WHO WE ARE & WHAT WE DO

TB CLINICAL RESEARCH AND IMPLEMENTATION
Aurum is a global leader in the field of TB, with over 20 years’ experience in TB-related epidemiology, clinical research, implementation science and programmatic implementation. The majority of its TB work has been conducted in South Africa and Sub-Saharan Africa, however Aurum has extended its reach to other continents.

The success of Aurum’s TB initiatives stems from the dynamic collaboration within its multidisciplinary team of experts ranging from epidemiologists, health economists and social scientists, to clinical trial specialists and programme managers, who deliver a comprehensive multi-faceted approach for optimal impact and outcomes.

A. Our Technical Expertise

1. TB Research

Aurum has extensive experience in TB research, specifically TB treatment clinical trials, TB prevention trials with vaccines, preventive therapy, epidemiological studies, implementation research and basic science research. Recognition for Aurum’s exceptional research capabilities is based on quality research conducted according to international standards.

Aurum’s resources and expertise in this area include:

- The ability to conduct investigator-led clinical trials, with competencies across the entire spectrum of research processes that include study design, protocol development, operational implementation of studies, database development, data management, trial monitoring, data analysis, study interpretation and write up.

- Four world-class clinical trial sites, eligible for participant enrolment on pharmaceutical trials at Thembisa Hospital, Klerksdorp, Rustenburg and Pretoria.

- Two laboratories that support the TB trials and other types of research required.
with one lab being a fully equipped BSL3 laboratory, which allows for live mycobacteria or any highly infectious pathogens requiring extreme caution, to be handled and grown. These labs exceed the capabilities of reference labs and university research labs, and are staffed by highly qualified scientists, technicians, technologists, pharmacists and clinicians.

- Dissemination of study results, contributing to over 200 publications in the past 10 years. See Annexure 1 for a list of selected TB-related publications.
- Excellent staff retention of well trained, highly experienced researchers.
- Exceptional systems and protocols to ensure safety, integrity and accuracy of research studies.
- Successfully conducting 20 Phase I, II and III TB clinical trials.
- Belonging to a number of influential networks, such as ACTG, HVTN, IAVI/AERAS and TB Alliance
- Being a member of consortia such as ASCENT, TB Sequel, Impaact4TB and PANACEA

1.1. TB vaccines and drug trials

As an international player in TB clinical research, Aurum has successfully conceptualised and implemented TB vaccine and drug trials in various roles, from leading landmark trials to co-leading or providing a significant supportive function with technical assistance at various stages of the clinical research process.

Aurum’s rigorous research process ensures that the findings of the various TB vaccine and drug trials contribute to the body of science and knowledge, and inform international TB guidelines for the prevention and treatment of TB.
Notable studies and their impact

**TB Prevention trials**
The findings of the AERAS GSK phase 2b vaccine trial, conducted in three countries, were a major contribution to the body of research, by providing evidence that the M72/AS01E vaccine had an efficacy of 50% against pulmonary tuberculosis disease in a phase 2B trial after 3 years of follow-up. This result represents the first tuberculosis vaccine in a century that has had significant efficacy.

**TB preventive therapy trials**
The MOI trial was one of the first trials focused on ascertaining whether people who were previously infected with TB, would benefit from TB preventive therapy to reduce TB incidence. The results were published and incorporated into the WHO guidelines for preventive therapy. The WHIP3TB trial was a randomised trial evaluating the use of the 3HP regimen for PLHIV in Ethiopia, South Africa and Mozambique. It investigated the use of preventive therapy once only vs the benefit of repeating after a year. This trial confirmed that periodic preventative treatment was not necessary even in high TB burden countries. The study was led by Aurum and was presented at the Conference of Retroviruses and Opportunistic Infections in March 2020 and contributed significantly to the international policy and guidelines.

The largest trial ever conducted by Aurum is the well-renowned Thibela phase 4 clinical trial that focused on the implementation of a nationwide preventive therapy strategy in a particular setting in the gold mines, with an accompanying epidemiological analysis. Findings of this trial showed that using mass preventive therapy in the form of isoniazid in mining houses did not reduce TB incidence. We were able to demonstrate the feasibility and safety of the use of isoniazid and results of this trial were used to inform international TB preventive therapy guidelines.

**TB treatment trials**
Aurum was involved in two of three TB treatment shortening trials (Remox and Rifafaquin) that were conducted from 2009-2014. Unfortunately, both of these trials found that this regimen did not decrease the duration of TB treatment from 6 months to 4 months., however, the results provided landmark information and contributed to the body of science around decreasing the duration of TB. Information from these trials was used to develop a shorter 4-month regimen which has recently been found to be effective.
Aurum is engaged in unique cutting-edge, exploratory research in Host Directed Therapy (HDT). HDT focuses on stimulating the host immunity response to overcome the bacteria rather than the bacteria itself. Treatment arms with CC-11050 and everolimus resulted in significant improvement in lung function, and trends toward earlier sputum culture conversion. If these outcomes are sustained during follow-up, and validated in a larger confirmatory trial, they could save millions of years of life and millions of DALYs over 10 years if implemented across South Africa. These findings were presented as a late-breaker at the American Thoracic Society annual meeting in Dallas in 2020. This has led to other trials are planned to test different compounds such as NIH metformin and NIH imatinib.

The panTB-HM sutezolid/HDT study (EDCTP, Wallis PI, €8.3M), is the first of its kind clinical trial investigating a candidate pan-TB regimen, and is projected to start late 2021. The study aims to validate a new treatment option for TB in patients, especially in contexts where TB testing is limited and the type of TB and drug resistance are unknown.

Refer to Annexure 2 which tabulates this selection and their impact.

1.2. Basic science research

Aurum’s competencies include basic science, which attempts to understand the immunology of TB and factors that show resistance to TB infection. A credible reputation, expertise in various settings and diverse published research have positioned Aurum as a valuable partner, drawing collaborators such as the University of Washington.

The LIFT IRIS study, Aurum’s first TB study using PET/CT and spirometry and specific end points to measure lung inflammation in HIV and TB, revealed worsened inflammation and lung function are common in patients with greater ART-mediated CD4 responses, and
are associated with persistent impairment of lung function. This research also explored host genetic risk factors and has contributed to accumulating evidence of harm due to unregulated immune reconstitution in patients with active MTB infection, and the findings have appeared in multiple publications.

Current studies include Aurum’s ongoing research in high-risk populations, which focuses on highly exposed Tuberculosis Uninfected (HETU) miners and aims to determine the risk factors and immunological factors for not being infected even after sustained high levels of TB exposure. Along the same theme, Aurum is also working to understand non-infection in household contacts. This study will define the functional αβ and γδ T-cell responses against Mycobacterium tuberculosis to ascertain an association of these responses with protective TB immunity. It is anticipated that these two studies will provide a roadmap for development of new TB tools or vaccines or immunotherapies aimed at preventing LTBI reactivation and TB disease.

For more information on clinical trials, refer to the clinical trials capability statement.

1.3. Epidemiology Research

With over 20 years’ expertise working in epidemiology, accomplished epidemiologists have conducted numerous studies in the field. Core strengths include:

- Monitoring TB disease trends, burden, risk factors and vulnerable populations and conducting research in these areas as needed.
- Conducting extensive TB transmission mathematical modelling to understand how different interventions may influence TB rates.
- Incorporating implementation science into epidemiological work when relevant, eg: establishing the effect or impact of the various interventions for TB.
- Conducting qualitative studies to understand patient experiences and preferences to various interventions.
- Conducting costing studies and cost-effectiveness evaluations of interventions.
- Collaborating with other high-profile institutions, such as the London School of Tropical Health and Johns Hopkins University.

Various epidemiological studies have been conducted to understand TB prevalence and incidence in different groups, e.g. miners, mini taxi drivers, prisoners, and has published systematic reviews in this area, which have informed the body of knowledge. Refer to the publications list in Annexure 1.

Aurum’s mathematical modelling experts ascertain the impact of various interventions on the TB epidemic and use data-driven TB programming to inform implementation models. In addition, our health economists ascertain the cost of treatment to determine the cost-effectiveness of an intervention, such as cost saving per TB case averted. This information is crucial in developing various business cases for the selection of interventions that should be rolled out and are disseminated within the various national working groups.
Performance in programmes and facilities are also evaluated to establish success factors and the information and data gathered from their routine programmatic activities are documented and disseminated and used to establish best practice. Data from these studies are also used to inform the National TB Strategic Plan in South Africa.

**The move towards Implementation Science**

Historically, Implementation Science/Implementation Research was categorised under epidemiology at Aurum. In recent years, implementation research has been integrated into a number of TB research initiatives and implementation programmes.

Implementation Research is an integrated concept that studies approaches to incorporating effective interventions into healthcare policy and best practice for programmatic implementation. In addition, it seeks to understand how research translates into practice.

