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Review Article

Group B streptococcus drug resistance in pregnant women in Iran: a meta-analysis

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ABSTRACT

Streptococcus (S.) agalactiae colonizes in the female genitourinary and lower gastrointestinal tracts and is responsible for a wide range of infections in newborns, pregnant women and non-pregnant adults. Therefore, antibiotic prophylaxis and infection treatment against *S. agalactiae* is important. The aim of this study was to determine the prevalence of *S. agalactiae* antibiotic resistance in Iranian patients, especially among pregnant women. A systematic literature search was conducted in PubMed, Scopus, Google Scholar and the Scientific Information Database (SID) databases by using related keywords and without any time limitation. A total of 26 studies reporting the prevalence of *S. agalactiae* antibiotic resistance in Iran met our predefined inclusion and exclusion criteria and were included in the meta-analysis. High rates of *S. agalactiae* antibiotic resistance in pregnant women were found against tetracycline (96.2%), trimethoprim-sulfamethoxazole (84.7%), cefotaxime (41.3%), clindamycin (26.8%) and erythromycin (21%). Additionally, resistance to penicillin (4.2%), ampicillin (2.7%), cefazolin (7.6%), vancomycin (2.4%), ceftriaxone (12.5%), ciprofloxacin (13.6%) and nitrofurantoin (0%) was low. Our results revealed that penicillin and ampicillin among penicillin-tolerant Iranian pregnant women, and vancomycin and cefazolin among penicillin-allergic women are still drugs of choice in intrapartum prophylaxis for preventing *S. agalactiae* vertical transmission and early-onset neonatal disease.

Introduction

Streptococcus (*S.*) *agalactiae* is a Gram-positive, β-hemolytic, facultative anaerobe and catalase-negative bacterium that has the group B antigen in the cell wall [1,2]. The natural habitat of this group B streptococcus (GBS) is in the urogenital tract and lower gastrointestinal tract. This microorganism can also be colonized in the vagina in 10–30% of pregnant women [1–3]. *S. agalactiae* is associated with life-threatening infections in both newborn children and adults including pregnant and non-pregnant women and men [3]. Early-onset neonatal disease occurs during the first 7 days of life and is characterized by bacteremia, pneumonia and meningitis. The disease is acquired in the uterus or during vaginal delivery from asymptomatic mothers. Late-onset neonatal disease occurs between the first week and the third month of life and is characterized by bacteremia with meningitis [1,2]. Adult diseases include endometritis, wound infections and urinary tract infections in pregnant women, as well as bacteremia, pneumonia, bone and joint infections, and skin and soft tissue infections in men and non-pregnant women [2]. The mortality rate is low among infants due to rapid diagnosis and varies between 2% and 4%; however, severe neurological sequelae may occur in 15–30% of infants [2,4]. Previous studies have estimated the maternal *S. agalactiae* colonization rate to be 18.0% globally [5]. This colonization rate was 15.5% among Iranian pregnant women [3]. According to the Centers for Disease Control and Prevention (CDC) guideline, vaginal-rectal screening should be performed in all pregnant women at weeks 35–37 of pregnancy for the prevention of perinatal GBS infection [6]. Intrapartum antibiotic prophylaxis is recommended in high-risk pregnant women in order to prevent maternal colonization of GBS [5]. For high-risk pregnant women with 1) history of childbearing with GBS infections, 2) GBS bacteriuria and positive culture for GBS in

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the current pregnancy, 3) intrapartum temperature of ≥38 °C, 4) preterm birth or rupture of membranes before childbearing (before 37 weeks) and 5) prolonged rupture of membranes more than 18 h after 37 weeks, chemoprophylaxis with intravenous penicillin G or ampicillin is recommended to prevent early-onset neonatal disease [2,6,7]. Additionally, to prevent penicillin-associated allergic reactions, cefazolin, clindamycin and vancomycin can be used in penicillin-allergic women [2]. β-lactam antibiotics, especially penicillin and ampicillin, are two drugs of choice for treating GBS infections [2]. Despite a 70% reduction in perinatal GBS infection incidence, there are serious concerns for emerging antibiotic resistance among GBS bacteria due to intrapartum antibiotic prophylaxis [8,9]. It should be noted that treating GBS infection with tetracyclines, macrolides and clindamycin is not recommended due to increased level of antibiotic resistance [2]. There has been no comprehensive data on *S. agalactiae* antibiotic resistance in Iran. Therefore, the objective of the present systematic review and meta-analysis was to increase our awareness regarding the epidemiology of *S. agalactiae* antibiotic resistance, especially in pregnant women, in Iran.

