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Prevalence of fluoroquinolone-resistant *Salmonella* serotypes in Iran: a meta-analysis

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ABSTRACT

The present study was conducted to investigate the antimicrobial susceptibility profiles of *Salmonella* serotypes, especially fluoroquinolone-resistant strains, recovered from clinical samples in Iran. A full electronic search using related keywords was conducted in Persian and English languages in ISI Web of Knowledge, PubMed, Scopus, Google Scholar and the Scientific Information Database (SID) search engines to find papers published between 1983 and 1 July 2019. According to the inclusion and exclusion criteria, 46 eligible articles were selected for the final analysis out of the initial 13,186 studies retrieved. The pooled prevalence of quinolone-resistant *Salmonella* serotypes in clinical specimens in Iran was 2.9% to ciprofloxacin and 48.1% to nalidixic acid. Additional data on antibiotic resistance was as follows: 54.3% to tetracycline, 50.6% to ceftizoxime, 50.2% to streptomycin, 37.9% to ampicillin, 36.5% to kanamycin, 33.5% to trimethoprim-sulfamethoxazole, 27.2% to chloramphenicol, 19.1% to cephalothin, 8.8% to ceftriaxone, 7.6% to cefotaxime, 7.4% to aztreonam, 7.2% to gentamicin, 7% to cefepime, 6.8% to ceftazidime, 5.8% to cefixime, 2.7% to imipenem and 2.2% to meropenem. Findings of the present study showed a rising trend of resistance to the drugs of choice for the treatment of *Salmonella* infections, i.e. ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole in Iran. However, ciprofloxacin, third-generation cephalosporins and carbapenems are still effective antibiotics especially against multi-drug resistant strains in Iran.

KEYWORDS

Antibiotic resistance; *Salmonella*; fluoroquinolone; Iran

Introduction

The genus Salmonella belongs to the family Enterobacteriaceae and includes two main species, i.e. *Salmonella enterica* and *Salmonella bongori*. This genus has around 2,600 unique serotypes, which are characterized as Gram-negative, facultative anaerobe, rod-shaped and motile with peritrichous flagella [1–3]. *Salmonella* serotypes are also known as enteric bacteria and cause zoonotic diseases that vary in severity from a local infection called gastroenteritis to systemic infections such as septicemia, paratyphoid fever and enteric fever (typhoid fever) [1,2,4]. Additionally, asymptomatic colonization of *Salmonella* serotypes adapted to humans in the gallbladder can establish human chronic carriers, which along with oral ingestion of contaminated water and food products such as poultry, eggs and dairy products are considered as the major dissemination routes for human diseases [2,4]. Individuals younger than 5 and older than 60 years as well as immunocompromised patients are more susceptible to *Salmonella* infections [2,4]. On the other hand, *Salmonella* infections are important in both developed and developing countries in terms of hospitalization as well as public health and economic impacts [5,6]. However, the efficacy of antibiotic treatment for *Salmonella* infections has been challenged by the emergence of antibiotic-resistant, especially multidrug-resistant (MDR), *Salmonella* serotypes [5]. Antibiotic therapy is not needed for *Salmonella*-induced gastroenteritis while for invasive *Salmonella* infections, ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole are used as the first-line treatments [1,2]. However, emerging MDR *Salmonella* species have changed the treatment regimen toward using fluoroquinolones and third-generation cephalosporins [1]. Nonetheless, the prevalence of fluoroquinolone-resistant *Salmonella* species is growing according to the World Health Organization (WHO) reports, warning that these species may become a great threat to human health [7]. The prevalence of antibiotic resistance of *Salmonella* serotypes has been studied sporadically in different cities of Iran but there has been no comprehensive study in this regard. Therefore, the present systematic review and meta-

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analysis were conducted to determine the antimicrobial susceptibility profiles of *Salmonella* serotypes, especially fluoroquinolone-resistant serotypes, recovered from clinical samples in Iran.

Methods

Search strategy

This systematic review and meta-analysis were performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [8]. Two authors searched both international and national databases including the Information Sciences Institute (ISI) Web of Knowledge, PubMed, Scopus, Google Scholar and the Scientific Information Database (SID) to find studies published between 1983 and 1 July 2019. Eligible studies were peer-reviewed scientific articles addressing antimicrobial susceptibility profiles of *Salmonella* serotypes, and published in English or Persian languages. Additionally, the references of included studies were manually searched to find missing studies. The search terms along with connectors (AND/OR) were 'drug resistan*' OR 'antibiotic resistan*' OR 'antimicrobial resistan*' AND '*Salmonella*' AND 'clinical sample' AND 'Iran'.

Study selection and quality assessment

The identified studies were further assessed in terms of eligibility for inclusion. We included studies reporting the prevalence of resistance, studies evaluating *Salmonella* serotypes isolated from clinical samples and studies limited to Iran. We excluded articles which had insufficient information, non-original articles, and data from other countries or on non-clinical samples. We only chose one of the articles with the same first author and the same time period of study. The Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data was used for the quality assessment of the included studies [9]. Articles were considered as a high-quality study when received more than 5 scores, medium-quality with 4–5 scores and low-quality with lower than 4 scores. We also excluded articles with quality scores lower than 4.

Data extraction and analysis

Important details of studies were extracted from articles that met the inclusion criteria (Table 1). These details included first author surnames, score of quality assessment, province of study, period of study, age group, sample size, type of tested samples, important *Salmonella* serotypes, antibiotic susceptibility testing method, number of *Salmonella* serotypes resistant to different antibiotics, number of *Salmonella* serotypes producing extended-spectrum β-lactamases (ESBLs) and number of multidrug-resistant *Salmonella* serotypes. Collected primary data on antibiotic resistance from eligible articles was transferred to Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ) and used for calculating microbial resistance profiles for each antibiotic. Data synthesis was done and expressed as a percentage and 95% confidence intervals (95% CIs) based on random- or fixed-effects models. The CMA software was also applied to assess two characteristics in the included studies, i.e. the existence of heterogeneity using I^2 statistic and Chi-square test (significance defined at $p < 0.1$), as well as publication bias using the funnel plots. I^2 values of 25%, 50% and 75% were considered as low, moderate and high levels of heterogeneity, respectively. At a low heterogeneity, i.e. $I^2 < 25\%$, a fixed-effects model was used for meta-analysis. The existence of visual asymmetry in funnel plots was considered as a sign of potential publication bias.

