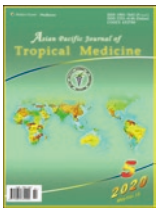

Review Article

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Current trends in the epidemiology and management of enteric fever in Africa: A literature review

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ABSTRACT

Enteric fever remains a tropical disease of public health significance in Africa, due to its high endemicity and transmission rates, more in sub-Saharan Africa with 7.2 million cases of typhoid fever annually and incidence rate of 762 per 100 000 person-years when compared with Northern Africa with a reported incidence rate of 557 per 100 000 person-years and lower. Recent studies show that almost all regions of sub-Saharan Africa are tending towards high incidence rates, especially Central and Western Africa. Though clinically indistinguishable from paratyphoid fever, typhoid fever causes more morbidity and mortality than paratyphoid fever, with a greater threat to children. Risk factors include consumption of contaminated water, patronizing food vendors and a history of contact with a case or a chronic carrier, amongst others. Environmental factors such as the rainy season, open sewers, contaminated water bodies and areas of low elevation have been implicated. Diagnosis in Africa is challenging due to resource constraints, as many centres still depend on clinical diagnosis and serodiagnosis using Widal test, in an era where more sensitive and specific tests exist. The polymerase chain reaction is one of the most sensitive diagnostic methods, while culture (particularly bone marrow) is considered to be one of the most specific. Quinolones (ciprofloxacin) and third-generation cephalosporins, amongst others, remain potent in the management of enteric fever, with resistance to quinolones gradually on the rise. Poor diagnostics, poor antibiotic stewardship and lack of drug (antibiotic) regulation are contributors to the problem of antibiotic resistance in Africa. Prevention of typhoid fever through vaccination, especially in children is still under investigation, with steady progress being documented. Overall, long term prevention strategies for typhoid fever should be based on improved sources of drinking water, good sanitation and hygiene, food safety and poverty alleviation.

KEYWORDS: Enteric fever; Typhoid fever; Epidemiology; Africa; Public health

1. Introduction

There are over 2 600 serovars of *Salmonella (S.) enterica* which have been classified based on their surface antigens, lipopolysaccharide (O) antigen and flagellar (H) antigen[1]. Serovars of *S. enterica* are divided into two groups according to their disease outcome in humans: typhoidal and nontyphoidal salmonellosis[2-5]. *S. typhi* and *S. paratyphi* are typhoidal Salmonellae that cause life-

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threatening systemic infections[6,7]. Non-typhoidal *Salmonella* cause self-limiting gastroenteritis in otherwise healthy humans (or animals), examples of which are *S. enteritidis* and *S. typhimurium*[8]. Enteric fever is a human-specific systemic illness that results from infection by two serovars of *S. enterica- typhi* and *paratyphi* (A, B, C), which result in typhoid and paratyphoid fever respectively. Humans remain the only source of these bacteria, with no animal or environmental reservoirs. It is transmitted *via* the ingestion of food or water contaminated by the faeces of an acutely infected, convalescent or chronic asymptomatic carrier[9]. The disease is much more common in Africa and Southeast Asia than in other regions of the world[10]. Poverty and poor hygiene are also known risk factors for transmission. Outbreaks of typhoid fever have been reported in Africa, with case fatality of up to 53%[11]. Typhoid fever contributes more to the global burden of enteric fever than paratyphoid fever[12]. Both illnesses are clinically indistinguishable, and they share some symptomatology with other diseases of high prevalence in Africa, especially malaria. Hence, reliance on clinical acumen alone, without laboratory confirmation can lead to misdiagnosis and over-reporting of enteric fever. In a bid to avoid missing positive cases of typhoid fever, clinicians may resort to treating febrile patients empirically to cover for enteric fever and other common causes of fever such as malaria[13].

Despite the plethora of existing knowledge on the epidemiology and management of enteric fever, especially typhoid fever, the disease remains a public health burden in Africa[14]. Contrasting statistical indices have been provided for various parts of the continent, putting in question the actual disease burden of enteric fever in Africa. Information on where Africa stands as regards the uptake and implementation of current practices such as antibiotic regimens, adequacy of investigative modalities and vaccination against *S. typhi* are also deficient. These have necessitated this review, to fill the gap in knowledge concerning the African position in combating this public health menace.

