

The global burden of vaccine preventable infectious diseases in children less than 5 years of age: Can we do better?

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Abstract

Globally an estimated 700,000 children under 5 years of age die of vaccine preventable diseases each year! Almost 99% of children who died lived in low-and middle-income countries. The leading risk factors for mortality include: lack of exclusive breast feeding, poor nutrition, indoor air pollution, low birth weight, crowding, poor hygiene, lack of access to health care, and most importantly lack of immunizations. Accurate specific pediatric infectious disease morbidity and mortality statistics are subject to many serious limitations, particularly in the less developed geographical regions (i.e., low-income). The major pathogens responsible for these deaths include: *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Bordetella pertussis*, influenza virus, measles virus, and rotavirus. Issues regarding, the burden of disease mortality, disease transmission, available vaccines, as well as vaccine successes and shortcomings for specific pathogens are discussed. Although much success in preventing these childhood deaths has been made globally, much remains to be done.

Citation: Frenkel LD (2020) The global burden of vaccine preventable infectious diseases in children less than 5 years of age: Can we do better? *Adv Pediatr Res* 7:40. doi: 10.35248/2385-4529.20.7.40

Received: May 07, 2020; **Accepted:** May 18, 2020; **Published:** May 25, 2020

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Competing interests: The authors do not have any competing interests.

Acknowledgments: The author would like to thank Dr. Fernando Gomez for editing the manuscript.

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Introduction

Infectious diseases are a leading cause of morbidity and mortality worldwide. As of 2018, the total world population of children less than 5 years of age was roughly estimated at 679 million [1]. Globally, an estimated 5.3 million of these children died in 2018 [2], with an estimated 700,000 dying from vaccine preventable infectious diseases (Table 1); 99% of the children who died, lived in low-and middle-income countries. Of these 5.3 million children, almost half die in their first month of life and many of the rest die during the first two years of life. A major cause of mortality in these children is a result of infectious diseases. Inspired by a recent review of global childhood mortality from infectious diseases [3] and the success of global elimination of two of the three strains of poliovirus responsible for decades of pandemic disease [4], the author undertook a review of the current status of

the major vaccine preventable infectious diseases worldwide. The focus of this article will be on six of these which remain significant causes of mortality and for which vaccines afford proven preventive success: Pneumonia (and to a lesser extent, meningitis and sepsis), caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b; disease caused by *Bordetella pertussis*, influenza virus, and measles virus; and enteritis caused by rotavirus.

Table 1: Pathogen specific global estimates of annual vaccine preventable infectious disease deaths in children between 1 and 59 months of age.

Causal organism	Number of Deaths and date of estimate	Reference
<i>Streptococcus pneumoniae</i>	294,000 - 2015	[7]

<i>Haemophilus influenzae type b</i>	29,500 - 2015	[7]
<i>Bordetella pertussis</i>	161,000 - 2014	[14]
Influenza virus	28,000-111,500 Year to year variation	[7]
Measles virus	74,015 - 2016	[38]
Rotavirus	215,000 - 2016	[50]

Methodology

Accurate specific pediatric infectious disease morbidity and mortality statistics are subject to many serious limitations, particularly in the less developed geographical regions (i.e., low-income). These limitations include: differences in case definition of the cause of death, lack of public health resources (including clinics, hospitals, diagnostic laboratories, imaging resources, and pathology), overlapping symptoms, and the inability to collect regional and national statistics [5]. It is clear that global child mortality is decreasing. Globally, the under-five years-of-age mortality rate dropped by more than half, from 93 in 1990 to 39.1 deaths per 1,000 live births in 2017 [6]. Much of this decrease is due to worldwide immunization efforts but there is still much to do.

Streptococcus pneumoniae and Haemophilus influenzae type b

Bacterial and viral acute lower respiratory tract infections (ALRIs) are the leading cause of childhood infectious disease mortality [7]. These generally manifest as pneumonia or bronchiolitis. *Streptococcus pneumoniae* and *Haemophilus influenzae* type b 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 pathogens associated with ALRI in children [7]. RSV is present in 22% and influenza virus in 7% of viral ALRIs [7]. *Bordetella pertussis* bacteria, influenza virus, and measles virus also may involve the lower respiratory tract.

