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# The Burden of Enteric Fever (Typhoid Fever) among Hospitalized Febrile Patients: An Insight in a Teaching Hospital in South East Nigeria

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## ABSTRACT

***Background:*** *Typhoid fever is a major public health problem in many developing countries, especially in sub-Saharan Africa, where access to safe water and sanitation is limited.*

*Different serovars of Salmonella constitute diverse geographical distribution, different host specificity and impose different syndromes during infections. In clinical settings, Salmonella infections are distinguished into typhoidal and non-typhoidal Salmonella serovars. Infected individuals usually suffer from prolonged fevers and headache, and later coupled with diarrhea and abdominal pain. Meanwhile, several other symptoms were also observed in the patients that include a non-productive cough, constipation, meningismus, deafness, confusion, as well as weight loss. On the occurrence of death, it has mainly associated with seizures, intestinal perforation, pneumonia, and coma. Nigeria, the most populous country in Africa, is highly endemic for typhoid fever, with an estimated incidence of 100 cases per 100,000 populations. Typhoid fever is a significant public health concern in Nigeria, and several studies have investigated the prevalence of the disease and its burden in the country. A systematic review and meta-analysis of studies conducted in Nigeria between 2000 and 2018 reported an overall pooled prevalence of typhoid fever of 20.9%.*

***Aims:*** *To determine the burden and frequency of typhoid fever among hospitalized febrile patient in David Umahi Federal University Teachiong Hospital, Uburu, between January 2023 to June 2023.*

***Methodology:*** *The 50ul of blood samples collected from hospitalized febrile patients were spun for 5minutes using 800D Centrifuge to separate the blood plasma from the serum. A drop of the antigens was added to the serum according to the labels on the 8 circles slide 4 circles for antigen O and 4 circles for antigen H. The content is mixed in each circle with separate wooden applicator stick and spread to fill the whole area of the individual circle, and then the glass slide was gently rocked back and forth for 2 minute and observed for agglutination. The ones that have the agglutinins are picked to find the titer. 5 drops of blood serum were made on a clean slide, for each of the reagent that agglutinated, a micropipette that is calibrated from 5ul to 50ul pipette was used. The following volumes of the agglutinated samples; 20ul, 40ul, 60ul and 80ul, 100ul, 120ul, 140ul, 160ml into the circles then a drop of the reagents hat caused the agglutination are added to each of the samples. The content was then mixed in each circle with a separate wooden applicator stick and spread to fill the whole area of the individual circle, then rocked the slides gently back and forth for 2 minute and observed for agglutination, it is then numbered 1 to 8 having them as 1 in 20 dilution, 1 in 40 dilution, 1 in 60 dilution, 1 in 80 dilution, 1 in 100 dillution, 1 in 120 dillution, 1 in 140 dillution and 1 in 160 dillution. (1/20ul, 1/40ul, 1/60ul 1/80ul , 1/100ul, 1/120ul, 1/140ul, 1/160ul) dilution continues until the titre is gotten. The positive agglutination is picked as the titre and are visible within 2 minute. Results were recorded according to the dilution and observed for the titer which was the sample with agglutinins. Negative results were indicated by the absence of agglutination between the patient's antibodies in serum and specific Salmonella antigens and results were noted as "non-reactive" (NR). For O antigen agglutination is said to be significant from 1/80 and above, for H antigen agglutination is significant from 1/160 and above.*

***Result:*** *There are 226 hospitalised febrile patient whose samples were analyzed for enteric (typhoid) fever between January to June 2023 at David Umahi Federal University Teaching Hospital, Uburu. 107 (47.3%) samples showed significant reaction of widal test (reaction from 1/80 and above) for both H and O antigen. The number of males tested positive, were 26 (33.3%) out of 78 male participants while 81(54.7%) out of 148 females participants were tested positive to vwidal tests. Ages 31-50years recorded the highest prevalence while 0-10years, recorded the lowest prevalence.*

***Conclusion:*** *Typhoid (Enteric) Fever still remain a disease of major public health importance and of significant burden to our health service delievery: Typhoid have similar symptom with other infections such as fever, headache, diarrhea or constipation, abdominal pain, fatigue and anorexia, therefore, treatment should be based on adequate laboratory diagnosis. The emergence of antibiotic-resistant strains of S. Typhi is a growing concern, the need for appropriate antibiotic stewardship can never been over emphasized.*