The aim of this study is to review the literature to determine current epidemiological trends of enteric fever, diagnostic methods used, antibiotic regimens favoured and the uptake and implementation of vaccination for *S. typhi* and other preventive modalities in Africa, particularly in the last decade (2010-2019).

Note: In the course of the review, typhoid fever and enteric fever may be used inter-changeable, as typhoid fever poses a greater threat and is of more public health significance than paratyphoid fever.

2. Epidemiology of enteric fever in Africa: burden of the disease

Typhoid and paratyphoid fever contribute significantly to annual morbidity and mortality, more so in low- and middle-income countries. Typhoid fever is of more public health significance globally, as it is estimated to have caused about 21.7 million illnesses and 217 000 deaths, while paratyphoid fever caused 5.4 million illnesses in the year 2000[15]. By the year 2010, there were 26.9 million cases of typhoid fever and 200 000 deaths[7]. However, a global decline in the number of cases of typhoid and paratyphoid fever was noted in 2017, to about 14.3 million cases, 12.1% (1.73 million) of which were from sub-Saharan Africa[12]. Data from Africa however, are limited due to inadequate epidemiological surveillance activities and restricted laboratory capacity, thus, the existing enteric fever estimates were extrapolated from studies that have been published over different time periods.

2.1. Regional epidemiology

The incidence of typhoid fever is often classified as low, medium, high and very high, corresponding to incidence bands of less than 10, 10 to 100, greater than 100 to less than 500, and greater than or equal to 500 per 100 000 person-years respectively[16]. In the year 2000, Africa was estimated to have a medium incidence[15]. Recent studies confirm a higher burden than previously estimated, with all regions of sub-Saharan Africa (excluding Southern and North Africa) having a great chance of being in the very high incidence category[17]. In a model designed recently (2017) by Antillón and colleagues, it was projected that 17.8 million cases of typhoid fever occur annually in low- and middle-income countries with 7.2 million cases in Sub-Saharan Africa at an incidence rate of 762 per 100 000 person-years. The incidence rates for Central, Eastern, Western, Southern sub-Saharan Africa and Northern Africa (and the Middle East) are shown in Table 1[17]. In a regional literature review from Mediterranean North Africa carried out in 2009, typhoid fever was found to be endemic in the region with an estimated incidence rate of 10-100 cases per 100 000 person-years, a rate much lower compared to the projection by Antillón *et al*[17,18]. The incidence rates for Algeria, Egypt, Libya, Morocco, and Tunisia are 3-22, 13-59, 7-21, 8-17 and 1-6 cases per 100 000 person-years respectively[18]. This may indicate a potential rising trend in the incidence of typhoid fever in North Africa, though the rates are much lower when compared with other parts of Africa. Another recent study on the global burden of typhoid fever modeled incidence rates for the entire globe. The incidence rates per 100 000 recorded for Africa were significantly lower than the Antillon model, however, the regional pattern was similar, with Western Africa having the highest incidence, followed by Eastern Africa, Central Africa, North Africa (and the Middle East) and Southern Africa in descending order (Table 1)[12,17].

In South Africa, where typhoid fever is a notifiable disease, the estimated annual incidence rate is 0.1 cases per 100 000 person-

years and this has remained constant for the last several years except in 2005 when there was an epidemic and it rose to 0.4 per 100 000 person-years[19]. However, previous data in South Africa revealed high incidence rates with over 4 000 cases being notified annually based on clinical, serological or microbiologically confirmed diagnoses[20]. The rest of Southern Africa suffers from upsurges in the incidence of typhoid fever, with outbreaks having been reported in Zimbabwe, Zambia, Mozambique, and Malawi[21–24].

Table 1. Incidence of typhoid fever in Africa by region.

Regions	Typhoid fever incidence rate (per 100 000)	
	Antillon model** Study period (1980-2014)	GBD model*** Study period (1990-2017)
Northern Africa*	557	39.3
Central Africa	1 459	81.4
Eastern Africa	620	151.9
Western Africa	753	161.1
Southern Africa	149	2.3

*Northern Africa's incidence rates were calculated with the Middle East. **Antillon model-refers to data got from a model developed by Antillon and colleagues[17]. ***GBD model-refers to data got from a model developed from the global burden of diseases, injuries and risk factors study (GBD) 2017[12].

