Global Estimated Disability-Adjusted Life-Years (DALYs) of Diarrheal Diseases: A Longitudinal Analysis of the Global Burden of Disease Study 2017

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GLOBAL ESTIMATED DISABILITY-ADJUSTED LIFE-YEARS (DALYs) OF DIARRHEAL DISEASES: A LONGITUDINAL ANALYSIS OF THE GLOBAL BURDEN OF DISEASE STUDY 2017

A Thesis
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Master of Science
Biological Sciences

by
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May 2020

Accepted by:
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Dr. Cheryl Ingram-Smith
Dr. Zhicheng Dou
ABSTRACT

Summary Background

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 is the most comprehensive study ever carried out to report on the state of global public health for the previous 28 years (1990-2017). In 2017, it covered 359 diseases and injuries for 195 countries and territories.

Our study sought to provide an up-to-date analysis of the progress that has been made to eradicate diarrheal diseases using the GBD2017 data. Although significant progress has been made in reducing the number of deaths due to diarrhea, diarrheal diseases incidences and associated morbidity have not experienced the same level of decline. Using disability-adjusted life-years (DALYs), a metric that tracks impact on life expectancy, prevalence, and impact on quality of life due to a specific disease, we performed a comparative analysis of the impact of diarrheal diseases by World-Bank (WB) Income regions, age, and sex.

Methods

Using multi-year GBD data that we accessed from the Institute of Health Metrics (IHME) tool (GBD Compare | Viz Hub), we analyzed the impact of diarrheal diseases using Microsoft Office Excel 2017 (Microsoft, Redmond, WA). We compared the disability-
adjusted life-year (DALY) metric due to diarrheal diseases among different demographic subsets including sex, age, country, and income level. One DALY is comparable to one lost year of “healthy” life, while the sum of DALYs across the population expresses the burden of disease caused by a gap between current health status and optimal health for the entire population impacting variables such as advanced age. All data estimates in the GDB2017 study were listed with 95% uncertainty intervals (UIs).

We also evaluated DALYs as a function of the socio-demographic index (SDI). This index, also developed by the GBD Project in 2015, is a measure of a region’s socio-demographic development and consists of data about the education levels, average income per person, and total fertility rate (TFR).

Findings

Diarrheal DALYs have decreased by approximately 54.64% from 1990 to 2017. In 1990 diarrheal diseases counts were estimated at 178,669,278.768251 (95% UI: 154,235,572.289659-203,868,117.467447) with an age-standardized DALY rate of 1,017.22180392645 per 100,000 people. On the other hand, in 2017, DALYs were estimated at 81,039,363.8553969 (95% UI: 70,120,051.7904495 - 972,33,423.453799); and an age-standardized DALY rate of 246 per 100,000 population globally. Interestingly, while DALYs have decreased, incidence and prevalence have increased by 52.16% and 47.22%, respectively. Age-standardization, otherwise known as age adjustment, makes it
possible to apply observed age-specific data from multiple populations to a standard age distribution that enables comparison across countries and regions.

Regardless of World Bank (WB) Income region, infants 28-364 days were the most vulnerable to diarrheal diseases. Since 1990, global diarrheal disease DALYs do not differ markedly between the sexes. In 2017, there seems to be a slight difference in WB High-income regions, where women have higher DALY rates (3.36% more), the rates in WB Low-income regions were higher for males in 2017 (24.23%). We also observed that the rate of diarrheal diseases highly correlates to socio-demographic index ($R^2 = 0.9937$).

**Interpretation**

Considerable progress has been made globally in reducing the burden of diarrheal diseases, as many socio-economic risk factors have been reduced. However, progress has not been up to par in all locations, Low-income countries are still substantially behind in reducing diarrheal diseases DALY rates compared to High-income countries and the burden of diseases infants still requires special attention.
ACKNOWLEDGEMENTS

First, I would like to sincerely thank my advisor Dr. Temesvari for mentoring and empowering me to finish this research. I am very fortunate to have had her guidance. Her work ethic, kindness, and patience, all qualities of a great educator, will stay with me for a long time. I would also like to thank my committee members, Dr. Cheryl Ingram-Smith and Dr. Zhicheng Dou, for their invaluable feedback and advice on this work.

Second, I would like to express my gratitude to my parents: Consolée and Vénuste, my siblings: Diane, Pamela, Arnaud, and Arthur, my fiancé, Thierry, and my adopted American family, Lisa and Jack, for being my greatest cheerleaders and source of support all these years.

Finally, I would like to thank The Department of Biological Sciences at Clemson University for financially supporting me with a teaching assistantship and funding my graduate education. Financial assistance for this work was also provided by the National Institute of General Medical Sciences Grant: GM109094, awarded to Dr. Lesly Temesvari. The funding agency played no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript. This content is solely the responsibility of the authors and does not necessarily represent the views of the National Institute of General Medical Sciences at the NIH.
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CHAPTER ONE
LITERATURE REVIEW

I. Introduction
Diarrheal diseases are a long-standing and leading cause of avoidable death. According to The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), in 2016, diarrhea diseases ranked 8th among leading causes of death for all ages with 1,655,944 deaths (95% uncertainty interval [UI] 1,244,073–2,366,552). This number has decreased by about 40% since 1990 (1). This is an astonishing lack of progress given that the risk factors of diarrheal diseases, such as consumption of contaminated food and water, can be easily avoided.

Children under two years of age are the most vulnerable to diarrheal diseases. This is alarming because early crucial cognitive development takes place before the age of 18 months. Children who experience multiple bouts of diarrheal disease start at an unequal footing for a quality life later in life, and experience less economic growth as adults (2). Multiple studies have also shown that there is a correlation between the burden of diarrheal disease and lower scores on the Test of Non-Verbal Intelligence-III and the Wechsler Intelligence Scale for Children, impairment of visual-motor coordination, and impaired auditory short-term memory and information processing in children who experienced multiple episodes of diarrheal as infants, and risk of diabetes, malnutrition, and cardiovascular disease (3-9). Further, diarrheal diseases have been linked to growth stunting in children. An analysis of nine separate studies, done over a 20-year time period
and in five countries, showed that stunting was directly linked to multiple episodes of diarrhea in infants under two years of age, where five or more episodes of diarrheal before 24 months increased the probability of stunting by 25% (95% CI 8-38%). The same study also showed that the likelihood of stunting was increased by 18% (95% CI 1-31%) for children who suffered from diarrheal diseases at least 2% of the time before 24 months of life (10).

The History of Diarrheal Diseases and Current Burden

The earliest recorded mention of diarrhea was in 460-370 B.C, where it was described by Hippocrates as “an abundant liquid stool at short intervals (11).” In the 17th century, diarrhea was classified into three categories by Jean Fernel according to severity: bilious diarrhea in which the yellow bile moves out freely, severe diarrhea caused by spleen dysfunction, and dysentery described as a bloody infection of the stomach with pains and ulcers. At the time, it was believed that diarrhea was caused by poor hygiene (12). By the 18th century, it was commonly understood that diarrhea was caused by poor environmental and individual hygiene; however, the mechanism of infection was still unclear (13). The first scientifically extensive study on diarrheal diseases was carried out from 1960 to 1965 in seven different developing countries. The data showed that there was a 40% prevalence of diarrheal diseases in children under six (14).

Diarrheal diseases still pose a major public health threat in developing countries. Every year, since 1990, diarrheal diseases have been consistently ranked in the top ten causes of morbidity and mortality for all age groups, while remaining in the top five causes of
morbidity and mortality for children under 5. Even though prevention and treatment strategies are known, it was the second leading cause of death among children under five years old, killing 525,000 in 2017. According to The World Health Organization (WHO) (15), in 2017, approximately 88% of individuals who died from diarrheal diseases were infected by drinking unsafe water or living in a region with inadequate sanitation and insufficient hygiene. Worldwide, 780 million individuals lack access to clean drinking-water and 2.5 billion have no appropriate sanitation (15).

Categorization of Diarrheal Diseases Causative Agents

Today, it is well known that diarrheal diseases are caused by a variety of bacterial, viral and parasitic organisms, and are propagated through the oral-fecal route. A list of communicable diarrheal diseases and their causative agents are shown in Table 1. In this review, we will explore the most common diarrheal diseases in each causative agent category, their clinical symptoms, pathogenesis and virulence, and current control strategies.
Table 1: Diarrheal Diseases Causative Agents.

<table>
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<tr>
<th>Causative Agent</th>
<th>Disease</th>
<th>Reviewed in</th>
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<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
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<tr>
<td>Vibrio cholerae</td>
<td>Cholera</td>
<td>Ref (16)</td>
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<tr>
<td>Salmonella typhi</td>
<td>Typhoid</td>
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<td>Listeriosis</td>
<td>Ref (20)</td>
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<td>Clostridium perfringens</td>
<td><em>C. perfringens</em> food poisoning</td>
<td>Ref (21)</td>
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<tr>
<td>Clostridium difficile</td>
<td><em>C. difficile</em> food poisoning</td>
<td>Ref (21,22)</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>Diarrhoeal syndrome</td>
<td>Ref (23)</td>
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<tr>
<td><em>Escherichia coli</em></td>
<td>EPEC</td>
<td>Ref (24)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>EHEC</td>
<td>Refs (24-26)</td>
</tr>
<tr>
<td>Shigella sonnei, Shigella boydii, Shigella dysenteriae and Shigella flexneri</td>
<td>Shigellosis</td>
<td>Refs (27,28)</td>
</tr>
<tr>
<td>Campylobacter</td>
<td><em>Campylobacter</em> infection</td>
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<tr>
<td>Aeromonas</td>
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<td><em>Blastocystis</em> hominis infection</td>
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<tr>
<td>Microsporidium</td>
<td>Microsporidiosis</td>
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Cholera

I. Clinical Features

Cholera is caused by *Vibrio cholerae*. It is an aquatic bacterium that replicates on the chitinous surface of copepods. *V. cholerae* strains are classified as serogroups based on their surface antigens. In humans, only two *V. cholerae*, serogroups O1 and O139, are known to cause disease. Serogroup O1 was discovered first and is the most common cause (45).

