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24 YEARS OF TB RESEARCH

satvi

TOWARDS A WORLD WITHOUT TB

ANNUAL REPORT 2024

vision and mission

OUR VISION

A World Without TB

OUR MISSION

Innovative and High-Quality TB Vaccine Research in Africa to impact the Global Epidemic

OUR VALUES

Innovation I Respect I Employee Recognition | Accountability Communication | Commitment | Honesty

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contents

director's foreword

The year 2024 marked significant advances across TB vaccine development, diagnostic innovation, and translational SATVI research that continue to drive meaningful progress toward addressing the global burden of TB.

The MTBVAC portfolio has successfully transitioned from early-phase safety studies and dose optimisation to large-scale efficacy evaluation in infants, and soon also in adolescents and adults. Almost a decade of MTBVAC clinical trials has demonstrated SATVI's capacity to shepherd promising interventions through the complete development pathway. Parallel development of the CFP-10-free interferon-gamma release assay has contributed towards resolution of the diagnostic challenge posed by MTBVAC-induced QuantiFERON conversions.

The completion of several major clinical trials has contributed essential knowledge to the TB vaccine field. The H56:IC31 Prevention of Recurrence trial, while not meeting its primary efficacy endpoint, provided critical insights into post-treatment vaccination strategies and immune recovery. Similarly, the results of the BCG Revaccination trial in adolescents, although not demonstrating protective efficacy against sustained Mycobacterium tuberculosis infection (IGRA conversion), offer new insights into the dynamics of TB sensitisation in high-burden settings.

In this report we revisit SATVI transcriptomic biomarker research, from completion of the CORTIS/HR projects, which generated valuable data on biomarker performance across diverse populations, including people living with HIV, and for community-based screening of asymptomatic TB among the 'walking well'. These findings have informed the development of more parsimonious signatures and advanced our understanding of transcriptomic biomarker limitations in the presence of concurrent viral infections. Ongoing work focuses on the potential of host blood transcriptomic signatures to predict TB treatment outcome.

SATVI's diagnostic innovation portfolio has expanded with successful validation of non-sputum approaches, such as oral swab, which achieved 90% sensitivity and 97% specificity using sequence-specific magnetic capture methodology. These advances and ongoing evaluation of exhaled breath analysis and blood-based biomarkers position SATVI at the forefront of next-generation TB screening and diagnostic tools.

Our commitment to the next generation of TB researchers is a cornerstone of the SATVI postgraduate programme. In addition to our investment in training a highly skilled group of MSc and PhD students and post-doctoral fellows to be the innovators and TB research leaders of tomorrow, we look to our own Breede Valley community to sensitise the youth to the possibilities of a career in science and research on the African continent.

Looking forward, SATVI is well positioned to weather the challenges that 2025 may bring. Our contribution to an expanding portfolio of TB vaccine trials reflects the dedication of the entire SATVI team, and the continued trust of our many collaborators and diversified funder base.

Professor Mark Hatherill
Director, SATVI

senior clinical leadership

EXECUTIVE COMMITTEE

PROFESSOR MARK HATHERILL, DIRECTOR

Dr **Mark Hatherill** (MD, FCPaed) is a clinical triallist, trained as a specialist paediatrician, who is active in the design and implementation of innovative trials of new tuberculosis (TB) vaccines and preventive strategies, through several consortia. His academic focus includes translational evaluation of new biomarkers and screening tests for TB, and clinical development of novel TB vaccine candidates. He is a full member of the Institute of Infectious Disease and Molecular Medicine (IDM) at the University of Cape Town (UCT), and the South African Principal Investigator of the Regional Prospective Observational Research in Tuberculosis (RePORT) South Africa Consortium.

Dr Hatherill is funded by institutional research grants from the Gates Medical Research Institute, the South African Medical Research Council (SAMRC), the US National Institutes of Health (NIH) and Civilian Research and Development Foundation (CRDF), and the European and Developing Countries Clinical Trials Partnership (EDCTP).

PROFESSOR TOM SCRIBA,

Dr **Tom Scriba** (PhD) directs the Clinical Immunology Laboratory at SATVI. He was trained in biological sciences at Stellenbosch University and obtained a DPhil (PhD) in T-cell immunology at Oxford University. He returned to South Africa in 2006 to complete a postdoctoral fellowship in paediatric and clinical immunology in TB and vaccinology at the IDM, UCT.

Dr Scriba's research interests include immuno-pathogenesis of infectious disease, and in particular *Mycobacterium tuberculosis (M.tb)*, development of immuno-diagnostics, development of novel TB vaccines, discovery of immune correlates of risk of TB disease and correlates of protection against *M.tb* infection and TB disease.

Dr Scriba is a full member of the IDM and of the Collaboration for TB Vaccine Discovery of the Gates Foundation (GF), and is funded by competitive grants from the GF, the SAMRC, Open Philanthropy, the Wellcome Trust, the US NIH and the European Union.

DR MASOODA KASKAR

Dr **Masooda Kaskar** joined SATVI's senior leadership team in 2016 to advance organisational excellence and drive innovation and growth. Her leadership experience spans corporate, public and philanthropic sectors, with a focus on strategic business development, governance and operations. In her current role she is a key driver of SATVI's transformation efforts and risk management plans to ensure the growth and long-term sustainability of the organisation.

Dr Kaskar previously occupied several senior leadership positions in the pharmaceutical industry. At Novartis she was instrumental in developing and implementing transformational growth plans that resulted in establishing Novartis's leadership position within the industry. She holds an MBChB degree from UCT and an MBA degree from UCT's Graduate School of Business.

MARWOU DE KOCK,

Marwou de Kock holds a master's degree in clinical research administration from UCT, as well as degrees in biomedical science and laboratory management. She has worked at SATVI since 2002 and has intricate knowledge of the site, the people and procedures in the laboratory, the clinical operations, and community engagement. She helped establish the SATVI Field Site Laboratory and developed it into a world-class facility that received SANAS accreditation in 2010. Ms de Kock is responsible for managing the SATVI Field Site, overseeing and managing service delivery for all operations, and coordinating and implementing multiple research projects.

CLINICAL INVESTIGATORS

PROFESSOR ELISA NEMES

Dr **Elisa Nemes** completed a PhD in HIV-specific T-cell immunology in Italy and France in 2008. She then worked on paediatric immune responses to HIV and TB in Cameroon. In 2011 Dr Nemes joined SATVI, where she has been involved in basic immunology studies; the development of immuno-diagnostics and clinical trials of new TB vaccines; studies of host correlates of risk of TB disease and correlates of protection from M.tb infection and TB disease in infants, adolescents and adults; and studies of BCG/TB immune reconstitution inflammatory syndrome (IRIS) in HIV-positive children. She is funded by competitive grants from the US NIH and the Gates Foundation. Dr Nemes was promoted to full professor ad hominem in 2025 and became a full member of the IDM in 2020.

ASSOCIATE PROFESSOR MICHÈLE TAMERIS

Assoc. Prof **Michèle Tameris** graduated from UCT with an MBChB degree in 1980. For many years she worked in the public health sector, in Cape Town and in Worcester. In 2003 she joined SATVI as a clinical researcher; she was promoted ad hominem to Senior Clinical Researcher in January 2019, and in January 2022 to Chief Research Officer, with the title of Associate Professor. Since 2005 she has been an investigator on all 34 vaccine trials of 11 candidate TB vaccines that have been conducted at SATVI, including 13 as principal investigator.

Prof Tameris has been awarded two Wellcome Trust International Engagement awards (2012 and 2014) for projects using drama to improve community understanding of TB research and remains actively involved in community engagement and advocacy programmes. She is a member of the UCT IDM Education Committee and the Stop TB Partnership Working Group on New Vaccines, leading the Advocacy sub-committee. She has served on two DSMBs and is currently clinical ethics advisor on the TBVAC-Horizon project.

ASSOCIATE PROFESSOR DR ANGELIQUE KANY KANY LUABEYA

Dr **Angelique Kany Kany Luabeya** graduated as a medical doctor in 1996 from the University of Kinshasa (Democratic Republic of Congo) and holds a master's degree in epidemiology from the London School of Hygiene and Tropical Medicine (LSHTM).

She joined SATVI in 2009 as a clinical investigator and has been involved as principal investigator in the implementation and conduct of the clinical trials of several TB vaccines (AERAS C035-456, IDRI-TBVPx-203, VPM1002-ZA-2.13TB, BCG REVAX and MTBVAC) in healthy adults and adolescents, TB patients and newborn infants.

Dr Luabeya led as SATVI principal investigator on two COVID-19 vaccine trials, the ENSEMBLE study and the SISONKE trial, which vaccinated healthcare workers in South Africa. She also contributed to the implementation of the NOVAVAX COVID-19 vaccine study. She was promoted to chief research officer in 2020. Dr Luabeya is the principal investigator on several diagnostic studies including TB case-finding by oral swab PCR, molecular confirmation of TB treatment and *M.tb* correlates of risk using molecular epidemiology, conducted in collaboration with the University of Washington and the Columbia University Mailman School of Public Health.

DR JUSTIN SHENJE, CHIEF RESEARCH OFFICER

Dr **Justin Shenje** graduated as a medical doctor from the University of Zimbabwe in 2004, then completed a master's degree in clinical epidemiology at the University of Pretoria, before joining the SATVI team as a clinical investigator in 2015. He has been an investigator on two groundbreaking TB drug clinical trials, the A5343 and A5349 studies. The A5343 study showed that

Delamanid and Bedaquiline, two new anti-TB drugs, can be safely combined in the treatment of MDR TB; and the A5349 study showed that a four-month Rifapentine-based drug-sensitive TB regimen was non-inferior to the standard six-month drug-sensitive treatment regimen.

Dr Shenje is principal investigator on a number of ongoing studies, including the A5300B study, which evaluates the effectiveness of the use of Delamanid in TB prophylaxis of MDR TB household contacts; the A5356 study, which seeks to evaluate the safety and efficacy of two linezolid-based MDR TB treatment regimens; the BNT164-02 phase 1 study, which investigates the safety and immunogenicity of two novel mRNA TB vaccines; and the A5406 study, which seeks to describe the pharmacokinetics of a twice-a-day Dolutegravir dosing regimen in patients with drug-sensitive pulmonary TB and HIV co-infection and on a Rifapentine TB treatment regimen.

DR SIMON MENDELSOHN, CHIEF RESEARCH OFFICER

Dr **Simon Mendelsohn** graduated from the University of Cape Town as a medical doctor in 2011. While on a Rhodes Scholarship he read for two master's degrees at the University of Oxford, in Immunology (2015) and International Health and Tropical Medicine (2016) and obtained a Diploma in Tropical Medicine and Hygiene from the Royal College of Physicians (London). He has experience in HIV and TB clinical medicine; most recently with Médecins Sans Frontières, implementing HIV and TB programmes in Malawi prisons.

