

Prevalence of Multiple Antibiotic Resistance Among *Salmonella* Isolates from Clinical Samples in Dhaka, Bangladesh

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Abstract

Objectives: Antibiotic resistance in clinical isolates is often correlated to poor disease management or prolonged hospitalization. The study aimed to determine the prevalence of multidrug-resistant *Salmonella* isolates in clinical samples collected from Dhaka, Bangladesh.

Methods: One hundred *Salmonella* isolates were obtained from 150 clinical samples. All isolates were tested against 12 antibiotics belonging to 9 different classes such as cephalosporins, carbapenems and fluoroquinolones to analyze their susceptibility pattern by Kirby- Bauer disk diffusion method on Mueller Hinton agar.

Results: *Salmonella* isolates were classified as multidrug-resistant and extensively drug-resistant based on resistance patterns against different antibiotics. The highest percentage of resistance was observed against penicillin-G (96%), cefuroxime (75%), and clindamycin (71%). The isolates exhibited 33% and 43% resistance against imipenem and meropenem respectively. Sixty percent of the isolates were sensitive to gentamicin and norfloxacin. Approximately 98% of isolates exhibited multidrug resistance. Twenty-three percent of the isolates were resistant to five classes of antibiotics, and 18% to six classes of antibiotics. Moreover, 20% of the isolates exhibited extensive drug resistance. Among the cell wall synthesis inhibitors, the highest resistance was recorded against penicillin G (31%), whereas the carbapenem group accounted for the maximum sensitivity (62%). Resistance rates varied between 20%-30% against protein synthesis inhibitors, which included clindamycin (29%), tetracycline (20%), and chloramphenicol (20%). Ninety percent of the *Salmonella* isolates showed multiple antibiotic resistance index ≥ 0.3 , whereas ≥ 0.5 was observed in 65% of the isolates.

Conclusions: The high prevalence of multidrug-resistant *Salmonella* isolates in clinical samples from Bangladesh indicates a serious threat to public health. Our findings emphasize the urgent need to control multidrug resistance through the appropriate use of antibiotics and public awareness.

Keywords: Multiple Antibiotic Resistance, MAR Index, Salmonella, Extensive Drug Resistance.

Introduction

The global rise of antibiotic resistance in recent years has given rise to resistant bacteria capable of causing life-threatening infections. The challenge is greater for a less developed country where antibiotics are widely misused and needlessly prescribed.¹ As a significant percentage of the population in Bangladesh does not have access to clean drinking water, *Salmonella* infections are highly prevalent.² The widespread occurrence of diseases caused by *Salmonella* requires frequent use of antibiotics. However, due to the rise of multidrug-resistant (MDR) species, commonly used antibiotics fail to combat infections.^{3,4} Evaluating the clinical efficacy of the available antibiotics is

critical to ensure adequate treatment of *Salmonella* infections. Therefore, it is important to determine the prevalence of antibiotic resistance among *Salmonella* species against the commonly used antibiotics.

Salmonella is one of the most common bacterial pathogens responsible for causing salmonellosis, typhoid fever, gastroenteritis and bacteremia.⁵ More than 2700 serotypes of *Salmonella* have been identified.⁶ Enteric infections caused by *Salmonella* are responsible for causing approximately 4500 deaths each year in Bangladesh.⁷ Chloramphenicol was used as a first-line therapy for the treatment of *Salmonella* infections. However, the emergence of resistance against chloramphenicol, as reported in numerous studies, limited its use.⁴⁻⁶ In a study carried out in Chattogram, Bangladesh,⁴ it was found that typhoid patients were not responsive to ciprofloxacin which is used as a second-line therapy. This indicates that the emergence of MDR *Salmonella* species is a serious public health concern that limits the therapeutic choices for the treatment. Antibiotic resistance is generally developed in *Salmonella* strains through mutations in chromosomal genes and plasmids. The transmission of the genes is promoted significantly by horizontal gene transfer.⁸ One of the main reasons behind the rapid emergence of MDR is the frequent and irrational use of antibiotics for prevention, treatment, and metaphylaxis.⁹ In a study carried out in southern rural Bangladesh, it was found that around 44% of doctors prescribe antibiotics without a clinical diagnosis.⁴ Another factor that significantly contributes to the rise in antibiotic resistance is the lack of patient adherence, as most patients do not understand the implications of incomplete doses.¹⁰ Also, the uncontrolled use of prophylactic antibiotics in animals for food production vastly contributes to the development of antibiotic resistance.¹¹

Infectious diseases in Bangladesh resulted in a high rate of mortality and morbidity due to the lack of statistics and comprehensive data on antibiotic resistance patterns which results in inadequate therapeutic choices for treating infections.⁴ Therefore, this study aimed to identify the prevalence of antibiotic resistance against commonly used antibiotics among *Salmonella* spp. isolated from clinical samples in Dhaka.

