Chapter 9

Diarrheal Diseases

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INTRODUCTION

The annual number of deaths from diarrheal diseases among the 0–4 year age group in low- and middle-income countries (LMICs) has dropped by 89 percent, from 4.6 million in 1980 to 526,000 in 2015 (Liu, Hill and others 2016). This striking improvement occurred without vaccines against the major pathogens, except for rotavirus, which is now being scaled-up in LMICs. The incidence of diarrhea has not significantly diminished, especially in young infants (Fischer Walker and others 2012). Therefore, success in reducing mortality appears to be driven largely by improved management rather than prevention (box 9.1). Each day, 4.7 million episodes of diarrheal disease occur, including 100,000 cases of severe diarrhea, along with nearly 1,600 deaths, approximately 9 percent of the mortality in children under age five years (chapter 4 in this volume, Liu, Oza, and others 2016).

Increasing awareness of the adverse effects of nonfatal episodes of diarrhea on infant and childhood growth and development, particularly the role of repeated illness and the potential impact of frequent subclinical infections with the same pathogens, presents a new challenge. Interventions will depend on enhanced understanding of causal pathways, pathogenesis, and sequelae of these infections, with or without symptomatic diarrhea.

Diarrheal diseases are good indicators of the stage of development of communities in LMICs because of the impact of proximal and distal determinants of diarrheal morbidity and mortality, including the availability of safe drinking water; sanitation; level of education, particularly of mothers; income; food security; nutrition; and access to health care, both preventive and therapeutic. Continued progress depends on recognition that intersectoral interventions are integral to required measures to reduce or eliminate diarrheal diseases as a public health concern.

This chapter explores the still-limited evidence on subclinical infections due to known microbial causes of diarrhea, and impacts on intestinal physiology, nutrient absorption, and nutritional status as plausible mechanisms underlying growth stunting and developmental delays. The potential interventions for clinical and subclinical intestinal infections are not necessarily identical, although they undoubtedly overlap. Accordingly, we consider epidemiology, transmission, and mechanisms of disease, as well as social and cultural factors instrumental in determining outcomes. Nutritional needs of infants and young children, breastfeeding practices, use of complementary foods, and management of nutritional rehabilitation of acute malnutrition are covered in greater depth in Das and others (2016, chapter 12 of this volume).

DIARRHEAL DISEASES

Definitions and Classification

Diarrheal diseases are most prevalent in and cause greater morbidity and mortality in children younger than age five years in low-income countries (LICs). The term covers a

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Box 9.1

Major Interventions in Diarrheal Disease

- Early use of oral rehydration solutions
- Appropriate use of antibiotics for bloody diarrhea and dysentery
- Continued breastfeeding
- Nutritional interventions for persistent diarrhea
- Rapid restoration of nutritional status in all diarrhea patients

multitude of infectious causes, ranging from viruses and bacteria to protozoa and occasionally worms, each with distinctive effects. There are three discernable epidemiological and clinical presentations with vastly different consequences for the individuals affected:

- Acute dehydrating watery diarrhea
- Acute inflammatory (bloody) diarrhea and dysentery
- Persistent diarrhea lasting 14 days or more.

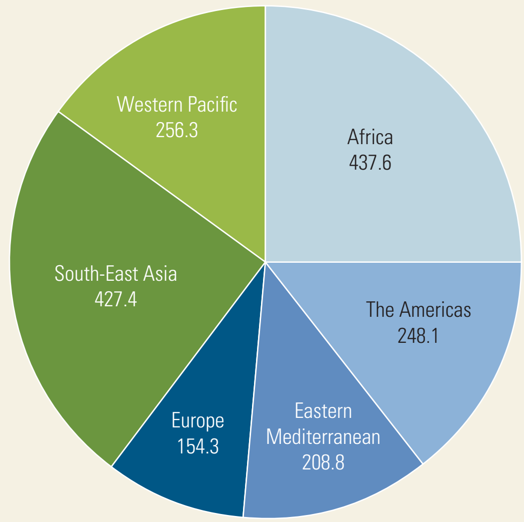
Burden of Infection

Children younger than age five years in LMICs in South Asia and Sub-Saharan Africa experience an average of 2.7 (uncertainty range: 2.1–3.2) episodes of diarrhea per year (Fischer Walker and others 2012). Most are mild and self-limited, lasting an average of 4.3 days. From 0.5 percent to 2 percent are severe, and last an average of 8.4 days (Lamberti, Fischer Walker, and Black 2012). Incidence rates vary but are higher in children in LICs and lower-middle-income countries, and highest in Sub-Saharan Africa (3.3 episodes per child per year) (Fischer Walker and others 2013) (figure 9.1).

Incidence

Despite targeted investments, estimated global diarrhea incidence rates have not changed significantly since 1980 (Bern and others 1992; Fischer Walker and others 2013; Kosek, Bern, and Guerrant 2003; Snyder and Merson 1982). Incidence consistently varies by age, peaking between 6 and 11 months, as immunity transferred from the mother in utero and via breastfeeding wanes; potentially contaminated complementary foods are introduced; and infant mobility increases, allowing for greater contact with sources of pathogens (Fischer Walker and others 2012). The consequences are also determined by

Figure 9.1 Regional Burden of Diarrhea, Ages 0–4 Years, 2010



Source: Fischer Walker and others 2013.

disease severity, although few studies separately analyze severe episodes or identify bloody diarrhea or dysentery or episodes that become persistent. One systematic review of the limited data available suggests that 5 percent to 15 percent of watery diarrhea cases progress to persistent diarrhea (Lamberti, Fischer Walker, and Black 2012). More than 50 percent of severe episodes occur in Sub-Saharan Africa and South-East Asia (figure 9.2).

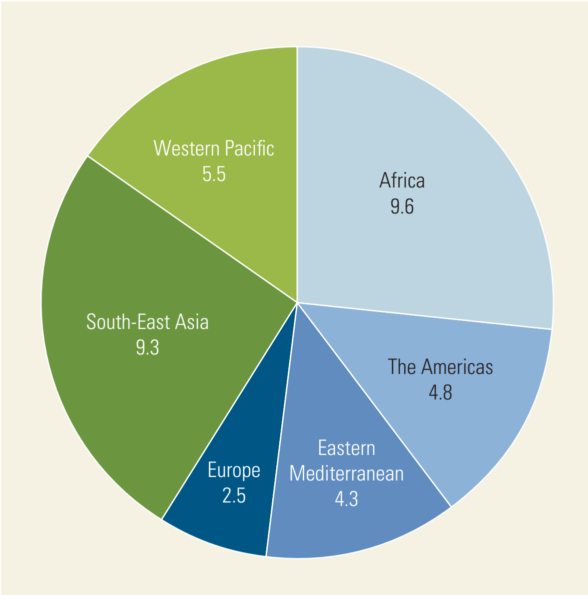
Mortality

The 2015 estimated number of deaths due to diarrhea—526,000 under age five years—represents an 89 percent decline from 1980 and a striking 58 percent reduction from 2000 to 2015 (Liu, Oza, and others 2016, chapter 4 in this volume), even though the total population in this age group increased by approximately 11 percent (figure 9.3). Because 72 percent of diarrhea deaths occur in the first two years of life, targeting this age group will yield the greatest future impact on mortality (Fischer Walker and others 2013). A thorough discussion of the cause-of-death structure and mortality decline is presented in Liu, Hill, and others (2016, chapter 4 in this volume); Sub-Saharan Africa and South Asia account for 90 percent of the total.

Etiologies

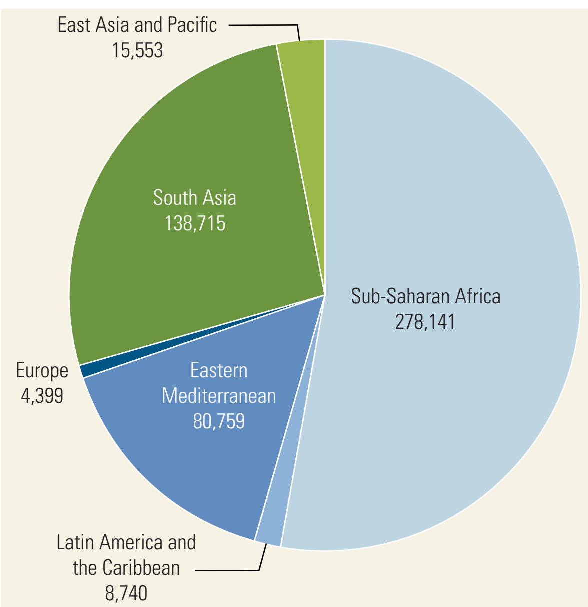
Although many agents cause diarrheal disease, a few account for a major portion of the burden. In one study, almost 40 percent of cause-specific attributable

Figure 9.2 Regional Burden of Severe Diarrhea Episodes, Ages 0–4 Years, 2010



Source: Fischer Walker and others 2013.