The single most commonly recognized symptom of Cholera is the profuse watery diarrhea, sometimes described as “rice-water stools.” Other symptoms include vomiting, rapid heart rate, loss of skin elasticity, dry mucous membranes, low blood pressure, thirst, muscle cramps, restlessness, and/or irritability. In severe Cholera cases, illness can progress into acute renal failure, severe electrolyte imbalances, and coma (45).

Despite being deadly within a few hours if left untreated, *V. cholerae* is fortunately inefficient at infecting humans compared to other bacteria. A person must ingest more than 500 *V. cholerae* bacteria to acquire a Cholera infection. Those who consume water directly from copepod-contaminated water, however, are likely to get infected as each copepod surface can carry up to 10,000 *V. cholerae* (45).
II. Epidemiology

Cholera is prevalent in areas of high poverty. It is concentrated in Asia and Africa for the most part, in countries that are ravaged by conflict, generally lack good infrastructure, have inadequate health systems, and are plagued by malnutrition (45). According to the WHO, there are between 1.3 and 4.0 million estimated cases of Cholera every year. Of those, about 21,000 to 143,000 result in death (45). Due to fear of alienation in tourism and trading, countries in endemic regions often underreport the number of Cholera cases. As an example, only 1,227,391 cases were reported to the WHO globally in 2017 despite a much larger estimate of actual cases (46). Another cause of underestimation of the number of Cholera cases is due to the difficulty of documentation. Of those who are infected, only 10% develop severe symptoms presenting watery diarrhea, vomiting and leg cramps (45). Those who are not severely infected generally do not consult a health practitioner limiting the documentation of illness.

Cholera is seasonal in endemic regions but can turn into large outbreaks in humanitarian crisis situations. Since *V. cholerae* grows on copepods, the number of Cholera cases surges during copepod growth season, which cycles with the seasonal proliferation of phytoplankton, the main food source of copepods. As copepods increase in numbers, they provide a rich growth medium for *V. cholerae* in waterways, leading to small outbreaks as people consume contaminated water and spread the disease in a cycle of poor sanitation (45).

Occasionally, these small outbreaks grow into epidemics in times of crisis. Since 2010, there have been over 12 serious Cholera outbreaks including in Nigeria, Haiti, Dominican
Republic, Venezuela, Democratic Republic of Congo, Somalia, Sierra Leone, Cuba, Ghana, Tanzania, Burundi, Algeria, Zimbabwe, and mostly recently, Yemen, where there is an active outbreak since 2017. Yemen's Cholera epidemic started as a result of war and became the largest recorded epidemic in one year since 1949, with 1.2 million cases between 2017 and 2018 alone (47).

III. Pathogenesis and Virulence

Cholera is mainly transmitted through consumption of food and water that have been contaminated by the feces of an infected person. Upon ingestion, most *V. cholerae* bacteria are killed on their journey through the digestive system. The surviving bacteria move to the small intestine where they secrete a toxin, known as Cholera toxin. The Cholera toxin is a heat labile heterotrimeric G protein-inhibiting exotoxin that is released by the bacteria into the surrounding milieu. It consists of an A subunit bound to five B subunits (48).

The first step in the Cholera toxin mechanism is the binding of its B subunit to the ganglioside, GM$_1$, receptor on host eukaryotic cells while the A subunit penetrates the plasma membrane of the cell. Upon entering the cell, the A subunit prevents GTPase activity by ribosylating its G alpha subunit. This activates adenylate cyclase, which in turn leads to the elevation of intracellular cAMP, which stimulates chloride secretion in the apical chloride channels on the intestinal epithelium which leads to hypersecretion of sodium. The second major virulence factor of *V. cholerae* is through the toxin-co-regulated pilus, which serves as a surface receptor for CTXφ. CTXφ is a filamentous bacteriophage that encodes the Cholera toxin. The pilus is encoded within a genomic island, vibrio
pathogenicity island (VPI-1). Virulence evolves through sequential acquisition of CTXφ and VPI-1 and culminates in a hypersecretion of fluids. The hypersecretion of fluids then leads to the signature high-volume “rice water” diarrhea that is usually associated with Cholera (49,50).

IV. Control and Therapies

The control of Cholera relies on four main strategies; prevention, monitoring and response in outbreak crises, treatment, and vaccination. For prevention, the most basic and most effective approach is improved sanitation. Better water and sewer infrastructure and water safety would limit contamination and Cholera transmission. One of the cheaper methods that have been used to prevent transmission is to filter copepods carrying V. cholerae out of water using saris in Bangladesh. Studies carried out in Bangladesh showed a 48% reduction in the transmission of Cholera using this method to filter drinking water (51).

Outbreak monitoring is important in endemic regions of Africa and Asia especially during copepod season by testing water sources, primarily for phytoplankton blooms or increased levels of V. cholerae. In non-endemic countries monitoring is also done after major natural or man-made disasters where sanitation infrastructure has been destroyed. Patient monitoring is also done by culturing stools for the presence of the bacterium. In addition, there are rapid diagnostic tests (RDT), the most common one being the dipstick, which, when dipped into stools, can signal the presence of V. cholerae in as fast as 15 minutes. There have been false negative cases; however, the Crystal VC test (by Span Diagnostics), for instance, has about a 90% sensitivity and only a specificity of about 70% (52). Here, sensitivity determines the ability to correctly identify those with the disease.
(true positive rate), whereas the specificity is the rate at which the test correctly identifies those without the disease (true negative rate).

Although *V. cholerae* is a bacterium, antibiotics are not enough to prevent death. Antibiotics kill the bacteria and reduce the duration of symptoms but have no effect on the already secreted Cholera toxin. For this reason, the most commonly recommended treatment for Cholera infection is oral or IV rehydration. According to the WHO 80% of people can be successfully treated with immediate oral rehydration therapy (15,52).

Vaccination against Cholera has been in use since the 1980s. In the beginning, an inoculated killed vaccine was widely used. However, the short-lived protection (approximately 6 months) made this vaccine expensive for the people that needed it the most. In addition to cost, this vaccine caused an inflammatory reaction at the injection site in patients. Since those who needed it the most could not afford it and those who could afford it did not want it due to side-effects, it got recommended by doctors less and less (16).

The Food and Administration (FDA) recently approved Vaxchora (lyophilized CVD 103-HgR) for adults 18-64 years, old who are traveling to an endemic or epidemic area. The effectiveness of this vaccine in persons living in endemic areas has not been established. The efficiency of protection is 90% after 10 days of inoculation and drops to 80% at 3 months after inoculation. Overall, protection is estimated to last between 3-6 months (53).
Currently, there are two WHO approved oral vaccines for the prevention of Cholera, Dukoral and Shanchol (also called mORCVAC depending on where it is produced). Both vaccines are approved in over 60 countries worldwide, but not available in the US. Dukoral (SBL Vaccin, Sweden) was produced and approved in Sweden in 1991. It is an oral vaccine that is administered in two doses over a period of 1-6 weeks. It consists of heat-killed *V. cholerae* organisms and recombinant Cholera toxin B subunit. The vaccine leads to antibacterial and antitoxic immunity due to this combination (53). In addition to its protection against Cholera, Dukoral has the added benefit of partial protection against diarrhea caused by enterotoxigenic *E. coli* (ETEC). The protection is due to the presence of the recombinant Cholera toxin B, which shares high homology with a toxin from ETEC. Although highly effective at protecting against Cholera, 85-90% protection only lasts for 4-6 months. Another weakness of Dukoral is that it only protects against O1 serotype *V. cholerae*. Because of the short duration of protection, Dukoral is mostly prescribed to short-term travelers and not to people living in endemic areas.

Shanchol (Shantha Biotechnics, India) or mORCVAC (VaBiotech, Vietnam) were approved in both India and Vietnam in March 2009. Shanchol received WHO prequalification, certifying that it meets the WHO international quality standards, in November 2011. Compared to Dukoral, both vaccines have protection against O139 serotype in addition to O1 serotype. They have also been shown to have a longer duration of protection in children and are cheaper to produce. The downside compared to Dukoral is that Shanchol and mORCVAC do not have protection against ETEC (16).
Shigellosis

I. Clinical Features

Shigellosis is caused by the bacteria of the genus *Shigella*. Typical symptoms include severe diarrhea, dysentery, abdominal cramps, fever, and rectal pain in mild cases. Stunted growth is a risk in children who have experienced multiple bouts of Shigellosis. Dysentery can lead to 200-300 mL of serum protein loss into feces daily. The loss of serum protein, in turn, leads to extreme reduction of nitrogen stores which provokes malnutrition and growth stunting (54).

*Shigella* is often referred to as “Traveler's diarrhea” as it is commonly seen among travelers, deployed military personnel, and expatriates to Low-income countries. Symptoms usually manifest within 24-48 hours of infection. It manifests as persistent diarrhea that can last up to 14 days (55,56). About 10-15% of patients develop chronic functional bowel disorders after acute episodes of Shigellosis. Unlike Cholera or ETEC that present as copious watery diarrhea, Shigellosis dysenteric stool is small and contains blood, mucus, and inflammatory cells which have been cited as causes for irritable bowel syndrome (57). *Shigella* is more dangerous than other gut pathogens because it can penetrate the lining of the intestine and cause severe inflammation of the intestine and systemic complications, which can lead to death if left untreated (54). In some children, Shigellosis can trigger seizures. In adults, it can lead to Reiter’s Syndrome, causing inflammation of the eyes and joints resulting in reactive arthritis (58).
II. **Epidemiology**

Humans are the primary hosts of *Shigella*. Shigellosis is transmitted through the oral-fecal route and is endemic in developing countries where there is inadequate sanitation. In developed countries, rare outbreaks are caused by uncooked contaminated food or contaminated water. In 2016, *Shigella* was the second leading cause of diarrhoeal mortality in 2016 among all ages, globally. It was the cause of an estimated 212,438 deaths (95% UI 136,979–326,913) and made up about 13.2% (95% UI 9.2–17.4) of all diarrhoeal deaths. About 30% of total *Shigella* deaths were children under 5 with 63,713 deaths (95% UI 41,191–93,611) (59). Repeated infection is common as there are multiple serotypes of *Shigella*, but evidence suggests that immunity is developed with age (60,61).

