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Antibiotic Resistance in *Salmonella Typhi*: Challenges and Strategies for Effective Typhoid Management in Uganda

Taliikwa Nicholas Ceaser

Department of Pharmacognosy Kampala International University Uganda
Email:ceaser.taliikwa@studwc.kiu.ac.ug

ABSTRACT

Typhoid fever, caused by *Salmonella enterica* serovar Typhi (*S. Typhi*), remains a significant public health concern in Uganda, particularly in densely populated urban centers and rural communities with limited access to clean water and sanitation. The emergence and spread of antibiotic-resistant *S. Typhi* strains especially multidrug-resistant (MDR) and extensively drug-resistant (XDR) types have complicated treatment strategies, increased morbidity, and posed substantial threats to disease control efforts. This review explores the current landscape of antibiotic resistance in *S. Typhi* in Uganda, evaluates contributing factors, and outlines comprehensive strategies to address this growing health challenge. The review also highlights gaps in surveillance, antibiotic stewardship, and public health infrastructure that hinder effective management. Finally, it recommends an integrated approach combining improved diagnostics, rational antibiotic use, vaccination, and public health interventions to curb the threat of resistant *S. Typhi* and improve outcomes in typhoid-endemic regions of Uganda.

Keywords: *Salmonella Typhi*, antibiotic resistance, multidrug-resistant, typhoid fever, Uganda.

INTRODUCTION

Typhoid fever is a life-threatening systemic bacterial infection caused by *Salmonella enterica* serovar Typhi (*S. Typhi*) [1]. It remains a major public health concern in many low- and middle-income countries (LMICs), particularly in sub-Saharan Africa and South Asia. In Uganda, typhoid fever continues to exert a significant burden on the healthcare system, disproportionately affecting children and young adults living in impoverished urban settlements and peri-urban areas [2]. The disease is primarily transmitted through the fecal-oral route, typically via ingestion of food or water contaminated with human feces containing *S. Typhi*. In regions like Uganda, where access to clean water, safe sanitation, and effective waste disposal is limited, typhoid persists as a major infectious disease challenge [3].

The prevalence of typhoid fever in Uganda is exacerbated by rapid urbanization, population growth, unregulated street food vending, and insufficient public health infrastructure [4]. These factors create a conducive environment for the continued transmission of typhoid-causing pathogens. Overcrowded slums in urban centers such as Kampala and Mbale often lack functional sewage systems, and residents are forced to rely on untreated water from wells or shallow boreholes. Furthermore, seasonal flooding and poor drainage worsen contamination and waterborne disease transmission during the rainy season. In rural areas, similar challenges exist, compounded by limited healthcare access and poor health-seeking behavior [5].

Historically, the treatment of typhoid fever has relied on the use of antibiotics. First-line antibiotics such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole were effective for many years; however, widespread use, misuse, and over-the-counter availability of these antibiotics have led to the emergence of multidrug-resistant (MDR) strains of *S. Typhi* [6]. More recently, strains resistant to fluoroquinolones, particularly ciprofloxacin, have become increasingly prevalent. Alarmingly, the global health community has reported extensively drug-resistant (XDR) *S. Typhi* strains that are resistant to all but a few last-resort antibiotics such as azithromycin and carbapenems [7]. Although most XDR outbreaks have been reported in Asia, the growing

interconnectedness of global populations and the presence of similar risk factors make such outbreaks increasingly likely in Uganda and other African countries [8].
The challenge of antimicrobial resistance (AMR) is compounded by a lack of routine diagnostic testing in many Ugandan health facilities. Many cases of febrile illness are treated presumptively as malaria or typhoid fever based on clinical suspicion without laboratory confirmation [4]. This empirical approach often results in inappropriate antibiotic use, which not only undermines treatment efficacy but also contributes to the further development of resistant bacterial strains. Furthermore, the high cost of second- and third-line antibiotics places an additional economic burden on patients and the healthcare system, making typhoid treatment increasingly unaffordable for many Ugandans [9].