Materials and methods

Search strategy and study selection

We conducted the current meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [10]. A list of the studies was collected in a reference management software by two authors independently through searching in different databases including PubMed, Scopus, Google Scholar and the Scientific Information Database (SID). There was no date limitation for searching electronic resources. Search terms were "antibiotic resistance" OR "drug resistance" AND "*S. agalactiae*" OR "*S. agalactiae*" OR "group B streptococcus (GBS)" AND "newborns" AND "pregnant women" AND "non-pregnant women" AND "men" AND "Iran". The search was managed through establishing an archive of relevant studies on *S. agalactiae* drug resistance in Iran by screening the titles and abstracts of the articles retrieved based on inclusion and exclusion criteria. Published cross-sectional studies in a language other than Persian and English languages, reporting antibiotic resistance of *S. agalactiae* isolated from samples other than clinical specimens and reporting antibiotic resistance of *S. agalactiae* from other countries were excluded from the meta-analysis. Articles with incomplete data, case reports, review articles and duplicate reports were also excluded. The reference lists of included articles were further checked to find any additional relevant study. The project was evaluated by Ardabil University of Medical Sciences and found to be in accordance to the ethical principles and the national norms and standards for conducting Medical Research in Iran (IR.ARUMS.REC.1398.127; 2019-06-23).

Data extraction and quality assessment

Relevant information obtained from the eligible studies included location of the study, year of the study, sample type, patients' properties, number of isolated *S. agalactiae* strains, antimicrobial susceptibility testing technique and drug resistance rates of *S. agalactiae* strains. The Joanna Briggs Institute (JBI) critical appraisal checklist was used to evaluate the quality of included cross-sectional studies. The quality of studies was classified as high (scores >5), medium (scores between 4 and 5) or low (scores <4).

Statistical analysis

Comprehensive Meta-Analysis software (Biostat, Englewood, NJ) was used for pooling of data and calculating antibiotic resistance rates, heterogeneity and publication bias in the meta-analysis. Percentage of *S. agalactiae* resistance to different antibiotics was calculated and expressed as 95% confidence interval (*CI*). Inconsistency among included studies was expressed as percentage (%) using I^2 statistic. If I^2 score was >25%, pooling of data was done by using random-effects model. Publication bias was assessed using funnel plots.

Results

Study selection

A total of 1091 articles, 1061 articles from international databases and 30 articles from an Iranian database, were identified (Fig. 1). Of these, 882 duplicate articles were removed by Endnote and 209 articles were evaluated based on the titles and abstracts. After screening the titles and abstracts, 157 articles did not meet our inclusion criteria and were excluded due to the fact that they were not relevant articles and reported the prevalence of *S. agalactiae* infection, *S. agalactiae* drug resistance in non-clinical samples and were not original articles. Thus, 52 full-text of the articles were assessed for eligibility. Of these, 28 articles were excluded with reasons such as inadequate data, not online availability of full-text of the article and abstract list of congresses. An additional 2 articles were added from searching reference lists of the included articles. Finally, there were 26 articles totally included in this meta-analysis with quality scores between 4 and 8.

Study characteristics

The 26 studies from 12 cities of Iran including Arak ($n = 3$), Ardabil ($n = 2$), Hamadan ($n = 3$), Kashan ($n = 1$), Kermanshah ($n = 1$), Kerman ($n = 1$), Khorramabad ($n = 1$), Mashhad ($n = 1$), Salmas ($n = 1$), Tehran-Alborz ($n = 11$) and Yazd ($n = 1$) were included in this study. Based on the data presented in Table 1, *S. agalactiae* strains were collected from different clinical specimens including vaginal and rectal swabs, urine, skin and soft tissue, bone, joint, blood, cerebrospinal fluid (CSF), pleural fluid, throat and external ear canals. Samples were also collected from newborns, pregnant women and non-pregnant adults. Additionally, microbiological methods including growth on Todd-Hewitt-Broth or 5% sheep blood agar mediums with 5% CO_2 at 33–37 °C for 18–24 h, typical colony morphology, Gram staining, β-hemolysis and other standard biochemical methods including negative catalase, positive hippurate hydrolysis and the Christie-Atkins-Munch-Petersen (CAMP) tests, bile esculin and 6.5% NaCl tests and finally resistance to trimethoprim-sulfamethoxazole and bacitracin disks were used for identifying *S. agalactiae* strains.

As shown in Fig. 3, funnel plot of the meta-analysis on the prevalence of antibiotic resistance of *S. agalactiae* to penicillin (A) and ampicillin (B) showed some evidence for publication bias due to asymmetric shape of funnel plots.

Characteristics of S. agalactiae antibiotic resistance

As presented in Table 1, Kirby–Bauer's disk diffusion method along with E-test and agar dilution methods were used to determine *S. agalactiae* antibiotic resistance characteristics in Iran. Based on the current meta-analysis, *S. agalactiae* resistance to different antibiotics among Iranian patients were as follows: 3.9% (95% *CI*: 1.1–13.0; $I^2 = 95.1\%$; $P = 0.0$) to penicillin (Fig. 2A), 7.1% (95% *CI*:

