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The Effect of Introduction of Pneumococcal Conjugate 13 Valent Vaccine on Severe Pneumonia among Hospitalized Children Under-Two years old

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A B S T R A C T

Severe pneumonia in children is a major forgotten killer globally. In Sudan the incidence among under-five children is 19% and it represents 27% of causes of hospital admission. Pneumonia is responsible for 10% of hospital deaths among under-five. Each year, more than 2 million children under-five die of pneumonia in the developing world. Objectives: The study has been conducted on Omdurman Pediatric Hospital; in the period from April to October 2014 to determine the effect of introduction of Pneumococcal Conjugated Vaccine (PCV13) on severe pneumonia in the second year after introduction of the vaccine in Sudan.375 children admitted in the hospital with severe pneumonia were included in the study. The study aimed to determine the coverage rate of the vaccine, the characteristics, pattern and presentation of severe pneumonia and to assess the prognosis and course of the disease among the vaccinated compared to non-vaccinated children. Methods: This study is a descriptive case finding clinical study among children who are categorized clinically as severe pneumonia at Omdurman Pediatrics Hospital, Sudan, according to discharge diagnosis in medical records with clinical evidence of severe pneumonia, in children between two and 24 months of age. The follow up of patient and information obtained after taking appropriate consents from guardian. Data analysis: The collected data was analyzed by computer using statistical package for social sciences (SPSS) version (16). The result obtained being presented in graphs and tables. Result: 375 children between 2-24 months of age were included. The patients less than 12 months of age were 268 represents 71.4% of the total number of patient. The total coverage rate of vaccination with PCV13 was 73.6%. The coverage rate of vaccination with first dose, second dose and third dose was 73.6%, 62.1%, and 48.3% respectively. There were no significant statistical differences in relation to age, sex, and length of stay in hospital, but the prognosis and outcome was significantly different between the vaccinated and non-vaccinated patients. The number of died patients was 19 and the case fatality rate was (5.06%). Conclusion: The coverage rate of the PCV13 was low because the vaccines have been introduced recently. The vaccination with PCV13 affects the invasiveness of the severe pneumonia infection, course, prognosis and outcome significantly.

Introduction

Pneumonia has been defined as an acute disease episode with cough or difficult breathing combined with tachycardia (Taneli Puumalainen *et al.,* 2008). It is a leading cause of morbidity and mortality worldwide in children under five years old. The estimated incidence is 156 million episodes per year (Rudan *et al.,* 2004).

The incidence of pneumonia shows wide-ranging geographical disparities, with two-thirds of the cases stemming from 10 countries (Igor Rudan *et al.,* 2008; WHO, 2006). Furthermore, Africa is one of the regions particularly heavily affected, with 35 million cases estimated to be from Africa (Rudan *et al.,* 2004), and Sudan is no exception, with 2 million cases per year (Igor Rudan *et al.,* 2008; WHO, 2006) and a yearly incidence of 19% among under-fives (http://www.gavialliance. org/library/news/gavi-features/2013).

Causes of pneumonia include viral and bacterial causes. In prospective, microbiology-based studies, the leading bacterial cause is pneumococcus, being identified in 30–50% of pneumonia cases (Shann, 1986; Adegbola *et al.,* 1994; Forgie *et al.,* 1991; Falade *et al.,* 1997).

Viral causes of pneumonia showed that respiratory syncytial virus is the leading viral cause, being identified in 15 – 40% of pneumonia or bronchiolitis cases admitted to hospital in children in developing countries, followed by influenza A and B, parainfluenza, human metapneumovirus and adenovirus (Weber *et al.,* 1998; Simoes *et al.,* 1999; Stensballe *et al.,* 2003).

The symptoms differ widely between individuals with pneumonia. A child may present with cough, fever and difficult breathing; they may also present with abdominal pain, headache and vomiting (Michael Harris *et al.,* 2011). In a healthcare setting where further diagnostic measurements are available, the care of the child can be based on a more thorough investigation than the clinical picture alone. The WHO guidelines suggest obtaining a chest X-ray in very severe pneumonia cases to identify possible complications (such as empyema and pericardial effusion) and in severe cases that do not respond to treatment, or that are associated with HIV-infection (WHO, 2005). Furthermore, Microbiological investigations can be helpful and should be considered in severe cases to determine the causative agent (Michael Harris *et al.,* 2011), and optimize antibiotic treatment.

