Chapter **19**

Diarrheal Diseases

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Diarrheal diseases remain a leading cause of preventable death, especially among children under five in developing countries. This chapter reviews and prioritizes a number of available interventions.

The normal intestinal tract regulates the absorption and secretion of electrolytes and water to meet the body's physiological needs. More than 98 percent of the 10 liters per day of fluid entering the adult intestines are reabsorbed (Keusch 2001). The remaining stool water, related primarily to the indigestible fiber content, determines the consistency of normal feces from dry, hard pellets to mushy, bulky stools, varying from person to person, day to day, and stool to stool. This variation complicates the definition of *diarrhea,* which by convention is present when three or more stools are passed in 24 hours that are sufficiently liquid to take the shape of the container in which they are placed. The frequent passage of formed stool is not diarrhea (Black and Lanata 2002). Although young nursing infants tend to have five or more motions per day, mothers know when the stooling pattern changes and their children have diarrhea (Ronsmans, Bennish, and Wierzba 1988). The interval between two episodes is also arbitrarily defined as at least 48 hours of normal stools. These definitions enable epidemiologists to count incidence, relapses, and new infections.

TRANSMISSION

Diarrhea is caused by infectious organisms, including viruses, bacteria, protozoa, and helminths, that are transmitted from the stool of one individual to the mouth of another, termed *fecal-oral transmission.* Some are well known, others are recently discovered or emerging new agents, and presumably many remain to be identified. They differ in the route from the stool to the mouth and in the number of organisms needed to cause infection and illness. Among bacteria, the ability to survive stomach acid is an important determinant of the inoculum size required to cause illness. For example, *Shigella* bacteria are resistant to low pH, and a few thousand organisms suffice, which are readily transferred by direct person-to-person contact or through contamination of inanimate objects, such as a cup. In contrast, bacteria readily killed by acid, such as *Vibrio cholerae,* require millions of organisms to cause illness, and therefore must first multiply in food or water to an infectious dose. Some pathogens, such as rotavirus, display a sharp host species preference, and others have a broad host range. Among *Salmonella* bacteria, certain bio-serotypes are adapted to infect animals and pose no threat to humans, and others are adapted to humans and do not infect animals. The majority, however, are not adapted to a specific host and can infect either humans or domestic animals, thus facilitating transmission of these organisms to humans. Less than a dozen of the more than 2,500 individual *Salmonella* cause the majority of human infections, reflecting the requirement for genes that encode essential virulence factors.

The ability to identify virulence genes and their products has led to new molecular approaches to epidemiology and diagnosis, and undoubtedly will lead to new measures to prevent and treat diarrhea. Molecular methods also allow the separation of organisms that otherwise appear to be identical. Nonpathogenic *Escherichia coli* in normal stool cannot be

separated from diarrhea-causing *E. coli* by standard methods; however, identification of virulence genes or factors distinguishes five groups of *E. coli* that cause illnesses ranging from cholera-like watery diarrhea to neonatal diarrhea, persistent diarrhea, and bloody diarrhea (Nataro and Kaper 1998).

LABORATORY DIAGNOSIS

Etiologic diagnosis of diarrhea is valuable for public health interventions and case management. Microbiological culture and microscopy remain the standard, despite their limited sensitivity. Their effectiveness is further reduced by antibiotic use, and patients with severe illness are more likely both to be cultured and to have taken antibiotics. Even when cultures are positive, the delay in laboratory identification limits their cost-effectiveness for managing individual patients. The information is always epidemiologically and clinically important; however, during epidemics, culturing every patient is unnecessary when the causative organism is known. Antimicrobial resistance data are essential to guide initial antibiotic choices.

New rapid tests to detect inflammatory mediators or white or red blood cells in stool offer the promise of distinguishing between secretory and inflammatory disease and optimizing case management (Huicho and others 1996). High background levels, probably from frequent infections, limits the use of such tests in developing countries, where they would be most useful (Gill and others 2003).

Simple microscopy for protozoa or helminths can be quick and effective when the proper sample is obtained and a well-trained technician is available to examine a fresh specimen, but these prerequisites are often not available in developing countries. Newer immunological and nucleic acid–based tests to detect pathogen-specific factors hold great promise for all diarrhea agents, but they are too expensive or require specialized instrumentation and trained technicians. For the foreseeable future, then, syndromic diagnosis will be the norm.

SYNDROMIC DIAGNOSIS

Three major diarrhea syndromes exist. They are acute watery diarrhea, which results in varying degrees of dehydration; persistent diarrhea, which lasts 14 days or longer, manifested by malabsorption, nutrient losses, and wasting; and bloody diarrhea, which is a sign of the intestinal damage caused by inflammation. The three are physiologically different and require specific management. Syndromic diagnosis provides important clues to optimal management and is both programmatically and epidemiologically relevant.

Acute watery diarrhea can be rapidly dehydrating, with stool losses of 250 milliliters per kilogram per day or more, a quantity that quickly exceeds total plasma and interstitial fluid volumes and is incompatible with life unless fluid therapy can keep up with losses. Such dramatic dehydration is usually due to rotavirus, enterotoxigenic *E. coli*, or *V. cholerae* (the cause of cholera), and it is most dangerous in the very young.

Persistent diarrhea is typically associated with malnutrition, either preceding or resulting from the illness itself (Ochoa, Salazar-Lindo, and Cleary 2004). Even though persistent diarrhea accounts for a small percentage of the total number of diarrhea episodes, it is associated with a disproportionately increased risk of death. In India, persistent diarrhea accounted for 5 percent of episodes but 14 percent of deaths, and a mortality rate three times higher than briefer episodes (Bhan and others 1989). In Pakistan, persistent diarrhea accounted for 8 to 18 percent of episodes but 54 percent of deaths (Khan and others 1993). In Bangladesh, persistent diarrhea associated with malnutrition was responsible for nearly half of diarrhea deaths, and the relative risk for death among infants with persistent diarrhea and severe malnutrition was 17 times greater than for those with mild malnutrition (Fauveau and others 1992). Persistent diarrhea occurs more often during an episode of bloody diarrhea than an episode of watery diarrhea, and the mortality rate when bloody diarrhea progresses to persistent diarrhea is 10 times greater than for bloody diarrhea without persistent diarrhea. HIV infection is another risk factor for persistent diarrhea in both adults and children (Keusch and others 1992). Management focuses on overcoming the nutritional alterations initiated by persistent diarrhea.

