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Review Article

Prevalence and Antimicrobial Resistance Patterns of *Shigella* in Ethiopia from 2000 to 2018: A Critical Review

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Abstract: *Shigella* is a non-motile, rod shaped, nonspore forming, and non-lactose fermenting facultative anaerobic Gram-negative bacterium that causes bacillary dysentery or also known as shigellosis. It is endemic throughout the world and it is among the most common causes of bacterial diarrheal diseases. Globally, it is estimated that shigellosis causes about 1,100,000 deaths per year, two-thirds of the patients being children under 5 years of age. The disease is transmitted faeco-orally, the commonest modes being person-to-person contact and contaminated food and water. It is a disease of overcrowding, insanitary conditions and poor personal hygiene, and affects mostly children of developing countries like Ethiopia. The treatment of shigellosis has currently become more challenging due to the emergence of drug resistant species and associated with a variety. of biological, pharmacological and societal variables with the worst combinations in low and middle income countries. Multidrug-resistant *Shigella* significantly varies from area to area of the world in relation with the practice of widespread use of antimicrobial agents. This review paper indicates isolation of *Shigella* infection increases time to time from under five children to hospitalized patients and also *Shigella* is becoming resistance to the commonly prescribed antimicrobial drugs in Ethiopia like ampicillin, Amoxicillin, chloramphenicol and tetracycline because of misuse of antimicrobials. Therefore, performing drug susceptibility test for each shigellosis case and creating awareness about the transmission, risk factors of shigellosis for the community is invaluable.

Keywords: *Shigella*, Ethiopia, Antimicrobial Resistance, Community

1. Introduction

Shigella is a non-motile, rod shaped, nonspore forming, and non-lactose fermenting facultative anaerobic Gram-negative bacterium that causes bacillary dysentery or also known as shigellosis [1]. Shigellosis is an acute invasive enteric infection often characterized by abdominal pain, fever and bloody diarrhea (dysentery).

Shigellosis is caused by *Shigella* species. However, three predominant strains are responsible for majority of shigellosis cases, S. sonnei, S. flexneri 2a and S. dysenteriae type 1. Of these, S. sonnei is encountered mostly in industrialized countries, S. flexneri 2a in developing countries and S. dysenteriae type 1 is the only epidemic as well as pandemic strain. They are pathogenic primarily due to their ability to invade intestinal epithelial cells. Shigellosis is a global human health problem. It is the most important cause of bloody diarrhea worldwide, especially in developing countries with substandard hygiene and poor quality of water supplies [2]. Shigellosis as a global human health problem is more severe than other forms of gastroenteritis. It is endemic throughout the world and it is among the most common causes of bacterial diarrheal diseases. Globally, it is estimated that shigellosis causes about 1,100,000 deaths per year, two-thirds of the patients being children under 5 years of age [3].

The disease is transmitted faeco-orally, the commonest modes being person-to-person contact and contaminated food and water. Infected food handlers can spread the disease Flies can breed in infected faeces and contaminate food. It is a disease of overcrowding, insanitary conditions and poor personal hygiene, and affects mostly children of developing countries [4]. Shigellosis typically evolves through several phases and manifestations of *Shigella* infection vary with the

infecting species, the age of the host, the presence of risk factors and the specific immune status of the host. The incubation period is 1 to 4 days, but may be as long as 8 days with S. dysenteriae [2].

The emerging of multi drug resistance is becoming a serious problem in the treatment of shigellosis. An increment of multidrug resistance to shigellosis is equivalent to a widespread uncontrolled use of antibiotics in developing countries. This emergency of drug resistance calls for the rational use of effective drugs and underscores the need for alternative drugs to treat infections caused by resistant strains [5]. Studies have been carried out in different parts of Ethiopia at different times to document the epidemiology of and drug Susceptibility pattern of *Shigella* species. Even though there are researches, there is no summarized prevalence data of this bacterial infection and its drug susceptibility pattern in Ethiopia. Therefore, the objective of this paper is to review the prevalence and antimicrobial resistance patterns of *Shigella* isolates conducted in Ethiopia.

