

ENTERIC AND DIARRHEAL DISEASES

STRATEGY OVERVIEW

OUR MISSION

Guided by the belief that all lives have equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. Our Global Health Program supports this mission by harnessing advances in science and technology to save lives in poor countries.

We focus on problems that have a major impact on people in the developing world but get too little attention and funding. Where proven tools exist, we support sustainable ways to improve their delivery. Where they don't, we invest in research and development of new interventions, such as vaccines, drugs, and diagnostics.

Our financial resources, while significant, represent a very small fraction of the overall funding needed to improve global health on a large scale. We therefore advocate for the policies and resources needed to provide people with greater access to health solutions. Strong partnerships are also essential to our success in making a difference and saving lives.

THE OPPORTUNITY

Diarrheal deaths have steadily dropped over the last 30 years due to advances in water and sanitation, per-capita income, antibiotics, and vaccines. Though these improvements have largely been seen in developed countries, the opportunity to prevent and treat enteric diseases in the developing world is greater than ever. Today there are established, low-cost interventions such as oral rehydration therapy, breastfeeding and good hygiene, and new tools such as zinc therapy. Most promising, there are now safe and effective vaccines for rotavirus, cholera, and typhoid.

Unfortunately, diarrheal diseases remain the second-leading cause of child death worldwide, killing nearly 1.7 million children annually and causing the hospitalization of millions.¹ Enteric and diarrheal diseases include infectious diarrhea and non-diarrheal enteric diseases such as typhoid (*Salmonella typhi*, *Salmonella paratyphi*),

hepatitis A and E, geohelminths (worms), and a host of other viral, bacterial, and parasitic pathogens. Only 4.4 percent of global health funding goes toward diarrheal-disease research and development, and it remains an issue with very few dedicated advocates.² Repeated bouts of diarrhea and persistent diarrheal disease—typically 2 to 10 episodes of diarrhea annually per child—radically impairs gut function, which is the single greatest contributor to childhood malnutrition and growth retardation.³

OUR STRATEGY

Our long-term vision is that children in developing countries are protected from or effectively treated for enteric and diarrheal diseases at the same rate as children in developed countries. A number of low-cost interventions exist and are effective for reducing child deaths due to these diseases, but today they are not available for many people in developing countries.

For those aspects of diarrheal disease that lack evidence-based solutions, we are investing in the research and development of new tools, and designing an integrated strategy for the delivery of both new and existing interventions (e.g., vaccines, oral rehydration solution with zinc supplements, and drug treatments). For prevention, we're supporting the development and delivery of safe and effective vaccines and other tools; the development of improved water, sanitation, and hygiene systems; and the promotion of nutritional practices that diminish diarrhea. We are also investing in treating diarrhea more effectively through the development and delivery of innovative interventions. Underlying this focus, we invest in epidemiology and biologic research to improve understanding of the burden and mechanisms of enteric diseases in developing countries. The global health community is not paying a great deal of attention to enteric and diarrheal diseases at the moment, but we're working to engage other partners.

INTERVENTION AREAS

Close critical science and knowledge gaps

There are major gaps in the global health community's understanding of diarrhea. Malnutrition and diarrheal diseases are linked in a complex, vicious cycle, as undernutrition contributes to the severity of diarrheal diseases, and diarrheal infections affect the gut's capacity to absorb nutrients.³ However, the mechanisms underlying these relationships are poorly understood. This lack of knowledge impedes the development of new and more effective interventions. Research initiatives aim to erase this knowledge gap and guide the rational development of better vaccines and treatments.

We are funding two initiatives that will provide comprehensive information on the pathogen epidemiology and the burden of diarrheal disease in developing countries. This includes the **Global Enterics Multicenter Study**, hospital programs in seven countries of Africa and Asia. This study will quantify the disease burden and identify the microbiologic (viral, bacterial, and parasitic) etiology of severe diarrheal disease among children younger than 5 years of age. It will also help better prioritize pathogen-specific interventions and establish data for subsequent trials targeting diarrhea, as well as calculate the financial cost of preventing and treating diarrhea. We also are funding a grant for the **Malnutrition-Enteric Disease (MAL-ED) Network**, which incorporates epidemiology and pathophysiology in a longitudinal study of children from birth to 24 months, to better understand pathogen-related undernutrition and impairment of gut and immune function.

