Global Journal of Medicine & Public Health

Antibiotic susceptibility and resistance patterns of diarrhoeagenic *Escherichia Coli*, *Shigella and Salmonella* species: A need for antimicrobial stewardship and surveillance programmes

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GJMEDPH 2020; Vol. 9, issue 6

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Conflict of Interest—none

Funding—none

ABSTRACT

Background

Diarrhoeal diseases caused by bacterial pathogens are a major cause of increased morbidity and mortality rates worldwide, especially in vulnerable populations such as children. The emergence of antibiotic resistance has affected antibiotics commonly used in the management of diarrhoea such as ampicillin, co-trimoxazole and tetracyclines. We assessed the antibiotic susceptibility and resistance patterns of diarrhoeagenic *Escherichia coli*, *Shigella*, and *Salmonella* species based on published studies.

Method

This was a narrative review in which PubMed, Google Scholar, and EMBASE databases were used to search for studies published between January 2010 and January 2021.

Results

This review shows that diarrhoeagenic *Escherichia coli*, *Shigella* species, and *Salmonella* species are among the microorganisms which have developed high resistance to antibiotics including ampicillin, co-trimoxazole and tetracyclines. However, the three diarrhoeagenic bacteria have a low resistance to ciprofloxacin, norfloxacin, and ceftriaxone and hence can be used as the drugs of choice in diarrhoeal infections.

Conclusion

There is a high prevalence of diarrhoea caused by *Escherichia coli*, *Shigella* species and *Salmonella* species. Many diarrhoeagenic bacteria have developed multi-drug resistance to antibiotics, more especially to ampicillin, co-trimoxazole and tetracyclines. Antibiotic susceptibility tests of diarrhoeagenic bacteria must be carried out before antibiotics are prescribed. More importantly, antimicrobial stewardship programmes and surveillance systems must be promoted to curb the emergence and spread of antimicrobial resistance both in public and private practicing sites.

Keywords: Diarrhoea, Diarrhoeagenic, Antibiotic Susceptibility Patterns, Antibiotic Resistance, *Escherichia Coli*, *Shigella*, *Salmonella*, Antimicrobial Stewardship, Surveillance

INTRODUCTION

Diarrhoeal diseases are a public health problem mostly in developing countries, due to a lack of access to proper health care, relevant microbiological diagnostics, good quality water, good sanitation, adequate healthcare facilities or good treatment interventions.[1] Globally, diarrhoeal diseases are among the major causes of human morbidity and

mortality; around 1.6 million people succumb to diarrhoeal diseases annually.[2] The morbidity associated with diarrhoea is more prevalent in children under the age of five years,[3,4] with mortality estimated at approximately 525,000 children every year globally.[2] Diarrhoea is caused by both infectious and non-infectious agents.[5] Infectious diarrhoea can be caused by bacterial pathogens, viruses and parasites.[6-8] Diarrhoeagenic bacteria include *Escherichia coli (E. coli)*, *Shigella* species (spp), *Salmonella* spp, and *Campylobacter* spp.[9] Diarrhoea caused by infectious agents such as bacteria should be treated with antibiotics only when there is need, evidenced after culture and sensitivity tests have been carried out.[10,11] Other adjuvants or supportive therapies used in the management of diarrhoea include oral rehydration solutions and zinc supplements.[12]

Unfortunately, in recent years, there has been a progressive increase in antibiotic resistance due to the overuse and misuse of antibiotics in the treatment of many conditions, including diarrhoea.[13,14,15] Empiric treatment of diarrhoea using antibiotics has been reported as a major cause of antimicrobial resistance (AMR)[16] and the emergence of AMR in enteric bacterial pathogens is a major public health problem that impacts negatively on the control of diarrhoea.[15-17] High rates of diarrhoeagenic-bacterial resistance to the commonly used and readily available antibiotics such as ampicillin, tetracyclines and trimethoprim-sulphamethoxazole (co-trimoxazole) have been reported.[17] Also, the emergence of AMR and multi-drug resistance (MDR) has changed the antibiotic susceptibility patterns of *E. coli, Shigella, and Salmonella* spp with time.[15]

Diarrhoea is a symptom of infections that are commonly spread via faeces, food and contaminated water.[18] The clinical features of diarrhoea include watery stool, increased frequency in passing stool, abdominal pain, nausea, vomiting, bloating, fever, loss of appetite, blood in the stool, dry mouth, low urine output and dehydration.[19]