Dr Mendelsohn joined SATVI as a clinical investigator in 2017, and in 2022 completed his PhD in Clinical Science and Immunology, which evaluated host-blood gene signatures for the diagnosis and prognosis of pulmonary TB. He is a Senior Researcher and Fellow of the Institute of Infectious Disease and Molecular Medicine, with a research focus on new tests for diagnosing *M.tb* infection and early (pre-symptomatic) TB disease, and on biomarkers for guiding TB preventive and curative treatment.

DR NICOLETTE TREDOUX, RESEARCH OFFICER

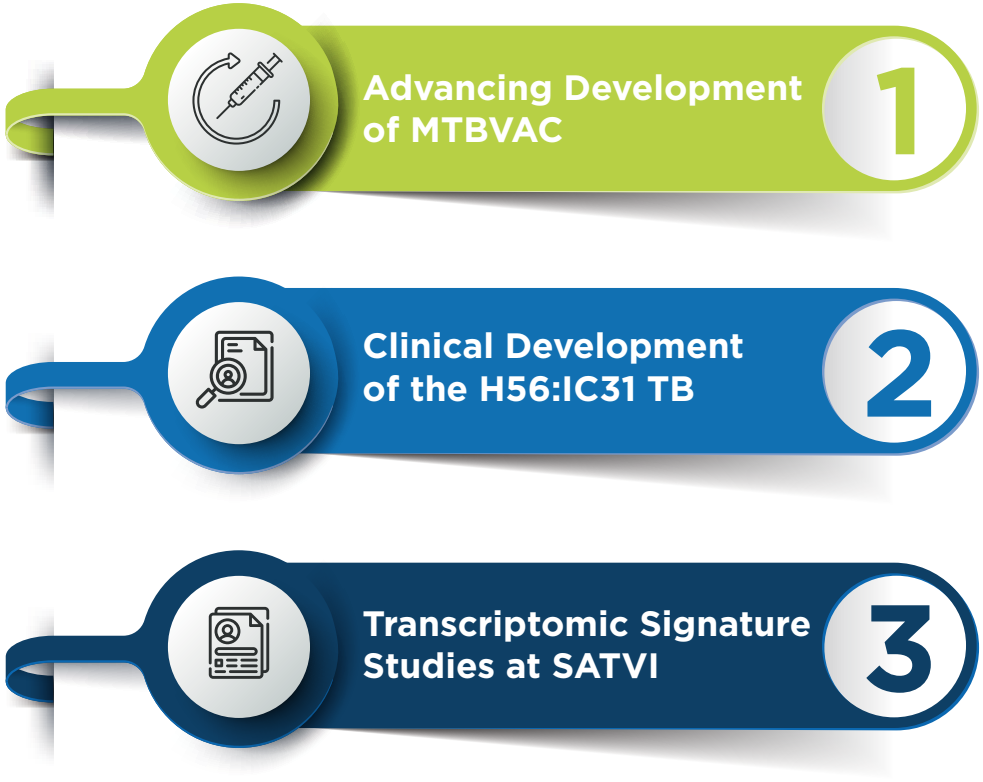
Dr **Nicolette Tredoux** graduated from the University of Stellenbosch in 1998 with an MBChB degree. She worked for many years in the public and private sector in Worcester and Robertson, both as a general practitioner and as a research medical officer. She obtained a postgraduate diploma in occupational medicine at Stellenbosch University in 2015. She is currently studying for her MSc in Clinical Epidemiology at the University of Stellenbosch. Dr Tredoux joined SATVI in 2021 as a part-time clinical investigator and has been working full-time since September 2022. She is principal investigator on two new studies due to start in the first quarter of 2025: the C113 IMAGINE trial, which will evaluate the safety and efficacy of a novel TB vaccine in the prevention of tuberculosis disease in adolescents and adults, and A5409 (RAD TB), which will evaluate the safety and efficacy of different combinations of TB drugs for the treatment of DS Tuberculosis.

DR THAKIERA ALLIE, CLINICAL INVESTIGATOR

Dr **Thakiera Allie** graduated as a medical doctor with a Bachelor of Medicine and Bachelor of Surgery (MBChB) from Stellenbosch University in 2020. Thereafter she conducted an internship in Pietermaritzburg, KwaZulu-Natal, where she rotated through different departments gaining valuable clinical experience.

Dr Allie completed her medical community service in 2023 at the Worcester Community Day Centre (CDC), as well as at the Worcester Hospital. Since joining SATVI she has been sub-investigator on several clinical trials. She is originally from Worcester and is deeply rooted in this community.

strategic highlights



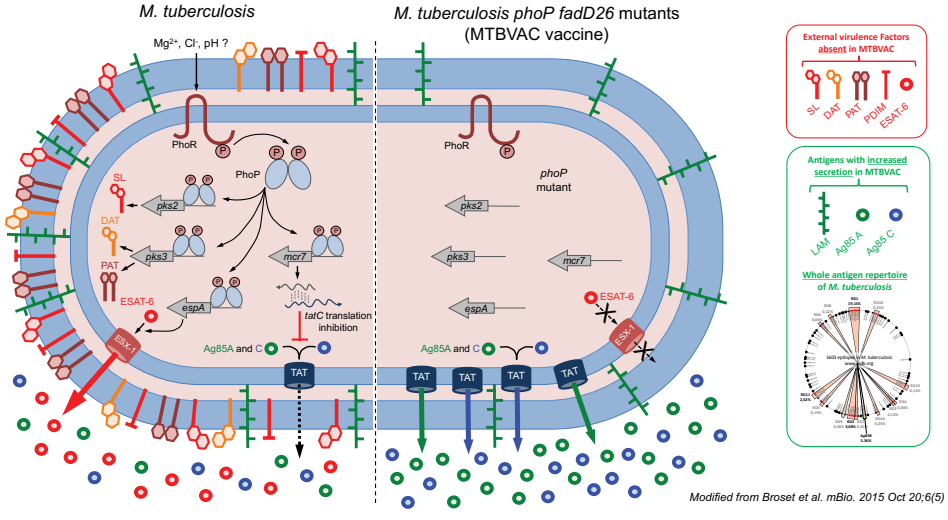
1. SATVI ADVANCING DEVELOPMENT OF MTBVAC: A NOVEL LIVE-ATTENUATED TUBERCULOSIS VACCINE CANDIDATE

Tuberculosis (TB) remains a significant global health challenge despite decades of prevention efforts. The Bacille Calmette-Guérin (BCG) vaccine, developed nearly a century ago from *Mycobacterium bovis*, has demonstrated variable efficacy worldwide, creating an urgent need for more effective alternatives.

Among promising candidates, MTBVAC stands out as the first live-attenuated vaccine derived from a human strain of *Mycobacterium tuberculosis (M.tb)* to enter clinical trials. SATVI has made critical contributions to MTBVAC development, from early safety studies to large-scale efficacy trials

MTBVAC: ORIGINS AND DESIGN

MTBVAC emerged from groundbreaking research conducted at the University of Zaragoza, Spain, where Dr. Carlos Martín and his colleagues engineered a genetically-modified version of human *Mtb* in 2008.



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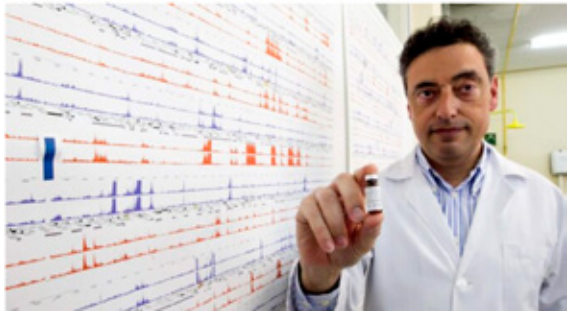


Professor Carlos Martin, University of Zaragoza.

Unlike BCG, which derives from the bovine tuberculosis pathogen, MTBVAC was created from a human strain of M.tb through the deletion of two key virulence genes – phoP and fadD26 – rendering the organism safe while preserving its immunogenic properties. This approach aimed to provide broader protection against TB than BCG, by maintaining the comprehensive antigenic profile of the human pathogen

MTBVAC 203 study team.

SATVI: A LEADER IN TB VACCINE CLINICAL RESEARCH

Since its establishment in 2001, in addition to studies in adults, SATVI has conducted 13 tuberculosis vaccine trials in infants and children, involving four novel TB vaccine candidates and the BCG vaccine. The first big study which SATVI conducted compared the efficacy between intradermal and percutaneous BCG administration in 11 680 babies.

This firmly established SATVI as a TB research group for future large-scale evaluations of vaccine candidates. Subsequent trials with candidates including MVA85A, AERAS 402, VPM1002 and H4:IC31 positioned SATVI as a premier site for clinical TB vaccine research in children as well as adults. This extensive experience made SATVI the natural partner for testing the efficacy and safety of the MTBVAC vaccine in a high-burden TB setting, particularly among infants and vulnerable populations in South Africa.

Professor Mark Hatherill addressed the UN High Level Meeting on TB, September 2023.

BABY STEPS: THE PHASE 1B TRIAL IN INFANTS

Following the first-in-human trial of MTBVAC in adults conducted by Francois Spertini and colleagues in Switzerland, SATVI conducted the first MTBVAC trial in infants in Worcester, South Africa between 2015 and 2018. This randomised, double-blind, dose-escalation study evaluated safety and immunogenicity in HIV-unexposed newborns.

Following a preliminary safety assessment in 18 adults, 36 infants were enrolled across three escalating dose cohorts: low (2.5×10^3 CFU), intermediate (2.5×10^4 CFU), and high (2.5×10^5 CFU), with a 3:1 randomisation ratio against BCG controls. An independent Data and Safety Monitoring Board (DSMB) reviewed day 28 safety and reactogenicity data from adult participants before infant enrolment commenced and subsequently reviewed each infant dose cohort before escalation to higher doses. The results were promising; MTBVAC demonstrated an acceptable safety profile across all doses with no serious adverse vaccine-related events. Reactogenicity was dose-dependent, but comparable to BCG. Immunologically, MTBVAC induced dose-dependent Th1-type immune responses characterised by polyfunctional $CD4^+$ T cells, with the highest dose eliciting significantly stronger responses than BCG.

THE QUANTIFERON DILEMMA: AN UNEXPECTED CHALLENGE

During the first infant trial, researchers identified an unanticipated phenomenon: MTBVAC recipients showed higher rates of QuantiFERON-TB Gold (QFT) test conversion compared to BCG recipients.

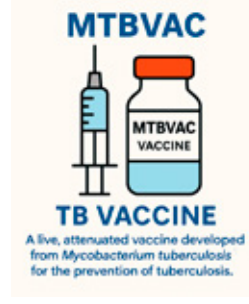
Professor Michèle Tameris noted: *"I recall during this time noting the positive QFT results received and referring the child for TB preventative therapy (TPT) – but then realising that there were far more positive QFT results overall than we expected from our experience in this population. Once unblinding occurred at the end of follow-up of each dose cohort, we realised that this was most likely a vaccine effect, and not a result of TB exposure."*

This observation presented a significant diagnostic challenge, as the QuantiFERON test, which measures interferon-gamma release in response to TB-specific antigens, could not differentiate between a vaccine-induced immune response and true *M.tb* infection. This finding necessitated development of alternative diagnostic tests for *M.tb* sensitisation, as well as adjusted criteria for preventive therapy in MTBVAC recipients.

