Confidence in typhoid fever diagnosis

TUBEX® TF is a rapid in vitro diagnostic test for detection of typhoid fever, a disease caused by *Salmonella typhi*. It enables diagnosis of acute phase disease by detection of infection-specific *S. typhi* anti-O9 IgM antibodies in patient serum. TUBEX® TF is based on a new technology; IMBI™ - Inhibition Magnetic Binding Immunoassay - a semi-quantitative colorimetric assay, completed within 10 minutes. A positive TUBEX® TF result, together with typical clinical symptoms, is a strong indication of acute typhoid fever.

**IMBI™ assay for infection-specific antibody detection.**

IMBI™ is a semi-quantitative assay technology, utilizing the advantages from the traditional Widal technique, being simple and based on visual interpretation of fluid; combined with specificity normally accorded to ELISAs, using purified antigens for detection.

The IMBI™ technology allows for detection of infection-specific antibodies in patient serum by assessing their ability to inhibit the reaction between the detector antigen, coated on magnetic particles, and the indicator antibody, coated on colored latex particles. The efficiency of the IMBI™ reaction is further made possible by specifically designed reaction wells. The reaction is separated using magnetic force. The color of the supernatant is proportional to the concentration of infection-specific antibodies found in patient serum. Scoring of results are performed by visual interpretation.

TUBEX® TF combines the antigen *S. typhi* LPS as detector with a specific monoclonal antibody directed against the *S. typhi* O9 antigen as indicator.

**Assay procedure.** TUBEX® TF is completed in a few steps as illustrated below.

1. **TUBEX® TF Brown Reagent (45µl).**
2. Sample or TUBEX® TF Control (45µl). Mix 10x.
3. Incubate 2 min.
4. **TUBEX® TF Blue Reagent (90µl).**
5. Cover strip Shake 2 min.
6. Separate 5 min on TUBEX® Color Scale Read results.

1. Add 45µl TUBEX® TF Brown Reagent (detector) to the TUBEX® Reaction Well Strip.
2. Add 45µl patient sample, TUBEX® TF Positive Control or TUBEX® TF Negative Control. Mix 10 times by pipetting.
3. Incubate on the bench for 2 minutes.
4. Add 90µl TUBEX® TF Blue Reagent (indicator).
5. Cover the TUBEX® Reaction Well Strip using the TUBEX® Sealing Tape. Tilt and shake the TUBEX® Reaction Well Strip for 2 minutes.
6. Place the TUBEX® Reaction Well Strip on the TUBEX® Color Scale. Allow separation for 5 minutes. Read and score the results by comparing the color of each supernatant to the TUBEX® Color Scale. The color scale range from 0 (negative test; clear pink) to 10 (positive test; intense blue).
**Typhoid fever diagnosis.** A clinical symptom of typhoid fever is high body temperature, a symptom applicable to a number of infectious diseases. For use in endemic areas, a test needs to be specific, easily accessible and having a short turnaround time. TUBEX® TF fulfills these criteria, being a rapid, stand-alone test for detection of current typhoid fever by its specific IgM detection.

The awareness of the clinical benefits of TUBEX® TF in endemic settings is increasing. A few examples on clinical trials forming the basis for this are presented below.

In a comparative trial in the Philippines, Kawano and co-workers found TUBEX® TF to be 95% sensitive at 80% specificity (75 culture-proven *S. typhi* infected patients, and 102 culture-negative non-typhoidal patients; see below). Being an IgM test, earlier detection of current disease compared to culture positivity is commonly seen. Thus, considering 14 TUBEX® TF positive, culture-negative cases as true positives, the TUBEX® TF specificity is increased to 93%. The positive predictive value was 78%, and the negative predictive value was 95%. In this comparative trial, TUBEX® TF was stated to score best among the assays analyzed. It fulfilled the required criteria for a serological test to be useful in a routine setting and to be a solid alternative to blood culture.

In a Vietnamese prospective trial, another 59 culture-proven *S. typhi* infected patients and 20 controls were included by Olsen and co-workers. A vast majority had taken antibiotics prior to visit, a factor known to negatively affect outcome of culture. Here, Widal sho- wed 64% sensitivity at 76% specificity, as compared to TUBEX® TF showing 78% sensitivity at 94% specificity. According to the authors, TUBEX® TF demonstrated promising results and was further the easiest test to use among the various assays analyzed.

In a prospective trial in Bangladesh by Rahman and co-workers, a total of 243 febrile outpatients (mainly children and adolescents) and 57 healthy controls were enrolled. Based on culture results, TUBEX® TF was 91% sensitive and 82% specific in febrile subjects. Specificity increased to 90% in nonfebrile, healthy subjects, suggesting that some culture-negative patients were truly typhoidal. For Widal, the corresponding figures were 82% sensitivity at 58% specificity.

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<thead>
<tr>
<th>Assay</th>
<th>IMBI™ (Inhibition Magnetic Binding Immunoassay)</th>
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</thead>
<tbody>
<tr>
<td>Antigen</td>
<td><em>S. typhi</em> LPS O9 (α-D-tyvelose)</td>
</tr>
<tr>
<td>Detection</td>
<td><em>S. typhi</em> IgM O9-antibodies</td>
</tr>
<tr>
<td>Samples</td>
<td>serum</td>
</tr>
<tr>
<td>Analytical sensitivity</td>
<td>15 – 20 µg/ml</td>
</tr>
<tr>
<td>Procedure</td>
<td>&lt; 10 minutes</td>
</tr>
<tr>
<td>Results</td>
<td>visual semi-quantitative scoring (0 – 10)</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>80 – 95%</td>
</tr>
<tr>
<td>Specificity</td>
<td>80 – 95%</td>
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</tbody>
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TUBEX® is a registered trademark of IDL Biotech AB. IMBI™ is a trademark of IDL Biotech AB.

**Modified after Kawano et al J Clin Microbiol 2007.**

**Modified after Lim et al J Clin Microbiol 1998.**

**References**


WHO. Background document: The diagnosis, treatment and prevention of typhoid fever. 2003; 11-16. WHO/V&B/03.07 (www.who.int/vaccines-documents/).