Methods

Clinical samples were collected from different diagnostics centers across Dhaka city during February 2023 to July 2023. A total of 150 samples (135 urine, 13 sputum, and 2 tracheal aspirates), collected in a sterile container, were transported to the laboratory and stored at 4°C for further analysis.

Salmonella spp. was isolated from the clinical samples by streak plate method using solidified Xylose- Lysine-Deoxycholate (XLD) agar and *Salmonella-Shigella* (SS) agar media. After incubation at 37°C, the bacterial growth was assessed. *Salmonella* species developed red colonies with a black center on XLD agar plate. In SS agar, non-lactose fermenting, colorless colonies with black centers, were identified as *Salmonella* isolates. The selected colonies were characterized by Gram staining. For standard biochemical assays, the Indole test, Triple Sugar Iron (TSI) test, Urease test, Methyl Red / Voges-Proskauer (MR-VP) test, Oxidase test, and Citrate Utilization test were carried out.^{12,13}

The antibiotic susceptibility test of the isolates was carried out using the Kirby-Bauer Disc Diffusion Method.¹³ The samples were spread on Mueller-Hinton Agar media and the antibiotic discs were placed. All the isolates were tested against 12 commercially available antibiotics which were as follows: tetracycline (30µg), penicillin G (30µg), clindamycin (10µg), meropenem (10µg), azithromycin (30µg), cotrimoxazole (25µg), gentamicin (10 µg), chloramphenicol (30µg), piperacillin (100µg), imipenem (10µg), norfloxacin (10µg), and cefuroxime (30µg). After incubation at 37°C, the diameter of the clear zones around the antibiotic discs was measured and the isolates were categorized as sensitive, intermediate, and resistant according to Clinical Laboratory Standard Institute (CLSI) guidelines.^{13,14} Standard strains were used as a control to validate the results.

The isolates showing resistance to at least three different classes of antibiotics were considered multiple drug resistant (MDR). The presence of extensive drug-resistant (XDR) isolates exhibiting susceptibility to only one or two classes of antibiotics, was also identified. The multiple antibiotic resistance (MAR) index was determined using the formula, "x/y, where 'x' is the number of isolates resistant to antibiotics and 'y' is the total number of antibiotics used" for each of the isolates.

Results

From a total of 150 clinical samples, 100 *Salmonella* isolates were obtained. A single isolate per sample was subjected to antibiotic susceptibility analysis to avoid redundancy or incidence of duplication. Ninety percent of the isolates were from the urine samples, 9% from sputum samples, and 1% from the tracheal aspirate samples.

Gram staining test on the *Salmonella* isolates revealed rod-shaped, pink-colored colonies forming a chain. All the isolates showed a positive citrate test evidenced by alkaline bluish media. A positive triple sugar test was confirmed by a reddish-black slant and yellow butt, and hydrogen sulfide gas was produced. The indole test was negative for the isolates due to the absence of a red-violet ring on the surface of the liquid culture media. The isolates showed a negative result in the Voges-Proskauer (VP) test and a positive result in the Methyl Red (MR) test, as evidenced by the development of a brownish-yellow color and a cherry red color, respectively. All the isolates showed positive results for motility tests. Catalase, oxidase and urease tests for the isolates showed negative results.

The susceptibility of all 100 *Salmonella* isolates was evaluated against 12 different antibiotics and the diameters of the zones of inhibition were measured (Table 1). The isolates were classified as resistant, intermediate resistant, or susceptible to a particular antibiotic using a zone diameter interpretive standards chart. The isolates showed a varying degree of resistance against all 12 antibiotics (Table 2 & Figure 1).

Table 1: Zone of inhibition (mm) obtained against different antibiotics for categorizing the isolates as resistant, intermediate resistant, or susceptible. Results are expressed as mean± SD.