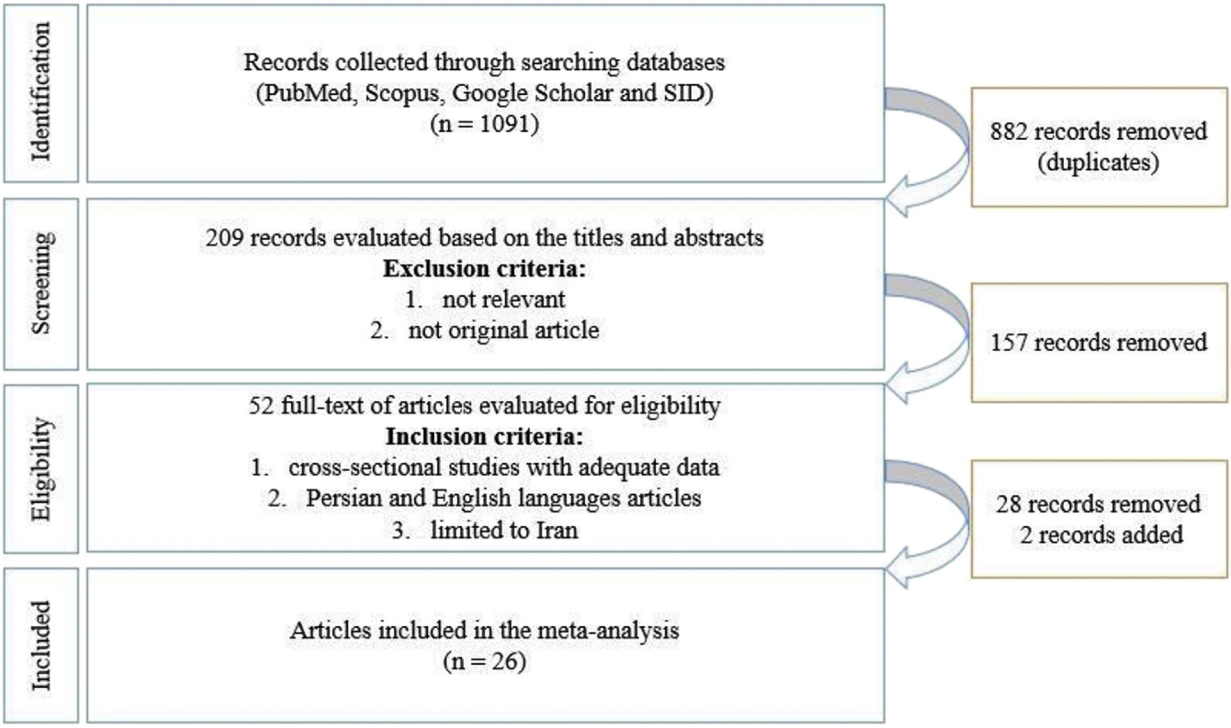


Fig. 1. The four-phase flow diagram of study selection process.

3.3–14.6; $I^2 = 91.3\%$; $P = 0.0$) to ampicillin (Figs. 2B), 26% (95% *CI*: 19.0–34.5; $I^2 = 89.8\%$; $P = 0.0$) to erythromycin, 30.7% (95% *CI*: 20.0–43.9; $I^2 = 94.3\%$; $P = 0.0$) to clindamycin, 3.2% (95% *CI*: 1.6–6.5; $I^2 = 77\%$; $P = 0.0$) to vancomycin, 7.5% (95% *CI*: 2.7–19.3; $I^2 = 80\%$; $P = 0.0$) to cefazolin, 25.1% (95% *CI*: 12.7–43.5; $I^2 = 85.7\%$; $P = 0.0$) to ceftriaxone, 18.5% (95% *CI*: 4.4–52.5; $I^2 = 93.3\%$; $P = 0.0$) to ciprofloxacin, 70.6% (95% *CI*: 60.1–79.3; $I^2 = 53.7\%$; $P = 0.0$) to trimethoprim-sulfamethoxazole, 46.1% (95% *CI*: 41.9–50.3; $I^2 = 0.0\%$; $P = 0.0$) to cefotaxime, 90.7% (95% *CI*: 85.4–50.3; $I^2 = 94.2\%$; $P = 0.0$) to tetracycline, 3.5% (95% *CI*: 1.5–7.9; $I^2 = 36.2\%$; $P = 0.16$) to nitrofurantoin, 31.5% (95% *CI*: 18.7–47.9; $I^2 = 84.9\%$; $P = 0.0$) to chloramphenicol, 0% to quinupristin/dalfopristin, 4.9% (95% *CI*: 3.2–7.5; $I^2 = 0.0\%$; $P = 0.63$) to levofloxacin and 0.08% (95% *CI*: 0.02–0.20; $I^2 = 0.0\%$; $P = 0.63$) to linezolid. Additionally, other antibiotic resistance patterns were as follows: azithromycin 41.9% (95% *CI*: 30.4–54.5), doxycycline 99.2% (95% *CI*: 88.5–100.0), ceftazidime 5.0% (95% *CI*: 1.6–14.4), ceftizoxime 54.1% (95% *CI*: 38.1–69.3), cephalothin 8.6% (95% *CI*: 0.8–51.2), norfloxacin 12.7% (95% *CI*: 0.8–73.5), moxifloxacin 8.9% (95% *CI*: 4.5–16.8), cefixime 80.2% (95% *CI*: 50.9–94.0), gentamicin 85.6% (95% *CI*: 60.6–95.8), kanamycin 66.6% (95% *CI*: 6.5–98.3), amikacin 81.1% (95% *CI*: 20.6–98.6), nalidixic acid 99.3% (95% *CI*: 89.2–100.0) and cephalexin 29.2% (95% *CI*: 0.6–96.7). Additionally, the prevalence rates of GBS drug resistance in pregnant women were as follows: 4.2% (95% *CI*: 1–16.2; $I^2 = 68.7\%$; $P = 0.0$) to penicillin, 2.7% (95% *CI*: 0.5–13.6; $I^2 = 78.7\%$; $P = 0.0$) to ampicillin, 21% (95% CI: 9.2–41.1; $I^2 = 82.8\%$; $P = 0.0$) to erythromycin, 26.8% (95% *CI*: 12.9–47.6; $I^2 = 82.6\%$; $P = 0.0$) to clindamycin, 2.4% (95% *CI*: 0.9–6.4; $I^2 = 0.0\%$; $P = 0.47$) to vancomycin, 7.6% (95% *CI*: 1.6–30; $I^2 = 83.4\%$; $P = 0.0$) to cefazolin, 12.5% (95% *CI*: 6.1–24; $I^2 = 0.0\%$; $P = 1.0$) to ceftriaxone, 13.6% (95% *CI*: 7.1–24.5; $I^2 = 0.0\%$; $P = 0.54$) to ciprofloxacin, 84.7% (95% *CI*: 73.5–91.7; $I^2 = 0.0\%$; $P = 0.48$) to trimethoprim-sulfamethoxazole, 41.3% (95% *CI*: 27.7–56.5; $I^2 = 21\%$; $P = 0.26$) to cefotaxime, 96.2% (95% *CI*: 87.8–98.9; $I^2 = 0.0\%$; $P = 0.68$) to tetracycline and 0% to nitrofurantoin.