Subsequent Trials and Diagnostic Solutions

Building on lessons from the initial study in infants, SATVI conducted two key trials designed to optimise MTBVAC dosing and develop companion diagnostics.

MTBVAC 202: DOSE REFINEMENT IN INFANTS



In this Phase 2a randomised, double-blind trial, 99 BCG-naïve, TB-unexposed infants were enrolled across three MTBVAC dose cohorts (2.5×10^4, 2.5×10^5, or 2.5×10^6 CFU) or BCG control. Key findings confirmed favourable safety profiles across all MTBVAC doses, with no serious adverse vaccine-related events.

Notably, the 2.5×10^5 CFU dose was associated with fewer solicited adverse events, including reduced injection site reactogenicity compared to BCG. Immunogenicity analysis showed that the 2.5×10^5 and 2.5×10^6 CFU doses induced similar CD4 T-cell response magnitudes, both exceeding the immunogenicity of BCG at 2-8 $x10^5$ CFU.

MTBVAC 050: SAFETY AND IMMUNOGENICITY IN ADULTS

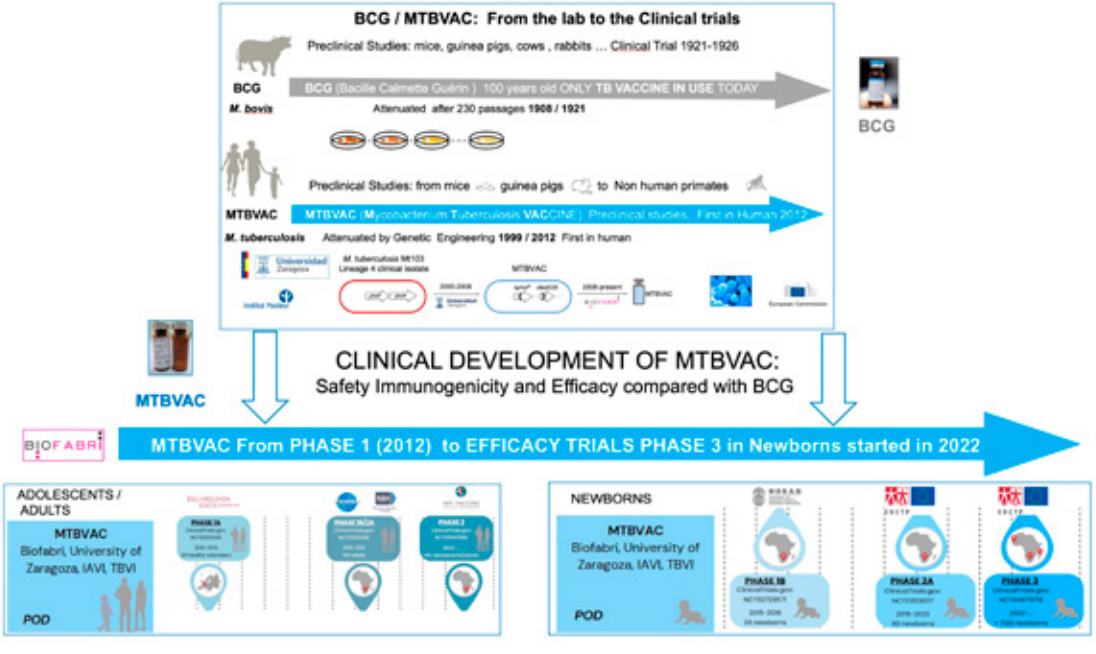
SATVI conducted a Phase 1b/2a trial, enrolling 144 HIV-negative adults aged 18-50 years, all previously BCG-vaccinated, in parallel with the MTBVAC 202 trial conducted in infants. Participants were stratified by QuantiFERON status and received either one of four MTBVAC doses (5×10^3, 5×10^4, 5×10^5, or 5×10^6 CFU) or standard-dose BCG revaccination.

Results showed acceptable tolerability across all MTBVAC doses with dose-dependent local reactogenicity. The 5×10^5 and 5×10^6 CFU doses induced stronger Th1 cytokine-expressing CD4 T-cell responses than BCG in both QFT-negative and QFT-positive individuals.

The CFP-10-Free IGRA: Addressing Diagnostic Challenges

To address the diagnostic conundrum created by MTBVAC-induced QFT conversions, SATVI researchers helped develop and evaluate the CFP-10-free interferon-gamma release assay (IGRA). This modified diagnostic test aimed to distinguish between vaccine-induced responses and actual M. tb infection.

The results showed that MTBVAC vaccination effectively induced T-cell responses to ESAT-6 and CFP-10 (and probably EspC), causing conversion of both standard QFT-Plus and the experimental CFP-10-free IGRA in vaccinees. While the CFP-10-free IGRA performed suboptimally in differentiating early, post-injection vaccine-induced responses from infection-induced responses, a promising pattern emerged: by one-year post-vaccination, most MTBVAC recipients had reverted to negative CFP-10-free IGRA status, suggesting potential utility for detecting true *M.tb* infection after this timepoint. The study demonstrated that CFP-10-free IGRA exhibited similar sensitivity and specificity to QFT-Plus in distinguishing TB patients from healthy individuals, supporting its further development as a companion diagnostic for future MTBVAC implementation.



ADVANCING TO PHASE 3: THE PATH TO LICENSURE

Based on cumulative safety and immunogenicity data, the 5×10^5 CFU dose of MTBVAC was selected for further clinical development. In October 2023, SATVI began enrolment for a pivotal Phase 3 trial as part of a multi-centre effort across six African sites. By December 2024, 949 infants had been enrolled at SATVI alone, with follow-up to continue until all participants complete two years of observation – anticipated to conclude in 2028.

In recognition of the importance of evaluating MTBVAC in populations with high TB-HIV co-infection rates, SATVI also participated in a trial in HIV-uninfected and HIV-infected adolescents and adults led by the HIV Trials Network (HVTN). Further expanding the evidence base, SATVI will participate in a pivotal Phase 2b efficacy trial of MTBVAC in IGRA-positive adolescents and adults starting in mid-2025.

SATVI's Comprehensive Contribution

Throughout the MTBVAC development pathway, SATVI has made substantial contributions to multiple clinical trials spanning phase 1/b through to phase 3 studies, enrolling 172 adults, including both IGRA-positive and IGRA-negative individuals, and people living with HIV; and 1 161 BCG-naïve newborns, including HIV-exposed but uninfected infants. These trials have consistently demonstrated MTBVAC's promising safety profile while generating critical immunogenicity data that informed dose selection for the ongoing Phase 3 efficacy trial.

CONCLUSION

SATVI's systematic approach to evaluating MTBVAC, from initial infant safety studies through to large-scale efficacy trials, has been instrumental in advancing this promising vaccine candidate. Our research has not only confirmed MTBVAC safety and enhanced immunogenicity in comparison with BCG, but also addressed crucial implementation challenges such as diagnostic differentiation between vaccination and infection.

The ongoing infant Phase 3 trial, and the pending adult Phase 2/b trial, represent the culmination of several years of painstaking clinical development that will determine whether MTBVAC can fulfill its promise as a more effective alternative to BCG, potentially transforming global TB prevention strategies after a century of reliance on this effective yet imperfect vaccine.

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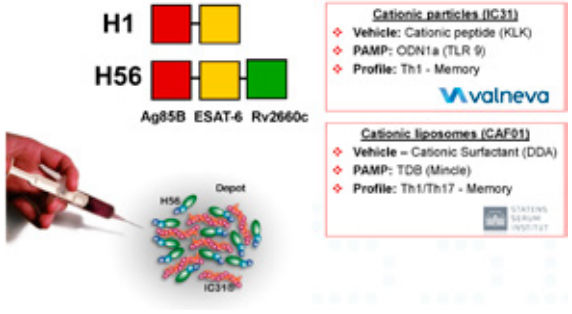
2. INSIGHTS FROM THE CLINICAL DEVELOPMENT OF THE H56:IC31 TB VACCINE

H56:IC31, a subunit tuberculosis (TB) vaccine developed by the Statens Serum Institut (SSI) in Denmark, was designed to provide protection across multiple stages of *Mycobacterium tuberculosis (M.tb)* infection and TB disease.

The vaccine comprises a fusion protein of three *M.tb* antigens, Ag85B, ESAT-6 and Rv2660c, formulated with the IC31 adjuvant. Ag85B is involved in cell-wall synthesis and expressed early during infection; ESAT-6 is a virulence factor absent in BCG strains; and Rv2660c is associated with latent infection. Formulated with the IC31 adjuvant, H56 was designed to elicit durable Th1-type immune responses, thought to be essential for controlling *M.tb*.

Preclinical studies demonstrated that H56:IC31 vaccination conferred protection against *M.tb* infection and reactivation in mice and nonhuman primates, reducing bacterial burden and lung pathology; this provided strong justification for clinical development.



PHASE 1: FIRST-IN-HUMAN CLINICAL TRIAL[1]

The initial clinical evaluation of the H56:IC31 vaccine was conducted by the South African Tuberculosis Vaccine Initiative (SATVI) between 2011 and 2012 in Worcester, South Africa. This open-label, dose-escalation Phase I trial enrolled 25 healthy adults, both *M.tb*. infected and -uninfected, to assess safety and immunogenicity. Participants received three intramuscular injections of either a low (15 µg) or high (50 µg) dose of H56:IC31 at 56-day intervals.

The vaccine was well tolerated, with no serious adverse events reported. Transient cardiovascular events were observed in 36% of participants but resolved without intervention. Immunologically, the vaccine induced antigen-specific IgG responses and Th1 cytokine-expressing CD4+ T cells. Notably, *M.tb*-infected individuals exhibited higher frequencies of H56-induced CD4+ T cells compared to uninfected participants, suggesting the vaccine's potential to boost pre-existing immune responses.

PHASE 2: DOSE SELECTION AND SCHEDULE OPTIMISATION

Following encouraging Phase 1 results, a larger Phase 2 dose-finding trial was conducted at SATVI. A total of 98 HIV-negative participants, stratified by *M.tb*. infection status, were randomised to receive two or three doses of the H56:IC31 vaccine at varying antigen concentrations (5 µg, 15 µg, or 50 µg).

The vaccine continued to demonstrate an acceptable safety profile, with no serious adverse vaccine-related events. Immunogenicity analyses showed that two or three doses at the lowest concentration induced durable, polyfunctional CD4+ T-cell responses in both *M.tb*-infected and uninfected participants. The findings supported the selection of the low-dose formulation for further clinical evaluation.

PHASE 2B: PREVENTION OF RECURRENCE TRIAL[3]

Given the early safety and immunogenicity data, the next critical step was an efficacy proof-of-concept study, which would evaluate whether the H56:IC31 vaccine could reduce TB disease recurrence after successful treatment.

Prevention of TB recurrence (POR) after successful treatment represents a novel and pragmatic strategy to evaluate the efficacy of TB vaccines, offering a faster, more efficient pathway to assess protective immunity in a small, high-risk population compared to traditional, large and costly trials evaluating prevention of primary TB disease in the general population.

