

## Antibiotic resistance: The overlooked threat in typhoid fever treatment in Nigeria.

**Okoye Amarachi Blessing**

*Department of Public Health, Ahmadu Bello University, Kaduna State, Nigeria*

*<https://orcid.org/0009-0009-3337-5646>*

*Email: amarachiblessingokoye@gmail.com*

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Dear Editor,

Typhoid, also referred to as typhoid fever, is one of the most prevalent diseases in many low and middle-income countries, and it is caused by the rod-shaped Gram-negative bacterium *Salmonella enterica* subtype Typhi (S. Typhi). This organism belongs to the Enterobacterales family. Among its symptoms are high temperature, lethargy, nausea, abdominal pain, and irregular bowel motions.<sup>1</sup> Clinical symptoms are considered when access to the required diagnostics is scarce, such as in endemic regions. However, several infectious diseases exhibit comparable clinical manifestations. An example is malaria; in these cases, the symptoms are not sufficiently sensitive or specific.<sup>2</sup> S. Typhi is typically transmitted through the fecal-oral route. Chronic carriers may expel the bacterium in feces or urine contaminating food and water.<sup>2</sup> An individual who has had typhoid fever for up to three of seven consecutive days in an endemic area, after traveling to such an area, or after coming into contact with a confirmed household incidence is said to have a suspected case of the disease.<sup>2</sup> To confirm a case of typhoid fever, however, the World Health Organisation [WHO] emphasized that a person must have undergone laboratory testing that yielded data showing the presence of S. Typhi and its DNA through culture or other molecular methods.<sup>3</sup> Blood culture is, therefore, the gold standard for diagnosing typhoid disease.<sup>4</sup> An estimated 12.5 - 16.3 million cases of typhoid fever have been documented worldwide each year, with 140,000 fatalities.<sup>5</sup> Sub-Saharan Africa remains a high-burden region.<sup>5</sup> In 2016, Nigeria documented 364,791 cases and 4,232 deaths, with 68% of the deaths occurring in children under the age of 15.<sup>6</sup> True incidences are likely higher due to poor surveillance, misdiagnosis, and limited access to diagnosis as blood confirmation is often unavailable in rural communities. Factors such as urbanization and migration, a lack of water, sanitation, and hygiene (WASH) programs, inadequate facilities for disposing of human waste, gaps in adequate healthcare, and the regional movement of immigrant workers all increase the spread of S. Typhi.<sup>7</sup> Furthermore, due of the inadequate coordination of the epidemiological surveillance system, vaccine exclusion, accurate reporting and documentation of typhoid fever cases in Nigeria is too difficult. The absence of better sanitary facilities is another barrier to lowering the incidence of typhoid fever in Nigeria.<sup>7</sup> Additionally, numerous studies from various Nigerian states have presented data on the high prevalence of typhoid fever.<sup>7</sup> Notably, Nigeria has not taken into consideration the inclusion of the internationally approved typhoid vaccine into its broader immunization program. According to trends in antibiotic resistance in Nigeria, rising antibiotic resistance in S. Typhi has led to prolonged hospitalizations, high cost of care, and mortality, particularly in high-burden areas. This concerning circumstance, which is frequently seen, poses a major public health risk.<sup>7</sup> The prevalence of multiple drug-resistant (MDR) S. Typhi appeared in the early 1970s. S. Typhi strains are resistant to the first line of antibiotics used to treat typhoid (ampicillin, trimethoprim/sulfamethoxazole, and chloramphenicol), as well as numerous others used today. In certain regions of Africa, ciprofloxacin resistance has been identified, which makes treatment alternatives extremely difficult. This pattern has been documented in Nigeria.<sup>7,8</sup>

A study by Ohanu et al. found that 56% of patients exhibited multi-drug antibiotic resistance (resistant to  $\geq 3$  first-line antibiotics), with ciprofloxacin, levofloxacin, and meropenem showing 100% resistance. This is concerning because antibiotics are usually the last line. In comparison, ceftriaxone revealed a 95.6% susceptibility rate.<sup>5</sup> A major concern. Ikimiukor et al. discovered a specific subtype of S. Typhi genotype 3.1.1 in a lab-based investigation. This genotype had previously been documented to be resistant to both ciprofloxacin and other drugs.<sup>6</sup> However, they discovered that all S. Typhi 3.1.1 isolates, with the exception of one from Obafemi Awolowo University (OAU), exhibited phenotypic resistance to nalidixic acid and carried Single Nucleotide Polymorphisms (SNPs) in the gyrA gene that give quinolone resistance. Furthermore, it was discovered that these 3.1.1 clone variants carried the tetA gene, which denotes tetracycline resistance, the

