Research Article

Is Penicillin-Nonsusceptible Streptococcus pneumoniae a Significant Challenge to Healthcare System? A Systematic Review and Meta-Analysis

Farzad Khademi¹ and Amirhossein Sahebkar²,3,4

¹Department of Microbiology, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran
²Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
³Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
⁴School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence should be addressed to Amirhossein Sahebkar; amir_saheb2000@yahoo.com

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Background. In recent years, antibiotic-resistant pathogens including penicillin-nonsusceptible Streptococcus pneumoniae (PNSP) have posed serious threats against human health. The aim of this meta-analysis was to investigate the prevalence of Streptococcus pneumoniae drug resistance particularly the incidence of PNSP strains in Iran.

Methods. A systematic search was done in national and international electronic databases using Persian and English keywords. Up until May 20, 2020, a total of 58 publications were detected as eligible articles based on the inclusion and exclusion criteria, and then the selected studies were enrolled for data extraction and meta-analysis according to the PRISMA guidelines.

Results. A high rate of PNSP (46.9%) and multidrug-resistant (MDR) S. pneumoniae (45.3%) in our isolates were evident. Furthermore, total frequency resistance to other drugs in S. pneumoniae was as follows: erythromycin 41.1%, azithromycin 53.2%, tetracycline 39.9%, levofloxacin 1.7%, rifampin 1.2%, clindamycin 31.7%, vancomycin 1.7%, trimethoprim/sulfamethoxazole 63.9%, chloramphenicol 20%, ceftriaxone 10.9%, amoxicillin 30.5%, ciprofloxacin 8.3%, imipenem 6.1%, linezolid 0%, and cefotaxime 8.3%. Conclusion. Although the overall prevalence of cephalosporin- and carbapenem-resistant Streptococcus pneumoniae was low, penicillin-resistant strains, especially PNSP, could become a significant challenge to the healthcare system in Iran. Hence, the prescription of penicillin as the first-choice antibiotic in the treatment of S. pneumoniae infections should be avoided.

1. Introduction

Streptococcus pneumoniae (S. pneumoniae) (pneumococcus) is a Gram-positive diplococcus that is an exclusively normal inhabitant in the oropharynx and nasopharynx of healthy individuals [1, 2]. Colonization rates are higher in the extreme of age (children under 5 and adults older than 65 years old) and immunocompromised patients especially in developing countries [3]. The bacterium enters the body through droplets and aerosols by person-to-person transmission. It then disseminates into other sites including circulation, brain, lungs, paranasal sinuses, and middle ears and causes severe diseases such as pneumonia, sinusitis, otitis media, bacteremia, and meningitis [1–3]. Pneumonia of any cause is an important disease affecting children under the age of five. In 2017, the World Health Organization (WHO) announced 808,694 pneumonia-related child deaths which accounts for 15% of total mortality in children younger than five years old [4]. The two most common bacterial causes of pneumonia in children are S. pneumoniae and Haemophilus influenzae type b, respectively [3]. Recently, a plan released by the WHO/UNICEF named the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD) with the aim of reducing the death rate to less than 3 children per 1000 live births by 2025 [4]. The main strategies to protect,
prevent, and treat children with pneumococcal pneumonia include exclusive breastfeeding, adequate complementary feeding, hand washing, reducing household air pollution, prevention of HIV, oxygen therapy, vaccinations, and also the administration of appropriate antibiotics [4]. Potent anticyclosal pneumococcal vaccines (PPSV23, PCV13, and PCV7) were developed based on the prevalent serotypes of *S. pneumoniae*; however, they are less effective in developing countries due to different distribution patterns of serotypes by geographic locations [1], and hence, they are not part of the childhood immunization plan in Iran. Over the last several decades, penicillin was the drug of choice for the treatment of pneumococcal diseases [1, 2]. However, up to 40% of these bacteria are found to be penicillin-resistant [5]. A list of antibiotic-resistant pathogens was released by WHO in February 2017 that urgently requires effective antibiotics [6]. Penicillin-non-susceptible *S. pneumoniae* (PNSP) strains are priority 3 (medium) on the list and known as increasingly drug-resistant pathogens which require further research and development of new antibiotics [6]. Given the distinct geographical distributions, which can affect bacterial phenotypic and genetic characteristics such as drug susceptibility, and self-medication of antibiotics in Iran, the current systematic review and meta-analysis was performed to follow four objectives: (1) to estimate the overall prevalence of *S. pneumoniae* strains resistant to different antibiotics among all age groups in Iran, (2) to determine *S. pneumoniae* drug resistance in Iranian children, (3) to assess the prevalence of PNSP strains, and (4) to investigate antimicrobial resistance profiles in different provinces of Iran.

2. Methods

2.1. Search Strategies. The current systematic review and meta-analysis is designed based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [7]. A comprehensive search was performed on studies published from October 1993 to May 2020. English keywords in the ISI Web of Knowledge, PubMed, Scopus, and Google Scholar databases and Persian keywords in national search engines including Scientific Information Database (http://www.sid.ir) and Magiran (http://www.Magiran.com) were used to find original articles addressing *S. pneumoniae* antibiotic resistance in Iran. For this purpose, the search terms (i.e., *S. pneumoniae*, antibiotic resistance, and Iran) were extracted from Medical Subject Headings (MeSH) and combined with connectors (AND/OR).