Typhoid fever has been endemic in Uganda for decades, with periodic outbreaks reported in both urban and rural areas. Despite public health campaigns and vaccination efforts, the disease continues to cause significant morbidity and mortality [5]. According to data from the Uganda Ministry of Health and WHO estimates, thousands of typhoid cases are recorded annually, with many more going undiagnosed or unreported due to under-resourced health systems [10]. Recent trends have shown an alarming rise in resistance to standard antibiotics used in typhoid management. The increased incidence of antibiotic-resistant *S. Typhi* has prompted a growing concern among healthcare providers, microbiologists, and policymakers regarding the sustainability of current treatment protocols. While new vaccines such as the typhoid conjugate vaccine (TCV) show promise in preventing infection, the availability, distribution, and affordability of these vaccines remain limited in many regions. Thus, antibiotics remain the primary tool for managing active typhoid infections [11]. However, with resistance to multiple classes of antibiotics on the rise, there is an urgent need to reassess treatment strategies and develop comprehensive antimicrobial stewardship programs.
The escalating burden of antibiotic-resistant *S. Typhi* strains poses a critical challenge to effective disease management in Uganda. Many health facilities continue to rely on outdated or less effective first-line antibiotics due to cost and availability, even as resistance to these drugs becomes more widespread [12]. The lack of diagnostic capacity further complicates the situation, leading to frequent misdiagnosis, inappropriate antibiotic use, and increased treatment failures. Additionally, the continued sale of antibiotics without prescription encourages self-medication and accelerates the development of resistance. If current trends persist, Uganda may face large-scale outbreaks of drug-resistant typhoid fever that will be difficult and expensive to control [13]. This could lead to increased morbidity and mortality, straining an already overburdened healthcare system. The objectives and research questions of this study aim to provide a comprehensive understanding of the growing challenge of antimicrobial resistance in *Salmonella enterica* serovar Typhi (S. Typhi) within Uganda, a country where typhoid fever remains a significant public health issue. The first objective seeks to assess the current patterns of antibiotic resistance among *S. Typhi* isolates across selected regions of Uganda, recognizing that updated resistance profiles are crucial for guiding clinical treatment. Building on this, the second objective focuses on evaluating the effectiveness of the antibiotics most commonly used in treating typhoid fever to determine which agents remain therapeutically viable. The third objective aims to uncover contributing factors driving the rise of antimicrobial resistance in typhoid treatment, including unregulated antibiotic use, poor sanitation, and limited diagnostic capacity. The fourth objective addresses the practices and awareness levels among healthcare providers, who often diagnose and treat typhoid fever empirically due to the unavailability of reliable laboratory tests. Finally, the study will propose actionable, evidence-based strategies for improving antimicrobial stewardship and resistance surveillance within the context of typhoid management. The corresponding research questions are designed to probe into key gaps: the current prevalence of antibiotic-resistant *S. Typhi*, the efficacy of treatment regimens, the underlying causes of resistance, healthcare providers' diagnostic behaviors, and the potential interventions that could curb resistance trends. The significance of the study lies in its potential to inform national health policy, optimize clinical practices, and shape public health interventions. By contributing to more rational antibiotic use and supporting preventive measures like vaccination and better diagnostics, this research will not only address the local typhoid burden but also align with global efforts to combat antimicrobial resistance—particularly in resource-limited settings such as Uganda.

Epidemiology of Typhoid and Resistance Trends in Uganda

Typhoid fever remains a major public health challenge in Uganda, with the country classified among those with a high endemic burden. The disease predominantly affects urban and peri-urban populations, particularly in densely populated areas such as Kampala, Mbale, and parts of Wakiso District, where access to clean water and sanitation services is limited [14]. Surveillance data from the Ministry of Health, along with findings from institutions such as the Uganda Virus Research Institute (UVRI) and Makerere University School of Public Health, have consistently shown recurring typhoid outbreaks, often linked to contaminated drinking water, poor waste disposal, and

unhygienic food handling practices. The epidemiological profile of typhoid in Uganda is increasingly complicated by the rise in antimicrobial resistance. Recent studies, including a 2021 multicenter surveillance report, have shown alarming resistance trends among *Salmonella enterica* serovar Typhi isolates [15]. Over 50% of cases displayed resistance to first-line antibiotics such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. Moreover, reduced susceptibility to fluoroquinolones, especially ciprofloxacin, is becoming more common. Emerging resistance to azithromycin and third-generation cephalosporins, although still sporadic, presents an additional threat to effective clinical management. These trends underscore the urgent need for improved water infrastructure, routine surveillance, and the implementation of typhoid vaccination strategies to curb transmission and resistance.

