Review Article

J Babol Univ Med Sci
23; 2021. P: 189-198

Evaluation of Frequency, Drug Resistance and Serotyping of Streptococcus Pneumoniae in Iran: A Systematic Review

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J Babol Univ Med Sci; 23; 2021; PP: 189-198

Received: Feb 11st 2020, Revised: Aug 9th 2020, Accepted: Aug 31st 2020.

ABSTRACT

BACKGROUND AND OBJECTIVE: Streptococcus pneumoniae is one of the main etiologies of meningitis, pneumonia, sinusitis, and middle ear infection associated with significant morbidity and mortality. This report aims to review and report the serotype distribution and antimicrobial resistance patterns and determine the frequency of S. pneumoniae in Iran.

METHODS: A systematic literature review of the literature published from January 1990 to August 2020 was performed to identify articles that have been published in Google Scholar, Scopus, PubMed, SID, IranMedex, and Magiran databases that describe the serotype distribution, antimicrobial resistance patterns and frequency of S. pneumoniae in Iran. The search terms were "Streptococcus pneumoniae, Antibiotic resistance, Serotyping, Systematic review, and Iran". The exclusion criteria were review articles or case reports, reports only emphasizing on serogroups rather than serotypes, and having isolates fewer than 10.

FINDINGS: Of 56 reports, 33 publications that met our inclusion criteria were selected for data extraction and analysis. The frequency of S. pneumoniae in patients and carriers was estimated at 1.5% and 20%, respectively. Highest levels of resistance were against co-trimoxazole followed by penicillin, and erythromycin. The most common serotypes were 23F followed by 19F, 6A/B, 19A, and 18C.

CONCLUSION: Based on the results of this study, the inappropriate use of antibiotics and the subsequent spread of resistant pneumococcal isolates in our country is worrisome.

KEY WORDS: *Streptococcus Pneumoniae, Antibiotic Resistance, Serotyping, Systematic Review, Iran*.

Please cite this article as follows:

Yousefi M, Mohammadi M, Afshar D, Nazari-Alam A. Evaluation of Frequency, Drug Resistance and Serotyping of Streptococcus Pneumoniae in Iran: A Systematic Review. J Babol Univ Med Sci. 2021; 23: 189-98.

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[DOR: 20.1001.1.15614107.1400.23.1.28.7]
[DOI: 10.22088/jbums.23.1.189]

Introduction

Streptococcus pneumoniae (pneumococcus) is a gram-positive bacterium. These types of microorganisms can be part of the natural flora of the nasopharynx in humans, and especially in children (1). This colonized bacterium is not dangerous, but it is able to migrate to other parts of the body, such as the ear, lungs, blood, and cerebrospinal fluid, and cause disruption in these organs (2). In addition, it may cause chronic infections such as pneumonia, meningitis, sinusitis, and otitis media in carriers. According to the World Health Organization (WHO), one million children die due to pneumococcal infections in the world every year (3, 4).

The colonization of this bacterium in the carriers plays an important role in the development of infection in the community (5). The S. pneumoniae is the main cause of a wide range of serious invasive diseases such as sepsis, bacteremia, and meningitis (6). These infectious diseases are causative of the life-threatening morbidity and mortality in pediatric patients and adults worldwide (7, 8). For the treatment of pneumococcal infections, the antibiotics of the group of macrolides, beta-lactams, fluoroquinolones, co-trimoxazole, and vancomycin have been frequently used (9, 10); however, during the past decades, drug resistance has increased and antibiotics biotypes become a further challenge (11, 12).

Vaccination is recommended to fight against this pathogen and control it (13). Vaccination greatly reduces the incidence of infections caused by this bacterium. The vaccines used today are multivalent conjugated vaccines (14). Generally, this bacterium includes over 93 serotypes. For the first time in 2000, a seven-valent pneumococcal conjugate vaccine (PCV7) has been used (13). These conjugate vaccines contain the most common serotypes that are the cause of pneumococcal disease. These serotypes include 4, 6B, 9V, 14, 18C, 19F, and 23F. However, after using the vaccine in the community for a while, it became clear that the vaccine did not have the desired efficacy. To overcome this problem, PCV10 and PCV13 were replaced. In addition to these strains, vaccines include 7 F/A, 19A, 1, 3, 5, and 6 A/C. But after using these vaccines, their impact was reduced again (13).

