Annals of Microbiology and Infectious Diseases
Volume 1, Issue 1, PP 24-38

Global Trends of Diarrhea Diseases in Children

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ABSTRACT

Diarrhea is a major cause of childhood morbidity and mortality. It results from contaminated food and water sources. Diarrhoea caused by infection is widespread throughout developing countries. This review focuses on diarrhea-related diseases in children worldwide. It looks at the pathogenesis, treatment, prevalence, and mortality rates of the major pathogens which cause diarrhea in children. The major pathogens include Rotavirus, Escherichia coli, Cholera, Shigella, Parasites (Protozoa and Helminthes), and waterborne-specific pathogens. Included are the associations between malnutrition, increased diarrheal prevalence and mortality rates, as well as Human Immunodeficiency Virus' (HIVs) association with increased mortality rates due to diarrhea. This paper explores the current treatment and prevention methods used to decrease the incidence, prevalence and mortality associated with diarrhea, and can help to promote diarrheal awareness and education.

Keywords: *Diarrhea, HIV / AIDS, Cholera, Escherichia coli, Parasites, Rotavirus, Salmonella, Shigella;*

INTRODUCTION

Diarrhea is a major cause of childhood morbidity and mortality. It results from contaminated food and water sources. The diagnosis of diarrhea is made when a person has loose or watery stools at least three times in a day or more frequently than normal for that individual. There are two subtypes of diarrhea i.e. acute diarrhea and chronic diarrhea. The main forms of acute diarrhea are acute watery diarrhea, bloody diarrhea, and persistent diarrhea. Acute watery diarrhea, which is caused mostly by *Vibrio cholerae*, *Escherichia coli*, and Rotavirus, is associated with massive fluid loss causing dehydration. Bloody diarrhea or dysentery is caused mainly by *Shigella sp.* and there is visible blood in the stools. Persistent diarrhea lasts for 14 or more days and can have bloody or non-bloody stools. Persistent diarrhea usually occurs in malnourished children or in children with HIV (1). Chronic diarrhea is a persistent, usually painless symptom with no bleeding, weight loss or fatigue. It is mainly caused by dietary problems like lactose deficiency or excessive caffeine intake. A few cases of chronic diarrhea may be caused by intestinal parasites (2). Diarrhea is a common symptom in numerous gastrointestinal infections. The infections can be caused by any number of bacteria, viruses, or protozoa. The leading cause of childhood diarrhea is Rotavirus. It accounts for 40% of all hospital admissions for diarrhea in children. The major bacterial pathogens are *E. coli, Shigella, Campylobacter, Salmonella,* and *V. cholerae* during epidemics, while the major causative protozoan is *Cryptosporidium* (1).

Children who are malnourished, or are not breastfed for six months or more, or children in poor health are more prone to acquiring severe diarrhea and at a higher risk for death(1). Environmental factors that increase the risk of developing diarrhea include unsanitary water sources, and poor overall hygiene (3). According to a UNICEF study there are around 2.5 million cases of diarrhea in children under the age of five with the highest incidence being in children under two years of age(1).

Almost 1.3 million children less than 5 years of age die each year from diarrhea which is the second leading cause of death in this demographic. The majority of these deaths occur in India, Nigeria, Afghanistan, Pakistan and Ethiopia (4). Diarrhea causes death in patients by depleting the body of its water and electrolytes (mainly sodium), which are required for normal functioning (5). Even if the child manages to survive the bout of diarrhea there

can be detrimental effects to the child's growth and cognitive development (3). To help decrease prevalence and mortality rates of childhood diarrhea it is first important to understand the causative pathogens and their modes of infection.

Epidemiology (Prevalence/Morbidity for the Several Causes of Diarrhea)

Currently, sub-Saharan Africa and Southeast Asia experience the highest burden of diarrhea-related diseases (Figures 1), with nearly 83% of deaths from diarrhea occurring in just fifteen countries (Figure 2). Despite falling diarrhea-related mortality in most of these countries, some areas are still experiencing a growing number of deaths each year, including Afghanistan, Burkina Faso, Democratic Republic of Congo, Cameroon, Chad and Mali(6).

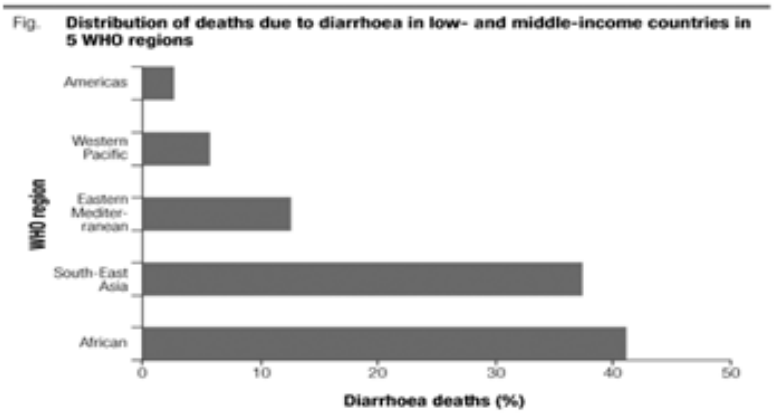


Figure1. *Diarrheal mortality by region (7)*

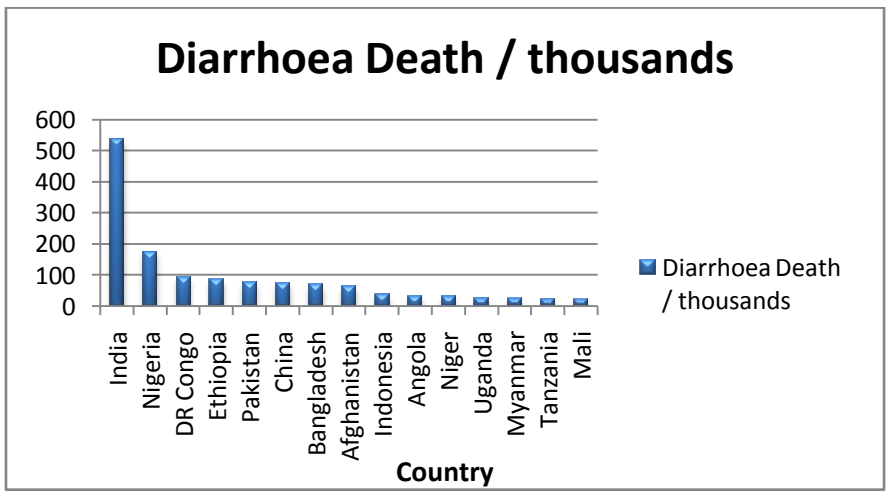


Figure2. *Countries accounting for three-quarters of deaths due to diarrhea in the developing regions of the world, 2004(7)*

