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Reassessing Malaria and Typhoid Co-Infection in Africa

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Abstract

Malaria and typhoid fever remain two of the most significant infectious diseases in Africa, contributing substantially to morbidity, mortality, and socioeconomic burden across the continent. Their overlapping geographic distribution, shared environmental risk factors, and similar clinical manifestations have led to a high burden of suspected and confirmed co-infections. However, the true epidemiology of malaria–typhoid co-infection remains poorly defined, largely due to diagnostic limitations, over-reliance on clinical symptoms, and the widespread use of poorly specific tools such as the Widal test. This review critically examines the current understanding of malaria and typhoid fever co-infection in Africa, highlighting the biological, environmental, and health-system factors that drive their coexistence. It explores the challenges associated with accurate diagnosis, including symptom overlap, inadequate laboratory capacity, co-circulation of other febrile illnesses, and the persistent use of suboptimal diagnostic methods. The review also assesses the consequences of misdiagnosis, such as inappropriate treatment, antimicrobial resistance, increased disease severity, and prolonged hospital stay. By synthesizing available evidence, we illuminate key knowledge gaps and underscore the need for integrated surveillance systems, improved diagnostic algorithms, point-of-care tools with higher sensitivity and specificity, and strengthened health-care infrastructure. Finally, we propose context-appropriate strategies for prevention, early detection, and effective management of co-infections in African settings.

Keywords: *Malaria; Typhoid fever; Co-infection; Africa; Diagnostic challenges; Antimicrobial resistance; Disease surveillance; Differential diagnosis.*

Introduction

Malaria is a life-threatening disease caused by a unicellular microorganism of the plasmodium group that are transmitted to people through the bites of infected female Anepheles mosquitoes. Approximately half of the world's population is at risk of malaria. Most of malaria cases and deaths occur in sub-Sahara Africa [1]. It is assumed to be responsible for about 1 to 3 million deaths and 300-500 million clinical cases annually [2]. According to the World malaria report 2019, there were about 228 million cases of malaria and an estimated 405, 000 deaths in 201 [3]. Most deaths are caused by *falciparum*, whereas *p. vivax, p. ovale* and *p malariae* generally cause a milder form of malaria; the specie p. Knowles rarely causes disease in humans –[4]. Typhoid fever, conversely, is an acute illness associated with fever caused by the Salmonella entrica serotype typhi and salmonella paratyphi bacteria. According to the most recent estimates, between 11 and 21 million cases and 128000 to 161000 typhoid-related deaths occur annually worldwide. Typhoid fever is contracted in most developing countries by drinking or eating the bacteria in contaminated water or food.

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People with acute illness can also contaminated their surrounding water supply through their faeces [5].

Malaria and typhoid fever co-infection is a significant public health concern in sub-Saharan Africa, particularly in tropical and subtropical regions where warm, humid environments favor the transmission of both diseases [6]. Although caused by different pathogens and transmitted through distinct mechanisms, these infections often coexist due to shared social determinants such as poverty, poor sanitation, and inadequate water supply, which increase vulnerability to both diseases [7]. The overlapping symptoms of malaria and typhoid fever complicate diagnosis, leading to frequent misdiagnosis and inappropriate treatment that can exacerbate morbidity and mortality [8]. Studies have shown that co-infection rates vary widely across African settings, with children and women often being the most affected groups, highlighting the need for age- and gender-sensitive interventions [6], [9], [10]. Reliable diagnostic methods are crucial to distinguish between these infections accurately to avoid misuse of drugs and reduce healthcare costs –[11]. Addressing diagnostic challenges and implementing integrated control strategies tailored to local epidemiological patterns are essential steps toward reducing the burden of malaria-typhoid co-infections in Africa[7], [12].

In this review, we tactfully revisited and discuss malaria and typhoid fever co-infection in Africa, explaining the challenges, including the diagnostic gap and the way forward as pertaining to the African context.

