ANNUAL REPORT

Fiscal Year 2022

(July 2021-June 2022)

Vanderbilt Tuberculosis Center

VANDERBILT UNIVERSITY

MEDICAL CENTER

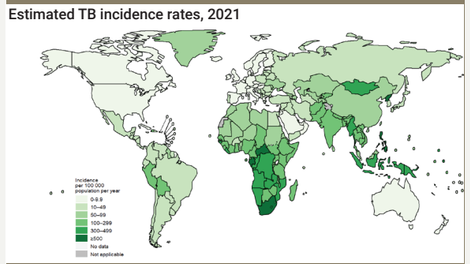
About the Vanderbilt Tuberculosis Center
The global burden of tuberculosis (TB) is enormous; approximately one-quarter of the world's population is infected with *M. tuberculosis*, and there are approximately 10 million new TB cases each year worldwide. Established in 2012, the Vanderbilt Tuberculosis Center (VTC) is a focal point for collaborative efforts in TB research that contribute to a reduction in the burden of TB and TB/HIV globally, including in Tennessee and Nashville. The VTC facilitates this in three ways:

- **Expand the Vanderbilt global research portfolio** in TB and TB/HIV, with a focus on epidemiology, clinical trials, and translational research.
- **Develop and mentor junior faculty members, fellows, and students** from Vanderbilt, Meharry, and collaborating health departments and international institutions. Particular attention is paid to investigators who are under-represented minorities and/or women, given the disproportionate burden of TB and HIV in these groups.
- **Provide technical assistance to the Vanderbilt-linked local and global service programs engaged in TB control**: the Metro Nashville Public Health Department, the Tennessee Department of Health, and PEPFAR/Global Health Initiatives in the Americas, Africa, and Asia.

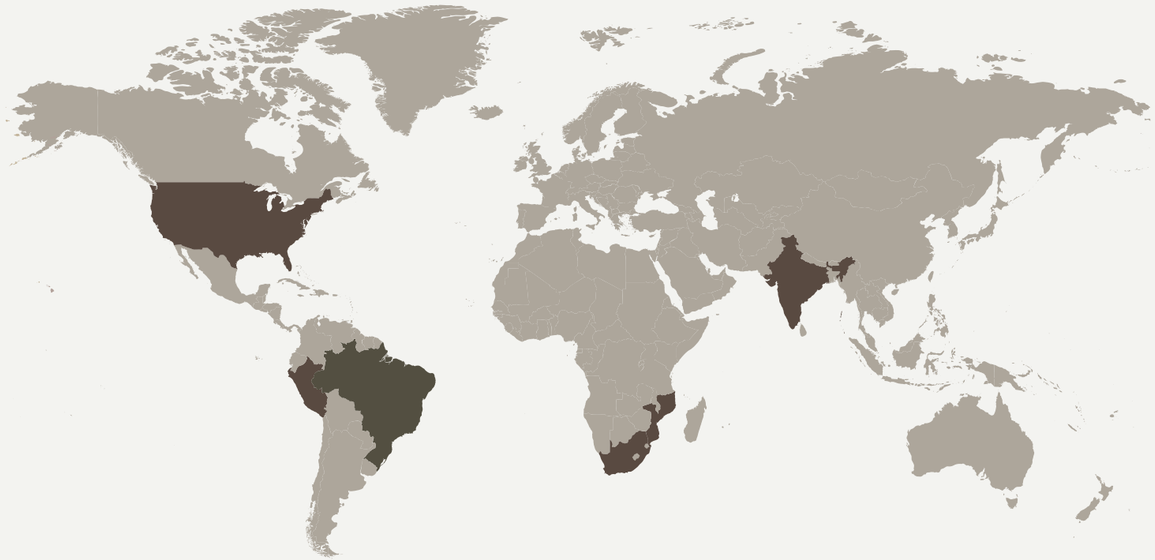
The VTC builds on the strengths of Vanderbilt University Medical Center and Vanderbilt University in clinical and translational research, and includes the full spectrum of discovery from bench to bedside to outcomes. With expertise in population data management, data quality, and study coordination, our research focuses particularly on epidemiology, host and pathogen factors that predispose to disease, clinical trials, and outcomes and implementation research. We do this in six broad area of research: Treatment and Prevention, Drug Resistance, TB/HIV, Transmission and Pathogenesis, Tools and Diagnostics, and Training the Next Generation of TB Scientists.

The Tuberculosis Epidemic
Tuberculosis (TB) is the **second leading cause of death from a single infectious agent** (behind COVID-19, higher than HIV/AIDS). In 2021 the World Health Organization (WHO) estimated that 10.6 million people developed TB disease, there were 1.4 million deaths among HIV-seronegative people and an additional 187,000 deaths from TB among persons living with HIV. The figure below details incidence by country (WHO Global TB Report 2022). The Vanderbilt TB Center works in many of the countries that have high TB incidence rates (see map on following page), and contributes to research to stop TB disease burden.

Estimated TB incidence rates, 2021



The severity of national TB epidemics, in terms of the number of incident TB cases per 100 000 population per year, varies widely among countries. In 2021, countries with the highest rates were mostly in the WHO African Region.



