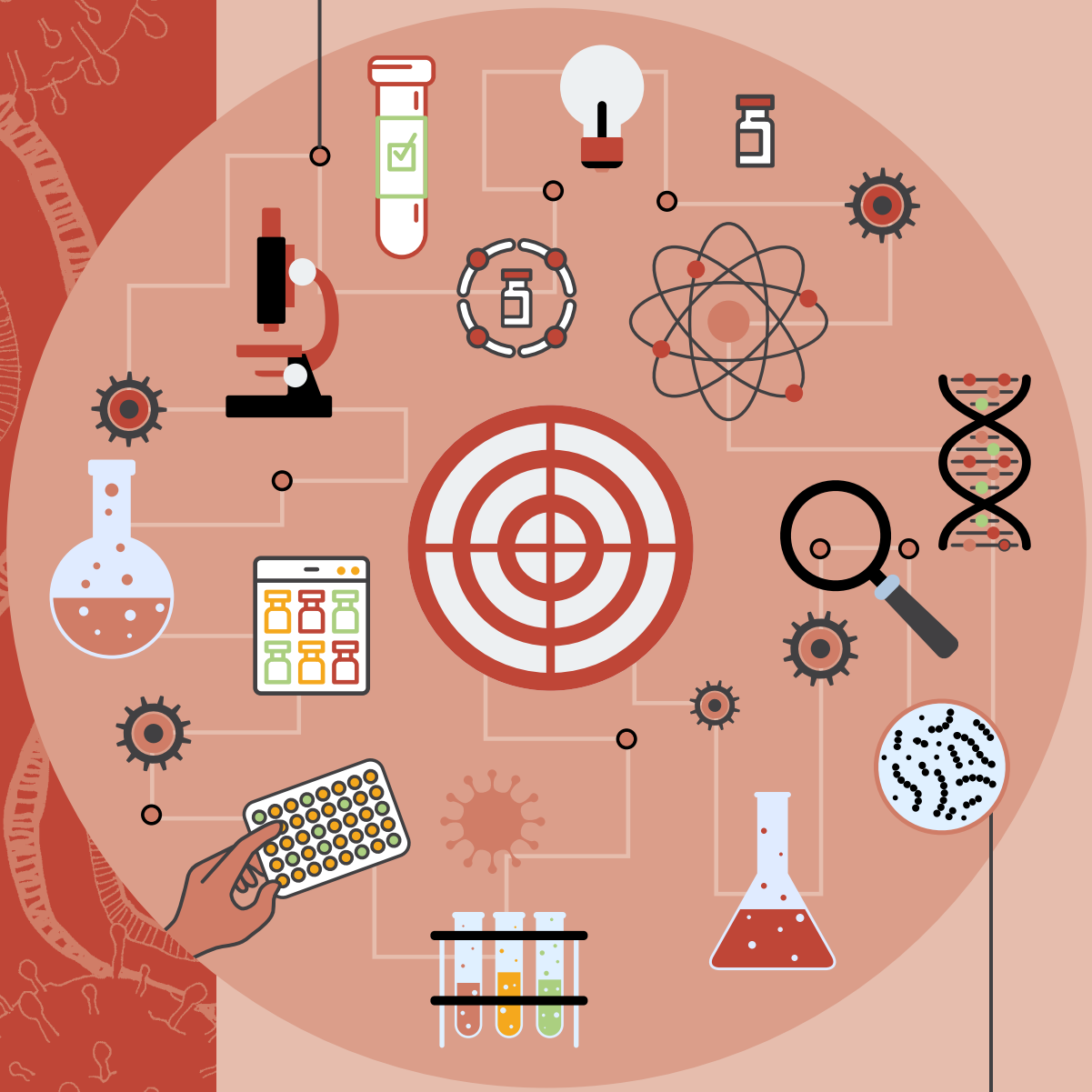
Target product profile for laboratory tests for acute typhoid fever surveillance



World Health Organization

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Contents

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Declarations of interest

All members of the TyDReP completed a declaration of interest form, according to WHO processes, that was used to assess and manage any conflicts of interest. WHO staff led by Dr Sandra Nwokeoha (WHO/HQ-EPS) also checked that there were no sanctions against any of the external members and conducted Google, LinkedIn and PubMed searches to identify any additional conflicts of interest that had not been declared.

Interests were assessed by a WHO panel including the TPP development team and a WHO , Office of Compliance, Risk Management and Ethics (CRE) where applicable. Decisions to enlist any expert into the TPP Development Group were based on whether any identified conflicts of interest were specific, personal, and/or financially significant.

All members of the TPP development group were not identified as having any interests that could conflict with the objectives of the TPP.

