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Diagnosis of Typhoid Fever: A Review Article

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Abstract

Typhoid fever, a well-known enteric disease caused by bacteria from the *Salmonella* species, poses a significant threat to public health. The accuracy of diagnostic tests for typhoid fever can vary, with widely used methods such as the TUBEX-TF, Typhidot, and Widal tests producing inconsistent outcomes. These tests often show differences in sensitivity and specificity based on the region and population being tested. This review assessed the diagnostic reliability of various rapid diagnostic tests (RDTs) for typhoid fever in regions such as Zimbabwe, Bangladesh, India, Indonesia, Cameroon, and others. A comprehensive literature search was conducted using databases like PubMed and Google Scholar to identify relevant studies published between 2015 and 2024. Studies assessed tests like TUBEX-TF, Typhidot, Widal, and newer systems such as the DPP Typhoid System. Results showed significant variability in sensitivity and specificity across regions, with TUBEX-TF showing sensitivities from 24% to 97.6% and specificity up to 99%, while the Widal test demonstrated high sensitivity but low specificity in some areas. Bayesian Latent Class Models were applied in several studies to refine accuracy assessments. The findings suggest that no single test is consistently reliable across all settings, and a combination of diagnostic approaches or the use of newer systems may improve accuracy. Further research is needed to validate the performance of emerging tests in diverse populations.

Keywords: Typhoid fever, rapid diagnostic tests, sensitivity, specificity.

Introduction

Typhoid fever is a systemic illness caused by *Salmonella enterica* serovar Typhi (S. Typhi), a Gram-negative, rod-shaped bacterium. This life-threatening disease has been a longstanding public health concern in developing and underdeveloped nations. A systematic analysis by typhoid and paratyphoid collaborators estimated that globally,

10.9 million cases of typhoid fever occurred in 2017, leading to 116.8 thousand deaths [1]. Despite a global decline in typhoid incidence per capita, particularly in high-income countries like Australia, Japan, New Zealand, Singapore, South Korea, and Taiwan, as well as in middle-income countries such as Malaysia and Thailand [2], certain countries like Ghana, Malawi, Fiji, China, Indonesia, Cambodia, and Iraq have seen a steady rise in incidence from 1990 to 2014. These figures are likely underreported, as many cases are either treated on an outpatient basis or go untreated. In Malaysia, between 2011 and 2015, it was estimated that 0.58 to 1.42 cases of S. Typhi infection per 100,000 people were reported annually, with most cases linked to travellers returning from endemic regions, migrant populations, and contamination in food chains through infected food handlers [3].

Typhoid fever poses a significant risk in regions characterized by poor-quality drinking water, unsanitary living conditions, and inadequate sanitation systems. Asymptomatic carriers are particularly crucial in spreading contamination and

The World Health Organization (WHO) recommends that countries where typhoid fever is endemic implement health facility-based surveillance systems with laboratory confirmation to accurately assess disease burden, monitor antimicrobial resistance, enable rapid outbreak detection, and evaluate the impact of vaccines [4]. Since the clinical symptoms of typhoid fever are often indistinguishable from other common acute febrile illnesses in these areas, such as malaria and dengue, laboratory confirmation—typically through blood culture—is essential for diagnosis [4]. However, blood culture has limited sensitivity, ranging from 40% to 60%, and its effectiveness is further diminished by the widespread use of antibiotics prior to diagnosis. Additionally, blood culture is not always readily available in many health care facilities, nor is it systematically collected from all febrile patients [4]. As a result, the number of confirmed S. Typhi cases likely represents only a small fraction of the true disease incidence.

facilitating disease transmission [2]. The illness is marked by a prolonged fever, which can reach temperatures as high as 103–104 °F (39–40 °C), accompanied by symptoms such as fatigue, headache, nausea, constipation or diarrhea, and abdominal pain. These symptoms typically emerge 6 to 30 days after infection [5]. In severe instances, complications such as intestinal perforation may occur, potentially leading to serious health issues or even death [6, 7].

Enhancing the quality of drinking water supplies and promoting better hygiene practices are likely the most effective strategies for eliminating typhoid fever. However, implementing these interventions quickly in endemic regions of Africa and South Asia poses significant challenges. Consequently, short-term control of typhoid primarily relies on extensive vaccination campaigns and appropriate treatment, both of which depend on the availability of rapid diagnostic tests (RDTs) that demonstrate strong performance. While several commercially available RDTs exist for diagnosing typhoid fever, identifying tests with high sensitivity and specificity remains difficult. This scarcity of reliable diagnostic assays hampers accurate assessments of the disease burden and can lead to misdiagnosis and inadequate treatment for patients. Additionally, the rising global prevalence of multidrug-resistant *S. Typhi* has heightened the demand for effective typhoid diagnostics [8-10].

