FIND

PROGRESS AND CHALLENGES TOWARDS TYPHOID DIAGNOSTICS

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BACKGROUND

It's not Typhoid – Tackling misdiagnosis of Typhoid fever in Nigeria

By Nigeria Health Watch ○ March 28, 2019 ○ 6 Mins read

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Editor's Note: *This week's blog is a personal story from a Nigeria Health Watch team member, Patience Adejo. She writes about her experience being diagnosed with Typhoid Fever multiple times using the Widal test, only to recently learn that the test does not give the most accurate diagnosis for typhoid fever. She delves into the standard procedure for diagnosing typhoid fever in Nigeria and the need for renewed scrutiny and adherence to diagnosis guidelines.*

https://articles.nigeriahealthwatch.com/its-not-typhoid-tackling-misdiagnosis-of-typhoid-fever-in-nigeria/

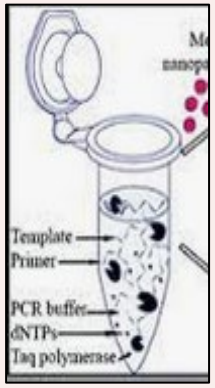
DIAGNOSTIC CHALLENGES

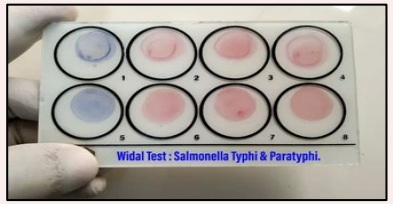
	Point of care testing	Drug susceptibility testing	Surveillance
Why?	• Guide treatment quickly • Rule antibiotic in or out • Provide confidence to HCW	• Guide choice of antibiotics • Keep abreast of susceptibility changes • Establish antibiogram	• Enable vaccine allocations • Guide WASH actions • Burden and incidence estimates
How?	• Most frequently used Widal test • Many other RDTs available ….“but”…..	• Blood culture and DST • Only available at the central level • Results too late to inform patient care	

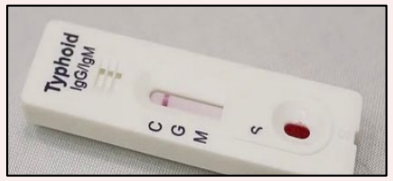
WHAT TESTS ARE CURRENTLY AVAILABLE?

Context

- **The majority of current typhoid tests are based on an innovation (Widal) that is over a century old.**