To compensate for this deficiency, the pneumococcal polysaccharide vaccine (PPSV23) was introduced (15). To increase the effectiveness of this type of vaccine in different societies, there is a need for relevant information, including the frequency of this pathogen in each community, the type of circulating serotypes in the community, and antibiotic susceptibility testing. Regarding this fact, various studies have been conducted about this issue in Iran; however, there is high inconsistency between the results. So far, pneumococcus vaccine has not been embraced in the Expanded Program on Immunization (16) in Iran and is advised only for at-risk groups.

In Iran, information about serotypes is rarely available due to the low level of positive reports, which is due to the improper use of antibiotics and the problems of culturing the bacteria themselves. The main purpose of designing this systematic review is to determine pneumococcal serotypes, antibiotic resistance and its frequency in Iran. The specific objectives of this review are to review the distribution of serotypes, patterns of antibiotic resistance of S. pneumoniae in Iran and to fill existing information gaps and provide basic and important information for pneumococcal vaccination policies.

Methods

Study design and search method: We have been done a systematic literature review of reports published from January 1990 to August 2020 about circulating pneumococcal serotypes in Iran by identifying articles that have been published in Google Scholar, Scopus, PubMed, SID, IranMedex, and Magiran databases that describe the serotype distribution, antimicrobial resistance patterns and frequency of S. pneumoniae in Iran. The search terms were "Streptococcus pneumoniae, Antibiotic resistance, Serotyping, Systematic review, and Iran". Articles that were published in Persian or English were reviewed. The study was registered with the ethics code IR.KAUMS.REC.1399.024

Inclusion and exclusion criteria: We considered observational studies (prospective, retrospective, analytical and descriptive) reporting data on frequency, serotypes distribution and antimicrobial resistance patterns of S. pneumoniae serotypes obtained from clinical samples (e.g., blood, CSF, pleural fluid, joint or peritoneal fluid, ear, eye, nasopharynx, or tracheal aspirates in clinical cases, or nasopharyngeal specimens in carriers) in Iran. The exclusion criteria were the relevant studies not carried out in Iran, studies in which type of patients and their age was unclear, studies whose sample size included less than 10 isolates, review articles, systematic reviews, case reports, and articles that were only available in abstract form.

[DOR: 20.1001.1.15614107.1400.23.1.28.7]
[DOI: 10.22088/jbums.23.1.189]

Data extraction: Our search results were combined by EndNote software, and duplicate documents were removed. Titles and abstracts were reviewed in terms of incompetence criteria and items that did not meet the target criteria were excluded from the study. The full texts of reports were read carefully, and organized pattern tables were built in Microsoft Excel spreadsheet and used to record the extracted data for the following variables: specified sample size, the specificity of the statistical population, number of isolates greater than 10, date of the study, date of publication, place of study, prevalence, antibiotics susceptibility results (penicillin, erythromycin, vancomycin, chloramphenicol, gentamicin, cefotaxime, ceftriaxone, tetracycline, rifampin, co-trimoxazole, ciprofloxacin, and ampicillin) and serotyping. Four researchers on the team freely perfumed literature review and explored all titles and abstracts of the articles. We assessed the quality of the articles by the adapted form of the Newcastle-Ottawa cohort scale for cross-sectional studies.

Data analysis: Analysis of the extracted data was performed using the Microsoft Excel spreadsheet program. The collected data were categorized into three areas: "Streptococcus pneumoniae prevalence", "Antibiotic resistance" and "Pneumococcal serotypes". The percentage of the serotypes was computed by dividing the number of isolates for each serotype by the total number of isolates included in all the reports. The frequency of antimicrobial resistance was defined as the percentage of isolates that were divided by the total number of isolates tested for resistance against the above specific antimicrobial agent.

Results

We screened 56 articles in our preliminary search, of which 33 studies fulfilled inclusion criteria and were included in the final analysis (Fig. 1) Among them, 23 articles that did not meet our criteria were excluded from the study (Fig. 1).

