been identified.

Both pre-emptive and reactive vaccination strategies would be aided by the use of a decision-making tool for the use of oral cholera vaccines in emergency situations, currently under development at WHO [WHO 2006, Chaignat and Monti 2007]. This three-part tool will assess: a) the risk of a cholera outbreak in an area (similar to a risk assessment tool developed by WHO for yellow fever), b) the capacity in the country to contain a potential outbreak, and c) the feasibility of implementing mass vaccination campaigns.

As recommended by WHO, all eligible ages should be vaccinated in mass campaigns to prevent or control cholera outbreaks.

We would also recommend a strategy similar to that used for the yellow fever vaccine stockpile in the mid-2000s. Priority for use of the yellow fever vaccine stockpile was to control outbreaks and any vaccine remaining at the end of the year was used for preventive campaigns the following year, upon request of countries. The entire stockpile was replenished with new vaccine at the beginning of the new year. Given the variability of outbreaks from year to year,

this approach guaranteed the producers a certain minimum demand each year, allowed them to plan production for the stockpile, and prevented them from having to throw out unused, soon-to-expire doses. In the case of cholera vaccine, priority for the stockpile could be given for pre-emptive vaccination in endemic areas following floods, cyclones or other natural disasters or for reactive vaccination during outbreaks. Vaccine left over at the end of the year could be used in vaccination campaigns in high-risk areas of endemic countries, such as urban slums and rural areas with poor water and sanitation systems.

4.   Estimated need and demand for a cholera vaccination stockpile

The demand for vaccine provided through a global stockpile will depend on a number of variables, including:

- whether the vaccine is to be used pre-emptively or reactively;

- the expected number of people at risk of epidemic cholera each year;

- the capacity of a country to implement mass vaccination campaigns, especially during floods and other emergencies that pose logistical challenges;

- the interest and political will among the country's health policymakers for cholera vaccination as part of an integrated approach towards the control of cholera outbreaks; and

- Whether the country has already introduced cholera vaccination for the control of endemic disease among high-risk populations.

We can roughly estimate the population at risk each year for epidemic cholera from the number of cases reported through the *Weekly Epidemiological Record*, GIDEON, ProMED and other sources used for the disease burden analysis (Appendix 1). This assumes that most cases reported were identified during outbreaks. The number of cases can then be divided by estimated attack rates of cholera during outbreaks to estimate the size of the population at risk. WHO uses the following estimated attack rates for different settings for planning cholera control interventions [WHO 2004]:

- 5-8% (50-80/1,000) in refugee camps, with high-risk populations (because of malnutrition);
- 0.2% (2/1,000) in open settings;
- 2% (20/1,000) in rural communities of 5,000 people or less.

Data from actual cholera outbreaks vary substantially from these guidelines. Attack rates were 12/1,000 during the 2003/04 outbreak in Lusaka, Zambia [Sasaki et.al. 2008], 19/1,000 on average in the refugee camps in Malawi during the 1987-1993 outbreaks [Paquet 1999], and 128/1,000 on average in rural villages during a 2002 outbreak in the Nicobar Islands [Suganan et. al. 2004]. For this exercise, we use attack rates of 3/1,000; 5/1,000 and 10/1,000. As shown in Table 3, the estimated average number of people at risk – based on reported cases world-wide – ranges from 13-43 million per year, depending on the assumed attack rate. Since these estimates depend on cholera reports, and a number of countries, especially in Asia, do not consistently report cholera outbreaks, the estimate for the WHO African region – where most cholera-affected countries appear to report cholera – is likely to be more reliable. Assuming an

attack rate of 10/1,000, there would be around 10 million people in AFR at risk of cholera outbreaks on average each year.

However, at least a portion of cases reported to WHO and other sources are likely to be endemic disease and not the result of outbreaks. Thus, this method could over-estimate the stockpile needs.

Table 3. Estimated numbers of people at risk of epidemic cholera each year based on cholera reports from 2001-2008, by WHO region

WHO region	Annual number of cases			Risk Population (Attack rate = 3/1000)	Risk Population (Attack rate = 5/1000)	Risk Population (Attack rate = 10/1000)
	minimum	maximum	mean			
AFR	32,000	150,000	98,000	33,000,000	20,000,000	9,800,000
SEAR	5,100	81,000	18,000	6,000,000	3,600,000	1,800,000
EMR	1,200	60,000	11,000	3,700,000	2,200,000	1,100,000
WRP	220	18,000	1,200	400,000	200,000	100,000
Total	**39,000**	**310,000**	**130,000**	**43,000,000**	**26,000,000**	**13,000,000**

Another way to estimate the demand for a cholera vaccine stockpile to is to look at the number of vaccines from other vaccine stockpiles distributed for each reported case of the targeted disease. In response to outbreaks of meningococcal meningitis in Africa, the stockpile of polysaccharide meningoccocal vaccine provided 42 to 131 doses for every reported case of bacterial meningitis – with the number of vaccines increasing in years with larger outbreaks (Table 4). Applying these ratios to cholera vaccine, but doubling the number of doses since cholera vaccine requires two doses, and using the mean number of reported cases per year from Table 3 (130,000), this would translate into an expected demand of 11-34 million doses per year (i.e., 130,000 cases x 2 doses x (42-131) doses per reported case). In Africa, assuming a ratio of persons vaccinated to cases of 40:1, the annual need based on a mean of 100,000 reported cases per year would be eight million doses. This is again a rough estimate, since it relies on reported cases of cholera, and since the comparison between meningitis and cholera may be limited. In addition, the number of doses required should decrease as countries adopt preventive cholera vaccination for high-risk populations.

Table 4. The number of reported meningitis cases and meningococcal vaccines distributed from 2005-2007 [from Perea 2007]

	2005	2006	2007
No. of cases	13,132	42,796	53,438
No. of epidemic districts	16	70	131
No. of vaccine requests	4	19	21
No. of vaccines supplied through the vaccine stockpile	550,000	6,000,000	7,000,000
No. of vaccines delivered per reported case	**42**	**140**	**131**

5. Proposed size and projected growth of a cholera vaccine stockpile

As mentioned above, the estimated need based on the size of the at-risk population is only one determinant of the demand for cholera vaccines for outbreak prevention or control. Other key factors in determining the number of doses needed for a vaccine stockpile include

countries' ability to rapidly implement cholera vaccination, the expected coverage rates, and the availability of funding – both from donors and from countries (e.g., for operational costs). Given all the uncertainties concerning the demand for vaccines provided through a global stockpile, the cholera vaccine stockpile could follow the examples of the yellow fever and meningoccocal vaccine stockpiles, which started small and grew with experience and as country demand increased. The yellow fever stockpile began with two million doses in 2001 and has grown more than eight-fold to more than 17 million doses per year, with GAVI support using the IFFIm financing mechanism

We therefore propose starting with a two million dose stockpile, enough to vaccinate nearly one million people each year. Starting small will enable those managing the stockpile to gain experience and improve its operation, determine the true demand for the stockpile, and seek funding for its growth. During this pilot phase, two critical activities should take place: 1) further testing of the decision-making tool for the use of oral cholera vaccines in complex emergencies; and 2) research to study the feasibility and impact of vaccination in halting ongoing outbreaks or in preventing their spread, as recommended by WHO in the 2010 position paper on cholera vaccines. The stockpile could be launched in 2011 or 2012, assuming production capacity is sufficient.

If demand for the stockpile is demonstrated, it could grow to five million doses after a few years – assuming sufficient funding and an adequate vaccine supply – and then to 10 million doses. It is anticipated that introduction of the vaccine into national immunization programs in endemic countries would eventually reduce the demand for vaccine through the stockpile. As with the yellow fever vaccine stockpile, vaccine remaining at the end of the year would be used the following year for preventive campaigns in high-risk areas.

In this investment case, we therefore assume a stockpile of two million doses from 2012 to 2013, five million doses from 2014 to 2015, and 10 million doses starting in 2016 (Figure 1).

Figure 1. Projected number of doses used per year
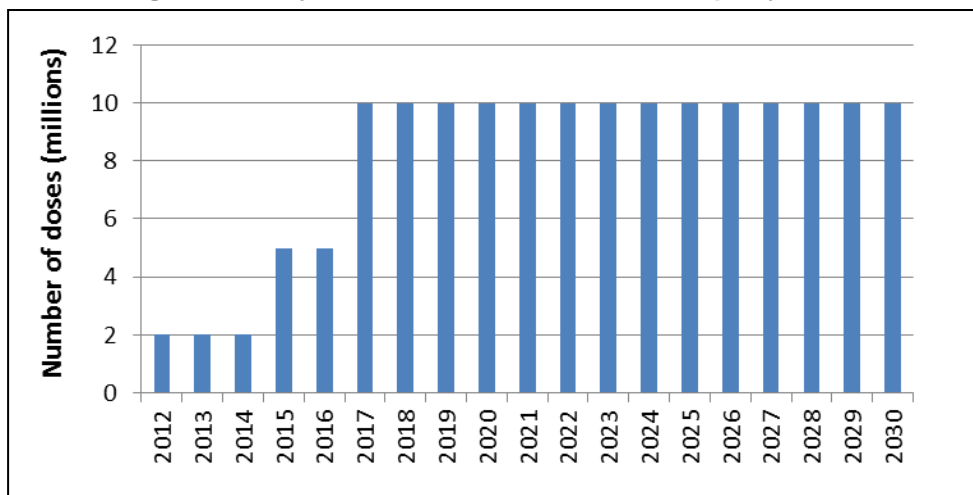
6.   Proposed management and operation of the cholera vaccine stockpile

The design and operation of a cholera vaccine stockpile can draw upon the more than 10 years of experience with the meningoccocal and yellow fever vaccine stockpiles, both of which are managed by WHO. WHO has identified key basic principles in establishing and managing a global vaccine stockpile [Costa 2009]. These include:

- using international partnerships to manage and govern it;
- working with manufacturers to ensure the availability of an emergency stock;
- the timely arrival of the vaccine for outbreak response; and
- the need for a financial mechanism to purchase the vaccines for the stockpile.

WHO has also established criteria for each vaccine stockpile about when to release vaccines from the stockpile to ensure that vaccines are sent at the right time – not too early or too late in the epidemic to have an impact – and to prevent false alarms [Costa 2009]. These criteria include: 1) laboratory-confirmed evidence of an outbreak, using pre-determined definitions of what constitutes an outbreak (an attack rate greater than the epidemic threshold of 10/100,000 cases in the case of meningitis and a single confirmed case in the case of yellow fever); 2) the availability of a country action plan for mass vaccination; and 3) the availability of adequate storage and materials to undertake vaccination campaigns.

Following these principles and based on the experience with other vaccine stockpiles, we propose that the design and operation of a cholera vaccine stockpile include the following elements:

- **Vaccine procurement and storage**: As with the meningoccocal and yellow fever vaccine stockpiles, vaccine procurement should be conducted by UNICEF or another central procurement agency, which would establish contracts with producers on an annual or longer basis. The full amount of the stockpile would be available at the beginning of each year and would be stored at the manufacturer(s) facilities.

- **Coordination of the stockpile and requests for its use:** An International Coordinating Group (ICG), made up of appropriate partners, would be responsible for making decisions about country requests for use of the stockpile. The ICG for both the yellow fever and meningoccocal vaccine stockpiles consists of representatives from four organizations: WHO, UNICEF, Medecins sans Frontieres (MSF), and the International Federation of the Red Cross and Red Crescent (IFRC). The secretariat for the ICG is at WHO headquarters. This mechanism is designed to ensure that decisions on the use of the stockpiles are made within 48 hours by consensus of all ICG partners, who communicate by email, phone and teleconference (Figure 2). Decisions are made based on the criteria described above. If the country request is approved, the producer is contacted and airships the vaccine to the country within seven days from the time the country makes the request.

- **Use of remaining vaccine for non-emergency situations:** As described above, priority for use of the stockpile would be given for emergency situations and any vaccine remaining at the end of the year could be given to countries – upon successful proposals – for use in preventive campaigns or as part of their cholera vaccine introduction. This guarantee of a minimum yearly demand provides an incentive for producers.

- **Country co-financing**: As with the yellow fever stockpile, countries using the cholera vaccine stockpile could be required to cover 50% of the operational costs of vaccination, with donors paying the remaining 50%, as well as the cost of the vaccine itself. Exceptions could be made for certain countries due to hardship. As has been the case with the yellow fever vaccine stockpile, middle-income countries could be required to pay back the cost of the vaccine once the emergency is over.

Figure 1. The process for accessing vaccines from the meningococcal and yellow fever vaccine stockpiles
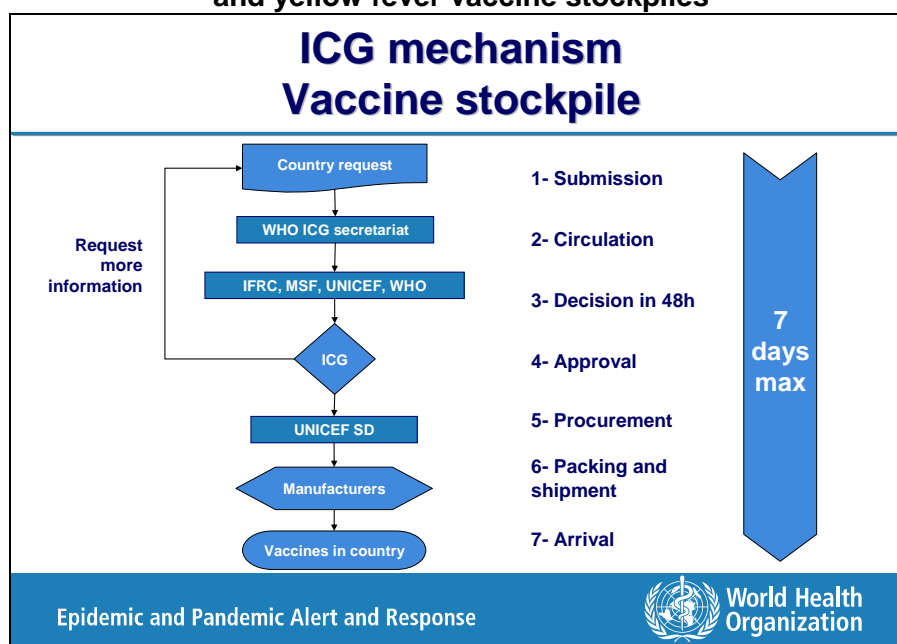
Source: WHO

7. Monitoring and evaluation of the use of the cholera vaccine stockpile

As recommended in the WHO position paper on cholera vaccines in 2010, research into the feasibility and effectiveness of cholera vaccination during emergencies should be conducted in conjunction with the use of the stockpile. This is especially true for any reactive vaccination, since data are lacking on the effectiveness and impact of vaccination using two-dose cholera vaccines in stopping cholera epidemics. Additional funds from other sources will be sought to conduct this research.

8. Cost-effectiveness of hypothetical reactive vaccination during large outbreaks

The incremental cost-effectiveness of reactive cholera vaccination during cholera epidemics was modeled using three published studies for the 2010-11 Haiti [Andrews and Basu 2011; Chao et al. 2011] and 2008-09 Zimbabwe [Reyburn et al. 2011] outbreaks. In each study, the authors reported the assumed number of people vaccinated as well as the number of cases and deaths averted (Table 5). A low wastage rate (5%) was assumed since the vaccine will be distributed via campaigns using single-dose vials. The potential treatment cost savings from the vaccine-induced reduction in cases were estimated from standard unit costs per inpatient day or outpatient visit as reported via WHO CHOICE. The treatment cost savings are conservative because these do not account for the need to import international doctors or establish

temporary treatment clinics. In addition, only the epidemic disease burden was considered, although cholera incidence persists in Zimbabwe and will likely continue in Haiti during the foreseeable future.

Even with very conservative estimates of potential cholera treatment cost savings, modeling results indicate that reactive cholera vaccination would have been very cost effective in both Haiti and Zimbabwe, assuming campaigns were implemented rapidly (*Table 5*). The Haiti results show that targeting high-risk populations would be two to four times more cost-effective than untargeted reactive vaccination. The Zimbabwe results clearly demonstrate that the intervention would have been more cost effective if vaccination activities are conducted rapidly.

Table 5. Modeled impact and cost-effectiveness of theoretical cholera reactive vaccination programs

Parameter/ measure	Chao et al., 2011		Andrews and Basu, 2011	Reyburn et al., 2010	
Country	Haiti		Haiti	Zimbabwe	
Projected time period	6 months		13 months	54 weeks (~14 months)	
Target population	3,000,000 (High-risk population)	10,000,000 (General population)	10,000,000 (General population)	13,349,000 (General population)	
Response time			4 months after cases identified	Rapid campaign (10 wks)	Slow campaign (33 wks)
Assumed coverage	30%	70%	10%	75%	50%
Estimated no. vaccinated people	3,000,000	7,000,000	1,000,000	10,011,750	6,674,500
Vaccination cost	$15,435,000	$36,015,000	$5,145,000	$51,510,454	$34,340,303
Averted cases	134,000	97,000	63,000	59,100	474
Averted deaths	2,690	1,940	900	2,570	21
YLD saved	246	178	116	129	1
YLL saved	58,270	42,024	19,496	87,939	705
DALY saved	58,516	42,202	19,611	88,067	706
COI saved	$3,135,693	$2,269,867	$1,474,244	$1,636,354	$13,124
Net program cost	$12,299,307	$33,745,133	$3,670,756	$49,874,100	$34,327,178
Cost/DALY saved	$210	$800	$187	$566	$48,600
Cost/Case averted	$92	$348	$58	$844	$72,420
Cost/Death averted	$4,572	$17,394	$4,079	$19,403	$1,665,107
GDP per capita, 2010	$673	$673	$673	$594	$594
Cost-effectiveness	Very CE	CE	Very CE	Very CE	Not CE

9. Conclusions

The establishment and use of a cholera vaccine stockpile has the potential to prevent cholera outbreaks and control epidemics once they begin. The availability of a stockpile, especially if donors are willing to cover the cost of the vaccine and subsidize operational costs, should also help to improve cholera surveillance and the speed of cholera control efforts due to the more efficient identification of outbreaks. Without the stockpile, it is less likely that cholera vaccines will be available from manufacturers in a timely manner in emergency or post-crisis situations to prevent or control outbreaks.

