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Review Article

Prevalence of Nasopharyngeal Carriage of *Streptococcus pneumonia* in Iran: A Meta-Analysis

Seyed Mehdi Hosseini (MSc)[a], Jalal Poorolajal (MD, PhD)[b], Manoochehr Karami (MSc, PhD)[c*], Pegah Ameri (MSc)[a]

[a] *Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran*

[b] *Research Center for Health Sciences and Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran*

[c] *Social Determinants of Health Research Center (SDHRC) and Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran*

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**** Correspondence***
Manoochehr Karami (MSc, PhD)
Tel: *+98 81 38380762*
Fax: *+98 81 38380762*
E-mail: *ma.karami@umsha.ac.ir*

ABSTRACT

Background: *Streptococcus pneumonia* is a major cause of childhood morbidity and mortality worldwide**.** Several studies have explored the nasopharyngeal carriage of *S. pneumonia* in Iran. This meta-analysis is aimed at exploring the overall prevalence of nasopharyngeal carriage of *S. pneumonia* among healthy children and its resistance to antibiotics.

Method: We have systematically reviewed published studies from international databases (PubMed, Web of Science, and Scopus) and national databases (Iranmedex, Magiran, Medlib, SID and Irandoc) and reference lists of articles published up to May 2015. Only cross-sectional studies supported with sensitivity test on samples collected from nasopharyngeal area were included and heterogeneity was assessed using Q-test and I^2 test statistic. Publication bias was explored using the Egger's and Begg's tests and the funnel plot. The overall prevalence of analyzed data were reported with 95% confidence intervals (CI) using the random-effects model.

Results: A total of 16 studies were included in the final analysis. The pooled prevalence of *S. pneumonia* nasopharyngeal carriage was 18% (95% CI: 14% - 23%). Antibiotic resistance rates were 26% (95% CI: 15% - 37%) to penicillin, 30% (95% CI: 10% - 49%) to erythromycin and 34% (95% CI: 10% - 57%) to tetracycline respectively.

Conclusions: This study could be able effectively estimate the overall prevalence of nasopharyngeal carriage of *S. pneumonia* and its antibiotics resistance rate among healthy children in Iran.

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Introduction

Streptococcus pneumonia, a gram-positive diplococcus, is a clinically important human pathogen that causes many infections such as pneumonia, sepsis, meningitis, sinusitis and acute otitis media[1-3]. Globally, it is one of the major causes of morbidity and mortality especially among children under the age of five years[2,4].

Streptococcus has several serotypes, which is characterized by its polysaccharide capsular[5]. Currently more than 90 different serotypes are distinguished[1]. However, not all serotypes have the same potential to cause disease. A limited number of serotypes are commonly found to cause disease among children under the age of five around the world[6]. Distribution of the disease-causing serotypes varies by geographic areas, age groups, socio-economic conditions, and seasonal variations[6,7].

Pneumococcus often colonizes the upper respiratory tract and human nasopharynx is the only natural reservoir for it[8]. Transmission of the microorganism is through contact with respiratory droplets[9]. A carrier of the bacteria in the nasopharynx is often asymptomatic. The bacteria usually cause local infections such as sinusitis and acute otitis media. Sometimes it enters the bloodstream and causes invasive pneumococcal diseases (IPD) such as septicemia, pneumonia, and meningitis[10-12].

Many factors including age, genetic background, socioeconomic status, immune status and geographic diversity influence the incidence of severe pneumococcal disease[13].

Nasopharyngeal carriage of pneumococcus is possible at any time during a person's life, but mainly occurs in the first year of life[14]. The prevalence of nasopharyngeal carriage of *S. pneumonia* in healthy children under the age of five years ranged from 20% to 93.4% in low-income countries[15]. Median period of the carriage status was 31 days in adults and 60.5 days in children. This period depends on the serotypes, previous exposure to the bacteria, age and immune status[16]. In 2013, WHO estimated 935,000 deaths among children under the age of five years due to pneumonia worldwide. Out of which the cause of death for about 15% the children was *S. pneumonia*[17].