Finally, we assessed antimicrobial resistance trends of *Salmonella* serotypes to important antibiotics, i.e. ciprofloxacin, nalidixic acid, ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole and third-generation cephalosporins in Iran from 1983 to 2019.

Results

Study characteristics

As shown in Figure 1, a total of 46 unique studies out of 13,186 records were included in this meta-analysis after screening titles, abstracts and full texts of eligible studies presenting data on the antibiotic resistance of *Salmonella* serotypes in Iran. Briefly, 12,081 records were initially excluded because of being duplicate studies obtained from different databases. Then, 735 duplicates, non-original and non-relevant articles were excluded through the evaluation of titles and abstracts. Among 370 studies identified for full-text screening, 185 duplicates and 39 articles with inadequate data were excluded along with 100 articles reporting antibiotic resistance in non-clinical samples. The included studies, 11 in Persian and 35 in English, were reported from different provinces of Iran and received quality scores between 5 and 8 (Table 1). Disk diffusion was the most commonly used method for antimicrobial susceptibility testing in the included studies. As shown in Table 1, *Salmonella* serotypes were isolated from all age groups, i.e. pediatric, juvenile and adult patients.

Quinolone-resistant Salmonella *serotypes*

Thirty-four and 35 studies evaluated antibiotic resistance rates of *Salmonella* serotypes against ciprofloxacin (Figure 2(a)) and nalidixic acid, respectively. The level of heterogeneity among the studies was high (>75%),

Table 1. Extracted information from eligible studies included in the meta-analysis.

Author (Ref)	Quality score	Province	Year	Age group	Sample origin	Strain (n)	*Salmonella* serotypes	AST	Antibiotic resistance (n) (%)						
									AMP	CHL	TMP-SMX	CIP	NAL	CAZ	CRO
Farahani [10]	7	Different cities	NA	NA	Stool	36	Enteritidis	Disk diffusion	NA	32 (91.2)	NA	8 (23.5)	32 (88.2)	1 (2.9)	NA
Soltan Dallal [11]	7	Different cities	2012-2013	<60	Stool	74	NA	Disk diffusion	17 (23)	NA	NA	74 (100)	65 (87.8)	NA	18 (24.3)
Saboohi [12]	6	Different cities	2008-2010	NA	Stool Blood Abscess Urine BM SF	85	NA	Disk diffusion	12 (14.1)	NA	NA	0 (0)	49	9 (10.5)	6 (7)
Iranshahi [13]	7	Different cities	2007-2008	<65	Stool Blood BM	53	NA	Disk diffusion	NA	NA	NA	0 0	28 (52.8)	NA	NA
Sepehri Rad [14]	7	NA	2008-2010	NA	Stool Blood Ascites Abscess Urine BM SF	83	Typhi Paratyphi Enteritidis	Disk diffusion	66 (79)	18 (21)	12 (14)	4 (4)	47 (56)	9 (10)	6 (7)
Amir Mozafari [15]	5	NA	2005-2006	NA	Stool	45	Typhi Paratyphi Enteritidis Typhimurium	Disk diffusion	NA	NA	NA	NA	11 (24.4)	NA	NA
Bialvaei [16]	7	East Azerbaijan	2009-2013	<70	Stool	91	Enteritidis Typhimurium	Disk diffusion	78 (85.7)	56 (61.5)	85 (93.4)	NA	NA	NA	NA
Aminshahidi [17]	7	Fars	2014-2015	<18	Stool	14	NA	Disk diffusion	2 (14.2)	NA	2 (14.2)	0 (0)	NA	1 (7.1)	NA
Anvarinejad [18]	8	Fars	2008 – 2014	NA	Blood	19	NA	Disk diffusion	3 (15.7)	4 (21)	3 (15.7)	0 (0)	6 (31.5)	0 (0)	0 (0)
Abdollahi [19]	7	Fars	NA	NA	Stool	96	Typhi Paratyphi Enteritidis Typhimurium	Disk diffusion	47 (49)	17 (18)	24 (25)	0 (0)	23 (24)	NA	NA
Yousefi-Mashouf [20]	6	Hamadan	2001-2004	<68	Stool Blood Urine	296	Typhi Paratyphi Enteritidis Typhimurium	Disk diffusion	214 (72.2)	105 (35.4)	94 (31.7)	8 (2.7)	NA	NA	NA
Afzali [21]	7	Isfahan	2000 – 2001	NA	Stool	66	NA	Disk diffusion	NA	1 (1.5)	29 (43.9)	7 (10.5)	25 (37.9)	NA	NA
Soltan Dallal [22]	7	Mazandaran	2013-2014	NA	Stool	4	Enteritidis	Disk diffusion	3	0 (0)	4 (100)	0 (0)	4 (100)	0 (0)	NA

(*Continued*)

Table 1. (Continued).