Timely and accurate diagnosis of enteric fever is crucial for reducing complications, hospitalizations, and mortality. However, obtaining laboratory confirmation within the first week of illness presents challenges due to the suboptimal performance of currently available laboratory testing methods. There is an urgent need for the development of rapid multiplex diagnostic tests that offer enhanced sensitivity and specificity to improve early diagnosis and management of the disease [11].

The laboratory diagnosis of typhoid fever predominantly relies on blood and stool cultures, which are considered the gold standard for confirming the infection. However, this method

presents significant challenges in resource-limited settings, where basic laboratory facilities for culturing may be lacking [12]. Additionally, the culture technique is time-consuming, often requiring several days to isolate and identify the causative agents [13]. The Widal test, currently the standard serological method for diagnosing typhoid, detects O and H antigens but has relatively low specificity due to cross-reactivity with other bacterial infections [14]. Consequently, there is a pressing need for a rapid and sensitive assay for the detection of *S. Typhi*, which would aid in clinical diagnosis and help prevent the spread of the disease [15]. In this context, developing a highly specific and sensitive immunodiagnostic test for typhoid fever represents a promising approach.

Several serology-based rapid diagnostic tests (RDTs) for typhoid fever, including Typhidot (Malaysia), TUBEX (Sweden), and Multi-Test Dip-S-Tics (USA), are commercially available and have been globally assessed for their performance. However, these tests have not provided satisfactory results when validated in various endemic settings [16]. This is largely attributed to inconsistencies in sensitivity levels, often resulting in false negatives. Numerous antigens, such as flagellin, hemolysin E (HlyE), YncE, and cytolethal distending toxin subunit B (CdtB), have been evaluated for their effectiveness in detecting *S. Typhi* [17, 18]. Nonetheless, due to the absence of comprehensive comparisons among the available data, the optimal antigen for *S. Typhi* detection remains undetermined.

The rationale for this systematic review is to assess the variability in diagnostic accuracy of rapid diagnostic tests (RDTs) for typhoid fever, including TUBEX-TF, Typhidot, Widal, and newer systems like the DPP Typhoid System, across diverse regions and populations. Given the global burden of typhoid and the inconsistent performance of available tests, this review aims to provide a clearer understanding of their reliability and limitations. By synthesizing findings from multiple studies, the review highlights the need for improved diagnostic

approaches to enhance accurate detection and effective treatment of typhoid fever.

Methodology

This study involves a systematic review of several diagnostic tests for typhoid fever, concentrating on the accuracy of rapid diagnostic tests (RDTs) like TUBEX-TF, Typhidot, Widal, and emerging systems such as the DPP Typhoid System across different regions and populations.

A comprehensive literature search was conducted using databases like PubMed and Google Scholar to recognize relevant studies published between 2015 and 2024. The search focused on key terms such as -TUBEX-TF, -Typhidot, -Widal test, -DPP Typhoid System, and -typhoid diagnostic accuracy. Studies were selected on the basis of their relevance to the diagnostic performance of these tests, reporting of sensitivity and specificity, and publication in peer-reviewed journals or validated clinical research.

The inclusion criteria for the selected studies required them to provide data on sensitivity and specificity of at least one typhoid diagnostic test, along with information on sample size, region, and testing methodology. Studies that did not report these values or lacked enough detail were excluded. Data extraction focused on essential parameters such as the sample size, demographic details (where available), sensitivity, specificity, and any additional methodologies applied, such as the use of Bayesian Latent Class Models for refining diagnostic accuracy.

Data were categorized based on the geographical location of the study (e.g., Africa, South Asia, Southeast Asia), allowing for comparison of test performance across different regions with varying typhoid burdens and healthcare infrastructure.

The primary outcome of the review was to assess the sensitivity (the ability to correctly identify patients with typhoid) and specificity (the ability to correctly identify patients without typhoid) of each diagnostic test. By comparing these outcomes across various regions, trends in diagnostic

accuracy were identified, highlighting the strengths and limitations of each test. This comprehensive approach allowed for a thorough assessment of typhoid diagnostic tests and provided valuable insights into their reliability and practical use in different settings.

