Jundishapur J Health Sci. 2021 April; 13(2):e114902. doi: 10.5812/jjhs.114902.

Published online 2021 June 22. **Review Article**

Frequency and Antimicrobial Resistance of *Shigella* Species in Iran During 2000-2020

Farhad Moradi [1,*], Nahal Hadi [1], Maryam Akbari [2], Zahra Hashemizadeh [1] and Reyhaneh Rouhi Jahromi [3]

[1]Department of Bacteriology and Virology, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Microbiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3]Zoonoses Research Center, Jahrom University of Medical Sciences, Jahrom, Iran

[*]*Corresponding author*: Department of Bacteriology and Virology, Shiraz University of Medical Sciences, Shiraz, Iran. Email: f.moradi1993@gmail.com

Received 2021 March 31; **Revised** 2021 June 01; **Accepted** 2021 June 08.

Abstract

Context: Numerous studies have shown the high frequency and antibiotic-resistant patterns of *Shigella* species in different provinces of Iran. In this study, we performed a comprehensive review from 2000 to 2020 in Iran to describe the prevalence rate and antibiotic-resistant patterns of *S. sonnei*, *S. dysenteriae*, *S. flexneri*, and *S. boydii*.

Evidence Acquisition: We systematically searched the biomedical databases including Scopus, Google Scholar, PubMed, SID, and Web of Science for related articles published in English or Persian. Finally, out of 70 articles, 34 studies were included in the study.

Results: From 44,292 clinical specimens, 2,742 cases were introduced as positive samples for *Shigella* species in Iran during 2000-2020. Also, *S. sonnei* (n = 1484, 54.1%) was the predominant species in Iran, followed by *S. flexneri* (n = 1100, 40.1%), *S. dysenteriae* (n = 80,3%), and *S. boydii* (n = 78, 2.8%). These *Shigella* species showed maximum resistance to ampicillin (n = 1759, 64%-96%), cotrimoxazole (n = 1220, 87%-100%), nalidixic acid (n = 649, 10%-82%), trimethoprim-sulfamethoxazole (n = 459, 80%-98.5%), cefotaxime (n = 410, 53%-63%), and tetracycline (n = 386, 36%-94%). No resistances were found against imipenem, meropenem, cefoxitin, norfloxacin, levofloxacin, azithromycin, and amoxicillin. Also, 308 and 359 cases were introduced as multidrug resistance (MDR) and extended spectrum beta lactamase (ESBL) producing species, respectively.

Conclusions: Evaluation of endemic shigellosis and antibiotic-resistant patterns through epidemiological studies are necessary to promote infection control strategies. These data may be useful to avoid empirical treatment, revise treatment guidelines, and decrease antimicrobial resistance of *Shigella* spp. in human societies.

Keywords: *Shigella*, Prevalence, Drug resistance, Iran

1. Context

Gastrointestinal infections caused by different enteric bacterial pathogens such as Escherichia and *Shigella* are the main public health threat worldwide. *Shigella* is a gram-negative and intracellular bacterium with the pathogenic subgroup (A-D) with different distribution in developing countries. *Shigella* species belong to the Enterobacteriaceae family, which includes *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*, with exclusive epidemiological features. They are spread through the fecal-oral route and produce acute infection in the intestine called shigellosis. However, this infection is mostly caused by *S. sonnei* in industrialized countries and *S. flexneri* in developing countries (1-3). Moreover, *S. dysenteriae* is known as an epidemic form of shigellosis in different countries. According to the estimations, 160 million disease cases and 600,000 deaths are due to *Shigella* infections annually worldwide. In Iran, the prevalence of *Shigella* infections is so variable geographically. For example, different studies have shown that the prevalence of diarrhea caused by *Shigella* is almost high in different Iranian cities such as Kashan, Tehran, Kerman, Zanjan, and Ahvaz. In late summer 2006, during the final stage of an outbreak of shigellosis in the Isfahan Province, a diarrheal outbreak appeared to be the result of shigellosis (1-5). Generally, shigellosis is related to insufficient sanitation, some environmental factors, person-to-person contact, especially in young children, contaminated water and foods, sexual activity, and traveling. Also, *Shigella* pathogenesis is related to various virulence factors located in the chromosome (such as invasion-associated locus (*ial*) and *Shigella* enterotoxin 1 genes (*set1A* and *set1B*)) and large virulent inv plasmids (for example; invasion plasmid antigen H (*ipaH*) and *Shigella* entero-

toxin 2 gene). These factors are associated with dissemination from cell to cell and the watery phase of diarrhea in the epithelial cells (1-6). The frequency and antibiotic-resistant patterns of *Shigella* species are changing rapidly over time. So, antibiotic treatments are typically suggested to decrease the symptoms of *Shigella* infections (6-9). Selecting an appropriate antibiotic for the treatment of *Shigella* infections is necessary because multidrug resistance (MDR) species can appear from many mechanisms, such as a decrease in cellular permeability, extrusion of drugs by active efflux pumps, and overexpression of drug-modifying in *Shigella* genomes (10-13). For example, the appearance of extended-spectrum-β-lactamases (ESBLs) producing strains of *Shigella* spp. and developing resistance to different treatment recommendations such as sulfonamides, tetracycline, chloramphenicol, ampicillin, fluoroquinolones, and ceftriaxone or azithromycin, which are recommended by the World Health Organization (WHO) for fluoroquinolones resistant species, are reported in different research studies worldwide. According to the WHO, effective treatment for *Shigella* spp. must be selected by the prevalence and antimicrobial susceptibility patterns of the endemic strains. Furthermore, some novel therapeutic strategies for *Shigella* treatment were suggested. For example, nanoparticles (NPs) have shown high antibacterial activity during in-vitro and in-vivo experiments, phage therapy, biotherapeutic agents (preferably probiotics), and natural and organic products (6, 10, 14). Today, different phenotypic and molecular methods have been used to diagnose *Shigella* species in human clinical specimens (11, 12, 14-16). Also, for epidemiological investigations, amplifying and non-amplifying DNA fingerprinting methods have been used for pathogenic strains. In Iran, different studies showed the prevalence and antimicrobial-resistant patterns of *Shigella* species isolated from clinical specimens of the adult and pediatric patients. In this comprehensive review, we tried to characterize and summarize this information in Iran during 2000-2020.

