

# Cholera, Diarrhea, and Oral Rehydration Therapy: Triumph and Indictment

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Cholera drove the sanitary revolution in the industrialized world in the 19th century and now is driving the development of oral rehydration therapy (ORT) in the developing world. Despite the long history of cholera, only in the 1960s and 1970s was ORT fully developed. Scientists described this treatment after the discovery of the intact sodium-glucose intestinal cotransport in patients with cholera. This new understanding sparked clinical studies that revealed the ability of ORT to reduce the mortality associated with acute diarrheal disease. Despite the steady reductions in mortality due to acute dehydrating diarrheal diseases achieved by ORT, the costly morbidity due to these diseases remains, the result of a failure to globalize sanitation and to control the developmental impact of diarrheal diseases and their associated malnutrition. New advances in oral rehydration and nutrition therapy and new methods to recognize its costs are discussed in this review.

The ability to use oral rehydration therapy (ORT) to control mortality associated with cholera and diarrheal diseases counts among the great triumphs of 20th century medicine. Intravenous therapy and ORT were fully developed only in the late 1960s and 1970s and have been hailed as “potentially the most important medical advance” in the 20th century [1, p. 25; 2, p. 300]. The intertwined stories of the fight against cholera and the development of ORT illustrate the critical cycle of clinical observations, physiologic research, and improved clinical outcomes. However, although cholera in the 20th century cata-

lyzed the creation of ORT, the developing world still awaits the sanitary revolution that, along with the fear of cholera, swept across the developed world in the 19th century.

Like immunization, pasteurization, and sanitation, ORT has dramatically reduced childhood mortality worldwide. ORT has primarily reduced mortality associated with diarrheal diseases in the first year of life [3]. However, there has been little if any reduction in the rates of morbidity or illness due to diarrheal diseases [3]. In fact, on the basis of growing populations living in poverty and emerging information on the long-term developmental impairment after diarrheal illnesses in the first 2 years of life [4, 5], the rate of morbidity associated with diarrheal diseases is increasing and is far more costly than ever appreciated. This global “tax” is becoming increasingly prohibitive not only in human terms, but also in microbiological, economic, and developmental terms. Thus, globalization of the sanitary revolution—provision of adequate water, sanitation, and

nutrition—may prove to be more cost-effective than has ever been appreciated.

## THE HORROR OF CHOLERA DRIVES THE SANITARY REVOLUTION THROUGHOUT THE INDUSTRIALIZED WORLD

Anyone who has seen the disease of cholera realizes its fearsome power as an instrument for societal fear and change. So dramatic is the rapid fluid loss into the intestines that the term “cholera sicca” has been used to describe the condition of a patient who dies of dehydration before having his first loose stool. When cholera first reached Paris in 1831, Magendie described it as “a disease that begins where other diseases end, with death” [1, p. 22].

For centuries, true “Asiatic” cholera resided in the Indian subcontinent until, in 1817, it broke out along routes of trade and spread into China and southern Russia. From there, the second pandemic erupted in 1829, spreading throughout Russia and western Europe. It crossed the

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Atlantic and tracked down the St. Lawrence River into New York, Philadelphia, and the southern United States, reaching Central America by the mid-1800s. Cholera continued to rage until the leaders of the sanitary revolution eradicated it from the Western Hemisphere in 1887. Their victory held for almost a century.

The seventh pandemic spread El Tor *Vibrio cholerae* from the Celebes, Indonesia, across the Middle East in the 1960s and across Africa in the 1970s. Then in 1991, El Tor cholera erupted in Peru, from which it has spread throughout nearly every country in the Western Hemisphere (figure 1) [6, 7]. In addition, the spread of the new serogroup O139 Bengal *Vibrio cholerae* began in Madras, India, in 1992. Both El Tor and O139 Bengal have remained endemic, along with classical cholera [8, 9].

