DIVERSITY IN TYPHOID DIAGNOSTIC PROTOCOLS AND RECOMMENDATION

FOR COMPOSITE REFERENCE STANDARD

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Abstract

Typhoid fever is a major public health burden which causes substantial global morbidity and mortality due to lack of decisive diagnostic protocols. The capacity of commonly use diagnostic test to validate the absence of typhoid fever is controversial. This study explores to evaluate new techniques for typhoid diagnosis and proposed a harmonised suitable standardized composite reference to be adopted. Published peer-reviewed articles indexed in PubMed, MEDLINE and Google scholar were reviewed for hospital-based studies. This study reveals new typhoid diagnostic techniques such as proteomics, serology, Rapid Diagnostic tests (RDTs), transcriptomics, genomics, and metabolomics. 34.4% of the studies use prospective study design. The study result establishes that, Widal test has a moderate diagnostic accuracy with average percentage sensitivity (52.9%), specificity (54%), positive predictive value (PPV) (56.8%) as well as negative predictive value (NPV) (55.6%) when compared with 29.4%, 28%, 29.5%, and 27.8%

of Typhidot respectively. The findings showed a statistically significant difference on the sensitivity between Widal and Typhidot t (40) = 2.639, *p* = 0.012 at *p*<0.05 using independent sample *t*-test. When there is no perfect reference standard that has an optimal diagnostic accuracy, the need for a harmonised suitable standardized composite reference is essential. Hence, this study recommends that, peripheral blood culture with established sensitivity of 60% and Widal test with average sensitivity of 52.9% be adopted as a consensus composite reference standard for typhoid fever diagnosis in other to improve confidence in prevalence estimates.

KEYWORDS: Typhoid fever; Diagnostic, Metabolomics, Composite reference standard, Accuracy, Sensitivity.

1.   INTRODUCTION

Enteric fever (EF), commonly called typhoid fever (TF) is a systemic infectious disease caused by *Salmonella* Typhi and *Salmonella* Paratyphi, which if left untreated could cause substantial ill health and death. The disease causes serious public health challenge, with approximately 12,000,000 to 27,000,000 cases annually [1,2]. The estimated death varies between 129,000 to 223,000 annually [3,4]. Typhoid fever causes overwhelming affliction in low and middle income countries, with a world-wide projection of 11.9 million cases and 120 000–220 000 mortality yearly [5, 6]. The prevalence of TF has been reported to be high in preschool children and infants [6-9]. In Africa, it has been observed that the burden of the disease is significantly high [6,10].

Lack of suitable diagnostic test as well as effective antibiotic treatment could result in TF death [11]. In perspective to the absence of decisive diagnostic protocols, the disease could lead to fatal complications such as intestinal perforations [12]. Research findings for the best enteric fever

diagnostic techniques are being carried out by many research groups globally, with elusive results [13]. The diagnostic accuracy of typhoid fever is a major challenge. The gap in TF diagnosis has led to under-diagnosis, imprecise disease burden estimates, inaccurate, and over-diagnosis that could result in inappropriate and excessive intake of antibiotics [14,15]. Various diagnostic techniques have been employed, including blood and bone marrow culture that were recommended as reference standard diagnostic tests [16,17]. The most sensitive and specific test for enteric fever is bone marrow culture, though, invasive with medical complications, requiring technical expertise and specialized equipment [18]. Blood culture is the most frequently used techniques among culture based methods with limited resources for proper culturing in many setting [19]. Blood and bone marrow culture sensitivity has been quantified at 40-80% and >80% respectively [19,20].

Rapid and accurate enteric fever diagnosis is significant and could reduce mortality, ill health and control the spread of the ailment [21-24]. Widal test is widely used due to its readily availability and affordability, but lack sensitivity and specificity and is not very reliable [25-28]. However, this cheap and quick Widal test is the reason for the extensive report on the incidence of typhoid fever in different areas of Nigeria [15]. Novel diagnostic techniques for enteric fever are in progress that could mitigate this deficit. New point-of-care technologies such as rapid magneto-DNA nanoparticle assay, proteomics, genomics, Loop Mediated Isothermal Amplification, Typhidot, Polymerase Chain Reaction (PCR), transcriptomic, and metabolomic has been establish [28-34]. Hemagglutination and enzyme linked immunosorbent assay (ELISA) are serological tests used for *Salmonella enterica* serova Typhi H and O antigens with poor sensitivity and specificity [35].

. The use of gold standard test with imperfect diagnostic accuracy could bring about newer and better technique [36]. The development of a composite reference standard (CRS) is alternative technique to improve diagnostic accuracy in the absence of a perfect reference test [37]. Composite

reference standard is the combination of more than one imperfect technique aimed at increasing diagnostic accuracy. This study discussed current biomarkers of enteric fever diagnosis and presented the diagnostic performance of typhoid fever test. However, based on the results of these findings, the study proposed a harmonised CRS for adoption as suitable standardized composite reference which would help to improved confidence in the prevalence estimates of typhoid fever infections.