Vanderbilt Tuberculosis Center Collaborators
The VTC is a joint effort of the Division of Infectious Diseases within the Department of Medicine and the Vanderbilt Institute for Global Health. In addition to other partners at Vanderbilt, local and international collaborators include:

- Metro Nashville Public Health Department
- Tennessee Department of Health
- Meharry Medical College
- Boston University
- Emory University
- Harvard University
- University of Massachusetts
- University of Washington
- Johns Hopkins University
- Rutgers University
- Southeastern National TB Center
- Instituto Nacional de Infectologia at FIOCRUZ, Brazil
- Centro Municipal de Saude de Duque de Caxias, Brazil
- Universidade Federal do Rio de Janeiro, Brazil
- Fundação de Medicina Tropical, Brazil
- Instituto Brasileiro para Investigação da Tuberculose, Brazil
- Fundação Jose Silveira, Brazil
- Universidad Peruana Cayetano Heredia, Peru
- University of Cape Town, South Africa
- Stellenbosch University, South Africa
- University of Witwatersrand, South Africa
- Aurum Institute, South Africa
- African Health Research Institute, South Africa
- Centro de Investigação em Saúde de Manhiça, Mozambique

The Vanderbilt TB Center participates in the following research networks:

- Regional Prospective Observational Research in Tuberculosis (RePORT), **Brazil, South Africa**, India, China, Philippines, Indonesia
- The Tuberculosis Trials Consortium (TBTC) of the Centers for Disease Control and Prevention (CDC)
- International Epidemiologic Databases to Evaluate AIDS (IeDEA)—NIH
  - » The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA
  - » The Caribbean, Central and South America Network (CCASAnet) for HIV Epidemiology-IeDEA
- The Antiretroviral Therapy Cohort Collaboration

Dr. Ribka Berhanu joined the Division of Infectious Diseases as an Assistant Professor in September 2021. She is an infectious diseases physician and clinical researcher, currently based in Johannesburg, South Africa. Dr. Berhanu's research is focused on improving the diagnosis and treatment of tuberculosis in high-burden countries. Her work is supported by an NIH K08 award to study the social networks and molecular epidemiology of drug-resistant tuberculosis transmission in two South African communities. She was previously the clinical manager of a specialized drug-resistant TB treatment unit at Helen Joseph Hospital, a public teaching hospital in Johannesburg, where she continues to see patients on the infectious disease consult service. She has collaborated extensively with researchers from the Health Economics and Epidemiology Research Unit (HERO) of the University of Witwatersrand, examining linkage to care in drug-resistant tuberculosis, treatment outcomes and toxicity, and cost-effectiveness. Dr. Berhanu will be an invaluable addition to our Division and our TB Center!

In March 2022, we participated in a grant submission led by **Eric Skaar** in response to NIH's call for support for biomedical research facilities (C06). VUMC proposed development of a new BSL3 research laboratory, that will markedly enhance our ability to perform laboratory-based TB research. The proposal, "Developing the VUMC MICRO facility to advance innovative BSL3 research", was successfully funded and we look forward to assisting with the development of the facility over the next 5 years!

Regional Prospective Observational Research in Tuberculosis (RePORT)-International is a global network of research sites in India, Brazil, Indonesia, South Africa, China, and the Philippines dedicated to collaborative tuberculosis research. A standardized research protocol (the Common Protocol) guides the enrollment of participants with active pulmonary tuberculosis and contacts into prospective observational cohorts. The VTC is involved in both the RePORT-Brazil and RePORT-South Africa networks, as well as the RePORT International Coordinating Center (RICC).

During the past year, we **re-competed for both the RePORT-Brazil network and the RePORT-International Coordinating Center**. These applications were submitted to NIH in December 2021 and March 2022, respectively. Rutgers led the submission of the RICC renewal, while we at Vanderbilt led the submission for RePORT-Brazil. Both applications received promising scores and are likely to be funded in 2023.

The VTC is the coordinating center for the **RePORT-Brazil** network. The RePORT-Brazil semi-annual meetings were held in October 2021 and March 2022 in Rio de Janeiro and Manaus, Brazil. Phase 2 enrollment began in June and to date, 151 participants have been enrolled. We have also been busy analyzing the existing data and specimens collected during Phase I, and have published several important manuscripts in the past year, including the following:

- "The Effect of Diabetes and Prediabetes on Mycobacterium tuberculosis Transmission to Close Contacts", Journal of Infectious Diseases, lead author: Maria Arriaga
- "A clinical prediction model for unsuccessful pulmonary tuberculosis treatment outcomes", Clinical Infectious Diseases, lead author: Lauren Peetluk
- "Determinants of losses in the latent tuberculosis infection cascade of care in Brazil", BMJ Global Health, lead author: Alexandra Souza

Additionally, Lauren Peetluk and Paul Wada both presented **abstracts from studies utilizing RePORT-Brazil data at the Conference on Retroviruses and Opportunistic Infections (CROI) 2022**. Lauren presented on "Isoniazid and rifampin plasma exposure are associated with TB treatment outcomes" and Paul presented on "Sex differences in latent tuberculosis infection among close contacts in Brazil."

We continue to collaborate with **Dr. Moises Huaman** at the University of Cincinnati. He and Yuri van der Heijden co-authored a publication this year on "Cytomegalovirus Infection Is Associated with Increased Prevalence of Latent Tuberculosis Infection". Moises continues to collaborate with the TB Center on his studies of latent tuberculosis infection and immune and vascular function.