Of particular concern in this study is severe pneumonia and very severe pneumonia. The former is categorized as having either lower chest wall in drawing or nasal flaring. Very severe pneumonia is categorized as having one of 4 features: Central cyanosis, inability to breastfeed/drink, convulsions/lethargy/unconsciousness, or severe respiratory distress (Taneli Puumalainen *et al.,* 2008).

The more severe presentations of pneumonia are a major source of morbidity and mortality worldwide among under-fives, with estimates indicating that 7-13% of the estimated 156 million yearly cases are possible life-threatening and requiring hospitalization (Rudan *et al.,* 2004). In Sudan this problem is no less severe, with 27% of hospital admissions among under-fives being caused by pneumonia (http://www.gavialliance.org/library/news /gavi-features/2013), as well as 10% of hospital deaths, second only to septicemia. Worldwide deaths are estimated to be 1.6 million, mainly in Africa and South-East Asia. Furthermore, it is suggested that such figures are underestimated, as the interquartile range for available case-fatality ratios was 1.3–2.6%, leading to an estimated 1.96–3.92 million expected deaths from pneumonia per year based on the basis of observed incidence. Therefore, two lines of evidence both indicate that there are more than 2 million deaths due to pneumonia each year in children aged less than 5 years (Igor Rudan *et al.,* 2008).

Pneumococcal pneumonia is of particular interest because it is the leading cause of bacterial pneumonia (Shann, 1986; Adegbola *et al.,* 1994; Forgie *et al.,* 1991; Falade *et al.,* 1997), and is a major cause of mortality. It has been estimated that up to 47% of deaths from pneumonia among under-fives are caused by *S. pneumoniae* (Javier Nieto Guevara *et al.,* 2013). Furthermore, Pneumococcal pneumonia, together with that caused by Haemophilus influenza type B(Hib) are the two causes of bacterial pneumonia that are vaccine preventable (Mulholland *et al.,* 1997; Madhi *et al.,* 2005).

The high morbidity and mortality rates resulting from pneumococcal diseases, including pneumonia, and the increase of multi-drug resistant strains have emphasized the urgent need for introduction of effective vaccines against diseases caused by *S. pneumoniae* (Maria Pavia *et al.,* 2009). Thus the PCV13 vaccine, covering serotypes which account for more than 80% of pneumococcal disease in most regions of the world (Peter

R. Paradiso, 2011) has been introduced. Some 1.3 million infants in Sudan have being targeted in a nationwide pneumococcal conjugate (PCV13) vaccination program starting in August 2013 (http://www.gavialliance.org/ library/news/gavi-features/2013), targeting the two most common killers among under-fives: sepsis and pneumonia.

Because Pneumococcal pneumonia is such a major cause of morbidity and mortality in young children and is preventable, this study has been done on children with severe pneumonia to determine the effect of the vaccine on the prognosis and course of children hospitalized for severe pneumonia from 1st of April 2014 to 31st of October 2014. The secondary objective was to determine vaccine coverage and its associated patterns.

Materials and Methods

This descriptive prospective case finding study took place from 1st of April 2014 to 31st of October 2014, and was carried out on infants categorized clinically as having severe pneumonia who were admitted into Omdurman Pediatric Hospital.

Omdurman Pediatrics Hospital is located in Omdurman, Khartoum State, Sudan. It serves as an out-patient and day-care hospital for children with variety of diseases. It provides services for children from different areas of Omdurman as well as the periphery. Additionally, it serves as a referral center for other parts of Sudan.

The study aimed to determine the coverage rate of the vaccine, the characteristics, pattern and presentation of severe pneumonia and to assess the prognosis and course of the disease among the vaccinated compared to non-vaccinated children.

Inclusion criteria included an age between 2 months and 24 months, residence at Omdurman locality, as well as an up to date immunization card. The sample size of 375 encompassed all patients who were admitted during the study period who fulfilled inclusion criteria.