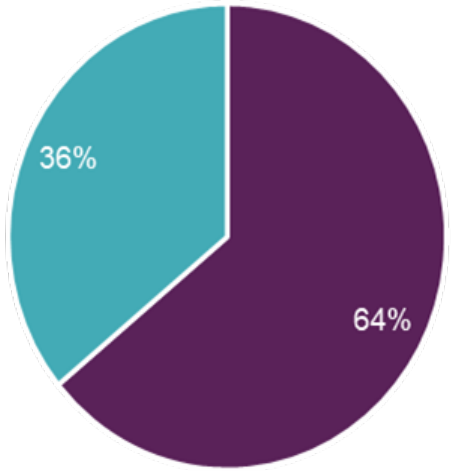




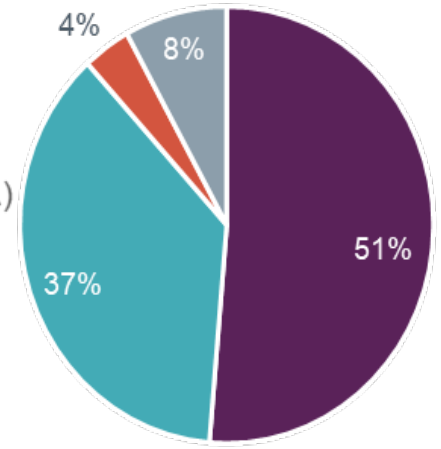
292 TESTS IDENTIFIED

TYPHOID FEVER DX LANDSCAPE – RESULTS OVERVIEW

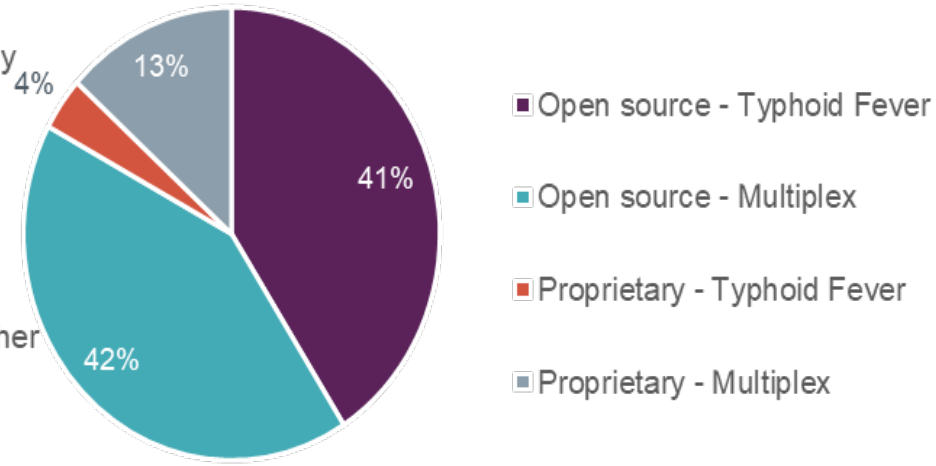
