American Journal of Clinical Medicine Research, 2018, Vol. 6, No. 1, 5-9
Available online at http://pubs.sciepub.com/ajcmr/6/1/2

DOI:10.12691/ajcmr-6-1-2

Invasive Pneumococcal Disease in Children below 14 Years before and after the Introduction of Pneumococcal Conjugated Vaccine

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Abstract **Background:** Invasive Pneumococcal Disease (IPD) is a life-threatening disease, which could be prevented by vaccination using Pneumococcal Conjugated Vaccine (PCV). Therefore, the aim of this study was compare the incidence before and after the introduction of the vaccine among children in King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, and to determine the extent of the disease prevention by the vaccine. **Methodology**: A retrospective cohort study including all children who are ≤ 14 years of age and microbiologically confirmed as infected (cases) with *Streptococcus pneumonia* (SP) from a sterile body fluid (blood or cerebrospinal fluid) before the introduction of the pneumococcal conjugated vaccine between the years of 2004-2008 and after the introduction of the pneumococcal conjugated vaccine (2009-2015) in KAMC, Riyadh, Saudi Arabia. **Results**: Out of 171 retrieved cases, 131/171(76.6%) were not vaccinated and 40/171(23.4%) were vaccinated. *Streptococcus Pneumonia* was isolated from blood in 163/171(95%) of the cases, and from cerebrospinal fluid in 23/171(13.5%) of the cases. **Conclusion**: The introduction of PCV7 has significantly decreased the incidence rates of IPD in children. The conjugate vaccines have shown a significant efficacy in reducing IPD among our population.

Keywords: *Invasive Pneumococcal Disease, Streptococcus pneumonia, Saudi Arabia, vaccine*

Cite This Article: Faiz Mohammed alruwaili, Abdullah Abdulrahman muharib, Turki seran alharbi, Abdulrhman Alnasser, Areej Abdullatif Madani, Esam Albanyan**,** Mohammed Alshaalan, Bassam Ahmed Almutlaq, and Hussain Gadelkarim Ahmed, "Invasive Pneumococcal Disease in Children below 14 Years before and after the Introduction of Pneumococcal Conjugated Vaccine." *American Journal of Clinical Medicine Research*, vol. 6, no. 1 (2018): 5-9. doi: 10.12691/ajcmr-6-1-2.

1. Introduction

Invasive Pneumococcal Disease (IPD) is defined as an infection in the blood or cerebrospinal fluid which leads to bacteremia and meningitis respectively. It is caused by a bacterium called *Streptococcus pneumonia* although *S. pneumoniae* is common inhabitants of the nasopharynx in up to 90% of healthy persons, it is the most common cause of community-acquired pneumonia in addition to other infections. It is a facultative anaerobic gram-positive diplococci bacterium that is seen in pairs under the microscope. IPD is a serious life-threatening condition that can affect immunocompetent and immunocompromised people at any age. *Streptococcus pneumonia* can also lead to noninvasive infections such as pneumonia, acute otitis media, and others [1]. Bacteremia with unknown site of infection is the most common invasive presentation of pneumococcal infection among children which accounts for about 70% of IPD among them.

One of the most common sites of infection that can lead to bacteremia are the lungs (pneumonia) which are accounting for about 14% of pneumococcal bacteremia among children. *Streptococcus pneumonia* by far is the most common cause of bacterial meningitis among children with an incidence that exceeds 3000 cases annually in the United States of America (USA). The using of the pneumococcal conjugated vaccine has significantly decreased the incidence of IPD. For example, the prevalence of pneumococcal meningitis before the introduction of the vaccine was about 10 per 100,000 in 1998 but after the introduction of the vaccine has been decreased by more than 60% in the USA [2,3].

The typical presentation of bacteremia in children caused by *Streptococcus pneumonia* is a brief fever for 1 to 2 days, with positive blood cultures. In addition, there are some aspects of the history have been highly associated of being affected with pneumococcal bacteremia such as rejection of breastfeeding or being an immunodeficient patient. Moreover, children who were treated with antibiotics in the preceding 30 days are more likely to have resistant pneumococcal bacteremia [4].

