TOWARDS a world without TB

20 Years of Research

20 YEARS OF TB RESEARCH | satvi

TOWARDS A WORLD WITHOUT TB

University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad

SPES BONA

vision and mission

Our Vision

A World Without TB

Our Mission

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

Our Values

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

University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad

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SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

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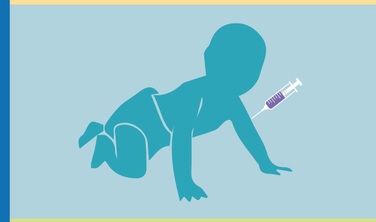
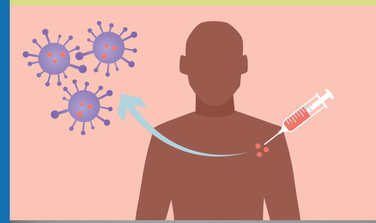




PREFACE

This SATVI History is the result of more than 20 interviews with SATVI staff and students, including many colleagues who have left, but are very much still part of the SATVI family. A small volunteer working group of SATVI historians set out to identify key events and to conduct the interviews with role players, a process that created a rich oral history of SATVI for our staff and students, our collaborators and the wider TB research community. We hope that it will inspire the many unsung SATVI TB research heroes to record their own stories, continue the narrative, and build on the incredible institutional memory that sustains the SATVI Mission: *Innovative and High Quality TB Vaccine Research in Africa to Impact the Global Epidemic*.

Ashley Veldsman
Julia Noble
Kelvin Vollenhoven
Linda van der Merwe
Mark Hatherill
Marwou de Kock
Michèle Tameris
Tom Scriba

May 2021

FOREWORD

SATVI celebrates 20 years of TB vaccine research on 26th March 2021, the anniversary of enrolment of the first participant in SATVI's first TB vaccine trial, a randomised controlled trial of intradermal vs percutaneous BCG vaccination (Hawkridge BMJ 2008).

As global TB vaccine stakeholders plan for ambitious new efficacy trials in infants and adults, we reflect on SATVI's contributions to the global TB vaccine development effort, including key epidemiological studies that laid the groundwork for development of new TB biomarkers, immunology studies of potential correlates of vaccine-mediated protection against TB, a large implementation trial of infant BCG vaccination, the first infant trial of a novel TB vaccine candidate in the 50 years, and two pivotal efficacy trials of BCG and the subunit vaccine candidate M72/AS01E. Our strong partnerships with the Breede Valley community, the Departments of both Health and Education, and our collaborators and funders have been critical to that effort.

Learning from this rich experience of TB research over two decades, which included valuable lessons from trials and tribulations as well as triumphs, has brought us closer to our vision – a world without TB.

Prof. Mark Hatherill
Director

CHAPTER 1

Early Beginnings

Randomised Controlled Trial of percutaneous and intradermal BCG vaccination (BCG-RCT).
Clinical trial .gov: Identifier: **NCT00242047**

4 FEBRUARY 2000
Meeting to launch the BCG RC trial.

2000 1 JULY
First SATVI staff appointed, based at Red Cross Hospital premises.

1 SEPTEMBER 2000
SA Medicines Control Council gives approval for the import and use of the Tokyo BCG vaccine.

2000 NOVEMBER
UCT Faculty of Health Sciences Human Research Ethics committee gives approval for the BCG RC Trial.

DECEMBER 2000
SATVI opens offices at the Brewelskloof Hospital nurses home.

2001 26 MARCH
First participant in the BCG RCT trial vaccinated.

Setting the scene for TB vaccine research

The South African Tuberculosis Vaccine Initiative (SATVI) was first known as the "BCG Study" research group, before the SATVI name was adopted. The research group was located within the Child Health Unit of the University of Cape Town's Faculty of Health Sciences.

A small group of health scientists associated with UCT and Rockefeller University, including Professors Greg Hussey, Maurice Kibel (deceased) (UCT), Gilla Kaplan and Willem Hanekom (Rockefeller University), conducted studies of TB epidemiology in children, BCG vaccine administration, and the immune response to TB and BCG vaccination. These early studies set the scene for later clinical trials of novel TB vaccine candidates. In South Africa, BCG vaccine (Tokyo 172 strain) was given percutaneously using a multi-pronged, BCG-coated administration tool. Vaccination policy in South Africa changed to intradermal administration of BCG (Danish 1331 strain) in 2000.

WHAT IS THE BCG VACCINE?

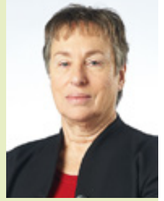
The bacille Calmette-Guérin (BCG) vaccine was developed by two French scientists, Albert Calmette and Camille Guérin in the 1900's (Luca, Mihaesca, 2013). The BCG vaccine was first used in humans in 1921. In South Africa the BCG vaccine is currently given at birth. BCG provides partial protection against TB in children, including severe forms of disease, but does not prevent TB occurring later in adulthood.

Professor Greg Hussey, Founding SATVI Director, current Director of Vaccines for Africa (VACFA):

"Maurice Kibel and my interest in the BCG vaccine and TB vaccines started when during hospital ward rounds, we would always look with interest to see whether paediatric patients with TB had received the BCG vaccine or not. We then became interested in finding out why children were getting sick with TB if they had received the BCG vaccine."

Professor Maurice Kibel,(deceased) was associated with SATVI since its establishment

Professor Gilla Kaplan, former Professor Rockefeller University, former Director Global Health Program at Bill and Melinda Gates Foundation:



"When I started working with Maurice Kibel and Greg Hussey in the period after the first democratic elections in 1994, they told me about what looked like the failure of BCG vaccination in protecting against paediatric TB because in the field they were observing a much higher rate of severe TB meningitis and other extra-pulmonary TB in children than was to be expected."

> We then became interested in finding out why children were getting sick with TB if they had received the BCG vaccine. - Greg Hussey

Developing the research concept

Greg Hussey, Maurice Kibel and Gilla Kaplan were awarded funding for the BCG RCT from the Bill and Melinda Gates Foundation through the Sequella Global TB Foundation.

Proposed research areas

At the heart of the research proposal was the establishment of a clinical research site which would undertake the Bacille Calmette Guérin Randomised Control Study (BCG-RCT) and future clinical trials of novel TB vaccine candidates. SATVI would have a strong focus on creating the infrastructure, human and organisational systems to support TB research and a world-class clinical research laboratory.

1 Comparing the protection against TB of percutaneous vs intradermal BCG vaccine administration in newborn infants:

The BCG RCT trial would assess whether the route of BCG administration to newborns was a factor in protection against TB.

2 Researching the immunology of BCG:

The Immunology case control study set out to determine the extent of specific immunity induced by BCG vaccination and how immunity correlates with resistance against tuberculosis disease.

3 TB observational study:

An observational study was conducted in Cape Town to compare the incidence of tuberculosis, and patterns of presentation and severity type of tuberculosis, in children in the Cape Town Metropole region aged between 0 and 2 years before and after the changeover from percutaneous Tokyo 172 BCG to intradermal Danish 1331 BCG.

4 Establish TB research capacity:

Establish a research site able to conduct clinical trials of emerging new TB vaccine candidates.

What was happening in the field?

GILLA KAPLAN: At that time, there were several new TB vaccines in development, including the recombinant BCG and Oxford vaccines and other groups were in the process of developing alternative vaccines. It was important for us to first use BCG to understand how efficacious BCG is, what do you need to do so that it does not fail to protect relative to the expectations of BCG.

WHAT WAS THE BCG RCT TRIAL?

The BCG RCT trial assessed whether the route of BCG administration to newborns affected the efficacy of BCG-mediated protection against TB. This study enrolled 11 680 infants, over 3.5 years.

Figure 1 Percutaneous administration tool.

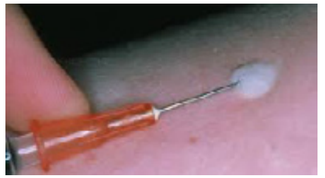


Figure 2 Intradermal administration tool.

Launching the BCG Randomised Control Trial

On the 4th February 2001 the BCG studies were launched in Cape Town. Present were Greg Hussey, Carol Nacy, Gilla Kaplan, Larry Geiter, Peter Donald, Bernard Fourie, Neil Cameron, David Coetzee and Zena Steyn.

Speakers at launch meeting:


Carol Nacy


Peter Donald


Bernard Fourie


Greg Hussey


Larry Geiter

Early SATVI Staff

On the 26 March 2001 the study commenced enrolling and completed follow-up during July 2006. The study recruited 11 680 newborn infants.


Photo 3SATVI BCG RCT Study team: From left to right Rachel Tobias, Linda vd Merwe, Lilly Denation, Stephanie Abrahams, Deon Minnies, Xolani Ndlakuhlola, Julia Noble, Sylvia Mlanjeni, Angelique Mouton, Ryan Karriem.

Ashley Veldsman, Professional Nurse, now Regulatory Specialist, July 2000 to present:

I can remember starting work early in the morning, meeting Tony Hawkridge at the office, collecting the prepared BCG vaccine from the bulk freezer from the 4th floor at Red Cross Children's Hospital. We would then rush to Worcester so we could get the vaccine there in time for use at the clinics.