2. Evolution of Shigellosis

Shigella was discovered in 1896 by a Japanese scientist, Dr Kiyoshi Shiga as bacteria causing dysentery in humans and primates [2, 6]. *Shigella flexneri* was described by Dr Simon Flexner in 1900. *Shigella boydii* was first isolated in India 1931 and was described by American bacteriologist and epidemiologist, Mark Frederick Boyd while *Shigella sonnei* was first isolated in 1904, but it was in 1915 that its pathogenicity was recognized by Dr Carl Olaf Sonnei [7, 8] and it was in 1950 that the Congress of the International Association of Microbiologists *Shigella* Commission adopted as the generic name *Shigella* and that species subgroups be designated A (*Shigella dysenteriae*), B (*S. flexneri*), C (*S. boydii*) and D (*S. sonnei*). Based on 16S rRNA sequencing, *Shigella* is from gamma Proteobacteria in the family *Enterobacteriaceae* phylum [7].

2.1. Shigellosis and Pathogenesis

Shigella causes disease by invading and replicating in cells lining the colonic mucosa. Epithelial cells of the colonic mucosa are the primary targets used by these bacteria and a key step in the pathogenesis of *Shigella* infection. The process of cell infection to be aided by the bacterial DNA encoding a number of plasmid and chromosomal proteins that assisted in adhesion of bacterial cells to epithelial cells with subsequent invasion through the M cells [9]. M cells are specialized epithelial cells which continuously sample material from the gut lumen and deliver them to the underlying mucosal lymphoid tissue, where immune responses can be initiated. This in turn facilitates transportation of bacteria [10].

Shigella infection is characterized by degeneration of the epithelium and inflammation of the lamina propria resulting in desquamation and ulceration of the mucosa with eventual leakage of blood and mucus into the lumen of the intestine. During infection, water absorption by the colon is negligible and this exacerbates diarrhoea. It is possible that prostaglandin interactions induced by the inflammatory response to bacterial invasion contribute to intestinal electrolytes and fluid movement resulting in colitis and diarrhoea [8, 11]. Central to its mechanism of virulence, *Shigella* expresses a type III secretion system (T3SS) that is responsible for the conveyance of a series of bacterial effectors into host cells, aimed at diverting host cellular processes that result in direct bacterial colonization and subsequent dissemination within the mucosal epithelium via subjugation of the host inflammatory response [8].

2.2. Health Impact of Shigellosis

Shigella is highly adapted to human as the only known natural hosts and incidences of shigellosis have been reported worldwide. According to [12], the average world annual incidences are estimated to be 80-165 million cases with 99% occurring in developing countries. About 1.1 million people die from *Shigella* infection each year of which 60% occur in children below 5 years of age. In endemic areas of the developing world, shigellosis is predominantly a pediatric disease [13]. The urban impoverished communities globally are hardest hit due to overcrowding, substandard sanitation, hygiene and lack of clean water. Institutions such as day-care centers, prisoners, military recruits and travellers are especially at high risk.

In developed countries shigellosis occurs erratically as outbreaks, while in developing countries reported incidences are probably 20 times more than in developed countries, yet a significant number of cases go unreported [14]. S. flexneri, the most frequently isolated species worldwide and accounts for 60% of cases in the developing countries, S. sonnei causes 77% of cases in the developed world as compared to 15% of cases in the developing countries while S. dysenteriae causes epidemics of dysentery particularly in confined populations like camps or schools [14]. *Shigella* species is one of the eight dangerous drug resistance bacteria. Worldwide, there are 700,000 deaths as a result of antimicrobial resistance (AMR) every year according to 2016 WHO report. The experts suggest that this figure will rise to 4.2 million in Africa and 10 million globally by 2050, if nothing is done [15].