The frequency of S. pneumoniae in carriers: The first studies were from 1998 to 2005 which examined the frequency of bacteria in 2629 subjects and 315 (12%) cases were reported in three studies (17-19). In four studies conducted from 2005 to 2012, 973 (24.3%) of the 4008 studied children were pneumococcus carriers (20-23). Ten studies were conducted from 2013 to 2020 and 240 (24.1%) subjects of 1450 studied people were pneumococcus carriers (16, 24-32). Based on all the mentioned studies, the average prevalence of Iranian carriers was estimated at 20%.

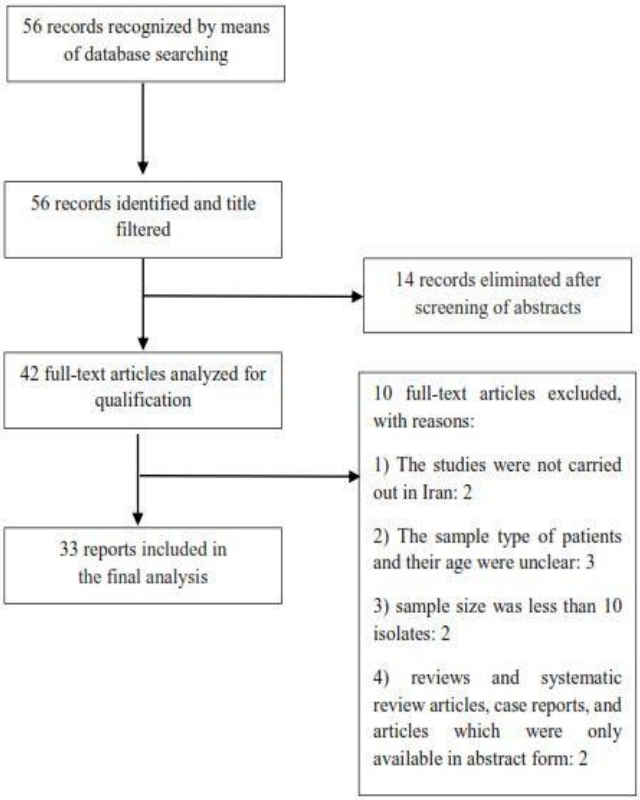

Figure 1. Flowchart of search method and selection of articles

Frequency of S. pneumoniae in patients: Two studies were conducted during the years 1997-2003, in which 57 pneumococcus isolates were obtained from 732 clinical specimens. The frequency of this bacterium was 7.79% (33, 34). In studies conducted from 2003 to 2013, 101 isolates of pneumococcus were obtained from 18519 clinical samples, and in other words, the frequency of pneumococcus was 0.55% (35-37). In other surveys, 1160 different clinical samples were collected from patients from 2013 to 2016 and were investigated for the presence of S. pneumoniae. In those studies, 148 (12.76%) bacterial isolates of pneumococcus were identified (12, 38, 39). Based on results of the mentioned studies, the average frequency of pneumococcus in Iranian patients was estimated at 1.5%.

Antibiotic Resistance: Of studies included in our analysis, the antibiogram test has been done in 31 studies (7, 12, 16, 18-24, 27-29, 32-37, 39-50). These antibiotics were penicillin, erythromycin, vancomycin, chloramphenicol, gentamicin, cefotaxime, ceftriaxone, tetracycline, rifampin, co-trimoxazole, ciprofloxacin,

[DOR: 20.1001.1.15614107.1400.23.1.28.7]
[DOI: 10.22088/jbums.23.1.189]

and ampicillin. Based on these results, on average, isolates were most resistant to co-trimoxazole, penicillin, and erythromycin. In these studies, the antibiotics with the least resistance were vancomycin, cefotaxime, and ceftriaxone, respectively. The complete results of the antibiogram extracted from 26 articles are given in Table 1.