Tony Hawkridge, Medical Officer to Clinical Director, August 2000 to June 2007:

This was a project to set up a large-scale TB vaccine trial in a high burden country, in a way that would allow for later trials to be done to the absolute highest quality standards.

Deon Minnies, Field Site Manager, October 2000 to 2011

For my first day, my main brief was to survey the environment to set up the field site. We had a one-man office in the hospital until we secured accommodation in what was called the old matrons' quarters or nurses home.

Linda Van der Merwe, Research Nurse, now Clinical Resource Manager, February 2001 to present:

At the time, we (research nurses) did not have study coordinators, so it meant that we would do all study functions which included consenting, recruiting, vaccination, follow-ups of participants.

Angelique Mouton, Data Capturer, July 2001 to present:

I started working on the BCG RCT study, which was the first big study of SATVI.

Lesley Workman Data Manager, 2001 to 2009:

Jane Hughes Laboratory Manager 2006 to 2013

Marijke Geldenhuys, Nursing Educator to Manager Training and Quality Assurance, July 2002 to January 2012:

I joined SATVI as nursing educator on 1 July 2002, when the BCG RCT trial started and SATVI needed someone to train the research nurses.

Julia Noble, Phlebotomy Assistant, now Quality Control officer, August 2001 to present:

In those early days we had to be at the office early in the morning, because you have to pack everything and get ready so that when the clinic opens, you must be there.

Sizulu Moyo, Clinical Investigator, June 2003 to 2011:

I joined SATVI before it was even called SATVI. My first trial I worked on, was the BCG study. My task as medical officer was to document serious adverse events, largely hospitalisations and mortality, partly to detect TB cases that could be missed.

Marwou de Kock, Lab Technologist, now Field Site Manager, June 2002 to present:

In my first few months at SATVI, I set up the laboratory at the nurse's home at Eben Dönges Hospital (Worcester).

Hassan Mahomed, Epidemiologist, then Co-Director, 2004 to 2012:

By the time I arrived, the BCG trial had concluded, and my job was to write this study up, look at all the data and convert it into a scientific publication.

Michèle Tameris, Medical Officer, now Principal Investigator, August 2003 to present:

On my first day at SATVI, I was introduced to the staff by Greg Hussey, at the monthly staff meeting and what amazed me was to see the whole SATVI staff complement around this one big table. Greg went around the whole table giving everyone a chance to speak.

Willem Hanekom, Laboratory Director, then Director, 2005 to 2012:

Before I joined SATVI in 2005, while working with Gilla Kaplan at the Rockefeller University in New York, I assisted Jane Hughes and Sebastian Gelderbloem in setting up the laboratory at Groote Schuur and also Marwou De Kock with setting up the (first) SATVI laboratory at the Eben Dönges Hospital.

Establishing infrastructure for a clinical research site.

MARWOU DE KOCK: In my first few months at SATVI, I had to set up the laboratory at the nurse's home at Eben Dönges hospital.

DEON MINNIES: The re-engineering of the old boiler house into the project offices was a major project, involving the provincial public works department, UCT building and architectural people. The project entailed constructing a second floor, with concrete partitioning and ceilings and a walk-in refrigerator.

MICHÈLE TAMERIS: SATVI has grown from an organisation which operated from the 2-bedroom matron's flat at Brewelskloof Hospital. All of the clinical staff, who went out to do case-control study bleeds, worked out of this one small office, sharing desks, sitting on either side of the desks.

■ Photo: The old hospital boiler house was converted into what is now known as the Project Office.

Growing impact

By 2008 SATVI was collaborating within a network of clinical trial sites created by Sequella/Aeras, with SATVI supporting capacity building at other research sites in Africa.

TONY HAWKRIDGE: I can remember going with Greg to Mozambique Kenya, Uganda, to help them set up their trial sites. The idea was already taking shape of creating a network of trial sites and not just one was already taking shape. We had to find out if they had similar capacity. It was exciting not just being focused on the Western Cape, to get out connect with these colleagues, with them, but also to bring our expertise to bear.

What were those early days like?

GREG HUSSEY: They were exciting times.

TONY HAWKRIDGE: It was a small team; it was easier because there were fewer people to consult. Greg was really the only one with experience of clinical trials, I knew about TB lab work and public health, but not TB vaccine trials.

WILLEM HANEKOM: I think we took a lot of liberty in getting things done, cross-subsidizing between research areas. Initially we had to build the laboratory from scratch, there were no students and no postdocs.

MICHÈLE TAMERIS: During this period the laboratory was moved from the single bedroom, at the Eben Dönges (where Worcester Hospital is now) in the nurses' home, to where the current storeroom is on the ground floor. It was a mission getting the minus 80 fridges through the doors, involving the removal of the door to manoeuvre the massive fridges from the nurse's home to the Project office.

JULIA NOBLE: It was a lot of work, and we covered a big area with just a few people. In the winter we used to put warm bottles into the incubator to keep the samples warm, because it gets very cold in the Ceres area.

What has the impact of the BCG trial been?

RESEARCH FINDINGS:

The study results "*Efficacy of percutaneous versus intradermal BCG in the prevention of tuberculosis in South African infants: Randomised trial*" were published in the British Medical Journal (Hawkridge, 2008).

This study which involved 11 680 newborn infants, found equivalence between intradermal BCG and percutaneous BCG in the incidence of tuberculosis in South African infants vaccinated at birth and followed up for two years.

Capacity development

GILLA KAPLAN: During the study it became clear to us that with the percutaneous tool, if the needles did not penetrate optimally, the needles sometimes bent, resulting in the device not delivering the full dose vaccine needed to induce an optimal response. From the onset we made sure that the nurses knew how to deliver the vaccine accurately. They were outstanding, because when we started to look for signs of sub-optimal delivery of vaccine in the percutaneous delivery, it was almost impossible to find a baby that did not have the perforations where the nine-pronged tool entered the skin.

Understanding BCG better

GILLA KAPLAN: Early in the BCG RCT study we learnt that the strain of BCG made a difference because the different vaccine strains commercially available had entirely different levels of side effects that were associated with the extent of immune activations. We found that

- Copenhagen BCG vaccine: The Copenhagen vaccine was ideal, because it was somewhere in the middle because it gave a strong immune response.
- Tokyo BCG vaccine: The Tokyo vaccine had a little more side effects but appeared to be more immunogenic.
- So the strain of BCG more or less conferring protection was another thing which emerged that time. We used T cell activation to measure it, but when we looked at the local reaction, there was a correlation between the local reaction and T cell activation.

Pioneering TB vaccine research

TONY HAWKRIDGE: The BCG RCT trial was invaluable to the TB research field because it allowed us to start exploring the incredibly complex field of why some kids respond to BCG in one way and some in another, why it is sometimes protective and other times not. The study placed the focus of the TB vaccine community on SATVI.

Setting up a large scale TB vaccine trial in a high burden country

TONY HAWKRIDGE: The BCG-RCT showed that it was possible to set up a large-scale TB vaccine trial site in a high burden country, in a way that would allow for later trials to be done to the absolute highest quality and that will allow later trials to be done that would satisfy regulatory requirements.

CHAPTER 2

Epidemiological & immunological studies to define the TB epidemic

Adolescent Cohort Study (ACS)
Follow-up visit complete

1 JULY
2005

Adolescent Cohort Study (ACS)
Study start enrolment

2009
FEBRUARY

NOVEMBER
2012

Adolescent Cohort Study (ACS)
Study results published

Between 2004 and 2009 SATVI conducted three large-scale epidemiological studies amongst various age groups and subpopulations to generate data about TB prevalence and incidence in this area to lay the basis for late phase TB vaccine studies. These studies were the Adolescent Cohort, the Neonatal Cohort and the Adult Prevalence Studies.

Study 1: Adolescent Cohort Study

"**HASSAN MAHOMED**: When I joined SATVI one of the first things I did was to look at routine data and I then produced a graph which showed that the incidence of TB in children was high, then it drops with very few TB cases in the school-going age (6 to 10), but then it takes off at around young adulthood. This analysis contributed to the discussion around studying the epidemiology of TB in adolescents, trying to understand what the rate of TB by age is, at what point does it start increasing, and understanding why you have the peak so early.

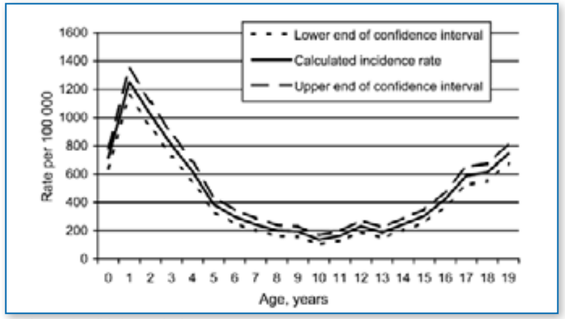
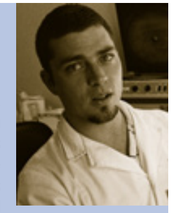


Figure 1: All tuberculosis incidence rate by the age (years) in Cape Town, July 2002-June 2003 (*n* = 5039). Source : City Health Directorate of the City of Cape Town (notified TB cases(and Census 2001 (population estimates).