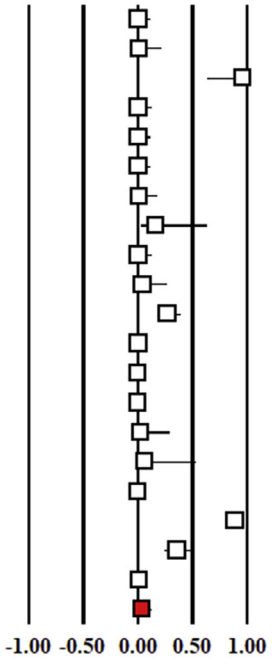
Discussion

S. agalactiae is associated with a wide range of infections in newborns, pregnant women and non-pregnant adults. Therefore, antibiotic prophylaxis in pregnancy and during vaginal birth, and post-delivery infections treatment against *S. agalactiae* are important. According to the guidelines from CDC, *S. agalactiae* remains susceptible to penicillin, ampicillin and first-generation cephalosporins [7]. Penicillin and ampicillin are two highly effective antibiotics in *S. agalactiae* intrapartum prophylaxis, which are intravenously administered for ≥4 h before delivery to prevent *S. agalactiae* vertical transmission and early-onset neonatal disease [7]. In this study, 3.9% and 7.1% of *S. agalactiae* strains isolated from the Iranian patients were resistant to penicillin and ampicillin (Fig. 2A and B). Resistance rate to these β-lactam antibiotics in this study was lower than that reported from Italy [37], while being higher compared to those reported from China [38], Switzerland [39], Brazil [40] and the Netherlands [41]. On the other hand, resistance to penicillin (4.2%) was higher and to ampicillin (2.7%) was notably lower among pregnant women compared to overall resistance rates (3.9% and 7.1%) in Iran. Therefore, these antibiotics can still be administered for intrapartum prophylaxis against *S. agalactiae* in the Iranian pregnant women with no risk for anaphylaxis. In penicillin-allergic mothers, macrolides (erythromycin), lincosamides (clindamycin), glycopeptides (vancomycin) and first-generation cephalosporins (cefazolin) are recommended for prophylaxis but their efficacy is unknown [7]. In the current meta-analysis, overall GBS resistance to erythromycin and clindamycin among Iranian patients were 26% and 30.7%, respectively. Furthermore, in the Iranian pregnant women, resistance to erythromycin (21%) and clindamycin (26.8%) was high. Resistance rate to these antibiotics was lower than Italy [37] and China [38] but higher than Switzerland [39], Brazil [40], the Netherlands [41] and Chile [42]. Total prevalence of vancomycin- and cefazolin-resistant *S. agalactiae* was low, being 3.2% to vancomycin and 7.5% to