Typhoid fever diagnostics: types of technologies (292 tests identified)



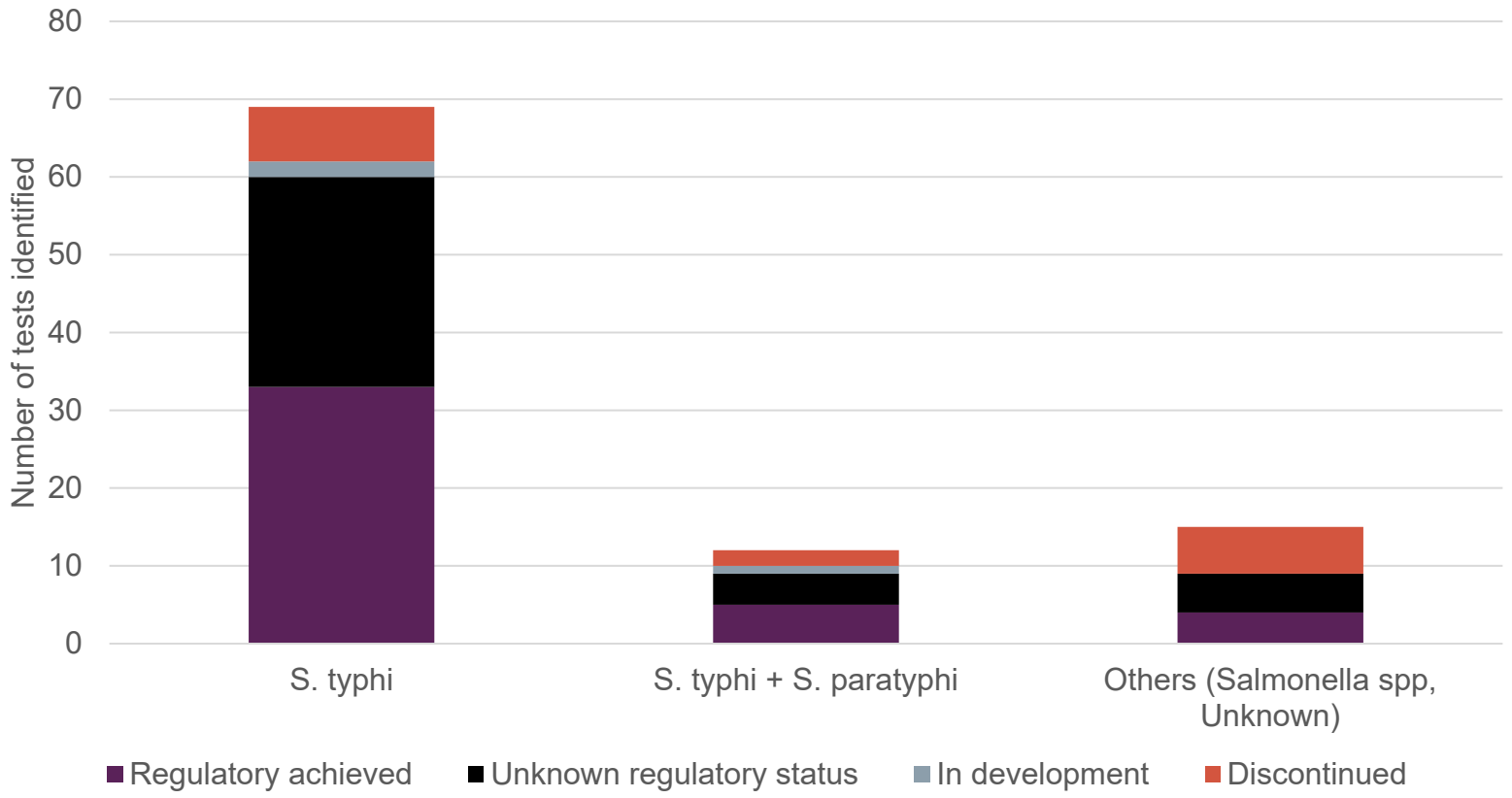
Typhoid fever diagnostics: types of immunoassays (187 tests identified)