In 2015, global mortality from *Streptococcus pneumoniae* (pneumococcal) infections in children between 1 and 59 months of age (without human immunodeficiency virus (HIV) co-infection) was

estimated to number 294,000 and from *Haemophilus influenzae* type b (Hib) 29,500 [8]. Most children who died of pneumococcus had pneumonia (81%), 12% with meningitis and 7% with sepsis [8]. It should be noted that confirming the diagnosis of pneumonia, is sometimes difficult because of subtle clinical signs and difficulty in getting or reading chest X-rays. This is a potential source of error in the numerical estimates of this diagnosis as is the difficulty of confirming the microbial etiology of pneumonia cases. Additionally, as is well appreciated by clinicians, the low sensitivity of diagnostic laboratory tests such as cultures further limits the ability to diagnose the etiology of pneumonia.

The leading risk factors for pneumonia mortality include: lack of exclusive breast feeding, undernutrition, indoor air pollution, low birth weight, crowding, lack of access to health care, and lack of immunization [9]. 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].

The dramatically decreased global mortality between 2000 and 2015 is ascribed to the increasing use of safe and effective vaccines against pneumococcus and Hib [10]! In the United States (US), the use of pneumococcal conjugate vaccines (PCV7 and 13) dramatically decreased the incidence of invasive pneumococcal infections, caused by vaccine serotypes [11]; the 13-serotype pneumococcal conjugate vaccine reduced the incidence of pneumococcal bacteremia by 95% in children between 3-months and 3-years of age [12]. Furthermore, even after seven years of use of PCV13 pneumococcal conjugate vaccine in the US, the protection against pneumococcal pneumonia seems to be unaffected by any emergence of non-vaccine serotypes [13]. Remarkably, in the United States and in other countries the widespread use of HIB vaccine has essentially eliminated invasive disease due to this pathogen. The increased global use of the 13-serotype pneumococcal and HIB conjugate vaccines should further decrease the global mortality from pneumococcal infections.

Pertussis

The causative organism of pertussis is *Bordetella pertussis*. This disease is very contagious and is spread via respiratory secretions. It generally presents in children as a distinct clinical syndrome also known as whooping cough. A global estimate of pertussis mortality in children less than 5 years of age in 2014 was reported to be 161,000 with 86,000 of these deaths in children less than 1 year of age [14,15]. The accuracy of pertussis mortality data in young children, in low-income countries, is limited by the difficulty of making a microbiologic diagnosis, the delayed onset of death, concomitant infections (such as with other respiratory viruses, measles, or malaria), and co-morbidities such as malnutrition [16].

Young infants, under 3 months of age, have smaller airways and the highest incidence of complications including pneumonia, encephalopathy with seizures, dehydration and death [17]. In addition, they would also be expected to have received less transplacental pertussis antibody from their mother during gestation unless their mothers received the currently recommended pertussis-containing vaccine during pregnancy [18]. A third reason for higher morbidity and mortality in infants is that they are more likely to have viral co-infections diagnosed at the time of the pertussis diagnosis [15,18]. It should be noted that pertussis vaccine is generally recommended at 2, 4, and 6 months of age.

Whole cell pertussis vaccine was introduced in developed countries in the 1940's and widely used in them by the 1970's [4]. With the global introduction of whole cell vaccine, pertussis deaths fell dramatically [16,19]. In the US, the number of reported pertussis cases per year decreased from a high of 250,000 to a low of 1,000 in the late 1980's. This whole cell pertussis vaccine was only moderately effective and was associated with a small incidence of febrile episodes and seizures, especially in young infants.

Neither natural pertussis infection nor immunization produces lifetime immunity [20]. Pertussis immunity wanes about 10 years after either natural infection or immunization [21]. Second or even third episodes of pertussis disease can occur during a person's lifetime after either naturally acquired infection or immunization. Evidence indicates that the switch from the more

reactogenic whole cell vaccine to the acellular vaccine in 1997 was largely responsible for an increase in pertussis cases [21]. Immunity wanes (the risk of pertussis infection increases) with each year after receipt of the fifth dose of DTaP vaccine [21]; vaccine effectiveness decreases from 95% to 71%. Recent data however, suggests that disease resurgence may also be due to genomic changes in the *Bordetella pertussis* organisms [22]. Although the most effective pertussis vaccine is not yet available, broad use of the current acellular vaccine is the best chance of reducing global childhood mortality from this disease.

