Chapter

Pneumococcal Carriage in Jordanian Children and the Importance of Vaccination

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Abstract

Pneumococcal carriage is a prerequisite for invasive and non-invasive infections, where children and elderly are the most vulnerable groups. Aims: Determine rates of carriage, resistance, and coverage of the pneumococcal conjugate vaccines (PCVs) in children attending day care centers (DCC) in north Jordan. Methods: Nasopharyngeal swabs (NP) were taken from healthy Jordanian children from north Jordan with ages ranging from 1 month to 14 years in the period from 2008 to 2019. Classical methods were used for cultivation, identification, resistance testing, and serotyping. Results: 1866 NP swabs were tested with carriage rate 39.3% (733 isolates). Resistance was variable; however, it showed highest rates for penicillin (89.3%) and trimethoprim-sulfamethoxazole (73.0%). Serotype 19F predominates with 17.6% of all serotypes. Coverage of the future PCV20 was 73.1% compared to the old PCV7 (41.7%). About 493 cases had a previous 1–3 PCV7 injections, among which 256 (51.9%) cases were pneumococcal carriers, distributed as non-PCV vaccine serotypes (31.6%), and with PCV types (68.4%). Conclusions: The potential inclusion of the PCV vaccination in the national immunization program of the country is necessary.

Keywords: *Streptococcus pneumoniae*, PCVs, coverage, nasopharyngeal carriage, resistance

1. Introduction

1.1 Describing the Jordanian situation

Jordan is an upper middle-income country with a total population of 10,806,000 inhabitants, where 44.3% of them are under the age of 19 years, and quite youthful with almost 75% under the age of 30. However, risk groups are the children below 15 years of age (34.4%), among which 11.1% are under the age of 5 years, and 3.67% are over 65 years of age. These age groups (children and elderly) are considered to be at risk from pneumococcal infections globally [1–3]. The prevalence of pneumococcal carriage was the only way in Jordan to detect the serotypes rotating in the Jordanian community, which reflects the clones of infections that might take place. The carriage rates in these areas were relatively high compared to other countries in the region. However, different serotypes were found in different areas. All of these isolates have

high resistance rates and are covered to a high percentage with the PCV13 or PCV20. This implies the necessity for a "strategic plan for vaccination in Jordan". *Streptococcus pneumoniae* is considered a leading causative agent of death because of pneumonia globally, especially in the developing countries or in Africa and Asia. In the case and history of Jordan, there is no data available on the pneumococcal infections or serotypes of invasive pneumococcal diseases (IPD), although parts of some publications have described infections with the pneumococci. However, to-date, the PCVs are not available in the National Immunization Program (NIP) of the country, but they are available in the private sector since the year 2000, followed by PCV13 in the year 2010. In Jordan, an average of 400–500 meningitis infections of different causative agents were reported annually, and many infections of otitis media and pneumonia with no identified causative agents, therefore surveillance of the carriage due to *Streptococcus pneumoniae* is essential. Another serious problem for Jordan is the antibiotic consumption, where no reported data are available. Although Jordan is one of the best countries in the region for medical tourism, but there is no numbers stating the antibiotic consumption of the country, where high resistance rates in antibiotics were found [4]. Causes for the high antibiotic resistance in the country are the misuse and abuse of the antibiotics [5, 6]. Furthermore, there are no statistics from the Ministry of Health (MOH) of Jordan regarding the statistics of IPD taking place in hospitals. However, only non-meningococcal meningitis is registered from the statistical department of the MOH, which includes a variety of causative agents including *Streptococcus pneumoniae* (i.e., pneumococcus). This fact is shown in **Figure 1** from the year 1990–2018. By checking these data in the figure, it appears that more than 50% of all cases are from Irbid (North Jordan), 1% from Madaba and 10% from Amman. However, almost 20% of the causative agents of non-meningococcal meningitis are due to the pneumococcus [7]. Another crucial point about Jordan is the absence of national centers working separately on different types of bacteria. These centers in the developed countries and other countries work together with the epidemiological national centers to develop statistics about the rate of invasive diseases caused by infectious agents and their resistance development. Such data are important for setting recommendations to develop new anti-infectious products or to set new treatment strategies. Furthermore, collection

