Chapter 9. Diarrheal Diseases

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Figures: 3
Maps: 0
Tables: 1

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Abstract
The past two decades have witnessed substantial progress in reducing the mortality and morbidity consequences of diarrheal diseases among infants and children under five years of age. For example, the absolute number of deaths in this age group has been reduced by 87 percent since 1980, and by 50 percent just since the millennium, even though the number of children under five years of age in the world has increased by more than 2 fold since 1980 to an estimated 640 million in 2009, over 90% living in low and middle income nations. Advances due to research and technology, increasing education, especially of women and girls, greater wealth, and improved infrastructure have all played major roles. Better nutrition, greater access to health care, high tech advances like medicines and vaccines, and low tech advances such as oral rehydration or zinc supplementation, have all played a role. Further improvements depend on continued investments in healthcare and research, particularly in developing countries where nearly all under 5 year diarrhea mortality occurs.

Major challenges persist. New infectious diarrhea agents continue to emerge, including viruses, bacteria, and protozoa, for which we may have no treatment or vaccines. The growing frequency of antibiotic resistant bacterial pathogens threaten to return us to the era before effective treatment became widely available just 60 years ago, while the paucity of antivirals and anti-protozoal agents remains problematic. Both under and over nutrition in young infants and children threaten their health, growth and development, and increase susceptibility to diseases in adulthood. Poverty, so closely linked to malnutrition, and to morbidity and mortality, remains prevalent as income disparities increase in all regions of the world. Research across the spectrum from basic, through translational, to health services research and delivery of health care, linking medical and social sciences in a common effort, is providing new insights, while capacity development within the research for health and healthcare systems in the most disease affected countries is advancing. And, as international assistance slows down, low and middle income countries are increasingly investing in their own national infrastructure.

This Chapter reviews what we have learned about the causes, epidemiology, clinical aspects, treatment and prevention of diarrheal diseases. It focuses on a set of interventions that are evidence based, feasible, and cost-effective, including biological, behavioral, and those related to the built environment and water and sanitation infrastructure. Many can be packaged together to gain economies of scale and the benefit of complementary effects. Many of the interventions and strategies have relevance beyond addressing the burden of diarrheal disease, and when considered in that context become even more cost-effective. In addition, new insights into early childhood stunting may lead us to new interventions. The world has done relatively well in addressing diarrheal diseases over the past three decades of attention and focus, and the way forward to achieve significant further improvements in the coming decade seems clear, if the attention, focus and investment is sustained.

Introduction
Since 1980 the annual number of deaths from diarrheal diseases among the 0-5 year age group in developing countries has dropped by 87 percent, from approximately 4.5-5 million to an estimated 619,000 (see below). This striking improvement occurred without vaccines against the major pathogens, except for rotavirus, only now being introduced in low-income countries (LICs). Even with universal coverage and no change in the dominant circulating strains, rotavirus deaths, currently estimated at 170,000 per year, would still be 85,000 to 95,000 per year in the under 5’s (Fischer Walker and Black, 2011).\(^1\)

Because the incidence of diarrhea has significantly diminished, especially in young infants (Fischer Walker and others, 2012),\(^2\) the success achieved appears to be largely driven by improved management, rather than prevention, of diarrhea. Several interventions are likely responsible, including the early use of oral rehydration solutions for dehydrating watery diarrhea; antibiotics for grossly bloody diarrhea and dysentery (a clinical syndrome consisting of a classical triad of frequent small volume bloody stools, abdominal cramps, and tenesmus or the perceived need to evacuate accompanied by straining and cramps); and nutrition interventions for persistent diarrhea, as well as post-illness nutritional rehabilitation for all patients. Although it may be
tempting to view such progress as tantamount to victory, 4.7 million episodes of diarrheal disease still occur each day, including 100,000 cases of severe diarrhea, and nearly 2,000 deaths, or approximately 10 percent of the mortality under age five years (Liu and others, 2012).³ That a diarrheal death occurs in a young child every 1.4 minutes is ample evidence that substantial challenges remain.

BOX 1: Major interventions in diarrheal disease
1. Early use of oral rehydration solutions
2. Appropriate use of antibiotics for bloody diarrhea and dysentery
3. Nutritional interventions for persistent diarrhea
4. Rapid restoration of nutritional status in all diarrhea patients

Increasing awareness of the adverse effects of non-fatal 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 represents a new challenge. The response will depend on enhanced understanding of the causal pathways and pathogenesis of enteric infections, with or without clinically manifest diarrhea, and their sequelae. This is the necessary starting point to identify effective and feasible new interventions for introduction and scale up, much like the oral rehydration revolution over 40 years ago. This Chapter will explore these issues.

Diarrheal diseases are good indicators of the stage of development of communities in the developing world because of the impact of proximal and distal determinants of diarrheal morbidity and mortality, including 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 in reducing mortality and morbidity depends on recognition that inter-sectoral interventions are an integral part of required measures to reduce or eliminate diarrheal diseases as a public health concern.

In contrast to previous assessments, we also consider the still limited evidence on subclinical infections due to microbial causes of diarrhea. Their effects on intestinal physiology, nutrient absorption, and nutritional status are now considered to be 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 the epidemiology, transmission, and mechanisms of disease as well as the 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 Chapter 12 of this volume.

Diarrheal Diseases

Definitions and Classification
Diarrheal diseases occur everywhere humans live, but are most prevalent and cause greater morbidity and mortality in children below age five years in LICs. However, the very term is simplistic, because it covers a multitude of infectious causes, ranging from viruses and bacteria to protozoa and occasionally worms, each with distinctive effects, and three distinct epidemiological and clinical presentations with vastly different consequences for the individuals affected:

- Acute dehydrating watery diarrhea
- Acute inflammatory (bloody) diarrhea or dysentery
- Persistent diarrheas that last 14 days or more.
The causes of these presentations, and their epidemiology, routes of transmission, pathogenesis underlying the clinical manifestations, and optimal treatment and prevention strategies differ considerably. These are discussed in greater detail later in this Chapter.

**Burden of Infection**

Children under age five years in low (LIC) and lower middle income countries in South Asia and Subsaharan Africa, experience an average of 2.7 (uncertainty range 2.1 – 3.2) episodes of diarrhea per year (Fischer Walker and others, 2013). Most are mild and self-limited. lasting an average of 4.3 days. From 0.5 percent to 2 percent are severe, lasting an average of 8.4 days (Lamberti, Fischer Walker, and Black, 2012). Incidence rates vary by region and country; they are higher in children in LICs and lower middle income countries and highest in Sub-Saharan Africa (3.3 episodes per child per year), where risk factors such as lack of access to water and sanitation, and undernutrition, are more common (Fischer Walker and others, 2013).

**Incidence**

Despite targeted investments over the past 35 years, estimated global diarrhea incidence rates have not changed significantly, from 2.2 to 3.0 episodes per child per year before 1980 (Snyder and Merson, 1982), to 3.2 in 1990 (Bern and others, 1992), 2.6 in 2000 (Kosek, Bern, and Guerrant, 2003), and 2.9 (2.3 to 3.4) in 2010 (Fischer Walker and others, 2013). 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 children’s mobility increases, allowing for greater contact with new pathogens (Liu and others, 2012). The consequences of diarrheal disease are also determined by disease severity, although few studies separately analyze severe episodes, or identify bloody diarrhea or dysentery, or episodes that become persistent. A recent 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). Figure 9.2 shows the regional burden of severe diarrheal disease.
Mortality

Unlike incidence, diarrhea mortality has declined dramatically since 1980. The 2012 estimated diarrhea mortality, 619,000 child deaths, represents an 87 percent decline from 1980 and a striking 50 percent decline since 2000 (Liu and others, 2012). Seventy-two percent of diarrhea deaths occur in the first two years of life; therefore targeting this age group will yield the greatest impact on mortality (Fischer Walker and others, 2013). A thorough discussion on cause of death structure and mortality declines is presented in Chapter 4 in this volume (Liu, and others). Figure 9.3. shows the regional burden of mortality; notably, Africa and Southeast Asia account for 79% of the total.
Etiological Causes