A

Meta-analysis

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total
Arak-1	0.008	0.001	0.118	-3.377	0.001	0 / 60
Arak-2	0.016	0.001	0.211	-2.883	0.004	0 / 30
Arak-3	0.967	0.634	0.998	2.341	0.019	14 / 14
Ardabil-1	0.009	0.001	0.125	-3.328	0.001	0 / 56
Ardabil-2	0.008	0.000	0.115	-3.401	0.001	0 / 62
Hamadan	0.008	0.000	0.115	-3.401	0.001	0 / 62
Kashan	0.014	0.001	0.182	-3.013	0.003	0 / 36
Kermanshah	0.167	0.023	0.631	-1.469	0.142	1 / 6
Kerman	0.009	0.001	0.127	-3.315	0.001	0 / 55
Khorramabad	0.045	0.006	0.261	-2.975	0.003	1 / 22
Mashhad	0.273	0.179	0.392	-3.549	0.000	18 / 66
Tehran-1	0.005	0.000	0.082	-3.666	0.000	0 / 90
Tehran-2	0.002	0.000	0.035	-4.307	0.000	0 / 222
Tehran-3	0.002	0.000	0.029	-4.430	0.000	0 / 264
Tehran-4	0.025	0.002	0.298	-2.558	0.011	0 / 19
Tehran-5	0.063	0.004	0.539	-1.854	0.064	0 / 7
Tehran-6	0.004	0.000	0.065	-3.840	0.000	0 / 115
Tehran-7	0.894	0.863	0.918	14.643	0.000	445 / 498
Tehran-8	0.360	0.240	0.501	-1.953	0.051	18 / 50
Yazd	0.010	0.001	0.068	-4.572	0.000	1 / 100
	0.039	0.011	0.130	-4.797	0.000	



B

Meta-analysis

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total
Arak-1	0.008	0.001	0.118	-3.377	0.001	0 / 60
Arak-2	0.367	0.216	0.549	-1.443	0.149	11 / 30
Arak-3	0.033	0.002	0.366	-2.341	0.019	0 / 14
Ardabil-1	0.009	0.001	0.125	-3.328	0.001	0 / 56
Ardabil-2	0.008	0.000	0.115	-3.401	0.001	0 / 62
Hamadan-1	0.008	0.000	0.115	-3.401	0.001	0 / 62
Hamadan-2	0.231	0.076	0.522	-1.829	0.067	3 / 13
Kashan	0.014	0.001	0.182	-3.013	0.003	0 / 36
Kerman	0.009	0.001	0.127	-3.315	0.001	0 / 55
Mashhad	0.007	0.000	0.108	-3.445	0.001	0 / 66
Salmas	0.617	0.472	0.744	1.589	0.112	29 / 47
Tehran-1	0.002	0.000	0.035	-4.307	0.000	0 / 222
Tehran-2	0.004	0.001	0.026	-5.562	0.000	1 / 264
Tehran-3	0.357	0.204	0.546	-1.490	0.136	10 / 28
Tehran-4	0.063	0.004	0.539	-1.854	0.064	0 / 7
Tehran-5	0.504	0.460	0.548	0.179	0.858	251 / 498
Tehran-6	0.040	0.019	0.082	-8.222	0.000	7 / 174
Tehran-7	0.420	0.292	0.559	-1.126	0.260	21 / 50
	0.071	0.033	0.146	-6.226	0.000	