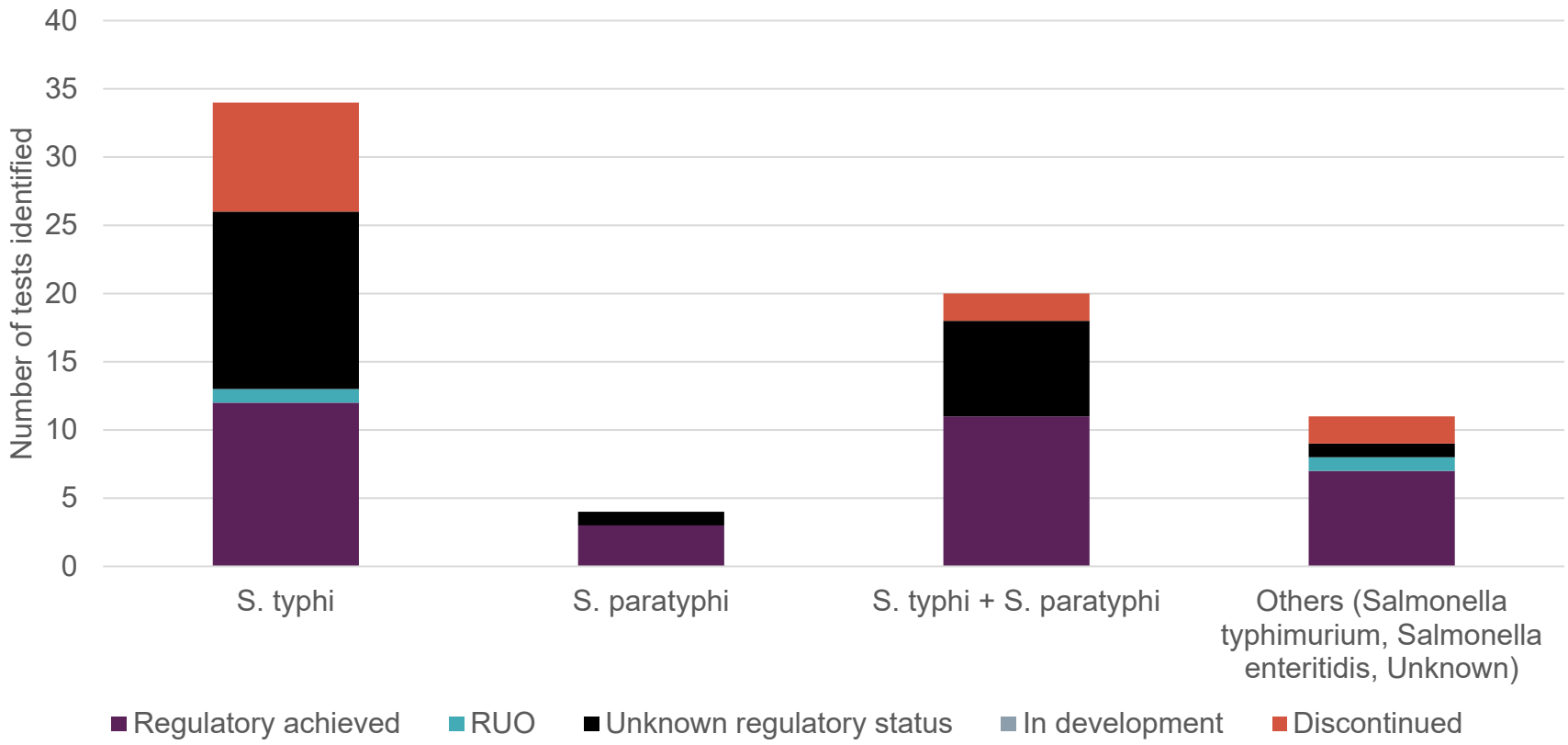
Typhoid fever diagnostics: types of molecular tests (105 tests identified)