**Aurum’s expertise and capabilities include:**

- Having conducted over 20 implementation research projects classified under TB prevention & TB treatment, predominantly as investigator led IR research.
- Leading large cluster randomised trials, investigating different strategies for TB, primarily in the area of TB case finding, TB prevention and TB/HIV integration.
- Incorporating all aspects of IR into the scope of work - study design, protocol development, database development, quantitative and qualitative skills, data collection and data management, implementation of the research, trial monitoring, analysis, interpretation and write up.

Aurum’s landmark studies have included, but are not limited to: TB screening (investigated the prevalence of undiagnosed TB in HIV-infected adults; a novel algorithm for TB screening and testing in HIV-infected adults (XPHACTOR); TB diagnosis (the use of GeneXpert point of care testing to accelerate entry into care - XTEND study); TB/HIV integration (use of TB/HIV integration officers to improve TB/HIV integration - MERGE, the use of presumptive TB treatment for ART patients - TB FastTrack, introduction of INH and Point of care CD4 in households for contact tracing - Inhibit TB); an evaluation of TB preventive therapy (Thibela study); and TB treatment (empirical TB treatment for HIV-infected adults).

Aurum’s large cluster-randomised trials have evaluated TB/HIV integration interventions, such as the use of presumptive TB treatment for ART patients (TB FastTrack), which evaluated the effect of a point-of-care TB test-and-treat algorithm on early mortality in people with HIV accessing ART, in 24 primary health centres and involving 3,023 participants. The trial confirmed that presumptive TB treatment was not helpful. Other studies include the use of TB/HIV integration officers in 18 primary healthcare clinics and 1,540 patients (MERGE). Contextual factors were explored to understand why this strategy was unsuccessful.
Programmatic TB implementation has been part of Aurum’s offering for over 20 years. Aurum’s expertise and capabilities include:

- Employing strong management personnel and well-trained human resources in all aspects of the HIV/TB treatment cascade.
- Establishing best practice and state-of-the-art practice for programmatic implementation.
- Informing national and global policy and guidelines.
- Operationalising the Implementation research into practice.
- Collaborating with international research institutions, government, civil society, and national and international academic institutions.
- Providing other implementors with technical support, training and materials to deliver programmes.
- Utilising exceptional project management tools, systems and processes, such as grants management to enhance programme management and coordination. Redcap, a server-based data collection system, allows for the collection of information in a systematic manner, while allowing programmers to support the team to collect and extract data as needed for monitoring purposes.

Using various methodologies in their TB programmes, Aurum’s implementation researchers identify, develop, test and evaluate the impact of various innovative strategies to improve TB service delivery and every aspect of the patient journey, while strengthening the national TB response. Identifying gaps, formulating universally relevant and important key questions, and conducting high quality research to answer these questions. E.g. ascertaining the advantages of using GeneXpert, finding the best algorithm for case finding, understanding the low uptake of a vaccine, establishing the best strategy to rollout a drug.

Examples include TB screening using symptoms and digital X-rays with CAD4TB software in correctional facilities that enabled over 400,000 people to be screened, and revealed TB prevalence was lower than anticipated in these settings. Routine programme evaluation in the mining sector has led to changes in practices in the detection and management of TB in this setting.

Previous work in the field of TB preventive therapy has led to the UNITAID-funded TB prevention project, IMPAACT4TB, a collaborative study taking place across 12 countries – Ethiopia, Zimbabwe, Malawi, Ghana, Mozambique, Brazil, India, Cambodia, Indonesia, Kenya, Tanzania, SA. Aurum is leading the implementation and scale up of 3HP in South Africa, Mozambique and Ghana, in addition to strengthening the healthcare system accordingly.

This will provide access to new and improved TB preventive therapy to over 400,000 patients, kick-starting the quest to reach the global target of 30M people accessing TB preventive therapy by 2022, and significantly catalysing the uptake of TPT in these countries and worldwide.
Various new diagnostic tests for active TB case finding, such as the Hain test when it was introduced, the use of Xpert in various population groups, and the TB-Lam test, have contributed to Aurum’s exceptional competence in establishing the practical applicability of these diagnostic tests and their impact on morbidity and mortality.

Aurum has developed a reputation as an expert in the evaluation of chest x-rays. Previous studies evaluated the chest x-ray utility in miners and the use of mini radiographs, which led to recommendations around the frequency of screening of miners in the South African mining industry. More recently, Aurum completed chest x-ray evaluations of digital radiography and computer-assisted technologies in both correctional settings and primary health clinics. The results contributed towards the body of knowledge, some of which were included in WHO reviews, and others informed international guideline development, and enabled Aurum to capacitate and train other screening teams.

Over the years, Aurum has obtained specialised experience in studying and implementing TB case finding in a number of different populations, such as screening for TB among HIV clinic attendees both in the era pre- and post-ART and pre- and post-GXP. Following the implementation of Xpert MTB Rif, another study investigated a clinical scoring system to identify those requiring further investigation for TB. Aurum’s XTEND study, conducted with the South African NDoH and NHLS, evaluated the scale up of Xpert for TB diagnosis, and addressed whether rapid testing, with quicker turnaround time for test results, would accelerate entry into care and improve health outcomes. Results showed that wide deployment of Xpert did not lead to reduced 6-month mortality compared with laboratory-based microscopy. Despite the advanced diagnostic tool, health outcomes did not improve as health systems were not equipped to handle the increased workload and patients did not receive their results immediately. This provided insights into the importance of health system strengthening and staff capacitation when introducing a new tool. TB screening and diagnosis among special populations including inmates, miners and minibus drivers have also been investigated. The studies showed high prevalence of undiagnosed TB in these populations, however, screening was shown to be difficult with each modality identifying different patients. TB screening using symptoms and digital X-rays with CAD4TB software in correctional facilities enabled over 400,000 people to be screened, and revealed that TB prevalence was lower than anticipated in these settings. Routine programme evaluation in the mining sector has led to changes in practices in the detection and management of TB in this setting.

2.1. TB screening and case finding in communities and special populations

Aurum has extensive experience in community TB screening, having screened over 160,000 household TB contacts, 428,000 community members and 220,000 prison inmates across more than 10 projects globally.

Approximately 200,000 patients have been initiated on TPT in the past 3 years.
Aurum is seasoned at evaluating household TB contact tracing, such as the “Ribolola” TB contact tracing project, in the Bojanala district of the North West Province, the recently completed INHIBIT-TB project, and the Centers for Disease Control (CDC)-Aurum contact tracing project. This work has contributed to systematic reviews and guideline development nationally and at WHO level. Currently, the Asibambisane project is investigating an enhanced system integrated with the ward-based outreach teams to deliver TB contact tracing. Extensive qualitative work to explore difficulties with the current programme has been conducted. Aurum’s work has progressed to the multi-country EDCTP grant, the CUT_TB project, which aims to investigate TB screening with Xpert for contacts and the relative contribution of community contacts compared to household contacts. The project is to begin in 2021 and will include sites in three countries, namely South Africa, Lesotho and Tanzania. These studies will inform the international guidelines.

We have also worked with public-private partnerships in the field of TB case finding.

In Ghana, a TB-Reach funded case finding project using pharmacies and other private entry points is being implemented and is being evaluated.

These projects have demonstrated the need for focused, high-quality TB symptom screening, sputum collection and HIV testing, with ongoing quality assessment and improvement.

Aurum’s vast expertise in this area enables effective implementation, as well as the provision of technical assistance to health workers, as follows:

- Training on TB household contact tracing and infection control (prioritising MDR-TB index patients and children < 5 years)
- Providing data on priority populations requiring targeted screening interventions
- Monitoring the yield of these interventions
- Ensuring facilitated entry into care.

“To seek, to find, to share, to care.”
2.2. TB/HIV Integration

In addition to early ART initiation for PLHIV as a preventive measure for TB infection, other key components of TB/HIV integration that Aurum has extensive experience in include:

- **Intensive case finding** in persons with HIV. We have evaluated Xpert MTB Rif among both newly diagnosed HIV patients and those already on treatment. The study found high prevalence of TB in newly diagnosed TB patients and proposed a scoring system to identify those who should be followed up for TB.

- **Optimal TB infection control** to prevent transmission of TB as outlined in National TB Infection Control Guidelines. Facilities require an infection control committee, biannual assessments, and infection control strategies.

- **Training of facility managers** to implement these measures is provided in the Aurum Manage Development Programme. Community outreach teams are trained on the principles of infection control, particularly for MDR-TB patients receiving decentralised care.

- **Isoniazid Preventive Therapy (TPT)** which reduces TB infections in PLHIV by up to 52%. QI methodologies are applied and used to identify and overcome clinic-level barriers to full IPT implementation.