2. NEW BIOMARKERS OF ENTERIC FEVER DIAGNOSIS

2.1 Proteomics

Serological markers that are available for enteric fever test are characterized with low sensitivity and specificity. In Nigeria, studies on children with acute enteric fever based on proteome microarray tested IgA, IgM and IgG ELISAs using S. Typhi LPS and hemolysin E (HlyE) proteins [38,39]. This study recognized putative sero-diagnostic biomarkers such as invasion (SipC), proteins targeted toward host cell attack (HlyE) and bacterial cell surface (OmpA) [28]. Other studies of S. Typhi proteome arrays have shown HlyE as a suitable sero-diagnostic biomarker based on IgG and IgA responses [28,38,40,41]. OmpA is also seen as a valuable biomarker from proteomic screening [30,41]. Salmonella Typhi proteome array screening has identified N-acetylmuramoyl-L-alanine amidase (t2002, STY0927) as a new putative biomarkers which is use in the catabolism of peptidoglycans.

During vaccination and cholera infection, antibody in Lymphocyte Supernatant assay (ALS) is used [42], tuberculosis [43] and influenza [44]. This has been used to detect S. Typhi antibodies in infected cohorts [45]. Antibody in Lymphocyte Supernatant assay is applied to translate new sero-diagnostic markers through immune-profiling to detect immune-dominant antigens [28,41].

Putative protein targets that should be considered for future diagnostic development in RDTs are IgA, S. Typhi LPS and IgG for better diagnostic results in resource-limited settings [28].

2.2 Metabolomics

Metabolomics is a new technique of scientific research, which was developed to identify and measure minute quantities of small chemicals in complex biological material using cutting-edge mass spectrometry [46]. Progress has been made to validate the diagnosis of enteric fever by using diagnostic metabolites in plasma from patients [47]. This technique is useful to several infectious diseases, detecting signatures of urinary tract infections, inflammatory disease and viral infections [48-50]. Furthermore, it is could predict disease outcomes, progression, and even onset, as was recorded in tuberculosis [51]. This technique was used to produce metabolites signatures on plasma samples by 2-dimensional gas chromatography with time of-flight mass spectrometry from 50 typhoid fever patients (25 with S. Typhi and 25 with S. Paratyphi A) against 25 febrile controls [47]. It has been identified and validated that significant and reproducible metabolomics signatures could separate typhoid and other febrile illness with asymptomatic controls in a Nepali patient cohort [47,52]. This diagnosis compares the metabolites profiles of healthy and infected persons with typhoid and paratyphoid. Threshold is determined to single out those with acute typhoid fever [53].

2.3 Transcriptomics

Transcriptomics require the measurement of gene expression in a given cellular compartment at a specific time. The transcript mRNA is measured and quantity by calculating the amount of mRNA transcribed from genomic DNA using microarrays and RNAseq high-throughput molecular technology. Profiles can be produced from a small quantity of biological sample, such as whole blood [54]. Therefore, transcriptomic has been used to generate detailed insights into the human

transcriptional response to several diseases [55-60] and other alternative immune perturbations [54,60-62]. The human challenge model has been the source of various gene expression datasets, which were generated in a highly controlled setting, allowing the interrogation of the human transcriptional responses to S. Typhi and S. Paratyphi A [59,63,64]. This technique use the response of the host as a possible biomarkers that are specific to identify typhoid fever patients. It confirms that gene expression profiles are specific enough to possibly differentiate diseases with similar clinical presentation [65]. This is a powerful tool to detect new diagnostic biomarkers for diseases and could represent the future of molecular diagnostics for typhoid fever.

2.4 Genomics

This technique has allowed for *S.* Typhi genome sequencing and assisted in the recognition of specific gene targets. DNA markers that are specific for *S.* Typhi have been identified using the genome database and nucleic acid sequence alignment tools (BLASTn). The primer sensitivities and specificities designed for amplifying specific gene sequences were authenticated using *S.* Typhi, non-Typhi *Salmonella* and non-*salmonella* clinical isolates [23].

2.5 Other Typhoid Diagnostic Techniques

Several other techniques aside the new approaches such as molecular detection of bacteria genes using PCR has being the focus of research towards developing an improved typhoid test. PCR technique is a non-culture based techniqus designed to identify the flagellin genes of *S.* Typhi, *S.* Paratyphi A and other specific targets [66,67]. A PCR-based technique has the capacity to identify bacterial DNA and do not recover living cell. Nevertheless, any pathogen-directed test for S. Typhi/S. Paratyphi A is limited by the low concentration of bacteria in the blood as well the inherent inhibitors in the sample [68]. Laboratory methods to lyse red blood cells have shown increasing yield [69], and extracting DNA from samples could generate increase yield, thus improving sensitivity and specificity [70].

