Rapid communication: TB antigen-based skin tests for the diagnosis of TB infection

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Background

Over a quarter of the world's population is estimated to be infected with *Mycobacterium tuberculosis* complex (MTBC). This infection is characterized by immune memory response to *Mycobacterium tuberculosis* (*Mtb*) antigens, with no evidence of clinically manifest tuberculosis (TB) disease.[1] People with TB infection are at risk for developing TB disease; hence, tests for TB infection are useful to identify those most likely to benefit from TB preventive treatment (TPT). The two currently available classes of tests – tuberculin skin test (TST) and interferon-gamma release assay (IGRA) – require a competent immune response to accurately identify TB infection. However, a positive test result by either method is not, by itself, a reliable indicator of the risk of progression to TB disease.

TST with a purified protein derivative were developed in the 1940s and were extensively used for detecting TB infection at all health care levels including at primary care level worldwide. However, false positive results occur in patients who have received a bacille Calmette-Guérin (BCG) vaccination and those with non-tuberculous mycobacterial (NTM) infection. In 2011, the World Health Organization (WHO) issued recommendations on the use of blood-based IGRA for the diagnosis of TB infection. These tests use *Mtb* specific antigens, making them more specific than TST; also, these are in vitro tests that do not require a repeat visit for reading the result. However, these tests do require laboratory infrastructure and qualified personnel; also, they are more expensive. In 2015, WHO updated its recommendations on the use of TST and IGRA for the diagnosis of TB infection, and in 2022 issued a policy statement extending these recommendations to cover the use of new and updated versions of blood-based IGRA.

Newer *Mtb* antigen-based skin tests (TBST) have been developed to measure the cell-mediated immunological response to *Mtb* specific antigens. Emerging evidence suggests that these tests may offer similar specificity to IGRA, and when compared with TST they may provide more reliable results in children and in people living with HIV. The TBST class is defined as skin tests for the detection of TB infection that use *Mtb* specific antigens (ESAT6 and CFP10).

In 2021, WHO commissioned a systematic review of published and unpublished data on this new class of tests for TB infection that had not been previously reviewed by WHO. A Guideline Development Group (GDG) was convened by WHO from 31 January to 3 February 2022, to discuss the findings of the systematic reviews and to make recommendations on this class of diagnostic technologies for TB infection. The following technologies were included in the evaluation: C-Tb (Serum Institute of India, India); C-TST (formerly known as ESAT6-CFP10 test, Anhui Zhifei Longcom, China); and Diaskintest (Generium, Russian Federation).

The objectives of the meeting were to assess the available data on TBST related to patient-important outcomes, diagnostic accuracy, safety, concordance, and economic and qualitative evidence, in comparison to TST and IGRA. This rapid communication aims to inform national TB programmes (NTPs) and other stakeholders about the key findings and considerations on the use of TBST for detection of TB infection, following the assessment by the GDG.

Key findings

Assessment of the evidence showed that TBST are accurate, appear to have a safety profile that is similar to that of TST, and are cost-effective, acceptable and feasible. However, the quantity and quality of the available evidence on

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[1] WHO consolidated guidelines on tuberculosis Module 1: Prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment).

the three tests evaluated varied, limiting the certainty of the findings. Also, the lack of a reliable reference standard for TB infection required the use of a hierarchy of proxy standards. Comparative analysis was performed with the previously WHO-endorsed tests TST and IGRA, to aid in the interpretation of the evidence on this new class of tests.

TBST were found to be accurate

Intervention: TBST were found to be accurate for detection of TB infection compared with IGRA and TST.

Data assessed: For sensitivity: 17 studies involving 1276 participants; for specificity (including difference in specificity): 14 studies involving 3792 participants; and for agreement: 16 studies involving 3198 participants. There were no identified studies on the efficacy of TPT based on diagnostic test results nor on the predictive value for progression to TB disease. Data on people living with HIV and children aged under 18 years were assessed where available.

Results: Diagnostic accuracy of TBST was confirmed for detection of TB compared with IGRA and TST. Overall, pooled sensitivity and specificity for TB infection detection were 76.0% (95% confidence interval [CI]: 70.0 to 81.0) and 98.0% (95% CI: 94.0 to 99.0), respectively. Difference in specificity between TBST and TST among those who were BCG vaccinated was 67.4% (95% CI: 24.0 to 110.7) and was higher for TBST. However, difference in specificity between TBST and IGRA among those who were BCG vaccinated was 9.7% (95% CI: –31.2 to 11.8) and was lower for TBST, although the confidence intervals overlapped. Agreement with TST in people without TB disease was 59.4% (95% CI: 45.4 to 72.1) and in people with TB disease was 88.3% (95% CI: 82.1 to 92.5). Agreement with IGRA in people without TB disease was 89.0% (95% CI: 82.6 to 93.2) and in people with TB disease was 85.7% (95% CI: 79.5 to 90.3).