#### DEVELOPMENT OF ORT: THE PARTNERSHIP OF CLINICAL MEDICINE AND PHYSIOLOGIC RESEARCH

Dating from prescriptions by the Indian physician Sushruta some 3000 years ago, rice water, coconut juice, and carrot soup

have been widely used throughout cholera's history [10]. But only when the second pandemic hit Russia was dehydration recognized as the cause of death due to cholera [11]. In 1831, O'Shaughnessy [12] analyzed the blood and stool specimens of patients with cholera and concluded that death was caused by a loss of water and salt. His recommendation that fluid replacement therapy be "effected by injection of powerful... salts directly into the veins" [12, p. 370] was probably the first therapy derived from experimental data. Latta [13], in 1832, concluded that saline provided orally or by enemas was either "useless or harmful," and he administered fluids intravenously, resulting in remarkable recovery of moribund patients. Despite these impressive early advances, cathartics and bloodletting prevailed throughout the 19th century. Cholera's mortality rate often exceeded 70% [1], and it was reduced to 40% only in 1906 with use of intravenous hypertonic solutions.

Physiological studies performed during the 1950s illustrated the cotransport of sodium and glucose and provided the physiologic underpinnings for the clinical use of ORT [14-17]. In 1960, the belief that cholera involved destruction of the intestinal mucosa was dispelled by histologic

and isotope studies [18], thus completing the rationale for fluid replacement in cholera. In 1961, Phillips and Wallace demonstrated that patients with cholera in Manila drank but did not absorb sodium chloride when provided orally, and that glucose provided with oral fluids was fully absorbed and enhanced sodium absorption [19]. In addition, Hirschhorn et al. [20] found that glucose-containing ORT substantially reduced the intravenous fluid requirement. Concurrent studies in Calcutta confirmed the effectiveness of the glucose solution provided orally [21]. Nalin, Cash, and colleagues [22-25] demonstrated a 70%-80% reduction in intravenous fluid requirements when ORT is used, and they also demonstrated the use of ORT alone in conscious patients. These results revealed the effectiveness of oral administration compared with administration via orogastric tubes, which was an important contribution to the feasibility of ORT use in remote rural areas.

When one of the authors (R.G.) arrived in 1970 at the Pakistan SEATO Cholera Research Laboratory (now the International Center for Diarrheal Diseases Research, Bangladesh; Dhaka), his commanding officer, Captain Robert A. Phillips, demanded that all cholera investiga-

