Review

Antimicrobial resistance pattern of Shigella species isolated from human stool in Asia: A systematic review

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Review

Antimicrobial Resistance Pattern of Shigella Species Isolated from Human Stool in Asia: A Systematic Review

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Abstract

Background: Shigella species are Gram-negative bacteria responsible for bacillary dysentery, particularly affecting children in low-income countries. The species are highly infectious and are primarily transmitted through contaminated food and water. Treatment typically involves antibiotics, but the rise of multidrug-resistant (MDR) Shigella strains has made management challenging. Methods: A comprehensive literature search was performed using PubMed and Google Scholar to identify studies on the prevalence of Shigella species and its antimicrobial resistance in Asia from 2000 to 2022. Results: The prevalence of Shigella varied widely, ranging from 1.31% to 40.34% in analysis of 25 studies. Among the four Shigella species, *S. flexneri* emerged as the most prevalent, accounting for 51.38% of isolates (n=6062/11797). *S. boydii* was the least encountered species, constituting only 1.5% of cases. Ampicillin resistance was high with rates exceeding 80% in eight studies. Tetracycline resistance exceeded 80% in nine out of 15 studies. Cotrimoxazole resistance was also very high with 15 studies showing rates over 80%. Chloramphenicol resistance was less common, with eight of 11 studies showing over 50% susceptibility. Gentamycin resistance was low, with 11 of 12 studies showing over 50% susceptibility. Ciprofloxacin low resistance with 100% susceptibility in five studies. Ceftriaxone resistance was also minimal. Conclusions: This systematic review highlights high burden of Shigella infection in Asia and significant drug resistance to tetracycline, ampicillin, nalidixic acid, and cotrimoxazole. Urgent actions include proper antibiotic use, and conducting clinical trials to develop effective management guidelines for Shigella infections is to be considered.

Keywords: Shigella; human stool; antimicrobial resistance; asia

Introduction

Shigella species are Gram-negative, rod-shaped, non-spore-forming, facultative anaerobic bacteria belonging to the family Enterobacteriaceae [1]. These bacteria are the primary causative agents of bacillary dysentery in humans, leading to diarrhea and dysentery [1]. *Shigella* species are categorized into serotypes and subserotypes based on the O-antigen present in the lipopolysaccharide of their cell envelope. This classification includes serogroup A (*S. dysenteriae*): 15 serotypes and 2 provisional serotypes, serogroup B (*S. flexneri*): 6 serotypes and 16 subserotypes, serogroup C (*S. boydii*): 20 serotypes, serogroup D (*S. sonnei*): 1 serotype [2]. In 1897, Kiyoshi Shiga, a Japanese scientist, first identified *S. dysenteriae*, a highly virulent strain producing exotoxins [3]. Globally, *S. flexneri* is the leading cause of diarrhea, particularly endemic in low- and middle-income countries, particularly 2a, 3a, 1a, 6, and 1b, are predominant in Asian countries [1,6].

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Shigellosis, caused by the human pathogen *Shigella spp.*, is a global health concern, disproportionately affecting chiefly the children below 5 years in low-income countries [4,5]. Notably, *Shigella* exhibits high transmissibility, requiring a low infectious dose of only 10-100 bacteria to cause illness, primarily spread through the fecal-oral route [3,5]. Transmission occurs through contaminated food, water, fomites, or direct contact with infected individuals [3] Sexual transmission, particularly among men who have sex with men, has also been reported [5]. Several outbreaks have been associated with consuming contaminated food and water, particularly foods that are manually handled, minimally processed, or eaten raw [7]. The clinical symptoms of shigellosis encompass a spectrum from mild watery diarrhoea to bloddy,mucoid diarrhoea accompanied by painful abdominal cramps and fever [10].

