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The increasing antimicrobial resistance of *Shigella* species among Iranian pediatrics: a systematic review and meta-analysis

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ABSTRACT

Background: Shigellosis remains one of the global causes of morbidity and mortality. However, the global emergence of antibiotic resistance has become the leading cause of treatment failure in shigellosis. This review aimed to provide an updated picture of the antimicrobial resistance rates in *Shigella* species in Iranian pediatrics.

Methods: A comprehensive systematic search was performed on PubMed, Scopus, Embase, and Web of Science until 28 July 2021. The meta-analysis was performed by computing the pooled using a random-effects model with Stata/SE software, v.17.1. The discrepancy within articles was surveyed by the forest plot in addition to the I^2 statistic. All statistical interpretations were reported on a 95% confidence interval (CI) basis.

Results: Totally, of 28 eligible studies published between 2008 and 2021. The pooled prevalence rate of multidrug-resistant (MDR) was 63% (95% CI 50–76). Regarding suggested antimicrobial agents for *Shigella* species, the prevalence of resistance for ciprofloxacin, azithromycin, and ceftriaxone as first- and second-line treatments for shigellosis were 3%, 30%, and 28%, respectively. In contrast, resistance to cefotaxime, cefixime, and ceftazidime was 39%, 35%, and 20%. Importantly, subgroup analyses indicated that an increase in resistance rates during the periods (2008–2014, 2015–2021) was recognized for ciprofloxacin (0 % to 6%) and ceftriaxone (6% to 42%).

Conclusion: Our findings revealed that ciprofloxacin is an effective drug for shigellosis in Iranian children. The substantially high prevalence estimation proposes that the first- and second-line treatments for shigellosis are the major threat to public health and active antibiotic treatment policies are essential.

KEYWORDS
Antimicrobial resistance; *Shigella* species; resistance; systematic review and meta-analysis

Introduction

Shigella, as a Gram-negative, non-spore-forming, and rod-shaped bacteria, are the causative agents of shigellosis which are considered by fever, diarrhea (watery or bloody), abdominal pain, and tenesmus (rectal spasms), and abundant leukocytes, blood and mucus in the stool [1]. Worldwide, shigellosis is a major public health concern especially in low-income countries because of overcrowding and low hygiene settings [2]. On a global scale, *Shigella* is estimated to cause 80–165 million cases of disease and 600,000 deaths each year (40,000 deaths per year in children under the age of 5 in 2015) [2]. In Iran, the prevalence of shigellosis is too varying geographically [3]. In Iran, shigellosis is one of the major causes of childhood diarrhea-related morbidity and mortality [3]. Based on the 2016 Global Enteric Multicenter Study report, the *Shigella* species is the primary bacteria among the top six attributable pathogens causing childhood diarrhea [4]. *Shigella* infection is transmitted through consuming contaminated food and water, the fecal – oral route, and person-to-person contact, particularly in adults during household contact with infected children [1]. The present WHO guidelines suggest the use of fluoroquinolones (first-line), beta-lactams (second-line), and cephalosporins (second-line) for shigellosis treatment in adults and children [2]. Azithromycin is now registered in WHO guidelines as second-line therapy for shigellosis in adults and as first-line for pediatrics in other guidelines [2]. *Shigella* strains have become resistant to first-line drugs (trimethoprim-sulfamethoxazole and ampicillin) and are

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

no longer prescribed to treat shigellosis due to the emergence of multidrug resistance (MDR) and have challenged the treatment of the disease in children [5,6]. Considering the increasing number of antimicrobial-resistant *Shigella* strains develops a life-threatening global concern and a major threat to public health [5,6]. Based on the WHO report 2016 [2], the *Shigella* species is one of the eight serious antibiotic resistant bacteria; thus, shigellosis treatment has presently become more challenging which has narrowed the option of antimicrobial agents and related to a diversity of biological, pharmacological and societal variables with the worst combinations in low and middle-income countries [7]. Several reports have reported the high-level antibiotic-resistant patterns of *Shigella* species in different provinces of Iran [8,9]. Therefore, in our study, we performed comprehensive metadata to characterize and summarize antimicrobial resistance patterns of *Shigella* species during 2008–2021 in Iranian children. It is proposed for the significance of constant monitoring of antimicrobial resistance of clinical isolates.

Methods

This study is conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [10].

Data sources and search strategy

Four databases (MEDLINE [PubMed], Scopus, and Embase, Web of Science) for studies were systematically searched (till 28 July 2021) by using the following keywords: ('*Shigella*' OR 'shigellosis'" OR '"bacillary dysentery"') AND "prevalence "OR 'epidemiology' AND ('Drug Resistance' OR 'antimicrobial Resistance' OR 'Antibiotic resistance' OR 'fluoroquinolone resistance' OR 'ciprofloxacin resistance' OR 'ceftriaxone resistance' OR 'azithromycin resistance') AND 'Iran' in the Title/Abstract/Keywords fields. The records found through database searching were combined and the duplicates were removed using EndNote X8 software (Thomson Reuters, New York, NY, U.S.A).

Inclusion and exclusion criteria

The following items were obtained from each included article: author, year of study, year published, province, number of clinical *Shigella* species isolates, number of resistant *Shigella* species isolates, diagnostic methods, antimicrobial susceptibility testing (AST; disk diffusion agar, agar dilution, micro broth dilution, E-test), and guideline of resistance. The exclusion criteria were as follows [1]: articles that included duplicate data [2]; animal studies, reviews, meta-analysis and/or systematic review, and conference abstracts [3]; resistance rates were not reported; and [4] studies without CLSI using guideline for interpretation of resistance.

Data abstraction

The reviewers screened all titles and abstracts separately and excluded irrelevant or duplicate articles first. The reviewers then independently assessed the remaining articles for inclusion. Also, the authors cross-check included articles reference list for any additional studies that may have been missed in the search. Three reviewers then distinctly assessed the lasting articles for inclusion. Differences were determined by discussion.