Tom Scriba, Postdoctoral Fellow, Deputy Director: Immunology and Laboratory, 2006 to present



While I was doing my PhD at Oxford University, I visited the SATVI site and Willem took me to a school in Worcester where the ACS study was running. There was this massive hall with large queues, divided up into the different aspects of the ACS study. It was very impressive and inspiring because as an Oxford student I was sheltered from clinical research.

MICHÈLE TAMERIS: For me, an important date in the history of SATVI is when we started the Adolescent Study and the Neonatal Study. Our staff numbers shot up from 40 to 120 and changed the dynamic of SATVI.

HASSAN MAHOMED: I think the ACS study had a major impact on the TB research field because from this study immunology blood samples provided data for many years to come.

ADOLESCENT COHORT STUDY (ACS) 2005 – 2009

A total of 6,363 adolescents were enrolled (58% of the school population targeted). During follow up, 67 cases of bacteriologically confirmed TB were detected giving an overall incidence rate of 0.45 per 100 person years (95% confidence interval 0.29-0.72). Black or mixed race, maternal education of primary school or less or unknown, a positive baseline QuantiFERON assay and a positive baseline TST were significant predictors of TB disease on adjusted analysis.

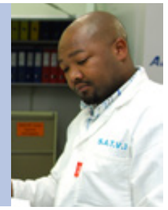
Photo From left to right: Dianne Gempies, Magda Van Rooy, Riley Joan Kock, Fazlin Kafaar, Mariaan Jacks

Fazlin Kafaar, Research Nurse now Study Coordinator, 2004:

I was appointed to work on the Adolescent Cohort Study in 2004.

Lebogang Makhethe, Laboratory Technologist:

I joined SATVI in Worcester from Cape Town in September 2007. The first study I worked on was the Adolescent Cohort Study.



"For me, an important date in the history of SATVI is when we started the Adolescent and Neonatal Cohort Studies."

Study 2: Neonatal study milestones

APRIL **2005** — Nenonatal study commences enrolment

NOVEMBER **2006** — Neonatal CS enrolment completed

DECEMBER **2008** — Data review December 2008

FEBRUARY **2012** — Results published

NEONATAL STUDY –2005–2008

The neonatal study, conducted between 2005 and 2008, enrolled 4 776 infants. The study aimed to compare TB case yield and disease profile among BCG vaccinated children using two case-finding strategies from birth until 2 years of age. The study found that home visits combined with record surveillance detected significantly more cases than record surveillance with a single visit.

Moyo *et al.*, 2012, IJTLD

SIZULU MOYO: I was the principal investigator on the Neonatal Cohort Study, from 2005 to 2009. This study eventually became the subject of my thesis.

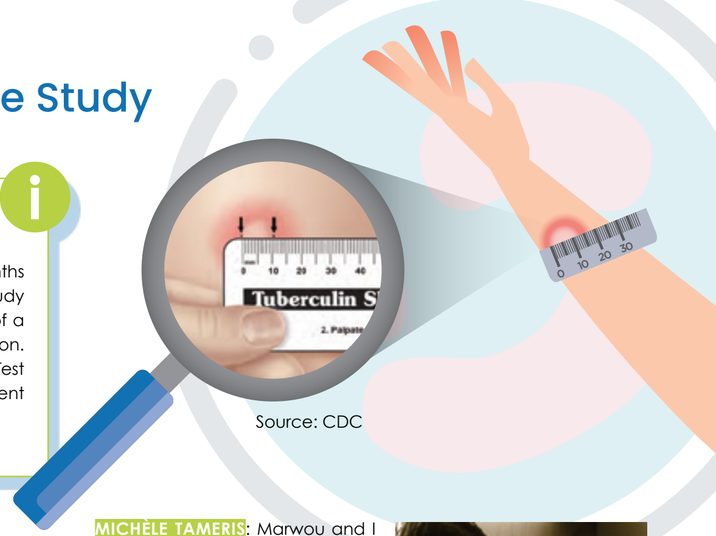
FAZLIN KAFAAR: When I joined SATVI in 2004, I first worked on the adult prevalence survey. We recruited 360 adults from workplaces in Worcester. During this study we did Mantoux and a chest x-ray.

Study 3: Adult Prevalence Study

WHAT WAS THE ADULT PREVALENCE SURVEY (APS) ABOUT?

The Adult Prevalence Study was conducted over three months during 2004 and recruited 358 adult participants. The study compared the Mantoux skin test with three generations of a whole blood IFN-γ assay as a test for tuberculosis infection. This study found poor agreement between Tuberculin skin Test (TST) and the different QuantiFERON tests in diagnosing latent TB infection.

Mahomed *et al.*, 2006



Source: CDC

Study 4: BCG HIV Study

IMMUNOLOGY STUDY: OBSERVATIONAL STUDY: HIV1 INFECTION AND BCG INDUCED IMMUNE RESPONSE (BCG-HIV)

The BCG-HIV study was conducted between 2003 and 2006 (Mansoor, 2010) amongst infants, born to HIV-infected and un-infected mothers, who received the BCG vaccine at birth.

The study found that BCG vaccination of HIV-uninfected infants induced a robust immune response, characterized by IFN-γ, TNF-α, and/or IL-2-expressing CD4 T cells. In contrast, HIV-infected infants had a markedly lower response throughout the first year of life. This result suggests that BCG vaccination may not protect HIV-infected infants against TB.

MARWOU DE KOCK: For my first study I was responsible for the BCG-HIV study which involved collecting cord blood from the placenta when the mothers gave birth. Once the baby was born, we had to prepare the blood assay tubes, accompany Michele Tameris and Sylvia Mlanjeni to draw the blood and process for shipment to the Cape Town Laboratory.

MICHÈLE TAMERIS: Marwou and I would go to maternity unit to collect blood from newborn babies. Sometimes if the baby was discharged, we would have to drive to the home to locate the baby. Marwou would hold the baby and tubes, while I was drawing blood. I can remember at the time satin bedware was fashionable, which made it a struggle to work with the baby sliding all over the bed.

CHAPTER 3

MVA85A

the first new generation infant TB vaccine candidate in 50 years

JUNE **2009**

Consenting starts on MVA85A study

2009
15 JULY

First participant vaccinated

JULY **2009**

First samples processed

2012
20 SEPTEMBER

Last participant follow up visits

Clinical development of the MVA85A vaccine

The period from September 2005 onward marked a major shift in SATVI's research focus from large epidemiological studies to conducting clinical trials of novel candidates in the growing TB vaccine pipeline.

On the 15th July 2009, the first infant was enrolled and vaccinated with the MVA85A TB vaccine in the first phase IIb, proof-of-concept infant efficacy trial of a novel TB vaccine candidate since BCG. The vaccine was developed by Oxford University as a booster to enhance the protective efficacy of the BCG vaccine.

WHAT WERE THE FINDINGS OF THIS STUDY?

Three phase I and IIA trials conducted at SATVI, and those conducted elsewhere had shown that MVA85A was safe and immunogenic. The phase IIb infant trial showed that MVA85A was safe, however, no significant efficacy against TB was observed. The study results were published in The Lancet (Tameris *et al*; 2013).

WHAT DOES MVA85A STAND FOR?

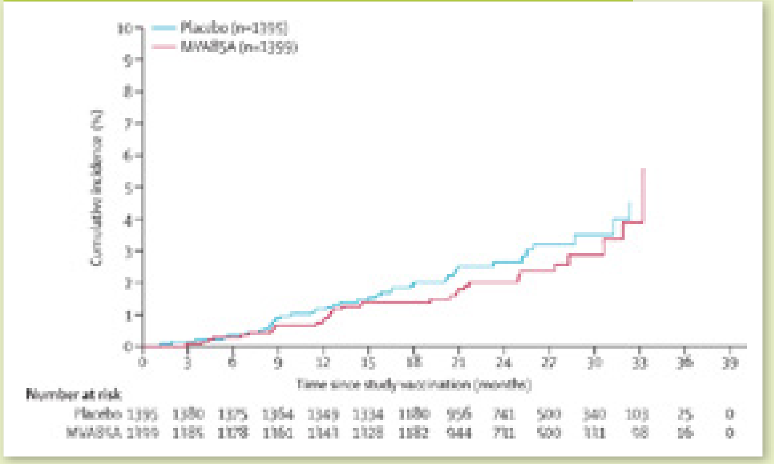
MVA stands for Modified Vaccinia Ankara, the attenuated viral vector that expresses the immunodominant *M. tuberculosis* protein, antigen 85A, which boosts the immune response to this protein induced by prior BCG vaccination.

MARK HATHERILL: The MVA85A trial established that SATVI had capacity to perform high quality TB vaccine trials, in parallel with evaluation of vaccine-induced immunogenicity, in a very high TB burden setting.