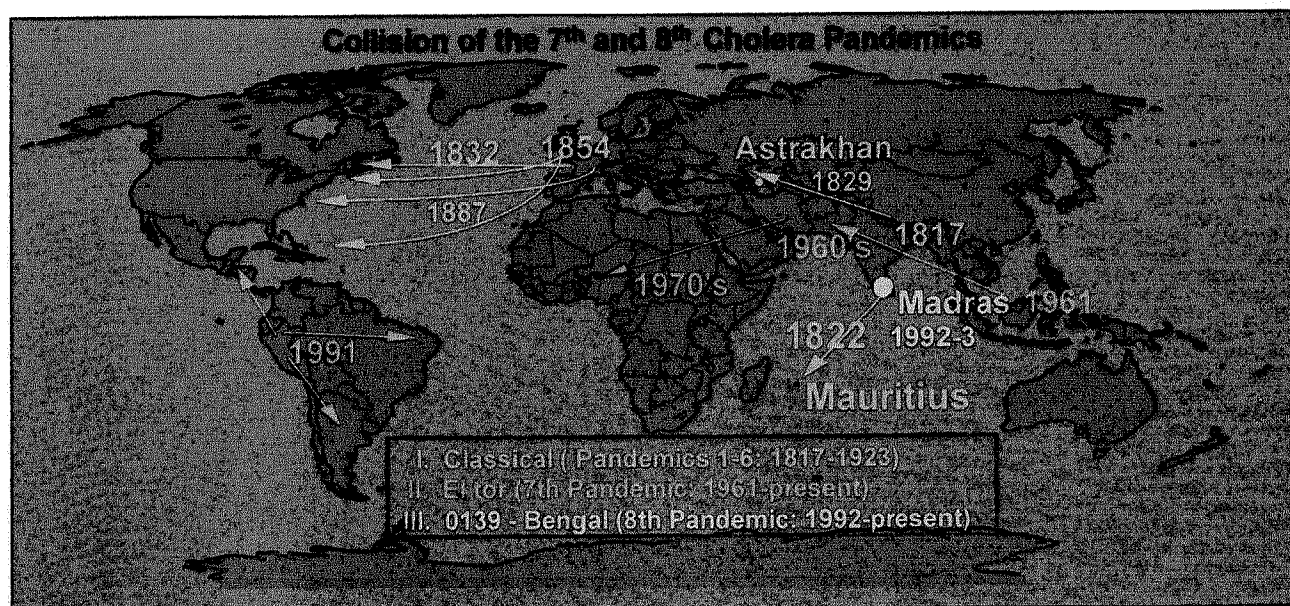
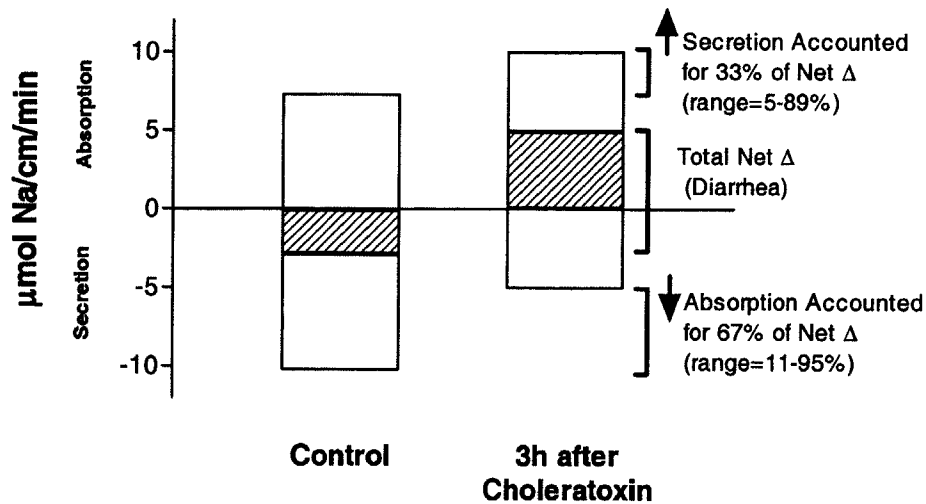


Figure 1. Spread of classical, El Tor, and O139 cholera epidemics. From [6].



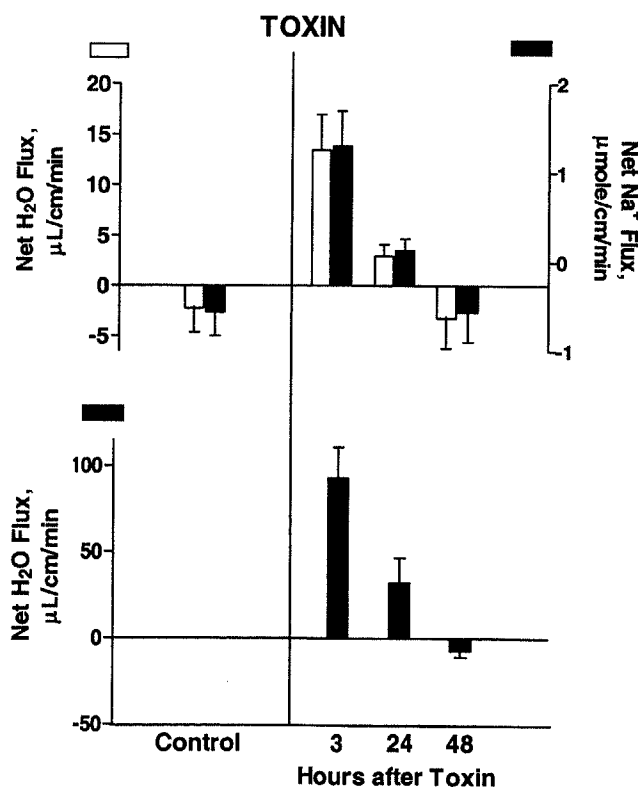
**Figure 2.** Effect of cholera toxin on unidirectional sodium fluxes in ligated canine jejunal segments. Three hours after treatment with cholera toxin, a significant increase in sodium and chloride secretion and a reduction in sodium absorption was observed. From [26].