It is difficult to predict the appropriate size of a cholera vaccine stockpile at this point in time. It is recommended that a stockpile with two-million doses be piloted to determine the demand for vaccines and the effectiveness of stockpile vaccine usage. If the pilot stockpile proves successful, it could grow to five million and then to 10 million doses. However, its size may decline in the future as countries implement periodic preventive campaigns in high-risk areas and/or improve their sanitation and water systems. The optimal size and vaccination strategies can only be determined through experience.

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Additional figures

Figure 3. Epidemic curve of the 2003-2004 cholera outbreak in Lusaka, Zambia
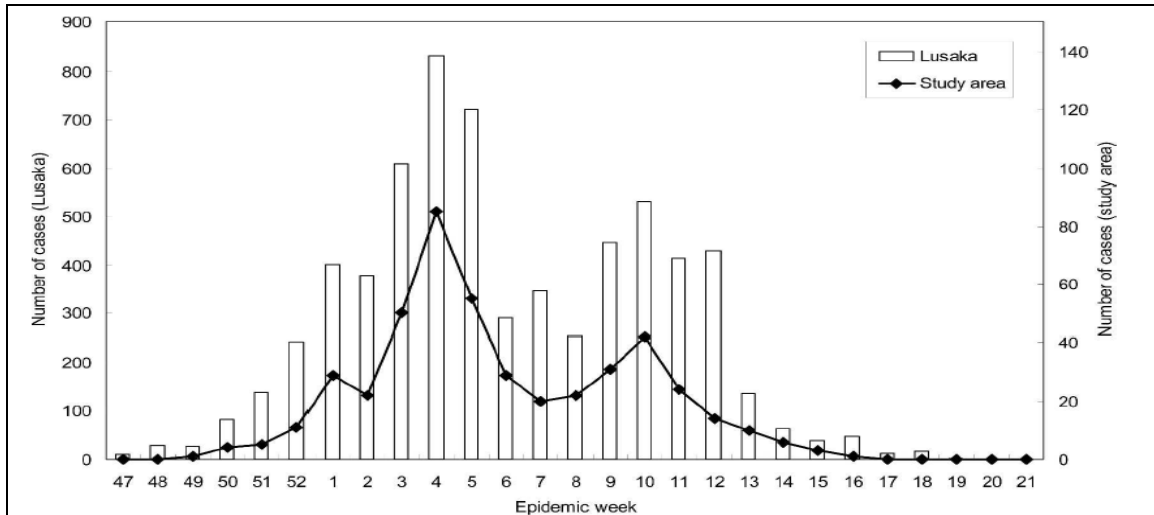
Source: Sasaki et al. 2008

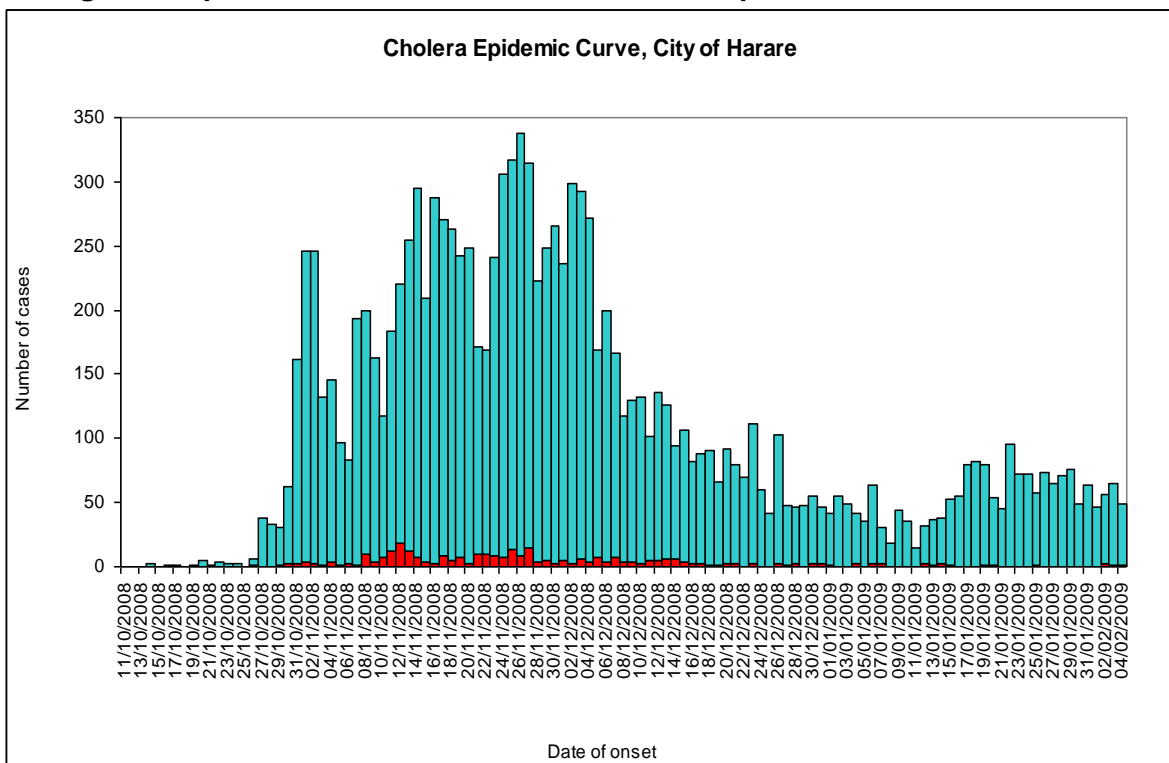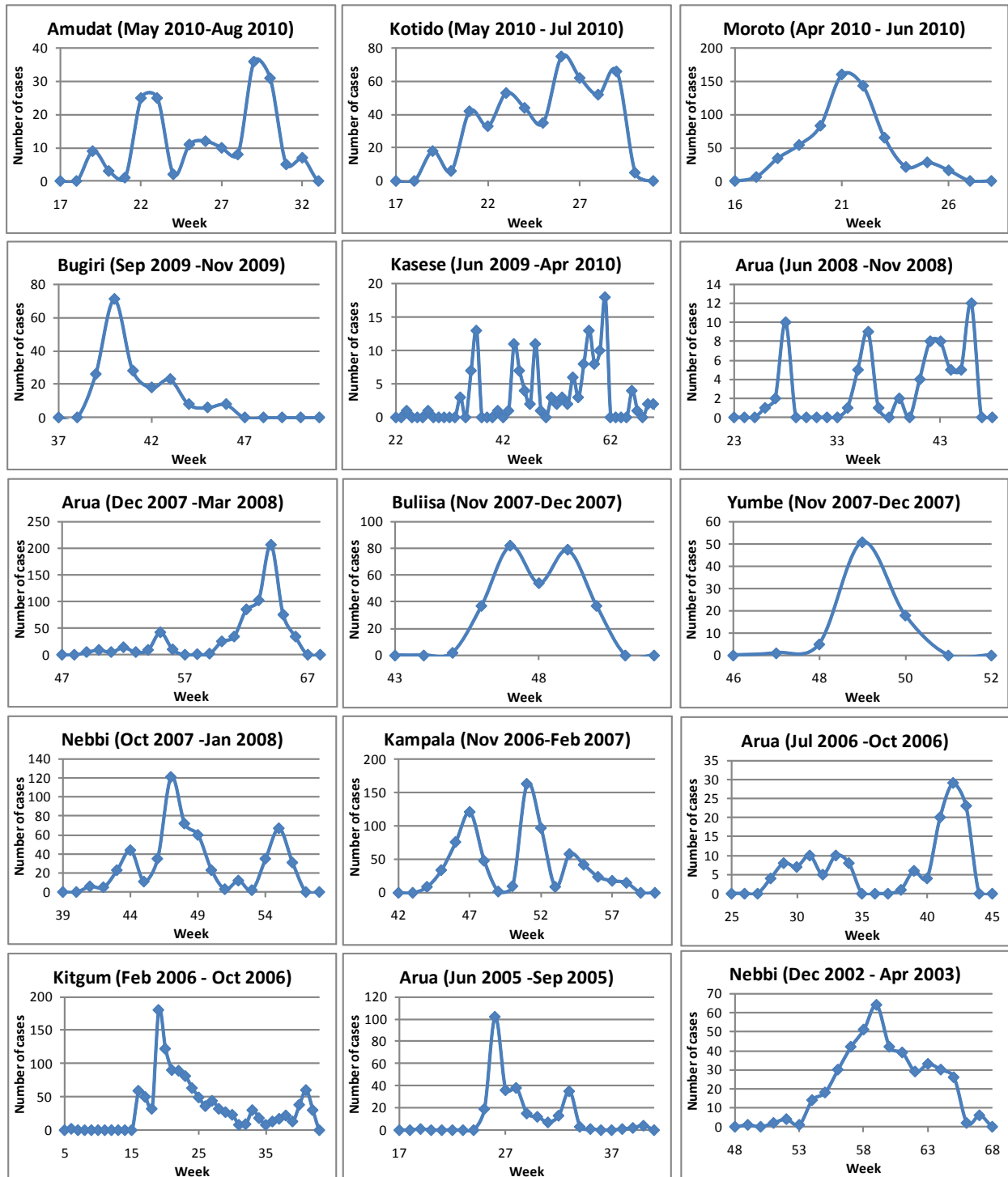**Figure 4. Epidemic curve of the 2008/09 cholera epidemic in Harare, Zimbabwe**

Figure 5. Area-specific epidemic curves of cholera outbreaks in Uganda, 2003-2010

Source: Ugandan Ministry of Health

Appendix 6. Cholera vaccine supply and pricing assumptions

1.   Current cholera vaccine producers and production capacity

Shantha Biotechnics (Shanchol™ O1/O139 killed whole-cell vaccine)

After acquiring the technology for the modified whole-cell only vaccine from the IVI and VaBiotech of Vietnam in the mid-2000s, Shantha achieved licensure of the vaccine in India in February 2009 and began sales to the private sector in India in 2010. The vaccine was pre-qualified in 2011.

According to Shantha, the current production capacity for Shanchol™ is around 2-2.5 million doses per year in its current facility, which is shared with other bacterial vaccines. Shantha has purchased land for a facility dedicated to the production of Shanchol™ and will begin construction if the company is confident of sufficient projected demand to warrant its investment in the new facility. It will take an estimated three years to complete and validate the facility. For this analysis, we assume that a new plant would be operational and validated by 2015. The production capacity is assumed to increase to around 20 million doses per year by 2015 and as much as 30 million doses, once the plant is at full capacity. Additional yield is limited by the time required to produce high concentrations of each of five different strains of *V. cholerae* contained in each dose of the vaccine (see Section 3 below).

VaBiotech (mORC/VAX® O1/O139 killed whole-cell vaccine)

VaBiotech, a public sector vaccine producer, developed the original WC-only vaccine (ORC-VAX) with technology transfer from Sweden, and began producing it in 1997. From 1997 to 2008, the company provided more than 20 million doses of the vaccine to the national immunization program for use in preventing outbreaks (e.g., during floods) and to control endemic cholera in high-risk areas. The producer worked with the IVI to modify the vaccine, and following bridging studies, had this new version licensed in 2009 in Vietnam (as mORC-VAX®). The producer would like to export the vaccine, including selling it to UN agencies. Before VaBiotech can apply to WHO for pre-qualification of the vaccine, however, the country's national regulatory authority – the National Center for Control of Medico-Biological Products (CENCOBI) – needs to receive a positive assessment from WHO. According to WHO informants, this could be achieved by 2013. We assume that pre-qualification of mORC-VAX® will take two years after CENCOBI is approved by WHO, that is, by 2015. According to VaBiotech, the company can produce up to 10 million doses per year of the new, modified vaccine. We project that 10 million doses can be available for export once the vaccine is WHO pre-qualified, assuming production can be expanded somewhat to accommodate both the domestic demand and the 10 million doses for export.

Crucell/SBL Vaccines

The WC-rBS vaccine, Dukoral®, is the only cholera vaccine currently pre-qualified by WHO. The vaccine achieved pre-qualification in 2001 following a recommendation that a global cholera vaccine stockpile be established. Dukoral® is sold in Europe as a traveler's vaccine and in the private sector throughout the world, where it is licensed in more than 60 countries.

According to the company, its current production capacity is limited, but capacity could increase quickly given sufficient demand.

While the vaccine is part of the global supply of oral cholera vaccines, we do not include it in the following projections of supply and demand, since the demand forecast assumes use of the modified WC-only vaccine, which has a different schedule for children under five years of age than Dukoral®. The O1/O139 WC-only vaccines have a two-dose schedule for 1-5 year olds and three years between revaccination. This compares to the three-dose schedule for 2-5 year olds with Dukoral® and revaccination every six months (children <2 are now eligible).

Other producers

The modified O1/O139 WC vaccine is not patent-protected and the technology for its production is relatively simple. The IVI has already transferred the modified O1/O139 technology to Eubioligics, a Korean biotechnology firm. This firm is seeking investment for a 25 million dose manufacturing facility that may begin operation as early as 2015/16. The timeline for availability on the global market will depend on 1) the ability to secure investment, 2) the speed of clinical development, and, finally, 3) the amount of time required for licensure and WHO prequalification.

It is also possible for additional vaccine manufacturers, besides Shantha, VaBiotech, and Eubiologics, to acquire the modified O1/O139 WC vaccine technology from IVI, if they believe that there would be sufficient demand and sufficient return on their investment. The estimated increase in production capacity required to meet the projected demand (discussed below) could be met by new producers entering the market, by current producers expanding their capacity, or by a combination of both.

Total planned capacity of pre-qualified O1/O139 WC vaccines by current producers

Based on current plans for Shantha and VaBiotech, the total supply of pre-qualified O1/O139 WC vaccines from its current producers will be around 2 to 2.5 million doses in 2012 and 2013 (all Shanchol™). It will then jump to around 30 million doses in 2015 and 40 million doses in 2016 (*Figure 1*). This assumes that Shantha will have built and validated the dedicated plant with a capacity of 20 million doses by 2015 and 30 million doses by 2016 and that mORC-VAX will be pre-qualified by 2015 and VaBiotech will have 10 million doses available for export per year.

Figure 1. Projected production capacity for WHO pre-qualified O1/O139 whole-cell only vaccines under current plans
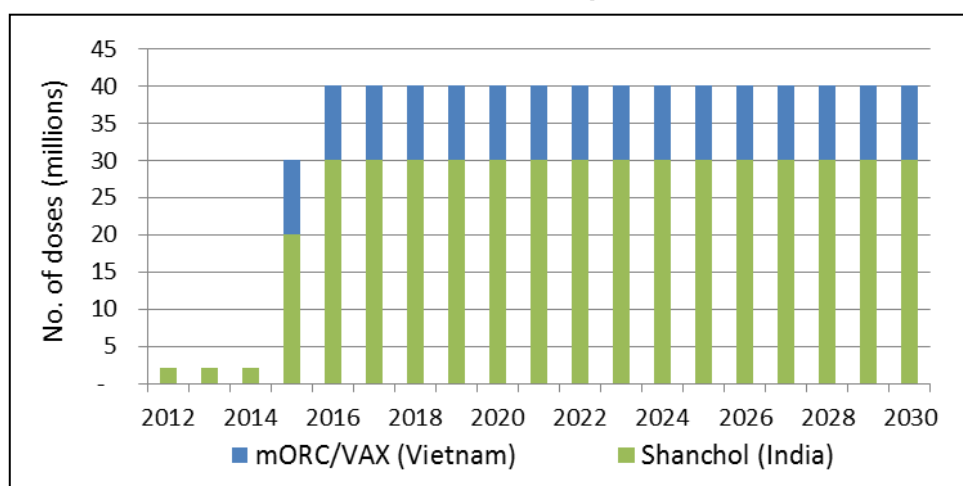
2. Required increase in production capacity of whole-cell only cholera vaccines to meet forecasted demand

The current production capacity of Shanchol™ will be sufficient to build an initial vaccine stockpile of two million doses, starting in 2012, assuming that the vaccine is pre-qualified by WHO in 2011 or in early 2012[13]. The planned maximum capacity of 40 million doses by 2016 of pre-qualified vaccine (from Shantha and VaBiotech) will be sufficient to supply the stockpile, plus meet the projected demand for all but the largest of the four vaccine options (Large Target all ages) until 2015 or 2016 (*Figure 2*). Specifically, the planned completion of Shantha's dedicated manufacturing facility in 2015 should coincide with expansion of the stockpile to five million doses annually and the potential introduction of the vaccine in Bangladesh, Zanzibar, and the Indian states of West Bengal and Orissa for the control of endemic disease.