We were able to host our first in-person meeting this year since COVID. In June 2022, **researchers from Brazil, South Africa, and the University of Washington visited Vanderbilt for a meeting** pertaining to our study entitled, "Immunogenetic predictors of active and incipient TB in HIV-negative and -positive close TB contacts" (NIH R01AI147765). It was a productive meeting, focused on project progress to date and data analyses; it was also great to finally see our colleagues in-person again!

The VTC **welcomed new Program Manager Cody Staats** in June 2022. Cody comes to us from Arizona State University's Center for Science and the Imagination. His experience includes nearly a decade of program and grant management overseeing pre-award, post-award, and closeout for gifts/grants from diverse funding sources. Cody will be focusing on RePORT-Brazil, while also taking on additional responsibilities in managing the portfolio of grant-funded projects at the TB Center.

Our colleagues at the University of Cape Town **successfully recompeted the HIV-Associated Tuberculosis Training Program (HATTP)** (D43TW010559) in August 2021; the new funding cycle began in May 2022. This grant's goal is to develop the next generation of clinician scientists in HIV-TB at UCT and accelerate transformation of the demographic composition of researchers at UCT to address disparities that persist from apartheid. David Haas leads this work at VUMC, and we look forward to welcoming new trainees to Vanderbilt during the next 5 years of the program.

During the 2022 Annual Conference of the National Tuberculosis Controllers Association, **the Vanderbilt TB Center was awarded the Joe B. Ware Partner Service Award**. The award "recognizes an organization that has made a significant effort and/or contribution to the mission of TB control and prevention through partnership activities with public health TB programs." Jason Cummins, Director of the TB Elimination Program for the Tennessee Department of Health nominated the Center. From Jason's nomination "The Center's research and influence reaches institutions both domestically and internationally. The Center and Dr. Sterling have been active in the TB Trials Consortium. On a local and state level, Dr. Sterling and others in the Center provide consultation and direct patient care to clients at the Metro Nashville Public Health Department TB Clinic." The TB Center is grateful for this recognition.

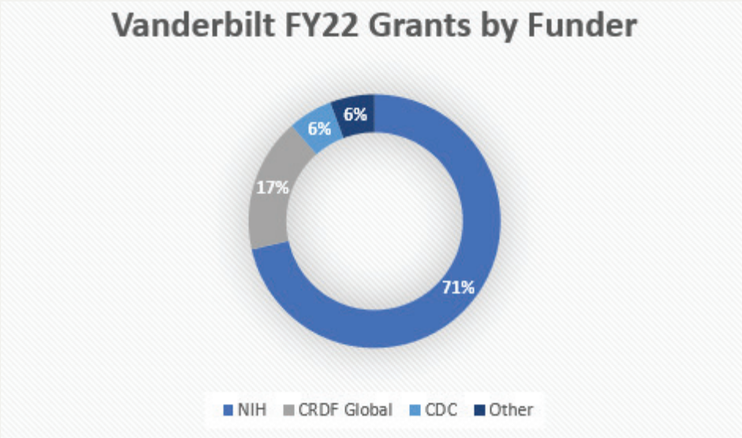
Fiscal Year 2022 Executive Summary

In the current fiscal year (July 1, 2021 – June 30, 2022), there were 35 TB research projects and total grant funding of $14,897,614 ($11,289,502 direct costs, $3,608,112 indirect costs), a 12% increase in total funding from FY21. Please see the funding table at the end of this document. Not included in the table is the endowed David E. Rogers Professorship, which provided partial support for Dr. Tim Sterling.

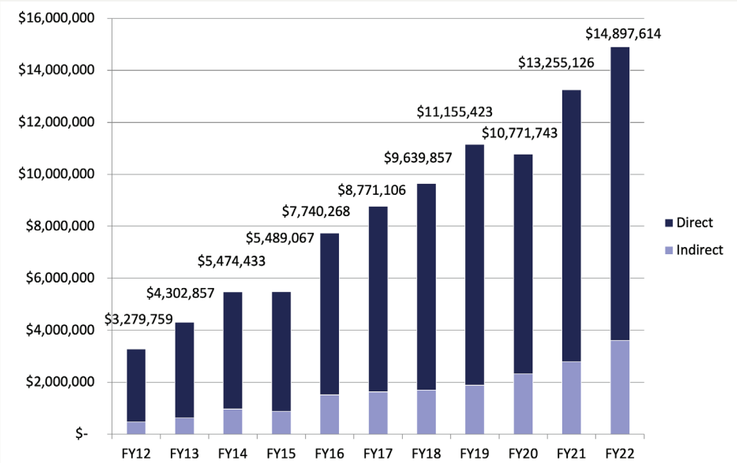
In the previous fiscal year (July 1, 2020 - June 30, 2021), there were 33 TB research projects with total grant funding of $13,255,126 ($10,476,444 direct costs, $2,778,683 indirect costs).

We acknowledge research funding from the U.S. National Institutes of Health, Centers for Disease Control and Prevention, Civilian Research and Development Foundation, Brazilian Ministry of Health, and South African Medical Research Council.

The number of submitted and awarded grants has steadily increased. We are pleased to report the amount of grant funding awarded for TB research at Vanderbilt has more than tripled since the center's inception in 2012, and we have exceeded $14 million in funding. We would like to acknowledge support from the Vanderbilt Institute for Global Health and the Division of Infectious Diseases in the Department of Medicine.