The POR TB study, a Phase 2/b randomised, placebo-controlled trial, was conducted at six sites in South Africa and Tanzania. It enrolled 831 HIV-negative adults who had completed more than five months of standard therapy for drug-susceptible pulmonary TB. Participants were randomised to receive two doses of the H56:IC31 vaccine or a placebo, spaced 56 days apart. They were followed for one year post-vaccination, with recurrent TB carefully categorised into either relapse and reinfection using whole-genome sequencing of baseline and recurrent Mtb isolates.

Importantly, a favourable safety profile was maintained for the vaccine. Mild to moderate local reactions at the injection site were more common in vaccinees, but no serious adverse treatment-related events were observed.

A 050/H56:IC31 Study team, Worcester.

While the H56:IC31 vaccine induced robust antigen-specific T-cell and antibody responses, it did not reduce the rate of TB recurrence in comparison to the placebo. The estimated vaccine efficacy was –73.8% (95% CI –246.9 to 9.8; p=0.10). No efficacy was observed for reinfection; but an unexpected excess of relapse cases was noted among vaccinees, although this finding was not statistically significant. The study was not designed with sufficient statistical power to allow the detection of significant differences between relapse and reinfection.

Several factors may explain these findings. It is possible that the immunological environment following TB disease and treatment is insufficiently restored to respond optimally to vaccination. Alternatively, vaccination may have influenced the reactivation of persisting *M.tb* bacilli in a subset of individuals.

The H56:IC31 POR TB trial was the first to test a subunit vaccine administered at the end of TB treatment for prevention of recurrence, providing critical insights for future vaccine strategies. The findings highlight the complexity of immunological recovery following TB treatment and raise important questions about how vaccination might interact with residual bacterial burden or immune perturbations.

Based on these findings, the clinical development of the H56:IC31 vaccine was terminated. Although the primary efficacy endpoint was not met, the trial demonstrated that post-treatment vaccination is feasible, safe, and capable of generating strong immunological responses. These results contribute valuable knowledge to the field and will inform the design of future POR and therapeutic vaccine trials.

SATVI's involvement in the H56:IC31 vaccine trials is a reflection of our capacity to conduct rigorous clinical evaluations and our commitment to advancing TB vaccine research through innovative trial design. The lessons learned from these studies will inform the approach to future trials of other candidates and contribute to the global effort to develop effective TB vaccines.

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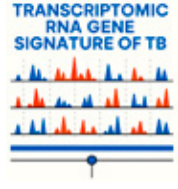
3. A REVIEW OF TRANSCRIPTOMIC SIGNATURE STUDIES AT SATVI



For the past 15 years, SATVI scientists have made substantial advances in the development of blood transcriptomic signatures.

This work began with the search for biomarkers that could identify individuals, particularly among those with *Mycobacterium tuberculosis (M.tb)* infection, who are at highest risk of developing tuberculosis (TB) disease and who would benefit from targeted intervention.

The completion of the **Adolescent Cohort Study (ACS)**, which followed healthy teenagers at high schools in Worcester, provided the first opportunity to develop transcriptomic signatures of TB risk **(Figure 1)**.

Teenage participant in ACS study.

A **blood transcriptomic signature is a** set of specific gene expression patterns detected in a person's blood, indicating that they may have existing TB disease. Such a signature may also predict the likelihood of a healthy person developing TB in the future.

These signatures are identified using high-throughput technologies such as RNA sequencing or microarrays, which quantify the expression levels of thousands of messenger RNAs (mRNAs) in blood samples. Once a signature is identified, it can be adapted for measurement by polymerase chain reaction (PCR), which is significantly cheaper, simpler, and faster than RNA sequencing or microarrays.

Transcriptomic signatures have the potential to serve as non-sputum-based biomarkers, enabling earlier, more accurate, and less invasive TB diagnosis and risk stratification, and helping to guide preventive interventions and treatment monitoring.

The ACS study collected blood in PAXgene tubes from thousands of participants, enabling RNA extraction to measure unique gene-expression patterns. In 2010, Willem Hanekom and Tom Scriba received a grant from the Gates Foundation, in collaboration with Alan Aderem and Daniel Zak at Seattle Biomedical Research Institute, to discover combinations of genes that are upregulated or downregulated specifically in ACS participants who ultimately develop TB disease.

Similarly, the Gates Foundation awarded another grant to Willem Hanekom and colleagues in the **Grand Challenges 6 (GC6) consortium**, including Stefan Kaufmann, Gerhard Walzl and others, to discover transcriptomic signatures in the GC6-74 study, which enrolled household contacts of TB patients from multiple African countries, including South Africa, Ethiopia, The Gambia and Uganda.

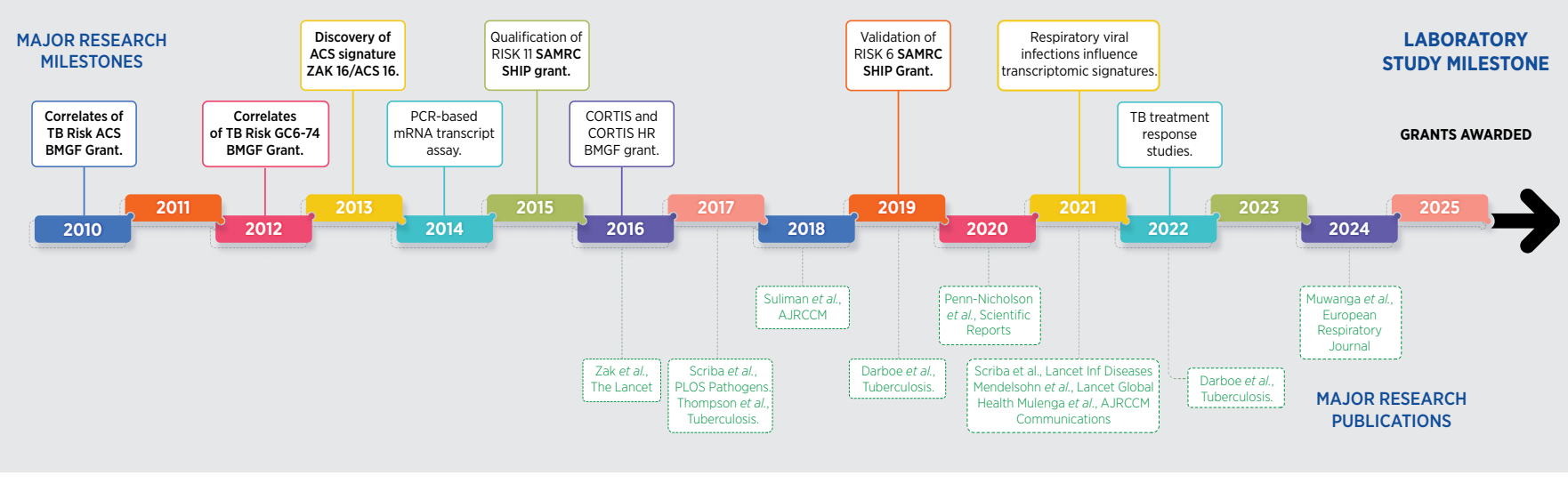


Figure 1. Timeline of SATVI's contributions to transcriptomic TB signature studies and scientific publications during the last 15 years.

A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Careful analyses of whole transcriptomes generated by RNA-seq from ACS participants led to the discovery of the first transcriptomic correlate of risk (COR) of TB, named **ACS-COR** or **Zak-16** (reflecting the 16 genes in the signature).

This signature was subsequently adapted for measurement by microfluidic real-time quantitative polymerase chain reaction RT-qPCR, allowing validation in the GC6 study and leading to a seminal publication in *The Lancet* (Zak, Penn-Nicholson, Scriba *et al.*, 2016).

More detailed analysis of gene expression patterns also allowed characterisation of sequential biological events and inflammatory processes that occur when individuals progress from M.tb infection to TB disease (**Figure 2**), published in *PLoS Pathogens* (Scriba, Penn-Nicholson, Shankar *et al.*, 2017).

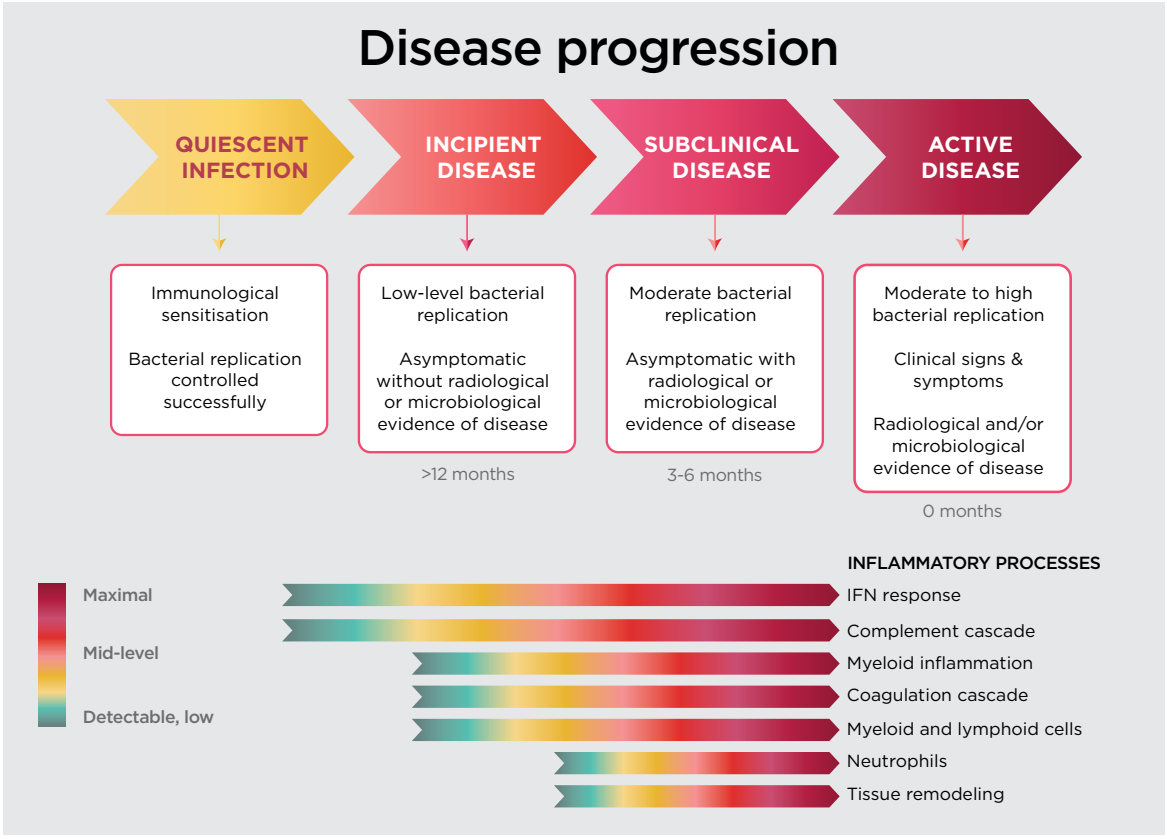


Figure 2. Biological and inflammatory processes during progression from infection to disease.