Although many agents cause diarrheal disease, just a few account for a major portion of the burden. One recent study demonstrated that almost 40 percent of the cause-specific attributable diarrhea mortality was due to two organisms, rotavirus (27.8 percent) and enteropathogenic E. coli (EPEC) (11.1 percent) (Lanata and others, 2013). In a large multisite, clinic-based prospective case-control study of children under 5 years, four pathogens - Rotavirus, Cryptosporidium, enterotoxigenic E. coli (ETEC), and Shigella – accounted for most of the attributable episodes of moderate-severe diarrhea (Kotloff and others, 2013). With rotavirus first during the first year of life, followed by Cryptosporidium. Rotavirus remained first in the 12-23 month cohort, followed by Shigella, but among children ages 24-59 months that relationship reversed. Children with moderate to severe diarrhea had an 8.5-fold (95% CI 5.8, 12.5, p < 0.0001) increased odds of dying during follow-up over a 90-day period. Most deaths were in infants (56 percent) and toddlers (32 percent). Notably, 55 percent of the deaths occurred at home or outside of a medical facility, and 33 percent occurred at least three weeks after the initial episode. Certain pathogens such as rotavirus, Shigella, Vibrio cholerae and adenovirus serotypes 40/41 were more commonly isolated from children with moderate to severe illness. Seventy two percent of controls without diarrhea also harbored one or more putative pathogens, and 31 percent had two or, reflecting the fecally contaminated environment they live in (Kotloff and others, 2013).

Transmission and Epidemiology

Understanding transmission routes and epidemiology is critical for effective prevention and mitigation strategies. Although transmission of diarrheal diseases is fundamentally the same for all agents, from the stool of an infected individual—whether human or an animal, with or without recent diarrhea—to the mouth of a new susceptible (termed fecal-oral transmission) there are diverse pathways and routes to infection, including direct person-to-person transmission mediated through contaminated fingers or inanimate objects (fomites), and indirect transmission via contaminated food or water, which also allows bacterial proliferation. Microbial
characteristics determine the number of organisms required to cause illness (the inoculum size); small inoculum pathogens are readily transmitted from person-to-person, but 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 non-specific host defenses, such as stomach acid. Some pathogens are inherently acid-resistant, such as *Shigella*, allowing small inocula to survive into the duodenum; others, like *V. cholerae*, are acid-sensitive, and large inocula are essential to survive passage through the stomach.

Reduced acid secretion significantly reduces the required inoculum size for acid-sensitive pathogens, for example when peptic ulcer disease is treated by gastric surgery or drugs to reduce acid-secretion. While infants, including preterm, produce acid, the amounts and response to stimuli such as feeding are diminished compared to 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 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, 2013), even though no increase was observed in diarrhea or other infectious disease morbidity.

Other factors include lack of refrigeration to store prepared but unconsumed food, or the presence of flies to transfer pathogens from feces in the environment to unprotected food or water in the household (Farag and others, 2013; Lindsay and others, 2012). A recent study of risk factors for *Shigella* infection in Thailand identified poor breastfeeding practices, poor water supply and sanitation (especially latrines and garbage disposal), lack of fly control, and inadequate personal hygiene, in particular, handwashing, as major targets for interventions (Chompook and others, 2006).

**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 prior exposure and preexisting immunity, including passively acquired immunity from breast milk consumption
- The health and nutritional status of the individual at the time of exposure.

The natural history following infection can vary from no symptoms, to mild-moderate but self-limited illness, to severe potentially life-threatening disease. Individuals healthier and better nourished at exposure are less likely to develop severe illness after exposure to 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 when between 5 to 10 percent, and severe and potentially life-threatening when it exceeds 10 percent. With increasing fluid losses, intravascular volume diminishes and blood pressure drops. Without replacement of losses (rehydration), hypotension can progress to circulatory failure resulting in dysfunction of critical organs and death. Early initiation of rehydration, for example using oral rehydration solutions (ORS), can mitigate and prevent progression to more severe dehydration. Such interventions are not only lifesaving, they can reduce duration of illness and extent of nutrient losses.
**Inflammatory Diarrhea and Dysentery**
Some pathogens cause inflammatory responses with leucocyte infiltration and damage to the bowel wall, resulting in mucosal ulcers, bleeding, leucocyte exudates, production of peptide cytokines that mediate dramatic, often prolonged, changes in appetite and metabolism, and direct nutrient losses with limited fluid losses. Bacterial pathogens causing inflammatory diarrhea and dysentery (defined below) generally require antibiotics to treat infection, resolve inflammation, allow the mucosa to heal, and reverse nutritional deterioration. Early effective antibiotic treatment shortens duration of illness, limits acute complications, and reduces longer-term impacts.

**Persistent Diarrhea**
Diarrhea episodes lasting from seven to 13 days are termed **prolonged** and are known to impair growth and increase the risk of progression to **persistent diarrhea** (episodes lasting 14 days or longer). In one study, prolonged diarrhea accounted for only 11.7% of episodes but 25.2% of all days of diarrhea, while persistent diarrhea accounted for only 4.7% of episodes but 24.5% of days with diarrhea (Moore and others, 2010). When an episode progressed from acute to prolonged the overall risk of persistent diarrhea increased from 4.8 percent to 29 percent (RR=6.09; 95% CI 4.96,7.45). Once diarrhea is persistent mortality rates increase sharply (Grimwood and Forbes, 2009); in some settings, they account for as much as 50 percent of overall diarrhea mortality. The continuing reduction in acute diarrhea deaths has focused attention on mortality associated with persistent diarrhea, which is relatively increased as a consequence.

A few pathogens have been particularly associated with persistence or are preferentially identified when an episode becomes persistent, including enteroaggregative *E. coli*, *Cryptosporidium parvum*, *Shigella flexneri*, *S. dysenteriae* type 1, and *Giardia lamblia*. As the duration of illness extends, malnutrition becomes increasingly evident due to ongoing mucosal injury, anorexia, malabsorption, and nutrient losses (Newman and others, 2000). *Shigella* infection, which is characterized by intense tissue catabolism and nutrient losses, almost doubles the risk of persistent diarrhea (Ahmed and others 2001) and bloody diarrhea (commonly due to *Shigella* infection) is a reported risk factor for persistent episodes (Mahalanabis and others, 1991). In Bangladesh, as the frequency of *Shigella* infection dropped from 1991 to 2010, 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, which requires careful dietary and nutritional management until the mucosal damage is reversed and new normally functioning epithelial cells are regenerated.

Even this brief summary of the three broad clinical categories of diarrheal disease makes it clear that the term **diarrheal diseases** encompasses a complex set of etiologies and manifestations that have different priorities for prevention, distinctive ways of management, and require individualized strategies to mitigate their clinical impact.

**New Frontiers: Subclinical Infections and Environmental Enteric Dysfunction**

**Subclinical Infections**
Historical interest in the composition and function of the microbial flora in the intestinal tract (Gorbach and others, 1967; Hentges, 1970) has progressed as sophisticated new methods have been developed to identify organisms that cannot yet be cultured (Lozupone and others, 2012). The gut microbiota is a remarkably diverse and complex community of microbes, acquired by infants after birth from their mothers and the environment, and thereafter influenced and shaped by the maturation of the immune system, diet, illness, and antibiotic use. Enormous numbers of widely diverse organisms coexist in the mouth, and while few reside in the harsher
Environmental Enteric Dysfunction

Almost 60 years ago, engineering ingenuity created devices to safely biopsy small bowel in living patients, leading to new concepts about the intestinal tract, e.g. demonstrating the presumed destruction of the small bowel mucosa in cholera patients was a post-mortem artefact (Gangarosa and others, 1960). The environment of the stomach and even fewer colonize the upper small bowel, very large diverse communities live in the terminal ileum and colon. The microbiome, “the combined genetic composition of all these symbionts, greatly outnumbers the host’s genome and contains information for metabolic processes that complement those of the host. It is likely that mutual metabolic benefit was the evolutionary driver of this interaction” (Mavrommatis, Young, and Kassiotis 2013, page 456). The acquisition of the microbiota (and its microbiome) after birth is necessary for development of the gut immune system, which is essential for protection against intestinal pathogens. Pathogens also can exist in equilibrium with their human hosts, even when they invade or colonize the mucosa as mutual adaptation may “result in acceptable levels of pathology”, that is with limited clinical consequences (Mavrommatis, Young, and Kassiotis 2013, page 456).