2.2. Typhoid versus paratyphoid fever

As regards paratyphoid fever, data on its burden in Africa are limited[6]. The majority of studies of enteric fever in these regions do not differentiate between *S. paratyphi* A and *S. typhi*; *S. paratyphi* B and C are also seldom reported[25]. A population-based study conducted in Kenya that utilized active surveillance for enteric fever in a population of 57 000 living in an informal settlement and rural area found no cases of *S. paratyphi* A[26]. In five hospital-based studies conducted in the West African countries of Nigeria, Togo, Senegal, and Benin, the proportion of enteric fever due to *S. paratyphi* A ranged from 0 to 34.4%[25]. Other works reported estimated incidence rates for paratyphoid fever in sub-Saharan Africa and North Africa/Middle East for the year 2010 to be 77.4 and 0.8 cases per 100 000 person-years respectively, while the mortality rates were 0.4 and <0.1 deaths per 1 000 person-years respectively[7].

Analysis of a five-year typhoid fever surveillance data in Ghana, West Africa showed a typhoid incidence rate of 0.68%-1.60%[27]. In Nigeria, typhoid incidence ranges from 3.9% to 18.6%, while in Burkina Faso, the annual incidence rate is between 107 and 402 per 100 000[28,29]. In the East-African region, typhoid fever occurs at variable incidence rates. For instance, in Kenya, the crude incidence of *S. typhi* is between 29 and 247 cases per 100 000 person-years[26], while in Uganda, outbreak proportions of typhoid fever incidence have been reported[30]; between 2013 and 2016, 210 204 cases were reported with an estimated incidence rate of 160 cases per 100 000 person-years in Uganda[31].

2.3. Transmission of enteric fever

S. typhi and *S. paratyphi* are transmitted through the ingestion of fecally contaminated food or water, improper hygiene, and unsafe food/water handling practices[7,17]. Individual-level risk factors include contaminated water supply, patronizing food vendors, ingestion of raw fruits and vegetables and a history of contact with a case or a chronic carrier. The risk of environmental transmission of typhoid fever is higher in the rainy season, proximity to open sewers and highly contaminated water bodies and residing in areas of low elevation[32–35]. Many typhoid outbreaks in African countries have been associated with consumption of untreated or sewage-contaminated water including South Africa, Zambia, Malawi, Uganda, Zimbabwe[36–39]. During outbreaks, a gradual decline in the number of cases is usually noted following patient treatment and in particular, public health interventions such as the provision of free water chlorination products, sensitization of residents on water treatment and establishment of safe alternative water sources in the affected communities[30,40]. Across Africa, enteric fever occurs in a range of seasonal patterns. A distinct seasonal pattern has been observed in Blantyre, Malawi with a peak in March-June following the rainy season, May and October in Kasese district, Uganda[31,41], but less clear associations with rainfall were found in Kenya[26,42]. Sustained precipitation in communities devoid of efficient drainage systems and water treatment presents considerable risk to its dwellers[31].

Socio-demographic factors such as gender and age influence the incidence of typhoid fever[43]. Children less than 20 years of age, especially those aged 0-14 years, bear the greatest burden of typhoid fever in sub-Saharan Africa[44]. Children have a poorly developed natural immunity (conferred by previous infection) and are also more likely to be exposed to fecal contamination in the immediate environment surrounding their home through outdoor play[45,46]. Some studies have observed a case distribution skewed towards the male gender and it reflects the association between masculine roles/activities and typhoid fever risk profile, as men often have a carefree attitude to the hygienic conditions of food or the environment where such is prepared[43,47]. Urbanization has a role in typhoid fever incidence as densely populated urban slums have a higher incidence of the disease than rural areas in Africa[26,48,49], though *S. typhi* is an important pathogen in both rural and urban settings[50].