Quality assessment

The quality assessment of the comprised articles was evaluated by two independent reviewers separately using an adapted version of the tool proposed by the Newcastle-Ottawa assessment scale adapted for cross-sectional studies [11]. Articles with scores≥6 points: high quality, ≤ 5 points: low quality were considered to be high and: low quality, respectively.

Definitions

People who were diagnosed with shigellosis by phenotypic and molecular methods. The resistance rate was according to the culture results and expressed as the number of resistant isolates divided by the total number of isolates tested. Results from phenotypic methods were recognized for the interpretation of resistance by CLSI guidelines.

Publication bias

The DOI plot and the LFK index were used to check for the existence of quantified asymmetry of study effects and publication bias. Simulation studies determine that the LFK index outperforms Egger's regression *P* value for the check of asymmetry. The closer the value of the LFK index to zero, the more symmetrical the DOI plot would be and zero characterizes complete symmetry.

Statistical analysis

The meta-analysis was performed by computing the pooled using a random-effects model with Stata/SE software, v.14.1 (StataCorp, College Station, TX). The discrepancy within articles was surveyed by the forest plot in addition to the I^2 statistic. Values of I^2 (25%, 50%, and 75%) were elucidated as the presence of low,

medium, or substantial heterogeneity, respectively. Thus, the DerSimonian and Laird random effects models were used [12]. Subgroup analyses were then employed by publication year. All statistical interpretations were reported on a 95% confidence interval (CI) basis.

Study outcomes

The main outcome was the weighted pooled resistance rate (WPR) of clinical *Shigella* species to drugs. A subgroup analysis was accomplished by publication date (2008–2014, and 2015–2021).

Results

Systematic literature search

686 records were recognized in our initial electronic database search. From these records, after an initial screening of the title and abstract, 616 articles were excluded due to their irrelevance and duplication. The full texts of the remaining 70 articles were reviewed (Figure 1).

42 of 70 articles were excluded for the below reasons: animal research, reviews, meta-analysis and/or systematic review, conference abstracts, resistance rates were not stated, and articles without a guideline for interpretation of resistance. Finally, 28 cross-sectional studies [13–39] were included in our meta-analysis. The reports included in our metadata assessed drug resistance to ciprofloxacin, ceftriaxone, azithromycin, tetracycline, nalidixic acid, chloramphenicol, trimethoprim/sulfamethoxazole, ampicillin, gentamicin, cefixime, ceftazidime, cefotaxime, and imipenem.

Study characteristics

The final 28 studies selected for this work were performed in 7 provinces and considered 2788 clinical *Shigella* species. The common reports originated in

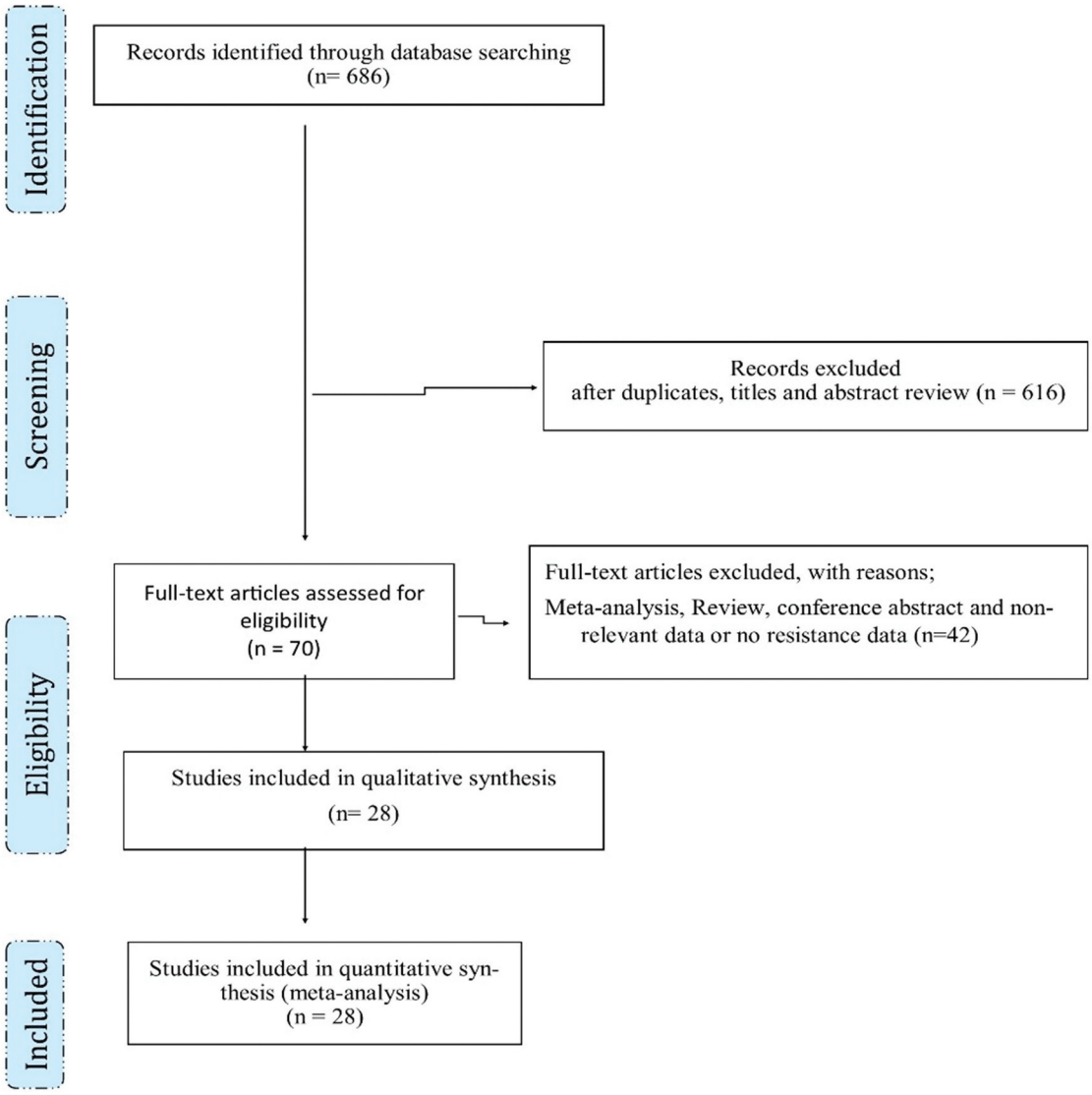

Figure 1. The PRISMA flowchart of included studies.