These relationships can be considered a form of asymptomatic infection without apparent harm to, and indeed potential benefits for, the host. In contrast, bacterial overgrowth (defined as a stable population in high concentration) by typical commensal colonic flora in the proximal small bowel, for example in malnourished individuals with diminished immune capacity, can impair nutrient absorption and exacerbate malnutrition (Neale and others, 1972). Some members of this flora also take advantage of opportunities such as immunosuppression to invade the host and cause systemic disease. While the major focus of microbiome research has been on the bacterial constituents, there are viral and fungal components of this community, although their impact is not yet understood. In addition to its positive metabolic role, the normal microbiota serves to limit the ability of pathogens to become established, while successful pathogens possess traits that allow them to effectively compete in an evolutionary “tug of war”.

It now appreciated that subclinical infections may cause physiological and structural alterations of the gut with adverse consequences on child nutrition and growth. For example, a handwashing intervention that reduced the number of episodes of diarrhea by 31 percent (4.3 vs. 3.0 episodes, P < 0.05) and days of diarrhea by 41 percent (9.67 versus16.33, P = 0.023) (Langford and others, 2011), showed that independent of diarrhea the infants with the highest values of a biomarker for mucosal damage (the ratio of lactose from breast milk to creatinine in the urine) and indicative of abnormal mucosal permeability had significantly lower height-for-age Z scores (P = .01), weight-for-age Z scores (P < 0.001), and weight-for-height Z scores (P = 0.034). This suggests that subclinical infections without evident symptoms might reduce nutrient absorption and impair growth by many of the same mechanisms present during clinical episodes. Although the reduction in absorption may be limited, chronicity, especially when dietary intake is marginal, may be sufficient to produce overt malnutrition over time.

Subclinical infections with pathogenic organisms can underlie growth faltering (Guerrant and others, 1999). Giardia intestinalis, for example, a known cause of diarrhea, often recurrent or relapsing, and associated with growth retardation in infants (Newman and others, 2001), is also commonly present in the stools of asymptomatic children in endemic areas. In some longitudinal studies, asymptomatic Giardia infection has correlated with growth faltering (Prado and others, 2005). Asymptomatic first Cryptosporidium infections in Peruvian infants have also been associated with slower weight gain compared to uninfected infants, but to a lesser extent compared to infants with initial symptomatic infections (Checkley and others, 1997). However, because asymptomatic infections were twice as common as diarrhea, their ultimate effect could even exceed those of clinical diarrhea. Despite some subsequent catch-up growth, infants infected with Cryptosporidium during the first six months of life remained stunted at one year of age (Checkley and others, 1998). Similar findings have been reported from studies in a peri-urban slum in Brazil (Bushen and others, 2007). Early colonization with Helicobacter pylori has also been identified as a precursor of growth faltering in children under five years in The Gambia (Thomas and others, 2004).
that mucosal glucose stimulated sodium absorption was preserved in cholera (Hirschhorn and others, 1968), successful oral rehydration therapy soon followed (Pierce and others, 1968).

Biopsy of the jejunum, the mucosal lining of the upper small intestine, in asymptomatic adults in tropical countries revealed structural differences compared to healthy adults from temperate countries (Baker, 1976), including shorter blunted villi which reduced the surface area covered by epithelial cells, and an increase in inflammatory cells in the subepithelial region (lamina propria). These changes were accompanied by diminished ability to absorb the pentose sugar xylose, and nutrients such as fat or vitamin B12. Limited data from infants and young children showed that stillborn babies had normal long finger-like villi, but older infants and children had similar structural and functional alterations as adults, suggesting the changes were acquired after birth (Baker, 1976).

Similar alterations also developed over one to two years in young adult expatriates living in Bangladesh (Lindenbaum, Kent, and Sprinz, 1966) or Thailand (Keusch, Piault, and Troncalle, 1972), generally 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; the findings reverted to normal over time when the subjects returned home (Lindenbaum, Gerson, and Kent, 1971). The jejunal mucosa of healthy South Asians living in the United States or the United Kingdom also increasingly normalized the longer they resided outside their home country (Gerson and others, 1971; Wood and others, 1991). However, the causes and significance remained unclear, and interest in this entity waned because there appeared to be no relationship to tropical sprue.

In retrospect, the extent of the weight loss associated with enteropathy in adults was dismissed too quickly. If the same decrement occurred in young infants, it would raise concerns about incipient malnutrition. Two decades later investigators in sub-Saharan Africa, using newer functional assessments of intestinal permeability, identified both functional alterations in young infants associated altered gut histology and poor growth in early childhood (Campbell and others, 2002; Campbell and others, 2004). The inflammatory cells present in the intestinal mucosa were further identified as immunoreactive T cells (Veitch and others, 1991) associated with strong pro-inflammatory local cytokine responses (Campbell and others, 2003). This finding sparked speculation about their role in pathogenesis, analogous to inflammatory bowel disease. While the mechanisms have remained uncertain, a nexus of microbial exposure, mucosal changes, reduced absorption and increased permeability, immune activation leading to poor response to mucosal vaccines, and growth stunting has been postulated (Prendergast and Kelly, 2012). Inadequacy of dietary intake, especially where diet quality is also marginal, likely exacerbates the effect of small reductions in absorption.

As a consequence, stunting is receiving increasing attention as a marker of chronic undernutrition, because of its prevalence in infants and children living in poverty in LMICs, its predictive role for increased childhood morbidity and mortality, and its association with poor longer term functional outcomes, including cognitive development and reduced years of schooling, and diminished productivity in adulthood, measured by income attained and other economic productivity markers (Dewey and Begum, 2011). The emerging concept is that changes in intestinal structure and function can develop in young infants in impoverished communities early in life, presumably due to environmental exposure to still unknown inciting factors, resulting in an initial malabsorption and early malnutrition, growth faltering, and increased susceptibility to diarrheal disease (Keusch and others, 2013). This acquired malabsorption has been termed environmental enteric dysfunction (EED), to stress the importance of the functional alterations.

Although systematic serial data on intestinal structure in these young infants is lacking, changes in a number of surrogate biomarkers of gut inflammation or immune activation have been identified (Kosek and others, 2013). These investigators have shown that children with combined activity scores of three biomarkers of intestinal inflammation (neopterin, alpha-anti-trypsin, and myeloperoxidase) in stool during periods without diarrhea inversely correlated with linear growth. Children with the highest score grew 1.08 centimeters less than children with the lowest score over the subsequent six months, after 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 conditions associated with intestinal inflammation, was predictive of linear growth in three-month-old birth cohorts in Bangladesh and Peru, independent of the LAZ score at the time the sample was taken (Peterson and , 2013). If confirmed, such assessments of intestinal health may become important biomarkers of EED and a predictor of growth (Box 2).

Box 2: Biomarkers to Assess Environmental Enteric Dysfunction

<table>
<thead>
<tr>
<th>Category</th>
<th>Biomarkers</th>
</tr>
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<tbody>
<tr>
<td>1. Intestinal absorption and</td>
<td>D-Xylose, mannitol or rhamnose absorption, lactulose paracellular uptake, α1-anti-trypsin leakage into gut lumen</td>
</tr>
<tr>
<td>mucosal permeability</td>
<td></td>
</tr>
<tr>
<td>2. Enterocyte mass and function</td>
<td>Plasma citrulline and/or conversion of alanyl-glutamine to citrulline, lactose tolerance test (as a marker of brush border damage)</td>
</tr>
<tr>
<td>3. Inflammation</td>
<td>Plasma cytokines, stool calprotectin, myeloperoxidase, or lactoferrin</td>
</tr>
<tr>
<td>4. Microbial translocation and</td>
<td>Stool neopterin, plasma LPS core antibody and/or LPS binding protein, circulating soluble CD-14</td>
</tr>
<tr>
<td>immune immune activation</td>
<td></td>
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</tbody>
</table>

As a cause of malnutrition and impaired immune function in early infancy, EED may increase susceptibility to and severity of subsequent diarrheal episodes. Repeated diarrhea is a major force for stunting, particularly when the rapid succession of infections restricts the capacity for catch-up-growth (Salomen and others, 1968). The effects of diarrheal diseases can be both short-term and long-term. In the short term, patients experience the adverse systemic impacts on appetite, metabolism, and nutrition due to the infection. In the longer term, patients are affected by mucosal changes that can alter digestion, absorption, and assimilation of nutrients from food. Bloody diarrheas and dysentery, structural mucosal damage also results in protein-losing enteropathy, as blood proteins leak into the gut lumen (Bennish, Salam, and Wahed, 1993). These effects have been shown to continue for weeks after shigellosis (Alam and others, 1994; Raqib and others, 1995), resulting in progressive malnutrition rather than convalescence and repair.