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Abbreviations and acronyms

CDC	Centers for Disease Control and Prevention
CRS	Composite reference standards
EIA	Enzyme immunoassay
EoI	Expression of Interest
IFU	Instruction for use
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMDRF	International Medical Device Regulators Forum
iNTS	Invasive non-typhoidal salmonellosis
LCM	Latent class model
LFA	Lateral flow assay
LMIC	Low- to middle-income countries
LPS	Lipopolysaccharides
NTS	Non-typhoidal *Salmonella*
OMP	Outer membrane proteins
PCR	Polymerase Chain Reaction
RDT	Rapid diagnostics test
SAGE	Strategic Advisory Group of Experts
TCV	Typhoid-conjugated vaccine
TF	Typhoid fever
TPP	Target product profile
TPTest	Typhoid/Paratyphoid diagnostic test
TyDReP	Typhoid Diagnostic Reference Panel
WHO	World Health Organization

Introduction

Typhoid fever (TF) is a severe systemic illness associated with abdominal pain, fever and occasionally can be life-threatening. TF also referred to as, typhoid, is caused by the Gram-negative *Salmonella enterica* serovar Typhi (*Salmonella* Typhi; *S. Typhi*). Individuals acquire *S. Typhi* after the consumption of contaminated drinking water or food with faeces of people who have typhoid or from people who are chronic carriers of *S.* Typhi. Annually, 9 million typhoid cases and up to 110 000 deaths are reported worldwide, with children at the highest risk of contracting typhoid *(1,2)* specifically, children aged 5-9 years are the most affected group *(3)*. The typhoid incubation period ranges between 7 and 30 days, after which patients can present with sustained fever, malaise, diarrhoea, constipation, splenomegaly and sometimes rose-coloured spots on the torso. Without hospitalization and appropriate antibiotic treatment, some patients' typhoidal disease can progress to manifest severe complications, including intestinal perforation, gastrointestinal haemorrhage, hepatitis, myocarditis, shock, pneumonia, anaemia, and even encephalopathy *(1,4)*. Paratyphoid fever, which is caused by *Salmonella* enterica serovar Paratyphi A, B and C presents as clinically indistinguishable from typhoid. However, patients infected with *S.* Typhi have more serious complications if untreated. The clinical syndrome of patients infected with either *S.* Typhi or *S.* Paratyphi A will be referred to as enteric fever.

Futhermore, there are several non-typhoidal *Salmonella* (NTS) serovars, of which Typhimurium, Dublin, Choleraesuis, and Enteritidis are the most prevalent and cause invasive non-typhoidal salmonellosis (iNTS) *(5,6)*. *Salmonella* species belong to the *Enterobacterales* order which includes several genera like *Escherichia*, *Klebsiella*, *Enterobacter*, *Shigella*, *Citrobacter*, and *Yersinia (2)*. The outer membrane of these Gram-negative bacteria is coated with highly variable antigens that can induce an immunological response. These bacteria are divided into serogroups based on the different antigen compositions. The three major types of antigens present on the cell surface of the bacterium are O (somatic), K (capsular), and H (flagellar). Different Gram-negative genera can share some of these antigens, thus, complicating the utilization of these targets in the rapid diagnostic tests (RDT) for *S.* Typhi identification.

This target product profile (TPP) will mainly address TF. Typhoid has contributed to significant morbidity and mortality in many resource-limited countries in South America, Africa, and Asia, because of the limited potable water supplies and suboptimal sanitation barriers *(4)*. To combat this human healthcare challenge, on 3 January 2018, the WHO announced the prequalification of a typhoid-conjugated vaccine (TCV) for children older than 6 months and in adults up to 45 years in typhoid-endemic countries. The decision came after the endorsement of the WHO Strategic Advisory Group of Experts (SAGE) on immunizations *(7)*. WHO recommends programmatic use of typhoid vaccines, though WHO notes that TCVs are the preferred products. TCV utilization is recommended for typhoid control in countries with high typhoid incidence or high prevalence of antimicrobial-resistant *S.* Typhi *(2,3)*. In addition, to understand the typhoid burden, the WHO recommends that countries conduct typhoid surveillance with a minimal surveillance standard of passive or active case-based laboratory-supported, facility-based sentinel surveillance of clinically suspected typhoid cases. Laboratory confirmation of *S.* Typhi is critical because clinical diagnosis is nonspecific; also, prevention of typhoid and response to a typhoid outbreak require specific measures *(1,3)*.

A forecasting study for TCV requests in 133 low- and middle-income countries (LMIC), estimated that between 2020 and 2025 TCV demand will predominantly come from African and Asian countries; many of which are eligible for Gavi (the Vaccine Alliance) co-financing and other support *(8)*. The TCV campaign demand is projected to end by 2030 *(8)*. Following the initial TCV campaign, demands are forecasted to track the birth

cohort of participating countries, which suggests an annual routine need for 90 to 100 million TCV doses. Peak demand was anticipated to occur between 2023 and 2026, with estimations of 300 million annual doses. This demand depends on whether the TCV campaign implementation is high *(8)*. As of December 2024, 9 countries introduced TCV vaccination in their national vaccine basket, including Pakistan, Samoa, Nepal, Liberia, Kenya, Malawi, Bangladesh, Ghana and Zimbabwe *(9, 10)*.