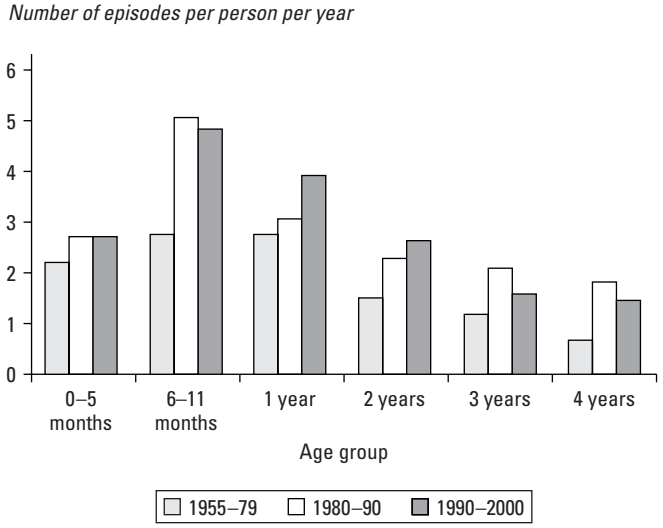
Bloody diarrhea, defined as diarrhea with visible or microscopic blood in the stool, is associated with intestinal damage and nutritional deterioration, often with secondary sepsis. Some dehydration—rarely severe—is common, as is fever. Clinicians often use the term *bloody diarrhea* interchangeably with dysentery; however, dysentery is a syndrome consisting of the frequent passage of characteristic, small-volume, bloody mucoid stools; abdominal cramps; and tenesmus, a severe pain that accompanies straining to pass stool. Those features show the severity of the inflammation. Agents that cause bloody diarrhea or dysentery can also provoke a form of diarrhea that clinically is not bloody diarrhea, although mucosal damage and inflammation are present, and fecal blood and white blood cells are usually detectable by microscopy. The release of host-derived cytokines causes fever, altering host metabolism and leading to the breakdown of body stores of protein, carbohydrate, and fat and the loss of nitrogen and other nutrients. Those losses must be replenished during convalescence, which takes much longer than the illness does to develop. For these reasons, bloody diarrhea calls for management strategies that are markedly different than those for watery or persistent diarrhea. New bouts of infection that occur before complete restoration of nutrient stores can initiate a downward spiral of nutritional status terminating in fatal protein-energy malnutrition (Keusch 2003).

DIARRHEA, ENVIRONMENT, AND POVERTY

Diarrheal disease affects rich and poor, old and young, and those in developed and developing countries alike, yet a strong relationship exists between poverty, an unhygienic environment, and the number and severity of diarrheal episodes—especially for children under five.

Poverty is associated with poor housing, crowding, dirt floors, lack of access to sufficient clean water or to sanitary disposal of fecal waste, cohabitation with domestic animals that may carry human pathogens, and a lack of refrigerated storage for food—all of which increase the frequency of diarrhea. Poverty also restricts the ability to provide age-appropriate, nutritionally balanced diets or to modify diets when diarrhea develops so as to mitigate and repair nutrient losses. The impact is exacerbated by the lack of adequate, available, and affordable medical care. Thus, the young suffer from an apparently never-ending sequence of infections, rarely receive appropriate preventive care, and too often encounter the health care system when they are already severely ill.

Although the presence of blood in the stool is a recognized danger signal, prompting more urgent care seeking, even these patients either are not treated early or receive poor medical care. Ironically, the poor spend considerable amounts on inappropriate care and useless drugs purchased from local shops and untrained practitioners. If antibiotics are properly prescribed, poverty often limits the purchase of a full course of treatment or leads to cessation of treatment as soon as symptoms improve, even though the infection has not been cured.



Source: Authors.

Figure 19.1 Median Age-Specific Incidences for Diarrheal Episodes per Child per Year from Three Reviews of Prospective Studies in Developing Areas, 1955–2000

PUBLIC HEALTH SIGNIFICANCE OF DIARRHEAL ILLNESSES

Continuing surveillance and longitudinal studies allow tracking of current levels and trends in diarrhea incidence and mortality and provide the basis for future projections and for evaluations of different control strategies.

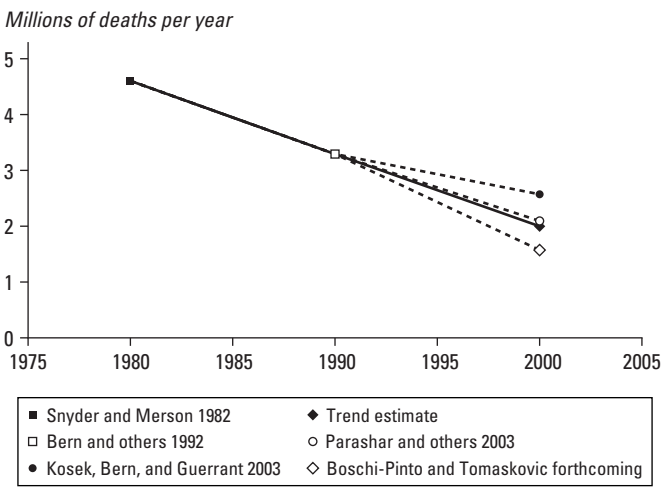
Morbidity

Comparisons over time of the global burden of diarrheal diseases have revealed secular trends and demonstrated the impact of public health interventions (Bern and others 1992; Kosek, Bern, and Guerrant 2003; Snyder and Merson 1982). The long-term consequences of diarrhea are only now being systematically assessed and are not reflected in earlier studies.

Reviews in 1992 (Bern and others) and 2003 (Kosek, Bern, and Guerrant) are similar in many ways—for example, assessing morbidity at least twice weekly—but differ significantly in the use of different sources for data on children under five and in the inclusion of studies differing in design and data collection protocols (and only the later study includes data from China). Remarkably, the estimated median incidence of diarrheal disease in children under five in developing countries has not changed much since the early 1990s (figure 19.1): 3.2 episodes per child per year in 2003 (Parashar and others 2003) compared with 3.5 episodes per child per year in 1993 (Jamison and others 1993). However, many fewer surveys were available for the most recent review (31 in 20 countries) compared with the 1993 consensus (276 in 60 countries), reflecting diminished support for the systematic collection of incidence data. Incidence rates in Sub-Saharan Africa and Latin America are clearly greater than in Asia or the Western Pacific, while subject to greater data limitations from individual countries. Incidence continues to show a peak in infants age 6 to 11 months, dropping steadily thereafter.

The seemingly lower estimates of diarrheal incidence before 1980 (Snyder and Merson 1982) are likely due to methodological differences. These estimates are not precise or directly comparable; the trends are most relevant. The persistently high rates of diarrhea throughout the 1990s despite intensive efforts at control, particularly among children age 6 to 24 months, is of particular concern. Early childhood diarrhea during periods of critical postnatal development may have long-term effects on linear growth and on physical and cognitive functions.

