Review Article

Typhoid fever in Ethiopia

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Abstract

This review focuses on the reports of salmonellosis by investigators in different parts of Ethiopia, in particular focusing on the levels of typhoid fever. Many of the reports are published in local journals that are not available online. There have been seven studies which diagnosed typhoid fever by laboratory culture and there is no coordinated epidemiological surveillance. All conducted research and reports from different health institutions in Ethiopia indicate that typhoid fever was still a common problem up to the most recent study in 2000 and that the extensive use of first-line drugs has led to the development of multiple drug resistance. In the sites covered by this review, the total number of published cases of typhoid fever dropped over time reflecting the decline in research capacity in the country. Data on the proportion of patients infected by different serovars of *Salmonella* suggest that the non-Typhi serovars of *Salmonella* are increasing. The published evidence suggests that typhoid fever is a current public health problem in Ethiopia although population based surveys, based on good microbiological diagnosis, are urgently needed. Only then can the true burden of enteric fever be estimated and the benefit of public health control measures, such as health education, safe water provision, improved food hygienic practices and eventually vaccination, be properly assessed.

Key Words: Ethiopia, *Salmonella*, Typhi, typhoid

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Introduction

In Ethiopia, as in other developing countries, it is difficult to evaluate the burden of salmonellosis because of the limited scope of studies and lack of coordinated epidemiological surveillance systems. In addition, under-reporting of cases and the presence of other diseases considered to be of high priority may have overshadowed the problem of salmonellosis [1]. The real situation of antibiotic resistance is also not clear since *Salmonella* are not routinely cultured and their resistance to antibiotics cannot be tested. As in a developed country, however, to control the spread of salmonellosis, surveillance for *Salmonella* serovars and the assessment of antimicrobial susceptibility is essential.

In Ethiopia there have been several studies conducted on salmonellosis which suggest an increase in the antibiotic resistance of *Salmonella* to commonly used antimicrobials in both the public health and veterinary sectors [2-7]. With the exception of *S*. Typhi, bacterial identification is usually to serogroup level, and sometimes only to genus level. Because of this, Paratyphi B and C isolates are reported with other serogroup B and C members and it is impossible to differentiate typhoidal from non-typhoidal salmonellae. So far there is only a single published study which uses serotyping to describe the different serovars of *Salmonella* circulating in Ethiopia [3]. The main objective of this review is to systematically summarize publications in local and international journals for evidence of culture-proven typhoid fever. The data is important for public health departments in the region as decisions need to be made on the implementation of vaccines against enteric fever.

Salmonella surveillance in Ethiopia

In 1972 statistics were reported for the years 1959 to 1963 from the Anti-Epidemic Service. During the five-year period an average of 3,469 cases of salmonellosis were reported per annum (17.3 cases per 100,000 inhabitants) [8]. It was noted that cases of enteric fever, diagnosed clinically as typhoid fever, were almost three times the number of that of the other types of salmonellosis. This suggests a typhoid fever

rate of approximately 4/100,000 inhabitants in the early 1960s. However, the diagnosis of typhoid fever was on clinical grounds and the only microbiological study at the time reported that less than 1% of over 700 stool specimens grew *S*. Typhi [9]. It is possible that either the clinical diagnosis of typhoid fever was not accurate, or that the methods used for stool analysis did not detect *S*. Typhi from either carriers or cases. It was not until 1981 that a comprehensive study on invasive *Salmonella* in Ethiopia was conducted [10]. A total of 165 *Salmonellae* were collected from various hospitals in the capital city, Addis Ababa, between 1975-80 and analyzed in the Microbiology laboratory of The Black Lion Hospital; 131 (79.4%) were from blood cultures, 18 (11%) from stool, and the rest 16 (9.7%) were from other specimens. Of the 165 isolates, 7 were group A; 16 were B; 1 was E; 17 were C; and the remaining 124 were *S*. Typhi. Most of the specimens available were collected from the blood of inpatients with suspected typhoid fever. It is clear, therefore, that typhoid fever in the late 1970s, in Addis Ababa was a major cause of community-acquired bacteraemia. These findings support the clinical survey data from the earlier Anti-Epidemic Service.