Since 2008, Gavi, prioritized TCV as part of its vaccine investment strategy in LMIC. With the prequalification of TCV by the WHO, Gavi strategically reported its commitment to providing co-financing support for Gavi-eligible countries that will introduce TCV into the routine immunization programme. In addition, Gavi committed to support a one-time catchup immunization campaign for children aged up to 15 years based on local TF burden. However, one of the major hurdles of introducing TCV is understanding the burden of *S.* Typhi in endemic regions. *S.* Typhi laboratory diagnostic challenges, particularly, the unavailability of reliable diagnostic assays may impact the implementing TCV in endemic regions due to the lack of typhoid surveillance diagnostic tools *(11, 12)*.

Gap Analysis of *Salmonella Typhi* surveillance laboratory tests

The WHO standard for the surveillance of vaccine-preventable diseases defines a confirmed typhoid case as the detection of *S.* Typhi by culture or detection of *S.* Typhi DNA from a normally sterile site (e.g. blood or cerebral spinal fluid). Blood cultures to isolate *S. Typhi* have been challenging because of the low-level of *S.* Typhi bacteraemia, 1—2 CFU/mL, and potential prior patient exposure to antibiotics. Blood cultures have been reported to have a clinical sensitivity of approximately 60% *(5)*. Other challenges in LMIC include the availability of blood culture media and systems, particularly in remote areas, and transportation of patient samples to an equipped laboratory in a timely and temperature-controlled manner *(5)*. Other bacterial cultures from other body sites like stool or urine have been reported to have lower sensitivity than blood cultures (31%) *(13)*.

An alternative approach to diagnose typhoid is to evaluate a patient's immunological response to *S.* Typhi. The Typhoid/Paratyphoid diagnostic (TPTest) assay is based on the detection of circulating immunoglobulin type A (IgA) antibodies targeting *S.* Typhi and *S.* Paratyphi in the blood of patients with enteric fever using a lymphocyte culture-based supernatant. It has been shown to have 100% sensitivity and specificity when compared to blood cultures *(14, 15)*. The drawbacks of this method include being time-consuming (24-48 hours) and requiring ex-vivo culturing of isolated lymphocytes and detection of IgA using an enzyme-linked immunosorbent assay (ELISA) *(11, 14)*.

Despite the wide-ranging availability of rapid *S.* Typhi/Paratyphi diagnostic serological assays, only a few of them meet the high-quality standards required for effective diagnosis or surveillance *(12, 15, 16)*. The current enzyme immunoassay (EIA)-based serological tests against Vi (virulence capsular polysaccharide), lipopolysaccharide (LPS), outer membrane proteins (OMP), O (somatic), and H (flagellar) antigens lack specificity in settings with a high burden of typhoid infections, as these antigens are also present in other members of the *Enterobacterales* family, including other *Salmonella* serovars *(12, 15, 16)*. These diagnostic challenges highlight the need for improved and more reliable diagnostic and surveillance methods.

Various RDTs and different forms of the Widal test are commonly used in health facilities around the world to diagnose *S.* Typhi and *S.* Paratyphi *(12, 17, 18)*. These tests are cheap, simple to use, do not require sophisticated laboratories, and deliver tests in a shorter time frame compared to blood culture, making them

very popular. However, such tests lack clinical sensitivity and specificity and therefore do not have sufficient accuracy to replace blood cultures as the main diagnostic/surveillance approach for typhoid *(12, 17, 18)*. The Widal test is the classical TF serological test that detects *S.* Typhi O and H immunoglobulin G (IgG) antibodies in a patients' blood sample. A positive Widal test requires testing acute and convalescent patient serum taken 10 days apart with a 4-fold increase in the antibody titer. Comparing the Widal results of acute and convalescent serum is rarely performed by health care providers. Like most serologic tests, a false-negative Widal test may occur early in the course of illness, and a false-positive Widal test may result from past infection or previous exposure to cross-reactive antigens or vaccination. Due to this, the clinical specificity of the Widal test is between 50—70% *(17)*.

Other RDTs like the Tubex® test (IDL Biotech, Sweden), a rapid immunochromatographic test that detects IgM antibodies against *S.* Typhi O:9 LPS antigens have been reported to have clinical sensitivity of 70-80% and a clinical specificity of 80-90% when compared against blood cultures *(18-26)*. Similarly, another commonly used TF RDT, Typhidot assay (Malaysian Biodiagnostic Research, Malaysia) that detects *S.* Typhi IgM and IgG against 50 kDa OMP has a similar sensitivity and specificity as the Tubex® test *(27)*. Like the Widal test, the sensitivity of the Tubex® test and Typhidot assay is lower in the first 2 weeks of illness *(27)*. More recently, serological assays targeting the *S.* Typhi and Paratyphi LPS and haemolysin E (HlyE), IgA have shown promising diagnostic sensitivity and specificity; however, these assays are not yet commercially available *(18-26)*.

Utilization of RDTs such as lateral flow assays (LFA) for the detection of S. Typhi antigens from patient stool samples, have been reported to show poor sensitivity and specificity when compared to blood cultures. These assays are not being widely used for the diagnosis of typhoid *(17)*.