Similarly, detailed analysis of transcriptomes from GC6 cohort participants from diverse African populations led to the discovery of the **RISK4** signature, which was also adapted for PCR measurement and validated in the ACS cohort (Suliman and Thompson *et al.*, *AJRCCM* 2018).

A major consideration in evaluating transcriptomic signature performance was the potential effect of underlying HIV infection, as most signatures included genes stimulated by interferons, molecules known to be upregulated during viral infections. The effect of HIV on transcriptomic signatures was specifically addressed in a study that formed the basis of PhD student Fatoumatta Darboe's PhD project, supported by the South African Medical Research Council (SA-MRC) through its Strategic Health Innovation Partnership (SHIP) (Darboe *et al., Frontiers Immunology* 2019).

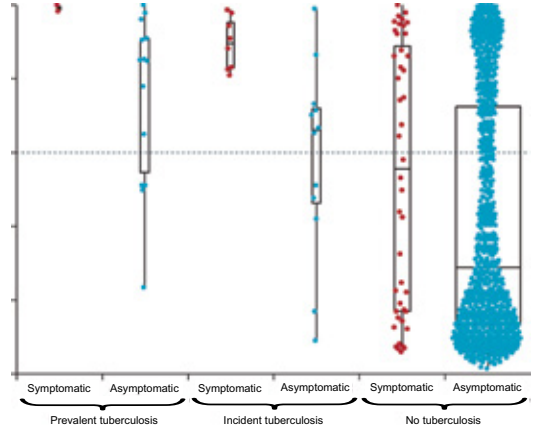
The SATVI transcriptomics team, taken at a progress meeting for the SA-MRC SHIP project in 2016. Back: Mark Hatherill, Michelle Fisher, Tom Scriba. Front: Fatoumatta Darboe, Sara Suliman, Adam Penn-Nicholson, Mbandi Kimbung.

These successes culminated in an opportunity to use a transcriptomic COR signature to identify individuals at high risk of developing TB, enabling targeted TB preventive therapy (TPT). Mark Hatherill secured a trial planning grant from the US National Institutes of Health (NIH) and led the design of the **Correlate Of Risk Targeted Intervention Study (CORTIS)**, with statistical support from Andrew Fiore-Gartland. In the laboratory, Tom Scriba, Adam Penn-Nicholson, Kate Hadley, Nicole Bilek, Zwai Erasmus and Fatoumatta Darboe converted the ACS-COR signature into RISK11, which could be measured more efficiently and which could be reproduced with a microfluidic RT-qPCR test with robotic RNA isolation from blood for much higher throughput processing.

Supported by the Gates Foundation and the SA-MRC, the CORTIS trial screened over 20 000 adults at five sites in South Africa, and enrolled RISK11-positive participants, at higher risk of developing TB disease, for randomisation to once-weekly Isoniazid and Rifapentine for 12 weeks (3HP), or no treatment. A subset of RISK11-negative participants was also randomly assigned to no treatment. Participants were screened at baseline for existing TB and followed for 15 months to monitor for the development of new TB disease.

The results of the trial showed that the RISK11 signature could distinguish between individuals with existing TB, those who developed new TB within 12 months of testing, and those who remained healthy. However, providing 3HP treatment to RISK11-positive individuals, after excluding those with baseline TB, did not significantly reduce progression to new TB over 15 months (Scriba and Fiore-Gartland *et al., The Lancet Infectious Diseases* 2021).

As part of his PhD project, Simon Mendelsohn assessed the performance of the RISK11 signature for diagnosing existing TB and predicting progression to new TB in people living with HIV in the CORTIS-HR study. The results were somewhat surprising, as the diagnostic and prognostic performance of RISK11 was similar in both HIV-negative and HIV-positive individuals (Mendelsohn *et al., The Lancet Global Health* 2021).



Signature scores for the RISK11 transcriptomic signature, measured by RT-qPCR at baseline (study enrolment) in people living with HIV from the CORTIS-HR study. A high signature score, seen primarily in symptomatic individuals with prevalent TB, or in those who ultimately developed TB during study follow-up (incident tuberculosis), indicates a high level of systemic inflammation. Those with asymptomatic disease had intermediate signature score levels, while controls, who did not develop TB during the CORTIS-HR study, had the lowest scores.

In the meantime, the global blood biomarker research community pushed for developing more parsimonious (simpler) signatures, as measuring gene expression levels of just a handful of genes is much cheaper, faster, and more efficient than using signatures that include many genes. This informed the development of **RISK6**, a PCR-based signature that was extensively validated for its performance as a diagnostic, prognostic and treatment-monitoring biomarker (Penn-Nicholson, Kimbung, Thompson and Mendelsohn *et al., Scientific Reports* 2020).

A PhD research project conducted by Simon Mendelsohn examined whether the findings from CORTIS and CORTIS-HR were unique to RISK11. He measured a set of eight parsimonious signatures, all by microfluidic RT-qPCR, demonstrating that multiple transcriptomic signatures yielded similar diagnostic and prognostic performance (Mendelsohn *et al., Communications Medicine* 2022).

The CORTIS trial also enabled further investigation of the effects of co-infection through a longitudinal sub study, involving participants who had blood samples collected at baseline, at month 3, and at month 12 for transcriptomic signature analysis, while nasopharyngeal and oropharyngeal swabs were collected at baseline and assessed for respiratory pathogens. By interrogating the longitudinal signature results, as part of a PhD project, Humphrey Mulenga found that a substantial proportion of healthy individuals had transient elevation of transcriptomic signature scores. Interestingly, detection of respiratory viruses – such as influenza A, rhinovirus, seasonal coronavirus and adenovirus – was associated with significantly elevated transcriptomic signature scores (Mulenga, Musvosvi, Mendelsohn *et al., AJRCCM* 2021). The implications of this result are relevant because chronic and especially acute viral infections appear to reduce the specificity of the vast majority of transcriptomic signatures, which typically detect interferon-stimulated genes.

A PhD research project conducted by Vanessa Muwanga aimed to investigate how transcriptomic signatures could differentiate TB from other respiratory diseases in symptomatic patients seeking care. She analysed the diagnostic performance of 20 blood transcriptomic signatures for TB in participants from six African countries. While no signature met the criteria set out in the target product profile, several showed strong performance in specific countries. This work contributes to advancing TB diagnostics, particularly for difficult-to-diagnose populations such as those with sputum-scarce or paucibacillary TB (e.g. children, extrapulmonary TB) and in resource-limited settings.

Perhaps the most promising application of transcriptomic signatures lies in their potential as tools to monitor the host response to TB treatment. Exciting new data from three independent studies suggest that several transcriptomic signatures can predict TB relapse in treated patients who appear to have been cured. This research, building on our 15 years of experience with biomarker and gene expression research, is expected to have a significant impact on the TB field.

Overall, transcriptomic signature research has been a major engine room for training of postgraduate students, with four PhD students graduating over the years: Fatoumatta Darboe, Simon Mendelsohn, Vanessa Muwanga and Humphrey Mulenga. The work has also supported four postdoctoral fellowships, those of Adam Penn-Nicholson, Sara Suliman, Mbandi Kimbung and Denis Awany.

Ongoing transcriptomic signature research is likely to lead to further advances and contribute to ‘A world without TB’.

selection of clinical trials

TB VACCINES

A Phase 3 randomised, double-blind, placebo-controlled, multicentre clinical trial to assess the prophylactic efficacy, safety and immunogenicity of the investigational M72/AS01$_E$ *Mycobacterium tuberculosis (M.tb)* vaccine when administered intramuscularly on a 0,1-month schedule to adolescents and adults.

STUDY STATUS

RECRUITMENT COMPLETE, FOLLOW-UP PERIOD ONGOING

Sponsors

GATES MEDICAL RESEARCH INSTITUTE

wellcome

Investigator

Angelique Luabeya

Study Coordinator:

Fazlin Kafaar

A previous phase 2b trial showed that the M72/AS01$_E$ vaccine provided ~50% protection against TB in IGRA-positive, HIV-negative adults. This phase 3 trial aims to confirm efficacy and assess safety, immunogenicity and effectiveness in IGRA-negative and HIV-positive populations. The primary goal is demonstrating efficacy in IGRA-positive, HIV-negative individuals, with secondary objectives including safety and exploratory efficacy in other groups. The trial enrolled 20 000 participants across 54 sites in five countries, with two doses administered one month apart. Recruitment ended in April 2025, and follow-up is ongoing. Results may support global vaccine licensure.

M72/AS01$_E$ Study team.

CLINICALTRIALS.GOV IDENTIFIER: NCT 06062238

HVTN605/A5421: Evaluating the safety and immunogenicity of MTBVAC in adolescents and adults living with and without HIV in South Africa.

STUDY STATUS

COMPLETED

Funders

NIH DAIDS

NIH

NIH

Principal Investigator

Michèle Tameris

Study Coordinator:

Elizabeth Filander

This multisite study is evaluating the safety and immunogenicity of the MTBVAC vaccine in adolescents and adults living with and without HIV in South Africa. It consists of three cohorts, based on the participants' HIV status and (for people living with HIV) their CD4+ T-cell count and WHO clinical stage prior to ART initiation/re-initiation. Within each cohort, participants are being stratified into subgroups based on IGRA status and randomised to receive MTBVAC or BCG as per protocol, and followed for 48 weeks after vaccination.

HVTN Study team.

By 31 December 2024 cohort 1 was fully enrolled, and Cohort 2 still had nine HIV+, QFT- adolescents to enrol. Following the completion of Cohort 2 enrolment and 28 days of follow-up, the Safety Monitoring Board (SMB) will meet to decide if enrolment into Cohort 3 may proceed.

CLINICALTRIALS.GOV IDENTIFIER: NCT05947890

A multicentre, Phase 3, double-blind, randomised, active-controlled study to evaluate the efficacy and safety of VPM1002 in comparison to BCG in prevention of *Mycobacterium tuberculosis* infection in newborn infants.

STUDY STATUS

COMPLETED

Funder	Principal Investigator	Study Coordinator:
SERUM INSTITUTE OF INDIA PVT. LTD.	 Angelique Luabeya	 Elizabeth Filander

This Phase 3, randomised, double-blind study compared the efficacy, safety and immunogenicity of the VPM1002 vaccine to BCG SII in 6 940 newborns. Designed as a single-dose, active-controlled trial, it aimed to assess protection against *Mycobacterium tuberculosis (M. tb)* infection. However, an interim analysis (July 2023) led to early termination in October 2024 due to insufficient cases.

VPM 1002 study team.

CLINICALTRIALS.GOV IDENTIFIER: NCT04351685

BNT164-02: A Phase 1b/2a two-part, randomised, placebo-controlled, observer-blind, dose-finding evaluation trial to describe the safety, reactogenicity and immunogenicity of two investigational vaccines against active tuberculosis in BCG-vaccinated, HIV-negative subjects and people living with HIV.