In shigellosis, the treatment approach depends on the severity of the disease. For mild symptoms, the focus is on hydration and electrolyte management due to water loss. In severe cases, especially for immunocompromised individuals, antibiotics are prescribed to shorten symptoms and reduce infection spread [13,17]. Antimicrobial resistance has complicated shigellosis treatment since the 1940s, starting with sulfonamide resistance in Japan [13]. Over the decades, Shigella developed resistance to tetracycline, chloramphenicol, and ampicillin, leading to the use of co-trimoxazole. However, by the mid-1980s, resistance to co-trimoxazole also emerged, drastically reducing its effectiveness [13]. Shigella spp. acquires drug resistance through several mechanisms: reducing the permeability of its outer membrane, actively pumping out drugs via efflux systems, enhancing the production of enzymes that inactivate or modify drugs, and altering drug targets through mutations. The rise of multidrug-resistant (MDR). Shigella strains and the progression of the disease have made case management more challenging [11]. Various factors, including geographic location, time period, class of antimicrobial usage, and the specific agents used, serotype of bacteria can influence the susceptibility patterns of Shigella [14,15].

The growing prevalence of multidrug resistance (MDR). to existing drugs, the lack of effective vaccines, the increasing global incidence, and the high rates of infection in vulnerable populations all highlight the need for this review.Despite the high prevalence of shigellosis, summary data on *Shigella* species are very few from Asia. Also the resistance pattern of bacteria may changes with time revealing resistance to newer drugs too. Therefore, this reviewer focused on prevalence and antimicrobial-resistant features of *Shigella* species in Asia from 2000 to 2023.

Methodology

Literature Search

The systematic review was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). guidelines [16]. A comprehensive literature search was conducted on the prevalence of *shigella* species and its antimicrobial resistance pattern among Asian population.Potentially relevant studies were identified through a computerized search using databases of PubMed and Google Scholar.The search was based on the combination of the following special index search terms (medical subject headings (MeSH). and Boolean operations: "*Shigella* "OR "Shigellosis" "OR "Bacillary Dysentery AND "Prevalence "OR "Epidemiology" AND ('Drug Resistance' OR 'antimicrobial Resistance' OR 'Antibiotic resistance'" OR antimicrobial susceptibility AND "Asia" in the title,abstract or keywords fields.Published in the English language, onwards from 2000 AD till dated 2022 AD. The records found through database searching were combined and the duplicates were removed using Covidence.The study initially screened all unique published articles based on title and abstract and further filtered out by reviewing full articles considering inclusion and exclusion criteria.This systematic review was exempt from Institutional Review Board review and was not registered.

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Inclusion Criteria

1. An article published in English from Asia, dating from 2000 AD to 2023 AD.
2. Shigella isolates only from human stool
3. Mentioned total number of Shigella isolates and antibiotic resistance/susceptible percentage of bacteria.
4. Study design been cohort study, cross sectional or hospital surveillance.

Exclusion Criteria

1. Studies having Shigella isolates from animal, or poultry origin.
2. Shigella isolates other than human stool like food, water sources and other environmental in origin.
3. Published between 2000AD and 2023 AD , language other than English , population included outside Asia
4. Study design been case report, case series and reviews, conference abstract
5. Resistance rates were not recorded

Data Extraction

The data extraction was done by two researcher (GB and AA). independently from included studies using a standardized and pretested format prepared in Microsoft Excel. A detailed review of each article was done to gather information about the first author, year of publication, enrollment time, country, type of study, population characteristics(percentage of male and female), age group of study participants, total stool sample, number of Shigella isolates, number and prevalence of different serogroups of Shigella, AST methods and resistance pattern of Shigella in eight different antibiotics including Ampicillin, tetracycline, cotrimoxazole, chloramphenicol, nalidixic acid, gentamycin, ciprofloxacin and ceftriaxone. The information was recorded in google sheet. Two researchers, AA and GB, performed data extractions separately to negotiate any possible errors. Disagreement on data extractions between researchers were resolved through discussion and consensus. The extracted data were checked at least twice for their accuracy.