Loop-mediated isothermal amplification (LAMP) is a method for the amplification of nucleic acid at a constant temperature, targeting specific *S.* Typhi gene [71,72].

An attractive approach for typhoid fever diagnostics is the detection of an antibody response signifying recent infection using serum and plasma. The most promising targets identified through serological response are (IgG) and (IgA) to hemolysin E and S. Typhi–specific lipopolysaccharide (LPS) [73], IgM and/or IgG to hemolysin E [74], and IgA to *S.* Typhi–specific LPS [75].

Widal test (WT) measures agglutinating antibodies against lipopolysaccharide (LPS) (O) and flagellar (H) antigens of *S.* Typhi in the sera of typhoid fever patient [76]. This technique is unreliable with low sensitivity and specificity [27]. Rapid diagnostic tests (RDTs) could detect antigens or antibodies with Typhidot-M® and TUBEX^{TM} as the current commercial RDTs for typhoid fever [13, 77]. *Salmonella* Typhi antibodies specific to LPS antigens are detected by Enterocheck WB techniques in a lateral flow format similar to ICT. Negative result is indicative of the absence of pink to pink-purple coloured band in the test area [18,28]. Blood culture technique is considered the reference standard for enteric fever diagnosis [78,79. The sensitivity of culture specimens differs considerably depending on the type and volume of fluid analysed, prior antimicrobial use, age of the infected person and period of ailment. Bone marrow culture is obtained through aspirate of the iliac crest or sternum with a sensitivity of approximately 90% when the culture is over 4 days [80-82].

3.   EXPLORATION APPROACH

3.1 Research design and methodology

The research design was a quantitative method with a survey approach which involves five respective steps: identification of studies; selection of articles; quality assessment of studies; extraction of data; and data analysis.

3.2 Search strategy for identification of relevant articles

A search strategy was designed to identify all articles in English that assessed enteric fever diagnostic protocols among humans. Published peer-reviewed articles of diagnostic protocol for enteric fever were identified from Google scholar, PubMed, and MEDLINE databases. The search words were enteric fever, novel typhoid diagnostic, cultural diagnostic test, diagnostic protocol of typhoid, rapid diagnostic test and widal test for trials in progress.

3.3 Search outcome

In all, three hundred and ninety two (392) articles were identified and screened (Figure 1). 355 articles were excluded after reviewing the articles based on the following: duplicates 94, misleading titles and abstract 102, articles without Widal and rapid diagnostic test 91, articles that do not meet quality criteria 68.

3.4 Inclusion and exclusion criteria

Studies in English language were included without restrictions on country, age, demographics, or time. Cross-sectional studies, paired comparative study, prospective cohort studies, and retrospective studies were included. Studies that do not meet quality criteria were excluded.

3.5 Ethics statement

All studies included were those approved by an institutional ethics review committee in addition obtained informed consent from all their participants. Ethics approval was not requisite for the present study as it is based on secondary data generated from the primary source.

3.6 Statistical analysis

The data obtained from the literature were entered into Microsoft Excel and Statistical Package for the Social Science (SPSS), version 25.0 for windows (SPSS Inc., Chicago, Illinois, USA) and were used for descriptive analysis of the data. The results are presented as percentages. Independent sample t-test was used to explore differences in the mean percentage sensitivity of diagnostic tests. The level of statistical significance was set at $P < 0.05$.

4.   RESEARCH OUTCOME AND ANALYSIS

4.1   Results of electronic search

The results of the synthesis from the studies collected by the literature review are presented in the Table 1. Of the 392 searched articles, 37(9.4%) articles met the inclusion criteria with 11,525 participants (Table 1). Exactly 27 studies use widal test, 5 use TUBEX, 15 use Typhidot (Typhidot, Typhidot-M, and TyphiRapid-Tr02), 1 use Diazo test, 2 use Enterocheck WB®, 2 use Multiplex PCR, 1 use ONSITE Typhoid Combo, 1 Multi-test dipstick, and 2 Panbio ELISA. Studies that used the gold standard for comparison were 31. All of the diagnostic tests were developed to identify *S.* Typhi infection and Paratyphi. 34.4% of the studies in this review used prospective study design.

4.2 Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)

The percentage sensitivity, specificity, PPV, and NPV of the data obtained are presented in Table 1. The average sensitivity of 52.9% (figure 2), average specificity of 54% (figure 3), average PPV of 56.8% (figure 4), and average NPV of 55.6% (figure 5) was determine in Widal test while 29.4%, 28%, 29.5%, and 27.8% was determine in Typhidot respectively. There was a statistical

evidence to demonstrate that there was a significant different between Widal test and Typhidot. The diagnostic accuracy of Widal was moderate compared to others.

