

DOI: 10.21767/2572-5483.100007

Potential Reduction of Mortality from Invasive Pneumococcal Infection among Children with Sickle Cell Disease in Haiti

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Rec date: Dec 16, 2015 Acc date: March 01, 2016 Pub date: March 07, 2016

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Abstract

Main problem background: Acute lower respiratory illness is the most common cause of death among children less than 5 years of age in Haiti. Because children with Sickle Cell Disease (SCD) have a very high risk of contracting invasive pneumococcal infection which may lead to bacteremia and pneumonia, childhood mortality among children with SCD will be significantly higher if they are not diagnosed and receive penicillin prophylaxis and appropriate immunizations. Currently, Pneumococcal 13-valent Conjugate Vaccine (PCV13) is not routinely given to any children in Haiti.

Importance: The institution of newborn screening and the routine administration of PCV13 in Haiti should decline the mortality of all children, and in particular the mortality of children with SCD.

New finding insights: There is no newborn screening program in Haiti. Limited data suggest that 1 in 173 children born in Haiti will have SCD. We will implement a newborn screening program in Cap-Haïtien, the second largest city in Haiti, with the purpose of identifying the children with SCD, and assuring they are vaccinated with PCV 13 and receive penicillin prophylaxis. Our hypothesis is that children who are identified through newborn screening with SCD will have a lower mortality rate compared to national statistics.

Conclusions: Newborn screening coupled with PCV13 and penicillin prophylaxis will reduce the mortality of infants with SCD as compared to national infant death statistics in Haiti.

Main Problem Background

Lower respiratory infection was the first and the second cause of death in the world in 1990 and 2013, respectively. In 2013, 2.7 million people died from this cause alone [1]. Young children are particularly affected by pneumonia when they are unprotected from infectious pathogens in developing countries. The World Health Organization estimates that 922,000 children less than age 5 died from pneumonia in 2015. *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia in children [2].

Information about the burden of lower respiratory infection in Haiti is limited, but it seems to be significant. A study at the Albert Schweitzer Hospital in Artibonite, Haiti, revealed that the most common cause of death (45%) in children less than 5 years of age was acute lower respiratory illness [3]. Currently, the GABRIEL Network, a multi-center case-control study, plans to elucidate the specific infectious etiologies for pneumonia among 1000 children less than 5 years of age in 9 low-income countries including Haiti [4]. Thus the GABRIEL Network will shed more light about the specific pathogens which cause pneumonia in Haiti.

Immunizations are key in order to reduce the risk to contract pneumonia and other infections. However, there is an unfortunate disparity that limits the access to immunizations which could prevent common communicable diseases in some developing countries. Whereas in developed countries, diphtheria, pertussis, tetanus, measles, mumps, rubella, polio, hepatitis A and B, varicella, *Haemophilus influenzae* and *pneumococcus* are routinely prevented, in resource-poor settings, not only is the immunization package offered considerably less extensive, but the penetration of immunization programs is much less. In Haiti, for example, the immunization package currently includes the pentavalent vaccine against diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b, but does not routinely include anti-pneumococcal vaccination. This omission should significantly impact the number of pneumonia cases by pneumococcus. Although Pneumococcal 13-valent Conjugate Vaccine (PCV13, Prevnar®) is commercially available in Haiti, its

Keywords: Haiti; Sickle cell disease; Immunization; Pneumococcus

cost is currently excessive for the majority of the population and most medical institutions. The lack of access to PCV13 is particularly critical for children with Sickle Cell Disease (SCD), who are particularly prone to pneumococcal infection.

Importance of the Problem on the Care of Children with Sickle Cell Anemia

The need to immunize children with Sickle Cell Anemia (SCA) is even more urgent. In the case of sickle cell anemia, the most severe form of SCD, the spleen, which makes opsonins that attack encapsulated organisms such as pneumococcus, undergoes a process termed "auto infarction" early in life. The BABY HUG Multicenter Clinical Trial (NCT00006400), a placebo-controlled study, assessed the benefit of hydroxyurea over placebo in infants with SCA at a mean age of 13 months. Only 12% of these infants at baseline had normal spleen uptake by 99m technetium sulfur-colloid liver-spleen scans, with the majority having decreased uptake, and some no uptake, indicating that hyposplenism occurs frequently in children with SCA younger than 1 year of age [5]. This early hyposplenism requires prompt identification of infants at risk and the institution of preventive measures, including prophylactic penicillin by 2 months of age and immunization with available vaccines against encapsulated bacteria. Without prophylaxis and immunizations, the prevalence of pneumococcal infection in children with SCA is 30 percent in the first three years of life and one-third of those infected may die [6].

In developing countries such as Haiti and the countries of Sub-Saharan Africa, diagnosis, immunization, and treatment of infectious complications of SCA have not been attempted on a large scale. Currently, there is no national newborn screening program in Haiti. Consequently, children with sickle cell disease are dying from preventable deaths because they are not identified early and penicillin prophylaxis and immunizations are not instituted.

