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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

[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