2. Evidence Acquisition

2.1. Search Strategy

We systematically searched the biomedical databases including Scopus, Google Scholar, PubMed, SID, and Web of Sciences in English and Persian to find the related studies from 2000 to 2020 with different keywords including "*Shigella* spp. AND Iran", "*Shigella dysenteriae* AND Iran", "*Shigella flexeneri* AND Iran", "*Shigella boydii* AND Iran", "*Shigella sonnei* AND Iran", "*Shigella* spp. AND human clinical specimens AND Iran", "*Shigella* spp. AND antimicrobial resistance AND Iran", "*Shigella dysenteriae* OR *Shigella flexeneri* AND antimicrobial resistance AND Iran", "*Shigella boydii* OR *Shigella sonnei* AND Iran", and "*Shigella* spp. AND multidrug resistance (MDR), and ESBLs AND Iran". To clarify the prevalence and development of antibiotic-resistance, we reviewed the published literature and their references to provide and categorize information about the prevalence and antimicrobial resistance of *Shigella* species isolated from different pediatrics and adult patients. Finally, out of 70 articles, we selected 34 papers published from 2000 to 2020 (Figure 1).

2.2. The Inclusion Criteria

There were four inclusion criteria:

1) Epidemiological and frequency studies were selected and categorized based on year, type of human clinical specimen, age groups, and the frequency of different *Shigella* species. The data was separated by the province and regions, sample collection, sample size, and number of positive specimens for different *Shigella* species.

2) Research studies with different phenotypic and molecular methods such as stool culture, biochemical detection, serotyping tests, Multiplex PCR, PCR-RFLP, and PFGE assay to identify *Shigella* spp.

3) Different clinical specimens such as watery and bloody diarrhea and rectal swabs were collected from hospitalized patients with different clinical signs and symptoms.

4) The studies that focused on antimicrobial susceptibility tests (AST) for *Shigella* spp. according to clinical laboratory standard institute (CLSI) and performed through disk diffusion (Kirby-Bauer) or molecular methods (Tables 1 and 2).

2.3. Exclusion Criteria

Case reports, duplicate documents, and the studies not exploring the prevalence and antimicrobial resistance for *S. sonnei*, *S. flexneri*, *S. dysenteriae*, and *S. boydii* were excluded from the study.

2.4. Data Analysis

In this review, data extraction was performed independently by three researchers to contradict any possibility of error. We used Microsoft Excel 2019 for storage, statistical analyses, numerical calculations, and chart designing. Also, for continuous variables, Wilcoxon rank-sum test (P-value ≤ 0.05) was used.

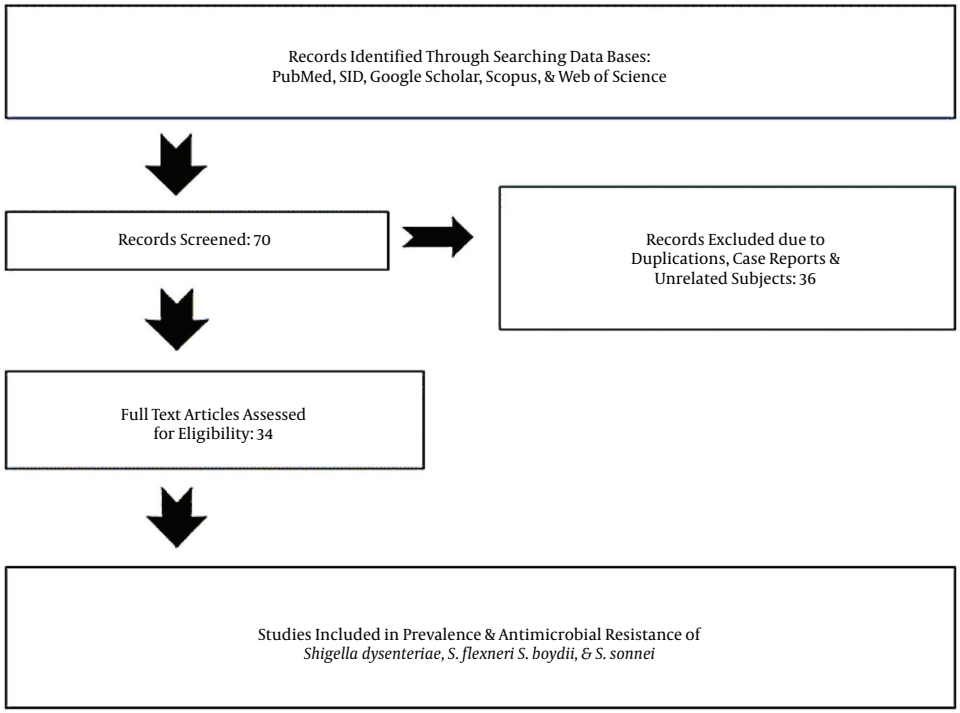

Figure 1. Flowchart of search strategies

3. Results

3.1. Prevalence Rates for Pathogenic Shigella Species

The epidemiological information and frequency of different *Shigella* spp. were categorized and presented in Table 1. In total, 44,292 human clinical specimens to find *Shigella* species in different provinces of Iran during 2000-2020 were investigated. Most studies (n = 12) had been performed during 2013-2016, and nine studies had been performed in 2015. We selected six observational cohort studies that were performed during five years. According to the collected data, 2,742 clinical sample cases were introduced as a positive sample for the *Shigella* species (Table 1). The frequencies of the *Shigella dysenteriae* (subgroup A), *Shigella flexeneri* (subgroup B), *Shigella boydii* (subgroup C), and *Shigella sonnei* (subgroup D) in Iran were compared (Figure 2). Furthermore, these studies were done in different provinces such as Tehran, Isfahan, Fars, and Mazandaran in Iran. According to different reports, most of the *Shigella* infections were discovered in Tehran (capital of Iran), Abadan, Isfahan, and Fars provinces. The geographic distribution of the prevalence studies in different provinces is shown in Figure 3. In these studies, different clinical stool specimens such as watery, bloody, and mucoid diarrhea and rectal swabs were collected from adult and pediatric age groups. Also, many of these specimens were isolated from hospitalized patients with different signs and symptoms. Some studies were defined in primary clinical outcome (i.e. diarrhea, fever, and abdominal cramps) in children. Also, the major manifestations of the disease for each species and strain were bloody, mucoid, and watery diarrhea. One study had been performed in six provinces of Iran and used other different samples such as urine, sputum, wound, respiratory fluids, vaginal secretions, biopsies, and blood culture. All isolates were confirmed as *Shigella* species by microbiological methods (e.g. culture, biochemical and serological tests by slide agglutination and a group-specific polyvalent antiserum) and molecular methods (e.g. Multiplex PCR, ERIC-PCR, and PCR-RFLP). Some studies used multilocus variable-number tandem-repeat (VNTR) analysis (MLVA) for genotyping of local *Shigella* strains. Also, the major phenotypic and genotypic methods to identify *Shigella* species were culture, biochemical test, slide agglutination, and Multiplex PCR. Out of 2,742 positive samples for *Shigella* species, *S. sonnei* (n = 1,484, 54.1%) was a predominant species in Iran, followed by *S. flexneri* (n = 1,100, 40.1%), *S. dysenteriae* (n = 80, 3%), and *S. boydii* (n = 78, 2.8%). Some of the studies reported the prevalence and relations between *Shigella* virulence genes and shigellosis in Iran. They reported some virulence genes

