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Microbiology Section

Drug Resistance in *Shigella*: A Cross-sectional Study from a Tertiary Care Centre in North Kerala, India

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ABSTRACT

Introduction: Shigellosis is an important cause of diarrhoeal mortality among children under five years. Even though shigellosis is mostly a self-limiting disease, antibiotics can attenuate the duration and severity of illness. However, drug resistance in *Shigella* is emerging as a significant public health problem. The choice of antimicrobial therapy for shigellosis should be made after accounting for local Antimicrobial Resistance (AMR) data.

Aim: To analyse the pattern of *Shigella* infection including clinical profile, treatment, common species causing shigellosis, and their antimicrobial susceptibility pattern.

Materials and Methods: This was a cross-sectional study conducted at Government Medical College, Kozhikode, Kerala, India from December 2017 to May 2019. A total of 60 *Shigella* isolates obtained from 1,646 stool samples of patients with suspected shigellosis were included in the study. Cultures were processed using standard microbiological methods. Identification was done using various biochemical tests and confirmed with agglutination using specific antiserum, followed by antimicrobial susceptibility testing using the Kirby-Bauer disc diffusion method and E-test. Multiplex Polymerase Chain Reaction (PCR) was done for every isolate to detect the presence of resistance genes. Culture-positive *Shigella* cases were evaluated for relevant demographic, clinical, therapeutic and microbiological variables.

Results: A total of 60 isolates (3.64%) were obtained from 1,646 stool samples during the study period. Out of 60 isolates, 51 (85%) were *Shigella sonnei*, 9 (15%) were *Shigella flexneri* and 41 (68.33%) isolates were Multidrug Resistant (MDR was defined as resistance to at least one agent in three or more antimicrobial classes). Third-generation cephalosporins were given for treatment in most cases. Ceftriaxone was resistant in 23 (38.3%) isolates and cotrimoxazole in 50 (83.3%) isolates. The commonest betalactamase gene identified was $bla_{CTX\text{-}M\text{-}1}$ in 23 (38.3%) isolates. Among the genes responsible for resistance to cotrimoxazole, *dhfr1A* was the predominant one in 51 (85%) isolates and in fluoroquinolone resistance, *qnrB* was present in six isolates (10%).

Conclusion: For tracking of AMR, especially regional monitoring among *Shigella* isolates is needed, since there is an emergence of multidrug resistance. Meropenem or azithromycin can be used as an alternative for the treatment of ceftriaxone-resistant shigellosis. Empirical therapy should be initiated in all shigellosis cases, and it should be based on the local antibiogram of *Shigella* isolates available.

Keywords: Antibacterial agents, Bacillary, Beta-lactam resistance, Dysentery, Genes

INTRODUCTION

Shigella species is an important cause of diarrhoea in children below five years [1]. Children are the highest risk group for shigellosis. However, it also affects some other groups, such as persons in custodial organisations, homeless persons, and Men having Sex with Men (MSM) [2]. There are four known species of this pathogen- *S. dysenteriae, S. flexneri, S. sonnei* and *S. boydii* [1]. Even though all four species can cause the disease, *S. flexneri* is the commonest species causing shigellosis in developing countries and *S. sonnei* in developed countries [3]. However, the prevalence of *S. sonnei* is reportedly increasing in developing countries [1,3]. Though the reason for this rising dominance of *S. sonnei* is not clear, the proposed reasons are, firstly, improving water quality, which prevents natural passive immunisation with the bacterium *Plesiomonas shigelloides* against *S. sonnei*. Secondly, *Acanthamoeba castellanii*, which has been shown to phagocytise *S. sonnei* efficiently and symbiotically, thus allowing the bacteria access to a protected niche in which to withstand chlorination and other harsh environmental conditions. Thirdly, the global spread of *S. sonnei* from Europe is aided by a strong selective pressure from localised antimicrobial use [4].