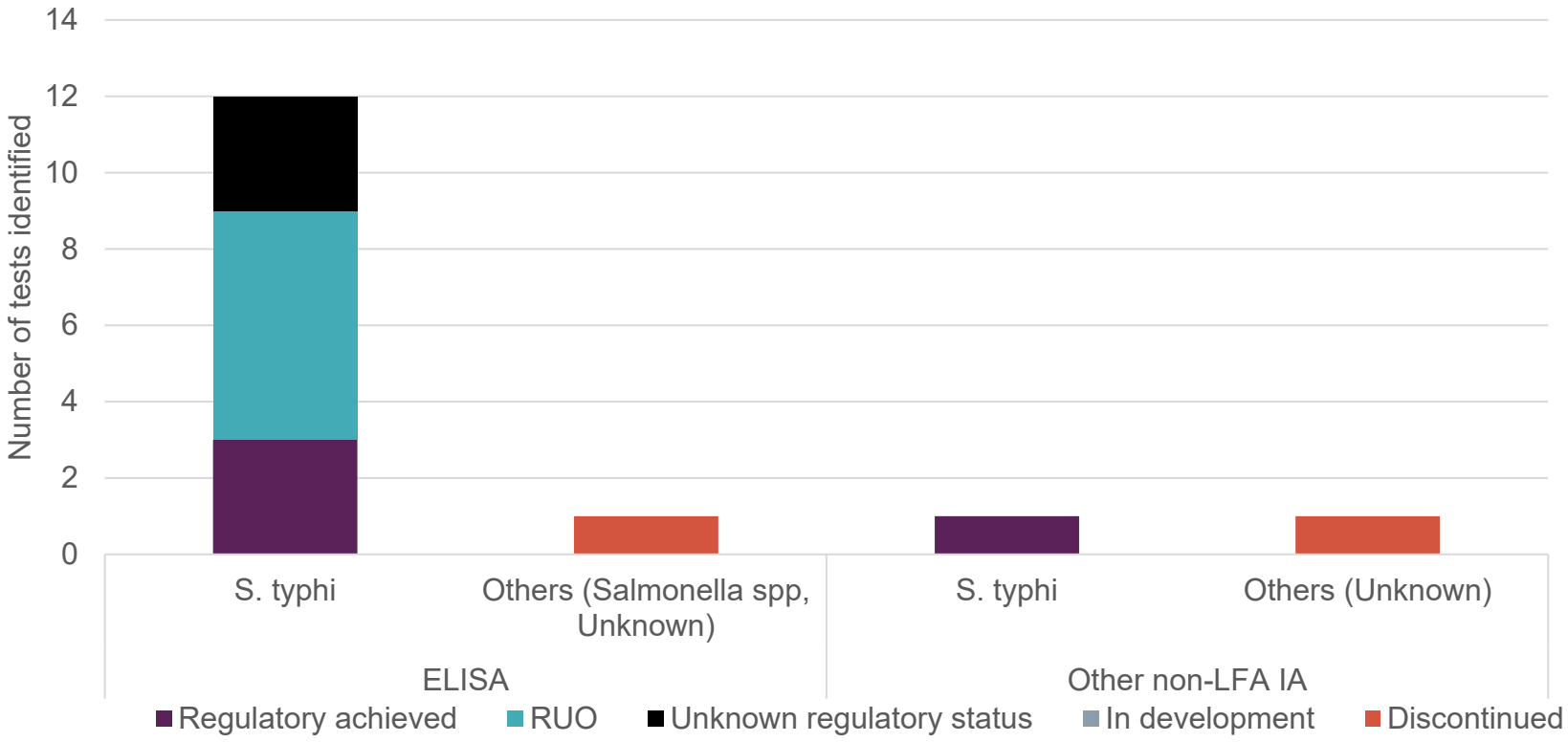
TYPHOID FEVER – 95 LATERAL FLOW TESTS – ANTIBODY