HASSAN MAHOMED: The MVA85A was our first big study which looked at efficacy, in other words to see if the vaccine works or not. Unfortunately, the results were negative, but it was an amazing ground-breaking experience for further studies into modern TB vaccines.

> The MVA85A trial was the first trial to test the efficacy and safety of a new TB vaccine in infants since BCG

Results depicting incidence of TB in infants who either received MVA85A vaccine (red line) or Placebo (blue line).



Source: Tameris *et al.*, 2013, Lancet.


Articles

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

TONY HAWKRIDGE: The MVA trials which started in 2005, leading up to the Phase IIb trial were like a book with many chapters. Even though the results were disappointing, the body of literature, the experience and the networks built up, were a huge achievement for SATVI.

SIZULU MOYO: I worked on the MVA85A study and my role included clinical assessments of participants, reading and interpreting their chest radiographs.

ANGELIQUE MOUTON: I captured the data on the MVA phase IIb study.

> Right from the start SATVI's focus was on TB vaccines.

Voices from the field

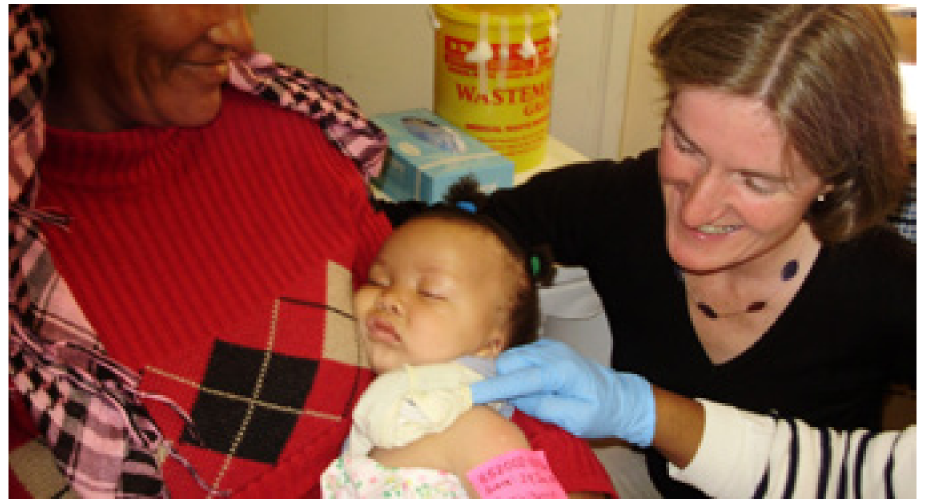
> If the trial is successful it will be exciting because we will have a vaccine that works better than BCG. BCG, does not prevent pulmonary TB, it only prevents disseminated TB in infants. BCG is not good enough in preventing lung TB, which is the most common form of TB, the one that spreads the bug.

Interview with Professor Tom Scriba, who was research officer at the time, about the potential impact of the MVA84A TB vaccine.

Video source: Hannah Madge, Oxford

Building collaborative partnerships

GREGORY HUSSEY: Our relationship with Oxford University evolved organically in a sense. They knew we were involved in setting up a trial site. They were working on a TB vaccine and were looking for sponsors and so the Wellcome Trust and Aeras became involved because our site had shown capacity and intent.



Professor Helen McShane (Oxford University) with participant in MVA85A trial

What were the lessons from the MVA85A trial?

The clinical, regulatory and research environment for modern efficacy trials of new TB vaccines are substantially different to that when BCG vaccine was first evaluated in infants.

Future infant vaccine trials need to allocate sufficient resources and optimise operational efficiencies.

A stringent case definition is necessary to maximise specificity and TB case accrual must be monitored carefully.

Tameris *et al.*, 2013.

> The beauty of working with Oxford University is that it is very much a partnership. It's not like they tell us do X and we do X. It's a more question of how we think we should do this. It's very much a question of "Together we will write the protocol and plan the study, discuss the program" working together.

Interview with Dr Michèle Tameris speaking on the partnership with Oxford University.

Video source: Hannah Madge, Oxford

CHAPTER 4

Multiple studies of TB vaccines, drugs, immunology and diagnostic tools

TB vaccine clinical trials: 2012 onwards

In the period 2000 to 2012, SATVI conducted clinical trials of BCG and 5 new TB vaccines in 11 different protocols. These studies included an infant efficacy trial of the viral vectored candidate vaccine MVA85A and early Phase 1-2 trials of Aeras-402 vaccine and the subunit candidate vaccines H4:IC31, M72/AS01$_E$ and H56:IC31.

Efficacy trials

SATVI played a key role in two pivotal efficacy trials, one that tested efficacy of the M72/AS01$_E$ candidate vaccine for prevention of progression to TB disease in *M.tuberculosis*-infected adults; and one that tested efficacy of BCG revaccination for prevention of *M.tuberculosis* infection in adolescents.

Prospects for a new TB vaccine for adults: Final results published of M72/AS01$_E$ efficacy trial

On the 29 October 2018, the final results of the M72/AS01$_E$ efficacy trial were announced at the 50th Union World Conference on Lung Health's TB Science 2019 symposium in Hyderabad, India, and published in the New England Journal of Medicine (Tait, NEJM 2019).

This ground-breaking trial assessed the safety and efficacy of the M72/AS01$_E$ candidate vaccine in *M.tuberculosis*-infected adult participants in South Africa, Kenya and Zambia. More than 3,500 participants, all HIV-negative and aged 18 to 50 years, received two doses of the candidate vaccine or a placebo 30 days apart and were followed for three years.

The results showed that vaccine efficacy of M72/AS01$_E$ against pulmonary tuberculosis, and vaccine-induced immune responses, were sustained for 3 years.

SATVI 018 Study team: From left to right: Balie Carstens, Veronica Baartman, Charmaine Abrahams, Cynthia Gintswa, Christel Petersen, Raida Onrus, Michele Tameris, Danelle van As, Georgette Shaw, Sonia Stryers, Miriam Moses, Roxanne Solomon.

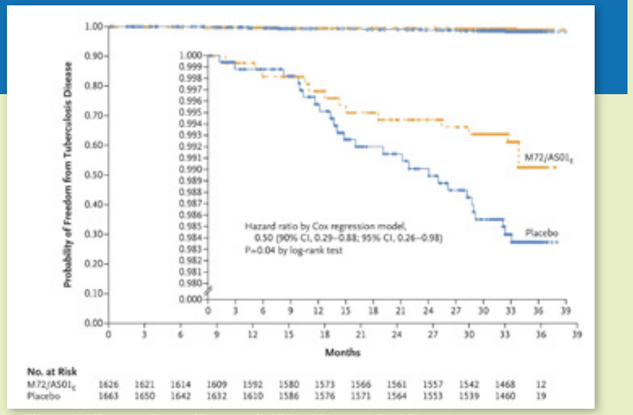


Figure 1 Efficacy- Blue efficacy of M72/AS01$_E$ and Red Placebo. Source: Van der Meeren 2018, NEJM.

WHAT IS THE M72/AS01$_E$ VACCINE?

The M72 antigen is a fusion of Mtb32A and Mtb39A, two MTB proteins. AS01$_E$ is an adjuvant system developed by GlaxoSmithKline (GSK) that contains two active compounds designed to stimulate the immune system: MPL (3-deacylated monophosphoryl lipid) and QS-21.

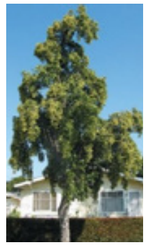
Number of participants: 3,573 HIV negative adults.

Sponsors: GlaxoSmithKline/GSK and IAVI.

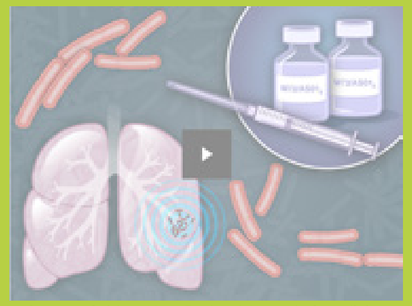
Research articles published: van der Meeren, NEJM 2018 and Tait *et al.*, 2019.

DID YOU KNOW?

A key component of the M72/AS01$_E$ TB vaccine candidate, the QS-21 molecule, comes from the soapbark tree, a medicinal resource recognized in the traditional knowledge of indigenous Andean peoples.



Quick take: M72 explained



Source of video: New England Journal of Medicine.

> These are game-changing results. If we can offer latently infected adults durable protection against pulmonary TB disease, we may be able to interrupt the cycle of TB transmission. - Mark Hatherill.

STUDY FINDINGS:

Out of the 1 626 participants who received vaccine, only 13 developed active TB disease, a reduction of 50%. In the placebo group, 26 people developed active TB.