Results

Study Selection

After conducting a comprehensive database search, 731 articles were initially retrieved. Following the removal of duplicates, 608 articles remained for further analysis. Subsequently, 482 papers were excluded during title and abstract screening due to non-compliance with inclusion criteria. The full text of the remaining 126 articles was obtained. Among these, 101 were rejected as they did not contain relevant findings. Ultimately, 25 articles were included in the review for our research paper. (Figure 1)

Study Characteristics

In this study, total 25 studies across different age groups were reviewed qualitatively. Among these studies, 19 were cross-sectional study, while 5 are surveillance. The primary countries represented were Iran (5 studies), China (4 studies), and India (4 studies). Additionally, 8 studies were conducted in the WHO Eastern Mediterranean region (including Iran, Pakistan, and Yemen), 7 in the WHO South-East Asia region (including Nepal and India), and 7 in the WHO Western Pacific region (including China, Malaysia, and South Korea). Two studies originated from Turkey. Notably, all the studies were hospital-based; no community-based research was included. The publication

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timeline spanned from 2001 to 2022, with enrollment occurring between 1999 and 2021.A detailed description of the characteristics of individual studies is provided in Table 1.

Table 1. Study Information.

Author	Country	WHO region	Enrollment Time	Published Year	Type of study	Age group included	Male%	Female%	Total Stool Sample	Number of Shigella Isolates
Tariq [17]	Pakistan	Eastern Mediterranean	2009-2010	2012	Cross sectional	NR	NR	NR	2500	95
Zhang [18]	china	Western Pacific	2006-2012	2015	Cross sectional	2-90 years	NR	NR	NR	2226
Chang [19]	China	Western Pacific	2004-2014	2016	Surveillance	All age group. 31.47% in under 5.More in child below 1	66	35	70802	6278
Maharjan [20]	Nepal	South East	2014	2017	Cross sectional	15-90.More in 15-30	56	54	640	29
Banajeh [21]	Yemen	Eastern Mediterranean	1998	2001	Cross sectional	1-60 month	NR	NR	561	37
Gharibi [22]	Iran	Eastern Mediterranean	2002-2008	2012	Cross sectional	NR	NR	NR	NR	121
SalimiyanRizi [23]	Iran	Eastern Mediterranean	2018-2019	2020	Cross sectional	Less than 14	NR	NR	233	94

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Saran [24]	Turkey	European Region	2008-2009	2013	Cross sectional	NR	NR	NR	NR	60
Mamishi [25]	Iran	Eastern Mediterranean	2021	2022	Cross sectional	1-16 yrs	51	49	7121	183
Taneja [26]	India	South East	2015-2019	2021	Retrospective	9 month to 78 years.34.3% in Child below 5	60	40	10456	137
Shakya [27]	Nepal	South East	2003-2007	2016	Surveillance	All age.24.5% Child below 10	More in male	Less		332
Zafar [28]	Pakistan	Eastern Mediterranean	2002-2003	2005	Cross sectional	NR	NR	NR	4688	193
Özmert [29]	Turkey	European Region	2003-2009	2011	Cross sectional	5-202 months(16.8 yrs).More in child under 5	57	43	14803	238
Srinivasa [30]	India	South East	2002-2007	2009	Cross sectional	All age.41.8% in child under 14 and 52.2% in adult	More	Less	2941	134
MoezArdalan [31]	Iran	Eastern Mediterranean	2001-2002	2003	Cross sectional	NR	NR	NR	734	123

