



Prevalence of Invasive *Streptococcus pneumoniae* Infections among Iranian Children: A Systematic Review and Meta-Analysis

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Abstract

Background: *Streptococcus pneumoniae* is an important pathogen of children, mostly in developing countries. We aimed to investigate the prevalence of invasive *S. pneumoniae* among Iranian children using a systematic review and meta-analysis.

Methods: A systematic search was carried out to identify papers published by Iranian authors in the Web of Science, PubMed, Scopus, and Google Scholar electronic databases from January of 2010 to December of 2017. Then, seven publications that met our inclusion criteria were selected for data extraction and analysis.

Results: Totally, one study was multicenter, and six were single-center based studies. Meanwhile, all of the included studied performed among hospitalized patients. Seven studies reported the prevalence of invasive *S. pneumoniae* isolated from children, of these the pooled prevalence of *S. pneumoniae* was 2.5% (95% CI: 0.7%-9.1%).

Conclusion: The overall prevalence of invasive *S. pneumoniae* infections among Iranian children is low (2.5%). However, further clinical studies are required to elucidate the burden of infections among Iranian children, especially in eastern regions.

Keywords: *Streptococcus pneumoniae*; Sepsis; Meningitis; Children; Meta-analysis

Introduction

Streptococcus pneumoniae is an important bacterial pathogen that can cause a variety of invasive diseases such as meningitis and sepsis, and considered a significant cause of morbidity and mortality in children (1, 2). *S. pneumoniae* is also causing a variety of community-acquired respiratory tract infections, such as otitis media, sinusitis, and non-bacteremic pneumonia (3, 4). Due to the lack of a

mature immune system and frequent contact with nasopharyngeal carriage of *S. pneumoniae*, infants and young children under 5 years of age are most susceptible to invasive pneumococcal disease (IPD) (5). The incidence of infections caused by *S. pneumoniae* in children varies around the world, the recent estimates showed *S. pneumoniae* causes



around 11% (8–12%) of all deaths in children under 5 years of age annually, mostly in developing countries (6).

Despite the high sensitivity of pneumococcal isolates against routine antibiotics especially to penicillins, recently, studies around the world have been reported increased antibiotics resistance trends of pneumococcal isolates to penicillin particularly in developing countries (7). In particular, penicillin-non-susceptible pneumococci (PNSP) has become a major public health concern among children and elderly patients (1, 8). Furthermore, the emergence of multidrug resistance among *S. pneumoniae* has become an important health challenge, especially in cases of meningitis which can be lead to treatment failures (9). Several resistance mechanisms including enzyme production such as β -lactamases, reduced penetration of the antibiotics to the target sites, or target mutations, decreased bacterial permeability, and increased drug efflux have been identified, which are responsible resistance to clinically used antibiotics (10).

The prevalence of *S. pneumoniae* infections and antibiotic resistance among children in Iran presented by local data, and there is a need for a systematic estimate of the burden of infection to guide public health policies. Therefore, this study aimed to estimate the prevalence of invasive *S. pneumoniae* infections in Iranian children by using a systematic review and meta-analysis. This finding can provide good epidemiological background contribute to the international data to estimate the burden of infections.

Methods

Search strategies

A systematic literature search was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify papers published by Iranian authors in the Web of Science, PubMed, Scopus, and Google Scholar electronic databases since January of 2010 to December of 2017. The systematic search was performed using a combination of terms and keywords including “*Streptococcus*

pneumoniae” OR “*S. pneumoniae*” OR “Pneumococcus” OR “Pneumococcal” AND “Bacteremia” OR “Sepsis” OR “Meningitis” AND “Neonate” OR “Children” OR “Pediatric” AND “Iran”.