5.   INTERPRETATION OF RESEARCH OUTCOME

This study reveals a moderate average diagnostic accuracy of Widal test in the diagnosis of TF. A clinically diagnosis requires high values for both sensitivity and specificity. TF diagnosis actually begins with the evaluation of clinical signs and symptoms. Different diagnostic tools are used for enteric fever diagnosis and include cultures from blood, bone marrow, urine and stool. Recently, diagnostic tools such as proteomics, transcriptomics, metabolomics and genomics have been exploited to detect biomarkers unique to *S.* Typhi [34]. The sensitivity of any diagnostic test is the percentage of patients that are positive and are appropriately identified with the ailment. However, specificity is the percentage of patients that are properly diagnosed as negative. The probability that those confirmed positive by the techniques are actually having the disease is positive predictive value (PPV) while the probability that those confirm negative by the techniques are actually not infected is negative predictive value (NPV).

Several gold standard techniques have been used to assess typhoid diagnostics, with blood culture being the most used techniques. The lack of perfect gold standards is a major challenge with assessing the accuracy of typhoid diagnostics. Blood cultures, which has a near perfect specificity, is only 50–65% sensitive. Storey *et al*. [116] reveal that no single test has adequately good performance but recommended that some existing techniques could be useful as composite reference standard.

The study reveals that the combinations of existing sensitive and specific techniques could surmount the limitations of accuracy that is intrinsic in single test. The application of composite reference standard could enhance better estimates for test performance based on combinations of tests. The purpose of this study is to evaluate typhoid diagnostic accuracy and the urgent need for

the best components of a typhoid CRS in other to establish a standardized composite reference as novel typhoid protocol. This will enable careful comparison of diagnostic accuracy data across studies, which is often difficult because of varying study designs and reference standards. To authenticate the diagnostic accuracy of a new test, results from several studies is required. Furthermore, the use of CRS will enhance confidence in prevalence estimates, which could help guide typhoid vaccination efforts. A new CRS for typhoid may still be imperfect compared to diagnostic truth, but there is much to gain from the approval of a standardized composite reference. There is an urgent need for better diagnostic tests to detect enteric fever in order to improve disease burden estimates and potentially accelerate the adoption of new typhoid vaccines [117,118]. In order to achieve this, standardization, and broad approval of a single reference standard based on a composite reference are required.

6. CHALLENGES AND FUTURE OUTLOOK

Identifying real typhoid patients with negative blood culture is a significant constrain in enteric fever diagnosis [119]. Indistinguishable clinical symptoms and the absence of a reliable gold standard test complicate typhoid diagnosis. About 20mL to 30mL of blood is needed for the detection of blood related infections and this poses a challenge for elderly and neonatal patients [120]. Additionally, lack of funding support, research capacity, and lack of institutional infrastructure are challenges facing TF diagnosis and other infectious diseases, especially in Nigeria. Absence of perfect test leads to unwise antibiotic use, resulting to complications, morbidity as well as drug resistance.

A diagnostic technique requiring small blood volumes with quick and correct detection is thus required. Furthermore, the quality of a reliable future evaluation of enteric fever diagnosis can be improved by the use of composite reference standard CRS, which will enhance assurance in

prevalence estimates and avoid inappropriate intake of antibiotics by patients that do not need it. Future research should employ a prospective cohort design with CRS as a diagnostic tool. From our outlook, metabolite profiles are possible future solution for diagnosing typhoid fever, but there are many challenges in making these indicative chemical signatures routinely accessible. The use of CRS as upgraded reference standard for typhoid fever diagnosis will improve the actual worldwide burden of typhoid widespread.

7. LIMITATIONS AND STRENGTHS OF THE STUDY

Limitations in this study arise from the variety of diagnostic technique used by several investigators, as well as the way those tests were conducted. As a result, many articles could not be included in the analysis. Also, this analysis was based on published literature only. Regardless of these limitations, the strength of this study is the thorough review of published peer review articles assessing the current trend and performance of various diagnostic protocols for the detection of enteric fever.

8. CONCLUSIONS AND RECOMMENDATIONS

In conclusion, it is a real possibility to eliminate typhoid fever, but novel diagnostics is necessary and should be factored into future trajectory for the disease control. This study found a diverse evidence of typhoid diagnostics with a substantial degree of variation in typhoid fever testing. The principle finding of this study reveals that the diagnostic performance of Widal test was moderate at a sensitivity of 52.9%. The combination of imperfect tests to determine typhoid fever disease status is a transparent technique to deal with the challenge of imperfect reference standard

However, the study proposes the combinations of peripheral blood culture and Widal test as a composite reference standard which will possibly improve confidence in prevalence estimate.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Author BEI got the concept. The study design and data analysis was performed by S.I.R.O. and B.E.I. Author B.E.I, I.B.O, IAE, and S.A.M participated in the drafting of the manuscript, which was critically reviewed for important intellectual content by S.I.R.O, A.B, U.J.O, and O.M.O. Interpretation of data obtained was done by S.A.M, S.I.R.O, I.B.O, I.A.E., U.J.O. and A.B. The statistical analysis was performed by B.E.I and O.M.O. All authors read and approved the final version of the revised manuscript for publication.