Antibiotics	Resistant	Intermediate	Sensitive
Tetracycline	9.43 ± 0.36	13.38 ± 0.38	18.35±0.46
Penicillin G	9.74 ± 0.43	0	29.41±0.52
Piperacillin	9.71 ± 0.40	0	16.09±0.38
Clindamycin	10.01 ± 0.45	15.15 ± 0.36	21.70±0.40
Meropenem	10.59 ± 0.58	17.27 ± 0.63	23.64 ± 0.57
Imipenem	9.90 ± 0.48	14.23 ± 0.46	19.97 ± 0.49
Azithromycin	10.22 ± 0.47	13.96 ± 0.38	18.64 ± 0.38
Cotrimoxazole	9.23 ± 0.52	13.15 ± 0.60	19.03 ± 0.63
Gentamicin	10.53 ± 0.55	13.50 ± 0.53	18.48 ± 0.55
Chloramphenicol	10.67 ± 0.59	11.85 ± 0.58	22.33 ± 0.58
Norfloxacin	11.45 ± 0.60	14.80 ± 0.83	20.85 ± 0.54
Cefuroxime	12.02 ± 0.58	18.72 ± 0.59	24.30 ± 0.49

Table 2: Antibiotic resistance in *Salmonella* isolates (n=100) against different antibiotics. n –number of isolates.

Antibiotics	Resistant (%)	Intermediate (%)	Sensitive (%)
Tetracycline	50	16	34
Penicillin G	96	0	4
Piperacillin	61	0	39
Clindamycin	71	12	17
Meropenem	43	8	49
Imipenem	33	11	56
Azithromycin	43	17	40
Cotrimoxazole	68	9	23
Gentamicin	32	8	60
Chloramphenicol	50	14	36
Norfloxacin	27	13	60
Cefuroxime	75	4	21

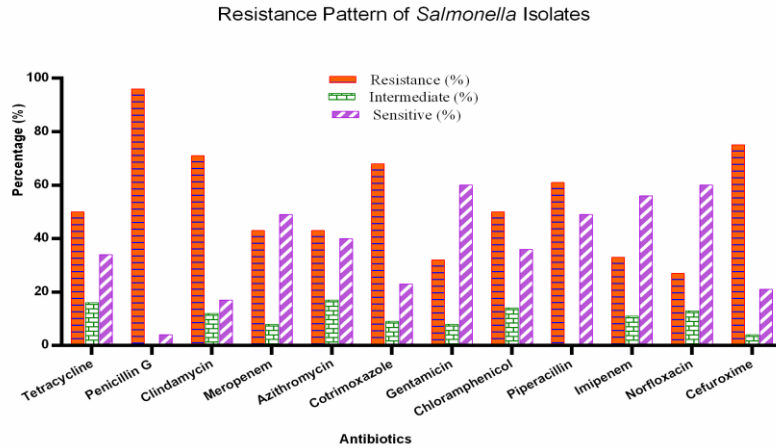


Figure 1: Antibiotic resistance pattern among *Salmonella* isolates.

As shown in Table 2, the highest percentage of resistance was observed against penicillin G (96% isolates) and the lowest against norfloxacin (27%). Followed by penicillin G, a high degree of resistance was recorded against cefuroxime (75%), clindamycin (71%), cotrimoxazole (68%) and piperacillin (61%). Fifty percent of the *Salmonella* isolates were resistant to tetracycline and chloramphenicol. A significantly high degree of resistance was also observed against meropenem (43%), azithromycin (43%), imipenem (33%) and gentamicin (32%).

Sixty percent of the isolates were sensitive to gentamicin and norfloxacin. Fifty-six percent of the isolates were sensitive to imipenem. Below 50% of the isolates were sensitive to all the antibiotics except gentamicin, norfloxacin, and imipenem. Only 4% of the isolates were sensitive to penicillin G with no isolate showing intermediate susceptibility. Seventeen percent of the isolates showed intermediate susceptibility towards azithromycin.

Twelve antibiotics selected for this study belonged to three major groups of antibiotics- bacterial cell wall synthesis inhibitors, bacterial protein synthesis inhibitors, and bacterial nucleic acid synthesis inhibitors.

The cell wall synthesis inhibitors included penicillin G and piperacillin from the penicillin group, imipenem and meropenem from the carbapenems and cefuroxime from the cephalosporins. Among these five antibiotics, *Salmonella* isolates exhibited the highest resistance against penicillin G (31%) and the lowest resistance against imipenem (11%) (Figure 2). The carbapenem group accounted for the highest percentage of sensitivity (62%) among all the cell wall inhibitory agents.