TBST safety profile appeared similar to TST

Intervention: The TBST safety profile was similar for detection of TB infection compared with TST.

Data assessed: Six studies involving 2931 patients.

Results: The safety profile of novel TBST appears to be similar to that of TST and is associated with mostly mild injection site reactions such as itching and pain. Relative risk for any injection site reaction in comparison with TST amounted to 1.05 (95% CI: 0.70 to 1.58). Relative risk for any systemic reaction in comparison with TST was 0.84 (95% CI: 0.60 to 1.10). From the reviewed studies, there appears to be no safety signal that might affect the choice between specific TBST and TST. However, the data on safety had significant limitations – the quantity of data and type of studies varied for different tests, including the availability of randomized and nonrandomized controlled trials and observational data. A full safety review would be required for each individual test before implementation, as part of the assessment by a regulatory authority.

TBST were found to be cost-effective

Intervention: TBST were found to be cost-saving or cost-effective for detection of TB infection compared with IGRA and TST, depending on the setting.

Data assessed: Eight studies, and a WHO-commissioned generalized model-based cost–effectiveness analysis representing Brazil, South Africa and the United Kingdom of Great Britain and Northern Ireland (United Kingdom).

Results: There were a few published studies on TBST costs and cost–effectiveness. Only eight studies were included from the primary review on novel TBST, and the quality of most of these studies was concerning. Diaskintest (Generium, Russian Federation) had sufficient available data to be included for the modelling analysis and used as a representative product of the class. For two other tests, the cost per test was not available. The model-based cost–effectiveness analysis showed that TBST are cost-effective (United Kingdom) or cost-saving (Brazil and South Africa) for selected scenarios relative to TST and IGRA.

TBST were found to be acceptable and feasible

Intervention: TBST were found to be acceptable and feasible for detection of TB infection compared with IGRA and TST.

<u>Data assessed</u>: Four studies, interviews (20 respondents) and a discreet-choice experiment (234 respondents).
<u>Results</u>: TBST were found to be an acceptable alternative to the TST but with many of the same limitations. The higher accuracy may help to avoid the negative consequences of false positives and may shift preferences towards the test. Careful communication during implementation and endorsement by providers and organizations will help to improve acceptability. TBST were found to be feasible to use in settings where the TST is already used, leveraging existing skilled staff, equipment, facilities and care pathways that are common to both tests. As with TST, the TBST are low-cost, portable tests that may be more suited than IGRA to use in low-resource settings. Feasibility factors (e.g. the need for a follow-up appointment and requirements for specialist staff and equipment) affect test preferences and are ongoing challenges to be addressed.

Overall conclusions

Overall, the new TBST class of tests were as sensitive as TST and IGRA, making them suitable alternatives. The specificity was similar to that of IGRA and better than that of TST, particularly in populations with prior BCG vaccination history. This is important to potentially reduce false positive diagnosis of TB infection in settings using TST. No safety signal was identified for the class of tests; however, regulatory evaluation for the individual products is essential before introduction of these in vivo tests. Where TST is already used, TBST implementation is expected to require some adaptation. Also, in many settings, TBST would be cost-saving relative to TST and IGRA. No evidence was identified on the predictive value of the tests or on the efficacy of TPT based on diagnostic test results; further research to address these gaps is needed, including comparison to TST and IGRA.

The findings were based on evaluation of data for the included assays that met the class definition: C-Tb (Serum Institute of India, India); C-TST (formerly known as ESAT6-CFP10 test, Anhui Zhifei Longcom, China); and Diaskintest (Generium, Russian Federation).

Extrapolation to other brand-specific tests cannot be made and any new in-class technologies will need to be evaluated by WHO.

Next steps

- The full policy guidelines, including specific recommendations, detailed justification and implementation considerations, will be released later in 2022, as part of the updated *WHO consolidated guidelines on tuberculosis Module 3: Diagnosis – rapid diagnostics for tuberculosis detection*. The release of the guidelines will be accompanied by an operational handbook.
- **NTPs and other stakeholders should seek approval from a local or internationally recognized regulatory authority before introducing these technologies.** The WHO recommendations on diagnostics are based on clinical research evidence; they do not include quality assessments of the products or the manufacturing process involved.

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