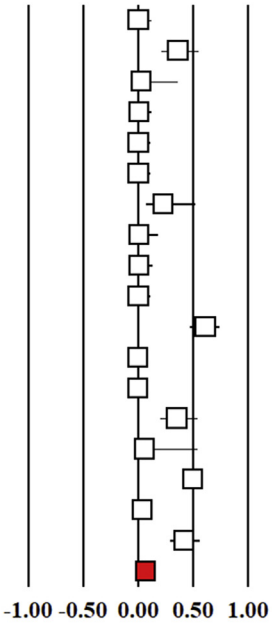
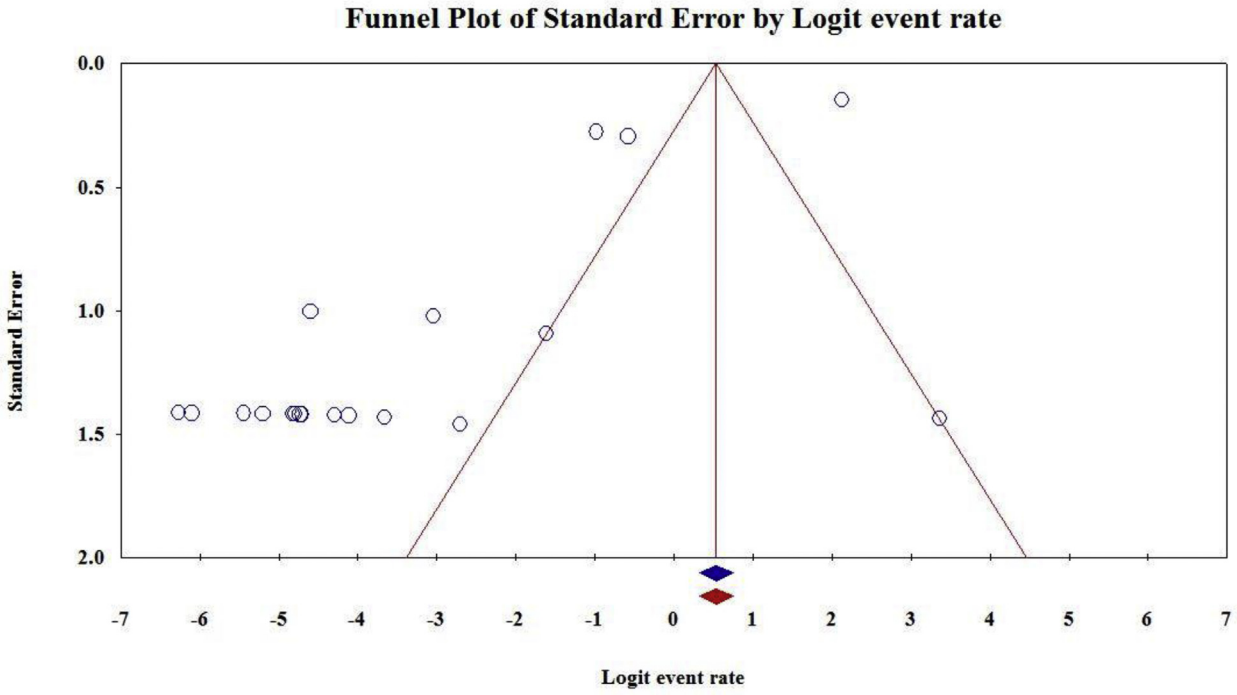
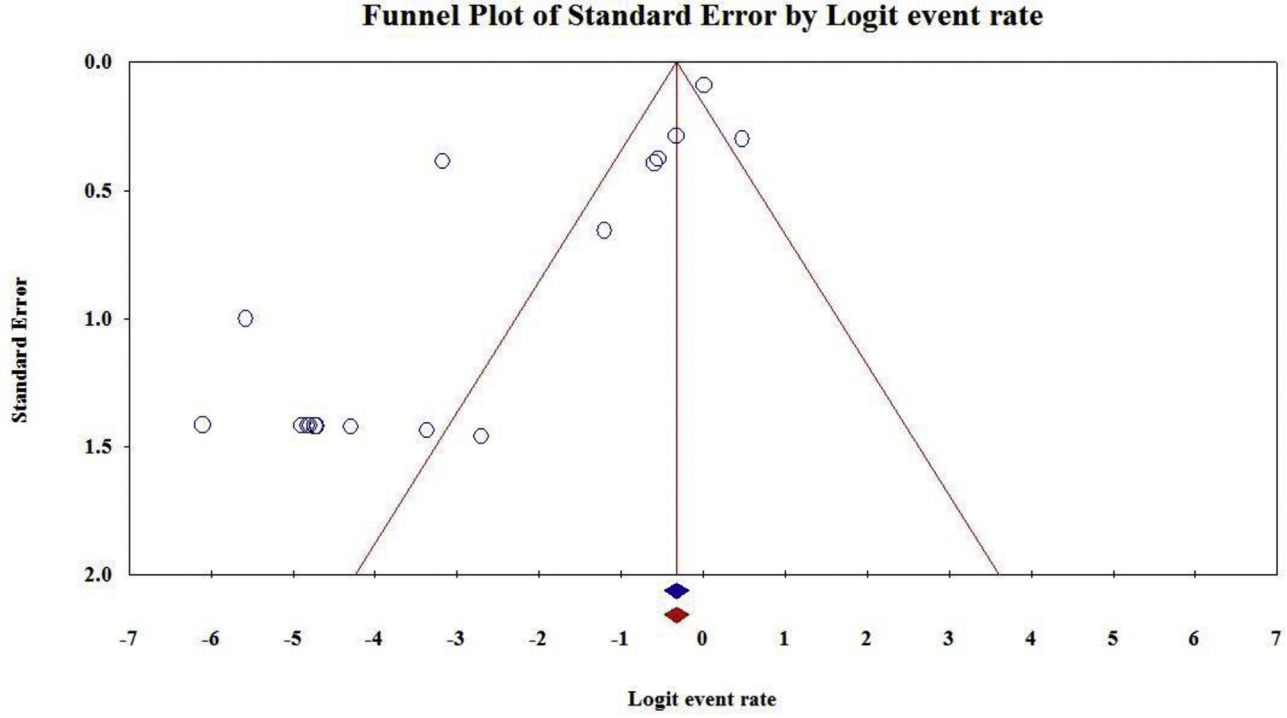


Fig. 2. Forest plot of the meta-analysis on the prevalence of antibiotic resistance of *S. agalactiae* to penicillin (A) and ampicillin (B) in Iran.



A



B

Fig. 3. Funnel plot of the meta-analysis on the prevalence of antibiotic resistance of *S. agalactiae* to penicillin (A) and ampicillin (B) in Iran.

Table 1
Profiles of included studies in the meta-analysis.