However, by 2015-2019, production capacity would have to be increased again to meet the projected growing demand for the vaccine. Based on Shantha's projections and for simplicity sake, we assume that each production facility will have an average capacity of 30 million doses per year. Therefore, new facilities will need to be built – by Shantha, VaBiotech or new producers entering the market, assuming their vaccines can be WHO pre-qualified. The sufficient supply for the first several years (from 2012 to 2016) will allow time for current or new producers to plan and bring on line new facilities to meet the growing demand. The lead time required for a new facility should be 24 to 36 months, assuming all vaccine development and pre-qualification work is complete.

As shown in *Figure 2b*, if all 33 countries in the demand forecast chose the smallest vaccination option – vaccinating 1-14 year olds in the Small Target areas (50% of urban slums and rural areas without adequate water supply) – demand would not outpace the currently planned supply until 2020. At that point, the demand would grow to 70-75 million doses per year, resulting in a gap of 30-35 million doses, which would require that at least one additional facility be built (Table 1). The gap between supply and demand would start earlier (in 2016), if all countries chose to vaccinate all ages one and above in the Small Target areas (*Figure 2a*). This scenario would require an additional capacity of 105 million doses by 2020, which would in turn require a total of four new production facilities.

If all countries adopted the option of vaccinating 1-14 year olds in Large Target areas (slums and entire rural populations without adequate water supply), this would eventually result in a gap of around 100 million doses (*Figure 2d*). This would require one additional facility by 2016 and three more in 2020 – for a total of four. The most expansive forecast – the Large Target program for all ages one and above – would result in a gap of almost 300 million doses (*Figure 2c*). This would require the building of a new facility each year from 2015 to 2018 and then five additional facilities once Investment 2 countries introduced the vaccine in 2020, for a total of nine new facilities. However, this scenario is probably the least likely.

In reality, different countries will likely choose different vaccination strategies, including ones not included in this investment case. This makes it difficult to predict with much certainty the gap between vaccine supply and demand over time. However, as countries indicate interest in introducing cholera vaccine and make plans for doing so, and as donors indicate their interest in providing financial support, more precise forecasting can be conducted to guide both current and potentially new suppliers in making decisions on whether and how to meet the anticipated demand.

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[13] See Section 4.2 and Appendix 5 on a discussion of the stockpile and its proposed growth over time.

Figure 2. Supply vs. projected demand for O1/O139 WC cholera vaccines under the four vaccination scenarios and proposed plans for a cholera vaccine stockpile

a. Small Target, 1-14 year olds

b. Small Target, 1+ year olds

a. Large Target, 1-14 year olds
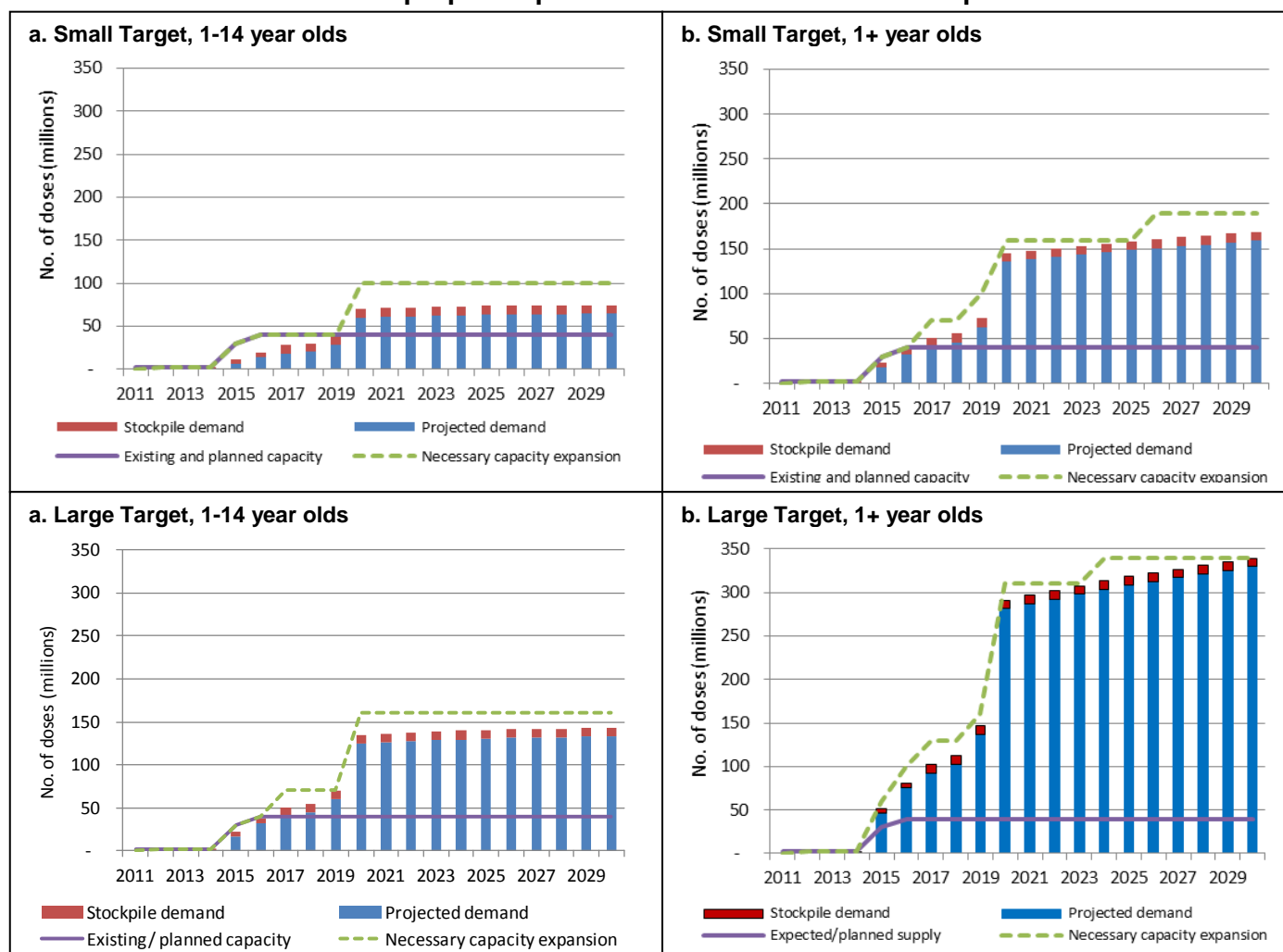

b. Large Target, 1+ year olds

Table 1. Difference between currently projected supply and demand for O1/O139 whole-cell cholera vaccines and additional production facilities required to meet demand*

Year	Small Target scenarios				Large Target scenarios			
	1-14 year olds		1+ year olds		1-14 year olds		1+ year olds	
	No. doses (millions)	No. new facilities required**	No. doses (millions)	No. new facilities required**	No. doses (millions)	No. new facilities required**	No. doses (millions)	No. new facilities required**
2012	0	0	0	0	0	0	0	0
2014	0	0	0	0	0	0	0	0
2016	+21	0	2	0	3	0	-41	2
2018	+10	0	-16	1	-14	1	-72	1
2020	-30	1	-105	3	-94	3	-251	6
Total new facilities required by 2020		1		4		4		9

* Demand is based on the results of the demand forecast for the control of endemic cholera (see Section 4 and Appendix 4) and the establishment of a vaccine stockpile increasing from two million doses per year in 2012 to ten million doses per year over five years. A "+" indicates a supply greater than projected demand, while a "-" indicates a supply less than demand.
** Assumes an average production capacity of 30 million doses per year per facility.

In summary, the production capacity from a dedicated Shanchol^TM facility plus the existing mORC-Vax® capacity would be insufficient for even the smallest potential demand projection. However, entry by Eubiologics or another new manufacturer may fill the gap for the smallest projection. For all other scenarios, significant increases in production capacity would be required.

3.   Vaccine price projections

Shantha has committed to selling its vaccine to the public sector for $1.85 per dose. VaBiotech has not set a public sector price for its vaccine outside of Vietnam. The current price of its mORC-VAX® vaccine is $0.75 per dose to the national immunization program (EPI) and $1.00 in the "free market".

Shantha reports that creating economies of scale in production by increasing yields are limited for the killed whole-cell cholera vaccine because of the time-per-dose required to grow whole cell bacteria to the necessary cell densities. Relative to other vaccines, the production of Shanchol™ and mORC-VAX® is facility-intensive, because each dose requires a large dose of each of five different *V. cholerae* strains. As a result, it is unlikely that these vaccines will ever be available at prices similar to those of the basic EPI vaccines, such as measles, oral polio vaccine or BCG. In addition, since both Shantha and VaBiotech are based in developing countries, relocating manufacturing facilities to less expensive countries will not reduce costs significantly.

Nonetheless, some economies of scale in production should be possible, and manufacturing processes could be improved, resulting in lower production costs. In addition, with increased demand, more firms could enter the market, increasing competition and putting downward pressure on price. For this investment case, we assume an average public sector price of $1.85 per dose from 2012 to 2017 (the current price of Shanchol™). We project that the price will decline to $1.45 per dose, starting in 2018 assuming increases in production efficiencies and in competition from new producers. In the sensitivity analysis, the lower bound of the price is $1.00, which is the current private sector price of the Vietnamese vaccine.

Appendix 7. Cost of introduction of oral cholera vaccine

1. Introduction

In this section, the cost analysis for introducing oral cholera vaccine with preventive campaigns into countries with endemic cholera is presented. Also, the estimated cost for stockpile is provided. The cost analysis for preventive campaigns in endemic settings is presented by WHO regions and for different age groups. This information will inform policymakers and potential donors on the estimated resource requirements needed to introduce oral cholera vaccine by region and globally.

2. Methods of Analysis

The costs of introducing oral cholera vaccine are estimated using the results of the demand forecast, the vaccine price per dose, and costs of delivering the vaccine to the target populations. The key parameters of the demand forecast are the age groups targeted, size of populations at-risk for cholera, predicted years of adoption and coverage rates for each country. The costs of delivering the vaccine include the projected cost per dose of vaccine and accompanying freight, insurance and customs charges, vaccine wastage rates, and delivery costs. The analysis assumes use of O1/O139 killed whole-cell vaccines, such as Shanchol™ and mORC-VAX (produced in Vietnam), once they are pre-qualified.

The costs are shown by Investment, with Investment 1 consisting of 11 countries projected to introduce cholera vaccination between 2015 and 2017, and Investment 2 consisting of 22 countries projected to adopt the vaccine between 2018 and 2020.

As discussed in the demand forecast (Appendix 4), this investment case proposes different options for targeting at-risk populations and ages (Table 1).

Table 1. Target groups for cholera vaccination

Large Target (urban slums and rural areas without safe water supply)	Small Target (50% of urban slum population and 50% of rural populations without safe water supply)
All persons aged 1 year and above	All persons aged 1 year and above
Children aged 1-14 years	Children aged 1-14 years

Table 2 shows the size of the target population by Investment and WHO region for the different targeting strategies and age groups.

As described in detail in the demand forecast (Appendix 4 and Section 4 of this report), we assume that vaccination will be rolled out in each country over a three-year period (i.e., one-third of the target population would be vaccinated each year) and that revaccination will take place after three years. Estimates of country-specific coverage rates for cholera vaccination were based on each country's coverage rate for measles containing vaccine (MCV). The coverage rate for children 1-14 years of age was assumed to be 80% of the country-specific coverage for MCV, while the coverage for persons 15 years and older was assumed to be 50% of the MCV coverage rates. The demand forecast also used a vaccine wastage rate of 5%, assuming the use of single-dose vials.

Table 2. Size of the target population for Investments 1 and 2

	AFR (millions)		SEAR (millions)		EMR (millions)	
	1-14	1+	1-14	1+	1-14	1+
Investment 1: 11 Countries						
2015-2017						
Large Target Population	20.6	38.4	31.5	88.3	0	0
Small Target Population	10.3	19.2	12.3	34.2	0	0
2018-2020						
Large Target Population	35.8	68.1	23.4	69.0	0	0
Small Target Population	17.9	34.1	9.1	26.7	0	0
Investment 2: 22 Countries						
2018-2020						
Large Target Population	33.7	70.0	8.3	23.8	7.4	17.1
Small Target Population	16.9	35.0	4.1	11.9	3.7	8.5

3. Cost assumptions

The price per vaccine is based on the current public sector price per dose for Shanchol™, US$1.85. The range of potential prices may fall to between US$1.00 and US$1.85. The price may fall if: 1) additional suppliers enter the market and provide competition to Shantha; 2) manufacturing process improvements lead to increases in the yield of vaccines produced; or 3) reliability of demand, increase of demand (volume) and long term commitment lead to economies of scale in production. It appears unlikely that the price per dose of a cholera vaccine with a composition similar to Shanchol™ could be sold for less than US$1.00 per dose because the yield of killed whole cells needed for the vaccine are small relative to the yields per reactor volume for other vaccines. For this analysis, we assume that the price of O1/O139 WC vaccines such as Shanchol™ will remain at $1.85 per dose until 2017 and then decrease if production volumes increase and that the base price estimate will be US$1.45 per vaccine. We also add FIC (freight, insurance, carrier) charges (15% of the cost of the vaccine) to the cost so that the cost per dose is $1.67-2.13.

The delivery cost of providing oral cholera vaccines has been estimated in three studies. Per fully vaccinated individual (two doses), a 1997 mass vaccination campaign in a Ugandan refugee camp cost about US$0.53 per person, while a 2004 mass vaccination campaign in an urban slum of Beira, Mozambique cost about US$2.09 with donated Dukoral vaccines [Legros et al., 1999; Cavailler et al., 2006].[14] A mass vaccination campaign in Hue, Vietnam only cost about US$0.27 per fully vaccinated individual using a locally manufactured vaccine similar to

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[14]These campaigns used the Dukoral vaccine, which requires a buffer solution prepared on site from a sachet of sodium bicarbonate and clean water. The transportation and advocacy campaign costs for the Beira demonstration project were very high, more than would be expected in a national program. The buffer sachets were shipped from the vaccine manufacturer in Sweden and weighed roughly the same amount as the vaccine.

Shanchol, i.e. no buffer was required [Thiem et al., 2003]. This may represent a lower bound since the vaccine is manufactured locally and because of the efficiency of the Vietnamese program. In 2008 US$, the delivery cost per dose without the vaccine from these demonstration projects varies from US$0.17 per dose to US$ 1.09.

Given the uncertainty in cholera vaccination campaign costs, it is helpful to review cost estimates from vaccination campaigns for other types of vaccines. WHO estimates that the cost per dose delivered via campaigns is typically between US$0.50 and US$0.70 [WHO, 2006]. These costs are similar to those estimated for measles vaccination campaigns. Table 3 summarizes the campaign costs per activity estimated by The Measles Partnership for measles vaccination through supplementary immunization activities [The Measles Partnership, 2005].

Table 3. Estimated operational cost per dose delivered in Measles Supplementary Immunization Activities (from The Measles Partnership 2005)

Measles Supplementary Immunization Activity line item operation costs	Cost per dose delivered
Financial costs	
Planning SIA	$0.040
Social Mobilization	$0.040
Training SIA	$0.040
Volunteer Incentives (vaccine delivery) SIA	$0.080
Volunteer incentives (0-dose monitoring)	$0.040 (Not applicable for Oral Cholera Vaccine)
Health Worker per diems	$0.160
Supervisor per diems	$0.010
Cold Boxes and Ice Packs for Catch-up SIAs	$0.050
Transport of Vaccines and Safety Boxes	$0.100
Monitoring and Evaluation	$0.020
Waste Management	$0.020
Financial costs Sub-total	*$0.56 (excluding 0-dose monitoring)*
Economic opportunity costs	
Health Worker Salaries	$0.100
Volunteer Time	$0.080
Cold Chain Equipment	$0.010
Household Transport and Time	$0.110
Opportunity Cost Subtotal	*$0.30*
Total cost	*$0.86*

Relative to measles vaccination, oral cholera vaccines should be easier to deliver because injections are not necessary. However, the single dose presentation of oral cholera vaccine may increase storage and transport costs per dose relative to the multi-dose presentations of MCV.

For the base case, delivery costs are estimated at US$0.60 per dose. For the sensitivity analysis, a range of US$0.30 –US$1.10 is examined. The lower bound is similar to costs estimated for the delivery of oral polio vaccines through mass campaigns in Bangladesh [Levin et al., 1999]. The upper bound is the delivery cost for the one-time Beira campaign.

4. Estimated cost for preventive campaigns

Table 4 shows the estimated cost of cholera vaccination from 2015 to 2020 for the 11 Investment 1 countries. The smallest program is the Small Target program for children 1-14 years old. For this program, a cumulative total of about 19 million children are expected to be vaccinated from 2015-2017 and 27 million children during 2018-2020. This program would require about 39 and 57 million doses in 2015-2017 and 2018-2020, respectively. The total cost would be approximately US$107 from 2015 to 2017 and $128 million from 2018 to 2020, in undiscounted 2010 USD. If vaccination were expanded to include all ages, about 44 million people would be vaccinated from 2015 to 2017 and another 61 million people from 2018 to 2020, at a cost of about $250 and $290 million per year, respectively.