Epidemiology of Diarrhea caused by Rotavirus

Prior to the introduction of vaccines, rotavirus accounted for an estimated 3 million cases per year with 95% of children infected by 5 years of age. Annually it was responsible for more than 400,000 physician visits, 200,000 emergency room visits, 55,000 to 70,000 hospitalizations and 20 to 60 deaths in the United States today (8). Africa tends to have more rotavirus mortality than most other countries. Developing countries and those with vaccines have decreased mortality significantly (9). In temperate climates, rotavirus is found more often during fall and winter (8). In the United States prior to vaccination, annual outbreak peaks usually started from the Southwest during November and December and progressed to the Northeast by April and May (8). Following the introduction of the vaccine, the seasons are shorter and have less notable differences in timing by geographic region. In tropical climates, the disease is even less seasonal than in temperate areas (8).

There are several sero groups of rotavirus, A-E, and depending on the proteins, VP, involved

they are further classified. From 1996 through 2005, five strains of rotavirus (G1-4, G9) accounted for 90% of cases from children younger than 5 years in the United States. Of these, the G1 strain accounted for more than 75% of cases (8). G9 strain is found most commonly in Africa, Asia and Latin America while G5 is most common to South America (10). The incidence of rotavirus is similar in developed and developing countries, suggesting that improved sanitation alone is not sufficient to prevent the infection (10).

Epidemiology of Diarrhea caused by E. coli

The transmission of *E. coli* infections most commonly occurs through the fecal-oral route. The most common forms of fecal-oral transmission include unhygienic food preparation, farm contamination due to manure fertilization, irrigation of crops with contaminated grey water or raw sewage, feral pigs on cropland, or direct consumption of sewage-contaminated water (11,12).

In the United States surveillance and recognition has increased over the past two decades. The increased surveillance has helped to cause a reduction in the incidence of *E. coli* in all populations including pediatric populations. According to the Food borne Diseases Active Surveillance Network (Food Net) of the Centers for Disease Control and Prevention (CDC) Emerging Infections Program, in 2007, the incidence of Shiga-toxin–producing *E. coli* (O157) was 1.20 cases per 100,000 populations, and the incidence of Shiga-toxin–producing *E coli* (non-O157) was 0.57 cases per 100,000 population). Since the beginning of surveillance in 1996, the incidence of Shiga-toxin–producing *E. coli* (O157) has decreased 25% (11,12). *E. coli* infections are quite common in most developing countries likely due to unsanitary conditions. The most common disease causing strain of *E. coli* in developing countries is Enterotoxigen *E.Coli* (ETEC) and it is estimated to cause over 600 million cases of diarrhea annually and 700,000 deaths in children younger than five years old (WHO). In May of 2011 an outbreak of *E. coli* began in Germany and eventually spread to eleven other countries (13). The outbreak was caused by a novel strain of *E. coli* designated as O104:H4; this strain was actually a form of Enteroaggregative *E. coli* (EAEC) that had acquired the genes required to produce the shiga toxin (13). A total of 3816 cases were confirmed with 54 deaths associated; 22% of cases developed Hemolytic uremic syndrome (HUS) (13). The outbreak predominantly affected adults, and adult women represented the majority of patients.

Epidemiology of Diarrhea caused by Shigella

Shigellosis is a severe and occasionally life-threatening bacteria cause of diarrheal infection. The organism Shigella spp. is the most common cause of acute, bloody diarrhea (dysentery) worldwide as well as significant morbidity and mortality associated with diarrheal disease. It is estimated that there are 125 million infections and 14,000 deaths caused by shigellosis annually in Asia (14). The genus *Shigella* has four species. *Shigella dysenteriae* is now rarely identified although it was historically responsible for large epidemics. Similarly, *S. boydii* is also not isolated frequently. *S. flexneri*, on the other hand, is common globally and often isolated frequently in resource-poor countries. *S. flexneri* has 15 different serotypes which are found heterogeneously across different regions. Lastly, *S. sonnei* which has only one serotype, is also found globally, although usually most commonly found in high-income regions (14)

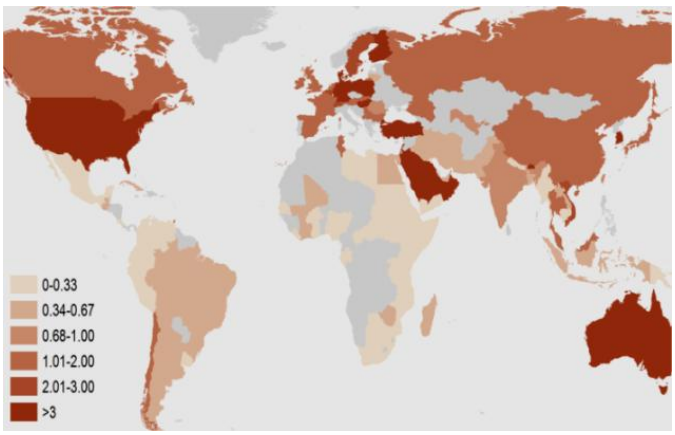


Figure3.*The ratio of S. sonnei to S. flexneri isolated from 100 countries, 1990–2014 (14).*

The above map (Figure 3) depicts the prevalence of *S. sonnei* versus *S. flexneri* worldwide, of note is the over 3:1 prevalence in the United States, Australia and the Middle East (14). According to the study on the rising dominance of *S. sonnei,* "the darker the color, the higher the proportion of *S. sonnei* isolated from each country; the lighter the color, proportionally

higher the proportion of *S. flexneri* isolated. Countries colored grey indicate no data on species were identified (14).

