THE STUDY OF PERFORMANCE AND DIAGNOSTIC EFFICACY OF WIDAL TEST AND STOOL CULTURE IN THE DIAGNOSIS OF TYPHOID FEVER AMONG SUSPECTED PATIENTS IN LOW INCOME COUNTRIES : A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: Typhoid fever is a significant health challenge in low- and middle-income countries (LMIC) due to inadequate access to clean water and sanitation infrastructure. The prevalence of typhoid fever, as determined by the Widal test, has quadrupled between 2014 and 2018, with sub-Saharan Africa having the highest infection load. Inadequate diagnosis and treatment are crucial to prevent complications. Rapid serological tests, lack of standard laboratory practices, and limited disease surveillance systems contribute to the uncertainty in disease burden.

Methods: Following PRISMA 2020 guidelines, this systematic review concentrated on full-text English literature published between 2014 and 2024. Editorials and review articles that appeared in the same journal as the submission were not accepted without a DOI. The literature was assembled using a variety of online databases, including ScienceDirect, PubMed, and SagePub.

Result: Utilizing reliable resources including Science Direct, SagePub, and PubMed, the study examined around 800 papers. After seven pieces were determined to be relevant for methodical investigation, a more thorough examination of the complete material was conducted.

Conclusion: Diagnostics for typhoid fever, a common illness in low- and middle-income countries, mostly depend on the Widal test. On the other hand, variables such as malaria parasitemia, antigen standardization, and patient population affect how accurate the test is. The suggested diagnostic strategy identifies Salmonella from blood, stool, and bone marrow cultures; this calls for significant upgrades to laboratory resources as well as continuous training.

Keyword: *Typhoid, LMIC, widal test, stool, diagnostic*

INTRODUCTION

Low- and middle-income countries (LMIC) continue to face health challenges and health security threats from typhoid fever as a result of inadequate access to clean water and inadequate sanitation infrastructure.[1-3] It is estimated that there are about 14 million cases of typhoid and paratyphoid fever worldwide, with sub-Saharan Africa (SSA) having the highest infection load with an incidence rate of 762 per 100,000 people annually.[4-6] A recent multi-centered population-based surveillance study found that S. Typhi was the most frequently isolated isolate among Salmonella spp., accounting for 24% of all bacterial pathogen infections in the SSA, accounting for over 33% of infections overall.[7] Per reports, children between the ages of two and four had the highest incidence of typhoid fever.[2,7,8] Typhoid fever requires effective diagnosis and treatment to prevent complications like intestinal perforation, hemorrhage, hepatitis, cholecystitis, myocarditis, shock, encephalopathy, pneumonia, and anemia. Risk factors include contaminated food and water, poverty, lack of hygiene, contaminated milk, and contact with chronic disease carriers, highlighting the need for timely and comprehensive care.[6]

The prevalence of typhoid fever, as determined by the Widal test, has quadrupled among patients of all ages between 2014 and 2018, rising from 9.2 to 37.4%, according to a five-year retrospective analysis.[9] Typhoid fever prevalence was estimated to be 5% among patients who were considered to be feverish, based on the biomarker's identification through blood culture.[10] This figure is considerably lower than the results of the traditional Widal test. Just 1 (0.7%) of the 288 blood samples that were taken produced isolates of Salmonella during blood culture and nearly half of those samples tested positive for the Widal test.[11] Furthermore, a study among feverish patients in Southern Ethiopia revealed that the pathogen's detection by blood culture indicated a 1.6% prevalence of typhoid fever.[12] Inadequate diagnosis still makes it difficult to effectively treat concurrent typhoid fever because of the disease's vague clinical presentation, a lack of funding, limited access to medical facilities, and a shortage of qualified medical professionals. In LMICs, when appropriate diagnostic instruments are unavailable, symptoms associated with febrile illness are frequently misinterpreted.[13,14] Rapid serological tests, which have a poor degree of sensitivity and specificity and produce inaccurate confirmed typhoid fever cases, are the only means of assessing the burden of typhoid fever in endemic areas. There is a significant knowledge gap that affects healthcare practices and policy in countries where typhoid fever is widespread because these countries lack well-established population-based national surveillance systems.[15]

