PROGRESS AND CHALLENGES TOWARDS TYPHOID DIAGNOSTICS

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Scientist
It’s not Typhoid – Tackling misdiagnosis of Typhoid fever in Nigeria

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

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.

**DIAGNOSTIC CHALLENGES**

**Point of care testing**
- Guide treatment quickly
- Rule antibiotic in or out
- Provide confidence to HCW

**Drug susceptibility testing**
- Guide choice of antibiotics
- Keep abreast of susceptibility changes
- Establish antibiogram

**Surveillance**
- Enable vaccine allocations
- Guide WASH actions
- Burden and incidence estimates

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**Why?**
- Most frequently used Widal test
- Many other RDTs available ....“but”.....

**How?**
- 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)
- 36% Immunoassay (IA)
- 64% Molecular

Typhoid fever diagnostics: types of immunoassays (187 tests identified)
- 51%
- 42% LFA - Other
- 13% ELISA and other LFA IA
- 8% LFA - Antigen
- 4% LFA - Antibody

Typhoid fever diagnostics: types of molecular tests (105 tests identified)
- 41%
- 42% Open source - Typhoid Fever
- 13% Proprietary - Typhoid Fever
- 4% Open source - Multiplex
- 8% Proprietary - Multiplex
TYPHOID FEVER – 95 LATERAL FLOW TESTS – ANTIBODY

- **S. typhi**: 60 regulatory achieved, 20 unknown regulatory status, 20 in development, 0 discontinued
- **S. typhi + S. paratyphi**: 10 regulatory achieved, 10 unknown regulatory status, 10 in development, 10 discontinued
- **Others (Salmonella spp, Unknown)**: 5 regulatory achieved, 5 unknown regulatory status, 5 in development, 5 discontinued

Legend:
- Regulatory achieved
- Unknown regulatory status
- In development
- Discontinued
TYPHOID FEVER – 69 LATERAL FLOW TESTS – ANTIGEN

Number of tests identified

- Regulatory achieved
- RUO
- Unknown regulatory status
- In development
- Discontinued

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Regulatory achieved</th>
<th>RUO</th>
<th>Unknown regulatory status</th>
<th>In development</th>
<th>Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. typhi</td>
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<tr>
<td>S. paratyphi</td>
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<tr>
<td>S. typhi + S. paratyphi</td>
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<tr>
<td>Others (Salmonella</td>
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<td></td>
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<tr>
<td>typhimurium, Salmonella</td>
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<tr>
<td>enteritidis, Unknown)</td>
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</tbody>
</table>
Note: Among “Other non-LFA IA” are included the TUBEX test and an unknown IA test.
TYPHOID FEVER – 87 MOLECULAR – OPEN SOURCE KITS

Molecular – Open source

Number of tests identified

S. typhi  S. paratyphi  S. typhi + S. paratyphi  Others (Salmonella spp, Unknown)  Multiplex

Regulatory achieved  RUO  Unknown regulatory status  In development  Discontinued

Only linked to Salmonella

Salmonella + other pathogens
TYPHOID FEVER – 18 MOLECULAR – PROPRIETARY KITS

![Bar chart showing molecular proprietary kits for typhoid fever.]

- **S. typhi + S. paratyphi**
  - Regulatory achieved
  - RUO
  - Unknown regulatory status
  - In development
  - Discontinued

- **Others (Salmonella spp, Unknown)**
  - Regulatory achieved
  - RUO
  - Unknown regulatory status
  - In development
  - Discontinued

- **Multiplex**
  - Regulatory achieved
  - RUO
  - Unknown regulatory status
  - In development
  - Discontinued