III. **Pathogenesis and Virulence Factors**

*Shigella* are Gram-negative bacteria transmitted in food or water contaminated with feces from an infected person. These bacteria like *Escherichia* are in the family of Enterobacteriaceae. *Shigella* species and their serotypes along with their typical geographic location are listed in Table 2.
Table 2: *Shigella* species and Serogroups. There are four different *Shigella* species with more than 20 serotypes. Serogroups A, B, and C are genotypically very similar. Positive β-D-galactosidase and ornithine decarboxylase biochemical reactions are used to differentiate *S. sonnei* from the other three serogroups.

<table>
<thead>
<tr>
<th><em>Shigella</em> species</th>
<th>Serogroups</th>
<th>Geographic location</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. dysenteriae</em></td>
<td>serogroup A, consisting of 12 serotypes</td>
<td>Epidemic outbreaks</td>
</tr>
<tr>
<td><em>S. flexneri</em></td>
<td>serogroup B, consisting of 6 serotypes</td>
<td>Developing world</td>
</tr>
<tr>
<td><em>S. boydii</em></td>
<td>serogroup C, consisting of 18 serotypes</td>
<td>Limited foci in India</td>
</tr>
<tr>
<td><em>S. sonnei</em></td>
<td>serogroup D, consisting of a single serotype</td>
<td>U.S. and other industrialized countries</td>
</tr>
</tbody>
</table>
Most of the current knowledge on mechanisms of *Shigella* pathogenesis is derived from studies of *S. flexneri*. The infection takes place in multiple steps. Infection is initiated when the bacteria enter the intestinal mucosa and proceed to penetrate the intestinal epithelium, the natural physical barrier that is meant to protect the body from pathogens (60). To cross the epithelial layer, *S. flexneri* triggers its own uptake by phagocytosis into microfold cells (M cells) and is released on the other side of the epithelium by vesicles trafficking and exocytosis (transcytosis) (62,63). M cells are specialized epithelial cells (EC), they transport antigens from the gut lumen and deliver them to the mucosal lymphoid tissue to initiate immune response (64). Once inside the intraepithelial layer, *S. flexneri* are immediately attacked by host macrophages. Normally, the macrophages engulf foreign particles to degrade them. However, *S. flexneri* quickly induces apoptosis of the macrophages as soon as they are engulfed to guarantee their survival (65-67).

With the macrophage death, there is subsequent release of cytokines interleukin-1 (IL-1) and IL-18 (68,69). Both cytokines play a central role in the regulation of immune and inflammatory responses to infections, in this case *S. flexneri* invasion. IL-1 signaling initiates intestinal inflammation, which is characteristic of Shigellosis, while IL-18 causes an antibacterial response by triggering natural killer (NK) cells and inducing the secretion of gamma interferon (IFN-γ) (68,70). IL-8 leads to an increased recruitment of polymorphonuclear neutrophil leukocytes (PMNs) to the site of infection (71,72). However, evidence suggests that *S. flexneri* secrete effector proteins that influence migration of PMN by modifying the transcriptional response of infected EC (73,74). As the PMNs are compromised so is the integrity of the epithelial lining, which enables *S. flexneri* to enter
the EC without the assistance of M cells (75,76). Eventually as infection gets worse, and more PMNs are recruited, the bacteria are killed, and the infection is cleared (77-79).

The severe tissue destruction caused by *Shigella*, namely macrophage death, destruction of the epithelial layer, and the massive influx of PMNs results in an impaired absorption of water, nutrients, and solutes, which cause watery diarrhea and the appearance of blood and mucus in Shigellosis stools (80). Another mechanism by which Shigellosis associated diarrhea is thought to occur is triggered by *Shigella* enterotoxin 1 (ShET1) and ShET2, which are produced by several *Shigella* strains. Evidence has shown that these two enterotoxins induce fluid secretion into the intestine, causing the watery phase of diarrhea (81,82).

Another toxin produced by *Shigella* is Shiga toxin, which is produced only by serotype 1. Shiga toxin is toxic to different cell types. It causes the formation of vascular lesions in the colon, the kidney, and the central nervous system (83). More so than *S. flexneri* and other serogroups, infections with *S. dysenteriae* serotype 1 is associated with a higher risk of life-threatening complications due to the high toxicity of Shiga toxin (80,84).

IV. Control and Therapies

Prevention of oral-fecal route transmission is the primary means of control of Shigellosis. The prevention is achieved through endemic population education and improvement of sanitation infrastructure. Like Cholera, antibiotics can be used to shorten the length of Shigellosis, however, to reduce the length of the disease and prevent death, they must be used in conjunction with oral rehydration therapy to replenish fluids. Antibiotic-sensitivity
tests are used to identify if the bacteria are resistant to antibiotics before prescribing a medication.

Generally, *Shigella* infection is diagnosed by testing patient stools for the bacteria. A stool sample is collected from the patient and placed on a growth medium for the bacteria. The bacteria are microscopically identified when there is growth.

Currently, there is no vaccine approved for Shigellosis in the US. No vaccine for Shigellosis is widely available. In China, a recombinant, live, oral, bivalent vaccine, produced by the Lanzhou Institute of Vaccines and Biological Products, is available for adults. The vaccine has approximately 60% efficacy for both *S. flexinari* and *S. sonnei* (28). The vaccine has never been evaluated or approved for use outside of China.

**III. Viral**

*Rotavirus*

**I. Clinical Features**

Worldwide, irrelevant of economic development, Rotavirus is the leading cause of diarrheal infection in children under 5 (85). Rotavirus infection presents with several symptoms including abdominal pain, watery diarrhea, vomiting, and approximately one-third of patients have a fever of >39°C.

According to different sources Rotavirus can lead to afebrile and febrile seizures and reduced consciousness. In afebrile cases, a study of 128 children in Italy showed that convulsions typically occur within four days of Rotavirus onset and last about 5 minutes
each (86). Febrile seizure symptoms tend to occur earlier after Rotavirus onset and last longer on average than afebrile cases (87,88). Rotavirus has also been shown to cause acute necrotizing encephalopathy (ANE) and cerebellitis/cerebellopathy (34).

After ingestion, Rotavirus travels to the small intestine, where it penetrates the epithelial cell lining. It then replicates in the cytoplasm causing cellular damage and fluid secretion, which result in profuse, watery diarrhea. The appearance of symptoms generally occurs suddenly, after an incubation period of 1-2 days. Diarrhea, vomiting, and fever can last between 4-7 days, during which time very large numbers of virus particles are shed in the feces (97). Rotavirus infection can be symptomatic or asymptomatic depending on the host. The main factor is age, but immunocompromised patients are at further risk of having the virus spread beyond the small intestine to other organs. If untreated, symptoms of Rotavirus can quickly lead to severe dehydration, electrolyte imbalance, metabolic acidosis, and death in extreme cases.

II. Epidemiology

Rotavirus is caused by ingestion of fecally-contaminated food and water and spreads via the fecal-oral route. Humans can serve as reservoirs for the virus. About $10^{10}$-$10^{11}$ virus particles can be shed in a single stool, and it takes less than 100 particles of Rotavirus to cause infection. Shedding of virus in feces has been shown to persist for weeks after symptoms have stopped. Because of its stability in the environment, it can also be transmitted through contact with contaminated objects or surfaces (32,35,89). Outbreaks
tend to quickly spread in institutional settings, such as daycares, schools, and hospitals (90).

Globally, in 2016, Rotavirus infection was responsible for more than 258 million episodes of diarrhea among children younger than 5 (95% UI, 193 million to 341 million). Of those cases, 128,500 resulted in death (95% uncertainty interval [UI], 104,500-155,600). Poverty, malnutrition, and low birth weight are some of the conditions that increase the risk of Rotavirus hospitalization. Over 80%, 104,733 deaths (95% UI, 83,406-128,842), of the total number of deaths occurred in Sub-Saharan Africa where there is limited access to vaccination (90).

III. Pathogenesis and Virulence Factors

Rotaviruses belong to the family Reoviridae. They derive their name from the Latin word rota meaning 'wheel', due to their round, wheel-like appearance when observed by electron microscopy. Structurally, Rotaviruses are made up of a genome composed of 11 segments of double-stranded RNA (dsRNA) surrounded by a nonenveloped, complex, triple-layered capsid structure. The triple-capsid layer is composed of an inner core, an intermediate capsid, and an outer capsid surrounded by short spikes. Each segment of RNA codes either a single viral structural protein (VP1 to VP4, VP6, and VP7) or nonstructural protein (NSP1 TO NSP4), except for segment 11 which codes for two nonstructural proteins (NSP5 and NSP6), in overlapping reading frames (91). The rotavirion consists of an inner core of RNA segments and molecules of VP1 and VP3 surrounded by VP2 protein (92,93). The middle core contains VP6 protein surrounded by
a layer VP4 protein spikes, that are embedded in a VP7 capsid. These two play an important role in enabling penetration of the virus into the epithelial lining.

The Rotavirus genus is classified into serological groups (A to E). Groups A to C infect humans, Group A causing most infections, and all the remaining groups infect animals (36). Rotaviruses are further classified into genotypes according to specific cut-off points in nucleotide sequence identities.

There are multiple mechanisms through which Rotavirus causes diarrhea including, villus ischemia, maladsorption caused by destruction of enterocytes or interference with their absorptive abilities, enterotoxin activity and triggering of intracellular fluid secretion by NSP4, and activation of the enteric nervous and vascular systems that lead to indirect secretion (94-96).