Typhoid fever management in LMIC faces challenges due to limited resources, insufficient staff, and reliance on blood culture for definitive diagnosis. This uncertainty in disease burden is due to inaccurate rapid diagnostic tests, lack of standard laboratory practices, and limited disease surveillance systems. Prevention methods like health education, vaccination, and antibiotic regimens have not yielded significant results in managing the disease in Africa. Addressing these issues requires a comprehensive approach to ensure the correct diagnosis and treatment of typhoid fever.[6] This study aims to provide a comprehensive overview of the literature on the performance and diagnostic efficacy of stool cultures and the Widal test in the diagnosis of typhoid fever among suspected patients in low-income countries that have been published during the last 10 years.

METHODS
PROTOCOL
Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were scrupulously followed by the work's author. This was done to make sure the study complied with all rules. The method of choice was laboriously created to guarantee the precision and coherence of the research outcomes.

CRITERIA FOR ELIGIBILITY
This paper offers a thorough analysis of research on the effectiveness of stool cultures and the Widal test in diagnosing typhoid fever in suspected patients in low-income nations. Through in-depth data analysis, this project aims to explain and enhance patient care procedures. This thesis' main goal is to highlight the importance of important topics that may be found in a range of literary works.

Strict inclusion and exclusion standards were put in place to ensure that the data utilized in this study was accurate. An item must have been published in English between 2014 and 2024 in order to be considered for inclusion. Among the exclusion criteria are editorials, submissions without a DOI, published reviews, and duplicate journal entries.

SEARCH STRATEGY
The study's keywords include "typhoid fever, widal test, low income, stool culture, diagnostic, efficacy, performance, outcomes". For this research, the following Boolean MeSH keywords were entered into the databases: (((("typhoid fever"[MeSH Terms] OR "typhoid fever "[All Fields] AND "widal"[All Fields]) OR ("typhoid fever"[MeSH Terms] OR "typhoid fever"[All Fields] AND "stool"[All Fields]) AND ("typhoid fever"[MeSH Terms] OR "diagnostic"[All Fields] OR "efficacy"[All Fields] OR "low income"[All Fields] OR "performance"[All Fields] OR "outcomes"[All Fields]))).

DATA RETRIEVAL

The writers carefully read the title and abstract of each article to determine its significance before starting this arduous examination. Greater weight was only assigned to studies that met the inclusion criteria and bolstered the goals of the article. A recurring pattern produced a definitive answer after several searches. Full-text entries were only accepted in the English language. Content that satisfied all predetermined inclusion criteria and had a clear connection to the study's topic matter was produced through the strictest screening procedure. Studies that deviated from these trends were typically disregarded and their conclusions were not given much weight. During the evaluation, a great deal of information was located and looked over, including factors, titles, authors, publication dates, places, and study methodologies.