Table 4. Estimated total costs of introducing oral cholera vaccine for Investment 1 countries from 2015 to 2020, by targeting scenario, USD (2010) millions*

Population Target	Target age group	Population size (millions)	No. doses (millions)	Vaccine cost (millions)**	Vaccine delivery cost) (millions)	Total cost (millions)
2015-2017						
Small Target areas	1-14	19	39	$83	$24	$107
	1+	44	91	$195	$55	$250
Large Target areas	1-14	43	89	$190	$54	$244
	1+	102	215	$457	$129	$585
2018-2020						
Small Target	1-14	27	57	$95	$34	$129
	1+	61	128	$213	$77	$290
Large Target	1-14	59	124	$207	$75	$282
	1+	137	288	$480	$173	$653
Total 2014-2020						
Small Target	1-14	46	96	$178	$58	$236
	1+	104	219	$408	$132	$539
Large Target	1-14	102	214	$398	$128	$526
	1+	239	503	$937	$302	$1,238

* Includes two Indian states (Orissa and West Bengal) as well as the countries of Bangladesh, Mozambique, Tanzania, Zambia, Gambia, Kenya, Malawi, Rwanda and Swaziland.
** From 2015-17Vaccine price includes $1.45 for the FOB price and $0.22 for customs, insurance and freight charges, for a total CIF price of $1.67 per dose.

The Large Target program would vaccinate about 43 million children from 2015 to 2017 in the 11 Investment 1 countries, at a cost of around $244 million over this three-year period. The all-ages program would vaccinate 102 million people, and cost around $585 million. During 2018-2020, the Large Target program would vaccinate a larger number of persons due to population growth – 59 million children or 137 million persons of all ages. The total program costs over this three-year period would be $282 million for children and $653 for persons of all ages.

Table 5 shows the cost of introducing oral cholera vaccine in the 22 Investment 2 countries from 2018 to 2020. For the Small Target program, a cumulative total of about 25 million children are expected to be vaccinated over the four years. This program would require about 52 million doses, and the total cost would be approximately US$118 million in

undiscounted 2010 USD. If vaccination were expanded to include all ages, about 55 million people would be vaccinated over the 2018-2020 period at a cost of about $264.

The Large Target program for the Investment 2 countries would vaccinate about 49 million children or 111 million people of all ages from 2018 to 2020. These programs would cost about US$236 million to vaccinate 1-14 year olds and $528 million to vaccinate all eligible ages over this three-year period.

Table 5. Estimated costs of cholera vaccination for Investment 2 countries from 2018 to 2020 by scenario, USD (2010) millions*

Population Target	Target age group	Population size (millions)	No. doses (millions)	Vaccine cost (millions)**	Vaccine delivery costs (millions)	Total cost (millions)
Small Target	1-14	25	52	$87	$31	$118
	1+	55	116	$194	$70	$264
Large Target	1-14	49	104	$173	$62	$236
	1+	111	233	$388	$140	$528
* Includes 22 countries and 10 Indian states (see Section 4 and Appendix 4 for a list of countries and Indian states).
** Vaccine price includes $1.45 for the FOB price and $0.22 for shipping and handling, for a total CIF price of $1.67 per dose.

5. Estimated cost of the cholera vaccine stockpile

The cost of the stockpile consists of the following components: 1) cost of the vaccine (including shipping and handling costs), 2) operational costs of delivering the vaccine to recipients in country, and 3) cost of managing the stockpile and conducting monitoring and research. Only the first two types of costs are included in this analysis, as the costs of managing the stockpile incurred by WHO and UNICEF and the participation of ICG members are relatively low and can be donated by the organizations involved. Funds for research and monitoring/evaluation can also be sought from other sources.

The pre-shipping or FOB[15] price of the vaccine for the stockpile is assumed to be $1.85 per dose – the current public sector price of Shanchol™ – from 2012 to 2017. It is then assumed to decrease to $1.45 starting in 2018, when adoption of the vaccine for high-risk populations of endemic countries is projected to begin. To these prices, we add 15% for customs, insurance and freight, for a CIF vaccine price of $2.13 from 2012 to 2017 and $1.67 from 2018 onwards. We assume a total vaccine delivery or operational cost of $0.60 per dose, based on the operational costs estimated for measles and yellow fever vaccination campaigns ($0.57-0.60). These costs include per diems for health workers, vaccine transport, cold chain, training and other local costs). Therefore, the estimated cost of vaccination per dose using vaccine from the stockpile would be $2.27- 2.73.

The total cost of vaccination through use of the stockpile, not including WHO and ICG costs, would be $5.5 million per year for a two-million dose stockpile during the first three years, $13.6 million for a five-million dose stockpile beginning in 2015, and $22.7-27.3 million, once it grows to 10 million doses (Table 6 and Figure 1). Assuming that the countries contribute 50% of the operational costs (i.e., $0.30/dose), the countries' contribution would be $600,000 to

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[15] FOB = Freight on board (the vaccine price before shipping, insurance, and customs costs are added). CIF = the vaccine price once customs, insurance and freight charges have been added.

$3,000,000 per year. Donors would contribute each year around $4.9 million for the two-million dose stockpile, $12.2 million when it grows to five million doses, and around $20-24 million for a 10-million dose stockpile.

Table 6. Projected annual costs of a cholera vaccine stockpile (including vaccine delivery costs) and possible share of financing (US$)

Years	No. doses	CIF vaccine price/ Dose*	Delivery cost/ dose**	Total cost/ dose	Total cost per year	Country contribution per year (50% of operational costs)	Donor contribution per year
2012 – 2014	2 million	$2.13	$0.60	$2.73	$5.46 million	$600,000	$4.86 million
2015 – 2016	5 million	$2.13	$0.60	$2.73	$13.7 million	$1.5 million	$12.2 million
2017 – 2030	10 million	$1.67-2.13	$0.60	$2.27-2.73	$22.7-27.3 million	$3 million	$19.7-24.3 million
Total 2012 – 2030 (undiscounted)	156 million				$366 million	$47 million	$319 million
* Based on pre-shipping price of $1.85 from 2012-2017 and $1.45 starting in 2018 and includes 15% for shipping, insurance and other handling charges. ** Operational cost of vaccination in the field and opportunity costs (described in text).							

Figure 1. Projected number of doses used per year and costs of a cholera vaccine stockpile
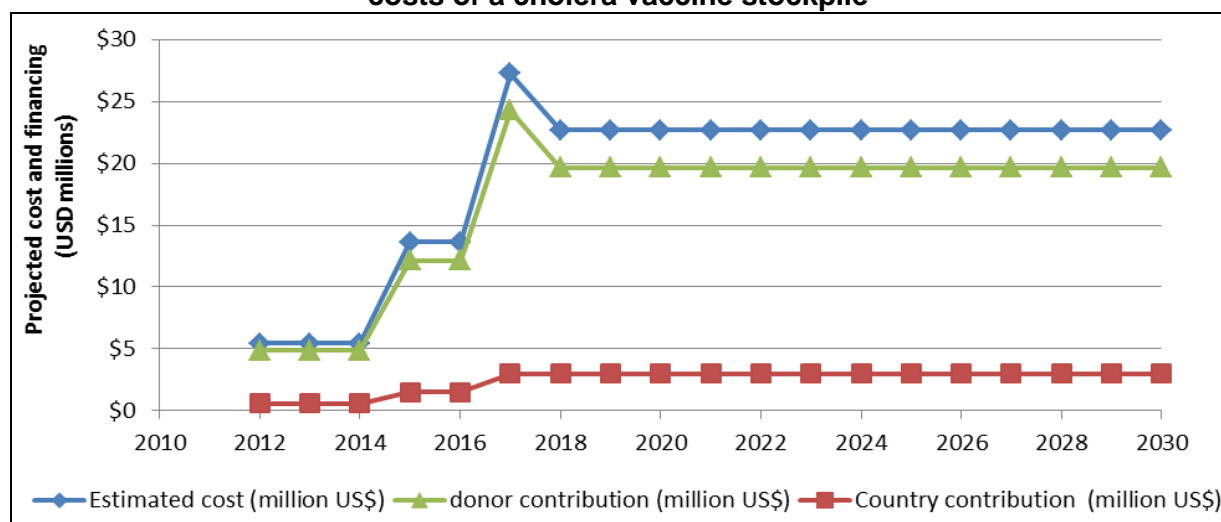
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Appendix 8. Description of the impact analysis and assumptions

1.   Background

A wide range of models for the dynamic transmission of cholera within at-risk populations have been published over the years which have explored the intricacies of disease dynamics and their interactions with environmental conditions. Several of these models have considered only indirect transmission via environmental exposure. For example, Codeço's [2001] model of indirect seasonal cholera transmission indicates that the threshold size of the susceptible pool which can trigger outbreaks depends on environmental, sociological and strain-specific factors, but that the existence of a permanent reservoir of infection causes this susceptible threshold to tend to zero – indicating that a community of any size is subject to an outbreak under these conditions. In this model the probability of becoming infected with cholera is dose-dependent, but since the model assumes transmission is environmental the optimal means of controlling infection is assumed to be via sanitation alone.

Hartley [2006] also considers cholera transmission via environmental exposure, as a function of the magnitude of the infective dose with respect to the threshold IC50. Within this model, the environmental reservoir is replenished via shedding by infectious individuals and is depleted via *V.cholerae* decay rates. Hartley's model also explores the possibility of an initial hyper-infectious state which decreases to lower infectiousness over several hours, indicating that "direct" within-household transmission may play a greater role as this initial period is more likely to occur at home.

The model developed by King [2008] further supports this theory, stating that:... while a relatively small dose of live bacteria induces a severe case of cholera when the innoculum is buffered, as by food, a large dose is needed when delivery is via contaminated water. Moreover, the fact that recently-shed vibrio are hyperinfectious implies that within-household transmission is more likely to result in severe infection. (p. S-6)

To accommodate these dynamics, transmission is represented in King's model as a dual function of both direct and indirect transmission with the environmental reservoir being critical to endemicity. This model also incorporates asymptomatic infection, such that some proportion of infected individuals never develop symptoms yet continue to shed vibrios until recovery. Upon recovery this model assumes immunity is very short-lived, with a difference in duration of immunity for asymptomatic and symptomatic individuals.

The models of Koelle & Pascual [2004] and Koelle [2009], on the other hand, explore only direct person-to-person transmission of cholera, indicating that the size of a cholera outbreak is a function of both population immunity and climate influences. Within these models fluctuations in herd immunity are captured by variation in the proportion of susceptibles within the population over time, and the effect of climate variability is captured in fluctuations in the cholera transmission rate over time, which are in turn affected by climate variability at multiple scales (local, regional and global) (see [Koelle 2009 p.30]) – seasonal variation is associated with timing of monsoon, long-term variation is inversely related to regional water cycles, and short-term variation is correlated with El Niño. However within these models even optimal climate conditions cannot trigger an outbreak if herd immunity is still high from previous outbreaks.

The stochastic model developed by Longini [2007] looks at both direct and indirect transmission of cholera over a single season within a community in Bangladesh, such that the probability of contact with sources of contamination is higher within households and significant population immunity exists due to prior infection. Within this model a two-dose vaccination strategy is implemented as a means of reducing morbidity over this period of time. The modeled vaccine is assumed to be "leaky" – that is, vaccination does not confer 100% immunity, but rather provides a reduced probability of infection and, once infected, a reduced degree of infectiousness. Based on proportional reductions in cholera incidence under different vaccination scenarios, Longini's model indicates that at surprisingly low levels of vaccination coverage there is significant herd immunity associated with vaccination.

Based on the methods developed by Longini [2007], we have developed an age-structured deterministic model of the transmission of cholera within at-risk populations, establishing transmission as a function of both direct and indirect exposure, simulated over a 50-year period between 2000 and 2050. Within our model (described below), we implement various vaccination strategies utilizing Longini's vaccine assumptions and explore the nonlinear change in morbidity and mortality over time as immunization is gradually adopted in populations, as well as the potential benefit of vaccination even to unvaccinated populations by simulating the reduction in infection loads due to the removal of segments of the susceptible population to protected status. We then evaluate resulting potential reduction in cholera incidence over the simulated period in an effort to provide insight into the outcomes associated with the adoption of cholera vaccine as an intervention to control cholera morbidity and mortality.

2   Methods

Model Description

We have modeled the dynamic transmission of cholera within age-structured at-risk populations (as defined by access to sanitation, see Appendix 1) for endemic and non-endemic countries within seven WHO regions (AFR-D, AFR-E, EMR-B, EMR-D, SEAR-B, SEAR-D, WPR-B) utilizing a compartmental structure, as described in detail in the Technical Section at the end of this appendix.

The compartmental flow of disease states within the model is described by a system of deterministic ordinary differential equations with homogeneous mixing between all age groups at the regional level (full detail is provided in the Technical Section). This structure is applied to all age groups (less than 1 year, 1 – 4 years, 5 – 14 years, and greater than 15 years), with age-specific attack rates representative of estimated age distribution of cases. Projected country-specific age-structured population numbers, birth rates and background death rates through the year 2050 were obtained from the UN Population Division.

Comparison with Previous Model

Though this model was parameterized and structured to parallel that developed by Longini [2007], there are significant differences which may impact direct comparability of results between the two models, including model type, resolution and population mixing, transmission intensity, and simulation period.

Both this model and Longini's incorporate seasonal dual-mode transmission, asymptomatic infection and age-structured vaccination utilizing a leaky vaccine. However, while Longini's model is a fully stochastic individual-based model of cholera transmission within a

spatially-structured single community (Matlab, Bangladesh), the model described here is deterministic with stochastic pulses to accommodate immigration of infection and probability of short- and long-term larger outbreaks.

When looking at the simulated populations, both models incorporate age structure. Longini's model simulates the population at the individual level with spatial structure within a single region of Bangladesh. The model described here is implemented at the whole population level over multiple countries within seven of the WHO regions, which are represented without spatial structure. Mixing within this model is homogeneous at the regional level, while within the Longini model mixing is assumed to occur heterogeneously at a local scale.

Incidence levels produced by Longini's model are established as representing higher-transmission years within the model described here, with average incidence levels being somewhat lower based on the disease burden estimates.

Finally, Longini's simulations are run over a 180-day high-transmission period, whereas this model is simulated over a 50-year period between the years 2000 and 2050. As a result of the longer duration of the simulation period in this model, multi-year waning of both natural and vaccine-induced immunity is incorporated into the disease dynamics, though this issue does not come into play in the 180-day cycle modeled by Longini.

Modeling Transmission Dynamics

Cholera transmission is modeled as a dual process involving both direct and indirect pathways. *Indirect disease transmission* is modeled as a function of contact with an infected water source (see for example [Hartley 2006] and [Codeço 2001]), which is re-contaminated by vibrio shedding from infected individuals within the simulated population, or immigrating into the region from outside areas. *Direct transmission* is modeled as a function of contacts between susceptible and infected individuals (both symptomatic and asymptomatic). The two types of transmission are then scaled by a seasonal forcing term, which represents seasonality as a periodic process [Koelle and Pascual 2004, Pascual and Dobson 2005], with short-term seasonality represented by semi-annual peaks occurring in spring and fall, and longer-term periodicity represented by an increased probability of large outbreaks on a roughly 20-year cycle. Direct and indirect transmission weight factors are then adjusted by region so that mean incidence values approximate the region-specific estimates summarized in Appendix 1.

Infected individuals can be either symptomatic or asymptomatic [Codeço 2001, Longini 2007], and the former are assumed to be 10 to 100 times as infective as the latter, shedding an accordingly larger amount of *V. cholerae* back into the environment [Codeço 2001]. Cholera-related mortality is assumed to occur in symptomatic infectives only. Infection-acquired natural immunity is assumed to wane over a period of 3 years, after which period the individual returns to full susceptibility.

Modeling Vaccination

The transmission model is initialized for a period of 10 years before vaccination scenarios are implemented. Vaccination scenarios are modeled utilizing age-specific strategies via campaigns which are assumed to occur every three years over a six-week period just before the spring peak in transmission. Vaccination is modeled in cholera endemic countries only with a range of coverage rates shown in Table 1. The coverage rate by country is then incorporated

into the modeling exercise by interpolating between coverage-specific overall effectiveness estimates by region.

Table 1. Vaccination scenario definitions for endemic transmission countries

Age Group	Coverage Rate			
	Baseline	Scenario 1	Scenario 2	Scenario 3
Less than 1 year	-	-	-	-
1 – 4 years	-	-	50-80%	50-80%
5 – 14 years	-	50-80%	50-80%	50-80%
Greater than 15 years	-	-	-	35-50%

As the vaccine is currently not applicable to infants under one year of age, this age group is not assumed to be vaccinated in any scenario. Coverage rates are representative of rates assumed to be achieved by age group, not of the total population. Full protection (based on age-specific vaccine efficacy) is conferred one week after receipt of the second dose of vaccine.

The vaccine itself is considered to be "leaky" [Durham 1998; Longini 2007], in that fully vaccinated individuals are still partially susceptible to infection, albeit at a lower level – within the first two years post-vaccination there is a 70% reduction in susceptibility, and a 50% reduction in the third year. Full susceptibility is assumed to resume in the fourth year post-vaccination. Vaccinated individuals who do become infected are similarly less infectious, in that they shed vibrios at a reduced rate.