IV. Control and Therapies

Like other diarrheal diseases, supportive rehydration therapy rather than medications is the recommended treatment for Rotavirus. Vaccination against Rotavirus has been available since 2006. Four Rotavirus vaccines are currently in use globally: the monovalent Rotarix (RV1), developed by GlaxoSmithKline, in Rixensart, Belgium and the pentavalent RotaTeq (RV5), developed by Merck in West Point, PA, USA. RV1 is made up of a single strain of Rotavirus derived from a human isolate and attenuated through multiple cell culture passages. RV5 contains five attenuated strains of Rotaviruses, four produced via the bovine Rotavirus isolate (G genotype) and one human isolate (P genotype). The other two newer, WHO-approved vaccines are Rotavac™, which is a
naturally occurring bovine-human reassortant neonatal G9P, also called 116E developed by Bharat Biotech in New Delhi, India, and RotaSiil™ a bovine-human reassortant with human G1, G2, G3 and G4 bovine UK G6P backbone also developed in India by Serum Institute of India (15).

Although vaccination does not entirely protect from contracting Rotavirus, both vaccines have successfully reduced global Rotavirus gastroenteritis with vaccine effectiveness ranging from 57% to 85% for RV1 and from 45% to 90% for RV5, lower childhood mortality countries coming up on the higher end of success (98).

IV. Parasitic

Cryptosporidiosis

I. Clinical Features

Cryptosporidium has many species; however, C. hominis and C. parvum are responsible for causing more than 90% of human cases of Cryptosporidiosis (99,100). Other species that are less commonly associated with human disease include C. meleagridis, C. cuniculus, C. felis, and C. canis.

The severity of a Cryptosporidium infection can vary from an asymptomatic shedding of oocysts to a severe and life-threatening disease. C. hominis patients typically have more severe symptoms including diarrhea, nausea, vomiting, and malaise, as well as other non-intestinal symptoms such as joint pain, eye pain, recurrent headaches, and fatigue. On the other hand, C. parvum-, C. meleagridis-, C. canis-, and C. felis-infected patients only
have diarrhea as a symptom (101). Regardless, of the responsible species, in rare cases, patients have other nonspecific symptoms such as myalgia, weakness, and anorexia as a result of Cryptosporidiosis (102).

Several parasite characteristics and host factors influence the virulence, persistence, and overall severity of the Cryptosporidiosis infection. Although not much is known about parasite factors, studies have shown that immunocompromised individuals such as HIV/AIDS patients, with T cell counts of <50, are at the greatest risk (103-109). Frequent exposure is another host-defining factor for individuals who live in areas that lack adequate sanitation (99).

When infected, otherwise healthy individuals (immunocompetent), can naturally eliminate the infection in two to three weeks. For immunocompromised individuals, however, the disease can evolve into a life-threatening condition causing dehydration and wasting (110-112), atypical gastrointestinal disease, biliary tract disease, respiratory tract disease, and pancreatitis, and in some cases leading to death (113-115).

II. Epidemiology

Cryptosporidiosis is the leading waterborne disease from recreational waters in the United States. Globally, Cryptosporidiosis was the fifth leading diarrheal disease in children younger than 5 years with more than 48,000 documented deaths (95% UI 24,600–81,900) and more than 4.2 million disability-adjusted life-years lost (95% UI 2.2 million–7.2 million) in 2016 (116).
The first cases of human Cryptosporidiosis were reported in 1976 (110,117). Cryptosporidiosis was established as a global public health threat when it was recognized as lethal to immunocompetent individuals (118,119). Its status as a significant waterborne disease was cemented with large-scale outbreaks of human Cryptosporidiosis in the UK (Swindon and Oxfordshire) and USA (Milwaukee, WI), where contaminated water was identified as the cause (120,121).

*Cryptosporidium* can be transmitted both through direct and indirect routes. The most common direct transmission is the fecal-oral route, where infected hosts shed contaminated stools. From there, parasites are transferred from animal-to-animal, animal-to-human (zoonotic), human-to-animal, or human-to-human (anthroponotic) (39,122,123). Human-to-human transmissions are well documented in outbreaks in closed settings such as daycare centers and hospitals (124). Zoonotic transmissions typically occur when veterinary students and researchers are exposed while treating animals in outbreaks where a strain that infects both humans and animals is involved. Indirect transmission usually occurs when the susceptible host encounters water, food, or surfaces that have been fecally-contaminated with *Cryptosporidium* (125,126). In rare cases, immunocompromised hosts and children can also get sick from inhaling oocysts from the environment (127-129). This form of contamination leads to laryngotracheitis, a respiratory disease, in addition to mild diarrhea.
III. Pathogenesis and Virulence

*Cryptosporidium* belong to the same phylum as other medically important parasites such as *Plasmodium* and *Toxoplasma*, which are called apicomplexan parasites. Like other diarrheal diseases, *Cryptosporidiosis* is transmitted through the oral-fecal route when a susceptible host consumes contaminated food and water.

The established infective life cycle of *Cryptosporidium* begins when the host ingests sporulated oocysts. The oocysts then undergo excystation and release four infectious sporozoites. Temperature and pH alone can induce excystation, however, reducing conditions, carbon dioxide, pancreatic enzymes, and bile salts have also been cited as causes of oocysts excystation (103,130-132).

Like most apicomplexan parasites, *Cryptosporidium* sporozoites possess gliding motility that enables them to move across the surface of the host cell (132). As sporozoites glide across the surface of the small intestine, the rhoptries and micronemes, in the parasite’s apical complex, release proteins that enable them to adhere to and invade the cell, and thereafter induce the host cell membranes to enclose the parasites into a parasite modified host membrane called the parasitophorous vacuole (PV) (133-137). Once inside the PV, each sporozoite matures into a spherical trophozoite, that undergoes merogony to asexually produce a type I meront containing eight merozoites (103). Each of the eight merozoites attaches to a neighboring epithelial cell after being released and undergoes merogony on its turn to produce either a second-generation type 1 meront or a type 2 meront (which only contains four merozoites).
Figure A: Cryptosporidium Life Cycle. Sporulated oocysts, containing 4 sporozoites, are excreted by the infected host through feces (1) (and possibly other routes such as respiratory secretions). Transmission of Cryptosporidium spp. occurs mainly through ingestion of fecally contaminated water (e.g., drinking or recreational water) or food (e.g., raw milk) or following direct contact with infected animals or people (2). Following ingestion (and possibly inhalation) by a suitable host (3), excystation (4) occurs. The sporozoites are released and parasitize the epithelial cells (5, 6) of the gastrointestinal tract (and possibly the respiratory tract). In these cells, usually within the brush border, the parasites undergo asexual multiplication (schizogony or merogony) (7, 8, 9) and then sexual multiplication (gametogony) producing microgamonts (male) (10) and macrogamonts (female) (11). Upon fertilization of the macrogamonts by the microgametes (12) that rupture from the microgamont, oocysts develop and sporulate in the infected host. Zygotes give rise to two different types of oocysts (thick-walled and thin-walled). Thick-walled oocysts are excreted from the host into the environment (13), whereas thin-walled oocysts are involved in the internal autoinfective cycle and are not recovered from stools (14). Oocysts are infectious upon excretion, thus enabling direct and immediate fecal-oral transmission. Extracellular stages have been reported, but their relevance in the overall life cycle is unclear (141). [https://www.cdc.gov/dpdx/cryptosporidiosis/index.html]
The type 2 merozoites are then released, but instead of undergoing merogony again, they begin gametogony to produce either microgamonts (male) or macrogamonts (female) (138,139). The molecular mechanisms governing gametogamy are poorly understood. Each microgamont goes through nuclear division and differentiates into 16 microgametes, while each macrogamont forms a unicellular macrogametocyte. Once released from the PV, the microgametes locate the unucleated macrogametocytes to fertilize them, forming zygotes. The zygote then goes through two asexual cycles of sporogony producing an oocyst that either has a thick wall or a thin wall, containing four sporozoites (140). Finally, the thick-walled infective oocysts are excreted from the host in feces enabling the repetition of the infective life cycle of Cryptosporidium if consumed by another susceptible host. Thin-walled oocysts remain inside the host and are involved in the internal autoinfective cycle (139).

IV. Control and Therapies

For the general public, the CDC recommends maintaining good sanitation by avoiding food and water that might be contaminated, and properly washing hands (alcohol-based hand sanitizers are not effective against the parasite) as a means of control of Cryptosporidium. In day care facilities, it is recommended to isolate children with diarrhea symptoms from groups to avoid small outbreaks (141).

Cryptosporidiosis symptoms disappear in healthy individuals within two to three weeks. However, children and pregnant women are at a greater risk of dehydration. Rehydration therapy is recommended in these cases. Where diarrhea symptoms are persistent, Nitazoxanide, an FDA-approved drug, is recommended. For immunocompromised
individuals, Nitazoxanide has not been documented as a cure for Cryptosporidiosis. However, taking anti-retrovirals reduces susceptibility and vulnerability to diseases that are AIDS-associated in HIV/AIDS patients by strengthening their immune system (141).
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CHAPTER TWO

GLOBAL ESTIMATED DISABILITY-ADJUSTED LIFE-YEARS (DALYs) OF DIARRHEAL DISEASES: A LONGITUDINAL ANALYSIS OF THE GLOBAL BURDEN OF DISEASE STUDY

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ABSTRACT

Summary Background

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 is the most comprehensive study ever carried out to report on the state of global public health for the previous 28 years (1990-2017). In 2017, it covered 359 diseases and injuries for 195 countries and territories.

