International Journal of Research in Medical Sciences
Umegbolu EI. Int J Res Med Sci. 2017 Aug;5(8):3400-3405
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20173530

Original Research Article

Sero-prevalence of *Salmonella typhi* antibodies among adult residents of some selected rural communities of Abia and Enugu States, Southeast Nigeria: a cross-sectional study

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Received: 10 June 2017
Accepted: 08 July 2017

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ABSTRACT

Background: *Salmonella typhi (S. typhi)* antibodies may be considered as biomarkers of typhoid fever, a severe febrile systemic illness caused by an invasive Gram-negative Bacterium *S. typhi*. Worldwide, about 21-26.9 million cases of typhoid fever and 200 000-215 000 deaths, occur annually. Between 2003 and 2005, statistics have shown a rising trend in the incidence of typhoid fever in Abia and Enugu States. The aim of the study was to determine the sero-prevalence of *S. typhi* antibodies in some rural communities of Abia and Enugu States as proxy indicators of prevalence typhoid fever (TF) in the two states.
Methods: This was a cross-sectional study of the sero-prevalence of *S. typhi* antibodies in ten rural communities of Umunneochi Local Government Area (LGA) of Abia State and Ezeagu LGA of Enugu State using 421 (200 in Abia and 221 in Enugu) blood samples for the Widal test to determine the titres of these antibodies.
Results: In the Abia communities the mean sero-prevalence of *S. typhi* antibodies was 68.2%, while in Enugu it was 87.1%. Between the two states, difference in the sero-prevalence of *S. typhi* antibodies was significant (p=0.03).
Conclusions: The sero-prevalence of *S. typhi* antibodies was higher (87.1%) in the Enugu communities, compared to the Abia communities (68.2%). To reduce the incidence and prevalence of TF in the communities, access to safe domestic water, improved sanitation and good food hygiene needs to be improved. Health-seeking behaviour also needs improvement.

Keywords: Abia, Antibodies, Enugu, Prevalence, *S. typhi*, Typhoid

INTRODUCTION

Salmonella typhi (*S. typhi)* antibodies may be considered as biomarkers of the typhoid fever diseases process. A biomarker is a chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in the human body.[1] The titres of *S. typhi* antibodies can be detected using the Widal test (WT). In many limited resource settings, the diagnosis of typhoid fever (TF) is still based on the WT, in spite of the limitations of the test caused by the possibilities of false positives (e.g. in persons who have received vaccines against *Salmonella*, in persons who have suffered from TF in the past and in antigen suspensions with fimbrial antigens). TF is a severe febrile systemic illness caused by infection with an invasive Gram-negative bacterium *Salmonella enterica*, subspecies *Enterica* serovar *typh*i (*S. typhi*).[2] It is one of the leading causes of infectious diseases in developing countries.[3] The disease process begins with the invasion of the small bowel (in the Peyer's patches) (although the large bowel may sometimes be involved), where the Salmonella organisms proliferate.[4] The incubation period of TF is about 7-14 days, during which the Salmonella

organisms invade macrophages and spread throughout the reticuloendothelial system. Clinically, the disease is usually characterized by gradual onset of fever, headache, malaise, anorexia, non-productive cough, constipation (or less commonly diarrhoea), abdominal pain, bradycardia and splenomegaly.[2,5,6] Complications of untreated TF include intestinal perforation, haemorrhage, typhoid encephalopathy, death (10%), relapse and chronicity or carrier stage (5%).[2,5] Chronic carriage, more frequently seen in middle aged and older people, those with gallstones and women, poses a public health risk, especially if the carrier works in the food industry, as exemplified by the well-known case of "Typhoid Mary" Mallon early last century.[7,8,5]

Although the definitive diagnosis of TF is based on the isolation of *S. typhi* from blood, stool, urine or other clinical specimens including bone marrow, this gold standard is hardly ever met in many limited resource settings, as it is expensive and impractical, and *S. typhi* may also prove difficult to culture.[2,6] Therefore in these poor resource settings, to diagnose TF, the time honoured WT (a serological method developed in 1896), which is a visual test that monitors agglutinating antibodies that react with *S. typhi*, is still commonly used.[2] However, because of the limitations of this test (low sensitivity and specificity), newer methods of diagnosis that are more sensitive and specific have found their ways into the diagnostic arsenal of TF. These new diagnostic tests include IDL Tubex® (which can detect IgM 09 antibodies from patients within a few minutes), Typhidot® (that can detect specific IgM and IgG antibodies against a 50kD antigen of *S. typhi*), Typhidot-M® (a modified and improved version of the Typhidot test) and Typhoid-paratyphoid diagnostic assay (which detects IgA).[9-12] But, like the WT, these new diagnostic tests also have their own limitations, that is why the search for even more sensitive, specific, and affordable diagnostic methods has continued till today. Some of the newer assays towards which intensive researches are presently being directed include antigen based rapid diagnostic test kits, multiplex PCR, stool dipstick tests, fast blood culture PCR method and onsite food testing kit.[2] Promising as these newer assays may seem, they are still rarely available in developing countries where resources are limited.[13]

