

Press Release:

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Results from innovative tuberculosis vaccine trial show potential for new BCG revaccination strategies and hope for subunit vaccines.

This is the first “prevention-of-infection” trial conducted for tuberculosis, the world’s leading infectious disease killer.

CAPE TOWN: 11 JULY 2018 - Scientists from the University of Cape Town-based South African Tuberculosis Vaccine Initiative (SATVI) and the Desmond Tutu HIV Foundation have announced publication in the *New England Journal of Medicine* of the results of an innovative clinical trial that provides encouraging new evidence that TB vaccines could prevent sustained TB infections in high-risk adolescents.

According to the World Health Organization (WHO), about one-quarter of the world’s population has latent TB infection, which means people have been infected by TB bacteria but are not ill with the disease and cannot transmit the disease. People infected with TB bacteria have a lifetime risk of falling ill with TB of 10%.

In a prevention-of-infection phase 2 trial conducted in Worcester and Cape Town, South Africa, revaccination with the Bacille Calmette-Guerin (BCG) vaccine significantly reduced sustained TB infections in adolescents. An experimental vaccine candidate, H4:IC31, also appeared to reduce sustained infections, although not at statistically significant levels. However, the trend observed for H4:IC31 is the first time a subunit vaccine has shown any indication of ability to protect against TB infection or disease in humans.

TB infections that developed during the study were measured using a QuantiFERON®-TB Gold in Tube (QFT-GIT) test, a commercially available blood test that helps diagnose TB infections. In the trial, individuals who tested negative for QFT-GIT were considered to not have TB infection. The trial measured the rate by which individuals converted to QFT-GIT positive, interpreted as evidence of TB infection. Those individuals who tested QFT-GIT positive consecutively over 6 months were considered to have a sustained infection.

H4:IC31 is a subunit TB vaccine candidate being developed jointly by Aeras and Sanofi Pasteur, and the Statens Serum Institute. BCG is the only licensed tuberculosis vaccine available globally. The clinical trial was conducted at SATVI and at the Emavundleni Research Centre (part of the Desmond Tutu HIV Centre). The trial was funded by Sanofi Pasteur, the United Kingdom’s Department for International Development, and Aeras. The study was approved by the Medicines Control Council of South Africa and the independent ethics committee of the University of Cape Town.

Mark Hatherill, MD, Director of the South African Tuberculosis Vaccine Initiative (SATVI) at the University of Cape Town, and the study's principal investigator, said: *"We are very pleased to publish the results of the first randomized, placebo-controlled prevention-of-infection trial for TB, which showed that vaccination may reduce the rate of sustained TB infection in a high-transmission setting. While neither vaccine proved to be statistically significant in preventing an initial TB infection, we are extremely encouraged by the efficacy findings against sustained TB infections. We believe the results from this novel trial design will provide significant scientific benefit to the field in understanding protection against TB infection, and based on this positive signal, we look forward to testing the potential of such vaccines to protect against TB disease among uninfected adolescents in a larger, more traditional prevention-of-disease clinical trial."*

Tom Scriba, PhD, Deputy Director Immunology of SATVI, said *"We are excited that this result provides an opportunity to identify the immune response that protects against sustained TB infection. This advance would accelerate rational development of new TB vaccines."*

Linda-Gail Bekker, MD, PhD, a lead investigator for the trial, the Chief Operating Officer at the Desmond Tutu HIV Foundation and President of the International AIDS Society, said: *"We would like to thank all the study participants and their families for participating in this novel clinical trial. We believe the results are important and warrant further investigation into other subunit vaccines and a re-evaluation of BCG revaccination as a potential strategy to prevent TB in high-incidence countries. An effective TB vaccine remains an urgent global goal."*

Jacqueline Shea, PhD, Chief Executive Officer at Aeras, said: *"These results highlight the importance of investing in new approaches to fighting the leading infectious disease killer and to evaluating new concepts in clinical trials. Further, the collaborative effort established between industry leaders, nonprofits and clinical sites during this trial showed how powerful combining such forces can be for developing new interventions against a global health threat. The BCG results are important findings with significant public health implications, especially with the rise of drug-resistant strains, that could lead to saving millions of lives. Likewise, the novel prevention-of-infection trial design can be used to inform clinical development of new vaccine candidates before entry into large-scale prevention-of-disease efficacy trials. We are very grateful to the trial participants and our partners and funders who enabled the conduct of this trial."*

Study Design and Results for H4:IC31 Vaccination and BCG Revaccination

The study involved 990 HIV-negative, healthy adolescents (12 to 17 years of age) who had previously been vaccinated as infants with BCG. All participants were randomized evenly into three study arms: placebo, H4:IC31, or BCG revaccination. All participants were screened to ensure they were not infected with *Mycobacterium tuberculosis* (Mtb) prior to vaccination in the study.