TYPHOID FEVER – 69 LATERAL FLOW TESTS – ANTIGEN

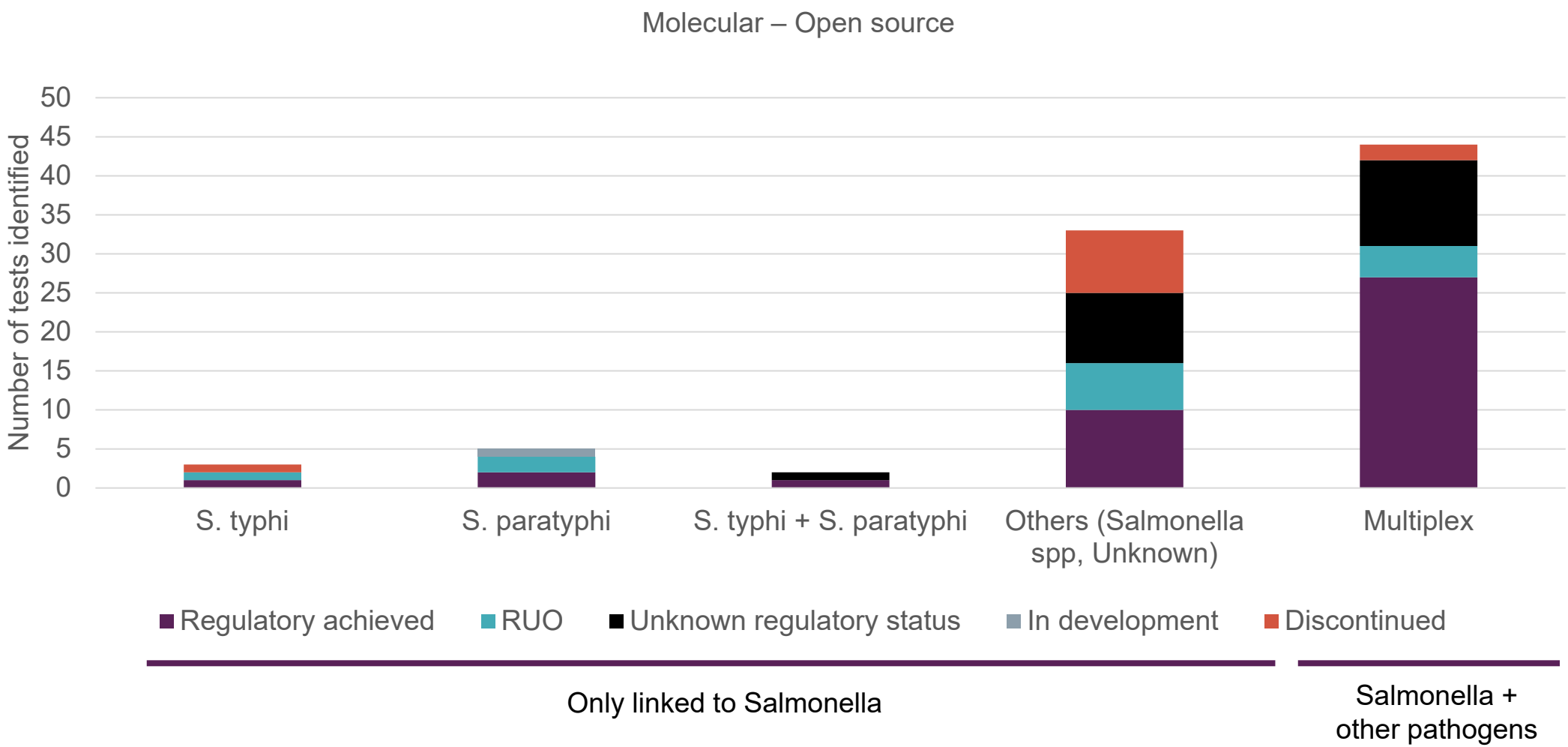


TYPHOID FEVER – 15 ELISA AND OTHER NON-LFA IA

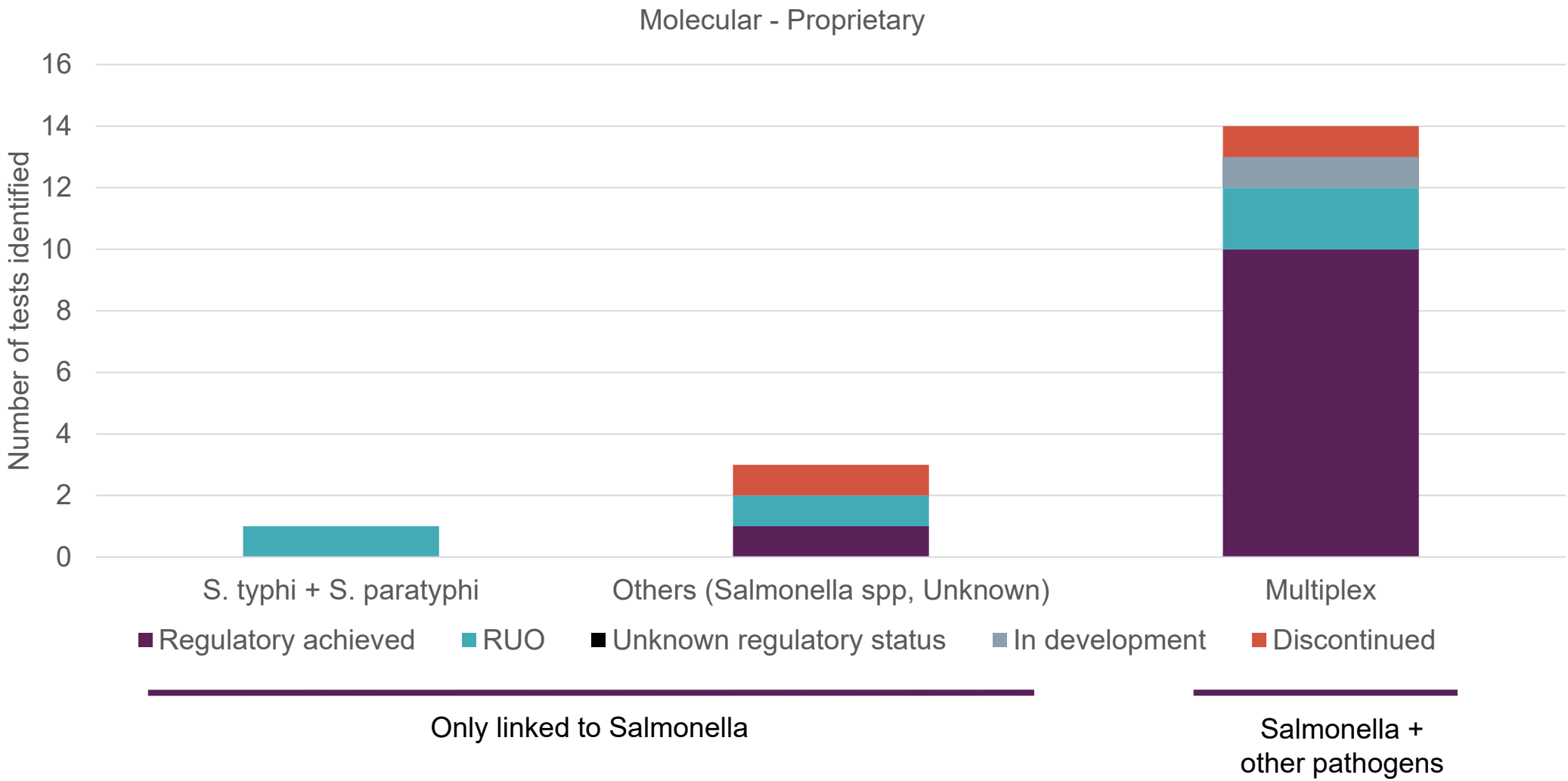


Note: Among "Other non-LFA IA" are included the TUBEX test and an unknown IA test

TYPHOID FEVER – 87 MOLECULAR – OPEN SOURCE KITS



TYPHOID FEVER – 18 MOLECULAR – PROPRIETARY KITS



7 COMMERCIALISED CARTRIDGE-BASED MOLECULAR TESTS

	Organisation Name (HQ country)	Test name	Target pathogen	Regulatory Status	Validated sample Types
1	BioFire Defense, llc (United States)	FilmArray Global Fever Panel RUO	Salmonella Typhi;Salmonella paratyphi;Chikungunya virus;Crimean Congo Hemorrhagic Fever virus;Dengue virus;Ebola virus;Lassa virus;Marburg virus;Plasmodium Species;West Nile virus;Yellow Fever virus;Zika virus; Leptospira spp; Bacillus anthracis; Francisella tularensis; Yersinia pestis; Leishmania spp; Plasmodium falciparum; Plasmodium vivax; Plasmodium ovale	None (RUO)	Whole Blood
2	Becton, Dickinson and Company (BD) (United States)	BD MAX Enteric Bacterial Panel	Salmonella spp.;Campylobacter spp;Escherichia coli;Shigella spp;Shigella dysenteriae	CE-IVD; US FDA 510k	Feces