In TF case definition, a case could be defined as a confirmed, probable, or chronic one.[12] A confirmed case is a patient with fever (38^{o}C and above) that has lasted for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S. typhi*, whereas a probable case is a patient with all the characteristics of a confirmed case except that there is no isolation of *S. typhi*. In a chronic case, there is prolonged excretion of *S. typhi* in stools, urine, bile or duodenal string cultures (for longer than one year) after the onset of acute TF. Paradoxically, some patients excreting *S. typhi* have no history of TF.[12] The first-line therapeutic agents currently in use for the treatment of TF in quinolone-sensitive areas are fluoroquinolones (especially ciprofloxacin and ofloxacin) and cephalosporines (specifically those of the third and fourth generations).[14] In quinolone-resistance areas, azithromycin and cefixime should be used. For complicated TF, in addition to the first-line drugs, ampicillin, amoxicillin and chloramphenicol can also be used. The treatment of carriers includes the use of ciprofolaxcin for 4 months or 52 weeks and cholecystectomy, where indicated.

The primary prevention of TF is hinged on ensuring access to safe water, food safety and proper sanitation infrastructures; health promotion and education to raise public awareness about safe water, sanitation and hygiene; and vaccination of at-risk individuals (laboratory staff, other susceptible individuals who are over 2 years of age and travelers to high risk areas) against TF.[15,16] However, vaccination does not offer 100% protection in TF. Its efficacy is about 50%-80%.[1] The early judicious use of efficacious antibiotics in patients with TF constitutes the Mainstay of secondary prevention.[17]

TF is endemic in less developed countries where poor sanitation and food hygiene and reduced access to treated water facilitate the spread.[15,18] Factors that affect its epidemiology include age (more in school-aged children and young adults), season (peaks in dry weather or at the onset of rains), and food habits (eating outside the home).[19,20] Studies have shown that about 50% or more cases of TF occur in children less than 5 years old in endemic regions; they also have the highest case fatality rate.[3,18] Sources of infection in TF include contacts or household members with a similar illness, contaminated drinking water and unwholesome meals.[6] The disease is transmitted through ingestion of food (shellfish, raw fruits and vegetables, contaminated milk and milk products) and water contaminated by faeces and urine of patients or carriers. The period of communicability in TF usually lasts from the first week of the illness up to the convalescence period.

Worldwide, about 21-26.9 million cases of TF, resulting in 200 000-215 000 deaths, occur each year.[14,16,21] Data from global burden of disease show that most cases of TF occur on the Indian Subcontinent and parts of Africa.[16,21-23] In Africa, the burden of TF is unknown, as appropriate technology to assess this is not available.[24] However, a crude estimate of an incidence rate of 724.6 cases per 100 000 has been reported by.[21]

For Nigeria (1999-2008), estimated incidence of 16 cases per 100 000 has been reported.[21] In Abia and Enugu States, available statistics indicate a rising trend in the reported cases of TF between 2003 and 2005.[25] In 2003, 966 cases were reported in Abia State and 1537 in Enugu State. Subsequently, in 2005, these cases increased to 5196 in Abia and 45211 in Enugu. From 2006 onwards, statistics on the prevalence of TF in Abia and Enugu States have not been available. This study therefore aims to determine the prevalence of *S. typhi* antibodies among

adult residents of some rural communities of Abia and Enugu States in order to bridge some of the gaps in data on the prevalence of TF, which have not been available in the two states since 2006. Granted the titre of a one-off WT is not usually diagnostic of TF, in low resource settings such as the rural communities of Abia and Enugu States, titres of one-off WT as determined by this study may be used as proxy indicators of the prevalence of TF in these communities.

METHODS

This was a cross-sectional study of the sero-prevalence of *S. typhi* antibodies among adult residents of ten rural communities of Umunneochi Local Government Area (LGA) of Abia State and Ezeagu LGA of Enugu State.