2.2. Inclusion and Exclusion Criteria. The articles were selected based on the title, abstract, and full text. First, the titles of cross-sectional studies on the prevalence of drug resistance were evaluated according to the author, bacterium, and country names, and then, abstracts and full texts were further assessed. Inclusion criteria were original articles assessing the prevalence of pneumococcus drug resistance, full-text availability, publication in English or Persian languages, and studies with sufficient data and limited to Iran. Exclusion criteria were studies reporting drug resistance patterns only at the level of *Streptococcus* genus or other than *S. pneumoniae*, evaluating the prevalence of *S. pneumoniae* resistance with low sample size, repetitive publications, nonoriginal articles, and articles available only in abstract form or abstracts from conferences.

2.3. Quality Assessment and Data Extraction. Included articles were further assessed in terms of quality using the Joanna Briggs Institute (JBI) critical appraisal checklist, and then, necessary data were extracted and tabulated in Table 1 [66]. The main data included the first author’s surname, study location, publication date, study enrollment date, age group, sample size, antibiotic susceptibility testing methods, the prevalence of *S. pneumoniae* resistance to different drugs, and the prevalence of multidrug-resistant (MDR) pneumococci.

2.4. Meta-Analysis. Meta-analysis of the extracted data on the *S. pneumoniae* antibiotic resistance was performed using the Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ), and the frequency of drug resistance was expressed as the percentage and 95% confidence intervals (95% CIs). Further analysis on the location of the study and age groups was also conducted. To evaluate the heterogeneity across the included studies, I² statistics and the chi-square test (χ²) with the Cochrane Q statistic (Q test) (p value <0.05 was considered statistically significant) were used. A random-effects model (DerSimonian–Laird method) was used to pool the data when heterogeneity was considered high (I² ≥25%). Distribution bias among published studies was calculated quantitatively using Begg’s and Egger’s tests (p value <0.05 indicates a significant bias) and visualized via the funnel plot graphs for each antibiotic.

3. Results

3.1. Results of Search and Characteristics of the Included Articles. Data were available from 15 provinces as follows: Ardabil (n = 1), Chaharmahal and Bakhtiari (n = 2), East Azerbaijan (n = 1), Fars (n = 6), Golestan (n = 1), Hamadan (n = 5), Isfahan (n = 2), Kermanshah (n = 1), Khuzestan (n = 1), Qazvin (n = 1), Tehran (n = 31), Sistan and Baluchestan (n = 3), West Azerbaijan (n = 1), Yazd (n = 1), and Zanjan (n = 1). Detailed characteristics of the selected articles are summarized in Table 1. A total of 1249 reports were identified for the analysis of *S. pneumoniae* antibiotic resistance in Iran. Finally, 58 articles (50 in English and 8 in Persian) were included in the study (Figure 1). Disk diffusion, E-test, and broth micro- and macrodilution were the most common methods used for antimicrobial susceptibility testing in the included articles.

3.2. Total *S. pneumoniae* Drug Resistance in Iran. The pooled prevalence of *S. pneumoniae* resistance to various antibiotics including erythromycin, azithromycin, tetracycline,
Table 1: Extracted information from eligible studies included in the meta-analysis.

