EMBARGO: **None**

A blood biomarker of tuberculosis discriminated between people at high risk for tuberculosis and those who remained healthy, but an effective preventive therapy for people at risk remains elusive.

The Lancet Infectious Diseases journal reports the findings of a study of a host blood signature of TB that differentiated between people who had or would develop active TB and those who remained healthy, and investigated in parallel the effect of giving TB preventive therapy based on a positive signature result.

25 JANUARY 2021: Researchers from the **South African Tuberculosis Vaccine Initiative** at the **University of Cape Town**, **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** have published the results from a study into a blood-based RNA biomarker which tested diagnostic and prognostic performance for TB and the efficacy of TB preventive therapy for biomarker-positive individuals 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 our 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 test 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 study was conducted between 2016 and 2019 across five distinct geographic communities across 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.

Results

A total 20,207 adult volunteers from communities in Worcester, Ravensmead, Durban, Klerksdorp and Rustenberg 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 6 months after testing, and individuals who remained healthy, with excellent performance. Disappointingly, the provision of a 3-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 6-month after testing.

This study was funded by the **Bill and Melinda Gates Foundation** and the **South African Medical Research Council.**

Comments from research study leaders

Prof Mark Hatherill (SATVI) 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."*

Prof Tom Scriba (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."*

Prof Gavin Churchyard (The Aurum Institute) said: *"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."*

Prof Naidoo (CAPRISA) said *: "This important study highlights the need to harness innovative TB diagnostic technologies that deliver results with accuracy and immediacy, particularly in settings with a high burden of disease. The findings of a high prevalence of asymptomatic TB serves as a grim reminder of ongoing high levels of TB transmission within our communities"*

Professor Fiore-Gartland (Fred Hutchison) said "This study also demonstrates the importance of large, rigorously designed, randomized clinical trials, which are the gold standard for moving clinical practice forward. The enormous collaborative effort that was required to screen 20K South Africans for this trial enabled us to ask and answer questions about TB disease progression that we couldn't previously. It was thrilling to take part in such a massive collaboration of scientists, clinicians and volunteers working to fight this deadly disease."

Prof Walzl (Stellenbosch University Immunology Research Group) said: *"The diagnostic performance of RISK11 as screening test for active TB and its prognostic ability for development of TB within 6 months are encouraging and future development could focus on the development of point-of-care, laboratory-free tests for use in low resource areas with high case loads."*

About the participating research groups

About SATVI.

The South African Tuberculosis Vaccine Initiative (SATVI) is a TB research group based at the Faculty of Health Sciences of the University of Cape Town. SATVI has conducted 29 Phase I–IV trials of 9 different TB vaccine candidates since 2005. SATVI's research also seeks to understand the risk for, and protection against, *M. tuberculosis* infection and disease, in order to develop more effective vaccines and preventive strategies for global impact on the TB epidemic. Read more at www.satvi.uct.ac.za

About the Aurum Institute.

Established in 1998, the Aurum Institute is an African Public Benefit Organisation whose mission is to improve the health of people and communities living in poverty through innovation in global health research, systems and delivery. It is rooted in Africa is dedicated to researching, supporting and implementing innovative, integrated approaches to Global Health with their headquarters in South Africa with offices in the USA, Ghana and Mozambique. The Aurum Institute has developed itself into a leading player, bridging the worlds of research, policy and implementation for impact. www.auruminstitute.org

About the Centre for the AIDS Programme of Research in South Africa (CAPRISA) .

CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy and hosts a DSI-NRF Centre of Excellence in HIV Prevention and a MRC HIV-TB Pathogenesis and Treatment Research Unit. The primary goal is to undertake globally relevant and locally responsive research that contributes to understanding HIV Pathogenesis, Prevention and Epidemiology, as well as the links between Tuberculosis and AIDS care. CAPRISA has diverse expertise in basic and molecular epidemiology, virology, immunology, infectious disease medicine, bioinformatics, statistics, ethics and health policy. Read more at www.caprisa.org

About the Stellenbosch University, Immunology Research Group.

The Stellenbosch University Immunology Research Group is part of the Division of Molecular Biology and Human Genetics at the Faculty of Medicine and Health Sciences, Stellenbosch University. The group focuses on the immunology of tuberculosis infection and disease and has a strong interest in host-based biomarker discovery and validation to aid the development of urgently needed tools in the fight against TB, particularly in resource constraint settings with high case loads.

About the London School of Hygiene and Tropical Medicine.

The London School of Hygiene and Tropical Medicine (LSHTM) TB Centre (https://www.lshtm.ac.uk/research/centres/tb-centre), established in 2012, supports cross disciplinary research to develop tools and interventions for the prevention and treatment of TB. As part of these efforts the TB Modelling Group (https://tbmodelling.lshtm.ac.uk/) uses mathematical and statistical models to understand the natural history and epidemiology of tuberculosis (TB) and to improve the contribution of TB modelling to policy decisions and implementation.

About the Fred Hutchinson Cancer Research Center

At Fred Hutchinson Cancer Research Center, home to three Nobel laureates, interdisciplinary teams of world-renowned scientists seek new and innovative ways to prevent, diagnose and treat cancer, HIV/AIDS and other life-threatening diseases. Fred Hutch's pioneering work in bone marrow transplantation led to the development of immunotherapy, which harnesses the power of the immune system to treat cancer. An independent, nonprofit research institute based in Seattle, Fred Hutch houses the nation's first National Cancer Institute-funded cancer prevention research program, as well as the clinical coordinating center of the Women's Health Initiative and the international headquarters of the HIV Vaccine Trials Network.

Journal article

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***
*Published **Online** January 25, 2021 https://doi.org/10.1016/ S1473-3099(20)30914-2*
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30914-2/fulltext

For enquiries:

Scientific Enquiries	*South African Tuberculosis Vaccine Initiative (SATVI) University of Cape Town: Professor Mark Hatherill at* mark.hatherill@uct.ac.za
Media enquiries	*Kelvin Vollenhoven at* kelvin.vollenhoven@uct.ac.za
cell	*074 585 2858*
Website	*www.satvi.uct.ac.za*