According to the National Population Commission (NPC), Umunneochi LGA has a population of 163,928, while Ezeagu LGA has a population of 170,603.[26] Applying the Taro-Yamane formula, a sample size of 399 households was obtained from Umunneochi LGA and 395 from Ezeagu LGA. However, out of the 604 (307 in Abia State and 297 in Enugu State) adult (18 years and above) respondents (representatives of the various households) who reside permanently in the ten communities of both states that were administered the questionnaire, only 421 (200 in Abia State and 221 in Enugu State) who gave their consents for blood sample collection were included in the study. Indigenes of these communities who reside outside the communities but were also present at the time of the study were excluded.

Multistage sampling technique was employed. Through balloting, Abia North Senatorial District of the State (out of 3), Umunneochi LGA of the Senatorial District (out of 7) and the five communities of the LGA (out of 29), namely Lokpanta, Lokpaukwu, Lekwesi, Leru and Obinolu were randomly selected in Abia State. Using the same technique, in Enugu State, Enugu West Senatorial District of the State (out of 3), Ezeagu LGA of the Senatorial District (out of 5) and the five communities of the LGA (out of 23)- Umusuru, Afor-Ugwu, Iwollo, Obinofia-Ndiagu and Mkpagu- were also randomly selected.

For the WT, blood samples were collected from the 421 (200 in the Abia and 221 in the Enugu communities) adult respondents who gave their consents (one sample per respondent), to determine the sero-prevalence of *S. typhi* antibodies in these communities. Blood samples were collected by applying a tourniquet on the lower one-third of the forearm, or on the mid-upper arm of the respondent in order to occlude the veins, after which the venepuncture site (the dorsum of the hand or antecubital fossa) was cleaned with a swab soaked in methylated spirit. With a sterile 5-ml syringe, the selected vein was punctured and about 3ml of venous blood withdrawn. The blood samples were then transferred into sterile specimen bottles placed in test tube racks and allowed to stand to enable the serum separate from the cells. After collecting the blood, pressure was then applied to the venepuncture site and the arm slightly raised for about a minute to stop the bleeding from the puncture site. Then the syringes and used swabs were discarded in the waste bin.

Using an adaptation of the slide test by Cruickshank, a drop of the patient's serum to be tested was pipetted on each of the eight reaction circles, after which one drop each of 'O' (*typhi*, *paratyphi* A, B, C) and 'H' (*typhi*, *paratyphi* A, B, C) antigens was also added to the eight reaction circles. The contents of each circle were mixed with separate mixing sticks and then the slide gently rocked back and forth while observing for agglutination macroscopically within one-two minutes. A titre of 1: 80 or more was considered clinically significant.[27] Only significant titres for *S. typhi* were included in the data for analysis.

A pilot study was conducted in two communities (Ihuezi and Adu-Achi) in May 2014 to test the questionnaire. Data were collected over a period of 20 weeks (from July to November 2014). The data so generated were analyzed as frequency distribution, t-test and Pearson product moment correlation using MaxStat (version3.60) statistical software. P-value ≤ 0.05 was considered significant.

RESULTS

604 copies of the questionnaire were administered to the adult respondents made up of 137 (44.6%) males and 170 (55.4%) females in the five communities of Abia State and 131 (44.2%) males and 166 (55.8%) females in the five Enugu communities. Blood samples were collected from 421 (200 from Abia and 221 from Enugu, representing 69.7% of those who were administered the questionnaire) respondents who gave their consents.

Table 1: Distribution of respondents by communities in Abia and Enugu states.

Abia	No. of respondents	Enugu	No. of respondents
LOKPANTA	60	UMUSURU	24
LOKPAUKWU	67	AFOR-UGWU	27
LEKWESI	60	IWOLLO	54
LERU	60	OBINOFIA-NDIAGU	126
OBINOLU	60	MKPAG	66
Total	307		297
Mean	61.4		59.4

Table 1 shows the distribution of respondents in the ten communities of both states. As shown in the table, the distribution of respondents in the communities of Abia State was more uniform, compared to the communities of Enugu State, where the distribution has a very wide margin of variation, from 24 (in Umusuru) to 126 (in

Obinofia-ndiagu). Mean distribution of respondents in the Abia communities was 61.4, while in Enugu it was 59.4.

The distribution of respondents by sex is shown in Table 2. The table shows that in the ten communities of Abia and Enugu States, the male to female ratio was approximately 44%: 55%.

Table 2: Distribution of respondents in Abia and Enugu states by sex.