Author (Ref)	Quality score	Province	Year	Age group	Sample origin	Strain (n)	*Salmonella* serotypes	AST	Antibiotic resistance (n) (%)						
									AMP	CHL	TMP-SMX	CIP	NAL	CAZ	CRO
Eshaghi Zadeh [23]	7	Tehran	2016-2017	<14	Stool	30	Typhi Paratyphi Enteritidis Typhimurium	Disk diffusion	NA	2 (6.7)	8 (26.7)	5 (16.7)	16 (53.3)	1 (3.3)	1 (3.3)
Fardsanei [24]	7	Tehran	2015-2016	NA	Stool	44	Enteritidis	Disk diffusion	NA	1 (2.3)	8 (18.2)	40 (90.9)	34 (77.3)	4 (9.1)	3 (6.8)
Ranjbar [25]	8	Tehran	2015-2016	NA	Stool	138	NA	Disk diffusion	11 (7.9)	NA	NA	0 (0)	NA	40 (28.9)	40 (28.9)
Ranjbar [26]	7	Tehran	2015	NA	Stool Blood Urine	21	Typhimurium	Disk diffusion	12 (57)	14 (67)	3 (14)	0 (0)	2 (9)	0 (0)	0 (0)
Abaspour shoushtari [27]	6	Tehran	2015	NA	Stool	60	NA	Disk diffusion	50 (83.3)	38 (38.3)	60 (100)	NA	NA	NA	27 (45)
Najafi [28]	7	Tehran	2015	NA	Stool Blood CSF Urine	48	Enteritidis Typhimurium	Disk diffusion	5	15 (31.2)	0 (0)	NA	NA	NA	5
Amiri [29]	7	Tehran	2015	NA	Stool	60	Typhimurium	Disk diffusion	NA	NA	13 (21.7)	0 (0)	42 (70)	NA	NA
Malehmir [30]	6	Tehran	2014-2015	NA	NA	138	NA	Disk diffusion	NA	NA	NA	0 (0)	92 (66.6)	NA	NA
Amini [31]	6	Tehran	2014	NA	Stool	46	Typhimurium	Disk diffusion	38 (82.6)	37 (80.4)	20 (43.1)	NA	NA	3 (6.5)	4 (8.6)
Mirjafari Tafti [32]	8	Tehran	2012 – 2014	<60	Stool	83	Enteritidis	Disk diffusion	47 (56.6)	38 (45.7)	71 (85.5)	2 (2.4)	10 (12)	NA	2 (2.4)
Salimian Rizi [33]	6	Tehran	2012 – 2013	NA	Stool Blood	110	NA	Disk diffusion	27 (24.5)	30 (27.3)	70 (63.6)	0 (0)	52 (47.3)	7 (6.4)	7 (6.4)
Farahani [34]	8	Tehran	2012-2016	<10	Stool	371	NA	Disk diffusion	45 (12.1)	NA	84 (22.6)	NA	230 (61.9)	NA	NA
Soltan Dallal [35]	6	Tehran	2011	<10	Stool	13	Typhi Paratyphi	Disk diffusion	10 (76.9)	1 (7.6)	1 (7.6)	NA	1 (7.6)	NA	NA
Bakhshi [36]	8	Tehran	2009-2012	<5	Stool	50	Enteritidis	Disk diffusion	NA	NA	19 (38)	3 (6)	26 (52)	NA	NA
Firoozeh [37]	5	Tehran	2009-2010	NA	NA	58	Paratyphi Enteritidis Typhimurium	Disk diffusion	13 (22.4)	10 (17.2)	12 (20.6)	1 (1.8)	43 (74.1)	7 (12.1)	3 (6.9)
Ranjbar [38]	8	Tehran	2008-2010	NA	Stool Blood Urine	38	NA	Disk diffusion	1 (2.6)	2 (5.2)	12 (31.5)	0 (0)	36 (94.7)	2 (5.2)	4 (10.5)
Tajbakhsh [39]	7	Tehran	2008-2010	NA	Stool	202	Enteritidis Typhimurium	Disk diffusion	29 (14.3)	27 (13.3)	70 (34.6)	0 (0)	90 (44.5)	9 (4.4)	9 (4.4)

(*Continued*)

Table 1. (Continued).

Author (Ref)	Quality score	Province	Year	Age group	Sample origin	Strain (n)	*Salmonella* serotypes	AST	Antibiotic resistance (n) (%) AMP	CHL	TMP-SMX	CIP	NAL	CAZ	CRO
Hamidian [40]	7	Tehran	2008-2009	NA	Stool	174	Typhi Paratyphi Enteritidis Typhimurium	Disk diffusion	NA	NA	NA	0 (0)	89 (51.1)	NA	NA
Rajaei [41]	7	Tehran	2008-2009	NA	Stool Blood Ascites Abscess Urine BM SF	84	Typhi Paratyphi Typhimurium	Disk diffusion	6 (7.1)	23 (27.4)	25 (29.8)	1 (1.2)	54 (64.3)	2 (2.4)	NA
Eshraghi [42]	5	Tehran	2008	NA	Stool	14	Enteritidis Paratyphi	Disk diffusion	NA	0 (0)	3 (21.4)	0 (0)	10 (71.4)	0 (0)	0 (0)
Hamidian [43]	8	Tehran	2007-2008	NA	Stool	129	Typhi Paratyphi Enteritidis	Disk diffusion	20 (15.5)	19 (14.7)	47 (36.4)	0 (0)	59 (45.7)	NA	NA
Ranjbar [44]	8	Tehran	2007-2008	<12	Stool Blood Urine	139	Enteritidis Typhimurium	Disk diffusion	22 (15.8)	19 (13.7)	30 (21.6)	0 (0)	85 (61.2)	6 (4.3)	6 (4.3)
Tajbakhsh [45]	8	Tehran	2007-2008	NA	Stool	71	Typhi Paratyphi Enteritidis	Disk diffusion	10 (14)	8 (11)	13 (18)	0	16 (22)	0 (0)	NA
Naghoni [46]	8	Tehran	2006-2008	NA	NA	138	Enteritidis Typhimurium	Disk diffusion	22 (15.9)	18 (13)	28 (20.3)	NA	89 (64.5)	6 (4.3)	6 (4.3)
Irajian [47]	6	Tehran	2007	NA	Stool	50	Typhi Paratyphi	Disk diffusion	13 (26)	23 (46)	32 (64)	0	31 (62)	1 (2)	NA
Morshed [48]	5	Tehran	2005-2007	NA	Stool	9	Enteritidis	Disk diffusion	3 (33.3)	1 (11.1)	1 (11.1)	0 (0)	7 (77.8)	0 (0)	0 (0)
Pourakbari [49]	7	Tehran	2001-2005	NA	Blood	42	NA	Disk diffusion	23 (54.7)	11 (26)	9 (21.4)	NA	NA	15 (35.7)	32 (76.1)
Bahrmand [50]	6	Tehran	1994	NA	Stool Blood	33	Typhi	Disk diffusion	29 (89.3)	22 (67.9)	22 (67.9)	0 (0)	2 (7.1)	NA	NA
Velayati [51]	8	Tehran	1986	<5	Stool	56	Enteritidis Typhimurium	Disk diffusion	52 (92.8)	49 (87.6)	NA	NA	1 (1.7)	NA	NA
Farhoudi-Moghaddam [52]	8	Tehran	1983-1986	<5	NA	508	Typhi Typhimurium	Disk diffusion	434 (85.4)	420 (82.7)	374 (73.6)	0 (0)	14 (2.7)	NA	NA
Araghinezhad [53]	7	Tehran	NA	NA	Stool	60	NA	Disk diffusion	NA	NA	10 (16.6)	NA	NA	NA	0 (0)
Bakhshi [54]	6	Tehran	NA	NA	Stool	36	NA	Disk diffusion	9 (25)	1 (2.8)	10 (27.8)	4 (11.1)	NA	NA	NA
Amini [55]	5	Tehran	NA	<5	NA	11	Enteritidis	Disk diffusion	1 (9)	3 (27.3)	0 (0)	NA	NA	NA	1 (9)