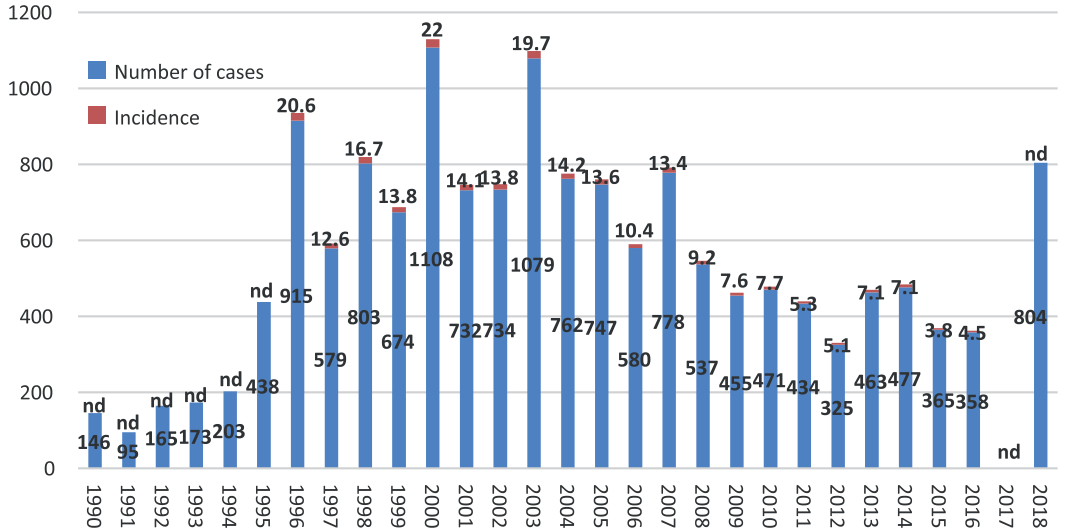

Figure 1.
Number of cases and incidence/100,000 of non-meningococcal meningitis in Jordan.

of invasive samples isolated at the hospitals is almost impossible, because the patients have consumed antibiotics prior to the microbiological sample testing. Therefore, shifting the surveillance to study the carriage of the pneumococci in children was the solution to find out all the possible serotypes rotating with their resistance data.

1.2 Global importance of *Streptococcus pneumoniae* (i.e., the pneumococcus)

S. pneumoniae, or the pneumococcus, is a lancet shape, Gram-positive diplococci, bile soluble, mainly optochin sensitive, and encapsulated. The diversity of capsular types is large, with more than 100 serotypes recognized to date based on the composition of the capsular polysaccharide. Many *S. pneumoniae* serotypes are capable of causing invasive diseases, including meningitis, septicemia, bacteremia, and non-invasive diseases like pneumonia, sinusitis and others; however, most of these diseases globally are caused by a small number of common serotypes [8]. The relative contribution of each serotype to the local burden of disease varies globally, with serotypes 1, 5, 23F, 19A, 19F, 6B and 6A more prominent in developing countries. *S. pneumoniae* infections may vary seasonally and large outbreaks exists but rarely found [8–10]. Meningitis due to *S. pneumoniae* occurs most commonly in early ages of children and in patients over 65 years of age, with an estimated incidence rate of 17 cases per 100,000 population in children less than five years of age [11]. This bacterium is widely spread and can also be found in pets [12]. As a comparison, the incidence of non-meningococcal meningitis for Jordan is estimated to be 4.5/100,000 cases in the year 2016 as shown in the figure. The case fatality rate for meningitis due to *S. pneumoniae* in children less than five years of age exceeds 73% in some parts of the world.

An important study done by the GBD 2016 Lower Respiratory Infections Collaborators in 2016 showed that the lower respiratory infections are the leading cause of morbidity and mortality around the world [13]. This study provides an up-to-date analysis of the burden of lower respiratory infections in 195 countries for the past 26 years, and shows how the burden of lower respiratory infection has changed in people of all ages. Their Findings In 2016 indicate that lower respiratory infections caused 652,572 deaths in children younger than 5 years, 1,080,958 deaths in adults older than 70 years, and 2,377,697 deaths globally in people of all ages. In this regard, *Streptococcus pneumoniae* was the leading cause of lower respiratory infection morbidity and mortality globally, contributing to more deaths than all other etiologies combined in 2016 [13].

S. pneumoniae was given the name as the forgotten killer in children in 2006 by the WHO in 2006 [14]. Furthermore, according to the WHO, 142 countries have introduced the PCV in the National Immunization Program. Jordan as one of the upper middle-income countries has not included this vaccine to the National Immunization Program (NIP) to-date.

The aim of this chapter is to show results of investigations of continuous surveillance on the carriage of *Streptococcus pneumoniae* from 2008 to 2019 in Jordanian children and to show the need of the inclusion of the PCVs in the NIP of the country.