| Author (ref)           | Province                 | Published time | Enrollment time | Age group | Strain (n) | AST | PNSP | ERY | AZM | TET | LVX | RIF | CLI | VAN | SXT | CHL | CRO | AMX | CIP | IPM | LZD | CTX | MDR |
|------------------------|--------------------------|----------------|----------------|-----------|------------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gharibani et al. [8]   | Ardabil                  | 2019           | 2015           | Children  | 43         | Disk diffusion | 41  | 32  | 31  | 18  | 0   | 12  | 0   | 35  | 7   | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | 32  |
| Khooshaei et al. [9]   | Chaharmahal and Bakhtiari| 2009           | 2007           | Children  | 38         | Disk diffusion | 11  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  |
| Imani et al. [10]      | Chaharmahal and Bakhtiari| 2007           | 2005           | ND        | 17         | Broth microdilution | 16  | 10  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | 1   | ND  | 2   | ND  | ND  | ND  | ND  |
| Abdinia et al. [11]    | East Azerbaijan          | 2014           | 2003–2013      | Children  | 37         | Disk diffusion | 14  | 6   | ND  | ND  | ND  | 1   | 0   | 12  | 2   | 4   | ND  | ND  | ND  | ND  | 3   | ND  | 3   | ND  |
| Hadi and Bagheri [12]  | Ardabil                  | 2019           | 2011–2016      | Children  | 10         | Disk diffusion | 7   | 3   | ND  | ND  | ND  | 3   | 0   | 9   | 1   | 4   | ND  | ND  | ND  | ND  | ND  | ND  | ND  |
| Kargar et al. [13]     | Chaharmahal and Bakhtiari| 2015           | 2011–2012      | Children/ | 45         | Disk diffusion | ND  | ND  | ND  | ND  | ND  | 31  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | 40  | ND  | ND  | ND  |
| Kargar et al. [14]     | East Azerbaijan          | 2012           | 2010–2011      | Children/ | 50         | Disk diffusion | 30  | 28  | 22  | 5   | 2   | ND  | ND  | 24  | 0   | ND  | ND  | ND  | ND  | 25  | 30  |
| Shishegar et al. [15]  | Fars                     | 2011           | 2007–2008      | Children  | 10         | Disk diffusion | ND  | 1   | ND  | ND  | ND  | ND  | ND  | 10  | ND  | 2   | 4   | 0   | ND  | 2   | ND  |
| Japoni et al. [16]     | Fars                     | 2010           | 2005–2006      | ND        | 13         | Disk diffusion | 5   | 3   | ND  | ND  | ND  | ND  | 1   | 0   | 6   | 1   | ND  | 1   | ND  | ND  | ND  | ND  | ND  |
| Kohanteb and Sadeghi [17]| Golestan                 | 2007           | ND             | Children/ | 115        | Disk diffusion | 39  | 21  | 15  | 28  | ND  | ND  | 0   | ND  | 9   | 7   | ND  | 9   | ND  | ND  | 5   |
| Ghaemi et al. [18]     | Chaharmahal and Bakhtiari| 2002           | 1998–1999      | Children  | 63         | Disk diffusion | 35  | 5   | ND  | 23  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  |
| Khademi et al. [19]    | Hamadan                  | 2016           | 2013–2014      | Children/ | 6          | Disk diffusion | ND  | ND  | ND  | ND  | ND  | ND  | 0   | 3   | ND  | 0   | ND  | 1   | ND  | ND  | 0   |
| Yousefi [20]           | Hamadan                  | 2014           | 2009–2013      | Children  | 35         | Disk diffusion | ND  | ND  | ND  | ND  | ND  | ND  | 9   | 12  | ND  | 19  | ND  | ND  | ND  | ND  | ND  |
| Yousefi [21]           | Hamadan                  | 2003           | 1998–2000      | Children  | 11         | Disk diffusion | ND  | ND  | ND  | ND  | ND  | ND  | 3   | 4   | ND  | 6   | ND  | ND  | ND  | ND  | ND  |
| Moskh et al. [22, 23]  | Hamadan                  | 2014           | ND             | ND        | 55         | E-test       | 52  | 14  | 10  | ND  | ND  | ND  | ND  | 0   | ND  | ND  | ND  | 6   | 55  | ND  | ND  | 12  |
| Yeganeh-Moghadam et al. [24]| Isfahan                | 2014           | 2011–2013      | Children  | 15         | Disk diffusion | ND  | 5   | 9   | ND  | ND  | ND  | ND  | 15  | ND  | 9   | 9   | 0   | ND  | ND  | 9   |
| Ghazikalayeh et al. [25]| Isfahan                  | 2014           | 2011–2012      | Children  | 291        | Disk diffusion | 47  | 10  | ND  | 74  | 0   | 5   | 0   | ND  | ND  | ND  | ND  | 0   | ND  | ND  | ND  |
| Sabory et al. [26]     | Kermanshah              | 2015           | 2012           | Children  | 83         | Disk diffusion | ND  | ND  | 53  | ND  | ND  | 34  | ND  | 31  | ND  | 3   | 47  | ND  | ND  | ND  | 34  |
| Khorrazi et al. [27]   | Khuzeestan               | 2007           | 2005–2006      | Adult     | 6          | Disk diffusion | ND  | ND  | ND  | 3   | ND  | ND  | 0   | ND  | 3   | ND  | ND  | ND  | ND  | ND  | ND  |
| Mosaf and Jassazadeh [28]| Qazvin                   | 2016           | 2013–2014      | Children  | 6          | Disk diffusion | ND  | ND  | ND  | ND  | ND  | ND  | 4   | 4   | ND  | ND  | ND  | ND  | ND  | ND  | ND  |
| Mamishki et al. [29]   | Tehran                   | 2019           | 2017–2018      | Children  | 4          | Disk diffusion | 1   | 4   | ND  | ND  | ND  | 2   | 0   | 1   | ND  | ND  | ND  | ND  | ND  | ND  | ND  |
| Ghafrarokhi et al. [30]| Tehran                   | 2020           | 2015–2019      | Children/ | 80         | Disk diffusion | 29  | 49  | ND  | 31  | ND  | 47  | 0   | 57  | 15  | 13  | ND  | ND  | ND  | ND  | 41  |
| Author (ref) | Province | Published time | Enrollment time | Age group | Strain (n) | AST | PNSP | ERY | AZM | TET | LVX | RIF | CLI | VAN | SXT | CHL | CRO | AMX | CIP | IPM | LZD | CTX | MDR |
|-------------|----------|----------------|----------------|-----------|------------|-----|------|------|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Azarsa et al. [31] | Tehran | 2019 | 2015 | Children/adult | 46 | Disk diffusion | 12 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Mousavi et al. [32] | Tehran | 2017 | 2014–2015 | Children | 76 | Disk diffusion | 76 | 65 | 65 | 4 | ND | 0 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | 76 |
| Ahmadi et al. [33] | Tehran | 2019 | 2013–2016 | Children/adult | 100 | Disk diffusion | 22 | 59 | ND | 57 | ND | 49 | ND | 92 | 23 | ND | 3 | ND | ND | ND | 54 |
| Houri et al. [34] | Tehran | 2017 | 2013–2016 | Children | 53 | Broth microdilution | 11 | 15 | ND | 13 | 0 | ND | 0 | 12 | ND | 4 | ND | ND | 0 | 3 | 9 |