Figure 9.3 Regional Burden of Diarrhea Mortality, Ages 0–4 Years, 2015



Source: Liu, Hill, and others 2016.

diarrhea mortality was due to two organisms: rotavirus (27.8 percent) and enteropathogenic *Escherichia coli* (11.1 percent) (Lanata and others 2013). Another large, multisite, clinic-based prospective case-control study of children under age five years with moderate to severe illness identified four pathogens—rotavirus, *Cryptosporidium*, enterotoxigenic *E. coli*, and *Shigella*—responsible for most attributable episodes of moderate to severe diarrhea (Kotloff and others 2013).

Rotavirus was the leading cause during the first year of life, followed by *Cryptosporidium*. Rotavirus remained first in the age 12–23 month cohort, followed by *Shigella*; among children ages 24–59 months, that ranking reversed. The odds of dying for children with moderate to severe diarrhea were 8.5 times higher (95 percent confidence interval 5.8–12.5, $p < 0.0001$) than for control subjects, with 33 percent of deaths occurring 21 days to 90 days following enrollment in the study. Most deaths were in infants (56 percent) and toddlers (32 percent); 55 percent of the deaths occurred at home or outside a medical facility. Certain pathogens, such as rotavirus, *Shigella*, *Vibrio cholerae*, and adenovirus serotypes 40/41, were more commonly isolated in children with moderate to severe illness. Almost three-quarters (72 percent) of controls without diarrhea also harbored one or more putative pathogens, and 31 percent had two or more, reflecting the fecally contaminated environment in which they live (Kotloff and others 2013). Future studies that include diagnostic capacity for noroviruses and other emerging pathogens may change these rankings.

Transmission and Epidemiology

Understanding transmission routes and epidemiology is critical for effective prevention and mitigation. Although transmission is fundamentally the same for all agents (fecal-oral transmission), there are diverse pathways and routes involved, including direct person-to-person transmission mediated through feces-contaminated fingers or inanimate objects (fomites); and indirect transmission via contaminated food or water in or outside the home, including agricultural fields or seafood sources irrigated or contaminated with pathogen-laden sewage. Microbial characteristics determine the number of organisms required to cause illness (the inoculum size); small inoculum pathogens are readily transmitted directly from person to person, whereas high inoculum pathogens first need to multiply in food or water. Host characteristics, such as immunity, often interplay with microbial characteristics. Pathogens also must survive diverse nonspecific host defenses, such as stomach acid. Some pathogens, for example, *Shigella*, are inherently acid resistant, so small inocula survive into the duodenum; others, like *V. cholerae*, are acid sensitive, and large inocula are essential to survive passage through the stomach.

Reduced gastric acidity significantly reduces the required inoculum size for acid-sensitive pathogens, for example, in individuals with peptic ulcer disease treated by gastric surgery or drugs to reduce acid secretion. Infants, including preterm, produce acid, but the amounts and response to stimuli are diminished compared with older children, potentially increasing their susceptibility. Malnutrition (Gilman and others 1988) and *Helicobacter pylori* infection of the stomach (Windle, Kelleher, and Crabtree 2007) also impair gastric acid production in young children. Sustained early infection with *H. pylori* in Gambian infants under age one year was associated with subsequent growth faltering, even though they had access to good primary health care, treatment of acute childhood illness, and nutritional supplements (Thomas and others 2004).

Other factors include lack of refrigeration for food, or flies that can transfer pathogens from feces in the environment to unprotected food or water in households (Farag and others 2013; Lindsay and others 2012). A risk factor study for *Shigella* infection in Thailand identified poor breastfeeding practices; poor water supply; unsafe sanitation; lack of fly control; and inadequate personal hygiene, in particular handwashing, as major targets for interventions (Chompook and others 2006). Multiple routes of transmission exist; hence any single intervention may have limited impact.

Natural History

Exposure to pathogens does not necessarily lead to infection, and infection does not necessarily result in clinical illness. Several factors explain the differences:

- The inoculum size and the biology of the pathogen, in particular, its virulence attributes
- The susceptibility of the host, including previous exposure and preexisting immunity, including passively acquired immunity in utero or from breast milk consumption
- The health and nutritional status of the individual at the time of exposure.

As a result, natural history following infection can vary from no symptoms, to mild-moderate self-limited illness, to severe life-threatening disease. Individuals who are healthier and better nourished at exposure are less likely to develop severe illness after a given inoculum of a specific pathogen. Early and appropriate management of clinical manifestations improves outcomes and can be effectively promoted at the community level.

Watery Diarrhea

Watery diarrhea is classified according to stool volume: mild when less than 5 percent of body weight, moderate between 5 percent and 10 percent, and severe and potentially life-threatening when in excess of 10 percent. With increasing fluid losses, intravascular volume diminishes and blood pressure drops. Without replacement of fluids (rehydration), hypotension can progress to circulatory failure, dysfunction of critical organs, and death. Early initiation of rehydration, for example, using oral rehydration solutions (ORS), can mitigate or prevent progression to more severe dehydration. Such interventions are not only life saving; they can also reduce duration of illness and extent of nutrient losses.

Inflammatory Diarrhea and Dysentery

Some pathogens cause inflammation of the bowel wall, with leukocyte (white blood cell) infiltration and damage resulting in mucosal ulcers; bleeding; leukocyte exudates; production of peptide cytokines that mediate dramatic, often prolonged, changes in appetite and metabolism; and direct nutrient losses. Bacterial pathogens causing inflammatory diarrhea and dysentery (a clinical syndrome of frequent small-volume bloody mucoid stools, abdominal cramps, and tenesmus [the urgency to pass stool]) generally require antibiotics to treat the infection, resolve inflammation, allow the mucosa to heal, and reverse nutritional deterioration. Early effective antibiotic treatment shortens duration of these illnesses, limits acute complications, and reduces longer-term impacts.

Persistent Diarrhea

Diarrhea episodes lasting from 7 days to 13 days, termed *prolonged,* impair growth and increase the risk of progression to *persistent diarrhea* (Moore and others 2010). Moore and others (2010) find that prolonged diarrhea accounted for only 11.7 percent of episodes but 25.2 percent of all days of diarrhea; persistent diarrhea accounted for only 4.7 percent of episodes but 24.5 percent of days with diarrhea. Progression from acute to prolonged diarrhea increased the overall risk of persistent diarrhea from 4.8 percent to 29.0 percent (relative risk 6.09, 95 percent confidence interval 4.96–7.45). Once diarrhea is persistent, mortality rates increase sharply (Grimwood and Forbes 2009), in some settings accounting for as much as 50 percent of overall diarrhea mortality. Continuing reductions in acute diarrhea deaths has increased attention to mortality associated with persistent diarrhea, which is relatively heightened as a consequence.

A few pathogens have been particularly associated with persistence or are preferentially identified when an episode becomes persistent, including a subgroup of diarrhea-causing *E. coli* designated enteroaggregative, *Cryptosporidium parvum, S. flexneri*, *S. dysenteriae* type 1, and *Giardia intestinalis (lamblia)*. Serial exposure to these or other pathogens may also be involved. As the duration of illness extends, malnutrition becomes increasingly prominent because of ongoing mucosal injury, anorexia, malabsorption, and nutrient losses (Newman and others 2000). *Shigella* infection, characterized by intense tissue catabolism and nutrient losses, almost doubles the risk of persistent diarrhea (Ahmed and others 2001). As the frequency of *Shigella* infection dropped from 1991 to 2010 in Bangladesh, the frequency of persistent diarrhea diminished as well (Das and others 2012). Mucosal injury also explains why the manifestations of persistent diarrhea are primarily those of malabsorption and malnutrition, and why careful dietary and nutritional management is needed until mucosal damage is reversed and new, normally functioning epithelial cells are regenerated.

NEW FRONTIERS: SUBCLINICAL INFECTIONS AND ENVIRONMENTAL ENTERIC DYSFUNCTION

Subclinical Infections

Mounting and diverse evidence suggests that subclinical infections with diarrhea pathogens can cause physiological and structural alterations of the gut with adverse consequences on child nutrition and growth. For example, a handwashing intervention not only reduced the number of diarrhea episodes by 31 percent (4.3 versus 3.0 episodes, $p < 0.05$) and days of diarrhea by 41 percent (9.67 versus 16.33, $p = 0.023$) (Langford, Lunn, and Panter-Brick 2011) but also showed that, *independent of clinical diarrhea*, infants with the highest values of a biomarker of mucosal damage (lactose-to-creatinine ratio) indicative of abnormal mucosal permeability had significantly lower height-for-age z-scores ($p = 0.01$), weight-for-age z-scores ($p < 0.001$), and weight-for-height z-scores ($p = 0.034$) (Langford, Lunn, and Panter-Brick 2011). This finding suggests that subclinical infections may reduce nutrient absorption and impair growth by many of the same mechanisms present during clinical episodes. Although the malabsorption may be limited, chronicity may be sufficient to produce overt malnutrition over time, especially when dietary nutrient intake is marginal.