Tehran ($n = 15$), followed by Khuzestan ($n = 5$), Fars ($n = 3$), Ardabil ($n = 2$), Qazvin ($n = 1$), Markazi ($n = 1$), and Khorasan Razavi ($n = 1$). The most frequent AST methods were disk diffusion agar and a combination of disk diffusion agar and MIC methods. The quality of data was high in 12 reports and low in 16 reports. The majority of the reports 27 (96.42%) selected in this study exposed the resistance to trimethoprim/sulfamethoxazole, ampicillin (24; 85.7%), nalidixic acid (23; 82.1%), and ciprofloxacin (23; 82.1%).

Ciprofloxacin resistance

The susceptibility to ciprofloxacin was determined in 23 studies including 1759 clinical *Shigella* species; the WPR was 3% (95% CI 1–6) with substantial

Table 1. Prevalence of antibiotic resistance of *Shigella* species among Iranian Pediatrics.

Variables	N. of studies	Prevalence (%) of Resistance (95% CI)	n/N	Heterogeneity Test (I^2)
Ciprofloxacin	23	3 [1–6]	81/1759	85.74
Publication date				
2008–2014	17	0 (0–0)	0/574	94.28
2015–2021	6	6 [2–10]	81/1185	83.19
Azithromycin	8	30 [15–46]	156/673	95.06
Publication date				
2008–2014	-	-	-	-
2015–2021	8	30 [15–46]	156/673	95.06
Ceftriaxone	18	28 [10–49]	741/1798	98.84
Publication date				
2008–2014	6	6 (0–53)	346/882	99.57
2015–2021	12	42 [26–57]	395/916	95.72
Cefixime	9	35 [12–61]	233/823	98.37
Publication date				
2008–2014	3	3 (0–11)	10/393	0.00
2015–2021	6	56 [30-]79)	223/430	96.12
Ampicillin	24	69 [56-]80)	1469/2549	97.03
Publication date				
2008–2014	6	37 [22–52]	272/889	91.95
2015–2021	18	79 [62-]86)	1197/1660	94.28
Chloramphenicol	11	24 [12–37]	345/1100	95.31
Publication date				
2008–2014	4	28 [11–48]	265/790	96.81
2015–2021	7	21 [4–45]	80/310	94.32
Trimethoprim/sulfamethoxazole	27	84 (73–93)	2122/2778	97.85
Publication date				
2008–2014	7	78 [40-]99)	543/971	99.16
2015–2021	20	87 (81–91)	1579/1807	88.46
Gentamicin	20	10 [1–22]	424/1871	98.28
Publication date				
2008–2014	6	11 (0–55)	323/882	99.43
2015–2021	14	8 [3–15]	101/989	88.98
Tetracycline	11	62 [37-]84)	563/820	97.70
Publication date				
2008–2014	4	79 [55-]96)	407/482	96.58
2015–2021	7	51 [21-]79)	156/338	96.40
Cefotaxime	13	39 [22–56]	526/1382	97.43
Publication date				
2008–2014	1	0 (0–2)	0	0
2015–2021	12	46 [34–56]	526/1182	91.84
Ceftazidime	12	20 [6–37]	334/1270	97.85
Publication date				
2008–2014	5	3 (0–29)	180/846	99.02
2015–2021	7	36 [28–43]	154/424	59.97
Amikacin	10	15 [1–39]	386/1181	98.84
Publication date				
2008–2014	3	19 (0–54)	306/679	0
2015–2021	7	14 [4–27]	80/502	93.56
Imipenem	8	4 (0–10)	24/513	88.12
Publication date				
2008–2014	-	-	-	-
2015–2021	8	4 (0–10)	24/513	88.12
Nalidixic acid	23	29 [16–42]	991/2560	98.15
Publication date				
2008–2014	7	21 [1–54]	358/971	99.09
2015–2021	16	33 [18–47]	633/1589	97.13
MDR	12	63 [49-]76)	799/1234	95.08
Publication date				
2008–2014	3	61 [47-]73)	388/590	-
2015–2021	9	65 [43-]83)	411/644	96.19

Abbreviations; I-squared; I^2, Confidence Interval; CI, Multiple drug resistance; MDR.

