

Infectious diseases as a cause of global childhood mortality and morbidity: Progress in recognition, prevention, and treatment

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Abstract

Child mortality and morbidity are far too high with almost 1% of all children around the world dying each year! Children living in underdeveloped countries (also referred to as “low-income”) and in those areas where crime and military actions are part of everyday life, come under increased threat from disease, starvation, trauma, and death. Infectious diseases are responsible for more than half of childhood deaths and an even greater level of morbidity. This article will review deaths in children, generally in those less than 5 years of age, from pneumonia and other respiratory infections (including bacterial pneumonia, pertussis, viral pneumonia respiratory syncytial virus (RSV), measles, and influenza, tuberculosis (TB), bacterial and viral enteric disease (including enterotoxigenic (ETEC) and enteropathogenic *E. coli* (EPEC), *Shigella*, cholera, infections, rotavirus norovirus, and malaria. Factors influencing disease epidemiology and mortality especially in underdeveloped countries will be noted. Much progress has been made in decreasing infectious disease morbidity and mortality during the last few decades, but much more progress can and should be made. The role of decreasing air pollution, improving sanitation, nutrition, mosquito control, immunization rates, and use of antimicrobial agents will be discussed.

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Introduction

Infectious diseases are a leading cause of morbidity and mortality worldwide. As of 2018, the total worldwide population of children less than 5 years of age was roughly estimated as 700 million. Globally, an estimated 5.6 million of these children died in 2016 [1], almost all of whom (99%) lived in low-and middle-income countries. The leading causes of death vary greatly depending on geographic factors such as location, socioeconomic development, parental education, and political stability. The overall leading causes of death in children less than 5 years of age are: preterm birth complications (18%), pneumonia (16%), intrapartum events (12%), diarrhea (8%), and malaria (5%). Almost 44% of all children die in the first month of their life. More than half of all children (51.8%) die of infectious diseases and

these deaths are concentrated in the first two years of life [2]. In addition to pneumonia, diarrhea, and malaria, the leading infectious disease killers in children worldwide include: tuberculosis (TB), and human immunodeficiency virus infection and disease (HIV/AIDS). Regrettably, measles and pertussis remain on the list of the major causes of infectious disease associated pediatric mortality globally, in spite of the fact that they are vaccine preventable or treatable with antimicrobial agents [3]. The good news is that child mortality has dramatically decreased worldwide since 1950 [4]. The world has made substantial progress in reducing child mortality in the past few decades. Globally, the under-five mortality rate dropped by more than half, from 93 deaths per 1,000 live births in 1990 to 41 in 2017 [2].

It is important to note that accurate specific pediatric infectious disease morbidity and mortality statistics are subject to many serious limitations, particularly in the less developed geographical regions. These limitations include: large differences in case definition and cause of death [5], lack of public health resources including clinics and hospitals, diagnostic laboratory and imaging resources, and the inability to collect regional and national statistics. Attempts to circumvent this problem often involve a variety of statistical modeling techniques. This article will focus on the following infectious diseases in children between one month and five years of age: acute lower respiratory tract infections (ALRI's), predominantly pneumonia and bronchiolitis, including pertussis, RSV, influenza, measles, TB, enteric bacterial and viral (including rotavirus) infectious diseases, and malaria.

Respiratory Infections

An estimated 920 thousand children died in 2015 of lower respiratory tract infections [6]. Pneumonia, as a diagnosis, includes the majority of acute lower respiratory infections (ALRI's), and is the leading cause of mortality in children less than 5 years of age [6]. ALRI's, including pneumonia and bronchiolitis, were attributed to four major etiologies in 2015. The bacterial causes of ALRI's, Pneumococcal pneumonia (pneumococcus) and *Haemophilis influenza* type b (Hib), together accounted for 64% of ALRI deaths in children less than 5 years of age. Respiratory Syncytial Virus (RSV) and Influenza Virus are the first and second most common viral pathogen associated with lower respiratory tract manifestations in children [7]. RSV is present in 22% and influenza virus in 7% of viral ALRI's. The bacteria, *Bordatella pertussis*, and measles virus also generally involve the lower respiratory tract, especially in fatal cases [5,3].