Subclinical infections with intestinal pathogens have been shown to underlie growth faltering (Guerrant and others 1999). *Giardia intestinalis*, which causes diarrhea associated with growth retardation in infants (Newman and others 2001), is often identified in the stools of asymptomatic children in endemic areas, and a correlation between asymptomatic *Giardia* infection and growth faltering has been reported (Prado and others 2005). Asymptomatic first *Cryptosporidium* infections in Peruvian infants are also associated with slower weight gain compared with uninfected infants, albeit to a lesser extent than infants with symptomatic infections (Checkley and others 1997). However, because asymptomatic infections were twice as common as diarrhea, their ultimate effects might exceed those of clinical diarrhea. Moreover, infants infected with *Cryptosporidium* during the first six months of life remained stunted at age one year, despite some interval catch-up growth (Bushen and others 2007; Checkley and others 1998). Early colonization with *H. pylori* has also been identified as a precursor of growth faltering in children under age five years in The Gambia (Thomas and others 2004).

Environmental Enteric Dysfunction

Intestinal biopsy studies of the upper small intestine from asymptomatic adults in tropical countries reported 30 years to 40 years ago documented structural differences compared with healthy adults from temperate countries, including shorter blunted villi, which reduced the surface area covered by epithelial cells, and increased inflammatory cells, accompanied by diminished ability to absorb test sugars, fat, or vitamin B12 (Baker 1976). Limited biopsies from infants and young children revealed normal, slender finger-like villi at birth, but jejunum of older infants and children resembled the adult gut, suggesting these changes were acquired after birth (Baker 1976). Similar changes occurred over one to two years in healthy young adult expatriates living in Bangladesh (Lindenbaum, Kent, and Sprinz 1966) and Thailand (Keusch, Plaut, and Troncale 1972), with few or no symptoms other than soft stools and mild weight loss. This constellation of findings was called *tropical* or *subclinical enteropathy/jejunitis/malabsorption*, and normalized after the subjects returned home (Lindenbaum, Gerson, and Kent 1971). The same resolution was observed in healthy South Asians living in the United States or the United Kingdom the longer they resided outside their home countries (Gerson and others 1971; Wood, Gearty, and Cooper 1991). However, the significance of enteropathy remained unclear, and interest waned because no relationship to pathogenesis of tropical sprue, a real disease, was apparent.

In retrospect, the extent of the weight loss associated with enteropathy in adults was dismissed too quickly; the same decrement occurring in young infants would raise concerns about incipient malnutrition. Recently, investigators in Sub-Saharan Africa, using newer assessments of intestinal permeability, identified alterations in young infants associated with altered gut histology and poor growth in early childhood (Campbell, Lunn, and Elia 2002; Campbell and others 2004). Inflammatory cells present in the intestinal mucosa were identified as immunoreactive T cells (Veitch and others 1991), linked to strong pro-inflammatory local cytokine responses (Campbell and others 2003). These findings have rekindled interest in their physiological significance, analogous to inflammatory bowel disease. Although the mechanisms have remained uncertain, a nexus of microbial exposure, mucosal pathology, increased permeability and malabsorption, immune activation leading to poor response to mucosal vaccines, and growth stunting has been postulated (Prendergast and Kelly 2012). Inadequacy of dietary intake, especially when diet quality is also marginal, would likely exacerbate the impact of any level of malabsorption.

In parallel, growth stunting, a marker of chronic undernutrition that is common among infants and children living in poverty in LMICs, is associated with increased childhood morbidity and mortality and poor longer-term functional outcomes, including cognitive development; reduced years of schooling; and diminished productivity in adulthood, measured by income attained and other economic productivity markers (Dewey and Begum 2011). If changes in intestinal structure and function develop in young infants in impoverished communities early in life, presumably due to environmental exposure to still-unknown inciting factors, the consequence may be initial malabsorption leading to early malnutrition, growth faltering, and increased susceptibility to diarrheal disease (Keusch and others 2013). This has been termed *environmental enteric dysfunction* (EED) to stress the importance of the functional alterations.

Although systematic serial observations of intestinal structure in these young infants remains limited, a number of surrogate biomarkers of gut inflammation or immune activation have been identified (Kosek and others 2013). A composite activity score of three stool biomarkers of intestinal inflammation (neopterin, alpha1-antitrypsin, and myeloperoxidase) during periods without diarrhea is inversely correlated with linear growth. Children with the highest score grew 1.08 centimeters less than children with the lowest score during the subsequent six months, even controlling for the incidence of diarrheal disease. Similarly, fecal levels of REG1B protein, which plays a role in cell differentiation and proliferation in the intestinal tract and is reported to be increased in other gut inflammatory conditions, was predictive of linear growth in three-month-old birth cohorts in Bangladesh and Peru, independent of their length-for-age z-score at the time the sample was taken (Peterson and others 2013). If confirmed, such assessments of intestinal health may become important biomarkers of EED and a predictor of growth (box 9.2).

If EED leads to malnutrition, impaired immune function, and increased susceptibility to and severity of subsequent diarrheal episodes in early infancy, it may be a major force for stunting, particularly when recurrent episodes restrict the capacity for catch-up growth (Salomon, Mata, and Gordon 1968). The effects of diarrheal diseases can be both short term and long term. In the short term, patients experience adverse systemic impacts on appetite, metabolism, and nutrition due to the infection. In the longer term, mucosal changes can alter digestion, absorption, and assimilation of nutrients from food. In bloody diarrhea and dysentery, structural mucosal damage leads to protein-losing enteropathy as blood proteins leak into the gut lumen (Bennish, Salam, and Wahed 1993). These effects can continue for weeks after shigellosis (Alam and others 1994; Raqib and others 1995), resulting

Box 9.2

Biomarkers to Assess Environmental Enteric Dysfunction

Category	Potential biomarkers
Intestinal absorption and mucosal permeability	D-Xylose, mannitol, or rhamnose absorption; lactulose paracellular uptake; α1-antitrypsin leakage into gut lumen
Enterocyte mass and function border	Plasma citrulline, conversion of alanyl-glutamine to citrulline, or both; lactose tolerance test (as a marker of microvillus damage)
Inflammation	Plasma cytokines, stool calprotectin, myeloperoxidase, or lactoferrin
Microbial translocation and immune activation	Stool neopterin; plasma lipopolysaccharide (LPS) core antibody, LPS binding protein, or both; circulating soluble CD14

in progressive malnutrition rather than convalescence and repair. As a consequence, mortality over the three months following successful discharge from an expert treatment center in Bangladesh almost doubled (2.8 percent versus 4.9 percent) in children with documented shigellosis compared with watery diarrhea without evidence of *Shigella* (Bennish and Wojtyniak 1991).

The early effects of EED can lead to repeated infection because of similar risk factors, including increased exposure to enteric pathogens, limited and poor quality water, lack of sanitary facilities, poor household hygiene, and poor diets. Understanding the pathogenesis of EED is a prerequisite to the selection of optimal interventions.

INTERVENTIONS FOR DIARRHEAL DISEASES

Interventions for diarrheal diseases can be divided into therapeutic and preventive (box 9.3). Some interventions, such as nutritional support and zinc supplementation, can be beneficial for both purposes. Interventions can also be classified by scale: individuals, households, or communities. Some depend on infrastructure; others are behavioral, determined by understanding and compliance at the level of the household, community, or health care system. Although most interventions are not new, innovations to make them more accessible or effective can have adverse unintended consequences, such as increased and inappropriate use of antibiotics.

Box 9.3

Interventions for Diarrheal Diseases

Category	Options
Therapeutic	Oral rehydration solutions
	Antimicrobials for bloody diarrhea or dysentery
	Nutritional treatment of persistent diarrhea
	Zinc supplementation
Preventive	Protected safe water
	Handwashing Sanitary disposal of fecal waste
	Vaccines
	Improved nutrition: vitamin A, zinc

Therapeutic Interventions

Treatment with therapeutic interventions focuses on reversing dehydration, providing antibiotics for inflammatory bacterial diarrhea and dysentery, and special nutritional interventions to overcome malabsorption associated with persistent diarrhea, although general dietary interventions to mitigate nutritional deterioration during and after diarrhea are relevant to all diarrheal diseases. Two analyses of a package of interventions individually shown to have an impact on mortality (ORS; zinc; antibiotics for dysentery; rotavirus vaccination; vitamin A supplementation; improved access to safe water, sanitation, and hygiene; and breastfeeding) estimate a reduction in mortality of 54 percent to 78 percent if implemented to a feasible level, and by 92 percent to 95 percent if universally applied (Bhutta and others 2013; Fischer Walker and others 2011).