QUALITY ASSESSMENT AND DATA SYNTHESIS

The authors separately assessed the research cited in the titles and abstracts of each article in order to determine whether papers require additional investigation. Examining every document that complied with the prerequisites in advance for review inclusion was the next step. The selection of the papers for the review is based on the evaluation findings. This criterion expedited the selection of publications for additional investigation, enabling a comprehensive appraisal of previous work and the circumstances that qualified it for assessment.
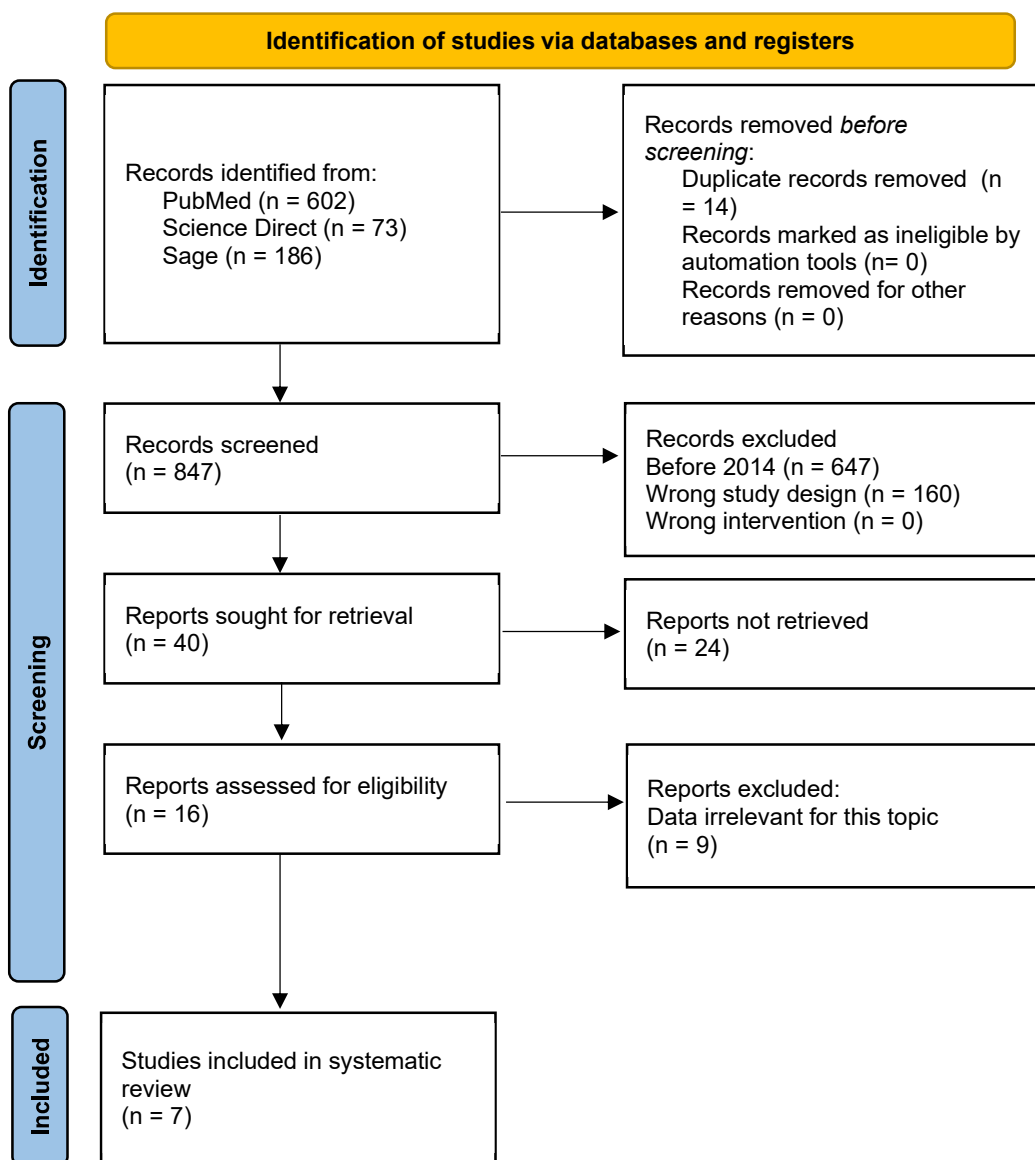

Figure 1. Article search flow chart

RESULT

Our research team first collected almost three thousand publications from reliable sources like PubMed, Science Direct, and SagePub. After a comprehensive three-tier screening procedure, only seven papers were judged to be immediately