The most commonly isolated diarrhoeagenic bacterial pathogens are from the *Enterobacteriaceae* family[20] such as *E. coli*, *Shigella* spp, and *Salmonella* spp.[21] *E. coli* is a Gram-negative, rod-shaped, coliform, facultative anaerobic bacterium and is a highly prevalent commensal inhabitant of the human gut. It is one of the most cardinal diarrheagenic pathogens.[22] *Shigella* is a Gram-negative, rod-shaped, non-spore-forming, nonmotile, facultative anaerobic bacterium.[23] *Shigella* spp. causes shigellosis, a very contagious acute enteric infection that is manifested by bloody diarrhoea.[24] Global studies have suggested that approximately 164.7 million people suffer from shigellosis annually, of which mortality of 1.1 million has been reported, mostly in children from developing countries.[25] *Salmonella* is a Gram-negative, rod-shaped, facultative anaerobic bacterium that is usually found along the digestive tracts of animal and human hosts and causes salmonellosis. *Salmonella* is transmitted to humans via the consumption of contaminated food products and from infected animals.[26] *Salmonella* can indirectly infect humans via transfer from animals and animal-derived food products, and thereby cause the potentially fatal diseases salmonellosis.[27] Globally, more than 250 million cases of diarrhoeal infections are caused by *Salmonella*, resulting in more than 3 million deaths annually.[28] Between 200 million to more than 1 billion cases of diarrhoea worldwide are due *to Salmonella* infections every year, leading to 3 million deaths.[28]

As a result of the diarrhoeal infections caused by *E. coli*, *Shigella*, and *Salmonella* spp., and other diarrhoeagenic pathogens, there is an urgent need for targeted treatment. However, antibiotic susceptibility tests (ASTs) are not routinely carried out before antibiotics are prescribed; hence empirical treatment is mostly considered. This has contributed to an increased rate of antibiotic-resistant bacteria[11,29] and the increased emergence of resistant strains of *E. coli, Shigella* and *Salmonella* spp. which have proved difficult to prevent and treat.[28] This can be partly attributed to lack of availability of ASTs and a long turnaround time of the test results. Widespread bacterial resistance to conventional first-line antibiotics such as ampicillin, co-trimoxazole, and chloramphenicol has been reported.[30] Bacterial resistance to fluoroquinolones is very low and they

must therefore be considered as the drugs of choice in circumstances where bacterial pathogens are resistant to the first-line antibiotics, provided the isolated pathogenic bacteria are sensitive to fluoroquinolones.[30] Therefore, the purpose of this review was to assess the antibiotic susceptibility patterns of diarrhoeagenic *E. coli, Shigella* and *Salmonella* spp. based on published studies.

METHOD AND MATERIALS

This study was a narrative review conducted through an extensive literature search using PubMed, Google Scholar and EMBASE. The reviewed literature was searched using the keywords diarrhoea, diarrhoeagenic, antimicrobial susceptibility patterns, antibiotic susceptibility patterns, antibiotic resistance, antimicrobial resistance patterns, *Escherichia coli, Shigella, Salmonella,* antimicrobial stewardship, and surveillance using the Boolean operator "AND". We performed this narrative review from July 2020 to February 2021. Our inclusion criteria were studies published in English between January 2010 and January 2021. Our exclusion criteria were studies published more than 10 years ago and those not published in English. Some of the reviewed articles' references were searched for further studies on the topic of study. A total of 103 articles were retrieved, of which 70 met the inclusion criteria and were included in our review.

RESULTS

Antibiotic Susceptibility and Resistance Patterns of Escherichia Coli, Shigella and Salmonella Isolates

Diarrhoea caused by enteric bacteria pathogens is among the major causes of morbidity and mortality rates in children 0–59 months at the University Teaching Hospitals in Zambia. A study by Chiyangi and colleagues analysing 271 stool samples reported that the most commonly isolated pathogen was Vibrio *cholerae 01* subtype, serotype Ogawa (40.8%), followed by *Salmonella* spp (25.5%), diarrhoeagenic *E. coli* (18%), *Shigella* spp (14.4%) and *Campylobacter* spp (3.5%), respectively.[31] Antibiotic susceptibility testing (AST) revealed that most of the pathogens tested were resistant to two or more antibiotics, mainly ampicillin and co-trimoxazole. They reported that all the diarrheagenic *E. coli* isolates were extended-spectrum β-lactamase (ESBL) producers.[31] Continued surveillance and monitoring of infectious diseases, good hygienic practices in various communities and public health education programmes are essential for controlling diarrhoeal infections caused by enteric bacterial pathogens.[32,33] Standard treatment guidelines in every country need to be revised based on local studies of antimicrobial susceptibility patterns in diarrhoea-causing microorganisms.