Other strategies, including pre- and probiotics to counter adverse changes in intestinal microecology, or fecal transplants to reconstitute a healthy microbiota after illness or antibiotic treatment, are not discussed further because available efficacy data are limited, often contradictory, of poor reliability, or difficult to interpret. Similarly, the use of drugs to restore physiological functions of the intestine is not considered because of limited reliable data in target human populations.

Oral Rehydration Solutions

ORS may prevent as many as 93 percent of diarrheal deaths (Munos, Fischer Walker, and Black 2010). The therapy works because the co-absorption of glucose and sodium is preserved during watery diarrheas; hence, ORS containing optimal concentrations of glucose and salt results in net uptake of sodium and chloride, effectively expanding the intravascular compartment regardless of age, and significantly reduces the need for intravenous fluids for all but the most severely dehydrated patients or those with intractable vomiting. New formulations with lower concentrations of glucose and sodium reduce the likelihood of hypernatremia during treatment of noncholera dehydration, reduce total stool output and vomiting, and reduce the need for supplementary intravenous fluids (Hahn, Kim, and Garner 2002); the World Health Organization (WHO) now recommends such formulations (WHO and UNICEF 2004).

Further modifications have been proposed, for example, rice-based formulations or the addition of certain amino acids (glycine, alanine, or glutamine) to further increase sodium absorption and hasten intestinal repair (Atia and Buchman 2009), or supplementation with zinc to improve outcomes (Awasthi and IC-ZED Group 2006;

Lazzerini and Ronfani 2013). However, the primary goal of ORS remains enhancing salt and water absorption. Although simple home-prepared ORS may be sufficient in mild diarrhea, the WHO formulation is preferred for more severely dehydrated patients.

Cholera and cholera-like enterotoxigenic *E. coli* infections raise additional issues because of prodigious volume losses; vomiting; and comorbidities, such as pneumonia, that affect outcomes. When intravenous rehydration is required because of shock, switching to maintenance ORS when clinical status improves is effective. Interest in antiemetic drugs, for example, ondansetron, is limited because safety and efficacy data in poorly nourished children under age five years are not available, and because of the added cost (Ciccarelli, Stolfi, and Caramia 2013).

Unfortunately, use of ORS for clinic- and home-based treatment has stagnated in most countries reaching, on average, 30 percent to 38 percent of the children who should receive it (Santosham and others 2010; WHO and UNICEF 2009). This absence of use is due in part to a lack of parental understanding of the benefit of ORS, because stool volumes may remain high even as hydration improves. Parental expectations of treatment are also influenced by previous experience. For example, Brazilian physicians recommend intravenous fluids for most children with moderate dehydration, which sends the wrong message to caregivers about professionals' trust in the efficacy of ORS (Costa and Silva 2011). Community-based initiatives, such as home visits by community health workers, and community-based delivery mechanisms have increased the use of ORS by an average of 160 percent, with an 80 percent increase in the use of zinc-ORS, as well as a 75 percent reduction in antibiotic use (Das, Lassi, and others 2013). Limited information precludes rigorous assessment of the impact of community case management on mortality, but trends suggest a decrease of 63 percent among children ages 0–4 years (95 percent confidence interval 7–85 percent) and 92 percent (95 percent confidence interval 13–100 percent) among children age 0–1 year.

Antibiotics

The pervasive, indiscriminate overuse of antibiotics is dangerous because it promotes emergence of drug resistance. Overuse is fostered by multiple causes: caregiver expectations; lack of knowledge; prescriber behavior; lack of etiology-specific point-of-care diagnostics; failure of regulation and its enforcement to control quality of and access to medicines; and availability without prescription in pharmacies, shops, and markets even when prescriptions are required (Adriaenssens and others 2011). Improved practitioner and parent knowledge and attitudes reduce inappropriate use (Clavenna and Bonati 2011).

Despite repeated pleas for more evidence-based use of antibiotics, better education of practitioners and the public, and systematic surveillance of antibiotic use and resistance, more than 50 percent of all medicines are still inappropriately prescribed, dispensed, or sold, and 50 percent of patients use them incorrectly (WHO 2010). Examples abound. Government health centers in The Gambia ordered antibiotics for 45 percent of young children with simple diarrhea without dehydration (Risk and others 2013). In the Democratic Republic of Congo, more practitioners relied on pharmaceutical companies for prescribing recommendations (73.9 percent) than on professional guidelines (66.3 percent) or university training (63.6 percent), and more practitioners used the Internet for guidance (45.7 percent) than used WHO publications (26.6 percent) (Thriemer and others 2013). Although 85 percent of caregivers in a peri-urban slum in Lima, Peru, expressed confidence in decisions made by physicians, even withholding antibiotics when advised, 65 percent of caregivers still believed antibiotics were necessary for acute diarrhea, and nearly 25 percent reporting leftover antibiotics at home said they would use them for a future illness (Ecker and others 2013). In Nigeria, 47 percent of young children with diarrhea seen at a third-level hospital had already received antibiotics without a clinician's recommendation (Ekwochi and others 2013). Caregivers in India and Kenya ranked antibiotics higher than ORS for diarrhea by more than two to one, partially explaining the low use of ORS and the high use of antibiotics (Zwisler, Simpson, and Moodley 2013).

Inappropriate use of antibiotics. Experts agree that antibiotics are usually unnecessary for acute watery diarrhea; most episodes are mild and self-limited, and many are due to viruses, especially among young children (Kotloff and others 2013). It is time to abandon routine use of antibiotics to shorten duration of illness in moderate to severe dehydration. Although *V. cholerae* has remained sensitive to most antibiotics, the long-term tradeoff of antibiotic use is selection for drug resistance, which is now increasing among *V. cholerae* strains (Ghosh and Ramamurthy 2011) and is potentially transferable to other enteric pathogens as well (Kruse and others 1995). The emergence of resistance in *V. cholerae* to quinolone (Kim and others 2010), the most useful antibiotic for grossly bloody diarrhea and dysentery, further raises the level of concern about routine inclusion of antibiotics for cholera. Routine use of quinolone may be appropriate in certain circumstances. These include treatment of the most severely purging cases (Harris and others 2012), during epidemics that overwhelm clinical capacity (Ernst and others 2011), or when elimination of viable *V. cholerae* in stool would diminish the potential for spread within or between countries (MacPherson and others 2009; Tatem, Rogers, and Hay 2006).

Appropriate use of antibiotics. Morbidity and mortality due to inflammatory diarrheas, most often caused by *Shigella* invading the intestinal mucosa, are not caused by dehydration but rather by tissue damage. Large numbers of leukocytes are recruited to the invasion site, leading to epithelial cell death and ulceration, with release of cytokine mediators of metabolism that result in nutritional deterioration. These metabolic responses persist for weeks after acute infection, and drive continuing malnutrition (Raqib and others 1995), a major reason why post-shigellosis mortality remains high for months after bloody diarrhea or dysentery ceases. The clinical hallmarks of inflammatory diarrhea for which antibiotics are indicated include grossly bloody stools or dysentery, usually with accompanying fever. Most episodes are bacterial in etiology, and *Shigella* or sometimes-related enteroinvasive *E. coli* serotypes are most common.

Without point-of-care diagnostics to identify specific causes, the pragmatic assumption is that bloody diarrhea is bacterial in origin and antibiotics appropriate for shigellosis should be initiated. This regimen will likely be adequate for other possible bacterial etiologies. However, resistance of *Shigella* species to some, or multiple, antibiotics is increasing (Bhattacharya and others 2011; Mota and others 2010), but the pattern is locale specific and dynamic (Das, Ahmed, and others 2013). Ongoing drug sensitivity surveillance is essential to guide therapeutic decisions (O'Ryan, Prado, and Pickering 2005). Because such surveillance is not yet feasible in most LMICs, empiric treatment decisions remain the norm. Ciprofloxacin, azithromycin, or pivmecillinam, where available, are reasonable initial choices, reserving ceftriaxone for treatment failures, defined as lack of clinical improvement within 48 hours to 72 hours (Erdman, Buckner, and Hindler 2008; Traa and others 2010).