Influenza

Influenza is easily transmitted via respiratory secretions and is characterized by global pandemics. It has a characteristic but not pathognomonic presentation with rapid onset of high fever, myalgia, cough, rhinorrhea, and headache [23,24]. Influenza accounts for 7 to 10% of severe ALRIs and has an appreciable but variable mortality [7]. Annual global mortality estimates, in children less than 5 years of age, range between 28,000 and 111,500, depending on seasonal epidemiology and methodology used [7]. Almost 99% of these deaths occur in low-income countries with case fatality rates greater than in high-income countries [7]. This is, in part, due to limited access to healthcare, limited health care personnel and facilities, limited access to antivirals and vaccines, and a higher incidence of co-morbidities such as tuberculosis and HIV/ AIDS (acquired immunodeficiency syndrome) [25].

Influenza virus evolves rapidly because of the high mutation rate associated with its multi-segmented genome, resulting in changes in the viral antigens (hemagglutinin and neuraminidase) against which host immunity and vaccines are targeted [26] with consequential variations in mortality. Genomic shifts are associated with a major change in the surface antigens and may result in global pandemics. A drift occurs when the genetic change results in only a minor antigenic change [4]. It is accepted that influenza A is generally more virulent than influenza B. Children less than 5 years of age, who are immunologically naive 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 and mortality than other age groups [23].

Inactivated influenza vaccine (IIV) was first available in 1957 [27]. The cold adapted live attenuated vaccine (LAIV) was licensed in the US in 2003 [28]. Regrettably, after several years of apparently good effectiveness, LAIV was no longer associated with acceptable protection against influenza disease [29,30]. The cause of this decreased efficacy of LAIV remains unclear but efforts to resolve this problem are being aggressively pursued and may have been resolved by the manufacturer in 2018 [31].

Efforts to develop new, safe, and more effective “universal” influenza vaccines are actively proceeding [32]. These efforts are meant to produce a vaccine, which will eliminate the necessity of developing seasonal reformulated vaccines for the drifted and shifted influenza viruses. Influenza vaccine effectiveness generally ranges between 10% and 60% depending on season; geographical region studied, and serotype matching. Strain mutations may even occur during the season after the vaccines are formulated and released for use around the world. In addition, it has been recently reported that the strains selected for that season may actually mutate in eggs during the manufacturing process, reducing vaccine efficacy [33].

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 [34]. Clearly, global efforts to implement routine seasonal immunization for all individuals over 6 months of age and maternal immunization [18] would be expected to reduce infant and childhood morbidity and mortality. High attack rates of severe respiratory disease including pneumonia were seen in children during the 2009 H1N1 pandemic [35]. Although pandemic influenza strains are usually associated with more severe clinical disease, some of the reported excess mortality in pandemics is thought to also be a result of secondary bacterial infections [35,36]. This would suggest that immunization against pneumococcus and HIB might also reduce pediatric morbidity and mortality associated with influenza infection. Regardless, influenza vaccine remains key to the global reduction of vaccine preventable mortality in children.

Measles

Measles, or rubeola, is a highly contagious illness. The causative virus is spread via respiratory secretions and the virus can infect exposed individuals not only in the same room but also via the air handling system from one room to another. Measles disease is manifest with a characteristic clinical presentation, including an erythematous macular heterogeneous rash, high fever, malaise, and an oral enanthema (Koplik spots) [37]. In spite of the availability of a safe and highly effective measles vaccine since 1963, measles remains a major killer of unimmunized young children globally with an estimated 74,015 deaths in children under 15 years of age in 2016 [38]. Measles provides lifelong immunity after recovery [4]. In the absence of “herd immunity” resulting from either natural infection or immunization, measles typically occurred in 3-year cycles during which the number of immune susceptible individuals reached the critical mass to support large outbreaks [4]. Measles virus is immunosuppressive which can lead to secondary bacterial infections, with bacterial pneumonia being a leading cause of measles associated mortality. Malnutrition, HIV/AIDS, and vitamin A deficiency are associated with more severe disease [39].