The Burden of Malaria and the Rise of Drug Resistance

Malaria remains a leading cause of morbidity and mortality in Africa. While the transmission process is known (Figure 1), the effectiveness of treatment is increasingly threatened by the rise of antimicrobial resistance (AMR), particularly resistance to antimalarial drugs. This dual challenge complicates malaria control efforts and poses a significant public health risk across the continent. Africa bears the highest global burden of malaria, with Plasmodium falciparum responsible for most severe cases and deaths, especially among children and pregnant women. Despite progress in reducing incidence and mortality through interventions like insecticide-treated nets, rapid diagnostic tests (RDTs), and artemisinin-based combination therapies (ACTs), the emergence and spread of drug-resistant malaria strains threaten these gains[2], [13], [14].

Resistance to older drugs such as chloroquine and sulfadoxine-pyrimethamine (SP) led to their replacement by ACTs. However, resistance to ACTs, especially artemisinin partial resistance (ART-R) linked to mutations in some genes, has now been documented in multiple African countries, including Rwanda, Uganda, and Eritrea [13], [15], [16], [17], [18]. This resistance is associated with delayed parasite clearance and, in some regions, reduced treatment efficacy [16], [17], [19]. Additionally, resistance to partner drugs in ACTs and the spread of multidrug-resistant strains further complicate treatment[14], [19].

Drug resistance in malaria parasites is driven by genetic mutations, often exacerbated by drug misuse, incomplete treatment courses, and limited access to quality healthcare [14]. Key resistance markers include mutations in pfcrt, pfmdr1, pfdhfr, pfdhps, and kelch13 genes, which confer resistance to chloroquine, SP, and artemisinin, respectively [14], [14], [20]. High prevalence of these mutations has been reported in East and Central Africa, undermining the effectiveness of both treatment and preventive strategies [20], [20], [20], [21].

AMR is not limited to malaria. Resistance among bacterial pathogens causing bloodstream infections, pneumonia, and meningitis is also rising, particularly in children, leading to higher mortality and complicating the management of co-infections [22], [23], [24]. Weak health systems, poor diagnostic capacity, and unregulated antibiotic use further fuel the spread of AMR [23], [24], [25]. Also co-infection of malaria and typhoid fever further complicates the treatment. Overall, malaria remains a major global health burden, especially in low- and middle-income countries, with Plasmodium falciparum causing the most lethal infections and deaths. Sustained investment in novel therapeutics, improved diagnostics, resistance monitoring, and integrated vector management is critical to counteract the growing threat of drug-resistant malaria and reduce its global burden.

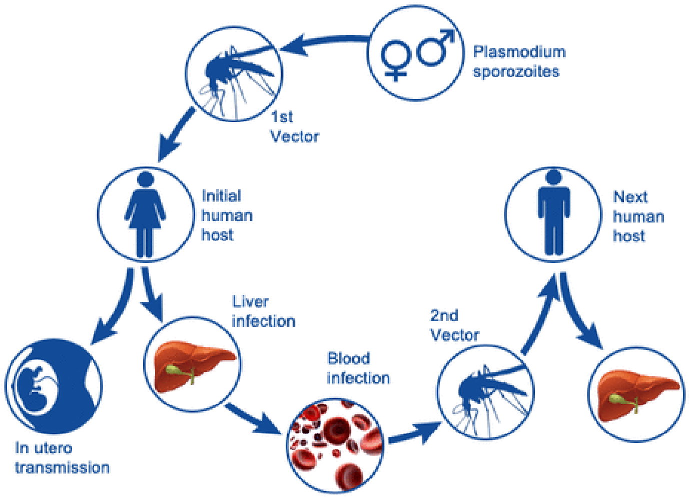

Figure 1: transmission and pathogenesis of malaria

Malaria and Typhoid Fever Co-Infection in Africa: an overview

Malaria and typhoid fever remain two of the most persistent infectious diseases affecting populations in tropical regions, particularly across Africa. Although they are caused by different pathogens. Plasmodium spp. causes malaria, and Salmonella enterica serovar Typhi causes typhoid fever [26], [27]. Their co-infection is frequently reported in clinical settings. This co-occurrence is not coincidental; rather, it is driven by a combination of environmental, socioeconomic, and health system–related factors that prevail across many African countries. Understanding these factors is crucial because co-infections often lead to diagnostic challenges, increased disease severity, and treatment complications.