Total Grant Funding by Year for TB-related projects at Vanderbilt



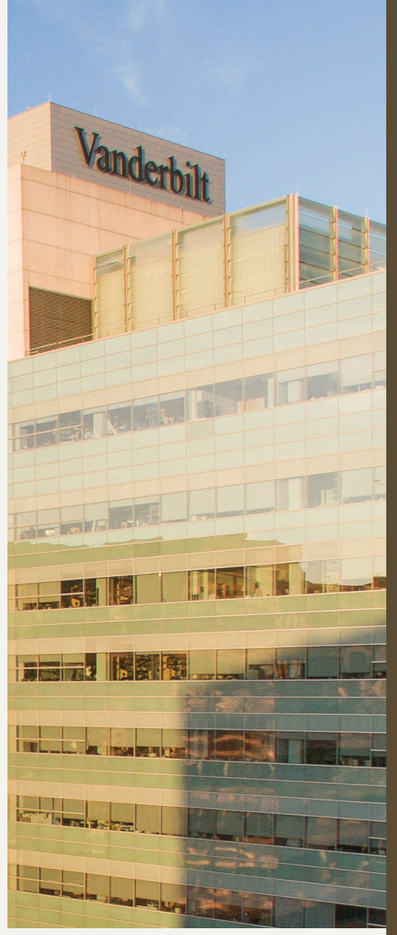
The **TB case conference** held monthly in collaboration between the Metro Public Health Department, the Tennessee Department of Health, Meharry Medical College, and Vanderbilt continued for its 19th year, led by Metro TB Medical Director, **Joanna Shaw-KaiKai**. With the assistance of **Jason Cummins** at the Tennessee Department of Health and **Christina Fiske** at Vanderbilt, this has been expanded to a **state-wide online case conference** that includes clinicians and staff from TB clinics throughout Tennessee. This has been a great platform to discuss complicated TB and LTBI cases, and get input from providers across the state of Tennessee. **Lauren Peetluk and Paul Wada** have also presented research results at this new conference. Additional consultation was provided by **Timothy Sterling and Ritu Banerjee** throughout the year. Vanderbilt infectious disease fellows continued to see patients with Drs. Shaw-KaiKai and Sterling on Friday mornings at the Metro Public Health Department TB Clinic.

In August 2021, Dr. Sterling served as a moderator for a meeting on the TB Research Landscape in the Philippines in the Midst of the COVID Pandemic. In September 2021, he served on an expert panel roundtable on TB pathogenesis and treatment at the 4th Annual Advanced TB Research Training Course sponsored by the University of Washington. On World TB Day (March 24, 2022), Dr. Sterling gave a talk at the symposium "O Brasil Inova—Quimoprofilaxia para TB" at the Fundacao Jose Silveira in Salvador, Brazil. Dr. Sterling also taught at the McGill Summer Institute in Infectious Diseases and Global Health in Montreal (June 2022), giving talks on TB Research Methods. And at the II Seminario Amazonico de Pesquisa Clinica em Tuberculose in Manaus, Brazil (June 2022), Dr. Sterling gave a talk entitled "Tratamento de curta duração da infecção por *M. tuberculosis*: opções atuais e estudos em andamento." Dr. Sterling continued to serve on the **U.S. Department of Health and Human Services Adult HIV Opportunistic Infection Guidelines Committee**.

Infectious Diseases Grand Rounds (IDGR) and **Vanderbilt Institute for Global Health Grand Rounds (VIGH GR)** continued to be held online and there were many TB-related presentations in FY2022: **Paul Wada** presented ID GR in May 2022 on "Sex Differences in Latent Tuberculosis Infection Among Close Contacts in Brazil". **Yuri van der Heijden** presented his work during the Vanderbilt Translational Research Forum on "Tuberculosis in South Africa: Preventing Resistance to Older and Newer Drugs."

The VTC continued to host meetings to foster collaboration in TB research at Vanderbilt and collaborating partner sites. In February 2022, guest lecturer **Kelly Dooley** presented on "Treatment of Tuberculosis: Advancing Toward a Better Future." In June 2022, **Nancy Séraphin** visited from the University of Florida and presented on "The public health importance of Mycobacterium tuberculosis intra-host genetic variability". Nancy also spent a few days on campus meeting with TB Center faculty and staff.

TB Center Program Manager **Hilary Vansell Riley** is participating in a new training grant in collaboration with the Institute for Global Health (**Holly Cassell**) and the Aurum Institute in South Africa. The NIH-funded G11 Global Infectious Disease **Research Administration**



Development Award training grant provides advanced training to senior administrators from LMIC institutions with the ultimate goal to improve oversight of NIAID grant awards and compliance with NIH funding policies and Federal research funding requirements for NIAID-supported foreign institutions in LMICs.

The **VTC website** continues to highlight VTC research and offer resources related to TB treatment and grant funding. The website is frequently updated with grant opportunities, publications, documents for grants and upcoming conferences and workshops. Please see the **Events** section for upcoming meetings and events. To receive VTC newsletters, **sign up here**.

Treatment and Prevention

Reducing the human reservoir of *M. tuberculosis* infection through early TB detection, treatment and prevention are vital to reducing the global burden of TB.