Shigellosis is a highly contagious disease due to its low infectious dose and high transmission in areas with crowding and poor sanitary conditions, making it an important agent of traveller's diarrhoea [5]. As per the World Health Organisation (WHO) recommendations, all cases of bloody diarrhoea should be treated promptly with an antimicrobial that is known to be effective against *Shigella* to reduce the risk of complications, duration of sickness and mortality and also reduce the risk of transmission to susceptible contacts [2].

Sulphonamides were the first drugs of choice for shigellosis when introduced in the early 1940s. In the late 1940s, sulphonamides became ineffective, and tetracycline, followed by chloramphenicol was recommended for shigellosis. Soon, resistance to both these drugs was also observed, and ampicillin and co-trimoxazole became the first-line drugs for treatment [5]. When resistance to both these drugs was reported during the 1980s, nalidixic acid was introduced. Later, resistance to nalidixic acid was reported in isolates from the Tripura outbreak in 1988 [6]. Then, fluoroquinolones succeeded as an effective treatment option for shigellosis. Following the higher incidence of fluoroquinolone resistance, cephalosporins were used to treat shigellosis. The first isolate showing ceftriaxone resistance was obtained in 2001, and an increase in the number of isolates resistant to third-generation cephalosporins was observed from 2005 onwards [5]. Currently, Centers for Disease Control and Prevention (CDC) recommends ciprofloxacin, ceftriaxone or azithromycin as the first-line options [7]. Concurrently, WHO advocate pivmecillinam, ceftriaxone and azithromycin as alternative drugs for ciprofloxacin-resistant infections [8]. Studies are being conducted to determine the resistance pattern of *Shigella* strains [2]. The rise of antibiotic-resistant enteric bacteria, particularly *Shigella*, has made the prevention of infectious diarrhoea and the need for an effective vaccine an even greater public health priority [9].

To know the local pattern of *Shigella* infection, which includes the commonest group of *Shigella* causing infection, and the antimicrobial susceptibility pattern, is important for the effective treatment of shigellosis. Considering the fact that our country is endemic for *Shigella* infections, it is important to study the above-mentioned factors [5]. Because regional research on this topic is scarce [5], this study targets to fill a significant gap in the literature.

This study aimed at the characterisation of *Shigella* isolates obtained in the clinical microbiological laboratory of a tertiary care centre in north Kerala, India.

MATERIALS AND METHODS

This was a cross-sectional study conducted at Government Medical College, Kozhikode, Kerala, India from December 2017 to May 2019. The study commenced after obtaining approval from the Institutional Ethics Committee (IEC) vide letter no: GMCKKD/RP2017/IEC/213.

Sample size calculation: The sample size for this study was calculated using the formula:

$N= (Z^2 \times pq) \div d^2$,

where, N is the required sample size, Z is the confidence level at 95% confidence interval (1.96), p is the prevalence of Shigella (3.8%, according to a previous study) [10], q is the complement of p (96.2%), and d is the desired precision (5%). Applying these values to the formula, the sample size calculated was 56 and finalised as 60.

Inclusion criteria: Stool samples from all inpatients, outpatients, and Intensive Care Unit (ICU) patients presenting with acute diarrhoea or dysentery were included in the study.

Exclusion criteria: Duplicate isolates from the same patient were excluded from the study.

Study Procedure

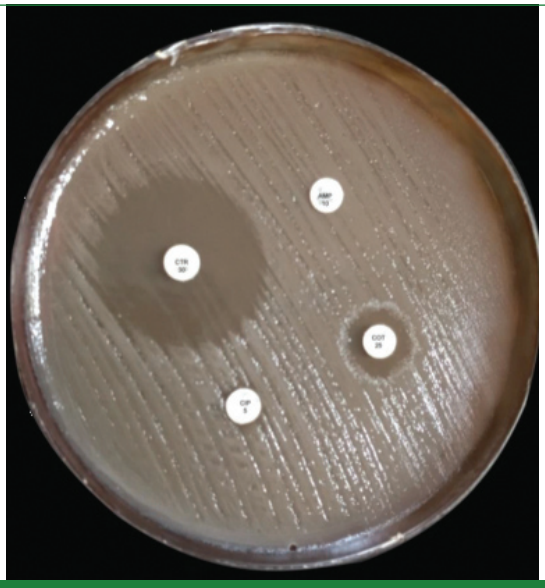
Stool samples from the patients with diarrhoea or dysentery were cultured onto MacConkey agar, Xylose Lysine Deoxycholate agar (XLD) and Selenite F broth after microscopic examination. After six hours, the Selenite F broth was subcultured onto MacConkey agar and XLD agar. All media were incubated at 37°C for 18 to 24 hours. After incubation, MacConkey agar plates were examined for non lactose fermenting colonies and XLD plates were examined for pink colonies. Such colonies were picked up for further identification.