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Dhital [32]	Nepal	South East	2014	2017	Cross sectional	Child under 5	NR	NR	717	15
Salmanzadeh-Ahrabi [33]	Iran	Eastern Mediterranean	2003-2005	2007	Cross sectional	NR	NR	NR	1350	155
Dutta [34]	India	South East	1995-2000	2002	Surveillance	Child under 5	NR	NR	2855	166
Karacan [35]	Turkey	European Region	2002	2007	Cross sectional	Range 1-16 Mean 4.83	57	43		198
Mamatha [36]	India	South East	2001-2006	2012	Cross sectional	NR	NR	NR	2100	77
Yang [37]	China	Western Pacific	2005-2011	2013	Surveillance	3month to 92 year.Median age 4.More common in child under 4	53	47		308
Gu [38]	China	Western Pacific	2002-2011	2017	Surveillance	NR	NR	NR		340
Koh [39]	Malaysia	Western Pacific	2007-2009	2012	Cross sectional	NR	NR	NR		70
Chuang [40]	Taiwan	Western Pacific	2001-2002	2006	Cross sectional	0-16 yrs included.Mean age 6.1	51	49		122
Jin [41]	South Korea	Western Pacific	1999-2008	2010	Cross Sectional	NR	NR	NR	NR	66

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Outcome

- **Population Demographics**

In our comprehensive review, we analyzed studies spanning various age groups. In 5 studies they had included people of all age group. Notably, 3 studies exclusively focused on children under five years, while 4 studies included children under 16 years. Age groups were unspecified in 10 studies. In most of the studies in which age distribution of disease were given, the prevalence of Shigella infection is more in children under 5 years. For instance, Taneja et al [40]. study in Indian population reported a prevalence of 34.3% in this age group. Similarly, Chang et al's [19]. surveillance study in China found 31.47% prevalence in children under 5, with an even higher incidence in those below 1 year. Additionally, 8 studies recorded gender-specific data, consistently revealing a male predominance of over 50% in all these studies.

- **Shigella Distribution**

Across 25 comprehensive studies, a total of **11,797** Shigella species were isolated (Table 2).

Table 2. Shigella Species Distribution.

Author	Number of Shigella Isolates	% of Shigella	*S.dysentriae %*	*No.S.dysentrie*	*S. flexneri %*	*No.S.flexeri*	*S. sonnei %*	*No.S.sonnei*	*S. boydii %*	*No.S.boydii*	*Unidentified*	AST Method
Tariq	95	3.8	29	28	49	47	13	12	9	8	0	Disc Diffusion
Zhang	2226	13.1	0	0	36	802	63.9	1424	0	0	0	Disc Diffusion
Chang	6278	8.87	0.61	38	63.86	4009	34.89	2191	0.63	40	0	Agar Dilution
Maharjan	29	4.5	10	3	59	17	8	8	3	1	0	Disc Diffusion
Banajeh	37	6.6	18	7	34	13	8	3	20	4	10	Disc Diffusion

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Gharibi	121	0	1	5	38	46	51	62	16	8	0	Disc Diffusion
SalimiyanRizi	94	40.34	1	1	23.4	22	70.2	66	0	0	5	Disc Diffusion
Saran	60	0	1.6	1	16.6	10	81.6	49	0	0	0	Disc Diffusion
Mamishi	183	2.5	0	0	30	55	70	128	0	0	0	Disc Diffusion
Taneja	137	1.31	0.7	1	63.5	87	8.8	12	6.6	9	28	Disc Diffusion
Shakya	332	0	28.6	95	50	166	27.54	34	6.6	15	22	Disc Diffusion
Zafar	193	4.1	11	21	58	112	16	31	15	29	0	Disc Diffusion
Özmert	238	1.6	0	0	10.5	25	87.8	209	1.7	4	0	Disc Diffusion
Srinivasa	134	4.6	3.7	7	64.9	87	21.6	29	8.2	11	0	Disc Diffusion
MoezArdalan	123	16.8	15	19	45	55	31	38	9	11	0	Disc Diffusion
Dhital	15	2	0	0	80	12	20	3	0	0	0	Disc Diffusion
Salmanzadeh-Ahrabi	155	11.5	4.5	7	30.8	48	55.1	85	9.6	15	0	Disc Diffusion
Dutta	166	5.8	5	8	58	96	28	47	9	15	0	Disc diffusion
Karacan	198	0	5.1	10	10.1	20	83.3	165	1.5	3	0	Disc Diffusion