A questionnaire was prepared to collect information regarding the following variables: age, sex, socioeconomic status, past history, vital signs and general examination findings, in addition to outcome of the management. The data was obtained from the caregiver, and the questionnaire was filled by the researchers.

Data entry, data analysis and vetting were done. The data obtained was coded, validated and entered into a computer and a master sheet was constructed to arrange the raw data, analysis was done using the Statistical Package for Social Science (SPSS) version 16.

Ethical approval was obtained from concerned administration. Consent was taken from parent or caregiver for both inclusion and sample collection after clear explanation.

Results and Discussion

This study was done on 375 infants between the ages of 2 and 24 months who fulfilled criteria for severe pneumonia. The gender distribution among these patients was biased towards males, who comprised 58.2% of the study population. Additionally, the age distribution showed that the bulk of the patients were below 1 year of age, at 71%, with 38% being between 2 months and 6 months and 33% being between 6 months and 12 months (Figure 1). 276 patients (74%) received the PCV-13 vaccine at least once. 166 (60%) of those vaccinated were male and 110 (40%) were female. Among the patients who received the vaccine, 203 (74%) received all three doses, 72 received two doses, and 23 received only one dose. Among the patients who were fully vaccinated, the majority (51%) were between 6 months and 12 months old. Furthermore, 19% were between 2 months and 6 months and 29% were between 12 months and 24 months (Figure 2).

The age among the unvaccinated tilted towards those who were older, with 29% of them being from 18 months to 24 months old, and only 20% being from 2 months to 6 months old, despite older patients forming a relatively smaller portion of the study sample (Figure 3).

Data pertaining to vaccination among patients with history of recurrent respiratory tract infections (RTI) was also collected. Among the 276 vaccinated patients, 104 (38%) had a history of recurrent RTI compared to 31.3% among the non-vaccinated. However, 41% of patients who had a history of recurrent RTI were vaccinated three times compared to 48% of the general study population. 30% of those with recurrent RTIs were vaccinated twice and 35% once (Figure 4).

In terms of the outcome of the patients; they were divided into three on the basis of length of hospital stay: Those who stayed for up to one day, those who stayed

between one and seven days and those who stayed for longer than 7 days. In the vaccinated patients, 13(61.9%) of those who had been given one dose of PCV13 only stayed one day in hospital and 156 patients (64.2%) stayed more than 1day and less than 7days.

Only 5(23.8%) of the patients who received two doses of the PCV13 stay one day in hospital and 67 patients (27.6%) stayed more than 1 day and less than 7 days. In the patients who received three doses of the PCV13, 3 patients (8.2%) stayed one day in the hospital, with 20 patients (8.2%) stayed (more than 1 day and less than 7 days) and no patient spend more than 7 days in the hospital (figure 5).

Despite forming 74% of the study population, only 47% of the 19 patients who died were vaccinated, and none of them were fully vaccinated. Of the 9 vaccinated patients who died, 5 (55%) were vaccinated twice and 4 (44%) were vaccinated once (figure 6). This is despite twice vaccinated patients out numbering once vaccinated patients by more than 3:1.

This study is one of the first descriptive case-finding clinical studies among children who are categorized clinically as severe pneumonia at Omdurman pediatrics hospital, Sudan, according to discharge diagnosis in medical record with clinical evidence of severe pneumonia, fulfilling the WHO classification, in children between two and 24 months age.

The study has been conducted to determine the effect of introduction of Pneumococcal Conjugated Vaccine (PCV13) on severe pneumonia in the second year of introduction of the vaccine in Sudan. The targets were to determine the coverage rate of the vaccine, the characteristics, pattern and presentation of severe pneumonia and to assess the prognosis and course of the disease among the vaccinated compared to non-vaccinated children.

Most of patients were less than 12 months of age, 268 represents 71.4% of the total number of patient in the study group. More than 2 months and less than 6 months were 143 making about (38.1%), and those who were between 6 and 12 months were 125 making (33.3%) of the study sample.