Catalase test and oxidase tests were performed initially. Catalase-positive and oxidase-negative isolates were further processed. The isolates were identified by standard biochemical tests: indole test, triple sugar iron test and mannitol motility test, 1% carbohydrate fermentation with glucose, lactose, sucrose and mannitol, and amino acid decarboxylation tests. The isolates, which were biochemically identified as *Shigella*, were subjected to a slide agglutination test using polyvalent antisera (DENKA SEIKEN CO., Ltd., Japan) for each of the four groups. A positive agglutination test confirmed the identification of the organism.

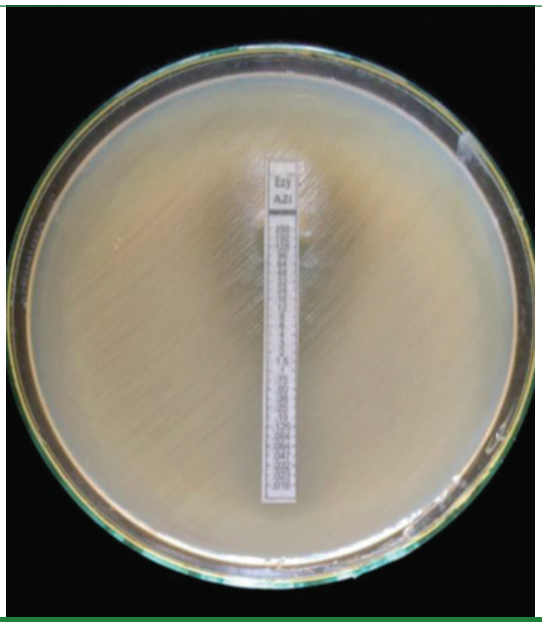
Antimicrobial susceptibility testing was done by Kirby-Bauer disc diffusion method according to Clinical and Laboratory Standards Institute (CLSI) M02 guidelines [11] using ampicillin (10 µg), ciprofloxacin (5 µg), cotrimoxazole (1.25/23.75 µg) and ceftriaxone (30 µg) discs [Table/Fig-1]. *Escherichia coli* ATCC 25922 was used as quality control strain.

For *Shigella sonnei* isolates which were resistant to ampicillin, cotrimoxazole and ciprofloxacin, the minimal inhibitory concentration of azithromycin was determined using E-test [Table/Fig-2]. Azithromycin E-test was performed and interpreted using CLSI M100 guidelines [12] for these *S. sonnei* isolates only and not for all isolates.

For *Shigella flexneri* isolates, the disc diffusion method was performed for azithromycin susceptibility testing. The results were interpreted using CLSI M100 guidelines [12]. The pattern of combination of drug resistance in MDR *Shigella* isolates were analysed like ampicillin- cotrimoxazole- ciprofloxacin- ceftriaxone and other combinations. Genomic DNA was extracted with the QIAamp DNA mini kit (Qiagen, Hilden, Germany). The presence of β-lactamase genes (bla_{OXA}, bla_{TEM}), ESC genes $bla_{CTX\text{-}M\text{-}1}$, AmpC ($bla_{MOX}$, bla_{CIT}, bla_{DHA}, bla_{ACC}, bla_{EBC} and bla_{FOX}), trimethoprim resistance gene (*dhfr1a*), sulphonamide resistance gene (*sulII*) and Plasmid-Mediated Quinolone Resistance (PMQR) (*qnrA, qnrB, qnrS*) genes were assessed by PCR as described earlier.