related to our continuing systematic inquiry. After that, a few passages were chosen for further study and a thorough examination of the whole document. For convenience of viewing, the content that was evaluated for this analysis has been condensed into Table 1.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Zorgani & Ziglam.[16] (2014)	Libya	Review	-	The Widal test, a crucial diagnostic tool in laboratories, is often influenced by the sensitivity and specificity of different populations, leading to potential misdiagnosis and mismanagement of patients. To improve the reliability of the test, it should be interpreted based on baseline antibody titers, not a single test.
Islam et al.[17] (2016)	Bangladesh	Bayesian	92 patients	Typhidot, Tubex, and TPTest were tested in 28 S. Typhi bacteremic patients, with varying sensitivity and specificity. TPTest showed a 96.0% sensitivity, while Tubex and Typhidot showed a 59.6% sensitivity. Bayesian latent class modeling estimated sensitivity at 96.6% for TPTest, 89.9% for Tubex, and 80.0% for Typhidot, respectively. These results highlight the importance of these tests in diagnosing S. Typhi.
Bundalian et al.[18] (2019)	Philippines	Meta Anaylsis	10 studies	The TUBEX® TF test has a sensitivity/specificity range of 55-100%/58-100%, Typhidot has a sensitivity/specificity range of 54-67%/54-95%, and the Widal test has a sensitivity/specificity range of 32-95%/4-98% in typhoid patients. In terms of the pooled meta-analysis estimations, the TUBEX® TF performed better than other methods in distinguishing between patients with typhoid fever and those with a febrile illness of unknown origin.
Ohanu et al.[19] (2017)	Nigeria	Prospective Study	810 patients	Typhoid suspects were aged 33.1±6.5 years, with 50.7% being women. Out of 810 tested, 14.1% had positive cultures for Salmonella enterica serovar paratyphi and S. enterica serovar Typhi. The Widal test had sensitivity, specificity, PPV, and NPV of 49.1%, 90.7%, 46.2%, and

				91.6%, respectively. Malaria parasitaemia was detected in 22.2% of febrile patients, with 63.9% having a positive Widal test for O/H antigens. Antibiotic multi-drug resistance was detected in 52.6% of patients.
Wilairatana et al.[20] (2021)	Thailand	Meta Analysis	81 studies	The Widal test was used to analyze the prevalence rates of typhoidal/NTS and malaria co-infection among febrile patients and malaria patients. The rates were 14% and 1%, respectively. The prevalence rates of malaria infection were 31% and 3%, respectively. Malaria infection was associated with typhoidal/NTS in children under 15 years. The case fatality rate was 16% in patients with malaria and NTS co-infections.
Mahmoud et al.[6] (2022)	Rwanda	Review	-	Typhoid fever, a major public health threat in Africa, relies on the Widal serological test for diagnosis. However, recent studies suggest blood culture, clinical findings, and laboratory confirmation. Treatment relies on fluoroquinolones, macrolides, and cephalosporins. Improvements in healthcare and vaccines are underway.
Teferi et al.[14] (2022)	Ethiopia	Meta Analysis	15 studies	Typhoid fever diagnosis in Ethiopia is influenced by blood and stool culture tests, with a prevalence of 3% and a Widal test of 33%. The Widal test, which is considered nonreliable, is used for the diagnosis of salmonella S. Typhi, causing high diagnostic uncertainties. The antimicrobial susceptibility of salmonella S. Typhi is low for most recommended antibiotics, and the Ethiopian Food and Drug Authority must strengthen its monitoring and antimicrobial surveillance system to address rising resistance.

Zorgani & Ziglam's 2014 study highlighted the importance of effective training in the laboratory for typhoid fever diagnosis. They highlighted the need for resources for bone marrow and blood culture, and the need for newer serological methods for early diagnosis.[16]

Islam et al.'s study revealed that diagnostic methods like TPTest, Tubex, and Typhidot have varying sensitivity and specificity. TPTest had a 96.0% sensitivity, while Tubex had a 60.2% sensitivity and Typhidot had a 59.6% sensitivity. The widal test had a low sensitivity but excellent specificity, while blood culture had intermediate sensitivity but 100% specificity. These findings highlight the importance of understanding and utilizing effective diagnostic methods.[17]

Bundalian's study on the Widal test revealed a sensitivity and specificity range of 68-86% and 84-97%, respectively, based on pooled diagnostic accuracy estimates. The test's results are difficult to interpret due to its limitations, such as high antibody concentrations and reliance on standardization and maintenance. The test's value depends on patient population and standardization.[18]