State	Total	Male	Female
Abia	307	137(44.6%)	170(55.4%)
Enugu	297	131 (44.2%)	166 (55.8%)

Table 3 shows the sero-prevalence of *S. typhi* antibodies in the ten communities of Abia and Enugu States using the significance of the Widal test titre. In the communities of Abia, the lowest sero-prevalence was found at Lekwesi (53.5%), while the highest was at Lokpaukwu (84.1%). Mean prevalence for the five communities was 68.2%.

Table 3: Sero-prevalence of *S. typhi* antibodies in some communities of Abia and Enugu states (No. of samples = 421).

Widal test titre			
Abia (No. of samples =200)	**Significant**	**Non-significant**	**Prevalence**
LOKPANTA	28	10	73.7%
LOKPAUKWU	56	11	84%
LEKWESI	23	20	53.5%
LERU	12	7	63.2%
OBINOLU	22	11	66.7%
Mean			68.2%
Enugu (No. of samples = 221)			
UMUSURU	22	2	91.7%
AFOR-UGWU	15	2	82.2%
IWOLLO	28	3	90.3%
OBINOFIA-NDIAGU 85	85	34	71.4%
MKPAGU	30	0	100%
Mean			87.1%
t			2.68
p			0.03

Table 4: Relationship between consent rates (for widal test) of respondents and sero-prevalence of *S. typhi* antibodies in some communities of Abia and Enugu states.

State	Total	Consent rate	Prevalence	r	p
Abia	307	200 (65.1%)	68.2%		
Communities					
LOKPANTA	60	38 (63.3%)	73.7%		
LOKPAUKWU	67	67 (100%)	84.0%		
LEKWESI	60	43 (71.7%)	53.5%		
LERU	60	19 (31.7%)	63.2%		
OBINOLU	60	33 (55%)	66.7%	0.61	0.28
Enugu	297	221 (74.4%)	87.1%		
Communities					
UMUSURU	24	24 (100%)	91.7%		
AFOR-UGWU	27	17 (63%)	82.2%		
IWOLLO	54	31 (57.4%)	90.3%		
OBINOFIA-NDIAGU	126	119 (94.4%)	71.4%		
MKPAGU	66	30 (45.5%)	100%	-0.75	0.15
Overall (for the ten communities)				-0.17	0.64

In the Enugu communities, the least sero-prevalence was at Obinofia-ndiagu (71.4%), while the highest was at Mkapgu (100%). Mean prevalence for the five Enugu communities was 87.1%. Between the two states, there was a significant difference in the sero-prevalence of *S. typhi* antibodies (p=0.03).

Table 4 shows the relationship between the consent rates of respondents for the Widal test and sero-prevalence of *S. typhi* antibodies by state and by communities. As shown in table, the overall consent rate of respondents in Abia State was lower (65.1%) with correspondingly lower mean sero-prevalence of *S. typhi* antibodies (68.2%) compared to Enugu State where the overall consent rate was 74.4% and sero-prevalence of *S. typhi* antibodies 87.1%. In the Abia communities the correlation between consent rate and sero-prevalence of *S. typhi* antibodies (r=0.61) was strong, positive, but not significant (p=0.28). In the Enugu communities, there was a strong negative (r=-0.75) but insignificant (p=0.15) correlation between consent rate and sero-prevalence of *S. typhi* antibodies. For the ten communities of both states, the overall correlation between consent rate and sero-prevalence of *S. typhi* antibodies was very weak (no

correlation), negative (r= -0.17) and not significant (p=0.64).

DISCUSSION

The endemicity of typhoid fever in less developed countries has been attributed to poor sanitation, poor food hygiene, and reduced access to treated water.[15,18] This study found a higher sero-prevalence of *S. typhi* antibodies in the five communities of Enugu State (mean sero-prevalence=87.1%), compared to the communities of Abia State where the sero-prevalence was 68.2%. Between the two states, there was a significant difference in the sero-prevalence of these antibodies (p=0.03). The study further demonstrated that the sero-prevalence of the antibodies did not depend on the consent rates of the communities for Widal test as the overall correlation between consent rate and sero-prevalence was very weak, negative (r= -0.17) and insignificant (p=0.64). Using the titres of Widal test (sero-prevalence) as proxy indicators of the prevalence of TF in these communities, this finding confirms the rising trend in its incidence in the two states reported by NBS.