The leading risk factors for pneumonia mortality include: lack of exclusive breast feeding, under-nutrition, indoor air pollution, low birth weight, crowding, lack of access to health care, and lack of measles immunization [5,8]. All of these factors, of course, are characteristics of under developed (aka low-income) nations [5]. Children in these countries are 18 times more likely to die of ALRI's than children who live in developed countries. Interestingly, children who were exclusively breast fed for the first six months of life had a one-third

decrease in acute respiratory infections [9]. Those who were in environments where hand washing was practiced had a one-quarter decrease [9]. Between 2005 and 2015, the number of deaths due to ALRI's decreased by almost 40% [3]. Prevention of infections through better nutrition, control of pollution, and immunization were largely responsible for this decrease. Globally, widespread use with the safe and effective vaccines against pneumococcus, Hib, pertussis, measles, and influenza could further dramatically decrease the burden of childhood mortality from ALRI's. Active attempts to develop a RSV vaccine have been mounted for almost 60 years. The major causes of bacterial pneumonia, pneumococcus and HIB can disseminate throughout the body via the blood stream and cause fulminant disease with subsequent death. However, they are generally treatable with effective antibiotics, especially with early diagnosis, but only one third of children with ALRI's in low income countries received antibiotics [6].

Bacterial Pneumonia

In 2015, global mortality from pneumococcal infections in children between 1 and 60 months of age (without HIV co-infection) was estimated to number 294 thousand and from Hib 29.5 thousand. These estimates include mortality from predominantly pneumonia, and to a lesser extent from meningitis, and sepsis. An estimated additional 23 thousand and one thousand deaths from pneumococcus and Hib, respectively, occurred in HIV infected children. It is important to note that pneumonia itself, is sometimes difficult to diagnose because of subtle clinical signs and difficulty in getting or reading chest X-rays. The difficulty of confirming the microbial etiology of pneumonia cases is well appreciated by clinicians because of the low sensitivity of diagnostic laboratory tests such as cultures. Dramatically decreased mortality between 2000 and 2015 is ascribed to the increasing use of effective vaccines against pneumococcus and Hib [10]. A 46% decrease in pneumococcal mortality in children less than 5 years of age, following the introduction of conjugate pneumococcal vaccine and improvements in HIV care in South Africa is reported [11]. It is important to note the significantly increased susceptibility to and mortality from bacterial infections in children with untreated HIV. An important consideration in

treatment of these two bacterial causes of pneumonia is the general availability of several effective antibiotics, especially when started early in the course of the infection.

Pertussis Infection

Pertussis generally presents in children as a distinct clinical syndrome known as whooping cough, because of its characteristic paroxysmal cough, which has been recognized for over 5000 years. The causative organism *Bordetella pertussis* was identified in 1906. The accuracy of pertussis mortality data in young children is limited by the difficulty of making a microbiologic diagnosis, delayed onset of death, concomitant infections (such as respiratory viruses, measles or malaria), and co-morbidities such as malnutrition (especially in low-income countries) [12]. As is true for many infectious diseases, mortality rates are highest during the first year of life. Young infants, generally under 3 months of age, may have complications including pneumonia, encephalopathy with seizures, and dehydration. These young infants would be expected to be more immunologically naïve since they had no previous contact with pertussis disease or vaccine, unless their mothers had received a dose of pertussis containing vaccine during pregnancy. Infants are also more likely to have viral co-infections diagnosed at the time of pertussis diagnosis [13]. As is to be expected, pertussis incidence and mortality in the undeveloped regions of the world is higher than in the developed regions. A global estimate of pertussis mortality in children less than 5 years of age was reported to be 161 thousand with 86 thousand of these deaths in children under 1 year of age [14].

Pertussis is a disease mediated by a variety of toxins [15]. The bacteria attach to the cilia of the respiratory epithelial cells. They produce toxins that paralyze the cilia, and cause inflammation of the respiratory tract. The clearing of pulmonary secretions is inhibited and with the inflamed respiratory tract coughing occurs. However, some infants never have coughing but manifest with vomiting and apnea. In addition, studies have suggested that the bacteria invade the lower respiratory tract and are present in alveolar macrophages [15]. Pertussis toxins: facilitate bacterial adhesion to respiratory epithelial cells, induce lymphocytosis, alter insulin secretion, and

enhance sensitivity to histamine and other mediators of pulmonary airway sensitivity.