Author (Ref)	Antibiotic resistance (n) (%)													
	CTX	ZOX	FEP	CFM	CEF	TET	GEN	MEM	IPM	STR	ATM	KAN	ESBLs	MDR
Farahani [10]	NA	NA	NA	NA	NA	NA	4 (11.2)	1 (2.9)	5 (14.7)	NA	NA	17 (47.1)	NA	NA
Soltan Dallal [11]	28 (37.8)	NA	NA	NA	NA	43 (58.1)	61 (82.4)	NA	NA	NA	NA	NA	NA	NA
Saboohi [12]	9 (10.5)	NA	5 (5.8)	6 (7)	NA	NA	NA	NA	NA	NA	NA	NA	2 (2.3)	NA
Iranshahi [13]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sepehri Rad [14]	6 (7)	NA	6 (7)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Amir Mozafari [15]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bialvaei [16]	35 (38.4)	35 (38.4)	NA	NA	NA	82 (91.1)	20 (21.9)	NA	NA	NA	NA	NA	29 (31.8)	NA
Aminshahidi [17]	2 (14.2)	NA	NA	NA	NA	NA	0 (0)	0 (0)	NA	NA	NA	NA	1 (7.2)	NA
Anvarinejad [18]	0 (0)	NA	0 (0)	0 (0)	NA	2 (10.5)	0 (0)	0 (0)	0 (0)	NA	0 (0)	NA	0 (0)	2 (10.5)
Abdollahi [19]	5 (5)	NA	NA	NA	NA	NA	NA	NA	0 (0)	NA	NA	NA	5 (5.2)	NA
Yousefi-Mashouf [20]	177 (59.7)	125 (42.2)	NA	NA	NA	NA	39 (13.1)	NA	NA	NA	NA	NA	NA	NA
Afzali [21]	NA	59 (89.4)	NA	NA	55 (83.3)	53 (80.3)	NA	NA	NA	NA	NA	NA	NA	NA
Soltan Dallal [22]	0 (0)	NA	NA	NA	NA	4 (100)	NA	NA	NA	NA	NA	NA	NA	NA
Eshaghi Zadeh [23]	1 (3.3)	NA	NA	NA	NA	11 (36.7)	NA	0 (0)	0 (0)	12 (40)	NA	NA	NA	NA
Fardsanei [24]	3 (6.8)	NA	5 (11.4)	NA	NA	8 (18.2)	NA	NA	0 (0)	18 (40.9)	NA	NA	NA	NA
Ranjbar [25]	6 (4.3)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	40 (28.9)	NA
Ranjbar [26]	0 (0)	NA	NA	NA	NA	17 (81)	0 (0)	NA	0 (0)	5 (24)	NA	3 (14)	NA	1 (4.7)
Abaspour shoushtari [27]	NA	NA	NA	NA	NA	28 (46.7)	60 (100)	NA	60 (100)	43 (71.7)	NA	NA	NA	NA
Najafi [28]	NA	NA	NA	NA	NA	27 (56.2)	0 (0)	NA	0 (0)	0 (0)	NA	NA	NA	NA
Amiri [29]	NA	NA	NA	NA	NA	NA	NA	0 (0)	0 (0)	NA	NA	NA	NA	NA
Malehmir [30]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Amini [31]	NA	NA	NA	NA	37 (80.4)	32 (69.5)	4 (8.6)	NA	NA	NA	NA	NA	1 (2.1)	NA

(*Continued*)

Table 1. (Continued).