One of the major drivers of malaria–typhoid co-infection is the overlapping endemicity of the two diseases. Africa's tropical climate, characterized by high temperatures, seasonal rainfall, and humidity, creates ideal conditions for both diseases to thrive. Stagnant water pools formed during the rainy season promote the breeding of Anopheles mosquitoes responsible for malaria transmission, while heavy runoff and flooding often contaminate water sources, increasing the risk of typhoid fever . In many rural and peri-urban communities where drainage systems are poor, the same environmental conditions that facilitate mosquito proliferation also support the spread of fecal contamination, making co-infection more probable.

Socioeconomic challenges further exacerbate the burden of co-infection . Malaria and typhoid fever are often referred to as "diseases of poverty," a term that reflects their strong association with inadequate housing, overcrowding, and lack of access to clean water. In low-income households, open defecation, poor sanitation, and reliance on untreated water are common realities. These conditions significantly increase typhoid transmission. At the same time, poor housing structures without window screens and the inability to afford or consistently use insecticide-treated nets leave individuals highly exposed to mosquito bites . Thus, the socio-economic vulnerabilities experienced by millions of Africans create an environment where both infections can occur simultaneously.

Furthermore, the weakness of health systems, environmental sanitation and human behavior also play important roles. Malnutrition and compromised immunity, which are common in many African settings, increase susceptibility to co-infections. Emerging evidence also suggests that antimicrobial resistance is complicating the epidemiology of typhoid. In many African regions, multidrug-resistant Salmonella Typhi strains have become increasingly common. Treatment failures prolong the duration of illness, leaving individuals more vulnerable to additional infections, including malaria, particularly in areas where both pathogens are widespread. Rapid urbanization and the growth of informal settlements contribute significantly to the rising rates of co-infection. Because both malaria and typhoid fever share the same social environment that are important to their transmission, true co-infection subsist. [7], [12]. In developing countries, co-infection of malaria and typhoid fever is often linked to poverty, overcrowding, and malnutrition, which create conditions conducive to both diseases . Anaemia caused by dyserythropoiesis is a well-established consequence of malaria, while haemolysis-induced anaemia leads to iron deposition in the liver. This iron overload can promote the growth of Salmonella bacteria, increasing susceptibility to typhoid fever . Studies have demonstrated that patients with severe anaemia show heightened vulnerability to Salmonellosis, supporting the biological mechanism behind this co-infection. The interplay between malaria-induced anaemia and typhoid infection highlights the importance of addressing nutritional and socioeconomic factors in managing these diseases. Effective diagnosis and treatment strategies must consider these underlying mechanisms to reduce morbidity associated with co-infections in endemic regions '.

High prevalence and variability of malaria and typhoid fever co-infection in Africa

Malaria and typhoid fever are both endemic in many African countries, often presenting with overlapping symptoms and leading to frequent co-infection. The prevalence of malaria-typhoid co-infection varies widely across regions, populations, and diagnostic methods. Hospital-based studies in Nigeria show co-infection rates from 5% to over 54%, with higher rates often reported in rural or low-income populations and among children aged 6–12 years. For example, a recent urban hospital study in Ibadan found monthly co-infection rates peaking at 9.7%, while other Nigerian studies report rates as high as 54.5% in Kano and 36.2% in Ebonyi State ––. In cameroon, prevalence rates of 30.3% and 6.74% have been reported, with higher rates among children and females. In Adamawa, 30.3% of febrile patients were co-infected, especially children aged 2–10 years . In Ghana, the situation is quite different – lower rates are observed, with blood culture-confirmed co-infection at 1.9% and Widal-based estimates at 5.7% . Studies in Ethiopia and Uganda using blood culture methods report lower co-infection rates (2.8–3.1%), suggesting that serological methods may overestimate prevalence (Table 1).