tors learn the Van Slyke copper sulfate method for field studies of plasma-specific gravity. Phillips patiently tolerated his young investigators' studies, including dual sodium isotopic studies of electrolyte transport by Guerrant and Rohde, which repeatedly showed both a reduction in sodium absorption and an increase in sodium and chloride secretion. However, this violation of the then-current theory of pathogenesis—that cholera toxin poisoned the sodium pump—prevented its publication until it was included in a chapter entitled "Pathophysiology of the Enterotoxic and Viral Diarrheas" in *Diarrhea and Malnutrition: Interactions, Mechanisms, and Interventions* in 1983 (figure 2) [26].

Subsequent studies that year in Dhaka revealed not only the activation of adenylate cyclase in human cholera [27], but also the apparent permanent "locking on" of adenylate cyclase in intestinal epithelial tissues for >24 h after a brief 10-min exposure to cholera toxin (figure 3) [28]. Recovery by 48 h was likely related to renewal of the intestinal epithelium over that period. The clinical consequence of this mechanism was the huge requirement for fluid replacement for 1–3 days even after all *Vibrio* microorganisms are killed with an effective antibiotic [28]. This ubiquitous activation of adenylate cyclase and its augmentation of hormone respon-

siveness [29] helped lead to the development of tissue culture bioassays [30] and, eventually, to Alfred G. Gilman's seminal work on G-proteins, for which he won the 1994 Nobel Prize.

The devastating conditions suffered by the Bangladeshi refugees as they fled the war with Pakistan offered ORT its definitive test. More than 350,000 refugees lived in the camp into which Dr. Mahalanabis



**Figure 3.** Time course of change in adenylyl-cyclase activity and net water and sodium flux in canine intestinal loops after exposure to cholera toxin. Significant increases in adenylyl-cyclase activity and net luminal movement of water and sodium were present at 3 h and at 24 h. At 48 h, both enzyme activity and net fluxes return to control values. From [28].

**Table 1. Prevention of morbidity and mortality related to diarrhea.**

Variable	Effectiveness for children aged <5 years, %		Cost, US\$	
	Decrease in morbidity	Decrease in mortality	Per averted episode	Per averted death
Oral rehydration therapy	—	41–71	—	1000–5000
Breast-feeding			45	890
Children aged <5 years	1–4	8.9		
Children aged <6 months	8–20	24–27		
Immunization				
Measles	1.8	13	6	130
Rotavirus	2.4	7.7	5	220
Cholera	0.1	1.7	220	2000
Improved water supply and sanitation	22–27	21–30	18–60	2900–9400

**NOTE.** Data are means or ranges of estimates. From [57, 58].

led his team. When the medical team ran out of intravenous fluids at the camp, oral glucose-salt packets were used to treat >3000 patients, resulting in a reduction in the mortality rate from 30% to only 3.6% [31]. Thus, the description of ORT and its physiologic basis may appropriately be called “potentially the most important medical advance of this century” [1, p. 25; 2, p. 300].

### NEW RESEARCH PATHWAYS FOR ORT

The argument that polyglucose (i.e., starch)-based ORT might provide more glucose that can be cleaved by disaccharidases at the mucosal brush border without the heavy osmotic load of glucose monomers has further improved ORT. Several studies have shown 32%–35% [32–34] reduction in fluid requirements when rice-based instead of glucose-based ORT is used (with 50–80 g of rice replacing the 20 g of glucose per liter) [35]. Although the results of rice-based ORT is less impressive in infants and in patients with noncholera diarrhea than it is in adults with cholera, it may be safer for household use because a sufficient quantity of water is needed to liquefy the cooked rice-based slurry for consumption. The added liquid helps to prevent the preparation of hypertonic solutions.