ORS may be useful but insufficient, because dehydration is minor and, unlike inflammation, does not drive severity or mortality. Mild shigellosis, typically associated with *S. sonnei* infection, without grossly bloody stools is generally self-limited and can be treated like other watery diarrheas with ORS alone, even if stool microscopy reveals some red or white blood cells. The challenge is to increase adherence to current principles and guidelines to limit the use of antibiotics unless clinical criteria are met.

Preventive Interventions

Preventive measures to reduce exposure to enteric pathogens involve improving the quality of water for drinking and cooking; the quantity of water available for personal and household hygiene; safe storage of food; handwashing; and sanitary disposal of fecal waste, including treatment of sewage to inactivate microbial pathogens. Vaccines to improve immunity are presently limited to rotavirus, the only vaccine approved and increasingly available to prevent moderate to severe rotavirus diarrhea. Improving health and immune function by improving nutritional status is another effective measure.

Vaccines

For public health, prevention is always preferable to treatment, but effective treatment is necessary when prevention fails. Immunization is among the more cost-effective public health tools when deployed at scale (WHO, UNICEF, and World Bank 2009). The complexity for diarrheal disease is that vaccines are pathogen specific and often serotype or serogroup specific. For example, different formulations would be necessary for *V. cholerae* O1 and O139; even if combined in the final product, a vaccine for each would be required. Unfortunately, vaccines for diarrheal diseases have met with developmental challenges, in part because the basis of effective immunity is poorly understood, and because diarrheal disease is most problematic in LICs where resources to purchase vaccines is limited, thereby reducing incentives for research and development.

Rotavirus. Two vaccines produced by Merck and GlaxoSmithKline are widely used in high-income countries and many middle-income countries but are only beginning to be introduced in LICs. Other rotavirus vaccines have been licensed in China or Vietnam for local use only. A less expensive Indian-manufactured vaccine named ROTAVAC® (Bharat Biotech) has been prequalified by the WHO and is approved for use in India. In efficacy trials, it reduced severe episodes by more than 56 percent in the first year of life, by nearly 49 percent in the second year of life, and overall by 55 percent (Bhandari and others 2014). It was also safe. The most important adverse event associated with rotavirus vaccines, intussusception, was assessed through active surveillance. Eight events occurred in India between 112 days and 587 days after vaccination, well beyond the known timing of vaccine-related intussusception, and so were unlikely to be vaccine related. Continued monitoring subsequent to introduction is necessary and is planned (Bhandari and others 2014).

Delayed introduction of rotavirus vaccines in LICs, where the vast majority of severe rotavirus infection and most mortality occurs, is a consequence of several factors:

- Price
- Lower reported efficacy than in high-income countries
- Uncertainty about the risk of complications, such as intussusception
- National policy failures to prioritize national childhood vaccine programs.

Gavi, the Vaccine Alliance has added rotavirus to its support program, and 19 of the 35 Gavi-eligible countries now include rotavirus vaccine in their routine immunization programs; this number is expected to increase to 30 during 2015 (Gavi Alliance 2014). ROTAVAC may ultimately be marketed outside of India in LICs. Universal implementation of rotavirus vaccine could prevent many episodes of severe diarrhea (Fischer Walker and Black 2011) and reduce the number of diarrhea deaths under age five years by 70,000–85,000 per year, and reduce hospitalizations and associated costs by an average of 94 percent (Munos, Fischer Walker, and Black 2010). The cost of hospital admission for rotavirus diarrhea in India may be as much as 5.8 percent of annual household income (Mendelsohn and others 2008), or about US$66 per hospitalization (Sowmyanarayanan and others 2012).

Cholera. The global burden of morbidity and mortality of cholera is high; an estimated 2.8 million cases and 91,000 deaths occur annually in endemic countries (Ali and others 2012). Incidence is highest in children under age five years, who may account for as much as 50 percent of cholera mortality. It is notable that 67 percent of inpatient cholera deaths in Bangladesh were actually associated with pneumonia rather than dehydration (Ryan and others 2000), increasing to 80 percent in children under age one year. Identification and appropriate treatment of these patients will reduce mortality.

Inexpensive oral killed whole bacteria cholera vaccines developed in India and Vietnam are effective (Clemens 2011); the former is WHO prequalified. Production and use of these vaccines remains limited, even for domestic needs, although widespread introduction could reduce incidence by as much as 52 percent (Das, Tripathi, and others 2013). Modeling based on clinical trials in Bangladesh suggests a herd immunity effect with as high as a 93 percent reduction in incidence if only 50 percent of the population is immunized (Longini and others 2007). Reduced incidence would also reduce the use of antibiotics (Okeke 2009).

In contrast to endemic cholera, the experience in Haiti following the introduction of cholera in 2010 is enlightening. In the first two years, 604,634 cases—with 329,697 hospitalizations and 7,436 deaths—were reported to the Ministry of Health (Barzilay and others 2013). With international support to improve case management, the case fatality rate rapidly decreased; within three months it was approximately 1 percent, a threshold indicator of effective case management for cholera (WHO 2012).

Mass immunization was under consideration as a way to prevent cholera from becoming endemic in Haiti. However, analyses concluded it should not be deployed because of serious obstacles, including limited vaccine availability, complex logistics, operational challenges of a multidose regimen, and population displacement and potential civil unrest (Kashmira and others 2011). Cholera has indeed become endemic in Haiti and is the leading etiology of diarrhea in hospitalized patients (Steenland and others 2013). A subsequent vaccine demonstration trial in Haiti showed that high coverage with two doses of vaccine was, in fact, feasible (Rouzier and others 2013). This paved the way for an ambitious immunization program, justified by the dreadful state of water and sanitation facilities in the country. The potential of vaccines to mitigate the extent of epidemic cholera and improve the impact of effective case management for dehydration has led to a proposal for an oral cholera vaccine stockpile that would be available for use in future emergency and humanitarian disaster settings (Waldor, Hotez, and Clemens 2010); this plan is being implemented through the WHO and the International Coordinating Group (WHO 2013).

Other pathogens. Vaccines for other enteric pathogens remain under research and development; no licensed products are available, particularly for agents highly associated with moderate to severe diarrhea, including enterotoxigenic *E. coli*, *Shigella*, and *Cryptosporidium*. More recently, norovirus has been identified as a potential significant cause of global diarrhea morbidity and mortality and a target for vaccine development (Patel and others 2008). Vaccines for these infections are a high priority, but it will be many years before licensed products become available for scale up in LICs.

It has long been recognized that measles immunization also reduces incidence and mortality from diarrheal disease (Feachem and Koblinsky 1983), presumably because measles is immunosuppressive and exacerbates malnutrition. The current campaign for measles elimination through universal immunization not only addresses measles, but has additional beneficial effects on diarrheal disease mortality and morbidity.

Nutrition

General Nutritional Support

Nutritional support is both a therapeutic and a preventive intervention. Malnutrition is a consequence of and a risk factor for diarrheal disease (Mondal and others 2012). Nutritional support during diarrhea and nutritional rehabilitation during convalescence reduce the severity of associated nutritional deficits and improves resistance to and recovery from future diarrheal episodes. Improving nutrition enhances the ability to respond to future exposure to diarrhea pathogens and mitigates the severity of nutritional losses when diarrhea occurs. Dietary management of acute diarrhea with locally available age-appropriate foods is effective for the majority of acute diarrhea episodes, even in the presence of lactose malabsorption; commercial preparations or specialized diets are not necessary (Gaffey and others 2013). Recent studies of community management of severe or moderate acute malnutrition using commercial ready-to-use therapeutic foods (RUTFs), which are energy dense, solid or semisolid, low-moisture-content preparations of peanut butter enriched with dried skimmed milk, sugar, vegetable oil, vitamins, and minerals that can be eaten direct from the package, have had positive effects (Santini and others 2013). Such products can also be locally made and will facilitate community management of malnutrition (Choudhury and others 2014; Schoonees and others 2013). Local production has certain benefits over imported commercially produced RUTF, which are more costly, can exert adverse impacts on breastfeeding, may medicalize and commercialize malnutrition treatment, and may be difficult to scale up to meet global needs (Latham and others 2010).

Exclusive breastfeeding is another fundamental nutritional support modality for very young infants, with many health impacts beyond improved nutrition and reduced susceptibility to diarrheal disease and other infections (Bhutta and others 2013; Dey and others 2013; Strand and others 2012). Alternating breastfeeding and ORS during acute watery diarrhea in infants combines the nutrient and resistance factors in breast milk with the impact of ORS on dehydration, but faces common cultural biases against feeding during diarrhea (Chouraqui and Michard-Lenoir 2007; King and others 2003). Strand and others (2012) conclude that breastfeeding is the most important modifiable risk factor to reduce the frequency of prolonged diarrhea.