[Table/Fig-1]: Antimicrobial susceptibility testing performed in cation-adjusted Mueller-Hinton agar by Kirby-Bauer disc diffusion method.



[Table/Fig-2]: E-Test for azithromycin performed in cation-adjusted Mueller-Hinton Agar.

STATISTICAL ANALYSIS

The data were entered in Microsoft Excel, and results were expressed in terms of frequency and percentage.

RESULTS

A total of 60 (3.64%) isolates obtained from 1,646 stool samples of patients with suspected shigellosis were processed during the study period. Out of 60 isolates, 51 (85%) were *Shigella sonnei* and 9 (15%) were *Shigella flexneri,* and 68.33% (41 isolates) were MDR. Out of the 60 patients from whom *Shigella* was isolated, the majority were children ≤5 years 31 (51.7%), followed by children in the 6-12-year age group 20 (33.3%), adults were only 9 (15%). About 55 (91.7%) of patients needed inpatient care, whereas 5 (8.3%) of patients were treated on an outpatient basis. Out of the 55 patients who were admitted, 11 (20%) were treated in ICU, and

44 (80%) were treated in the wards. An average of three days of hospital stay was needed for the inpatients.

The majority of the patients 41 (68.3%) had only gastrointestinal symptoms such as abdominal pain, diarrhoea or dysentery with or without fever and dehydration. However, some of the patients presented with features of *Shigella* encephalopathy 19 (31.7%).

For the treatment of shigellosis, ceftriaxone and cefixime (both are third generation cephalosporins) were the commonest drugs used (given for 59 patients- 98.3%). The details of antibiotics given for shigellosis cases are summarised in [Table/Fig-3].

Antibiotic given	N (%)
Cefixime	32 (53.3)
Ceftriaxone	25 (41.67)
Ciprofloxacin	1 (1.67)
Ceftriaxone and ciprofloxacin	1 (1.67)
Ceftriaxone followed by azithromycin	1 (1.67)

[Table/Fig-3]: Antibiotics given to Shigellosis cases.

One patient received combination therapy with ceftriaxone and ciprofloxacin and another patient was given azithromycin after three days of ceftriaxone therapy. No deaths were reported in the study and all patients recovered following the antibiotic and supportive therapy.

The resistance pattern of *Shigella* isolates shows a high degree of resistance against ampicillin, cotrimoxazole, and ciprofloxacin among both species of *Shigella* isolated [Table/Fig-4].

	S. sonnei (n=51)	*S. flexneri* (n=9)	Total isolates (n=60)
Antibiotics	N (%)	N (%)	N (%)
Ampicillin	36 (70.6)	8 (88.9)	44 (73.3)
Cotrimoxazole (Trimethoprim-sulfamethoxazole)	45 (88.2)	5 (55.6)	50 (83.3)
Ciprofloxacin	48 (94.1)	9 (100)	57 (95)
Ceftriaxone	18 (35.3)	5 (55.6)	23 (38.3)

[Table/Fig-4]: Resistance pattern of *shigella* isolates by disc diffusion (N=60).

Shigella sonnei isolates, which were resistant to ampicillin, cotrimoxazole and ciprofloxacin, were 30 in number. These were tested for azithromycin MIC using the E-test. Only one was sensitive, two were intermediate, and the remaining 27 were resistant (90%). Among the *S. flexneri* isolates, azithromycin was resistant in 8/9 isolates by disc diffusion (88.9%).

The resistance pattern of MDR *Shigella* isolates (n=41) is shown in [Table/Fig-5].

Resistance pattern	*S. sonnei* (Total=34) N (%)	*S. flexneri* (Total=7) N (%)
Ampi- Co- Cip- Ceftri	11 (32.3)	2 (28.6)
Ampi- Co- Cip	19 (55.9)	2 (28.6)
Ampi- Co- Ceftri	2 (5.9)	-
Ampi- Cip- Ceftri	1 (2.9)	3 (42.9)
Co- Cip- Ceftri	1 (2.9)	-

[Table/Fig-5]: Pattern of drug resistance in MDR *Shigella*.