Without the introduction of new tools, modelling exercises to ascertain the impact of current TB interventions in South Africa show that comprehensively implementing a combination of these interventions has the potential to achieve the WHO 2025 targets for TB. Aurum is engaged in interventions that will significantly contribute to achieving these targets, such as improved linkage to TB care, eliminating initial default, ensuring a cure for every patient, and providing IPT to PLHIV.

2.3. Controlling TB during pregnancy

This is critical as maternal to infant TB transmission has an eight-fold higher risk of early infant mortality. In addition to ART, pregnant women should receive a TB symptom screen at each visit and IPT if indicated.

Furthermore, optimised paediatric TB care is also a critical gap in TB prevention and treatment and Aurum provides training to Clinical Technical Assistants and Mentors involved in paediatric TB care, which contributes to the TB/HIV integration support provided to facilities.
2.4. MDR TB treatment

Aurum’s capabilities include designing and decentralising national MDR-TB treatment programmes and supporting sub-national readiness efforts. Primary healthcare workers and TB focal point persons are trained to use standardised WHO documentation, and manage side effects.

Aurum has previously supported the recent introduction of bedaquiline (BDQ) into the South African MDR programme, which requires close monitoring. Aurum’s pilot mHealth monitoring system includes pharmacovigilance for patients receiving BDQ, and Aurum’s TB Technical Leads provide guidance to MDR programme review committees in monitoring programmatic rollout. A result of Aurum’s quality improvement methodology is the development of a sputum collection instruction video for increasing TB screening yield that has been distributed widely in South Africa. Available in six local languages as DVD or mobile application, it assists patients to provide high quality sputum samples, which are critical for TB diagnosis.

2.5. Digital technologies for TB management

MHealth digital, mobile and wireless technologies are being used to support the achievement of health objectives. Digital technologies are increasingly being used to support case findings and treatment in persons with TB.

Aurum is evaluating the use of digital adherence tools (MERM devices) to support patients initiated on TB treatment. A trial is being conducted in clinics across three provinces in South Africa, to evaluate the effectiveness of using such adherence tools to improve adherence to treatment and to reduce the occurrence of poor consequences of TB. This work will provide a basis for further implementation. The ASCENT TB project is implementing a number of digital adherence technologies (99-DOTS, MERMS and Vide-DOT) across five countries, with the aim of initiating 55 000 TB patients to support TB treatment. This will be extended to drug-resistant TB and latent TB infection treatment.

Refer to Annexure 3 for a comprehensive list of MHealth projects.
3. Quality Improvement

Aurum’s Quality Improvement methodology is core to providing technical assistance to the various departments internally and to external institutions. The objective is to institutionalise QI into all programmes receiving support, through healthcare staff and patients’ collective responsibility. Training, mentoring, peer learning, and the use of data, enables facilities to identify gaps in service delivery and implement changes that improve HIV and TB health outcomes. The process includes identifying problematic areas and gaps in healthcare processes with view to addressing the root cause, analysing the situation, generating change ideas, testing the ideas, and implementing the effective ones. Aurum uses several methods to develop and spread innovations in HIV and TB care such as:

- **Innovation hubs**, i.e. facilities where ‘Innovators’ and ‘Early Adopters’ are willing to test change ideas.
- ‘**Rapid Learning Collaboratives**’ that draw on peer learning to improve a common indicator of interest across a number of facilities.
- **Improvement summits** to benchmark improvement projects.
4. Monitoring & Evaluation

The Implementation Research Division has significant experience in conducting evaluations contributing to a broad evidence base, with support from the M&E department.

Aurum has extensive data management and M&E skills and capabilities for internal processes and to assist partners, sub-partners and the Department of Health to collect, process, analyse and store data, enabling insights into data to inform evidence-based decision making and to report on progress and trends. A dedicated Data Management Department ensures data quality, availability and archiving; and a monitoring and reporting team is responsible for routine reports and data analytics.

Routine monitoring of programme data consists of weekly data collection and monthly reporting. Aurum uses standardised tools for data monitoring and recording, including DoH mandated registers (HTS, VMMC, patient records), stationery, attendance registers, meeting minutes and reporting tools such as Tier.net. Where possible we also utilise a performance management app or a combination of paper-based and electronic systems.

Routine project data quality assurance to monitor and improve data quality record keeping and reporting. Routine data quality audits (DQAs) help to improve data completeness, data quality, and data accuracy and address gaps that otherwise could negatively impact patient care. DQAs are conducted at a subset of sites by multi-sectoral teams from Programmes, Data, M&E.

5. Policy Development

Aurum was instrumental in establishing the South African TB Think Tank and has served as the Secretariat since its inception in 2014. Its role was to develop the Terms of Reference and to ensure support of various stakeholders and organisations through a collaborative and inclusive process culminating in the development of the National TB plan (NTP).

The Think Tank has supported the South African Government in developing numerous TB and HIV guidelines, that have informed 2017 National Strategic Plan for HIV, TB and STIs.

Refer to the Staff Bios which show national and international involvement in TB policy making.
OUR EXPERTS

Aurum has a dedicated team of international and local experts who are available to provide technical and programmatic support to successfully start up and implement TB programmes. The following are some of our world-renowned TB experts:

Professor Gavin Churchyard

Prof Churchyard is specialist physician, internationally renowned for his contributions in TB research. In addition, he is the founder and Group Chief Executive Officer of the The Aurum Institute. He has extensive clinical trials experience, having conducted numerous TB treatment, TB vaccine, TB prevention, TB diagnostics, Host Directed Therapy for TB, HIV vaccine, and microbicide trials. Furthermore, he has conducted research on TB-related morbidity and mortality. Prof Churchyard’s own investigator-initiated studies have involved large, multi-site and often complex studies in South Africa and internationally.

He is currently the principal investigator/Chair of: the WHIP3TB trial evaluating 3HP, a short course TB preventive therapy regimen, given once or annually (ongoing in 8 sites in 3 countries); A5300B/PHOENIx MDR TB trial evaluating delamanid versus isoniazid for preventing TB among MDR TB exposed household contacts in 27 sites in 12 countries; and IMPAACT4TB that aims to scale up and evaluate 3HP (safety and PK with dolutegravir and in children, models of delivery, cost-effectiveness and modelled impact) in 12 high burden countries. He has also served as principal investigator of the following multisite trials: Thibela TB, a large cluster randomised trial of community-wide isoniazid preventive therapy among 80,000 South African gold miners in 20 sites in 3 provinces (Churchyard et al, NEJM, 2014); and XTEND, a large cluster randomised trial to evaluate the impact of the national roll-out of GeneXpert in South Africa on patient, program and population level outcomes in 20 sites in 4 provinces (Lancet Global Health, 2017).

Professor Churchyard sits on various national and international working groups and committees including the AIDS Clinical Trials Group (ACTG) Transformative Science Group for TB where is chair. He is also Chair of the ACTG TB vaccine and Immunology Working Group; member of both the ACTG Scientific Advisory Steering Committee (SASC) and the New Chemical Entities Working Group; Chair of the HVTN Network Evaluation Committee; co-Chair of the HIV Vaccine Trials Network (HVTN) TB vaccine committee; member of the HVTN Scientific Governance Committee; and Chair of the ACTG/HVTN/IAVI TB vaccine Working Group.
**Professor Violet Chihota**

Prof Chihota is a Lead Senior Scientist in the Aurum Global Division. She has been a researcher in global health for over 10 years, designing, managing and conducting clinical research studies in South Africa, Zimbabwe, Botswana, Cameroon, Georgia, India and Malaysia. She previously worked as a Senior Scientific Officer at the Foundation for Innovative New Diagnostics (FIND), Switzerland. She is also a Senior Researcher at the University of Witwatersrand, School of Public Health. Prof Chihota holds a BSc Honours Biological Sciences from the University of Zimbabwe, an MSc Medical Microbiology from London School of Hygiene and Tropical Medicine, a PhD in Medical Biochemistry from Stellenbosch University and is trained in Epidemiology and Statistics from the Johns Hopkins University. She has straddled both the basic science, epidemiology and implementation research fields. Her work has focused on the epidemiology of TB, and evaluating TB-related diagnostic tools and strategies for improving health outcomes in people with TB in the Southern Africa region. Her current interests include diagnosis and treatment of latent tuberculosis infection (LTBI) and resistance to TB infection. She is also a skilled manager of complex interventional implementation research projects, having managed and worked with diverse teams at both Aurum and FIND. Prof Chihota has published widely on HIV/TB co-infection, particularly focusing on the molecular epidemiology of drug sensitive and resistant TB, diagnosis, case finding and linkage to care.