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1   TABLE 1: Diversity of Typhoid fever diagnostic protocols and accuracy values

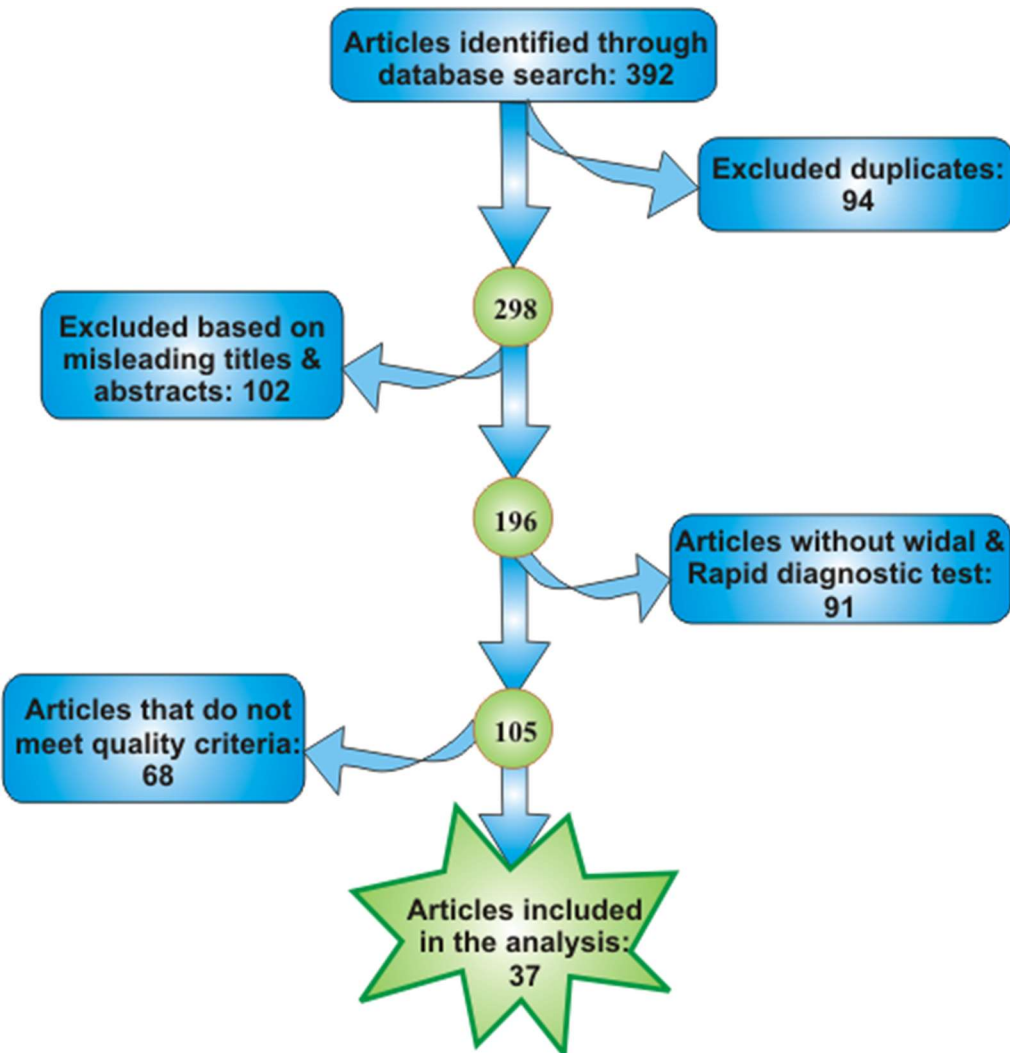
Diagnostic tests	Study design	Sample size (11,525)	Gold Standard	Country	Prev (%)	Sen (%)	Spec (%)	PPV (%)	NPV (%)	Citations
Widal	Cross-sectional	372	Stool culture	Ethiopia	56.2	80	44.5	3.8	98.8	[83]
Widal	Cross-sectional	95	Stool culture	Ethiopia	68.4	84.2	35.5	24.6	90	[84]
Widal	Randomized design	125	Stool Culture	Nigeria	17.6	78.3	93.6	68.2	98.1	[85]
Widal	Cross sectional	158	Stool Culture	Tanzania	81	81.5	18.3	10.1	89.7	[86]
Widal	Prospective study	810	Blood and stool culture	Nigeria	NR	49.1	90.7	46.2	91.6	[87]