Our study sought to provide an up-to-date analysis of the progress that has been made to eradicate diarrheal diseases using the GBD2017 data. Although significant progress has been made in reducing the number of deaths due to diarrhea, diarrheal diseases incidences and associated morbidity have not experienced the same level of decline. Using disability-adjusted life-years (DALYs), a metric that tracks impact on life expectancy, prevalence, and impact on quality of life due to a specific disease, we performed a comparative analysis of the impact of diarrheal diseases by World-Bank (WB) Income regions, age, and sex.
Methods

Using multi-year GBD data that we accessed from the Institute of Health Metrics (IHME) tool (GBD Compare | Viz Hub), we analyzed the impact of diarrheal diseases using Microsoft Office Excel 2017 (Microsoft, Redmond, WA). We compared the disability-adjusted life-year (DALY) metric due to diarrheal diseases among different demographic subsets including sex, age, country, and income level. One DALY is comparable to one lost year of “healthy” life, while the sum of DALYs across the population expresses the burden of disease caused by a gap between current health status and optimal health for the entire population impacting variables such as advanced age. All data estimates in the GDB2017 study were listed with 95% uncertainty intervals (UIs).

We also evaluated DALYs as a function of the socio-demographic index (SDI). This index, also developed by the GBD Project in 2015, is a measure of a region’s socio-demographic development and consists of data about the education levels, average income per person, and total fertility rate (TFR).

Findings

Diarrheal DALYs have decreased by approximately 54.64% from 1990 to 2017. In 1990 diarrheal diseases counts were estimated at 178,669,278.768251 (95% UI: 154,235,572.289659-203,868,117.467447) with an age-standardized DALY rate of 1,017.22180392645 per 100,000 people. On the other hand, in 2017, DALYs were
estimated at 81,039,363.8553969 (95% UI: 70,120,051.7904495 - 972,33,423.453799); and an age-standardized DALY rate of 246 per 100,000 population globally. Interestingly, while DALYs have decreased, incidence and prevalence have increased by 52.16% and 47.22%, respectively. Age-standardization, otherwise known as age adjustment, makes it possible to apply observed age-specific data from multiple populations to a standard age distribution that enables comparison across countries and regions.

Regardless of World Bank (WB) Income region, infants 28-364 days were the most vulnerable to diarrheal diseases. Since 1990, global diarrheal disease DALYs do not differ markedly between the sexes. In 2017, there seems to be a slight difference in WB High-income regions, where women have higher DALY rates (3.36% more), the rates in WB Low-income regions were higher for males in 2017 (24.23%). We also observed that the rate of diarrheal diseases highly correlates to socio-demographic index ($R^2 = 0.9937$).

**Interpretation**

Considerable progress has been made globally in reducing the burden of diarrheal diseases, as many socio-economic risk factors have been reduced. However, progress has not been up to par in all locations, Low-income countries are still substantially behind in reducing diarrheal diseases DALY rates compared to High-income countries and the burden of diseases infants still requires special attention.
I. Introduction

Diarrheal diseases have long been distinguished as a serious global health problem, particularly in developing countries. Acute diarrhea is normally caused by infection with viral (e.g., Norovirus (1), Rotavirus (2)), bacterial (e.g., Campylobacter (3), Escherichia coli (4), Salmonella (5), Shigella (6)), or parasitic (e.g., Entamoeba histolytica (7), Giardia lamblia (8), Cryptosporidium enteritis (9)) etiological agents. On the other hand, chronic diarrhea can have non-communicable derivations such as food allergies and intolerances, celiac disease, Crohn’s disease, ulcerative colitis, or long-term use of medicines such as antibiotics, antacids or other drugs.

According to World Health Organization (WHO) Global Health Observatory (GHO) data, in 2016, diarrhea was the ninth leading cause of mortality globally, responsible for more than 1.3 million total deaths (10). Many factors including age, environment, and sex can exacerbate the impact of diarrhea for various demographic groups. For example, the impact of diarrheal disease on children is substantial. In 2017, global data show that diarrheal diseases rank third among all causes of mortality in children younger than five (11). This demographic made up more than a quarter (33.38%) of global diarrheal deaths altogether and multiple reports have explored reasons for this burden (12-14). Furthermore, there is a growing body of evidence that shows that children, who suffer from multiple bouts of diarrhea, especially before the age of two, experience poor physical growth(15), poor cognitive development(16,17), and are at higher risk for the development of type 2 diabetes, metabolic syndrome, obesity and related co-morbidities (18,19).
Location is another critical factor that has bearing on the number of diarrheal diseases deaths. Evidence has shown that Low-income regions, with poor access to health care, safe water, and sanitation, and with higher numbers of marginalized populations are the most vulnerable. For example, 87% of diarrheal deaths occurred in South Asia and sub-Saharan Africa in 2015(20).

Women made up more than half (52.23%) of all diarrheal deaths in 2017. Cultural factors influence this disparity among sexes. For instance, in some sub-Saharan Countries, especially in more unstable, violent settlements, many women have reverted to using unclean forms of sanitation such as bucket toilets even when clean forms are available. This may be the result of fear of physical and sexual violence that comes with using public sanitation facilities (21,22). Other research suggests that women's sanitation use may be affected by their fear of contracting infections from unclean sanitation facilities (23,24).

Despite these statistics, if we consider mortality rates overall, global health has improved tremendously as life-expectancy has almost doubled since the 1950s [6–7]. Much of this progress has to do with the improvements made that have led to a reduction of child mortality rates. For example, since 1990, mortality for children under five has declined by 57% and 68% for all causes and diarrheal causes, respectively (25,26). Despite this drop-in diarrhea-related mortality, the incidence of diarrheal disease, in this same age group, has experienced a less pronounced declivity (26), decreasing only by on 24% during the same time period.
Ageing populations further challenge the ability to limit diarrheal disease. According to UN estimates, individuals older than 60 years of age will grow from 962.3 million in 2017 to 2080.5 million in 2050 (27). This growth will occur mainly in Africa, for which it is estimated that individuals over the age of 60 will increase by 230% over this time period. In 2016, diarrhea mortality was approximately three times higher in adults older than 70 years of age than in children younger than 5 years (28).

An important framework for the eradication of diarrheal diseases is that they mostly occur in Low-income countries. Low-income countries do not have suitable infrastructure and enough resources that can be dedicated to this task (24). It is, therefore, important for there to be a focus not only on measuring mortality rates, but also on lost healthy years. A disability-adjusted life-years (DALY) is a metric that can track disease burden as it incorporates both current and long-term burden and expresses morbidity as years of life lost as a result of premature mortality as well as years lived with disability (29).

In this study, we examined the burden of diarrheal diseases from 1990 to 2017 based on the data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GDB2017) (26). Specifically, we conducted a longitudinal analysis of DALYs associated with diarrheal diseases by country, age, and sex.
II. Methods

Overview

The Global Burden of Disease (GBD) Project was initiated in 1990, to provide wide-ranging, global-level, assessments of data human health. A consortium of project collaborators has tracked the mortality and morbidity associated with 359 diseases (communicable and non-communicable) (30), with 3484 sequelae and 84 risk factors for each of 195 countries and territories and the globe from 1990 to 2017. The data in the GBD2017 are extracted from 68,781 data sources and are reported by region, age, and sex, allowing for a variety of comparisons by time, sex, population and other demographic groupings (28). The first data set (for the initial year 1990) was published in the World Development Report 1993 (30). This international consortium is managed by the Institute for Health Metrics and Evaluation (IHME; Seattle, WA).

Analysis of Data

Using multi-year GBD data, we analyzed the impact of diarrheal diseases using Microsoft Office Excel 2019 (Microsoft, Redmond, WA). Specifically, we compared the disability-adjusted life-year (DALY) metric due to diarrheal diseases among different demographic subsets including sex, age, country, and income level.

The latter followed World Bank (WB) income categories: High income, Low income, Lower middle income, Upper middle income. One DALY is comparable to one lost year of “healthy” life, while the sum of DALYs across the population expresses the burden of
disease caused by a gap between current health status and optimal health for the entire population impacting variables such as advanced age. Simply put, one DALY equals the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences. Further details on the methods used in data modeling for the GDB2017 can be found in other publications (31,32).

When comparing WB High-income regions to WB Low-income regions, and males to female, we used age-standardized data, which is essentially age adjusted data, to enable comparison across populations with varying age demographics.

We also evaluated DALYs as a function of the socio-demographic index (SDI). This index, also developed by the GBD Project in 2015, is a measure of a region’s socio-demographic development and is comprised of data about the education levels, average income per person, and total fertility rate (TFR). The SDI is expressed on an interpretable scale of zero to one, where zero represents the lowest educational achievement, lowest income per capita, and highest TFR, and one represents the highest educational achievement, highest income per capita, and lowest TFR. All data estimates in the GDB2017 study were listed with 95% uncertainty intervals (UIs).

Data Visualization

To compare data, we used MS Excel 2016 to model and visualize data exported from the IHME tool (GBD Compare | Viz Hub) (26).
Ethics Statement

This study was based on secondary databases which are publicly available, without identification of individual data.

III. Results

Summary of Global DALYs due to Diarrheal Disease

To assess the global impact of diarrheal diseases, many previous studies have focused on mortality statistics (32-35). However, given that global mortality rates are decreasing, and given that individuals are living longer, it is imperative to also look at the burden of diseases, including diarrheal diseases, from the perspective of disability. Therefore, we examined yearly DALYs attributable to diarrheal diseases using GBD Project data. To the best of our knowledge, this is the only longitudinal study of diarrheal diseases DALYs that encompasses all 28 years of data available from the GBD. The GDB2017 categorizes diseases, causes and their sequelae into four hierarchical levels (Figure1).
**Figure 1: GBD Hierarchical Levels:** Level 1 consists of three broad cause groups: communicable, maternal and neonatal conditions and nutritional diseases (CMNN); non-communicable diseases (NCDs); and injuries. There are 21 diseases and injuries categories at Level 2. Level 3 and Level 4 break down causes to the smallest level of detail with 167 causes, and 288 causes, respectively. Diarrheal diseases are classified in level 3 causes under enteric infections.
Appendix 1 summarizes the global estimates for DALYs, incidence, and prevalence for diarrheal diseases from 1990 and 2017. Appendix 1 also includes the annual socio-demographic index as reported in the GBD2017 results. In 1990 DALYs counts were estimated at 178,669,278.77 (95% UI: 154,235,572.29 - 203,868,117.47) with an age-standardized DALY rate of 1,017.22 per 100,000 people. On the other hand, in 2017, DALYs were estimated at 81,039,363.85 (95% UI:70,120,051.79 - 972,33,423.45); and an age-standardized DALY rate of 246.01 per 100,000 population globally. Thus, diarrheal DALYs have decreased by approximately 54.64% since 1990.