STUDY STATUS

ONGOING

Funder	Investigator	Study Coordinator:
BIONTECH	 Justin Shenje	 Christel Petersen

Currently, the Bacillus Calmette-Guérin (BCG) vaccine remains the sole approved TB vaccine, despite conferring only partial protection. This dose escalation study seeks to evaluate the safety and immunogenicity of two novel mRNA TB vaccines, BNT164a1 and BNT164b1, both encoding immunogenic antigens of Mycobacterium tuberculosis.

The study is sponsored by BioNTech. Participants will receive three doses of either one of the two vaccines or a matching placebo and will be followed up for a duration of one year. The study commenced in July 2023, is progressing well and is scheduled to come to an end in May 2028.

CLINICALTRIALS.GOV IDENTIFIER: NCT05547464

BCG REVAX: A randomised, placebo-controlled, observer-blind Phase 2b study to evaluate the efficacy, safety and immunogenicity of BCG revaccination in healthy adolescents for the prevention of sustained infection with *Mycobacterium tuberculosis*.

STUDY STATUS

MANUSCRIPT PUBLISHED

Funder: GATES MEDICAL RESEARCH INSTITUTE

Investigator: 
Angelique Luabeya

Study Coordinator: 
Fazlin Kafaar

A Phase 2/b randomised, double-blind trial in South Africa assessed BCG revaccination for preventing sustained *M.tb* infection in 1 836 IGRA-negative, HIV-negative adolescents (10–18 years). Participants received either BCG (n=918) or a placebo (n=917). After 30 months, sustained IGRA conversion occurred in 62 (BCG) vs. 59 (placebo) participants, yielding a hazard ratio of 1.04 (95% CI: 0.73–1.48) and VE of −3.8% (95% CI: −48.3 –27.4). BCG induced Th1 CD4+ T-cell responses but showed no protective efficacy. Injection-site reactions were more frequent with BCG. Findings suggest BCG revaccination does not prevent sustained *M.tb* infection in this population.

READ STUDY RESULTS

CLINICALTRIALS.GOV IDENTIFIER: NCT04152161

TREATMENT STUDIES

Phoenix MDR Study: Protecting households on exposure to newly diagnosed index multidrug-resistant tuberculosis patients (PHOENIx MDR-TB).

STUDY STATUS

RECRUITMENT COMPLETE IN FOLLOWUP

Sponsor: GATES MEDICAL RESEARCH INSTITUTE

Funder: NIH National Institutes of Health

Principal Investigator: 
Justin Shenje

Study Coordinator: 
Libby Briel

This Phase 3 study aims to evaluate the efficacy and safety of Delamanid in comparison with Isoniazid in preventing active TB disease in high-risk household contacts (HHC) of MDR-TB patients. Participants were randomised to receive either Delamanid or Isoniazid, which they received for a duration of 26 weeks, and are being followed up for a period of 96 weeks. The primary outcome is the occurrence of either confirmed or probable TB at any time between enrolment and 96 weeks. The study started in the fourth quarter of 2019 and is now fully enrolled. The SATVI site enrolled 64 index cases and 153 HHCs.

CLINICALTRIALS.GOV IDENTIFIER: NCT03568383

Project to accelerate new treatments for tuberculosis (PAN-TB).

STUDY STATUS

DATA ANALYSIS

Sponsor and funder: Gates Foundation

Principal Investigator: 
Angelique Luabeya

Study Coordinator: 
Lisa Beyers

This Phase 2b/c trial tested two novel TB regimens (DBQS and PBQS) combining existing and new drugs (Bedaquiline, Delamanid, Pretomanid, Quabodepistat and Sutezolid) to shorten treatment for drug-sensitive TB (DS-TB) without resistance testing. The goal was to identify a pan-TB regimen for Phase 3. Using a two-stage design, it compared 4-month DBQS/PBQS against 6-month standard care in ~129 participants (18–65 years with DS-TB).

READ MORE ABOUT THIS STUDY

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

A5406: Pharmacokinetics and safety of double-dose Dolutegravir when used with Rifapentine for HIV-associated tuberculosis.

STUDY STATUS

RECRUITMENT COMPLETE (IN FOLLOW-UP)

Sponsor	Principal Investigator	Study Coordinator:
NIH National Institutes of Health	 Justin Shenje	 Libby Briel

Dorman *et al.*, 2021 were able to demonstrate that the 17-week Rifapentine, Isoniazid, Moxifloxacin and Pyrazinamide regimen was non-inferior to the standard first-line, 6-month anti-TB regimen for drug-sensitive TB. However, Rifapentine is a potent liver enzyme inducer and has been shown to reduce Dolutegravir drug concentrations. The study therefore set out to describe the pharmacokinetics of a dosage of 50 mg Dolutegravir twice daily, when co-administered with the 17-week Rifapentine-based regimen.

The study enrolled patients with newly diagnosed drug-sensitive pulmonary TB who also had HIV co-infection. Participants were put on the 17-week Rifapentine regimen and a Dolutegravir-based anti-retroviral therapy regimen and followed up for 48 weeks. Intensive pharmacokinetic samples were collected at week 8 and week 21, while sparse pharmacokinetic samples were collected at weeks 2, 4, 10, 14 and 17. The study aims to conduct a pharmacokinetic analysis to evaluate whether the twice-daily 50 mg Dolutegravir dose is sufficient when co-administered with Rifapentine. The study had an enrolment target of 30 participants and has completed enrolment, with the SATVI site having enrolled five participants, and is now in the follow-up phase.

CLINICALTRIALS.GOV IDENTIFIER: NCT05630872

A5356: Safety/tolerability of two Linezolid dosing strategies in combination with a short-course regimen for Rx of drug-resistant TB.

STUDY STATUS

RECRUITMENT COMPLETE (IN FOLLOW-UP)

Funder	Principal Investigator	Study Coordinator:
NIH National Institute of Allergy and Infectious Diseases	 Justin Shenje	 Libby Briel

Linezolid is a new, highly efficacious anti-TB drug, which in combination with other new anti-TB drugs has shown efficacy rates that exceed 90%. However, Linezolid is associated with myriad debilitating adverse events. This study aims to optimise Linezolid dosing by comparing two Linezolid dosing strategies: Linezolid 1 200 mg daily for 4 weeks followed by Linezolid 1 200 mg three times a week for 22 weeks, versus Linezolid 600 mg once daily for 26 weeks, in an experimental regimen which also includes Bedaquiline, Dalamanid and Clofazimine.

ACTG Study team.

The study enrolled patients with newly diagnosed MDR-TB, who were randomised to receive either of the Linezolid dosing strategies and were followed up for a duration of 72 weeks. The primary outcomes were time to sputum conversion up to 26 weeks, and proportion of participants with permanent discontinuation of at least one study drug due to adverse events, intolerance or death. The study started enrolment in September 2022 with a target of enrolling 132 participants and has completed enrolment, with the SATVI site having enrolled 13 participants; the study is now in the follow-up phase.

DIAGNOSTICS

Biomarker approaches for tuberculosis screening, diagnosis and treatment response (RePORT SA-003).

STUDY STATUS

STUDY ONGOING

Funders

Principal Investigator

Michèle Tameris

Study Coordinator:

Lisa Beyers

The purpose of this study is to test new blood, sputum, urine, mouth swab and oral rinse tests to diagnose TB, to predict who will get TB disease, to test the immune response to TB, and to predict what types of TB are most easily cured and what types of TB are most difficult to cure, in adults and children, and in people with and without HIV; and to create a database and a biobank, for future use by collaborators.

Enrolment into Cohort B (household contacts of confirmed index TB cases) commenced in October 2024, with the plan being to enrol 300 participants and follow them up for 12 months. Anyone diagnosed with pulmonary TB at enrolment (prevalent TB) will be referred to the public health clinics and offered enrolment and follow up in cohort A, which will follow them throughout treatment and for 12 months post-treatment completion. Participants in Cohort B diagnosed with TB during follow-up (incident TB) will be referred to the public health clinics for further management.

Bucal Swab: Study into tuberculosis case-finding by oral swab polymerase chain reaction (PCR).

STUDY STATUS

MANUSCRIPT PUBLISHED

Funders

Principal Investigator

Angelique Luabeya

Study Coordinator:

Christel Peters

This study investigates the feasibility of diagnosing tuberculosis (TB) using oral swabs as a non-sputum alternative, leveraging Polymerase Chain Reaction (PCR) test to detect *Mycobacterium tuberculosis (M. tb)* DNA. Previous research (Luabeya *et al*., 2019) confirmed *M.tb* DNA presence in oral samples, supporting this approach. While earlier studies showed lower sensitivity than sputum, this work (analysed by Olson *et al.*, 2024) tested two enhanced methods:

1. **Centrifugation** concentrated bacteria from foam swab eluates, followed by Mechanical Lysis and dual-target qPCR (IS6110/IS1081). This achieved **83% sensitivity** and **100% specificity** in 124 South African patients.
2. **Sequence-Specific Magnetic Capture (SSMaC)** used probes and magnetic separation to enrich MTB DNA, yielding **90% sensitivity** and **97% specificity** in 128 participants.

Both methods demonstrate high accuracy, with SSMaC being particularly promising for automation. Oral swabs could expand TB diagnosis accessibility, especially where sputum collection is challenging. The findings underscore the potential for scalable, sensitive alternatives to sputum-based testing.

Studies in the validation of non-sputum TB tests.

1. **Non-invasive, non-sputum screening tests for TB.**
2. **Integration of COVID-19 and tuberculosis case-finding by face mask sampling.**
3. **Molecular detection of Mycobacterium tuberculosis DNA in blood as a marker of infection and TB disease.**

STUDY STATUS

STUDY ONGOING

Funders

Principal Investigator

Simon Mendelsohn

Study Coordinator:

Lisa Beyers

Study team: Studies in validation of non-sputum TB tests.

This study will validate new, non-sputum tests for diagnosing *M.tb* infection and TB disease. Enrolment of healthy adults and patients newly-diagnosed with TB started in July 2023, with 231 (68 TB cases; 163 healthy adults) enrolled until the end of December 2024. Some of the new tests being evaluated include face masks fitted with sampling patches, exhaled breath and skin patch chemical signature measurements, oral rinse and swab testing, and blood collection for specific biomarkers of infection such as M.tb-specific T-cell activation assays, *M.tb* cell-free DNA in serum, and *M.tb* complex DNA in CD34+ stem cells.

IMMUNOLOGY AND BIOMARKER STUDIES

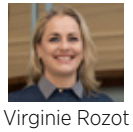
Natural Killer cell determinants of immunity to *M.tb* in humans.

STUDY STATUS

COMPLETED
MANUSCRIPT BEING PREPARED

Funders: NRF National Research Foundation; EDCTP

Principal Investigator & Supervisor



Virginie Rozot

Scientist

Carly Young-Bailie

Co-Supervisor

Tom Scriba

In this study we characterised NK cells in *M.tb*-exposed adolescents over two years using a CyTOF-based intracellular cytokine staining (ICS) assay to understand peripheral blood NK cell functional changes that occur during progression to TB disease. We also investigated the influence of bystander activation on NK cell cytokine and cytotoxic marker expression by comparing the effects of cytokine neutralisation in TB cases and healthy controls, using a flow cytometry ICS assay.