These extended effects partially explain why mortality over three-months following successful discharge from an expert treatment center in Bangladesh was 2.8 percent in children with watery diarrhea without evidence of *Shigella* but 4.9 percent for children with documented shigellosis (Bennish and Wojtyniak, 1991). The early effects of EED and the impact of repeated infection represents a double jeopardy due to similar risk factors, including increased exposure to enteric pathogens, limited and poor quality water, lack of sanitary facilities, and poor household hygiene. Understanding the pathogenesis of EED is a prerequisite to the selection of optimal interventions.

**Interventions for Diarrheal Diseases**

Interventions for diarrheal disease can be divided into *preventive*, primarily interrupting the routes of transmission and improving resistance to infection, and *therapeutic*, treating illness when it occurs. They can also be classified by scale: individuals, households, and communities. Some interventions 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, some innovations to make them more accessible or effective have had serious unintended consequences, e.g. increased and inappropriate use of antibiotics.
Preventive measures to reduce exposure to enteric pathogens involve improving quality of water for drinking and cooking, the quantity available for personal and household hygiene, and sanitary disposal of fecal waste. Vaccines to improve resistance are presently limited to Rotavirus, the only vaccine currently approved and widely available to prevent diarrhea; other vaccines lag behind in distribution or development. Improving health and immune function through improving nutritional status is another effective measure. Treatment 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 recent analyses of a package of interventions individually shown to have an impact on mortality (ORS, antibiotics for dysentery, rotavirus vaccination, vitamin A supplementation, improved access to safe water, sanitation and hygiene, and breastfeeding) estimated a reduction in mortality of 54 to 78 percent if implemented to a currently feasible level, and by 92 to 95 percent if universally applied (Bhatta and others, 2013; Fischer Walker and others, 2011).

Box 3. Interventions for diarrheal diseases

<table>
<thead>
<tr>
<th>Category</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive</td>
<td>Protected safe water</td>
</tr>
<tr>
<td></td>
<td>Sanitary disposal of fecal waste</td>
</tr>
<tr>
<td></td>
<td>Vaccines</td>
</tr>
<tr>
<td></td>
<td>Improved nutrition – vitamin A, zinc</td>
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<tr>
<td></td>
<td>? Pre- or probiotics</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>Oral rehydration solutions</td>
</tr>
<tr>
<td></td>
<td>Antimicrobials for bloody diarrhea/dysentery</td>
</tr>
<tr>
<td></td>
<td>Nutritional treatment of persistent diarrhea</td>
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<td></td>
<td>Zinc supplementation</td>
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<td>? Pre- or probiotics</td>
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Other proposed interventions, 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 because the available efficacy data are limited, contradictory, of poor reliability, or difficult to interpret. Similarly, the use of drugs to restore physiological functions of the intestine are not considered because of limited reliable data in target human populations.

**Oral Rehydration Solutions**

It is over 45 years since the efficacy of oral rehydration solutions was clearly demonstrated (Ruxin, 1994). ORS is estimated to prevent approximately 93 percent of diarrheal deaths (Munos and others, 2010). ORS is based on observations that a normal mechanism to absorb glucose and sodium together is preserved in watery diarrheas, and that oral solutions containing the right amount of glucose and salt resulted in the net uptake of sodium and chloride along with water. This effectively expanded the intravascular compartment in all age groups (Nalin and others, 1970) and for all but the most severely dehydrated patients or patients with intractable vomiting; it significantly reduced the need for intravenous fluids (Sack and others, 1978). Subsequent formulations with lower concentrations of glucose and sodium reduce the likelihood of hyponatremia during treatment of non-cholera dehydration, and reduce total stool output, vomiting, and the need for supplementary intravenous fluids (Hahn and others, 2002). WHO now recommends such formulations (WHO and UNICEF 2004). While further modifications have been proposed, for example cereal (rice)-based formulations or the addition of certain amino acids (glucose, alanine, or glutamine) to further increase sodium absorption and hasten...
intestinal repair (Atia and Buchman, 2009),

or supplementation with zinc to improve outcomes (Awasthi, 2006; Lazzerini and Ronfani, 2013), the primary goal of ORS remains enhancing salt and water absorption.

Cholera and cholera-like enterotoxigenic *E. coli* infections raise additional issues because of the prodigious volume losses or vomiting, and comorbidities, such as pneumonia, that affect outcomes. When intravenous rehydration is required because of shock, switching to maintenance ORS is effective when clinical status improves. Although there is interest in antiemetic drugs, such as odansetron, limited safety and efficacy data in poorly nourished children under age five years, and the added cost, diminish current enthusiasm (Ciccarelli and others, 2013).

Unfortunately, the use of ORS for clinic- and home-based treatment has stagnated in most countries, with an average coverage of 30-38 percent of the children who should receive ORS (Santosham and others, 2010; WHO/UNICEF, 2009). In part, this is due 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 may be influenced by prior experience when physicians recommend intravenous fluids. In Brazil, for example, most children with moderate dehydration are rehydrated with intravenous fluids, which sends the wrong message to caregivers about physician preferences (Costa and Silva, 2011). Community-based initiatives, such as home visits by community health workers and community-based delivery mechanisms, can increase 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% reduction in antibiotic use (Das and others, 2013). Limited information precludes an assessment of the impact of community case management on mortality, but trends suggest a decrease of 63 to 92 percent among children ages 0 to four years and 0 to one year, respectively.

**Antibiotics**

The pervasive overuse of antibiotics is dangerous because of emerging 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 the quality of and access to medicines, and because many antibiotics are readily available in pharmacies, shops, and markets without prescriptions. Overuse can occur even where prescriptions are required (Adriaenssens and others, 2011), but it can be reduced by practitioner and parent knowledge and attitudes (Clavenna and Bonati, 2011).

Despite repeated reports calling for more evidence-based use of antibiotics, better education of practitioners and the public, and systematic surveillance of antibiotic use and resistance, WHO estimates that more than 50 percent of all medicines are inappropriately prescribed, dispensed, or sold, and 50 percent of patients use them incorrectly (WHO, 2010). 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 (73.9 percent) than professional guidelines (66.3 percent) or university courses (63.6 percent), and more practitioners used the internet (45.7 percent) than 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. 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 tertiary hospital had already received antibiotics without a clinician’s recommendation (Ekwochi and others, 2013). Caregivers in India and Kenya ranked antibiotics over ORS by more than 2:1 as the “strongest medicine for diarrhea”, partially explaining the low use of ORS and the high use of antibiotics (Zwister and others, 2013).

Experts agree that antibiotics are usually unnecessary for acute watery diarrhea; most episodes are mild and self-limited, and especially among young children many are due to viruses, (Kotloff and others, 2013). It is time to
abandon routine adjunctive use of antibiotics to shorten duration of illness in moderate to severe dehydration. Although effective antibiotics for cholera can reduce fluid losses and replacement requirements by up to 50 percent, and stop the shedding of viable organisms in one to two days (Harris and others, 2012), a systematic review of antibiotics for cholera found the evidence for reduced mortality too weak to make any recommendation (Das, Ali, and others, 2013). While V. cholerae has remained sensitive to most antibiotics, the long-term tradeoff is selection for drug resistance which is now rapidly increasing (Ghosh and Ramamurthy, 2011). This raises the likelihood of horizontal transfer of multidrug resistance among V. cholerae and potentially to other enteric pathogens as well (Kruse and others, 1995). The emergence of quinolone resistance in V. cholerae (Kim and others, 2010), the most useful antibiotic for grossly bloody diarrhea and dysentery, further raises the level of concern about routine adjunctive antibiotics for cholera except perhaps the most severe purging (Harris and others, 2012), or epidemics that overwhelm clinical capacity (Ernst and others, 2011). Elimination of viable V. cholerae in stool would also diminish the potential for spread within or between countries (Macpherson and others, 2009; Tatem and others, 2006).