**Associate Professor Salome Charalambous**

Associate Professor Charalambous is the Deputy Chief Scientific Officer at The Aurum Institute. She holds a medical degree from the University of the Witwatersrand and an MSc and PhD in Epidemiology at the London School of Hygiene and Tropical Medicine. She has vast medical research experience in the fields of HIV and TB. She is the Deputy Chief Scientific Officer at Aurum. She has been involved in TB and HIV implementation research since 1998, and has published in areas of TB-HIV research including TB case finding, TB-HIV integration and HIV programme management. From 2003 – 2010, she led an HIV programme implementation, including ART, in settings with private practitioners, mining companies, public sector hospitals and correctional services. Following this period in predominantly programmatic implementation, she focused again on operational research in the fields of HIV and TB and has published extensively on the topics. For TB HIV integration, she has led individually randomised trials, including involvement as the South Africa Principal Investigator on the WHIP3TB trial, which evaluated periodic 3HP in HIV-infected populations, and cluster-randomised trials such as the TB FASTTRACK trial (which evaluated presumptive TB treatment in patients with advanced HIV) and the MERGE trial (which evaluated TB-HIV integration strategies). She is currently leading the Secretariat for the South African National TB Think Tank. She also holds a joint appointment with Wits and Yale Schools of Public Health.
**Professor Bob Wallis**

Prof Wallis is a physician-scientist with training in Internal Medicine and Infectious Diseases, and expertise in the development of biologics, vaccines, and small molecules.

He assumed the role of Aurum Chief Science Officer in January 2014. He holds adjunct appointments as Professor at Case Western Reserve University and Rutgers-New Jersey Medical School, where he previously held full-time positions. He has published approximately 140 manuscripts, review articles and book chapters, mainly in the areas of tuberculosis biomarkers, immunotherapy, and anti-infective drug development. He has particular expertise in the use of innovative models to evaluate new drugs and vaccines. Prof. Wallis came to Aurum after nearly 10 years in the pharmaceutical industry, most recently at Pfizer, where his leadership in anti-infective R&D included the TB candidate sutezolid. He is a member of the editorial board of the Journal of Infectious Diseases and is a Fellow of the Infectious Diseases Society of America and the Royal College of Physicians of Edinburgh. Prof Wallis is presently leading multiple studies of adjunctive host-directed therapies in TB at Aurum.

**Dr Regina Osih**

Dr Regina Osih has 14 years’ experience in infectious disease and public health. She brings to the team technical expertise in infectious diseases, specifically HIV and TB as well as epidemiology and operational research. She has previously worked on projects in several countries in Africa and has spent the last 6 years working in the public health realm in South Africa. Dr Osih was previously employed as the director for TB Access at the Clinton Health Access Initiative, where she oversaw the global TB programme for the organisation. Prior to this, she was the clinical and health programmes director at the Wits Reproductive Health and HIV Institute with oversight of HIV, TB and MTCT programmes within the organisation. In addition, she has had several short periods as an independent consultant in South Africa and Switzerland, managing projects in the fields of clinical research, public health research, HIV prevention and health policy development. Dr Osih holds an MD from the University of Lausanne, Switzerland, an MPH from Johns Hopkins University and is board-certified in Internal Medicine and Infectious Diseases through the University of Maryland.
Dr Yuri van der Heijden

Dr Yuri van der Heijden is an infectious diseases specialist and a Senior Researcher at Aurum. He is also an Assistant Professor of Medicine in the Division of Infectious Diseases at Vanderbilt University Medical Center in Nashville, Tennessee, USA. He has a long-standing interest in global health. His primary research objective is to optimise the care of patients with tuberculosis, with a focus on multidrug-resistant tuberculosis. He is currently collaborating with several investigators in different areas of South Africa to study the clinical and molecular epidemiology of drug-resistant tuberculosis, limitations and opportunities for improvement in programmatic tuberculosis data, and the influence of co-morbidities on tuberculosis outcomes. His qualifications include a medical degree and Master of Public Health from Vanderbilt University School of Medicine, and Bachelor of Science degree from Furman University in Greenville, South Carolina, USA.

Ms Karin Kanewske Turner

Ms Turner has extensive experience in health systems, human capacity development, PEPFAR and other presidential initiative programmes, international health and donor programme management. Before joining Aurum, she was the Global Business Development Director at BroadReach Corporation. Prior to that, she worked at USAID for 12 years, starting at the Global Health Bureau in Washington DC, prior to PEPFAR. She then moved to the USAID Regional HIV/AIDS Programme, based in Pretoria covering Southern and Eastern African countries. Ms Turner was the Director of the Health Systems team at USAID Mozambique for 4 years. She worked in Uganda in HIV/AIDS community programmes, and East Timor with the UN as an Environmental Health Advisor. She also worked in Washington D.C. for the World Bank in the Gender and Water Sanitation Section and at a private healthcare foundation focused on chronic disease care. She began international work as a Peace Corps volunteer in Morocco and a teacher in the Czech Republic. Earlier in her career, she also worked with the University of Colorado as a genetics/molecular biology research assistant under 2 NIH grants. She received her undergraduate degree in Molecular Biology and Biochemistry at the University of Colorado at Boulder, and Masters of Public Health degree in healthcare management from Johns Hopkins School of Public Health.
Noriah Maraba

Ms Noriah Maraba is a Senior Research Manager in the Research Management Department. She has a BSc Medical Science (Hons) degree from University of Limpopo, a Master degree in Epidemiology and Biostatics and PhD in Public Health at WITS University. Her interests are in the use of digital technologies to address gaps within the TB care cascade, and in TB mortality studies and TB linkage to care studies. She is currently involved in studies evaluating the use of digital adherence technologies (medication monitors) to improve TB adherence in DSTB patients, as well as the programmatic roll-out of these digital adherence technologies for DSTB and DRTB patients in SA.
C. Our Experience

The tables below contain selected studies and programmes. Please contact Aurum for an exhaustive list.

Flagship TB programmes

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<tr>
<th>Project name</th>
<th>Thibela TB: design and methods of a cluster randomised trial of the effect of community-wide isoniazid preventive therapy on tuberculosis amongst gold miners in South Africa</th>
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<td>Funder</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<td>Funding period</td>
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**Project Goal:** To establish whether community-wide isoniazid preventative therapy (IPT), administered to an entire ‘at-risk’ community, was more effective than TB preventative therapy given to high-risk individuals only, particularly those with HIV/AIDS or silicosis.

Thibela’s primary objective was to accomplish a 60% reduction in the incidence of TB in the community wide IPT arm, compared to the control arm. If successful, such a programme would have the added advantage of reducing the transmission of TB between people, resulting in fewer cases of TB, which would in turn lead to improved control of the disease. The Thibela study offered IPT treatment to eight mine shaft clusters of gold miners at three mining companies in South Africa over a five-year period. A further seven clusters were enrolled as control groups. Nearly 80 000 mine workers were enrolled into the various components of the study.

Almost 24 000 goldmine workers were started on IPT; the largest number of people to date ever given IPT in a clinical trial.

<table>
<thead>
<tr>
<th>Project name</th>
<th>Xpert for TB: Evaluating a New Diagnostic ‘XTEND’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funder</td>
<td>Bill &amp; Melinda Gates Foundation</td>
</tr>
<tr>
<td>Funding period</td>
<td>2011-2015</td>
</tr>
</tbody>
</table>

**Project Goal:** The aim of the study was to determine whether healthcare worker (HCW) practice in investigating people with TB symptoms was altered when the initial test for TB was changed from smear microscopy to Xpert MTB/RIF.

The XTEND evaluation was conducted in 40 primary health clinics in South Africa. A cross-sectional sub-study at clinics participating in a pragmatic cluster randomised trial, which evaluated the effect of Xpert MTB/RIF implementation in South Africa. Consecutive adults exiting PHCs reporting at least one TB symptom (defined as any of cough, weight loss, night sweats and fever) were enrolled. The main outcome was the number of patients who self-reported having sputum requested by HCW during the clinic encounter just completed. A large proportion of people exiting PHCs reporting TB symptoms did not get tested. Implementation of Xpert MTB/RIF did not substantially change the probability of getting tested for TB. Better systems are needed to ensure that opportunities to identify active TB among PHC attendees are not missed.
**IMPAACT4TB (www.impaact4tb.org)**

<table>
<thead>
<tr>
<th>Funder</th>
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<th>Funder ref. no.</th>
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<tr>
<td>Funding period</td>
<td>Sep 2017 – Aug 2021</td>
<td>Funding amount</td>
<td>$ 58,887,058</td>
</tr>
</tbody>
</table>

**Project Goal:** To reduce TB incidence and deaths among people living with HIV (aged 15-49) and child contacts <5 who are exposed to TB in 12 low- and middle-income countries by scaling up 3HP, a short-course TB preventive regimen of high-dose INH and rifapentine weekly for 3 months.