Calculating Vaccine Effectiveness Ratios

The benefit derived from the implementation of the various vaccination scenarios is measured through the calculation of four different vaccine effectiveness ratios, based on definitions derived by Longini [2007] (see Figure 1). These are as follows:

Overall Vaccine Effectiveness (OVEF) - Compares incidence in the total population (vaccinated + unvaccinated) (Longini's Sub-region 1) to that in a comparable completely unvaccinated population (Sub-region 2);

Indirect Vaccine Effectiveness (IVEF) - Compares incidence in the unvaccinated subpopulation of a larger population within which some people are receiving vaccination ("Nonvac" in Sub-region 1) to that in a comparable completely unvaccinated population (Sub-region 2);

Total Vaccine Effectiveness (TVEF) - Compares incidence in the vaccinated subpopulation of a larger population within which some people are receiving vaccination ("Vac" in Sub-region 1) to that in a comparable completely unvaccinated population (Sub-region 2);

Direct Vaccine Effectiveness (DVEF) - Compares incidence in the vaccinated subpopulation ("Vac" in Sub-region 1) to that of the unvaccinated subpopulation ("Nonvac" in Sub-region 1) in a larger population within which some people are receiving vaccination.

Herd immunity is accommodated within the model due to the fact that vaccination reduces the number of infected individuals over the simulation period, which in turn also reduces the amount of contamination in the environment, and thus the risk of infection to non-vaccinated groups. Thus, persons would be less likely to be exposed to persons infected with

144

cholera or water bodies contaminated with vibrios. The impact of vaccination on herd immunity is measured through the calculation of IVEF.

Figure 1. Calculation of vaccine effectiveness ratios, from Longini et al. (2007)
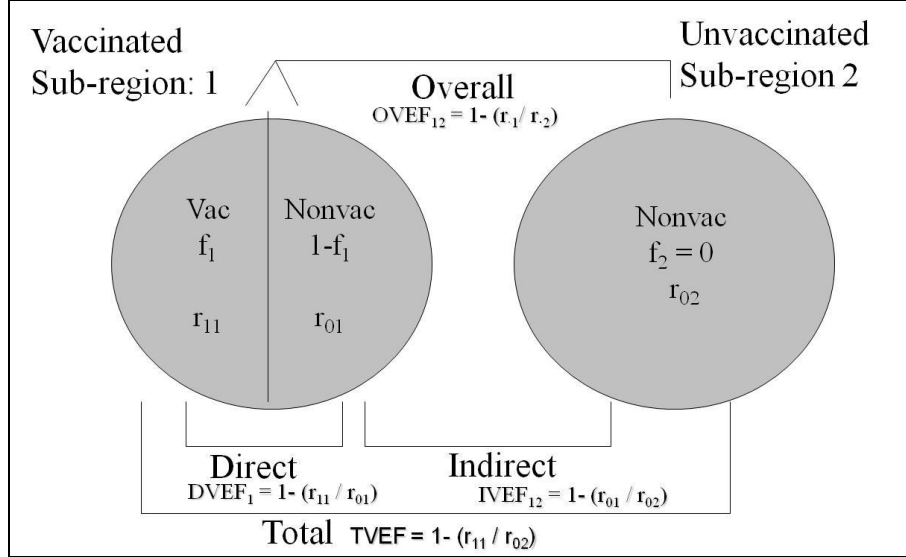
The effectiveness ratios are calculated not from the total number of cases for the entire simulation period, but rather from the mean incidence per 1,000 population over all simulation years, which is in turn calculated from the annual incidence. The annual incidence for subpopulations (and the total population) is based on the following equation (symptomatic cases only):

$$Incidence_{subpop} = 1000 * cases_{subpop} / population_{subpop} \qquad (1)$$

Vaccine effectiveness ratios are calculated as follows:

$$
\begin{aligned}
OVEF &= 1 - (Incidence_{total}[scenario] / Incidence_{total}[baseline]) \\
IVEF &= 1 - (Incidence_{unvacc}[scenario] / Incidence_{total}[baseline]) \\
TVEF &= 1 - (Incidence_{vacc}[scenario] / Incidence_{total}[baseline]) \\
DVEF &= 1 - (Incidence_{vacc}[scenario] / Incidence_{unvacc}[scenario]) \qquad (2)
\end{aligned}
$$

3.   Results

Model Validation

Simulation results for endemic countries within each region were validated against the incidence rates reported in Appendix 1 to confirm that the age distribution of cases and incidence in the absence of vaccination approximated expected values (see Tables 2 and 3)[16].

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[16] The simulated disease burden, both age-specific and total numbers of cases, vary from year to year due to inter- and intra-year stochasticity incorporated into the simulation model. This allows for fluctuations in the short- and long-term transmission of cholera within the region and importation of disease from outside the region via immigration. Additional variation particularly in the SEAR-B, SEAR-D and WPR-B regions may be associated with differences in the modeled populations, as discussed in section 8.4 below.

Age-specific incidence rates agree fairly well between the simulation and our disease burden estimates.

Table 2. Expected endemic cholera incidence per 1,000 population by age group and by WHO sub-region, 2010 (from Appendix 1)

	<1y	1-4y	5-14y	15y+	Total
AFRO-D	6.2	6.1	1.9	0.8	2.0
AFRO-E	12.5	12.2	3.8	1.6	4.0
EMRO-B	0.42	0.41	0.13	0.05	0.10
EMRO-D	5.6	5.5	1.7	0.7	1.6
SEARO-B	1.8	1.8	0.57	0.24	0.45
SEARO-D	6.2	6.1	1.9	0.8	1.6
WPRO-B	0.44	0.43	0.13	0.06	0.10

Table 3. Calculated endemic cholera incidence per 1,000 population by age group and by WHO sub-region in the absence of vaccination, averaged over entire simulation period

	<1y	1-4y	5-14y	15y+	Total
AFRO-D	6.7	6.1	2.4	0.9	2.0
AFRO-E	15.2	12.7	4.0	1.9	4.0
EMRO-B	0.48	0.47	0.14	0.06	0.10
EMRO-D	6.0	5.5	1.9	0.8	1.6
SEARO-B	1.7	1.6	0.6	0.3	0.4
SEARO-D	7.2	6.6	1.9	1.0	1.6
WPRO-B	0.40	0.39	0.16	0.07	0.10

As additional model verification, the endemic countries within each region were simulated with varying levels of vaccinated coverage for all individuals older than one year of age. These results were validated against those of Longini [2007] and Ali [2005] to confirm that the expected vaccine effectiveness values (Figure 8.2) were reflected by the simulation model. This figure shows the impact of vaccination if all age groups are vaccinated at the same coverage rate.

The calculated indirect effectiveness values (Figure 2) from the dual-transmission simulation for the endemic-transmission regions fall between the estimates provided by Ali [2005] and Longini [2007], with the exception of the three lowest-transmission regions EMR-B, SEAR-B and WPR-B, in spite of the relatively good fit of simulated age-specific incidence to estimated incidence for these regions.[17]

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[17] One potential cause is that these regions have smaller fractions of children relative to total population. Thus, there would be fewer people vaccinated. This is especially evident in the WPRO-B region in which children compose the smallest fraction of total population.

Figure 2. Calculated indirect effectiveness (IVEF) for endemic-transmission countries at various levels of vaccination coverage versus 14% coverage, compared with Lancet (Ali 2005) estimates and PLoS (Longini 2007) calculations
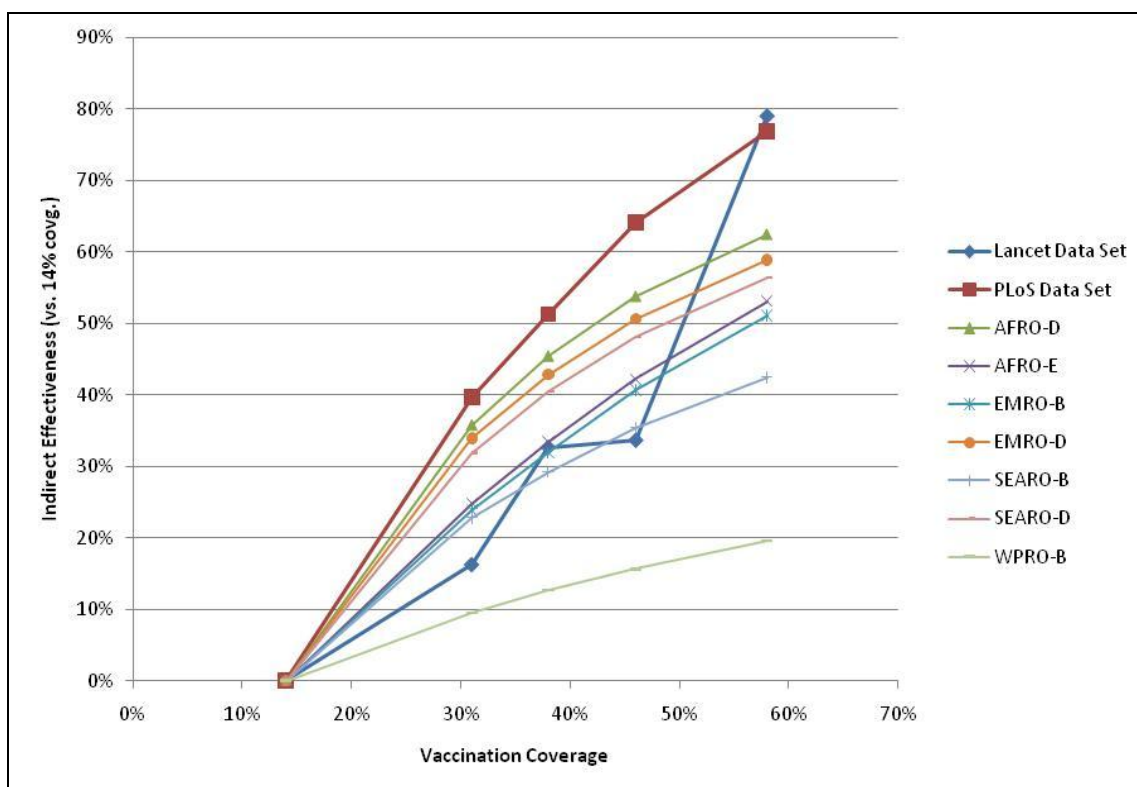
Endemic Countries Scenario Results

The three vaccination scenarios shown in Table 4 were simulated in each of the endemic regions to evaluate the potential impact of the various strategies on age-specific and overall morbidity and mortality during the time period. The same age-specific coverage rates are assumed for each region, although these coverage assumptions are varied in the technical appendix. Impacts are estimated based on the number of cases with and without vaccination by subgroup. Global results, showing the overall impact of the vaccination program for the entire endemic population (including both vaccinated and unvaccinated individuals) are presented in Table 4 below. There is regional variation in the estimates. The sub-region-specific vaccine effectiveness ratios are shown in Tables 8A.3 (a) – (g) in the Technical Section at the end of this appendix.

Differences between Scenarios

As expected, incidence rates in vaccinated groups are predictably lower than in the unvaccinated groups for all scenarios. When adding high-transmission/high incidence 1-4 year-olds to the existing school-age vaccination campaign (that is, moving from scenario 1 to scenario 2), there is a large increase in total protection, from 30% overall reduction to 52% overall protection. In moving from Scenario 2 (all children 1-14 years old) to Scenario 3 (all children and adults greater than 1 year), there is a similar increase in overall protection. However, it requires a much larger increase in the number of people vaccinated than in moving from scenario 1 to 2. This is because the population of adults is much larger than the population

of children aged 1-4 years. This is because adults are a relatively low-incidence/low transmission group.

Table 4. Calculated age-specific overall vaccine effectiveness ratios for vaccination scenarios for endemic-transmission countries averaged over all regions

Age Group:	< 1 yr	1-4 yr	5-14 yr	15+ yr	TOTAL
Scenario 1 - School-age children, 65% coverage	28%	26%	41%	27%	30%
Scenario 2 - All children > 1 yr, 65% coverage	48%	58%	58%	46%	52%
Scenario 3 - All children > 1yr, 65% coverage; adults, 50% coverage	65%	72%	71%	66%	69%

For all regions, scenario 3 provides the greatest reduction in incidence for both vaccinated and unvaccinated individuals and for the population as a whole, though the *magnitude of the improvement in vaccine effectiveness ratios* – particularly direct protection as represented by DVEF and indirect protection as measured by IVEF – resulting from adding adults to vaccination campaigns depends intimately on the age structure of the population as well as the cholera incidence in the region in the absence of vaccination.

Vaccination impact

Overall effectiveness ratios, similar to those shown in Table 8.4 may be used to predict the impact of vaccination. The model results by WHO sub-region are included in Table 8A.4 (a) – (g) of the Technical Section. It is expected that adoption timing, vaccination strategies and coverage rates will vary across countries. Thus, a sensitivity analysis of the relationship between coverage rates and overall effectiveness is provided as Table 8A.7. The number of cases averted in a given year for a given country can be calculated depending on the coverage rate achieved, the baseline incidence rate (assuming no vaccination), and the population at-risk. The average overall effectiveness estimates of children-only and all ages vaccination programs given the expected country-specific coverage rates are shown in Figure 3.

Herd Immunity

The greatest improvement in herd immunity for infants (who are excluded from vaccination in all scenarios), as measured by indirect protection IVEF, is seen in the AFR-D, AFR-E, EMR-D and SEAR-D regions – all of which experience expected total cholera incidence greater than 1.5 cases per 1,000 population (Appendix 1) – have the high-incidence infant and 1-4 year-old subpopulations representing roughly 15% of the total population, and the lower-incidence adult subpopulation representing roughly 55% of the total population. For these regions, the combination of *high total incidence* along with population structure weighted toward the higher-incidence *younger ages* results in greater improvements in morbidity associated with implementation of vaccination scenarios in general. This is particularly apparent with scenario 2, in which high-incidence 1-4 year-olds are included in vaccination campaigns, and with scenario 3, in which the adult subpopulation is vaccinated as well.

Figure 3. Average expected impact of vaccination programs by WHO region
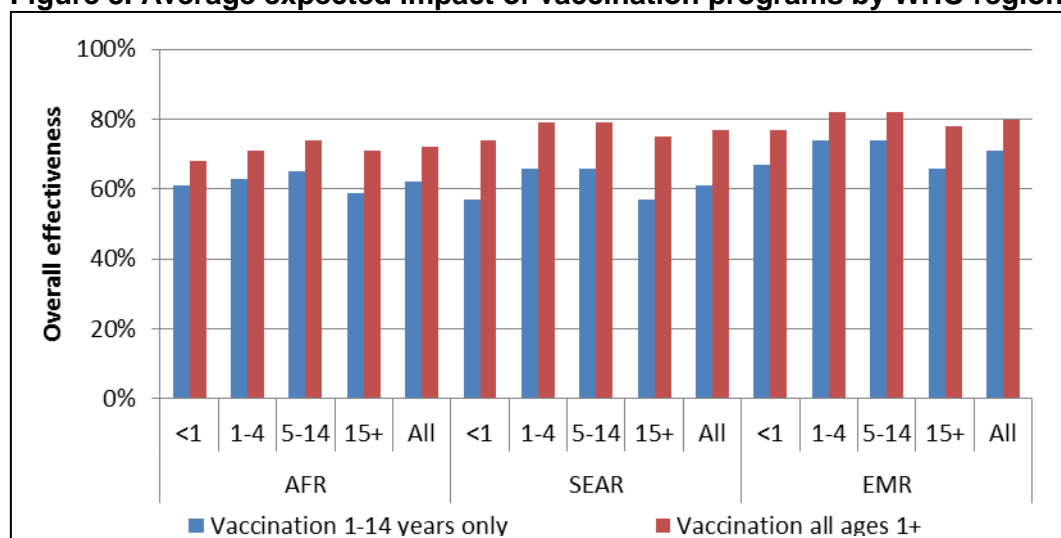
The lowest improvement in infant indirect protection – though still an improvement – is seen in the EMR-B, SEAR-B and WPR-B regions. These regions each experience expected total cholera incidence less than 0.5 cases per 1,000 population, each have infant and 1-4 year-old subpopulations representing less than 10% of the total population, and the lowest-incidence adult subpopulation representing roughly 70% of the population. For these regions, the combination of *lower total incidence* along with population structure weighted toward the lower-incidence *older age groups* results in relatively smaller improvements in morbidity associated with implementation of vaccination until the 15+ year-old largest subpopulation is included in vaccination campaigns (that is, scenario 3).

Average Age of Infection

As expected, implementation of vaccination in younger age groups causes the average age of infection to shift upward, however vaccinating adults shifts this back down to baseline or younger ages (see tables 8A.4 (a) – (g) in the Technical Section).

4.   Model Limitations

The model described above assumes homogeneous mixing at the regional level for all at-risk populations within all the countries within a given region, however it has been shown that there are numerous variations in cholera transmission and seasonality dynamics (such as the timing of the rainy season) between local areas which can dramatically affect transmission (see for example Gaffga et al. [2007], Griffith et al. [2006], Mendelsohn et al. [2007], Lucas et al. [2005]). For example, within the endemic-transmission countries of AFR-D region alone the rainy season can occur at complete opposite times of the year depending on the location of the country. Treating an entire region homogeneously obscures these local variations and may introduce uncertainty into results particularly as incidence drops to very low levels, when local heterogeneity may allow transmission to persist.