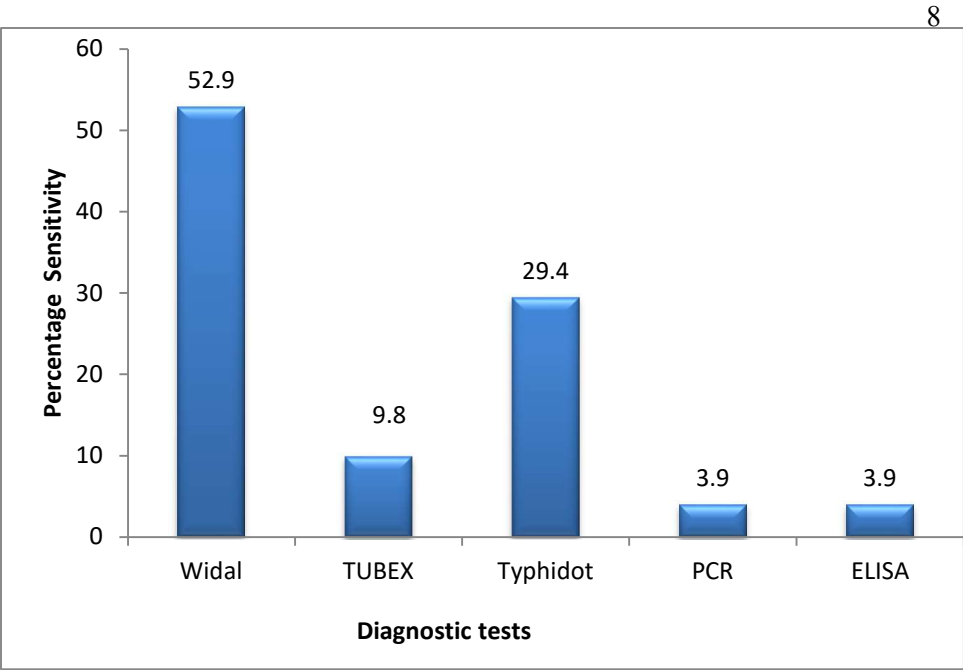
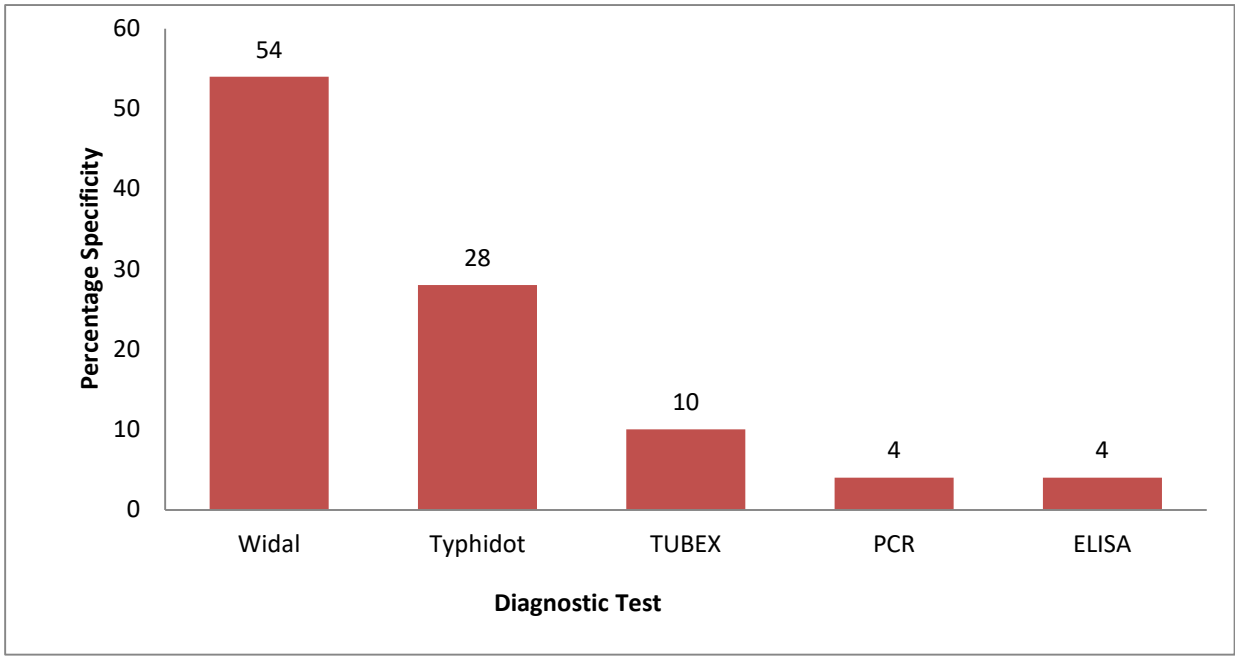
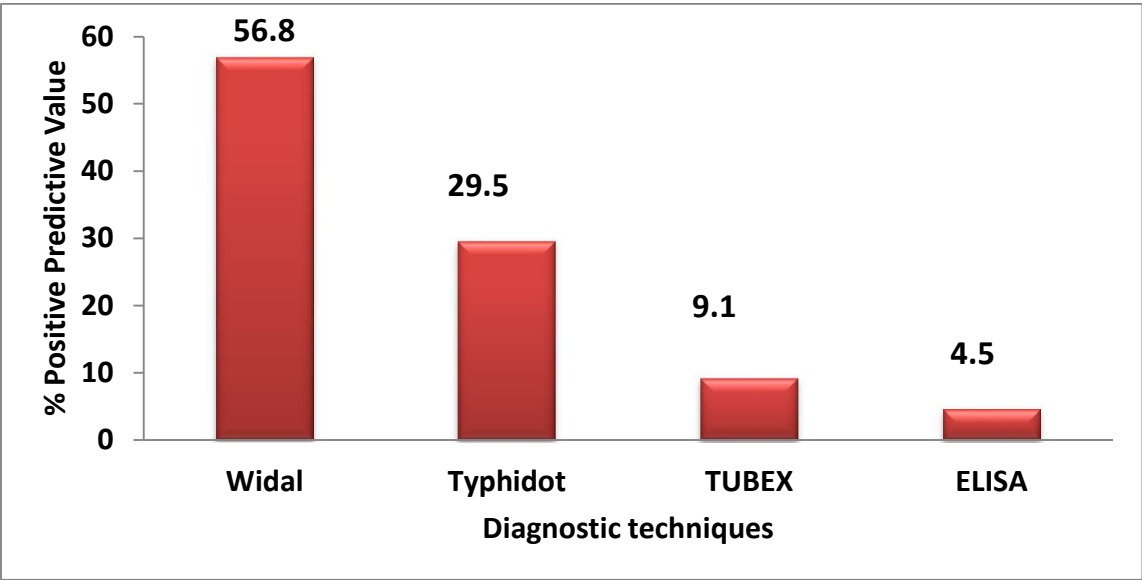
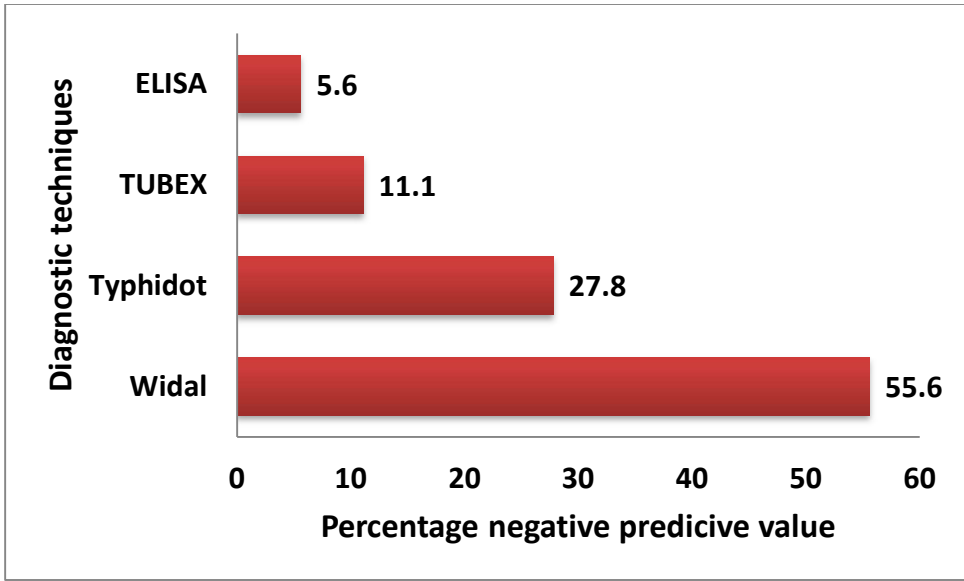
Widal	Cross-sectional	91	Stool culture	Nigeria	62.5	71.4	66.7	83.3	50	[88]
Widal	NR	71	PCR	India	NR	50	50	92.8	39.5	[89]
Widal	Comparative study	112	Stool culture	Cameroon	57.1	40.9	32.4	6.44	28.1	[90]
Widal	Cross-sectional	158	Stool and blood culture	NR	81	81.5	18.3	10.1	89.7	[91]
Widal	Retrospective study	100	Blood Culture	India	NR	71.4	47.3	9.25	95.7	[92]
Widal	Prospective study	270	Blood culture	Ethiopia	32.6	71.4	68.4	5.7	98.9	[93]
Widal	Prospective study	163	Blood culture	India	54	65.4	89.8	NR	NR	[94]
Widal	Cross-sectional	271	Blood culture	Nigeria	45.76	35	51	17	73	[95]