Molecular diagnostic approaches to diagnose typhoid directly from patients' whole blood is also met with limited success because of the low bacteraemia and the molecular diagnostic inhibitors present in the patient's blood samples. Blood culture-PCR assay that is based on incubating patients' heparinized blood in ox bile/tryptone soya broth at 37 °C for 5 hours after which, PCR is performed on the extracted DNA from the pelleted bacteria, has been reported to improve the laboratory diagnosis of typhoid. However, such molecular diagnostic assays are currently not widely available *(28-31)*.

The need for additional typhoid diagnostic tests

New typhoid diagnostic innovations are needed for individual patient care decisions as well as for surveillance to guide vaccine and other public health measures. Improved typhoid diagnostics would strengthen surveillance by providing reliable incidence data. Comprehensive mapping of disease burden enables health authorities to identify hotspots suitable for typhoid conjugate vaccine (TCV) introduction. Not only that, but post-vaccination rollout, sensitive and specific diagnostics tools would allow monitoring of vaccine impact on circulating *S.* Typhi strains and detection of breakthrough infections. Integration of reliable diagnostic tests with vaccination campaigns can optimize resource allocation, ensure high-risk populations are reached, and measure progress toward elimination. Investing in additional typhoid diagnostics is therefore essential to reduce mortality, preserve antibiotic efficacy by reducing the emergence of antibiotic-resistant S. Typhi strains, and guide effective vaccine deployment. Enhanced diagnostics may also identify asymptomatic carriers, supporting targeted health interventions and breaking the chains of transmission. The current typhoid diagnostic challenges emphasize the need for new and innovative *S.* Typhi RDTs and EIAs that will help in the surveillance of acute typhoid cases.

The role of target product profiles

The first step towards accelerating the development of surveillance tests for typhoid is to develop TPPs. TPPs are strategic planning tools for guiding the development of new tests and other health care products and serve to inform public health programme requirements, thereby shaping future market offerings. The primary audience for TPPs are manufacturers, suppliers and researchers developing new assays. A TPP outlines the key characteristics that a product should possess to meet the needs of its intended users, target population and public health programmes in their intended settings of use. For each characteristic, the TPP states a *preferred* criterion that is to be achieved by product developers if feasible and a *minimal* criterion if the preferred criterion is not feasible, as long as the minimal criterion is acceptable to a national public health programme.

This document describes two typhoid TPPs:

1. A RDT TPP (**Table 1**), intended to enable decentralized typhoid surveillance testing, away from referral laboratories in LMIC settings.
2. An EIA TPP (**Table 3**) to assist in evaluating EIA tests as alternative surveillance tools enabling the confirmation of acute typhoid in LMIC settings if an RDT assay cannot be developed.

Manufacturers of typhoid tests that meet the criteria detailed in these TPPs will be eligible to submit an Expression of Interest (EoI) for their performance claims to be evaluated by WHO assessment via an expert review panel on diagnostics and/or other assessment mechanisms. Products that successfully obtain a recommendation after WHO assessment will be prioritized for procurement by WHO, Gavi and United Nations Children's Fund (UNICEF) to support surveillance and inform vaccination strategies for TCV maximum impact.

Methods

This TPP was developed according to the WHO standard procedure for TPPs. Initial TPP drafts were developed by the WHO TPP drafting team (the authors), through scientific literature reviews and horizon scanning to identify the unmet clinical needs. The authors established a TPP development group of 17 external individuals, comprising of scientists, public health officials and intended user representatives, who were selected according to the WHO standard procedure, with due attention paid to geographical and gender diversity. The TPP development group was referred to as the Typhoid Diagnostic Reference Panel (TyDReP). The TyDReP compromised of 9 males and 8 females from all WHO Regions (African, 2; Americas, 4; Eastern Mediterranean, 2; European, 3; South-East Asia, 5 and Western Pacific, 1).

The first TyDReP meeting outlined the TPP development process and aimed to establish the core characteristics of the TPPs. TyDReP members were asked to complete a Delphi-like online survey to establish their level of agreement on each minimal and preferred characteristic criterion in the TPP. Their agreement rating was determined using a 4-point Likert-type scale: 1, fully disagree; 2, mostly disagree; 3, mostly agree; 4, fully agree; members could also mark "No opinion". Comments were requested on all items and were required when members indicated that they did not agree (Likert score 1 or 2). Of the 17 TPP TyDReP members, 14 (88%) completed the survey. The overall levels of agreement (the count of responses of Likert score 3 or 4 divided by all Likert responses for each characteristic), while not judged against a consensus threshold at this stage, were generally high, averaging 97% for the minimal characteristics and 98% for the preferred characteristics. Upon stratifying the TPP by RDT and EIA, the overall agreement of the RDT and the EIA minimal and preferred characteristic were greater than 95% agreement. No single TPP characteristic received less than 86% agreement, which is above the requirement for consensus of ≥ 75% agreement. All the comments received were compiled and reviewed by the authors, and the TPP was jointly revised to address constructive feedback, incorporate suggestions, and refine language for the avoidance of misunderstanding. A subsequent TyDReP meeting was held to review the development group survey results and agree upon the changes proposed to the TPP.