| Talebi et al. [35] | Tehran | 2019 | 2013–2015 | ND | 161 | Disk diffusion | 93 | 96 | ND | 121 | ND | 84 | ND | 151 | 95 | ND | ND | ND | ND | 69 |
| Moghadam et al. [36] | Tehran | 2017 | 2013–2015 | Children/adult | 100 | Disk diffusion | 26 | 64 | ND | 77 | 0 | ND | 56 | 0 | 96 | 44 | 0 | ND | 0 | ND | ND | 71 |
| Farshad et al. [37] | Tehran | 2016 | 2013 | Adult | 48 | Disk diffusion | 40 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Rahbar et al. [38] | Tehran | 2019 | 2012–2016 | Children/adult | 50 | E-test | 15 | 36 | 35 | 28 | 1 | ND | 26 | 0 | 32 | 13 | ND | ND | ND | ND | ND | ND |
| Tabatabaei et al. [39] | Tehran | 2017 | 2012–2015 | Children/adult | 73 | Broth microdilution | 16 | 61 | ND | 59 | ND | 0 | 11 | 23 | ND | ND | ND | ND | 31 | ND |
| Talebi et al. [40] | Tehran | 2016 | 2011–2013 | Children/adult | 100 | Disk diffusion | 28 | 60 | ND | 85 | ND | 78 | 0 | 93 | 48 | 0 | ND | 0 | 0 | 0 | 50 |
| Azadegan et al. [41] | Tehran | 2015 | 2011–2013 | Children/adult | 186 | Disk diffusion | ND | 88 | ND | 186 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Abdollahi et al. [42] | Tehran | 2018 | 2011–2012 | Children | 102 | Disk diffusion | 61 | 24 | ND | 11 | 0 | ND | 70 | 23 | ND | ND | ND | 0 | ND |
| Ahmadi et al. [43] | Tehran | 2013 | 2011 | Children/adult | 88 | Disk diffusion | ND | 47 | ND | 55 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Soltan Dallal et al. [44] | Tehran | 2013 | 2011 | Children/adult | 15 | Disk diffusion | 12 | 10 | ND | 0 | ND | 8 | ND | 8 | ND | 12 | ND | ND | ND | ND |
| Sadeghi et al. [45] | Tehran | 2015 | 2010–2012 | Children/adult | 80 | E-test | 36 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Ahmadi et al. [46] | Tehran | 2015 | 2010–2012 | Children/adult | 70 | Disk diffusion | 60 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Mahmoudi et al. [47] | Tehran | 2013 | 2009–2011 | Children | 7 | Disk diffusion | 5 | ND | ND | ND | ND | ND | ND | 7 | ND | 4 | ND | ND | ND | ND |
| Khoramrooz et al. [48] | Tehran | 2012 | 2009–2010 | Children | 23 | Disk diffusion | 6 | 11 | 13 | ND | 0 | ND | 8 | 0 | 23 | ND | 3 | ND | 0 | ND | ND |
| Rahimi et al. [49] | Tehran | 2015 | 2008–2012 | Children/adult | 38 | NA | 3 | 2 | ND | 8 | ND | ND | 2 | 29 | 4 | ND | ND | 6 | ND | ND |
| Habbibi et al. [50] | Tehran | 2013 | 2008–2012 | ND | 50 | Broth microdilution | 9 | ND | ND | ND | ND | ND | 4 | ND | ND | ND | 2 | ND | ND | ND |
| Dashti et al. [51] | Tehran | 2012 | 2008–2009 | Children | 573 | Disk diffusion | 53 | ND | 315 | 377 | ND | 0 | ND | 9 | 68 | 34 | 26 | 23 | ND | ND | 17 |
| Ashhtiani et al. [52] | Tehran | 2014 | 2001–2011 | Children | 194 | Disk diffusion | 89 | 99 | ND | ND | ND | 0 | 139 | 58 | 23 | ND | ND | ND | 25 |
| Pourakbari et al. [53] | Tehran | 2012 | 2001–2005 | Children | 46 | Disk diffusion | 14 | 29 | ND | ND | ND | 3 | ND | 38 | 8 | ND | ND | ND | ND | ND | ND | ND |
| Author (ref)          | Province                        | Published time | Enrollment time | Age group | Strain | AST          | Antibiotic resistance (n) |
|----------------------|---------------------------------|----------------|-----------------|-----------|--------|--------------|--------------------------|
| Aligholi et al. [54] | Tehran                          | 2009           | 2001–2005       | Children  | 50     | Agar dilution| PNSP: 15, ERY: 29, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: ND, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Oskoui et al. [55]  | Tehran                          | 2010           | 2000–2008       | ND        | 54     | Disk diffusion| PNSP: 10, ERY: 9, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: ND, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Jahanmehr et al. [56]| Tehran                          | 2004           | 1999–2001       | ND        | 66     | Disk diffusion| PNSP: 12, ERY: ND, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: ND, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Oskoui et al. [57]  | Tehran                          | 2003           | 1998–2000       | ND        | 130    | Disk diffusion| PNSP: 114, ERY: 10, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: 28, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Rezaeizadeh et al. [58]| Tehran                       | 2012           | 1998–2008       | Children  | 30     | Disk diffusion| PNSP: 17, ERY: 6, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: ND, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Modarres et al. [59] | Tehran                          | 1998           | 1993–1995       | Children  | 51     | Disk diffusion| PNSP: 1, ERY: 1, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: 29, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Gharailoo et al. [60]| Sistan and Balouchistan         | 2016           | 2013–2014       | Children  | 42     | Disk diffusion| PNSP: 42, ERY: 23, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: 39, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Bokaeian et al. [61]| Sistan and Balouchistan         | 2012           | 2008–2010       | Children  | 75     | Disk diffusion| PNSP: 62, ERY: 66, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: 47, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Bokaeian et al. [62]| Sistan and Balouchistan         | 2011           | 2007–2008       | Children/ adult | 136 | Broth microdilution| PNSP: 43, ERY: 25, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: 11, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Rahbar et al. [63]   | West Azerbaijan                 | 2005           | 1999–2001       | ND        | 24     | Disk diffusion| PNSP: 8, ERY: ND, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: ND, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Behnaz et al. [64]   | Yazd                            | 2004           | 2002            | Children  | 72     | Disk diffusion| PNSP: 36, ERY: 45, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: 45, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |
| Karami et al. [65]   | Zanjan                          | 2009           | 2006–2007       | Children/ adult | 57 | Broth microdilution| PNSP: 33, ERY: ND, AZM: ND, TET: ND, LVX: ND, RIF: ND, CLI: ND, VAN: ND, SXT: ND, CHL: ND, CRO: ND, AMX: ND, CIP: ND, IPM: ND, LZD: ND, CTX: ND, MDR: ND |