Vaccination is the straight way to reduce pneumococcal disease and its nasopharyngeal carriage. There are several types of vaccines that two-polysaccharide vaccines (PCV13 and PCV7) are recently introduced. These vaccines include 7-valent pneumococcal conjugate vaccine (PCV7) which contains the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, 23F and 13-valent pneumococcal conjugate vaccine (PCV13) and capsular antigens of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F [18,19].

Epidemiological studies in Iran reported nasopharyngeal carriage rates of *S. pneumonia* ranging from 5.9% to 44.1%[7,20,21]. The resistance of *S. pneumonia* against commonly used antibiotics is another concern. Studies reported resistance rates of as high as 80% for some antibiotics[22-24] and variations by country[7,20,21].

There is knowledge gap regarding the current prevalence of *S. pneumonia* nasopharyngeal carriage. This meta-analysis was conducted to estimate nasopharyngeal carriage rate and antibiotics resistance to *S. pneumonia* in Iran.

Methods

Criteria for including studies

Reports that included healthy children from whom nasopharyngeal samples were taken using swabs were eligible for this analysis. Reports on cross-sectional studies in Iran supported with investigations using samples collected from nasopharyngeal area were included. Other cross-sectional studies that had used samples from other body areas, and cohort, case-control, and interventional studies were excluded.

The primary outcome of interest was to determine the prevalence of nasopharyngeal carriage of *S. pneumonia* among healthy children under the age of 15 years; and the second outcome was to determine antibiotic resistance among the carriers against common antibiotics.

Search methods

The search strategy was based on key words presented as follows: (sepsis OR septicemia OR septic OR encephalitis OR meningitis OR *Streptococcus* OR streptococcal OR streptococci OR pneumonia OR pneumococcal OR pneumococci) AND (Iran).

The PubMed, Scopus, Web of Science, Medlib, SID, Iranmedex, Magiran and Irandoc websites were accessed using the key words. Eligible materials reports done up to May 2015 were included. The reference lists of all included studies were also scanned for additional sources. Besides, attempt was made to contact the authors of included studies for additional sources of information to include in the study but without response.

Data collection and analysis

Two authors (SMH and PA) independently made the decision as to which studies met the inclusion criteria to achieve the objectives of this meta-analysis. Two potentially eligible studies and presented fully in texts reports were excluded from the analysis. Provinces with only one study were not included in the analysis. In all phases of the research process, issues faced among the authors, were reached agreement through discussions.

The quality of the included studies was evaluated using STROBE checklist[25,26]. Heterogeneity across the studies was explored using Chi-squared (χ^2) test at the 5% significance level ($P < 0.05$) and was quantified using I^2statistic.[27,28]. Publication bias was assessed using Begg's and Egger's tests and visualized using the funnel plot[29-32].

Stata software version 11 was employed for the data analysis. Results are reported using a random effect model with 95% confidence interval (CI).

Results

Description of study

We reviewed 3876 references from international databases and 4937 references from national databases until May 2015. We excluded 4936 duplicates and 3717 clearly irrelevant references through reading of the topics and abstracts of the reports. One hundred and sixty articles were potentially eligible. Through further screening, 144 studies were excluded because they did not meet the inclusion criteria. Eventually, 16 studies[7,20,21,33-45] were included in the meta-analysis (Figure 1), out of which eight articles were in English and the remaining eight article were in Persian. One article used the samples taken from oropharyngeal area.