A cross-sectional study by Karambu *et al*. (2014) was conducted in Igembe District Hospital in Meru County, Kenya, to characterise enteric bacterial pathogens that cause diarrhoea in children aged five years and below.[34] The study was conducted among 308 children aged between 2 to 60 months, with a mean age of 27.25 months and a median age of 26 months. The isolation rates of enteric bacteria were reported to be 9.1% for Enterotoxigenic *E. coli* (ETEC), 6.8% for Enteropathogenic *E. coli* (EPEC) and 12.3% Enteroaggregative *E. coli* (EAEC), 10.4% for *Salmonella paratyphoid*, 1.9% for *Shigella flexineri* and 0.9% for *Shigella dysenteriae*. More than 95% of the isolated enteric bacteria were reported to be resistant to cotrimoxazole, amoxicillin and sulphinatozole.[34]

Similarly, another study in Sudan by Saeed *et al*. (2015) reported that bacterial pathogens were found to be a significant cause of diarrhoea in children aged five years and below.[35] There was a higher resistance established to several commonly prescribed antibiotics.[34] Several factors have been significantly associated with diarrheal diseases in children, and these include insufficient hand washing before eating and after visiting the toilet, drinking untreated water from rivers, children not exclusively breastfed, occupation of the parent, and the parent or guardian not washing hands after changing the baby's nappies.[34] Therefore, strategies and measures that will help to reduce diarrheal infections must be put in place to reduce the morbidity and mortality rates associated with diarrheal diseases.

A study in Ethiopia by Demissie *et al*. (2014) reported on the prevalence and antimicrobial susceptibility

patterns of diarrheagenic Shigella spp. and Salmonella spp. A total of 372 diarrhoeic stool samples were collected from patients suffering from diarrhoea and cultured on MacConkey and Salmonella-Shigella agars, and ASTs of the isolates were determined following the standard bacteriological methods.[28] From the findings, the isolation rate was 4.57% for *Shigella* spp. and 1.08% for *Salmonella* spp. *Shigella* isolates were highly resistant to ampicillin (94.1%), amoxicillin (88.2%) and tetracycline (88.2%), while *Salmonella* isolates were highly resistant to amoxicillin (100%), tetracycline (100%) and ampicillin (75%). Conversely, all the isolates of *Shigella* and *Salmonella* were fully (100%) susceptible to norfloxacin and ciprofloxacin.[28] This makes fluoroquinolones the first-choice antibiotics in patients suffering from diarrhoea caused by *Enterobacteriaceae* bacteria.[27] The researchers concluded that the high rates of bacterial resistance to antibiotics in the above study from Ethiopia could have been a result of poor prescribing patterns and the misuse of antibiotics, empirical treatment and wrong indications.[36]

The shigellosis and salmonellosis infection rates were very high due to differences in awareness about personal and environmental hygiene among different populations. Health educators and promoters must ensure people are informed about the importance of hygiene in the prevention of diarrheal diseases.

Another study in Ethiopia by Huruy *et al*. (2014) revealed a higher prevalence of *Shigella* than *Salmonella* isolates from diarrhoeal samples, while *E. coli* was not detected.[37] Other diarrhoeagenic microorganisms that were isolated included parasites such as *Cryptosporidium*, *Isospora Beri*, and *Strongyloides*. From the ASTs that were done, it was found that *Salmonella* spp. were resistant to tetracycline and ampicillin while *Shigella* spp. were resistant to tetracycline, cefaclor, and gentamicin.[37] Huruy *et al*. also reported on the importance of personal and environmental hygienic practices in infection prevention and control, and emphasized the need for improving prescribing patterns and performing antibiotic sensitivity tests whenever possible.