Table 1. Prevalence Studies for *Shigella* spp. Based on Clinical Human Specimens (ND: Not Detected)

Reference, Publication Year	Performed Year	Region	Human Sample	Age, y; Male & Female	Detection Methods	Sample Size	Positive for *Shigella* spp., No. (%)	Frequency of *Shigella* spp., No. (%)			
								S. flexneri	*S. sonnei*	*S. boydii*	*S. dysenteriae*
Salimiyan Rizi et al., 2020 (17)	2018-2019	Mashhad	Stool samples	< 14	Culture, biochemical, serotyping tests.	233	89 (22.3)	22 (23.4)	66 (70.2)	ND	1 (1)
Karimi-Yazdi et al., 2020 (8)	2017-2018	Tehran	Diarrheal stool	≤ 14	Culture, PCR, slide agglutination	141	141 (100)	28 (19.9)	111 (78.7)	2 (1.4)	ND
Sheikh et al., 2019 (18)	2016-2017	Ahvaz	Bloody, mucoid and watery diarrhea	2-65	Culture, PCR, Slide agglutination	522	69 (13.2)	34 (49.3)	22 (31.9)	9 (13)	4 (5.8)
Avakh Majalan et al., 2018 (6)	2016	Tehran	diarrheal stool	Randomly	Culture, biochemical, serotyping tests.	300	26 (8.7)	11 (42.3)	15 (57.7)	ND	ND
Teimourpour et al., 2019 (13)	2015-2017	Ardabil	Stool samples	< 10	Culture, PCR	1280	113	22 (19.4)	79 (69.9)	9 (9.9)	3 (6.2)
Moghanloo et al., 2018 (19)	2015-2017	Kashan	Diarrheal stool	1-69	Culture, biochemical, serotyping tests.	528	98 (18.5)	31 (31.63)	57 (58.1)	2 (2)	8 (8.1)
Yaghoubi et al., 2017 (7)	2015-2016	Tehran	Stool samples	1-15	Culture, serotyping tests. Multiplex PCR	946	75 (7/7)	33 (44);1a (11), 2a (22)	40 (53.3)	1 (1.3)	1 (1.3)
Shahin et al., 2020 (20)	2015-2016	Isfahan, Fars, Hormozgan, Kohkiloyeh va Boyer Ahmad	Not define	Not define	Biochemical, PCR, serogroup test	70	70 (100)	26 (37.1)	44 (62.8)	ND	ND
Beladi Ghannadi et al., 2019 (21)	2015-2016	Tehran	Stool samples	Randomly	Culture, serotyping tests. Multiplex PCR	945	52 (5.5)	12 (23)	23 (44.2)	5 (9.6)	12 (23)
Pour et al., 2016 (22)	2015	Ahvaz	Diarrheal stool	≤ 2-8	Culture, biochemical, ERIC-PCR	50	50	31 (62)	16 (32)	3 (6)	ND
Yousefi et al., 2018 (23)	2015	Kerman	Stool samples	15-79	Culture, biochemical	241	5 (19)	ND	ND	ND	5 (19)
Abbasi et al., 2019, (2)	2015	Arak	Mucoid and bloody diarrhea	1-10	Culture, PCR, slide agglutination	230	19 (8.2)	4 (21)	15 (78.9)	ND	ND
Shokoohizadeh et al., 2017 (24)	2015	Ahvaz	Diarrheal stool samples	≤ 2-8	Microbiologic tests, ERIC-PCR, MLST	80	50 (62.5)	31 (62)	16 (32)	3 (6)	ND
Aminshahidi et al., 2017 (3)	2014-2015	Shiraz	Loose stools with WBC+	≤ 18	Culture, PCR	269	41 (15.2)	33 (80.5)	8 (19.5)	ND	ND
Soltan Dallal et al., 2015 (25)	2013-2014	Tehran	Stool samples	≤ 14	Culture, biochemical test	200	6 (3)	ND	6 (3)	ND	ND
Hosseini Nave et al., 2016 (26)	2013-2014	Kerman	Stool samples	Randomly	Biochemical, serological test, Multiplex PCR	624	56 (9)	31 (55.4)	18 (32.1)	7 (12.5)	ND
Talebreza et al., 2015 (27)	2013-2014	Tehran	Stool samples	< 10	Culture, PCR, slide agglutination	938	36	10 (27.8)	22 (61.1)	3 (8.3)	1 (2.8)
Nikfar et al., 2017 (4)	2013-2014	Ahvaz	Stool samples	≤ 12	Culture, slide agglutination	193	193 (100)	125 (64.8)	63 (32.6)	4 (2.1)	1 (0.5)
Nodeh Farahani et al., 2018 (28)	2012-2016	Tehran	stool samples	1-10	Culture, slide agglutination	5300	472 (8.9)	185 (39.2)	287 (60.8)	ND	ND
Zahedi Bialvaei et al., 2016 (16)	2012-2013	Tehran, Fars, Kurdistan, Mazandaran, Khuzestan, Sistan va Baluchestan	Urine, blood, sputum, wound, respiratory and vaginal secretions, biopsies, body fluids	Randomly	Culture, biochemical test, slide agglutination	443	52 (11/7)	ND	ND	ND	ND
Alizadeh-Hesar et al., 2015 (11)	2012-2013	Tehran	Bloody and loose stools	< 5	Culture, PCR, PFGE	5291	70 (1.32)	8 (11.43)	61 (87.14)	1 (1.43)	ND
Jomezadeh et al., 2014 (1)	2011-2013	Abadan	Stool samples	≤ 1-15	Culture, biochemical test, Slide agglutination	705	36 (5.1)	19 (52.7)	11 (30.5)	4 (11.1)	2 (5.5)
Mostafavi et al., 2016 (29)	2010-2015	Isfahan	Stool samples	< 5-15 <	Culture, biochemical test, slide agglutination	45	45 (100)	15 (34.1)	28 (63.6)	ND	1 (2.3)
Zahedi Bialvaei et al., 2017 (30)	2009-2013	Tabriz	Stool samples	3-70	Culture, biochemical test, Slide agglutination, PCR	58	58 (100)	7 (12)	45 (77.6)	ND	6 (10.3)
Esmaeili Dooki et al., 2014 (31)	2009	Mazandaran	Fecal specimen and Rectal swab	≤ 1-14	Culture, biochemical test	1072	7 (0.65)	ND	6 (85)	ND	1 (15)
Ranjbar et al., 2013 (5)	2008-2010	Tehran	Rectal swabs	≤ 12	Culture, biochemical test, Slide agglutination	55	55 (100)	ND	ND	ND	ND
Ranjbar and Mirsaeed Ghazi, 2013 (32)	2008-2010	Tehran	Rectal swabs	≤ 5-12 ≤	Culture, biochemical test, ERIC-PCR	950	89 (9.3)	28 (31.5)	54 (60.7)	5 (5.6)	2 (2.2)
Khaghani et al., 2014 (9)	2008-2010	Ahvaz	Stool samples	≤ 1-12	Culture, biochemical test, slide agglutination	4380	175 (4)	87(49.8); type 1=19(21.8), type 2=50 (57.5), type 3=1 (1), type 4=3(3.4), type 6=7(8.1)	ND	ND	ND
Ranjbar and Memariani, 2015 (33)	2008-2010, 2002-2003	Tehran	Watery, loose and bloody stools	≤ 12	Culture, slide agglutination, MLVA assay	950	47 (4.9)	ND	47 (100) 21 genotypes	ND	ND
Dibaj et al., 2013 (34)	2006	Isfahan	Rectal swabs	Randomly	Culture, biochemical test, slide agglutination, Ribotyping	146	13 (8.9)	2 (15.4)	6 (46.1)	1 (7.7)	4 (30.8)
Soltan Dallal et al., 2019 (35)	2005-2006	Esfahan, Tehran, Kurdistan, Yazd Ghazvin, Zanjan, Semnan, Golestan	Fecal swab samples	Randomly	Culture, serogroup test, PCR	1012	29 (2.86)	13 (44.8)	16 (55.2)	ND	ND
Farshad et al., 2015 (36)	2003	Shiraz	Stool samples	≤ 1-14	PCR-RFLP and PFGE	719	82 (11.4)	16 (19.51)	61 (74.3)	3 (3.6)	2 (2.4)
Gharibi et al., 2012 (15)	2002-2008	Bushehr	Stool samples	Randomly	Culture, biochemical test, slide agglutination	121	121 (100)	46 (38.1)	62 (51.2)	8 (6.6)	5 (4.1)
Pourakbari et al., 2010 (12)	2001-2006	Tehran	Stool samples	Randomly	Culture, biochemical test, slide agglutination	15,255	397 (2.6)	190 (47.9)	179 (45.1)	8 (2)	20 (5)