Author (Ref)	Antibiotic resistance (n) (%)													
	CTX	ZOX	FEP	CFM	CEF	TET	GEN	MEM	IPM	STR	ATM	KAN	ESBLs	MDR
Mirjafari Tafti [32]	NA	NA	NA	3 (3.6)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Salimian Rizi [33]	3 (2.7)	NA	NA	NA	NA	37 (33.6)	1 (0.9)	NA	0 (0)	NA	6 (5.5)	NA	4 (3.6)	3 (2.7)
Farahani [34]	25 (6.7)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	63 (17)	NA
Soltan Dallal [35]	NA	0 (0)	NA	NA	3 (23)	NA	1 (7.6)	NA	NA	NA	NA	NA	NA	1 (5)
Bakhshi [36]	NA	NA	NA	NA	NA	31 (50)	1 (2)	NA	NA	26 (52)	NA	NA	NA	NA
Firoozeh [37]	2 (3.4)	NA	NA	4 (6.9)	1 (1.8)	ND	4 (6.9)	NA	0 (0)	39 (67.3)	5 (8.6)	13 (22.4)	NA	6 (10.3)
Ranjbar [38]	4 (10.5)	NA	NA	NA	NA	34 (89.4)	0 (0)	NA	NA	29 (77.1)	NA	24 (63)	NA	NA
Tajbakhsh [39]	10 (4.9)	NA	NA	NA	NA	80 (39.6)	1 (0.4)	NA	NA	NA	NA	NA	7 (3.4)	8 (3.9)
Hamidian [40]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rajaei [41]	NA	NA	NA	NA	NA	NA	NA	NA	NA	25 (29.8)	NA	NA	NA	NA
Eshraghi [42]	0 (0)	NA	NA	NA	NA	4 (28.6)	0 (0)	0 (0)	0 (0)	1 (7.1)	NA	NA	NA	NA
Hamidian [43]	NA	NA	NA	NA	8 (6.2)	56 (43.4)	0 (0)	NA	NA	NA	11 (8.5)	NA	3 (2.3)	9 (6.9)
Ranjbar [44]	6 (4.3)	NA	NA	NA	6 (4.3)	72 (51.8)	0 (0)	NA	0 (0)	59 (42.8)	ND	31 (22.3)	6 (3.2)	NA
Tajbakhsh [45]	0 (0)	NA	NA	NA	0 (0)	18 (25)	0 (0)	NA	0 (0)	NA	NA	10 (14)	NA	NA
Naghoni [46]	6 (4.3)	NA	NA	NA	6 (4.3)	70 (50.7)	NA	NA	NA	59 (42.7)	NA	31 (22.5)	NA	NA
Irajian [47]	NA	NA	NA	NA	NA	NA	14 (28)	NA	NA	NA	NA	17 (34)	1 (2)	6 (12)
Morshed [48]	NA	NA	NA	0 (0)	1 (11.1)	3 (33.3)	0 (0)	NA	0 (0)	3 (33.3)	NA	2 (22.2)	NA	NA
Pourakbari [49]	NA	NA	NA	NA	21 (50)	NA	6 (14.2)	NA	NA	NA	NA	13 (30.9)	NA	NA
Bahrmand [50]	NA	NA	NA	NA	NA	20 (60.7)	NA	NA	NA	27 (82.1)	NA	4 (10.7)	NA	15 (45.4)
Velayati [51]	NA	NA	NA	NA	31 (55.3)	44 (78.5)	50 (89.2)	NA	NA	53 (94.6)	NA	53 (94.6)	NA	NA

(*Continued*)

Table 1. (Continued).

Author (Ref)	Antibiotic resistance (n) (%)														
	CTX	ZOX	FEP	CFM	CEF	TET	GEN	MEM	IPM	STR	ATM	KAN	ESBLs	MDR
Farhoudi-Moghaddam [52]	NA	NA	NA	NA	80	406 (80)	0 (0)	NA	NA	390 (76.8)	NA	412 (81.1)	NA	NA
Araghinezhad [53]	NA	NA	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bakhshi [54]	NA	NA	NA	NA	NA	17 (47.2)	NA	NA	NA	17 (47.2)	NA	NA	NA	NA
Amini [55]	NA	NA	NA	NA	NA	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA	NA	NA	NA

Abbreviations: AMP-ampicillin; CHL-chloramphenicol; TMP/SMX-trimethoprim-sulfamethoxazole; CIP-ciprofloxacin; NAL-nalidixic acid; CAZ-ceftazidime; CRO-ceftriaxone; CTX-cefotaxime; ZOX-ceftizoxime; FEP-cefepime; CFM-cefixime; CEF-cephalothin; TET-tetracycline; GEN-gentamicin; MEM-meropenem; IPM-imipenem; STR-streptomycin; ATM-aztreonam; KAN-kanamycin; AST-antimicrobial susceptibility testing; ESBLs-extended-spectrum β-lactamases; MDR-multidrug-resistant (combined resistance to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole); BM-bone marrow; SF-synovial fluid; CSF-cerebrospinal fluid; NA-data not available.

hence a random-effects model was used to calculate the weighted average. Additionally, in publication bias evaluation, we observed a visual asymmetry of the funnel plot (Figure 2(b)). Overall resistance prevalence of quinolone-resistant *Salmonella* serotypes isolated from clinical specimens in Iran was as follows: 2.9% (95% *CI*: 1.4–6; I^2 = 84.4%; Q = 212.7; p = 0.00) to ciprofloxacin and 48.1% (95% *CI*: 39.9–56.4; I^2 = 92.8%; Q = 475.6; p = 0.00) to nalidixic acid. As shown in Figure 3(a) and Table 2, we also evaluated the trends of antimicrobial resistance during 12-year intervals. From 1983 to 2019, the resistance trend of *Salmonella* serotypes to ciprofloxacin and nalidixic acid in Iran was increasing with a gentle and fast slope, respectively.

Salmonella serotypes resistance profiles to the first-line treatments for invasive infections

Meta-analyses with random-effects models were used to assess *Salmonella* serotypes resistance profiles to ampicillin (I^2 = 96.9%; Q = 1035.6; p = 0.00), chloramphenicol (I^2 = 95.3%; Q = 716.2; p = 0.00) and trimethoprim-sulfamethoxazole (I^2 = 93.8%; Q = 582.7; p = 0.00). In Iran, 37.9% (95% *CI*: 26.2–51.3) of *Salmonella* serotypes were resistant to ampicillin, 33.5% (95% *CI*: 26–42) to trimethoprim-sulfamethoxazole and 27.2% (95% *CI*: 18.7–37.8) to chloramphenicol were resistant. There were signs of publication bias in the included studies evaluating the resistance of *Salmonella* serotypes to each of the three above-mentioned antibiotics. As shown in Figure 3(a), the susceptibility of *Salmonella* serotypes to the first-line antibiotics increased from 1983 to 2008 but showed a decreasing trend from 2008 to 2019. Additionally, the prevalence of MDR serotypes of *Salmonella* was 9% (95% *CI*: 4.3–18; I^2 = 83.4%; Q = 48.4; p = 0.00) in Iran.