Selection criteria

Two reviewers independently reviewed the search results at the databases with the related keywords and analysis the titles, abstracts, and full texts to determine articles that met the inclusion criteria, and inconsistencies between reviewers were resolved by consensus. No language restrictions were applied in our search, but at least the abstract must be available in English. Then, articles that were indexed in PubMed or Scopus and had the following criteria were included in our study, a standard method was used for detection of *S. pneumoniae*, cross-sectional or retrospective studies investigating the prevalence of *S. pneumoniae* in children, and samples collected from patients. Articles excluded if did not use a standard detection method, the sample size was less than 10 isolates, origin of samples was unclear, or focused on pneumococcal colonization or nasopharyngeal carriage of *S. pneumoniae*. Furthermore, grey literature, book chapters, reviews, and systematic review articles, case reports, and articles that were only available in abstract form without necessary information were excluded.

Quality assessment

The validity of studies was evaluated independently by two authors using the Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data, (11) and disagreements were resolved by consensus. Items related title and abstract, introduction, methods, results, discussion, and other information were determined and a score was assigned to each item.

Data extraction

Data on authors, performed time, publication date, research location, study setting, patients' age, primary sample size, source of isolation, and *S. pneumoniae* detection rate were extracted from included studies.

Statistical analysis

Analysis of data was performed by Comprehensive Meta-Analysis Software Version 2.2 (Bio stat Company). Meta-analysis was performed by using random-effects model to estimate the pooled prevalence and corresponding 95% confidence interval (CI). Statistical heterogeneity between and within groups was estimated with the Q statistic and the I² index. The funnel plot, Begg's rank correlation test, and Egger's weighted regression tests were used to evaluate possible publication bias ($P < 0.05$ was considered as indicative of statistically significant publication bias).

Results

Initially, a total of 1,655 titles were found by database search. Among them, 1,647 were removed by index, title and abstract screening and eight were accessed in full text. Of eight full text reviewed articles, one study did not report primary sample size. Finally, seven studies matched with eligibility criteria and were subjected to meta-analysis (12-18). A flowchart of the literature search, the selection procedures and reasons for exclusion are presented in Fig. 1. The detailed characteristics of the selected studies in the meta-analysis are available in Table 1.