3	BioFire Diagnostics, llc (United States)	FilmArray Gastrointestinal (GI) Panel	Salmonella spp.;Adenovirus;Campylobacter spp;Clostridioides difficile;Escherichia coli;Vibrio cholerae;Yersinia enterocolitica;Plesiomonas shigelloides; Vibrio spp; Cryptosporidium spp; Cyclospora cayetanensis; Entamoeba histolytica; Giardia lamblia; Astrovirus; Norovirus; Rotavirus	CE-IVD; US FDA 510k	Feces
4	Great Basin Scientific (United States)	Stool Bacterial Pathogens Panel	Salmonella spp.; Campylobacter coli; Campylobacter jejuni; Shigella spp.; Escherichia coli	US FDA 510k	Feces
5	Luminex Corporation (United States)	VERIGENE Enteric Pathogens Test	Salmonella spp.;Campylobacter spp;Shigella spp;Yersinia enterocolitica;Vibrio spp; Norovirus; Rotavirus	CE-IVD; US FDA 510k	Feces
6	Mobidiag/Hologic (United States)	Novodiag Bacterial GE +	Salmonella spp; Campylobacter coli;Campylobacter jejuni;Clostridioides difficile;Escherichia coli;Shigella spp;Vibrio cholerae;Yersinia enterocolitica;Yersinia pseudotuberculosis; Yersinia pestis; Vibrio parahaemolyticus	CE-IVD	Feces
7	Molbio Diagnostics Pvt ltd. (India)	Truenat Salmonella	Salmonella spp.	CE-IVD	Whole Blood

Direct from Whole Blood (≥200uL)