Salmonella serotypes resistance profiles to the third-generation cephalosporins

Antibiotic resistance profiles of *Salmonella* serotypes to the third-generation cephalosporins were as follows: 50.6% (95% *CI*: 26.5–74.4; I^2 = 92.7%; Q = 41.1; p = 0.00) to ceftizoxime, 8.8% (95% *CI*: 5.1–14.9; I^2 = 89.1%; Q = 202.4; p = 0.00) to ceftriaxone, 7.6% (95% *CI*: 3.8–-14.6; I^2 = 95%; Q = 425.6; p = 0.00) to cefotaxime, 6.8% (95% *CI*: 4.3–10.7; I^2 = 79.2%; Q = 106; p = 0.00) to ceftazidime and 5.8% (95% *CI*: 3.4–9.5; I^2 = 0.0%; Q = 1.4; p = 0.83) to cefixime. Apart from cefixime, the prevalence of antibiotic resistance was pooled using random-effects models. The trends of antimicrobial resistance to ceftizoxime was decreasing, while it was almost constant for ceftazidime, ceftriaxone, cefotaxime and cefixime over the time period from 1995 to 2019 (Figure 3(b)). Additionally, the prevalence of ESBLs

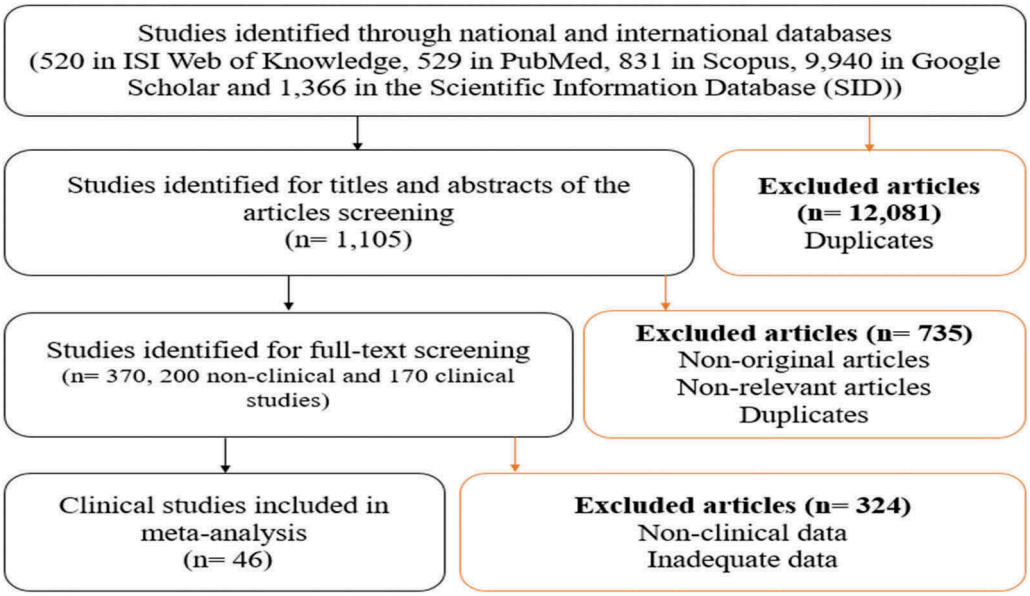


Figure 1. Systematic review flowchart.

producing *Salmonella* serotypes was 6.5% (95% *CI*: 3.5–-11.7; I^2 = 89.4%; Q = 113.8; p = 0.00) in Iran.

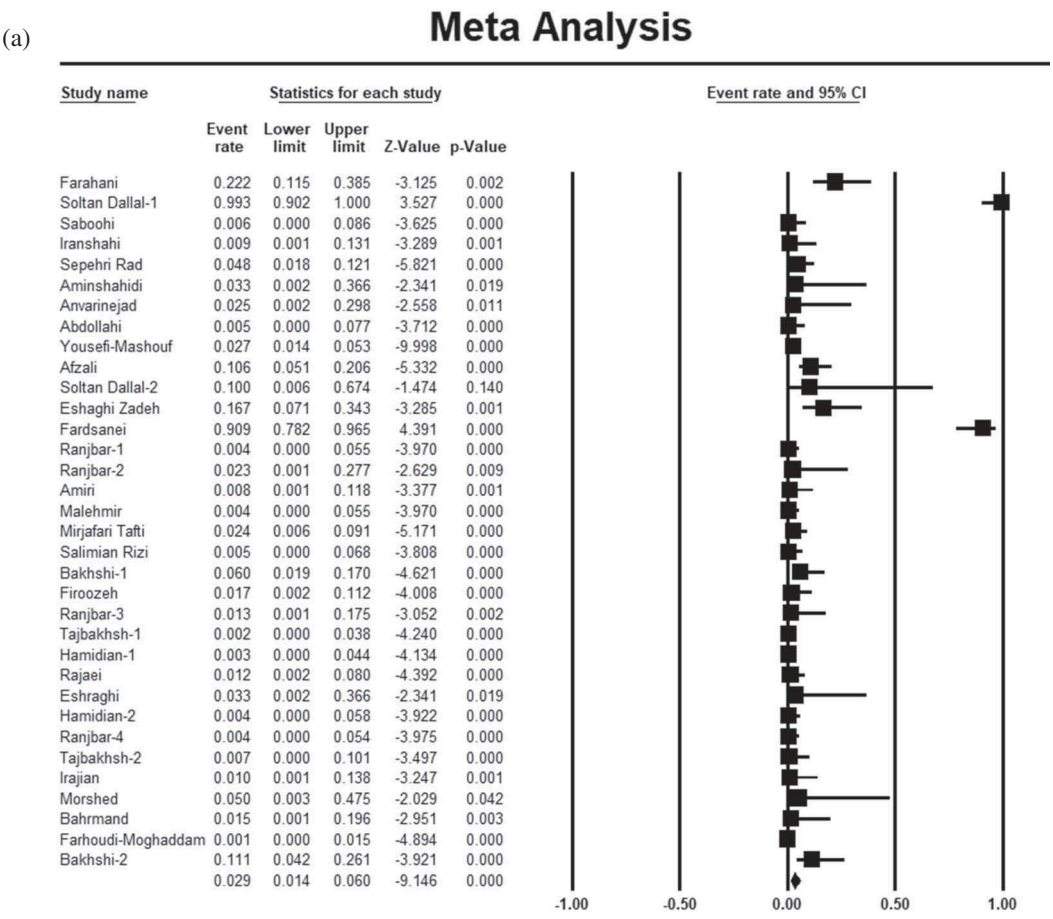
Other Salmonella *serotypes resistance profiles*

