Decline in Child Hospitalization and Mortality after the Introduction of the 7-Valent Pneumococcal Conjugative Vaccine in Rwanda

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Abstract. Pneumonia is a public health problem in the tropics, and the 7-valent pneumococcal conjugative vaccine (PCV-7) has been introduced in an effort to prevent the disease and therefore reduce childhood mortality. In Rwanda, PCV-7 was introduced in 2009, and we aimed to determine its impact on the rate of child hospitalization/mortality due to pneumonia. A retrospective survey was conducted on hospitalization rates and pediatric deaths between two periods, that is, before the introduction of PCV-7 (2007–2009) and after the introduction of PCV-7 (2010–2013) in Kabutare District Hospital. There was a 53% reduction in hospitalization, with a significant decline in in-hospital deaths between the two periods. There was also a significant correlation between vaccination coverage and decline in hospitalization rates between 2009 and 2013. We conclude that PCV-7 vaccine is associated with significant reduction in the rate of child hospitalization and mortality but more mechanistic studies are warranted to determine the immunological impact, especially in the context of coinfections and malnutrition.

INTRODUCTION

Pneumonia is a serious infection that is common in sub-Saharan African infants and young children. It affects approximately 450 million people globally per year and results in about 4 million deaths, mostly in the third world countries.¹ In 2011, an estimated 1.3 million children under the age of 5 years died of pneumonia, accounting for 18% of all deaths of children under 5 years of age worldwide.² Pneumonia affects children and families everywhere, but is most prevalent in southeast Asia and sub-Saharan Africa where it is the leading cause of death among children in low-income countries.³ In 2008, pneumonia occurred in approximately 156 million children—151 million in the developing world and 5 million in the developed world.⁴ Though the causes may be diverse, it has been reported that *Streptococcus pneumoniae* is the most common cause of severe bacterial pneumonia in developing countries.⁵

In 2000, a 7-valent pneumococcal conjugate vaccine (PCV-7) was introduced to the national pediatric immunization program in the United States and resulted in a rapid and dramatic decrease in invasive pneumococcal disease in both children and adults.⁶

In Rwanda, PCV-7 was introduced in April 2009, and is now part of the routine vaccination program. PCV-7 is administered in a three-dose primary series, administered at six, 10, and 14 weeks of age. In 2007, pneumonia was reported to be the leading cause of infant mortality in Rwanda, with 154,000 children (mainly in rural areas) dying each year before their fifth birthday (DHS 2007).⁸ Whether the PCV-7 vaccine has been effective in reducing this mortality in Rwanda is not yet documented.

METHODS

We retrospectively analyzed data on children under 5 years of age from Kabutare District Hospital, a hospital

located in the Southern Province of Rwanda, comparing two periods: 2007–2009 (before PCV-7 introduction) and 2010–2013 (after PCV-7 was introduced). In Kabutare hospital, pneumonia is diagnosed by physical examination by a medical doctor and when necessary by gram staining and blood culture. In the latter case, *S. pneumoniae* is considered. Severe cases (i.e., in case of persistent infection) are referred to the Butare University Teaching Hospital where an antibiogram is performed.

We analyzed records of child (0–5 years of age) hospitalization and mortality due to pneumonia as defined by physicians and/or confirmed by laboratory tests (blood culture and gram staining) done at Kabutare District Hospital for the period 2007–2013. Information related to malnutrition and coinfection was also considered. Statistical analyses were performed using GraphPad Prism 7 (San Diego, CA), and $P \leq 0.05$ was considered significant. Comparisons between the two periods (before versus after PCV-7 introduction) were done using independent t tests, and correlation between vaccination coverage and hospitalization rates was done using Pearson's correlation coefficients. In both cases, two-sided P values were considered.

RESULTS

Overall, in Kabutare District Hospital, there were 621 children admitted for pneumonia prior the introduction of PCV-7 (2007–2009) versus 297 cases post PCV-7 introduction (2010–2013). In-hospital death cases due to pneumonia amounted 72 prior PCV-7 introduction versus 30 post-PCV-7 introduction. Statistical analyses showed a 53% reduction in child hospitalization due to pneumonia between the two periods. Furthermore, an independent t test (Table 1) showed significant declines in hospitalization ($t = -2.9$, $df = 5$, $P = 0.0338$) and mortality ($t = 3.002$, $df = 5$, $P = 0.03$) due to pneumonia between the two periods. Interestingly, there was no significant change in overall hospitalization cases (i.e., when all causes were considered, $t = 1.871$, $df = 5$, $P = 0.12$).