Children, especially those aged 6–12 years, and females are more frequently affected by co-infection –. Not surprisingly, poor sanitation, use of untreated water, rural residence, and low education levels are consistently associated with higher co-infection rates . Co-infection rates often peak during the rainy season, coinciding with increased malaria transmission and waterborne typhoid outbreaks . Diagnostic and public health implications are quite enormous. Overlapping symptoms lead to frequent misdiagnosis and unnecessary concurrent treatment, emphasizing the need for laboratory confirmation to avoid inappropriate antibiotic and antimalarial use –.

Table 1: Prevalence of Malaria-Typhoid Co-Infection in Selected African Studies

Country/Region	Prevalence (%)	Population/Setting	Diagnostic Method	Citations
Nigeria (Ibadan)	5.7–9.7	Urban hospital	Hospital records	[6]
Nigeria (Kano)	54.5	Hospital patients	Widal/microscopy	[41]
Nigeria (Ebonyi)	36.2	Community adults	Widal/microscopy	[36]
Cameroon (Adamawa)	30.3	Febrile patients	Widal/microscopy	[9]
Ghana (Ga West)	1.9–5.7	Febrile patients	Blood culture/Widal	[38]
Ethiopia (Arba Minch)	3.1	Febrile patients	Blood culture	[39]
Uganda (Western)	2.8	Febrile children	Blood culture	[40]

Misdiagnosis and overuse of antibiotics in malaria-typhoid coinfection significantly increase antimicrobial resistance risk

Misdiagnosis and empirical treatment of malaria and typhoid coinfection, especially without laboratory confirmation, drive the overuse of antibiotics and accelerate the emergence of antimicrobial resistance (AMR), posing a major threat to public health. In regions where malaria and typhoid are co-endemic, clinicians frequently treat both infections concurrently based on clinical suspicion or unreliable diagnostics like the Widal test, rather than laboratory confirmation. This practice leads to unnecessary antibiotic use, which increases selective pressure on pathogens and fosters the development and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, particularly in Salmonella Typhi and non-typhoidal Salmonella [4], [38], [38], [42], [43], [44], [45], [46].

Studies show that true malaria-typhoid coinfection rates are low, yet empirical treatment for both is common. The Widal test, often used for typhoid diagnosis, has poor specificity and sensitivity, resulting in frequent false positives among malaria patients and subsequent unwarranted antibiotic prescriptions [4], [38], [42]. This over-prescription is a key driver of AMR, with high rates of resistance observed to commonly used antibiotics such as ampicillin, tetracycline, co-trimoxazole, and chloramphenicol [4], [38], [42], [43], [44], [45].

The rise of MDR and XDR typhoid, especially in South Asia and sub-Saharan Africa, is directly linked to inappropriate antibiotic use and poor diagnostic practices. These resistant strains limit treatment options, increase morbidity and mortality, and threaten global health security through international spread –[43], [44], [45], [46], [47]. Inappropriate antibiotic use is also prevalent in pediatric and community settings, further compounding the problem [48], [49].

Limitations of typhoid and malaria diagnostic methods in Africa

Accurate diagnosis of typhoid and malaria in Africa is hampered by overlapping symptoms, limited laboratory infrastructure, and the suboptimal performance of commonly used tests. These challenges contribute to misdiagnosis, inappropriate treatment, and increased morbidity and mortality. One of the major limitation is overlapping clinical presentation. Both diseases present with similar symptoms (fever, malaise, gastrointestinal distress), making clinical differentiation unreliable and leading to frequent misdiagnosis, especially in children and pregnant women [50], [51].