3. Antimicrobial Resistance

3.1. Global Trends of Antimicrobial Resistance

Antibiotic resistance becomes a critical public health problem around the globe in recent years. Antibiotic resistance is a natural phenomenon that occurs whenever antibiotics are in use. However, there are human behaviors that contribute to the rapid development and spread of bacterial antibiotic resistance. According to [14] availability and use of broad spectrum antibiotic without prescriptions facilitate the development of resistance by *Shigell*a species.

The treatment of Shigellosis has currently become more challenging due to the emergence of drug resistant species and associated with a variety of biological, pharmacological and societal variables with the worst combinations in low and middle income countries [15]. Multidrug-resistant *Shigella* significantly

varies from area to area of the world in relation with the practice of widespread use of antimicrobial agents [15].

In the late 1980s, fluoroquinolones (norfloxacin, ciprofloxacin and ofloxacin) were introduced and were found to be very effective in the treatment of shigellosis cases including those caused by multi-drug resistant S. dysenteriae type 1 strain [4]. Recent outbreak investigations in India and Bangladesh showed high level of resistance even to norfloxacin, ciprofloxacin and ofloxacin [16]. A case–control study to characterize the epidemiology of bloody diarrhea in rural western Kenya reported that 80% of the bacterial pathogens isolated were *Shigella* species of which approximately 49% was caused by S. flexneri [17]. Shigellosis is also an important cause of infectious diarrhea in Iran [3], mostly community acquired, caused mainly by S. flexneri and S. dysenteriae.

Table 1. *Prevalence and antimicrobial resistance profiles of Shigella isolates in Ethiopia.*

Year	Location	Specimen	No. of sample Tested	Prevalence No. (%)	MDR	Predominant serogroup Isolated	Common resistance pattern	Maximum drug resisted No.	References
2000	Jimma	Stool	384	77 (20.1)	66 (85.7)	*Serogroup B (flexneri)*	TET, AMP, SXT, CHL, CF, CB	10	[28]
2001-2005	Gondar	Stool	2891	214 (7.4)	188 (87.8)	-	COT, AMP, TET, CHL	6	[31]
2003/4	Gondar	Stool	391	29 (7.42)	28 (96.6)	-	AMP, CHL, TET	9	[20]
2005	Gondar	Stool	384	65 (16.9)	53 (81.5)	-	AMP, TET, SXT, CHL	6	[24]
2006/7	Gondar	Stool	384	60 (15.6)	48 (80)	-	AMP, TET, SXT, CHL	6	[32]
2007	Harar	Stool	244	17 (6.7)	-	-	TET, AMP, AMX	5	[33]
2006-2008	Gondar	Stool	1200	90 (7.5)	71 (79)	*Serogroup A (S. dysenteriae)*	AMP, TET, COT, CHL	7	[25]
2009	Bahir Dar	Stool	215	32 (14.9)	32 (100)	-	S, AMP, TET, AMX, COT, CF, CHL	9	[34]
2011	Hawassa	Stool	158	11 (7)	11 (100)	*Serogroup B (flexneri)*	AMP, TET, ERY, CRO, AMX	7	[35]
2011	Harar	Stool	384	56 (14.6)	46 (82.1)	-	TET, AMP, COT, CHL	5	[36]
2011/12	Mekelle	Stool	260	18 (6.9)	16 (88.9)	*Serogroup D (s. sonnei)*	AMP, TET, CHL, COT	6	[21]
2011/12	Butajira	Stool	382	17 (4.5)	9 (56.25)	*Serogroup D (s. sonnei)*	TET, AMP, SXT	7	[22]
2012	Jimma	Stool	260	6 (2.3)	6 (100)	-	AMP, COT, AMX	5	[23]
2012	Addis Ababa	Stool	253	23 (9.1)	20 (87)	-	AMP, AUG, SXT	8	[27]
2014	Gondar	Stool	372	17 (4.57)	16 (94.1)	*Serogroup B (s. flexneri)*	AMP, TET, AMX, SXT, CF, KAN, GEN	9	[30]
2014	Mekelle	Stool	216	15 (6.9)	12 (80)	-	AMX, COT, CIP, NOR, GEN	8	[19]
2014	Jimma	Stool	176	2 (1.1)	2 (100)	-	COT, NAL, AMP, TET	4	[37]
2015	Arbaminch	Stool	376	10 (3)	-	-	CLR, AMX, AMC	10	[38]
2015/16	Debre Markos	Stool	220	5 (2.3)	-	-	AMP, CHL, TET	5	[39]
2015/16	Nekemte	Stool	422	9 (2.1)	3 (33.3)	-	AMX, GEN, CHL	4	[40]
2015/16	Harar	Stool	417	6 (1.4)	6 (100)	-	CHL, COT, TET	8	[41]
2016	Wegera	Stool	225	5 (2.2)	-	-	TET, AMP, AMX, GEN	6	[42]
2016	Robe/Goba	Stool	422	18 (4.3)	18 (100)	-	CHL, TET, DOX, AMX	4	[18]
2016/17	Wolkite	Stool	170	4 (2.4)	3 (75)	-	AMP, AMX	2	[43]
2017	Arbaminch	Stool	167	8 (4.8)	5 (62.5)	-	AMP, ERY, CHL	7	[44]
2017	Dire Dawa	Stool	218	6 (2.8)	2 (10.5)	-	AMP, AMX, CHL, TET	5	[45]
2017	SNNP	Stool	204	17 (8.3)	15 (88.2)	-	AMP, GEN, SXT, CHL	6	[26]
2017	Adama	Stool	232	22 (9.5)	-	*Serogroup A (s. dysenteriae)*	AMP, TET, CIP	7	[46]
2018	Gondar	Stool	257	26 (10.1)	10 (38.5)	*Serogroup A (s. dysenteriae)*	AMP, SXT, TET, AMX	8	[29]
2018	Gondar	Stool	272	29 (10.7)	17 (58.6)	-	AMX, CHL, TET, SXT	7	[47]