Area	Year	Sample type	Patients' properties	Strain (n)	AST	Antibiotic resistance (n)															Ref
						PEN	AMP	ERY	CLI	VAN	CFZ	CRO	CIP	TMP/SXT	CTX	TET	NIT	CHL	Q-D	LVX	LZD	
Arak	2013	Vaginal and rectal swabs	Pregnant women	60	Disk diffusion	0	0	17	9	0	2	ND	ND	ND	ND	58	ND	ND	ND	ND	ND	[11]
Arak	2010	Vaginal and rectal swabs	Pregnant women	30	Disk diffusion	0	11	7	ND	0	12	NA	ND	ND	14	ND	ND	ND	ND	ND	ND	[12]
Arak	ND	Vaginal and rectal swabs	Pregnant women	14	Disk diffusion	14	0	8	13	0	3	ND	ND	ND	4	ND	ND	ND	ND	ND	ND	[13]
Ardabil	2008	Vaginal and rectal swabs	Pregnant women	56	Disk diffusion E-test	0	0	0	2	0	0	7	8	47	ND	ND	ND	ND	ND	ND	ND	[14]
Ardabil	2008	Vaginal and rectal swabs	Pregnant women	62	Disk diffusion E-test	0	0	1	11	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	[15]
Hamadan	2013–2014	Vaginal swab Urine Blood	Pregnant and none-pregnant women	62	Disk diffusion	0	0	22	0	0	0	ND	ND	ND	ND	62	ND	2	0	3	0	[16]
Hamadan	2013–2014	Urine	ND	2	Disk diffusion	ND	ND	ND	ND	0	0	0	1	0	0	ND	0	ND	ND	ND	ND	[17]
Hamadan	1998–2002	ND	ND	13	Disk diffusion	ND	3	ND	ND	ND	ND	ND	ND	6	ND	ND	ND	9	ND	ND	ND	[18]
Kashan	2011–2012	Vaginal swab	Pregnant women	36	Disk diffusion	0	0	2	3	ND	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	[19]
Kermanshah	ND	Vaginal swab	Pregnant women	6	Disk diffusion	1	ND	3	2	1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	[20]
Kerman	2006–2007	Vaginal swab	Pregnant women	55	Agar dilution	0	0	6	14	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	[21]
Khorramabad	2012	Vaginal and rectal swabs	Pregnant women	22	Disk diffusion	1	ND	22	22	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	[22]
Mashhad	ND	Vagina, urethra and prostate secretion Urine	ND	66	Disk diffusion E-test	18	0	16	13	2	ND	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	[23]
Salmas	2015	Urine	None-pregnant women and Men	47	Disk diffusion	ND	29	ND	41	ND	ND	ND	25	35	ND	36	3	ND	ND	ND	ND	[24]
Tehran-Alborz	2014–2015	Vaginal swab Urine Blood Spermatic fluid	Pregnant and none-pregnant women	90	Disk diffusion	0	ND	27	89	1	ND	ND	ND	ND	ND	89	ND	ND	ND	6	ND	[25]
Tehran	2013–2015	Urine Skin and soft tissue Bone Joint Blood CSF Pleural fluid	ND	222	Disk diffusion	0	0	127	149	0	ND	ND	ND	ND	ND	194	ND	73	ND	ND	ND	[26]
Tehran	2014	Urine	ND	264	Disk diffusion	0	1	43	38	0	ND	ND	13	ND	ND	212	1	ND	ND	11	0	[27]
Tehran	2013	Throat External ear canals	Newborns	19	Disk diffusion	0	ND	5	6	0	ND	ND	ND	ND	ND	19	ND	ND	0	ND	0	[28]
Tehran	2012–2013	Urine	ND	28	Disk diffusion	ND	10	27	ND	0	ND	15	ND	19	ND	ND	0	7	ND	ND	ND	[29]
Tehran	2011–2012	Urine	ND	104	Disk diffusion	ND	ND	22	24	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	[30]
Tehran	2010–2011	Vaginal and rectal swabs	Pregnant women	7	Disk diffusion	0	0	ND	ND	ND	ND	ND	0	7	ND	7	0	ND	ND	ND	ND	[31]
Tehran	2010	Urine	ND	115	Disk diffusion	0	ND	40	40	ND	ND	ND	ND	ND	ND	110	ND	51	0	ND	1	[32]
Tehran	2010	Urine	Pregnant and none-pregnant women	498	Disk diffusion	445	251	120	84	80	ND	218	ND	ND	232	ND	ND	ND	ND	ND	ND	[33]
Tehran	2010	Urine	ND	Variable	ND	ND	7	ND	ND	9	16	ND	ND	126	ND	146	7	ND	ND	ND	ND	[34]
Tehran	ND	Vaginal swab Urine	ND	50	Disk diffusion	18	21	8	9	12	ND	12	ND	ND	ND	ND	ND	ND	ND	ND	ND	[35]
Yazd	2015	Vaginal swab	Pregnant and none-pregnant women	100	Disk diffusion	1	ND	8	10	ND	ND	ND	ND	ND	ND	95	ND	ND	ND	ND	ND	[36]

Abbreviations: PEN-penicillin; AMP-ampicillin; ERY-erythromycin; CLI-clindamycin; VAN-vancomycin; CFZ-cefazolin; CRO-ceftriaxone; CIP-ciprofloxacin; TMP/SXT-trimethoprim-sulfamethoxazole; CTX-cefotaxime; TET-tetracycline; NIT-nitrofurantoin; CHL-chloramphenicol; Q-D-quinupristin/dalfopristin; LVX-levofloxacin; LZD-linezolid; ND-not determined; AST-antimicrobial susceptibility testing; CSF-cerebrospinal fluid.

cefazolin. Moreover, the prevalence rates of vancomycin- and cefazolin-resistant *S. agalactiae* among Iranian pregnant women were 2.4% and 7.6%, respectively. According to the results of this study, due to high rates of erythromycin and clindamycin resistance, vancomycin and cefazolin are drugs of choice in intrapartum prophylaxis among penicillin-intolerant Iranian pregnant women.