Epidemiology of Diarrhea caused by antibiotic resistant strains

Resistant strains in the U.S. are usually found to have decreased sensitivity to Ampicillin, or Trimethoprim-Sulfamethoxazole, and in rare cases, both. These resistant cases are reported in only about 27,000 subjects per year (~5.5%). Elsewhere in the world, particularly in developing countries, there seems to be a prevalence of drug resistant bacteria that are least likely to be susceptible to ciprofloxacin or azithromycin or both (15). These resistant strains are commonly found in India, the Middle East, Africa, and parts of Europe; with multi-drug resistant strains found in Australia, Europe and parts of North America (15). According to the Thompson study, there is a rising dominance of the *S. sonnei* variety of the bacteria and this is hypothesized as a multi factorial causation. First the study posits that some of the expansion of infection is actually due to improved quality of drinking water in the areas that are seeing the infection the most, particularly Asia, Latin America, and the Middle East as well as due to a potential unproven ability to acquire and/or maintain a wider array of antimicrobial resistance genes. Her theory is that the improved drinking water actually keeps the population from developing a resistance to the bacteria, and makes it more susceptible to infection. She also posits that these same egions have a prevalence of *Acanthamoeba castellani*, which phagocytoses these bacteria, and transport them in a type of symbiotic relationship, thus making them less susceptible to host defenses (14).

Epidemiology of Diarrhea caused by Cholera

Cholera is transmitted by ingestion of contaminated food or water that is infected with the feces of an infected individual. Cholera has previously, swept the world with six pandemic outbreaks. Some of these places include India and East Pakistan, and later receded into their ancestral home in the Indo-Pakistani subcontinent (16). During the course of outbreaks, the El Tor biotype *Vibrio cholerae* strain was discovered. This particular strain is a subset of *Vibrio cholerae* that was not involved in the previous pandemic cholera outbreaks, but was found to be responsible for the seventh pandemic cholera outbreak. Cholera has been heavily dispersed within the African and Southeast Asian countries since 1961(16). It is not as widely disturbed in European countries and Japan (16). The last cholera outbreak reported was in India and Bangladesh, with the emergence of 0139 *V. cholera*. It appeared that it would replace 01 strain, but it has exhibited dormant periods when 01 strain re-emerges. Cholera outbreaks tend to occur in areas where there is poor sanitation. It occurs occasionally as a limited outbreak in advanced countries.

Studies had shown that the global burden of cholera is high in developing countries. One particular study estimated that there were 2.8 million cases of cholera (uncertainty range: 1.2-4.3 million) and about 91,000 deaths (uncertain range: 28,000-142,000) worldwide. There are high incidents of cholera in Southern Asia and Africa. Data from these regions show that about half of the cases and mortality occur in children under the age of five (17). The table below shows the annual incidence rate (per 1,000) by age group, in two Asian and one African country (17).

	Kolkata, India (May 2003–Apr 2005)			**Jakarta, Indonesia (Aug 2001–Jul 2003)**			**Beira, Mozambique (Jan-Dec 2014)**		
Age (years)	**Population**	**Cases**	**Rates**	**Population**	**Cases**	**Rates**	**Population**	**Cases**	**Rates**
Less than 1	698	10	7.1	3121	25	4.01	-	-	-
1-4	3782	53	7.1	12620	39	1.55	1686	9	8.8
5-14	11440	50	2.1	29003	17	0.29	17861	38	3.5
Greater than 14	42143	78	0.9	115432	62	0.27	-	-	-
Total	58063	191	1.6	160257	143	0.45	19547	47	4.0

The annual numbers of deaths from cholera in an endemic country in 2005 was estimated by WHO based on the age specific mortality rates populations. The summary is represented below in the graph (Figure 4).

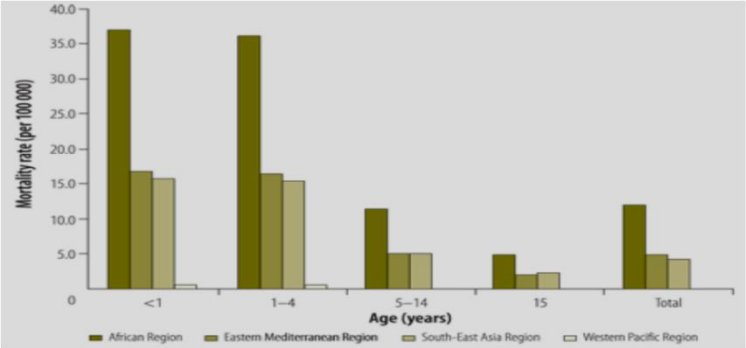


Figure4. *Age-specific mortality rates for at-risk populations by WHO stratum in cholera-endemic countries, 2005 (17)*

Epidemiology of Diarrhea caused by contaminated Water

An estimated 1.8 billion people (25% of the world's population) are without access to adequate sanitation (18). An approximately 2.4 billion people or 1/3rd of the world population is without access to a toilet, which is a significant contributing factor in the contamination of drinking water (18). 780 million people, which is twice the population of the United States or 1/10th the population of the world, do not have access to a safe water source (18). One third of all schools lack access to safe water and adequate sanitation (18). Pneumonia and diarrhea account for over a quarter of all deaths in children worldwide, and were responsible for around two million child deaths in 2011(19). Diarrhea caused some 800,000 of those deaths in children under five and thus means that approx. 2200 children die every day due to diarrhea-related disease (19). Nearly 72 percent of deaths from diarrhea are in children under two year's old(19). One third of all healthcare facilities in low and middle-income countries lack a safe water source (5).