Data on the incidence of shigellosis, the principal cause of bloody diarrhea in developing countries, are even more limited. Kotloff and others' (1999) review of studies on *Shigella* infection estimates that more than 113 million episodes occur every year in children under five in developing countries, or 0.2 episodes of bloody diarrhea per year caused by S*higella* species.



Source: Authors.

Figure 19.2 Estimates of Diarrhea Mortality, 1975–2000

Mortality

Bern and others (1992); Kosek, Bern, and Guerrant (2003); and Snyder and Merson (1982) also estimate diarrheal mortality using data from longitudinal studies with active surveillance in place (figure 19.2). The estimate before 1980 was 4.6 million deaths per year. This estimate dropped to 3.3 million per year between 1980 and 1990 and to 2.6 million per year between 1990 and 2000. Two other studies (Parashar and others 2003; Boschi-Pinto and Tomaskovic forthcoming) report even lower figures for 1990–2000: 2.1 million and 1.6 million deaths per year, respectively. Methodological variations (inclusion of studies with different designs and data collection methods and inclusion of data from China, different sources for estimating the number of children under five, and different strategies for calculating mortality for this age group) may account for some of the striking differences. However, the end of the 20th century witnessed significant reductions in diarrheal deaths in children under five.

This steady decline in diarrheal mortality, despite the lack of significant changes in incidence, is most likely due to modern case management (introduced since the 1980s) and to the improved nutrition of infants and children. Major recommendations include the following:

- counseling mothers to begin suitable home-prepared rehydration fluids immediately on the onset of diarrhea
- treating mild to moderate dehydration early with oral rehydration solution (ORS), reserving intravenous electrolytes for severe dehydration
- continuing breastfeeding and complementary foods during diarrhea and increasing intake afterward
- limiting antibiotic use to cases of bloody diarrhea or dysentery and avoiding antidiarrheal and antimotility drugs
- advising mothers to increase fluids and continue feeding during future episodes.

Victora and others' (2000) review provides evidence that this strategy, and especially oral rehydration therapy (ORT), has influenced the outcome of dehydrating diarrhea. Data from 99 national surveys carried out in the mid 1990s and compiled by the United Nations Children's Fund (UNICEF) increasingly show that diarrhea patients are appropriately managed in most parts of the world, with overall use rates of ORS or recommended home fluids reaching 49 percent. Country case studies in Brazil, the Arab Republic of Egypt, Mexico, and the Philippines showed a dramatic reduction of diarrhea mortality as ORT use rates increased from close to zero in the early 1980s to 35 percent in Brazil, 50 percent in Egypt, 81 percent in Mexico, and 33 percent in the Philippines in the early 1990s. Hospital admissions for diarrhea also plummeted (Victora and others 2000). As mortality attributable to acute dehydration decreased, the proportionate mortality associated with persistent diarrhea increased. Data from Brazil and Egypt suggest that even relatively low ORT use rates can positively affect mortality, because ORT use tends to be much higher for severe illness (Victora and others 2000).

Worldwide mortality caused by *Shigella* infection is estimated to be 600,000 deaths per year among children under five, or a quarter to a third of all diarrhea-related mortality in this age group (Kotloff and others 1999). Because mortality caused by bloody diarrhea is not tracked separately, it is difficult to assess the impact of standard case management recommendations, and disease-specific trends cannot be tracked. In the past few years, however, data from the International Centre for Diarrheal Disease Research, in Bangladesh, have shown a marked decrease in the rate of hospitalization caused by *Shigella,* especially *S. dysenteriae* type 1, the most severe form of shigellosis. Some investigators have suggested that this decrease may be because *Shigella* infections are now in the low part of a 10-year cycle (Legros 2004). The observed change could also be explained by better case management with more efficacious antimicrobials. More comprehensive, syndrome-specific surveillance data will be required if rational control priorities are to be set, because the options for dehydrating and bloody diarrheal diseases differ substantially.

Despite national data that indicate a significant decline in mortality (Baltazar, Nadera, and Victora 2002; Miller and Hirschhorn 1995), diarrheal diseases remain among the five top preventable killers of children under five in developing countries and among the top two in many.

Long-Term Consequences

The long-term consequences of diarrheal diseases remain poorly studied, and analyses of global trends have not considered them. Niehaus and others (2002) recently evaluated the

long-term consequences of acute diarrheal disease on psychomotor and cognitive development in young children. Following a cohort of 47 children in a poor urban community in northeastern Brazil, they correlated the number of diarrheal episodes in the first two years of life with measures of cognitive function obtained four to seven years later. They found a significant inverse correlation (average decrease of 5.6 percent) between episodes of early diarrheal disease and overall intellectual capacity and concentration, even when controlling for maternal education or helminth infection, which are known to be independent predictors of malnutrition and cognitive defects. Test scores were also 25 to 65 percent lower in children with an earlier history of persistent diarrhea.

Recent evidence suggests that genetic factors may also be involved in the developmental response to repeated diarrhea (Oria and others 2005). Better and more sensitive assessment tools are needed to define the relationships between diarrheal diseases and developmental disorders and to calculate individual and societal costs and the cost-effectiveness of interventions. In addition, early childhood malnutrition resulting from any cause reduces physical fitness and work productivity in adults (Dobbing 1990).

PREVENTIVE STRATEGIES

Strategies for controlling diarrheal diseases have remained substantially unchanged since the 1993 edition of this volume (Martinez, Phillips, and Feachem 1993). The World Health Organization (WHO 2004) recently reevaluated these interventions to determine the extent to which they have been effectively implemented and their effect.

Promotion of Exclusive Breastfeeding

Exclusive breastfeeding means no other food or drink, not even water, is permitted, except for supplements of vitamins and minerals or necessary medicines. The optimal duration of exclusive breastfeeding is six months (WHO 2001). A meta-analysis of three observational studies in developing countries shows that breastfed children under age 6 months are 6.1 times less likely to die of diarrhea than infants who are not breastfed (WHO Collaborative Study Team 2000). Exclusive breastfeeding protects very young infants from diarrheal disease in two ways: first, breast milk contains both immune (specific) and nonimmune (nonspecific) antimicrobial factors; second, exclusive breastfeeding eliminates the intake of potentially contaminated food and water. Breast milk also provides all the nutrients most infants need up to age 6 months. When exclusive breastfeeding is continued during diarrhea, it also diminishes the adverse impact on nutritional status.

Those data underpin the global campaign to promote exclusive breastfeeding for the first six months of life by increasing both the initiation and the duration of exclusive breastfeeding. The strategies include the following:

- hospital policies and actions to encourage breastfeeding and discourage bottle feeding
- counseling and education provided by peers or health workers
- mass media and community education
- mothers' support groups.