Filamentous hemagglutinin, pertactin, and fimbrial components are bacterial adhesion molecules. They are both important factors in disease pathogenesis and components of the acellular pertussis vaccine [16]. Unlike other causes of ARTIs, pertussis tends to involve the upper respiratory tract with only occasional spread of the bacteria from the upper to the lower tract. Although the clinical symptoms may last for several weeks because of the protracted action of the toxins there is no evidence of chronic infection [15]. It is possible that the persistent clinical symptoms also reflect toxin mediated immune sensitization of the airway in susceptible individuals analogous to reactive airway disease.

Whole cell pertussis vaccine was introduced in industrial countries in the 1940's and widely used by the 1970's. With the global introduction of pertussis vaccine, pertussis deaths have fallen, by nearly 50% [14]. As is the case with naturally acquired pertussis disease, immunity wanes after about 10 years [17] and second or even third episodes of pertussis disease can occur during a person's lifetime. These second and third episodes are generally somewhat less severe. A few years after the introduction of the less reactogenic acellular vaccine, to replace whole cell pertussis in 1997, the incidence of pertussis slowly begun to increase slightly [18,13]. The reasons for this continue to be debated. However, there is no question but that widespread global use of pertussis vaccines can decrease morbidity and mortality dramatically, and that the use of a dose of pertussis vaccine given to pregnant women can reduce the infant mortality even further.

Viral Pneumonia

Clear data concerning the incidence and etiology of viral pneumonia is difficult to obtain because, in addition to the factors noted above, of costly and technically demanding microbiologic diagnostic assays, the common occurrence of dual infectious agents isolated from patients with clinical pneumonia, the discovery of new respiratory pathogens, and the usual lack of fatal cases. RSV and Influenza Virus associated ALRI's, the first and second most common viral pathogens, present often dramatically, with pneumonia and bronchiolitis. RSV and influenza virus manifest with significant

seasonal or epidemic disease clusters and are responsible for 15-40% and 10%, respectively, of microbiologically documented pneumonia. The third, fourth, and fifth most common agents causing ALRI's are respectively: Parainfluenza Virus, Human metapneumovirus, and Adenovirus [5]. Mycoplasma organisms also cause ALRI's but will not be further discussed.

Influenza

Estimates of mortality from influenza respiratory tract infections vary from year to year depending on seasonal variations of influenza disease including epidemics and methodologies of confirming the diagnosis of influenza. It should be noted that influenza has a characteristic but not pathognomonic presentation with rapid onset of high fever, myalgia, cough, rhinorrhea, and headache. Influenza accounts for 7 to 10% of severe ALRI's. Nair and colleagues estimated the global number of new cases of influenza was about 90 million and severe acute respiratory tract disease in young children worldwide in 2008 was one million [6]. Annual mortality estimates range between 28 and 111.5 thousand children less than 5 years of age, depending on seasonal epidemiology and methodology used. Most of the reported cases or severe influenza and death occur in the first year of life [18]. Almost 99% of the deaths occurred in developing countries with case fatality rates 12 times that of developed countries [6]. Influenza mortality in low-income countries is higher than in high-income countries due to access to healthcare, limited health care personnel and facilities, limited access to antivirals and vaccines, and a higher incidence of co-morbidities such as HIV/AIDS [19]. Wide variation from year to year would be consistent with the seasonal variability of influenza subtypes and the associated variability of disease severity, and epidemiology. It is accepted that *Influenza A* is more virulent than *Influenza B* and that pandemics of shifted subtypes are associated with higher global mortality. As might be expected, children less than 5 years of age, who are immunologically naïve to influenza because of the lack of previous natural infection and/or lack of immunization against that season's influenza virus, have a higher attack rate than other age groups, in addition to a higher mortality rate (Rut) [20].

Influenza vaccine was first available in 1957 [21]. The efficacy of influenza vaccines is highly

variable from season to season because of genetic shift and drift of the viral serotypes. This occurs in spite of diligent selection of new vaccine serotypes from season to season to cover the expected serotypes for each new season. If the selected vaccine serotypes are well matched with the actual circulating virus serotypes the efficacy is better. In addition, it has been recently reported that the strains selected for that season may actually mutate in the eggs during the manufacturing process, reducing vaccine efficacy. At best overall influenza vaccine efficacy varies between 40 and 80% from season. It is clear, however, that individuals, including pregnant women who are immunized have less complications, hospitalization rates, and mortality than unimmunized individuals. In addition, influenza immunization provides the benefits of herd immunity decreasing both household and community transmission [19]. Clearly, global efforts to implement routine seasonal immunization for all individuals over 6 months of age would be expected to reduce childhood mortality. The use of antiviral agents in the treatment of influenza is limited by marginal efficacy and development of viral resistance. There is some evidence that prompt institution of the neuraminidase inhibitor oseltamivir can shorten the duration of symptoms and reduce complications, including otitis media in children [19].