Table 2. Characteristics of Antimicrobial Resistance Patterns of *Shigella* spp. in Studies Performed in Iran

Antimicrobial Agents	Number of Studies	Resistant Strains Reported, Number (from 2742 *Shigella* spp.)	Rate of Resistance Reported, No. (%)	Reference
Ampicillin	14	1759	64-96%	(1, 6, 8, 9, 12, 14, 17, 18, 20, 21, 25, 28, 30, 31)
Trimethoprim-sulfamethoxazole	8	452	80-98.5%	(1, 3, 8, 9, 14, 18, 21, 30)
Chloramphenicol	10	299	10-61%	(1, 2, 6, 9, 12, 14, 18, 20, 25, 30)
Nalidixic acid	16	649	10-82%	(1-3, 6, 8, 9, 11-15, 17, 18, 20, 28, 31)
Gentamicin	15	260	1.5-36%	(1-4, 6, 9, 11-14, 17, 18, 25, 30, 31)
Erythromycin	2	51	57-68%	(18, 31)
Cefixime	6	169	22-68%	(1, 2, 8, 17, 18, 31)
Ceftazidime	6	217	27-39%	(2, 3, 12, 18, 21, 27)
Ceftriaxone	10	311	0-63%	(1-4, 6, 13, 14, 17, 18, 31)
Ciprofloxacin	14	105	0-40%	(1-3, 6, 8, 13-15, 18, 20, 21, 25, 31, 35)
Tetracycline	11	386	36-94%	(1, 2, 6, 11, 14, 15, 20, 21, 25, 27, 30)
Cotrimoxazole	7	1220	87-100%	(2, 11, 12, 15, 17, 25, 28)
Cefotaxime	10	410	53-63%	(2, 3, 8, 14, 20, 25, 27, 28, 30, 31)
Ceftizoxime	5	74	6-41%	(2, 12, 15, 30, 31)
Cefoxitin	1	3	15%	(2)
Norfloxacin	2	6	4-5%	(2, 14)
Azithromycin	4	131	0-47%	(2, 3, 13, 17)
Imipenem	2	0	0	(2, 13)
Meropenem	1	0	0	(3)
Amikacin	6	176	0-63%	(3, 12, 13, 21, 30, 31)
Levofloxacin	1	16	11%	(8)
Minocycline	1	158	66-93%	(8)
Streptomycin	3	144	98-100%	(11,21,36)
Tobramycin	1	112	20%	(12)
Kanamycin	1	358	60%	(12)
Cephalothin	1	311	42-67%	(12)
Aztreonam	1	19	34%	(14)
Ofloxacin	2	8	4-5%	(13, 14)
Amoxicillin	2	30	40-83%	(17, 27)
ESBL producing	5	359	5.7-56%	(2, 3, 5, 16, 28)
MDR	6	308	76-98%	(2, 5, 6, 8, 9, 21)

such as *ipaH*, *ipaBCD* (necessary for invasion and intracellular survival), *VirA* (intracellular spreading factor), *stx*, *set1A*, *set1B*, and sat among *Shigella* species in pediatric or hospitalization diarrhea. For example, one of the studies showed the prevalence of enterotoxins ShET-2 (*sen*), *ipaH*, *ipaBCD*, sat, *virA*, *ial*, *set1A*, and *set1B* genes in *Shigella* species isolated from hospitalizing bloody diarrhea or other study revealed the high prevalence of *ipaH*, *ipaC*, *sen*, *ipaD*, *virA*, *ipaB*, and *ipgD* genes in *Shigella* isolates (7, 8).

3.2. Antibiotic-Resistance Patterns of Shigella Species

The antibiotic-resistance information for positive samples (n = 2,742 *Shigella* species) against 30 most common antibiotic agents was investigated in Iran during 2000-2020. The AST for *Shigella* isolates was completed by phenotypic according to CLSI guidelines and genotypic methods. In different studies, *Shigella* isolates (n = 2,742) showed maximum resistance to Ampicillin (n = 1,759, 64%-96%), Cotrimoxazole (n = 1,220, 87%-100%), Nalidixic acid (n = 649, 10%-82%), Trimethoprim-sulfamethoxazole (n = 459, 80%-98.5%), Cefotaxime (n = 410, 53%-63%), and Tetracycline (n = 386, 36%-94%). No resistances were found against imipenem, meropenem, cefoxitin, norfloxacin, levofloxacin, azithromycin, and amoxicillin. Furthermore, MDR phenotypes were seen in six studies for 308 *Shigella* species with different resistance patterns to antibiotic agents. Also, 359 *Shigella* isolates in five studies could produce ESBLs, and some of them were positive for *bla*TEM, *bla*CTX-M-1, *bla*CMY 2, *bla*CIT, and *bla* CTX-M-15 (Table 2 and Figure 4) (2, 3, 5, 16, 28).