There are two indicators to achieving this goal:
1. Modelled reduction of TB incidence among PLHIV (all age groups) and child contacts < 5 years in our project countries.
2. The modelled reduction of TB deaths among PLHIV (all age groups) and child contacts < 5 years in project countries.

The project aims to contribute to the sustainable scale up of affordable, quality-assured 3HP, a short-course TB preventive therapy regimen consisting of high-dose isoniazid and rifapentine weekly for three months or over 30 days (3HP/1HP). Thus far, research shows that the current 6-month INH regimen has not significantly decreased the pool of latent TB due to poor uptake. 3HP’s lesser toxicity and shorter regimen may address some barriers to adherence, and has lower risk of generating resistance, with similar efficacy.

The study is taking place in Brazil, Cambodia, Ethiopia, Ghana, India, Indonesia, Kenya, Malawi, Mozambique, Tanzania, South Africa & Zimbabwe.

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**CDC/PEPFAR Care & Treatment Programme**

<table>
<thead>
<tr>
<th>Funder</th>
<th>PEPFAR-CDC</th>
<th>Funder ref. no.</th>
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<tbody>
<tr>
<td>Funding period</td>
<td>2006-present</td>
<td>Funding amount</td>
<td>$283,392,950</td>
</tr>
</tbody>
</table>

**Project Goal:** Aurum has been a leading care and treatment programme implementing partner under PEPFAR, funded through the Centers for Disease Control (CDC) SA since 2006, to provide programmatic implementation and technical assistance for HIV/AIDS and tuberculosis prevention, care, and treatment services throughout the health system in South Africa.

Aurum leads a consortium with exceptional experience and skills to implement evidence-based epidemic control activities in four priority districts in South Africa. Aurum implements a programme of activities to support the decentralised delivery of comprehensive, integrated HIV and TB services, with robust monitoring and evaluation in the priority districts.
Project name: Targeted HIV Testing Services and Tuberculosis interventions in four informal settlements in the eThekwini Metro, and Farm workers and their Families in uMgungundlovu District, KwaZulu-Natal

Funder: Global Fund

Funding period: 2018-2019

Funding amount:

Project Goal: In February 2018, the KZN Treasury Awarded Aurum a contract to implement targeted TB and HIV testing services (HTS) interventions in 8 Wards in eThekwini Metro and 15 Wards in uMgungundlovu district.

Key objectives of the project for TB

- Increase knowledge on HIV, AIDS, TB and STIs to the people living in four informal settlements by the 31 March 2019.
- To increase uptake of HIV, TB and STI testing services by 50% of all people living in the four informal settlements by 31 March 2019.
- To successfully initiate 90% of all TB positive target population on TB treatment according to the National TB guidelines by 31 March 2019.
- To reduce loss to follow up of ART and TB patients by 75% by March 2019.

Project highlights

Three Career Jamborees were conducted at uMgeni, Richmond and at Pietermaritzburg in 2018. Pietermaritzburg hosted the biggest jamboree of all that took place on 4 September 2018 at the YMCA in uMgungundlovu with the below mentioned outcomes:

- A total of 232 youth attended (168 girls and 64 boys).
- 53 youth were tested for HIV (37 of these were girls)
- 161 youth were screened for TB (108 girls and 53 boys).
- 123 youth were screened for STIs – 90 girls and 42 boys.
- 132 CAO application forms were submitted and 58 applicants were accepted by institutions of high learning around KZN.
- uMgungundlovu managed to exceed the stipulated targets for TB.
- All TB initiated patients were provided with nutritional support through food parcel distribution.

eThekwini conducted 5 Health jamborees at Cato Crest, Amatikwe and Amaoti.

- In eThekwini distribution of 202 food parcels in relation to the nutritional support indicator.
- Most sites achieved 70% in all target areas, with one site meeting all targets for TB and HIV cascades.
- Three sites in eThekwini exceeded their TB screening targets, and one site achieved 94% of the target.

Stakeholder collaboration and partnerships were successfully maintained. War room attendance and Municipal DAC and nerve centre meetings were attended. War room equipment was purchased for 20 wards.

Overall project achievements for TB

- 88,803 members of vulnerable populations were screened for TB at eThekwini and uMgungundlovu, achieving 115% of the target. People were initiated onto TB treatment, achieving 115% of the target.
### Comprehensive Prevention Package (CPP) to Key Populations

<table>
<thead>
<tr>
<th>Project name</th>
<th>Comprehensive Prevention Package (CPP) to Key Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funder</td>
<td>Global Fund</td>
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<tr>
<td>Funding period</td>
<td>2016-2019</td>
</tr>
</tbody>
</table>

**Project Goal:** The National Department of Health (NDoH) under the Global fund, selected the Aurum Institute as a Sub-Sub Recipient (SSR) with the mandate of providing a Comprehensive Prevention Package (CPP) to Key Populations. The Aurum Institute was responsible for the provision of this package comprising, HIV counselling and testing services, TB screening using symptoms and digital X-ray screening, STI screening and linkage to care for Peri-mining communities, Informal settlements, and inmates in the Department of Correctional Services (DCS). These services are provided by direct service delivery.

**Outcome for inmates over 3 years:**
- Inmates provided with a CPP in correctional centres – 147,211
- Inmates screened for TB in the correctional centres – 429,993
- Inmates screened for TB with chest x-ray – 125,541
- Number of Clients Presumptive of TB – 26,732
- Number of Clients tested for TB with GXP – 20,758
- Number of Clients Tested TB Positive – 891
- Initiated on TB Treatment – 847

**Peri mining over 3 years**
- Clients screened for TB - 397,431
- Tested for TB – 64676
- Positive for TB – 1574
- Initiated on TB treatment - 1543

**Informal settlements for year 3**
- Clients provided with CPP in informal settlements – 36,413
- TB screening - 35,243
- Tb testing - 6,506
- Positive for TB - 69
- Clients linked to care and initiated on treatment – 62

### A randomized controlled trial of two adjunctive host-directed therapies in rifampin-resistant tuberculosis (DRTB-HDT)

<table>
<thead>
<tr>
<th>Project name</th>
<th>A randomized controlled trial of two adjunctive host-directed therapies in rifampin-resistant tuberculosis (DRTB-HDT)</th>
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<tr>
<td>Funder</td>
<td>Johnson &amp; Johnson Trust, Janssen Pharmaceutica Pty Ltd, European Union</td>
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<tr>
<td>Funder ref. no</td>
<td>GPH-01112018 847465</td>
</tr>
<tr>
<td>Funding period</td>
<td>2015-2021</td>
</tr>
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</table>

**Project Goal:** To examine the safety, tolerability, and preliminary efficacy of two adjunctive TB-HDTs (one anti-inflammatory, and one antimicrobial) in patients with rifampin-resistant pulmonary tuberculosis. Efficacy endpoints will include measures of recovery of lung function and eradication of M tuberculosis infection.

This Phase 2 trial is a randomised, open-label, 3-arm, parallel group trial in RIF-R-TB patients with moderately advanced or far advanced pulmonary disease by chest x-ray. Willing patients providing informed consent are undergoing screening evaluations to establish eligibility. Patients meeting all the inclusion and none of the exclusion criteria are randomly assigned to one of three treatment arms within 14 days after starting screening. All patients are receiving a full course of treatment for RIF-R-TB according to national and WHO recommendations. Those randomised to an experimental arm are concurrently receiving adjunctive HDT during the first 6 months of therapy. HIV-1-infected patients on ART continue ART. Those not on ART, start ART during the period of study participation. All patients are undergoing safety and efficacy assessments no less than monthly during the study treatment period.
Project name: Evaluation of the Effect of 3HP vs Periodic 3HP vs 6H in HIV-Positive Individuals (WHIP3TB)

Project Goal: Weekly isoniazid (900mg) and rifapentine (900mg) for 12 weeks (3HP) has similar efficacy to 6 months of daily isoniazid (6H) as TB preventive therapy. We compared treatment completion rates and effectiveness of 3HP vs. 6H and the effectiveness of 3HP given annually vs. once among HIV-positive people.

Method: HIV-positive people in South Africa, Ethiopia and Mozambique aged ≥2 years, without active TB and on antiretroviral therapy (ART) for ≥3 months or ineligible were randomised 9:9:2 to periodic (annual) 3HP (p3HP), 3HP, or 6H. Participants in the 3HP/p3HP and 6H arms were followed for 24 and 12 months, respectively; all were seen monthly for the first three months of each participation year. Medication doses were directly observed at dispensing visits and otherwise self-administered. Participants in the 6H arm were dispensed 3 months treatment at month 3. Participants were screened for TB with symptoms, chest X-ray and sputum culture after 12 and 24 months. Completion of the initial treatment course in the combined 3HP/p3HP arms vs. 6H was compared using pill counts. TB incidence and all-cause mortality over 12 months was compared in the 3HP and 6H arms, and TB incidence, all-cause mortality, and permanent discontinuation of 3HP for adverse events over 24 months was compared in the p3HP and 3HP arms.