Sample extraction done prior to testing using Trueprep cartridge and device

9 POC INCLUDING WIDAL TEST EVALUATED IN FIND STUDY

RDTs evaluated	STUDY		PAKISTAN		KENYA	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
WIDAL	47.7%	79.4%	48.3%	75.1%	45.8%	93.5%
SD Bioline Salmonella Typhi IgG/IgM	21.6%	100%	19.5%	100%	28.8%	100%
Typhidot Rapid IgG/IgM	**46.2%**	**82.8%**	**32.7%**	**93.2%**	**93.2%**	**40.4%**
Enterocheck WB	72.7%	86.5%	69.8%	88.3%	83.1%	96.8%
Test-it Typhoid IgM	**63.6%**	**95.1%**	**58.5%**	**94.6%**	**81.4%**	**96.8%**
CTK Typhoid IgG/IgM combo rapid test CE	1.5%	100%	0%	100%	6.8%	100%
Spectrum Typhoid IgG/IgM Rapid cassette	49.6%	78.7%	58.0%	74.6%	20.3%	91.9%
TUBEX-TF	60.6%	94.0%	63.4%	92.2%	50.8%	100%
Diaquick S.Typhi/Paratyphi Ag cassette	0%	100%	0%	100%	0%	100%

Commonly used

Africa vs Asia

Comparative Analysis of Commercially Available Typhoid Point-of-Care Tests: Results of a Prospective and Hybrid Retrospective Multicenter Diagnostic Accuracy Study in Kenya and Pakistan

Jyotshna Sapkota,[a,b,c] Rumina Hasan,[d,e] Robert Onsare,[f] Sonia Arafah,[a] Sam Kariuki,[f] Sadia Shakoor,[d] Farah Qamar,[d] Sheillah Mundalo,[f] Frida Njeru,[f] Rael Too,[f] Elizabeth Ndegwa,[f] Jason R. Andrews,[g] Sabine Dittrich[a,h]

WHAT WE HAVE IS SUBOPTIMAL:

What would an ideal test look like?

A next-generation typhoid diagnostic test should improve **patient management** through the diagnosis and treatment of infection with acute *Salmonella enterica* serovars Typhi or Paratyphi with a sensitivity **≥90% and specificity ≥95%.**

The test would ideally be used at the lowest level of the healthcare system in settings **without a reliable power** or water supply and provide results in **<15 min at a cost of <US$1.00.**

Mather et al. 2019

INNOVATION NEEDS

Point of care testing: to guide patient management at local level

- Widal test developed in 1896 and is unchanged since then
- No good reference standard available
- Ability to differentiate between many fevers

Drug susceptibility testing: to inform what drugs work

- S. Typhi has an extremely low pathogen load in the blood (approximately 1 CFU/ml blood)
- Simplified amplification steps needed to be linked to the molecular application
- Expansion of infrastructures

Surveillance: to inform global and local decision public health decision making

- Specific information to guide vaccine interventions
- Scalable tools that can be used outside of large centers and provide representative data
- High-thought ability to support public health surveys.

WAY FORWARD: TECHNOLOGY

- New diagnostic tools:
  - Expand to detection of IgA (using HlyE/LPS targets)
    Preliminary data showing promising results but not yet commercially available
  - ? multiplex

- Amplification- innovation are needed to enable molecular detection
  - At POC for decentralized use
  - As improved reference test

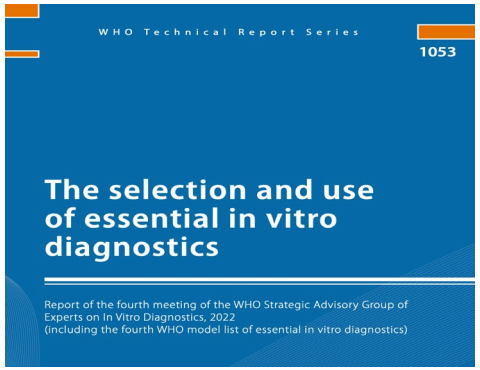
WAY FORWARD: IMPLEMENTATION

- Digital tools to help guide the use of appropriate diagnostic
- Algorithm and testing pathways (recommended by WHO EDL)

WAY FORWARD: ACCESS

- Strong advocacy:

- Submit data and provide evidence to Essential Diagnostic List at Global and National level



Applications for Do Not Do recommendations

Serological tests for detection of typhoid antigen and immunoglobulin M/immunoglobulin G antibodies

Unavailability of alternative rapid tests, while acknowledgeing the suboptimal performance of currently avalable tests.

FIND

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KENYA MEDICAL RESEARCH INSTITUTE
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The Vaccine Alliance

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