Determination of pneumococcal serotypes: Of 32 articles reviewed in our study, only 9 articles provided information about prevalent serotypes in Iran. Based on these studies, different serotypes were found in Iran: 1, 2, 3, 4, 6 , 6A/B, 7F, 8, 9, 9V, 10A, 11, 11A, 13, 14, 15, 15A, 15C, 17, 18C ,19, 19A, 19B, 19C, 19F, 20, 21, 22F, 23, 23A, 23F, 29, 31, 33, 34, 35A, 35B, and 37 (16, 20, 23, 24, 26, 32, 49, 51, 52). Among serotypes mentioned above, the most common serotypes were 23F, 19F, 6A/B, 19A, and 18C. In most studies, there were serotypes that were non-typable which in some cases were up to 26% of all strains.

Table 1. Antimicrobial resistance pattern of S. pneumoniae isolates

First author	Year	Province	Sample size	Antibiotic resistance (%)											
				PEN	ERY	VAN	CAM	GEN	CTX	CRO	TCN	RPM	SXT	CIP	AMP
Khajeh	1998-1999	Mashhad	90	38	-	-	-	-	-	-	-	-	-	-	-
Khotayi	1997-2000	Tehran	46	17	-	-	-	-	-	-	-	-	-	-	-
Yousefi Mashouf	1998-2000	Hamadan	11	-	-	-	36	0	-	0	-	-	27	-	63
Oskouei	1998-2000	Tehran	130	-	8	0	22	-	-	-	36	-	44	-	0
Jahanmehr	1999-2001	Tehran	66	18	-	0	-	-	-	-	-	-	-	-	7.5
Rajabi	2000	Tehran	66	28.8	-	0	-	-	-	-	-	-	-	-	7.5
Oskouei	2000-2008	Tehran	54	26	16.6	-	-	-	3.7	-	18.5	-	52	-	-
Behnaz	2002	Yazd	75	50	62.5	-	-	-	-	-	30.6	-	62.5	4.2	-
Rezaeizadeh	1998-2008	Tehran	30	56.7	20	0	20	76.7	-	-	-	-	63.3	-	20
Haghi Ashtiani	2001-2011	Tehran	194	46	51	0	30	63	13	12	-	-	72	-	24
Zargarizadeh	2002-2003	Tehran	50	44	26	0	16	-	8	6	20	2	65	-	-
Abdinia	2003-2013	Tabriz	44	37.8	16.2	0	5.4	22.8	8.1	10.8	-	2.7	32.4	8	-
Fahimzad	2004-2006	Tehran	20	35	-	0	10	-	-	-	-	10	60	-	-
Bakhshaei	2005-2006	Mashhad	102	48	43.1	-	-	-	-	-	-	-	80.4	-	-
Shishegar	2007-2008	Shiraz	12	-	10	-	-	-	20	-	-	-	100	0	50
Bokaeian	2008-2009	Zahedan	136	9.5	18	0	8	-	2.2	3.6	9.5	-	-	1.4	-
Sanaei Dashti	2008-2009	Tehran	573	9.2	-	1.5	6	-	3	4.5	66	0	11.8	1.5	-
Kargar	2010-2011	Shiraz	50	60	18	-	0	0	50	-	10	-	48	-	56
Soltan Dalal	2012	Tehran	15	80	65	53	53	0	-	-	0	-	-	-	65
Mirzaei	2011-2012	Kashan	291	-	3.4	0	-	-	-	-	25.5	0	-	-	-
Sabory	2012	Kermanshah	83	-	-	-	-	-	-	31	-	41	4	-	-
Tabatabaei	2012-2015	Tehran	73	20.5	83.6	7	-	-	42.5	31.5	-	-	15	-	-
Gharailoo	2013-2014	Sistan-Baluchestan	74	-	56	0	16	46	0	-	61	-	93	-	-
Houri	2014	Tehran	53	19.1	71.4	0	-	-	4.7	9.5	66.9	-	57.1	-	-