In 2003, the number of reported cases of typhoid fever in Abia State was 966 and in Enugu State 1537, while in 2005 these cases increased to 5196 in Abia State and 45211 in Enugu State.[25] The NBS statistics also show that between 2003 and 2005, there were more reported cases of TF in Enugu State, compared to Abia State. Higher sero-prevalence of *S. typhi* antibodies in the Enugu communities compared to their Abia counterparts found in this study has also confirmed the difference in incidence of TF previously reported for the two states. Furthermore, the findings of this study are in agreement with records from three Government Hospitals in Enugu State, which showed that in 2013, 2014 and 2015, diagnosed cases of typhoid fever were 1200, 1392 and 1632 respectively, indicating a rising trend in the incidence of TF in the State.

The observed difference in the sero-prevalence of *S. typhi* antibodies in the communities of Abia and Enugu States may be attributed to a possible difference in the levels of sanitation, food hygiene and access to safe domestic water supplies in the states, for these have been identified as risk factors that fuel the development and spread of TF. The implication of this finding is that there could be more enabling conditions for the spread of TF in the Enugu communities than in their Abia counterparts. Although it may not be totally correct to equate the sero-prevalence of *S. typhi* antibodies to the prevalence of TF in these communities using one-off titres of the Widal test, however, a direct relationship between the prevalence of the disease and the sero-prevalence of these antibodies could be inferred, considering the settings of the communities of the study. In such limited resource settings as the rural communities of Abia and Enugu States, the titres of *S. typhi* antibodies determined by the Widal test may be used as proxy indicators of the prevalence of the diseases caused by *S. typhi* since the use of more sensitive methods such as blood and bone marrow cultures, IDL Tubex® test, Typhidot®, Typhidot-M®, Multiplex PCR, stool dipstick tests, fast blood culture PCR method and onsite food testing kit which are rarely available in developing countries, is not feasible.[12] As has already been reported, absence of appropriate technology in Africa makes it difficult to assess the actual burden of disease on the Continent.[24]

Besides lack of appropriate technology to determine the disease burden, not all who suffer from TF usually end up in the hospitals for proper diagnosis and treatment, as was the case in the ten communities of the study. As a result of this, appropriate data on TF are usually not available, hence the difficulty encountered in determining the burden of the disease in many African countries, including Nigeria.

In line with case definition of TF, these cases with significant titres of antibodies to *S. typhi* as found in the study, may represent healthy carriers of the disease in the communities, and these carriers in turn could be a part of the pool of the disease in the areas of study, where, apart from the other conditions that aid its spread, low health-seeking behaviour among the residents could also be another factor that plays a significant role. Since there could also be healthy carriers of TF without a history of the disease, the cases with significant titres of the Widal test are indeed of importance from the public health perspective.[12] Involvement of these healthy carriers in the food industry might give rise to food borne TF, as was the case with the legendary 'Typhoid' Mary Mallon in the 19th Century.

Lastly, considering the settings of the communities of the study, the findings of this study could help to fill some of the gaps in data on TF disease burden, unmasking the problem of the carrier stage of the disease (with its associated public health risk) in the communities, and by extrapolation the States (Abia and Enugu) and the country in general. Timely detection of these cases would help to protect the public health.

Limitation of the study was to unequal sample sizes (200 blood samples in Abia and 221 in Enugu states) for the Widal tests which could have affected the sero-prevalence data. This disparity arose because the study was on opt in or opt out basis, and as such only consenting adult respondents who allowed blood samples for the Widal tests to be collected from them were recruited into the study.

CONCLUSION

Although the result of a one-off Widal test is not usually diagnostic of typhoid fever, especially when there are no suggestive clinical symptoms, in limited resource settings such as the rural communities of Abia and Enugu States, such a test may be employed for population screening to

detect the healthy carriers of the disease who pose risk to the public health as they inadvertently aid the continuous transmission of *S. typhi* in the communities. The sero-prevalence of *S. typhi* antibodies was quite high in the ten communities of both states, however it was higher for the Enugu communities (87.1%) compared to the Abia communities (68.2%). To reduce the incidence and prevalence of TF in these communities, access to safe domestic water, improved sanitation and good food hygiene needs to be improved. The residents of the communities also need to improve on their health-seeking behaviour.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee Abia State University Teaching Hospital, Aba Campus, Nigeria

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Cite this article as: Umegbolu EI. Sero-prevalence of *Salmonella typhi* antibodies among adult residents of some selected rural communities of Abia and Enugu States, Southeast Nigeria: a cross-sectional study. Int J Res Med Sci 2017;5:3400-5.