This corresponded with the study done in Australia on the Effectiveness of 7-valent pneumococcal conjugate vaccine against radiologically diagnosed pneumonia according to World Health Organization (WHO) criteria in indigenous infants on period from 1st April 1998 to 28th February 2005 in which the incidence of pneumonia is highest among children under one year old, 183/526 episodes of pneumonia represent (34.8%) occurred before 5 months of age and 247/526 (47.0%) by 7 months (Morris *et al.,* 2003). In other study done in South African, between May 29, 2012 and May 31, 2014, Incidence of community-acquired pneumonia increased from the second month to 1 year, highest in the third month, from one to six months old 106/141 represent 75% episode of pneumonia (David M le Roux *et al.,* 2015).

This coverage rate differ from the study done in South African, between May 2012 and May 2014, in which high immunization coverage recorded of primary series vaccinations: 512 (98%) of 561 infants received a 6-week vaccine, first dose, with PCV13, 521 (94%) of 552 received a 10-week Vaccine, second dose, with PCV13, and 477 (89%) of 534 received a 14-week, third dose, vaccine with PCV13 (David M le Roux *et al.,* 2015).

In an Indian study coverage rates were 98%, 55%, 30%, and 7% for one, two, three, and booster doses, respectively (O'Grady *et al.,* 2010). The coverage rate in our study is low compared with the other two previous studies. This could be explained by fact that the PCV13 was introduced recently in Augusts 2013, 8 months before the study was undergone.

The total fatality rate is corresponded with study done in our country, Sudan, in which the fatality rate was 9/224 (4.01%) (Salih *et al.,* 2011). Other study done in South African, between 2012 and 2014, after introduction of PCV13 the case fatality was 13/513(2.53%). Another study done on factors determining the outcome of children hospitalized with severe pneumonia in India between May 2004 and February 2006. Children of either sex, between 2–60 months of age hospitalized with severe community acquired pneumonia (CAP) fulfilling the WHO criteria of severe and very severe pneumonia were enrolled within 24 hours of admission in which the fatality rate was 21/200 represent 10.5%, it is higher in compare with our study (O'Grady *et al.,* 2010).

Most importantly, vaccinated patients showed better outcome, as unvaccinated patients tended to have longer hospital stay. Furthermore, 6.7% of completely vaccinated patients stayed in the hospital for longer than 7 days as compared to 9.1% of unvaccinated patients.

Figure.1 Distribution of patients in the study groups according to ages in months