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Yang	77	3.7	1.3	1	94.8	73	3.9	3	0	0	0	Disc Diffusion
Gu	308	0	0.9	3	84.4	260	13	40	0.7	5	0	Agar Dilution
Koh	340	0	0	0	0	0	All	340	0	0	0	Disc Diffusion
Chuang	70	0	0	0	0	0	All	70	0	0	0	Disc Diffusion
Mamatha	122	0	0	0	0	0	All	122	0	0	0	Disc Diffusion
Jin	66	0	0	0	0	0	All	66	0	0	0	Disc Diffusion

These samples were collected from patients presenting with symptoms such as diarrhea and other gastrointestinal issues. Total number of stool sample was reported in 15 studies ranged from 70802 in Chang et al to 233 in SalimiyanRizi et al. The prevalence of Shigella varied widely, ranged from 1.31% to 40.34%. In 9 studies we identified that the Shigella isolates from human stool sample was less than 5%.

Among the four Shigella species, *S. flexneri* emerged as the most prevalent, accounting for an impressive 51.38% (6062/11797). of isolates. Remarkably, in 10 studies, *S. flexneri* prevalence exceeded 50%. Conversely, S. boydii was the least encountered species, constituting a mere 1.5% of cases (178/11,797). Intriguingly, six studies reported no S. boydii isolates at all. *Shigella sonnei*, a common cause of shigellosis, represented 44.39% of cases (5237/11,797). and *S.dysenteriae* 2.1%(255/11797). Additionally, total 65 species were unclassified Shigella species.

- **Antimicrobial Resistance**

The antibiotic-resistance information for Shigella species in different countries of Asia was studied against 8 most common antibiotic agents during 2000-2022 (Table 3). .

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Table 3. Antimicrobial Resistance Pattern.

Author	Number of Shigella Isolates	Ampicillin %	Tetracycline %	Cotrimoxazole %	Chloramphenicol %	Nalidixic acid %	Gentamycin %	Ciprofloxacin%	Ceftriaxone%
Tariq	95	97	94	97	73	66	17	13	20
Zhang	2226	87	79	79	27	98	56	11	0
Chang	6278	89	88	0	0	89	34	22	0
Maharjan	29	58	0	55	7	76	0	52	0
Banajeh	38	0	0	84	52	19	48	0	0
Gharibi	121	0	93	86	0	12	0	4.3	0
SalimiyanRizi	94	57	0	83	0	16	27	3.8	44
Saran	60	27	68	92	0	0	0	0	0
Mamishi	183	96	0	96	0	64	2	18	0
Taneja	137	68	71	76	21	0	7.6	62	45
Shakya	332	88	0	76	0	80	0	39	0
Zafar	193	56	0	88	0	39	0	0	0
Özmert	238	36	0	70	0	4.7	0	0	0
Srinivasa	134	55	0	81	43	62	0	21	0
MoezArdalan	123	0	74	70	0	1	0	3.1	2

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Dhital	15	0	80	67	0	80	0	67	6.7
Salmanzadeh -Ahrabi	155	81	99	94	28	2.6	0	0	0
Dutta	166	67	92	96	46	29	3	4	0
Karacan	198	14	0	90	0	0	0	0	2
Yang	308	93	91	81	76	96	39	28	27
Gu	340	68	74	69	0	75	36	0	0
Koh	70	10	40	38	10	2.5	0	0	0
Chuang	122	32	0	98	0	98	0	0	27
Mamatha	77	100	84	90	0	100	0	87	2.5
Jin	66	41	94	95	0	65	9	0	1.5

In 23 studies AST was done by disc diffusion method and in only 2 it was done by agar dilution method.

Ampicillin

Among 25 studies,ampicillin resistance was recorded in 21 studies.One study noted a 100% resistance rate among all Shigella species. In eight studies, resistance levels exceeded 80%, while only six studies showed susceptibility rates above 50%. Notably, one study reported a resistance rate as low as 10%

Tetracycline

Tetracycline resistance was investigated in 15 studies.In 9 different studies,the resistance was more than 80%.The resistance pattern of tetracycline ranged from 98.7% to 40%.Only 2 out of 9 studies reported the susceptibility of more than 50%.