Inadequate and inaccurate diagnostic tools is a major limitation that hinders malaria diagnostic in Africa. Widal test is widely used due to low cost and ease of use, but it suffers from low specificity and sensitivity, high rates of false positives/negatives, and cross-reactivity with malaria and other infections. Its accuracy is further affected by lack of antigen standardization and varying baseline titers in endemic populations [32], [50], [51], [52], [53], [54], [55]. Blood and stool cultures are often considered gold standards for typhoid, but are expensive, require skilled personnel, and have limited sensitivity, especially after antibiotic use or in low-resource settings. They are often unavailable in rural or primary care facilities [40], [51], [52], [56], [57], [58]. Also while Malaria Rapid Diagnostic Tests (RDTs) are simple and accessible, their sensitivity varies by brand, parasite species, and genetic diversity (e.g., HRP2 gene deletions). They may miss low-level parasitemia and mixed infections, leading to false negatives [32], [50], [59].

Most RDTs detect malaria by using antibodies that recognize a parasite protein called histidine-rich protein 2 (HRP2) or its close counterpart, HRP3. Over time, however, some Plasmodium falciparum strains have developed deletions in the genes responsible for producing these proteins (pfhrp2 and pfhrp3). Parasites with these gene deletions are not picked up by the tests. In several countries, the number of these deletion-carrying strains has increased to the point where RDTs may give misleading results. As a result, a test may appear negative even when the blood contains malaria parasites, simply because the parasites lack the proteins the test is designed to detect. On the other hand, microscopy which is the old standard for malaria, requires skilled microscopists and functional infrastructure, which are often lacking [51].

Furthermore, systemic and operational barriers exist. Many facilities lack adequate laboratory equipment, trained personnel, and reliable supply chains for diagnostic reagents [50], [53]. Delays in test results and inefficient health information systems hinder timely and accurate diagnosis [60]. Finally, community Factors: Self-medication, traditional beliefs, and lack of public awareness further complicate diagnosis and management [50].

There are many consequences of diagnostic limitations. Misdiagnosis and Overtreatment can leads to unnecessary use of antibiotics and antimalarials, contributing to drug resistance and increased healthcare costs [38], [61]. It also lead to missed alternative diagnoses. A significant proportion of febrile illnesses are neither malaria nor typhoid, but limited diagnostics mean other causes often go undetected [38], [52].

Also poor diagnostic accuracy undermines disease surveillance and public health interventions [53], [57], [58].

Need for molecular diagnostics and genomic surveillance

Accurate diagnosis and effective surveillance are critical for controlling malaria and typhoid fever, especially given their overlapping symptoms and the risk of co-infection in endemic regions. Malaria and typhoid fever frequently present with similar clinical symptoms, leading to frequent misdiagnosis and inappropriate treatment, which can worsen patient outcomes and contribute to drug resistance [8], [62], [63], [64]. Traditional diagnostic methods, such as microscopy for malaria and the Widal test for typhoid, have limitations in sensitivity and specificity, particularly in detecting low-density infections or distinguishing between mono- and co-infections [55], [63], [65] This diagnostic ambiguity is compounded in resource-limited settings, where advanced laboratory infrastructure is often lacking[55], [63].

Molecular diagnostic tools, including PCR-based assays and metagenomic sequencing, offer higher sensitivity and specificity for detecting both malaria and typhoid pathogens, even at low pathogen densities or in mixed infections [65], [66], [67]. Multiplex and point-of-care molecular platforms can rapidly differentiate between malaria, typhoid, and other febrile illnesses, reducing misdiagnosis and enabling timely, targeted therapy [67], [68]. These approaches are especially valuable in settings where co-infection is common and clinical presentation is non-specific[8], [62], [64].

Genomic surveillance enables the detection and monitoring of antimicrobial resistance (AMR) in both Plasmodium and Salmonella Typhi, informing treatment guidelines and public health interventions –[5], [69], [70], [71]. For malaria, genomic tools can track the emergence and spread of drug-resistant strains and diagnostic escape variants, supporting evidence-based policy decisions [65], [69], [70]. For typhoid, whole-genome sequencing and targeted amplicon sequencing can identify high-risk lineages, resistance genes, and transmission patterns, facilitating outbreak response and vaccine prioritization[5], [67], [71], [72], [73].