ONLINE: LIVE PRESS CONFERENCE: M72/AS01$_E$ efficacy trial results presented, Union World Conference on Lung Health.
https://www.youtube.com/watch?v=6btCJZGfZko

The evaluation H4:IC31 and BCG revaccination in healthy adolescents

AN INNOVATIVE PROOF OF CONCEPT TRIAL IN ADOLESCENTS

This was the first randomized, controlled, prospective Prevention of Infection (POI) trial conducted to study whether vaccination can prevent *Mycobacterium tuberculosis* (Mtb) infection in high-risk, healthy adolescents. Conducted in the Western Cape Province of South Africa, the trial tested the efficacy of **Bacille Calmette-Guérin** (BCG) and new vaccine candidate **H4:IC31** to prevent an initial or a sustained TB infection.

Research findings:

- The experimental vaccine candidate H4:IC31 did not reduce sustained infections at statistically significant levels.
- BCG revaccination significantly reduced sustained infections with 45% efficacy.

Funded by: Sanofi Pasteur, the UK Department for International Development and Aeras/IAVI.

Ethics approval: Medicines Control Council of South Africa and the Human Research Ethics Committee of the University of Cape Town.

Clinical Trials.gov Identifier: NCT02075203
Published research article: Nemes *et al.*, 2018, New England Journal of Medicine.

> Sustained infection can be prevented by BCG revaccination of adolescents with 45% efficacy - (*Nemes et al*, NEJM 2018).

SATVI Aeras 040 study team

On July 12 2018, the first prevention of *M.tuberculosis* infection (POI) trial results were presented which showed that sustained infection can be prevented by BCG revaccination of adolescents with 45% efficacy (*Nemes et al, NEJM 2018*). These results provide proof-of-concept for the novel prevention of infection trial design and highlight the crucial question of whether BCG revaccination of *M.tuberculosis*-uninfected populations could have long-term impact on TB disease.

ONGOING FOLLOW-UP STUDY: BCG REVACCINATION OF HEALTH ADOLESCENTS FOR THE PREVENTION OF MYCOBACTERIUM TUBERCULOSIS SUSTAINED INFECTION (BCG REVAX).

The purpose of this study is to demonstrate the efficacy of Bacille Calmette Guerin (BCG) revaccination against sustained *M. tuberculosis* infection versus a placebo in previously BCG vaccinated QuantiFERON®-TB Gold Plus (QFT) negative, healthy adolescents. The study started in November 2019 and will enrol 1,800 participants.

Clinicaltrials.gov Identifier: NCT04152161BCG

New TB vaccines

Safety and immunogenicity study of the VPM 1002 TB vaccine candidate with BCG in HIV exposed newborn infants.

This multi-site trial to evaluate the safety and immunogenicity of the candidate recombinant BCG vaccine VPM1002, in HIV exposed and unexposed neonates, compared with BCG is being prepared for publication. Enrolment and follow up completed in September 2019.

VPM1002

VPM1002 is an investigational vaccine co-developed by scientists from the Max Planck Society (MPG) and the Hanover-based VPM.

Development of this vaccine had started in the 1990s with the aim to improve BCG by endowing it with the capacity to stimulate a broader, more efficacious T cell response (Kaufmann 2020).

Photo: On the 27 August 2015 the first infant participant was vaccinated. Study team Leticia Swanepoel, Elisma Schoeman, Mother, infant and Doreen Willemse

WHAT IS MTBVAC?

MTBVAC was developed by the University of Zaragoza, Spain. This vaccine is the first live-attenuated Mycobacterium tuberculosis vaccine to start clinical evaluation in newborns and may offer greater protection than BCG. The vaccine, which has been previously tested in a phase I trial in Switzerland, is intended as a BCG replacement vaccine.

MTBVAC vaccine trial in adults

On 20 October 2015 SATVI vaccinated the first participant in the MTBVAC study, a clinical trial which would evaluate the safety of the novel TB vaccine MTBVAC, first in adults, followed by a dose escalation trial of the safety and immunogenicity of MTBVAC compared to BCG in newborns.

Photo: First adult participant vaccinated on MTBVAC trial in South Africa. From left to right: Dr Hennie Geldenhuys, participant, Sandra Kruger, Yolande Greg and Fazlin Kafaar October 2015.

TB treatment studies

The Rifaquin trial found that a once weekly treatment was as good as six months of daily treatment.

The RIFAQUIN trial investigated both shortening and simplifying treatment and used higher doses of Rifapentine than other studies that tested shortening TB treatment using Fluroquinolones. The 6-month regimen that included weekly administration of high-dose Rifapentine and Moxifloxacin was as effective as the control regimen.

MARK HATHERILL: "The burden of taking tablets is huge for TB patients. Consequently, even with the best will in the world, patients sometimes stop their treatment once they begin to feel better. Over a long period of time this has led to more drug resistant strains."

DANELLE VAN AS: Research Nurse to study Coordinator. "This study was very exciting because of the possibility that TB patients may take less tablets daily and that the time of treating TB could be shortened."

The study was conducted between August 15, 2008, and August 1, 2011.

The study participants were patients with newly diagnosed, smear-positive, drug-sensitive tuberculosis who were assigned to three arms receiving:

- **Control regimen** that included 2 months of ethambutol, isoniazid, rifampicin, and pyrazinamide administered daily followed by 4 months of daily isoniazid and rifampicin;
- **4-month regimen** in which the isoniazid in the control regimen was replaced by moxifloxacin administered daily for 2 months followed by moxifloxacin and 900 mg of rifapentine administered twice weekly for 2 months.
- **6-month regimen** in which isoniazid was replaced by daily moxifloxacin for 2 months followed by one weekly dose of both moxifloxacin and 1200 mg of rifapentine for 4 months.

Results were published in the New England Journal of Medicine of 23 October 2014 (Jindani et al)

The RIFAQUIN trial, which was published in the New England Journal of Medicine, made us realise we could do high quality drug trials

The main focus was to establish a laboratory that is functional and that can adopt any assay

CHAPTER 5

Immunology

A selection of key immunology milestones

- Analyses based on BCG-RCT Nested Immunology Study, initiated in 2002, show that BCG-induced T cell responses do not correlate with reduced risk of TB.
- Study of BCG vaccination of HIV-positive children, conducted between 2003 and 2006, shows that T cell responses are impaired.
- SATVI Laboratory receives accreditation from the South African National Accreditation System (SANAS) in January 2010.
- Immunology assays to measure T cell responses of TB vaccines, performed in in clinical trials of 9 different TB vaccine candidates and BCG between 2005 and 2019, allow inter-vaccine comparison of vaccine immunogenicity.
- Performance of a novel immunodiagnostic test for M.tb infection (QuantiFERON-TB Gold) in the Adolescent Cohort Study informed epidemiological and immunological interpretation of the test.
- First application of QuantiFERON-TB test as clinical endpoint for efficacy trials of vaccine candidates testing prevention of M.tb infection. Partial efficacy of BCG revaccination enabled, for the first time, studies to discover vaccine-induced correlates of protection against sustained M.tb infection in humans.
- Analyses based on the Adolescent Cohort Study lead to discovery of a blood signature that can predict onset of TB. This signature was ultimately assessed in the prospective clinical trial, CORTIS.

Immune responses to BCG vaccination

Since its establishment in 2000, SATVI has established two Good Clinical Laboratory Practice compliant immunology laboratories with excellent scientific teams that facilitate the conduct of cutting-edge immunology studies in a rural field-site setting at the heart of the TB epidemic. SATVI has completed many seminal immunology projects that have contributed substantially to advancing global understanding of immune responses to Mycobacterium tuberculosis and to TB vaccination in humans. Much of the early work focused on developing and optimising practical and rigorous methods to collect and process immunology samples in rural field site settings. SATVI has also established state of the art immunology technologies and relevant expertise to measure and understand the complex interactions between the immune system, Mycobacterium tuberculosis and vaccines.

BCG RCT nested immunology study, initiated in 2002

The very first flagship immunology project conducted at SATVI was the "BCG-RCT Nested Immunology Study", which was embedded into the BCG RCT, and allowed collection of blood samples to determine correlates of risk of TB following newborn vaccination with BCG.

WHAT WAS THE BCG-RCT NESTED IMMUNOLOGY STUDY ABOUT?

This study enrolled 5,675 infants, who were routinely vaccinated with BCG at birth. Blood was collected at 10 weeks of age, processed and cryopreserved, and infants were followed for at least 2 years to identify those who developed TB and those who did not. The research team then retrieved the cryopreserved blood cells to identify immune responses that correlate with risk of developing TB disease. The key finding was that frequencies or quality of BCG-specific T cell responses, previously thought to correlate with protection against TB, did not correlate with risk of TB. The work was published in 2010 (Kagina et al., AJRCCM).

Voices from the field

GREG HUSSEY: "the intent was to develop the capacity at the Worcester site as well as the immunology capacity in Cape Town."

GILLA KAPLAN: "In those early days our thinking was to understand how BCG works"

TONY HAWKRIDGE: "The BCG-RCT samples were a valuable resource for the research community, allowing us to explore the incredible complex field of why some kids respond to BCG in one way and other times not".

TB is the biggest killer of humans due to bacterial infection. In 2019, 10 million people were estimated to develop TB, and 1.4 million died. The only available vaccine against TB, BCG, is given to infants to prevent severe forms of the disease. But protection against lung disease is very variable – particularly in countries where TB is most common, such as South Africa.