2. Material and methods

Research studies on the carriage of Streptococcus pneumoniae were approved by the Independent Ethical Committee (IEC) of the Ministry of Health (MOH) of Jordan, followed by approval of the Ministry of Health (MOH) with approval number

8/75/2/2257, and other approvals of the directorates of each day care center (DCC). Informed written consent for the participants and the use of NP swabs was obtained from parents prior to collecting the swabs. Parents were educated on the benefits of future vaccination with the available PCVs. Nasopharyngeal swabs were taken from children attending the governmental Day Care Centers (DCCs) from the governorates of Ajlun (n = 415) [15], Madaba (n = 761) [1, 16], private clinic in Amman (n = 149) [16], Irbid (n = 423) [1], Wadi Alseer (n = 118) [17], with total number of samples 1866. Only one NP-swab was obtained from each child with exception to the research project from Ajlun, where 3 consequent samples were taken at 2 months at the time of the first vaccination, then at 4 months of age at the time of the second vaccination and finally a third sample was taken 2–3 months after the third vaccination with PCV7. NP-samples were collected in the period from 2008–2019. Processing, culturing and identification were done by classical methods [1, 18]. Resistance testing was performed according to the latest CLSI standards using *S. pneumoniae* ATCC 49,619 as a control strain [19]. The Neufeld's Quellung reaction method was used for Serotyping using type and factor sera provided by the Statens Serum Institute (SSI), Copenhagen, Denmark.

3. Results and discussion

Four governorates and the capital of Jordan were tested during the whole period of carriage surveillance in Jordan. The total carriage rate for the whole period and for the whole population tested was 39.3% as presented in **Table 1**. The highest carriage rate was in the governorate of Ajlun with 58.1%, because three samples were obtained from the same child over one year period. Nevertheless, this carriage rate of Ajlun was not significantly different ($p > 0.05$) from the carriage rate obtained from Wadi Al Seer, even with only one NP-swab obtained from each child. Wadi Al Seer and Ajlun were tested almost at the same period. The most interesting finding of all cities is the findings in the capital of Amman, where only 13.4% of the children involved in the study were carriers and that the coverage of the PCVs was minimal as found in **Table 1**. This was due to the reason that 69 cases from 149 (46.3%) were vaccinated with PCV7. Only 11 cases from the vaccinated children of Amman were carriers, but none of them was carrier of PCV7 serotype. The second highest carriage was shown in Madaba with 37.1% carriage rate, followed by Irbid with carriage rate of 29.6%. Coverage rates of the PCVs were highest (76.0%) for Irbid with PCV20, and this coverage was not significantly different from the PCV20 coverage for Irbid city ($p < 0.05$). To-date, there are at least 220 publications all over the world investigating carriage or nasopharyngeal carriers of Streptococcus pneumoniae. Our findings are comparable with other studies all over the world; in the region as an example, a study done in Palestine in 2013 has found carriage rates in 11 cities of Palestine to be from 34.1% in Ramallah up to 66.7% in Tubas [20]. In the kingdom of Saudi Arabia, carriage rate was found in 2014 to be 6% [21]. Another study done in 11 countries of Asia and the Middle East on 4963 children below 5 years of age found nasal carriage rate of 22.3% of antibiotic-resistant pneumococci isolates [22]. In Israel, carriage rates tested on ages between 2 and 24 months was shown to increase with age from 2 months with 26% carriage rate to 62% at age of 24 months [23]. In a recent study about carriage of the pneumococcus in Indonesia showed high carriage rate of 73% in school children with acute otitis media (AOM) [24]. Dominant serotypes of the school children were 23A (11 %), 6A/6B (10 %), 3 (8 %), 14 (7 %), 6C/6D (7 %), 11A/11D (6 %), 15B/15C

City	Year from–to	No. of samples	Carriage rate (%)	Coverage of PCV7 (%)	Coverage of PCV10 (%)	Coverage of PCV13 (%)	Coverage of PCV20 (%)
Wadi Al Seer	Mar. 2008–Nov. 2009	118	55.1	52.3	52.3	58.5	73.0
Ajlun	Jun. 2009–Nov. 2010	415	58.1	32.1	32.1	50.4	70.9
Amman	May 2015–Apr. 2016	149	13.4	5	5	10	35
Irbid	Dec. 2017–Mar. 2019	423	29.6	51.2	51.2	65.6	76.0
Madaba	May 2015–Mar. 2019	761	37.3	50.7	51.1	65.1	75.7
Total	Mar. 2008–Mar. 2019	1866	39.3	42.4	42.7	58.4	72.4

Table 1.
Carriage rate of S. pneumoniae *in 5 cities of Jordan with the coverage rate of PCVs including the future PCV20.*