PNSP: penicillin-nonsusceptible *S. pneumoniae* (intermediately resistant and fully resistant); ERY: erythromycin; AZM: azithromycin; TET: tetracycline; LVX: levofloxacin; RIF: rifampin; CLI: clindamycin; VAN: vancomycin; SXT: trimethoprim/sulfamethoxazole; CHL: chloramphenicol; CRO: ceftriaxone; AMX: amoxicillin; CIP: ciprofloxacin; IPM: imipenem; LZD: linezolid; CTX: cefotaxime; MDR: multidrug-resistant (resistant to ≥3 antibiotic classes); AST: antimicrobial susceptibility testing; ND: not determined.
Records identified through national and international databases searching (1249) 

Titles and abstracts of the articles assessed for screening (n = 1089) 

Full text of the articles assessed for eligibility (n = 139) 

Included articles in the meta-analysis (n = 58) 

Records excluded: Duplicates 
Nonoriginal articles 

Figure 1: Flow diagram of literature search and study selection.

Prevalence (%)

100
60
80

1998 2005 2010 2015 2020

Year

Prevalence (%)

PNSP
MDR

Figure 2: Total trend in the prevalence rate of PNSP and MDR strains in all age groups in Iran over time (based on the year of publication).

levofoxacin, rifampin, clindamycin, vancomycin, trimethoprim/sulfamethoxazole, chloramphenicol, ceftriaxone, amoxicillin, ciprofloxacin, imipenem, linezolid, and ceftaxime was 41.1% (95% CI: 32.9–49.7; I² = 93%; Q = 545.1; p = 0.00), 53.2% (95% CI: 38.9–67.1; I² = 92.4%; Q = 118.4; p = 0.00), 39.9% (95% CI: 30.2–50.4; I² = 95%; Q = 506.8; p = 0.00), 1.7% (95% CI: 0.2–11.1; I² = 90.9%; Q = 110; p = 0.00), 1.2% (95% CI: 0.1–13.2; I² = 91.1%; Q = 67.6; p = 0.00), 31.7% (95% CI: 20.7–45.2; I² = 91.9%; Q = 172.8; p = 0.00), 1.7% (95% CI: 0.7–4.1; I² = 85.8%; Q = 218.4; p = 0.00), 63.9% (95% CI: 52.3–74; I² = 94.6%; Q = 672.5; p = 0.00), 20% (95% CI: 14.2–27.3; I² = 91.4%; Q = 303.5; p = 0.00), 10.9% (95% CI: 6.6–17.6; I² = 84.7%; Q = 130.8; p = 0.00), 30.5% (95% CI: 12.8–56.8; I² = 95.2%; Q = 187.6; p = 0.00), 8.3% (95% CI: 3.6–17.7; I² = 89.6%; Q = 154.3; p = 0.00), 6.1% (95% CI: 0.1–89.4; I² = 91.8%; Q = 36.6; p = 0.00), 0%, and 8.3% (95% CI: 3.7–17.4; I² = 92.5%; Q = 189; p = 0.00), respectively. The frequency of MDR S. pneumoniae strains in Iran was 45.3% (95% CI: 34.3–56.8; I² = 91.3%; Q = 150.7; p = 0.00). As illustrated in Figure 2, the prevalence of MDR S. pneumoniae in Iran showed an increasing trend from 16.7% in 2010 to 51.3% in 2020. A random-effects model was used to estimate pooled effect in terms of the heterogeneity among studies.

3.3. S. pneumoniae Drug Resistance in Different Provinces of Iran. The results of the subgroup analysis of the prevalence of S. pneumoniae antibiotic resistance based on the different geographic locations in Iran are shown in Table 2. A random-effects model was used to combine studies within each subgroup and obtain the overall effect. The highest rates of S. pneumoniae antibiotic resistance among different provinces in Iran were as follows: 74.4% to erythromycin in Ardabil, 72.1% to azithromycin in Ardabil, 50% to tetracycline in Khuzestan, 24.2% to levofloxacin in Fars, 41% to rifampin in Kermanshah, 50.1% to clindamycin in Tehran, 2.5% to vancomycin in Hamadan, 96.9% to trimethoprim/sulfamethoxazole in Isfahan, 66.7% to chloramphenicol in Qazvin, 60% to ceftriaxone in Isfahan, 60% to amoxicillin in Isfahan, 20.1% to ciprofloxacin in Fars, 99.1% to imipenem in Hamadan, and 60% to ceftaxime in Isfahan. In addition, the highest rates of PNSP and MDR S. pneumoniae strains were detected in Ardabil (95.3% and 74.4%, respectively).