Develop innovative vaccines

It is estimated that existing vaccines for rotavirus, cholera, and typhoid could address approximately 25 percent of child deaths due to enteric and diarrheal diseases. In particular, vaccination offers the best hope for preventing severe rotavirus illness, as the disease cannot be treated with antibiotics or other drugs, and can infect children regardless of hygiene practices or access to clean water. We support the development of more affordable vaccines against enteric and diarrheal diseases. To ensure access to such vaccines in the developing world, our strategy prioritizes the development of first- or second-generation vaccines by low-cost manufacturers in endemic countries. Details of our investment activities by disease follows.

Rotavirus

Our investments helped support the development, licensure, and current rollout of two orally administered, live, attenuated vaccines against the disease—Rotarix®

from GlaxoSmithKline and RotaTeq® from Merck & Co.—through the rotavirus ADIP (Accelerated Development and Introduction Plan) funded by the **GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation)**.

Based on results from recent trials, both vaccines are now licensed for use and are recommended by the **World Health Organization (WHO)** to be included in the routine immunization schedules of countries around the world.⁴

To help ensure the availability of rotavirus vaccines in endemic countries, we are supporting **PATH** in accelerating the development of safe, effective, and affordable new vaccines by developing-country manufacturers. **Bharat Biotech International** in India is currently developing a naturally attenuated strain (116E) isolated from infants.

Cholera

Until recently, there was one internationally licensed oral cholera vaccine available (Dukoral®, a killed, whole-cell plus toxin B subunit vaccine produced by Crucell/SBL Vaccines). However, only Vietnam, which began using a locally produced version in 1997, has employed the vaccine, due to its prohibitive cost.

In July 2006, we provided funding to the **International Vaccine Institute (IVI)** to implement the **Cholera Vaccine Initiative (CHOVI)**, which aims to develop and deploy safe and effective oral cholera vaccines in populations at risk for endemic or epidemic cholera. The initiative is focusing on the development and testing of two oral cholera vaccines: 1) a newly reformulated killed, whole-cell vaccine based on the one used in Vietnam, and 2) a live, attenuated Peru-15 strain vaccine.

Because the approved killed, whole-cell cholera vaccine requires two doses and provides only moderate levels of protection (60 percent to 80 percent), IVI is also developing a live-attenuated oral cholera vaccine that could confer high-grade, long-term protection after a single dose.

Typhoid

Two types of vaccine for typhoid are currently licensed and widely used worldwide: a subunit (Vi) vaccine administered by intramuscular injection, and a live, attenuated *S. typhi* strain (Ty21a) for oral immunization. Several typhoid vaccination programs that involve annual child-vaccination campaigns using the Vi vaccine have been carried out in Asia. A recent study showed the vaccine was effective in young children and protected unvaccinated neighbors of Vi vaccinees.⁵

We are supporting the IVI and its work with **Shantha Biotech International (Shantha)** in India toward the development and licensure of a second-generation

conjugate vaccine that can be effective in younger age groups. This vaccine is currently in pre-clinical trials and is expected to start Phase I/II clinical trials in 2010.

Escherichia coli and *Shigella* vaccines

The leading bacterial causes of diarrhea are enterotoxigenic *Escherichia coli* (ETEC) and *Shigella*, which, combined, are responsible for approximately 200,000 deaths of children each year. Both are becoming increasingly more resistant to the antibiotics most commonly used for treatment. Therefore, we see the development of vaccines against both bacteria as critical in preventing disease in populations most at risk, especially young children.

We are supporting PATH to develop ETEC and *Shigella* vaccines that induce potent, broadly reactive, and persistent immunity and are effective in preventing disease in developing-country populations.

Our short-term focus is to ensure proper execution of the ongoing and planned Phase I and II vaccine trials. In the long term, we will monitor our success based on the number of vaccines that successfully make it through all stages of development, licensure, WHO prequalification, the GAVI Alliance adoption, vaccine procurement, and vaccine dosage delivery.