From 1974 to 1981, Gebre-Yohannes conducted a study to identify the prevalent serovars and their susceptibility to drugs in Addis Ababa. This study serves as a base-line of data for all subsequent surveillance studies in Ethiopia [3]. *Salmonella* strains were isolated from adult patients referred to the Central Laboratory and Research Institute, Addis Ababa, between January 1974 and October 1981. Of 216 *Salmonella* isolates studied, 54.6% were from stool and 45.4% from invasive sites: blood 34.7%; pus 5.6%; and urine 5.1%. There were 26 different serovars, of which *S*. Typhi (48.6%) was the most common, followed by *S*. Concord (12.5%), *S*. Typhimurium (11.1%) and *S*. Paratyphi B (5.6%). The high isolation rate of *S*. Concord in Ethiopia is unusual and is in contrast to the other regions in Africa where *S*. Typhimurium or *S*. Enteritidis are more common [11,12]. Further study of this serovar is necessary to establish whether it remains in the human population and to investigate possible animal or food sources.

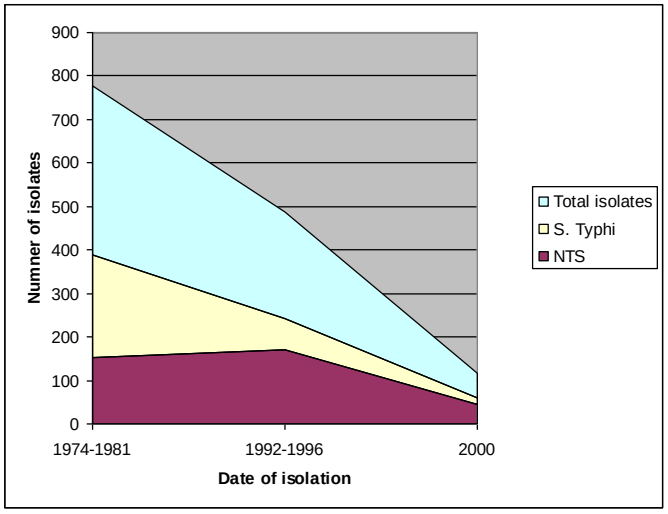
In 1985, Ashenafi and Gedebou reported a study from 1982-83 to determine the aetiology of diarrhoea in adult out-patients in Addis Ababa [4]. A total of 1,000 adult diarrhoeal cases from different hospitals and clinics were investigated and 45 *Salmonella* strains were isolated in the order of prevalence: group C, group B, *S*. Typhi, other group D, group A, and group E. This again raises the possibility that *S*. Concord (a group C *Salmonella*) is the most common cause of gastrointestinal salmonellosis and shows that *S*. Typhi was present. In a study conducted in a rehabilitation camp in Korem [13], a total of 42 (21.1%) of the camp residents had a stool positive culture of *Enterobacteriaceae*, of which only 2% were *Salmonella* species. These were not examined further. There is little information in this study but there is a suggestion of a low level of typhoid carriage in this camp population. Between February 1992 and January 1993 a similar study was conducted in Tikur Anbessa Hospital, Addis Ababa, to determine the prevalence of enteric pathogens (*Campylobacter*, *Salmonella* and *Shigella spp*, *Y. enterocolitica* and enteropathogenic *E. coli*) in 630 adult patients with diarrhoea and 220 patients without diarrhoea [14]. The prevalence of *Salmonella spp*. was 3.8% and 5.9% in patients with diarrhoea and without diarrhoea respectively. The most commonly isolated serogroup was group B (81.1%), followed by *S*. Typhi (10.8%) and group C (8.1%). This patient group may represent the population more closely than that of the camp in Korem and given the level of isolation of *Salmonella* from non-diarrhoea patients suggests the existence of fairly high numbers of carriers of *Salmonella*, including *S*. Typhi, or undiagnosed typhoid cases. This is in agreement with some previous studies in Ethiopia [4,15], and shows that in the 1980s *S*. Typhi was present in the stool of a fairly high percentage of patients who were not clinically diagnosed as having typhoid fever. A similar study conducted in Addis Ababa to determine *Salmonella* serogroups in adult diarrhoeal outpatients in 1995 [5] reports forty-five *Salmonella* strains from 700 stool specimens. Among the isolates, serogroup C (possibly *S*. Concord) comprised 31.1%; B 24.4%; *S*. Typhi 15%; D (other than *S*. Typhi) 13.3%; A 8.9%; and E 6.7%. Of all the *Salmonella* isolates in this study, 15.6% were *S*. Typhi. This is a relatively high percentage from diarrhoea patients and again suggests that a substantial number of typhoid carriers were present in the community at this time. Also in the 1990s, Wolday reported that 43.6% (48/110) of *Salmonella* from hospitalized patients were *S*. Typhi in Addis Ababa [16]. This isolation rate again corroborates previous studies in Ethiopia [3,5,17], showing that typhoid fever was a common cause of hospital admission.