Pneumococcal bacteremia that occurs in children who present with fever, lethargy, and irritability, but without signs of focal infection or toxic appearance is called occult pneumococcal bacteremia. The primary cause of pneumococcal bacteremia is usually unknown, but there are some primary causes that can be revealed after the physical examination (e.g. acute otitis media, pneumonia, and meningitis) [5]. In the USA, there are more than 50,000 cases of pneumococcal bacteremia that occur annually with the prevalence of 23.2 per 100,000 [2]. A study conducted in 1999–2003 in Saudi Arabia has estimated the incidence of IPD to be 17.4/100,000 children younger than 5 years of age with a mortality rate of 12.2% [6].

In addition, rising pneumococcal antimicrobial resistance has become a worldwide issue, with over 90 serotypes vaccine development was challenging. However, the introduction of PCV7 which cover the serotype (4, 6B, 9V, 14, 18C, 19F, and 23F) in the US back in 2000 resulted in significant reduction of vaccine serotypes by 77% decrease among children aged <5 years and a 39% decrease in hospital admissions for pneumonia among children aged <2 years [7]. Furthermore, the prevalence of pneumococcal meningitis before the introduction of the vaccine was about 10 per 100,000 in 1998 but after the introduction of the vaccine has been decreased by more than 60%. Unfortunately, this was followed by a slight rise in non-vaccine serotypes such 19A, which were also showing higher incidence of antimicrobial resistance. The introduction of PCV13 in 2010 again resulted in a decrease in serotypes covered by the vaccine and that of PCV7 stereotype [8].

Post vaccine data on IPD in this region is lacking, yet urgently needed, in order to understand the impact of vaccine introduction on pneumococcal disease locally.

However, there an urgent need for studies to highlight the epidemiology and incidence of IPD over a 9 year period that covered a pre-vaccine and post vaccine era, allowing us to evaluate the impact of the vaccine on this community. Therefore, the aim of this study was compare the incidence before and after the introduction of the vaccine among children in King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, and to determine the extent of the disease prevention by the vaccine.

2. Methods

A retrospective cohort study including all children who are ≤ 14 years of age and microbiologically confirmed as infected (cases) with *Streptococcus pneumonia* (SP) from a sterile body fluid (blood or cerebrospinal fluid) before the introduction of the pneumococcal conjugated vaccine between the years of 2004-2008 and after the introduction of the pneumococcal conjugated vaccine (2009-2015) in KAMC, Riyadh, Saudi Arabia.

2.1. Ethical Consent

Our study protocol was conformed according to the 2013 Declaration of Helsinki.

2.2. Statistical Analysis

Statistical analysis was performed using SPSS software for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Categorical variables are given as frequencies and percentages, and continuous variables. For all statistical comparisons, a p value below 0.05 was considered statistically significant.

3. Results

In the present study about 171 cases of IPD were retrieved from KAMC. Out of 171 patients, 87/171(51%) were males and 84/171(49%) were males. Out of 171 retrieved cases, 131/171(76.6%) were not vaccinated and 40/171(23.4%) were vaccinated. *Streptococcus Pneumonia* was isolated from blood in 163/171(95%) of the cases, and from cerebrospinal fluid in 23/171(13.5%) of the cases. No isolate from other body fluids. Pneumonia was ascertained in 45/171 (26%) of the cases. The commonest presenting symptoms was fever in 158/171(92.4%) followed by seizures in 20/171(12%) and shock in 19/171(10.9%). Other symptoms like rash, headache, and photophobia were also experienced by some patients, as indicated in Table 1, Figure 1.

Around 89/171(52%) of the patients have comorbid conditions including; respiratory diseases in 41 (24%), genetic diseases in 20(12%), acute lymphocytic leukemia in 11(6.4%), gastro-esophageal reflux in 7(4%) and Down syndrome in 6(3.5%). Some complications occurred in 14(8%) of the cases; 3(1.8%) of them were hearing loss and 11(6.4%) were mortality.

The distribution of the study population by incidence of IPD and vaccination status during 2004-2008 was summarized in Table 2 and shown in Figure 2. The distribution of the study population by incidence of IPD and vaccination status during 2009 to 2015 was summarized in Table 3 and shown in Figure 3.

Approximately 25% of the isolates were resistant to penicillin (both intermediate and high resistance), as indicated in Table 4, Figure 4.

13 cases of meningitis occurred below one year of age resulting in 3(23%) deaths. No mortality among meningitis cases that occurred after one year of age. Complications occurred in 9(43%) of the survivors of meningitis cases including three cases of hearing loss.