The assumption regarding the length of natural immunity after symptomatic infection may be conservative in the sense that the numbers of cases with and without vaccination are

higher than if a longer assumption had been used. Since the numbers of symptomatic cases remain low relative to the population size, it is unlikely that this assumption has a large impact on model results.

There are a number of differences between the simulation results and the disease burden estimates in Appendix 1. Although IVI estimates represent only a subset of provinces within Indonesia, within this model SEAR-B simulations include the country Indonesia as a whole, since population projections through 2050 from UN Population Division do not break down to the province level. This is also the case with WPR-B (China) and SEAR-D (India). Also, age distribution of cases within SEAR-D may differ from IVI estimates since district level population numbers in India available from the World Health Organization only represent populations up to 80 years, whereas country-level projections represent up to 100 years.

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Appendix 9. Description of the analysis of the macro-economic impact of cholera in Mozambique

1. Introduction

In this appendix, an analysis by Oxford Economic Forecasting (OEF) on the economic impact of a cholera outbreak in Mozambique is presented. This analysis uses the Oxford Economics macroeconomic model which forecasts the impact of a shock to the economy caused by disease outbreaks or other events. The model was used to capture the main channels of transmission, including demand and supply effects. Since the Oxford Economics' model does not include Mozambique, they used a model for South Africa and scaled the shocks according to the economic features of Mozambique. South Africa shares many similar economic features that imply that the transmission of the shock through the economy is likely to be similar to what would happen in Mozambique.

This appendix explains the Oxford Economic Forecasting approach and results.

2. Benchmark from Previous Episodes and Studies

A few studies have estimated the economic costs of a cholera epidemic. Suarez & Bradford [1993] compute a fuller estimate of the cost of the 1991 cholera epidemic in Peru. They calculated the supply channels outlined by Kirigia et al. [2009] and three demand effects: reduced tourism revenue, reduced revenue on exports of goods and lower domestic consumption. The tourism channel is significant, with revenues from international visitors reduced by 72% of their level in 1990. Export revenues were also expected to decline drastically, as importers put up barriers to prevent transmission of the disease. However, this was not the case, as it was found that the disease was not transmitted in most food products. As a result, only fresh fish exports were limited and total exports in 1991 were just 0.5% lower than the previous year.

Turning to consumption effects, unlike influenza, cholera is not easily spread through human-to-human contact, at least not outside the household, and as a result, there is no need for people to isolate themselves to avoid the epidemic. Suarez and Bradford found that the only sectors significantly affected were fresh fish, where demand fell by 33.6%, and street food vendors, although the authors mention that this estimate may be exaggerated. However, they note that there are likely to be general equilibrium effects, as consumers substitute potentially infected food with safe alternatives, and a fall in discretionary spending as consumers avoid restaurants. WHO quotes an estimated cost of US$770 million to Peru's GDP in 1991 (around 2% of GDP) from the epidemic, citing a food trade embargo and the impact on tourism as the main channels.

Despite WHO guidelines in the International Health Regulations (IHRs) of 2005 that suggest that travel and trade do not need to be restricted during an epidemic, many countries limit imports from infected areas. Kimball et al. [2005] estimates the loss of export earnings with data from Mozambique, Kenya, Tanzania and Uganda. The four countries experienced cholera epidemics in the period of 1997-2002 and were subject to EU restrictions on fish imports. They find that these countries lost around 4% of total export earnings in 1998, increasing to more than 10% in 2002. However, this study suggests that for poorer, less developed countries that are more reliant on fresh food exports, this economic channel could be significant.

Poulos et al [2011] calculate the short-term costs of illness from endemic cholera, including "public costs" (e.g., treatment and hospitalization costs incurred by the public sector) and "private costs, such as out-of-pocket payments for medical care, and lost earnings of the patient and caretakers at home, using patient data from Bangladesh, Mozambique, India and Indonesia. They found that the majority of costs are borne by the public sector, but that, from an individual level, private costs can be significant, particularly if the patient has to be hospitalized. Kirigia et al (2009) conduct a similar analysis, calculating both the short-term and long-term costs of illness from cholera in the WHO's Africa Region in 2005. Their costs include hospitalization and treatment, laboratory diagnosis of the disease, short-term loss of earnings of patients and their families and lost productivity and output due to limited working ability and premature death. They estimate a total economic loss of US $53.2 million as a result of the 125,018 cases reported in the WHO Africa Region in 2005, equivalent to slightly less than 1% of the GDP of the region.

These studies addressed some of the main transmission channels of the economic impact of a cholera epidemic on the economy. In this report, Oxford Economics' macroeconomic model is used to obtain quantitative estimates of the overall economic impact, accounting for spillovers throughout the economy.

3. Economic channels

In this section, macro-economic impacts that are likely to result from a cholera outbreak are discussed. In particular, there is a discussion of how shocks are implemented in Oxford Economics' macroeconomic model.

OEF's global macroeconomic model encompasses both demand and supply aspects of each economy. On the demand side, consumers' expenditure is a function of incomes, employment and real interest rates. So, if a cholera outbreak has a negative impact on economic activity that reduces demand for labor, this will feed through to consumer spending via lower incomes, which in turn will affect overall GDP and demand for labor (amongst other variables). Investment is determined by the level of real interest rates and competitiveness, but is mainly driven by an 'accelerator' mechanism – that is, lower output leads to lower investment. On the supply side, the long-run trend rate of growth of the economy depends on the growth in the population of working age, the speed with which the capital available to workers increases, and total factor productivity growth. So, if a cholera outbreak affects the availability of labor, that will tend to dampen potential growth. In turn, the mismatch between demand and supply has an impact on prices. If weaker demand leaves large amounts of production capacity unused, this will tend to depress prices as companies are forced to reduce margins.

These are examples of the economic transmission channels at play in the estimation of the macro-economic impact of a cholera epidemic. The remainder of this section details the main economic transmission channels and the assumptions used in these studies.

Supply channels

Labor supply

Epidemiological data used from the IVI used in the Investment Case were used to calibrate the size of the shock on the labor supply for Mozambique. These data (shown in Table 1) include an average cholera attack rate of 2.75% during an outbreak, a case fatality rate of 3.8% (based on the disease burden analysis for the AFRO-D and AFRO-E mortality strata, and an average

duration of illness of six days. The assumed duration of the outbreak that is modeled is nine months.

Based on these parameters, the temporary negative impact on labor supply in Mozambique is 0.13% over nine months. The permanent negative impact on labor supply is 0.05%.

At the macroeconomic level, these shocks are very small and are unlikely to represent significant costs. With around half the work force employed in agriculture, employers should be able to find replacements for absent employees.

Total factor productivity

A cholera outbreak is likely to restrict the ability of companies to carry out business normally. For instance, Oxford Economics has carried out some work on air travel and total factor productivity (TFP). They estimated that a 10% reduction in air travel reduces TFP by 0.6% in the long term. This estimate was based on a sample of countries with higher income levels than Mozambique. In this study, OEF assumes that the elasticity of TFP to business travel is half as large, at 0.3%. Given the assumed 60% drop in travel, this implies a productivity shock of 1.8%.

Production costs

The impact of a cholera outbreak on production costs is ambiguous and is likely to depend on when the outbreak occurs in the country's economic cycle. Disruptions in transport and logistics could lead to a rise in production costs if spare capacity is scarce. But if the outbreak occurs when the economy has surplus capacity, the impact of the epidemic on production costs is likely to be minimal. In practice, it is likely that prices of some goods like food go up while prices of other goods and services for which demand falls go down. Agricultural products account for 16% of total imports in Mozambique (WTO data). A rise in food prices would therefore have a significant impact on overall prices in the economy. Since food consumption tends to be price-inelastic, this would put a significant burden on households' purchasing power.

Demand channels

International travel and tourism

In Mozambique, travel and tourism make up 7% of total exports and 1.5% of GDP. Suarez & Bradford [1993] suggest that the impact of a cholera epidemic on international travel and tourism can be very large. They estimate that the cholera outbreak in Peru in 1991 resulted in a fall in tourism revenue of 72%. OEF uses the Peru example to calibrate the shock to travel and tourism in this study. Tourism is then assumed to gradually return to more normal levels. It should be noted that this may overstate the actual impact of the cholera outbreak since other factors, such as terrorist attacks at the time, are likely to have deterred tourists. Different countries have very different exposures to travel and tourism. A given fall in tourism inflows will therefore affect various economies very differently.

<u>Exports of goods</u>

Although WHO states that embargoes are unnecessary, a country affected by a cholera outbreak is likely to experience a fall in exports of food, as reported in Kimball et al (2005). In Mozambique, food exports account for 2.6% of GDP and 12.2% of total exports.

To calibrate the shock, OEF takes the data from Kimball et al. using the estimate from the Kimball study of a 4% shortfall in total exports as a result of a cholera outbreak, and given that food accounted for around 50% of exports of these four countries from 1997 to 2002, they therefore estimate an 8% shortfall in food exports from a cholera outbreak in Mozambique.). Since the estimates of declines in total exports in the Kimball study ranged from 4-10% in any given year, the 8% decline in food exports is therefore conservative. As with travel and tourism, exports of foods are assumed to return to normal levels gradually once the epidemic is over.

<u>Discretionary consumer spending</u>

Experience suggests that consumers cut spending on non-essential goods and services during epidemics and health scares as they seek to avoid crowded places such as markets and restaurants. For cholera however, this channel is likely to be of little significance. As mentioned in Suarez & Bradford, there may be cuts in food consumption from street vendors and restaurants, but the fall in overall discretionary consumer spending is likely to be much smaller.

OEF makes the assumption that consumption of food away from home drops by 20%. Data on the share in total consumption of spending on food away from home are not available for Mozambique. However, looking at other countries in the region, we can assume that this share is around 5%.

<u>Fixed investment</u>

Beyond the dampening impact of slower activity and higher interest rates (see below), domestic and foreign investment is also likely to be postponed while the economic impact of the epidemic is uncertain. Estimating this shock is more difficult. There was no visible impact on investment in Peru in 1991 during the cholera epidemic, for instance. The experience of other epidemics or health scares like the SARS episode in 2003 shows no clear and consistent fall in investment in the affected countries either.

In this study, OEF assumes a shock of the same size as the productivity shock explained above (-1.8%). This is the assumption that they have retained in previous analyses of the economic impact of epidemics. If anything, the risk is that investment falls by a larger amount.

Summary of assumptions

Table 1 summarizes the assumptions for the macro-economic modeling of a cholera outbreak in Mozambique. The shocks are applied from the beginning of 2011 – when the outbreak is presumed to begin – and continue for three quarters, before gradually tapering off.

Table 1. Summary of assumptions for Mozambique

Assumption	Value
Epidemiological assumptions:	
Incidence rate	2.75%
Case fatality rate	3.80%
Duration of illness	6 days
Duration of epidemic	9 months
Economic assumptions:	
Productivity shock	1.8%
Shock to travel and tourism	72%
Shock to exports of food	-8%
Consumption shock	-1%
Investment shock	-1.8%
Monetary policy	No change
Fiscal policy	Endogenous
Short-term impact on labor supply (9 months)	0.13%

4. Scenario results

Table 2 summarizes the estimated macro-economic impact of a nine-month long cholera epidemic in Mozambique. The GDP would be lowered by around 2-2.5% in the year of the epidemic and 0.5-1% in the following year. This represents a loss of around US$303 million for the two years combined, with much of the loss due to the loss in exports. In the year of the epidemic, consumer spending would be reduced by US$114 million (1.2%). The impact on consumer prices would be small, with only a slight increase. In terms of jobs, the epidemic would cause the loss of more than 56,000 in the first year of the outbreak and 72,000 jobs over two years.

Table 2. Scenario results – Impact of cholera epidemic in Mozambique

Indicator	Year 1	Year 2
GDP	-2.1%	-0.5%
GDP (US$ million)	-245	-58
GDP per capita (US$)	-10	-2.5
Private consumption	-1.2%	-0.3%
Private consumption (US$ million)	-114	-28
Private consumption per capita (US$)	-5	-1
Consumer prices	0.2%	0.5%
Employment	-0.7%	-0.2%
Employment ('000s)	-56.3	-16.1

These results are consistent with the findings of previous studies that estimated the impact of a cholera epidemic at 1-2% of GDP. This analysis suggests that an epidemic can have significant, albeit manageable, adverse economic effects. A GDP loss of the order of 2-2.5% can typically be recouped within a few years. In this study, OEF has assumed that the epidemic is contained to Mozambique. If the epidemic were to spread across countries, the impact on international trade and the economy as a whole would be larger.

5. Conclusions

The economic impact of cholera in Mozambique was analyzed. The analysis is based on assumptions about the severity of the epidemic provided by IVI. Other assumptions included the

drop in business and tourism travel to the country, in food exports and in consumption of food away from home, and were drawn from historical experience of previous cholera and other infectious diseases epidemics.

The economic cost of an outbreak would amount to around 2.1% of GDP in the first year of the epidemic. This represents a significant, albeit manageable cost. In some sectors, such as tourism, some of this loss would probably be temporary. In others such as food exports, some of the loss could last several years.

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Appendix 10. Analysis of global cost effectiveness of cholera vaccination: methods, assumptions and results

1. Introduction

This appendix draws upon results from a number of other appendices to estimate the cost effectiveness of introducing oral cholera vaccine through preventive campaigns over the period 2015 to 2030. This section uses the vaccination program costs discussed in Appendix 7, the reductions in direct and indirect cholera cost of illness after vaccination, as well as the number of cases, deaths, and disabled adjusted life years (DALYs) averted to calculate cost-effectiveness. With this information, estimates of cost per case, death, and DALY averted by WHO region are made.

Results are shown for programs in which vaccination is provided for all ages one year and older and for programs that are limited to children age 1-14 years. This appendix also includes a sensitivity analysis to identify the greatest sources of uncertainty and how these parameters would influence the cost effectiveness estimates. The cost-effectiveness of using vaccines from the stockpile reactively is not included in this analysis due to a lack of data. However, results from existing studies on cost-effectiveness of introducing the vaccine in Haiti and Zimbabwe are discussed in Appendix 5.

2. Methods

Cost-effectiveness analysis is a standardized framework for comparing the costs and benefits of interventions. The costs of a vaccination program include both the fees paid to vaccine suppliers as well as program implementation costs. The benefits of vaccination include both improvements in health indicators based on averted illnesses as well as reduced cholera treatment costs and productivity losses. In order to compare cholera vaccination with other potential health investments, the following cost-effectiveness metrics will be calculated: cost per case averted, cost per death averted, or cost per DALY averted [Cook et al., 2008; Jeuland et al., 2009].

The incremental cost per DALY averted is calculated from the changes in cholera control program costs and health outcomes with and without introduction of cholera vaccination.[18] The incremental cost of vaccination includes the purchase price of vaccines plus freight and insurance and operational costs of cholera vaccination. In addition, the savings from direct costs of not treating cholera and indirect costs of time spent away from work for illness or for taking care of sick patients are also calculated. The net cost of the program is calculated by subtracting treatment cost savings and opportunity cost of time spent ill with cholera from total vaccination program costs.

The number of cases, deaths, and DALYs averted are used as health indicators to quantify the impact of cholera vaccination. The cost effectiveness of cholera vaccination is calculated with and without herd protection effects. Without consideration of herd protection,

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[18]For this analysis, we assume that cholera vaccination would occur in isolation. However, in many locations, it may be more efficient to combine cholera vaccination activities with other interventions such as health and hygiene education, or point of use water treatment programs.

only vaccinated persons are assumed to be protected at rates equivalent to the direct protection of vaccination.

Indirect or herd protection effects of cholera vaccination are based on the 1985 oral cholera vaccine trial in Matlab [Ali et al., 2005; Longini et al., 2007], as discussed in Appendix 8. As part of the global investment case for cholera vaccination, a dynamic model of cholera vaccination was undertaken for each WHO sub-region and is described in Appendix 8. The estimation of herd protection depends on both the number of people in each population group as well as group-specific coverage rates. The overall protection achieved through vaccination is thus a function of the coverage rates achieved.

DALYs averted are calculated using standard age weights and standard life expectancy following Fox-Rushby and Hanson [2001].

Table 1 shows the parameter assumptions on characteristics of cholera infection, the oral cholera vaccine, and costs by WHO region used in the cost-effectiveness analysis. The incidence rates are shown by four age groups.

The populations that are projected to be vaccinated vary by target and age group and estimates of the numbers of these populations are described in Appendix 7.