## Keywords
Enteric fever, vwidal test, Prevalence, Serovar.

## Introduction
Typhoid fever is a bacterial infection caused by the bacterium *Salmonella enterica serotype Typhi*, which is transmitted through contaminated food, water, and occasionally by person-to-person contact [1]. Typhoid fever is a major public health problem in many developing countries, especially in sub-Saharan Africa, where access to safe water and sanitation is limited [2]. Ebonyi State is located in the Southeastern region of Nigeria and has a population of approximately 3.8 million people [3]. Like many other states in Nigeria, typhoid fever is a significant public health concern in Ebonyi State, with a high burden of morbidity and mortality.

Salmonella is an intracellular pathogen that causes a variety of diseases termed salmonellosis, ranging from gastroenteritis to enteric fever in humans and animals [4]. Its genus comprises of two distinct species which are Salmonella bongori and Salmonella enterica, the former is a commensal to cold-blooded animals while the latter comprises six subspecies; enterica, salamae, arizonae, diarizonae, indica, and houtenae [5]. These subspecies are further divided into 50 serogroups characterized based on O (somatic) antigen and more than 2600 serovars by H (flagellar) antigens in the genus [6]. However, only 50 serovars within the subspecies enterica are known for common cause of infections in humans and warm-blooded animals [5]. Different serovars of Salmonella constitute diverse geographical distribution, different host specificity and impose different syndromes during infections [5]. In clinical settings, Salmonella infections are distinguished into typhoidal and non-typhoidal *Salmonella serovars* [5].

Genetic diversity observed in Salmonella strains is attributed to the ability of lysogenic bacteriophages to mediate gene transfer to the bacterial chromosome (horizontal gene transfer) or by gene degradation, besides other factor [6,7]. However, association of Salmonella with human infections only involves a small fraction of its serovars, which most pertain to *Salmonella enterica ssp* [6]. In humans, Salmonella infection is mainly routed from ingestion of contaminated food or water that causes gastroenteritis which is a localized infection, or enteric fever, a severe systemic infection [6]. Of the prominent salmonellosis in humans are typhoid fever, an infection caused by *Salmonella enterica serovar Typhi*, and paratyphoid fever. Paratyphoid fever is another undistinguishable clinical condition caused by *Salmonella enterica serovar* Paratyphi A, B or C [8]. Infected individuals usually suffer from prolonged fevers and headache, and later coupled with diarrhea and abdominal pain. Meanwhile, several other symptoms were also observed in the patients that include a non-productive cough, constipation, meningismus, deafness, confusion, as well as weight loss. On the occurrence of death, it has mainly associated with seizures, intestinal perforation, pneumonia, and coma [9]. *S. Typhi* is the main causative agent for typhoid fever, a systemic illness contracted mainly via ingestion of contaminated food or water [10,11]. Unlike the other *serovars* of Salmonella such as *S. Typhimurium* and *S. Enteritidis* which often associated with

gastroenteritis and can infect a wider host range, *S. Typhi* infection is specific to humans [12].

In *Salmonella species*, penetration of epithelial cells plays the most important step in pathogenesis [13]. Similarly, *S. Typhi* also initiate infection by invading intestinal epithelial cells and transferred to lamina propria [14,15]. However, unlike *S. Typhimurium*, *S. Typhi* allows the process of colonization in deeper body tissues by avoiding triggering early inflammatory response in the human intestine [15]. This technique is achieved by producing factors that inhibit inflammatory response thus enabling systemic invasion and colonization of the gallbladder [14]. Invasion of intestinal mucosa is done by the activation of two Type III secretion systems (T3SS-1 and T3SS-2) encoded by SPI-1 which deliver bacterial proteins into non-phagocytic epithelial cells [14-16]. These factors interfere with host cell function thus promotes bacteria uptake into the intestinal epithelial cells and allows survival and multiplication in the host macrophage [14]. When infection reaches threshold level which is determined by number of bacteria, virulence and host immune response, the bacteria are disseminated systemically which starts bacteremia phase to colonize macrophages in other organs [14]. The most common sites for secondary infection are liver, spleen, bone marrow, gallbladder and Peyer's patches in the terminal ileum. It's infection in the gallbladder leads to asymptomatic carrier of the pathogen [14].