Results: Between November 2016 and November 2017, 4593 participants were screened, 4027 enrolled and 4014 analysed. The median age was 41 years (19 (0.5%) <18 years), all were on ART, 70% were female, 38% were QuantiFERON-TB GOLD Plus positive; 63%, 22% and 15% were from South Africa, Ethiopia and Mozambique, respectively. Treatment completion in the combined 3HP (n=3610) and 6H (n=404) arms was 90.4% versus 50.5% (risk ratio: 1.79; 95%CI:1.62-1.79). TB incidence and mortality by study arm are shown in the table. TB incidence and mortality from month 0 to month 12 was similar in the 3HP and 6H arms. TB incidence over 24 months and from month 12 to month 24 was similar in the p3HP (n=1808) and 3HP (n=1802) arms. Over 24 months, TB incidence among QuantiFERON Plus positive participants, incidence of rifampicin resistant TB, and mortality were similar in the p3HP and 3HP arms. Treatment discontinuation in the p3HP and 3HP arms was 1.2% vs. 0.6% (OR2.11, 95%CI:0.95-5.02).

Conclusion: Treatment completion was higher in the 3HP arms vs. 6H. In high TB transmission settings, annual 3HP did not provide additional benefit to people receiving ART.

Project name: Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR-TB)

Project Goal: This Phase 2 randomised trial aimed to evaluate the safety preliminary efficacy and biomarker response of host directed therapies added to rifabutin-modified standard therapy in adults with drug-sensitive smear-positive pulmonary TB.

The trial is taking place at 27 sites in at least 12 countries, including Botswana, Brazil, Haiti, India, Kenya, Peru, the Philippines, South Africa, Tanzania, Thailand, Uganda and Zimbabwe. The study team has enrolled 5,610 participants, including 2,158 adults ages 18 and older who were being treated for confirmed active MDR-TB through their country’s national TB treatment programme and 3,452 members of their households who were at high risk for developing active TB disease. The participating household members were assigned at random to receive either oral delamanid daily for 26 weeks or oral isoniazid plus vitamin B6 daily for 26 weeks. All at-risk members of the same household received the same drug regimen.
## Project name: Community and Universal Testing of TB Contacts (CUT-TB)

<table>
<thead>
<tr>
<th>Funder</th>
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<th>Funder ref. no.</th>
<th>RIA2019IR-2877</th>
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<tr>
<td>Funding period</td>
<td>2020-2024</td>
<td>Funding amount</td>
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</table>

**Project Goal:** To evaluate a Test-and-Treat strategy that includes universal TB testing of all household contacts regardless of symptoms, complimented by treatment of either TB disease or latent TB infection (LTBI).

A multidisciplinary team of African and European researchers will evaluate this Test-and-Treat strategy in three countries including South Africa, Tanzania and Lesotho. A cluster-randomised trial (CRT), with randomisation at TB source case level will be conducted. Investigators will enroll and randomise 600 TB source cases in each country, and their household or community contacts, to either universal TB Test-and-Treat or standard TB screening and preventive therapy. The aim is to increase TB yield, defined as the proportion of new microbiologically confirmed contacts with TB (primary outcome), and increase the proportion started on TPT among identified contacts. The CRT will be preceded by a LTBI prevalence study in 100 households of TB patients in each country to inform whether LTBI testing should be included in evaluation of contacts in high TB burden settings.

CUT-TB will include socio-behavioural, economic and modelling, paediatric and microbiology work packages to determine: the impact of stigma on both household and community contact tracing; the cost effectiveness of the intervention; strategies to improve case finding and TPT with a specific focus on children; and evaluate TB transmission by comparing mycobacterial strains. Capacity development is a cross-cutting theme which will involve development of clinical expertise in paediatric TB, development of trials expertise in a new TB research site in Lesotho, clinical training on paediatric TB, three PhDs and seed projects for junior investigators.

## Project name: Phase 2b Controlled Trial of M72/AS01E Vaccine to Prevent Tuberculosis (AERAS GSK phase 2b study)

<table>
<thead>
<tr>
<th>Funder</th>
<th>AERAS Global TB Vaccine Foundation (AERAS)</th>
<th>Funder ref. no.</th>
<th>n/a</th>
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<tbody>
<tr>
<td>Funding period</td>
<td>2008-2017</td>
<td>Funding amount</td>
<td></td>
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</table>

**Project Goal:** To assess the safety of M72/AS01E and its efficacy against progression to bacteriologically confirmed active pulmonary tuberculosis disease.

A randomised, double-blind, placebo-controlled, phase 2b trial of the M72/AS01E tuberculosis vaccine was conducted at 3 sites in Kenya, South Africa, and Zambia. Human immunodeficiency virus (HIV)–negative adults 18 to 50 years of age with latent M. tuberculosis infection (by interferon-γ release assay) were randomly assigned (in a 1:1 ratio) to receive two doses of either M72/AS01E or placebo intramuscularly 1 month apart. Most participants had previously received the bacille Calmette–Guérin vaccine. Clinical suspicion of tuberculosis was confirmed with sputum by means of a polymerase-chain-reaction test, mycobacterial culture, or both.

Results showed that M72/AS01E provided 54.0% protection for M. tuberculosis–infected adults against active pulmonary tuberculosis disease, without evident safety concerns.
Project name: Evaluation of a point-of-care tuberculosis test-and-treat algorithm on early mortality in people with HIV accessing antiretroviral therapy (TB Fast Track study): study protocol for a cluster randomised controlled trial - flagship

**Project Goal:** Existing rapid diagnostic tests for tuberculosis lack sensitivity among HIV-positive people, and consequently, tuberculosis treatment is either delayed or started empirically (without bacteriological confirmation). This trial aimed to test whether a primary care-friendly management algorithm enables nurses to identify HIV-positive patients at the highest risk of tuberculosis, to facilitate prompt treatment and reduce early mortality.

The TB Fast Track study was an open, pragmatic, cluster randomised superiority trial, with 24 primary health clinics randomised to implement the intervention or standard of care. Adults (aged ≥18 years) with a CD4 count of 150 cells/μL or less, who had not received any tuberculosis treatment in the last three months, or ART in the last six months, were eligible. In intervention clinics, the study algorithm was used to classify individuals as at high, medium or low probability of tuberculosis. Those classified as high probability started tuberculosis treatment immediately, followed by ART after two weeks. Medium-probability patients followed the South African guidelines for test-negative tuberculosis and were reviewed within a week, to be re-categorised as low or high probability. Low-probability patients started ART as soon as possible. The primary outcome was all-cause mortality at six months. Secondary outcomes included severe morbidity, time to ART start and cost-effectiveness.

The trial confirmed that presumptive TB treatment was not helpful. There remains an urgent need for better diagnostic tests for tuberculosis, especially for people with advanced HIV disease, which may render empirical treatment unnecessary.

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Project name: TB Sequel: Pathogenesis and Risk Factors of Long-term Sequelae of Pulmonary TB

**Project Goal:** TB Sequel is a large cohort study of over 1,600 TB patients followed up over 2 years to measure post-TB lung sequelae in four countries (South Africa, Mozambique, Tanzania, The Gambia). The project aims to systematically assess and describe lung outcomes in African TB patients: understand clinical, microbiologic, host immune, genetic, behavioural, environmental risk factors affecting the long-term sequelae of pulmonary tuberculosis; determine occurrence of reversible and irreversible costs and socioeconomic consequences for TB patients and design and facilitate novel host interventions to restore and preserve overall health and well-being in patients with TB.

This study is an integral part of an overall strategy to fill a knowledge gap needed to improve TB treatment outcomes globally. The main scientific goal is to identify the major pathogenic mechanisms associated with poor TB treatment outcomes, so that such pathways can be interrupted to avert long term TB sequelae.
<table>
<thead>
<tr>
<th>Project name</th>
<th>TB Monitoring Adherence &amp; Treatment Endpoints (TB MATE) project</th>
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<tr>
<td><strong>Funder</strong></td>
<td>Stop TB Partnership Secretariat (Stop TB), Medical Research Council - Sa (Mrc-Sa), Bill &amp; Melinda Gates Foundation (BMGF)</td>
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<td><strong>Funder ref. no.</strong></td>
<td>STBP/TBREACH/GSA/W6-34 SAMRC-SHIP-DST-NDOH OPP1205388</td>
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<td><strong>Funding period</strong></td>
<td>2018-2021</td>
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**Project goal:** The aim of this study is to implement and evaluate the use of an adherence monitoring system (using the Wisepill evriMED device) with a differentiated response to patient care, among drug-sensitive TB patients (DSTB) in three provinces (Gauteng, KwaZulu-Natal and Western Cape) of South Africa.