In contrast, morbidity and mortality due to inflammatory diarrheas, most often caused by Shigella invading the intestinal mucosa, are not due to dehydration, but rather tissue damage. Large numbers of leukocytes are recruited to the invasion site, leading to epithelial cell death and ulceration, and release of cytokine mediators of metabolism underlying nutritional deterioration. These responses persist for weeks after acute infection, drive continuing malnutrition (Raqib and others, 1995), and are 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 are bacterial in etiology and Shigella or related enteroinvasive E. coli serotypes are most common. Without point-of-contact diagnostics to identify specific causes, a pragmatic assumption is that it is bacterial and antibiotics appropriate for shigellosis should be initiated, which is likely to be adequate for other bacterial etiologies. While resistance to some, or multiple, antibiotics is increasing (Mota and others, 2010; Battacharya and others, 2011), the pattern is locale-specific and dynamic (Das and others, 2013). Surveillance needs to be in place to continually identify agents and antimicrobial sensitivity to guide therapeutic decisions (O’Ryan and others, 2005). Because this is not yet feasible in most LMICs, empiric treatment decisions remain the norm. Currently, ciprofloxacin, azithromycin, or pivmecillinam (if available) are reasonable initial choices, reserving ceftriaxone for treatment failure, with no clinical improvement within 48 hours to 72 hours (Erdman and others, 2008; Traa and others, 2010).

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

Vaccines

The public health perspective is that 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/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 been 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 which reduces incentives for R&D.
Rotavirus
The only approved diarrhea vaccine marketed at a global scale is rotavirus. Two vaccines are available and while widely used in HICs and MICs they are only beginning to be introduced in LICs. Other rotavirus vaccines are licensed in China or Vietnam for local use only, however an Indian vaccine has recently been prequalified by WHO, a process to provide early evaluation of quality, safety and efficacy of products pre-licensure. This product would be lower in cost and has recently been shown to reduce severe episodes by over 56% in the first year of life and 54% overall (Bhandari and others, 2014).98 Importantly, no evidence of increased incidence of intussception, the major adverse reaction to rotavirus vaccines, was detected.

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

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

The Global Alliance for Vaccines and Immunization (GAVI) has now added rotavirus to its support program, and 19 of the 35 GAVI eligible countries are including rotavirus vaccine in their routine immunization programs; the number should increase to 30 in 2015 (GAVI, 2014).99 Universal implementation of rotavirus vaccine could reduce the number of under five diarrhea deaths by 75,000 to 85,000 per year (Fischer Walker and Black, 2011),1 prevent many episodes of severe diarrhea, and reduce hospitalizations and associated costs by an average of 94 percent (Munos and others, 2010). The cost of hospital admission for rotavirus diarrhea in India may be as much as 5.8 percent of household annual income (Mendelsohn and others, 2008),100 or about US$66 per hospitalization (Sowmyanarayanan and others, 2012).101

Cholera
The global burden of morbidity and mortality of cholera is high, with an estimated 2.8 million cases and 91,000 deaths annually in endemic countries (Ali and others, 2012).102 Incidence is highest in children under five years, who may account for as much as 50 percent of cholera mortality. Inexpensive oral killed whole bacteria cholera vaccines developed in India and Vietnam are effective (Clemens, 2011),103 and the former is also WHO prequalified. Production and use of these vaccines, even for domestic use, remains limited even though widespread use could reduce incidence by as much as 52 percent (Das and others, 2013).104 Modeling based on clinical trials in Bangladesh suggests as much as 93 percent reduction in cholera if only 50 percent of the population is immunized, i.e. herd immunity (Longini and others, 2007),105 potentially reducing the use of antibiotics as well (Okeke, 2009).106

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).107 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).108 Approximately two thirds of inpatient “cholera deaths” in endemic countries are actually associated with pneumonia rather than dehydration (Ryan and others, 2000),109 increasing to 80 percent in children under age one year.

Mass immunization was considered for Haiti to possibly prevent cholera from becoming endemic, however a careful analysis concluded it should not be introduced because of limited vaccine availability, complex logistics, operational challenges of a multidose regimen, and population displacement and potential civil unrest as serious obstacles.(Kashmira and others, 2011)110 Cholera has indeed become endemic in Haiti and is the leading etiology of diarrhea in hospitalized patients (Steenland and others, 2013).111 A subsequent vaccine demonstration trial in Haiti showed that it was feasible to achieve high coverage with two doses of vaccine (Rouzier and others,
This has paved the way for an ambitious immunization program, justified by the dreadful state of water and sanitation facilities in the country. While early deployment of cholera vaccine might have mitigated the extent of the epidemic and improved the impact of effective case management for dehydration, some supported creation of a cholera vaccine stockpile, available for use in future emergency and humanitarian disaster settings (Waldor and others, 2010). This is being implemented through WHO and the International Coordinating Group (WHO. 2013).

**Other Pathogens**

Vaccines for other enteric pathogens remain in research and development; no licensed products are available, particularly for agents highly associated with moderate to severe diarrhea, including ETEC, *Shigella*, and *Cryptosporidium*. While a high priority, it will be many years before a licensed product becomes 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. In India 25 percent of children admitted to hospital in the late 1980’s because of measles had diarrhea, and 22 had both diarrhea and pneumonia (Deivanayagam and others, 1994). The case fatality rate in measles associated diarrhea, often dysenteric, was 5 percent, however, this is a minimal estimate because 33% were discharged in critical condition again medical advice, with no follow up. Measles vaccine is now a high priority to prevent measles, which will have additional effects to reduce mortality and morbidity from diarrheal disease.

**Nutrition:**

**General Nutrition Support**

Malnutrition is both a consequence of and a risk factor for diarrheal disease (Mondal and others, 2013). Nutritional support during and nutritional rehabilitation post-diarrhea will reduce the severity of associated nutritional deficits, and improve resistance to and recovery from future diarrheal episodes. Prevention of malnutrition improves the ability to respond to future exposure to diarrhea pathogens, and mitigates the severity of nutritional losses when diarrhea occurs. A recent review of dietary management of acute diarrhea (Gaffey and others, 2013) concluded that locally available age-appropriate foods should be promoted for the majority of acute diarrhea episodes, even in the presence of lactose malabsorption, instead of commercial preparations or specialized diets. There is considerable interest in community management of severe or moderate acute malnutrition using ready-to-use therapeutic foods (RUTF) which are energy dense, solid or semisolid, low moister content preparations of peanut butter enriched with dried skimmed milk, sugar, vegetable oil, vitamins and minerals that can be eaten direct from the package. Such products, whether imported commercial versions or locally made, facilitate community management of malnutrition (Choudhury and others, 2014; Schoonees and others, 2013).

Imported commercially produced RUTF has been criticized because of high price and limited affordability, adverse impacts on breastfeeding, medicalization and commercialization of malnutrition treatment, and difficulty in scale up to meet global needs (Latham and others, 2010).

Exclusive breast feeding is a key nutritional support mechanisms for very young infants, with many health impacts beyond nutritional status and reduced susceptibility to diarrheal disease and other infections (Bhutta and others. 2013; Dey and others. 2013; Strand and others. 2012). Continued breast feeding during acute watery diarrhea in infants alternating with ORS combines the nutrient and resistance factors in breast milk with the impact of ORS on dehydration, and is highly recommended despite common cultural biases against feeding during diarrhea (Chouraqui and Michael-Lenoir. 2007; King and others. 2003. In fact, 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 common, especially in LICs, due to low dietary intake and/or inadequate absorption (Haider and Bhutta, 2009). Zinc deficiency is associated with increased risk of intestinal infections, adverse effects on structure and function of the gastrointestinal tract, and impaired immune function (Gebhard and others, 1983; Bhan and Bhandari, 1998). WHO currently recommends zinc supplementation for children with acute diarrhea, at a dose of 10 mg per day for those under six months of age or 20 mg per day for children over 6 months old for 10 – 14 days.