Cotrimoxazole

Cotrimoxazole resistance was recorded in 24 out of 25 studies. Fifteen studies revealed resistance rates exceeding 80%, with overall resistance ranging from 37.5% to 97.5%. Except for one study, none showed susceptibility rates above 50%

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Chloramphenicol

The resistance to chloramphenicol was investigated in 11 studies.One study reported of 100% susceptibility to chloramphenicol and 8 revealed the susceptibility of more than 50% whereas 2 study reported the resistance of more than 70%.

Nalidixic Acid

Most studies (22 out of 25). reported antimicrobial resistance to nalidixic acid. One study found a 100% resistance rate among all Shigella species. Seven studies reported resistance rates higher than 80%, while one study showed a minimal resistance rate of 1%. Only eight studies indicated susceptibility rates above 50%

Gentamycin

Only 12 studies reported the resistance of Shigella to gentamycin.11 studies showed the susceptibility to gentamycin of more than 50% .The resistance pattern ranged from 56.3% in one study to no resistance at all in one study.

Ciprofloxacin

20 out of 25 studies reported the resistance to ciprofloxacin.5 studies revealed 100% susceptibility of ciprofloxacin in all Shigella species and 11 studies showed resistance of less than 20%.Only four studies reported the resistance of more than 50% to ciprofloxacin.

Ceftriaxone

The resistance of Shigella to ceftriaxone was reported in 13 studies.3 studies revealed no resistance of ceftriaxone to Shigella.9 out of 13 studies showed resistance of less than 20%.The maximum resistance recorded was 45.2% in one study.Only 2 studies showed the resistance of more than 30%.

Most *Shigella* species isolates tested sensitive for gentamycin ciprofloxacin and ceftriaxone. Even though the reports varied in research locations and times, *Shigella* species were resistant to tetracycline, ampicillin,chloramphenicol, and co-trimoxazole.

Discussion

This review analyzed the distribution of Shigella serogroups and antimicrobial resistance patterns, based on data from 25 eligible studies conducted in Asia. The infection caused by this pathogen can be highly life-threatening for infants and children under five years old It has been estimated that approximately 188 million individuals worldwide contract shigellosis each year with 1 million deaths annually [42]. In Asia alone, it is estimated that there are 125 million infections and 14,000 deaths due to shigellosis annually [43]. The burden of disease is exacerbated by multiple serotypes that contribute to repeated infections. While immunity develops with age, shigellosis remains a significant risk for travelers in endemic areas, often manifesting as persistent diarrhea.Changing patterns of antimicrobial susceptibilities among *Shigella* isolates pose major difficulties in selecting an appropriate drug for the treatment of shigellosis [12].

According to the review and meta-analysis conducted by Basilua Andre Muzembo among five South Asian countries, Shigella flexneri was the most prevalent serogroup, accounting for 58% of the isolates, followed by Shigella sonnei at 19% [44]. In our study, we found a similar pattern, with Shigella flexneri being the most prevalent, representing 51.38% of the isolates, followed by Shigella sonnei at 44.39%. It has been documented that while Shigella flexneri remains the dominant serogroup in underdeveloped countries, its prevalence is declining in many rapidly developing and developed nations. In contrast, Shigella sonnei is on the rise in these rapidly developing and developed regions.This statement is further validated by a study conducted in United states(1999-

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2002)in which Shigella sonnei accounted for 71.7%, Shigella flexneri accounted for 18.4% [45].Such shift in prevalence has also been noted in some asian countries as in a study conducted in southern Vietnam [46].There was a significant species shift from *S. flexneri* to *S. sonnei* between period (1995-1996). (29% *S. sonnei*). and period (2007-2008). (78% *S. sonnei*). with an approximate 1:1 ratio of *S. flexneri* to *S. sonnei* in the intermediate period (2000-2002).