The issue of bacterial co/secondary infection has been of interest since before the viral etiology was known. The organism *Haemophilus influenzae* was named when pathological specimens from individuals who died of influenza were examined and these gram-negative organisms were found. Influenza viruses were first isolated in the 1930's [21]. During the great Spanish flu epidemic of 1918-1919, in addition to the very young and old, an unusual number of previously healthy individuals between 20 and 40 years of age (the so called "W" shaped mortality curve) died of severe pneumonia thought to be caused by *Staphylococcus aureus* organisms. A number of studies have implicated *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pyogenes* as organisms responsible for bacterial co/secondary infection in influenza and increased mortality [22]. The majority of studies reported pneumococcus as the single major pathogen responsible for bacterial co/secondary infection in those with influenza [22].

Primary influenza viral pneumonia can be severe and life threatening, with a mortality of 10-20% but is thought to generally be acute and self-limited [23]. High attack rates of severe respiratory disease and pneumonia were seen in children during the 2009 H1N1 pandemic and found to be associated with bacterial infection [23]. It should be noted that antibiotic treatment early in symptomatic influenza could alter the incidence and microbiology of bacterial co/secondary infection in patients with influenza.

Respiratory Syncytial Virus Infections

RSV is a Paramyxovirus related to Parainfluenza Virus and Human Metapneumovirus; there are two clinically important types in humans: A and B. It is the most frequent cause of ALRI's including pneumonia and bronchiolitis in young children (Table 1) [24]. An estimated, 59.6 thousand hospitalized children younger than 5 years of age died from RSV in 2015 [25]. RSV is the second most important pathogen causing death globally (the first being malaria) in infants younger than one year of age [26]. It is important to note that fewer than half of RSV deaths in low-income countries occur in a hospital [26]. Morbidity and mortality of RSV infections tend to be higher in premature infants, in those with chronic lung disease, and in those with congenital heart disease. The airway lumen of a newborn is narrow and the smooth muscle of the airway is more hyper reactive than in the adult [27]. As is true for several viruses, airway lumen structure and airway smooth muscle reactivity explain why RSV is an important cause of exacerbations of asthma. In addition, RSV infection is associated with eosinophilic infiltration of the airways, providing another link to the exacerbation of asthma. RSV has a predilection for replication at the terminal bronchioles and result in exuberant cellular infiltration, viscous mucosal secretions, sub mucosal edema, and loss of ciliated epithelium. These lead to mucous plugging of the small airways with subsequent air trapping leading to the clinical manifestations of bronchiolitis [24].

Prior infection with RSV, especially during the first two years of life may result in antibody production but does not result in persistent immunity. Subsequent re-infection can occur but tends to be less severe [24]. In the early 1960's, the first RSV vaccine was developed and first tried on infants in 1966. It was a formalin-inactivated vaccine and

tragically, it enhanced natural RSV disease. Two infants died in the trial. In spite of: the need for a vaccine against this very common infectious agent and the burden of serious disease in infants, efforts to develop a safe and effective RSV vaccine were understandably delayed. It is hypothesized that an effective RSV vaccine must be able to induce high affinity IgA antibody in respiratory secretions against epitopes on the RSV-fusion glycoprotein [26]. Other potential problems hindering the development of a RSV vaccine include mutational genetic shifts in the RSV subtypes, analogous to those seen with influenza virus, the fact that RSV infection and replication occurs in the external immune compartment rather than systemically, and the fact that the vaccine should be targeted to infants who have immature immune responses. RSV recombinant subunit vaccines are continuing to be developed [26].

RSV specific intravenous immunoglobulin has been fairly widely and successfully used in premature infants and immune deficient individuals for the prevention of RSV infections. It was withdrawn from market when monoclonal anti-RSV antibody became available which can be used intramuscularly. Both products are expensive and not universally recommended. Aerosolized Ribavirin is the only RSV antiviral agent, which has received some use, is. Because of concerns regarding its toxicity to health care personnel, including teratogenicity, its use has become somewhat cumbersome.