Vaccination impact

The impact of vaccination is estimated with and without consideration of herd protection impacts. Without consideration of herd protection, the impact of vaccination is simply the product of the baseline number of cases, vaccination coverage, and the direct effectiveness of vaccination by age group. The minimum number of cases averted by year and by age group within countries is

$$No\,cases\,averted_{i,t} = \cdot N_{i,t} \bullet I_i \cdot COV_{i,t} \cdot Effd_i \tag{1}$$

where $N_{i,t}$ is the number of people targeted for vaccination in group i in year t, I_i is the baseline incidence, $Effd_i$ is the direct effectiveness of vaccination, and $COV_{i,t}$ is the coverage rate. The total number of averted cases is the sum of age-specific cases across countries and over time

With consideration of herd protection, the entire community receives some protection through vaccination, although vaccinated persons are protected at a greater rate than unvaccinated persons. Herd protection effects for cholera vaccination are estimated via a series of dynamic models of cholera transmission with different vaccination strategies. The overall protection is calculated based on the number of cases predicted with and without the introduction of a vaccination program, assuming homogenous mixing of the populations targeted for vaccination. Comparison of herd protection effects between vaccinating two different age groups, only children or both children and adults, suggests a non-linear increase in protection relative to population-averaged coverage rates. For example, assuming coverage rates of 65% for adults and 50% for children in SEAR, vaccinating only children renders 58% protection overall for the population, while vaccinating both children and adults renders 75%.

Table 1. Parameter estimates for cost-effectiveness analysis

WHO region and mortality stratum	AFR					SEAR					EMR					Sensitivity Analysis
Age group	<1	1-4	5-14	15+	All	<1	1-4	5-14	15+	All	<1	1-4	5-14	15+	All	Range
Annual incidence rate (/1,000)	6.2-12.5	6.1-12.2	1.9-3.8	0.8-1.6	1.9-4.0	6.8	6.6	2.1	0.9	1.7	5.6	5.4	1.7	0.7	1.6	50-150% base case
Case fatality rate (%)			3.8%					2.5%					3.2%			1%-5%
Vaccination program operational assumptions																
Vaccine duration of protection			3 years					3 years					3 years			3-5 years
Vaccine wastage			5%					5%					5%			3-15%
Vaccine coverage of targeted population	0%	80% MCV	80% MCV	50% MCV		0%	80% MCV	80% MCV	50% MCV		0%	80% MCV	80% MCV	50% MCV		
Direct vaccination protection (without herd protection impact)	NA	70%	70%	70%	NA	NA	70%	70%	70%	NA	NA	70%	70%	70%	NA	Between effectiveness estimates with and without herd protection
Vaccination protection for 1-14years, with consideration of herd protection																
Overall protection	61%	63%	65%	59%	62%	57%	66%	66%	57%	61%	67%	74%	74%	66%	71%	
Vaccination protection for 1+ years, with consideration of herd protection																
Overall protection	68%	71%	74%	71%	72%	74%	79%	79%	75%	77%	77%	82%	82%	78%	80%	
Vaccination cost assumptions																
Vaccine procurement cost per dose, 2010 US$ (weighted average)*			$1.86					$1.86					$1.86			1.15-2.13
Vaccine delivery cost per dose, 2010 US$			$0.60					$0.60					$0.60			0.30-1.10
Assumptions for economic valuation																
Direct COI per case, 2010 US$			$11-15					$9					$9			0-300% of base case
Indirect COI per case, 2010 US$			$7-9					$7					$8			
Duration of illness			5 days					5 days					5 days			3-10 days
DALY weight			0.105					0.105					0.105			
Discount rate			0.03					0.03					0.03			0-10%

* This is the average weighted cost of the vaccine from 2014 to 2020, including 15% shipping and handling charges. The assumed vaccine price is $1.85 from 2015 to 2017 and $1.45 from 2018 to 2020.

The overall protection from the dynamic model is the weighted average reduction in cholera incidence rates for vaccinated and unvaccinated persons by age group. In the dynamic model, uniform coverage rates across WHO regions (e.g., 65% for children age 1-14 years and 50% of adults) are assumed. However, predicted demand is a function of MCV coverage rates by countries, and the impact by country is based on interpolation of dynamic model runs in which the coverage rates were varied.

Averted cost of illness through vaccination

Detailed cholera treatment cost estimates are available for four discrete locations: Kolkata, India, Matlab, Bangladesh; Beira, Mozambique, and Jakarta, Indonesia [Poulos et al., 2011]. Treatment costs were estimated from interviews of patients with laboratory-confirmed cases of cholera, examination of public facility treatment records, and operational costs. In Matlab and Beira, surveillance was undertaken at hospitals. In Kolkata and Jakarta, surveillance incorporated outpatient and inpatient treatment sites. The hospitalization rates were 22% and 37% for Jakarta and Kolkata, respectively, and average length of stay were 1.7 days in Matlab, 2.3 days in Kolkata, and 3.1 days in Beira. The sum of public facility and private out-of-pocket inpatient treatment costs varied from US$24 in Matlab to about US$180 in Jakarta. For outpatient treatment, the average cost of illness was about $22 in Jakarta.

The estimated direct cost of illness (COI) by WHO regions is summarized in Table 2. Proposed treatment regimens are based on standard WHO guidelines [WHO 2005]. It is assumed that all patients receive a series of antibiotics (erythromycin) and zinc. Mild cases (75%) are assumed to be treated with oral rehydration salts (ORS) at outpatient clinics. Severe cases (25%) require overnight stays at hospitals and rehydration with IV solutions. Drug costs are estimated from a published volume of standard drug costs [Management Sciences for Health, 2008]. Outpatient treatment costs and inpatient costs per night are estimated using standardized rates from the WHO Choice web site [WHO-CHOICE, 2009]. Based on WHO-CHOICE estimates, it is assumed that outpatient treatment requires services from community clinics, which is accessible to 80% of the surrounding population, and that inpatient treatment occurs at secondary hospitals with 80% occupancy.[19]

Using estimates of the average length of stay, the estimated inpatient treatment costs vary from US$23 in SEAR to US$35 in AFR in 2010 US$. Outpatient treatment costs are considerably less, about US$3.50-3.70 per case across regions. Inpatient treatment costs are similar to those reported by Poulos et al., US$26 in Matlab, US$29 in Kolkata, and US$43 in Beira and much less than reported for Jakarta US$190 in 2005 US$.

The indirect costs of cholera illness consist of the value of days of work lost due to cholera. In the surveys conducted by Poulos et.al. [2011], respondents were asked about whether other family members or friends were able to substitute their efforts to reduce productivity losses. Thus, estimates are less than if such substitution was not accounted for in the analysis. In Table 3, the average productivity losses are estimated at the four sites. The estimates vary from US$8 in Matlab to US$25 in Jakarta for hospitalized patients. For outpatient treatment, average productivity losses per case varied from US$3 in Kolkata to US$7 in Jakarta in US$2005. The estimated average productivity losses as a percentage of per capita GDP were used to estimate expected productivity losses in other countries using average rates of

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[19]In some locations, cholera patients are treated in isolation wards, which may increase costs. These potential extra costs are not accounted for in the analysis.

0.3% of GDP for outpatient cases and 1.8% of GDP for inpatient cases. All cost of illness estimates are varied between 0-300% in the sensitivity analysis.

Table 2. Estimates of direct (treatment) costs of cholera illness by WHO region, US$2010[*]

	AFR	EMR	SEAR	Source
Direct cost of illness (COI) per outpatient				
Cost per outpatient visit	2.5	2.6	2.4	WHO-CHOICE 2011
Medication cost for outpatient:				Management Sciences for Health (MSH) 2009
▪ ORS, weighted average for all ages	0.5	0.5	0.5	
▪ Antibiotics, weighted average for all ages	0.3	0.4	0.4	
▪ Zinc Supplement, weighted average for all ages	0.3	0.3	0.3	
Total Direct COI per outpatient	**5.3**	**4.5**	**3.9**	
Direct COI per inpatient				
Cost per hospital inpatient stay	30.9	19.9	18.4	
Average length of hospital stay, days	3	2	2	
Cost per hospital inpatient day	10.3	10.0	9.2	WHO-CHOICE 2011
Medication cost for inpatient:				Management Sciences for Health (MSH) 2009
▪ IV (Ringer Lactate Solution) weighted average for all ages	3.2	3.4	3.6	
▪ Antibiotics, weighted average for all ages	0.3	0.4	0.4	
▪ ORS, weighted average for all ages	0.7	0.7	0.7	
▪ Zinc Supplement, weighted average for all ages	0.3	0.3	0.3	
Total Direct COI per inpatient	**35.4**	**24.6**	**23.4**	
Average direct COI per case[*]	**11.5**	**9.0**	**8.5**	
* Patients are assumed to consist of 75% of outpatients and 25% of inpatients.				

The total (direct and indirect) costs of illness per patient are shown by region in Table 4.

162

Table 3. Estimates of indirect costs of cholera illness by WHO region, US$2010

	Matlab	N. Jakarta	Kolkata	Beira	Average
Indirect cost per hospitalized patient	8.7	26.5	13.4	17.1	
Indirect cost per outpatient	NA	7.3	3.3	NA	
GDP per capita	641	2,963	1,176	473	
Indirect cost as percentage of GDP per capita, hospitalized	1.4%	0.9%	1.1%	3.6%	1.8%
Indirect cost as percentage of GDP per capita, outpatient	NA	0.2%	0.3%	NA	0.3%

WHO region	AFR	EMR	SEAR
GDP per capita	1,152	1,189	1,041
Indirect cost per hospitalized patient	18.7-24.6	21.7	19.0
Indirect cost per outpatient	3.1-4.1	3.6	3.2
Indirect cost per patient*, weighted average	**7.0-9.2**	**8.2**	**7.1**
* Patients are assumed to consist of 75% of outpatients and 25% of inpatients.			

Table 4. Estimates of total costs (direct and indirect) of cholera illness per patient by WHO region, US$2010

WHO region	AFR	EMR	SEAR
Direct costs (weighted average of hospitalized and outpatient cases)	17.3	11.9	9.7
Indirect costs (weighted average of hospitalized and outpatient cases)	7.0 – 9.2	8.2	7.1
Total costs per patient	**24.3 – 26.5**	**20.1**	**16.8**

3. Results

Table 5 summarizes the cost-effectiveness estimates by WHO region. It should be noted that insufficient data were available to differentiate incidence and case fatality rates in the Small and Large target areas. Thus, the cost-effectiveness is the same for Small and Large Target areas. The discounted treatment cost savings and averted indirect cost-of-illness divided by discounted program costs are summarized in the table. Projected treatment cost savings and averted indirect COI are small relative to the expected cost of the intervention, across all programs and regions. As shown in Table 6, the direct treatment cost savings vary between 1-5% of program costs depending on region and consideration for herd protection. Averted indirect COI estimates also appear to be small relative to program costs, varying between 1-3.5%.

The net cost of vaccination was calculated based on the total cost of treatment less projected treatment cost savings and averted productivity losses. Table 4 summarizes the net cost per case averted, the net cost per death averted, and net cost per DALY averted, with and

without consideration for herd protection. The cost per case, death, and DALY averted are always lower for programs that target children relative to programs that target all ages.

In general, child vaccination programs are about twice as cost effective as the all-age vaccination programs. The cost per case, DALY, and death averted is smallest in the AFR region due to its high incidence and case fatality rates. The estimates for the other regions tend to be similar in magnitude. In general, it costs about US$190-330 per case averted for vaccination programs for children ages 1-14 after accounting for herd protection. The cost per case averted increase to about US$320-640 for programs in which all ages are vaccinated. The cost per death averted varies between US$4,800-11,700 for child vaccination programs and US$8,500-23,900 for all-age programs. The cost per DALY averted varies between US$150-780 for all types of vaccination programs when herd protection effects are accounted for.[20]

Table 5. Program cost effectiveness estimates by WHO region, 2014-2030

| WHO region	AFR		SEAR		EMR	
Number of countries	26		5		2	
Vaccination target (age group)	1-14	1+	1-14	1+	1-14	1+
With consideration of herd protection, using best estimate of vaccination costs						
Net vaccination cost/case averted, US$ 2010	185	322	303	618	333	644
Net vaccination cost/death averted, US$ 2010	4,856	8,465	11,747	23,925	10,391	20,135
Net vaccination cost/DALY averted, US$ 2010	151	268	383	785	329	640
Treatment cost savings (% of total cost)	5.4%	3.2%	2.9%	1.5%	2.4%	1.3%
Productivity savings (% of total cost)	3.5%	2.1%	1.9%	0.9%	2.2%	1.2%
Without consideration of herd protection, using best estimate of vaccination costs						
Net vaccination cost/case averted, US$ 2010	422	670	595	1,043	804	1,354
Net vaccination cost/death averted, US$ 2010	11,094	18,564	23,835	42,201	25,130	42,326
Net vaccination cost/DALY averted, US$ 2010	324	540	694	1,348	733	1,316
Treatment cost savings (% of total cost)	2.5%	1.6%	1.6%	0.9%	1.0%	0.6%
Productivity savings (% of total cost)	1.6%	1.0%	1.0%	0.5%	0.9%	0.6%

The consideration of herd protection effects has a large impact on cost effectiveness. When herd protection effects are accounted for, programs become about twice as cost effective.

These results were then compared to the weighted average Gross Domestic Product (GDP) per capita of the countries included in the analysis, by region, which were ≈$1,000 - $1,200. Using the thresholds established by the 2002 *World Health Report*, interventions with a cost/DALY averted of less than the GDP per capita are considered "very cost-effective", while

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[20]The incremental cost per DALY averted is calculated based on the difference in net vaccination costs divided by the difference in DALYs averted by region. The incremental cost per DALY estimates vary from US$150-890 with consideration for herd protection and from US$310-1,600 when herd protection effects are omitted. The incremental cost per DALY is a better benchmark for determining whether to target adults in addition to children because this approach does not combine the very cost effective child vaccination program with the less cost effective adult vaccination program in a single average cost measurement.

those with a cost/DALY averted of less than three times the per capita GDP are considered "cost-effective". The cholera vaccination programs for 1-14 year olds were found to be "very cost effective" across the WHO regions whether or not herd effects were incorporated into the analysis. The vaccination programs for all ages and above were found to be very cost effective when herd protection is accounted for and are cost effective when herd protection effects are omitted.[21]

Figure 1. Estimates of cost per DALY averted by cholera vaccination by WHO region[a], with and with herd effects taken into account
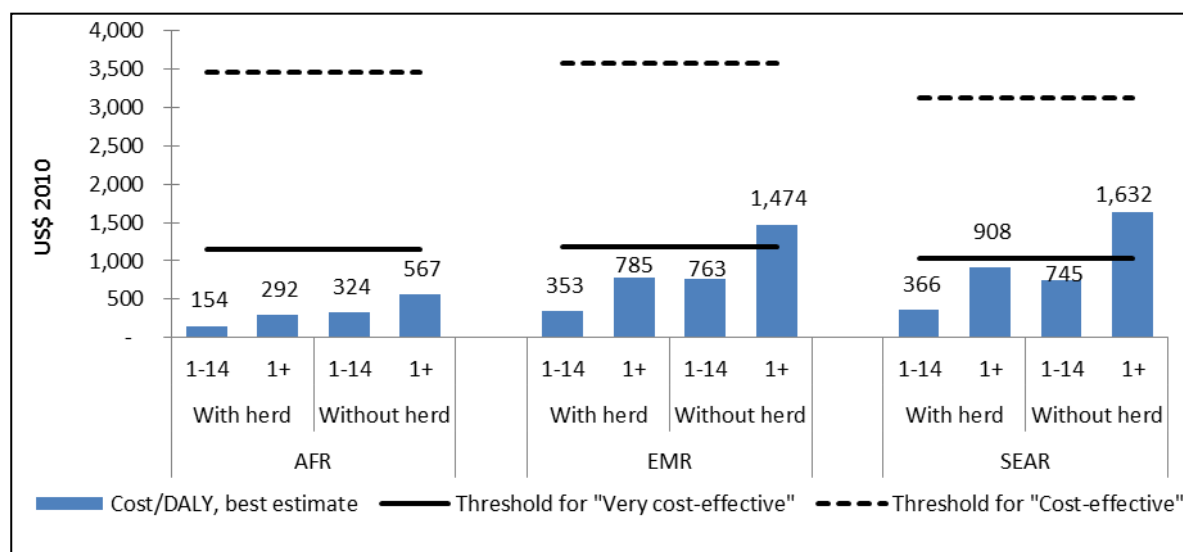
[a] For North Korea, the regional average GDP per capita is used as a threshold for "Very cost-effective"

Sensitivity analysis

This section examines the uncertainty in cost effectiveness analyses. The estimates for the sensitivity analyses use the baseline values and uncertainty ranges indicated in Table 1 Figure 2 presents the very cost effective isoquants for varying incidence rates, case fatality rates, and vaccination price + delivery costs. Each line represents a 'very cost effective' threshold for incidence and costs at varying case fatality rates. If the incidence and costs are to the upper left of the lines, the program would not be very cost effective. If the incidence and costs are to the lower right, the program would be very cost effective. In addition, the best estimates of incidence and cost per person, including the price and delivery costs for two doses, are shown in the figure. Findings are similar for the EMR regions, of which the latter are not shown here.

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[21] Again one should consider the incremental cost per DALY in adding adult vaccination to child vaccination programs when determining cost effectiveness.