So far, despite their promise, the integration of molecular diagnostics and genomic surveillance into routine practice faces challenges, including cost, infrastructure, and the need for trained personnel –[70]. However, recent advances in cost-effective sequencing technologies and open-source bioinformatics tools are making these approaches increasingly accessible in low-resource settings [71], [72]. Strengthening laboratory capacity and fostering collaboration between research and public health sectors are essential for maximizing the impact of these technologies [71].

By analysing parasite genomes from many regions — with the MalariaGEN Pf7 database now containing more than 20,000 whole-genome sequences from 33 countries — researchers can track how common hrp gene deletions are in different areas and monitor changes over time. This information helps decide whether rapid diagnostic tests are still reliable or if they should consider using alternative diagnostic tools. Genomic surveillance also shows whether these gene deletions are spreading from one location to another or emerging independently in different places.

Emerging solutions and prospects in preventing malaria and malaria-typhoid fever coinfection in Africa

Preventing malaria and its coinfection with typhoid fever in Africa requires innovative, integrated, and context-specific strategies due to overlapping risk factors and persistent public health challenges. Recent advances include the rollout of malaria vaccines (RTS,S/AS01 and R21/Matrix-M), which are being integrated into routine immunization programs in several African countries and are expected to significantly reduce childhood deaths and overall malaria burden[74], [75]. Next-generation vaccines and transmission-blocking approaches are under development, aiming to improve efficacy and address different parasite stages [74]. Vector control remains central, with innovations such as next-generation insecticide-treated nets (ITNs), indoor residual spraying (IRS) with new insecticides, and larviciding, especially in areas with insecticide resistance '[76], [77], [78]. Integrated Vector Management (IVM), including environmental management, housing improvements, and community-driven interventions, is also gaining traction [77], [79].

Coinfection rates vary widely across regions, with higher prevalence in children and areas with poor sanitation ––[6], [9], [11], [39], [80]. Overlapping symptoms complicate diagnosis, often leading to mismanagement and increased risk of antimicrobial resistance [39]. Enhanced laboratory diagnostics, including rapid diagnostic tests and blood cultures, are essential for accurate detection and targeted treatment [11]. Public health interventions must focus on improving water quality, sanitation, and hygiene to reduce typhoid transmission, alongside malaria control efforts[81].

Improved sanitation, health education, and targeted interventions for high-risk groups are critical. Laboratory-based diagnosis should be prioritized to guide effective treatment and reduce drug resistance –[36], [40], [81]. For diagnostics, newer approaches using artificial intelligence and multiplex assays show promise but are limited by data quality, computational demands, and infrastructure needs [51], [60]. There is an urgent need for affordable, sensitive, and specific point-of-care diagnostics that can distinguish between malaria, typhoid, and other febrile illnesses in resource-limited settings[31], [50], [51], [59], [68].

The future of prevention lies in combining technological innovation with robust health systems and community engagement. Digital tools, genomic surveillance, and data-driven decision-making are being adopted to monitor resistance and optimize interventions [76], [77], [82]. Plant-based nanoparticles and green nanotechnologies show promise for targeted malaria management and vector control [82].

Strengthening cross-sector partnerships, sustainable financing, and policy support are critical for scaling up these solutions[76], [79], [79].

Since the mid-20th century, several effective malaria medicines have been introduced, only for Plasmodium parasites to eventually develop resistance and render those drugs less useful. In the early 2000s, the World Health Organization (WHO) shifted strategy and recommended artemisinin-based combination therapies (ACTs). These treatments pair an artemisinin-derived drug with one or more additional "partner drugs" to improve effectiveness and slow the development of resistance. Unfortunately, partial resistance to artemisinin has already appeared in a number of regions, causing the drugs to clear parasites from the bloodstream more slowly. The major worry is that if parasites also become resistant to the partner drugs — as has already happened with some combinations — ACTs may stop working as a reliable treatment. Artemisinins are not the first antimalarial drugs to encounter parasite resistance, but this is the first time researchers have identified an early warning sign: a genetic marker called PfKelch13. With targeted tools like amplicon sequencing, genomic surveillance can track mutations in the PfKelch13 gene and alert health officials when artemisinin resistance is emerging or spreading in their region. The Pf7 dataset, released in 2023, provides information on how well different drugs are expected to work by analysing more than 20,000 parasite samples from 97 sites worldwide. In addition, whole-genome sequencing (WGS) offers a wider view of the parasite's DNA, making it possible to detect new mutations linked to resistance — including resistance to the partner drugs used alongside artemisinin.