Zinc may curtail the severity of diarrheal episodes and prevent future episodes because zinc is vital for the synthesis of protein, cell growth and differentiation, and immune function, and promotes intestinal transport of water and electrolytes (Castillo-Duran and others, 1987; Shankar and Prasad, 1998). Zinc also has a vital role in normal growth and development of children, with or without diarrhea. A recent meta-analysis suggests that preventive zinc supplementation at a dose of 10 mg zinc/day for a duration of 24 weeks leads to a net a gain of 0.19 (±0.08) cm in children under the age of five years (Imdad and Bhutta, 2011). Various zinc formulations (sulfate, acetate, and gluconate) are acceptable options. Zinc sulfate is low-cost, safe, efficacious, and 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.

Walker and Black (2010) reviewed 13 studies of zinc supplementation in diarrhea from LMIC’s and concluded that zinc was associated with a significant 46% (RR:0.64; 95% CI: 0.32, 0.88) reduction in all-cause mortality and 23% (RR: 0.77 95% CI: 0.69, 0.85) reduction in diarrhea-related hospital admissions, although the impact on diarrhea related mortality and subsequent prevalence were not significant. One limitation was the inability 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. Similar efficacy has been documented in children less than six months of age (Mazumder and others, 2010). Zinc supplementation may also be useful in the treatment of persistent diarrhea. A randomized control trial in 6 - 18 month old children concluded that persistent diarrhea led to depletion of zinc while oral zinc administration improved zinc status (Sachdev and others, 1990). A pooled analysis of the effect of supplementary oral zinc in children under the age of five with persistent diarrhea showed a 24% lower probability of continuing diarrhea (RR: 0.76; 95% CI: 0.63, 0.91) and a 42% lower rate of treatment failure or death (RR: 0.58; 95% CI: 0.37, 0.90) (Bhutta and others, 2000). Another review on zinc supplementation for greater than 3 months in children less than 5 years of age to prevent diarrhea in LICs and MICs showed a 13% (RR = 0.87; 95% CI: 0.81, 0.94) reduction in incidence of diarrhea (Yakoob and others, 2011). To date there have been no reports of severe adverse reactions from any form of zinc supplementation used in the treatment of diarrhea.

Despite evidence of benefit, introduction of low osmolarity ORS and zinc for the treatment of diarrhea remains limited. Many countries have changed diarrhea management policies to add zinc to ORS, but there is a gap between policy change and effective program implementation (Bhutta and others, 2013). Bottlenecks include limited knowledge among care providers and parents, price, availability and barriers at the policy level. Scaling up the use of zinc, including promotion and distribution through community programs, have increased its use by 80% (Das and others, 2013). Free distribution, social marketing, education of caregivers and the provision of zinc through both government and private providers at the community level and co-packaging of zinc and oral rehydration solution, are additional strategies to increase coverage.

**Water and Sanitation**
Because of diarrhea is transmitted by the fecal-oral route, provision of adequate amounts of clean water and safe disposal of feces have major impacts on diarrhea incidence. If EED is also a consequence of continuing ingestion of fecal microorganisms, as suspected, these improvements should also reduce EED as a cause of early malnutrition. A recent review suggests reductions in diarrhea risk of 17 percent and 36 percent for improved water quality and excreta disposal, respectively (Cairncross and others, 2010). One analysis of demographic health surveys conducted between 1986 and 2007 suggests that improved sanitation reduces diarrhea mortality (OR: 0.77, 95% CI 0.68,0.86), incidence (R = 0.87, 95% CI 0.85,0.90), and risk of mild to moderate stunting (OR: 0.73, 95% CI 0.71,0.75) while access to improved water reduces risk of diarrhea (OR: 0.91, 95% CI 0.88,0.94) and mild-severe stunting (OR: 0.92, 95% CI 0.89,0.94) (Fink and others, 2011).

Handwashing is a closely related intervention; it depends on water supply and interacts positively with sanitation to reduce exposure to fecal contamination. A review of 42 studies estimated that just 19% of the world’s population wash their hands with soap after contact with excreta (Freeman and others, 2014). Meta-regression of risk estimates suggested that handwashing reduced the risk of diarrheal disease by as much as 40% (risk ratio 0.60, 95% CI 0.53-0.68) or as little as 23% (risk ratio 0.77, 95% CI 0.32-1.86) when the data were adjusted for unblinded studies. Handwashing is discussed in greater detail as a behavioral intervention in the following section.

Somewhat surprising, a 2005 meta-analysis of water, sanitation, and hygiene—collectively known as WASH—interventions failed to document greater effectiveness of combinations over single interventions (Fewtrell and others, 2005). Current assessments are not sufficiently robust to influence investing in one WASH strategy over another, although these interventions all make sense and improve quality of life (Arnold and others, 2013). A World Bank analysis of trends in Demographic and Health Studies data suggested that open defecation explains almost twice as much (54 percent versus 29 percent) of the international variation in child height compared to gross domestic product (GDP) (Spears, 2013). A 20 percent reduction in open defecation predicted a 0.1 SD increase in child height.

As infrastructure projects, water and sanitation improvements may be built at the community, neighborhood, or individual household levels, may be more or less technically complex, and more or less expensive. A thorough discussion of water and sanitation infrastructure will appear in the DCP3 volume on Injury Prevention and Environmental Health (Briceno and Hutton, forthcoming). In 2008, the World Bank and WHO estimated the global cost of water and sanitation projects to meet the 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), or US$4-14 billion per year for water and sanitation projects, respectively, or US$8 to 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 must be maintained; this ongoing requirement represents substantial additional financial as well as human capacity investments, however without them infrastructure deteriorates and the initial investment is lost.

Limited evidence suggests that combining development and health interventions results in facilities that are better built and maintained, and in improved practices. Six years after completion of a project in Bolivia, an assessment indicated that the use of facilities in intervention communities was 44 percent higher than in control communities, and more than two-thirds of households continued to practice selected maternal and child health behaviors promoted by the interventions compared to less than half of the households in control communities (Eder and others, 2012). Unfortunately, current assessments indicate that the 2015 MDG 7 goal for water and sanitation targets will not be met in five of nine regions (WHO and UNICEF, 2013).

**Behavioral Interventions**
A number of actions or decisions by caregivers, providers, and public health officials require behavior changes wherein some volition is required to act, but if the practice became the norm it could reduce risk of, and morbidity and mortality from, diarrhea. Each of these behaviors is often difficult to sustain, but each would, if accomplished, have 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, even door knobs (Abad and others, 2001),\(^{147}\) is a common route for the transmission of low inoculum diarrheal (as well as respiratory) pathogens. Contaminated hands readily inoculate food or water which allows high inoculum pathogens to multiply. Implementation of simple handwashing procedures significantly reduce transmission rates in health care facilities (Bolon, 2011),\(^ {148}\) households (Bloomfield, 2003),\(^ {149}\) schools (Lee and Greig, 2010),\(^ {150}\) and even day care and preschool settings, which are notoriously difficult environments to enforce good hygiene (Churchill and Pickering, 1997);\(^ {151}\) implementation can also reduce respiratory disease, another major infectious cause of childhood death (Luby and others, 2005).\(^ {152}\)

For example, handwashing with soap in a refugee camp in Malawi reduced the number of diarrhea episodes by 27 percent, even though only 38 percent of the households had soap available on interview days (Peterson and others, 1998).\(^ {153}\) Provision of soap and a weekly meeting with trained health care workers from the same communities to reinforce the behavior in an urban squatter community in Karachi, Pakistan, showed a 39 percent reduction (95% CI -61.16%) in days with diarrhea among infants versus controls over one year (Luby and others, 2004).\(^ {154}\) Even severely malnourished children (WAZ < -3.0) had 42 percent (95% CI -69.16%) 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% CI -65.34%). Although the use of soap improves effectiveness, handwashing with water alone is worthwhile. In Bangladesh the risk of diarrhea diminished when caregivers washed both hands with water before preparing food (OR: 0.67, 95% CI 0.51,0.89), although the effect was greater if one or both hands were washed with soap (OR: 0.30, 95% CI 0.19,0.47) (Luby and others, 2011).\(^ {155}\) Risk was also reduced when caregivers washed their hands with soap after defecation, but not with water alone (OR: 0.45, 95% CI 0.26,0.77). There are five key times for handwashing: after defecation, after handling children’s feces or cleaning the anus, before preparing food, before feeding children, and before eating. Direct observations determined that this results in more than 20 situations per day for handwashing, a frequency considered impossible to achieve, especially when the added cost of soap was considered. The key lesson distilled from the data emphasized handwashing before preparing food because it was the single most effective opportunity.