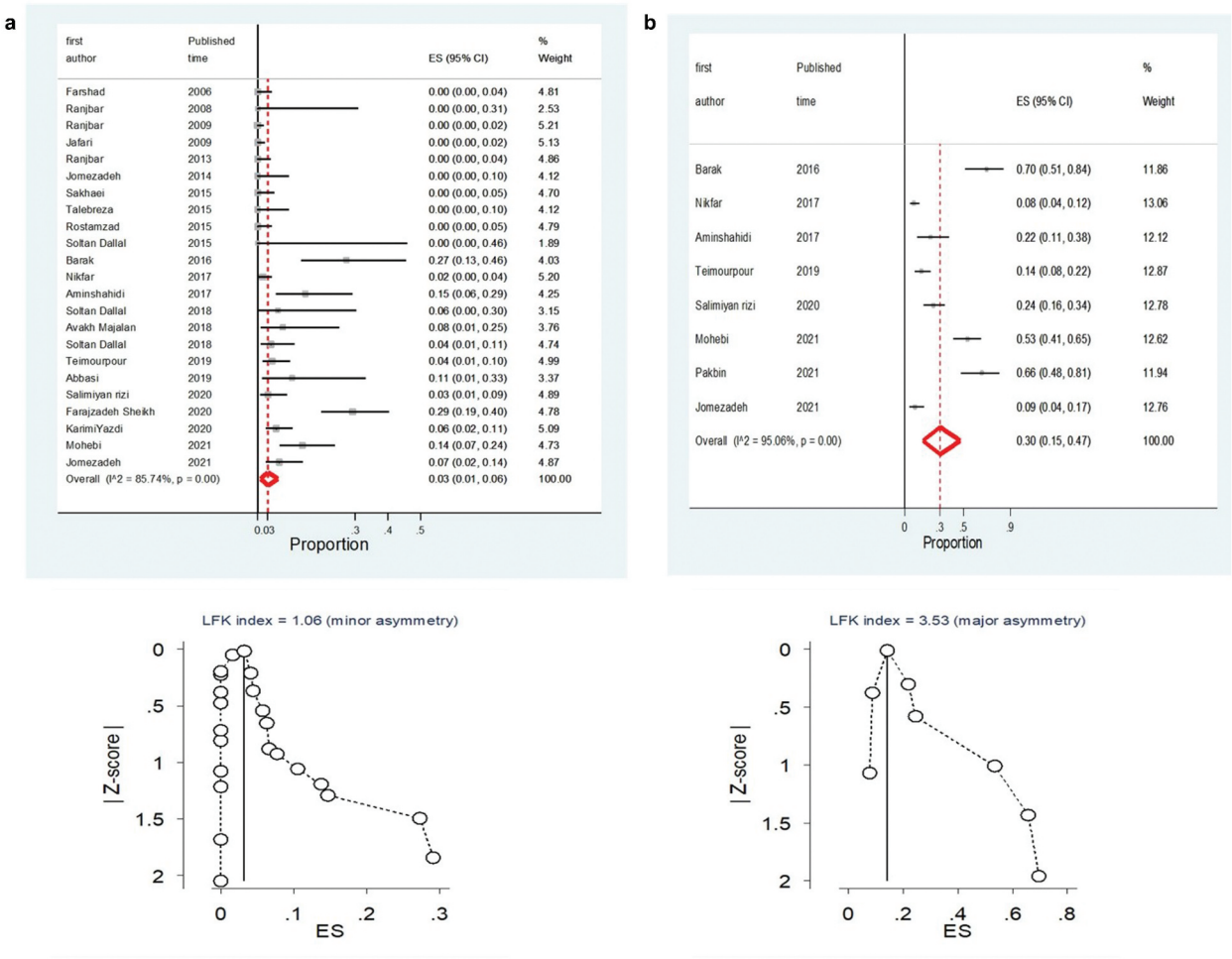

Figure 2. Forest plots and DOI plots of the prevalence of clinical *Shigella* species resistant to ciprofloxacin (A) and azithromycin (B) in Iran.

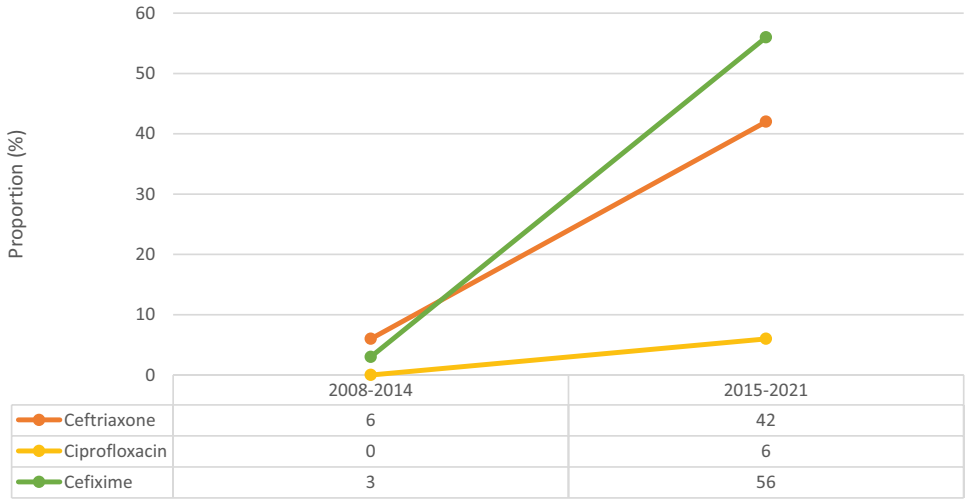

Figure 3. Forest plots and DOI plots of the prevalence of clinical *Shigella* species resistant to ciprofloxacin (A) and azithromycin (B) in Iran.

heterogeneity ($I^2 = 85.74\%$) (Table 1 and Figure 2). To analyze the trends for changes in the prevalence of ciprofloxacin resistance in more recent years, we performed a subgroup analysis for two periods (2008–2014 and 2015–2021) (Table 1 and Figure 3). The subgroup analysis that compared the data from 2008–2014 (WPR 0%; 95% CI 0%-0%), and 2015–2021 (WPR 6%; 95% CI 2%-10%) indicated a relative increase in the resistance rate. Nevertheless, this difference was not statistically significant ($P > 0.05$). Based on the provinces of the studies, the highest resistance rate was reported in