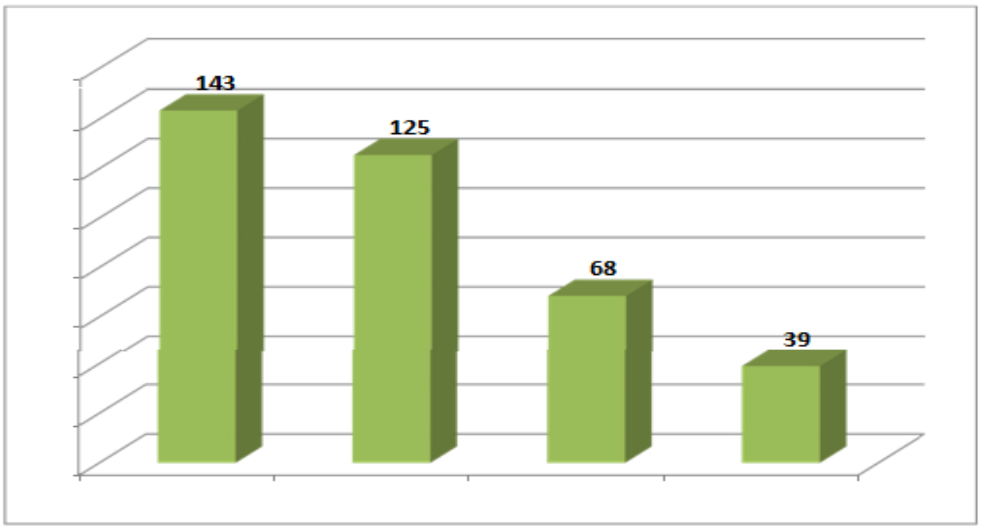


Figure.2 Distribution of doses of PCV13 given to in relation to gender

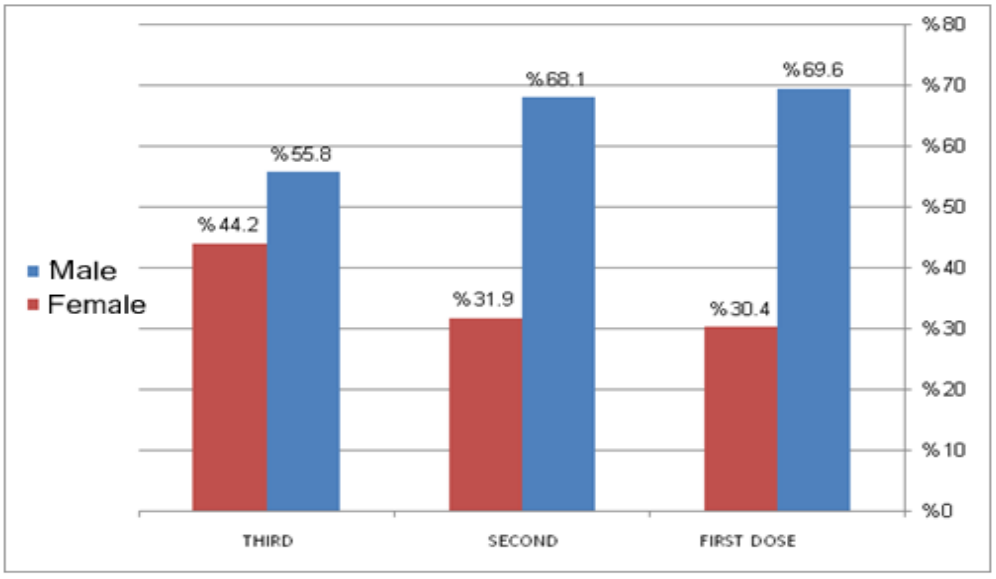


Figure.3 Vaccination status with pcv13 in relation to ages in months

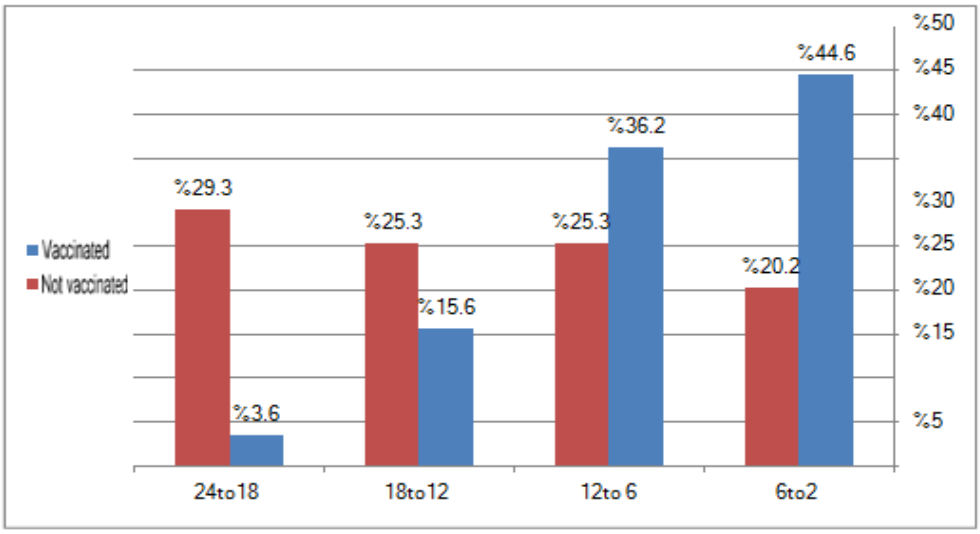


Figure.4 Number of doses of PCV13 received by patients in relation to history of recurrent RTI