4. Discussion

Several studies reported that the prevalence and antibiotic-resistant patterns of *Shigella* spp. are on the rise in Iran. According to the WHO, exploring the epidemiology of the infectious disease in developing countries is necessary because annual reports have shown that about 200,000 infectious diseases are related to this *Shigella* spp. Hence, to explain the prevalence and antibiotic-resistant patterns of *Shigella* spp., we reviewed the related studies published from 2000 to 2020 in Iran. Overall, *Shigella* virulence or pathogenicity is related to the immunity of patients, and severe clinical findings with low infectious dose (10-100 organisms) can be seen in children, elderly adults, and immunodeficient patients. This bacterial species is transmitted by the oral-fecal pathway and causes self-limiting diarrhea or invasive bacillary dysentery with bleeding or inflammatory diarrhea, fever, and abdominal cramps. Unfortunately, antibiotic therapy is a main strategy to combat and control the *Shigella* spread, and excessive use of antibiotics agents can develop MDR strains in different countries. According to the Centers for Disease Control and Prevention (CDC), *Shigella* infections are treated with ciprofloxacin and Ceftriaxone, especially for children with shigellosis. Hence, understanding the prevalence and antibiotic-resistance patterns of *Shigella* species is necessary for efficient treatment and increasing the public hygiene (17, 22, 34, 36-39). Different countries such as Bangladesh, Maldives, Tanzania, Nepal, Myanmar, and Sri Lanka reported the prevalence of *Shigella* spp. in symptomatic and asymptomatic children (40). In Iran, different studies were performed to evaluate the prevalence and antibacterial resistance patterns for *Shigella* subgroup (A-D) in pediatric and adult patients. For example, in Thailand and United States, *S. sonnei* had the highest prevalence, followed by *S. flexneri* during 1997-2006. Similarly, our comprehensive review showed the *S. sonnei* (54.1%) was a predominant species in Iran during a 20 year period. But other studies in China, Bangladesh, Pakistan, Indonesia, Nepal, and Vietnam documented *S. flexneri* as the foremost species in these regions (33, 41-44). Furthermore, various studies documented the *S. sonnei* and *S. flexneri* outbreaks in Maharashtra, West Bengal, and Kerala (26). In addition, some of the studies showed different antibiotic-resistance patterns for *Shigella* species in Iran and other countries. For instance, according to different reports in Iran, *Shigella* species have a maximum resistance to ampicillin, cotrimoxazole, nalidixic acid, trimethoprim-sulfamethoxazole, cefotaxime, and tetracycline. compared to other countries, resistance to ciprofloxacin, amoxicillin, and cotrimoxazole was detected in *Shigella* species in Pakistan, Bangladesh, Vietnam, and China (33, 42, 43). Some of these antibiotics agents were described in the National Antimicrobial Resistance Monitoring system (NARMS 2015) Report for *Shigella* species. The NARMS introduces *Shigella* as an important MDR phenotype, including resistance to at least ampicillin, trimethoprim-sulfamethoxazole, tetracycline, and sulfisoxazole. These antibiotics and the results from antibiotic resistance are similar to AST platforms performed according to the CLSI in Iranian clinical research. Also, for *Shigella*, fluoroquinolones and macrolides are important agents in the treatment of severe infections (33, 44). Moreover, different studies (for example, in Chandigarh from 2001 to 2009 and Korea from 1991 to 2002) reported a high level of ESBL positive in *Shigella* strains (26, 33, 42-44). Also, in Iran, 11 studies introduced 667 clinical isolates as MDR and ESBLs producing species.

4.1. Some Information About

Shigella infections in Iran is still unknown as follows: prevalence rate, predominant species, and antibacterial

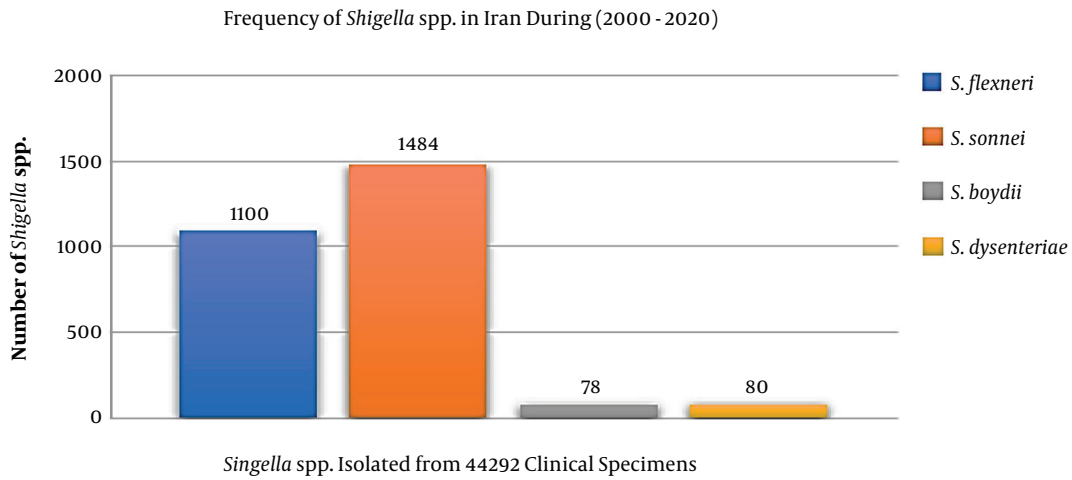

Figure 2. The frequency of the *Shigella dysenteriae* (subgroup A), *Shigella flexeneri* (subgroup B), *Shigella boydii* (subgroup C), and *Shigella sonnei* (subgroup D) in Iran during 2000-2020

Figure 3. The geographic distribution of the prevalence studies for *Shigella* spp. in different provinces of Iran during 2000 -2020

resistant studies from all provinces, role of *Shigella* virulence factors in various infections, and type of experimental treatment of the shigellosis in different provinces. Also, understanding the resistance and susceptibility to different antibiotics for *Shigella* species may assist in revising treatment procedures and develop an active treatment for shigellosis in pediatric and adult patients. In this study, we determined the prevalence of different *Shigella* species,