An 84% drop in measles deaths between 2000 and 2016 prevented an estimated 20.4 million deaths worldwide! This decrease illustrates the possibility of the worldwide elimination of measles disease with the optimal uptake of measles vaccine. Mothers who have recovered from wild type measles infection generally provide protective levels of transplacental antibodies after 27 weeks gestation; this lasts until the newborn is 12 to 15 months old. Unfortunately, this maternal gift of antibodies may block the efficacy of measles vaccine up to a year of age. Therein lies the basis for the recommendation for the first measles immunization dose be given between 12 and 15 months of age, except during outbreaks when the immunization can be given as early as 6 months of age [37,40]. Lesser and unquantifiable transplacental protection is provided by immunized mothers. Genotypic mutations of wild measles virus are unusual and do not have the same implications that mark influenza virus [41].

A decade ago an unethical scientist published fraudulent data linking autism with measles

immunization [42,43]. This resulted in dramatically increased measles vaccine hesitancy and refusal, especially in high-income countries, leaving those individuals and their unimmunized contacts susceptible to community wide outbreaks of measles disease. As is often the case, such setbacks affect immunization rates for an uncomfortably long period of time. Regretfully in the US, this has now resulted in a markedly elevated number of outbreaks in religious communities where parents have refused to allow their children to be immunized [4]. These cases might threaten the celebrated “elimination” of measles in the US in 2000 [44]. The one potential positive result of this situation is that it may lead to the elimination of non-medical exemptions for immunizations prior to preschool and school attendance [45,46].

Rotavirus

Rotavirus is recognized as the most common cause of acute gastroenteritis [47,48]. Rotavirus is very infectious; it affects children in upper, middle, and lower income countries reflecting the usual transmission from a symptomatic child to another immune susceptible child, rather than by food and water [48]. Therefore, improvements in water quality are unlikely to have a complete impact on transmission. Prior to the widespread global introduction of rotavirus vaccine, the estimate of global deaths in children under 5 years of age in 2008 was 453,000 [49]. In 2016 the estimate of deaths declined to 128,500 [50]. By 2016 rotavirus caused 30% of diarrheal deaths in children less than 5 years of age, resulting an estimated 1.5 million hospitalizations and 128,500 deaths [50]. These deaths occur mostly in children under the age of 2 years. More than 85% of rotavirus deaths continue to occur in low-income countries in Africa and Asia secondary to limited health care resources [50]. However, deaths also occur in unimmunized children in the high-income countries [50].

The development of two live attenuated recombinant rotavirus vaccines since 2006 have dramatically decreased morbidity and mortality in those countries where they are used currently preventing an estimated 44% of rotavirus deaths per year in children less than 5 years of age [51]. The finding of ‘herd immunity’ for non-vaccinated children was a surprising, but welcomed, “side effect” [52] and may contribute to the high efficacy of these vaccines in high-income countries.

Regretfully, for unexplained reasons, the rotavirus vaccines are not as effective in low-income countries [53,54]. Malnutrition, zinc deficiency, vitamin deficiency, co-infections, differences in gut microbiota, and genetic factors may all play a role [54]. The decreases could be greater if more than the current global coverage rates of 15% were accomplished [50]. The disappointing coverage level in low-and high-income countries suggests that improvement from increased rotavirus vaccine use is possible [50-54].

Discussion and Conclusion

It is estimated that more than 700,000 children around the world die from vaccine preventable infections each year. There are several basic reasons why this occurs. One, which is particularly important in underdeveloped nations, is the lack of public health resources to buy and administer vaccines or to mount other basic disease prevention efforts. A second, and especially sad, reason is when misinformed parents, or populations in conflict areas, block immunization efforts. The third is the lack of acceptable efficacy of some immunizing agents. Major efforts on the part of international organizations and inspired national programs to bring resources to bear on immunization efforts have allowed for much progress but much more has to be done. Efforts to educate parents and populations in conflict have been of limited success. The development of more effective vaccines and legislative efforts to mandate immunizations for school and child care attendance offer some promise.

Be aware that childhood immunization rates have dramatically decreased in the US during the COVID 19 pandemic [55]. It is likely that funding available for childhood immunizations will be less available in the less developed nations because of the economic costs of the pandemic.

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