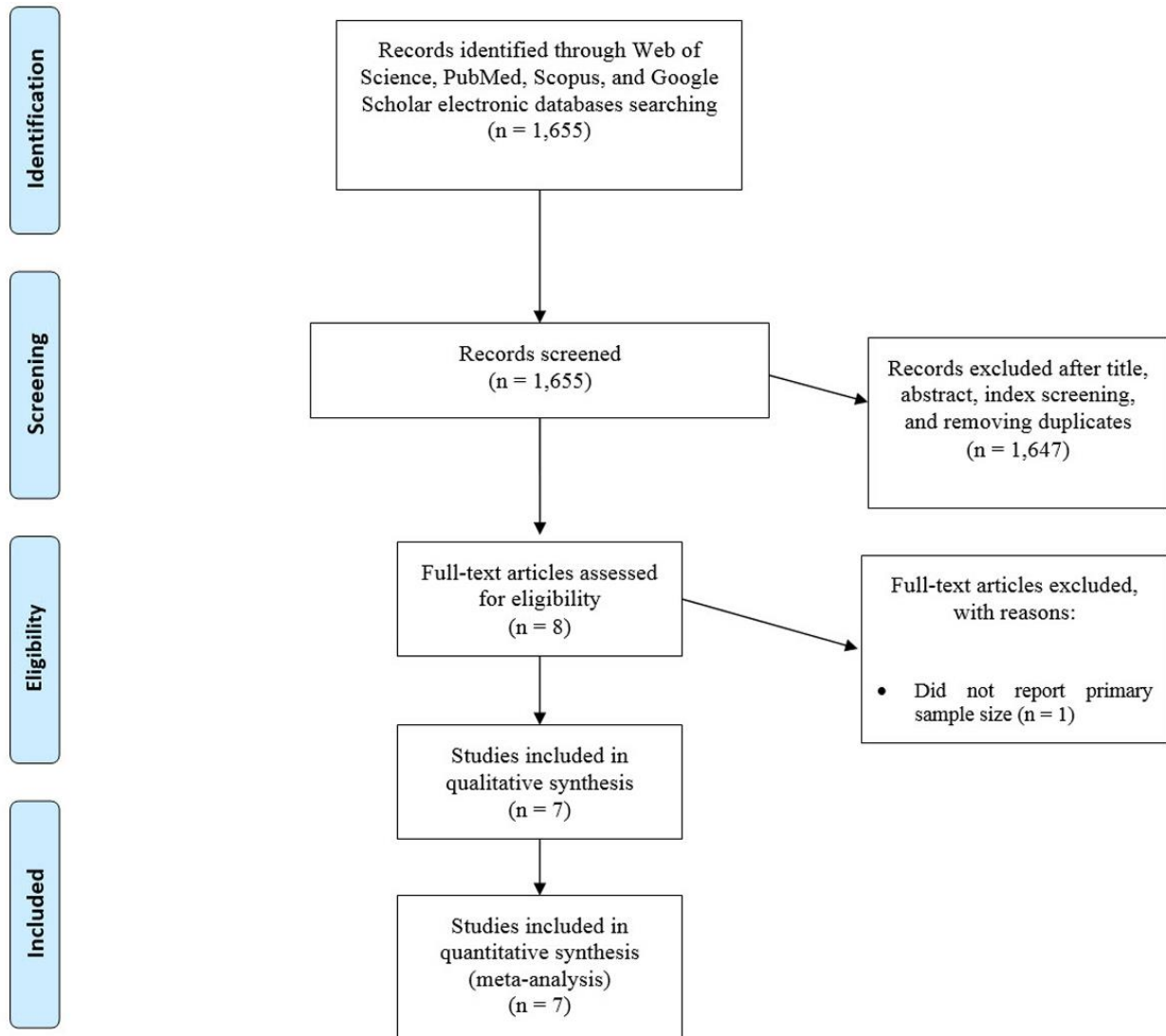


Fig. 1: Flow chart of the literature search strategy and study selection

Table 1: Characteristics of studies included in the meta-analysis

Performed year	City/Region	Multicenter or Single center based	Hospitalized or Community	Age range	Detection methods	Sample source	Sample size No.	<i>S. pneumoniae</i> No.	Quality assessment score	Ref
1998-2008	Tehran/North	Single center	Hospitalized	Pediatric	Culture	CSF	11,269	30	9	(12)
2008-2009	Tabriz/Northwest	Single center	Hospitalized	11 days-14 years	Culture and PCR	CSF	277	8	9	(13)
2009-2011	Tehran/North	Single center	Hospitalized	5 months - 10 years	Culture	CSF, Blood	31	7	6	(14)
2003-2013	Tabriz/Northwest	Single center	Hospitalized	2 days-13 years	Culture	CSF, Blood	7,112	44	9	(15)
2014-2015	Ahvaz/Southwest	Single center	Hospitalized	Under 5 years	Culture and PCR	CSF	196	5	7	(16)
2007-2013	Tabriz/Northwest	Single center	Hospitalized	2 months - 13 years	Culture	Blood	96	2	8	(17)
2013-2016	Tehran/North	Multicenter	Hospitalized	Under 5 years	Culture and PCR	Blood, CSF	585	53	8	(18)

Abbreviations: PCR, Polymerase chain reaction; CSF, Cerebral spinal fluid

Totally, one study was multicenter, and six were single-center based studies. Meanwhile, all of the included studies performed among hospitalized patients. Seven studies reported the prevalence of *S. pneumoniae* isolated from clinical samples in children, of these the pooled prevalence of *S. pneumoniae* was 2.5% (95% CI: 0.7%-9.1%) (Fig. 2). There was a significant heterogeneity among the studies ($P < 0.001$; $I^2 = 98.26\%$). The sensitivity

analyses were performed by removing one study at a time to evaluate the impact of each study on the summary results and between-study heterogeneity (Fig. 3). The symmetric funnel plot (Fig. 4) showed no evidence of publication bias and confirmed by the results of Begg's rank correlation ($\alpha = 0.30$, $P = 0.76$) and Egger's regression result ($t = 0.32$, $P = 0.76$).