Interventions focused on hospital practices apply where most women deliver in such facilities. Such interventions have shown up to a 43 percent increase in exclusive breastfeeding with good institutional policies and retraining of health staff (Westphal and others 1995). Interventions focused on education and counseling increase exclusive breastfeeding by 4 to 64 percent (Sikorski and others 2002). Peer-counseled women are less likely to stop exclusive breastfeeding than are those who receive either professional support or no support, and their infants are 1.9 to 2.9 times less likely to have diarrhea (Barros and others 1995; Haider and others 1996). No large-scale peer counseling programs exist; therefore, feasibility is unknown. Community-based mother's support groups are sustainable, but they have low coverage and are biased toward women who are already motivated to breastfeed (Bhandari and others 2003). Mass media can be effective where media coverage is high, where production skills are good, and where it addresses barriers to breastfeeding instead of just proclaiming its benefits. We found no studies that examined the relationship between breastfeeding promotion and diarrheal disease mortality; however, estimates suggest such promotion could decrease all-cause mortality in children under five by 13 percent (Jones and others 2003).

Maternal HIV infection has put a new wrinkle in the "breast is best" dogma because of the risk of transmission of infection to the infant (De Cock and others 2000). There is a trade-off, however, between the risk of mortality associated with replacement feeding and the risk of HIV infection, especially where safe replacement feeding is difficult. For women who are HIV-negative or whose status is unknown, WHO currently recommends exclusive breastfeeding for at least six months (WHO 2000). The best option for HIV-positive women is acceptable, affordable, sustainable, and safe replacement feeding. If this option is not possible, there are four alternatives: (a) heat-treated breast milk, (b) HIV-negative wet nurses, (c) uncontaminated donor milk, or (d) exclusive breastfeeding for six months and rapid discontinuation thereafter (WHO 2003).

A danger of promoting replacement feeding is that uninfected women or women with unknown HIV status will adopt the practice. Even in high-prevalence communities, the best

option for women with unknown status for the overall health of their children appears to be exclusive breastfeeding for six months. In Coutsoudis and others' (1999) cohort study in South Africa, the risk of mother-to-infant transmission of HIV after three months of exclusive breastfeeding was similar to that with no breastfeeding and significantly lower than that with mixed feeding. Providing antiretroviral therapy to the mother should significantly extend the period of safe breastfeeding for the initially HIV-negative infants of HIV-positive mothers.

Improved Complementary Feeding Practices

Ideally, complementary foods should be introduced at age 6 months, and breastfeeding should continue for up to two years or even longer to increase birth intervals (WHO 2003). There is a strong inverse association between appropriate, safe complementary feeding and mortality in children age 6 to 11 months. Malnutrition is an independent risk predictor for the frequency and severity of diarrheal illness. There is a vicious cycle in which sequential diarrheal disease leads to increasing nutritional deterioration, impaired immune function, and greater susceptibility to infection. The cycle may be broken by interventions to decrease infection incidence to reduce malnutrition (Keusch and Scrimshaw 1986) or improving nutritional status to reduce the burden of infection (Victora and others 1999).

Improved feeding practices to prevent or treat malnutrition could save as many as 800,000 lives per year (Jones and others 2003). Pediatricians have long been aware of an increase in diarrhea incidence during weaning from exclusive breast milk feeding. Microbial contamination of complementary foods (Mondal and others 1996) and nutritionally inadequate diets during and after diarrhea episodes (Badruddin and others 1991) increase the risk. Contamination of complementary foods can potentially be reduced by educating caregivers on hygienic practices (Guptill and others 1993), improving home food storage (English and others 1997), fermenting foods to reduce pathogen multiplication (Kimmons and others 1999), or ingesting nonpathogenic probiotic microorganisms that colonize the gut and help resist pathogens (Allen and others 2004). These interventions have not been evaluated at scale in communities, and effectiveness trials are lacking.

We could not find any reports on the effects of complementary feeding interventions on mortality. Five efficacy trials to improve the intake of complementary foods noted a net increase in energy intake of between 65 and 300 kilocalories a day and improvements of 0.25 to 0.46 standard deviations in weight-for-age and 0.04 to 0.35 standard deviations in height-for-age (Caulfield, Huffman, and Piwoz 1999). By extrapolation, this increment in growth should translate into a 2 to 13 percent reduction in deaths associated with malnutrition (Black and others 1995).

Brown, Dewey, and Allen (1998) reviewed experiences with large-scale complementary feeding interventions in 14 countries. They demonstrate that it is possible to provide nutritionally improved complementary foods in diverse cultural settings and that poor mothers are willing to prepare new foods their children will eat. However, caregivers face considerable time and resource constraints in providing such foods, especially during episodes of illness. A pilot study in Brazil that implemented nutritional counseling through the Integrated Management of Childhood Illness Program reported significant weight gain in children age one year or more, but not in younger children (Santos and others 2001).

Unfortified complementary foods do not meet all essential micronutrient requirements. Although improvements in vitamin A status do not significantly reduce the incidence of diarrhea and other common childhood illnesses, vitamin A supplementation can reduce the frequency of severe diarrhea (Barreto and others 1994) and mortality (Ross and others 1995). Chapter 28 describes interventions to promote vitamin A intake. Zinc supplementation also reduces the incidence of diarrhea.

Rotavirus Immunization

Almost all infants acquire rotavirus diarrhea early in life, and rotavirus accounts for at least one-third of severe and potentially fatal watery diarrhea episodes—primarily in developing countries, where an estimated 440,000 vaccine-preventable rotavirus deaths per year occur (Parashar and others 2003), compared with about a dozen in a developed country such as France (Fourquet and others 2003). An effective rotavirus vaccine would have a major effect on diarrhea mortality in developing countries.

In 1998, a quadrivalent Rhesus rotavirus–derived vaccine that reduced the frequency of severely dehydrating rotavirus—but not the overall incidence of rotavirus infections—was licensed in the United States (Glass and others 1999). It was cost-effective, even at US$100 for a full course of immunization, when direct economic losses resulting from health care expenses and indirect costs of lost productivity and wages for the caretakers were considered (Tucker and others 1998). The strategy was clear: use the high-priced vaccine routinely in industrial countries to subsidize its use in developing countries. However, postmarketing surveillance detected an apparent increase in a relatively rare event, intussusception, a condition in which the intestine telescopes on itself, causing a potentially serious obstruction (CDC 1999a). The relationship was strongest with the first dose of vaccine given with the first or second dose of diphtheria-pertussis-tetanus vaccine (Peter and others 2002), although this was counterbalanced by a decrease in the incidence of intussusception in older children (Murphy and others 2003).