In October 2024, a public consultation was conducted. The public consultation was initially published for 28 days and later extended by 10 working days to increase the number of public responses. A total of 17 public respondents from 8 countries participated in the consultation. These included: USA (N=8), China (N=2), India (N=2), Benin (N=1), Ethiopia (N=1), Nepal (N=1), Turkey (N=1) and United Kingdom (N=1). Results from the public consultation were discussed at a subsequent TyDReP meeting and TyDReP members agreed upon the proposed changes to the TPP.

Resulting TPPs developed for laboratory tests for acute typhoid fever surveillance

Table 1.
Target product profiles on rapid diagnostic tests for acute typhoid surveillance

RDT parameter	Minimal characteristic	Preferred characteristic	Notes
Scope			
Goal of the test	To detect *Salmonella* Typhi and Paratyphi infection/illness. To be used for surveillance and determining disease burden in a population.	To detect *Salmonella* Typhi and Paratyphi infection/illness. To be used for surveillance and determining disease burden in a population. Detection and differentiation between *Salmonella* enterica serovars Typhi and Paratyphi A.	According to WHO and the International Medical Device Regulators Forum (IMDRF) categories of test purposes *(37)*. Not intended as an aid to diagnosis or for other clinical purposes.

RDT parameter	Minimal characteristic	Preferred characteristic	Notes
Target population	All patients that meet the WHO surveillance standard case definition of a suspected typhoid case *(4)* [1]		Refer to: World Health Organization, Typhoid and other invasive salmonellosis. Vaccine-Preventable Diseases Surveillance Standards, 2018 *(4)*. [1]Fever for at least three out of seven consecutive days in an endemic area or following travel from an endemic area. Or fever for at least three out of seven consecutive days within 28 days of being in household contact with a confirmed case of typhoid or paratyphoid fever.
Target use settings	Primary health care (level 1) without access to a laboratory or higher level of health care professionals at higher levels. Higher health care levels, including their laboratories.		For definitions of levels, see Table 2 below, adapted from *(38)*.
Target users	Health workers with minimal training and any health care professional with similar or more advanced training.		
Test kit			
Test format and kit	Point of care; a single-use, disposable test that requires no specialized instrument or additional laboratory equipment to perform the test procedure, including specimen preparation. The test includes all materials required for the test procedure, including devices, reagents, and other consumables to test one individual, in a packaged, self-contained kit. Additional consumables may be needed for specimen collection.	Point of care; a single-use, disposable test that requires no specialized instrument or additional laboratory equipment to perform the test procedure, including specimen preparation. The test includes all materials required for the test procedure, including devices, reagents, and other consumables to test one individual, in a packaged, self-contained kit. Additional consumables may be needed for specimen collection. Battery-operated reader as an optional tool for reading and interpreting results.	
Result format	Qualitative (example: positive or negative)		
Result interpretation	Visual interpretation of qualitative results by the naked eye, with minimal instructions for interpretation by the user.		Refer to: World Health Organization. Target product profile for readers of rapid diagnostic tests. 2023 *(32)*. Patient results could also be obtained via an optional reader *(32)*.
Assay targets	Any acceptable analyte, or combination of analytes, that can meet clinical sensitivity and specificity thresholds for detection of *Salmonella* Typhi/Paratyphi.	Any acceptable analyte, or combination of analytes, that can meet clinical sensitivity and specificity thresholds for detection and differentiation of *Salmonella* enterica serovars Typhi.	Refer to: Redefining typhoid diagnosis: what would an improved test need to look like? BMJ Global Health. 2019 *(33)*.

RDT parameter	Minimal characteristic	Preferred characteristic	Notes
Specimen	≤ 50 µL of whole capillary blood ≤ 25 µL of serum [2] ≤ 25 µL of plasma [2]	≤ 50 µL of whole capillary blood ≤ 25 µL of serum [2] ≤ 25 µL of plasma [2] Plus other specimen types.	[2]To enable use in laboratories where these specimens are used. Whole capillary blood is the sample type for use in level 1 facilities where phlebotomy is not available.
Performance			
Clinical sensitivity	≥ 85%	≥ 90%	These levels should be met at the lower bound of the two-sided 95% confidence interval. Assessment should be based on comparison with well-characterized typhoid composite reference standards (CRS). These CRS have been characterized by multiple typhoid diagnostic tools including "Blood cultures", the typhoid reference diagnostic standard and latent class model (LCM) statistical analysis. Performance should be described in the instruction for use (IFU) for each specimen type in the product claims and for all target populations described in the TPP.
Clinical specificity	≥ 90%	≥ 95%	See note for *Clinical sensitivity* above.
Interference	Minimized interference from common human diseases, especially those presenting with similar signs and symptoms to typhoid infection (e.g., invasive non-typhoidal salmonellosis [iNTS]), and common exogenous and endogenous interferents [3]	Same as Minimal except for no cross-reactivity with patients with iNTS.	[3]Interferents should be tested at clinically relevant concentrations, included in a risk evaluation and listed in the IFU. See The Clinical and Laboratory Standards Institute (CLSI) EP07 *(35)*; also, see Box 1 for a list of relevant interferents to be considered.
Test failure (invalid) rate	≤ 5%	≤ 1%	Rates based on acceptable standards for existing WHO prequalification products *(34)*.
Test procedure			
User training	User can conduct the test correctly after half a day of training.	User can conduct the test correctly after a brief review of the IFU.	
Ease of use	Easy-to-perform test procedure and result interpretation by the intended user, with minimal steps; no precision pipetting, and no timed steps (except for reading the test result).		Specimen collection is excluded from this characteristic.
Language support	For each country of deployment, the packaging and IFU are provided in one commonly used language, such as the official language or the de facto national language, as well as any language mandated by local regulatory or trade compliance requirements.	Same as minimal plus additional languages to enable use by other residents of that country.	Preferred languages include French, English.