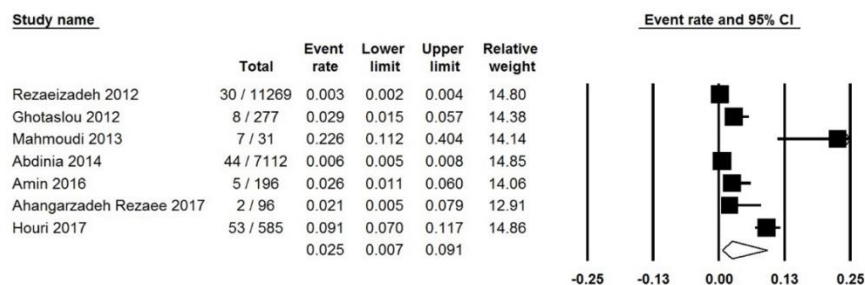


Fig. 2: Forest plot of the meta-analysis on the prevalence of invasive *S. pneumoniae* in Iranian children

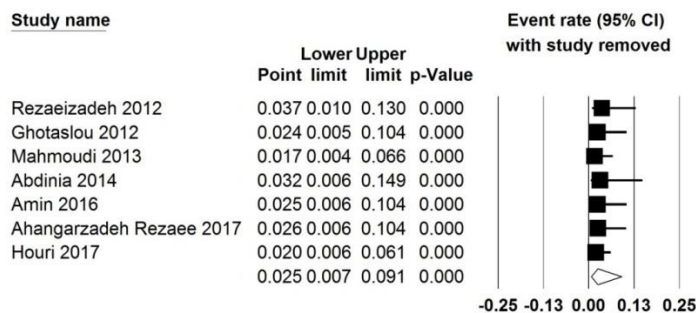


Fig. 3: The sensitivity analyses results performed by removing one study at a time

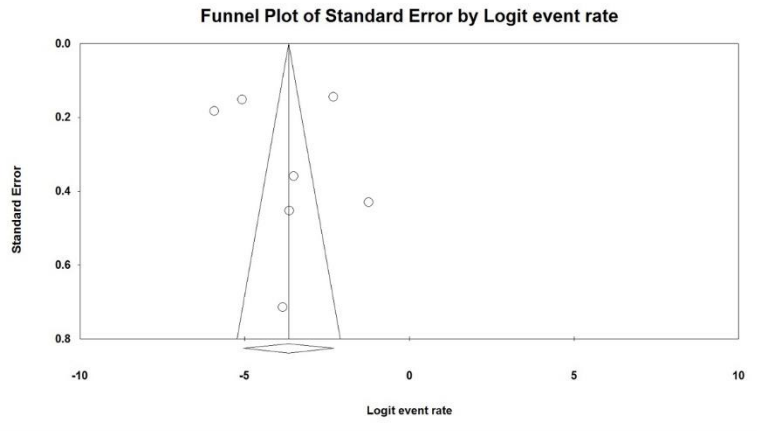


Fig. 4: Funnel plot of the meta-analysis on the prevalence of invasive *S. pneumoniae* in Iranian children

Subgroups analysis based on detection methods was done and results are presented in Fig. 5. According to the results, using PCR along with culture significantly increases the reported rates compared to using culture alone (4.2% vs. 2.1%). Finally, subgroups analysis between geographical regions was done and results are presented in Fig.

6. However, it must be considered that our estimates could not fully indicate the prevalence of *S. pneumoniae* in Iranian children since as seen in our results the geographical distribution of the studies was limited to only three geographical regions.

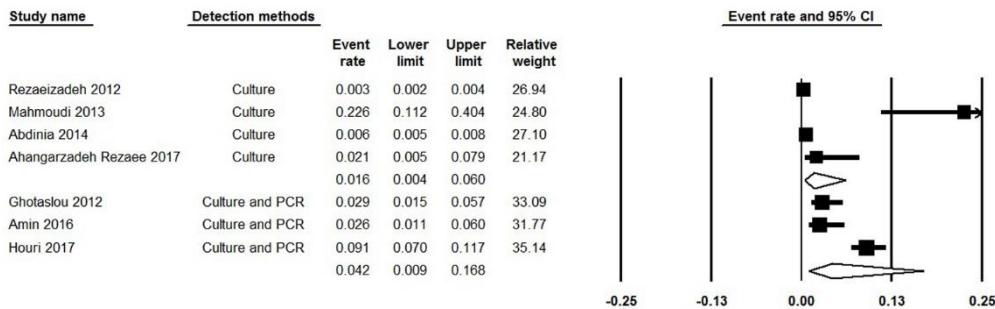


Fig. 5: Subgroups analysis of the pooled prevalence of invasive *S. pneumoniae* based on detection methods