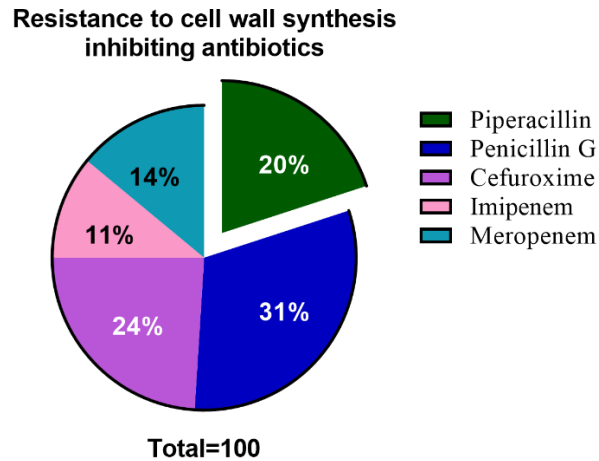


Figure 2: Resistance pattern among *Salmonella* isolates based on cell wall synthesis inhibitors.

Five antibiotics selected from the bacterial protein synthesis inhibitors included azithromycin, chloramphenicol, clindamycin, gentamicin and tetracycline. The highest percentage of resistance was observed against clindamycin (29%), followed by tetracycline (21%), chloramphenicol (21%), azithromycin (18%), and gentamicin (11%) (Figure 3). On the other hand, the *Salmonella* isolates showed the highest sensitivity towards gentamicin (32%), followed by azithromycin (22%), and chloramphenicol (19%) among the bacterial protein synthesis inhibitors.

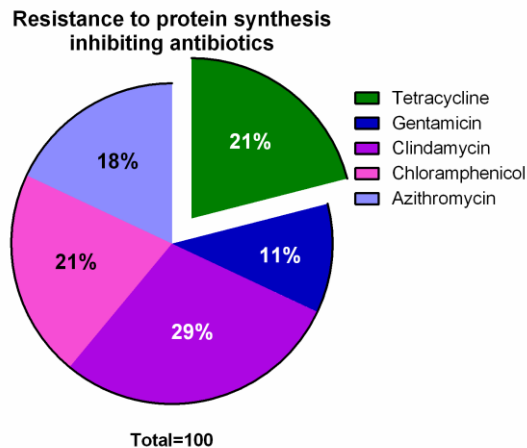


Figure 3: Resistance pattern among the *Salmonella* isolates based on protein synthesis inhibitors.

In this study, the resistance of the isolates was examined against two nucleic acid synthesis inhibitor antibiotics; norfloxacin and cotrimoxazole. The results showed a higher degree of resistance to norfloxacin (72%) compared to cotrimoxazole (28%).

Among the 90 isolates obtained from urine samples, the highest resistance was observed against penicillin G (96%) and cefuroxime (77%) followed by clindamycin (70%) and cotrimoxazole (65.5%). Resistance to piperacillin, tetracycline, chloramphenicol, and azithromycin varied between 40% and 60%. A high prevalence of resistance was recorded against carbapenem antibiotics which included imipenem (32%), and meropenem (38%). The results obtained from antibiotic susceptibility analysis showed gentamicin as the most effective antimicrobial against isolates obtained from both urine (65%) and sputum (78%) samples. Nine *Salmonella* strains were isolated from sputum samples and the highest resistance was observed against penicillin G (89%) and meropenem (89%), followed by

clindamycin (78%), and cotrimoxazole (78%). Resistance towards tetracycline, imipenem, piperacillin and chloramphenicol varied between 45% and 55% among the sputum samples.

As shown in Figure 4, 98% isolates showed a MAR index value of 0.2 and above, while 90% of the isolates exhibited a MAR index value ≥ 0.3 . MAR index ≥ 0.5 was observed with 65% of the isolates. The results revealed a high prevalence of multidrug resistance as 98% of the isolates showed MDR, while 23% of them were resistant to 5 classes of antibiotics (Figure 5). As shown in Figure 5, 17% of the isolates showed resistance towards six classes of antibiotics, and 16% of the isolates exhibited resistance against four classes of antibiotics. Two of the isolates were resistant to all the nine classes of antibiotics used in this study. Moreover, in the current study, 20% of the isolates showed extensive drug resistance (XDR).