Results

In 2015, a study was conducted to evaluate the clinical performance of the TUBEX-TF and OnSite Typhoid IgG/IgM Combo rapid tests for detecting *Salmonella enterica* serovar Typhi infection during a typhoid outbreak in Harare, Zimbabwe. The study included a sample size of 136 participants, although their age and gender were unspecified. The findings showed that both the TUBEX-TF and OnSite Typhoid IgG/IgM Combo rapid tests demonstrated high diagnostic accuracy, with 100% sensitivity and specificity values of 94.12% and 94.35%, respectively.

In 2016, conducted a study in Bangladesh comparing the performance of various immunodiagnostic assays, including TPTest, Tubex, Typhidot, and Widal tests, alongside blood cultures, in detecting patients with typhoid fever. The study involved a sample size of 92 participants, though their age and gender were unspecified. The sensitivity and specificity of the TPTest were found to be 60.2% and 89.9%, respectively. Tubex showed higher accuracy with 96.0% sensitivity and 96.9% specificity, while Typhidot demonstrated a sensitivity of 59.6% and specificity of 80.0%. The study also applied a Bayesian Latent Class Modeling approach to further analyze the data.

In 2024, Nurmawati S, et al. conducted a study in Indonesia to assess the clinical characteristics of enteric fever and evaluated the performance of the TUBEX TF IgM test in hospitals. The study involved a sample size of 301 participants. The results showed a wide range of sensitivity for the TUBEX TF test, varying from 97.6% to 70.7%, and specificity from 38.3% to 67.2%. Additionally, the acute IgG test demonstrated a sensitivity of 90.7% and specificity of 82.7%.

Another study conducted a comparative analysis of commercially available typhoid point-of-care tests in 2022. The study, a prospective and hybrid retrospective multicenter diagnostic accuracy evaluation, was carried out in Kenya and Pakistan. A total of 531 serum samples were analyzed, though details regarding the participants' age and gender were unspecified. The study found that the Enterocheck-WB (RDT) demonstrated 72.7% sensitivity and 86.5% specificity in detecting typhoid fever across the two countries.

In 2015, conducted a study in Bangladesh to evaluate the diagnostic accuracy of three rapid diagnostic tests for typhoid fever. Using a Bayesian latent class model, the study involved participants with a median age of 13.5 years (IQR: 5-31 years). One of the tests, TUBEX TF, demonstrated a sensitivity of 24% and a specificity of 96%, highlighting its limitations in sensitivity despite high specificity.

In 2021, conducted a study in Fiji assessed the Rapid Diagnostic Tests for Typhoid Diagnosis. This study included 179 patients with a median age of 29 years (IQR: 20-46), of whom 51.4% were male, and 73.2% were indigenous. The sensitivity of the TUBEX TF test was 77.6%, with a specificity of 60.5%. Additionally, the Typhifast IgM test had a sensitivity of 75.5% and a specificity of 85.5%.

In 2021, performed a cross-sectional comparative study in Cameroon with 558 patients. The study compared the Widal test and Typhidot immunoassay for diagnosing typhoid fever. The Widal test showed a sensitivity of 94.44% and a specificity of 48.35%, while the Typhidot test demonstrated a sensitivity of 80.56% and a specificity of 94.03%.

Another study in 2019, studied the prevalence of typhoid fever among febrile Nigerian patients. The study included 1,098 participants: 810 cases (114 children, 669 adults) and 288 controls (48 children, 240 adults). The Widal test had a sensitivity of 49.1% and a specificity of 90.7%.

In 2020, conducted a cross-sectional comparative study in India with 121 participants aged 12-65 years. The Typhifast IgM test had a sensitivity of

55.22% and specificity of 74.04%, while the Enterocheck WB test showed a sensitivity of 85.07% and a specificity of 62.96%. The DPP Typhoid System had a sensitivity of 97.01% and specificity of 68.52%.

In 2024, Singh R, and colleagues, performed a cross-sectional comparative study in India, evaluating the TUBEX-TF test for typhoid diagnosis. The study, involving 94 participants, found a sensitivity of 25% and specificity of 84% for the Widal test, while the TUBEX-TF had a sensitivity of 44% and specificity of 59.1%. The DPP Typhoid System showed a sensitivity of 75% and a specificity of 79.55%.

In 2015, another study conducted a comparative study in India, evaluating the TUBEX TF (Inhibition Magnetic Binding Immunoassay) for typhoid fever. The study included serum samples from 50 patients with typhoid, 50 with non-typhoid fever, and 100 healthy individuals. The TUBEX TF test showed a sensitivity of 76% and a specificity ranging from 96-99%.