This systematic review highlights significant variability in antimicrobial resistance patterns in Shigella species across different antibiotics. Ampicillin resistance was notably high, with several studies showing rates exceeding 80%, and some even reaching 100%. Tetracycline resistance was also prevalent, with rates over 80% in some studies. Co-trimoxazole resistance was reported in many studies, with 15 showing resistance rates above 80%. Chloramphenicol resistance varied significantly, with some studies showing high susceptibility rates and others showing high resistance. Nalidixic acid resistance was similarly high, with one study reporting 100% resistance and several others reporting over 80% resistance.

This result is consistent with the findings of Andaman Islands study (2000–2011). in which 100%the shigella isolates were resistance to ampicillin [47]. Another article from China (2010). states 85.4% of shigella isolates were resistant to ampicillin [48].These findings align with a previous review on antimicrobial resistance patterns of *Shigella* species in Africa, Asia, and South America (2001–2014), which noted that most studies from Africa and Asia demonstrated significant resistance to tetracycline, chloramphenicol, and co-trimoxazole among *Shigella* serogroups [49]. Additionally, a multicenter study conducted in six Asian countries revealed high resistance rates to ampicillin and co-trimoxazole across all sites, while resistance to nalidixic acid varied widely: 100% of *S. flexneri* and 98% of *S. sonnei* strains in China were resistant, compared to 75% of *S. sonnei* and 48% of *S. flexneri* strains in Bangladesh, with little or no resistance reported at other sites [50].

The World Health Organization (WHO). guidelines for treating Shigella and dysentery, first issued in 2005 and updated in 2013, recommend ciprofloxacin as the primary treatment [14]. The advised dosage is 15 mg/kg for children and 500 mg for adults, taken twice daily for three days and azithromycin and ceftriaxone are suggested as second line drugs [12]. The guidelines also stated that ceftriaxone and pivmecillinam (amdinocillin pivoxil). are "the only antimicrobials that are usually effective for the treatment of multi-resistant strains of Shigella in all age groups," but their use is restricted due to their expensive formulation (parenteral administration for ceftriaxone, and four times daily dosing for pivmecillinam). As a result, ciprofloxacin-resistant local strains of Shigella were the only circumstances in which pivmecillinam and ceftriaxone were approved for usage.

In our study also the resistance of shigella against ciprofloxacin is relatively low in most studies. Out of 25 studies, 20 reported some level of resistance to ciprofloxacin. However, five studies found 100% susceptibility, meaning no resistance was observed in those cases. In 11 studies, resistance rates were less than 20%, suggesting ciprofloxacin remains largely effective. Only four studies reported higher resistance rates, with over 50% of *Shigella* strains showing resistance. This suggests that while resistance is emerging in some areas, ciprofloxacin is still generally effective against *Shigella* in most regions. Also, resistance of *Shigella* to ceftriaxone was generally low, with most studies showing minimal resistance and only a few reporting higher levels.

Although ,A systematic review examined the evolving resistance patterns to ciprofloxacin in the Asia–Africa regions (combined). and found a significant rise in resistance, increasing from 0.6% (95% CI 0.2–1.3%). in 1998–2000 to 29.1% (95% CI 0.9–74.8%). in 2007–2009. This represents a 49-fold increase over 12 years [51]. In another review they conducted between 1999 and 2012, They found a significant increase in ceftriaxone resistance in asia africa region rising from 0.83% (1998-2000) to 14.2% (95% CI 3.9–29.4%). by 2012(52). Ceftriaxone may not be suitable for treating shigellosis in Asia-Africa, according to the authors' conclusion.