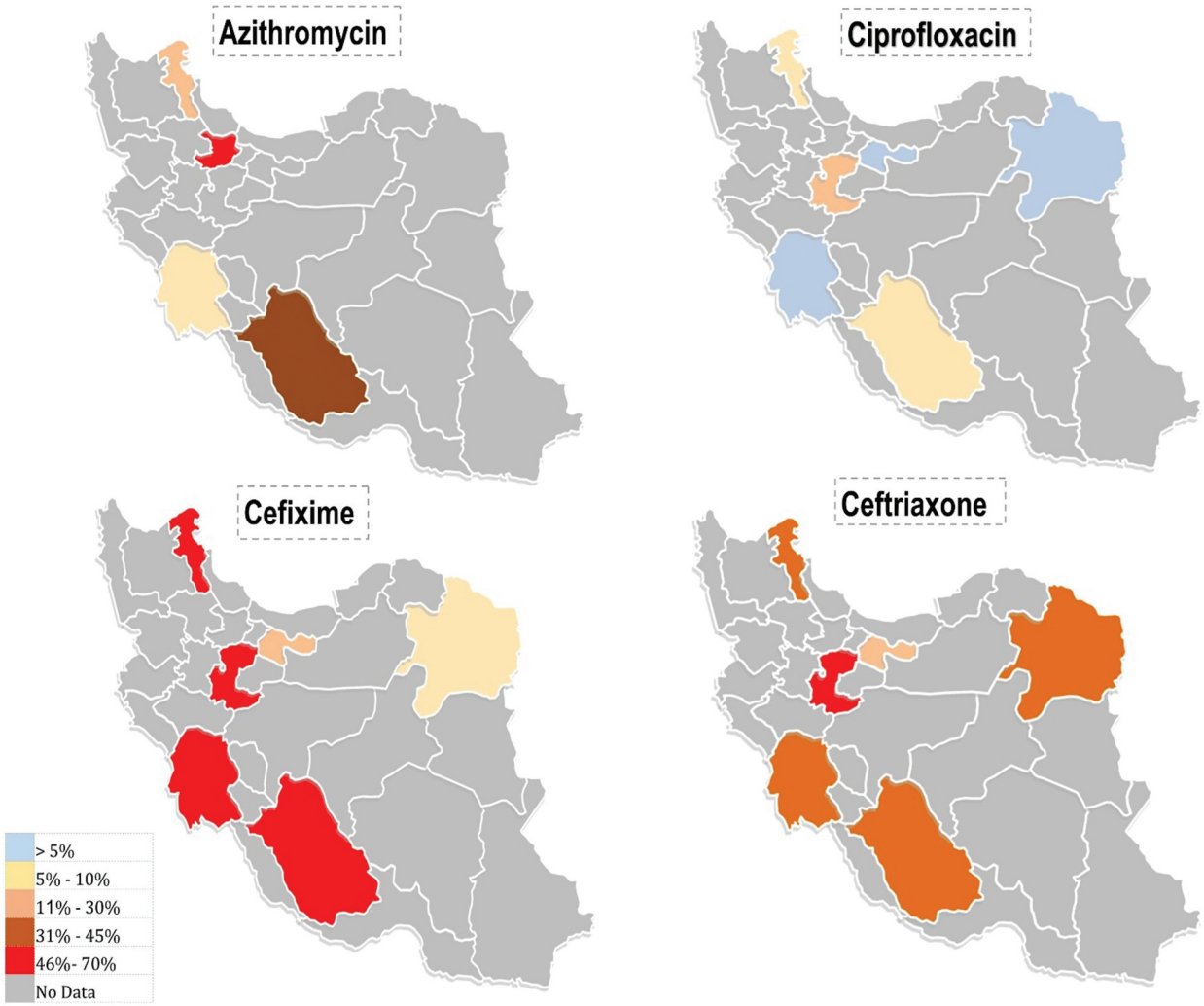

Figure 4. The prevalence of ciprofloxacin, ceftriaxone, and cefixime weighted pooled resistance in Iranian children stratified by published year.

Markazi (11%), followed by Ardabil (8%) and Fars (7%) (Figure 4).

Azithromycin resistance

The susceptibility to azithromycin was determined in 8 studies that included 673 clinical *Shigella* species; the WPR was 30% (95% CI 15–47) with substantial heterogeneity ($I^2 = 95.06\%$) (Table 1 and Figure 2). Based on the provinces of the studies, the highest resistance rate was reported in Qazvin (66%), followed by Fars (42%) (Figure 4).

Third-generation cephalosporins resistance

Ceftriaxone

The susceptibility to ceftriaxone was determined in 18 studies and included 1798 *Shigella* species. The WPR to ceftriaxone was 28% (95% CI 10–50; Table 1, Figure 5) ranging from 11% in Tehran to 63% in Markazi with substantial heterogeneity ($I^2 = 98.84\%$; Figure 4). Subgroup analysis showed a significant increase in ceftriaxone resistance ($p = 0.001$) from 6% (95% CI 0–53) in 2008–2014 to 42% (95% CI 27–58) in 2015–2021 (Table 1, Figure 3), with significant heterogeneity between subgroups ($p = 0{\cdot}01$).

Cefixime

The susceptibility to cefixime was determined in 9 studies and included 823 *Shigella* species. The WPR to ceftriaxone was 35% (95% CI 12–62; Table 1, Figure 5) ranging from 10% in Khorasan Razavi to 70% in Ardabil with substantial heterogeneity ($I^2 = 98.37\%$; Figure 4). Subgroup analysis showed a significant increase ($p = 0{\cdot}01$) in cefixime resistance ($p = 0.001$) from 3% (95% CI 0–11) in 2008–2014 to 56% (95% CI 31–79) in 2015–2021 (Table 1, Figure 3).

Cefotaxime

The susceptibility to cefotaxime was determined in 13 studies including 1382 clinical *Shigella* species; the WPR was 39% (95% CI 23–57) with substantial