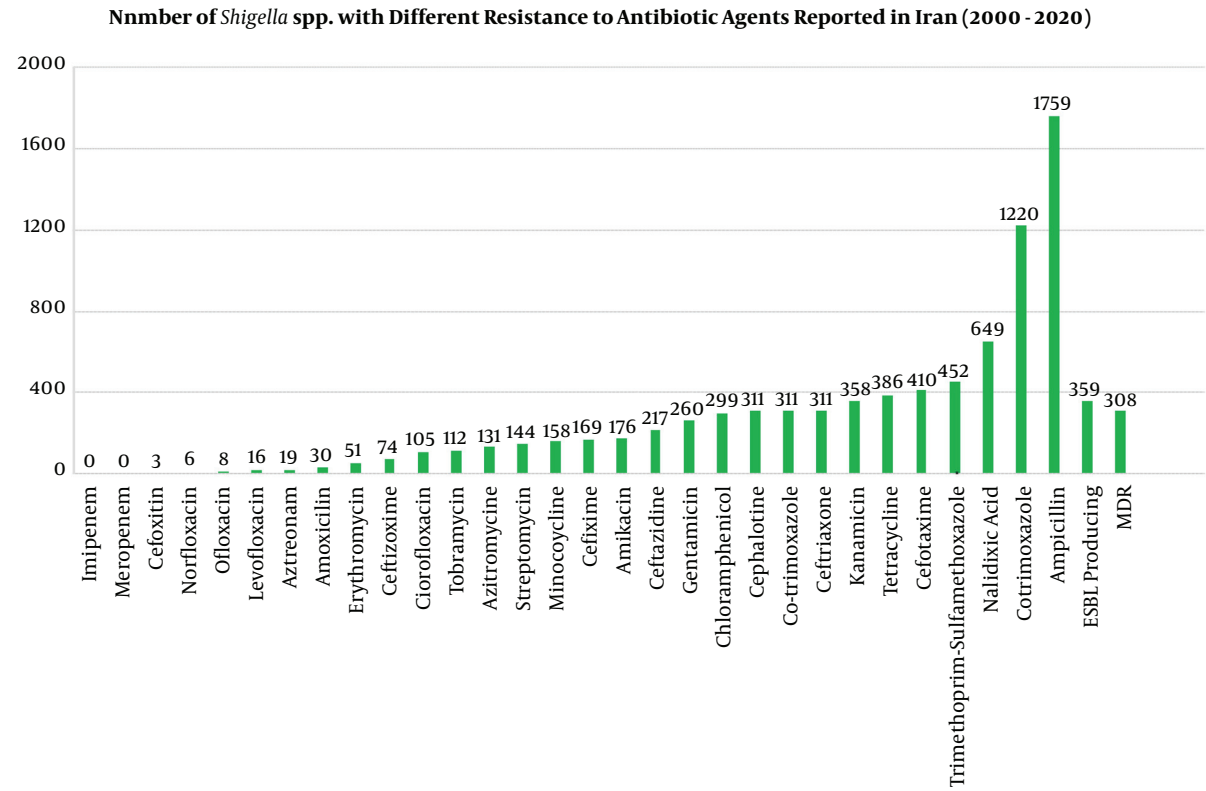

Figure 4. Antibacterial resistant patterns of *Shigella* spp. in Iran during 2000-2020

predominant species, the provinces that have an important role in *Shigella* detections, and the main laboratory diagnostic methods in Iran. We also introduced the maximum and minimum resistance to different types of antibiotics in Iran for 20 years. According to different studies in Iran, it is not possible to conclude the main sources of infection in Iran, the relations between *Shigella* virulence factors in various infections, and the main transmission mechanisms responsible for antibiotic resistance.

5. Conclusions

Evaluation of endemic shigellosis through epidemiological studies is necessary to define the source of infection and promote infection control policies. Future studies in Iran should determine the prevalence, antibiotics resistance rates, sources of infection, virulence factors in various infections, and transmission of the antibiotic resistance mechanisms of *Shigella* spp. in all provinces. This data can be useful to avoid empirical therapy, choose the best antibiotics for effective treatment, and improv public health in human society.

Footnotes

Authors' Contribution: FM did study concept design and writing the first draft of the article. MA, RR, and FM did collection and interpretation of data. NH and ZH did critical revision of the manuscript.

Conflict of Interests: The authors declare that they have no conflict of interests.

Funding/Support: There was no funding or support.

References

1. Jomezadeh N, Babamoradi S, Kalantar E, Javaherizadeh H. Isolation and antibiotic susceptibility of Shigella species from stool samples among hospitalized children in Abadan, Iran. *Gastroenterol Hepatol Bed Bench*. 2014;**7**(4):218–23. [PubMed: 25289136]. [PubMed Central: PMC4185876].
2. Abbasi E, Abtahi H, van Belkum A, Ghaznavi-Rad E. Multidrug-resistant Shigella infection in pediatric patients with diarrhea from central Iran. *Infect Drug Resist*. 2019;**12**:1535–44. doi: 10.2147/IDR.S203654. [PubMed: 31239729]. [PubMed Central: PMC6559769].