Clinical features of typhoid fever are variable ranging from mild fever to marked toxaemia and associated complications [15]. Early onset of the fever may include headache, diarrhea or constipation and abdominal pain [17]. In average cases of non-complicated typhoid fever, the incubation period for the fever is between 10-14 days and may persist up to 4 weeks if left untreated [15,17]. Other symptoms also include dull frontal headache, a dry bronchitic, anorexia, nausea, bradycardia, and rose-spots on abdomen and chest [15,17]. Since the presentations of the disease vary, there is a challenge to differentiate the typhoid fever symptoms from other diseases with similar onsets like, malaria fever, tuberculosis, brucellosis, sepsis of other bacterial pathogens [15]. The clinical symptoms for typhoid and paratyphoid fever are similar; therefore, a better diagnosis is needed for clear differentiation from other fever causing diseases [8,17]. However, complications may also occur mainly in endemic regions involving between 10%-15% of patients. Most common complications are gastrointestinal bleeding, hepatitis, pancreatitis, seizures which in some cases are fatal [17].

Early treatment with antibiotics has shown to be highly effective in fighting infections but improper administration of the antibiotics has led to emergence of multidrug-resistance strains of the pathogen [18].

The Widal test is a widely used serological test for the diagnosis of typhoid fever. The test detects antibodies to *Salmonella enterica serovar Typhi*, the causative agent of typhoid fever. Although it lacks specificity and its inability to differentiate between current and past infections, however its ease of performance and interpretation and its low cost compared to other diagnostic tests, place vwidal as one of the most commonly performed test in resource poor setting like ours. However, blood culture, stool culture and PCR and other support test for further accuracy for typhoid fever are usually recommended. The principle of the Widal test is based on the detection of agglutinins (antibodies) in the patient's serum that react with the antigens (O and H) present on the surface of *S. Typhi*. The test is performed by mixing the patient's serum with antigens and observing for agglutination.

The interpretation of the Widal test depends on the titre of antibodies detected in the patient's serum. A four-fold rise in the titre of agglutinins (from baseline to convalescent phase) is considered diagnostic of typhoid fever. However, the test has several limitations, including low sensitivity and specificity, cross-reactivity with other *Salmonella serovars*, and false-positive results due to previous infection or vaccination with related organisms. The Widal test is a commonly used serological test for the diagnosis of typhoid fever. Despite its limitations, it has several advantages that make it a valuable diagnostic tool.

### Problem Statement

A few studies provided some insights into the surveillance activities and devastating effects of typhoid fever in Ebonyi State and currently none is available in Ohaozara and Uburu where David Umahi Federal University Teaching Hospital is located. Despite its significant impact on the health of the population, there is limited information on the prevalence of typhoid fever in Uburu and its eviron where David umahi federal university teaching hospital is located.

### Aims

To determine the prevalence of typhoid fever among hospitalized febrile patients that attended DUFUTH between January 2023 to June 2023.

### Objectives

1. To determine the age and sex of hospitalized febrile patients diagnosed of typhoid fever between January to June 2023 in David Umahi federal University Teaching Hospital Uburu.
2. To determine the prevalence of typhoid fever among hospitalized febrile patients that attended David Umahi federal university teaching hospital between January to June 2023.

## Materials and Methods

### The Setting

This study was carried out in the department of clinical microbiology at David Umahi federal university teaching hospital, Uburu, Ebonyi state**.** The hospital is one of the leading tertiary health care facilities in South-East Nigeria and has a functional Medical Microbiology Department with an average yearly sample turnover rate of 1350 to 2000 blood specimens.

## Study Design

This is a retrospective study carried out at David Umahi Federal Teaching Hospital Uburu (DUFUTH) on blood samples tested for all cases of hospitalized febrile patients between January 2023– June 2023 to determine the occurance of positivity of salmonalla typhi.

## Study Population

The study included 226 pateints were admitted and managed for fever related ailment and their blood samples were sent to Medical Microbiology Department, David Umahi Federal University Teaching Hospital Uburu for analysis for Enteric fever. It involved patients of all age groups, and sex.

## Inclusive Criteria

All cases of fever that presented in DUFUTH between January and June 2023 were analyzed. Consent was also obtained from the caregivers of minors.

## Collection of Samples

Exactly 50ul of blood sample was collected from these hospitalized patients presented with fever into vacutainer tubes containing no preservatives/additives. Amongst the symptoms, most of the patients presented clinically with fever having temperatures above 37.5ºC Fatigue, headache, abdominal pains, constipation and anorexia which are common symptoms of typhoid fever.