New Finding Insights

In Haiti, one of us (JF) estimated that the incidence of SCD (including SS and SC) is 1.35% (or 1 in 74) when infants less than 6 months of age were screened for SCD during a population screening [7]. However, the percentage of individuals with SCD significantly decreased in the older age groups, suggesting that many children were not surviving childhood. In 2010, Rotz and colleagues conducted a newborn screening pilot for hemoglobinopathies at a hospital in Port-au-Prince. In this study, the incidence of SCD was 1 in 173 [8]. As the current birth rate in Haiti is 22 per 1000 (which translates into 233,000 births per year in a population of 10.6 million), 1,350 children with SCD are expected to be born each year in Haiti [9]. In reality, few of these children will survive beyond age 5 due to the lack of systematic newborn screening. Pneumococcal infection should be a significant contributor to the high early childhood mortality, although this has not been investigated.

In 2016, Haiti will initiate a GAVI-sponsored pneumococcal vaccine campaign with PCV13. This GAVI program will, therefore, provide an ideal platform to demonstrate the potential of PCV13 vaccine to improve the survival of children in Haiti. However, the campaign may not be sufficient to reach all children. Therefore, other steps may be taken to assure that at the minimum children who have SCD will be identified and immunized.

We plan to begin a pilot newborn screening study at the Justinien University Hospital in Cap-Haïtien, the second largest city in Haiti, over 2-year period. This study will train local physicians, nurses, and other health professionals in newborn screening techniques, and will educate the population at-large about newborn screening and SCD. The purpose of this study will be to create the necessary infrastructure in order to continue screening children who are born locally, and to obtain information about the prevalence of SCD and the impact of newborn screening and preventive measures on the mortality of Haitian children with SCD. Tracking of the affected children will be conducted by community health workers. All children with SCD will receive free penicillin and PCV13 at age 2, 4, 6 and 12 months. Mortality data at 1 year of follow-up will be compared to national statistics for all infant mortality. All children identified will be followed by a trained pediatrician. The episodes of bacteremia, pneumonia, and other complications will be documented. Our hypothesis is that children who are identified through newborn screening with SCD will have a lower mortality rate compared to national statistics.

Comments and Conclusions

We have the opportunity to decrease the mortality of children with SCD in Haiti. The preventive role of pneumococcal vaccination on pneumococcal infection has been documented in the general pediatric population and in children who are at the highest risk for contracting such infection as discussed below. The results in Haiti should not be different, but should be studied. In the US, prior to the introduction of 7-valent Pneumococcal Conjugate Vaccine (PCV7), the highest rates of Invasive Pneumococcal Infection (IPD) occurred in children less than 2 years of age. In 2014, data from the Active Bacterial Core Surveillance (ABCs) Program of the Centers for Disease Control and Prevention (CDC) estimated that IPD rates (cases per 100,000 population per ABCs areas) were 15.4, 10.1, and 6.2/100,000 children for those infants < 1, 1, and 2 - 4 years of age, which were markedly reduced rates compared to decades ago [10]. In the United States, PCV7 decreased the prevalence of invasive pneumococcal infection by 74% in the general pediatric population and by 57% in children with SCD.5 Outside the United States, a study from South Africa demonstrated that immunization with PCV7 reduced the overall mortality of pneumococcal disease by 50% [11].

A recent literature review summarized vaccine trials completed, demonstrating the benefit of PCV7, PCV9, PCV13 and 23-serotype Pneumococcal Polysaccharide Vaccine (PPSV23) in children. Fifty-eight studies were identified; of

which 28 were conducted in children and 9 were conducted in both children and adults. These studies evaluated different regimens of either polysaccharide or conjugate and polysaccharide vaccines, and antibody titers were measured. These studies demonstrated that the administration of pneumococcal immunization prompted antibody responses in children with SCA, similar to responses seen among healthy children, and that there were no unexpected adverse events [12]. PCV13 substituted PCV7. Therefore, the American Academy of Pediatrics (AAP) Committee on Infectious Diseases recommends that children receive PCV13 [13]. In addition to PCV13, the AAP recommends PPSV23 for high risk populations, such as asplenic children, including children with SCD, and children with HIV infection [13]. The latter population is also threatened for early death from invasive pneumococcal infection as a result of their depressed T-cell function.

In order to decrease morbidity and mortality of children with SCD in Haiti, the University of Miami Family Medicine, the University of Miami Sickle Cell Center and the Justinien University Hospital are joining efforts to initiate a newborn screening and SCD treatment program in Cap Haitien.. Our program will assure that children who are born and screen positive for SCD, will be contacted and immunized with all childhood immunizations including PCV13, and started on penicillin prophylaxis.

Acknowledgment

This acknowledgment is in memoriam to one of the authors, Dr. Jean Fleurival, whose passion was to serve children and adults with sickle cell disease in Haiti for many decades.

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