The overall reduced incidence in immunized infants compared with nonimmunized infants in these studies suggested that the vaccine may actually protect against later adverse events. Nonetheless, the ensuing controversy led to a reversal of the recommendation for universal immunization in the United States and withdrawal of the vaccine from the market, precluding the possibility of its deployment in developing countries (CDC 1999b). Because very young infants are less prone to develop intussusception, initial immunization at birth might have been entirely safe.

Despite this setback, efforts to produce an effective and safe rotavirus vaccine continue. The Rhesus vaccine has been relicensed to another manufacturer, and new vaccines derived from human or bovine rotavirus are undergoing field trials in developing countries (Dennehy 2005). A monovalent human rotavirus vaccine was introduced in Mexico in 2005. The entry of both China and India into rotavirus vaccine development and their potential for manufacturing quality vaccines at low cost will make it easier to deploy an effective vaccine where it is really needed.

Cholera Immunization

Endemic cholera is primarily a pediatric disease, although adult morbidity and mortality are significant, especially during epidemics. The lethality of cholera is due to the physiological consequences of rapid and profound dehydration. Oral rehydration therapy has dramatically improved survival and reduced the cost of treatment. Wherever parenteral and oral rehydration is readily available, even in epidemic situations, a cholera mortality rate above 1 percent indicates failure of the public health system to provide appropriate case management.

A vaccine would further reduce the morbidity and mortality associated with cholera in endemic areas; however, developing an effective, safe vaccine has proven difficult. The most immunogenic and protective vaccines tested thus far are administered orally. Two such vaccines have been licensed: an attenuated live vaccine and a heat-killed vaccine combined with recombinant cholera toxin B subunit, which functions as an immunoadjuvant (Graves and others 2000; Ryan and Calderwood 2000). Many developing countries can produce the killed vaccine, especially without cholera toxin B. Current oral cholera vaccines appear to be safe and offer reasonable protection for a limited period; however, the main users have been individual travelers from industrial countries who may be exposed to the risk of cholera while traveling in endemic areas.

The use of oral cholera vaccine in mass vaccination campaigns as an adjunct to good case management, disposal of fecal waste, and access to safe water during humanitarian disasters has recently been reviewed (WHO 1999). Analysis of an outbreak in Micronesia suggested that a single dose was useful in limiting the spread of cholera (Calain and others 2004). But because ORT is so inexpensive and useful in preventing death, immunization is not a high priority. Only Vietnam routinely deploys cholera vaccine.

Operational information on the costs, logistics, and availability of vaccines for use by global programs and on the vulnerable populations in high-risk settings who would benefit from cholera vaccine remains limited. Although scientific interest in a cholera vaccine remains high, its public health priority is less than that of a vaccine for rotavirus or *Shigella*.

Measles Immunization

Measles is known to predispose to diarrheal disease secondary to measles-induced immunodeficiency. Feachem and Koblinsky (1983) estimate that measles vaccine given to 45 to 90 percent of infants would prevent 44 to 64 percent of measles cases, 0.6 to 3.8 percent of diarrheal episodes, and 6 to 26 percent of diarrheal deaths among children under five. Global measles immunization coverage is now approaching 80 percent, and the disease has been eliminated from the Americas, raising hopes for global elimination in the near future (GAVI 2005), with a predictable reduction in diarrhea as well.

Improved Water and Sanitary Facilities and Promotion of Personal and Domestic Hygiene

Human feces are the primary source of diarrheal pathogens. Poor sanitation, lack of access to clean water, and inadequate personal hygiene are responsible for an estimated 90 percent of childhood diarrhea (WHO 1997). Promotion of hand washing reduces diarrhea incidence by an average of 33 percent (Huttly, Morris, and Pisani 1997); it works best when it is part of a package of behavior change interventions. Effects on mortality have not been demonstrated. However, the required behavior change is complex, and significant resources are needed. Antiseptic soaps are more costly than plain hand soap and confer little advantage. Washing hands after defecating or handling children's feces and before handling food is recommended, but it entails an average of 32 hand washes a day and consumes 20 liters of water (Graef, Elder, and Booth 1993). If soap is too costly, ash or mud can be used, but access to water remains essential (Esrey 1996).

Six rigorous observational studies demonstrated a median reduction of 55 percent in all-cause child mortality associated with improved access to sanitation facilities (Esrey, Feachem, and Hughes 1985). The greatest effect of improving sanitation systems will be in areas of high population density and wherever the entire community, rather than single households, adopts the intervention. Current technology can be costly and difficult to maintain, and in some settings it is simply not feasible.

CASE MANAGEMENT

Two recent advances in managing diarrheal disease—(a) newly formulated ORS containing lower concentrations of glucose and salts and (b) zinc supplementation—used in combination with promotion of exclusive breastfeeding, general nutritional support, and selective and appropriate use of antibiotics, can further reduce the number of diarrheal deaths among children. Families and communities are key to achieving case management goals by making these recommendations routine practice in homes and health facilities.

New Oral Rehydration Solutions

For more than 25 years, UNICEF and WHO have recommended a single formulation of glucose-based ORS considered optimal for cholera, irrespective of cause or age group affected. This formulation has proven effective and without significant adverse effects (Ruxin 1994), but because watery stools persist and duration of diarrhea is not reduced, mothers' and health workers' acceptance of current ORSs has been suboptimal.

During the past 20 years, efforts to improve ORS to treat dehydration from all types of diarrhea and reduce stool output or duration have continued—for example, by reducing the sodium content in line with sodium losses for noncholera diarrhea. Compared with standard ORS, lower sodium and glucose ORS reduces stool output, vomiting, and the need for intravenous fluids (Hanh, Kim, and Garner 2001). If household use increases, new ORS can reduce childhood deaths from noncholera diarrhea (Duggan and others 2004), and it appears to be as effective as standard ORS for children or adults with cholera. A WHO expert group now recommends that ORS containing 75 milliequivalents of sodium and 75 millimoles of glucose per liter (total osmolarity, 245 milliosmoles per liter) be used everywhere (WHO and UNICEF 2004).

Zinc Supplementation

A review of all relevant clinical trials indicates that zinc supplements given during an episode of acute diarrhea reduce both duration and severity and could prevent 300,000 deaths in children each year (Black 2003). WHO and UNICEF now recommend that all children with acute diarrhea be given zinc in some form for 10 to 14 days during and after diarrhea (10 milligrams per day for infants younger than 6 months and 20 milligrams per day for those older than 6 months) (WHO and UNICEF 2004).

Pilot studies in Brazil, Egypt, Ethiopia, India, Mali, Pakistan, and the Philippines that include zinc routinely in the management of acute diarrhea not only show an improvement over ORS alone but also suggest two important new effects: (a) use rates of ORS increase, and (b) use rates of antidiarrheals and antimicrobials decrease significantly (Baqui and others 2004). Large community-based studies are being implemented to corroborate these potentially important findings.