3. Aminshahidi M, Arastehfar A, Pouladfar G, Arman E, Fani F. Diarrheagenic Escherichia coli and Shigella with High Rate of Extended-Spectrum Beta-Lactamase Production: Two Predominant Etiological Agents of Acute Diarrhea in Shiraz, Iran. *Microb Drug Resist*. 2017;**23**(8):1037–44. doi: 10.1089/mdr.2017.0204. [PubMed: 29106325]. [PubMed Central: PMC5709696].
4. Nikfar R, Shamsizadeh A, Darbor M, Khaghani S, Moghaddam M. A Study of prevalence of Shigella species and antimicrobial resistance patterns in paediatric medical center, Ahvaz, Iran. *Iran J Microbiol*. 2017;**9**(5):277–83. [PubMed: 29296272]. [PubMed Central: PMC5748446].
5. Ranjbar R, Mirsaeed Ghazi F, Farshad S, Giammanco GM, Aleo A, Owlia P, et al. The occurrence of extended-spectrum beta-lactamase producing Shigella spp. in Tehran, Iran. *Iran J Microbiol*. 2013;**5**(2):108–12. [PubMed: 23825726]. [PubMed Central: PMC3696844].
6. Avakh Majalan P, Hajizade A, Nazarian S, Pourmand MR, Siyavoshani KA. Investigating the Prevalence of Shigella Species and Their Antibiotic Resistance Pattern in Children With Acute Diarrhea Referred to Selected Hospitals in Tehran, Iran. *J Appl Biotechnol Rep*. 2018;**5**(1):70–4. doi: 10.29252/jabr.05.02.06.
7. Yaghoubi S, Ranjbar R, Dallal MMS, Fard SY, Shirazi MH, Mahmoudi M. Profiling of Virulence-associated Factors in Shigella Species Isolated from Acute Pediatric Diarrheal Samples in Tehran, Iran. *Osong Public Health Res Perspect*. 2017;**8**(3):220–6. doi: 10.24171/j.phrp.2017.8.3.09. [PubMed: 28781945]. [PubMed Central: PMC5525559].
8. Karimi-Yazdi M, Ghalavand Z, Shabani M, Houri H, Sadredinamin M, Taheri M, et al. High Rates of Antimicrobial Resistance and Virulence Gene Distribution Among Shigella spp. Isolated from Pediatric Patients in Tehran, Iran. *Infect Drug Resist*. 2020;**13**:485–92. doi: 10.2147/IDR.S238559. [PubMed: 32104018]. [PubMed Central: PMC7025676].
9. Khaghani S, Shamsizadeh A, Nikfar R, Hesami A. Shigella flexneri: a three-year antimicrobial resistance monitoring of isolates in a Children Hospital, Ahvaz, Iran. *Iran J Microbiol*. 2014;**6**(4):225–9. [PubMed: 25802704]. [PubMed Central: PMC4367937].
10. Rahman M, Shoma S, Rashid H, El Arifeen S, Baqui AH, Siddique AK, et al. Increasing spectrum in antimicrobial resistance of Shigella isolates in Bangladesh: resistance to azithromycin and ceftriaxone and decreased susceptibility to ciprofloxacin. *J Health Popul Nutr*. 2007;**25**(2):158–67. [PubMed: 17985817]. [PubMed Central: PMC2753991].
11. Alizadeh-Hesar M, Bakhshi B, Najar-Peerayeh S. Clonal dissemination of a single Shigella sonnei strain among Iranian children during Fall 2012 in Tehran, I.R. Iran. *Infect Genet Evol*. 2015;**34**:260–6. doi: 10.1016/j.meegid.2015.06.024. [PubMed: 26117443].
12. Pourakbari B, Mamishi S, Mashoori N, Mahboobi N, Ashtiani MH, Afsharpaiman S, et al. Frequency and antimicrobial susceptibility of Shigella species isolated in Children Medical Center Hospital, Tehran, Iran, 2001-2006. *Braz J Infect Dis*. 2010;**14**(2):153–7. doi: 10.1590/s1413-86702010000200007. [PubMed: 20563441].
13. Teimourpour R, Babapour B, Esmaelizad M, Arzanlou M, Peeri-Doghaheh H. Molecular characterization of quinolone resistant Shigella spp. isolates from patients in Ardabil, Iran. *Iran J Microbiol*. 2019;**11**(6):496–501. doi: 10.18502/ijm.v11i6.2221.
14. Ranjbar R, Farahani A. Shigella: Antibiotic-Resistance Mechanisms And New Horizons For Treatment. *Infect Drug Resist*. 2019;**12**:3137–67. doi: 10.2147/IDR.S219755. [PubMed: 31632102]. [PubMed Central: PMC6789722].
15. Gharibi O, Zangene S, Mohammadi N, Mirzaei K, Karimi A, Gharibi A, et al. Increasing antimicrobial resistance among Shigella isolates in the Bushehr, Iran. *Pak J Biol Sci*. 2012;**15**(3):156–9. doi: 10.3923/pjbs.2012.156.159. [PubMed: 22866547].
16. Zahedi Bialvaei A, Kafil HS, Asgharzadeh M, Aghazadeh M, Yousefi M. CTX-M extended-spectrum beta-lactamase-producing Klebsiella spp, Salmonella spp, Shigella spp and Escherichia coli isolates in Iranian hospitals. *Braz J Microbiol*. 2016;**47**(3):706–11. doi: 10.1016/j.bjm.2016.04.020. [PubMed: 27268117]. [PubMed Central: PMC4927670].
17. Salimiyan Rizi K, Farsiani H, Sasan MS. High rate of resistance to ceftriaxone and azithromycin among Shigella spp. isolates at three children's referral hospitals in Northeast Iran. *J Infect Chemother*. 2020;**26**(9):955–8. doi: 10.1016/j.jiac.2020.04.022. [PubMed: 32446727].
18. Sheikh AF, Moosavian M, Abdi M, Heidary M, Shahi F, Jomehzadeh N, et al. Prevalence and antimicrobial resistance of Shigella species isolated from diarrheal patients in Ahvaz, southwest Iran. *Infect Drug Resist*. 2019;**12**:249–53. doi: 10.2147/IDR.S187861. [PubMed: 30774392]. [PubMed Central: PMC6348961].
19. Moghanloo E, Khorshidi A, Badameh P, Ghadirian Abarghuei A, Valipour M, Akbari H. Prevalence of Shigella and Other Pathogenic Gram-negative Bacteria in the Patients with Diarrhea in Kashan City, Iran During 2015-2017. *J Hum Environ Health Prom*. 2018;**4**(3):106–10. doi: 10.29252/jhehp.4.3.2.
20. Shahin K, Bouzari M, Komijani M, Wang R. A New Phage Cocktail Against Multidrug, ESBL-Producer Isolates of Shigella sonnei and Shigella flexneri with Highly Efficient Bacteriolytic Activity. *Microb Drug Resist*. 2020;**26**(7):831–41. doi: 10.1089/mdr.2019.0235. [PubMed: 32031907].
21. Beladi Ghannadi S, Ghane M, Babaeekhou L. Determination of Antibiotic Resistance Pattern and frequency of CTX-M, TEM, and SHV Β-Lactamase Encoding Genes among Shigella Isolates from Inpatients in Tehran, Iran. *Med Lab J*. 2019;**13**(2):8–15. doi: 10.29252/mlj.13.2.8.
22. Pour MBMG, Shokoohizadeh L, Navab-Akbar FT. Analysis of clonal relationships among Shigella spp. isolated from children with shigellosis in Ahvaz, Iran. *Arch Adv Biosci*. 2016;**7**(2):45–51.
23. Yousefi M, Dehesh MM, Askarpour S, Saeidi R. A Food Poisoning Outbreak by Shigella boydii in Kerman-Iran. *Arch Clin Infect Dis*. 2018;**13**(6). 82350. doi: 10.5812/archcid.82350.
24. Shokoohizadeh L, Kaydani GA, Ekrami A. Molecular characterization of Shigella spp. isolates from a pediatric hospital in Southwestern Iran. *Gastroenterol Hepatol Bed Bench*. 2017;**10**(4):319–22. [PubMed: 29379598]. [PubMed Central: PMC5758741].
25. Soltan Dallal MM, Eghbal M, Sharafianpour A, Zolfaghari MR, Yazdi MKS. Prevalence and multiple drug resistance of Shigella sonnei isolated from diarrheal stool of children. *J Med Bacteriol*. 2015;**4**(3-4):24–9.
26. Hosseini Nave H, Mansouri S, Sadeghi A, Moradi M. Molecular diagnosis and anti-microbial resistance patterns among Shigella spp. isolated from patients with diarrhea. *Gastroenterol Hepatol Bed Bench*. 2016;**9**(3):205–10. [PubMed: 27458513]. [PubMed Central: PMC4947135].
27. Talebreza A, Memariani M, Memariani H, Shirazi MH, Eghbali Shamsabad P, Bakhtiari M. Prevalence and Antibiotic Susceptibility of Shigella Species Isolated From Pediatric Patients in Tehran. *Arch Pediatr Infect Dis*. 2015;**4**(1). doi: 10.5812/pedinfect.32395.
28. Nodeh Farahani N, Masjedian Jazi F, Nikmanesh B, Asadolahi P, Sadeghi Kalani B, Amirmozafari N. Prevalence and antibiotic susceptibility patterns of salmonella and shigella species isolated from pediatric diarrhea in Tehran. *Arch Pediatr Infect Dis*. 2018;**6**(4). 57328. doi: 10.5812/pedinfect.57328.
29. Mostafavi N, Bighamian M, Mobasherizade S, Kelishadi R. Resistance of Shigella strains to extended-spectrum cephalosporins in Isfahan province. *Med J Islam Repub Iran*. 2016;**30**:428. [PubMed: 28210593]. [PubMed Central: PMC5307619].
30. Zahedi Bialvaei A, Pourlak T, Aghamali M, Asgharzadeh M, Gholizadeh P, Kafil HS. The Prevalence of CTX-M-15 Extended-spectrum beta-Lactamases Among Salmonella spp. and Shigella spp. Isolated from three Iranian Hospitals. *Eur J Microbiol Immunol (Bp)*. 2017;**7**(2):133–7. doi: 10.1556/1886.2017.00004. [PubMed: 28690880]. [PubMed Central: PMC5495085].
31. Esmaeili Dooki MR, Rajabnia R, Barari Sawadkohi R, Mosaiebnia Gatabi Z, Poornasrollah M, Mirzapour M. Bacterial entropathogens and antimicrobial susceptibility in children with acute diarrhea in