2.4. Disease surveillance

The Typhoid Fever Surveillance in Africa program was created in response to the World Health Organization's call for more epidemiological data to address the knowledge gaps in the incidence and antimicrobial resistance patterns of invasive *Salmonella*

infections in different countries in sub-Saharan Africa with previous typhoid fever studies. It was conducted between 2010 and 2013 across 13 surveillance sites in 10 countries. The results of this study represent a comprehensive analysis done in sub-Saharan Africa with the aim of supporting policymakers with information to aid preventive efforts against typhoid fever[51]. However, a recent study to investigate severe typhoid fever burden [the Severe Typhoid in Africa (SETA) study] was carried out in rural and urban sites with high typhoid endemicity across sub-Saharan Africa. It aimed to explore the burden of severe typhoid fever infections, clinical characteristics, immune response, and bacterial shedding patterns, as well as a public and private cost burden. This information would be vital for policymakers on planning immunization strategies as well as effective typhoid control and prevention policies[52].

3. Diagnosis of enteric fever-peculiarities in Africa

3.1. Clinical diagnosis

The role of clinical judgment in the diagnosis of typhoid fever cannot be overstated. However, care must be taken in order to distinguish it from other gastrointestinal diseases and febrile illnesses. This is majorly done *via* meticulous history taking and physical examination. Differential diagnoses include malaria, appendicitis, amebiasis, tuberculosis, leishmaniasis, toxoplasmosis, brucellosis, typhus, influenza, rickettsial disease and lymphoma[53]. These can be excluded by carefully analyzing the symptoms and laboratory investigations.

The classical syndrome begins 7-14 days after the ingestion of the organism and usually spans 4 weeks. There is an initial prodromal phase that is characterized by non-specific symptoms which include dull frontal headache, delirium, and malaise[54,55]. During this stage, the salmonellae stimulate inflammation in the bowel and in return causes monocytic infiltration of the Peyers patches; this is responsible for the abdominal symptoms such as right upper quadrant pain and constipation. The fever pattern is characterized as a rising body temperature during the day which falls subsequently by morning (step ladder pattern)[53,54]. The peaks and troughs progressively increase with time. By the end of the first week of illness, the fever plateaus. At this time, the individual develops salmon-colored, blanching, truncal, maculopapular rash called rose spots. These are visible in races of light skin color and may not be of any diagnostic use in individuals of dark skin color. However, they appear for a short period of 2-5 days[55].

During the second week of illness, most of the aforementioned symptoms worsen. There may be abdominal distension and splenomegaly. Relative bradycardia (when associated with fever-Faget's sign), a dicrotic pulse and meningismus may be noticed[53,54]. By the third week, the patient continues to deteriorate, with weight loss and anorexia. Some individuals have green-yellow diarrhea (pea soup)[54]. At this point, they enter into a typhoid state characterized by confusion, apathy, psychosis; some have bowel perforation that can lead to peritonitis, others may develop myocarditis or intestinal hemorrhage (rare)[53]. The fourth week, a stage of defervescence is characterised by resolution of fever and general improvement in clinical status, if the patient survives prior stages.

3.2. Laboratory diagnosis

Culture has been considered the gold standard for diagnosing enteric fever for decades; however, it is not without its drawbacks. *S. typhi* and *S. paratyphi* can be isolated from the specimen such as bone marrow, blood, intestinal secretions, stool, and urine, in decreasing order of sensitivity. Despite a high specificity (100%), cultures demonstrate variable sensitivity rates-less than 50% in stool culture[56,57], 66% in blood culture[58] and up to 90% in bone marrow[59]. A bone marrow specimen is considered the best for culture, found superior to the blood which may miss some true positive cases[58]. Bone marrow culture can remain sensitive for up to 5 days after the commencement of treatment, but the collection of a bone marrow sample is considered hectic and potentially harmful to the patient, especially when deemed unnecessary[60]. When the specimen is collected, it is advised that multiple series of cultures be conducted to increase the sensitivity[61]. The specimen is cultured using selective media and incubated for at least 7 days. A preliminary result can be gotten after 2-3 days[53]. The time taken to obtain a result using traditional culture techniques, lack of manpower and infrastructure and the often low sensitivity of cultures limit their use. The polymerase chain reaction is a more sensitive and efficacious test in the detection of *S. typhi* genetic sequences in blood and/or urine; it has been found to detect culture-negative typhoid fever[62,63]. However, the unavailability of this test, especially in resource-poor regions limits the use of the test in Africa[64].