Epidemiology of Diarrhea linked to children with parasitic infection

Results found in a cross-sectional study that was undertaken to document the pathogens suspected to be involved in community-acquired childhood diarrhea in Dakar, the capital city of Senegal showed that parasitic agents were detected in 25 (14%) children, namely *Giardia lamblia* (15 patients), *Entamoeba histolytica / Entamoeba dispar* (8 patients), *Ascaris lumbricoides* (4 patients) and *Trichuris trichiura* (1 patient) (20). One patient had three different parasites present in their stool (21).

However the study did not account for *Cryptosporidium sp.*, which is significantly associated with childhood diarrhea in West Africa (21). It was found in Ghana that *Cryptosporidium sp.* was not only the most prevalent parasite detected, but also it is significantly associated with diarrhea (21). *Cryptosporidium sp.* was also discovered to be significant in Peru where a great deal of attention has been given to parasitic roles in diarrhea following El Nino weather patterns (22). The significance of the El Nino study was Population-based data that found more detailed changes in disease rates. Finally, population-based data made it possible to collect information on individuals over time and correlate that weather patterns and not just malnutrition were to blame for parasitic induced diarrhea (22). Limitations to attributing *Cryptosporidium sp.* and *C. hominis* subtype families were noted in a study by Cama and colleagues. They brought to light especially low first exposure risks in a 4-year longitudinal birth cohort of 533 children in Peru. They caution that data may under represent the true prevalence of *Cryptosporidium sp.* because children who are constantly exposed to this parasite and its subfamilies could have a lower risk of infection with just one exposure (23). Furthermore, it has been noted that older children in conditions not related to malnourishment, may be having a higher prevalence of parasitic diarrhea because they are more likely to play outside and find themselves exposed to contaminated water (22). Moving our focus to Asia, in Nepal, a study was done using 507 stool samples from students' aged 3-14 years (24). These samples were examined at the time of May through November

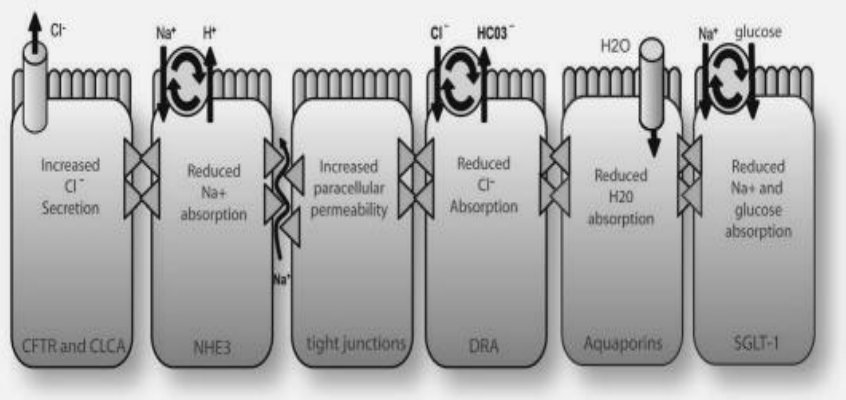
2014 and showed 22.68% (115/507) children to have at least one or even more intestinal parasites present (24). *Giardia lamblia* was identified to be the most common parasite in the sample of children with 10.45% (53/507) turning up to be positive cases (24).

Epidemiology of Diarrhea related to children with HIV/AIDS

Diarrhea is the second leading killer globally of children of under five (after pneumonia), responsible for nearly one in five childhood deaths (~1.5 million each year). Around 40% of these deaths occur in Africa. Studies have suggested that diarrhea was even more likely in children with HIV, and the leading cause of death among HIV-infected infants. Persistent diarrhea adds to mortality by causing malnutrition and wasting that weaken the child. It was observed in a study that persistent diarrhea was eleven times as likely to be associated with death in children with HIV as in those without, even though other complications could be contributing factors. Despite these factors, persistent diarrhea is still considered to be a marker for rapid progression of HIV disease (25, 26, 27). Over the years, there had been changes which has improve the outlook for children at risk of diarrhea, including those with HIV; these includes wider promotion of simple interventions (such as vitamin A and zinc supplementation) that has improve survival; most especially oral rehydration therapy (ORT) used for the management of dehydration related to diarrhoea (25,26,27).

Types of Diarrhea

Diarrhea is either an inability of the intestine to absorb water, or an increase in the secretion of water/fluid into the intestine's lumen. At the cellular level certain ions and channels are particularly involved in the mechanism of diarrhea; the image below illustrates this involvement (28).



There are different classifications of diarrhea based on their mechanisms of action, which are described below.

Osmotic

Retention of excess solutes in the lumen of the intestine, shifts the osmotic balance; drawing water into the lumen and away from systemic circulation. This results in abundant, increasingly watery stool. Also known as malabsorptive, due to inability to absorb certain carbohydrates, most commonly lactose, through intestinal epithelium (28, 29).

Secretory

During digestion water in the lumen of the intestine is usually absorbed in the large intestine after being secreted by the small intestine. In this condition the amount of water secreted into the lumen of the intestine in the small intestine overwhelms the large intestine's capacity to absorb, and leaves a watery stool. This increased secretion is usually in response to some one or more of the following factors: laxatives; hormones, which can be secreted by tumors; drugs, especially asthma medications, antidepressants, cardiac drugs; heavy metals, organic toxins, and plant products, most notably, arsenic, insecticides, mushroom toxins, caffeine (29).

Inflammatory/Infectious

In this type there is a bacterial, viral or protozoal infection in the intestine, and the infection injures, or destroys the epithelial cells lining the lumen of the intestine. This results in a primary loss of the intestine to absorb water, and a secondary malabsorptive diarrhea ensues. To worsen the condition, inflammation activates white blood cells, which, causes them to release

inflammatory mediators, which stimulate secretions and augment the amount of fluid in the intestinal lumen. Leukocytes tend to release oxygen free radicals, which kill intestinal epithelial cells, which are then replaced with immature cells that typically are deficient in the brush border enzymes and transporters making them poor for absorption of nutrients and water. In the end, inflammatory infectious diarrhea can eventually consist of all types of diarrhea in one patient, which is quite dangerous and increases the condition's effect and burden on the patient (28).