Vanderbilt works closely with the **Tennessee Department of Health** and **Metro Nashville Public Health Department** to better treat and prevent TB disease among populations locally and internationally.

Tim Sterling continued as Protocol co-Chair of the **Tuberculosis Trials Consortium (TBTC) of the Centers for Disease Control and Prevention's Study 37 (ASTEROID)**, a trial for latent TB infection. Study 37 is assessing six weeks of daily rifapentine vs a comparator arm of 12-16 week rifamycin-based treatment for latent *M. tuberculosis* infection. Enrollment started in August 2019, but had to pause in early 2020 due to COVID, but has since resumed.

Collaborator **Larissa Otero** from Universidad Peruana Cayetano Heredia was awarded a **K43 grant** in September 2018 from Fogarty International Center (FIC). Her grant is titled "Patient-centered intervention to prevent TB among children <5 years old", and Tim Sterling is one of her faculty advisors. Larissa is the first investigator in Latin America to receive the K43 award.

Elizabeth Phillips collaborates with **Graeme Meintjes** at the University of Cape Town on an R01 project investigating "Immune-mediated adverse drug reactions to HIV and TB treatments in South Africa: predict, prevent and improve long-term outcomes (IMARI SA study)".

In the annual cross-consortium competition for RePORT-focused scientific projects, we had **two projects funded by CRDF Global this past year**. The first involves RePORT-Brazil, India, and South Africa, and will research the effects of **COVID-19 and tuberculosis** on one another, "Associative BRICS Research in COVID-19 and Tuberculosis (ABRICOT)". The second project involves RePORT-Brazil and India, and explores **innovative modelling methods for predicting TB treatment outcomes**.

Drug Resistance

Multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid and rifampin, and extensively drug-resistant TB (XDR-TB), defined as MDR-TB strains that are also resistant to fluoroquinolones and second-line injectable agents, are a growing concern. Researchers at Vanderbilt, with collaborators in Tennessee as well as Lima, Peru and Cape Town and Durban, South Africa, study resistance to TB drugs, with a particular focus on the fluoroquinolones. These agents are widely used to treat other bacterial infections, which can increase the risk of drug resistance in TB, and also affect the diagnosis and treatment of TB.

Work has continued on the **PRE-EMPT study** (Predictors of Resistance Emergence Evaluation in MDR-TB Patients on Treatment, R01AI134430), which is led by **Robert Horsburgh** at Boston University. This is an observational study of multi-drug resistant TB in which patients are being enrolled through RePORT-Brazil and RePORT-India. To date, more than 300 participants have been enrolled. Results of the TBTC OptiQ study of levofloxacin dose-ranging, conducted at the Cayetano site in Peru and in South Africa are expected in 2022.

Neil Osheroff continued work on a VA grant, which was renewed in 2018 for an additional four years. This research focuses on interactions between fluoroquinolones (and related compounds) with DNA gyrase from wild-type and mutant *M. tuberculosis* strains. Understanding the basis of drug-gyrase interactions is a key concept in designing novel drugs that display greater activity against the enzyme and can overcome resistance. Recent findings have shown promising results, by **making a slight chemical change to the drug moxifloxacin, it has much better activity against the wild-type gyrase enzyme**; it maintains activity against resistant enzymes; and in all cases, it forms more stable DNA strand breaks. In addition, the **laboratory is working on a group of gyrase-targeted drugs** called "novel bacterial topoisomerase inhibitors" as well as other drug classes that are showing excellent activity against wild-type and fluoroquinolone-resistant *M. tuberculosis* gyrase. This exciting work could have important therapeutic implications.

Yuri van der Heijden continued work on his R01 grant entitled, "**Poor Treatment Response and Outcomes in Bedaquiline-Based Treatment Regimens for Drug-Resistant Tuberculosis in South Africa**" (R01AI158605-01). Collaborators include Peter Rebeiro and Gustavo Amorim at VUMC; Violet Chihota and Gavin Churchyard at the Aurum Institute; Rob Warren and Anzaan Dippenaar at Stellenbosch University; and Gary Maartens and Paolo Denti at the University of Cape Town. In this study, the group aims to determine the clinical, pharmacokinetic, and mycobacterial genotypic and phenotypic predictors of programmatic poor treatment response and outcomes of drug-resistant tuberculosis in South Africa, which will allow targeted interventions among high-risk individuals. Currently the study team is working through regulatory and start-up requirements before enrollment begins. In May 2019 he became a Senior Researcher of the **Aurum Institute in Johannesburg**. He remains on the Vanderbilt faculty, and splits his effort between South Africa and the United States.

Work is nearing completion on an NIH-funded R56 grant, "Fluoroquinolones and Efflux-Mediated Cross Resistance in HIV-related TB", which builds on work done by **Brandon Eilertson, Fernanda Maruri**, and **Amondrea Blackman** on the role of DNA gyrase mutations and efflux pumps in fluoroquinolone resistance. This project was in collaboration with **David Sherman**, **Tige Rustad**, and **Bob Morrison** from the Center for Infectious Disease Research (CIDR) in Seattle, and **Yan Guo** at the University of New Mexico. **Fernanda Maruri**, together with **Amondrea Blackman, Yuri van der Heijden**, and **Peter Rebeiro**, identified an optimal frequency of genetic mutations in *M. tuberculosis* that identifies fluoroquinolone resistance. This has implications for future diagnostic tests of drug-resistant TB.