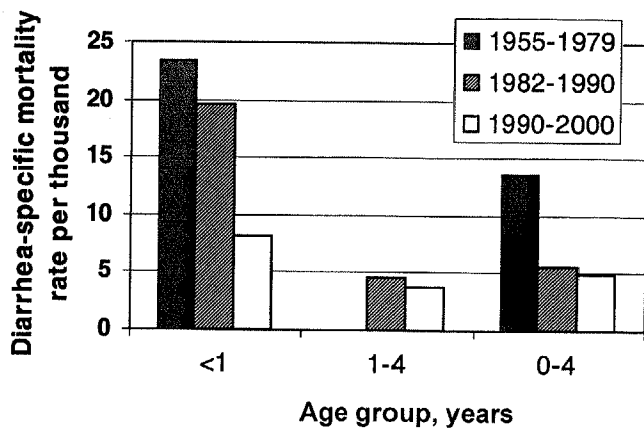
Studies have attempted to exploit the

additive sodium absorption seen with neutral amino acids, such as alanine and glycine, without striking clinical benefit [36]. In addition, amylase-resistant maize starch-based ORT has been tested to provide colonic butyrate to reduce cholera diarrhea. In the colon, short-chain fatty acids enhance the absorption of salt and water and provide an additional source of energy [15]. Indeed, Ramakrishna et al. [37] showed further reductions in fluid requirements for patients with cholera over the first 48 h with maize-based ORT. However, this requires that antibiotics be delayed, presumably to allow the colonic flora to act on the nonhydrolyzed maize starch and to produce butyrate and other short-chain fatty acids.

The amino acid glutamine has also received interest as a component of ORT on the basis of considerable *in vitro* and *in vivo* evidence. Glutamine, a crucial source of energy for the intestinal mucosa, is involved in important metabolic processes that regulate intestinal epithelial repair and barrier function [38, 39]. It also stimulates sodium absorption [40], as demonstrated in experimental models of cholera [41–43], rotavirus enteritis [44], cryptosporidiosis [45, 46], and intestinal perfusion in adults with cholera [47]. An oral rehydration solution (ORS) containing glutamine was well tolerated and was as effective as the standard World Health Organization ORS in infants (1 month to

1 year old) with noncholera diarrhea and dehydration [48]. Moreover, Lima et al. [49] demonstrated that the stable and highly soluble glutamine-containing dipeptide, alanyl-glutamine, enhanced water and electrolyte intestinal absorption even better than glutamine or glucose in an animal model of cholera. These findings strengthen the rationale for further clinical studies of stable glutamine derivative-based ORT in cholera and other infectious diarrheal syndromes [50]. These derivatives can help overcome the unfavorable chemical properties of glutamine (instability during heat sterilization and prolonged storage and limited solubility), which compromise its use in routine clinical settings. These same properties may account for the absence of striking superiority of glutamine-based ORS reported by some [51].

Micronutrients have also emerged as potential adjunct therapy for cholera and other diarrheal episodes. Several studies have demonstrated that zinc supplementation during acute diarrhea reduces the duration and severity of illness and the risk of prolonged diarrhea [52–55]. A combined analysis from 2 studies (1250 children) showed that zinc supplementation reduced the rate of prolonged diarrhea by 38% [56]. Another study found a 42%–47% reduction in the risk of prolonged diarrhea when zinc was provided daily during diarrhea until 7 days after recovery (1.9–3.1 mg/kg or 3 recommended daily allowances per day) [55]. In addition, in pooled analyses of trials performed in Asia, vitamin A supplementation during acute diarrhea reduced the rate of persistent diarrhea by 55% but had no effect on the duration of the acute episode [53]. Although these results were not studied in patients with cholera, they provide a solid rationale for investigating the use of micronutrients as adjuncts to ORT. These micronutrients (perhaps in combination with glutamine derivatives) may help address the failure of ORT to provide the nutritional support needed by most children with diarrhea. They may also help



**Figure 4.** Decreasing global diarrhea mortality, 1955–2000. Diarrhea-specific mortality trends are from 3 prospective studies in developing areas. Only 2 studies presented data for 1955–1979 for children 1–4 years old. From [3].

reverse the vicious cycle of persistent diarrhea and malnutrition, given their effect on reducing the risk for chronic diarrhea.