Table 1. Global Etiology of Acute Respiratory Infections in Young Children (Piedimonte).

RSV	63%
<i>Mycoplasma</i>	9%
Pneumococcus	8%
<i>HIB</i>	6%
<i>H parainfluenzae</i>	2%
Adenovirus	7%
Influenza virus	5%

Measles Infections

Measles, or rubeola, was first described by Aricenna in the seventh century [28]. It typically

occurred in 3 year cycles during which the number of immune susceptible individuals reached the critical mass to support large outbreaks. In spite of an 84% drop in measles deaths between 2000 and 2016, preventing an estimated 20.4 million deaths worldwide, 90 thousand deaths still occurred, mostly in children, in 2016 [29]. Measles virus is a highly contagious, febrile, exanthema-producing, respiratory virus with a characteristic Koplik's spots) [28]. Measles is usually self-limited but this potentially fatal disease provides lifelong immunity after recovery from the initial infection. Measles virus infection is associated with infection of the upper and lower respiratory epithelium (particularly the alveolar macrophage) followed by viremia and systemic spread (to dendritic cells in the dermis and systemically to lymphoid cells), including to the brain and gastrointestinal tract [30]. Measles virus is immunosuppressive which can lead to bacterial super-infection, including pneumonia, a leading cause of measles associated mortality. Diarrhea and dehydration can also be a dangerous complication especially in low-income countries. Malnutrition, HIV/AIDS, and vitamin A deficiency are associated with more severe disease in these low-income countries where 95% of global measles deaths occur [29]. In spite of the availability of a safe and highly effective measles vaccine since 1963 and its near elimination of this disease in the US and most of the Americas, measles remains a major killer of young children globally. Although there are genotypic mutations of wild measles, it does not seem to have the same virologic and immunologic implications that mark influenza. Mothers who have recovered from wild type measles infection generally provide protective levels of transplacental antibody after 27 weeks gestation that lasts until the newborn is 12 to 15 months old and may block the efficacy of measles vaccine given to an infant for that time. Lesser and unquantifiable transplacental protection is provided by immunized mothers. Therein is the basis for the recommendation for routine infant immunization at 12 to 15 months of age, except during outbreaks when the recommendation is to start measles immunization at 6 months of age. A decade ago an unethical scientist published fraudulent data linking autism with measles immunization. This resulted in dramatically increased vaccine hesitancy and refusal, leaving those individuals and their unimmunized contacts susceptible to outbreaks of

measles disease. As is often the case, such setbacks affect immunization rates for an uncomfortably long period of time with the danger of harm to innocent unimmunized individuals in their surrounding communities. There are no antiviral agents recommended for the treatment of measles. Vitamin A is recommended worldwide, especially for all individuals with measles and reportedly can reduce mortality by 50% [29].

Tuberculosis Infections

Tuberculosis infections are responsible for more global deaths than any other infectious disease. It is estimated that 10-15% of cases in TB endemic areas occur in infants and young children, who are especially susceptible to developing severe or disseminated tuberculosis. However, global TB mortality is a factor in all age groups. TB is estimated to have killed 191 thousand children less than of 5 years of age in 2015, with the majority (70%) occurring in Southeast Asia and sub-Saharan Africa, where the human immunodeficiency virus epidemic continues unabated. HIV co-infection in children with TB increases the mortality due to TB; HIV infected children less than 5 years of age accounted for 27% of deaths from TB in the low-income countries. Most of these children were not on treatment [31]! TB is an unfortunate example of a disease of poverty, with the majority of cases and deaths occurring among poor and marginalized people in low-income countries. Weak health systems hinder efforts to stop the spread of TB and to treat those already infected. And even when people get treatment, the first-line drugs may not work because of multidrug-resistant TB, a growing problem. Indeed, TB is the leading infectious cause of death in individuals of all ages worldwide and a top ten cause of death in children [31].