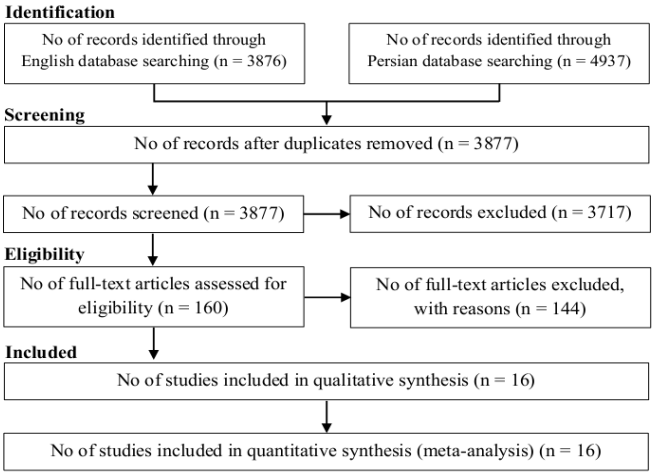

Figure 1: Flow chart of the study selection process

Table 1 presents the years when and where the researches were conducted, other main characteristics that are included in the final analysis of this study. Altogether, the studies included 11,874 participants. Among these study reports, the highest and lowest prevalence of carriage status was reported from studies conducted in Tehran by Safari et al [45] and Noorbakhsh et al [43] respectively. The average nasopharyngeal *S. pneumonia* carriage rate of the healthy children was 18% (95% CI: 14%, 23%).

Antibiotics drug resistance

Among the studies resistance to three common antibiotics were reported. Five studies reported resistance to erythromycin, eight studies resistance to penicillin and another five studies reported resistance to tetracycline that accounted for 30% (95% CI: 10%, 49%), 26% (95% CI: 15%, 37%) and 34% (95% CI: 10%, 57%) respectively (Table 2).

Heterogeneity and publication bias

The results of heterogeneity assessment are presented in Figure 2-4. The findings show the existence of a statistically significantly high heterogeneity (I^2=98%, *P*=0.001) among the studies (Figure 2). Similarly, a statistically significantly high heterogeneity in *S. pneumonia* carriage rates by province (I^2=98.6%, *P*=0.001) and in children under the age of 7 years (I^2=96.8%, *P*=0.001) were observed. However, a statistically significant moderate heterogeneity was found in children over the age of 7 years (I^2=68.7%, *P*=0.012) (Figure 3 and Figure 4, respectively).

Table 1: Summary of studies results

1st author, year	Province	Age (yr)	Sex	Sample	Case	Prevalence	Antibiotic resistance (%)		
							Ery[a]	Pen[b]	Tet[c]
Behnaz, 2004	Yazd	3.2	Both	200	75	0.38	16	38	23
Bakhshaee, 2006	Mashhad	4.2	Both	1161	102	0.09	44	49	-
Bakhshaee, 2012	Mashhad	5.1	Both	1125	114	0.10	-	-	-
Bokaeian, 2011	Zahedan	14.7	Both	865	136	0.16	25	13	13
Fahimzad, 2008	Tehran	2-6	Both	296	96	0.32	-	-	-
Ghaemi, 2002	Gorgan	6-12	Both	1268	138	0.11	14	19	51
Jalilinejad, 2014	Bandar Abbas	4.3	Both	402	63	0.16	53	-	-
Khoshdel, 2009	Shahrekord	2.5	Both	244	38	0.16	-	11	-
Khoshdel, 2014	Shahrekord	1-5	Both	363	107	0.29	-	-	-
Kordi, 1998	Isfahan	1-7	-	234	17	0.07	-	5	-
Mirzaei, 2014	Kashan	13.1	Both	2100	291	0.14	10	-	74
Mirzaei, 2014	Kashan	13.1	Both	1289	181	0.14	-	-	-
Mousavi, 2013	Tehran	1-5	Both	150	40	0.27	-	-	-
Noorbakhsh, 2001	Tehran	3.9	Both	170	4	0.02	-	4	-
Safari, 1997	Kashan	-	Both	707	92	0.13	-	-	-
Sanaei, 2012	Tehran	7.0	Both	1300	573	0.44	-	53	376

Ery: Erythromycin, Pen: Penicillin, Tet: Tetracycline

Table 2: Antibiotic resistance rate for three common antibiotics

Antibiotic	No. of studies	Sample size	Resistance rate (%)	95% CI (%)
Erythromycin	6	805	30	(10, 49)
Penicillin	8	1083	26	(15, 37)
Tetracycline	5	1213	34	(10, 57)

The findings from the Begg's (*P*=0.012) and Egger's (*P*=0.071) tests indicated the presence of publication bias among the studies.