Ohanu's study revealed that typhoid patients had a significantly higher prevalence of typhoid than controls. Of the 810 patients tested, 114 (14.1%) were bacteriologically positive for typhoid pathogens, with S. typhi being the most common pathogen. The clinical features of febrile patients showed significant differences compared to those with negative typhoid culture results. Of the 114 febrile patients with culture-confirmed typhoid fever, 63 (55.3%) had positive Widal titers for the O antigen, while 6 (5.3%) had positive Widal titers for the H antigen.[19]

The study by Wilairatana et al. showed that the Widal test was used to estimate the prevalence rate of typhoidal/NTS and malaria co-infections among febrile patients in Africa. The highest prevalence rate was found in Cameroon and Nigeria, while lower rates were found in Sierra Leone, Ethiopia, Pakistan, Ghana, India, and Tanzania. The highest prevalence of co-infections was observed in all age groups, with 1% in Africa and 1% in Asia. The prevalence rate of malaria and typhoid co-infections was highest in 2016 and 0% in 2012 and 2016.[20]

Mahmoud's study highlights the challenges in diagnosing typhoid fever in Africa due to resource and personnel limitations. The gold standard is bone marrow culture, but diagnosis often relies on blood culture or the widal test. A new surveillance model aims to improve diagnosis, but antibiotic self-medication and resistant bacterial strains could undermine typhoid prevalence.[6]

Teferi's study revealed a 3% typhoid prevalence among eligible studies, with significant heterogeneity. The study used a random-effects model for meta-analysis, revealing a 2% prevalence in febrile patients compared to 6% in suspected patients. The stool culture test identified a higher proportion of salmonella S. Typhi than blood culture, with a 4% prevalence. The Widal test, however, had a 33% prevalence, higher than blood and stool culture.[14]

DISCUSSION

Diagnosing typhoid fever involves a range of methods, both direct and indirect. The gold standard is the Widal test, which examines the production of IgM and IgG antibodies against the somatic O-antigen or flagellar H-antigen of Salmonella. However, it is not specific and may lead to false positive results due to cross-reactivity with other Salmonella and Plasmodium species. Rapid tests like the TUBEX® TF assay have shown promise for acute diagnosis and treatment monitoring. Other serologic tests, such as TUBEX® TF (IgM), Typhidot (IgM/IgG), IgM/IgG ELISA, IgM dipstick, and Widal test (hemagglutination) are also used for typhoid fever diagnosis.[18] However, the Widal test's accuracy depends on the laboratory and patient population, as well as the antigen's standardization and maintenance.[21] Additionally, using the Widal test in regions where typhoid is endemic may be challenging due to patients' exposure to S. Paratyphi A or malaria.[18]

The prevalence of typhoid fever has been reported to be 14.1% in Africa and Asia. This is compared to previous studies where the prevalence was found to be between 11.3% and 18.7%. Differences in factors such as age, gender distribution, and sample size may explain the disparity between the current study and previous studies. However, the larger sample size and higher use of antibiotics may have affected the prevalence rates.[19] Positive cultures for typhoid fever are most frequently found in blood (81%), followed by stool (50%) and urine (2.1%).[22] In African settings, late presentation is common, and simultaneous blood, urine, and stool cultures increase the probability of detection. S. paratyphi is more common than S. typhi, accounting for 63.2% of cases with culture-proven typhoid fever.[19] According to a study by Ohanu et al., malaria parasitemia is a common cause of acute febrile illness. The study found a high proportion of individuals with malaria parasitemia have positive Widal reactions, suggesting that the Widal test alone may not accurately diagnose typhoid fever. 48% of patients with malaria parasitemia would have been misdiagnosed.[19]