Salmonellosis is particularly common in children of developing countries and Ethiopia is no exception [18]. In a study conducted in Jimma Hospital, South West Ethiopia, from March to July 2000, a total of 59

Salmonella strains were isolated from 384 pediatric outpatients with diarrhoeal illness [20]. Of these, Serogroup A comprised 5 (8.5%) isolates; B 17 (28.8%); C 13 (22%); D 8 (13.6%, other than *S.* Typhi); E 3 (5.1%); and *S.* Typhi 13 (22%). This increased isolation rate of *Salmonella* from diarrhoeal pediatric outpatients may indicate poor sanitary conditions. Further studies [21] indicated that the local practice of sanitation was far from satisfactory and that the personal hygiene status of parents responsible for food preparation and child rearing was poor. This study also showed that, of all *Salmonella* isolates, 78% (46/59) belonged to non-Typhi serogroups, which in turn indicates, not surprisingly, that these serogroups are responsible for the majority of diarrhoea in children. Although diarrhoea in children is associated with salmonellosis and with human immunodeficiency virus (HIV)-infection, it is not clear whether *S.* Typhi is more common where HIV has a high prevalence. To address this question a retrospective study was carried out on cases of *Salmonella* infections occurring in both HIV-infected and uninfected patients [18]. Of 28 non typhoidal *Salmonella* (NTS) isolates, 18 were from sero-positive subjects and 10 from sero-negative subjects; for 21 *S.* Typhi isolates, 9 were from sero-positive subjects and 12 from were from sero-negative subjects. Although it would be expected for NTS to be more common in HIV positive patients: HIV+ NTS+ versus HIV- NTS+ (HIV+/HIV-) 18 versus 10 (1.8), perhaps the surprising finding from this study is that HIV positive patients were less likely to have *S.* Typhi infection: HIV+ *S.* Typhi+ versus HIV- *S.* Typhi+ (HIV+/HIV-) 9 versus 12 (0.75). Similar findings had been reported from Zimbabwe, where 27.5% (14/51) of *S.* Typhi isolations and 62.5% (32/51) of NTS isolations were from HIV positive subjects [19]. While not conclusive, the evidence is that NTS is more readily able to infect HIV positive subjects whereas *S.* Typhi is less common in HIV positive cases than in HIV negative subjects. A properly designed case control study is needed to investigate this question further. In many developing countries, NTS have become serious pathogens, especially among immunosuppressed adults, and particularly in those with HIV/acquired immunodeficiency syndrome (AIDS) [22]. If it is true and HIV actually protects against typhoid fever, then valuable insights into the host-pathogen interaction during typhoid fever could be gained.

Other studies from Ethiopia on HIV co-infection include a study conducted between February and July 2001 in Jimma Hospital [23]. The study identified potential bacterial pathogens in the stool of HIV positive and HIV negative patients. However, of 372 patients (192 HIV+ and 180 HIV-) including 99 HIV-positive patients with diarrhoea, a total of only 8 *Salmonella* strains were isolated. This result is in agreement with studies conducted in Rwanda (11%) and Argentina (5%) [24,25] but much lower than the previous study conducted in Ethiopia (55.1%) [18]. Why such a low level of salmonellosis was seen is not clear. Something which we can conclude from the published data, however, is that NTS isolation is increasing in comparison with the isolation of *S.* Typhi (Figure 1). This could be due to the increase of HIV/AIDS and the amplification of NTS in combination with high levels of drug resistance. If so, NTS represents a real threat to public heath for the population as a whole.

Figure 1. Relative number of *Salmonella* Typhi and non-typhoid *Salmonella* reported in the scientific literature over time.



Research infrastructure in Ethiopia

As shown in the figure, reports of both *S.* Typhi and NTS seem to be decreasing over time. This may mean that *Salmonella* infection in the country as a whole is decreasing but a more likely explanation is that the research capacity of the country has declined. In the early 1970s and 80s there were two laboratories with bacteriology facilities: The Central Laboratory Research Institute and The Black Lion Hospital. Almost all hospitals in the country were referring cases of suspected salmonellosis to these laboratories which then published the results of their investigations. Later, more laboratories were established in different parts of the country and referrals became less common. These new

smaller laboratories did not have a research capacity and so it seems, therefore, that despite the presence of more cases of salmonellosis, indicated by the *Salmonella* isolates recorded in the daily record books of hospital microbiology laboratories, there is less published data.

Drug resistance profile

The extent of antibiotic resistance in developing countries such as Ethiopia is difficult to assess because *Salmonella* are not routinely cultured and so their resistance to the antibiotics cannot be tested. The results from the publications we were able to access are presented in Table 2.