gyrA\_S83Y mutation (ciprofloxacin and levofloxacin resistant), and the IncY plasmid (Multi-drug resistance through horizontal transfer).<sup>6</sup> According to Akinyemi et al., there is a general rise in the frequency of typhoid fever in Lagos, and about 80% of the isolates in their investigation showed antibiotic resistance.<sup>7</sup> Another study in Nigeria reported *Salmonella* organisms that produced Extended-Spectrum  $\beta$ -Lactamase (ESBL) were found to be resistant to certain cephalosporin medications, including ceftazidime and cefotaxime.<sup>9</sup> Therefore, study confirmed nonetheless, further stating that not every isolate of *Salmonella* that exhibited antibiotic resistance produced Extended-Spectrum  $\beta$ -Lactamase. This entails resistance that can arise from chromosomal mutation and plasmid-mediated, e.g., gyrA\_S83Y. This result is consistent with a related study conducted in Keffi, Nigeria, by Tsaku et al.<sup>10</sup> This implies that to manage resistant *Salmonella* infections effectively, there is an urgent need for enhanced diagnostic capability, regular surveillance, and antibiotic stewardship. Even though, typhoid fever is still common in Nigeria, millions of individuals continue to receive incorrect diagnoses as a result of the Widal test's continuous use. Even in patients with a history of prior infection, many doctors base their diagnosis and treatment of typhoid fever on a single Widal test result.

False positives and needless antibiotic use are frequent results of this approach, which dramatically adds to the expanding issue of antibiotic resistance.<sup>5,7</sup> Studies show that single widal agglutination testing of a serum specimen is unreliable and frequently results in a misdiagnosis, which influences antibiotic resistance and improper use in typhoid-endemic nations like Nigeria.<sup>3</sup> While there is a rising in antibiotic resistance, it becomes more difficult to effectively treat typhoid fever with antibiotics.<sup>1</sup> Furthermore, antibiotics are widely accessible over-the-counter in Nigeria, where individuals frequently buy them without a prescription or the necessary dose information. This has a significant impact on the nation's growing antibiotic resistance and issues with medication therapy. Self-medication is common and frequently results in insufficient treatment plans, which not only makes the therapy inefficient but also gives infectious bacteria more chances to become resistant. Additionally, multidrug-resistant variants of *Salmonella Typhi* have been related to the use of antibiotics in animal husbandry. These strains can transfer to people and make treating typhoid fever even more difficult.<sup>1,5,7</sup>

Nigeria's antibiotic resistance issue is caused mainly by the poor healthcare infrastructure.<sup>7</sup> Healthcare professionals' capacity to correctly identify resistant strains of *Salmonella Typhi* is influenced by limited access to laboratory testing, which frequently results in empirical treatment option which is dependent on antiquated resistance patterns rather than the needs of specific patients. These poor antibiotic prescribing habits among healthcare providers are the result of insufficient training and limited access to current prescribing recommendations, including a lack of information about current resistance tendencies and evidence-based treatment approaches.

Furthermore, structured training programs can increase physicians' awareness of antibiotic stewardship and promote more rational sales of antibiotics and usage, helping to combat rising resistance levels. Antibiotic prescribing and dispensing policies should be tightly enforced to ensure that antibiotics are only used when clinically indicated, prescribed by certified practitioners, and administered under appropriate regulatory monitoring. Immunization programs and laboratory tests should be accessible at all times. WASH programs should be made available to vulnerable communities in Nigeria in order to promote health, improve quality of life, and drive socioeconomic growth.

## Conclusion

Typhoid fever is a serious health concern in Nigeria, primarily transmitted by contaminated food or water infected with *S. Typhi*, as well as poor sanitation and hygiene from person to person. The disease manifests in a variety of ways and, in some cases, can be deadly. Despite current control measures, the growing challenge of antibiotic resistance, particularly in *Salmonella Typhi* strains, has made effective treatment of typhoid fever more difficult. Misdiagnosis due to inaccurate diagnostic procedures such as the Widal test, unregulated antibiotic access, widespread self-medication practices, and antibiotic use in animal farming are all influencing factors. A comprehensive strategy is required, including incorporating typhoid vaccination into national immunization plans, improving WASH practices and health infrastructures, strengthening laboratory diagnostics, regulating antibiotic sales, encouraging rational prescribing, and implementing national surveillance through antibiotic stewardship programs. Without immediate response, the incidence of antibiotic-resistant typhoid fever in Nigeria will continue to rise, endangering the health and well-being of millions of Nigerians, particularly the most vulnerable group.

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### **Completing interests**

The author declares no conflict of interests.

### **Ethical Approval**

Not applicable