Frequencies of cytokine-expressing peripheral blood NK cells changed over time during TB progression. These cells were lower in samples collected at distal timepoints from TB diagnosis in progressors but increased significantly to frequencies exceeding controllers at timepoints proximal to TB diagnosis. Interestingly, cytokine expression by peripheral NK cells was mediated by IL-2 and IL-12/IL-18 signalling, probably expressed by T cells and myeloid cells respectively. Neutralising T cell-associated IL-2 signalling also significantly reduced peripheral NK cell cytotoxic potential, particularly in TB patients. Our findings indicate marked modulation of NK cell functions during TB progression, which are likely to be secondary to systemic TB disease processes such as immune activation, inflammation or cytokine expression.

These data highlight the dynamic nature of NK cell function during disease progression and suggest that bystander cytokine activation is an important effector of NK cell responses.

Immunopathology of TB in humans.

STUDY STATUS

DATA ANALYSIS
MANUSCRIPT BEING PREPARED

Funder

leap

Collaborating Scientists

Carly Young-Bailie

Tim Reid

Principal Investigator

Virginie Rozot

Digby Warner
Atica Moosa
Dharanidharan Ramamurthy
Ben Loos
Alex K Shalek

This study used state-commissioned autopsies to collect tissue and blood samples within 24 hours of death for immune investigations. Of 177 autopsies, consent was obtained from family members or next of kin for 104 decedents and could be included in this research study (65.4% consent rate), of which 23 had TB pathology. Among the 81 without TB pathology, ~70% had *Mycobacterium tuberculosis* DNA/RNA in their thoracic lymph nodes, suggesting a high prevalence of infection. Ongoing analyses using histology, microscopy, mass cytometry and single-cell RNA sequencing aim to uncover immune signatures of *M.tb* control or disease pathology, with the goal of informing future diagnostic and vaccine strategies.

WATCH A SHORT VIDEO EXPLAINING THIS STUDY

Developing a simple and automated method to measure a T cell-based TB biomarker.

STUDY STATUS

STUDY ONGOING

Funders

Gates Foundation

LifeArc

Principal Investigator

Munyaradzi Musvosvi

Study Coordinator:

Elizabeth Filander

Mycobacterium tuberculosis-specific T-cell activation, a proxy for the in vivo presence of *M.tb* antigens, is a promising blood-based TB biomarker. To move this biomarker to clinical significance, we must overcome certain technical challenges. The test requires trained laboratory technologists to process the blood samples and requires expertise in the analysis of flow cytometry data to interpret results. We are developing a platform to automate blood processing and flow cytometry analysis to measure this biomarker.

research 2024

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staff honours accreditations and impact at conferences

PROFESSOR TOM SCRIBA ELECTED TO UCT COLLEGE OF FELLOWS

Professor Tom Scriba was elected to the UCT College of Fellows.

TO READ THE FULL ARTICLE SCAN THE QR CODE

SATVI AT THE 7TH GOBAL FORUM ON TB VACCINES

7 GLOBAL FORUM ON TB VACCINES
Driving innovation from discovery to access

SATVI made a significant contribution at the 7th Global Forum on TB vaccines, which took place in Rio de Janeiro, Brazil from the 8 to 10 October 2024, with no fewer than eight SATVI members presenting their research and taking part in discussion sessions.

- **Michèle Tameris** presented a poster on the safety, reactogenicity and immunogenicity of the MTBVAC vaccine, comparing results across 3 dose cohorts in BCG-naïve infants compared with BCG, in the MTBVAC 202 phase 2a clinical trial in infants.
- **Angelique Luabeya** presented a poster on the safety and immunogenicity of the MTBVAC vaccine in HIV-negative adults, with or without *M.tb* sensitisation (assessed by QFT test), at different MTBVAC dose levels. QFT-positive MTBVAC recipients reported more injection site reactions than QFT-negative MTBVAC recipients.
- **Mark Hatherill** (above) moderated a panel discussion on 'How to make new TB vaccines a reality', which highlighted technological advancements learned from the COVID-19 vaccine response; the need for new funding initiatives to expand the limited pool of philanthropical funders; the need for investment in technological capacity

Professor Mark Hatherill.

Dr Carly Young-Bailie.

Professor Elisa Nemes.

and infrastructure to support manufacturing in preparation for roll-out, including tech transfer to high-burden countries; and the necessity of involving affected communities in TB vaccine research and development from the start.

- **Simon Mendelsohn** presented a poster on mRNA signatures measured prior to H56:IC31 vaccination predicting TB relapse in HIV-negative adults successfully treated for drug-sensitive pulmonary TB.
- **Monika Looney** presented a poster that reported responses by CD4+ and CD8+ T cells to the four *M.tb* antigens (CFP-10, PE13, PPE18, and Wbbl1) intended for inclusion in the TITAN mRNA vaccine candidate, which is being developed by a South African mRNA vaccine consortium led by **Munya Musvosvi**.
- **Carly Young-Bailie** presented an oral abstract on a study that aims to investigate lymph nodes as niches for *M.tb* infection in humans with or without evidence of TB, and profiles associated host immune responses. The findings suggest that *M.tb* is highly prevalent in the population served by the Western Cape Forensic Pathology Services in this high TB-burden setting. The programme has demonstrated feasibility as a valuable resource for gaining deeper insights into the tissue-level spectrum of M. tb infection and TB immunopathology in humans, which could inform correlates of the clinical outcomes of *M.tb* infection.
- **Elisa Nemes** presented an update on a large consortium that focuses on the identification of immune correlates of protection in human TB vaccine trials.
- **Tom Scriba** presented a talk about the safety, immunogenicity and efficacy results of the H56-POR phase 2/b trial, which assessed prevention of recurrent TB disease in TB patients with the H56:IC31 vaccine.

our staff

TRAINING

Study Coordinators Training, October 2024.

Health and Safety training, October 2024.

ANNUAL STAFF AWARDS, NOVEMBER 2024

Long Service awards

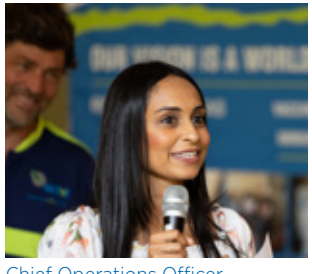
SATVI staff who have worked for 15 years and longer received Long Service awards in Cape Town. Fabio Julies (15 years), Marcia Steyn (Ad hominem promotion), Elizabeth Filander (15 years), Hashley Oliphant (15 years), Lena Douw (15 years) Habibullah Valley (Ad hominem promotion.). Not in picture are Angelique Kany Kany Luabeya (15 years), Libby Briel (15 years), Lynnett Stone (15 years), Humphrey Mulenga (15 years), Munyaradzi Musvosvi (15 years).

SATVI ANNUAL AWARDS

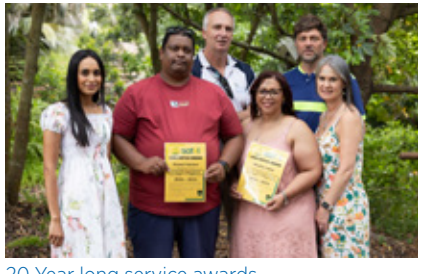
Annual Staff Meeting

Director, Professor Mark Hatherill.


Deputy Director, Professor Tom Scriba.


Chief Operations Officer, Dr Masooda Kaskar.

Field Site Manager, Ms Marwou de Kock.


20 Year long service awards.


SATVI EXCO.


15 Year long service awards.


10 Year long service awards.


5 Year long service awards.


Values ambassadors.

communications, community engagement and advocacy

WORLD TB DAY

This year's World TB Day Programmes have included:

Date	Venue	Audience
20 March '25	Brewelskloof Hospital	Patients
20 March '25	Worcester CDC	Patients
20 March '25	Empilisweni Clinic,	Patients
28 March '25	Youth Research Advisory Group	Youth
3 April '25	Steenvliet Primary School	Learners
5 April '25	Esselen Park High School	Learners
15 & 16 April	Boland Nursing College	Nursing students

WORKPLACE TB EDUCATION: RAINBOW CHICKEN FOODS, WORCESTER

Ms Patricia Magawu, Clinical Research Worker addressing Rainbow Chicken employees.

TB survivor from Rainbow Chicken sharing his experiences.

Mr Kelvin Vollenhoven, Communications Manager speaking about signs and symptoms, diagnosis and treatment adherence.

WORCESTER HIGH SCHOOL

Learners from Worcester Secondary High School who participated in the program.

Mr Kelvin Vollenhoven, Communications Manager speaking to learners on TB, signs and symptoms, diagnosis and treatment adherence.

BREEDE RIVER HIGH SCHOOL

Mr Kelvin Vollenhoven, speaking to Grade 7 learners on TB, signs and symptoms, diagnosis and treatment adherence.

BOLAND NURSING COLLEGE

Dr Sarah Nyanyu, sharing the work that SATVI does to develop research strategies to deal with the complexities of TB, with nursing students from the Boland Nursing College.

Ms Marwou de Kock, Field Site Manager, talking to nursing students about signs, symptoms, diagnosis and treatment adherence.

Ms Christel Peters, Study Coordinator, sharing her experiences as study coordinator with prospective nurses at Boland Nursing College.

Other events took place at (1) Brewelskloof Hospital, (2) Worcester Community Day Clinic, (3) Steenvliet Primary School (4) Esselen Park High and (5) Empilisweni Clinic

RESEARCH COMMUNICATION: VIDEO TITAN VACCINE RESEARCH PROJECT

We have produced an in-house video in which **Dr Munyaradzi Musvosvi** explains the Titan Vaccine research project, which will allow the selection of the most promising TB vaccine candidates.

WATCH A VIDEO EXPLAINING THE VIDEO TITAN VACCINE RESEARCH PROJECT

COMMUNITY ADVISORY BOARD (CAB)

2024 was a special year for us, because it marked the 10th anniversary of the CAB in its current form. Roughly 40% of the original CAB members who joined in 2014 were still members at the end of 2024.

SATVI's relationship with the local community extends as far back as 2008, when the very first CAB was established. This relationship has been complemented by various Community Engagement Programmes, through which it has a much broader connection with, reach into and impact on the broader community where it works.

CAB meeting, March 2024.

CAB EXCO with Doreen Willemse (FAMCRU Site Manager) and Kelvin Vollenhoven (SATVI Communications Manager).