## Methodology

The 50ul blood samples collected from patients were spun for 5 minutes using 800D British standard Search-tech instrument Centrifuge to separate the blood plasma from the serum**.** Test was done using Swe Health Samonella Antigen reagent set. The antigens used for VWidal test were the somatic antigen (antigen O) and the flagella antigen (antigen H), the O antigens include: O, AO, BO, and CO, the H antigen has H, HA, HB, and CH. This test was done to get the agglutinins by observing the reaction between the serum and the reagents. The testing procedure included adding a drop of the antigens to the serum according to the labels on the 8 circles slide 4 circles for antigen O and 4 circles for antigen H. The content is mixed in each circle with separate wooden applicator stick and spread to fill the whole area of the individual circle, and then the glass slide was gently rocked back and forth for 2 minute and observed for agglutination.

The ones that have the agglutinins are picked to find the titer. 5 drops of blood serum were made on a clean slide, for each of the reagent that agglutinated, use a micropipette that is calibrated from 5ul to 50ul, pipette the following volumes of the agglutinated samples:, 20ul, 40ul, 60ul and 80ul, 100ul, 120ul, 140ul, 160ul into the circles then a drop of the reagents that caused the agglutination are added to each of the samples. The content was then mixed in each circle with a separate wooden applicator stick and spread to fill the whole area of the individual circle, then rocked the slides gently back and forth for 2 minute and observed for agglutination, it is then numbered 1 to 7 having them as 1 in 20 dilution, 1 in 40 dilution, 1 in 60 dilution and 1 in 80 dilution 1/20, 1/40, 1/60 (dilution continues until the titre is gotten) The positive agglutination is picked as the titre and are visible within 2 minute. Results were recorded according to the dilution and observed for the titer which was the sample with agglutinins. Negative results were indicated by the absence of agglutination between the patient's antibodies in serum and specific *Salmonella* antigens and results were noted as "non-reactive" (NR). For O antigen agglutination is said to be significant from 1/80 and above, for H antigen agglutination is significant from 1/160 and above.

## Result

There are 226 hospitalized patient managed for febrile related ailment between January and June 2023 in David Umahi Federal University Teaching Hopsital, Uburu. Out of these 226 whose samples were analyzed, 107 (47.3%) showed significant reaction to antigen H and O of salmonella typhi (reaction from 1/80 and above). Other 119 (52.7%) of patient hospitalized in dufuth were of other fever related ailment like malaria, Urinary tract infection, Upper respiratory tract infection, Lower, respiratory trac t infection, Tonsilitus, etc.

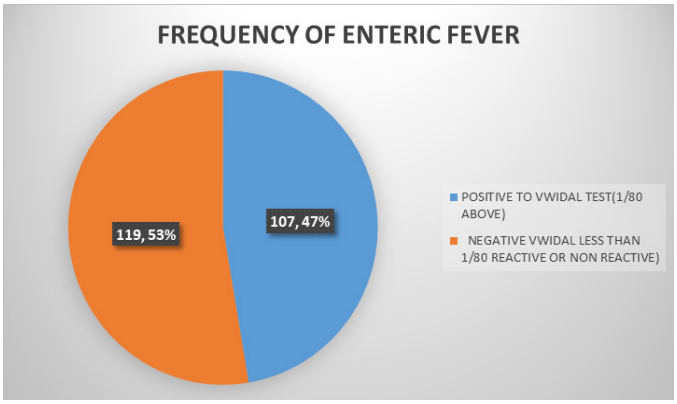


**Figure 1:** Showing the prevalence of typhoid fever among hospitalized febrile patient within the study period.

## Sex Distribution

Among the participants, 78 (34.5%) were male while 148(65.5%) were female participants.