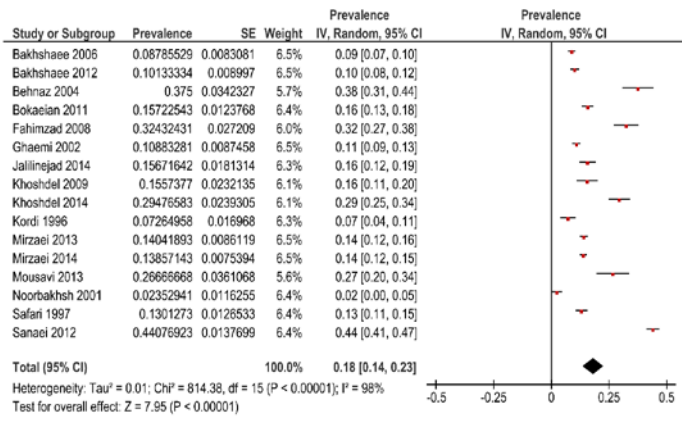

Figure 2: Meta-analysis of *S. pneumonia* carriage in healthy children

Subgroup analysis

Analysis revealed variation in the prevalence of *S. pneumonia* nasopharyngeal carriage rates by province. For example, the prevalence was 9% (95% CI: 7%, 10%) in Mashhad, 26% (95% CI: 2%, 51%) in Tehran, 23% (95% CI, 9%, 36%) in Shahrkord and 14% (95% CI: 13%, 15%) in Kashan (Figure 3). In addition, the prevalence *of* carriage was 18% (95% CI: 13%, 23%) in children under the age of 7 years and 13% (95% CI: 12%, 15%) in children over the age of 7 years (Figure 4).

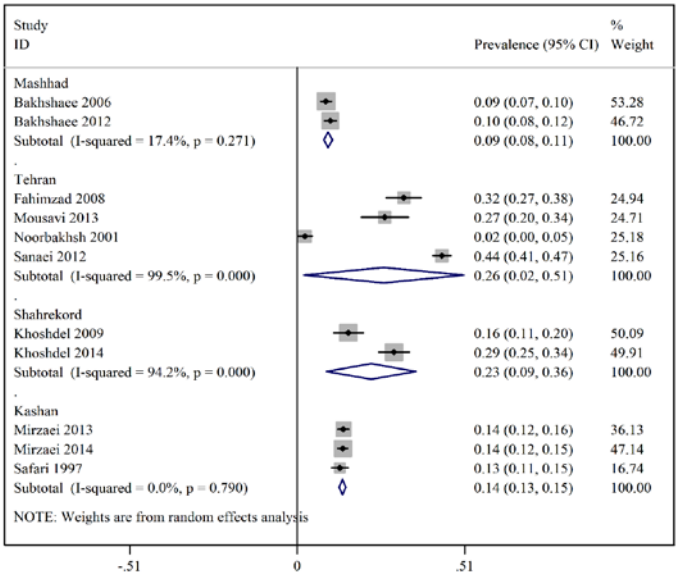

Figure 3: Meta-analysis of *S. pneumonia* carriage in healthy children by province

Discussion

This meta-analysis included 16 studies that reported *S. pneumonia* carriage status. The overall prevalence of nasopharyngeal *S. pneumonia* carriage was 18%. This shows that the nasopharyngeal *S. pneumonia* carriage rate in Iran to be moderate.