The data showed that both vaccines appeared to be safe and produced an immune response in the adolescents studied. No vaccine-related serious adverse events were reported in the study, and the most common vaccine-related adverse event was injection site swelling in BCG revaccinated participants, typical for BCG vaccination.

For the primary efficacy outcome, 134 participants tested positive for an initial Mtb infection as measured by QFT-GIT conversion from negative to positive. When compared to the placebo, neither vaccine prevented initial Mtb infection (i.e., QFT-GIT conversion).

For the secondary efficacy outcome, 82 participants exhibited a sustained QFT-GIT conversion which remained positive for at least 6 months. In the BCG revaccination arm, the

vaccine efficacy for preventing a sustained infection was 45.4% and was statistically significant. In the H4:IC31 arm, vaccine efficacy was 30.5%, but did not meet rigorous criteria for statistical significance.

This convincing BCG efficacy signal provides impetus for trials of BCG revaccination for prevention of TB disease in adolescents without Mtb infection, which would be needed to confirm direct clinical benefit of the prevention-of-infection approach. The modest efficacy effect of H4:IC31 encourages further testing of next generation subunit TB vaccines.

About TB and Vaccine Development

Tuberculosis is designated a priority infectious disease by the WHO (www.who.int/tb/en/). It causes more deaths than any other single infectious disease and is increasingly characterised by antimicrobial resistance. There were 10.4 million new cases of TB in 2016 and 1.7 million deaths.

Introduced in 1921, BCG is the only vaccine currently licensed to prevent TB disease. Past observational studies have indicated that primary BCG vaccination may offer partial protection against initial Mtb infection. It has also been hypothesized that revaccination with BCG might provide additional protection against Mtb infection. However, prior to this proof-of-concept trial, this hypothesis had not been tested in a prospective, randomized, placebo-controlled trial. The results to be published in the *New England Journal of Medicine*, indicating that sustained QFT-GIT conversions are preventable by BCG revaccination, provide novel insights into possible mechanisms of protection in humans. These results are consistent with the hypothesis that vaccine-induced immune responses may increase the ability to control or even clear an Mtb infection.

About South African Tuberculosis Vaccine Institute (SATVI)

SATVI is a leading TB vaccine clinical research group at the University of Cape Town, with a field site in the town of Worcester. The goal of SATVI is the development of new and effective vaccination strategies against TB through conduct of clinical trials of new vaccine candidates and immunology studies to better understand risk for and protection against TB. SATVI has conducted 24 clinical trials of 9 novel TB vaccine candidates and BCG, involving more than 25,000 infants, children and adults in partnership with the Worcester community. For more information visit www.satvi.uct.ac.za

About Desmond Tutu HIV Foundation

The Desmond Tutu HIV Foundation, housed within the Desmond Tutu HIV Centre at the University of Cape Town, is committed to the pursuit of excellence in research, treatment, training and prevention of HIV and related infections in South Africa. Its vision for the future includes the continuation of current TB/HIV related work of treatment, care, prevention and education particularly in the most vulnerable populations, whilst staying abreast of new developments and continuing to contribute to cutting edge information in HIV and TB public health, social and clinical research. For more information: www.desmondutuhivfoundation.org.za

About Aeras

Aeras is a nonprofit organization advancing the development of new tuberculosis vaccines for the world in partnership with other biotech, pharmaceutical and academic organizations. Aeras is primarily funded by The Bill & Melinda Gates Foundation, the UK Department for International Development (DFID), and other parties committed to ending the TB epidemic. Aeras also receives support from the U.S. government and through partnerships and collaborations with universities and pharmaceutical companies around the world. Aeras is headquartered in Rockville, Maryland (USA), with a clinical development and operations office in Cape Town, South Africa. For more information, please visit www.aeras.org.

About Sanofi

Sanofi is dedicated to supporting people through their health challenges. We are a global biopharmaceutical company focused on human health. We prevent illness with vaccines, provide innovative treatments to fight pain and ease suffering. We stand by the few who suffer from rare diseases and the millions with long-term chronic conditions.

With more than 100,000 people in 100 countries, Sanofi is transforming scientific innovation into healthcare solutions around the globe.

About Statens Serum Institut (SSI)

SSI is under the auspices of the Danish Ministry of Health. Its main duty is to ensure preparedness against infectious diseases and biological threats as well as control of congenital disorders.

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