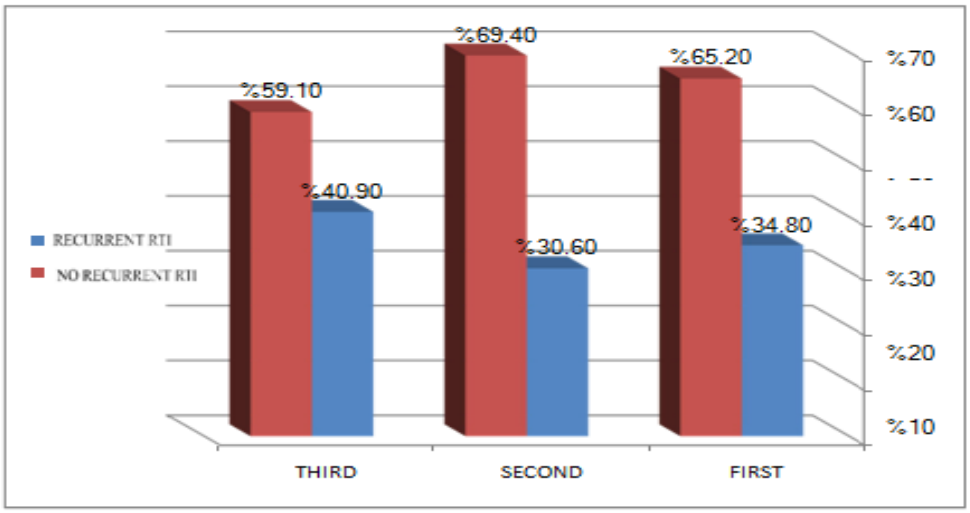


Figure.5 Number of doses of PCV13 given to patients in relation to duration of hospital staying in days

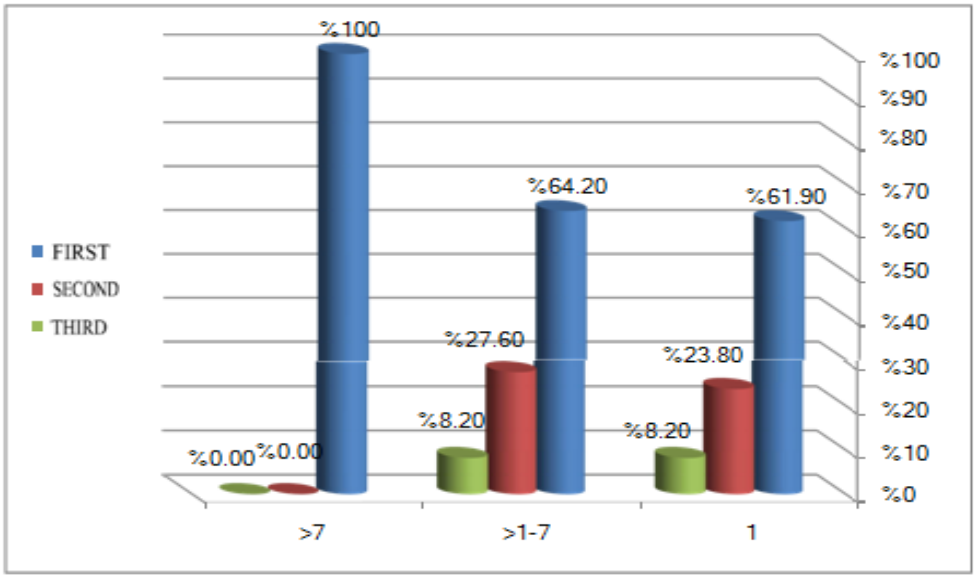
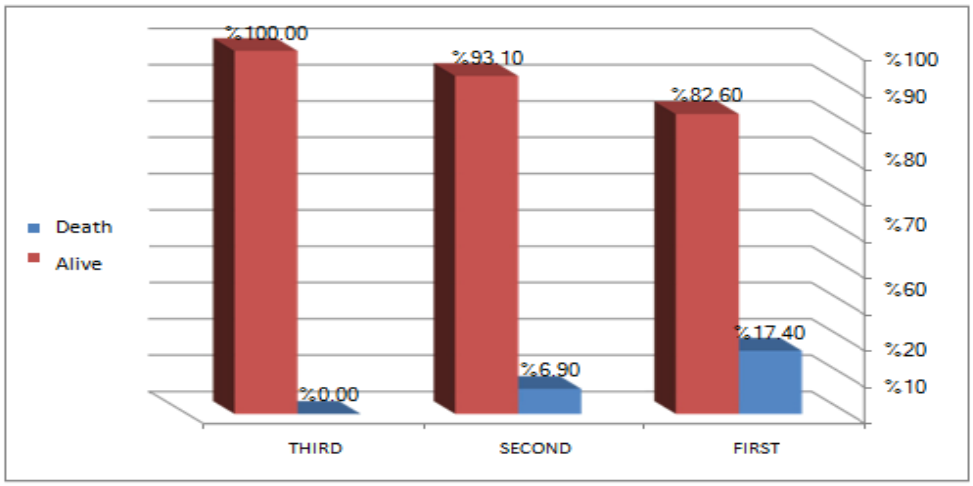