Zinc Supplementation

Zinc deficiency is associated with increased risk of diarrhea, adversely affects intestinal structure and function, and impairs immune function (Bhan and Bhandari 1998; Gebhard and others 1983). Zinc administration may curtail the severity of diarrheal episodes (Haider and Bhutta 2009) and prevent future episodes because it is vital for protein synthesis, cell growth and differentiation, and immune function, and promotes intestinal transport of water and electrolytes (Castillo-Duran and others 1987; Shankar and Prasad 1998). A systematic review of 13 studies from LMICs of zinc supplementation in diarrhea finds a significant 46 percent (relative risk 0.64, 95 percent confidence interval 0.32–0.88) reduction in all-cause mortality and 23 percent (relative risk 0.77, 95 percent confidence interval 0.69–0.85) reduction in diarrhea-related hospital admissions (Fischer Walker and Black 2010). No statistically significant impact on diarrhea-related mortality and subsequent prevalence was found; however, it was not possible to completely separate the effect of zinc from that of ORS in large-scale effectiveness trials, because introduction of zinc also increased ORS use rates. Zinc supplementation for more than three months was associated with a 13 percent (relative risk 0.87, 95 percent confidence interval 0.81–0.94) reduction in incidence of diarrhea in children under age five years in LMICs (Yakoob and others 2011). Efficacy has also been documented in children younger than age six months (Mazumder and others 2010). There have been no reports of severe adverse reactions from any form of zinc supplementation used in the treatment of diarrhea, and the WHO recommends therapeutic zinc supplementation for children with acute diarrhea for 10 days to 14 days.

Zinc supplementation may also be useful in the treatment of persistent diarrhea. A randomized controlled trial in children ages 6–18 months showed that persistent diarrhea led to depletion of zinc whereas oral zinc administration improved zinc status (Sachdev, Mittal, and Yadav 1990). A pooled analysis of the effect of supplementary oral zinc in children under age five years with persistent diarrhea reduced the probability of continuing diarrhea by 24 percent (relative risk 0.76, 95 percent confidence interval 0.63–0.91) and decreased the rate of treatment failure or death by 42 percent (relative risk 0.58, 95 percent confidence interval 0.37–0.90) (Bhutta and others 2000).

Zinc also plays a vital role in normal growth and development of children, with or without diarrhea. Preventive zinc supplementation at a dose of 10 milligrams per day for 24 weeks leads to a net gain of 0.19 (±0.08) centimeters in height in children under age five years (Imdad and Bhutta 2011). Zinc sulfate is low cost, safe, and efficacious, and tablets can be crushed and fed to children or dispersed in breast milk, ORS, or water. Baby zinc sulfate tablets and formulations in syrup form are also available.

Although many countries have changed diarrhea management policies by adding zinc to ORS, a gap remains between policy change and effective program implementation (Bhutta and others 2013). Bottlenecks include limited knowledge among care providers and parents, price, and availability. Scaling-up use of zinc, including promotion and distribution through community programs, can increase use by 80 percent (Das, Lassi, and others 2013). Free distribution, social marketing, education of caregivers, and provision of zinc through both government and private providers at the community level, and copackaging of zinc and ORS are additional strategies to increase coverage.

Water, Sanitation, and Hygiene

Because diarrhea is ultimately transmitted from infected stools, clean water and safe disposal of feces have major impacts on diarrhea incidence. If, as suspected, EED is also a consequence of continuing ingestion of fecal microorganisms, water and sanitation improvements should also reduce EED as a cause of early malnutrition. Reductions in diarrhea risk of 17 percent and 36 percent have been shown for improved water quality and excreta disposal, respectively (Cairncross and others 2010). Demographic and Health Surveys between 1986 and 2007 also suggest that access to improved water reduces risk of diarrhea (odds ratio 0.91, 95 percent confidence interval 0.88–0.94) and mild or severe stunting (odds ratio 0.92, 95 percent confidence interval 0.89–0.94), while improved sanitation reduces diarrhea mortality (odds ratio 0.77, 95 percent confidence interval 0.68–0.86), incidence (odds ratio 0.87, 95 percent confidence interval 0.85–0.90), and risk of mild to moderate stunting (odds ratio 0.73, 95 percent confidence interval 0.71–0.75) (Fink, Günther, and Hill 2011).

Water, sanitation, and hygiene interventions are collectively known as *WASH*. Somewhat surprisingly, a 2005 meta-analysis of WASH interventions failed to document greater effectiveness of combinations over single interventions (Fewtrell and others 2005). Current assessments are not sufficiently robust to influence investment decisions in one strategy over another, although all make sense and improve quality of life (Arnold and others 2013).

As infrastructure projects, water and sanitation improvements can be built at the community, neighborhood, or individual household levels; may be more or less technically complex; and may be more or less expensive. Unfortunately, the majority of sanitation systems fail to treat sewage to render it safe; as a result, irrigation water or seafood sources may become contaminated (Hutton and Chase, forthcoming, volume 7). In 2008, the World Bank and the WHO estimated that the global cost of water and sanitation projects to meet Millennium Development Goal (MDG) targets would be US$42 billion and US$142 billion in 2005 dollars through 2014 for water and sanitation, respectively, exclusive of programmatic costs beyond the intervention delivery point (Hutton and Bartram 2008). This investment equates to US$4 billion and US$14 billion per year for water and sanitation projects, respectively, or US$8 and US$28 per capita, respectively. When maintenance, the cost of replacing existing infrastructure and facilities, and the extension of coverage to include future population growth are added, expenditures increase to US$360 billion for each intervention. Once built, however, water and sanitation infrastructure need to be maintained; this ongoing requirement leads to substantial additional financial as well as human capacity investments, without which infrastructure deteriorates and the initial investment can be lost. Further economic analysis of WASH interventions is provided in Hutton and Chase (forthcoming).

Limited evidence suggests that combining development and health interventions results in facilities that are better built and maintained, and used more effectively. Six years after completion of a project in Bolivia, the use of facilities in intervention communities was 44 percent higher than in control communities; from 66 percent to 86 percent of intervention households continued to practice four promoted maternal and child health behaviors compared with 14 percent to 30 percent of households in control communities (Eder and others 2012). Unfortunately, current assessments indicate that the 2015 MDG 7 for water and sanitation targets will not be met in five of nine regions (WHO and UNICEF 2013).

Behavioral Interventions

Many actions or decisions by caregivers, health care providers, and public health officials require behavior changes and the decision to act. If improved practices became the norm, risk of diarrhea and morbidity and mortality rates would diminish. Each of these behaviors may be difficult to sustain, but each would have a major impact.

Handwashing

The transfer of infectious agents via the hands directly between individuals or indirectly through contamination of inanimate objects (fomites), such as dishes, utensils, and other objects (Abad and others 2001), is a common route for the transmission of low inoculum diarrhea pathogens (as well as respiratory infections). Contaminated hands readily inoculate food or water, allowing high inoculum pathogens to multiply. Simple handwashing procedures significantly reduce transmission rates in health care facilities (Bolon 2011); households (Bloomfield 2003); schools (Lee and Greig 2010); and even day care and preschool settings, which are notoriously difficult environments in which to enforce good hygiene (Churchill and Pickering 1997). Handwashing has an additional benefit in also reducing transmission of respiratory infections (Luby and others 2005).

Provision of soap to an urban squatter community in Karachi, Pakistan, supported by weekly meetings with trained health care workers from the same communities to reinforce the behavior, reduced days with diarrhea by 39 percent (95 percent confidence interval −61 percent to −16 percent) among infants compared with controls over one year (Luby and others 2004). Even severely malnourished children (weight-for-age z-score < −3.0) had 42 percent (95 percent confidence interval −69 percent to −16 percent) fewer days of diarrhea, compared with equally malnourished children in the control group. An additional benefit was a 50 percent reduction in the incidence of pneumonia (95 percent confidence interval −65 percent to −34 percent).

Handwashing with water alone is also worthwhile. In Bangladesh, the risk of diarrhea diminished when caregivers washed both hands with water before preparing food (odds ratio 0.67, 95 percent confidence interval 0.51–0.89); the effect was greater if one or both hands were washed with soap (odds ratio 0.30, 95 percent confidence interval 0.19–0.47) (Luby and others 2011). Risk was also reduced when caregivers washed hands with soap after defecation, but not with water alone (odds ratio 0.45, 95 percent confidence interval 0.26–0.77). Five key times for handwashing were identified: after defecation, after handling children's feces or cleaning the anus, before preparing food, before feeding children, and before eating. Direct observations identified more than 20 opportunities per day for handwashing, a frequency considered impossible to achieve, especially when the added cost of soap is considered. Handwashing after contact with feces is poorly practiced globally (Freeman and others 2014), and Luby and others (2011) recommended prioritizing handwashing before food preparation because it was the single most effective opportunity to reduce diarrhea risk.

