

Diarrheal Diseases Fact Sheet

Diarrheal diseases account for approximately 2 million deaths annually in children under the age of 5. Disease and death caused by diarrhea is a global problem, but is especially prevalent in developing countries. International programs encouraging the use of oral rehydration therapy (ORT) have greatly reduced infant mortality in recent years by treating dehydration. However, diarrheal diseases remain a serious public health problem and continue to be a leading cause of disease and death in children worldwide. With approximately 4 billion acute cases annually among children, there is an urgent need for safe and affordable anti-diarrheal drugs to treat infants and children in conjunction with ORT.

OneWorld Health's Role

The Institute for OneWorld Health is assembling a portfolio of product candidates that will address various aspects of diarrheal diseases, with a special focus on the needs of young infants and children.

OneWorld Health has conducted searches to license potential drug candidates and consulted with leading researchers to evaluate promising products and identify the key challenges in development. In 2004, with a grant from the Bill & Melinda Gates Foundation, the Institute for OneWorld Health also undertook a landscape analysis to survey vaccine candidates for diarrheal diseases, and examine infrastructure necessary to support a concerted effort in enteric vaccine development. In collaboration with NIAID and the FDA, OneWorld Health organized a workshop with international vaccine experts in April 2004.

OneWorld Health also raises awareness of the toll of diarrheal diseases among the tropical health scientific community, by sponsoring symposia, such as *"Enhancing ORT: Current status and future directions"* in 2005 and *"Getting In-Zinc: A discussion of zinc supplementation to combat diarrheal and other infectious diseases"* in 2006, to create opportunities for experience sharing and discussion.

A grant from the Lehman Brothers Foundation in 2005 is enabling OneWorld Health to evaluate early-stage pediatric diarrhea compounds and accelerate the selection of promising drug leads.

A grant from the Bill and Melinda Gates Foundation in 2006 for \$46.07M is enabling OneWorld Health to develop safe, effective and affordable anti-secretory drugs to be used as an adjunct to ORT in adults and children with life-threatening secretory diarrhea, such as cholera and enterotoxigenic E.coli (E.coli), which are responsible for up to 40% of reported cases of diarrheal disease in developing countries. OneWorld Health is collaborating with Professor Alan Verkman of the University of California at San Francisco (UCSF) and BioFocus (UK) to further optimize and develop novel anti-secretory drug candidates that block the cystic fibrosis transductance regulator (CFTR) which is a key mechanism by which cholera and E.coli toxins drive massive intestinal fluid loss. OneWorld Health is also collaborating with the Centre for Health and Population Research in Bangladesh (ICDDR,B) on other research opportunities related to iOWH's emerging diarrheal disease portfolio.

Disease Transmission

A major challenge to combating diarrhea is the number of disease-causing pathogens including bacteria, viruses and parasites.

- **Bacteria:** Several types of bacteria, often consumed through contaminated food or water, can cause diarrhea. Common culprits include *E. coli*, salmonella, shigella and cholera.
- **Viral infections:** Rotavirus is the most significant viral pathogen, causing diarrhea particularly in young children.
- **Parasites:** Parasites can enter the body through food or water and settle in the digestive system. Parasites that cause diarrhea include *Giardia lamblia*, *Entamoeba histolytica* and *Cryptosporidium*.

Disease Characteristics

The primary cause of death from diarrheal diseases is dehydration. As dehydration worsens, symptoms progress from thirst, restlessness, decreased skin turgor and sunken eyes to diminished consciousness, rapid and feeble pulse and low or undetectable blood pressure. Studies suggest that diarrhea within the first two years of life has long-term, lasting effects on growth, fitness, cognition and school performance. The significant impact on growth is due to reduction in appetite, altered feeding practices and decreased absorption of nutrients. Diarrheal disease is also often a coinfection with other diseases, such as malaria and HIV, and is frequently comorbidity factor in deaths due to these diseases.

Geographic Distribution and Prevalence

Diarrheal diseases are a global problem, but are especially prevalent in developing countries in conditions of poor environmental sanitation, inadequate water supplies, poverty and limited education. The epidemiology of diarrheal diseases in many developing countries is still poorly understood. Prospective studies, surveillance systems and outbreak investigations have attempted to describe the epidemiology of diarrheal diseases. However incidence data is quite variable, likely due to methodological differences and underreporting of episodes. Incidences vary by region, season and with the timing of epidemics, such as outbreaks of cholera.

Generally, the highest incidence occurs in the first two years of life, followed by a decline with increasing age. In children under the age of 5, an estimated 4 billion acute cases of diarrhea occur each year, resulting in 2 million deaths. Although global diarrheal disease mortality declined from 1980 to 1990, death rates from 1990 to 2000 appear to have stabilized. In addition, diarrheal disease-associated morbidity has increased slightly between 1990 and 2000.

Current Therapies

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 resistance in many different bacterial pathogens. Recently, a new compound that treats *Giardia*- and *Cryptosporidium*-induced diarrhea has been approved for use in both children and adults; however, this compound is available only in the United States and Latin America, is ineffective against bacterial and viral pathogens and is unaffordable to most people in the developing world.

Since the 1980s, the administration of oral rehydration therapy (ORT), which counters dehydration associated with diarrhea, has been the cornerstone of international programs for the control of diarrheal diseases and has greatly reduced mortality due to dehydration. However, while ORT is extremely useful, it does not treat the cause of diarrhea directly. This most widely used treatment helps counter fluid loss due to diarrhea and actually promotes intestinal fluid absorption, but ORT neither stops the symptoms nor kills the pathogens responsible for disease. There is therefore an urgent need for the development of safe, effective and affordable drugs to treat infants and children with diarrheal diseases.

Sources

World Health Organization, <http://www.who.int/health-topics/diarrhoeal.htm>

Centers for Disease Control and Prevention, <http://www.cdc.gov>

Black RE. Diarrheal diseases. In: *Infectious disease epidemiology: theory and practice* Editors: Nelson KE, Masters-Williams C, Graham NMH. Aspen Publisher, Inc. June, 2000.

Black RE, Merson MH, Huq I, Alim AR, Yunus M. *Incidence and severity of rotavirus and Escherichia coli diarrhoea in rural Bangladesh. Implications for vaccine development.* Lancet 1981; 1(8212):141-3

Dupont, HL. *Diarrheal diseases in the developing world*, Infect Dis Clin North Am 1995; 2:313-324

Guerrant RL, Kosek M, Moore S, Lorntz B, Brantley R, Lima AA. *Magnitude and impact of diarrheal diseases*, Arch Med Res 2002; 33(4):351-5

Kosek M, Bern C, Guerrant RL. *The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000.* Bull World Health Org 2003; 81: 197-204

Victoria CG, Bryce J, Fonatiane O, Monasch R. *Reducing death from diarrhoea through oral rehydration therapy*, Bull WHO 2000; 78:1246-55