**Table 1:** Showing the sex distribution of the participants.

| S/N | Sex | Frequency | Percentage |
|---|---|---|---|
| 1 | MALE | 78 | 34.5% |
| 2 | FEMALE | 148 | 65.5% |

## Age Distribution

**Table 2:** Showing age distribution among participants

| Age groups | Frequency | Percentage |
|---|---|---|
| 0 to 10 years | 28 | 12.4% |
| 11 to 20 years | 22 | 9.7% |
| 21 to 30 years | 34 | 15.1% |
| 31 to 40 years | 50 | 22.1% |
| 41 to 50years | 48 | 21.3% |
| 51 to 60year | 20 | 8.8% |
| 61 above | 24 | 10.6% |
| Total | 226 | 100% |

### Prevalence of Enteric Fever in Relation to Gender

Out of the 226 blood symptomatic patient samples analyzed, 107 were reactive for *Salmonella enterica serovar typhi*. The number of males tested positive were 26 (33.3%) out of 78 male participants, while 81(54.7%) out of 148 females participants were tested positive to salmonella enterica serovar typhi antigen. Using chi-square ($\chi^2$) statistical to determine the significant in relation to sex with the P-Value approach comparing the P-Value (P=0.00113) with $\alpha <$ (0.05) shows that the prevalence is statistically significant in relation to sex.

**Table 3:** Sex distribution of Enteric fever among participants.

| Sex | Number tested | Number tested positive | Tested positive % |
|---|---|---|---|
| Male | 78 | 26 | 33.3 |
| Female | 148 | 81 | 54.7 |
| Total | 226 | 107 | 100% |

### Age Related Prevalence

Ages 0 to 10 year, 28 samples were tested with number of reactive 6, which is 5.6%. Ages 11 to 20 years 22 were tested and 14 were reactive which is 13.1%. Ages 21 to 30 years, 34 were tested and have 10 reactive which is 9.3%. Ages 31 to 40 years, 50 samples were tested and have 24 reactive which is 22.4%. Ages 41 to 50 year, 48 samples were tested and have 22 reactive which is 20.6%. Ages 51 to 60years 20 samples were tested 15 reactive which is 14.1%. Ages 61 years and above 24 samples were tested and 16 were reactive which is 14.9%. Using chi-square ($\chi^2$) statistics to determine the significant in relation to sex with the P-Value approach comparing the P-Value (P=4.865) with $\alpha >$ (0.05) shows that the prevalence is statistically significant in relation to age.

**Table 4:** Distribution by age group of typhoid infection in patients that attending "David Umahi Federal Teaching Hospital Uburu Ebonyi State.

| Age groups | Number tested | Number reactive | % frequency | Number non-reactive | % frequency |
|---|---|---|---|---|---|
| 0 to 10 years | 28 | 6 | 5.6% | 22 | 18.5% |
| 11 to 20 years | 22 | 14 | 13.1% | 8 | 6.7% |
| 21 to 30 years | 34 | 10 | 9.3% | 24 | 20.2% |
| 31 to 40 years | 50 | 24 | 22.4% | 26 | 21.8% |
| 41 to 50years | 48 | 22 | 20.6% | 26 | 21.8% |
| 51 to 60year | 20 | 15 | 14.1% | 5 | 4.3% |
| 61 above | 24 | 16 | 14.9% | 8 | 6.7% |
| Total | 129 | 107 | 100% | 119 | 100% |

## Discussion

Nigeria, the most populous country in Africa, is highly endemic for typhoid fever, with an estimated incidence of 100 cases per 100,000 populations [19]. Typhoid fever is a significant public health concern in Nigeria, and several studies have investigated the prevalence of the disease in the country. A systematic review and meta-analysis of studies conducted in Nigeria between 2000 and 2018 reported an overall pooled prevalence of typhoid fever of 20.9% [19] with prevalence higher in rural areas (23.1%) compared to urban areas (17.9%) and was more common among children under the ages of five years (28.2%) [19]. However, our findings in this research demonstrated a prevalence of 47.3% among hospitalized febrile patients that attended DUFUTH within the study period. This tallies with similar of the indigenous findings in previous researches in Unwana Afikpo north local government area which recorded 49.4% [20]. *Nevertheless, other studies conducted in other parts of the state and other neighbouring states in Nigeria recorded lower prevalence. Examples of such include;* study conducted in Abakaliki showed a prevalence of 21.2% [21], Benin city Nigeria reported a prevalence of 8.8% among febrile patients attending a tertiary hospital [22], Lagos recorded 11.6% among febrile patients attending a tertiary hospital [23]. In Ghana, a study reported a prevalence of 10.7% among febrile patients attending a teaching hospital [24]. Similarly, a study in Tanzania reported prevalence of 17.2% among febrile patients attending a referral hospital [25].