How feasible is it to embed handwashing in daily behavior? A randomized intervention in Pakistan compared provision of soap for handwashing with a method to disinfect water or no intervention, including weekly visits over nine months to encourage either practice (Luby and others 2006). The study documented a 55 percent reduction in diarrhea (95 percent confidence interval 17 percent to 80 percent) compared with control neighborhoods, but no difference between the soap or water disinfection groups. When reenrolled in a follow-up surveillance 18 months later, handwashing intervention households were still 1.5 times more likely to wash with soap and water (79 percent versus 53 percent, $p = 0.001$) and 2.2 times (50 percent versus 23 percent, $p = 0.002$) more likely to rub their hands together compared with controls (Bowen and others 2013). During weekly follow-up throughout the 14 months without active educational intervention there was no difference between the groups in the proportion of person-days with diarrhea (1.59 percent versus 1.88 percent, $p = 0.66$) or the amount of soap purchased. Three years later, however, the investigators reengaged 461 original households (69 percent) and found the original intervention households were 3.4 times more likely than controls to have soap available (97 percent versus 28 percent, $p < 0.0001$), more commonly reported handwashing before cooking (relative risk 1.2, 95 percent confidence interval 1.0–1.4) and before meals (relative risk 1.7, 95 percent confidence interval 1.3–2.1), and purchased more soap per person per month (0.91–1.1 bars versus 0.65 for controls, $p < 0.0001$).

The critical question is not whether improving handwashing practices is effective, but rather how to best promote consistent behavior. The behavior requires availability of water and household handwashing stations designed and located to facilitate rather than inhibit the practice (Hulland and others 2013). Educational support from health care workers is useful, but how much is feasible and affordable remains in question. Increasingly, integrated behavioral models will be needed to improve the outcome of WASH interventions (Dreibelbis and others 2013).

Health Care Seeking

To ensure optimal care of infants and children with diarrheal disease, caregivers must recognize there is a problem, know what to do and do it, be alert to signs of clinical deterioration needing professional care, and know how to access such care without delay. Knowledge and experience are necessary but not sufficient; caregivers must also have the authority to act promptly. Initiatives to scale up prompt decision making and action generally focus on technical details and acquisition of practical skills, but frequently overlook social and cultural dimensions. These factors may influence whether a caregiver recognizes that fluid losses are beyond normal limits, are becoming dangerous, and require professional intervention (Larrea-Killinger and Muñoz 2013).

Higher levels of education promote quicker care-seeking action; however, cultural influences, for example, gender discrimination, can delay action for female infants (Malhotra and Upadhyay 2013). In rural Burkina Faso caregivers failed to recognize mild diarrhea, especially among infants, and made intervention choices that were not clinically based and recommended (Wilson and others 2012). Only 55 percent of caregivers sought care outside of the household, and 22 percent of these were with traditional healers or drug vendors, only 12 percent of whom recommended ORS. In rural Kenya, where caregivers understood the significance of diarrhea and dehydration, their primary concern was stopping the diarrhea, preferring antibiotics or antidiarrheals over ORS (Blum and others 2011). Cost of treatment is the major pragmatic impediment to care seeking outside of the home (Nasrin and others 2013). Anthropological and ethnographic approaches may help improve educational messaging and responses, but cost, travel and access to facilities, and wait times are likely to be critical determinants of behavior, and these require very different inputs to address.

Community-Based Interventions

Limited access to health facilities with trained primary care workers means that many children fail to receive simple but effective early interventions when diarrhea develops. However, a systematic review (Das, Lassi, and others 2013) concludes that community-based interventions improve care seeking by 9 percent (relative risk 1.09, 95 percent confidence interval 1.06–1.11), increase ORS use by 160 percent (relative risk 2.6, 95 percent confidence interval 1.59–4.27), produce a 29-fold increase in use of zinc supplements (relative risk 29.8, 95 percent confidence interval 12.33–71.97), and reduce antibiotic use by 75 percent (relative risk 0.25, 95 percent confidence interval 0.12–0.51).

Because diarrheal disease risk not only depends on the behavior of individuals and households but also on the practices of neighbors and communities, a systems approach to increase "attention to multiple transmission pathways, and highlight the need to widen the causal lens and pay more conceptual attention to socioeconomic status, gender, remoteness, and ecosystem changes" (Eisenberg and others 2012, 242) can improve outcomes. However, measuring these effects will require innovative study designs that reveal social patterns of interaction and the movement of pathogens through the environment.

Community-Led Total Sanitation

Interventions to improve the safe disposal of human excreta can be difficult to implement and maintain, and documenting a positive result is challenging, especially in rural settings in LMICs (Clasen and others 2010). For full impact, children and adults must learn to consistently use improved sanitation, and stools from infants and toddlers must be handled safely as well. Because water and sanitation improvements are often implemented together, separating the influence of each, and under which circumstances, can be difficult. Community-Led Total Sanitation (CLTS) is a participatory approach to improving sanitation in communities, in which communities mobilize to achieve total abandonment of open defecation and replace it with subsidized construction of facilities, household by household. The goal is to generate social pressure on all members of a community to understand the health implications of open defecation, and convince the community to join together, without external resources except guidance and facilitation, to agree on and act to completely eliminate open defecation and build a community sanitary infrastructure (Kar 2003). Its relevance is suggested by an analysis of Demographic and Health Survey data indicating that open defecation explains almost twice as much (54 versus 29 percent) of the international variation in child height compared with gross domestic product (Spears 2013). A 20 percent reduction in open defecation predicted a 0.1 standard deviation increase in child height.

CLTS begins with a facilitator engaging a community or village to promote understanding of the link between open defecation and illness. Initial engagement is followed by a survey and mapping of actual practices, often led by motivated school-age children. Finally, community deliberations lead to communal decisions to make the necessary changes. In the process, the facilitator may "provoke people through… tactics that trigger powerful emotions such as disgust, shame and fear… [to] enable local people to confront an unpleasant reality, and in doing this deliberately shocks, provokes, jokes and teases. Sparking these emotions and affects is key to triggering CLTS" (Deak 2008, 11). Although some have criticized the use of shame or social stigma to promote compliance (Bartram and others 2012), others have noted that shame, social pressure, and peer monitoring with government subsidies to build latrines markedly increases the adoption of improved sanitation (Pattanayak and others 2009).

Many tensions continue to surround the CLTS movement because organizations, government ministries, and development funders may be committed to different models of improving sanitation infrastructure; yet many examples of success and the spread of CLTS exist. This juxtaposition of tensions and successes indicates the need for careful analysis of the role of CLTS and how and where to introduce it most effectively. A number of issues must be considered, such as how to promote learning by doing; careful training of facilitators; cultural changes in institutional environments to a more participatory, responsive, transparent, and downward-accountability approach; and changing from a top-down to a bottom-up development model that is sensitive to local context and the longer time horizon required (Deak 2008).

COST AND COST-EFFECTIVENESS OF INTERVENTIONS

Several cost-effective and low-cost interventions are available to help prevent and treat diarrhea (table 9.1). Since the analysis of cost-effectiveness of interventions for diarrhea in LMICs in the second edition of *Disease Control Priorities in Developing Countries* (Keusch and others 2006), the ranking of various modalities has changed because of new evidence on the benefits of zinc as adjunct therapy for diarrhea (optimally in combination with ORS), substantial decreases in the cost of rotavirus vaccine, and additional research separating the cost-effectiveness of water supply from that of sanitation. The large gains in measles immunization have stopped additional work on its cost-effectiveness for diarrhea because it has become standard care. Although it is self evident that breastfeeding promotion reduces diarrhea, this practice has not been as high on the research and policy agenda.

The following is a brief discussion of the cost-effectiveness of selected diarrhea interventions. Details are presented in table 10.1 (Feikin and others 2016, chapter 10 in this volume). Das and others (2016, chapters 10 and 12 in this volume), and Stenberg and others (2016, chapter 16 in this volume) provide relevant information on vaccines and nutrition.

The most cost-effective interventions currently available for diarrhea (as measured in 2012 U.S. dollars per disability adjusted life year [DALY] averted) are prophylactic zinc supplementation (alone and as an adjunct to ORS), ORS, rotavirus vaccine, and household-level water treatment (primarily in rural areas using chlorination or solar disinfection) (see table 10.1). The second most cost-effective group includes rural sanitation, piped water, and in selected countries, cholera vaccine. Nutrition interventions are the least cost-effective for diarrhea; however, they have other major benefits, and cost-effectiveness of community management of severe acute malnutrition is addressed in Lenters, Wazny, and Bhutta (2016, chapter 11 in this volume).