RDT parameter	Minimal characteristic	Preferred characteristic	Notes
Time to result[4]	≤ 60 min	≤ 30 min [5]	[4]Including time from the start of specimen preparation to test result, not including the duration of specimen collection. [5]To meet the preferred characteristic, time to result is less critical for surveillance tests.
Stability of valid result	≥ 30 min (after which, results may be false or invalid).	≥ 1 h (after which results give invalid rather than false results).	
Internal controls	Procedural reagent-addition control in each test as an indicator of test validity.	Procedural specimen-adequacy control in each test as an indicator of test validity.	
External controls	Positive and negative controls are specified in the IFU and available for purchase separately.	Positive and negative controls are included in the test's price and are delivered with the test kits.	RDTs are single-use tests without quality control for individual results. External Quality Assurance programmes should be defined by the laboratory where testing is performed and outside the scope of this TPP.
Operational			
Shipping conditions	72 h at 1–45 °C fluctuating, with indicator of temperature or humidity excursions that would result in invalid or low-performance results.	72 h at 1–50 °C fluctuating, with indicator of temperature or humidity excursions that would result in invalid or low-performance results.	
Storage and operating conditions	≥ 18 months at 1–30 °C and ≤ 70% humidity, including 3 months at 40 °C, at ≤ 2500 m altitude.	≥ 24 months at 1–40 °C and ≤ 90% humidity, at ≤ 4000 m altitude.	
Stability of each test once opened [6]	≥ 30 min	≥ 1 h	[6]Including time from opening the test kit to completely adding reagents to the specimen.
Biosafety	None, apart from the use of non-sterile gloves.		
Waste disposal	Standard biohazard waste disposal.	All components of the kit are designed to minimize environmental footprint during standard biohazard waste disposal.	
Pricing and market access			
Target list price per test[7]	≤ US $ 3	≤ US $ 1	[7]List price: Pricing from manufacturers should be as low as sustainably possible while maintaining quality, based on evidence of the true cost of goods sold accounting for material, manufacturing process, operational logistics and commercialization efforts. Pricing should also include and clearly define all facets of end-to-end implementation (e.g. support, maintenance). Pricing must account for production at scale with defined volume thresholds. Ultimately, pricing should intersect sustainable long-term viability for the manufacturer with affordability to support widespread access to testing in LMICs and should be transparently published.
Quality Management	Compliant with ISO 13485	Compliant with ISO 13485 or equivalent	

Table 2.

Low- to middle-income countries use setting definitions. Adapted from *(38)*.

	Self-Testing	Level 0 (L0) - Community	Level 1 (L1) - Primary Care	Level 2 (L2) - District Hospital Lab	Level 3 (L3) - Regional/ Provincial Lab	Level 4 (L4) - Reference/ National Lab
Use setting	• Home testing	• Community outreach • Home testing	• Primary care facility	• Near-patient laboratory • Referral hospital laboratory • Emergency Department testing	• Near-patient laboratory • Referral hospital laboratory • Emergency Department testing	• Reference laboratory
Lab infra-structure	• No mains power • No water • No lab equipment • No environmental control (e.g., temp, dust, humidity)	• No mains power • No water • No lab equipment • No environmental control (e.g., temp, dust, humidity)	• No mains power (unreliable) • Minimal lab equipment (may not support cold chain) • BSL-1 containment • No environmental control (e.g., temp, dust, humidity)	• Mains power (may be intermittent) • Basic lab equipment (biosafety cabinet, centrifuge, calibrated pipets, fridge) • -20 freezers (some) • BSL-2/1 containment (some) • Environmental control (e.g., temp, dust, humidity) (some)	• Mains power (may be intermittent) • Basic lab equipment (biosafety cabinet, centrifuge, calibrated pipets, fridge) • -20 freezers • BSL-2/1 containment • Environmental control (e.g., temp, dust, humidity)	• Mains power (reliable) • High infrastructure facility • -20 freezers • -80 freezers (some) • BSL-2/3 containment • Environmental control (e.g., temp, dust, humidity)
Operator skill	• Self-testing • Simple reagent/ sample transfer	• Nurse/ pharmacist • Community health workers • Simple reagent/ sample transfer	• Nurse • Trained laboratory worker • Minimal sample processing (≤ 3 steps)	• Laboratory technician (1-2 year certif) • Sample processing with calibrated volumes (≤ 3 steps)	• Laboratory technician (1-2 year certif) • Sample processing with calibrated volumes (≤ 3 steps)	• Science research specialists • Laboratory technician (1-2 year certif)
Specimen capacity	• Can process minimally invasive samples: fingerstick blood, nasal swabs, saliva, urine	• Can process minimally invasive samples: fingerstick blood, nasal swabs, saliva, urine	• Can process upper respiratory specimens; clinic may not have capacity for lower respiratory, venipuncture, plasma	• Can process most BSL-2 specimens; depends on clinic sample capacity	• Can process most BSL-2 specimens; depends on clinic sample capacity	• Can process most BSL2/3 specimens
Test capacity	• True-POC MDx (some) • RDT	• True-POC MDx • RDT	• True-POC MDx • Basic microscopy • RDT	• Near-POC MDx • ELISA with simple reader • Microscopy • RDT • Clinical chemistry (some)	• Blood culture and microbiology capacity (some) • Near-POC MDx • ELISA with simple reader • Microscopy • RDT • Clinical chemistry	• Blood culture and microbiology capacity • Lab MDx / PCR / LDT • ELISA/EIA/ CLIA/PRNT • Fluorescence microscopy • Clinical chemistry • Sequencing (some) • Mass spectrometry (some)