There has been considerable improvement in global TB statistics; the TB mortality rate (per 100,000 population) fell by 37% between 2000 and 2016. The accuracy of the mortality statistics in young children is limited by the difficulty of obtaining diagnostic specimens. The use of molecular diagnostic blood tests may help resolve this problem in those countries where this technology can be made available. Household contact investigation can reveal infected children. However, only 7% of young child contacts received preventive antimicrobial treatment in 2015 [31]. The number of household contacts less than 5 years

of age, reported to have been started on TB preventive treatment, increased by 85% between 2015 and 2016 (from 87,242 to 161,740). This was still only 13% of those estimated to be eligible [32]. Most importantly, as noted above, far too many children with TB never received any appropriate antimicrobial treatment for their TB! An estimated 50% of children less than 5 years of age fall into this group [33]. Additionally, HIV infected children should receive antiretroviral treatment (ART) for the HIV infection in addition to that for TB but most do not. Pregnant women should also receive ART to decrease mother-to-child HIV transmission. BCG vaccination should be provided as part of national childhood immunization programs, as indicated by a country's TB epidemiology. In 2016, 154 countries reported providing BCG vaccination as a standard part of TB prevention programs; 111 countries reported coverage above 90% [32]. Finally, treatment of latent TB infection is critical to the control and elimination of TB infection. It is now easier to treat latent TB with once-weekly isoniazid and rifapentine for 12 weeks, preferably using directly observed administration of the medications [34].

Enteric Infections (Diarrheal Diseases)

Diarrhea is a leading killer of children, second only to pneumonia, accounting for approximately 8% of all deaths among children less than 5 years of age, worldwide, in 2016. This translates to an estimated 480 thousand children dying in 2016, despite the availability of rotavirus immunization, water purification, effective oral rehydration regimes, and effective antimicrobial treatment. An estimated 25% of the deaths from diarrhea occur among children living in South Asia and sub-Saharan Africa. These deaths are attributed to enteric infections [35]. As is true for almost all of the causes of global infectious disease mortality, the burden is highest in children under two years of age and in low-income countries. More than half of these deaths occur in children less than 5 years of age and were attributed to rotavirus, EPEC, calcivirus, and ETEC [36].

The lack of access to sophisticated diagnostic capabilities has hindered the ability not only to target treatment but also to ascertain the full epidemiology of diarrheal disease. Historically, studies of enteric pathogens have focused on those with diarrhea, which is under reported, even in

developed countries [37]. A high burden of enteric pathogens in the underdeveloped countries is common, even in the absence of diarrhea. This represents another confounding problem in determining the burden of diarrhea and enteric infection because enteropathogenic organisms are isolated from 83% of children with diarrhea and from 72% of "well" children [37,38]. Continual challenge by pathogens, in conjunction with an inadequate diet, stimulates an inflammatory response that alters the structure of the intestines, alters metabolic and immunological pathways, and changes the microbiome, thus explaining some of the pathogenesis of enteric infections. Both diarrhea and enteropathogen infections have been associated with reduced growth and cognitive development as well as impaired responses to immunization [37].

Despite this heavy toll, progress is being made. One of the major causes of death in individuals with diarrheal diseases is severe dehydration progressing to shock. In 1968 an article was published reporting dramatic results with the use of an oral rehydration solution (ORS) in those cases where iv treatment was not available for those patients with life threatening cholera diarrhea [39]. The concentration of glucose and electrolytes in the ORS and the observation that stool losses had to be replaced cc for cc is responsible for its success [40]. A second observation was that individuals sick with severe diarrhea could and should be carefully fed orally to aid in the healing of the injured bowel epithelium. From 2000 to 2016, the total annual number of deaths from diarrhea among children less than 5 years of age, decreased by 60%. Sadly however, in 2016 in spite of the dramatic successes of ORS in severe diarrhea due to a variety of causes, only 45% of young children were offered this life-saving treatment [40].

Many more children could be saved through basic interventions including water purification, improved nutrition, increased breast feeding of infants, improved hygiene and sanitation, improved molecular diagnostic technology, use of rotavirus and measles vaccine, use of oral rehydration and more effective antimicrobials, used judiciously [35]. Of interest is the finding that a significant proportion of mortalities from childhood diarrheal disease actually occurred after discharge from clinic/hospital, most often in younger children. This is at odds with the traditional conception of diarrhea-related mortality being closely tied to

dehydration and hypovolemic shock (this finding is left unexplained). The children in this study were statistically more likely to have had infection with *enteropathogenic Escherichia coli* (EPEC), *Enterotoxigenic E. coli* (ETEC), and *Cryptosporidium* [35].