Research diarrhea biomarkers and host mechanisms

We are assessing the potential role and impact of clinical diagnostics and more elaborate tests of the biology of enteric infections and their impact on the host. Improved and increased availability of diagnostics for acute diarrhea could improve the impact of therapy through better drug selection and reduction in the risk of antibiotic resistance.

We are also funding a learning agenda on tropical enteropathy, gut immune dysfunction, and biomarkers and genomic markers for these conditions, to identify key gaps in knowledge. Understanding such gaps may allow insights into next-generation vaccine and adjuvant design as well as better micronutrient and therapeutic approaches to gut health. Identification of protection biomarkers, due to either natural or induced immunity, will assist in better candidate selection and improve vaccine trials.⁶ In recognition of these significant needs, we are also beginning to test bold and unconventional ideas within the Grand Challenges Explorations (GCE) initiative, through a streamlined application and funding process. GCE grants in the area of diarrheal diseases include funding for:

- improving vaccine responses by manipulating gut flora
- interrupting cholera colonization by stopping cell-to-cell signaling

- developing a self-adjuvanting vaccine for ETEC

We need new tools and improved biomarkers to further develop therapeutic interventions; to manage the effects of infectious pathogens, including stunting (impaired growth) and immune dysfunction; and to aid our understanding of disease pathogenesis. Sensitive, accurate, non-invasive markers of early gut dysfunction, micronutrient/nutritional status, and mucosal immune status are essential to finding and developing the next generation of vaccines, therapeutics, and nutritional tools. Investigations of genetic and environmental risk factors of impaired childhood development will shed light on the critical roles and interplay of nutrition, gut function, microbiome, and population genetics that lead to biomarkers for assessment of health status and nutrition inadequacy in children. These markers will likely include profiles of pathogen and communal gut microbes (gut microbiome) and indicators of the host (child) response.

Develop and increase uptake of novel therapeutic interventions

Very few treatments for specific diarrheal pathogens exist. In many parts of the world, diarrhea is routinely treated with antibiotics, regardless of the underlying cause. However, antibiotics are ineffective against many pathogens, and indiscriminate use of such drugs contributes to drug resistance.

Since the 1980s, the administration of oral rehydration therapy (ORT) using oral rehydration salt (ORS) solution has been the cornerstone of international programs for the control of diarrheal diseases. An estimated 50 million lives have been saved due to the use of ORS, which counters dehydration.⁷ However, while ORS helps counter fluid loss due to diarrhea and promotes intestinal fluid absorption, it is ineffective in reducing stool output in acute watery diarrhea and in killing the pathogens responsible for diarrhea.

Recently, zinc taken with ORS has been shown to significantly reduce deaths when used as part of the ORT regimen.⁸ Zinc considerably reduces the duration and severity of diarrhea episodes, decreases stool output, lessens the need for hospitalization, and may also prevent future diarrhea for up to three months.⁹ In 2004, WHO and the **United Nations Children's Fund (UNICEF)** recommended the use of a 10- to 14-day zinc treatment together with ORS as a two-pronged approach to treat acute diarrhea in children.¹⁰

Considering the great promise the ORS-zinc combination holds in reducing diarrheal disease and deaths, we are investing in approaches to drive the adoption of this intervention on a much larger scale than has been achieved

so far. We are investing in the identification of optimal products and formulations of the ORS-zinc combination, and working with manufacturers to ensure a reliable and affordable supply.

Through a grant to the **Institute for OneWorld Health (iOWH)**, we are also investing in the development of novel, safe, effective, and affordable therapies to complement ORS and zinc. iOWH is developing therapies that would reduce the impact of secretory diarrhea by preventing fluid loss, dehydration, and death.

We are also learning about other treatments, such as antimicrobials or nutrient supplements, that would shorten the duration of diarrhea, decrease transmission of the microbe, and decrease the risk of long-term gut dysfunction.