Management of Bloody Diarrhea

The primary treatment for shigellosis, the most common and severe cause of bloody diarrhea, is antimicrobials. The choice of effective, safe, and inexpensive oral drugs for use in developing countries has, however, become problematic because of the increasing prevalence of antimicrobial drug resistance (Salam 1998). Tetracycline, ampicillin, and the fixed-ratio combination of trimethoprim and sulfmethoxazole, once used as first-line treatment, are no longer reliably effective. When epidemic dysentery caused by multidrug-resistant *S. dysenteriae* type 1 appeared in Africa and Asia in the 1980s and 1990s, nalidixic acid was pressed into use (Salam and Bennish 1988). Nalidixic acid is a drug used primarily for urinary tract infections, but it is also effective against *Shigella*. Clinical responses were initially excellent, but with continued use, resistance to nalidixic acid has been increasing in many parts of the world (Dutta and others 2003).

A number of other drugs have been tested and shown effective, including ceftriaxone, azithromycin, pivmecillinam, and some new generation 5-fluoroquinolones, such as ciprofloxacin (Salam 1998). Because of its effectiveness, safety, ease of administration by the oral route, short course, and low cost (US$0.10 for a three-day course for a 15-kilogram child), ciprofloxacin is the current drug of choice for shigellosis (Zimbasa Dysentery Study Group 2002). However, ciprofloxacin-resistant strains are already appearing (Pazhani and others 2004), and it is only a matter of time before resistance becomes widespread, especially if the drug is readily available and indiscriminately used. Because of these concerns, development of a vaccine for *Shigella* is critical. The Diseases of the Most Impoverished initiative, supported by the Bill & Melinda Gates Foundation (Nossal 2003), which promotes vaccine development for *Shigella*, cholera, and typhoid, is a significant advance since the previous edition of this volume.

COST-EFFECTIVENESS OF INTERVENTIONS

Cost-effectiveness ratios of diarrheal disease interventions were calculated by World Bank region in terms of disability-adjusted life years (DALYs) averted for a model population of 1 million, following the standardized guidelines of the Disease Control Priorities Project for economic analyses (see chapter 15). Europe and Central Asia were excluded because data were lacking owing to the low prevalence of disease. Input variables included (a) region-specific diarrhea morbidity rates adapted from Kosek, Bern, and Guerrant (2003); (b) region-specific

underlying mortality rates and age structures provided by the Disease Control Priorities Project; (c) median intervention effectiveness rates (that is, percentage of diarrheal morbidity reduction and percentage of diarrheal mortality reduction); and (d) median per capita intervention costs gathered from the literature and from personal communications (table 19.1).

Because approximately 90 percent of all cases in the developing world occur in children under five, the analysis focused on this age group alone. Uniform intervention effectiveness rates were assumed for all regions because region-specific information was not available. Regional variations in cost-effectiveness were due to regional variations in the prevalence of diarrheal disease, in the diarrhea-attributable morbidity and mortality, and in the intervention cost, where region-specific information was available.

Disability-adjusted life years are averted through the avoidance of cotemporaneous disability and mortality attributable to diarrhea. We did not consider long-term developmental and cognitive effects of childhood diarrhea or the external benefits of interventions unrelated to diarrhea (for instance, benefits of measles immunization unrelated to diarrhea or other health benefits of improved public water and sanitation). Therefore, our estimates err on the conservative side.

We explored two general categories of interventions: early interventions that take place within the first year of life—breastfeeding promotion and immunizations for rotavirus (with the prototype Rhesus reassortant tetravalent vaccine), cholera (with live oral vaccine), and measles—and other interventions that treat an entire cohort of children under five simultaneously (improved water and sanitation). For early interventions, cost-effectiveness ratios were calculated by considering the cost of treating all newborns in a single year and the benefits (DALYs averted) from those treatments that occur over the first five years of life. These benefits include avoided mortality that allows individuals to live to the expected life expectancy for the region. Other interventions included ORT and improved water and sanitation infrastructure. Because a single year of these interventions yields only cotemporaneous benefits—because effectively treated individuals do not necessarily live to life expectancy given that they are likely to be reinfected the next year—we calculated cost-effectiveness of a five-year intervention. Analysis of a five-year intervention enabled us to consider the case in which an entire cohort of children age zero to four avoids early childhood diarrheal mortality because of the intervention and receives the benefit of living to life expectancy.

Disability and deaths averted for those benefiting from improved water and sanitation were calculated from only the fraction of the model populations currently without access. For each region, the proportion of rural and urban children age zero to four currently without access to improved water and sanitation was calculated using region-specific information from *World Bank Development Indicators* (World Bank 2002) for 2000. Infrastructure improvements for rural and urban populations were considered separately because of differences in infrastructure type and cost, although the same effectiveness rates were used for both.

The per child treatment costs and effectiveness rates used are presented in table 19.1. Cost per treatment of ORT varied widely depending on the type and method of ORT implemented. Oral rehydration therapy can be as inexpensive as US$0.02 per child treated—the cost of a home remedy with sugar and salt. However, treatment can become substantially more expensive if commercially manufactured ORS is used or if there are substantial personnel or infrastructure costs (Martinez, Phillips, and Feachem 1993). Finally, our analysis considered only long-run marginal costs (which vary with the number of individuals treated) and did not include fixed costs of initiating a program where none currently exists.

Figure 19.3 shows the cost-effectiveness of all interventions over the first five years of life. Two interventions administered during the first year of life—breastfeeding promotion (US$930 per DALY) and measles immunization (US$981 per DALY)—were the most cost-effective. ORT (US$1,062 per DALY) and water and sanitation in rural areas (US$1,974 per DALY) were the next most cost-effective, but only if they were implemented continuously for five years, thereby allowing an entire cohort of effectively treated children age zero to four to survive past the age at which they are most at risk for diarrheal infection, disability, and mortality. Rotavirus immunization (US$2,478 per DALY), cholera immunization (US$2,945 per DALY), and water and sanitation in urban areas (US$6,396 per DALY) were the least cost-effective.

Among the early interventions, breastfeeding promotion was less effective than other interventions but also less expensive than rotavirus and measles vaccination (table 19.1). Cholera vaccination was less expensive than breastfeeding promotion, but it was also many times less effective because of the significantly higher prevalence of diarrhea that is not related to cholera—making cholera vaccination the least cost-effective of the early interventions considered. Oral rehydration therapy and water and sanitation interventions were more effective than breastfeeding and vaccination interventions in reducing morbidity and mortality caused by diarrhea, but they were also more expensive. However, our analysis for water and sanitation did not consider the benefits of this intervention other than those related to health, and the high cost-effectiveness ratio is more a limitation of our methodology than of the intervention itself.