**Primary Objective:** To evaluate whether implementation of the Wisepill evriMED device with real-time monitoring and differentiated care is able to increase the proportion of patients with >90% adherence to DS-TB treatment.

**Secondary Objectives:**
1. To evaluate whether implementation of the system is able to increase the proportion of patients who successfully complete DS-TB treatment.
2. To evaluate whether the system is able to reduce the proportion of patients with recurrence of TB, a year following end of treatment.
3. To explore the feasibility, acceptability, and fidelity of implementing the adherence monitoring system and differentiated care in drug-sensitive TB patients.
4. To evaluate the cost-effectiveness of this intervention.

**Methods:** 18 clinics in three districts will be selected where patients will receive patient education and implementation of TB treatment adherence monitoring. In each clinic, 145 patients will be enrolled over a six-month period, enrolling up to 2610 patients in total. In the intervention arm, patients will receive the Wisepill evriMED 1000 device reminders and differentiated care in response to real-time adherence monitoring.

This real time (daily) monitoring will be undertaken from a central database. The approach will include automated weekly messages to patients reinforcing good adherence and automated SMS reminders to any patient with one missed dose in a week. A second or third missed dose will trigger a counsellor- or nurse-initiated call to the patient and 4 or more missed doses in a week will trigger a home visit. Should 4 or more doses again be missed, additional measures will be implemented including motivational counselling. The control arm will receive education, provision of the medical device to measure adherence, which will be downloaded at clinic visits. For the control arm, normal follow up procedures using Tier.net reporting will be implemented.

**Significance:** By implementing a programme to improve adherence, we hope to improve treatment completion, reduce rates of loss to follow-up, and reduce TB relapse among TB patients, thereby improving overall TB control and ultimately TB transmission in South Africa.
Project name: Adjunctive host-directed therapies for pulmonary tuberculosis: a prospective, open-label, phase 2, randomised controlled trial

Funder: Bill & Melinda Gates Foundation, Medical Research Council

Funder ref. no.: OPP1127276

Funding period: 2015-2020

Project Goal: To assess the safety and preliminary efficacy of four host-directed therapies for tuberculosis.

Method: In this prospective, open-label, phase 2, randomised controlled trial, patients with pulmonary tuberculosis were recruited at three clinical sites in South Africa. Eligible patients were aged 18–65 years, HIV-1-negative, and had rifampicin-susceptible Mycobacterium tuberculosis, a sputum Xpert cycle threshold of less than 20, and moderately advanced or far advanced disease on chest radiography. By use of numbers generated in blocks of ten and stratification by site, eligible patients were randomly assigned (1:1:1:1:1) to receive one of the four host-directed treatments plus standard tuberculosis treatment or standard treatment alone (the control group). Host-directed treatments were: 200 mg twice daily of CC-11050 with food (day 1–112); 0·5 mg/day of everolimus (day 1–112); 6 mg/day of auranofin after seven doses of 3 mg/day (day 1–112); and ergocalciferol (5 mg on day 1, then 2·5 mg on day 28 and day 56). All study participants received rifabutin-substituted standard tuberculosis treatment for 180 days. Patients and clinicians were not masked to treatment assignment. Spirometry and sputum culture with solid and liquid media were done at baseline and up to 180 days at specified intervals throughout treatment. The primary endpoint was safety and tolerability during treatment. Secondary preliminary efficacy endpoints were treatment effects on sputum microbiology (culture status at day 56 and time to culture conversion up to day 180) and lung function (FEV1 and forced vital capacity [FVC]) measured by spirometry at day 56, day 180, and day 540. Safety was analysed in the intention-to-treat population and preliminary efficacy primarily in the per-protocol population. The trial is registered at ClinicalTrials.gov (NCT02968927), and post-treatment follow-up was completed in 2020.

Findings: Between November, 2016, and September, 2018, 200 patients were randomly assigned to different treatment groups (n=40 per group, apart from n=39 in the everolimus group after one patient withdrew consent). 11 treatment-emergent serious adverse events occurred in total, of which three were attributable to a host-directed treatment. Life-threatening thrombocytopenia occurred in an auranofin recipient; apparent intra-abdominal sepsis leading to death occurred in another auranofin recipient and was classified as a suspected unexpected serious adverse reaction. Tuberculous spondylitis occurred as an apparent paradoxical reaction in a patient receiving ergocalciferol. Two patients in the control group had life-threatening, treatment-attributable liver injury. No treatment-attributable serious adverse events occurred in patients receiving CC-11050 or everolimus. Mean FEV1 in the control group was 61·7% of predicted (95% CI 56·3–67·1) at baseline and 69·1% (62·3–75·8) at day 180. Patients treated with CC-11050 and everolimus had increased recovery of FEV1 at day 180 relative to the control group (mean difference from control group 6·30%, 95% CI 0·06–12·5; p=0·048; and 6·56%, 0·18–12·9; p=0·044, respectively), whereas auranofin and ergocalciferol recipients did not. None of the treatments had an effect on FVC during 180 days follow-up or on measures of sputum culture status over the course of the study.

Interpretation: CC-11050 and everolimus were safe and reasonably well tolerated as adjunctive therapies for tuberculosis, and analysis of preliminary efficacy suggests they might also enhance the recovery of FEV1, a key measure of lung function and predictor of all-cause mortality. Further studies of these candidates are warranted.

Project name: DRTB Data Management Support project

Funder: Johnson & Johnson Corporate Citizen Trust (J&J Trust), Janssen Pharmaceutical Pty Ltd (Janssen Pharma), European Union - European Commission (Eu)

Funder ref. no.: GPH-01112018 847465

Funding period: 2015-2024

Project goal: The IRD project team conducted a monitoring and support for Bedaquiline (BDQ) implementation and provision of quality data on effectiveness of DRTB treatment. The main objectives of this study are to 1) support routine DRTB data quality 2) Strengthen BDQ data reporting (patient information register) and 3) Support Ototoxicity Prevention Programme.
Annexure 1

The tables below contain selected studies and programmes. Please contact Aurum for an exhaustive list.

Selected list of publications

1. A Multicentre Randomised Clinical Trial to Evaluate High Dose Rifapentine with a Quinolone for Treatment of Pulmonary Tuberculosis: The RIFAFQUIN Trial. 20th Conference on Retroviruses and Opportunistic Infections 2013 3-6 March 2013; Atlanta, United States.


11. Xpert MTB/RIF misses the vast majority of TB among symptomatic household contacts. 45th Union World Conference on Lung Health, 2014; Barcelona, Spain.


15. EP-14-228-02, ed. Evaluating the addition of digital chest radiography to routine symptom screening for diagnosing TB within correctional facilities 50th Union conference on Lung Health; 2019; Hyderabad, India.


## Annexure 2

### Selected clinical trials and their impact

<table>
<thead>
<tr>
<th>Trial</th>
<th>Role</th>
<th>Impact/Achievement</th>
</tr>
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<tbody>
<tr>
<td><strong>TB Prevention</strong></td>
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</tr>
<tr>
<td>AERAS GSK phase 2b study represents the first tuberculosis vaccine in a century that had significant efficacy of 50%.</td>
<td>Participating centre</td>
<td>Contributed to the body of research providing new hope for an efficacious vaccine</td>
</tr>
<tr>
<td>MOI Trial - The first TB prevention therapy trial that proved TB incidence did not decrease when people previously infected with TB had additional TB preventive therapy</td>
<td>Led</td>
<td>Results were published and incorporated into the WHO guidelines for preventive therapy.</td>
</tr>
<tr>
<td>The WHIP3TB trial looked at using preventive therapy once only vs benefit of repeating after a year in PLWA in 3 countries, and the evidence showed repeating the dose was not necessary.</td>
<td>Led</td>
<td>The study was presented at CROY, and contributed significantly to the international policy and guidelines</td>
</tr>
<tr>
<td><strong>TB prevention therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 TB treatment shortening trials using Remox and Rifquin were conducted to establish if treatment could be reduced from 6 months to 3 months. The trials ruled out this regimen</td>
<td>Participating centre</td>
<td>Provided landmark information which contributed to the body of science around decreasing the duration of TB, which has eventually led to the discovery of an effective shorter 4-month regimen</td>
</tr>
<tr>
<td><strong>Phoenix Trial</strong></td>
<td>Leading</td>
<td></td>
</tr>
<tr>
<td><strong>Unique exploratory trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDT with CC-11050 and everolimus is unique exploratory research in Host Directed therapy</td>
<td>Leading</td>
<td>Contributed to the field of TB research by increasing understanding and gaining evidence on efficacy of specific compounds in the treatment of TB. These findings were presented as a late-breaker at the American Thoracic Society annual meeting in Dallas. This is a unique area of research that paves the way for other trials planned to test different compounds such as NIH metformin and NIH imatinib.</td>
</tr>
<tr>
<td>panTB-HM sutezolid/HDT study</td>
<td>Leading</td>
<td>First ever clinical trial of a candidate pan-TB regimen; to start late 2021.</td>
</tr>
<tr>
<td>NAC trial in Tanzania</td>
<td>Leading</td>
<td>Has the potential to restore and preserve overall health and wellbeing in patients with TB, which is a significant contribution to patient quality of life.</td>
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</table>
Annexure 3