The AMR genes detected in the *Shigella* isolates by multiplex PCR [Table/Fig-6]. The distribution of genes showed that, *dhfr1A* was predominant (85%, 51 isolates) among genes responsible for cotrimoxazole resistance, while *qnrB* was the fluoroquinolone resistance gene detected in six isolates (10%).

In this study, $bla_{CTX-M-1}$ was the commonest β-lactamase gene identified in 23 isolates (38.3%) [Table/Fig-7].

S. No.	Organism	Resistance genes	S. No.	Organism	Resistance genes
1	*S. sonnei*	*dhfr1A, sul2*, DHA	31	*S. sonnei*	*dhfr1A*, $bla_{CTX-M-1}$
2	*S. sonnei*	*dhfr1A, sul2*, $bla_{CTX-M-1}$	32	*S. sonnei*	*dhfr1A*, TEM, DHA, *qnrB*
3	*S. sonnei*	No resistance genes identified	33	*S. sonnei*	*dhfr1A, qnrB*
4	*S. sonnei*	*dhfr1A, sul2*	34	*S. sonnei*	*dhfr1A*
5	*S. sonnei*	*dhfr1A, qnrB, DHA*	35	*S. sonnei*	*dhfr1A, TEM*
6	*S. sonnei*	*dhfr1A, DHA*	36	*S. sonnei*	*dhfr1A*
7	*S. sonnei*	*dhfr1A*	37	*S. sonnei*	*dhfr1A*
8	*S. sonnei*	*dhfr1A, sul2, TEM*	38	*S. sonnei*	*dhfr1A, sul2*
9	*S. sonnei*	*sul2*, $bla_{CTX-M-1}$	39	*S. sonnei*	*dhfr1A, sul2*
10	*S. sonnei*	*dhfr1A*, $bla_{CTX-M-1}$	40	*S. sonnei*	*dhfr1A*
11	*S. sonnei*	*dhfr1A, sul2*, $bla_{CTX-M-1}$	41	*S. sonnei*	*dhfr1A*
12	*S. sonnei*	*dhfr1A, sul2*, $bla_{CTX-M-1}$	42	*S. sonnei*	No resistance genes
13	*S. sonnei*	*dhfr1A*, $bla_{CTX-M-1}$	43	*S. sonnei*	*dhfr1A*, $bla_{CTX-M-1}$
14	*S. sonnei*	*dhfr1A*	44	*S. sonnei*	*sul2*, $bla_{CTX-M-1}$
15	*S. sonnei*	*dhfr1A, sul2*	45	*S. sonnei*	*dhfr1A, ACC*
16	*S. sonnei*	*dhfr1A*	46	*S. sonnei*	*dhfr1A, sul2*
17	*S. sonnei*	*dhfr1A*, $bla_{CTX-M-1}$	47	*S. sonnei*	$bla_{CTX-M-1}$, *blaDHA*
18	*S. sonnei*	*dhfr1A, sul2*	48	*S. sonnei*	*dhfr1A*, $bla_{CTX-M-1}$
19	*S. sonnei*	*dhfr1A, blaCTX-M-1*	49	*S. sonnei*	*dhfr1A*
20	*S. sonnei*	*dhfr1A, sul2*, $bla_{CTX-M-1}$, *qnrB*	50	*S. sonnei*	*dhfr1A*
21	*S. sonnei*	*dhfr1A, sul2, qnrB*	51	*S. sonnei*	*dhfr1A*
22	*S. sonnei*	*dhfr1A, sul2*, $bla_{CTX-M-1}$	52	*S. flexneri*	*TEM, DHA*
23	*S. sonnei*	*dhfr1A, sul2*, $bla_{CTX-M-1}$	53	*S. flexneri*	No resistance genes
24	*S. sonnei*	*dhfr1A*, bla_{CMY}	54	*S. flexneri*	*sul2*, $bla_{CTX-M-1}$, *qnrB*
25	*S. sonnei*	*dhfr1A*, $bla_{CTX-M-1}$	55	*S. flexneri*	*sul2*, $bla_{CTX-M-1}$, *qnrS*
26	*S. sonnei*	*dhfr1A, sul2*, $bla_{CTX-M-1}$	56	*S. flexneri*	*dhfr1A, sul2*
27	*S. sonnei*	*dhfr1A, sul2*	57	*S. flexneri*	*dhfr1A*, $bla_{CTX-M-1}$
28	*S. sonnei*	*dhfr1A*, $bla_{CTX-M-1}$	58	*S. flexneri*	*dhfr1A*
29	*S. sonnei*	*dhfr1A*	59	*S. flexneri*	*dhfr1A, qnrS*
30	*S. sonnei*	*dhfr1A*	60	*S. flexneri*	*dhfr1A*, $bla_{CTX-M-1}$