[DOR: 20.1001.1.15614107.1400.23.1.28.7]
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First author	Year	Province	Sample size	Antibiotic resistance (%)										
				PEN	ERY	VAN	CAM	GEN	CTX	CRO	TCN	RPM	SXT	CIP	AMP
Najafi Mosleh	2015	Hamedan	55	-	25.5	0	-	-	-	-	-	-	-	11	-
Mousavi	2014-2015	Tehran	76	-	86	-	-	94	-	-	5	0	-	-	-
Mohammadi Gharibani	2015	Ardabil	43	95.34	74.4	-	16.3	-	-	-	-	-	81.4	-	-
Ahmadi	2016	Tehran	100	22	59	-	23	-	-	-	57	-	92	3	-
Talebi	2013-2015	Tehran	161	58	60	-	59	-	-	-	75	-	94	-	-
Emaneini	2016-2017	Tehran	44	16	73	-	14	-	-	-	66	-	86	-	-
Ghahfarokhi	2015-2017 And 2018-2019	Tehran	80	8.7 27.5	55 68	-	18 20	-	-	-	20 15	-	63 80	-	-

Pen: penicillin, ERY: erythromycin, VAN: vancomycin, CAM: chloramphenicol, GEN: gentamicin, CTX: cefotaxime, CRO: ceftriaxone, TCN: tetracycline, RPM: rifampin, SXT: co-trimoxazole, CIP: ciprofloxacin, AMP: ampicillin

Discussion

In this review, we have shown that the most frequent serotypes obtained from Iranian Patients were 23F followed by 19F, 6A/B, 19A, and 18C. The main findings of our report are the frequency of S. pneumoniae in patients and carriers, which were estimated at 1.5% and 20%, respectively. The highest resistance rates were against co-trimoxazole followed by penicillin, and erythromycin. In other parts of the world, the most common serotypes are 14, 1, 4, 6 A / B, 3, and 8 (53). The frequency of serotypes in Iran is very different from other parts of the world (2, 8), but is in agreement with a systematic review by Singh et al. in 2017 in India, according to which, the serotypes 14, 1, 19F, 6B, 5, 6A, 9V, and 23F were the most common ones (54).

The prevalence of these serotypes may increase in cases where blood cultures are performed exclusively for hospitalized patients (55). Thus, infectious serotypes appear to cause serious infectious diseases that require hospitalization (4, 5). Polyvalent vaccines (seven, ten, thirteen, twenty-three) are used to prevent pneumococcus (13, 56). The use of this type of vaccine should be based on the type of serotype circulating in the community, but in Iran, it is recommended to provide a comprehensive study on the frequency of pneumococcal serotypes in all regions of Iran. In agreement with a report by Azarsa et al. in 2015 in Tehran on 560 clinical samples, the most prevalent serotypes in penicillin non-susceptible S. pneumoniae isolates were 23F, 19F, 14, 3 and 9V (26) and in a report by Abdoli et al. in 2020 in Bojnurd, of 106 cases of S. pneumoniae, serotypes 23F, 19F, 19A, 1, 14 were the most prevalent (25) and similar to in our report, the major serotypes were 23F and 19F. In other current reports, a similarity was observed in serotype distribution in Iran. In a report by Ahmadi et al. in 2019, the most common serotypes were 14, 19F, 23F (28). In a report by Talebi et al. in 2019, the most frequent serotypes among the penicillin non-susceptible S. pneumoniae were 14, 23F, and 19F (50) and in a report by Ghahfarokhi et al. in 2020 in Tehran, the most common serotypes were 23F, 14, 3 19F, and 19A (32).

All of the previous reports revealed that major serotypes in Iran in recent years are 23F and 19F which can be used in vaccine preparation for our social situations. Opposite to the report by Rafiei Tabatabaei et al. in 2019, in which the identified serotypes were the serotypes 1, 4, 6A/B, 7F, 9V, 11A, 14, 15A, 19A, 19F, and 23F (2), our major serotype was 23F. Genetic mutations can change in specific areas, and the causes must be evaluated. A study by Beheshti et al. in 2020 demonstrated that all of the penicillin-resistant isolates were multidrug-resistant (MDR) and the most common capsule types detected in 64% of the pneumococcal isolates were 6A/B, 19A, 15A, 23F (16). One can presume that the isolated MDR can be our major problem in Iran because this result was very similar to our results. By comparing studies performed in Iran and

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studies in other parts of the world (1, 4, 5, 55, 57-59), it can be seen that there is a significant difference with the prevalence of pneumococcal meningitis in Iran, which is low. Thus, one can say that the main cause of bacterial meningitis in Iran is a microorganism other than pneumococcus. To prove this claim, it is necessary to make a comprehensive study in this regard. The frequency of pneumonia caused by this bacterium is reported to be 25% and 28% in the United States and Germany, respectively (60, 61). In a study by Edmond et al., pneumococcus prevalence was reported to be 15.5% (62).