Only linked to Salmonella

Salmonella + other pathogens
## 7 COMMERCIALISED CARTRIDGE-BASED MOLECULAR TESTS

<table>
<thead>
<tr>
<th>Organisation Name (HQ country)</th>
<th>Test name</th>
<th>Target pathogen</th>
<th>Regulatory Status</th>
<th>Validated sample Types</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> BioFire Defense, llc (United States)</td>
<td>FilmArray Global Fever Panel RUO</td>
<td>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</td>
<td>None (RUO)</td>
<td>Whole Blood</td>
</tr>
<tr>
<td><strong>2</strong> Becton, Dickinson and Company (BD) (United States)</td>
<td>BD MAX Enteric Bacterial Panel</td>
<td>Salmonella spp.;Campylobacter spp;Escherichia coli;Shigella spp;Shigella dysenteriae</td>
<td>CE-IVD; US FDA 510k</td>
<td>Feces</td>
</tr>
<tr>
<td><strong>3</strong> BioFire Diagnostics, llc (United States)</td>
<td>FilmArray Gastrointestinal (GI) Panel</td>
<td>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</td>
<td>CE-IVD; US FDA 510k</td>
<td>Feces</td>
</tr>
<tr>
<td><strong>4</strong> Great Basin Scientific (United States)</td>
<td>Stool Bacterial Pathogens Panel</td>
<td>Salmonella spp.; Campylobacter coli; Campylobacter jejuni; Shigella spp.; Escherichia coli</td>
<td>US FDA 510k</td>
<td>Feces</td>
</tr>
<tr>
<td><strong>5</strong> Luminex Corporation (United States)</td>
<td>VERIGENE Enteric Pathogens Test</td>
<td>Salmonella spp.; Campylobacter spp;Shigella spp;Yersinia enterocolitica;Vibrio spp; Norovirus; Rotavirus</td>
<td>CE-IVD; US FDA 510k</td>
<td>Feces</td>
</tr>
<tr>
<td><strong>6</strong> Mobidiag/Hologic (United States)</td>
<td>Novodiag Bacterial GE +</td>
<td>Salmonella spp; Campylobacter coli;Campylobacter jejuni;Clostridioides difficile;Escherichia coli;Shigella spp;Vibrio cholerae;Yersinia enterocolitica;Yersinia pseudotuberculosis; Yersinia pestis; Vibrio parahaemolyticus</td>
<td>CE-IVD</td>
<td>Feces</td>
</tr>
<tr>
<td><strong>7</strong> Molbio Diagnostics Pvt ltd. (India)</td>
<td>Truenat Salmonella</td>
<td>Salmonella spp.</td>
<td>CE-IVD</td>
<td>Whole Blood</td>
</tr>
</tbody>
</table>
### 9 POC Including Widal Test Evaluated in FIND Study

<table>
<thead>
<tr>
<th>RDTs evaluated</th>
<th>Study</th>
<th>Pakistan</th>
<th>Kenya</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Widal</td>
<td>47.7%</td>
<td>79.4%</td>
<td>48.3%</td>
</tr>
<tr>
<td>SD Bioline Salmonella Typhi IgG/IgM</td>
<td>21.6%</td>
<td>100%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Typhidot Rapid IgG/IgM</td>
<td>46.2%</td>
<td>82.8%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Enterochek WB</td>
<td>72.7%</td>
<td>86.5%</td>
<td>69.8%</td>
</tr>
<tr>
<td>Test-it Typhoid IgM</td>
<td>63.6%</td>
<td>95.1%</td>
<td>58.5%</td>
</tr>
<tr>
<td>CTK Typhoid IgG/IgM combo rapid test CE</td>
<td>1.5%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Spectrum Typhoid IgG/IgM Rapid cassette</td>
<td>49.6%</td>
<td>78.7%</td>
<td>58.0%</td>
</tr>
<tr>
<td>TUBEX-TF</td>
<td>60.6%</td>
<td>94.0%</td>
<td>63.4%</td>
</tr>
<tr>
<td>Diaquick S.Typhi/Paratyphi Ag cassette</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Commonly used: Widal

Africa vs Asia: SD Bioline Salmonella Typhi IgG/IgM
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

Unavailability of alternative rapid tests, while acknowledging the suboptimal performance of currently available tests.