In the overall analysis of means to prevent diarrhea-associated morbidity and mortality (table 1) ORT is one of the most important interventions in the reduction of mortality. Indeed, striking reductions in infant diarrhea-related mortality emerged from a recent analysis (figure 4) [3]. By means of methods similar to those used in studies conducted during 1955–1990 [59, 60], the latest 10-year update reveals continued reductions in diarrhea-specific mortality rates, almost entirely in infants aged <1 year [3]. Undoubtedly, part of this improvement is due to the implementation of ORT in developing countries. However, there is no reduction in morbidity, because ORT saves lives lost to acute dehydration (and likely speeds recovery) but fails to remove the causative factors contributing to diarrheal illnesses or their long-term consequences. This observation is supported by the finding of a stable or increasing median number of diarrheal episodes per child per year (figure 5).

#### POTENTIAL LONG-TERM IMPACT OF NONFATAL DIARRHEAL DISEASE

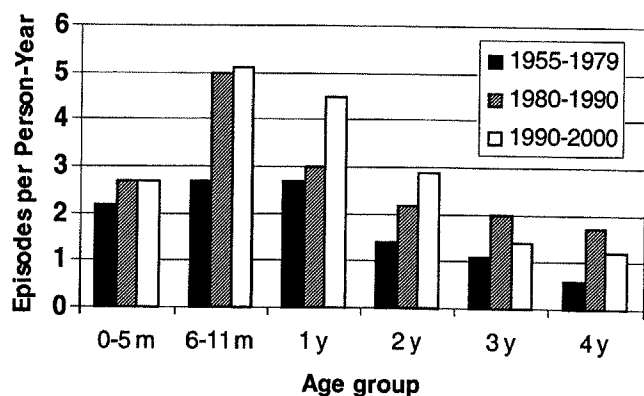
The morbidity associated with multiple episodes of diarrheal diseases is increas-

ingly recognized to have potentially devastating consequences. Clues to the importance of these long-term consequences of diarrhea in the formative first 2 years of life arise from studies in northeast Brazil and Lima, Peru.

Initial studies of short-term impact of intestinal helminthic infections on physical fitness [61], physical activity [62], and cognitive function [63, 64] fostered long-term prospective studies of the association between early childhood diarrhea burdens and physical fitness, growth, and cognitive impairment 4–7 years later. A significant correlation between the amount of diarrhea in the first 2 years of life and physical fitness and cognitive function 4–7 years

later was observed in children in northeast Brazil [5]. This association was confirmed after controlling for potential confounders (i.e., anthropometric variables, helminthic infections, anemia, and socioeconomic status) and suggested an impact of early diarrhea on children's motor and cognitive development. In addition, early childhood (0–2 years) diarrheal burden was associated with linear growth shortfalls beyond age 6 years, even after controlling for nutritional status and socioeconomic variables (maternal education and family income) [65]. Helminthiasis (*Ascaris lumbricoides* and *Trichuris trichiura*) during the same period (0–2 years) also correlated with long-term stunting [5]. Surprisingly, this association seemed to be true also for certain asymptomatic enteric infections. Studies from Brazil and Peru have shown that enteric infection with enteroaggregative *Escherichia coli* (EAggEC) and *Cryptosporidium* species is associated with growth impairment even without overt diarrhea [66–68].

Coupled with growth and physical fitness impairment, significant reductions in cognitive function in later childhood (i.e., 6–9 years of age) were also associated with early childhood diarrheal burdens [5, 69]. Repeated bouts of diarrhea (mean, 10.2 episodes of diarrhea in the first 2 years of life) were associated with 5.6% reduction in cognitive function. When considering only the impact of persistent diarrheal ill-



**Figure 5.** Increasing global diarrhea morbidity, 1955–2000. Median age-specific incidence rates in diarrheal episodes per child-year from 3 prospective studies in developing areas. m, Months; y, years. From [3].

nesses on later childhood cognitive performance, the reduction on the Wechsler Intelligence Scale for Children was 25%–65%. This lasting disability carried far-reaching consequences. Data show increased age at starting school and age-for-grade among the children with the heaviest diarrheal burdens in their first 2 years of life [70]. Studies in Peru and The Philippines corroborate these findings [71, 72].