(4 %) and 35 B (4 %). Coverage of the PCV13 in the Indonesian study was 41%. Other study in south Italy on healthy children aged 1–7 years attending day-care centers and schools showed nasopharyngeal colonization rate of Streptococcus pneumoniae to be 18.29%. PCV13 serotypes of this study covered 60.34% of the isolates with serotypes 19A, 19F, 14, 6B, or 23F; and that 8.62% of the strains were intermediately resistant to penicillin, 65.5% were erythromycin-resistant, and 17.2% were resistant to Co-trimoxazole [25]. To date, there is no data describing the invasive Streptococcus pneumoniae infections in Jordan, but this bacterium was identified as the causative agent in 30% of meningitis cases in Yemen, 16% in the UAE, 19–21% in Kuwait, 13% in Qatar, 23–31% in Saudi Arabia, and 21–30% in Egypt [26].

Resistance rates to antibiotics are increasing worldwide. The main reasons for this global threat of resistance are the misuse and abuse of the antibiotics [27]. Streptococcus pneumoniae is one of the major pathogens of community-acquired respiratory tract infections, where Alexander Project in 1997 for resistance showed the variation of antibiotic resistance in Europe [28]. In our studied 5 regions in Jordan as found in **Table 2**, resistance rates to penicillin varied from 80% to 95.4%, and for erythromycin from 55% to 73.6%, for clindamycin from 20%–44.4%, and for Co-trimoxazole (SXT) from 30%–78.5%. Extreme differences in antibiotic resistance were observed in this surveillance in the last 13 years. This resistance is increasing in Europe and in the United states [29, 30]. More than 80% of the resistance is covered by the new PCV20 [27].

In **Table 3**, an uneven distribution of the serotypes in each city was found. Certain clones of the serotypes were found only in one city or two, but not in others. As an example, Serotype 5 was only found in Madaba. This serotype 5 is prevalent in many countries [31–35]. Serotype 4 was only found in Ajlun, but it is also prevalent in many countries as causative agent of an outbreak in a home for aged people [36, 37]. Serotype 13 was also only found in Ajlun, which was found as multidrug resistant in Russia [38]. Serotypes 19A and 19F were mainly found in Ajlun and Madaba.

Table 4 gives an insight about the differences and comparisons of the Jordanian carriage rate, resistance and coverage of PCVs with other countries worldwide. In literature, pneumococcal nasopharyngeal carriage was studied in different directions,

City	No. of isolates	% PEN R	% ERY R	% CLI R	% TET R	% SXT R	% CHA R
Wadi Al Seer	63/118	80.0	61.5	33.8	53.8	73.8	9.5
Ajlun	241/415	82.0	55.7	36.3	46.8	62.3	2.5
Amman	20/149	90.0	55.0	20.0	45.0	30.0	0.0
Irbid	125/423	86.3	75.0	30.8	45.5	68.6	2.4
Madaba	284/761	95.4	73.6	44.4	52.8	78.5	3.7
Total	733/1866	89.4	64.8	36.3	47.6	73.0	3.1

Abbreviations: PEN (Penicillin), ERY (Erythromycin), CLI (Clindamycin), TET (Tetracycline), SXT (Sulfamethoxazole-Trimethoprim), CHA (Chloramphenicol), R (Resistance).

Table 2.
Resistance rate of S. pneumoniae in 5 cities of Jordan.

Serotype	Total no. (%)	Ajlun no.	Wadi Al Seer no.	Amman no.	Irbid no.	Madaba no.
3	12 (1.6%)	4	0	0	1	7
4	1 (0.14%)	1	0	0	0	0
5	1 (0.14%)	0	0	0	0	1
13	1 (0.14%)	1	0	0	0	0
14	40 (5.5%)	9	2	0	9	20
21	1 (0.14%)	1	0	0	0	0
28A	8 (1.1%)	1	0	0	1	6
34	4 (0.55%)	0	2	0	0	2
42	1 (0.14%)	1	0	0	0	0
10A	10 (1.4%)	4	0	0	1	5
10F	1 (0.14%)	1	0	0	0	0
11A	44 (6.0%)	21	3	3	4	13
15A	19 (2.6%)	10	3	1	3	2
15B	23 (3.1%)	13	1	0	3	6
15C	17 (2.3%)	6	0	0	5	6
15F	1 (0.14%)	0	1	0	0	0
16A	2 (0.27%)	0	0	0	0	2
16B	1 (0.14%)	1	0	0	0	0
16F	13 (1.8%)	7	1	0	4	1
17F	12 (1.6%)	4	1	0	1	6
18A	1 (0.14%)	0	1	0	0	0
18C	9 (1.2%)	0	0	0	1	8
19A	38 (5.2%)	19	2	0	4	13
19F	129 (17.6%)	29	12	1	26	61
22A	2 (0.27%)	0	0	0	0	2