Another study in 2024, conducted a cross-sectional comparative study in Bafoussam City, Cameroon, involving 336 febrile patients. The Typhidot immunoassay revealed 100% sensitivity and 82.3% specificity in diagnosing typhoid fever.

In 2015, conducted a comparative study in Kathmandu, Nepal, involving 1,371 participants aged 46-60. The ELISA test showed a sensitivity of 72% and specificity of 58%, while IgG sensitivity and specificity were 96% and 95%, respectively, and IgM sensitivity and a specificity were 95% and 94%.

Table I: Assessment of sensitivity and specificity of different rapid diagnostic tests.

SNo.	Publication year	Study Design	Country	Sample size	Age	Gender	Widal Test	Enterocheck-WB (RDT)	TUBEX TF (RDT)	Typhifast IgM (RDT)	TYyphidot test
1.	2015	a review and meta-analysis of TUBEX® TF clinical performance	Zimbabwe	136	unspecified	unspecified	----	----	100% sensitive and 94.12% specific,	100% sensitive and 94.35% specific,	----
2.	2016	Comparative study	Bangladesh	92	Unspecified	----	----	----	Sensitivity 60.2% Specificity 89.9%		Sensitivity 59.6% Specificity 80.0%
3	2024	----	Indonesia	301	----	----	----	----	sensitivity of 97.6% to 70.7% specificity of 38.3% to 67.2%	Acute IgG revealed Sensitivity90.7% specificity82.7%	----
4.	2022	prospective and retrospective multicenter	Kenya and Pakistan	531 serum samples	Unspecified	Unspecified	----	72.7% sensitivity, 86.5% specificity	----	----	----
5.	2015	Bayesian latent class model.	Bangladesh		median (IQR) age of 13.5 (5-31) years	----	----	----	----	Sensitivity 24% and Specificity96%	----
6.	2021	----	Fiji	179 patients	median (IQR) age was 29 (20-46) years.	92 (51.4%) male and 131(73.2%) were indigenous	----	----	sensitivity 77.6% Specificity 60.5%	----	sensitivity 75.5 % Specificity 85.5%
7.	2021	Cross-Sectional Comparative Study	Cameroon	558 patients	Unspecified	Unspecified	Sensitivity 94.44% Specificity 48.35%	----	----	Sensitivity 80.56% Specificity 94.03%	----
8.	2019	Case-control	Nigeria	1098	Cases: 810 (114 children, 669 adults.), Control: 288 (48 children, 240 adults)	Unspecified	Sensitivity 49.1%, Specificity 90.7%	----	----	----	----

9.	2020	Cross-sectional comparative study	India	121	12-65 years	Unspecified	Sensitivity 55.22%, Specificity 74.04%	Sensitivity 85.07%, Specificity 62.96%	----	Sensitivity 97.01%, Specificity 68.52%	----
10.	2024	Cross-sectional comparative study	India	94	Unspecified	Unspecified	Sensitivity 25%, Specificity 84%	Sensitivity 44%, Specificity 59.1%	Sensitivty 75%, Specificity 79.55%	----	----
11.	2015	Comparative study	India	50 patients of typhoid , 50 patients of PUO and 100 normal healthy	Unspecified	Unspecified	----	----	Sensitivity of 76% and specificity of 96-99%	----	----
12.	2024	Cross-sectional study a	Bafoussam City, Cameroon	336	Unspecified	Unspecified	----	----	----	----	sensitive (100%) and specific (82.3%)
13.	2015	Comparative study	Kathmandu, Nepal.	1371	46-60 years	2:1	----	Sensitivity 72.0% and specificity 58.0%	----	sensitivity and specificity of IgG (96.0% and 95.0%) and IgM (95.0% and 94.0%)	----

Discussion

Numerous studies reflect a wide range of geographic areas, methodologies, and diagnostic methods used for detecting typhoid fever. There is significant variability in the performance of diagnostic tests such as TUBEX-TF, Typhidot, Widal, and others, depending on the region and population. For instance, in Zimbabwe, the TUBEX-TF and OnSite Typhoid IgG/IgM tests exhibited impressive results, with 100% sensitivity and specificities over 94% [19]. However, these results stand in stark contrast to findings from Bangladesh and India, where the sensitivity of TUBEX-TF ranged from 24% to 97.6%, raising concerns about its ability to reliably detect all typhoid cases in those regions [20-22].