Malnourishment

Malnourishment is actually an exacerbating factor that increases the lethality of diarrhea. This means that the diarrhea is attributed to another source, such as infection, but an underlying state of malnourishment worsens the effects of the diarrhea, and leaves the patient susceptible to overwhelming dehydration and other factors, such as vitamin deficiency, which can prolong the course of the infection, and keeps the patient from recovery, thus, leading to death (5).

Etiological Factors and Its Pathophysiology

Table2. *Most Common etiological agents of acute diarrhea in children*

Enteropathogenic *Escherichia coli*	**Shiga toxin-producing *E. coli***
Entero aggregative *E. coli*	Enteroinvasive *E. coli*
Shigella sp	*Campylobacter sp*
Cryptosporidium sp	*Giardia lamblia*
Rotavirus	*Vibrio cholerae*

Rotavirus

Rotavirus is the single most common cause of severe diarrhea. Other viruses, like adenovirus, and measles can cause diarrhoea as well. Cytomegalovirus can be associated with colitis in HIV disease while infection with HIV could directly cause or contribute to malabsorption and diarrhea (25). Rotavirus is a double-stranded RNA virus of the family *Reoviridae*. It enters through the mouth and replicates in the small intestine(8). Rotavirus alters the structure of the enterocytes, which leads to malabsorption. The incubation period for rotavirus is relatively short, usually less than 48 hours, and clinical symptoms vary and depend on whether it is the first infection or a reinfection. Most symptomatic rotavirus infections occur between 3 months and 2 years of age, with a peak incidence between 7 and 15 months (8). Rotavirus infection in infants and young children can progress to severe diarrhea, which can lead to dehydration, electrolyte imbalance, and metabolic acidosis (8). Transmission is by fecal-oral route, both through close person-to-person contact and by fomites that can be left on surfaces(8). Once infected they can shed large quantities of virus in their stool starting 2 days before the onset of diarrhea and for up to 10 days after onset of symptoms and even up to 30 days in an individual that is immune deficient (8,10). Some studies demonstrated that naturally acquired rotavirus infections provide protection against rotavirus disease upon reinfection and that protection is greatest against the most severe disease outcomes (9). Recovery from a first rotavirus infection usually does not lead to permanent immunity. One study found that after the first infection 38% of children are protected against any subsequent rotavirus infection, 77% are protected against rotavirus diarrhea, and 87% are protected against severe diarrhea (8).

Escherichia coli

Disease-causing *Escherichia coli*, *Enterobacter* species, *Shigella* species, *Salmonella species*, *Campylobacter*, *Mycobacterium avium intracellulare (MAI)*, or disseminated TB, and *Yersinia* species are among bacteria that can cause diarrhea (25). *Escherichia coli (E. coli*) is a gram-negative facultative anaerobic, non-sporulating, rod-shaped bacterium (30). *E. coli* is a normally occurring member of the intestinal flora and many strains of *E. coli* are considered harmless and some are even beneficial to their hosts by producing useful substances such as vitamin K_2 (31). *E. coli* infections are the second leading cause of pediatric diarrhea behind rotavirus induced diarrhea; specific serotypes of *E. coli* have been identified to be pathogenic. It is also known that normally nonpathogenic strains of *E. coli* can produce disease in an immunocompromised host or if the normal bacterial flora has been altered significantly. Currently, there are five serotypes identified as being diarrheagenic strains of *E. coli*: Enterotoxigenic *E. coli* (ETEC) Enterohemorrhagic *E. coli* (EHEC) Enteropathogenic *E coli* (EPEC) Enteroinvasive *E coli* (EIEC) Enteroaggregative E coli (EAEC) (30). These five serotypes

account for the vast majority of E. coli induced diarrhea in pediatric patients. The pathogenic serotypes of E. coli each have their own unique pathogenesis.

The transmission of *E. coli* infections most commonly occurs through the fecal-oral route. The most common forms of fecal-oral transmission include unhygienic food preparation, farm contamination due to manure fertilization, irrigation of crops with contaminated greywater or raw sewage, feral pigs on cropland, or direct consumption of sewage-contaminated water (11,12).

Strain Specific Pathogenesis of E. coli

ETEC is the specific strain that most commonly causes what is known as traveler's diarrhea. ETEC is capable of adhering to the mucosa of the small intestine by using fimbrial colonization factor antigens (30,32). If ETEC successfully colonizes the mucosa, release of a heat labile toxin (LT) and heat stable toxin (ST) will occur with the ST toxin being the more virulent of the toxins (30, 32, 33). These toxins stimulate the lining of the intestines to secrete excessive fluid and electrolytes, which can lead to severe dehydration. Patients typically present with watery diarrhea and abdominal cramps. Symptoms often last for three to four days. Most patients are able to recover with supportive measures, mainly fluid and electrolyte replacement, making hospitalization and antibiotics unnecessary in most cases. Furthermore, immunity to the surface antigens tends to develop which tends to confine serious infection to the immune-compromised and the very young (30, 32, 33).

EHEC is also referred to as shiga-toxin producing *E. coli* (STEC) and causes an estimated 110,000 cases in the United States annually (30, 32). Children under the age of five and the elderly are considered the most at risk for developing serious complications from EHEC infection (32). After colonization, which produces an attaching and effacing (AE) lesion in the large intestine, EHEC releases the shiga toxin, which is cytotoxic to the vascular endothelium (32). EHEC often presents with an acute bloody diarrhea with abdominal cramps. In some cases, the shiga toxin enters the circulation where it is capable of causing hemolytic-uremic syndrome (HUS); HUS is a very serious complication of EHEC and is characterized by the clinical triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure (30, 32). HUS can be fatal especially in very young children, even with proper treatment. Patients under the age of five are most at risk for developing life-threatening complications of HUS. Uncomplicated EHEC tends to resolve itself in about one week's time, but hospitalizations are required in 23-47% of cases (30, 32).