How feasible is it to embed this practice in daily behavior? A randomized intervention in Pakistan providing soap for handwashing or a method to disinfect water, with weekly visits over nine months to encourage the practice, documented a 55 percent reduction in diarrhea (95% CI 17,80%) versus control neighborhoods, with no difference between the soap or water disinfection groups (Luby and others, 2006).\(^ {156}\) When reenrolled in a follow-up surveillance 18 months later, intervention households were still 1.5 times more likely to wash with soap and water (79% versus 53%, P = 0.001) and 2.2 times (50% versus 23%, P = 0.002) more likely to rub their hands together compared with controls (Bowen and others, 2013).\(^ {157}\) Weekly follow-up over the 14 months without active educational intervention demonstrated no difference between the groups in the proportion of person-days with diarrhea (1.59% versus 1.88%, P = 0.66) or the amount of soap purchased. Three years later, however, the investigators re-engaged 461 original households (69 percent) and found the original intervention households were 3.4 times more likely than controls to have soap available (97% vs. 28%, P < 0.0001), more commonly reported handwashing before cooking (RR: 1.2, 95% CI 1.0,1.4) and before meals (RR: 1.7, 95% CI 1.3,2.1), and purchased more soap per person/month (0.91 to 1.1 bars for intervention households versus 0.65 for controls, P < 0.0001).
To habituate health behaviors that should persist throughout life, it is postulated that individuals must first choose to do so until the behaviors become automatic (Ouellette and Wood, 1998) through three stages, planning, motivation, and finally habituation (Curtis, Danquah, and Aunger, 2009). Speculatively, the interval surveillance may have triggered motivation among the prior intervention group, which was subsequently sustained over a longer time. Evidence suggests that protection of infants from disease does not motivate handwashing as effectively as the desire to nurture, revulsion of feces, and social acceptance and status afforded by cleanliness (Scott and others, 2007). The key question is not whether improving handwashing practices is effective, but rather how the consistency of the practice can best be promoted. Design and location of a household handwashing station can either facilitate or inhibit the practice (Dreibelbis and others, 2013).

Additional intervention by health care workers is useful, but how much is feasible and affordable, and what they address remains in question? Increasingly, integrated behavioral models are being developed 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 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; they often overlook social and cultural dimensions. This can influence when a caregiver’s focus on rehydration changes because they recognize that fluid losses are beyond the limits of “normal” and becoming dangerous, requiring professional intervention (Larrea-Killinger and Muñoz, 2013).

Higher levels of education promote quicker care seeking action, whereas cultural influences, for example, gender discrimination, can delay this for female versus male infants (Malhotra and Upadhyay, 2013). Two problems were identified in a rural setting in Burkino Faso: first, failure to recognize mild diarrhea, especially among infants; second, intervention choices that do not match international recommendations (Wilson and others, 2012). Although 784/10,262 children included in the sample had diarrhea by clinical criteria (3 or more liquid or semiliquid stools in 24 hours), only 55% of caretakers answered yes when asked during an interview if the child had diarrhea. Only 55 percent of caretakers sought care outside of the household for children with clinically defined diarrhea, of which 22 percent were with traditional healers or drug vendors, only 12 percent of whom recommended ORS (in only 12 percent of cases). In rural Kenya, where caregivers had a good understanding of diarrhea and dehydration, what most concerned them was to stop the diarrhea, preferring antibiotics or antimicrobials over ORS (Blum and others, 2011). Continued diarrhea was an important reason to seek care at a health facility; however, caretakers expected “Western medicines” (e.g. antibiotics) would be provided. Cost of treatment represents the major pragmatic impendiment to care-seeking outside of the home (Nasrin and others, 2013). While anthropological and ethnographic approaches may help improve educational messaging and responses, cost, access to facilities, travel and wait times are likely to be critical determinants of behavior, and require very different inputs to address.

Community-Based Interventions

Because of continuing limitations in access to health facilities and trained primary care workers, large numbers of children fail to receive simple but effective early interventions when diarrhea develops. A recent systematic review (Das and others, 2013) concluded that community-based interventions improve care seeking by 9 percent (RR: 1.09, 95% CI 1.06-1.11), increase use of ORS by 160 percent (RR: 2.6, 95% CI 1.59-4.27), produce a 29-fold increase in the use of zinc supplements (RR: 29.8, 95% CI 12.33,71.97), and reduce antibiotic use by 75 percent (RR: 0.25, 95% CI 0.12,0.51).
Because diarrheal 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” has been recommended (Eisenberg and others, 2012, page 242). They argue that measuring these effects will require different study designs that elucidate social patterns of interaction and the movement of pathogens through the environment.

**Community-Led Total Sanitation (CLTS)**

Interventions to improve the safe disposal of human excreta can be difficult to implement, maintain, and document a positive result, especially in rural settings in LICs (Clasen and others, 2010). Since 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 improve sanitation in communities, originally proposed in 1999. Using CLTS as the approach, communities mobilize to achieve total abandonment of open defecation, and replace it with subsidized construction of facilities, household-by-household. The idea is to generate social pressure on all members of a community to understand the health implications of open defecation, and get the community to join together, without external resources except for guidance and facilitation, to agree on and act to completely eliminate open defecation and build a community sanitary infrastructure (Kar and Kamal, 2003).

CLTS can be a powerful technique for change. It begins with a facilitator engaging a community or village to promote understanding of the link between open defecation and illness. Engagement is followed by a survey and mapping of actual practices, often carried out 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 incite self and community analysis [and] 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, page 11). While some observers have critiqued the use of shame or social stigma to promote compliance as a violation of ethical principles and an infringement on human rights (Bartram and others, 2012), others have noted the combination of 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 from organizations, government ministries, and development funders who may be committed to different models to improve sanitation infrastructure, at the same time many examples of success and spread of CLTS exist. This juxtaposition of tensions and successes indicates the need for careful analysis of the role of a program like CLTS and how best to introduce it. It will be important to consider 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 top-down to bottom-up development, sensitive to the local context and the longer time horizon required (Deak, 2008).

**Cost and cost-effectiveness of interventions**

There are cost-effective and low cost interventions to help prevent and treat diarrhea (Table 9.1). Since the analysis of cost-effectiveness of interventions for diarrhea in LMICs in DCP-2 (Keusch and others, 2006) the ranking of various modalities has changed because of evidence on the use 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 has stopped additional work on its cost-effectiveness for diarrhea because it is now “standard
Althou the it is self-evident that coverage with breastfeeding promotion reduces diarrhea, this has not been as high on the research and policy agenda.