TB/HIV

TB is closely linked to HIV; HIV has been a key contributor to the TB epidemic. People with living with *M. tuberculosis* and HIV infection are significantly more likely to develop TB than persons who are HIV-negative. To control TB in high HIV-prevalence settings, it is imperative to coordinate efforts for TB and HIV control. Vanderbilt collaborates with international organizations and performs studies in population-based cohorts to identify ways to reduce the burden of TB among persons living with HIV.

Work continued on the R01 project, "**Predictors of treatment toxicity, failure, and relapse in HIV-related tuberculosis**" (R01 AI120790), which began in August 2016. This study builds on the existing **RePORT-Brazil** Cohort, for which Vanderbilt serves as the coordinating center. The over-arching goal of this project is to optimize the treatment of HIV-related tuberculosis in a large, genetically diverse cohort in Brazil, by characterizing the relationship between human genetic single nucleotide polymorphisms (SNPs), tuberculosis and HIV drug levels, and tuberculosis treatment outcomes. The project involves colleagues at all RePORT-Brazil sites (including **Valeria Rolla and Felipe Ridolfi**) as well as Vanderbilt investigators Tim Sterling, David Haas, Digna Velez Edwards, Jacqueline Piekos, Brian Hachey, Gustavo Amorim, and Stephany Duda, and Ed Acosta from the University of Alabama-Birmingham. Participant enrollment and laboratory assays are complete; data analyses are underway.

In the past year, the **Caribbean, Central, and South America Network (CCASAnet) for HIV epidemiology**, led by **Catherine McGowan** and **Stephany Duda** has continued to collect and synthesize data through the Vanderbilt Data Coordinating Center (VDCC). CCASAnet has created a shared repository of HIV patient data that has been merged from 10 sites throughout Latin America. This dataset has allowed high-quality analyses of HIV and TB. The most recent published analyses were led by **Tim Sterling and Brenda Crabtree**, and investigated TB treatment intermittency in the continuation phase and mortality in HIV-positive persons receiving antiretroviral therapy. The findings were published in BMC Infectious Diseases in April 2022.

Work has continued on **Bryan Shepherd's R01** grant titled "**Statistical methods for correlated outcome and covariate errors in studies of HIV/AIDS**". This project involves two sites from CCASAnet in Peru and Mexico, and two sites from IeDEA-East Africa in Uganda and Kenya. The goal of this project is to create novel statistical methods, study design, and tools to assist with the validation of patient records and improve the estimation of outcomes for HIV/TB studies. The group is currently developing a study on the timing and type of test for bacteriologically

confirmed TB and associated outcomes and will compare the validated and non-validated datasets, and data audits of TB data have begun at both EA and CCASAnet sites.

Yuri van der Heijden and John Koethe continued work on a grant from CRDF Global **exploring immune activation and dysglycemia in TB patients with and without HIV**. This project is a collaboration between the VUMC CFAR site and the RePORT-South Africa AHRI site. Analyses are ongoing and results are expected to be published in 2023.

C. William Wester leads a large **CDC/PEPFAR**-funded initiative in Mozambique entitled, the "**Avante Program**" where the Vanderbilt University Medical Center (VUMC)/Friends in Global Health (FGH) team provides technical assistance supporting the scale-up of comprehensive HIV and TB services, including the provision of combination antiretroviral therapy (ART). This program (CoAg# GGH002367) received a 5-year renewal (9/30/2021 thru 9/29/2026). As part of this new award the VUMC/FGH team is continuing to make great strides in across numerous programmatic areas, as they now provide extensive support to 144 sites that are providing potentially life-saving ART, a significant increase from 18 ART sites when the initiative began in late 2012. Significant progress in terms of performance related to key TB indicators was made during the recently completed five-year reporting period. A total of 18,405 patients were diagnosed with TB during COP20 (9/30/2020 thru 9/29/2021), the last year of the cooperative agreement, a 2- fold increase compared to COP16, the first year of the cooperative agreement. HIV testing coverage among TB infected patients was above 95% in all reporting years of the Avante Program. ART coverage improved from 88% in COP17 to 100% during the last year (COP20) of this recently completed 5-year grant award.

Transmission and Pathogenesis

A better understanding of the pathogenesis of TB is key to developing novel approaches to combating this disease. Researchers at Vanderbilt along with international collaborators have been working to improve our understanding of the mechanisms behind *M. tuberculosis* transmission and pathogenesis.

Tim Sterling, Bruno Andrade (Brazil), and Thomas Hawn (UW) were awarded a **R01** in 2019 and two associated administrative supplements, titled "**Epidemiologic, immunologic, and genetic predictors and mechanisms of incipient, sub-clinical, and active TB in HIV-infected and -uninfected close TB contacts**" (R01AI147765). This project seeks to understand the protective and predisposing factors for progression from *M. tuberculosis* infection to TB disease. The group will evaluate innate immune responses in macrophages and their correlates with human genetic polymorphisms, acquired immunity to *M. tuberculosis*, and epidemiologic factors associated with the risk of incipient and active TB. These studies are being performed in the Regional Prospective Observational Research in Tuberculosis **(RePORT)-Brazil** cohort. This work may identify host pathways associated with protection against TB (for future host-directed therapies and vaccines), and to identify persons infected with *M. tuberculosis* who would benefit most from TB preventive therapy. Collaborators include Spyros Kalams, Simon Mallal, and Peter Rebeiro at Vanderbilt; Bruno Andrade, Valeria Rolla, Afranio Kritski, Marcelo Cordeiro Santos, Solange Cavalcante, Cristina Lourenco, and Maria Arriaga in Brazil; Thomas Hawn and Javeed Shah at the University of Washington; and Mark Hatherill, Thomas Scriba, Simon Mendelsohn, and Prisca Thami at the University of Cape Town.