Mediterranean North Africa is a region where typhoid and paratyphoid fevers are common. Among S. Typhi and S. Paratyphi isolates, multidrug resistance is common. There are issues with the Widal test's systematic usage for diagnosis and antibiotic treatment because of its variable sensitivity and specificity among populations. As of right now, Libyan laboratories lack a defined protocol for identifying and reporting S. Typhi, which results in subpar laboratory practices and incorrect interpretation. The Widal test should not be interpreted based only on the manufacturer's titers, but also on baseline antibody titers to guarantee consistent results. The recommended diagnostic approach is to identify Salmonella from bone marrow, blood, and stool cultures; this calls for extensive laboratory resource improvements and ongoing

training.[16] Enteric fever is a significant global health concern, particularly in infrastructure-limited countries like Bangladesh. The sensitivity of microbiologic culturing of bone marrow is considered the gold standard for confirming the disease, but it is not practical for young children in endemic areas.[17] Blood culturing is often used as an alternative diagnostic option, but its sensitivity is only 40-80% due to the low burden of organisms in blood and prior use of antimicrobial agents.[23] Improved diagnostic assays are needed to target antimicrobial agents with activity. The Widal assay has low sensitivity and specificity, while nucleic acid amplification assays show promise but face challenges in clinical situations.[17]

The Widal test is a commonly utilized diagnostic tool for detecting typhoid fever, but studies have shown that it may also report high rates of malaria and typhoidal/NTS co-infections in febrile patients in Cameroon, Nigeria, and Sierra Leone. Nigeria, in particular, has the highest prevalence of co-infections, indicating a potential relationship between the two diseases.[20] However, the test has been found to have a wide margin of error in detecting malaria and co-infections due to its inability to differentiate between Salmonella species and cross-reactivity with other Enterobacteriaceae. False-positive results have also been reported, leading to overdiagnosis and unnecessary treatment with antibiotics, which can contribute to microbial resistance and poor outcomes in resource-limited areas.[24,25] Combining the Widal test with blood and stool cultures is recommended for diagnosing Salmonella spp. infections in febrile or malaria patients, this method can be costly.[20] Recent studies in Ethiopia have found the Widal test to have poor reliability, with low specificity and a high rate of false positive and negative results. Therefore, it should not be solely relied upon in detecting typhoid fever.[14]

In LMIC, particularly in Africa, the diagnosis of Typhoid fever is impeded by resource and personnel limitations. Developed nations have relied on serology or agglutination tests, such as the Widal test, for over 50 years. While many Typhoid fever diagnostic guidelines advise against using it as the sole diagnostic criteria, Africa has made progress in improving diagnosis through various projects.[26] A new surveillance model has been developed, which includes clinical findings, Widal test confirmation by two separate technicians, and ruling out other febrile illnesses. This protocol has proven successful in Sierra Leone and Malawi, resulting in more Typhoid fever cases being identified than ever before.[19,26] However, the reliance on cheaper serology tests like the Widal test, as well as antibiotic self-medication, may undermine the prevalence of Typhoid fever in Africa. The emergence of resistant bacterial strains of Typhoid fever in Africa has changed the medications of choice, with blood culture now being the preferred diagnostic standard. PCR may be used to identify resistant strains, but its use in Africa is highly limited.[6] Typhoid fever diagnosis faces numerous challenges, including high healthcare costs, differing baseline data for the Widal test, and missed diagnoses due to patients using pharmaceutical medications.[27] Additionally, false positives from serology tests and stool cultures can complicate investigations.[26,27] The lack of data in various African countries also poses significant challenges for the public health sector in identifying chronic carriers and sensitivity regarding stool culture, as most fecal specimens do not reveal bacteria presence.[6]

CONCLUSION

Typhoid fever is a common disease in LMIC countries, with the Widal test being the gold standard for diagnosis. However, the test's accuracy depends on factors such as laboratory and patient population, antigen standardization, and the presence of malaria parasitemia. The prevalence of typhoid fever is 14.1% in Africa and Asia, with S. Paratyphi A and malaria being more common. The Widal test's sensitivity and specificity are also a concern, with Libyan laboratories lacking a defined protocol for identifying and reporting S. Typhi. The recommended diagnostic approach is to identify Salmonella from bone marrow, blood, and stool cultures, which requires extensive laboratory resource improvements and ongoing training. The Widal test has a wide margin of error in detecting malaria and co-infections, leading to overdiagnosis and unnecessary treatment with antibiotics. In LMIC countries, the diagnosis of typhoid fever is impeded by resource and personnel limitations, and the emergence of resistant bacterial strains has changed the preferred diagnostic standard.

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