Mamuye *et al*. (2015) conducted a study among children under-five in rural Mozambique in which 190 enteropathogens were isolated.[38] The isolates included 24.1% *E. coli*, 9.1% *Shigella*, (3.95%) *Salmonella* and *Citrobacter* spp., and 34% were parasites respectively. The resistance rates of *Shigella* spp. were high for ampicillin (95.7%) and amoxicillin+clavulanic acid (augmentin) (91.4%), while resistance rates for *Salmonella* spp. were also high for ampicillin (80%) and amoxicillin+clavulanic acid (80%). *Shigella* isolates were highly sensitive to ciprofloxacin (91.3%) and ceftriaxone (100%). *Salmonella* isolates also showed high sensitivity to ciprofloxacin (91.4%) and ceftriaxone (100%). More than 87% of *Shigella* spp. were reported to have multiple resistance for two or more antibiotics, compared with 70% for *Salmonella* spp.[38] The results obtained by Mamuye *et al*. (2015) on the prevalence and antimicrobial susceptibility patterns of *Shigella* and *Salmonella* isolates are in tandem with those reported by Reda *et al*. in Ethiopia, Hui in China, Demisse *et al*. in Ethiopia, and Huruy *et al*. in Ethiopia.[14,26,28,37]

A study by Esmaeili Dooki *et al.* (2014) among Iranian children under 14 years of age showed a high prevalence of *E. coli*, followed by *Shigella*, and *Salmonella* spp. with all the isolates being susceptible to ciprofloxacin, cefixime and ceftizoxime.[39] The tested bacteria showed cross-resistance to antibiotics that were a result of the pathogens carrying an ESBL-producing plasmid that exerts TGC resistance. These ESBL-producing plasmids were transferred to susceptible strains of bacteria via the process of conjugation.[40, 41]

In India, Rajeshwari *et al*. (2015) reported that the prevalence of enteropathogenic *E. coli* was found to be 10% while that of *Shigella spp.* was reported to be 1.3% from a total of 400 stool samples collected from children aged from 2 to 36 months with a mean age of 12 months.[42] ASTs of enteropathogenic *E. coli* showed that *E. coli* was resistant to nalidixic acid (95%), amoxicillin (90%), cefotaxime (77.5%), norfloxacin (77.5%), ceftriaxone (75%), ciprofloxacin (72.5%), ofloxacin (70%), nitrofurantoin (27.5%), azithromycin (25%), gentamicin (17.5%), and

amikacin (12.5%).[42] Gentamicin and amikacin proved to have lower levels of AMR and can be used as drugs of choice in this region but can only be administered via the parenteral route as injectables. The high rates of AMR seen with nalidixic acid and amoxicillin may be attributed to the poor prescribing patterns of the commonly used antibiotics in children. To reduce the high prevalence of AMR among the tested antibiotics, infection prevention and control is needed in addition to better feeding practices, increased and routine susceptibility tests, and better antibiotic prescribing and usage.[43]

A study by Pourakbari *et al*. (2010) in Iran evaluated children's stool samples from the national laboratory and reported a *Shigella* spp. prevalence of 4.5%.[44] Antibiotic sensitivity tests showed that *Shigella* was highly sensitive to ceftriaxone (95%), ceftizoxime (94%), and nalidixic acid (84%). Conversely, resistance to co-trimoxazole and ampicillin was reported to be at 87% and 86%, respectively. Even if this study focused on Shigellosis, other diarrhoeagenic pathogens such as *Salmonella* should be considered as they contribute the several diarrhoeal cases and deaths.[44] This study by Pourakbari *et al*. showed that *Shigella* was highly resistant to ampicillin and co-trimoxazole, but more sensitive to ceftriaxone, ceftazidime, and nalidixic acid.[44] Therefore, ampicillin and co-trimoxazole must be avoided in the treatment of diarrhoea caused by *Shigella* spp. Conversely, this supports the need for conducting ASTs before prescribing antibiotics so that the specific therapy is prescribed, dispensed and administered to the right patient.