WILLEM HANEKOM: "In those early days we were looking for what we called correlates of protection, but which were actually correlates of risk."

Study of immunogenicity of BCG in HIV-positive children, 2003 to 2006

The BCG-RCT nested Immunology Study was later followed by research to evaluate the immunogenicity of BCG in HIV-positive children at a time when concerns were raised about the safety of BCG in HIV-positive infants and when antiretroviral treatment was not universally available through the public health system. The study, which showed that BCG induced T cell responses were significantly impaired in HIV-positive infants and may thus be of limited benefit (Mansoor *et al.*, 2009), contributed to international policy around BCG vaccination in HIV infected infants (Hanekom, 2012). With universal provision of antiretroviral treatment, the revised WHO guidelines now recommend that children born to HIV-infected mothers do receive BCG vaccination.

WHY IS THIS WORK ON BLOOD TESTS FOR TB RISK SO IMPORTANT?

It is very clear that better and earlier diagnosis of TB is necessary if we are to control the TB epidemic. This is because TB diagnosis is not optimal, relies on those who are unwell to seek healthcare at clinics or hospitals, and is restricted to people who can expectorate sputum. A test that is not based on sputum and can identify people very early during the course of TB disease, would allow treatment before the onset of severe lung damage and before they transmit the bacterium to others. SATVI has led many research projects to develop blood biomarkers that allow early identification of those at risk of TB, or who may already have undiagnosed disease. Blood gene expression (transcriptomic) signatures developed by SATVI researchers include the 16-gene ACS signature (Zak, 2016), RISK11 (Darboe et al., 2018) and RISK6 (Penn-Nicholson, 2020). We have also developed a protein signature of risk of TB (Penn-Nicholson *et al.*, 2019).

> SATVI has led many research projects to develop blood biomarkers that allow early identification of those at risk of TB, or who may already have undiagnosed disease.

Blood biomarkers discovered in the Adolescent Cohort Study, 2005 to 2009

The epidemiological Adolescent Cohort Study (ACS), conducted between 2005 and 2009, laid the foundation for the second, very large immunology project at SATVI. Blood collection from 6,363 adolescents who were followed for 2 years allowed identification of those who progressed to active TB (progressors) and those who remained healthy despite evidence of *M. tuberculosis* infection (non-progressors). RNA sequencing of blood samples from progressors and non-progressors allowed identification of correlates of risk of TB disease, based on expression levels of genes that changed more than a year before individuals were diagnosed with TB. This facilitated the development of a gene expression (or transcriptomic) signature, essentially a blood test, that can predict the risk of a person developing TB. The finding was published in 2016 (Zak *et al.*, Lancet 2016). Refinement of this signature led to several other key publications. It also ultimately culminated into the prospective clinical trial, CORTIS, which determined if the gene expression signature can lead to biomarker-targeted preventive treatment of those at highest risk of TB (Scriba *et al.*, Lancet Inf Dis 2021).

HASSAN MAHOMED: "From the ACS study we collected blood samples for immunology and the analysis continued long after I left SATVI"

MARK HATHERILL: "The data from the ACS brought RNA signatures into the mainstream as biomarkers to predict TB"

TOM SCRIBA: "It is amazing to see that the blood collected into PAXgene tubes during the Adolescent Cohort Study, which was ongoing when I joined SATVI in 2006, has led to the development of multiple blood transcriptomic signatures. This work has been pivotal in informing our understanding that TB exists as a disease spectrum instead of the two defined states of latent and active TB."

Biomarker discovery offers hope for identification of those at high risk of TB

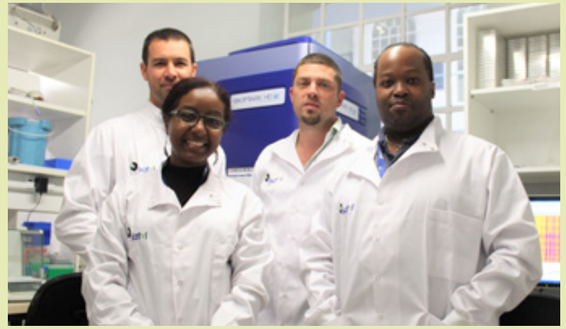
On 12 April 2016 SATVI published the discovery of a blood based biomarker that can indentify those at risk of TB (Zak *et al*, 2016)

> The gene signature which emerged from studies essentially evolved from the understanding that T cells are not going to predict, the level of T cell activation is not going to predict protection, or that it is not the only measure of immunity. – Gilla Kaplan

Growing portfolio of clinical immunology studies

The initial immunology work laid the platform for the generation of a substantial body of literature on the human immune response to BCG and *M. tuberculosis* infection. Notable findings include examining if delayed BCG vaccination would result in an enhanced immune response (Kagina *et al.*, 2009) , a description of the differences in antigen-specific immune responses to BCG administered by percutaneous or intradermal injection (Davids *et al.*, 2006), a study of the longitudinal T cell responses to neonatal BCG vaccination to understand to which degree this response wanes (Soares et al., 2013), a study which demonstrated that BCG vaccination of newborns induces CD8 T cells (in addition to the more prominent CD4 T cell response) (Murray *et al.*, 2006) and a study which reported that IL-17- and IL-22-producing CD4 T cells contribute to the anti-mycobacterial immune response (Scriba *et al.*, 2008).

- **Building RNA research capacity**
  During June 2016 SATVI acquired a Tecan Freedom EVO 150, a core liquid handling and robotics workstation to increase the capacity for high-volume RNA extraction from blood samples. This equipment allowed screening of more than 20,000 individuals for possible inclusion in the CORTIS-01 trial. Depicted is Senior Technologist Mzwandile Erasmus with the Tecan Freedom EVO workstation.



- From left to right: Dr Adam Penn-Nicholson, Dr Sara Suliman, Professor Tom Scriba and Mzwandile Erasmus.

This also facilitated implementation of highly standardized measurements of T cell responses in phase 1, 2 and 2b trials of investigational TB vaccine candidates (Hanekom *et al.*, 2012; Kagina *et al.*, 2015), and led to the first comparison of CD4 and CD8 cell responses induced by 6 different TB vaccines tested at the SATVI field site (Rodo *et al.* 2019). This work provides a data-driven approach for rational selection of TB vaccine candidates for advancement to advanced clinical trials.

We also implemented this standardized measurement of T cell responses as a measure of vaccine immunogenicity in the first phase IIb trial of the MVA85A vaccine in infants, which was conducted at the SATVI field site in Worcester (Tameris, 2013) and contributed to a study of immune correlates of risk of TB in infant participant of this trial (Fletcher *et al.*, 2016), in collaboration with Professor Helen MacShane of Oxford University, who developed the MVA85A vaccine.

This collaborative team measured 22 immune-response characteristics in blood samples from infants in the phase 2 b trial of the MVA85A vaccine and found that elevated activation of CD4 T cells was linked to higher TB disease risk. Higher levels of IFNγ-expressing cells that responded to the BCG vaccine were linked to reduced risk of TB. Interestingly, higher levels antibodies to the mycobacterial Ag85A protein were also associated with lower TB risk.

> "We looked at a number of factors that could be used as immune correlates, to try and find biomarkers that will help us develop a better vaccine," said Professor Helen MacShane of Oxford University, MVA85A lead investigator.

Blood-based biomarker identifies people who have TB or would develop TB in the CORTIS trial

On the 26 January 2021, SATVI published the landmark findings of a prospective clinical trial of a host blood gene expression signature of TB, which differentiated between people who had or would develop active TB, and those who remained healthy. The trial also investigated the efficacy of giving TB preventive therapy based on a positive signature result (Scriba *et al.*, 2021).

Articles

Biomarker-guided tuberculosis preventive therapy (CORTIS): a randomised controlled trial

CORTIS-01 TRIAL

Study aim: 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

Findings:

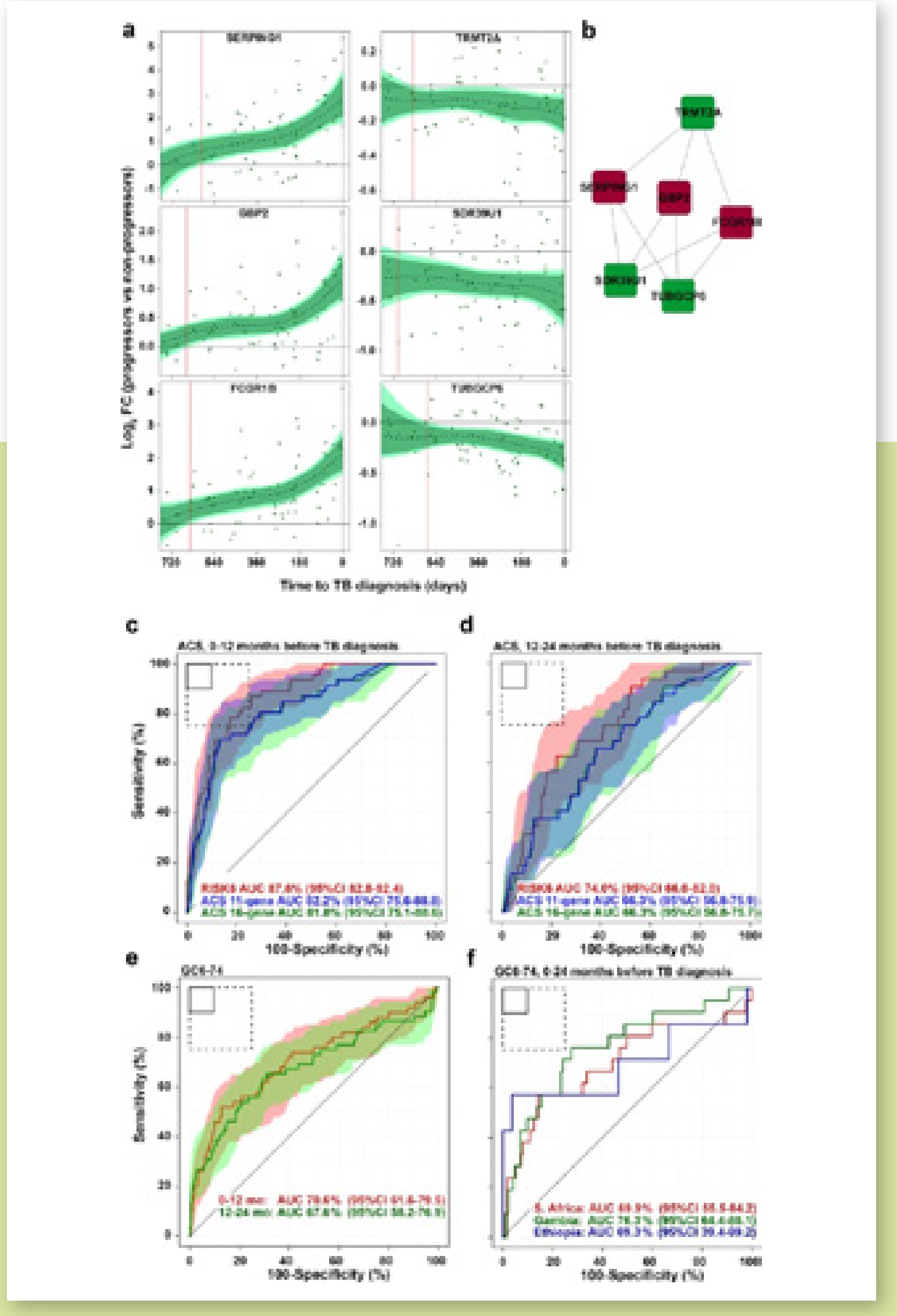
1. The RISK11 blood test discriminated between individuals with current TB disease or those who would progress to incident TB within 6 months after testing, and individuals who remained healthy, with good performance.
2. Disappointingly, the provision of a 3-month preventive therapy regimen of once-weekly, high-dose isoniazid and rifapentine (3HP), which is effective in treating *M. tuberculosis* infection, did not reduce the rate of TB disease in RISK11-positive participants over 15 months of follow-up.
3. The RISK11 signature predicted 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 months after testing.

WHY WAS THIS STUDY CONDUCTED?

Only 5-10% of people with evidence of *M. tuberculosis* infection are at risk of progression to TB disease and would benefit from antibiotic treatment. Treatment of all people who are infected with the TB bacterium is not a feasible prospect in high-burden settings such as South Africa, because the majority of our population is infected. Many people would be treated unnecessarily and the logistical and financial challenges are virtually insurmountable. A test that can be used to identify those at highest risk, who would benefit from preventive treatment, is therefore urgently needed.

RISK6, a robust and simple 6-gene transcriptomic signature of TB disease risk, diagnosis and treatment response

By further building on the gene expression signature work done in the Adolescent Cohort Study, SATVI scientists established a robust and simple, PCR-based host-blood transcriptomic signature, RISK6. This signature can be used to identify individuals at high risk of incident disease, as a screening test for subclinical or clinical tuberculosis, and for monitoring tuberculosis treatment. RISK6 utility was validated by blind prediction using quantitative real-time (qRT) PCR in seven independent human cohorts. Prognostic performance for identification of incident TB significantly exceeded that of previous host-blood transcriptomic signature signatures discovered in the same cohort. The findings were published in 2020 (Penn-Nicholson et al., Scientific Reports).



> The immunology work is groundbreaking research which has informed groups around the world that are working on TB vaccines.
> - Tony Hawkridge

Laboratory and Immunology: Capacity development in support of clinical trials within a Pan African context

From its inception, SATVI has played a key role supporting the broad research agenda by rendering support and training to other clinical research groups within network studies. For example, Tom Scriba and Elisa Nemes have been co-organizers, faculty and teachers of a biannual African Flow Cytometry for more than a decade – work that has led to significant immunology and flow cytometry capacity development in many different African countries (Nemes *et al.*, Cytometry Part A 2015). Also, as part of an European Developing Countries Clinical Trials Partnership (EDCTP) project, SATVI has assumed the role as network training partner, providing training to clinical research groups based in Senegal and Madagascar in performing whole blood ICS assays, Quantiferon assays and differential leukocyte count and immunophenotyping of cryopreserved ex vivo blood (DLC-ICE_ Assay). This included the development of a special instructional video as training aid.

SATVI has built up a world-class clinical immunology infrastructure and laboratory team that operates under Good Clinical Laboratory Practice (GCLP) standards. Our track record in training the next generation of immunologists and clinical scientists and our capacity and expertise in gene expression analyses, flow cytometry, cytometry by time-of-flight (CyTOF), interferon-gamma release assays and many other immunological techniques at the coalface of the TB epidemic places us in a unique position to contribute significantly to achieve "a world without TB".

Whole blood ICS Assay

Whole Blood Intracellular Cytokine Staining (ICS) Assay - Training: Procedure to prepare the sample tubes and perform the whole blood short-term stimulation assay to detect the frequency of antigen specific cytokine producing CD4+ and CDS+ lymphocytes in peripheral blood.

DLC blood assay

Differential Leukocyte Count and Immunophenotyping of Cryopreserved Ex vivo blood (DLC-ICE) Assay: This assay is for determination of relative proportions and absolute numbers of peripheral blood myeloid and lymphoid cell subsets and detection of activated T cells using flow cytometry.

Quantiferon-TB Gold Plus Training

CHAPTER 6

Building the SATVI team

Capacity development was a focus from the early days of SATVI, building not only research infrastructure and operating systems, but investing in our people - The SATVI Team.

I found it amazing that once the laboratory was established in Worcester, it recruited local people and really became outstanding. Every time I visited Worcester, there was more capacity, more knowledge. - Gilla Kaplan

Capacity development at a rural laboratory

The Cape Town and Worcester Immunology Laboratories were accredited as ISO 15 189 compliant medical laboratories during January 2010.

MARWOU DE KOCK: "The SANAS accreditation was blood sweat and tears, involving many documents with many version controls."

CAPACITY DEVELOPMENT WITHIN A GLOBAL CONTEXT

In 2010 the SATVI laboratory hosted technologists from Uganda, Zimbabwe, Tanzania, India and South Africa clinical research laboratories for two one-week training programs in Whole Blood assays as part of the International Maternal Pediatric Adolescent Adolescent AIDS Clinical Trials Group (IMPAACT).

From left to right: Andrea Gutschmidt (SUN, Cape Town), Marwou de Kock (SATVI, Cape Town), Shivali Agiwal (BJMC & SGH, India), Bosco Kafufu (MU– JHUR, Uganda)

Building research capacity at a field research site

Capacity development was high on the SATVI agenda in the early days, because clinical research was a relatively new field in South Africa, there were very few capacity development programs or benchmarked job descriptions.

We insisted on a few non-negotiables, one of which was capacity development. I always used to say that you cannot do anything without developing the capacity of individuals - Greg Hussey

MARIJKE GELDENHUYS: "The first training was focused on the BCG-RCT. Aeras had the idea to build the vaccine research site so that when the Phase 3 trial would start, the site would be ready. The aim of the capacity development program, in addition to building the staff knowledge base, was also to develop clinical research as a profession.

The Siyathinga Professional Development Program (PDP) officially started in January 2003 when Aeras Global TB Foundation brought Professors Silvia Silver and Jennifer Page on board. The goal was to develop a core standard for clinical research and TB knowledge.

WHAT WAS THE SIYATHINGA PROFESSIONAL DEVELOPMENT PROGRAM ABOUT?

The training focused on the developmental needs of every research team member and included topics like clinical infectious diseases, good clinical practice (GCP), clinical research management, epidemiology, biostatistics and laboratory practices. The overall aim was to make research principles practical and understandable.

From left to right: Veronica Dirks, Sunelza Lakay, Nathan Maasdorp, Fazlin Kafaar, Rachel Tobias, Elmarie Simon, Benita van Stavel, Julia Noble.

Poster developed as training aid about the clinical research process.