Serotype	Total no. (%)	Ajlun no.	Wadi Al Seer no.	Amman no.	Irbid no.	Madaba no.
22F	2 (0.27%)	0	1	1	0	0
23*	5 (0.68%)	0	0	0	1	4
23A	26 (3.5%)	9	2	1	2	12
23B	1 (0.14%)	0	0	0	0	1
23F	59 (8.0%)	11	8	0	15	25
24F	7 (0.95%)	7	0	0	0	0
33A	3 (0.4%)	2	1	0	0	0
33F	7 (0.95%)	6	1	0	0	0
35A	3 (0.4%)	0	1	0	1	1
35B	12 (1.6%)	8	4	0	0	0
35C	1 (0.14%)	1	0	0	0	0
35F	2 (0.27%)	2	0	0	0	0
6A	65 (8.9%)	29	2	1	13	20
6B	58 (7.9%)	14	11	0	12	21
6C	4 (0.55%)	0	0	1	2	1
7B	5 (0.68%)	2	1	0	0	2
7C	1 (0.14%)	1	0	0	0	0
7F	1 (0.14%)	1	0	0	0	0
9N	9 (1.2%)	3	0	3	0	3
9V	9 (1.2%)	3	1	0	1	4
Pool C	6 (0.81%)	0	0	0	5	1
Pool D	2 (0.27%)	0	0	0	1	1
Pool E	4 (0.55%)	0	0	0	2	2
Pool F	1 (0.14%)	0	0	0	1	0
Pool G	9 (1.2%)	0	0	0	1	6
Pool I	6 (0.81%)	0	0	0	1	5
Mixed 14 & 6B	1 (0.14%)	0	0	0	0	1
NT	18 (2.5%)	7	1	0	2	8
Others*	15 (2.0%)	0	0	8	0	7

**Isolates from antisera pools C, D, E, F, G, I, which are not included in the PCVs*

Table 3.
Serotypes detected in the surveillance studies with numbers isolated in each city.

either to find out the carriage rate, to check the impact of the PCVs on colonization, or to check the rate of carriage before and after vaccination strategies, or the carriage rates after certain infection, and many other issues related. The data available in **Table 4** are from the region, from Africa, from Europe, and Latin America. As an example, in Palestine 11 cities were tested for pneumococcal carriage with rates ranging from 34.1% in Ramallah to 77.7% in Salfeet [20].

Country	Study period	Rate of carriage	PEN R (%)	ERY R (%)	CLI R (%)	SXT R (%)	PCV7 coverage	PCV13 coverage	Reference
Jordan	2008/19	39.3	89.4	64.8	36.3	73.0	42.4	58.4	[1, 15–17]
Palestine	2013	55.7	10.9	30.3	nd	45.9	55.7	nd	[20]
Ethiopia	2017	18.4	15.0	23.9	nd	nd	nd	nd	[39]
Turkey	2017	14.0	nd	nd	nd	nd	12.6	nd	[40]
Palestine (EJ)	2014	30.7	nd	nd	nd	nd	47.0	62.0	[41]
Palestine	2014	28.6	nd	nd	nd	nd	41.2	54.8	[41]
Gaza Strip	2009	50.0	70.0	nd	nd	nd	54.0	71.0	[42]
Pakistan	2013	73.6	nd	nd	nd	nd	38.9	53.1	[43]
Gambia	2009	72.0	nd	nd	nd	nd	24.7	46.8	[44]
Finland	1994/95	49.0	nd	nd	nd	nd	nd	nd	[45]
Brazil	2008/09	55	38.4	nd	nd	73.8	nd	nd	[46]

Abbreviations: nd = not defined; PEN (Penicillin), ERY (Erythromycin), CLI (Clindamycin), SXT (Sulfamethoxazole-Trimethoprim), R (Resistance), PCV7 (7-Valent Pneumococcal Conjugate Vaccine), PCV13 (13-valent Pneumococcal Conjugate Vaccine).

Table 4.
Comparison of carriage rate, resistance and coverage of PCV7 and PCV13 in other locations (regional and international).

4. Conclusions

The prevalence of pneumococcal carriage was the only way in Jordan to detect the serotypes rotating in the Jordanian community, which reflects the clones of infections that might take place. The carriage rates in these areas were relatively high compared to other countries in the region. However, different serotypes were found in different areas. All of these isolates have high resistance rates and are covered to a high percentage with the PCV13 or PCV20. This implies the necessity for a strategic plan for vaccination in Jordan.

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Conflict of interest

The author declares no conflict of interest.

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