Table 1. Description of the study population by sex and clinical symptoms

Variable	Category	Frequency
Sex		
	Males	87
	Females	84
Symptoms		
	Fever	158
	Seizure	20
	Shock	19
	Neck stiffness	10
	Headache	8
	Rash	6
	Photophobia	3

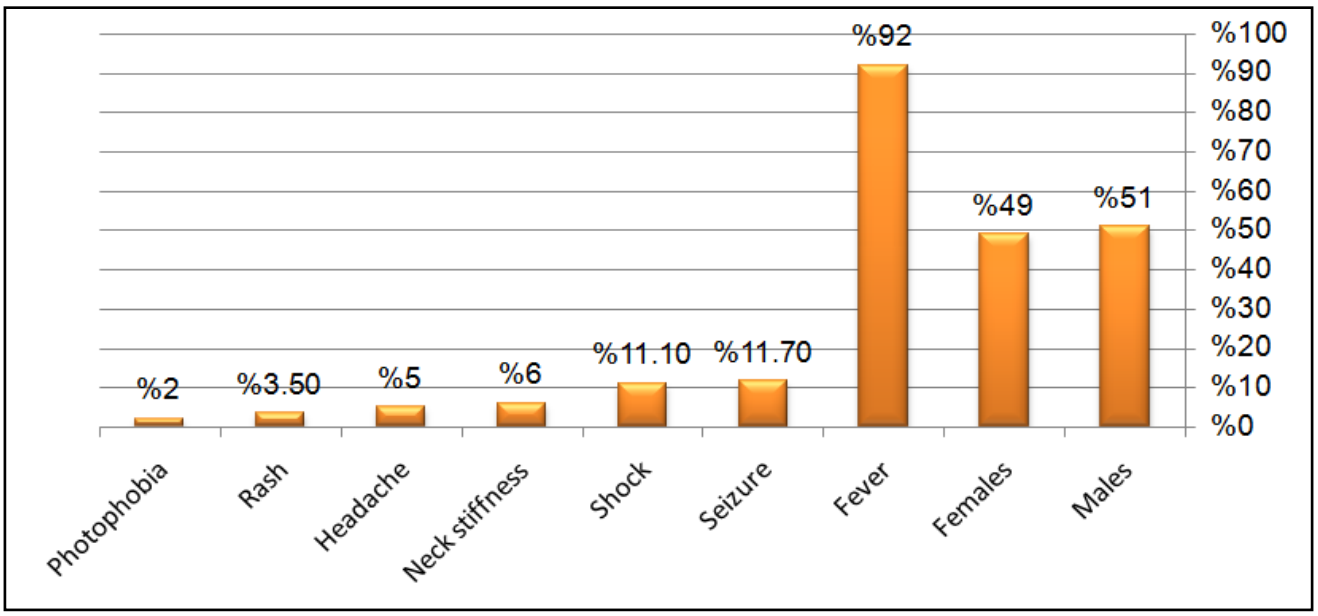

Figure 1. Description of the study population by sex and clinical symptoms

Table 2. Distribution of the study population by incidence of IPD and vaccination status during 2004-2008.

Year	Served children ≤14 year	IPD in Vaccinated	IPD in Non-vaccinated	IPD incidence
2004	143908	0	17	11.81
2005	146100	0	8	5.5
2006	148325	0	19	12.8
2007	150584	0	22	14.6
2008	152879	0	13	8.5
Total	741796	0	79	53.21