MAR indices of *Salmonella* isolates (n=100)

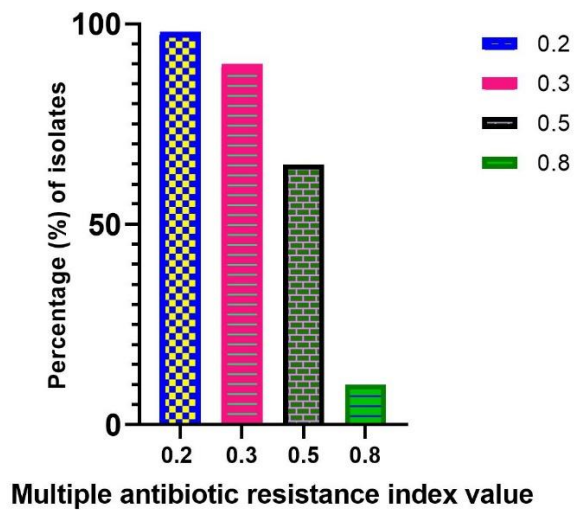


Figure 4: Percentage of isolates with varying Multiple Antibiotic Resistance (MAR) index values.

Resistance to multiple classes of antibiotics

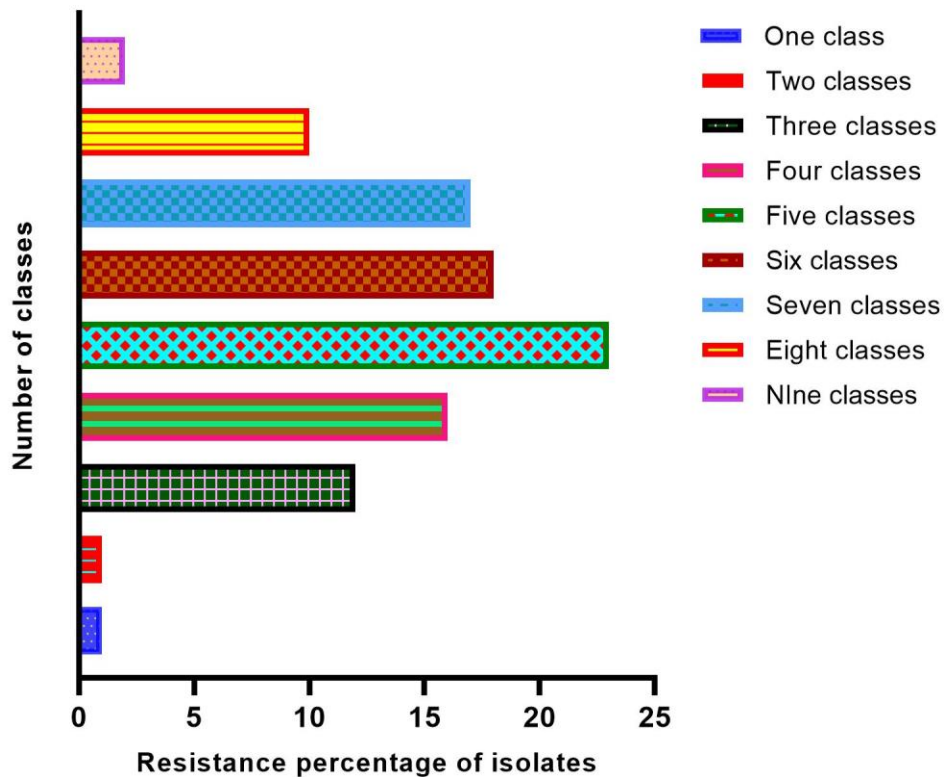


Figure 5: Resistance of *Salmonella* isolates against multiple classes of antibiotics.