S. agalactiae resistance to other cephalosporins such as cephalexin (29.2%), ceftriaxone (25.1%), cefotaxime (46.1%), ceftizoxime (54.1%) and cefixime (80.2%) was high, except for cephalothin (8.6%) and ceftazidime (5.0%). One possible reason for the high rate of resistance of this bacterium is lower effectiveness of cephalosporins on Gram-positive bacteria [1,2]. In our study, cephalothin, cefotaxime and ceftriaxone resistance rates were higher than those reported from China (0%), Brazil (0%) and the Netherlands (0%) [38,40,41].

We observed a lower percentage of resistance to quinupristin/dalfopristin and linezolid, while resistance to other protein synthesis inhibitors including azithromycin, doxycycline, tetracycline, chloramphenicol, gentamicin, kanamycin and amikacin was higher. The same rate of linezolid resistance (0.08%) was found in Italy (0%) and Switzerland (0%) [37,43]. Also, tetracycline resistance rate (90.7%) was similar to those of China (83.9%), Brazil (97.0%) and Switzerland (89.0%) [38,40,43]. However, azithromycin resistance rate (41.9%) was lower than that of China (87.5%) [38], and gentamicin resistance rate (85.6%) was higher than that of Switzerland (0.8%) [43].

The prevalence of *S. agalactiae* resistance to quinolones was variable. Resistance rate to the narrow-spectrum quinolone, nalidixic acid, was found to be high (99.3%) in the current study. This is an expected result because nalidixic acid is an effective quinolone against Gram-negative rods and has no activity against Gram-positive bacteria [2]. Our results also showed that *S. agalactiae* resistance to broad-spectrum quinolones including levofloxacin (4.9%) and ciprofloxacin (18.5%) as well as extended-spectrum quinolones including norfloxacin (12.7%) and moxifloxacin (8.9%) was low. These results are also in accordance with the fact that antimicrobial activity of broad- and extended-spectrum quinolones is higher against Gram-positive bacteria [2]. *S. agalactiae* resistance rates to quinolones in other countries were reported to be as follows: Italy: levofloxacin 9.23% and moxifloxacin 0% [37], China: levofloxacin 35.7% [38], Brazil: levofloxacin 0% [40], and Switzerland: levofloxacin 1.6% [43]. In the present study, nitrofurantoin resistance rate was 0%, which is similar to that reported by Simoes et al. [44]. Therefore, nitrofurantoin can be a drug of choice for treating asymptomatic and symptomatic bacteriuria in the Iranian pregnant women due to low resistance rate and its ability to achieve adequate concentrations in the urine [44]. However, it is not useful in intrapartum prophylaxis due to its low level in the maternal bloodstream and inability to cross the placenta [44]. However, 84.7% of *S. agalactiae* were resistant to trimethoprim-sulfamethoxazole, suggesting that it is not an effective drug for treating urinary tract infection in the Iranian pregnant women. We observed variable resistance rates to this drug in different studies. This difference may be due to differences in the geographical area, patients' properties and specimen type. Lack of access to complete data from all cities of Iran on *S. agalactiae* antibiotic resistance and a high level of heterogeneity among the included studies were the main limitation of the current systematic review and meta-analysis.

Conclusion

Given the low prevalence of *S. agalactiae* resistance to penicillin and ampicillin in the Iranian pregnant women, these antibiotics can still act as two highly effective antibiotics in intrapartum prophylaxis for preventing *S. agalactiae* vertical transmission and early-onset neonatal disease in Iran. Furthermore, due to the high rate of erythromycin and clindamycin resistance, vancomycin and cefazolin are drugs of choice for intrapartum prophylaxis in penicillin-allergic Iranian women. Additionally, resistance rates to nitrofurantoin, quinupristin/dalfopristin, levofloxacin, linezolid, ceftazidime, norfloxacin, cephalothin and moxifloxacin were low in Iran; therefore, using these agents is suggested for the treatment of *S. agalactiae* infections. Investigation of bacterial resistance mechanisms especially among resistant bacteria to erythromycin, clindamycin, ceftriaxone, ciprofloxacin, trimethoprim-sulfamethoxazole, cefotaxime, tetracycline, chloramphenicol, azithromycin, doxycycline, ceftizoxime, cefixime, gentamicin, kanamycin, amikacin, nalidixic acid and cephalexin is recommended.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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