One of the clinical researchers Eunice Sinanile came up with the name Siyathinga which means "we are moving" - Marijke Geldenhuys

SATVI obtained accreditation for its GCP program when the South African health regulatory authorities decided that there should be a standard for GCP training in South Africa.

By 2005, the PDP was implemented at clinical research sites in India that were part of the Aeras network. It was also extended to sites in Uganda, Kenya and Mozambique.

Angelique Mouton: "I participated in the Siyathinga Professional Development Program which started in 2003 and in December 2007 there was a specialised module on Informed consent"

This program was later presented as part of a two week UCT summer program "Clinical Trials Research Methods" (2011) with a five-year grant from the Fogarty Institute (NIH, undated).

Academic impact

SATVI has established itself as an interdisciplinary TB research group that offers an established clinical research field site and an accredited laboratory research environment to scholars of epidemiology, infectious diseases, immunology or vaccinology, all within the context of TB vaccine research. SATVI has attracted students from Africa and Europe to the postgraduate and postdoctoral fellowship programs, produced more than 300 peer-reviewed papers, and graduated SATVI alumni who have taken leading roles in the Department of Health and non-governmental research organizations, both in South Africa and internationally.

> SATVI is a global brand, everyone in the research space knows of SATVI. It built this brand, through not through marketing, but through the quality of the work it has produced, and so it is still the place to be for anyone wanting to do TB vaccine research
> - Willem Hanekom

TOM SCRIBA: "I joined SATVI as postdoctoral fellow. Before that I was based at Oxford University and there, I was sheltered from clinical research environment.

WILLEM HANEKOM: "SATVI has made an incredible impact and contributed to the two major advances in TB research, the M72/AS01E vaccine and BCG revaccination."

Growing research partnerships

A major contributor to the SATVI success story was the series of productive partnerships with local, national and international networks, including Aeras, the European and Developing Countries Clinical Trials Partnership, the AIDS Clinical Trial Group (ACTG) and at a local level, the Departments of Health and Education.

Photo From left to right: Andrea Soares, Tom Scriba, Willem Hanekom, Gwen Tena-Coki, Ben Kagina and David Kagina (Ben's son).Supervisors Tom and Willem.

Photo: Munyaradizi Muzvosvi (PhD) 2015. With co-supervisor Adam Penn Nicholson.

> What stands out for me was the relationships that you build, not just with the clinic staff, but with the participants. Some people would share personal stuff, which made me feel good because I could do something for others, even if it were by just listening.
> - Julia Noble

Voices from the field

GREG HUSSEY: "In those early days, we had the best collaborative relations with Stellenbosch University in terms of infectious diseases."

"We were also in good standing with the provincial Department of Health and national government, and with the City of Cape Town."

HASSAN MAHOMED: "Working with the Department of Health was not always easy because they were always busy, but we developed a good working relationship with them."

FAZLIN KAFAAR: "When I joined SATVI to work on the Adult Prevalence Study, Hassan arranged for the City of Cape Town to bring a mobile x-ray bus to Worcester."

GILLA KAPLAN: "We believed that SATVI had to have a strong relationship with Brewelskloof Hospital, even if they functioned independently, the relationship was important. In many places, the health workers think that research gets in the way, but in Worcester that was avoided because SATVI was set up in the right way and was supported and liked and that meant you could set up clinics in the hospital, you could have your participants come there."

High level visits to SATVI

SATVI hosts Bill and Melinda Gates

On 2 August 2006, SATVI hosted Bill and Melinda Gates at UCT to gain first-hand insight into the progress of the BCG RCT.

TONY HAWRIDGE: "We then had to decide what we would show the BMGF delegation. The trial had already finished and what was most recent was the work on ascertaining TB in infants. Coming up with a watertight TB disease endpoint in kids was going to be difficult. What we figured out was that if you look at kids from a radiological perspective you get one answer and if you look at it from clinical perspective you get a different answer. We had this set out in tables and then Jerry said: " Why don't you just put this in a Venn diagram", and that is what we presented to Bill Gates.

So Bill listened politely and his comment was "That's terrible, there is hardly any overlap". The findings told us that diagnosis of TB in infant vaccine trials was going to be tricky. I don't know if it has been solved yet."

Click here to read UCT article online.

Advocacy: SATVI briefs the National Parliamentary Portfolio Committee on Health, January 2011.

On 24 January 2011, SATVI and Aeras briefed the national portfolio on Health about the current TB research program, the need for funding and support for TB research. Dr Hassan Mahomed and Dr Willem Hanekom represented SATVI and Sebastian Gelderbloem represented Aeras.

Meeting details:
Summary: https://pmg.org.za/committeemeeting/12458/

Link to presentations:
SATVI presentation: https://pmg.org.za/files/docs/110125SATVI-edit.pdf
Aeras presentation: https://pmg.org.za/files/docs/110125aeras_0.ppt

Stop TB ambassador Craig David visits SATVI

On the 24 March 2010 Craig David, the Stop TB ambassador visited SATVI where he spoke with SATVI clinical investigator Dr Sizulu Moyo during a video interview.

SATVI audiovisual library

Why we need a TB vaccine.

Professor Greg Hussey explains why a new TB vaccine is needed.

Youtube: https://youtu.be/4FGgKxBSdrQ

Target population of the MVA85A study.

January 2010, Professor Hassan Mahomed explains the target population groups of the MVA85 phase IIb trial.

Youtube: https://youtu.be/wN2pl8FLstA

Stop TB Partnership. Craig David interviews Dr Sizulu Moyo.

Youtube: https://youtu.be/4FPS-X3k7Pc

Professor Helen MacShane explains the importance of the MVA85A clinical trial.

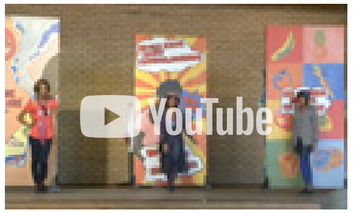
BBC Fergus Walsh conducts interview with Professor Helen MacShane at the Worcester field site about the MVA85A TB vaccine trial.

Youtube: https://youtu.be/FuKQh7fxBzE

Interview on SABC Hello doctor

During 2010 Professor Willem Hanekom featured with TB Ambassador Gerry Rantseli-Elsdon on the Hello Doctor television program where they spoke about TB, the dangers and stigma attached to it.

Youtube: https://youtu.be/BFd9VP6ac1s



Performance of Carina's Choice drama.

Carina's Choice, a video production developed by the SATVI and the Mothertongue community theatre project with the support of the Wellcome Trust.

Youtube: https://www.youtube.com/watch?v=pAosgZO-O0k&t=68s

Focus on research partnership between SATVI and Oxford University on researching TB vaccines, Oxford University.

Professors Val Mizrahi, Mark Hatherill and Doctor Michèle Tameris speak on the challenges of TB and the work that SATVI does.

Youtube: https://www.youtube.com/watch?v=9qtJprCHg3U

Union TV

During November 2015 the work that SATVI does was featured on the Union TV, a conference audio visual channel running for the duration of the 46th *Union World Conference* on Lung Health held in Cape Town from 2-6 December 2015.

Youtube: https://youtu.be/997LEBsXovc

Lienkie's lungs drama performed on SABC Hectic Nine 9 youth magazine program.

During May 2017 the cast of Lienkie's Lungs and Dr Michèle Tameris featured on the SABC Hectic Nine 9 youth magazine program. The drama was developed in a collaboration between Mothertongue a community-based theatre program and SATVI with a Wellcome Trust Public Engagement grant.

Dr Michèle Tameris & Vanessa

During May 2017 SATVI featured Michèle Tameris and Vanessa, as well as the Beat TB drama group.

Youtube: https://youtu.be/GMcdl7edX_8

Movers and shakers Mothertongue drama group.

Youtube: https://www.youtube.com/watch?v=PIXbiTt1TJU&t=3s

Credits

Creative writing, archival content, interview transcription: Kelvin Vollenhoven

Desktop publishing and art advisor: Samantha Mouton

SATVI History working group

1. Ashley Veldsman
2. Julia Noble
3. Kelvin Vollenhoven
4. Linda van der Merwe
5. Mark Hatherill
6. Marwou de Kock
7. Michèle Tameris
8. Tom Scriba

People we interviewed:

1. Angelique Mouton
2. Ashley Veldsman
3. Brian Abel
4. Cheryl Day (Associate Professor)
5. Deon Minnies (Dr)
6. Elmarie Simon
7. Fazlin Kafaar
8. Gregory Hussey (Professor)
9. Gilla Kaplan (Professor)
10. Hadn Africa
11. Hassan Mahomed (Professor)
12. Jane Hughes
13. Julia Noble
14. Lebogang Makhethe
15. Lesley Workman
16. Linda van der Merwe
17. Marijke Geldenhuys
18. Mark Hatherill (Professor)
19. Marwou de Kock
20. Michele Tameris (Dr)
21. Sizulu Moyo (Dr)
22. Tony Hawkridge (Dr)
23. Lesley Workman
24. Tom Scriba (Professor)
25. Willem Hanekom (Professor)

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SPES BONA

20 YEARS OF TB RESEARCH

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TOWARDS A WORLD WITHOUT TB