A study by Banga *et al*. (2011) on antimicrobial susceptibility of *Shigella* spp. in Northeast Malaysia reported similar findings as those found in the study by Pourakbari *et al*. described above.[45] It was reported that there has been an increase in AMR over the past years. Hence, it is important that antibiotic susceptibility studies are carried out regularly and empirical treatment guidelines updated.[45] Bacterial resistance to antibiotics is dynamic and thus it is important to keep these bacterial strains under surveillance to monitor the local susceptibility patterns, and subsequently formulate and implement policies for the prudent and rational use of antibiotics.[25,46] In Turkey, Ince *et al*. (2012) conducted a study on salmonellosis.[47] They reported that the *Salmonella* spp. were resistant to ampicillin (25.8%), chloramphenicol (18.2%), co-trimoxazole (7%), ceftriaxone (4.7%), and ciprofloxacin (0.3%) respectively. Fortunately, nationwide implementation of the diarrhoea training and treatment programmes that promote the limited and rational antibiotic use proved to have led to the lower levels of AMR reported in Turkey than some other countries.[47]

In New South Wales, Australia, Brown *et al*. (2017) isolated 160 *Shigella* spp. From these 160 *Shigella* isolates, it was found that 86.9% were susceptible to azithromycin, 65.0% were susceptible to ciprofloxacin while 23.7% were susceptible to co-trimoxazole.[48] Besides, this shows a high rate of *Shigella* resistance to co-trimoxazole.[48] Furthermore, the study revealed that bacteria developed some resistance even to ciprofloxacin, the drug recommended by the World Health Organization (WHO). This indicates the need for specific countries to develop their own treatment guidelines based on antimicrobial susceptibility studies.[49] In the USA, *Salmonella* resistance to azithromycin has been reported and it varied amongst the different centres where the study was conducted.[29] Azithromycin resistance has been reported to be high due to its misuse.[29,30,50,51] This shows a rise in AMR of diarrhoeagenic bacteria such as *E. coli*.[52] The resistance of bacteria to tetracyclines, penicillins, cephalosporins, fluoroquinolones, aminoglycosides and other classes of antibiotics has been reported,[53,54] which heightens the need to call for prudent and rational use of antibiotics.

Antimicrobial Stewardship and Surveillance of Infections and Antibiotic Resistance

Well-established and functional Antimicrobial Stewardship Programmes (ASPs) play a vital role in promoting the rational use of antibiotics, infection control and curbing AMR.[55-58] There is a need to put in place leadership, qualified personnel working in a multidisciplinary team, and to enhance the availability of ASTs to promote targeted treatments,

advocacy and updated policies. Healthcare workers such as pharmacists are key players in a multidisciplinary team that can initiate and implement ASPs in health facilities.[59,60]

The cornerstone for the management of infections caused by *E. coli*, *Shigella,* and *Salmonella* spp. are effective control of disease source and the appropriate use of antibiotics.[20] In the case of an empirical selection of an antibiotic, it needs to be broad enough to cover the most common pathogens that cause diarrhoea.[25] In some settings, empirical treatment is recommended when there is a need.[61] Healthcare workers can help in curbing AMR by enhancing infection prevention and control; prescribing and dispensing antimicrobials only when they are truly needed; and prescribing and dispensing the right antibiotic(s) to treat the diagnosed infectious disease.[62,63] It is highly recommended that whenever possible, microscopy, culture and sensitivity tests should be undertaken before antibiotics are prescribed and dispensed.[45,62] ASPs discourage self-medication and inappropriate use of antibiotics as these are factors that lead to the escalation of antibiotic-resistant bacteria.[64-67]

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Globally, there is a need for strengthened surveillance systems to monitor infectious diseases and AMR.[68,69] Robust surveillance systems are essential as they help to identify infectious disease-causing microorganisms and implementation of control measures.[70]

CONCLUSION

Diarrhoea and antibiotic resistance are a global public health problem. *Escherichia coli*, *Shigella* species, and *Salmonella* species have developed resistance to more than one antibiotic, especially to ampicillin, co-trimoxazole and tetracyclines. Future studies should focus on how to implement preventive measures to reduce antibiotic resistance against diarrhoeagenic pathogens and should promote basing antibiotic prescription on the antibiotic susceptibility profiles of the microorganisms. Antimicrobial stewardship and surveillance programmes must be promoted in all healthcare facilities to strengthen infection prevention, control and curb antimicrobial resistance. Further, treatment protocols need to be updated to be in line with antimicrobial resistance patterns.

ACKNOWLEDGEMENT

We wish to express our profound gratitude to the Department of Pharmacy at the University of Zambia for guidance and support throughout the research process. We are also grateful to the University of Zambia e-library for providing access to many articles used in the review manuscript.

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