Table 1. Summary of findings from published literature which identifies *Salmonella* Typhi in Ethiopia.

Reference	Resistance **	Location in Ethiopia	Strains collected	Total *Salmonella*	*Salmonella* Typhi
[9]	0	Addis Ababa	1975	7	7
[10]	<1%	Addis Ababa	1975-80	165	124
[3]	Not stated	Addis Ababa	1974-81	216	105
[4]	Not stated	Addis Ababa	1982-83	45	*
[5]	43%	Addis Ababa	1995	45	7
[15]	Not stated	Gondar	1994-6	80	17
[16]	6%	Addis Ababa	1993-6	110	48
[20]	54%	Jimma	2000	59	13

*Serogrouping was performed but the results were not presented.
** Resistance to first line drugs: Ampicillin, chloramphenicol or Co-trimoxazole.

Gedebou and Tassew report that of 124 *S.* Typhi tested against 11 drugs from 1974-81, all were essentially susceptible to all of the clinically relevant drugs [10]. Similar results were obtained by Gebre-Yohannes for 105 *S.* Typhi collected between 1974 and 1981 [3]. By 1996 the first resistant isolates appeared and Wolday reported that of 48 *S.* Typhi isolates collected between 1993 and 1996 from hospitalised patients in The Black Lion Hospital, Addis Ababa, 52.1% of strains were resistant to co-trimoxazole, 6% to ampicillin and a single isolate showed resistance to chloramphenicol [16]. By 1995, 28.6% of *S.* Typhi isolates were resistant to chloramphenicol [5] and in 2000, the most recent study, reports that 30.8% of the isolates of *S.* Typhi were resistant to chloramphenicol, 54% to ampicillin, and 38% to co-trimoxazole [20]. These data show clearly the emergence of a significant resistance problem in the last decade in *S.* Typhi isolated in Ethiopia, especially in Jimma.

Table 2. Percentage antimicrobial susceptibility of *Salmonella* Typhi over time in Ethiopia.

Date	N					
		NA	AM	CB	CE	CL
1974-81		NR	NR	NR	NR	100
1975-80	124	NR	99.2	98.4	99.2	100
1993-96	48	NR	94	96	97	99
1995	7	NR	57	57	42	71
2000	13	92	46	62	54	69
Date	N					
		GM	K	PB	TE	SxT
1974-81		100	NR	100	NR	100
1975-80	124	100	100	99.2	98.4	100
1993-96	48	99	100	NR	94	47.9
1995	7	100	57	100	28	57
2000	13	100	77	100	46	62

Amp: ampicillin, CL: chloramphenicol, PB: polymyxin B, TE: tetracycline, NA: Nalidixic acid, CB: carbenicillin, GM: gentamicin, SxT: trimethoprim-sulphamethoxazole, Cep: cephalothin, K: kanamycin, NR: Not reported.

Conclusion and Recommendations

All the studies on salmonellosis conducted by different investigators in Ethiopia have shown the widespread distribution of *Salmonella* isolates in the community. Several serovars, including *S.* Typhi were, by the year 2000, associated with multiple drug resistance to clinically relevant drugs. The only study to type at the serovar level shows that multi-drug resistant *S.* Concord was very common in Ethiopia by 1980. This serovar is rare elsewhere [26-28]. Typhoid fever and carriage of *S.* Typhi was present in 2000 but there has been no reliable data since then. We must therefore assume that typhoid fever is still present in Ethiopia.

Based on published literature we conclude the following:

The epidemiology of salmonellosis in Ethiopia has not been well investigated and that funding is needed for continuous surveillance both nationally and locally in order to develop national and local guidelines for antibiotic treatment. One way to move towards this goal would be to set up a central bacteriological reference facility.

This central facility should be able to identify *Salmonella* to the level of serovar and measure quantitatively antibiotic susceptibility, so that comparison with serovars isolated from humans, animals and food products could be possible. In the

longer term the introduction of molecular typing tools is essential.

To decrease the incidence of salmonellosis in Ethiopia, besides giving attention in identification, susceptibility testing and reporting during routine bacteriological analysis, public health measures such as improving personal and food hygiene and intensive health education has to be given.

The advantages of continuous surveillance of *Salmonella* serovars include:

Epidemiology: Early warning of new strains emerging in humans or in the food chain.

Improved empirical treatment: Information to guide best clinical practice for specific therapy (systemic antibiotics may be required for treatment of typhoidal salmonellae).

Public health: Improved knowledge for education and awareness of good sanitation practice.

Health policy: Evidence base for decisions on the control and prevention of salmonellosis including the introduction of vaccination.

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