Contrary to these reports, the frequency of *S. pneumoniae* in patients was estimated at 1.5% in other regions of Iran, which is very low in comparison with other countries. The frequency of S. pneumoniae in the Netherlands, Spain, and China was reported to be 22%, 36%, and 16.6%, respectively (58, 63, 64), which is very higher in comparison with our report indicating 1.5% prevalence in Iran. On the other hand, this is in agreement with the study of Ahangarzadeh Rezaee et al. which was performed on children with cancer, and showed that 2% of patients had pneumococcal infection (65). In this study, it has been shown that pneumococcal bacteria can be considered as a life-threatening infectious agent in cancer patients.

The second issue in pneumococcal infections is the status of carriers and one of the limitations of these studies was that the age of the evaluated carriers was not the same. The average number of pneumococcal carriers in the world is between 3% and 18% (53) but the frequency of S. pneumoniae in carriers was estimated at 20%. Based on these studies, the number of pneumococcal carriers in different regions of Iran is higher than the global average. Factors involved in this phenomenon include non-observance of health care and lack of regular vaccination in the exposed age groups. Scientific documents on S. pneumoniae antibiotic resistance at global level have greatly increased in recent years. Scientists and physicians need to differentiate antibiotic resistance patterns for meningitis and non-meningitis isolates. According to the results of studies, the highest drug resistance of pneumococcus in Iran is related to co-trimoxazole (maximum range), erythromycin and penicillin, respectively. In Africa, the highest resistance is related to co-trimoxazole and tetracycline (57).

In Asia, the highest resistance is related to erythromycin and penicillin (66), which is somewhat similar to the studies conducted in Iran. Studies on antibiotic susceptibility of pneumococcus are carried out periodically and regularly in most Asian countries (59, 66, 67), but there are few studies available in Iran. One of them is the study of Rafiei Tabatabaei et al. in 2017 in Tehran. In their study, among 73 S. pneumoniae isolates, antibiotic susceptibilities were 95.9% to ofloxacin, 93% to vancomycin and 78% to penicillin, revealing an increase in *S. pneumoniae* isolates that were resistant to conventional drugs in the course of treatment (39). This is in agreement with the study of Mohammadi Gharibani in 2019 in Ardabil, according to which 74.4 % of the isolates were resistant to erythromycin, 95.3% to penicillin, 81.3 % to co-trimoxazole (27).

We can claim that the current therapeutic strategies are not suitable in Iran and they need a change. The vancomycin resistance was very rare in our results but in a report by Nazari Alam et al. in 2017 in Tehran, 5 S. pneumoniae isolates were found to be resistant to vancomycin. Their results demonstrated that an alarming rate of vancomycin-resistant pneumococci may result from the uncontrolled use of vancomycin and self-medication (8).

Considering the existing gap, it is necessary to conduct regular studies under the supervision of a single unit in Iran and we must consider correct management of the antibiotics, reduction in the cost of treatment and timely treatment of patients with the pneumococcal disease based on the obtained information. In conclusion, although regular studies have not been performed on pneumococcus in different regions in Iran, the frequency of carriers and types of serotypes can be estimated based on our systematic review data and based on that strategy, the vaccination strategy can be revised and fundamental changes can be made. In addition, while considering drug resistance in pneumococcal isolates, proper treatment program should be performed for pneumococcal patients. The inappropriate use of antibiotics and the spread of resistant strains in the community have led to increased drug resistance of pneumococci, which is worrying in the future; to solve this problem, it is necessary to prepare and introduce an appropriate antibiotic prescription for pneumococcus.

Acknowledgment

We express our thanks to Vice Chancellor for Research and Technology of Kashan University of medical sciences for accompanying us in this research.

[DOR: 20.1001.1.15614107.1400.23.1.28.7]
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