EPEC is also known to produce AE lesions but does not secrete the shiga toxin. EPEC lack fimbriae and instead use an adhesin molecule called intimin to bind to host intestinal cells (30, 32). The adherence to host cells causes a derangement of actin filaments, which elicits an inflammatory response from the host. The derangement of the mucosal structure by attachment and effacement is the primary mechanism behind diarrhea in EPEC infections (30, 32). EPEC is one of the more common causes of pediatric diarrhea especially in hospital settings. EPEC causes a watery diarrhea and may even cause dysentery; if the diarrhea becomes chronic in a young infant, failure to thrive may occur (32).

EIEC invades the epithelial cells of the large intestine and produces enterotoxins that are often lactose non-fermenting and tend to produce the local colonic inflammatory response (30, 32, 33). The enterotoxins and inflammation lead to colonic epithelial cell death, which causes a watery diarrhea and potentially dysentery. EIEC predominantly affects children in the developing world and is relatively uncommon in the developed world (12, 33).

EAEC uses aggregative adherence fimbriae (AAFs) to adhere to human epithelial cells type 2 (HEp-2) cells of both the large and small intestine (30, 32, 33). After colonization, enterotoxins and cytotoxins are produced that interact with the toll-like receptor 5, which recruits inflammatory cells through release of interleukin 8. EAEC causes a water diarrhea and may lead to dysentery. EAEC is believed to cause chronic diarrhea in HIV-infected patients (32).

Cholera

Cholera is an acute and severe form of watery diarrhea. It is caused by the ingestion of contaminated food or water with the Gram-negative bacterium, *Vibrio cholerae* (18). The most commonly affected population includes young children (infants to the age of four years

old). Research has reported an estimate of 1.4 to 4.3 million cases of cholera every year. The worldwide data on cholera mortality show that 28,000 to 142,000 deaths occur annually due to the disease (18).

Cholera is transmitted by fecal and oral transmission. Acidic environments are not suitable for *cholera* bacteria growth. Organs in the human body such as the stomach do not yield a high survival rate for cholera bacteria due to the low pH environment. The bacteria that manage to survive in the gastrointestinal tract colonize in the intestines (small or large). They grow and secrete potent cholera enterotoxin that causes diarrhea (16). The mechanism of action of the cholera enterotoxin work to bind on the plasma membrane of the intestinal epithelia wall and they release active enzyme subunits that cause the rise in cyclic adenosine 5-monophosphate (cAMP) production. Excess production of intracellular cAMP levels lead to substantial increase in the amount of electrolyte and water into intestinal lumen (16). Thus, activating the loss of electrolytes and water causing diarrhea.

Parasitic Infections

Parasitic infections that can cause diarrhea are Cryptosporidiosis, Isosporiasis, Microsporidiosis, Cyclosporiasis, Giardiasis, Strongyloidiasis and Entamoebiasis (25). In a study to determine the prevalence of intestinal parasites and its association with diarrhea in Ugandan children admitted with severe acute malnutrition, the prevalence of protozoa (20.9%) was higher than helminth (13.9%) infections *Giardia lamblia* had the highest prevalence at 15.4% followed by hookworm at 9%. Other noteworthy intestinal parasites like *Entamoeba histolytica*, *Cryptosporidium* species, *Entamoeba coli*, and *Isospora* species, *Ascaris lumbricoides*, *Hymenolepis nana*, *Schistosoma mansoni*, *Trichuris trichiura*, *Strongyloides stercoralis* and *Taenia* species showed a span of prevalence from 2.5 to 5%. Children presenting with *Giardia lamblia* were 3.53 times more likely to have diarrhea. Overall, Children who had parasites in their stool were 3.14 times more likely to present with diarrhea when compared to children with diarrhea who didn't have parasites present, the overall prevalence of intestinal parasites was 32.8% (34).

Children with HIV/AIDS

Infants and children with a HIV infection have more frequent and more severe diarrhea than children without HIV. The severity of acute diarrheal episodes can range from mild to moderate to severe cases that can lead to hospitalization or death. Severity is influenced by many factors, including the causative pathogen and host characteristics, such as immunodeficiency and age (4).

A study in the United States showed a higher prevalence of *Pneumocystis carinii* in intestinal tissue from 19 HIV-positive children than in controls (35). *Cryptosporidium* and cytomegalovirus were linked to a particularly severe, prolonged form of chronic diarrhea in HIV-positive children, with some evidence of increased rates of colonization of *Cryptosporidium* in these children (36). In addition to *Cryptosporidium*, *Microsporidium* and *Giardia* species were also reported at high prevalence in HIV-infected children in Malawi (4).

Diagnosis and Lab Work

A wide range of etiological agents have been associated with infectious diarrhea, including viruses, bacteria, and parasites (37). Diagnostically, various lab tests are available, including culture, microscopy, and antigen-based tests. Each combination of pathogen and test has distinct performance characteristics, and there are limitations to all. Culture methods are often low yield for enteropathogens, particularly in the setting of antibiotic use (38). Microscopy for parasites is widely used because it is inexpensive, but it is insensitive and requires substantial time, equipment, and training. Antigen-based tests have represented a substantial advance for diarrheal diagnostics; however, the test characteristics are variable, and commercial assays are not available for all relevant pathogens (39, 40). Diagnosis of rotavirus may be made by rapid detection of rotavirus antigen in stool specimens. Strains may be further characterized by enzyme immunoassay or reverse transcriptase polymerase chain reaction, but such testing is not commonly done(10). Specific investigations are not routinely required in the majority of patients with acute diarrhea as the illness is usually self-limiting. Lab diagnosis is useful for people who have a risk of spreading the infection or have infection that could benefit from specific therapy (41).