**Table 9.1: Cost-effectiveness and Unit Cost of Interventions for Diarrheal Diseases**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Oral rehydration Solution (vs no ORS)</td>
<td>AFR-E</td>
<td>&lt;$200</td>
<td>$2.26/diarrhea episode</td>
</tr>
<tr>
<td>Prophylactic zinc with ORS (vs ORS alone)</td>
<td>AFR-E and SEA-D</td>
<td>&lt;$100</td>
<td>$0.63/diarrhea episode</td>
</tr>
<tr>
<td>Rotavirus vaccine (vs no vaccine)</td>
<td>Low income countries</td>
<td>&lt;$200 at $5/dose (less at $0.20/dose)</td>
<td>$5/dose for 2 doses (GAVI price); GAVI-eligible countries pay $0.20/dose for 2 doses</td>
</tr>
<tr>
<td>Clean water (at household: chlorination/solar disinfection, vs untreated water)</td>
<td>AFR-E and SEA-D</td>
<td>&lt;$200</td>
<td>$0.06/person/year SEA-D $0.17/person/year AFR-E</td>
</tr>
<tr>
<td>Improved rural water and sanitation (vs unimproved)</td>
<td>AFR-E and SEA-D</td>
<td>&lt;$2000</td>
<td>$27/household (well); $50 household (latrine)</td>
</tr>
<tr>
<td>Piped water and sewer connection (vs no connections)</td>
<td>AFR-E and SEA-D</td>
<td>&lt;$2000 ($3000)</td>
<td>$130/household (water); $153/household (sewer)</td>
</tr>
<tr>
<td>Cholera vaccine (vs no vaccine)</td>
<td>High-endemicity countries</td>
<td>$2000-$10,000</td>
<td>$1.20/person</td>
</tr>
<tr>
<td>Behavior change</td>
<td>Low income countries</td>
<td>Large variation</td>
<td>Large variation</td>
</tr>
<tr>
<td>RUTF added to standard rations (vs standard rations)</td>
<td>AFR-E</td>
<td>&gt;$10,000 considering only benefits for diarrhea</td>
<td>$576 /child/year</td>
</tr>
</tbody>
</table>

Source: see Chapter 17. AFR-E refers to high mortality Africa and SEA-D to high mortality Southeast Asia (WHO subregions). Costs and cost per DALY are higher in other regions. Interventions costing less than $240/DALY in 2012 would be very cost-effective even in the poorest low income country, and those costing less than $720 would be cost-effective, even in the poorest low income country (Burundi’s per capita GNI was $240 in 2012: World Bank 2014). Unit costs are converted from original year using US CPI.

Detailed discussion on the cost-effectiveness of selected diarrhea interventions is presented in Chapter 10 (Preventive care), table 10.1. Chapters 10 and 12 (Infant and young child growth) also provide relevant information on vaccines and nutrition. Chapters 10 and 16 review Cost-effectiveness of rotavirus and cholera vaccines. This information is summarized only briefly here.
The most cost-effective interventions currently available for diarrhea (as measured in US $ of 2012 per DALY) are prophylactic zinc supplementation (also as an adjunct to ORS), ORS, rotavirus vaccine, and household-level water treatment (using chlorination or solar disinfection primarily in rural areas) (also see Table 10.1). The next most cost-effective group includes rural sanitation, piped water and (in selected countries) cholera vaccine. Finally, nutrition interventions are the least cost-effective for their impact on diarrhea, however they have important other benefits. Cost-effectiveness of community management of severe-acute malnutrition is covered in Chapter 11.

Table 9.1 includes just one study of behavior change, obtained from a focused search in PubMed. Behavior change interventions tend to have very heterogenous results; the one surveyed here (see Table 10.1 for more details), a hand-washing education intervention in Burkina Faso (Borghi and others, 2010), would fall into the most cost-effective group. Well-designed behavior change interventions to increase the use of clean water, latrines (where available), 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 did not yield any relevant citations. Typically searches on drug names yield many cost-effectiveness study results when a drug is new, or is being tested for a new use, however this is not the case here. Drug treatment for dysentery is known to be highly effective if the pathogens are sensitive, and with the high case fatality rates for dysentery drug treatment is extremely likely to be cost-effective.

However, it is not sufficient for an intervention to be cost-effective in order to be adopted. Cost or affordability in relation to health expenditures also matters. One big change over the last decade has been the addition of zinc as a complementary therapy to ORS. Since it is an add-on to an existing treatment, it appears particularly cost-effective, and is also relatively affordable. Robberstad and others (2004) estimated that zinc tablets cost approximately $0.63 for a three week course of treatment on top of the $2.26 in recurrent costs per course of treatment with ORS (US $ of 2012, although they do not provide any allowance for personnel costs in their analysis.

Introduction of rotavirus vaccine is progressing through GAVI support, although the negotiated price for the vaccine is $5 per dose for the 2-dose course, this is still a substantial addition to the current cost of the Expanded Program of Immunization (EPI). GAVI provides the vaccine at a highly subsidized price to eligible countries ($0.40 for two doses), but countries which “graduate” from eligibility (such as India) are required to pay 20% of the GAVI cost in the first year, increasing gradually by $1 per year until the full price is paid (see Chapter 20, “Health gains and financial risk protection”). Since diarrhea rates (and mortality rates) are higher in LICs, the vaccine is particularly cost-effective in LICs, which are also likely to face the greatest hurdles regarding affordability.

Sanitation and, to a lesser extent, water supply interventions, are subject to the issue of affordability. Initial investment costs per household for standard urban requirements, namely water piped to the house and a sewer connection, are $130 and $153, respectively. The lowest-cost clean water interventions in rural areas are still substantial at $26/household for a dug well, $29 for a borehole, and for sanitation (pit latrine) $50/household (Haller and others, 2007), in US $ of 2012. Household disinfection of water at point of use (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 run to decrease diarrhea, stunting, and intestinal parasites, the investment costs make the transition likely to be slow.

Most of the results in Tables 9.1 and 10.1 describe the cost-effectiveness of adding a single intervention. If interventions are combined, the incremental cost-effectiveness of each additional intervention can diminish. One ambitious study (Fischer Walker and others, 2011) estimated the combined effect of ten interventions designed to reduce diarrhea, in 68 countries with high child mortality, using the LiST model (Lives Saved Tool). Two scenarios were modelled: an ambitious strategy (designed to reach MDG4 goals in a realizable way), and a universal strategy (designed to bring coverage of many interventions to 90% or more, and water, sanitation and
hand-washing interventions to 55% or more). Both strategies were scaled up from current coverage to the target over five years. The ambitious strategy saved 3.8m lives over a five year period, at a cost of $49.2bn, i.e. $12,847 per death averted (or approximately $405/DALY: US $ of 2008, assuming one life saved in infancy/early childhood is about 32 DALYs). The universal strategy saved 5m lives for a cost of $19,460 per death averted (or $608/DALY). These would be considered cost-effective or very cost-effective range for most countries. However affordability is an obstacle. The water and sanitation component is the main issue, accounting for 84% of the cost of the ambitious package, and 87% of the universal strategy.

Extended cost-effectiveness analysis (ECEA) provides further insight. Chapters 19 ("ECEA of rotavirus vaccination in India") and 20 present ECEA analyses of water and sanitation improvements, and the introduction of rotavirus vaccine in India, respectively. Both Chapters show that these interventions are pro-poor, as 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 their children have poorer nutritional status and are at higher risk of mortality from diarrhea-related illness.

Conclusions

There have been dramatic reductions in the burden of diarrheal diseases in the under 5 year population in low and middle income countries as a result of focused attention and resources applied, originally through vertical programs and advocacy through WHO and international donor agencies, and more recently through more integrated programs for primary care and community based programming. There are no magic bullets yet to control the incidence of, let alone eliminate, diarrheal diseases. Reductions in severity and mortality have not been achieved by reducing the frequency of diarrhea episodes. Rather, improving nutrition of young children results in a healthier host able to respond better to infection, water and sanitation improvements reduce the number of microorganisms the host is exposed to, and use of simple but highly effective interventions such as oral rehydration solutions has enabled early treatment and mitigation of dehydration due to watery diarrhea. When antibiotics are used appropriately for inflammatory diarrheas survival is enhanced, however this is difficult to target to individuals who truly need antibiotic treatment and most use of these drugs is not only ineffective (for example treatment of a viral infection) but counterproductive as well, as this creates a selective pressure for drug resistance; many important diarrheal disease agents now exhibit serious often multi-drug resistance. Improved understanding of the pathogenesis of persistent diarrhea has helped the development of nutritional interventions useful in the face of the malabsorption and malnutrition that characterize persistent diarrhea and lead to serious morbidity and increased mortality.

We have reviewed a number of interventions and policy strategies that independently are effective, can often be packaged together, and can be delivered at the community level. Among these, many have impact far beyond diarrheal disease, and these additional rationales for implementation represent benefits that enhance their cost-effectiveness. Some are both effective and highly inexpensive, so there is no a priori reason not to promote them, for example the early use of oral rehydration solutions. Continued attention to delivering the appropriate package of interventions, coupled with monitoring and continuous quality improvement of healthcare delivery services, can be expected to continue to drive down the mortality and sequelae of diarrheal diseases in the forthcoming decade.
References


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