Resistance to other antibiotics were as follows: 54.3% (95% *CI*: 45–63.3; I^2 = 91.9%; Q = 310.1; p = 0.00) to tetracycline, 50.2% (95% *CI*: 38.4–62; I^2 = 91.6%; Q = 202.7; p = 0.00) to streptomycin, 36.5% (95% *CI*: 20–56.9; I^2 = 96.5%; Q = 344.1; p = 0.00) to kanamycin, 19.1% (95% *CI*: 8.2–38.6; I^2 = 95.6%; Q = 253.8; p = 0.00) to cephalothin, 7.4% (95% *CI*: 4.9–10.9; I^2 = 0.0%; Q = 1.5; p = 0.66) to aztreonam, 7.2% (95% *CI*: 3.4–14.5; I^2 = 91.4%; Q = 292.7; p = 0.00) to gentamicin, 7% (95% *CI*: 4.4–11; I^2 = 9.3%; Q = 4.4; p = 0.35) to cefepime, 2.7% (95% *CI*: 0.9–8.4; I^2 = 71.9%; Q = 53.4; p = 0.00) to imipenem and 2.2% (95% *CI*: 0.8–6.2; I^2 = 0.0%; Q = 0.7; p = 0.97) to meropenem.

Discussion

Recently, it has been reported that the prevalence of *Salmonella* strains resistant to antimicrobial agents, especially quinolone-resistant *Salmonella* serotypes, is increasing. This increasing prevalence poses a serious public health concern in both developed and developing countries [1,56]. Therefore, obtaining epidemiological information on drug resistance can help physicians and health-care professionals choosing proper antimicrobial agents and avoid treatment failure. Ciprofloxacin is a known fluoroquinolone antibiotic in the treatment of life-threatening *Salmonella* infections [57]. However, according to the WHO report, *Salmonella* serotypes are becoming increasingly drug-resistant bacteria and fluoroquinolone-resistant *Salmonella* serotypes have been placed in the high-priority category in terms of the urgency of the need to new antibiotics [7]. Resistance rate to ciprofloxacin in *Salmonella* strains in the present meta-analysis was low (2.9%) (Figure 2(a)). Our findings showed higher rates of resistance compared with those reported from Korea, France, the United States, Greece, Turkey (0%) and Thailand (0.3%) while the rates were lower compared with China (9.2%) [57–60]. On the other hand, tracking the antibiotic resistance trends of *Salmonella* serotypes during successive years is important for sustaining treatment regimens and preventing treatment failure. The trend of ciprofloxacin resistance in *Salmonella* serotypes in Iran showed a rather mild increase from 1983 to 2019 (0.4% to 3.5%) (Table 2 and Figure 3(a)). It shows that ciprofloxacin can still be used as an effective antibiotic against infections due to *Salmonella* serotypes in Iran. Contrary to ciprofloxacin, resistance rate to another quinolone, i.e. nalidixic acid was increasing during the monitored years (2.9% to 56.7%). Overall resistance to nalidixic acid in Iran was high (48.1%), which is similar to Korea (43.3%) and China (56%) [58,60]. Differences in results can be attributed to different *Salmonella* serotypes and regional variations. The main mechanisms involved in resistance to fluoroquinolones in *Salmonella* strains include mutations in the DNA gyrase genes, efflux pumping and maybe alterations in the expression of outer membrane proteins or lipopolysaccharides [59]. In the present study, *Salmonella* serotypes displayed a higher level of resistance to conventional antibiotics used as the first-line treatments for *Salmonella*-induced enteric fever infection, i.e. ampicillin (37.9%), chloramphenicol

(a)



(b)

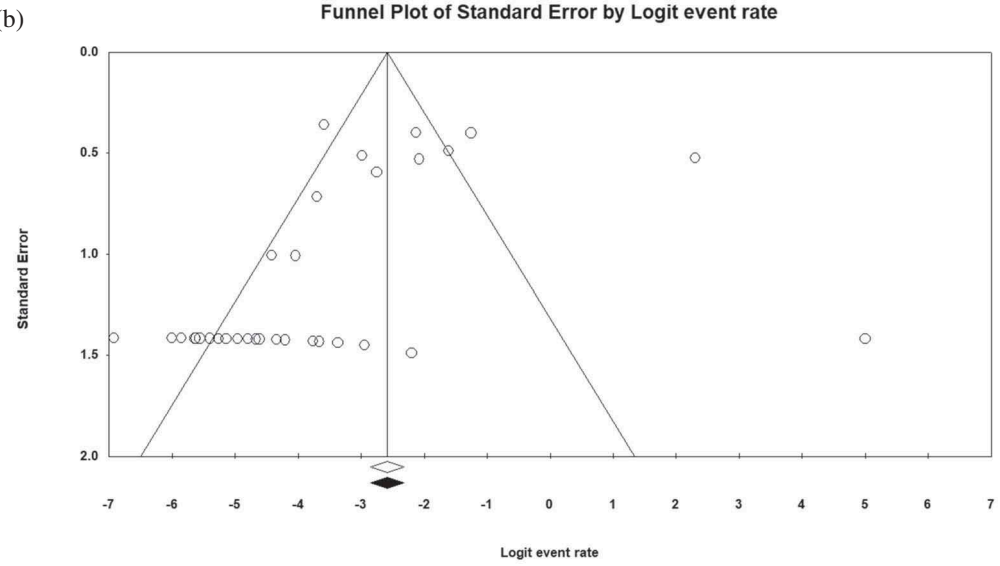


Figure 2. Forest plot (a) and funnel plot (b) showing the prevalence of antibiotic resistance of *Salmonella* serotypes to ciprofloxacin.