When stool specimens from the original study were re-analyzed using highly sensitive quantitative polymerase chain reaction (PCR) methods, it was found that the leading pathogens causing diarrhea in young children were (in descending order), *Shigella* spp., rotavirus, adenovirus 40/41, ETEC, *Cryptosporidium* spp. and *Campylobacter* spp. [35].

Viral Enteric Infections

Rotavirus is the most common cause of acute gastroenteritis in children, both in upper, middle, and lower income countries. In 2016 it causes 30% of diarrheal deaths in children less than 5 years of age; resulting an estimated 129 thousand deaths [41], mostly in children under the age of 2 years [38]. Other diarrhea producing viral pathogens isolated from hospitalized children, less than 5 years of age include: adenovirus, norovirus, calcivirus, and astrovirus [36]. More than 85% of rotavirus deaths occur in low-income countries in Africa and Asia [35]. Rotavirus is very infectious, transmitted by fecal-oral route, usually however, spread by direct contact rather than in water or food, and therefore, improvements in water quality are unlikely to have significant impact on transmission [42].

The development of rotavirus vaccines has dramatically decreased morbidity and mortality in those areas where they are used. In the US, its success was so dramatic that currently norovirus is the leading cause of medically attended gastroenteritis. Regrettably, for unexplained reasons, the rotavirus vaccines are not as effective in low-income countries [35]. Nonetheless, diarrhea-associated mortality in children less than 5 years of age has decreased 65% because of improvements in the availability of safe water, sanitation, and improved nutrition. The decreases could be greater if more than the current coverage rates globally of 15% were accomplished [41]. This disappointing coverage level in low-income countries, the remaining appreciable burden of rotavirus deaths in these same countries, as well as the estimated 7% of diarrheal episodes in children less than 5 years of

age in the US and 10% in Canada all suggests that there is still more improvement of rotavirus vaccine possible [41].

Currently, the second most common cause (18%) of all diarrheal disease is norovirus, which is estimated to result in 70 thousand deaths annually. As is true for all enteric infections, norovirus deaths occur mostly in children less than 5 years old in developing countries. Norovirus, which includes the Norwalk virus is in the calcivirus family, is a ubiquitous virus with similar incidence of disease in high, middle, and low-income countries. Norovirus is extremely contagious, is transmitted by the fecal-oral route as well as by contaminated water and food but seems to cause a milder disease than rotavirus [43]. Estimates of the burden of norovirus disease is fraught with difficulty because: laboratory diagnostic testing is difficult even in high-income countries, reinfection is common, the virus is shed for weeks following an episode of diarrheal disease, and the virus can be isolated from healthy asymptomatic individuals [43]. Other enteric viruses include astrovirus and adenovirus which together may account for 7% of global deaths in children less than 5 years of age [36].

Bacterial Enteric Infections

Enterotoxin producing *Escherichia coli* (ETEC) and *Shigella* species are a major part of the burden of bacterial enteritis [35]. In addition, *Enteropathogenic Escherichia coli* (EPEC), *Vibrio cholerae*, *Salmonella* spp., and *Campylobacter* spp. as well as three parasites: *Cryptosporidium* spp., *Entamoeba histolytica*, and *Giardia lamblia* are also on some lists of non-viral pathogens [34] (these latter three will not be further discussed in detail). There is a concern that current interventions of viral enteritis (oral rehydration, continued feeding, and Zinc) will not be effective in treating disease caused by parasitic pathogens [38]. In addition, antibiotic resistance to these bacteria is a growing problem. As compared to the percentage of viral enteric pathogens causing death of children less than 5 years of age (42%) and the estimated number of 422 thousand deaths, the 6 most common bacterial pathogens cause 27% of deaths in young children for a total estimated number of 275 thousand deaths (Table 2). It should be noted that the childhood mortality estimates vary widely from author to author depending on many factors: global locations included, year of estimate,

diagnostic methods, modeling parameters, etc. Most of the bacterial diarrheal disease is a result of contaminated food and water. Cholera is manifest with profuse watery diarrhea and untreated, can result in death within hours. Cholera outbreaks can spread rapidly and require aggressive attention to sanitation, hygiene, and water treatment [44]. A combined ETEC and Shigella vaccine is reported to be close to approval. Three cholera vaccines have been tested and found to give as high as 77% protection after two years and 65% protection after 5 years. A fourth FDA approved oral Cholera vaccine is used in adults traveling to Cholera affected areas. It is estimated that herd immunity with 50% coverage could prevent transmission in endemic areas [35].