The prevalence of *S. pneumonia* carriage in under 5 year old children is most commonly reported. This study compared *S. pneumonia* carriage status in children below and over the age of 7 years. The prevalence was higher in children under the age of 7 years (18%) than in children over the age of 7 years (13%).

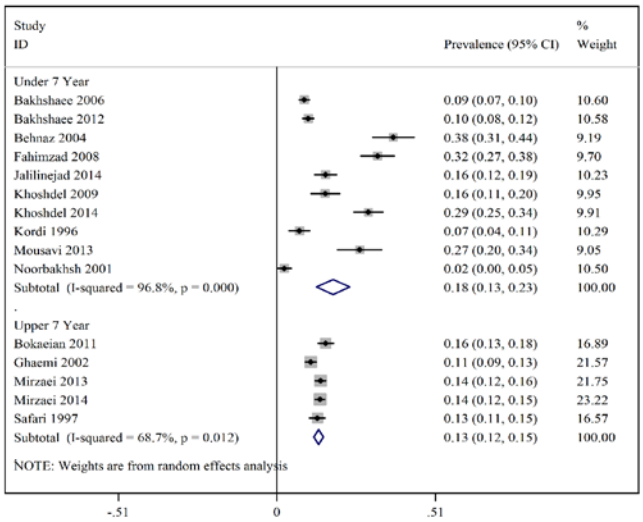

Figure 4: Meta-analysis of *S. pneumonia* carriage in healthy children by age group

Furthermore, since the prevalence of *S. pneumonia carriage* varies by province in Iran, a subgroup analysis by province was made. However, lack of study reports from the entire provinces was one of the limitations of this analysis. This analysis demonstrated that the highest prevalence (26%) was reported from Tehran and the lowest (0.09%) was from Mashhad.

Antibiotic resistance rate of *S. pneumonia* particularly in children is an important issue worldwide. Nine of studies included in the meta-analysis reported antimicrobial resistance for three common antibiotics. The subgroup analysis by antibiotics indicated that resistance rate was 30% for erythromycin, 26% for penicillin and 34% for tetracycline respectively.

The Q-test and I^2 statistical tests indicated heterogeneity among the included studies. The majority of the observed heterogeneity may be attributable to the quality of the included studies, variations in population sizes, socio-demographic characteristics, and potential confounding factors that were not controlled in the studies. However, these statistical tests should be interpreted with caution. The Q-test is likely to have low statistical power when the sample size or the number of studies included in the analysis is small. On the other hand, when the sample size or the number of the studies included is high such as in ours with 16 studies involving 11,784 participants, the test is more likely have high power in detecting a small amount of heterogeneity that may be clinically unimportant[46].

Adegbola et al.[15] conducted a similar study to estimate the carriage rate of *S. pneumonia* among healthy children below the age of 5 years and adults in low and lower-middle income counties. They retrieved 11 articles, of which 5 were from low income and the remaining 6 were from lower-middle income counties. The study reported a higher prevalence of *S. pneumonia* carriage among children in low-income than in lower-middle income countries. In addition, the prevalence was higher in young children than in adults. The high prevalence of *S. pneumonia* carriage among the younger age group children in the current study is consistent with previous study. However, the current finding indicated that prevalence of carriage is lower than that reported from low income, 64.8% (95%CI: 49.8%, 79.1%), and low-middle income countries, 47.8% (95% CI: 44.7%, 50.8%), before the introduction of PCV.

The poor quality of the reports included in the analysis, small sample sizes (in some study) and not controlling potential confounding factors were the main limitations and potential sources of biases for the current meta-analysis.

Conclusions

Despite the limitations, this study could effectively estimate the overall prevalence of nasopharyngeal carriage of *S. pneumonia* and antibiotics resistance rate among children in Iran. This study could contribute to the change in general view about the necessity of vaccination.

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Conflict of interest statement

The authors declare that they have no conflicts of interest in this study.

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