The Widal test, despite being widely used, also shows considerable variation in performance. While it demonstrated high sensitivity (94.44%) in Cameroon, its poor specificity (48.35%) indicated a high rate of false positives. This variability makes it less reliable for diagnostic accuracy, particularly in regions where the burden of febrile illnesses is high [23]. These tests may be useful for ruling out typhoid but less effective at confirming infections, especially in the early stages.

Newer diagnostic tools, such as the TUBEX TF IgM and DPP Typhoid System, have emerged with some promising results. The TUBEX TF IgM test in Indonesia exhibited sensitivity between 70.7% and 97.6%, but specificity was lower, ranging from 38.3% to 67.2% [24]. On the other hand, the DPP Typhoid System in India showed a more balanced sensitivity of 75% and specificity of 79.55%, making it a potentially more reliable diagnostic option [25]. Despite these developments, the trade-offs between sensitivity (identifying true positives) and specificity (correctly identifying negatives) continue to challenge clinicians, as seen with the Widal test's poor specificity and the variable performance of Typhidot and TUBEX TF.

Moreover, the use of Bayesian Latent Class Models in studies from Bangladesh and Fiji suggests a more sophisticated approach to understanding the

accuracy of these tests in the absence of a perfect diagnostic standard. These models allow for a more nuanced assessment of the tests' performance in specific populations. Overall, the variation in results across regions and test types indicates that relying on a single diagnostic tool may not suffice for accurate typhoid diagnosis [26, 27]. Instead, a combination of methods, or the use of emerging test systems like DPP Typhoid, may help improve diagnostic accuracy. Nonetheless, more studies are needed to confirm the reliability of these newer tests across diverse populations and outbreak settings.

In a systematic review of typhoid point-of-care diagnostic tests, studies conducted across various countries highlight significant variability in the sensitivity and specificity of the tests. Sapkota et al. performed in Kenya and Pakistan, where the Enterocheck-WB (RDT) exhibited a sensitivity of 72.7% and specificity of 86.5% [28]. In Nigeria, Ohanu et al. evaluated the Widal test, which showed lower diagnostic performance with a sensitivity of 49.1% and specificity of 90.7%, indicating that while the test effectively rules out disease, it may miss many true cases of typhoid fever [29]. Likewise, Piankeu et al. in Cameroon demonstrated that the Typhidot immunoassay had perfect sensitivity (100%) but a specificity of 82.3%, signalling the test's ability to detect all true typhoid cases but with a risk of overdiagnosis [30]. In Nepal, Adhikari et al. found that the ELISA test had moderate diagnostic accuracy with a sensitivity of 72% and specificity of 58%, while IgG and IgM tests demonstrated higher sensitivity (96% and 95%, respectively) and specificity (95% and 94%, respectively) [31]. Across these studies, the balance between sensitivity and specificity varied, highlighting the challenges of achieving optimal diagnostic accuracy. Tests like Typhidot and DPP Typhoid System, with high sensitivity, are more suited for high-prevalence areas, where minimizing missed diagnoses is critical, whereas tests like Widal, with higher specificity, may be useful in low-prevalence settings to avoid unnecessary treatment. The review underscores the importance of selecting appropriate diagnostic tools based on

local epidemiology and the trade-offs between false positives and negatives in clinical settings.

The limitations of the studies highlighted include small sample sizes, variability in study design, and the potential for selection bias, which may affect the generalizability of the findings. Additionally, some studies lacked demographic details such as age and gender, limiting the ability to assess the impact of these factors on test performance. The varying methodologies and cut-off values for determining sensitivity and specificity among different rapid diagnostic tests may also contribute to inconsistencies in results. Therefore, it is recommended that future studies utilize larger, more diverse populations and standardized protocols to enhance comparability. Moreover, integrating multiple diagnostic methods, including blood cultures and serological tests, could provide a more comprehensive approach to diagnosing typhoid fever, ultimately leading to improved patient outcomes and more effective management of febrile illnesses.

In conclusion, the study review demonstrated varying diagnostic performances of rapid diagnostic tests (RDTs) for typhoid fever across different countries and patient populations. Tests like TUBEX TF, Typhidot, Enterocheck WB, and others showed considerable variation in sensitivity and specificity, with TUBEX TF generally having lower sensitivity but higher specificity in some studies. The Typhidot test, on the other hand, displayed high sensitivity in certain settings, while the Widal test often showed inconsistencies, particularly with lower specificity. The results highlight the importance of selecting the appropriate diagnostic tool based on the clinical context and regional prevalence of typhoid fever to improve diagnostic accuracy.

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