Table 9.1 includes just one study of behavior change, identified through a focused search in PubMed. Such interventions tend to have very heterogeneous results; the one reviewed here (see table 10.1 for further details), a handwashing education intervention in Burkina Faso

Table 9.1 Cost-Effectiveness and Unit Cost of Interventions for Diarrheal Diseases

Intervention	Region	Cost-effectiveness (US$/DALY averted)	Unit cost (US$)
Oral rehydration solution (versus no ORS)	AFR-E	< 200	2.20/diarrhea episode
Prophylactic zinc with ORS (versus ORS alone)	AFR-E and SEA-D	< 100	0.61/diarrhea episode
Rotavirus vaccine (versus no vaccine)	Low-income countries	< 200 at 5/dose (less at 0.20/dose)	5/dose for two doses (Gavi price); Gavi-eligible countries pay 0.20/dose for two doses
Clean water (at household: chlorination or solar disinfection versus untreated water)	AFR-E and SEA-D	< 200	0.07/person/year SEA-D 0.13/person/year AFR-E (in 2000 U.S. dollars)
Improved rural water and sanitation (versus unimproved)	AFR-E and SEA-D	< 2,000	28/household (well); 52/household (latrine)
Piped water and sewer connection (versus no connections)	AFR-E SEA-D	< 2,000 < 3,000	136/household (water); 160/household (sewer)
Cholera vaccine (versus no vaccine)	High-endemicity countries	2,000–10,000	1.33/person
Behavior change	Low-income countries	Large variation	Large variation
RUTF added to standard rations (versus standard rations)	AFR-E	> 10,000 considering only benefits for diarrhea	527/child/year

Source: See Horton and Levin 2016, chapter 17, on cost-effectiveness in this volume.
Note: AFR-E = high-mortality Africa (WHO subregion); DALY = disability adjusted life year; Gavi, the Vaccine Alliance; ORS = oral rehydration solution; RUTF = ready-to-use therapeutic foods; SEA-D = high-mortality South-East Asia (WHO subregion). Costs and cost per DALY averted are higher in other regions. Interventions costing less than US$240 per DALY in 2012 would be very cost-effective even in the poorest low-income country; those costing less than US$720 would be cost-effective even in the poorest low-income country (Burundi's per capita gross national income was US$240 in 2012) (World Bank 2014). All costs converted to 2012 U.S. dollars (except as noted otherwise).

(Borghi and others 2002), falls into the most cost-effective group. Well-designed behavior change interventions to increase use of clean water, latrines, ORS, prophylactic zinc, and vaccines could all be cost-effective. Neither table 9.1 nor table 10.1 contains cost-effectiveness results for drug treatment of dysentery because focused searches in PubMed returned no relevant citations. Typically, cost-effectiveness studies are performed when a drug is new or is being tested for a new use, which is not the case here. Drug treatment for dysentery is known to be highly effective if the pathogens are sensitive; the high case fatality rates for dysentery indicate that drug treatment is extremely likely to be cost-effective.

It is not sufficient for an intervention to be cost-effective to be adopted. Cost or affordability in relation to health expenditures also matters. One major advance has been the addition of zinc as a complementary therapy to ORS; as an adjunct to an existing treatment, it appears to be particularly cost-effective and affordable. Robberstad and others (2004) estimate that zinc tablets cost approximately US$0.61 for a three-week course of treatment, in addition to the US$2.20 in recurrent costs per course of treatment with ORS, excluding personnel costs in delivering the intervention.

Introduction of rotavirus vaccine is progressing as a result of Gavi interventions, although the negotiated price for the vaccine at US$5 per dose for the two-dose course remains a substantial addition to current costs of the WHO's Expanded Program on Immunization. Gavi provides the vaccine at a highly subsidized price to eligible countries (US$0.40 for two doses); countries that graduate from eligibility are required to pay 20 percent of the Gavi cost in the first year, increasing by US$1 per year until the full price of US$5 per dose is paid (Verguet and others 2016, chapter 19 in this volume). Given that diarrhea rates and mortality rates are higher in LICs, the vaccine is particularly cost-effective in these countries.

Sanitation and, to a lesser extent, water supply interventions, are subject to affordability considerations. Initial investment costs per household for standard urban requirements—water piped to the house and a sewer connection—are US$136 and US$160, respectively. The lowest-cost clean water interventions in rural areas are still substantial at US$28 per household for a dug well, US$31 per household for a borehole, and US$52 per household for a pit latrine (Haller, Hutton, and Bartram 2007). Household point-of-use disinfection of water (using chlorine or solar disinfection) costs pennies per capita per year in recurrent costs, but requires behavior change. Although improved water supply and sanitation are essential in the long term to decrease diarrhea, intestinal parasites, and stunting, the investment costs mean the transition is likely to be slow.

Most of the results in tables 9.1 and 10.1 describe the cost-effectiveness of implementing a single intervention. If interventions are combined, the incremental cost-effectiveness of each additional intervention can decline. Fischer Walker and others (2011) estimate the combined effect of 10 interventions designed to reduce diarrhea in 68 countries with high child mortality, using the Lives Saved Tool. Two scenarios were modeled: an ambitious strategy designed to reach MDG 4 goals (to reduce child mortality) in a realizable way; and a universal strategy designed to bring coverage of many interventions to 90 percent or more of the target population, and water, sanitation, and handwashing interventions to 55 percent or more. Both strategies were scaled up from current coverage to the target over five years. The ambitious strategy saved 3.8 million lives during a five-year period, at a cost of US$52.5 billion, or US$13,700 per death averted, approximately US$432/DALY averted assuming one life saved in infancy or early childhood is about 32 DALYs averted. The universal strategy saved 5 million lives at a cost of US$20,752 per death averted, or US$648 per DALY averted. Although these rates would be considered cost-effective or very cost-effective for most countries, affordability is still an obstacle. The main issue is the water and sanitation components, which account for 84 percent of the cost of the ambitious package and 87 percent of the universal strategy.

Extended cost-effectiveness analysis provides further insight. Chapters 18 and 19 in this volume (Ashok, Nandi, and Laxminarayan 2016; Verguet and others 2016) present extended cost-effectiveness analyses of the introduction of rotavirus vaccine in India and water and sanitation improvements in Ethiopia. These interventions are pro-poor—the poor benefit disproportionately from reduced child mortality and from out-of-pocket savings on treatment costs, because they bear a disproportionately higher burden of ill health from diarrhea. They have less access to clean water and improved sanitation, and therefore their children have poorer nutritional status and are at higher risk of mortality from diarrhea-related illness.

CONCLUSIONS

The burden of diarrheal diseases in children under age five years in LMICs has been reduced dramatically. These reductions are the result of focused attention and resources applied, originally through vertical programs and advocacy through the WHO and international donor agencies, and more recently through more integrated programs for primary care and community-based programming. Although there are no magic bullets to control the incidence of diarrheal diseases, the following are highly effective: improved nutrition of young children to increase their ability to respond to infection; water and sanitation improvements to reduce the number of microorganisms in the environment; handwashing; and implementation of simple but highly effective interventions, such as ORS, that have enabled early treatment and mitigation of dehydration due to watery diarrhea.

When antibiotics are used appropriately for inflammatory diarrheas, survival is enhanced; however, targeting only those individuals who truly need antibiotic treatment remains problematic. Most uses of antibiotics are not only ineffective, for example, in the treatment of viral infections, but counterproductive, due to selective pressure for drug resistance. Indeed, many important diarrheal disease agents now exhibit serious resistance to multiple medications. Improved understanding of the pathogenesis of persistent diarrhea has helped the development of nutritional interventions to address the malabsorption and malnutrition that characterize persistent diarrhea and lead to serious morbidity and increased mortality.

This chapter reviews interventions and policy strategies that are effective, can often be packaged together, and can be delivered at the community level. Many of these interventions have impacts far beyond diarrheal disease, and these additional rationales for implementation enhance their cost-effectiveness. Some are both effective and highly inexpensive, for example, the early use of ORS, so there is no reason not to promote them. Continued attention to delivering an appropriate package of interventions, coupled with monitoring and continuous quality improvement of health care delivery services, can be expected to continue to drive down the mortality and sequelae of diarrheal diseases in the coming decade. In addition to the development of point-of-care diagnostics, medications, and vaccines, many issues need continuing study, including better water and safe sanitation methods, food and water safety behavior within households and along the food chain, and the cause and role of EED and asymptomatic infection on intestinal function and nutrition.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  a) lower-middle-income = US$1,046–US$4,125
- b) upper-middle-income (UMICs) = US$4,126–US$12,745
- High-income countries (HICs) = US$12,746 or more.

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