Mechanisms of Antibiotic Resistance in *Salmonella enterica* serovar Typhi

Salmonella enterica serovar Typhi (*S. Typhi*) has developed multiple mechanisms to evade the effects of commonly used antibiotics, contributing to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains [16]. One major pathway involves plasmid-mediated resistance genes, which allow the bacterium to acquire resistance traits against antibiotics such as ampicillin, chloramphenicol, and co-trimoxazole historically first-line therapies for typhoid fever. In addition to horizontal gene transfer, point mutations in chromosomal genes encoding DNA gyrase (gyrA) and topoisomerase IV (parC) have been identified, conferring resistance to fluoroquinolones, a widely used class of antibiotics. Furthermore, *S. Typhi* can reduce intracellular antibiotic concentrations through the activation of efflux pump systems and modifications in outer membrane porins, limiting drug uptake. Of particular concern is the acquisition of resistance islands, especially those associated with IncHI1 plasmids, which can carry multiple resistance genes. These plasmids have been central to the spread of MDR and XDR *S. Typhi* in South and Southeast Asia, and their potential dissemination to Africa represents a significant public health threat. Understanding these resistance mechanisms is essential for guiding treatment strategies and informing the development of next-generation antimicrobial agents and diagnostic tools [17].

Implications for Clinical and Public Health and Contributing Factors in Uganda

The clinical and public health implications of increasing *Salmonella Typhi* resistance in Uganda are significant and multifaceted. The rise in antimicrobial-resistant strains has led to delays in effective treatment, resulting in severe complications such as intestinal perforation, sepsis, and even death, particularly among vulnerable populations [18]. Patients often require second- and third-line antibiotics, which are more expensive and less accessible, thereby escalating treatment costs and financial strain on both families and the healthcare system. Additionally, these resistant infections lead to prolonged hospitalizations, putting pressure on already overstretched health facilities and contributing to bed shortages and higher operational costs. The risk extends beyond Uganda's borders, as the spread of resistant *S. Typhi* through regional and international travel poses a global health threat. Multiple factors are driving this trend within the country. Inappropriate antibiotic use is widespread, with many individuals resorting to self-medication and purchasing antibiotics without prescriptions, a practice exacerbated by weak pharmaceutical regulations. Furthermore, the limited availability of laboratory diagnostics forces healthcare providers to rely on empirical treatments without confirming drug susceptibility, often leading to ineffective therapy and further resistance. Poor sanitation and hygiene conditions in many communities perpetuate the cycle of transmission, while underdeveloped surveillance systems hinder early detection and containment of resistant outbreaks. Collectively, these challenges underscore the urgent need for a comprehensive national strategy that includes antibiotic stewardship programs, improved diagnostic infrastructure, enhanced surveillance, public health education, and investment in water, sanitation, and hygiene (WASH) interventions to curb the growing threat of drug-resistant typhoid in Uganda [19].

Strategies for Effective Management

Effective management of typhoid fever requires a multifaceted approach encompassing improved diagnostics, antibiotic stewardship, vaccination, WASH interventions, and research. Establishing nationwide diagnostic capacity including sensitive blood culture systems and improved Widal tests—can enhance early detection and case confirmation [20]. Strengthening antimicrobial resistance (AMR) surveillance by integrating it into Nigeria's National Action Plan for AMR is essential for tracking resistance trends. Rational antibiotic use must be promoted through the enforcement of prescription-only policies and tighter regulation of antibiotic sales, alongside the implementation of antimicrobial stewardship programs in healthcare settings. Vaccination efforts should focus on introducing and scaling up typhoid conjugate vaccines (TCVs), particularly among vulnerable groups such as school-aged children, while post-introduction surveillance ensures effectiveness and high coverage. Water, sanitation, and hygiene (WASH) initiatives are critical to typhoid prevention, necessitating expanded access to safe drinking water, improved sanitation infrastructure, and public education on hygiene and food safety [20]. Finally, advancing local research into resistance patterns, vaccine performance, and molecular epidemiology, in partnership with

international collaborators, will inform evidence-based policies and long-term control strategies, strengthening Nigeria's ability to mitigate typhoid's public health impact.

CONCLUSION

The escalating threat of antibiotic-resistant *Salmonella enterica* serovar Typhi in Uganda demands urgent and coordinated public health action. The growing prevalence of multidrug-resistant and extensively drug-resistant strains has significantly undermined the effectiveness of conventional treatment options, increased disease burden, and raised the cost of care. These challenges are compounded by widespread misuse of antibiotics, inadequate diagnostic infrastructure, and poor sanitation conditions that facilitate transmission. This review underscores the need for a robust, multisectoral response involving improved diagnostic capabilities, strengthened antimicrobial stewardship, and the introduction of typhoid conjugate vaccines (TCVs). In addition, expanding WASH infrastructure and enforcing policies to regulate antibiotic use are essential for sustainable disease control. Investing in research and surveillance will further guide evidence-based interventions and support early detection of emerging resistance trends. Addressing antibiotic resistance in *S. Typhi* not only improves health outcomes in Uganda but also contributes to the broader global effort to contain antimicrobial resistance and safeguard the efficacy of life-saving antibiotics for future generations.

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