The **Regional Prospective Observational Research for TB (RePORT)-Brazil** cohort is co-funded by the NIH and the Brazilian Ministry of Health. This multi-year observational cohort has been established to perform translational studies of the pathogenesis of *M. tuberculosis* infection and TB disease. The cohort consists of approximately 1,200 TB cases and 2,000 of their close contacts across 5 sites in three cities in Brazil (Rio de Janeiro, Salvador, and Manaus) and will lay the groundwork for many important future studies and funding opportunities for VTC members. It is coordinated with similar networks in India, South Africa, China, Indonesia, and the Philippines. Enrollment began in June 2015 in Rio de Janeiro, in January 2016 in Manaus, and in Salvador in June 2016. The first phase of enrollment ended June 30, 2019; follow-up was complete by June 30, 2021. There have been > 200,000 specimens collected, processed, and stored in the biorepository. Phase 2 began enrollment in June 2022 and to date has enrolled 151 participants.

The VTC is also a partner site for the **Regional Prospective Observational Research for Tuberculosis (RePORT)- South Africa**. Phase 2 of RePORT-South Africa was funded in October 2020, led by the University of Cape Town. Mark Hatherill (UCT) and Tim Sterling are the Co-PIs for this phase, and participant enrollment is underway. The Vanderbilt team has been heavily involved in data quality assessments, as well as database development through REDCap, ensuring that the data collected are harmonized across other RePORT networks.

Bruno Andrade, Salvador site-PI for the RePORT-Brazil network and an adjunct faculty member at Vanderbilt, studies biomarkers for susceptibility to TB disease. Through a CRDF Global supplement, he and **John Koethe, Henrique Serezani**, and **Tim Sterling** are investigating prospective profiling of eicosanoid and inflammatory balance in TB-diabetes. This study will evaluate participants from RePORT-Brazil and RePORT-South Africa and will also utilize the Eicosanoid Core at Vanderbilt. The results were recently published.

Another CRDF Global grant awarded to **Thomas Hawn, Bruno Andrade**, and **Tim Sterling** is investigating **macrophage immunogenetics and incipient tuberculosis in Brazil**. This project involves the RePORT-Brazil sites and the UW CFAR site and builds on work on latent infection already happening in the cohort.

RePORT-Brazil also collaborates with **Neel Gandhi** at Emory University on an R01, "**Characterization of Genomics and Metabolomics among Individuals Highly-Exposed, but resistant to Mtb Infection**" (R01AI139406). Such persons are considered "resistors", and may provide important insights into protection against *M. tuberculosis* infection.

Tools and Diagnostics

Rapid and accurate diagnosis is critical for timely initiation of TB treatment, but many people with TB (or TB symptoms) do not have access to adequate initial diagnosis. New tools and diagnostics are needed that can accurately diagnosis TB disease and be utilized in settings across the globe.

David Wright and Rick Haselton continue work on their R01, "**A 100-fold more sensitive TB diagnostic based on magnetic concentration and "coffee ring" formation**". In many settings, inspection of a stained sputum sample under a microscope remains the primary diagnostic tool for tuberculosis. This project proposes a simple modification of this well-established procedure to increase its sensitivity and extend its capabilities to detect drug resistant strains. The approach is based on a magnetic gathering of tuberculosis bacilli from the total sputum volume and, using the microfluidics of "coffee ring" formation, concentrate any tuberculosis present into a pre-selected region of a slide for inspection by standard bright field microscopy.

Rick Haselton was also awarded a new R21 grant investigating, "**Urine TB diagnostic by amplicon reconstruction for PCR detection of DNA fragments**". Current diagnostic methods are most often based on detection of biomarkers in a sputum sample which is difficult to obtain in children and HIV-infected individuals. The much more easily obtained urine sample has been suggested as an alternative patient sample for diagnosis.

There are two additional diagnostic projects in Brazil. The first is an evaluation of a **novel urine lipoarabinomannan (LAM) test** developed by **David Wright** that his doctoral student **Michaela Jorge** will evaluate in RePORT-Brazil specimens, in collaboration with Valeria Rolla and Adriano Gomes. The second is a **sputum PCR-based test (Truenat)** for the diagnosis of TB that is similar to the current GeneXpert test. This study is being led by Afranio Kritski in Brazil, in collaboration with other RePORT-Brazil investigators.

Training the Next Generation of TB Scientists

The VTC aims to train the next generation of TB scientists, enabling them to succeed in their research and academic goals, and provide opportunities for TB training.