Table 3.

Target product profiles on enzyme immunoassays for acute typhoid surveillance

EIA parameter	Minimal characteristic	Preferred characteristic	Notes
Scope			
Goal of the test	To detect *Salmonella* Typhi and Paratyphi infection/illness. To be used for surveillance and determining disease burden in a population.	Same as minimal plus detection and differentiation between *Salmonella enterica* serovars Typhi and Paratyphi A.	According to WHO and the International Medical Device Regulators Forum (IMDRF) categories of test purposes. Not intended as an aid to diagnosis or for other clinical purposes.
Target population	All patients that meet the WHO surveillance standard case definition of a suspected typhoid case *(4)* [1].		Refer to: World Health Organization, Typhoid and other invasive salmonellosis. Vaccine-Preventable Diseases Surveillance Standards, 2018 *(4)*. [1]Fever for at least three out of seven consecutive days in an endemic area or following travel from an endemic area. Or fever for at least three out of seven consecutive days within 28 days of being in household contact with a confirmed case of typhoid or paratyphoid fever.
Target use setting	Regional or provincial laboratory (level 3) or above.	District hospital (level 2) or above.	For definitions of levels, see Table 2.
Target users	Laboratory staff trained in serological diagnostics.		
Test kit characteristics			
Test format and kit	An EIA in a kit that contains all materials required for the procedure, including controls, reagents and consumables, but excluding specimen collection materials and reagent-grade water for rehydration or dilution of kit components.		Manufacturers should define the reagent-water grade needed in the instructions for use (IFU).
Result format	Qualitative interpretation (for example, reactive, non-reactive or equivocal)	Qualitative interpretation (for example, reactive, non-reactive or equivocal) A software that will perform calculations to get to a qualitative read-out is needed.	
Equipment compatibility	Kit and IFU compatible with manual and automated equipment for standard 96-well microplates[34].	Kit and IFU compatible with manual and automated equipment for standard 96-well microplates[34]. Or equivalent high-through put format equipment.	
Test configuration	96-well microplate	Offered in two configurations: • 96-well microplate • 8-16-well strip-plates	The smaller configuration enables more cost-efficient execution of small batches for reduced turnaround time.

EIA parameter	Minimal characteristic	Preferred characteristic	Notes
Assay targets	IgM or IgA antibodies specific to antigens of *S.* Typhi and Paratyphi	IgM or IgA antibodies specific to antigens of *S.* Typhi and Paratyphi Includes other *Salmonella* Typhi and Paratyphi A biomarkers	
Specimen	• ≤ 0.1 mL of serum or • ≤ 0.1 mL of plasma	• ≤ 0.05 mL of serum or • ≤ 0.05 mL of plasma • Dried blood spots or swabs of oral fluid	
Time to result	≤ 6 h (i.e. same-day result)	≤ 2 h	
Language support	For each country of deployment, the packaging and IFU are provided in one popular language, such as the official language or de facto national language, and any language mandated by local regulatory or trade compliance requirements.	For each country of deployment, the packaging and IFU are provided in one popular language, such as the official language or de facto national language, and any language mandated by local regulatory or trade compliance requirements. Additional languages to enable use by other residents of that country.	Preferred languages include French, English
Performance characteristics			
Clinical sensitivity	≥ 85%	≥ 90%	These levels should be met at the lower bound of the two-sided 95% confidence interval. Assessment should be based on comparison with well-characterized typhoid composite reference standards (CRS). Thes CRS have been characterized with multiple typhoid diagnostic tools including "Blood cultures", typhoid reference diagnostic standard and latent class model (LCM) statistical analysis. Performance should be described in the IFU for each specimen type in the product claims and for all target populations described in the TPP.
Clinical specificity	≥ 90%	≥ 95%	See note for *Clinical sensitivity* above.
Interference	Minimized interference from common human diseases, especially those presenting with similar signs and symptoms to typhoid infection (e.g. invasive non-typhoidal salmonellosis [iNTS]), and common exogenous or endogenous interferents.		Interferents should be tested at clinically relevant concentrations, included in a risk evaluation and listed in the IFU. See CLSI EP07 *(35)*; also, Box 1 includes a list of relevant microbial pathogens that induced patient's immunological response, after which it might cross-react with the assay.
Equivocal results	Acceptable if the IFU explains how to address them (e.g. report equivocal, retest if possible and if necessary, request a second specimen)		