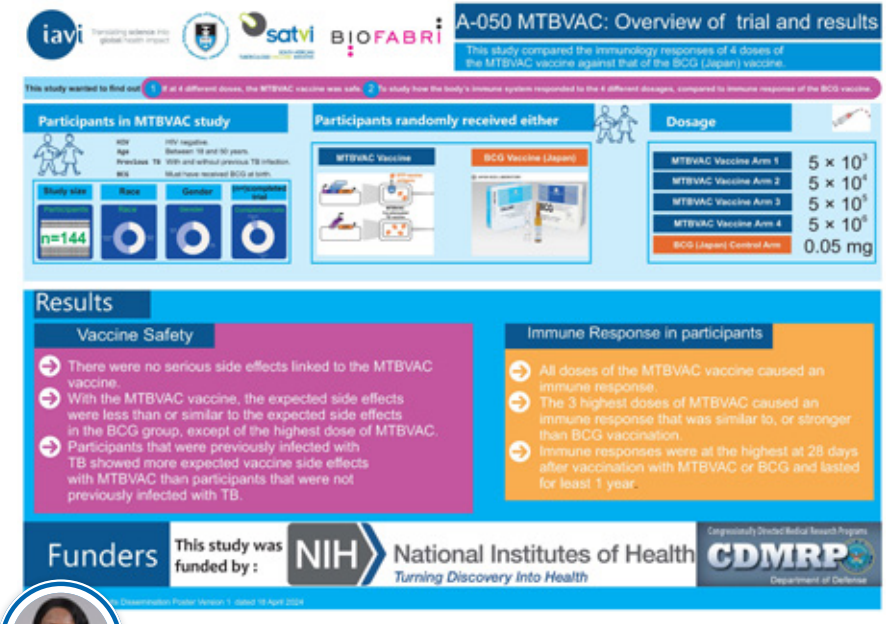
Dr Nicolette Tredoux, SATVI Clinical Investigator leading a discussion on the C113 Imagine TB vaccine trial.

The CAB held 5 meetings during 2024. SATVI's responsiveness has been recognised in several CAB meetings where CAB members expressed appreciation for the rapid response which SATVI provided to communities in need, ranging from food parcels to providing basic supplies a local soup kitchen run by a community leader.

CAB SKILLS AUDIT

We have developed a CAB skills audit survey tool which identifies the training needs of CAB members, and the site has started responding to the skills gaps identified – for example, covering topics such as how to read a research study protocol.

RESULTS DISSEMINATION OF THE A-060 MTBVAC TB CLINICAL TRIAL



Associate professor Angelique Luabeya, presented the results from the MTB Vac A-050 study.

YOUTH RESEARCH ADVISORY GROUP

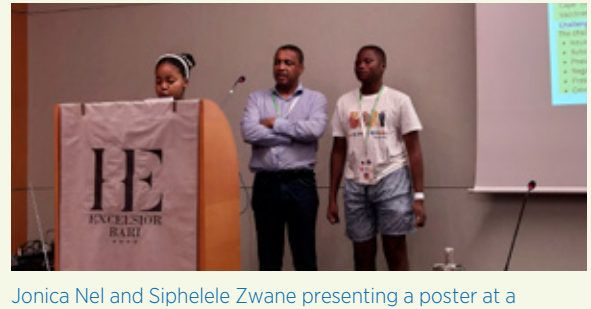
We have grown our involvement with the youth by establishing a Youth Research Advisory Group, in partnership with schools and youth organisations. The YRAG participates in the review of adolescent study materials, posters and brochures.

In July 2024, two members from our Youth Research Advisory Group, **Jonica Nel** and **Siphelele Zwane**, together with SATVI Communications Manager **Kelvin Vollenhoven**, participated in an international children's research conference in Italy, where they presented a poster. We developed an online video clip which was screened at the International Children's Advisory Network Summit in Bari, Italy, and at an ACTG Africa Regional Meeting on 23 October 2024 exploring involving youth in research.

Establishment of Youth Research Advisory Group, March 2024.

Healthy Health discussions during CAB meetings.

Marking Womens Day, August 2025.



Jonica Nel and Siphelele Zwane presenting a poster at a children's research conference held in Bari, Italy, July 2024.

Poster presented at ICAN Conference, July 2024.

WATCH A VIDEO TO LEARN MORE ABOUT THE YOUTH RESEARCH ADVISORY GROUP

Video about the Youth Research Advisory Group.

Standard NEWS 26 July 2024

Boland youth wow research network in Italy

The Youth Research Advisory Group, associated with -the South African Tuberculosis Vaccine Initiative (SATVI) has just returned from an international conference in Bari, Italy where they presented a poster on the work their youth advisory group is doing.

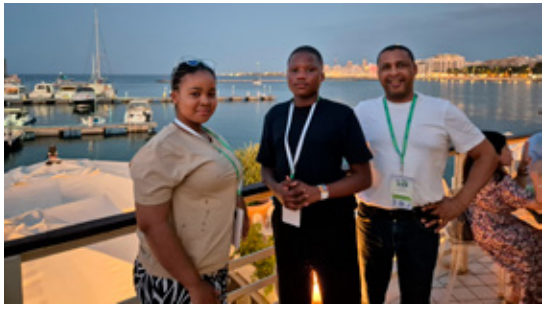
The conference, organised by the international children's research network ICAN, provides a place where young people from all over the world can make input into the design, implementation and evaluation of research studies, and the development • of educational materials.

During the conference· they visited a children research hospital and the Pharmaceutical Science Faculty of the University Degli Studi Bari, where they learnt how scientists design and make medicines, even the latest techniques in using 3-D printers to make medicines

Our local youth advisory group, which is supported by SA TVI, aims to promote an understanding of research among young people, allow them to give input on research done by researchers, as well as assist young people in doing their own Science Technology Engineering and Mathematics (STEM) research projects.

The Escom Expo for Young Scientists is one such place where young people can showcase their research. Some of the current research projects members are working on are studying the prevalence of Covid in Worcester using data obtained from wastewater processing plants. The long-term aim is to create an interest among learners in STEM subjects and expose them to careers in this area.

If you have any ideas about helping youth learn about science contact Kelvin Vollenhoven at SATVI: . kelvin.vollenhoven@uct.ac.za



Here in Italy are (from left to right) Jonica Nel (Esselen Park High), Siphele Zwana (Somerset High) and Kelvin Vollenhoven (SATVI)

In the news, August 2024.

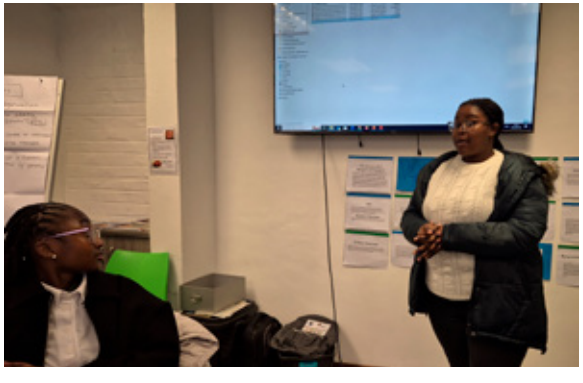
TRAINING FOR YOUTH RESEARCH ADVISORY GROUP, DECEMBER 2024

Professor Mark Hatherill and Dr Simon Mendelsohn engaging with members of the Youth Research Advisory Group, December 2024.

Professor Malk Hatherill and Dr Simon Mendelsohn with the Youth Research Advisory Group during their visit to the Cape Town SATVI offices.

SCIENCE CAPACITY DEVELOPMENT: GROWING THE NEXT TIER OF RESEARCHERS

In August 2024, five of our Youth Research Advisory Group participated in the Stellenbosch Eskom Expo for Young Scientists, where they presented five posters on research they had conducted.



Reananetse Mbizo, presenting a research poster to her peers at YRAG on a research project she did in Robertson on HIV: Mother-to-child transmission.

Two young female scholar scientists from Robertson and Worcester won silver medals, and another female student from Worcester received a special commendation for her research topic.

From left to right: Paul Museke (Somerset High), Akanya Tyaliti (Somerset High), Ms Zizipho Mhlungulwana (Mathematics and Physics teacher, Somerset High), Grace Maunga (Zwelethemba High), Reananetse Mbizo (Masakheke High), Mpariwa (Somerset High), and Kelvin Vollenhoven (SATVI).

Reananetse Mbizo, Masakheke High School, Robertson. Research Topic: Vertical transmission of HIV in pregnant mothers to their infants.

Akanya Tyaliti, Somerset High. Research Topic: Can humans distinguish between Artificial Intelligence (AI)-generated text and human-written text?

SATVI POSTGRADUATE STUDENTS INVOLVED IN JUDGING SCIENCE PROJECTS SUBMITTED BY SCHOOL LEARNERS

SATVI has been involved with the Science Expo, with a number of SATVI postgraduate students serving as judges.

From left to right: Tsholofelo Tshuma, Alisha Chetty, Lauren Cruywagen, Dominique Ariefdien and Gabriela Jackson.

DISTRICT STEM TEACHER TRAINING PROGRAMME

On Saturday 2 November 2024, **Kelvin Vollenhoven** presented a talk on Ethics in School STEM Research Projects at a district teachers' training programme convened by the organisers of the Eskom Expo for Young Scientists.

From left to right: **Kelvin Vollenhoven** (SATVI), **Kimberly Coetzer** (Stellenbosch Division of Molecular Biology and Human Genetics (SDMBHM)), **Dannielle Kenny** (SDMBHM), **Pebetsi Kgole** (SDMBHM) and Prof **Prathieka Naidoo** (professor in Chemical Engineering at Stellenbosch University, coordinator of STEM@Maties at Stellenbosch University, and steering committee member of the Expo for Young Scientists).

SOAPBOX SCIENCE ENGAGEMENT

Elisa Nemes and **Carly Young-Bailie** co-organised the Soapbox Science Cape Town 2024 event, which is an initiative to promote the visibility and boost the career prospects of female and non-binary scientists through the establishment of annual public grassroots engagement. The Soapbox Science event follows the format of London's Speaker's Corner in Hyde Park, which is historically an arena for public debate. Hosted at the V&A Waterfront, Soapbox Science Cape Town recruited leading female scientists from several tertiary institutions across South Africa to share some of our county's most groundbreaking scientific research. For more info, visit **www.soapboxscience.org**

MANDELA DAY 2024

For Mandela Day we supported the Avian Park Community Clinic with the establishment of a food garden.

WATCH A VIDEO OF OUR NELSON MANDELA DAY ACTIVITIES AT AVIAN PARK, WORCESTER

funders

ACTG AIDS CLINICAL TRIALS GROUP

Gates Foundation

GATES MEDICAL RESEARCH INSTITUTE

BIOFABRI

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Congressionally Directed Medical Research Programs CDMRP Department of Defense

iavi Translating science into global health impact

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NRF National Research Foundation

science & innovation Department: Science and Innovation REPUBLIC OF SOUTH AFRICA

European Commission Horizon 2020 European Union funding for Research & Innovation

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EDCTP

wellcome

novavax

saMRC advancinglife

the HARRY CROSSLEY foundation

TBVI TuBerculosis Vaccine Initiative

CRDF U.S. Civilian Research & Development Foundation

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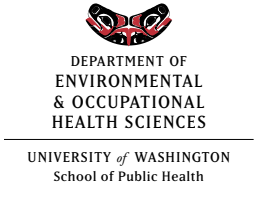
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South African Tuberculosis Vaccine Initiative (SATVI)

Institute of Infectious Disease and Molecular Medicine (IDM),
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