AMP: Ampicillin; AMX-CAL: amoxicillin-clavulinic acid; CHL: chloramphinicol; CF: cephalothin; CIP: ciprofloxacin; GEN: gentamycin; CLR: clarithromycin; KAN: kanamycin; CEF: cefaclor; CRO: ceftriaxone; NOR: norfoxacillin; DOX: doxycycline; S: streptomycin; SXT (COT): trimethoprim-sulfamethoxazole; TET: tetracycline; CB: carbenicillin; AUG: augumentin; ERY: erythromycin; MDR: multiple drug resistance.

Table 2. *Shigella resistance patterns for the antibiotic tested in some selected reports in Ethiopia.*

Authors	Antibiotics tested							
	AMP (%)	AMX (%)	CIP (%)	TET (%)	CHL (%)	CRO (%)	GEN (%)	SXT (%)
[28]	29.9	-	-	36.4	59.7	-	98.7	67.5
[25]	78.9	-	2.2	90	67.8	0	12.2	84.6
[30]	94.1	88.2	0	88.2	17.6	-	41.2	58.8
[19]	100	86.7	6.7	-	46.7	-	13.3	66.7
[29]	61.5	34.6	0	65.4	7.7	3.9	23.1	38.5

Authors	Antibiotics tested							
	AMP (%)	AMX (%)	CIP (%)	TET (%)	CHL (%)	CRO (%)	GEN (%)	SXT (%)
[47]	-	93.1	-	89.7	44.8	-	-	41.4
[45]	83.3	100	-	50	66.7	0	0	16.7
[26]	82.4	-	17.6	-	47.1	17.6	76.5	64.7
[23]	100	100	0	-	16.7	0	0	100
[22]	47.1	-	5.9	82.4	29.4	0	17.6	76.5
[33]	100	100	-	70.6	29.4	-	0	-
[35]	63.6	100	0	54.5	9.1	54.5	27.3	0
[41]	33.3	-	0	83.3	50	16.7	33.3	66.7
[39]	100	100	0	80	80	0	0	20
[32]	80	-	8.3	85	48.3	-	10	76.7
[24]	81.5	-	9.2	87.7	50.8	-	10.7	75.4
[36]	94.6	-	0	96.4	53.6	-	21.4	73.2
[31]	79.9	-	8.9	86	52.8	-	7.9	73.4
[21]	88.9	-	0	77.8	55.6	0	27.8	55.6
[42]	100	100	-	60	40	0	60	40
[34]	93.8	75	0	93.8	53.1	-	18.8	62.5
[27]	95.7	91.4	4.3	-	21.7	4.3	17.4	52.2