We postulate that these long-term effects are due to the negative impact of the diarrheal burden on nutritional status during this critical and vulnerable period of cerebral synapse formation [73]. The diarrheal episodes may cause persistent intestinal injury leading to malabsorption and greater susceptibility to further infections. These sequelae may compromise the absorption of critical micronutrients for brain development like iron and vitamin B<sub>6</sub> [74], leading to irreversible structural and biochemical brain damage. Last, intestinal inflammation seen in asymptomatic children infected with EAaggEC [66] and in symptomatic *Cryptosporidium*-infected children [75, 76] may play a role in the pathogenesis of these long-term deficits. Studies to further evaluate these mechanisms remain to be performed.

The vicious cycle of diarrhea and malnutrition must now encompass persistent as well as acute diarrhea and must also encompass the long-term interactions with fitness, growth, cognitive development, and even school performance. If one includes such long-term developmental consequences, the disability-adjusted life years (DALYs) impact of diarrheal diseases more than doubles [4].

### **COSTS OF THE FIGHT AGAINST DIARRHEA**

However, what is the cost of initiatives that would reduce not only the acute disease burden but also the long-term effects of childhood diarrheal illnesses? One good measure is the cost of reducing child malnutrition in developing countries, because

better nutritional status could allow children to better resist infection and to better recover from infections they do experience. It has been estimated that overall investments by developing countries in 5 instrumental sectors (irrigation, rural roads, agricultural research, clean water supply, and education) need to increase from the current projected \$25 billion annually to \$35 billion to achieve a 43% reduction in the number of malnourished children [77]. These expenditures represent only ~5% of the annual expenses of developing countries [77].

Knowing that ~88% of diarrheal diseases in the world are attributable to unsafe water, sanitation, and hygiene, the World Health Organization estimated that to increase the number of people with access to safe water by the year of 2015 by 50% would cost ~\$37.5 billion international dollars (I\$; a floating adjustment of US\$ for international purchasing power) over 10 years [78]. This investment would reduce the number of DALYs worldwide by 30 million and carry a cost-effectiveness ratio of I\$1250 over 10 years per DALY averted. Our doubling or quadrupling of the early childhood diarrhea-associated DALYs [4] could double or quadruple the cost effectiveness of such interventions (i.e., reduce the cost per DALY averted in the above example to only I\$625 or I\$312 over 10 years).

### **LATE 20TH-CENTURY REMINDERS OF THE IMPORTANCE OF WATER AND SANITATION**

Recent tragedies also point to our failure to work toward the globalization of the sanitary revolution. On 14 February 1992, 75 of 336 Aerolineas Argentinas passengers arrived in Los Angeles with cholera acquired from ingestion of a cold seafood salad picked up at Lima, Peru. Although 10 patients were hospitalized with severe cholera and 1 died, careful follow-up revealed no secondary cases, thus suggesting the importance of sanitation and water in pre-

venting the spread of cholera [79, 80]. Another tragic reminder came when nearly 10% of more than a half million Rwandan Hutu refugees died in their first month in a refugee camp in Zaire in July 1994. More than 12,000 died of cholera, with a mortality rate reaching 48% as a result of inadequate supplies of water, sugar, and salts [81].

In summary, the story of cholera, diarrhea, and ORT illustrates the importance of the fundamental measures of clean water provision and sanitation in controlling infectious diarrhea, and it exemplifies how the basic science can be translated into lives saved. However, diarrhea-associated morbidity and its long-term developmental impairment continue unabated. The continued diarrhea-associated morbidity now likely exceeds its still staggering mortality. The huge human and societal costs of largely preventable cholera and other diarrheal diseases thus reveal not only the triumphs of ORT but also provide an indictment of our failure to see that basic, affordable measures undertaken in the industrialized world more than a century ago must now be undertaken worldwide. This is a costly failure that we cannot afford.

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