Serologic techniques used in the diagnosis of enteric fever include the tube/slide agglutination test (Widal test), indirect hemagglutination, indirect fluorescent Vi antibody and enzyme-linked immunosorbent assay (ELISA), amongst others. The Widal test, developed in 1896, detects antibodies against purified O and H antigens in sera of patients suspected to be infected with *S. typhi* or *S. paratyphi*, by agglutination reaction (clumping)[65]. Antibodies to the Vi capsular antigen though useful, have limited use in the diagnosis of acute typhoid fever infection but high titres do occur in carriers[66,67]. Serial dilutions of unknown sera are tested against antigens from representative Salmonellae. At least two serum specimens, obtained at intervals of 7-10 days, are needed to prove

a rise in antibody titre. However, obtaining a second sample for confirmation may prove challenging due to the possible lack of follow-up for repeat sample collection. The interpretative criteria when single serum specimens are tested vary, but a titre against the O antigen of >1:320 and against the H antigen of >1:640 is considered positive[68]. In interpreting the Widal test, the interpreter should bear in mind that the presence of cross-reactive antibodies to other illnesses such as non-typhoidal *Salmonella* infections, malaria, dengue fever, miliary tuberculosis, endocarditis, chronic liver disease, and brucellosis, can confound the result[65]. In developing countries, the Widal test has been used as the sole means of diagnosis of typhoid fever for many years[56,69,70]. In the majority of the regions in Africa, it is used because of its relatively cheap cost and the fact that it is easy to perform and requires minimal skill and basic equipment[69,71,72]. However, studies have raised alarm about the apparent increase in the incidence of typhoid fever in healthcare facilities in Nigeria and other parts of Africa where this test is used[56,71,73-75]. In contrast, in developed countries, the Widal test if used at all is used as an aid in the diagnosis of enteric fever in the acute phase of illness, rather than the sole diagnostic methods[65].

There are several commercially available immunodiagnostic kits, and the Tubex®, Typhoid/Paratyphoid (TP) test, Typhidot®, TyphiRapid®, and Cromotest® O and H (semiquantitative slide agglutination) have shown promise with documented high sensitivities and specificities[64]. These methods deserve further exploration in terms of feasibility, cost analysis, technical and infrastructural provisions, by stakeholders in developing countries where they would be of use in improving enteric fever diagnostics and help to phase out the use of Widal test in such settings. Another emerging diagnostic technique that has found use in the rapid identification of microbial infections is the Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) mass spectrometry. It is able to differentiate the *S. typhi* serovar from other Salmonellae. It is said to provide rapid, reliable results within minutes and is also labour and cost friendly[76-78]. However, the cost-effectiveness of this investigative modality is relative, as the studies quoted are from developed, resource-rich climes. The cost of acquiring and maintaining the needed equipment runs into tens of thousands of US dollars[78]; hence, the cost-appropriateness of this test for the developing, resource-poor climes is queried.

Histology can also be used to make a diagnosis, although reserved for research purposes as it is not a practical means of making a diagnosis. The hallmark histologic finding in enteric fever is the infiltration of tissues by macrophages that contain the bacteria, degenerated lymphocytes, and erythrocytes. The aggregation of these is called a typhoid nodule. They can be found in the mesenteric nodes of the small intestine, spleen, kidney, bone marrow and liver[5].