Interestingly, while DALYs have decreased, incidence and prevalence have increased by 52.16% and 47.22%, respectively (Appendix 1). Specifically, diarrheal disease incidence was estimated at 4,135,836,824.13 (95% UI: 3,811,339,413.89 - 4,500,759,366.83) in 1990, compared to 6,292,936,671.74 (95% UI: 5,808,374,688.14 - 6,816,675,433.15) in 2017. Diarrheal disease prevalence was estimated at 63,492,658.0347 (95% UI 59,217,728.40 – 68,111,097.50) in 1990, compared to 93472768.36 (95% UI: 86857153.63 - 99961050.16) in 2017. Overall, these data suggest that treatments may have improved, which has led to a lower number of lost healthy years due to diarrheal disease; however, there may be a lack of progress in prevention methods.

SDI is a summary measure of where countries or other geographic areas are on the spectrum of development. The SDI measure is expressed on a scale of 0 to 1 and incorporates three different aspects of development: income per capita, education, and fertility. A zero SDI value indicates a Low-income region, while an SDI value of one
indicates a High-income country. The global SDI value increased from 0.52 in 1990 to 0.65 in 2017 indicating that there has been global economic progress overall. The increase in SDI may be an indicator of enhanced access to health care, and specifically enhanced availability of treatments for diarrheal diseases, leading to the decrease in associated DALYs.

Global Diarrheal Disease DALYs Differ by World Bank (WB) Economic Region

Economic stability is another important factor that affects the number of DALYs in each region. Although global DALYs, due to diarrheal disease, decreased from 1990 to 2017, it is important to understand if different WB economic regions vary in their progress toward treatment and eradication of diarrheal diseases. Therefore, we compared diarrheal diseases DALYs per 100,000 people in WB Low-income regions to that of WB High-income regions from 1990 to 2017.

In 1990, DALYs per 100,000 were highest in Niger with an estimate of 17,633.63 (95% UI: 12,873.65 - 22,679.68) and lowest in North Korea with an estimate of 370.910371233981 (95% UI: 705.48 - 238.14) (Figure 2). In 2017, the DALYs per 100,000 were highest in Central African Republic with an estimate of 8,590.04 (95% UI: 5,449.51 - 12,230.82) and, once again, lowest in North Korea with an estimate of 381.568756222037 (95% UI: 270.49 - 808.57) (Figure 2).
Figure 2: World Bank Low-income DALYs per 100,000 Age-standardized for Both Sexes (1990-2017).
In 1990, in the WB High-income regions (Figure 3), Saudi Arabia exhibited the highest DALYs per 100,000 with an estimate of 962.35 (95% UI 1374.01- 662.02), and the Netherlands had the lowest DALYs per 100,000 with an estimate of 16.52 (95% UI: 21.60 - 12.27). In 2017, Guam had the highest DALYs per 100,000 with an estimate of 483.37 (95% UI: 663.90 - 335.04) while Malta had the lowest DALYs per 100,000 with an estimate of 25.90 (95% UI: 33.28 - 19.58).

We also compared the highest DALYs per 100,000 in both economic regions. Not surprisingly, there were substantially more DALYs per 100,000 in WB Low-income regions than in High-income regions with a ratio of 697:1. However, there was an interesting temporal trend observed. In the case of WB Low-income regions, there was a steady decline in DALYs per 100,000 with an overall decrease of 58% from 1990-2017 (Figure 2). On the other hand, in the case of WB High-income regions, there was a decline of DALYs per 100,000 from 1990 to 1998, after which there was an increase almost every year up to 2017 (Figure 3). Thus, the cumulative decrease, from 1990 to 2017, in DALYs per 100,000 of 2% in WB High-income regions is markedly lower than that of WB Low-income regions. An annual increase in diarrheal disease DALYs per 100,000 in Bahrain, Bermuda, Demark, Germany, and the US Territories of Guam, the Northern Mariana Islands and Puerto Rico as well as the little change in Antigua and Barbuda, Chile, Barbados, Estonia, Trinidad and Tobago, may have contributed to this apparent lack of progress in WB High-income regions.
Figure 3: World Bank High-income DALYs per 100,000 Age-standardized—Both Sexes (1990-2017).
Global Diarrheal Diseases DALYs Do Not Differ Markedly Between the Sexes in 2017

Previous data suggest that diarrheal diseases disproportionately affect boys compared to girls (32). The specific reasons for this uneven distribution among the sexes are still unclear. One hypothesis state that boys younger than five years old are more likely to be exposed to infectious pathogens in Low-income countries due to social and cultural reasons including their general ability to move and play outside the home more than girls (31). To determine if the diarrheal diseases in males and females were differentially contributing to the unusual temporal pattern of DALYs in WB High-income regions, we compared age-standardized DALY rates per 100,000 by sex in both economic regions.

As shown in Figures 4 and 5, temporal patterns of DALYs for both males and females, in WB High-income regions, separately, was similar to that for both sexes combined (Figure 3) in that there was an apparent decline in DALYs per 100,000 from 1990 to approximately 1998, after which there was an increase almost every year up to 2017. For both males and females, Saudi Arabia reported the highest DALY rates per 100,000 in 1990 with 1869.28 (95% UI: 3073.62 - 1125.10) and 1093.24 (95% UI: 1785.80 - 624.55), respectively, in WB High-income regions. In 2017, Guam had the highest diarrheal diseases DALY rates for both males and females at 474.16 (95% UI: 659.41 - 328.91) and 490.68 (95% UI: 674.91 - 336.08), respectively.
Figure 4: World Bank High-income DALYs per 100,000 Age-standardized—Female (1990-2017).
Figure 5: World Bank High-income DALYs per 100,000 Age-standardized—Male (1990-2017).
We also combined the data for the diarrheal diseases DALYs for males and females in Figure 6. Females consistently had higher DALY rates per 100,000 both in 1990 and 2017 both in Saudi Arabia and in Guam, the two most affected countries in WB High-Income countries. In 1990, in Saudi Arabia, the rate of diarrheal diseases in females was 41.5% higher than that in males. That gap was considerably smaller in Guam in 2017, where there was a 3.36% difference in diarrheal diseases rates between females and males. The lower rates of diarrheal diseases for both sexes in 2017 in the High-income region are encouraging, however, work remains to be done to increase the speed at which diarrheal diseases are eradicated.
Figure 6: WB High-income Male and Female DALY Rates Combined 1990 vs. 2017.
In Figures 7 and 8, we repeated the analysis by sex, but this time in the World Bank Low-income regions. Niger had the highest diarrheal disease DALY rates for females in 1990 at 40,880.10 (95% UI: 26,685.78 - 56,133.80), while Chad had the highest DALY rates per 100,000 in 2017 at 11,109.24 (95% UI: 7,993.22 - 15,282.68). Chad reported the highest DALY rates for males both in 1990 and 2017 at 27,230.37 (95% UI: 17,459.49 - 40,318.61) and 14,662.02 (95% UI: 10,053.10 - 20,477.33), respectively.
Figure 7: World Bank Low-income DALYs per 100,000 Age-standardized—Female (1990-2017).
**Figure 8:** World Bank Low-income DALYs per 100,000 Age-standardized—Male (1990-2017).
Figure 9 summarizes these data for both sexes. Like WB High-income regions, Low-income regions had disproportionate DALY rates per 100,000 for women in 1990, in Niger, diarrheal diseases DALY rates were 38.39% higher in females than in males. However, this dynamic changed in Chad in 2017, where males had 24.23% higher rates of diarrheal disease than females. A hypothesis for this progress seen in women in Low-income countries since 1990, can be attributed to their progress in other areas such as education which has enabled them to be aware of preventable diseases such as diarrheal diseases (36).

North Korea stands out in Figure 9, barely having any DALY rates reported. Reliable estimates of the burden of diseases in North Korea are widely unavailable and the WHO ranks available raw data at the lowest level of credibility.

Overall, these data suggest that the disproportionately higher number of diarrheal diseases DALY rates observed for boys versus girls in children under five years old does not remain true in age-standardized DALY rates. Since 1990, the gap between males and females in both economic regions have been narrowed.
Figure 9: Comparison of Diarrheal Disease Burden Between Sexes from 1990 to 2017 in WB Low-income.
Diarrheal Diseases DALYs Rates by Age in WB Low-income Countries and WB High-income Countries

Up to this point, we based our analysis on age-standardized DALY rates comparing WB High-income and WB Low-income. Previous data have shown that young children under five are particularly vulnerable to diarrheal diseases (32). In many Low-income countries, lack of sanitary facilities and hygienic practices, fly infestations, and regular consumption of street food constitute some of the leading causes of diarrheal disease (37-39).

In Figure 10, we compared different age categories’ vulnerability to diarrheal diseases using DALYs by age category in WB Low-income regions. The 28-364 days age group emerged as the most vulnerable demographic to diarrheal diseases by far with 13,949,996.98 DALYs (95% UI: 1,172,1297.30 – 1,622,0597.90) in 1990, and 8,170,515.87 DALYs (95% UI: 7,028,902.56 – 9,511,204.72) in 2017.