A 2013 systematic review examined 48 high-quality randomized controlled trials, mostly conducted in low- and middle-income countries (LMICs). The review showed that following the current WHO treatment guidelines using ciprofloxacin, pivmecillinam, or ceftriaxone reduced clinical failure rates by 82% (95% CI 67–99%). It also found that these treatments successfully

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eliminated *Shigella* pathogens in 96% of cases (95% CI 88–99%). The authors concluded that there is strong evidence supporting the effectiveness of these antimicrobial guidelines in reducing serious morbidity and mortality [53]. However, a study conducted in Bangalore between 2002 and 2007 found that while all shigella isolates were sensitive to ciprofloxacin between 2002 and 2004, the resistance pattern gradually increased up to 48% over the course of the year [54]. As a result, the author concluded that ciprofloxacin cannot be used to treat shigellosis. In another study done in Iran ,ciprofloxacin resistance among shigella isolates were found to be 73%.

Given the research highlighting rising resistance to ciprofloxacin and ceftriaxone, a review of international literature was conducted to explore alternative antimicrobials for the treatment of *Shigella* dysentery.In our review , only 12 studies found resistance to gentamycin and 11 reported over 50% susceptibility suggesting it could be effective against Shigella. In contrast,Global patterns of aminoglycoside resistance in Shigella (from 1999 to 2010). were evaluated in a 2013 comprehensive review, which also showed rising levels of in vitro gentamicin resistance in the Asia–Africa area, reaching 32.4% in 2005–2007 [55]. The 2010 Cochrane study confirmed aminoglycosides' inefficacy, as they typically have poor oral absorption, thus reducing their utility [56].

Azithromycin, a macrolide antibiotic, is recommended as an alternative second-line treatment for adults in both current WHO guidelines and most international guidelines.In earlier (1995-1996) study done in Dhaka [57], azithromycin was effective in the treatment of adult men with moderate to severe shigellosis with clinical rate of cure (82% [CI, 70% to 95%]). and the bacteriologic rate of cure (94% [CI, 80% to 99%]).By 2010/11,azithromycin susceptibility was still 74% [58]. More recently, there have been growing reports of Shigella strains resistant to azithromycin, including documentation by the Centers for Disease Control and Prevention (CDC) [59]. In areas where ciprofloxacin-resistance is evident, azithromycin can be an appropriate second-line alternative therapy owing to its oral administration and affordability [60].

The World Health Organization (WHO). guideline that recommends ciprofloxacin as a first-line treatment and ceftriaxone, pivmecillinam, and azithromycin as alternatives remains effective in many regions but many studies have depicted their inefficacy owing to to rising resistance rates. The global rise in antibiotic resistance presents a significant challenge to managing infectious diseases, and WHO has classified it as a critical issue. The drug resistance pattern in a country typically reflects how effective the current treatment plans are for various diseases and helps guide future strategies. To address the global challenge of antimicrobial resistance and limit its spread, constant monitoring of susceptibility patterns is necessary. It is for selection of appropriate antimicrobial agents for therapy when indicated.

This growing resistance demands the urgent development of new antibiotics and strategies to preserve the effectiveness of existing ones. Evidence suggests that antibiotic prescribing contributes to resistance not only on a societal scale but also at the individual patient level, making this information crucial for clinicians [61]. In light of the rapid development of multi-drug resistance, focusing on vaccine development against the most common Shigella strains could offer a promising alternative. It is essential to carefully monitor any changes in the prevalence of serotypes and resistance patterns of Shigella strains in different regions to adapt treatment strategies accordingly [47].

Conclusions

This review study suggests that the current treatment mechanism might not be addressing the full burden of *Shigella*-associated mortality in Asia. The pooled estimate provides high burden of *Shigella* infection and its high proportion of drug resistance pattern to tetracycline, ampicillin, chloramphenicol, and cotrimoxazole in Asia. Clinicians should continue to aggressively aware shigellosis, particularly vulnerable children with diarrhea, such as those younger than 5 years or identification and treatment of *Shigella* infection which might be life-saving. As a result, initiating and scaling-up drug susceptibility testing for each shigellosis case, educating the community and health care providers on appropriate antibiotic use, and conducting clinical trials are all urgently needed to

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List of abbreviations

AMR-Antimicrobial Resistance

MDR-Multi Drug Resistance

WHO-World Health Organization

CDC-Centre for Disease Prevention and Control

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