Discussion

This study was conducted to identify the antibiotic resistance pattern among *Salmonella* spp. isolated from clinical samples in Dhaka. Among the 100 clinical *Salmonella* isolates, 98% were multidrug-resistant, which showed resistance against at least three different classes of antibiotics. The rising incidence of antimicrobial resistance caused by MDR pathogens raises serious concerns regarding the therapeutic usability of the available antibiotics in the near future.¹⁵

Seventeen percent of the isolates were resistant to seven classes of antibiotics, 18% to six classes of antibiotics, and 23% to five classes of antibiotics. The results revealed that the most effective antibiotics were gentamicin and norfloxacin, against which 60% of the isolates showed sensitivity, followed by imipenem (56%) and meropenem (49%). Ninety-six percent of the isolates exhibited resistance to penicillin G, 75% to cefuroxime, 61% to piperacillin, 43% to meropenem and 33% to imipenem. Broad-spectrum antibiotics like imipenem or meropenem are frequently used as therapeutics due to the rising incidence of antimicrobial resistance among pathogens. These antibiotics are typically more damaging to the healthy microbiota. In a study carried out in the United States, KPC-2 β -lactamase-producing strain of *Salmonella* was found to be resistant to most beta-lactam antibiotics, including oxyimino-cephalosporins and imipenem.¹⁶ In this study, a high percentage of isolates showed resistance to carbapenems which indicates a reduced possibility of the therapeutic effectiveness of carbapenems against pathogenic organisms. The results obtained in this study are in line with a study conducted in Pakistan,¹⁷ which reported 48% of the resistance to meropenem among *Salmonella* isolates, indicating a similar pattern to carbapenem resistance. The diminishing efficacy of the limited antibiotic options against MDR pathogens suggests the urgent need to search for alternatives to carbapenem therapy.¹⁸

In a study conducted by Uddin *et al.* (2018),¹⁹ 40% of the total isolates were found resistant to azithromycin. This is similar to the findings from this study, where 43% of the isolates were resistant to the same drug. However, a much higher percentage of resistance to tetracyclines (50%) was observed in this study than that reported by Uddin *et al.* (28%).¹⁹ Dallal *et al.* (2016)²⁰ reported 100% resistance against tetracyclines among *Salmonella* spp. isolated from resident patients in a study in Northern Iran. The variation in the resistance could be attributed to different disease patterns in the sampling regions.²¹ Different studies have reported varying degrees of resistance against chloramphenicol among clinical *Salmonella* isolates across different countries such as 100% in Saudi Arabia,²² 44% in Burkina Faso,²³ 50% in Kenya,²⁴ and 60% in Pakistan.²⁵ In this study, 50% of the isolates showed resistance to chloramphenicol. This is in line with a study by Islam *et al.* (2018)²⁶ which reported 32.5% of chloramphenicol resistance among the isolates obtained from clinical samples in Bangladesh. This indicates the significant development of resistance against chloramphenicol in Bangladesh. The higher prevalence of antibiotic resistance in Mediterranean, eastern and southern countries has also been reported previously.¹

By the end of the 20th century, the use of fluoroquinolones was recommended to treat diseases caused by *Salmonella* in Southeast Asia due to the rise of multi-drug resistance against chloramphenicol and other antibiotics and has remained the treatment of choice since then.²⁷ However, particularly in Southeast Asia, reports showed a significant rise in resistance to fluoroquinolones over the years.²⁸ Ali Shah *et al.*¹⁷ and Qamar *et al.*²⁹ from Pakistan reported 95% and 91.7% resistance, respectively, against ciprofloxacin, a fluoroquinolone molecule. A study from India also reported a very high incidence of resistance against ciprofloxacin (97%).³⁰ From Bangladesh, Mannan *et al.*³¹ and Habib *et al.*³² reported 51% and 20% ciprofloxacin-resistant isolates, respectively, from clinical samples. A study conducted in China documented 20% of clinical *Salmonella* isolates to be resistant to ciprofloxacin.³³ In this study, approximately one-fourth (27%) of the isolates showed resistance to norfloxacin, a fluoroquinolone molecule, which indicates the need for alternative antibiotics.

The results obtained in this study also indicate the development of high resistance against cotrimoxazole, a sulfonamide drug, as 68% of the isolates were found resistant to cotrimoxazole. This is consistent with the findings of published studies from Pakistan¹⁷ and Bangladesh,²⁶ where 66.7% and 48.4% resistance were reported against cotrimoxazole respectively. A large number of *Salmonella* isolates (65.5%) obtained from urine samples were found resistant to cotrimoxazole. In a similar study by Farhan *et al.*³⁴ from Pakistan, 38.5% resistance was reported against cotrimoxazole. Although the number of isolates from sputum samples (9%) was smaller than urine samples (90%) in this study, equivalent or higher resistance was observed against all antibiotics except cefuroxime, norfloxacin, and azithromycin.