The high burden of enteric fever in sub sahara Africa is attributed to poor sanitation and hygiene practices, inadequate access to clean water, and poor hygiene practices. According to the World Health Organization (WHO), an estimated 11-20 million cases of typhoid fever occur annually in sub-Saharan Africa, with approximately 116,000 deaths [19]. Studies conducted in various sub-Saharan African countries have reported high prevalence rates of typhoid fever with almost no exception. Typhoid fever is also associated with poverty and overcrowding, which are prevalent in many parts of sub-Saharan Africa majorly Nigeria which facilitate the spread of the disease. The burden of typhoid fever in the region highlights the urgent need for interventions to improve access to clean water, sanitation, and hygiene practices. Vaccination against typhoid fever is also recommended as a preventive measure. Suffices to say that DUFUTH is situated in a remote village of Uburu and every indication for typhoid fever ranging from poor hygiene, poverty and poor sanitation is at its highest in the immediate environment of DUFUTH; hence the high incidence didn't come as a surprise.

Incidence of typhoid fever remains a global challenge in many geographic areas, mainly in developing countries associated with poor sanitation systems and improper water treatment of water supplies, and particularly high in South-central and Southeast Asia [26]. The annual occurrence of the disease is estimated to reach 21 million illnesses with a death toll of approximately 216 000 [27]. The disease is endemic in Bangladesh with a recent record of the illness is estimated to be 390 cases per 100 000 persons [28], while in Malaysia, it periodically gives an outbreak with annual incidence of 10.2 – 17.9% cases per 100 000 persons [9]. The gender distribution of typhoid disease in this study was 33.3% for males and 54.7% for females, suggesting that typhoid fever was more prevalent in females than in males among the gender in this locality, this is contrary to the investigation carried out in Afikpo south by [20] which showed higher prevalence in males 57% than females 42%. Also, Similar research done [29,30] in Bangladesh and South Africa showed that typhoid fever correlated with gender and case fatality is higher in females compared to males.

Prevalence of 5.6% is noted in children 0 to 10 years of age, this

age group has the lowest prevalence compare to other age groups in this study this may probably be due to their controlled diet and drinking water as well as exclusive breast feeding at these tender ages by their parents. Most reported cases of typhoid fever in clinical settings revealed that many of infections occur mainly in children as young as 5 years old to young adults. However, in some countries where typhoid fever is endemic; India, Indonesia, Bangladesh, Thailand and Vietnam, typhoid fever is also commonly seen in 1 to 5 years old children [15]. The persistence of this fever remains a problem in these developing countries by which prolonged use of antibiotics together with misapplications and self-prescribing of the antibiotics lead to a higher health concern of drug resistance and dissemination of resistant strain in these areas and children are not left behind [5].

Ages 21 to 30 years have a prevalence of 13.1%, this could be attributed to increase in conscious cleanliness, young adult tends to create more time for their personal hygiene also have right to what to eat or drink and what not. This study shows higher prevalence among older adults within the age group 31 to 40 that show a prevalence of 22.4% and ages group 41 to 50 showed a prevalence of 20.6%. This could be attributed to a much busy life style that could result to poor personal hygiene. Research indicated that household contact is a major risk factor associated to the spread of typhoid infection [25]. This further reported that the prevalence of typhoid was higher in households containing more than 6 members. Crowding was seen to be a risk factor associated with typhoid fever among households. This age group faces higher risk of infection due to increase in household members. Most epidemiological studies have related the risk factors to typhoid fever of being waterborne or food borne [31]. A prevalence of 14.9% was seen among aged adult from 61years and above, this could be because of low immunities and poor hygiene

## Conclusion

In view of this study, Typhoid (Enteric) Fever still remain a disease of major public health importance: Typhoid have similar symptom with other infections such as fever, headache, diarrhea or constipation, abdominal pain, fatigue and anorexia, therefore, treatment should be based on adequate laboratory diagnosis.

The emergence of antibiotic-resistant strains of *S. Typhi* is a growing concern, the need for appropriate antibiotic stewardship [32] can never been over emphasized.

## Recommendation

1. Since Typhoid is mostly caused by poverty, overcrowding and poor hygiene, efforts should be made to improve on the living conditions of the people in Uburu and Ohaozara local government of Ebonyi state.
2. There should be public enlightenment of the good sanitation and personal hygiene as major control measures of the diseases.

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