3.4. S. pneumoniae Drug Resistance in Iranian Children. The results of subgroup analysis based on the age group indicated that 27 studies investigated the prevalence of S. pneumoniae antibiotic resistance profiles in Iranian children. Based on the current meta-analysis, S. pneumoniae resistance to different antibiotics was as follows: 38.5% (95% CI: 25.7–53.2; I² = 93.4%; Q = 290.2; p = 0.00) to erythromycin, 66.5% (95% CI: 54.8–76.5; I² = 81%; Q = 26.4; p = 0.00) to azithromycin, 33% (95% CI: 20.2–49; I² = 95.9%; Q = 223.1; p = 0.00) to tetracycline, 0.8% (95% CI: 0.3–2.1; I² = 0.0%; Q = 1.9; p = 0.92) to levofloxacin, 1.2% (95% CI: 0.1–13.2; I² = 91.1%; Q = 67.6; p = 0.00) to rifampin, 17.3% (95% CI: 7.3–35.6; I² = 86.8%; Q = 45.5; p = 0.00) to clindamycin, 1.7% (95% CI: 0.4–7.1; I² = 90.7%; Q = 151; p = 0.00) to vancomycin, 63.7% (95% CI: 48.3–76.7; I² = 94.8%; Q = 407.2; p = 0.00) to trimethoprim/sulfamethoxazole, 17.7% (95% CI: 11.4–26.3; I² = 86.1%; Q = 93.6; p = 0.00) to chloramphenicol, 12.6% (95% CI: 6.5–22.9; I² = 84.9%; Q = 73; p = 0.00) to ceftriaxone, 35.1% (95% CI: 12.3–67.6; I² = 96.3%; Q = 162.4; p = 0.00) to amoxicillin, 5.5% (95% CI: 1.1–22.7; I² = 90.7%; Q = 53.7; p = 0.00) to ciprofloxacin, 0.7% (95% CI: 0.0–9.7; I² = 0.0%; Q = 0; p = 1.00) to imipenem, 0% to linezolid, and 8.3% (95% CI: 3.2–19.8; I² = 88.6%; Q = 61.4; p = 0.00) to ceftaxime. Besides, 57.4% (95% CI: 33.1–78.6; I² = 91%; Q = 44.8; p = 0.00) of S. pneumoniae isolated from Iranian children were MDR strains. Random- or fixed-effects models were used to estimate pooled effect.
3.5. *Penicillin-Nonsusceptible S. pneumoniae* in Iran. According to the random-effects model ($I^2 = 93.6\%$; $Q = 712.6$; $p = 0.00$), the total prevalence of PNSP strains in Iran was 46.9% (95% CI: 38.6–55.4). In addition, the rate of PNSP strains isolated from Iranian children was 46.9% (95% CI: 33.4–60.8; $I^2 = 94.4\%$; $Q = 363.1$; $p = 0.00$) as well (Figure 3(a)). As shown in Figure 3(b), publication bias was detected in the current study due to the evidence of asymmetry in the funnel plot whereas the results of Begg’s ($z = 0.21, p = 0.83$) and Egger’s tests ($t = 1.86, p = 0.07$) were not statistically significant. Finally, as presented in Figure 2, we assessed the frequency of PNSP strains from 1998 to 2020. Figure 2 shows an increasing trend of PNSP strains in Iran.

### Table 2: *S. pneumoniae* antibiotic resistance profiles in different provinces of Iran.

| Province                           | PNSP | ERY | AZM | TET | LVX | RIP | CLI | VAN | SXT | CHL | CRO | AMX | CIP | IPM | LZD | CTX | MDR |
|------------------------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ardabil                            | 95.3 | 74.4| 72.1| 61.9| 1.1 | 1.1 | 27.9| 1.1 | 81.4| 16.3| ND  | ND  | ND  | ND  | ND  | ND  | 74.4|
| Chaharmahal and Bakhhtiari         | 69.2 | 58.8| ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | 5.9 | ND  | 11.8| ND  | ND  | ND  |
| East Azerbaijan                    | 37.8 | 16.2| ND  | ND  | ND  | 2.7 | ND  | 1.3 | 32.4| 5.4 | 10.8| ND  | ND  | ND  | ND  | 8.1 |
| Fars                               | 48.6 | 27.4| 25.5| 17  | 24.2| ND  | 18.5| 1.9 | 66.2| 7.3 | 17.1| 40  | 20.1| ND  | ND  | 18.6|
| Golestan                           | 55.6 | 7.9 | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  |
| Hamadan                            | 94.5 | 25.5| 18.2| ND  | ND  | ND  | 2.5 | 29.1| 34.8| 7.1 | 54.3| 11.6| 99.1| ND  | 7.1 |
| Isfahan                            | 16.2 | 11.4| 60  | 25.4| 0.2 | 0.2 | 1.7 | 0.2 | 96.9| 60  | 60  | 3.1 | ND  | 0   | 60  |
| Kermanshah                         | ND   | ND  | 63.9| ND  | ND  | 41  | ND  | 37.3| 3.6 | 56.6| ND  | ND  | ND  | 41  |
| Khuzeastan                         | ND   | ND  | ND  | 50  | ND  | ND  | ND  | ND  | ND  | ND  | 7.1 | ND  | 50  | ND  | ND  |
| Qazvin                             | ND   | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | 66.7| 66.7| ND  | ND  | ND  |
| Tehran                             | 40.2 | 47.3| 68.1| 45.7| 1.1 | 0.4 | 50.1| 2.2 | 69.5| 24.1| 9.8 | 12.8| 5.9 | 0   | 5.4 |
| Sistan and Balouchestan            | 79.3 | 55.4| ND  | 38.1| 0.9 | ND  | 0.7 | 81.3| 12.1| 2.6 | 16.7| 0.7 | ND  | 2   | 31.2|
| West Azerbaijan                    | 33.3 | ND  | ND  | ND  | 2   | 0.2 | 2   | ND  | ND  | ND  | 12.8| 5.9 | 0.7 | ND  | 5.4 |
| Yazd                               | 50   | 62.5| ND  | 30.6| ND  | ND  | ND  | 62.5| ND  | ND  | ND  | ND  | ND  | ND  |
| Zanjan                             | 57.8 | ND  | ND  | 50  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  | ND  |