Promote effective nutritional practices

There is a strong interaction between infectious enteric disease and undernutrition. For many years, it has been recognized that poor nutrition contributes to enteric and other infections, but we now appreciate that in these vulnerable populations the reverse is also true. We are working toward developing and delivering a set of proven interventions to ensure adequate nutrition of infants and young children. These include exclusive breastfeeding for the first six months of life; the addition of nutrient-dense complementary foods beginning at age six months; and the use of proper feeding practices, such as immediate and continued breastfeeding for 24 months. Additional details about this work are included in our Nutrition strategy.

Improve water, sanitation, and hygiene

Enteric and diarrheal diseases thrive where people don't have safe water, adequate sanitation facilities, or effective handwashing routines. Through our Global Development Program, we work with partners around the world to provide improved water, sanitation, and hygiene services and technologies.

PROGRESS

We have made global investments in enteric and diarrheal diseases since 1999. Through the work of many great partners, we now have new insights regarding pathogen burden and some early discoveries of new vaccines and other interventions that are in varying stages of development.

Vaccines

Rotavirus vaccine

- A recent WHO recommendation for rotavirus vaccine worldwide has led GAVI to plan to roll out vaccine introduction in 42 GAVI-eligible countries.

- Two orally administered, live, attenuated vaccines against rotavirus—Rotarix® from GlaxoSmithKline and RotaTeq® from Merck & Co.—are now licensed for use and are recommended by WHO to be included in the routine immunization schedules of countries around the world.¹¹

Cholera vaccine

- IVI successfully completed the technology transfer of the modified killed, whole-cell vaccine to Shantha in India, and the vaccine was licensed in India in February 2009. Shantha will apply to WHO for pre-qualification of the vaccine.
- The live, attenuated vaccine candidate Peru-15 was found to be safe and immunogenic in Phase I/II trials in children and adults conducted in Bangladesh, and may represent a next-generation cholera vaccine.¹²

Typhoid vaccine

- A study published in 2009 of the administration of the Vi polysaccharide vaccine in more than 37,000 slum-dwelling residents in Kolkata, India, showed an overall protective effectiveness of 61 percent, and 80 percent for children between the ages of 2 and 5.⁵

Therapeutics

Zinc and ORS

- A project completed in early 2009 by ICDDR,B, **Scaling up Zinc Treatment for Young (SUZY)** in Bangladesh, was the first national scale-up program to introduce zinc. This project made “Baby Zinc” into a household name in Bangladesh, recognized by two-thirds of families living in urban slums and more than half of those living in rural areas across the country. While actual use of zinc to treat diarrhea lagged behind awareness, the outputs of the project included a novel vanilla-flavored dispersible tablet formulation, a strong media-marketing campaign, commitments of provider networks to incorporate zinc into their treatment protocols, technical assistance to other countries, and a series of groundbreaking research reports.^{13,14,15,16,17,18}

CHALLENGES

Our biggest challenge in reducing enteric and diarrheal diseases is that the global community, in both the private and public sectors, is still not sufficiently committed to this cause. Other than rotavirus, diarrheal vaccines do not have a large enough market for investment by major vaccine manufacturers. Therefore, funding for core research support has been dependent on governments' investments in product development, which have been limited. We are working to remedy this by developing partnerships with stakeholders and donors to improve awareness of the problems and

opportunities, better define barriers to investment, and identify solutions to address the funding deficiency.

THE WAY FORWARD

The fight against diarrhea cannot be won without our partners in advocacy, science, academia, government, health, development, and philanthropy. We look toward to working with our partners to rebuild momentum and overcome the devastating toll diarrhea takes on children, families, and communities around the world.

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TO LEARN MORE

About the Global Health Program:
www.gatesfoundation.org/global-health

About Enteric and Diarrheal Diseases:
www.gatesfoundation.org/diarrhea

Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people's health and giving them the chance to lift themselves out of hunger and extreme poverty. In the United States, it seeks to ensure that all people—especially those with the fewest resources—have access to the opportunities they need to succeed in school and life. Based in Seattle, Washington, the foundation is led by CEO Jeff Raikes and Co-chair William H. Gates Sr., under the direction of Bill and Melinda Gates and Warren Buffett.

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