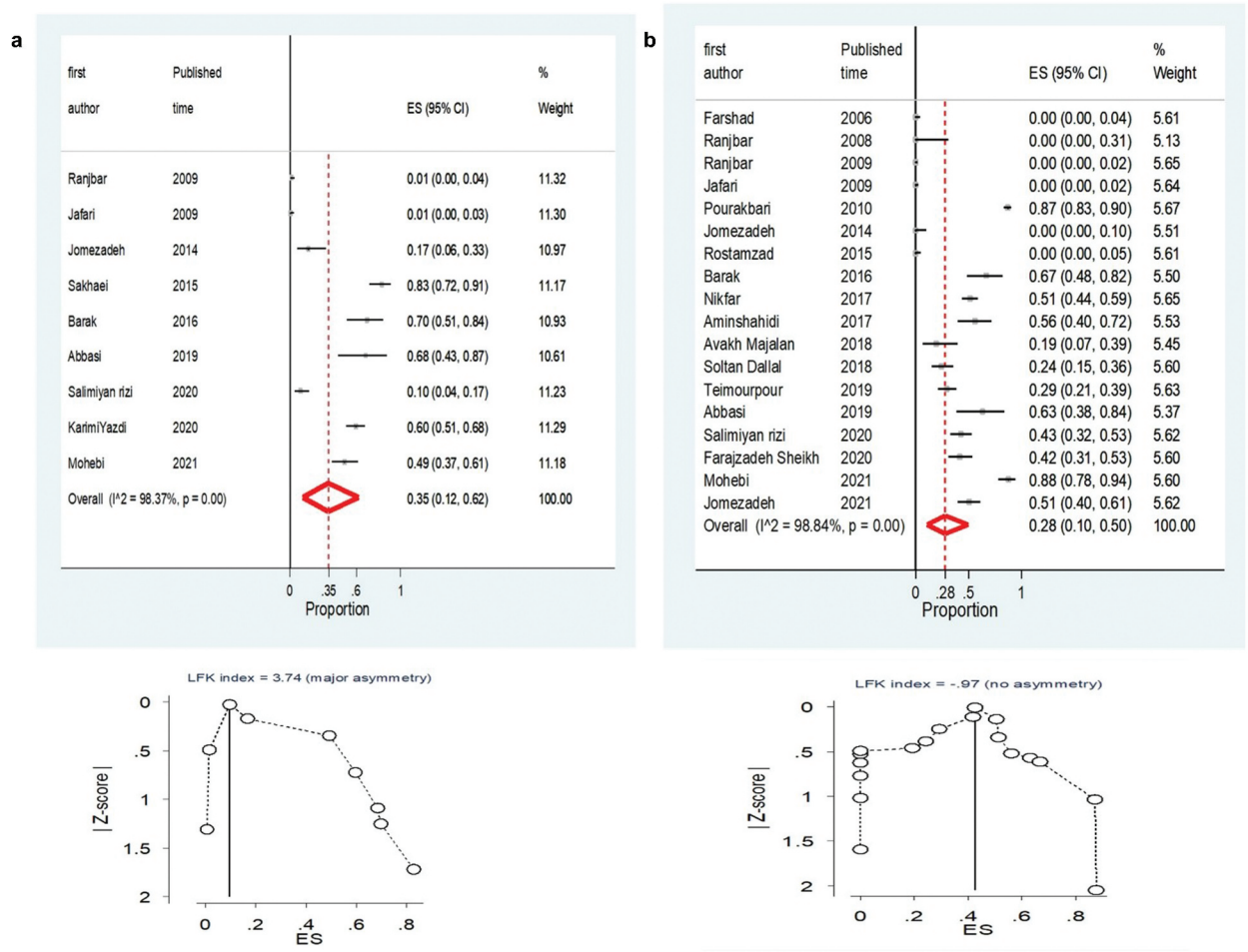

Figure 5. The prevalence of azithromycin, ciprofloxacin, ceftriaxone, and cefixime weighted pooled resistance in Iranian provinces.

heterogeneity ($I^2 = 97.43\%$) (Table 1). There was a high increase in cefotaxime resistance between 2008–2014 and 2015–2021 years (Table 1).

Ceftazidime

The susceptibility to ceftazidime was determined in 12 studies including 1270 clinical *Shigella* species; the WPR was 20% (95% CI 6–38) with substantial heterogeneity (I2 = 97.85%) (Table 1). There was a 12-fold increase in ceftazidime resistance between 2008–2014 (3%) and 2015–2021 years (36%) (Table 1), although, this increase was not significant ($p > 0{\cdot}05$).

Ampicillin resistance

The susceptibility to ampicillin was determined in 24 studies and included 2549 *Shigella* species. The WPR to ceftriaxone was 69% (95% CI 57–80; Table 1) with substantial heterogeneity ($I^2 = 97.03\%$). Subgroup analysis showed a 2-fold increase in ampicillin resistance from 37% (95% CI 23–53) in 2008–2014 to 79% (95% CI 70–86) in 2015–2021 (Table 1).

Imipenem resistance

The susceptibility to imipenem was determined in 8 studies and included 513 *Shigella* species. The WPR to imipenem was 4% (95% CI 0–10; Table 1) with substantial heterogeneity ($I^2 = 88.12\%$).

Chloramphenicol resistance

The susceptibility to chloramphenicol was determined in 11 studies and included 1100 *Shigella* species. The WPR to chloramphenicol was 24% (95% CI 12–38; Table 1) with substantial heterogeneity ($I^2 = 95.31\%$). Subgroup analysis showed a minor decrease in chloramphenicol resistance from 28% (95% CI 11–49) in 2008–2014 to 21% (95% CI 4–46) in 2015–2021 (Table 1).

Trimethoprim/Sulfamethoxazole resistance

The susceptibility to trimethoprim/sulfamethoxazole was determined in 27 studies and included 2778 *Shigella* species. The WPR to trimethoprim/sulfamethoxazole was 84% (95% CI 73–93; Table 1) with substantial heterogeneity ($I^2 = 97.85\%$). Subgroup analysis showed an increase in resistance from 78% in 2008–2014 to 87% in 2015–2021 (Table 1).

Aminoglycosides resistance

Gentamicin

The susceptibility to gentamicin was determined in 20 studies and included 1871 *Shigella* species. The WPR to gentamicin was 10% (95% CI 1–23; Table 1) with substantial heterogeneity ($I^2 = 98.28\%$). Subgroup analysis showed a decrease in gentamicin resistance from 11% (95% CI 0–55) in 2008–2014 to 8% (95% CI 3–15) in 2015–2021 (Table 1).

Amikacin

The susceptibility to amikacin was determined in 10 studies and included 1181 *Shigella* species. The WPR to amikacin was 15% (95% CI 1–40; Table 1) with substantial heterogeneity ($I^2 = 98.84\%$). Subgroup analysis showed a decrease in amikacin resistance from 19% in 2008–2014 to 14% in 2015–2021 (Table 1).