Treatment

The major approaches to the treatment of diarrhea include supportive therapy which

involves replacement of fluid and electrolytes, symptomatic treatment which aims to reduce stool frequency and relieve patient's other symptoms such as abdominal pain, specific therapy such as antimicrobial chemotherapy to reduce duration and severity of the illness (42).

Supportive Therapy

Fluid and electrolyte therapy is the most important approach towards treating diarrhea and is usually sufficient, except when the patient is vomiting or has a severe case of diarrhea. This can be accomplished by using Oral Rehydration Solution (ORS) (42). Table 3 shows the components of ORS. Deaths from diarrhea are due to the dehydration and deprivation of nutrients necessary for growth, especially when the diarrhea lasts for days and depletes the sufferer of essential salts and water. It is therefore very important to start fluid replacement therapy as soon as possible (5).

Symptomatic Treatment

Antisecretory drug therapy-Racecadotril, an enkephalinase inhibitor that has pro absorptive activity is effective or reducing amount and frequency of stool. It potentiates endogenous enkephalins in the intestine and is safe for pediatric use. Bismuth salicylate has been shown to be effective in the treatment of traveler's diarrhea; it is an effective antidiarrhoeal and is also thought to have antibacterial and anti-inflammatory properties (42).

Antimotility Therapy-The most commonly used antimotility agents such as loperamide and diphenoxylate-atropine combination act by increasing intestinal transit time and enhancing the potential for reabsorption of fluid and electrolytes but are not recommended in children because of central nervous system side effects (42).

Antimicrobial Therapy

Antimicrobial use is not necessary in mild and quick recovery cases. However, they are useful in reducing the severity and duration of diarrhea. Their use is recommended in dysenteric shigellosis, cholera, pseudomembranous enterocolitis, parasitic causes of diarrhea, and sexually transmitted diseases. Conversely, use of antimicrobials in the treatment of *E coli* O157:H7 causes lysis of the organism and toxin release, which leads to hemolytic uremic syndrome and is therefore not recommended (42). Patients should be treated if they are debilitated, immunosuppressed, having abnormal cardiovascular system, having valvular, vascular, or orthopedic prostheses, having hemolytic anemia (e.g. cases with salmonellosis), or are extremely young or old. Treatment is also recommended for those that relapse and those with prolonged symptoms (42).

Table3. *Composition of the new ORS formulation (43)*

New ORS	**Grams/litre**	**%**	**New ORS**	**Mmo/litre**
Sodium chloride	2.6	12.683	Sodium	75
Glucose, anhydrous	13.5	65.854	Chloride	65
Potassium chloride	1.5	7.317	Glucose-anhydrous	75
Trisodium citrate, dihydrate	2.9	14.146	Potassium	20
			Citrate	10
Total	**20.5**	**100.00**	**Total Osmolarity**	**245**

The current recommendations for assessing and treating diarrhea involve evaluating dehydration, appropriate fluid replacement that includes salt and water to balance the electrolytes, continued feeding or increased breastfeeding, antibiotic regimens when indicated and appropriate referral and follow-up. Interventions including vitamin A, zinc and cotrimoxazole may contribute substantially to preventing diarrhea in children with HIV infection or exposure to HIV (4). Administration of ART (Acute rehydration therapy) and restoring immune function are critical for the prevention and treatment of diarrhea in children with HIV infection(44). Probiotics have been proven to shorten the diarrhea by average of one day (42).

Rotavirus

There are currently two rotavirus vaccines licensed for use in the United States. RV5 (RotaTeq) is a live oral vaccine manufactured by Merck and licensed by the Food and Drug Administration in February 2006. RV5 contains five rotaviruses developed from human and bovine parent rotavirus strains. RV1 (Rotarix), a live oral vaccine manufactured by

GlaxoSmithKline, was licensed by the FDA in April 2008. RV1 contains one strain of live attenuated human strain 89-12 (type G1P1A (8)) rotavirus (CDC, 2015). Efficacy of the vaccines varies greatly. Both vaccines have reduced the number of physician visits and rotavirus related hospitalizations (45). It is 74%-87% effective with any rotavirus gastroenteritis and 85%-98% against severe gastroenteritis. The vaccinations require 2 (RV1) or 3 (RV5) oral doses beginning at 2 months of age but may be started as early as 6 weeks of age with a minimum of 4 weeks in between doses (8).

E. coli

The mainstay of treatment for *E. coli* infections that produce diarrhea in children is hydration therapy to replenish lost fluids and electrolytes (30, 32). Severe dehydration may require hospitalization with administration of fluids intravenously. Antibiotics may be required if the disease persists for more than a week or if the symptoms are severe. The antibiotics of choice for *E. coli* are fluoroquinolones, azithromycin, and rifaximin (30, 32). While most cases of *E. coli* do not require aggressive therapy, development of HUS especially in children under five years old should be treated as a severe condition that requires hospitalization and careful care. In developed countries, most *E. coli* infections are self-limited and do not require extensive therapy. In developing nations, *E. coli* infections cause significant morbidity and mortality often because of poor sanitation and low availability of resources.

Parasitic Infection

In humans, nitazoxanide (thiazolide antiparasitic) is an effective treatment of parasites; among them are *Giardia lamblia, Entamoeba histolytica, Cryptosporidium parvum, Cyclospora cayetanensis, Trichomonas vaginalis, Vittaforma corneae, Encephalitozoon intestinalis, Isospora belli, Blastocystis hominis, Balantidium coli, Enterocytozoon bieneusi, Ascaris lumbricoides, Trichuris trichiura, Taenia saginata, Hymenolepis nana, and Fasciola hepatica* (46). In vitro antimicrobial activity has been shown against various gram-positive and gram-negative anaerobic bacteria, especially *Bacteroides species, Clostridium species, and Helicobacter pylori*, as well as aerobic gram-positive bacteria (46).