The high cost-effectiveness ratio for ORT is attributable to the high variation in reported treatment costs, which may inflate the median cost used in this analysis (table 19.2). Given the range of reported treatment costs (table 19.1), the cost-effectiveness ratio of ORT could be as low as US$4 per DALY or as high as US$2,124 per DALY in low- and middle-income countries. High variation in reported treatment costs results in

Table 19.1 Cost and Effectiveness Values Used to Calculate Cost-Effectiveness Ratios for Select Interventions for Diarrhea for Children under Age Five

Model regions	Sources	Source regions or countries	Median cost/child (2001 US$)	Cost/child range (2001 US$)	Median diarrhea morbidity reduction (percent)	Morbidity reduction range (percent)	Median diarrhea mortality reduction (percent)	Mortality reduction range (percent)
Breastfeeding promotion								
Costs								
LMICs, EAP, MENA, SA, SSA	Horton and others 1996; Martinez, Phillips, and Feachem 1993	LMICs, Brazil, Honduras, Mexico	8.98	0.46–17.50				
LAC	Horton and others 1996	Brazil, Honduras, Mexico	1.86	0.46–3.26				
Effectiveness (age 0 to 5)								
All	Feachem and Koblinsky 1984	LMICs			4.5	1–8	10.5	4–17
Rotavirus immunization with RRV-TV								
Costs								
LMICs, EAP, LAC, MENA, SSA	Martinez, Phillips, and Feachem 1993; Narula, Tiwari, and Puliyeh 2004	LMICs, India	53.80	3.33–104.30				
SA	Narula, Tiwari, and Puliyeh 2004	India	104.30	—				
Effectiveness (age 0 to 5)								
All	Parashar and others 1998[a]	Brazil, Peru, R. B. de Venezuela			8.54	—	24.1	—
Cholera immunization with live oral vaccine								
Costs								
LMICs, EAP, MENA, SA, SSA	Cookson and others 1997; Martinez, Phillips, and Feachem 1993	LMICs, Argentina	3.65	1.70–5.60				
LAC	Cookson and others 1997	Argentina	1.70	—				
Effectiveness (age 0 to 5)								
All	de Zoysa and Feachem 1985	Bangladesh			0.095	0.06–0.13	1.5	1–2

Measles immunization								
Costs								
LMICs, LAC, MENA, SA	Duke 1999; Feachem and Koblinsky 1983; Phillips, Feachem, and Mills 1987; Martinez, Phillips, and Feachem 1993; Shann 2000	LMICs, Côte d'Ivoire, Ghana, Indonesia, Papua New Guinea, Zambia	13.26	0.52–26.00				
EAP	Duke 1999; Phillips, Feachem, and Mills 1987; Shann 2000	Indonesia, Papua New Guinea	1.62	0.52–1.10				
SSA	Feachem and Koblinsky 1983; Phillips, Feachem, and Mills 1987	Côte d'Ivoire, Ghana, Zambia	15.00	4.00–26.00				
Effectiveness (age 0 to 5)								
All	Feachem and Koblinsky 1983	LMICs			2.2	0.6–3.8	16	6.4–25.6
Water supply and sanitation improvement								
Costs (rural)								
All	Esrey, Feachem, and Hughes 1985	LMICs	25.00	—				
Costs (urban)								
All	Esrey, Feachem, and Hughes 1985	LMICs	81.00	—				
Effectiveness (age 0 to 5)								
All	Esrey, Feachem, and Hughes 1985; Esrey and others 1991	LMICs			24	22–26	65	—

(Continues on the following page.)

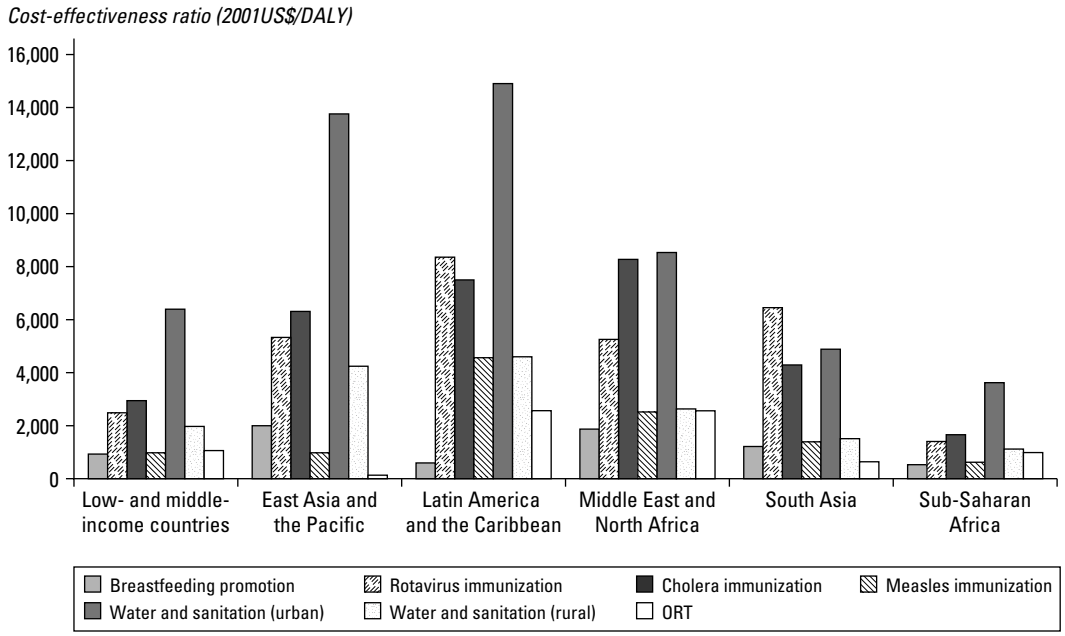
Table 19.1 Continued

Model regions	Sources	Source regions or countries	Median cost/child (2001 US$)	Cost/child range (2001 US$)	Median diarrhea morbidity reduction (percent)	Morbidity reduction range (percent)	Median diarrhea mortality reduction (percent)	Mortality reduction range (percent)
Oral rehydration therapy								
Costs								
LMICs	Horton and Claquin 1983; Islam, Mahalanabis, and Majid 1994; Qualls and Robertson 1989; Shepard, Brenzel, and Nemeth 1986; WHO and UNICEF 2001	Bangladesh, Arab Rep. of Egypt, The Gambia, Honduras, Indonesia, Malawi, Swaziland, Turkey	5.50	0.02–11.00				
EAP	Shepard, Brenzel, and Nemeth 1986	Indonesia	0.71	0.02–1.40				
LAC	Shepard, Brenzel, and Nemeth 1986	Honduras	2.59	0.02–5.16				
MENA	Shepard, Brenzel, and Nemeth 1986	Arab Rep. of Egypt	4.89	0.02–9.75				
SA	Horton and Claquin 1983; Islam, Mahalanabis, and Majid 1994	Bangladesh	2.91	0.02–5.80				
SSA	Shepard, Brenzel, and Nemeth 1986; Qualls and Robertson 1989	The Gambia, Malawi, Swaziland	5.51	0.02–11.00				
Effectiveness (age 0 to 5)								
All	Boschi-Pinto and Tomaskovic forthcoming	LMICs			0	—	95	—

Source: Authors.