Tetracycline resistance

The susceptibility to tetracycline was determined in 11 studies and included 820 *Shigella* species. The WPR to tetracycline was 62% (95% CI 38–84; Table 1) with substantial heterogeneity ($I^2 = 97.70\%$). Subgroup analysis showed a decrease in tetracycline resistance from 79% (95% CI 56–96) in 2008–2014 to 51% (95% CI 22–79) in 2015–2021 (Table 1).

Nalidixic acid resistance

The susceptibility to nalidixic acid was determined in 23 studies and included 2560 *Shigella* species. The WPR to nalidixic acid was 29% (95% CI 16–43; Table 1) with substantial heterogeneity ($I^2 = 98.15\%$). Subgroup analysis showed a significant increase in nalidixic acid resistance from 21% (95% CI 1–55) in 2008–2014 to 33% (95% CI 19–48) in 2015–2021 (Table 1).

Mdr

The MDR was determined in 12 studies and included 1234 *Shigella* species. The WPR to MDR was 63% (95% CI 50–76; Table 1) with substantial heterogeneity ($I^2 = 95.08\%$). Subgroup analysis showed an increase in MDR resistance from 61% (95% CI 48–73) in 2008–2014 to 65% (95% CI 44–83) in 2015–2021 (Table 1).

Discussion

To our knowledge, this is the first study that presents comprehensive evidence for the ongoing expansion of antimicrobial-resistant *Shigella* species in Iranian pediatrics during the 13-year timeframe. Therefore, this study has significant implications for understanding the trafficking of antimicrobial-resistant bacterial pathogens from Iran and it could support to plan *for Shigella* species control and prevention policies in Iran. It has been estimated that approximately 188 million individuals worldwide contract shigellosis each year with 1 million deaths annually [1]. The emergence and spreading of antimicrobial resistance amongst *Shigella* strains complicate the therapeutic management of severe *Shigella* cases. Furthermore, shifts in the patterns of antimicrobial resistance amongst *Shigella* strains make it challenging to suggest a drug of choice. The global crisis of drug resistance is an extensively increasing public health concern, especially in developing countries like Iran [3]. *Shigella* species as one of the primary pathogens causing childhood diarrhea is highly antibiotic resistant among eight drugs resistance bacteria [3]. A high prevalence of antimicrobial-resistant *Shigella* infections in Iran is related to high numbers of childhood morbidity and mortality becoming an overlooked problem [3]. The choice of antibiotics has been different over the years as antibiotic resistance has arisen, with diverse patterns of resistance being described worldwide. The WHO guidelines recommend the use of fluoroquinolones, beta-lactams, cephalosporins, and azithromycin for adults and/or children with shigellosis [2]. However, *Shigella* species are adept at receiving antimicrobial-resistant-related genes via plasmids, and the emergence of MDR isolates with reduced susceptibility to fluoroquinolones and third-generation cephalosporins is rising worldwide [40].

The WHO recommended the use of ciprofloxacin, as an alternative empiric antimicrobial treatment for shigellosis [41]. Ciprofloxacin, which was previously used as a backup antibiotic to treat shigellosis, is presently suggested as first-line treatment for all cases of all ages presenting with bloody diarrhea; with ceftriaxone and azithromycin as second-line treatments [2]. However, the emergence and dissemination of resistance have also been reported to first- and second-lines shigellosis drugs [42]. From our metadata, ciprofloxacin showed the lowest resistance rate (3%, 95% CI 1–6) and suggesting its fitness for inclusion in a treatment scheme as WHO guidelines recommend [2]. Although, a considerable increase was observed in resistance to ciprofloxacin when the WPR was 0% (95% CI, 0–0) in 2008–2014 and 6% (95% CI, 2–10) in 2015–2021. Our results are in line with other findings in previous reports, which showed that the emergence of resistance to ciprofloxacin in *Shigella* species is raising worldwide [42–46]. Gu et al. [45] conducted a systematic review to analyze the trend in the resistance of *Shigella* to ciprofloxacin in Europe – America and Asia – Africa. They reported resistance rates to ciprofloxacin in the area of Asia – Africa (5%) was 16.7 times those of Europe – America (0.3%). The number of causes might be due to the rising trend of *Shigella* resistance to ciprofloxacin. First, the high capacity of

Shigella for rapidly acquiring antibiotic resistances determinants reduced previous first-line shigellosis treatments, such as ampicillin and trimethoprim-sulfamethoxazole, ineffective and shifted treatment recommendations global to alternative drugs (e.g. ciprofloxacin, azithromycin, and ceftriaxone) [47]. Second, in Iran a developing country, empiric prescriptions arise frequently at the community level [48]. The unheeding medicine of these antibiotics, combined with the absence of guidelines for antibiotic use, self-medication, and the high burden of infectious disease may have stimulated the emergence of ciprofloxacin-resistant *Shigella* strains in Iran. However, in response to the increase of *Shigella* strains with reduced ciprofloxacin susceptibility, the United States Center for Disease Prevention and Control (CDC) [49] recommended clinicians treating patients with MDR shigellosis for whom antibiotic treatment is shown should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is≥0.12 µg/mL even if the laboratory report identifies the isolate as susceptible, and should work closely with their clinical microbiology laboratory and infectious disease specialists to determine proper antibiotic therapy. Contrary to ciprofloxacin, resistance to ampicillin was shown to be too constant in Iran (69%) advising that the use of ampicillin in the *Shigella* species control and prevention scheme could increase treatment failure. This result is consistent with the previous studies performed in Germany and Ethiopia [50,51].