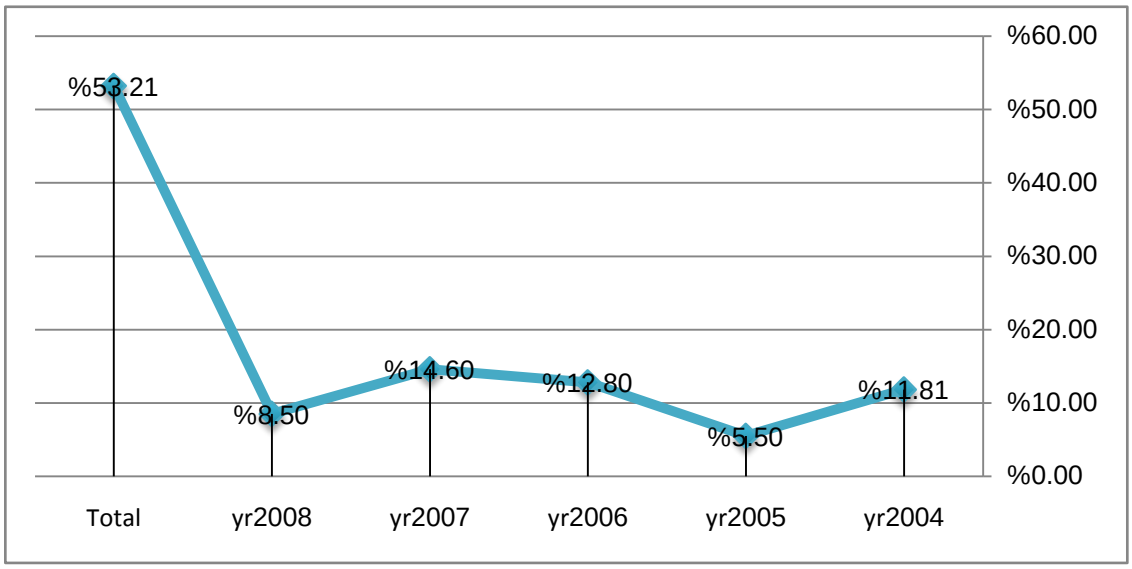

Figure 2. Description of the study population by incidence of IPD in non-vaccinated children during 2004 – 2008

Table 3. Distribution of the study population by incidence of IPD and vaccination status during 2009 to 2015

Year	Served children ≤14 year	IPD in Vaccinated	IPD in Non-vaccinated	IPD incidence	
				Vaccinated	Non-vaccinated
2009	155309	1	16	0.64	10.3
2010	157675	8	16	5.07	10.14
2011	160077	4	5	2.4	3.12
2012	162515	11	5	6.7	3
2013	164990	7	5	4.24	3
2014	167503	5	4	2.98	2.38
2015	170053	4	1	2.35	0.58
Total	1138122	40	52	24.38	32.52

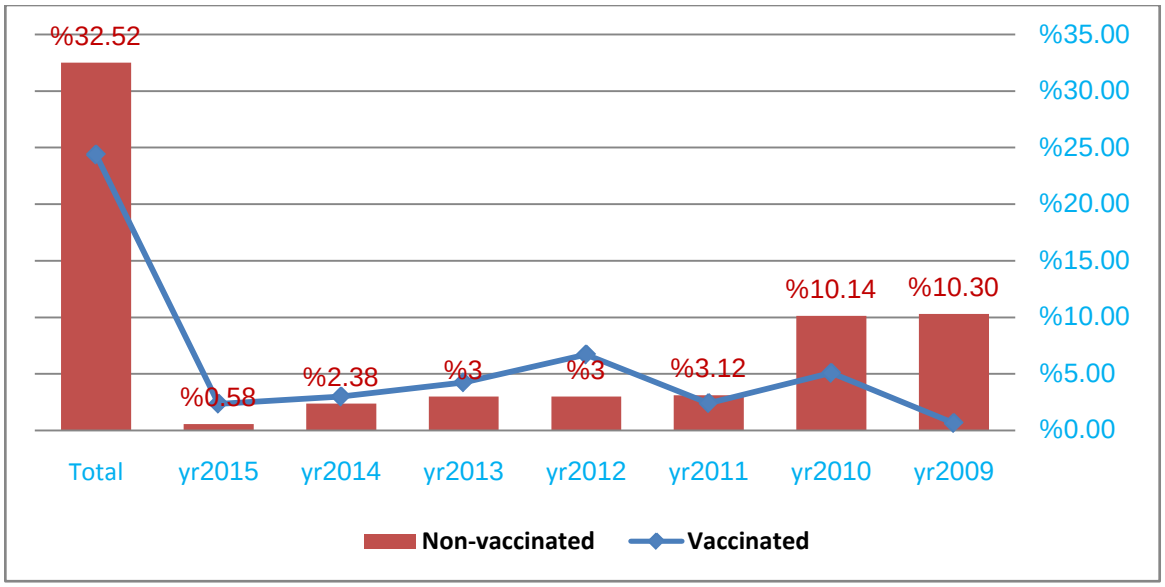

Figure 3. Description of the study population by incidence of IPD and vaccination status during 2009 to 2015

Table 4. Distribution of the study subjects by drug sensitivity

Drug	Sensitive	Resistant	intermediate	Total
Penicillin	128	10	33	171
Ceftriaxone	170	1	0	171
Vancomycin	171	0	0	171