4. Management of enteric fever

The choice of antibiotics depends on the susceptibility of *S. typhi* strains in the area of residence or travel. With the emergence of new resistant strains of *S. typhi* over the years, there have been concomitant modifications in treatment modalities with respect to antibiotics. Prior to the antibiotic era, mortality averaged 10%-15% for untreated typhoid[79]. Following the introduction of chloramphenicol in 1948, this plummeted to <1% and the duration of fever from 14-28 days to 3-5 days. A high relapse-rate (10%-25%), bone marrow toxicity, high rate of chronic carriage, together with the emergence of plasmid-mediated resistance to chloramphenicol occurred in the 1970s[79], which birthed the use of ampicillin and trimethoprim-sulphamethoxazole (TMP-SMZ) as the mainstay of treatment[80]. In the 1980s, however, Multi-drug resistant (MDR) *S. typhi* emerged. These bacteria are resistant to chloramphenicol, ampicillin, TMP-SMZ, streptomycin, sulfonamides, and tetracycline. Plasmid-mediated resistance is also implicated in this. The fluoroquinolones were the next, coming into use from the 1980s to the 2000s. MDR strains of *S. typhi* are common in Africa but remain susceptible to ciprofloxacin, thus, ciprofloxacin is currently the treatment of choice for typhoid fever in Africa[81]. Ciprofloxacin has also been shown to be effective against infections due to *S. paratyphi*[82]. However, resistance to ciprofloxacin (*via* specific mutations in *gyrA* and *parC*, which code for the binding region of DNA gyrase and topoisomerase Ⅳ respectively) is on the rise and has also been reported from the African continent[21], though uncommon when compared with Asia[81,83]. Norfloxacin, ofloxacin and perfloxacin are other quinolones that have been shown to be effective in some clinical trials.

Cefotaxime, cefoperazone, ceftriaxone and some other third-generation cephalosporins have remarkable success in the treatment of typhoid fever with shorter courses (3 days), compared to the usual 10 to 14-day regimens[84,85]. These drugs should be reserved for quinolone-resistant cases. Growing numbers of extensively drug-resistant (XDR) *S. typhi* have been identified, in which case there is resistance to classical first-line antibiotics (ampicillin, chloramphenicol, TMP-SMZ), fluoroquinolones and third-generation cephalosporins[83,86]. Aztreonam (a monobactam), azithromycin, carbapenems (meropenem) and tigecycline have been shown to be effective in such cases[83,87,88].

Good nursing care and supportive management are key to the management of typhoid fever. Salicylates and antipyretics should be avoided as they cause severe hyperhidrosis and hypotension. Though the role of surgery remains controversial, segmental resection and anastomosis appear to be the best treatment for typhoid perforation[89].

5. Current public health concerns

5.1. Typhoid vaccines

There are two commercially available vaccines for typhoid fever: the live oral vaccine (Ty21a) and the Vi polysaccharide vaccine (ViCPS or Vi)[90-92]. Ty21a is an attenuated vaccine strain of *S. typhi*[91-93]. Ty21a induces cell-mediated and humoral immunity against *S. typhi* and can be used in people age 5 years and above[90-92]. It is known that Ty21a vaccine-induced antibodies have the ability to cross-react with *S. paratyphi* A and B which shows that the vaccine may provide some immunity against paratyphoid fever, as there are no available vaccines against *S. paratyphi*[6,91,94].

ViCPS vaccine is based on the *S. typhi* Vi antigen. Both *S. typhi* and *S. paratyphi* C express ViCPS, while *S. paratyphi* A and B do not. ViCPS induce a T-cell independent humoral immune response[90]. Its safety for use in children as young as two years old emphasizes its importance because children have a higher risk of infection with *S. typhi* in endemic areas[90,95]. Studies have shown that the cumulative efficacy of the Ty21a vaccine and ViCPS vaccine is 51% and 55%, respectively[96]. The use of this vaccine in school-aged children (older than 2 years) may be beneficial in decreasing the risk of transmission in the short to medium term by conferring herd immunity. A limitation in the use of typhoid vaccines is the short duration of immunity conferred, which diminishes within the first three years[97].

Efforts on typhoid vaccines are being made internationally on the development of vaccines that are more efficacious and can protect children less than two years of age. Conjugate vaccines that combine ViCPS with inactive forms of bacterial exotoxins have been developed and are being investigated. ViCPS conjugated with tetanus toxoid (Vi-TT or Typbar-TCV) appears to be the most promising, has been approved for private use in India and Nepal and has recently been prequalified by the WHO[98-101]. The Vi-TT vaccine has proven to stimulate strong immune responses in children even in those younger than two years of age[99].