4. Discussion

Antibiotic resistance is consistently growing and has become a global public health crisis. According to the European Center for Disease Prevention and Control (ECDC) and the Center for Disease Control and Prevention (CDC), antibiotic-resistant bacteria in Europe and the USA are associated with an annual mortality rate of 25,000 and 23,000, respectively. Also, nearly 700,000 deaths worldwide are due to antibiotic resistance [5, 67]. It is estimated that antimicrobial resistance will lead to 10 million deaths a year by 2050 [5, 67]. Factors such as antibiotic overuse/misuse in humans and also in the food/veterinary industry along with reduced development of new antibiotics play key roles in the incidence of both Gram-positive and Gram-negative resistant bacteria [5]. Penicillin-resistant *S. pneumonia* was first detected in Australia in 1967. PNSP strains are listed as one of the most serious emerging bacterial threats as of 2017 [3, 6]. The current rate of penicillin-resistant *S. pneumoniae* in Iran is 46.9%, whereas it is found to be 1–5% in the UK, Germany, Austria, Norway, and Sweden, 5–10% in Italy, 10–25% in Portugal, Ireland, Finland, and Turkey, 25–50% in Spain, France, Greece, and Israel, 20% in Brazil, and 66.4% in China [68–70]. The results of subgroup analysis based on the age group showed a similarly high rate of PNSP among Iranian children (46.9%) which could be due to the common use of antibiotics in these patients [39]. Therefore, the prescription of penicillin as the first-choice antibiotic in the treatment of *S. pneumoniae* infections such as meningitis and pneumonia should be avoided. The prevalence of PNSP isolates in Iran has shown a rising trend from 1998 to 2020 (Figure 2). While there was high pneumococcal resistance to amoxicillin in Iran, resistance to other beta-lactam antibiotics such as cephalosporins and carbapenems was rather low. Thus, the extended-spectrum cephalosporins are suitable alternative drugs in the treatment of penicillin-resistant infections including pneumococcal meningitis in Iran. Modification of penicillin-binding proteins (PBPs) particularly PBP1a, PBP2x, and PBP2b as well as mutations in *cpoA, ciaH, murM*, and *murN* genes has been described as the main mechanisms of resistance in *S. pneumoniae* to beta-lactam antibiotics [3]. Pneumococcal resistance to macrolides, fluoroquinolones, and tetracyclines has also been reported [1]. The prevalence of macrolide-resistant *S. pneumoniae* is geographically variable as it ranges from 25 to 50% in France, Italy, and Greece, 10 to 25% in Spain, Portugal, the UK, Germany, Poland, Norway, and Finland, and 1 to 5% in Latvia and Sweden [68]. In Iran, 41.1% and 53.2% of *S. pneumoniae* isolates were resistant to erythromycin and azithromycin, respectively. Ribosomal modification, efflux system, and point mutations are involved in the emergence of macrolide-resistant *S. pneumoniae* [3]. An important mechanism of *S. pneumoniae* resistance to clindamycin is the alteration of the ribosomal target through *erm(B)* gene which encodes a 235 RNA methylase [71]. Clindamycin has shown a strong activity against community-acquired infections of *S. pneumoniae* [71]. However, the rates of clindamycin-resistant pneumococcal strains in the current study were high (31.7%) and included 25% in Egypt, 35.1% in Turkey, and 21.8% in the United States [3,71]. Penicillins and macrolides have been largely applied in the treatment of community-acquired pneumonia and other respiratory tract infections by *S. pneumoniae* [72]. However, a high resistance
rate to these antibiotics has led to the use of quinolones against important bacterial respiratory tract pathogens [72]. Hence, a combination of vancomycin and gentamicin is proposed for treating infections caused by penicillin- and cephalosporin-resistant \textit{S. pneumoniae} strains [3]. The findings of the present study on the prevalence of fluoroquinolone-resistant strains of \textit{S. pneumoniae} indicated a low resistance rate to levofloxacin (1.7%) and ciprofloxacin (8.3%) in Iran. The prevalence of fluoroquinolone-resistant pneumococcal strains in other countries was as follows: 4%