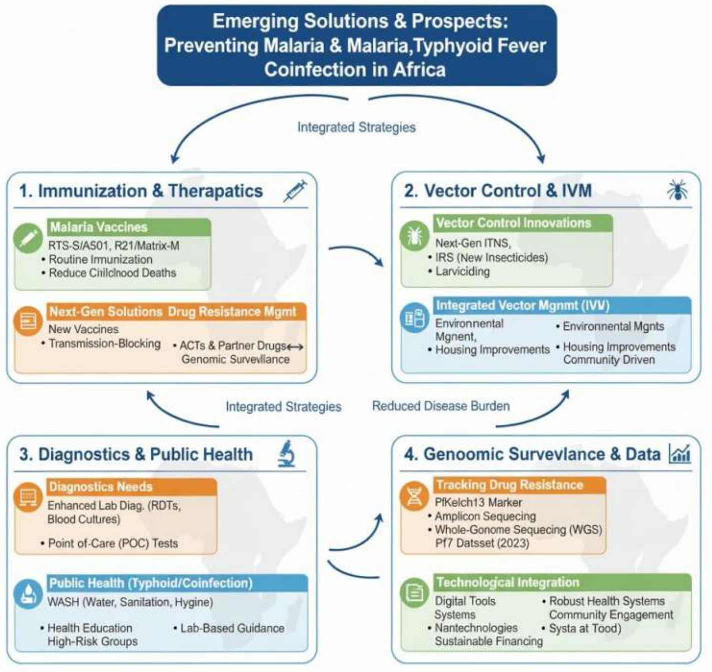

Figure 2: Integrated strategies for preventing malaria and malaria-typhoid fever coinfection in Africa

Conclusion

Malaria and typhoid fever co-infection remains a major public health challenge across Africa, with reported prevalence varying widely depending on geographical location, population characteristics, and diagnostic methods. This variability underscores the urgent need for accurate, standardized, and context-appropriate diagnostic approaches. Misdiagnosis not only impedes effective treatment but also contributes significantly to the inappropriate use of antimicrobials.

The growing threat of AMR, especially to frontline antimalarial drugs, further complicates disease management in co-endemic regions. Strengthening surveillance systems, enhancing health system capacity, and developing innovative treatment and prevention strategies are essential to preserve drug efficacy and sustain progress toward malaria elimination. Improving diagnostic accuracy for both malaria and typhoid fever requires substantial investment in laboratory infrastructure, personnel training, and the development of affordable, reliable point-of-care tests suitable for resource-limited settings. Addressing these diagnostic gaps is critical for reducing mismanagement, improving clinical outcomes, and mitigating the spread of AMR. Importantly, the overuse and misuse of antibiotics, often driven by diagnostic uncertainty in febrile illnesses, remains a major catalyst for AMR. To combat this, African health systems must prioritize laboratory-based confirmation of infections, implement robust antimicrobial stewardship programs, and maintain continuous surveillance of resistance patterns. Public and healthcare provider education on the risks of empirical antibiotic use is equally vital. Overall, tackling malaria–typhoid co-infection in Africa requires a coordinated and sustained effort that integrates improved diagnostics, targeted treatment, responsible antimicrobial use, and broader socioeconomic and environmental interventions. Only through such a comprehensive approach can the burden of these diseases be effectively reduced and public health safeguarded.

Statements and Declarations

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