[Table/Fig-6]: Antimicrobial Resistance (AMR) genes detected in the *Shigella* isolates.

Betalactamase gene	No. of isolates (%)
$bla_{CTX-M-1}$	23 (38.3)
bla_{DHA}	6 (10)
bla_{TEM}	3 (5)
bla_{CMY}	1 (1.7)
bla_{ACC}	1 (1.7)

[Table/Fig-7]: Distribution of β-lactamase genes.

DISCUSSION

In the current study, the number of *S. sonnei* (51/60, 85%) was much higher than the number of *S. flexneri* (9/60, 15%) isolated. Some of the previous studies from India reports *S. flexneri* as the common serotype [13-15]. However, findings consistent with this work had been reported previously from Kerala, which reported *S. sonnei* as the commonest serogroup (62.5%) [16]. Certain studies

with comparable findings had been reported from other developing countries like Iran and Iraq, where 57% and 55.8% was *S. sonnei*, respectively [17,18]. Gradually increasing trends were reported in the yearly isolation rates of *S. sonnei* in a study from South India [1]. Similar to this study finding, *Shigella* infection is common in children less than five years of age [5,17]. With proper hydration, shigellosis is usually self-limited. However, severe cases can lead to mortality. In a contemporary study from our institute by Jayakrishnan MP et al., with a protracted study period, 26% mortality was reported among children who were positive for either *Shigella* PCR or culture [19]. Nevertheless, the present study did not report any mortality.

MDR *Shigella* is already reported from various parts of the world [20-22]. In this study, among all the *Shigella* isolates, high resistance was seen among ampicillin (73.3%), cotrimoxazole (83.3%) and ciprofloxacin (95%). Also, 41 isolates (68.3%) were MDR. A similar pattern was observed for cotrimoxazole (91.6%) and ciprofloxacin (85.4%) and a lower resistance for ampicillin (60.4%) in a previous study from Kerala [16]. Some studies from Kolkata [14] and Delhi [23,24] report lower resistance to ampicillin (54-60%) and varying resistance to ciprofloxacin (53-83%) and cotrimoxazole (65-93%). At the same time, the annual report of the AMR surveillance network, Indian Council of Medical Research (ICMR) reports an increasing susceptibility to cotrimoxazole over the years 2017-2023 and decreasing susceptibility to ampicillin [15]. A study from Iran reported lower resistance to ciprofloxacin (7.69%) but comparable resistance rates for ampicillin and cotrimoxazole (61.5% for both) [17].

Escalating resistance to third-generation cephalosporins is a great concern in the current times, especially since it is the first-line drug for shigellosis in areas where ciprofloxacin resistance is high. In this study, overall ceftriaxone resistance was 38.3%; 35.3% for *S. sonnei* and 55.6% for *S. flexneri*. Higher resistance rates were reported in a previous study from South India [1], where cefotaxime resistance rates were 67% for *S.sonnei* and 43% for *S. flexneri*. In the previous study from Kerala [16], ceftriaxone resistance reported was 17%. Studies from Kolkata report low levels of resistance (6%) [5], but increasing trends in resistance [14]. Research articles from various parts of the country report varying resistance rates to 3rd generation cephalosporins from 8-9% [25] to rates up 50% [15,23,26,27]. Decreased susceptibility to azithromycin is another regard that is reinforced by the current study, in which azithromycin resistance was 89.7%. Zhang C et al., report 20.4% isolates with decreased susceptibility [28] in China. It is interesting to note that Baumgart S et al., reports 71.4% resistance to azithromycin in resource-rich settings [21], while the ICMR AMR surveillance network reports 83.3% susceptibility to azithromycin for *S.flexneri* isolates [15] in India. However, the majority of the Asian countries have developed high resistance rates to azithromycin according to the review article by Salleh MZ et al., [20].

