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New study finds that blood biomarker of TB discriminates between people with high risk and those who remained healthy

Researchers from the South African Tuberculosis Vaccine Initiative (SATVI) at the University of Cape Town, in collaboration with various partners in their field, have published the results from a study into a blood-based RNA biomarker. The study, which tested diagnostic and prognostic performance for TB and the efficacy of TB preventive therapy for biomarker-positive individuals, was published in *The Lancet Infectious Diseases* journal**.**

Treatment of all people who have a latent infection with the TB bacterium is not a feasible prospect because the majority of the South African population is infected and due to the logistical and financial challenges. Importantly, only 5-10% of people with latent infection are at risk of progression to TB disease and would benefit from antibiotic treatment.

The strategy proposed in this publication advances the development of a point-of-care blood test with which health practitioners could accurately identify people who have TB disease, or who are likely to progress from latent infection to active TB disease, and make it possible to apply available TB preventive and treatment regimens selectively, and with greater accuracy to those who are most likely to benefit, to impact on transmission in communities.

The other partners in the study are the Aurum Institute, the Centre for the AIDS Programme of Research in South Africa, Stellenbosch University, the London School of Hygiene and Tropical Medicine and the Fred Hutchinson Cancer Research Center.

The study was conducted between 2016 and 2019 across five distinct geographic communities in South Africa. The research team set out to test the performance of a transcriptomic signature of tuberculosis (RISK11), as well as the efficacy of signature-guided preventive therapy using a parallel, three-arm hybrid study design.

A total 20 207 adult volunteers from communities in Worcester, Ravensmead, Durban, Klerksdorp and Rustenburg were screened for participation. More than 80% of detected TB cases did not have any symptom compatible with TB disease and would not have been detected by current TB screening strategies that require symptoms as the entry point to investigation. The RISK11 blood test discriminated between individuals with current TB disease or those who would progress to incident TB within six months after testing, and individuals who remained healthy, with excellent performance. Disappointingly, the provision of a three-month regimen of once-weekly, high-dose isoniazid and rifapentine (3HP), which is effective in treating latent TB infection, did not reduce the rate of TB disease in RISK11-positive participants over 15 months of follow-up.

Performance of RISK11 as a screening test for active disease in people with TB symptoms exceeded the WHO requirements for a triage test. But diagnostic performance in asymptomatic participants did not meet these requirements, highlighting how challenging

diagnosis of asymptomatic TB can be. The RISK11 signature was able to predict risk for TB disease progression in this trial population with TB incidence exceeding one case per 100 person-years, but optimal prognostic performance was limited to a period of six months after testing.

SATVI's Professor Mark Hatherill said: "These results demonstrate proof of concept for host blood signature TB screening in high burden communities and will advance development of simple point-of-care testing platforms. However, the missing piece of this TB screening strategy is an effective biomarker-guided preventive therapy regimen, which remains elusive."

Professor Tom Scriba, also from SATVI, said: "This large study was a very impressive collaborative effort between many excellent teams. One of the key findings is the high prevalence of asymptomatic TB in South African communities, which highlights the critical and urgent need to develop effective interventions that can prevent this devastating disease."

"Having a test that is able to predict risk of progressing to TB disease is an important new tool in the TB prevention armamentarium. Further research, however, is required to evaluate treatment regimens to prevent progression to TB disease," said Professor Gavin Churchyard from the Aurum Institute.

The study

Biomarker-guided tuberculosis preventive therapy (CORTIS): a randomised controlled trial. Scriba T.J, Fiore-Gartland A., Penn-Nicholson A., Humphrey Mulenga H., Mbandi S.K., Borate B., Mendelsohn S.C., Hadley K., Hikuam C., Kaskar M., Musvosvi M., Bilek N., Self S., Sumner T., White R.G., Erasmus M., Jaxa L., Raphela R., Innes C., Brumskine W., Hiemstra A., Malherbe S.T., Hassan-Moosa R., Tameris M., Walzl G., Naidoo K., Churchyard G., Hatherill M., and the CORTIS-01 Study Team. ***Lancet Infect Dis 2021***
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