In Figure 11, we removed the first ten years of life to analyze how the remaining age demographics fare. Two additional peaks emerged, one at ages 20-24 and the other at 60-64 years. The Peak at 20-24 has not been explained in previous literature. Our hypothesis is that the sudden spike in diarrheal DALY rates is contamination of young mothers and fathers by their infants and toddlers. Previous studies have reported that diarrhea impacts at least 9% of the elderly population at any given time. This has a significant negative impact on their quality of life, increasing their hospital visits and
hospitalization (51). Other studies have reported that diarrheal diseases in the elderly population are a significant cause of fecal incontinence (52), morbidity (53,54), and mortality (35). Long-term care facility stay for the elderly was cited as a risk factor for diarrheal diseases (35). Consumption of multiple medications was also reported as a risk factor for diarrheal disease, with a 11.0% increase of diarrheal disease prevalence in patients who were taking 3–5 drugs, and an 11.7% increase in patients taking 6 or more drugs at once (55).
Figure 10: Diarrheal Disease DALYs Counts by Age (1990-2017) in WB Low-income.
Figure 11: Diarrheal Disease DALYs Counts by Age (1990-2017) in WB Low-income.
Figure 12: Diarrheal Disease DALYs Counts by Age (1990-2017) WB High-income.
In Figure 12, we repeated the same age group comparison in WB High-income countries. Overall, in High-income countries, infants 28-364 days old, were the most vulnerable to diarrheal diseases with 206,133.79 (95% UI: 145,965.76–292,139.86) DALYs in 1990. However, in 2017, the most vulnerable group was the 1-4-year-olds with 83,578.53 (95% UI: 53,231.443–124,013.45) DALYs. There doesn’t seem to be a clear explanation for this shift.

On a global scale, infants, 28-364 days old were again the most vulnerable to diarrheal diseases in 1990 and 2017 at 72,710,222.04 (95% UI: 63,366,316.83–82,038,201.88) DALYS and 25,200,783.96 (95% UI: 22,457,911.40–28,191,106.60) for males and females.

In Figure 13, we compared 1990 DALYs to 2017 DALYs by age and by sex. Males had slightly higher DALYs at 37,050,104.87 (95% UI: 29,642,441.65–43,624,887.49) versus 35,660,117.17 (95% UI: 30,938,542.58–40,580,555.92) DALYs for females 28-364 days old.

The same trend is observed in 2017, with males having higher DALYs at 13,552,012.55 (95% UI: 11,551,907.13–15,808,093.94) compared to females at 11,648,771.41 (95% UI:10,140,980.26–13,443,270.64) DALYs.
Figure 13: Global DALY Counts by Gender and Age (1990-2017).
Relationship Between DALY Rates and SDI

By comparing WB High-income to WB Low-income countries throughout this paper, we aimed to report on the impact of economic and infrastructure development on health, in this case as it relates to diarrheal diseases. In all areas of our analysis, WB High-income citizens fared better than citizens of WB Low-income regions. The SDI metric measures a region’s socio-demographic development considering data about the education levels, average income per person, and total fertility rate (TFR) then reports a value between zero and one, one indicating the greatest development.

The global SDI is a good summary of the socio-economic progress that has been made globally. In Figure 13, we plotted global DALY rates from 1990 to 2017 against average WB High-income, WB Low-income, and Global SDI values for each year, respectively. We observe a cubic polynomial relationship in the WB high-Income regions, where SDI values are highest and DALYs lowest. Looking at the curve of the graph, it imitates the trend we saw in Figure 3 where, there was at first a decrease in the number of DALYs from 1990 to 1998, where the number of DALYs started to increase for unclear reasons. In contrast, DALY rates in WB Low-income regions and Globally have a linear relationship with SDI value. As the SDI increases, DALY rates per 100,000 decrease over time. Looking at the data, it seems that SDI has a great impact on DALY rates in Low-income countries with Low-income, but that impact is lost as the SDI increases.
Figure 14:


**Middle:** DALY Rates vs. Average WB Low-Income Regions SDI 1990-2017.

**Bottom:** DALY Rates vs. Average Global SDI 1990-2017.
IV. Discussion

In this study, we have discerned the impact of diarrheal diseases by examining DALYs, a measure that reports the number of lost “healthy” years in a population due to a specific illness. Overall, our analyses show that global diarrheal diseases DALYs have decreased. Surprisingly, the decline in DALYs was more dramatic for WB Low-income regions than for WB High-income regions. While DALYs have decreased, incidence and prevalence have increased by 52.16% and 47.22%, respectively. Regardless of WB income regions infants 28-364 days were the most vulnerable to diarrheal diseases. However, there were unexplained peaks of DALYs for the 20-24 and 60-64 age groups. Since 1990, global diarrheal disease DALYs did not differ markedly between the sexes. We also observed that the rate of diarrheal diseases highly correlates to socio-demographic index ($R^2 = 0.9937$).

We hypothesized that socio-economic status would have a great impact on the overall health of a population. For that reason, for most of our analyses, we compared the data between WB High-income countries and WB Low-income countries, after which we refined our analyses by age and sex. Although mortality rates have declined, these data show that diarrheal diseases still affect the quality of life of individuals of all ages, particularly in WB Low-income regions.

In each year since 1990, DALYs for children 28 to 364 days old were the highest suggesting that this group continues to be the most vulnerable population regardless of income region. This is also the group for which mortality is highest (14,32), albeit this metric has declined from 1990 to 2017 (26). This progress in lowering childhood
mortality is due to several factors including, female education, which has contributed to improvements in hygiene and sanitation, wider access to better nutrition, increased breastfeeding, better supplemental feeding, increased use of oral rehydration therapy (ORT), and measles immunization (40-42). Several studies have shown the impact that improvements in children nutrition, access to clean safe water and food, as well as treatment with rehydration therapy have had on reducing the number of diarrheal diseases related deaths (14,43).

The significant lag of WB Low-income countries compared to WB High-income countries in yearly DALY rates observed is alarming, particularly for children under five. Children who experience multiple bouts of diarrheal disease start at an unequal footing for a quality life later in life, experience less economic growth as adults (44). The impact of diarrheal diseases on crucial early cognitive development is well documented. Children who experienced multiple episodes of diarrheal have lower scores on the Test of Non-Verbal Intelligence-III and the Wechsler Intelligence Scale for Children, they also suffer visual-motor coordination impairment, slowed auditory short-term memory and information processing; and are at a higher risk of malnutrition, diabetes, and cardiovascular disease in adulthood (15,17,19,45,46). Further, diarrheal diseases have been linked to growth stunting in children. An analysis of nine separate studies done over a 20-year time period and in five countries showed that stunting was directly linked to multiple episodes of diarrhea in infants under two years of age, where the proportion of stunting attributed to five or more episodes of diarrheal before 24 months increased the probability of stunting by 25% (95% CI 8-38%). The same study also showed that the likelihood of stunting was increased by 18% (95% CI 1-31%) for
children who suffered from diarrheal diseases at least 2% of the time before 24 months of life (47).

It is well known that diarrheal diseases disproportionately affect populations in poverty and conflict-ridden countries. It is therefore unsurprising that we found a strong negative correlation between SDI and diarrheal diseases’ DALYs globally ($R^2 = 0.9937$). Data shows that caregiver knowledge as it relates to Water, Sanitation, and Hygiene (WASH) is an important factor in preventing diarrhea (48-50). As the SDI value for a country goes up so does the education level of its population, notably its women. Since women are the primary caregivers in most cultures, their education on WASH leads to a significant decrease in diarrheal rates among children (48-50). However, we saw that SDI’s impact on diarrheal diseases weakens as a region’s SDI value increases.

Our analysis has shown a small spike in diarrheal diseases DALYs in the elderly at 60-64 years in WB Low-income countries and 80-84 years in WB High-income countries. Previous studies have reported that diarrhea impacts at least 9% of the elderly population at any given time. This has a significant negative impact on their quality of life, increasing their hospital visits and hospitalization (51). Other studies have reported that diarrheal diseases in the elderly population are a significant cause of fecal incontinence (52), morbidity (53,54), and mortality (35). Long-term care facility stay for the elderly was cited as a risk factor for diarrheal diseases (35). Consumption of multiple medications was also reported as a risk factor for diarrheal disease, with a
11.0% increase of diarrheal disease prevalence in patients who were taking 3–5 drugs, and an 11.7% increase in patients taking 6 or more drugs at once (55).

To our knowledge, our study is the first to make a longitudinal analysis of DALYs associated with diarrheal diseases. Our data show that diarrheal disease associated DALYs have not markedly changed (WB High-income regions). There was a slight decrease until around the year 2000, where DALY rates started to slowly increase in high income countries for unclear reasons. In contrast, WB Low-income regions experienced a more dramatic drop in DALY rates from 1990 to 2017 although yearly DALY counts are still noticeably higher than in WB High-income regions. Overall, diarrheal diseases DALYs have been declining at a slower pace than that for mortality (26). This indicates that increased intervention is necessary.

V. Acknowledgements

This work was supported by a National Institute of General Medical Sciences Grant: GM109094 (LAT). The funding agency had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This content is solely the responsibility of the authors and does not necessarily represent the views of the National Institute of General Medical Sciences or the National Institutes of Health.
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### APPENDIX 1: Summary of DALY Counts, Incidence Counts, Prevalence Counts, DALY Rates Due to Diarrheal Diseases and Global SDI Values (1990-2017).