Babol, Iran. *Caspian J Intern Med*. 2014;**5**(1):30–4. [PubMed: 24490011]. [PubMed Central: PMC3894468].
32. Ranjbar R, Mirsaeed Ghazi F. Antibiotic sensitivity patterns and molecular typing of Shigella sonnei strains using ERIC-PCR. *Iran J Public Health*. 2013;**42**(10):1151.
33. Ranjbar R, Memariani M. Multilocus variable-number tandem-repeat analysis for genotyping of Shigella sonnei strains isolated from pediatric patients. *Gastroenterol Hepatol Bed Bench*. 2015;**8**(3):225–32. [PubMed: 26328045]. [PubMed Central: PMC4553163].
34. Dibaj R, Aslani MM, Heidarieh P, Hashemi A, Ataei B, Daei-Naser A, et al. Conventional and molecular investigation of Shigella isolates in relation to an outbreak in the area of Isfahan, Iran. *Iran J Microbiol*. 2013;**5**(4):339–44. [PubMed: 25848502]. [PubMed Central: PMC4385158].
35. Soltan Dallal MM, Ghahremani R, Akhavan SA, Rajabi Z. Frequency, Antimicrobial Resistance and Serotyping of Shigella-Contaminted Food Samples in Foodborne Disease Outbreaks in Iran. *SJSPH*. 2019;**17**(2):110–20.
36. Farshad S, Ranjbar R, Hosseini M. Molecular Genotyping of Shigella sonnei Strains Isolated From Children With Bloody Diarrhea Using Pulsed Field Gel Electrophoresis on the Total Genome and PCR-RFLP of IpaH and IpaBCD Genes. *Jundishapur J Microbiol*. 2015;**8**(1). e14004. doi: 10.5812/jjm.14004. [PubMed: 25789126]. [PubMed Central: PMC4350046].
37. Samie A, Guerrant RL, Barrett L, Bessong PO, Igumbor EO, Obi CL. Prevalence of intestinal parasitic and bacterial pathogens in diarrhoeal and non-diarroeal human stools from Vhembe district, South Africa. *J Health Popul Nutr*. 2009;**27**(6):739–45. doi: 10.3329/jhpn.v27i6.4325. [PubMed: 20099757]. [PubMed Central: PMC2928113].
38. Cunningham SA, Sloan LM, Nyre LM, Vetter EA, Mandrekar J, Patel R. Three-hour molecular detection of Campylobacter, Salmonella, Yersinia, and Shigella species in feces with accuracy as high as that of culture. *J Clin Microbiol*. 2010;**48**(8):2929–33. doi: 10.1128/JCM.00339-10. [PubMed: 20519461]. [PubMed Central: PMC2916566].
39. Sur D, Ramamurthy T, Deen J, Bhattacharya SK. Shigellosis : challenges & management issues. *Indian J Med Res*. 2004;**120**(5):454–62. [PubMed: 15591629].
40. Muthuirulandi Sethuvel DP, Devanga Ragupathi NK, Anandan S, Veeraraghavan B. Update on: Shigella new serogroups/serotypes and their antimicrobial resistance. *Lett Appl Microbiol*. 2017;**64**(1):8–18. doi: 10.1111/lam.12690. [PubMed: 27783408].
41. Gupta A, Polyak CS, Bishop RD, Sobel J, Mintz ED. Laboratory-confirmed shigellosis in the United States, 1989-2002: epidemiologic trends and patterns. *Clin Infect Dis*. 2004;**38**(10):1372–7. doi: 10.1086/386326. [PubMed: 15156473].
42. von Seidlein L, Kim DR, Ali M, Lee H, Wang X, Thiem VD, et al. A multicentre study of Shigella diarrhoea in six Asian countries: disease burden, clinical manifestations, and microbiology. *PLoS Med*. 2006;**3**(9). e353. doi: 10.1371/journal.pmed.0030353. [PubMed: 16968124]. [PubMed Central: PMC1564174].
43. Chompook P, Samosornsuk S, von Seidlein L, Jitsanguansuk S, Sirima N, Sudjai S, et al. Estimating the burden of shigellosis in Thailand: 36-month population-based surveillance study. *Bull World Health Organ*. 2005;**83**(10):739–46. [PubMed: 16283050]. [PubMed Central: PMC2626425].
44. CDC. *National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Human Isolates Surveillance Report for 2015 (Final Report)*. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC; 2018. Available from: http://wwwn.cdc.gov/narmsnow.