Cholera

Oral or intravenous hydrations are first line of therapy for cholera. Patients who are severely ill have their first line of therapy that includes antibiotic treatment with hydration. Antibiotics are also recommended for those that are hospitalized (15). The drug of choice is dependent on the regional location. In most countries, Doxycycline is recommended as first-line treatment for adults, while azithromycin is recommended as the first line treatment for children and pregnant women (15). Antibiotics are contraindicated for use as prophylactics in cholera prevention. Preventive treatments involve health promotion by educating the communities about the importance of good sanitation and hygiene as well as providing adequate education to health care workers, supplying adequate resources, and monitoring the usage of antibiotics (15). There is the also the need to increases disease awareness about cholera and promote health and wellness.

Malnutrition

If children are fed properly as soon as their diet allows, they recover quicker than children that are starved. Supplementation with Vitamin A has no effect on the overall attack rate but reduces the severity of diarrhea (number of bowel movements); and, supplementation with Zinc reduced the incidence of diarrhea by 20% (47).

Preventing Spread and Education

Diarrhea is among the most common travel related illness in children which is easily preventable. Sanitation and good hygiene are critical for one's well being and it reduces the risk of many diseases. Diarrhea can be caused by ingestion of contaminated food and beverages, infrequent hand washing while traveling to a developing country. When water and soap are not available, use of hand sanitizer with at least 60% alcohol is crucial (5,48). Proper technique should be used such as lathering with soap for at least 20 seconds before washing (5). Avoidance of raw fruits and vegetables while travelling can help reduce the risk. Food borne illness is more prevalent than water borne; therefore one should pay more attention to the dietary option such as food items that are well cooked and freshly served (48). Also, washing of work surfaces frequently to

avoid contamination and using of refrigerator to thaw items instead of leaving it outside (5). Beverages such as un-iced carbonated drinks or sealed fruit juice or water are recommended. Ice cubes are regarded as contaminated as it could have been prepared from the stored rainwater that may not have been purified, hence, unsafe to drink. Pasteurized, refrigerated dairy products are recommended if powdered formula is unavailable, which would be prepared using boiled water. The relationship between diarrhea and malnutrition is bidirectional in the sense that diarrhea leads to malnutrition (47, 49). Malnourished children are more susceptible to diarrhea[5] and malnutrition determines the duration and severity of diarrhea (47, 49). For infants, breastfeeding is the best way to reduce the risk of food borne or waterborne illness (12). Breastfeeding infants have higher lactoferrin levels, which is bactericidal to enteric pathogens thus, it aids in prevention (50).

Water purification can be done via several different options, such as: Portable electric water heater; filters along with chemical decontamination with halogen are recommended as filters alone only protect against bacteria and parasites but not viruses; adding halogen such as iodine, chlorine or chlorine dioxide can be directly added to the water (12).

Rotavirus is the leading cause of acute diarrhea and accounts for 40% of hospitalization of children under five; hence proper vaccination should be given to decrease the risk (12). Antibiotics as prophylaxis can be used but its effectiveness is undetermined in infants under the age of two, therefore it is not recommended (12, 50). If planning on traveling to prevalent areas, it is highly recommended to check the Centers for Disease Control and Prevention website for warnings and tips for the specific destination to reduce any risk and for prior awareness (50).

Recommendations for parasitic eradication should include but not be limited to: Steps to control the increased risk of diarrheal disease that occurs at notable season changes and recognition of poor sanitation conditions in at-risk communities (23). Secondly, pediatric hospitals must equip themselves with effective methods of diagnosing *Cryptosporidium*, such as the use of Polymerase chain reaction (PCR) or modified Ziehl-neelsen staining (MZN) for *Cryptosporidium* oocyst diagnosis in low risk patients (51). Lastly, increase availability of affordable diagnostic equipment that can aid in the management of diarrhea in infants and children, which can lead to the appropriate use of antimicrobial medications (21).

According to the World Health Organization and UNICEF, the regions with the lowest coverage of safe sanitation in 2006 were sub-Saharan Africa (31%), Southern Asia (33%) and Eastern Asia (65%). This study also showed that seven out of ten people without access to safe sanitation were rural inhabitants (5). Also according to the United Nations and UNICEF, one in five girls of primary-school age are not in school, compared to one in six boys. The fact that more girls are not attending school can be attributed, in part, to the lack of sanitation facilities for girls reaching puberty, and that girls are also more likely to be responsible for collecting water for their family, making it difficult for them to attend school during school hours. The installation of toilets and latrines may enable school children, especially menstruating girls, to further their education by remaining in the school system, and at the same time significantly improving water sanitation and reducing infection (48).

CONCLUSION

Childhood diarrhea is very prevalent in the world and is the second leading cause of death in children. Watery diarrhea causes a rapid depletion of water and electrolytes in the body while bloody diarrhea may cause substantial blood loss leading to hypovolemic shock. Left untreated these situations can lead to death. Diarrhea, which is a symptom of intestinal infection, is still a burden on the world today due to inadequate access to water, sanitation, and treatment.

Most of the pathogens that can cause diarrhea in children are transmitted via the fecal oral route and are found in drinking water. In less developed countries that are uneducated on the importance of water sanitation, there is an increased risk of contracting a diarrheal disease through ingestion of water. Better education about sanitation and the importance of proper hygiene can lower the number of infections

caused by waterborne pathogens. Rotavirus is the main causative agent of viral diarrhea in children. This virus is preventable through use of the vaccine rotavac, which unfortunately is less accessible in developing countries.

E. coli is a major bacterial pathogen that can cause both watery diarrhea and dysentery. Through the use of surveillance methods by food suppliers and proper preparation of food this pathogen is less likely to pose a threat. Oral Rehydration therapy (ORT) is the main treatment used when dealing with life-threatening diarrhea. ORT includes replenishment of fluids and electrolytes and it is an easy way to prevent deaths caused by diarrhea. Depending on the pathogen involved other medical interventions may be needed but for self-limited infections ORT is all that is required to prevent death. Following the simple practices of proper hygiene, food preparation and access to basic medical treatments can decrease the large number of diarrheal infections and deaths. Since access to proper medical treatment is not available in developing countries it is paramount that these infections be prevented.

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