<table>
<thead>
<tr>
<th>Year</th>
<th>DALYS(COUNT)</th>
<th>Yearly % change (1990-2017)</th>
<th>Incidence (COUNT)</th>
<th>Incidence Yearly % change (1990-2017)</th>
<th>Prevalence (COUNT)</th>
<th>Prevalence Yearly % change (1990-2017)</th>
<th>DALYS Rate per 100,000</th>
<th>DALYS Rate per 100,000 Yearly % change (1990-2017)</th>
<th>Global SDI value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>178669278.768251 (154235572.289659 - 203868117.467447)</td>
<td>-1.38%</td>
<td>4135836824.13 (3811339413.89 - 4500759366.83)</td>
<td>1.03%</td>
<td>63492658.0347 (59217728.4013 - 68111097.4995)</td>
<td>0.61%</td>
<td>1017.22 18</td>
<td>-5.48%</td>
<td>0.52</td>
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<td>1991</td>
<td>176211231.975992 (152417710.105072 - 203868117.467447)</td>
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<td>4178680590.28 (3862369247.75 - 4546537194)</td>
<td>1.14%</td>
<td>63879563.7307 (59687506.0553 - 68353071.6295)</td>
<td>0.74%</td>
<td>964.375 95</td>
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<td>1992</td>
<td>171391104.702396 (148048548.745833 - 195423133.839874)</td>
<td>-2.37%</td>
<td>422696642.33 (3911282047.24 - 459488290.47)</td>
<td>1.20%</td>
<td>64354761.6535 (60216614.2833 - 68748674.8797)</td>
<td>0.83%</td>
<td>913.410 15</td>
<td>-5.66%</td>
<td>0.53</td>
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<td>1993</td>
<td>167336245.367074 (144492458.9642 - 190729559.825914)</td>
<td>-2.27%</td>
<td>4278217512.01 (3963190862.66 - 4641663372.13)</td>
<td>1.33%</td>
<td>64893253.9959 (60865663.3427 - 69276193.9801)</td>
<td>1.01%</td>
<td>864.453 62</td>
<td>-5.72%</td>
<td>0.54</td>
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<td>1994</td>
<td>163531094.361715 (141140449.762872 - 185920622.828311)</td>
<td>-2.58%</td>
<td>4335761075.1 (4021226056.65 - 4701326266.54)</td>
<td>1.51%</td>
<td>65553334.1273 (61573352.4542 - 69964587.0143)</td>
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<td>817.651 78</td>
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<td>4402215884.49 (408555694.08 - 4772086653.91)</td>
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<td>66386638.7427 (62353581.3153 - 70879899.7971)</td>
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<td>153873908.661665 (133776006.168749 - 174777925.406401)</td>
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<td>4484297876.71 (416481442.09 - 4861829301.19)</td>
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<td>67510156.653 (63422181.5192 - 72023108.5209)</td>
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<td>1.69%</td>
<td>651.443 02</td>
<td>-6.00%</td>
<td>0.57</td>
</tr>
<tr>
<td>Year</td>
<td>DALYS(COUNT)</td>
<td>Yearly % change 1990-2017</td>
<td>Incidence (COUNT)</td>
<td>Incidence Yearly % change 1990-2017</td>
<td>Prevalence (COUNT)</td>
<td>Prevalence Yearly % change 1990-2017</td>
<td>DALYS Rate per 100,000</td>
<td>DALYS Rate per 100,000 Yearly % change 1990-2017</td>
<td>Global SDI value</td>
</tr>
<tr>
<td>------</td>
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<td>--------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>2000</td>
<td>137477671.468813 (119619790.521677-156919816.875076)</td>
<td>-3.54%</td>
<td>4884897582.21 (4542372128.38-5299281709.2)</td>
<td>1.19%</td>
<td>73265259.8259 (68959087.3693-77779798.8537)</td>
<td>0.95%</td>
<td>614.584 89</td>
<td>-6.03%</td>
<td>0.57</td>
</tr>
<tr>
<td>2001</td>
<td>132617150.351318 (115367283.21441-151733021.850822)</td>
<td>-3.62%</td>
<td>4943837569.91 (459503282.45-5357286521.92)</td>
<td>0.61%</td>
<td>73965543.9256 (69694539.9109-78441687.4816)</td>
<td>0.26%</td>
<td>579.637 5</td>
<td>-6.03%</td>
<td>0.58</td>
</tr>
<tr>
<td>2002</td>
<td>127817914.757423 (112012414.87639-147229894.071081)</td>
<td>-3.55%</td>
<td>4973994368.72 (4629036494.45-5384716718.55)</td>
<td>0.30%</td>
<td>74155996.0217 (70002507.3735-78620590.4761)</td>
<td>-0.09%</td>
<td>546.669 54</td>
<td>-6.00%</td>
<td>0.58</td>
</tr>
<tr>
<td>2003</td>
<td>123279674.410709 (108332371.69601-142012414.87639-147229894.071081)</td>
<td>-2.85%</td>
<td>4988404828.18 (4648432090.04-5396015933.82)</td>
<td>0.25%</td>
<td>7409120.0219 (69913356.1542-78561557.6038)</td>
<td>-0.10%</td>
<td>515.725 85</td>
<td>-5.96%</td>
<td>0.59</td>
</tr>
<tr>
<td>2004</td>
<td>119766167.975616 (105442211.52549-138373762.376267)</td>
<td>-2.49%</td>
<td>5001354629.58 (4663710243.92-5384716718.55)</td>
<td>0.54%</td>
<td>74019231.7028 (69870184.9237-78475500.0168)</td>
<td>0.33%</td>
<td>486.725 57</td>
<td>-5.90%</td>
<td>0.59</td>
</tr>
<tr>
<td>2005</td>
<td>116788626.814903 (102742156.94292-135020314.92497)</td>
<td>-1.64%</td>
<td>5028649926.53 (4687626674.81-5384716718.55)</td>
<td>0.48%</td>
<td>7426281.7028 (7008278.3286-78475500.0168)</td>
<td>0.46%</td>
<td>459.613 66</td>
<td>-5.94%</td>
<td>0.6</td>
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<tr>
<td>2007</td>
<td>112212485.901006 (98809042.04359-130286506.168655)</td>
<td>-1.81%</td>
<td>5059634422.65 (4728264918.95-5447581637.74)</td>
<td>0.18%</td>
<td>7480220.9738 (70621050.1784-79117542.0882)</td>
<td>0.38%</td>
<td>409.127 49</td>
<td>-6.11%</td>
<td>0.61</td>
</tr>
<tr>
<td>2008</td>
<td>110181306.352133 (96998856.458766-127941188.92497)</td>
<td>-1.23%</td>
<td>5068828295.18 (4738222250.22-5452172271.14)</td>
<td>0.59%</td>
<td>7508878.9012 (70889515.0868-79305348.9356)</td>
<td>0.78%</td>
<td>385.583 27</td>
<td>-6.15%</td>
<td>0.61</td>
</tr>
<tr>
<td>2009</td>
<td>108824183.682178 (95897049.061446-126426141.106932)</td>
<td>-1.66%</td>
<td>5099126336.86 (4767508341.72-5485887189.72)</td>
<td>1.36%</td>
<td>7567820.6528 (71431928.8358-79819137.9986)</td>
<td>1.45%</td>
<td>363.240 42</td>
<td>-6.17%</td>
<td>0.62</td>
</tr>
<tr>
<td>2010</td>
<td>107018962.602547 (93454209.9631604-124889985.741479)</td>
<td>-4.95%</td>
<td>5169542216.71 (4833451585.31-5556928325.15)</td>
<td>2.02%</td>
<td>76789507.0786 (72456555.2358-81053303.3758)</td>
<td>2.02%</td>
<td>342.134 92</td>
<td>-6.15%</td>
<td>0.62</td>
</tr>
<tr>
<td>Year</td>
<td>DALYS(COUNT)</td>
<td>Yearly % change 1990-2017</td>
<td>DALYS(COUNT)</td>
<td>Yearly % change 1990-2017</td>
<td>DALYS(COUNT)</td>
<td>Yearly % change 1990-2017</td>
<td>DALYS Rate per 100,000 Yearly % change 1990-2017</td>
<td>DALYS Rate per 100,000 Yearly % change 1990-2017</td>
<td>Global SDI value</td>
</tr>
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<td>------</td>
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</tr>
<tr>
<td>2011</td>
<td>101725967.347824 (89644459.9831456-119068365.99207)</td>
<td>-5.02%</td>
<td>5275902290.88 (4920054852.45-5665447574.68)</td>
<td>2.30%</td>
<td>78374946.7055 (73913067.4149-82791160.1963)</td>
<td>2.31%</td>
<td>322.3187 -6.03%</td>
<td>0.62</td>
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<tr>
<td>2012</td>
<td>96617580.817008 (85160652.2047593-113591584.175086)</td>
<td>-4.94%</td>
<td>5400283887.57 (5025690557.65-5801308983.15)</td>
<td>2.58%</td>
<td>80228490.5323 (75541509.5601-84874468.7924)</td>
<td>2.58%</td>
<td>303.9823 -5.70%</td>
<td>0.63</td>
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<tr>
<td>2013</td>
<td>91843279.9738443 (80612660.6996005-108043934.094889)</td>
<td>-4.56%</td>
<td>5543032980.65 (5152024164.31-5964838486.52)</td>
<td>2.77%</td>
<td>82356346.493 (77356532.7585-87174559.0467)</td>
<td>2.77%</td>
<td>287.5799 -5.48%</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>87650670.122366 (76585397.9347087-103537964.791569)</td>
<td>-4.27%</td>
<td>5700740396.17 (5288676893.47-6146170370.65)</td>
<td>2.90%</td>
<td>84706121.3446 (79257785.5891-89847391.0056)</td>
<td>2.90%</td>
<td>272.6297 -5.34%</td>
<td>0.64</td>
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<tr>
<td>2015</td>
<td>83908966.8746052 (72856397.2085521-99796525.7447586)</td>
<td>-3.06%</td>
<td>5870845742.81 (5439192572.83-6344083193.4)</td>
<td>3.27%</td>
<td>87232204.1209 (81513437.2364-92749672.126)</td>
<td>3.25%</td>
<td>258.80148 0.00%</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>81339102.296204 (70651187.060819-97118555.3102732)</td>
<td>-0.37%</td>
<td>6069024218.27 (5610378301.88-6570441210)</td>
<td>3.56%</td>
<td>90165742.5137 (84064543.7691-96111684.5052)</td>
<td>3.54%</td>
<td>258.80148 -5.20%</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>81039363.8553969 (70120051.7904495-97233423.453799)</td>
<td>0.00%</td>
<td>6292936671.74 (5808374688.14-6816675433.15)</td>
<td>47.22%</td>
<td>93472768.3654 (86857153.63-99961050.1615)</td>
<td>47.22%</td>
<td>246.01081 0.00%</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Overall % change 1990-2017</td>
<td>54.64%</td>
<td>52.16%</td>
<td>47.22%</td>
<td>75.82%</td>
<td></td>
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</tbody>
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