| Study name | Event rate | Lower limit | Upper limit | Z value | p value | Total |
|------------|------------|-------------|-------------|---------|---------|-------|
| Gharibani  | 0.953      | 0.832       | 0.988       | 4.171   | 0.000   | 41/43 |
| Khoshdel   | 0.289      | 0.168       | 0.451       | -2.510  | 0.012   | 11/38 |
| Abdinia    | 0.378      | 0.239       | 0.542       | -1.465  | 0.143   | 14/37 |
| Hadi       | 0.700      | 0.376       | 0.900       | 1.228   | 0.220   | 7/10  |
| Ghaemi     | 0.556      | 0.432       | 0.673       | 0.880   | 0.379   | 35/63 |
| Ghazikalyeh| 0.162      | 0.124       | 0.208       | -10.339 | 0.000   | 47/291|
| Mamishi    | 0.250      | 0.034       | 0.762       | -0.951  | 0.341   | 1/4   |
| Mousavi    | 0.994      | 0.905       | 1.000       | 3.545   | 0.000   | 76/76 |
| Houri      | 0.208      | 0.119       | 0.337       | -3.956  | 0.000   | 11/53 |
| Abdollahi  | 0.598      | 0.500       | 0.688       | 1.967   | 0.049   | 61/102|
| Mahmoudi   | 0.714      | 0.327       | 0.928       | 1.095   | 0.273   | 5/7   |
| Khoramrooz | 0.261      | 0.122       | 0.472       | -2.193  | 0.028   | 6/23  |
| Dushti     | 0.092      | 0.071       | 0.119       | -5.837  | 0.000   | 53/573|
| Hagh Ashtiani| 0.459   | 0.390       | 0.529       | -1.147  | 0.251   | 89/194|
| Pourakbari | 0.304      | 0.189       | 0.451       | -2.580  | 0.010   | 14/46 |
| Aligholi   | 0.300      | 0.190       | 0.440       | -2.746  | 0.006   | 15/50 |
| Rezaei-zadeh| 0.567    | 0.388       | 0.729       | 0.728   | 0.467   | 17/30 |
| Modares    | 0.020      | 0.003       | 0.126       | -3.873  | 0.000   | 1/51  |
| Gharailoo  | 0.988      | 0.840       | 0.999       | 3.123   | 0.002   | 42/42 |
| Bokacian   | 0.827      | 0.724       | 0.987       | 5.121   | 0.000   | 62/75 |
| Behnazz   | 0.500      | 0.387       | 0.613       | 1.000   | 0.000   | 36/72 |
|           | 0.469      | 0.334       | 0.608       | -0.438  | 0.661   |       |

\textbf{Figure 3:} Forest plot (a) and funnel plot (b) showing the prevalence of penicillin-nonsusceptible \textit{S. pneumoniae} in Iranian children.
in Egypt, 1.8% in Turkey, 1-2% in the USA, and <10% in Belgium [3, 71, 72]. A low incidence of vancomycin-resistant \textit{S. pneumoniae} was found in Iran (1.7%), and no resistance has been reported in many other countries [3]. Factors associated with resistance to fluoroquinolones in clinical pneumococcal isolates include mutations in the quinolone-resistance-determining regions (QRDRs) of \textit{gyrA}, \textit{gyrB}, \textit{parC}, and \textit{parE} genes as well as the overexpression of \textit{pmrA} gene (codes for an efflux pump) and \textit{patA} and \textit{patB} genes (code for an ABC transporter) [3, 71]. Point mutation in a histidine kinase gene (\textit{vncS}) is associated with the emergence of vancomycin-tolerant pneumococcal strains [3]. The highest drug resistance rate among pneumococcal isolates in Iran was observed to folate pathway inhibitors (i.e., trimethoprim/sulfamethoxazole (63.9%)). Cotrimoxazole-resistant \textit{S. pneumoniae} were isolated in 25–45% of strains in the USA, 55% in Egypt, 100% in Saudi Arabia, and 67.2% in Turkey [3, 71]. Mutations in dihydrofolate reductase (DHFR) and in dihydropteroate synthase (DHPS) are the mechanisms of resistance to folate inhibitors [3, 71]. Studies from the Middle East and the USA have reported a high rate of \textit{S. pneumoniae} resistance to tetracycline which could be attributed to extensive use of this antimicrobial agent [3, 71]. A similar result was observed in the current study (39.9%). Resistance to chloramphenicol (a bacterial protein inhibitor) was high whereas there was no resistance to linezolid. Two other important findings of the study included a high prevalence of MDR pneumococci in Iranian people (45.3%), especially children (57.4%) with a rising trend from 2010 to 2020 (Figure 2), and also the isolation of \textit{S. pneumoniae} with multidrug resistance in children less than five years old from Shahrekord, Iran, with the high consumption of nonprescribed antibiotics in Iran. Available data from CDC showed that MDR \textit{S. pneumoniae} is responsible for more than 30% of invasive pneumococcal disease throughout the United States [73, 74]. Therefore, timely vaccination in Iranian children and ongoing surveillance on drug resistance trend along with the use of combination therapy or the use of newer antibiotics are needed to improve microorganism susceptibility.

5. Conclusion

The current study indicated a high prevalence of PNSP and MDR strains in Iran among all age groups. Similar results were also observed in the frequency of erythromycin-, azithromycin-, tetracycline-, clindamycin-, trimethoprim/sulfamethoxazole-, chloramphenicol-, and amoxicillin-resistant \textit{S. pneumoniae} strains. These findings could be due to the high consumption of nonprescribed antibiotics in Iran. Hence, strategies to prevent emerging drug-resistant pneumococcal infections and treatment failure in Iran include (1) continuous regional monitoring of nasopharyngeal carriers of antibiotic-resistant \textit{S. pneumoniae} in children, (2) controlled administration of antibiotics to improve microorganism susceptibility, (3) use of combination therapies or drugs with low resistance rate in accordance with local resistance patterns, and (4) identification of the most common pneumococcal serotypes and their drug resistance rates in Iranian population to produce effective pneumococcal vaccines. The most effective antibiotics for the treatment of pneumococcal infections in Iran based on the current study are levofloxacin, rifampin, vancomycin, ceftriaxone, ciprofloxacin, imipenem, linezolid, and cefotaxime.

Data Availability

There are no raw data associated with this systematic review and meta-analysis.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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