EIA parameter	Minimal characteristic	Preferred characteristic	Notes
Lot–to–lot stability	Controlled by a setup procedure that the manufacturer defines in the IFU, and which the laboratory performs with each new lot. The setup procedure may involve external controls, patient specimens or both.	Controlled entirely by the manufacturer so the laboratory does not need to perform a setup procedure with each new lot.	This does not imply that laboratories should deviate from their quality control procedures of verifying each new lot.
Operational			
Shipping conditions	• 72 h at either 2–8 °C • or ≤ -15 °C (frozen), by choice of the manufacturer, with ≤ 1 h excursions to 37 °C.	72 h at a fluctuating temperature between 1 and 50 °C	
Storage conditions	12 months at either 2–8 °C or ≤ -15 °C (frozen), by choice of the manufacturer, and ≤ 70% humidity at ≤ 2500 m elevation.	24 months at 2–8°C and ≤ 90% humidity at ≤ 4000 m elevation, with an indicator of temperature or humidity excursions that would render invalid or low-performance results.	
Operating conditions	15–30 °C and ≤ 80% humidity at ≤ 2500 m altitude.	10–37 °C and very low-to-condensing humidity at ≤ 4000 m elevation.	
Stability of the kit once opened[2]	≥ 1 month	≥ 3 months	[2]Applies only if multiple strips or plates are provided in one kit. The environmental conditions and overall duration in Storage conditions apply.
Biosafety	Standard specimen collection safety precautions recommended. All materials are free of substances with a GHS classification of H340, H350 and H360, with minimal inclusion of any materials with other GHS classification H (36). The test can be performed under core biosafety requirements, similar to those previously referred to as biosafety level 2, with heightened control measures applied based on local risk assessment.		
Waste disposal	Standard biohazardous waste disposal or incineration of consumables; no high temperature incineration required.	All components of the kit are designed to minimize environmental footprint during standard biohazard waste disposal.	
External controls	Positive and negative controls are provided with each test kit. Low-positive controls for monitoring longitudinal test performance are specified in the IFU and available for purchase separately.	Same as minimal except low-positive controls provided with each test kit.	

EIA parameter	Minimal characteristic	Preferred characteristic	Notes
Pricing and market access			
Target list price [3]	96-well microplate: < US $ 300	96-well microplate: < US $ 250 96 tests in 8-well strips: < US $ 300	[3]List price: the price the manufacturer has determined for the product, taking into account the cost of goods sold and other factors (e.g., a reasonable profit margin); the list price does not include any discounts, potential mark-ups for distribution or other costs, including freight, taxes, etc. This cost is assumed at volume production and the prices listed in the TPP are considered for public health preferential pricing in LMICs only.
Quality Management	Compliant with ISO 13485	Compliant with ISO 13485 or equivalent	

Box 1.

Lists of potential interferents, as applicable

Potential cross-reactivity antibodies to pathogens:

- *Salmonella* Paratyphi A, B and C
- *Samonella* Worthington
- *Salmonella* Typhimurium
- *Salmonella* Gallinarum
- *Salmonella* Enteritidis
- *Salmonella Dublin*
- *Salmonella* iNTS serovars
- *Plasmodium malariae*
- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Brucella abortus*
- *Brucella melitensis*
- *Brucella suis*
- *Rickettsia rickettsia*
- *Rickettsia conorii*
- *Rickettsia typhi*
- *Leptospira interrogans*
- *E. coli*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Enterobacter* species
- *Citrobacter* species
- Dengue
- Influenza A and B viruses
- *Orientia tsutsugamushi*
- Chikungunya virus
- *Leishmania donovani* complex
- *Trypanosoma brucei gambiense*
- *Trypanosoma cruzi*
- *Shistosoma* species
- *Strongolodies* species

Other potential interferents:

- Haemoglobin
- Bilirubin (conjugated and unconjugated)
- Plasma proteins (e.g. fibrinogen)
- Serum proteins (e.g. human serum albumin)
- Triglycerides
- Cholesterol
- Antibodies against the expression systems used to generate recombinant antigens (e.g. *E. coli*, yeast, insect cells)
- Human anti-mouse and other heterophile antibodies
- Biotin
- Rheumatoid factor
- Rhesus factor
- Anti-nuclear antibodies

Conclusion

New typhoid diagnostic innovations are needed for typhoid surveillance to guide the introduction of TCV and other public health measures. The current typhoid diagnostic challenges emphasize the need for new and innovative *S.* Typhi RDTs and EIAs that will help in the surveillance of acute typhoid cases.

These two typhoid TPPs will guide the assessments of which typhoid diagnostic tests perform well enough to warrant use for acute typhoid surveillance. The provided guidance is expected to stimulate manufacturers toward the development of test kits that demonstrate the specified level of performance.

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