(27.2%) and trimethoprim-sulfamethoxazole (33.5%) compared with newer agents, i.e. fluoroquinolones and extended-spectrum cephalosporins. However, the trend of resistance of *Salmonella* serotypes to these antibiotics was variable from 1983 to 2019 in Iran (Figure 3(a)). On the other hand, frequency of MDR strains, combined resistance to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole, was low in Iran (9%). However, the prevalence of MDR strains is variable worldwide. This is due to the widespread use of the mentioned antibiotics that has caused these drugs to become obsolete in some regions [56]. Given the results of this study, continuing these antibiotics in Iran can lead to a similar outcome. Resistance rates to the above-mentioned three drugs in Iran were much higher than those reported for the United States,

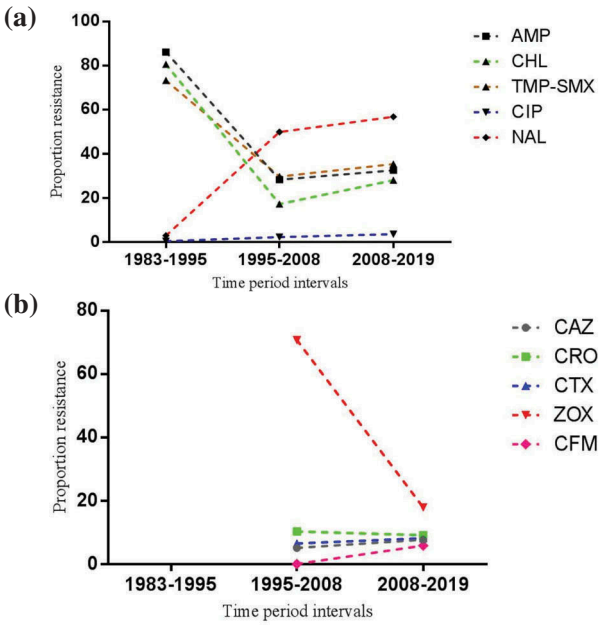


Figure 3. Antimicrobial resistance trends of *Salmonella* serotypes to different drugs in Iran over time. (a) ciprofloxacin, nalidixic acid, ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole trends and (b) third-generation cephalosporins trends.

Greece, Turkey and Italy [59]. Extended-spectrum cephalosporins are another class of antibiotics, which can be used in severe infections when ciprofloxacin is contraindicated [57]. Fortunately, the resistance of *Salmonella* serotypes against both classes of antibiotics, i.e. fluoroquinolones and extended-spectrum cephalosporins, was low in Iran, except for ceftizoxime (50.6%) (6.8% to ceftazidime, 8.8% to ceftriaxone, 7.6% to cefotaxime and 5.8% to cefixime). Furthermore, the frequency of ESBLs which confer *Salmonella* serotypes resistance to the third-generation cephalosporins was low in Iran (6.5%). On the other hand, the trend of resistance of *Salmonella* serotypes to these drugs in Iran was not worrisome (Figure 3(b)). However, given the ability of *Salmonella* serotypes to establish zoonotic infections as well as the human chronic carriers, overuse of fluoroquinolones and extended-spectrum cephalosporins in both clinical settings and animal industry can lead to the spread of antimicrobial resistance [59]. In addition to foods of animal products, which can act as the primary source of antimicrobial-resistant *Salmonella* infection, the bacterium is able to acquire resistance genes from other enteric pathogens through transferable plasmids, transposons, and integrons [59]. Therefore, it is necessary to apply strategies to decrease drug-resistant *Salmonella* infections, such as stopping the use of antimicrobial agents in food animal industries and continuous monitoring of drug resistance of foodborne *Salmonella* in both clinical and non-clinical specimens via routine susceptibility testing. In addition to the third-generation cephalosporins, the use of azithromycin has been recommended as the treatment of choice against infections caused by MDR and fluoroquinolone-resistant *Salmonella* serotypes [56]. In addition to azithromycin, carbapenems and tigecycline are drugs of choice for the treatment of *Salmonella* infections resistant to classical first-line antibiotics, fluoroquinolones and third-generation cephalosporins [61]. In accordance with the reported results from Korea (0%) [58], the prevalence of imipenem-resistant *Salmonella* serotypes was low in Iran (2.7%). Our results showed that meropenem resistance rate was also low in Iran (2.2%). However, there was not enough information on azithromycin- and tigecycline-resistant *Salmonella* serotypes in Iran.

Conclusion

Findings of the present study showed a rising trend of resistance to the drugs of choice for the treatment of *Salmonella* infections, i.e. ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole in Iran. Therefore, to prevent the emergence and spread of MDR strains in Iran, the following measures are recommended: prudent use of antibiotics, performing continuous antimicrobial susceptibility testing, using effective antibiotics with low bacterial resistance rates such as ciprofloxacin, third-generation cephalosporins and carbapenems, and testing bacterial resistance to other effective antibiotics such as azithromycin and tigecycline. Additionally, there is a need for additional comprehensive systematic reviews and meta-analyses in Iran to obtain information on the prevalence of

Table 2. Proportion of *Salmonella* serotypes resistant to therapeutic antibiotics during a 12-year intervals.

		Proportion of resistant isolates (%) (95% CIs)									
Year	Strain (n)	AMP	CHL	TMP-SMX	CIP	NAL	CAZ	CRO	CTX	ZOX	CFM
1983-1995	597	86.1 (83–88.6)	80.5 (69.7–88.1)	73.2 (69.3–76.7)	0.4 (0–5.2)	2.9 (1.8–4.7)	NA	NA	NA	NA	NA
1995-2008	1052	28.3 (12.8–51.7)	17.2 (10.5–26.8)	29.7 (22.3–38.2)	2.2 (0.9–5.4)	49.8 (39.3–60.4)	5.1 (1.5–16.1)	10.3 (1.2–52.6)	6.5 (0.7–40.3)	70.7 (18–96.4)	0
2008-2019	2341	32.5 (21–46.5)	28 (18.5–40)	35.4 (25.1–47.2)	3.5 (1.1–11)	56.7 (48.6–64.4)	7.7 (4.6–12.5)	9.1 (5.3–15.2)	8.2 (4.5–14.5)	17.9 (1.5–76)	5.8 (3.4–9.6)

Abbreviations: AMP-ampicillin; CHL-chloramphenicol; TMP/SMX-trimethoprim-sulfamethoxazole; CIP-ciprofloxacin; NAL-nalidixic acid; CAZ-ceftazidime; CRO-ceftriaxone; CTX-cefotaxime; ZOX-ceftizoxime; CFM-cefixime; NA-data not available.

resistant *Salmonella* isolates in non-clinical samples. This information will help reducing the spread of resistance from animal to human pathogens.

Disclosure statement

No potential conflict of interest was reported by the authors.

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