AMP: ampicillin; AMX: amoxicillin; CIP: ciprofloxacin; TET: tetracycline; CHL: chloramphenicol; CRO: ceftriaxone; GEN: gentamicin; SXT (COT): trimethoprim-sulfamethoxazole; - (not tested); 0 (susceptible).

3.2. Antimicrobial Resistance in Ethiopia

Antimicrobial resistance is a global problem in general, but it might be more severe in Ethiopia where there is lack of rigorous regulations. There have been studies conducted in Ethiopia on shigellosis (Table 1) which suggest an increase in the antimicrobial resistance of *Shigella* to commonly used antimicrobials [18-27].

77 and 17 *Shigella* strains were isolated from 384, 382 stool samples. Among the isolates 40.3%, 29.5% were caused by S. flexneri respectively [28, 22]. High prevalence of *Shigella* species (16.9%) was also reported from South Ethiopia [24]. Similarly, a study conducted in northwest Ethiopia (Gondar) from 2006 to 2008 showed that *Shigella* species was isolated from 7.5% (90 isolates) of the total 1,200 stool specimens. The study also indicated that S. flexneri was the most frequently isolated species which constituted 72.2% of *Shigella* isolates [25]. Other studies in Gondar also showed that *Shigella* species were the most frequently identified etiological agents for diarrhea [25]. In addition, a study conducted by [21, 29, 30] reported the majority of isolate was s. flexneri, s. dysenteriae and s. sonnei respectively.

Antibiotic resistance patterns of *Shigella* to commonly prescribed drug like chloramphenicol, gentamycin, ampicillin and trimethoprim-sulfamethoxazole in different studies on different parts of Ethiopia are presented in table 2.

4. Control and Prevention of Shigellosis

Rehydration therapy is an essential first step which can be used to correct dehydration due to diarrhea of any etiology and has greatly decreased the number of deaths due to diarrhea. Without antimicrobial treatment, or if an ineffective antimicrobial is given, an episode of shigellosis lasts from 2-10 days, or longer, and the risk of serious complications or death is greatly increased, especially for infection caused by S. dysenteriae type 1 or S. flexneri.

Inadequately treated shigellosis is an important cause of persistent diarrhea [2]. The main antibiotics used are ampicillin, tetracycline, amoxicillin, cotrimoxazole, chloramphenicol and trimethoprim-sulfamethoxazole. However, treatment has become increasingly difficult due to emerging resistance to these commonly prescribed antibiotics. It is emphasized that hands should be washed before eating, before feeding children, after defecation and after disposal of children's excreta. These measures are further reinforced in epidemic situations, when, because of the very low infective dose of the organism and its potential for rapid spread, stringent control measures need to be instituted through simple but effective health education messages to the common masses [4].

5. Conclusion and Recommendation

This review paper indicates isolation of *Shigella* infection increases time to time from under five children to hospitalized patients. Besides, *Shigella* is becoming resistance to the commonly prescribed antimicrobial drugs in Ethiopia like ampicillin, amoxicillin, chloramphenicol and tetracycline because of misuse of antimicrobials. Therefore, minimizing the expansion of antimicrobial resistance by different strategies and collaboration of stakeholders is important. Performing drug susceptibility test for each shigellosis case and creating awareness about the transmission, risk factors of shigellosis for the community is invaluable.

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