Figure.6 Number of doses of PCV13 given to patients in relation out come



Regarding the vaccination with PCV13 status of the patient died in our study group, 10 patients out of 19 representing (52.6%) were not vaccinated. 9 patients (47.4%) were vaccinated with the PCV 13, despite vaccinated patients forming 74% of the study group.

None of the patients who died were completely vaccinated despite the latter forming 48% of the study population. This consistent with a Meta-Analysis study; performed to determine the efficacy in reducing the incidence of invasive disease caused by *Streptococcus pneumoniae*, pneumonia, and acute otitis media in healthy infants younger than 24 months, the result reveal the efficacy of pneumococcal conjugate vaccine in the reduction of invasive pneumococcal disease was 89% involving vaccine serotypes in both the intention to- treat and per-protocol analyses and ranged from 63% to 74% for all serotypes. The pneumococcal conjugate vaccine produces a significant effect regarding prevention of invasive pneumococcal disease (Williams *et al.,* 2002). Weaknesses of this study is that PCV-13 only targets *S. pneumoniae*, but this study was a general study which uses pneumonia of all microbiological types as a surrogate for *S. pneumonia*. Although *S. pneumonia*e is

the most common cause of bacterial pneumonia in our study sample, this still may lead to biases.

We recommend encouragement of children under 5 all over the country and the establishment of a program to that effect. Furthermore, we recommend further, well controlled studies on the efficacy of PCV-13 on incidence and severity of pneumonia.

This study is one of the first descriptive case-finding clinical studies among children who are categorized clinically as severe pneumonia at Omdurman Pediatrics Hospital, Sudanin children between 2 and 24 months age. We concluded that the childhood pneumonia remains an important public health problem despite the introduction of new conjugate vaccines. We also notice a high incidence of pneumonia, with a high proportion of cases in the first year of life and it's the major killer of children less than 2 years of age. We find that the coverage rate of the vaccine in the study groups was (73.6%) which is low because the vaccine has been introduced in August 2013. No significant difference in our study in the clinical presentations, symptom and sign, at admission between the vaccinated and non-vaccinated patients after we exclude the risk factor and the antibiotics received by patients. The vaccinations mainly affect the invasiveness of the severe pneumonia infection, course, prognosis morbidity and mortality, and outcome significantly.

Recommendations

Since severe pneumonia continues to be the main killer, the incidence among under-five children is 19% and it represents 27% of hospital admission. The pneumonia is responsible for 5.06 % of hospital deaths among our study groups, the coverage rate of the vaccine is low, and the target goals should be to;

1. Encourage the vaccination with PCV13 in under-five years old children specifically less than two years in all over the country.
2. Establish specific program and develop new strategy to increase the awareness of mother and parent about importance of vaccination with PCV13, not to discontinue the vaccination to complete the dose and take the dose on time to increase the coverage rate of the vaccine and catch up full immunity.
3. Further studies are needed for long period after complete introduction of PCV13 to reflect the actual effect on incidence and invasiveness of pneumonia.
4. Encourage the domestic and international fund to support the vaccination with PCV13, to bring sufficient quantity of vaccines to support achievement to vaccination of all under-five year old children in Sudan as soon as possible.

Compliance with Ethical Standards

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- Disclosure of conflict of interest: Nil to disclose.
- Consent: Ethical approval for this study was obtained from the concerned administrations. Written informed consent was obtained from all parents/care-givers of all patients included.

Author Contributions

Nurallah Elnaji Ahmed: Investigation, formal analysis, writing—original draft. Ibrahim Ali Adlan: Validation, methodology, writing—reviewing. Ahmed Sarar Mohamed:—Formal analysis, writing—review and editing. Omer Saeed Magzoub: Investigation, writing—reviewing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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