Data published in the annual report from the Ministry of Health (MOH) indicated a PCV-7 vaccination coverage of 40% in 2009, 80% in 2010, 82% in 2011, and 100% in 2012 and 2013 (MOH, Expanded program on immunization,

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TABLE 1
Hospitalization and death cases due to pneumonia at Kabutare District Hospital

Period	Year	Total number of children hospitalized	Comparison (overall hospitalization)	Number of children hospitalized due to pneumonia	Comparison (hospitalizations)	Deaths due to pneumonia	CFR (%)	Comparison (deaths)
Before PCV-7	2007	1,117	$t = -1.871$, $df = 5$, $P = 0.12$	200	$t = -2.9$, $df = 5$, $P = 0.0338$	31	15.50	$t = -3.002$, $df = 5$, $P = 0.030$
	2008	1,087		120		16	13.30	
	2009	1,555		301		25	8.30	
After PCV-7	2010	902		94		14	14.90	
	2011	1,185		71		13	18.30	
	2012	914		88		2	2.30	
	2013	856		44		1	2.30	

CFR = case fatality rate; PCV-7 = 7-valent pneumococcal conjugative vaccine. The t , df , and P values were obtained from unpaired t tests comparing the two periods.

Comprehensive multi-year plan 2011–2015).⁹ Statistical analysis showed a significant negative correlation between vaccination coverage and hospitalization cases due to pneumonia ($r = -0.938$, $P = 0.0183$).

In 2012 and 2013, 30% of children with pneumonia had malaria, 11% had bronchiolitis, 7% had infestation with intestinal parasites, 7% were malnourished, and 2% were human immunodeficiency virus (HIV) positive.

DISCUSSION

Findings from the current study are consistent with those found in other countries indicating reductions in pneumonia cases after PCV-7 introduction. Thus, in the United States, there was a 39% reduction of all-cause pneumonia admission rates for children younger than 2 years after PCV-7 introduction.⁶ In Uruguay, there was a 56% reduction in pneumonia among children < 2 years of age after the introduction of PCV-7,⁷ whereas in Poland, the reduction of pneumonia after the introduction of PCV-7 vaccine was 65%.¹⁰ Cohen and others also demonstrated that PCV-7 was highly effective among HIV-infected and HIV-exposed and uninfected children in South Africa.¹¹ Our data thus extend these observations that demonstrate a positive impact of the introduction of PCV-7 vaccine.

Our results showed that HIV coinfection occurred in 2% of all pneumonia cases between 2012 and 2013 (post PCV-7 introduction). Pneumonia is a leading cause of morbidity and death in HIV-infected children, and an important cause of hospitalization.¹² Children with HIV have a higher risk than immune competent children of developing pneumonia, associated with a more severe disease and worse outcome.^{12,13} Indeed, HIV has contributed substantially to increased incidence, severity, and mortality of childhood pneumonia in the developing world, particularly in sub-Saharan Africa.¹⁴

In our study, 7.4% of hospitalized children (with pneumonia) were also diagnosed with intestinal parasites. Intestinal parasites are the main causes of malabsorption of nutrients in intestine, leading to malnutrition. Many intestinal parasites also cause diarrhea. Chronic diarrhea reduces the time necessary for proper absorption of nutrients, and causes malabsorption, which in turn weakens the immune system. A weakened immunity makes it easier for pathogens to invade.

Interestingly, 6.7% of pneumonia-positive cases post vaccination presented signs of malnutrition. It has been argued that improving child nutrition may substantially prevent childhood pneumonia.¹⁵ It is therefore conceivable that pneumonia in our vaccinated population may have been an indirect consequence of malnutrition and infectious diseases (intestinal parasites, malaria, and HIV) that are usually associated with malnutrition.

The limitation of our study is that it fails to demonstrate whether the surveyed children were all vaccinated. However, the published report by the World Health Organization and United Nations Children's Emergency Fund on immunization coverage in Rwanda indicates a pneumococcal vaccination coverage of 97–99% between 2010 and 2014.¹⁶ Furthermore, hospitalization rates recorded from Kabutare Hospital negatively correlated with vaccination coverage reported by the Rwandan MOH in the period 2009–2013.

A further limitation could be other unmeasured interventions such as the reduction in malaria incidence and universal access to antiretroviral therapy for the period 2005–2010,¹⁷ which may have impacted on improved health status of children in Rwanda. Indeed, a study in Kenya has shown that the peak of pneumonia incidence coincides with the high malaria seasons¹⁸ while others have shown high immunogenicity of the PCV after antiretroviral therapy in children.^{19,20} It is worth noting however that there was no significant change in overall hospitalization rates (when all causes were considered) in this study.

Overall, our study is consistent with studies by others that demonstrate an association between the introduction of the PCV-7 vaccination and reduction of the incidence and severity of childhood pneumonia. We also demonstrate that a high number of children hospitalized due to pneumonia post-vaccination had other important coinfections including malaria, HIV, and intestinal parasites, which may favor the occurrence of pneumonia. It is therefore possible that the PCV-7 vaccination effort may be hindered by these other coinfections, but further mechanistic studies are warranted to demonstrate this.

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