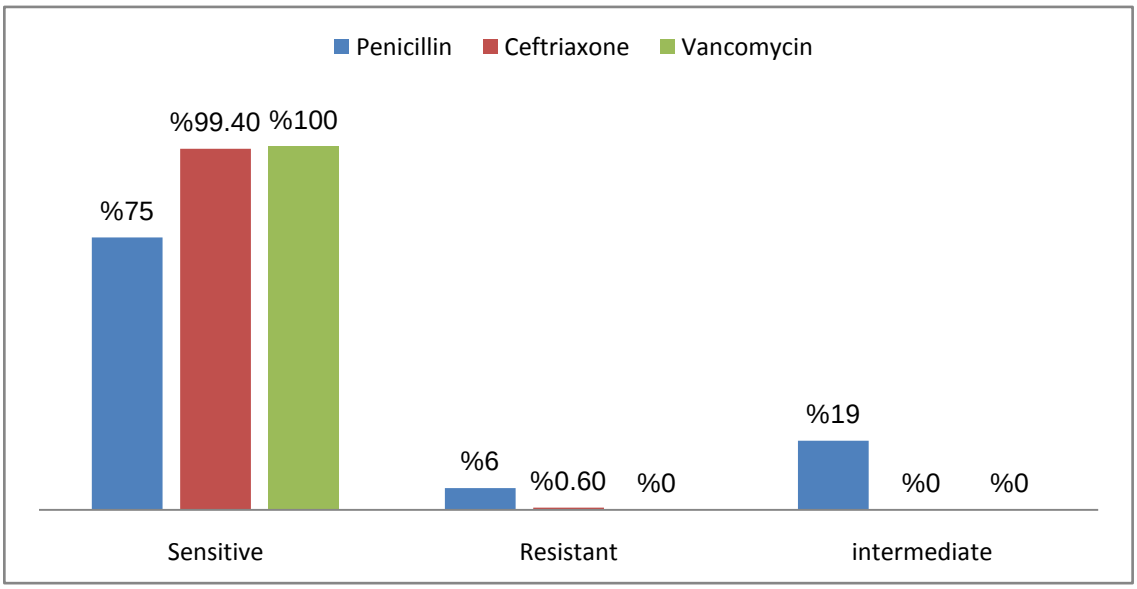

Figure 4. Description of the study subjects by drug sensitivity

4. Discussion

Streptococcus Pneumonia is a major cause of focal and systemic IPD infections in children including otitis media, sinusitis, pneumonia, meningitis, septicemia, cellulitis and rarely skeletal infections. There are almost 14 million cases of severe illnesses and 800000 deaths among children at or below age 5 years occurring annually worldwide. This high impaction on child health is attributed to pneumococcal high serotypes number, variable virulent factors, and wide geographical distribution.

Most of the Saudi studies showed variability in serotype causing IPD; however certain serotypes were the cause of the majority of the cases of IPD including 1,3,4,5,6B,7, 14, 18C, 19A, 19F,23F, and rarely 3,9V,11 and 22. Serotype prevalence varies significantly in different countries and in different seasons [9]. It also has a cycling pattern every 3-5 years. There are also some reports of inducing serotype replacement by currently available conjugate vaccines with a good example of 19A serotype surge in different countries [10].

Previous studies reported IPD incidence of 2 – 25/100000 live Saudi children ≤ 5 years of age in different studies [11]. Our study showed similar trend with an annual incidence of around 7.2 per 100000 prior to introduction of conjugate vaccine and 2.15 per 100000 after introducing conjugate vaccination.

However, we are not able to screen the breakthrough infections to discern whether they were caused by the vaccine or non-vaccine types. Pneumococcal vaccine

implementation requires a vigilance in tracing braking infections and define their serotypes in order to advise for further vaccine strategies and modification.

The most common presenting complaint was fever followed by seizure and shock indicating the severity of such illnesses. All invasive diseases in our patients were in the form of bacteremia, pneumonia, and meningitis. There were no other manifestations such as cellulitis, pericarditis or musculoskeletal manifestations.

Streptococcus pneumonia resistance to penicillin is rising worldwide [12]. This is mainly attributed to the inappropriate and excessive use of antibiotics. However, the emergence of resistant serotypes may be a contributory factor. We found 25% of our isolate being resistant to penicillin. Other Saudi studies showed a higher rate of resistance at 70% and 36% [13].

5. Conclusion

The introduction of PCV7 has significantly decreased the incidence rates of IPD in children. The conjugate vaccines have shown a significant efficacy in reducing IPD among our population.

Conflict of Interest

Authors declare no conflict of interest to declare.

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