In developing countries, the evolution of multidrug-resistant bacteria is a significant public health concern.³⁵ The problem is most commonly related to the frequent use of antibiotics without proper diagnosis.³⁶ In the current study, sixty-five percent of the isolates showed a MAR index equal to or higher than 0.5, indicating a high prevalence of resistance among the clinical samples in Bangladesh. Moreover, 20% of the isolates showed XDR in this study. In a study by Qamar *et al.*³⁷ in 2020, no XDR isolates were reported from Bangladesh and Nepal. However, the findings of a significant level of drug resistance among the bacterial isolates in that study (2016-2019) on enteric fever in Asia indicate a severe threat to the people.³⁷ A study carried out in Lahore, Pakistan by Zahid *et al.* in 2021²⁵ reported the presence of 67% MDR along with 34% XDR among *Salmonella* isolates from clinical samples. Several other studies from Pakistan also demonstrated the strong presence of XDR isolates such as 35% by Klemm *et al.*³⁸ and 41.6% by Ambreen *et al.*³⁹ High prevalence of extensive drug-resistant isolates (33.3%) has also been reported among clinical *Salmonella* isolates by El-Aziz *et al.* in 2021,⁴⁰ from Egypt.

Globally, *Salmonella* is responsible for causing a wide range of enteric diseases. The development of MDR and XDR *Salmonella* spp. is a public health threat. The presence of *Salmonella* has also been correlated with urinary tract infections (UTIs).^{41,42} Moreover, a correlation between UTIs caused by *Salmonella* and the high incidence of chronic illnesses such as cardiopulmonary or liver disease, gastric resection, and diabetes mellitus has been documented previously.⁴³ Numerous reports documented the occurrence of UTI due to *Salmonella* in healthy individuals.^{44,45} Twenty-three UTI cases were identified in a study conducted in Australia, among which only three had urological complications.⁴⁶ Due to disease recurrence or chronic asymptomatic bacteriuria, *Salmonella* UTIs require follow-up urinary cultures and prolonged antibiotic therapy for two weeks or more.⁴⁷⁻⁴⁹ Apart from UTIs, infections caused by extensive drug-resistant *Salmonella* can result in complications in the treatment of immunocompromised patients.⁴⁴

Non-typhoidal *Salmonella* species were found to result in septic arthritis of the hip after UTI.⁵⁰ Therefore, the presence of MDR and XDR *Salmonella* spp. might cause a wide variety of resistant infections resulting in higher mortality.

The results obtained in this study demonstrate the alarming rise of MDR and XDR pathogens in Bangladesh, which could be attributed to the irrational use of antimicrobials combined with inadequate AMR surveillance.¹³ In resource-limited countries such as Bangladesh, the habit of self-medication among patients, and the indiscriminate use of antibiotics in agriculture and farming is a major contributor to the emergence of resistant bacterial strains along with poor healthcare standards.⁵¹ Moreover, data to monitor trends and susceptibility patterns against antibiotics are infrequently produced.^{4,13,51} Hence, the implementation of strong antibiotic stewardship programs is crucial to track the spread of MDR pathogens in Bangladesh. As the problem of AMR is multi-sectoral, a multi-disciplinary and holistic approach is necessary to ensure the best use of antibiotics, prescribe the right antibiotics, and preserve the 'last resort' antibiotics.^{1,51} The overall findings of the present study will provide helpful information to the local authorities towards the development of a strong antimicrobial stewardship program.

The major limitation of this study was that the clinical samples were collected from the Dhaka region only, which might not represent the country as a whole. For tracking the resistance patterns of *Salmonella* spp., a more detailed study with a larger sample size, including broader areas, is highly desirable. Routine investigations are required to minimize the misuse of antimicrobials and find out the root causes of resistance development. Finally, the identification of genes responsible for resistance could provide a deeper insight into the resistance patterns and the mechanisms involved.

Conclusion

To reduce the rise in antibiotic resistance, the overuse and incorrect prescriptions of antibiotics need to be monitored. It is crucial to conduct systematic and focused studies on the prevalence and incidence of antibiotic resistance including MDR and XDR patterns. Strategies to prevent the transmission and spreading of resistant species need to be designed to combat the problem of antibiotic resistance. The current study has documented the high prevalence of multiple drug-resistant *Salmonella* isolates in Dhaka, Bangladesh. This necessitates the implementation of suitable actions to monitor and regulate the use of antibiotics. Countrywide screening of microbial infections and causative agents using standardized approaches is highly desirable.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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