LMICs = low- and middle-income countries; EAP = East Asia and the Pacific; LAC = Latin America and the Caribbean; MENA = Middle East and North Africa; SA = South Asia; SSA = Sub-Saharan Africa; — = not available.

a. Effectiveness calculated based on vaccine efficacy reported in Parashar and others (1998) and under the assumption that rotavirus infection is responsible for 20 percent of all diarrheal morbidity and severe infection is responsible for 33.3 percent of all diarrheal mortality.



Source: Authors.

Figure 19.3 Cost-Effectiveness: Intervention at Birth through Age 5 with Benefits that Occur over Five Years (age 0–4)

Table 19.2 Cost-Effectiveness Ratios of Oral Rehydration Therapy Interventions Based on Minimum, Median, and Maximum per Capita Costs (2001 US$/DALY)

Region	Minimum cost	Median cost	Maximum cost
Low- and middle-income countries	4	1,062	2,124
East Asia and the Pacific	4	132	260
Latin America and the Caribbean	20	2,570	5,120
Middle East and North Africa	10	2,564	5,113
South Asia	4	642	1,279
Sub-Saharan Africa	4	988	1,972

Source: Authors.

high variation in cost-effectiveness for the other regions as well. There remains little doubt, however, about the effect of widespread use of ORT on diarrhea morbidity and mortality and about the associated direct and indirect cost savings for treatment and hospitalization.

RESEARCH AGENDA

Good evidence now supports the view that promoting ORT in conjunction with other key interventions, preventive as well as curative, has had a large role in the marked reduction in deaths of children caused by diarrhea (Victora and others 2000). Preventive strategies—such as breastfeeding, improving complementary feeding and using micronutrient supplementation or fortification, and increasing coverage with the full set of Expanded Programme on Immunization vaccines (especially measles vaccine)—are all useful and effective (GAVI 2005). Failure to separately track the full impact of bloody diarrhea—especially *Shigella* infection—on morbidity and mortality or to effectively implement good clinical management (including guidelines for and control over the use of antibiotics) has contributed to the continuing burden of bloody diarrhea and dysentery worldwide and the alarming increase in antibiotic resistance. The challenges for the next decade will be to increase or ensure universal appropriate implementation of these interventions in developing countries and to avoid a situation in which they compete for funding and staff time. Delivery of good-quality services is essential, and much remains to be learned through research before this requirement can be met.

Other interventions, such as vaccines against rotavirus, *Shigella,* or cholera, are either not yet available or not ready for universal administration. Progress toward the development of these vaccines, with the highest priority for the first two, is encouraging, but further investments in research and development will be required before large-scale implementation of these interventions can be considered. The cost of these vaccines will remain a major constraint for poor people, who cannot pay for the costs of development and ensure reasonable profits for industry. However, increased public investment in

fundamental and applied research, vaccine purchase schemes, and development of low-cost, high-quality manufacturing capacity in developing countries may change the prevailing dynamics. By creating public-private partnerships for vaccine development, organized as targeted product development programs, the public sector, private foundations, and industry are taking steps toward these goals.

Because of the fecal-oral transmission of enteric pathogens, improving the supply of safe water and the ability to safely dispose of fecal waste are the best ways to reduce the burden of morbidity and mortality. However, major investments and critical improvements in water and sanitary waste disposal on the necessary scale are unlikely to occur in the next decade or two. Local low-tech solutions can be useful, and enhanced efforts to find ways to improve water cleanliness at the point of use and to build simple latrines that will be used consistently are needed (chapter 41). However, in the face of HIV and the attention being given to tuberculosis and malaria, coordinated efforts to build safe water and sanitation capacity at the local level, one village at a time, that are sufficient to significantly influence the burden of illness are unlikely—even though many more infants and children die each year of preventable and treatable diarrhea than of HIV/AIDS.

The cycle of research, followed by implementation, followed by research has enabled the development of improved tools to manage diarrheal diseases—tools that have the potential to further drive down diarrhea mortality. The challenge is to achieve high coverage and good practice with ORT and correct diarrhea case management, including antimicrobial and nutrition interventions. Interventions to integrate health care through programmatic initiatives such as the Integrated Management of Childhood Illness program, critically evaluated elsewhere in this book (chapter 63), could be essential to ensure this high coverage. Some concern remains that in low-resource settings such targeted vertical programs may be abandoned, to the detriment of the goals for disease burden reduction that they were established to achieve.

The challenge posed by the case management of bloody diarrhea is a different matter. Until a vaccine is available, the keystone for managing bloody diarrhea will continue to be the early use of effective antimicrobial agents. That is made difficult by increasing drug resistance, aided by the widespread indiscriminate and inappropriate use of antimicrobials, and the increasingly difficult task of finding a safe, inexpensive, and effective oral agent and then ensuring that the drug is given in a clinically optimal manner. From a technical perspective, the development of a vaccine against *Shigella* infections is still in its infancy and in need of greater investment. For both watery and bloody diarrhea, the challenge of developing drugs to normalize the pathophysiology caused by the infection remains a scientific challenge and a distant hope.

CONCLUSIONS

Existing interventions to prevent or treat diarrheal diseases have proven their efficacy in reducing mortality, but a major challenge for the next 10 years will be to scale up these interventions to achieve universal utilization coverage. The United Nations Millennium Development Goal to reduce the mortality rate among children under five by two-thirds by 2015 will be easier to attain if the scale-up goals are reached. New products and tools could significantly improve the efficacy of these interventions—for example, rapid specific diagnostics, new treatment strategies based on reversing the pathophysiology of the infection, simple and effective ways to produce clean water and control human waste, and vaccines to prevent illness. However, these products and tools will not become widely available in time to influence the achievement of the Millennium Development Goals. Continued investment in diarrheal disease research across the spectrum of basic, social and behavioral, and applied investigations is, therefore, essential, including expanded behavioral research to understand how parents assess risk and how actionable health messages can be presented in different cultures and settings.

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