Figure 2. Very cost effective thresholds for AFR and SEAR by target age
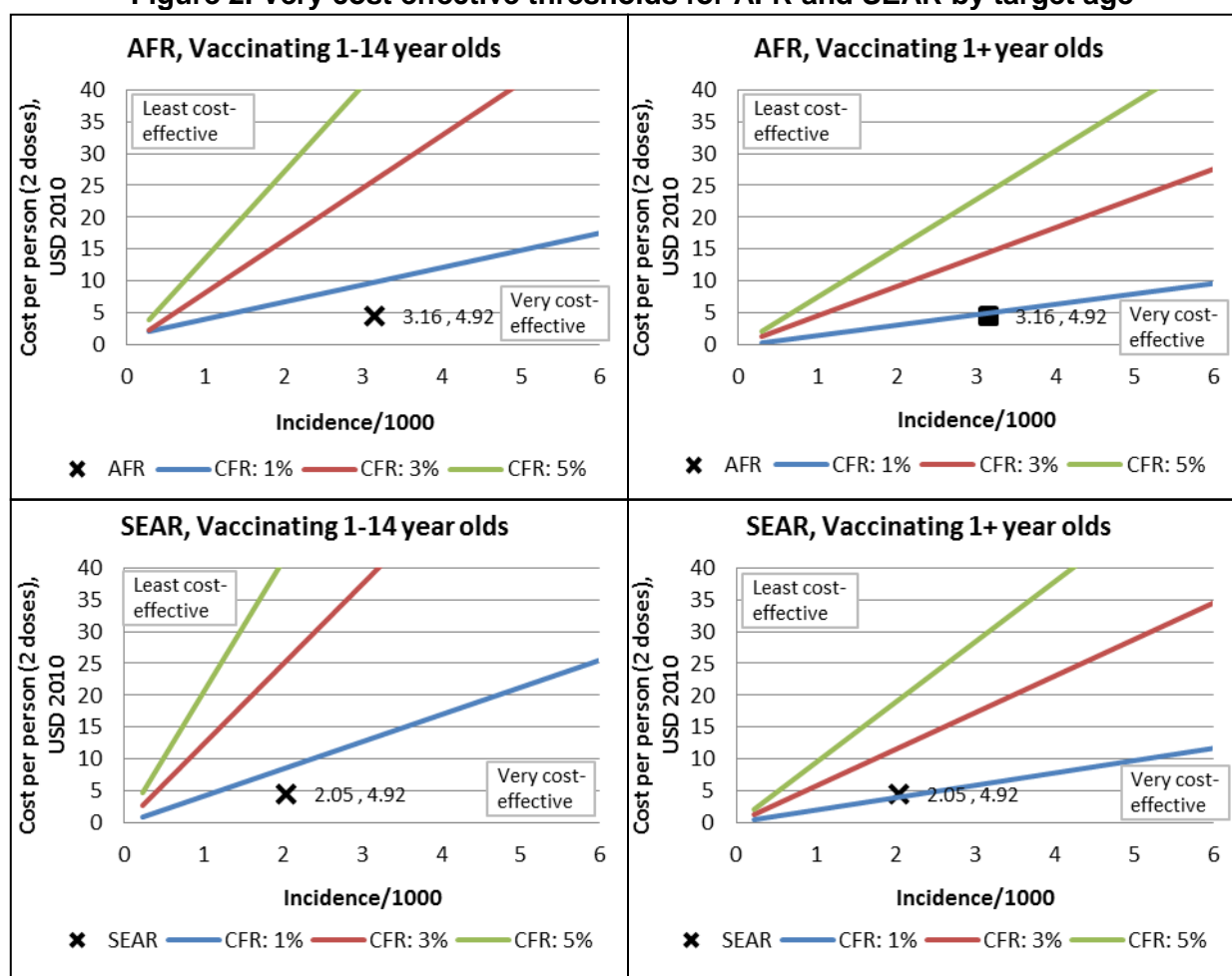
The uncertainty in case fatality rates is very important for determining cost effectiveness. The 3% and 5% rates allow for a large range of incidence rates and/or cost estimates to be very cost effective. For case fatality rates equal to or less than 1%, programs become much less likely to be very cost effective. The 1% isoquants intersect the baseline estimates of incidence rates and cost per person estimates for both AFR and SEAR, indicating that programs would not be very cost effective at lower incidence rates or higher costs than the assumed baseline values. For the all-age vaccination programs, programs would not be very cost effective if case fatality rates were 1%.

The tornado charts in Figures 3a and 3b indicate the range in cost per DALY as each parameter is varied across its uncertainty range, one variable at a time, using Monte Carlo simulations. For each random variable, the probability density function (pdf) is assumed to be triangular, based on the median estimate and bracketed lower and upper bound values summarized in the table. The cost per DALY averted is calculated for each of 10,000 random parameter draws by WHO region and by program type (children only versus all ages).

Figure 3. Tornado charts of parameter uncertainty in cost per DALY estimates for AFR

a. Vaccinating children aged 1-14 years

b. Vaccinating persons aged 1 year and above
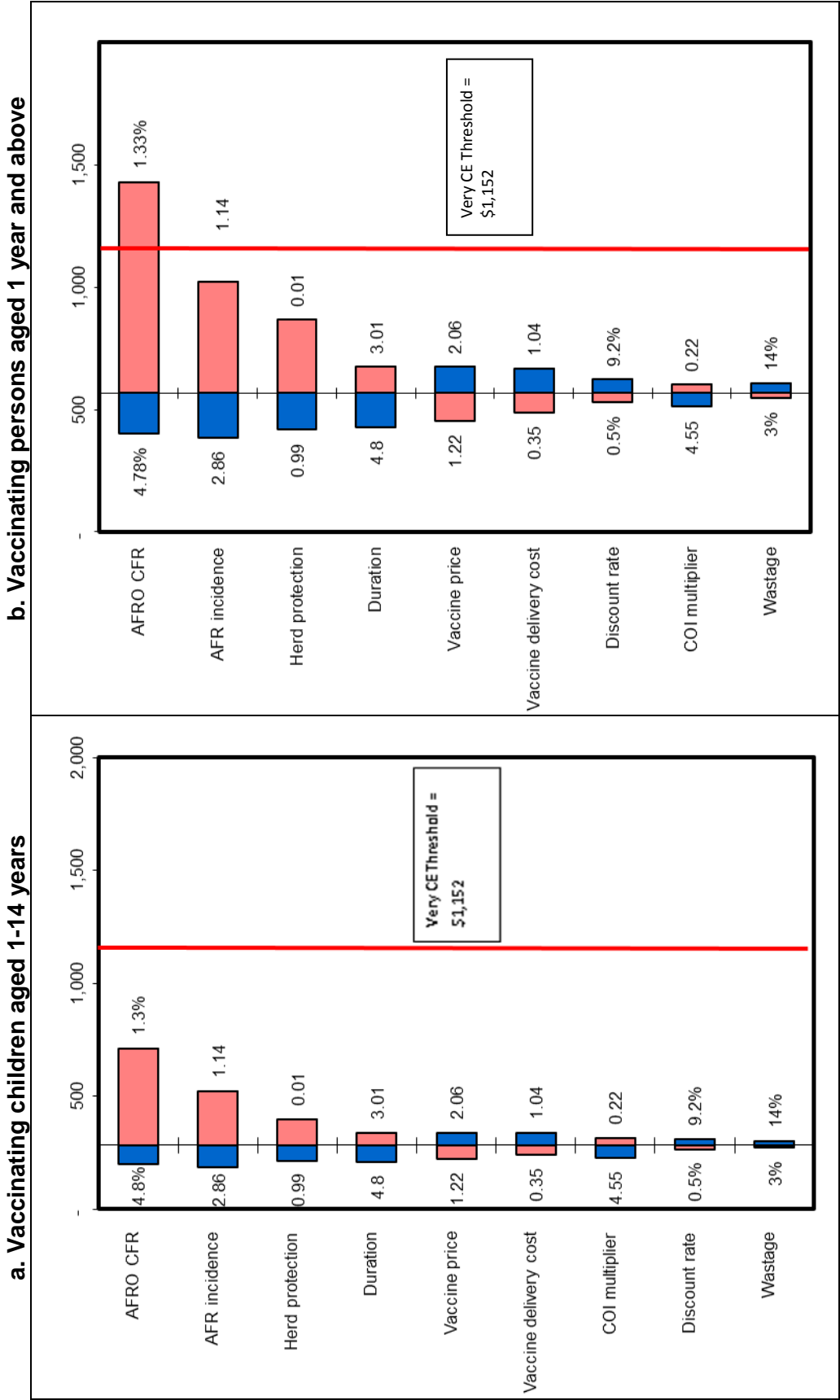
In the tornado chart, the baseline estimate is indicated by the vertical line. The largest spread is identified for the case fatality rate, followed by incidence rates, and the herd protection parameter. Thus, assuming regional variation in incidence and case fatality rates, cholera vaccination would be most cost-effective in areas with higher incidence and case fatality rates and where herd protection effects would be most likely. Figures 3a and 3b shows results for the AFR region; similar results are found for the other sub-regions. The spread in cost effectiveness is about twice as great for the all ages vaccination program relative to the children-only program.

After incidence, CFR, and herd protection, the next most important parameters are the vaccination costs (both price and delivery costs) and the duration of protection. Finally, the COI multiplier, discount rate, and wastage rate have relatively minor impacts on cost effectiveness. An analysis of variance for the multivariate results indicates similar findings. The parameters with the greatest impact on variances in the multivariate analyses are case fatality rate (35%), incidence rate (25%), and herd protection effect (20%). Uncertainty in program costs (7.5%) and vaccine duration (7%) are also important. Uncertainty in COI estimates, wastage rates and discount rates account for less than 3% of the uncertainty combined.

The findings that cholera vaccination is very cost effective for children in at-risk populations as well as cost-effective for adults hold across a broad range of parameter estimates, although cholera incidence and case fatality rates should be reconsidered if other public health interventions succeed in reducing cholera risks.

4. Conclusions

This appendix examines the cost effectiveness of cholera vaccination. Child vaccination programs appear to be very cost effective across a range of parameter estimates while vaccination for adults is cost-effective. The parameters with the greatest associated uncertainty include case fatality rates, incidence rates and herd protection assumptions. Specifically, cholera vaccination is found to be very cost effective at case fatality rates greater than 1%. Where case fatality rates are reduced to less than 1%, cholera vaccination becomes less cost effective. Thus, prior to introducing cholera vaccines, surveillance should be conducted to verify incidence rates and case fatality rates due to cholera. After initiating vaccination campaigns, it will be useful to continue surveillance efforts to verify expected herd protection effects of cholera vaccination.

The impact of herd protection is another important consideration for assessing the cost effectiveness of cholera vaccination. Currently, the only published estimates are available from the Matlab trial. Additional assessments are underway for the Kolkata trial and a Zanzibar demonstration project with Dukoral®; however, results are currently unpublished. The herd protection resulting from child vaccination programs should be evaluated for comparison to the Matlab, Kolkata, and Zanzibar trials in which adults were also vaccinated.

As cholera case fatality and incidence rates decline, the decision to maintain vaccination should be revisited based on estimated cholera incidence and case fatality rates assuming vaccination were to cease. In addition, public health decision makers should monitor the progress of new approaches to predict cholera outbreaks associated with specific climactic events such as El Nino [Pascual et al., 2000; Anyamba et al., 2006; Olago et al., 2007]. These may help to identify when vaccination efforts should be expanded beyond communities at greatest baseline risk. At the same time, special attention should be paid to the influence of global warming on the global incidence and geography of cholera. Many studies suggest that global warming may increase cholera incidence rates [Lipp et al., 2002; Emch et al., 2008;

Fernández et al., 2009]. Thus, cholera surveillance outside of areas targeted for vaccination should continue to determine if vaccination efforts should be expanded in light of increased spatial occurrence of cholera due to global warming.

This cost-effective analysis differs from other analyses [MacPherson and Tonkin, 1992; Murray et al., 1998; Naficy et al., 1998] since it makes different assumptions about case fatality rates, incidence rates, price per dose and other parameters. A cost effectiveness analysis of cholera vaccination was recently published for Kolkata, India; Beira, Mozambique; Matlab, Bangladesh; and Jakarta, Indonesia [Jeuland et al., 2009] where lower case fatality rates (3-3.8% vs. 1%) and vaccine efficacy rates (61-70% vs. 50%) were assumed. In addition, the price per vaccine dose was assumed to be higher in these analyses (US$1-1.85 per dose vs. US$0.60 per dose). The higher case fatality rates are assumed in our analysis because better treatment is likely to be available in the selected sites in Jeuland et al. than in the general at-risk population for cholera. The higher vaccine efficacy rates were assumed because of additional findings on the vaccine observed after the publication of the earlier study.

In general, the findings of this study and the earlier Jeuland study (2009) are similar. Cholera vaccination is shown to be very cost effective for child vaccination programs when herd protection is accounted for. In this study, cholera vaccination is still generally cost effective without consideration of herd protection due to the higher efficacy and case fatality rate estimates. All of the other studies are based on either limited populations or hypothetical population groups, while this analysis uses a global perspective.

In conclusion, it appears that cholera vaccination is very cost effective for children in at-risk populations as well as cost-effective for adults. These findings hold across a broad range of parameter estimates, although cholera incidence and case fatality rates should be reconsidered if other public health interventions succeed in reducing cholera risks.

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Appendix 11. Summary of the country investment case study on cholera vaccination: Bangladesh

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, its Expanded Program on Immunization (EPI), and other information needed to conduct the study. This information was supplemented by data from past research conducted by the 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 grey 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 [Sur et al. 2005]. 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 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 high risk for cholera.

These districts contain 51% of the entire population and have an estimated average annual incidence rate of 3/1,000. 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 [Sack et al. 2003] — 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 (Harris et al. 2008). 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 for the World Health Assembly calling for intensified global efforts to control cholera, including through mass vaccination campaigns.

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) [Poulos et al. 2011]. 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 alone cost the shrimp industry almost $15 million in 1997 [Cato and Subasinge 2003].

Current cholera control measures in Bangladesh

An estimated 22% of the rural population does not have access to safe drinking water [UN Statistics Division 2009], 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; only around one-half of Dhaka's population is now estimated to have access to a safe, 24-hour water supply [ADB 2007]. Only an estimated one-third of the rural population and 58% of the urban population have access to adequate sanitation facilities [UN Statistics Division 2009].

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. It currently, consists 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 [Pathey 2007] — 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

In February 2009, 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. 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 traveler's 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 applied for WHO pre-qualification of the vaccine.

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. 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.

Since it is not yet certain how many producers will enter the cholera vaccine market, the future global production capacity of the vaccine is not yet known. However, Shantha has made plans to build at least one dedicated cholera vaccine facility, each with an initial annual capacity of 10-20 million doses, potentially growing to 25-30 million doses.

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 efforts 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 a 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 [Bangladesh EPI 2009]:

- 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 2014.

The analyses assume use of the WC (Shanchol™) vaccine, which has a current public sector price of $1.85/dose. We assume that by 2014 the price of the WC vaccine will be reduced to $1.45 per dose, as a result of improvements increasing production yield and efficiencies, and 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.

Table 1. Estimated cost, impact and cost-effectiveness of four scenarios of cholera vaccination in Bangladesh

Parameter	Large Target (entire populations in high-risk districts		Small Target (urban slums +selected rural populations in high-risk district)	
	1-14 year olds	1+ year olds	1-14 year olds	1+ year olds
Estimated number people vaccinated per year	6.1 million	15.8 million	2.1 million	5.5 million
Number doses required per year (2 doses + 5% wastage)	12.8 million	33.2 million	4.5 million	11.6 million
Annual vaccination costs (US2010 $)	$28 million	$72.7 million	$9.8 million	$25.5 million
Cases prevented per year	154,000	194,000	54,000	68,000
Percent reduction in annual incidence	43%	54%	15%	19%
Cases averted from 2014-2030	2.6 million	3.3 million	900,000	1.1 million
Deaths averted from 2014-2030	39,000	49,000	14,000	17,000
Cost-effectiveness ratio (cost/DALY saved)	$350	$760	$350	$760
Degree of cost-effectiveness per WHO definition	Very cost-effective	Cost-effective	Very cost-effective	Cost-effective

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 million per year, save $2.6 million per year in cost-of-illness, prevent 154,000 cases each year (≈2.6 million from 2014 to 2030), and ≈39,000 deaths over this time period, reducing the national cholera incidence by 43%. This program would be "very cost-effective" (cost/DALY averted of $350), using the WHO definition of cost/DALY averted is less than or equal to the country's gross domestic product (GDP) per capita [WHO 2001].

Vaccinating all persons one year and older under the Large Target scenario would increase the numbers of persons vaccinated each year to almost16 million, cost ≈$73 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 17-year period from 2014 to 2030, this program would prevent 3.3 million cases and 49,000 deaths. This option is less cost-effective than the

children's only program (with a cost/DALY averted of $760, 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 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 17 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 ≈$25.5 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's-only Small Target option, by 26-29% for either the children's only Large Target option or the all-ages Small Target option; and by 75% if all ages are vaccinated under the Large Target scenario. The cost of the program to vaccinate 1-14 year olds throughout the 28 high-risk districts (Large Target) — at $28 million — would be around 50% of the annual cost of vaccinating infants with either rotavirus vaccine or the seven-valent conjugate pneumococcal vaccine (estimated to cost $55 million and $58 million per year, respectively), if one considers the full cost of the programs and assumes the Government will eventually assume their costs. Vaccinating all eligible ages under the Large Target scenario would cost roughly the same as nation-wide rotavirus or pneumococcal vaccination for infants.

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.

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International Vaccine Institute
SNU Research Park, San 4-8
Nakseongdae-dong, Kwanak-gu
Seoul 151-919 Korea