Guidelines for acute diarrheal diseases without blood in the stool, have cautioned against the use of antimicrobials in children.

Antibiotics effective against Shigella are recommended for these children who have bloody stools. There is some evidence that use of narrow spectrum antibiotics targeted against sensitive organisms cultured from stool in severe cases of enteritis can improve outcomes [35].

Table 2. Global Estimates of Infectious Disease Mortality in Young Children*.

All infectious diseases	700 million
Respiratory infections	704 thousand [4]
Bacterial pneumonia	324 thousand [10]
Pertussis	161 thousand [14]
Viral pneumonia	
Influenza	28-112 thousand [7]
RSV	60 thousand [25]
Measles	63 thousand [4]
TB	191 thousand [31]
Enteric infections	499 thousand [4]
Viral enteric infections	422 thousand [36]
Rotavirus	272 thousand [36]
Calicivirus (norovirus)	98 thousand [36]

Astrovirus and Adenovirus	52 thousand [36]
Bacterial enteric infections	275 thousand [36]
EPEC	109 thousand [36]
ETEC	59 thousand [36]
Shigella	38 thousand [36]
Camphylobacter	31 thousand [36]
Salmonella	25 thousand [36]
Cholera	13 thousand [36]
Malaria	306 thousand [35]

*Statistics do not always add up, depending on methodology and year of estimates.

Malaria

Malaria is a systemic disease caused by plasmodium and transmitted by the female anopheles mosquito found mainly in tropical areas around the world, specifically in sub Saharan Africa (90%), Asia, and Latin America, and to a lesser extent in blood transfused from an infected individual. *Plasmodium falciparum* is the most severe of the four causative plasmodium organisms. In 2015, malaria globally accounted for 5% of deaths in children less than 5 years of age and in 10% in sub Saharan Africa. In 2016, there were 216 million malaria cases that led to 440,000 deaths. Of these about two thirds (306 thousand) were in children less than five years of age, with 91% of the deaths in sub Saharan Africa [45]. Malaria in pregnant women is associated with stillbirths, abortion, infant mortality and low birth weight [46].

Recurrences of malaria can be associated with recrudescence when symptoms return after a symptom free period due to ineffective treatment. Relapse occurs when parasites are cleared from the blood but reactivate in the liver cells. Reinfection reflects the incomplete immunity associated with an episode of malaria that allows for a subsequent second or third malaria infection. Relapse with *P. vivax* has been described to occur years after the initial symptomatic infection. Today, 3.2 billion (almost half of the world population) are at risk. Despite this heavy toll, major inroads have been made against the disease. Since 2010, mortality rates among children less than five years of age

have fallen by 34% [45]. This has been accomplished, in part, as a result of stepped-up funding and programming, draining and spraying (mosquito control) of low-lying swampy areas where the mosquitoes breed, the adoption of sleeping under insecticide-treated mosquito nets, particularly under long lasting insecticide treated nets, on a regular basis. The use of these nets is one of the most effective ways to prevent malaria transmission and reduce malaria related deaths. However, household ownership of mosquito nets is uneven across countries in the region, with an average coverage of 66 per cent in the countries of sub-Saharan Africa; ranging from less than 30 per cent to approximately 90 per cent [45].

In addition, an obvious factor in decreasing mortality is the use of effective treatment. Artemisinin-based combination therapy (ACT) is the most effective antimalarial therapy for *P. falciparum*, the most lethal malaria parasite and the one most pervasive in sub-Saharan Africa. Regretfully, only a relatively small proportion of children treated for malaria were actually receiving ACT. Other less effective antimalarial drugs are still commonly used. In 2015, the median proportion of children less than 5-years of age with evidence of recent or current *P. falciparum* infection and a history of fever who received any antimalarial drug was only 30% [45]. Although extensive efforts to develop a vaccine against malaria have been attempted during the past several decades, none has yet been totally successful.

Conclusion

Too many children are still dying from preventable and/or treatable infectious diseases. This burden is greatest in children less than 5 years of age and in underdeveloped, low-income countries. Table 1 lists the global etiology of acute respiratory infections in children less than 5 years of age and Table 2 lists global estimates of infectious disease mortality in children less than 5 years of age.

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