Another ViCPS conjugate that is likely to succeed is the Vi-rEPA in which ViCPS is combined with a recombinant exoprotein A from *Pseudomonas aeruginosa*[102]. It has been shown that Vi-rEPA has the potential to be effective in children that are not up to two years of age. A study carried out on Vietnamese children showed that Vi-rEPA was immunogenic in children between age two to five, with an effectiveness rate of 91.5%[103]. Vi-DT is also another ViCPS conjugate vaccine that is being actively investigated. Vi-DT consists of ViCPS conjugated to recombinant diphtheria toxoid, an inactivated diphtheria toxin produced by Corynebacterium diphtheria[104]. Vi-CRM197 is made from the conjugation of ViCPS with CRM197, a non-toxic, genetically-detoxified mutant of diphtheria toxin. Though it has shown less promising results in certain populations, further investigations are required for this conjugate vaccine[105].

Currently, the two commercially available typhoid vaccines have not been incorporated into the Expanded Immunisation Program of Nigeria's health policy[28]. Studies on the development and uptake of typhoid vaccines in Africa are limited.

5.2. MDR typhoidal Salmonellae

The spread of MDR *S. typhi* strains has been reported. Resistant strains to drugs like ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole (cotrimoxazole) and recently, ciprofloxacin have been reported in Africa and Asia, which could make the treatment of the disease more difficult[106]. A retrospective cohort study by Akinyemi *et al*. in Nigeria (Lagos, Kano and Abuja), amongst patients (adults and children) clinical diagnosed with enteric fever and confirmed with blood culture, from 1993-2015 showed that there was an increase in the trend of MDR *S. typhi* over the study period, particularly in Lagos. Cefuroxime, cefotaxime and ciprofloxacin-resistant *S. typhi* were also noted to be on the rise in recent years[28]. In another study conducted in North-central Nigeria in 2015, MDR *S. typhi* was prevalent, however, no resistance was documented to ciprofloxacin or imipenem[107]. Use of un-prescribed antibiotics, over-the-counter antibiotic sales, and non-completion of the prescribed dose of antibiotics may account for the high prevalence of antimicrobial resistance noted in Nigeria, where the sale of antibiotics in patent medicine stores and pharmacies is not strictly regulated. Antimicrobial resistance (MDR strains) and reduced ciprofloxacin susceptibility are gaining ground in different regions of Africa, with copious evidence in East, West and South Africa (Ghana, Kenya, Tanzania, Uganda, Burkina Faso, Guinea Bissau, and Madagascar to mention a few)[29,44,108-110]. Some South African researchers discourage the use of ciprofloxacin as a first-line agent, as up to 50% resistance was documented in a study of *S. paratyphi* isolates, and isolated cases of clinical treatment failure and mortality in another study in the region, from ciprofloxacin-resistant *S. typhi*, have been documented[111,112].

6. Conclusions

Enteric fever, particularly typhoid fever is a significant public health problem in Africa. The burden of the disease is variable across different regions of the continent, with higher morbidity and mortality in children. Poverty, personal and environmental hygiene, food and water safety are important determinants that can serve as focal points for public health interventions. It is recommended that efforts be made by stakeholders in Africa, to make available means

for accurate, yet rapid diagnostic tests, as the prevalent method for diagnosis in many parts of the continent (Widal test), lacks the sensitivity and specificity required of a diagnostic test. There is also a need for antibiotic stewardship and drug (antibiotic) regulation, to prevent the spread of mutant species of *S. typhi* which fail to respond to a wide range of antibiotics (XDR *S. typhi*). Efforts towards typhoid vaccination in endemic regions need to be intensified, both in the lab (research and development) and in the field. There is a need to fill a knowledge gap in the uptake and utilization of typhoid vaccination in various regions of the continent. Efforts must be intensified in the use of long term prevention strategies for enteric fever such as protection of water sources, good sanitation and hygiene (personal and environmental), food safety and poverty alleviation.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Authors' contributions

OAA conceptualized and designed the research idea, and was involved in the literature review, drafting of the manuscript and final review of the manuscript. OOA, OE, DFR, TOB and OBN participated in the literature review, drafting and review of the manuscript. BAA provided editorial support, and reviewed the final draft of the manuscript. AOI and AO provided supervisory support to the project.

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