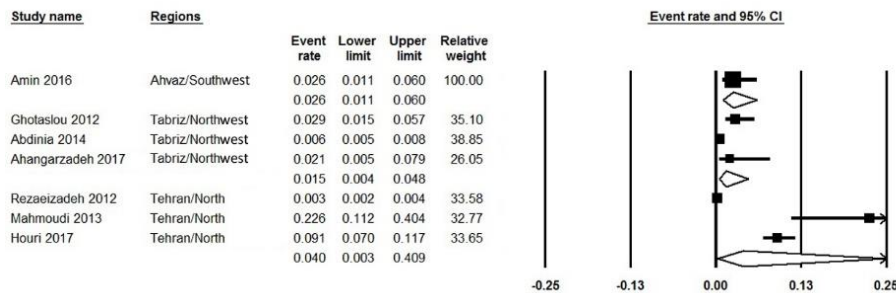


Fig. 6: Subgroups analysis of the pooled prevalence of invasive *S. pneumoniae* based on geographical regions

Discussion

Invasive *S. pneumoniae* infections continue to be one of the most common causes of morbidity and mortality worldwide, particularly in children (19). Thus, is essential to gain a close estimation of the burden of IPD for the development of effective healthcare practice. To the best of our knowledge, this study is the largest comprehensive survey to date estimated the prevalence of invasive *S. pneumoniae* in Iranian children with 2.5% (95% CI: 0.7%-9.1%). Despite the several comparable reports with our findings, due to multifactorial nature of the prevalence of IPD its international comparison is challenging. Besides the geographical distribution, variations may arise from differences in type of infection, seasonal variability, and studied population. The prevalence of invasive *S. pneumoniae* in children has a large variation among other Asian countries. *S. pneumoniae* introduced as a causative agent of bacterial meningitis ranging from 2.5% to 33.2% from different neighboring and eastern Asian countries including Pakistan, Iraq, Qatar, Turkey, India, China, and South-Korea (20-28). The report of *S. pneumoniae* blood-stream infections in Asian countries is rare and in China reported 16.7% (29). Moreover, the overall average of *S. pneumoniae* detection in children experiencing otitis media in several neighboring and eastern Asian countries including Saudi Arabia, Turkey, Japan, Taiwan, and Thailand estimated 27.8%, ranging from 9.9% to 49.9% (30, 31). Another factor that plays a key role in epidemiology of *S. pneumoniae* infections is capsular type, which can vary geographically (18, 32). The polysaccharide capsule of *S. pneumoniae* is one of the major virulence factors of organism invasiveness (32). To date more than 90 capsular types of pneumococci are recognized; while, it seems that only certain number of capsular types are responsible for the majority of invasive disease (32). Also, the majority of antibiotic-resistant *S. pneumoniae* has been linked to the spread of pediatric pneumococcal serotypes including 6A, 6B, 9V, 14, 15A, 19F, 19A, and 23F (33). Regard the distribution of capsular serotypes, among the included studies, only

Houri et al. showed the prevalent of 23F and 19F serotypes in Iranian pediatric (18, 30).

Meta-analysis studies often are not without limitations. In the present study, the included studies were performed on hospitalized patients so the burden of infection would be expected to be different in the community.

Conclusion

The overall prevalence of invasive *S. pneumoniae* infections among Iranian children is low (2.5%). However, further clinical studies are required to elucidate the burden of infections among Iranian children, especially in eastern regions. Meanwhile, results recommended using PCR for detection of invasive *S. pneumoniae* infections since the detection rates were higher than using conventional culture alone.

Ethical consideration

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

None declared.

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