TUBEX	Comparative study	139	Blood culture	Tanzanian	NR	79	89	NR	NR		[96]
TUBEX	Retrospective study	970	Blood culture	Pakistan	1.86	41.9	96	31.6	97.3		[97]
Typhidot	Retrospective study	42	Blood culture	NR	NR	92.7	NR	97.4	NR		[98]
Typhidot	Cross-sectional	211	Blood culture	NR	95.9	95.9	26.5	30.3	96		[99]
Typhidot	Prospective study	500	NR	Cambodia	63.6	63.6	82.9	26.4	95.9		[84]
Typhidot	Retrospective study	145	Blood Culture	NR	32.4	26.7	61.5	7.4	87.9		[100]
Multiplex PCR	Prospective study	680	Blood culture	Bangladesh	20	95	92.9	NR	NR		[89]
Enterocheck	Prospective study	145	Blood Culture	NR	NR	85.5	88.6	51.1	97.7		[13]

Widal	Prospective	80	Blood		62.5	71	62	91	31	
Widal	study		culture	India	NR	71	62	91	31	[101]
PCR	Comparative		Blood			100	86.5			
Widal	study	76	culture	NR	NR	88.6	62.5	NR	NR	[102]
Widal	Comparative		Blood		45.7	34.1	42.8			
Typhidot	study	105	culture	India	74.3	92.6	37.5	NR	NR	[103]
Typhidot			Blood		97.36	96	89.5	95		
Widal	NR	124	culture	NR	73.68	72	87	87	NR	[104]
Widal	Comparative		Blood		35	86.7	89.5	79.5	93.4	
Typhidot	study	140	culture	Egypt	36.5	93.3	90.6	82.3	96.6	[105]
Widal	Comparative	100	NR	India	48.1	NR	NR	94	NR	
Widal	study				26			52		[106]
Widal	Comparative		Blood		57	57	83			
Typhidot	study	-	culture	New Delhi	79	79	87.5	NR	NR	[107]

Test	Study	n	Sample	Country		Sens	Spec	PPV	NPV	Ref
ONSITE Typhoid Combo	NR	136	NR			100	94.4	63.2	100	
TUBEX				Zimbabwe	NR	100	94.1	63.2	100	[108]
Typhidot			Blood and bone			70	70	77	89	
Widal	NR	97	marrow	Pakistan		54	55	81	89	NR	[109]
Widal	Prospective		Blood			68	86	94	57	
Typhidot	study	100	culture	India	NR	85	100	100	75	[23]
Typhidot	Comparative		Blood			97.3	88.1	97.4	87.8	
Enteroscreen	study	2699	culture	India	NR	98.2	92	96.2	82.3	[110]
Widal	Comparative		Blood			84.1	52.7	25.3	94.5	
ELISA	study	1371	culture	Nepal	NR	95.5	94.7	77.7	99.1	[111]
Typhidot M						90	100	100	92.1	
Diazo test	Prospective study	145	Blood culture	India	NR	86.7	85.7	83.9	88.2	[112]
Widal						40	91.4	80	NR	

Test	Study type	Sample size		Reference test	Location						Ref
Panbio ELISA	Prospective study	144	NR	NR		84	78	80	68.4	87.4	
Widal							98	76.6	69	98.6	
Typhidot							98	76.6	98.6	69	[113]
TUBEX						15	51.1	88.3	0.31	0.95	
Typhidot						23	70	80.1	0.26	0.96	
TyphiDot Rapid (TR-02)	NR	500		Blood culture	New Guinea	22	89.4	85	0.38	0.99	[114]
Widal						8	51.1	95.8	0.56	0.95	
Multi-test Dipstick							89	50	85	60	
Typhidot	Prospective study	80	NR		Vietnam	NR	79	89	96	59	
TUBEX							78	94	98	59	
Widal							64	76	88	48	[115]

5   FIGURE 1   Flowchart of published peer-reviewed journals detected through databases and

6   included in the analysis.

17  FIGURE 2: The mean percentage sensitivity of typhoid fever diagnostic techniques

19   FIGURE 3: Mean percentage specificity of typhoid fever diagnostic techniques

24   FIGURE 4: Mean percentage positive predictive value of typhoid fever diagnostic technique

28   FIGURE 5: Mean percentage negative predictive value of typhoid fever diagnostic techniques