Generally, third-generation cephalosporins are active and effective for the treatment of shigellosis due to the wide spectrum of activity, robust antimicrobial activity, and few allergic reactions [52]. However, due to the overuse or misuse of antibiotics, third-generation cephalosporins resistance is extremely severe [53]. The rapid emergence and dissemination of resistance to third-generation cephalosporins in *Shigella* species are important in shigellosis management [52]. In our study, ceftazidime showed a relatively low WPR rate (20%, 95% CI 6–38%), a substantial increase was detected over time: from 3% (95% CI 0–29) in 2008–2014 to 36% (95% CI 29–44) in 2015–2021. The same time-span variation was detected with cefixime, where the resistance to this drug increased meaningfully ($p \leq 0.05$) from 3% (95% CI 0–11) in 2008–2014 to 56% (95% CI 31–79) in 2015–2021. In Iran, a significant increase in antibiotic resistance was shown for ceftriaxone from 6% (95% CI 0–53) in 2008–2014 to 42% (95% CI 27–58) in 2015–2021. In line with our findings, the relatively high resistance rates to ceftriaxone and ceftazidime were up to 14·2% and 6·2% during 2010–2012 in Asia-Africa [53]. Moreover, a comparison between countries showed that currently, the most serious problem concerning resistance to third-generation cephalosporins appeared in the Pakistani pediatric population (34.5%) [54]. Our findings suggest that the uses of third-generation cephalosporins in an antimicrobial therapy scheme should be used more cautiously and monitoring of the drug resistance of *Shigella* strains should be supported and that rational use of antibiotics is essential. Physicians should be concerned about this fact and perform susceptibility testing on all clinical isolates, varying the empirical antibiotic consequently.

Comparable to our data, the increasing antibiotic resistance used for the eradication of *Shigella* species concurs with the global data collected in the WHO Regions [2]. Azithromycin as a macrolide, that blocks bacterial protein synthesis has been applied in Iran, azithromycin is the most frequently recommended antimicrobial for the treatment of children infected with shigellosis, mainly for infections caused by MDR organisms or ciprofloxacin-resistant *Shigella* species [40]. Clinical evidence for the efficacy of azithromycin in treating shigellosis is inadequate [40]. Similar to our data (30%), the emergence of the azithromycin-resistant *Shigella* species has been reported in Southeast Asia [40], Palestine [55], Australia [56], Canada [57], and the United States [58] where susceptibility to azithromycin is decreased. The lower rate of decreased susceptibility to azithromycin indicated from Southeast Asia has been related to limited azithromycin usage in the region [40]. Previous studies presented that the age of the patients had a substantial impact on the rate of decreased susceptibility to azithromycin isolates among children suffering from shigellosis [59,60]. The high prevalence of the azithromycin-resistant *Shigella* species in our study (30%) may show that azithromycin resistance has evolved as a result of antimicrobial selection pressures and unsuitable use of azithromycin. The rise emergence of azithromycin-resistant *Shigella* species underlines the necessity for alternative options for the treatment of shigellosis.

The high resistance rate for tetracycline recognized in this metadata (WPR 62%, 95% CI 38–84) is consistent with data from Peru (74%), Senegal (94%), Spain 83%, and China (87%) [61,63–65]. From other antimicrobials analyzed in our study, slightly higher resistance rates against gentamycin and nalidixic acid were observed in Ethiopia [50] and Asia – Africa [45] (WPRs 17.3%, 95% CI 11.2–25.9 vs 33.6%, 95% CI 21.8–46.6).

The emergence and spreading of MDR strains of *Shigella* are principally substantial in developing countries, particularly when this is entangled with other highly prevalent major health challenges such as human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis, malnutrition, and malaria [66,67]. The recent and prompt emergence of MDR amongst *Shigella* species has been designated around the world [68,69]. MDR strains of *Shigella* limited the option of active

antibiotics, thus decreasing the effective treatment choices for shigellosis and becoming the main problem for the control of shigellosis [62]. Similar to the data from China [70], Ethiopia [50], and the United States [71] the emergence of MDR among *Shigella* isolates in our meta-analysis was high (63%). Several reasons can cause the emergence and dissemination of MDR strains of *Shigella*. The most significant reason is the selection of MDR strains harboring certain resistance mechanisms because of overuse or misuse of drugs.

Several limitations of our analysis should be considered. 1) as the articles included for prevalence estimation did not involve all provinces of Iran, these results may not truly represent the magnitude of antimicrobial resistance in *Shigella* strains in Iran and should be interpreted with caution. 2) the cumulative estimations of prevalence using a random-effect model may not completely invalidate the heterogeneity between studies. 3) due to the unavailability of data from the primary studies, the potential effect of age, sex, ethnicity, socioeconomic status, and lifestyle of the patients on antimicrobial resistance in *Shigella* strains could not be analyzed.

Conclusion

The high increasing rates of resistance to trimethoprim/sulfamethoxazole followed by ampicillin and tetracycline in Iranian children *Shigella* species isolates were identified. Ciprofloxacin, imipenem, and amikacin were shown to be the best drugs versus *the Shigella* species, with the lowest resistance rate. Importantly, a decrease in resistance rates during the two time periods was recognized for chloramphenicol, amikacin, gentamicin, and tetracycline. Time-based fluctuations in antibiotic resistance rate showed in this metadata reinforcing the importance of continuous monitoring of antimicrobial resistance in *Shigella* to scrutinize the development of antibiotic resistance and introduce plans for prevention and control to decrease the burden of shigellosis in Iran. Constantly, high resistance to ampicillin was shown in Iranian pediatrics, we propose that ampicillin should not be comprised in the *Shigella* species control and prevention scheme. In addition, we recommend that azithromycin, cefixime, ceftriaxone, ceftazidime, and cefotaxime should be used more cautiously in Iran.

Authors' contributions

AB, SA, RSH, NM, and MKS contributed to the conception, design, searching and data extraction of the work. TA and SA contributed to the data curing of the work. LM contributed to the analysis of the work. EK contributed to the drafting and final approval of the version to be published. BZTA contributed to revising and final approval of the version to be published. All authors agreed and confirmed the manuscript for publication.

Availability of data and material

All the data in this review are included in the manuscript.

Ethical approval and consent to participate

The study protocol was approved by the Health Research Ethics Committee (reference no. IR.GOUMS.REC.1401.138).

Disclosure statement

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