List of MHealth projects in TB

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<thead>
<tr>
<th>Name of project</th>
<th>Description</th>
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<tr>
<td>TB-MATE</td>
<td>Evaluation of a digital adherence technology (DAT) which uses pill boxes to improve adherence to TB treatment. Patients are provided with a pill box fitted with an electronic module which records the number of times the box is opened. Opening a box is regarded as a proxy for adherence. The module also beeps to remind the patient to take their treatment if the box is not opened.</td>
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<td>i-Beat TB</td>
<td>A completed project conducted to reduce initial loss to follow up. The project digitised TB diagnostic information usually found in paper registers. This was to enable faster availability of TB results reducing unnecessary visits to the clinic by people who don’t have TB. Health workers/project staff used a tablet loaded with an electronic register to record all patient data for TB tests. Software was developed by Mobenzi. This digital technology hastened the receipt of TB results. Patients would choose to have their results either sent to them as text messages, (via call) and be asked to collect them at the nearest health clinic. This part of seamless relaying of TB test results was a huge success and received positive reviews by patients and health workers from the quantitative interviews. This pilot has been developed further and the proposal was submitted as an R01 to the NHI led by Dr Violet Chihota.</td>
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<td>Project Ascent</td>
<td>Builds from the idea of pill boxes in used in TB-MATE. The project aims to scale up and distribute the pill boxes in different countries including South Africa. In the project, the patient will have treatment support from text message and a mobile application where they receive individualised information about their treatment. Patients are also empowered to decide when they will take their own treatment with correct instruction on the correct medication to take and when. The patient will also benefit from text message prompts for actions required of them such as reminders about appointment or when to take their medication if they have forgotten. A mobile application also allows the patients to access information of how they are performing in terms of adhering to their treatment. An added feature allows the patients to communicate with health workers via an application or simple text message.</td>
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<td>The USSD contact tracing</td>
<td>This project proposes the use of a USSD technology, which is available of the most basic feature phone, to improve and optimise contact tracing especially for the hard-to-reach TB contacts. The current methods for contact tracing where community health workers visit home to screen is not cheap, confined to contacts who are in the house, has no definitive effective model yet and hence the need to innovate more in order to improve contacts that are found and screened. In the USSD project, the contacts of TB patients will dial a USSD code which will provide them with the same TB symptom screening questions as would have been done by the health worker. The answers to these questions will be processed in real time and a symptom screen result availed to the contact. Those who results suggest TB disease will be asked to visit their nearest or preferred clinics for further evaluation just as would have happened with community health worker. The USSD technology has strengths of its low cost, familiarity with most cell phone users (a key feature for loading airtime &amp; cell phone banking), ubiquity and the availability on the most basic phone which most people are likely to own.</td>
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<td>Keheala</td>
<td>A new initiative which draws from recent evidence of a study/project conducted in Kenya where health promotion/behavioural economics strategies in the form of nudges and socio-behavioural approaches are used on mobile platforms as interventions to prevent TB. Such interventions include sending positive messages to improve how patients behave. This same approach can also be applied to the current programme of scaling the uptake and adherence to 3HP by patients seeking to prevent TB. The rationale for using this idea in 3HP stems from the uncertainty in the uptake and adherence to 3HP in routine care. The current UNITAID grant which is scaling up the availability of 3HP in public facilities could benefit from this technology. However, its effectiveness and costs have not been evaluated. A grant application was submitted to evaluate the idea therefore in the South African context. In the grant application, the main endpoint is treatment completion. Feasibility and acceptability and feasibility will also be evaluated. Regina Osih stated that Sanofi approached Aurum to pilot an idea like the Kaehla in two countries. There was no talk about conducting an evaluation, but the idea can be explored, and Sanofi may not be opposed to it. Further details of can be obtained from Professor Churchyard or Karin Turner who had the call with representatives from Sanofi.</td>
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<td>CommCare app</td>
<td>A mobile application use in the community with an aim to improve how data are captured and how the people found in the community can be linked back to the clinic. It’s an app that was put together by Demagi which is a Boston company but also has offices in Cape Town. They also did the same in Mozambique where the US government handed over the application to PEPFAR partners to start using the application. Similarly, in South Africa both CDC and USAID partners will start using the application. Aurum will be responsible for rolling this out to entire country and it is aiming to have 40 000 users. Discussion with Demagi are that Aurum could take over the overall app not just the roll out but also the training and data capturing. Currently, the CommCare application is being managed by Lauren de Kock’s team because it is in the training and management phase. The team is however currently seeking to identify a technical. Discussion indicate that it could end up Marinda Bouwer.</td>
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<td>AitaHealth app</td>
<td>This was an application used in an Aurum study where ward-based outreach workers (WBOTs) used tablets loaded with a mobile application called AitaHealth which replaced the paper-based data collection methods performed in the household during household visits. It was hypothesised that using the application would improve accuracy of data collection as a result of reducing the workload usually imposed by paper-based methods. Using AitaHealth would also improve monitoring and evaluation of the community interventions because data and location of the household visits are available to supervisors through a monitoring dashboard. AitaHealth was also expected to improve follow-ups and home visits through reminders on the app where WBOTs are provided with the numbers, location and other identifying information for successful visit to occur. Unsuccessful visits would also be tagged with an automated reminder loaded with information about the exact location and date of follow up. This further reduced the administrative burden of scheduling initial and repeat visits therefore making the contact tracing intervention more efficient. Data from this project are still being analysed. Results from the AitaHealth app could be included in the December report to the MRC to show that they were used to get the CommCare application up and running.</td>
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<td>Digital X-ray</td>
<td>Aurum Innova has been implementing screening programmes using their mobiles fleets fitted with hi-tech but simple and cheap solar powered digital X-ray machines. The fleet also has artificial intelligence application (AI) which reads the images from the X-ray and provides an indicative diagnosis. The accuracy of the AI is also high, therefore can eliminate the volume of X-ray images that would have been read trained radiographer (which would have a redundant and costly exercise). Radiographers are therefore able to concentrate on other productive duties such as the reading of the only those images that require their attention thereby producing higher quality outputs. The X-ray has also been able to read other lung pathologies beyond TB. The Aurum Innova fleet was also fitted with Gene-Xpert machine which also allows added value of a confirmatory diagnosis of TB disease. Aurum Innova has used the digital X-ray in projects conducted in South Africa such as; the prevalence survey, gold mine screening programme, department of correctional services (DCS) screening programme through the Global Fund. They have also conducted similar screening in Namibia and for the prevalence survey Swaziland. Currently, two state of the art vehicles have been shipped to Zambia to performed more similar work. Data from these programmes which is vast has not been sufficiently evaluated and no publication has been produced.</td>
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<td>MBOB x-ray reading AI app</td>
<td>Aurum Innova is also working with the Medical Bureau for Occupational Disease (MBOD) to develop a machine learning algorithm to read spirometry results to determine lung function. In developing the algorithm, clinicians were asked to about the key factors/ indicators they consider when determining lung function. A machine learning algorithm was then built using these key indicators to also produce a lung function diagnosis without the need for human intervention. Lung function results from this the algorithm were compared independently to the physical clinician’s diagnosis and more than 90% of the results were congruent. Once developed, this could eliminate the need for using imported algorithms that are not developed locally.</td>
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<td>X-ray scheduling app</td>
<td>Stemming from the high demand for distributing digital X-rays to underserved areas, there has is growing need to develop a scheduling app which will facilitate the deployment of the vehicles to areas where X-rays are more required. The app will also be intelligent enough to immediately communicate the results of the diagnosis to the providers and partners.</td>
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<td>Electronic tick registers project</td>
<td>A project that is running in Ekurhuleni that’s been run through the HSD. In the project, they have “electronified” the ticket registers which are found at each clinic and the data would feed that into DHIS. It should have now been turned into an electronic application. It was also presented by the Gauteng province at the TB innovations meetings as something to take forward and get funding for.</td>
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<td>CRD mHealth app</td>
<td>To provide more information on the mHealth technologies that have been used in clinical trials. Get Tanya or Naydene for the next meeting</td>
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“To seek, to find, to share, to care.”

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