The commonest betalactamase gene detected in this study was CTX-M-1 (38.3%), which was the same as reported by Anandan S et al., from South India [1]. However, Sethuvel DPM et al., from same region reported blaOXA and blaTEM as the commonest genes [13]. Taneja N et al., reports blaTEM and $bla_{CTX\text{-}M\text{-}15}$ to be the commonest betalactamase genes [5]. CTX-M-type β-lactamases contain at least 40 enzymes, and these can be readily transferred among *Shigella* isolates by conjugative plasmids [29]. *Shigella* producing CTX-M ESBL have been previously reported from various countries [2]. The finding of a high prevalence of ESBL producing genes which spread by horizontal transfer and/or mobilisation of genetic mobile elements by orofaecal route, has serious implications in terms of further spread of resistance to third generation cephalosporins to other regions [5]. The presence of dfrA1 genes among *Shigella* isolates is the main mechanism of trimethoprim resistance [29] and in the current study, 85% isolates had this gene. sul2 gene mediating sulphonamide resistance was present in 22 isolates (36.7%). Similar observations were reported by Sethuvel DPM et al., from Vellore [13]. These genes associated with drug resistance in *Shigella* has been reported from different parts of the world [29]. PMQRs namely qnr genes is the main reason for resistance to quinolones among *Shigella* isolates, and they are usually associated with transposable or mobile elements on plasmids [29]. Although *qnrB* is the commonest *qnr* gene in this study (6 out of 60), the low frequency precludes the generalisability of this observation. Thomas S et al., had reported *gyrA* and *parC* gene mutations [chromosomal genes] causing fluoroquinolone resistance in *Shigella* from Kerala [30]. Asad A et al., from Bangladesh reports the presence of both chromosomal gene (*gyrA* and *parC*) mutations and transferable genes (*qnrA, B, S*) in their isolates [31].

It is to be noted that there was a set of isolates in this study that were phenotypically sensitive organisms, but had resistance genes in their genome, which indicates non expression of AMR genes. Also, some of them were phenotypically resistant but negative for the targeted genes. This might be because of other mechanisms responsible for resistance [13]. Even though MDR *Shigella* infections are associated with mortality, this study did not report any associated mortality. This may be due to the self-limiting nature of the infection.

Limitation(s)

The present study had some limitations. Firstly, the small sample size of this study may limit the generalisability of the findings. Especially the number of *S. flexneri* isolates being only nine, arriving at statistical conclusions is difficult. Secondly, financial considerations necessitated a selective approach to azithromycin MIC testing among the isolates. Therefore, MIC determination was prioritised for *Shigella sonnei* isolates displaying resistance to ampicillin, cotrimoxazole and ciprofloxacin. This has affected the comparison of azithromycin resistance levels between the two species accurately. Furthermore, alternative resistance mechanisms, such as efflux pump or other genetic variants may have contributed to the resistant phenotype but were beyond the diagnostic scope of the current study.

CONCLUSION(S)

The study underscores the escalating threat of AMR in *Shigella*. Resistance to multiple therapeutic options can lead to lethal complications in shigellosis cases. The emergence of MDR *Shigella* necessitates robust regional monitoring to effectively track AMR trends. Empirical management of shigellosis should be tailored to the resistance profiles found in local antibiograms. In cases of ceftriaxone resistance, meropenem and azithromycin may be considered as alternative options based on susceptibility patterns. Significant reductions in infection rates are achievable through the successful development and implementation of vaccines.

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