David Haas collaborates with **Graeme Meintjes** at the University of Cape Town on the **HIV-Associated Tuberculosis Training Program (HATTP)** (D43TW010559). This grant's goal is to develop the next generation of clinician scientists in HIV-TB at UCT and accelerate transformation of the demographic composition of researchers at UCT to address disparities that persist from apartheid. VUMC hosted two Ph.D. students from South Africa as part of the

training grant, **Zinhle Cindi** spent January-October 2019 under the mentorship of David Haas, and **Phuti Choshi** spent December 2019-June 2020 under the mentorship of Elizabeth Phillips. The grant was successfully renewed for a second funding cycle, which began in May 2022; we look forward to welcoming new students to Vanderbilt over the next 5 year period.

The **Vanderbilt Infection Pathogenesis and Epidemiology Research Training Program (VIPER)** (T32AI007474), led by **Spyros Kalams**, was successfully refunded in August 2021 for another funding cycle. The objective is to prepare postdoctoral fellows for careers in infectious diseases basic science, translational research, and epidemiology in infectious diseases.

Leonardo Barreto, Public Health Technologist at **Instituto Nacional de Infectologia Evandro Chagas – FIOCRUZ**, spent March-August 2022 in the Sterling Lab evaluating subtle changes in drug resistance (Minimum Inhibitory Concentration - MIC) in *M. tuberculosis* isolates from study participants from the NIH-funded project "Predictors of treatment toxicity, failure, and relapse in HIV-related tuberculosis" (R01AI120790). This work was conducted in collaboration with Cindy Nochowicz, Research Specialist Sr., and accompanied by Evan Peace, an undergraduate student from Wheaton College, who interned with VUMC over the summer as part of the Undergraduate Clinical Research Internship Program (UCRIP). Their work in the BSL3 lab with 175 *M. tuberculosis* isolates, has opened doors to a variety of collaborative opportunities. In early August, Leo visited the Sarah Fortune Lab at Harvard's T.H. Chan School of Public Health, where together with the Christopher Sassetti Lab at UMass's Chan Medical School, work is underway to interpret changes in MIC in the context of the underlying whole genome sequencing, based on this work.

Next Steps and New Submissions

There are currently several NIH grants in development or under review. Program Managers Hilary Vansell Riley and Cody Staats will continue to seek out and announce TB funding opportunities as they are posted and offer support in developing the necessary components.

We also wish to add a laboratory-based investigator with strengths in latent *M. tuberculosis* infection, including methods to improve its detection, and factors associated with progression to tuberculosis disease. A background in host and/or pathogen genomics would be beneficial for both the VTC and the Division of Infectious Diseases. Such a scientist would provide synergy with the current strengths of the VTC, including expertise in population-based work, and access to large, well-characterized cohorts.

Selected Recent Publications (2021-2022)

1. Queiroz ATL, Araújo-Pereira M, Barreto-Duarte B, Gomes-Silva A, Costa AG, Andrade AMS, Miguez-Pinto JP, Spener-Gomes R, Souza AB, Benjamin A, Sant'Anna F, Figueiredo MC, Mave V, Salgame P, Ellner JJ, Sterling TR, Cordeiro-Dos-Santos M, Andrade BB, Rolla VC. Immunologic Biomarkers in Peripheral Blood of Persons With Tuberculosis and Advanced HIV. Front Immunol. 2022 Jun 10;13:890003. doi: 10.3389/fimmu.2022.890003. PMID: 35757685; PMCID: PMC9226490.
2. Porter M, Choshi P, Pedretti S, Chimbetete T, Smith R, Meintjes G, Phillips E, Lehloenya R, Peter J. IFN-γ ELISpot in Severe Cutaneous Adverse Reactions to First-line Anti-tuberculosis Drugs in an HIV Endemic Setting. J Invest Dermatol. 2022 Jun 1:S0022-202X(22)01500-7. doi: 10.1016/j.jid.2022.05.1059. Epub ahead of print. PMID: 35659939.
3. Anderson K, Pietersen E, Shepherd BE, Bian A, Dheda K, Warren R, Sterling TR, van der Heijden YF. High mortality among patients hospitalized for drug-resistant tuberculosis with acquired second-line drug resistance and high HIV prevalence. HIV Med. 2022 May 24. doi: 10.1111/hiv.13318. Epub ahead of print. PMID: 35608016.
4. Walker NF, Karim F, Moosa M, Moodley S, Mazibuko M, Khan K, Sterling TR, van der Heijden YF, Grant AD, Elkington PT, Pym A, Leslie A. Elevated Plasma Matrix Metalloproteinase-8 associates with Sputum Culture Positivity in Pulmonary Tuberculosis. J Infect Dis. 2022 May 1:jiac160. doi: 10.1093/infdis/jiac160. Epub ahead of print. PMID: 35510939.
5. Antimycobacterial Susceptibility Testing Group. Updating the approaches to define susceptibility and resistance to anti-tuberculosis agents: implications for diagnosis and treatment. Eur Respir J. 2022 Apr 14;59(4):2200166. doi: 10.1183/13993003.00166-2022. PMID: 35422426; PMCID: PMC9059840.
6. Holzman SB, Perry A, Saleeb P, Pyan A, Keh C, Salcedo K, Narita M, Ahmed A, Miller TL, Pettit AC, Khurana R, Whipple M, Katz D, Largen A, Krueger A, Shah M. Evaluation of the latent tuberculosis care cascade among public health clinics in the United States. Clin Infect Dis. 2022 Apr 1:ciac248. doi: 10.1093/cid/ciac248. Epub ahead of print. PMID: 35363249.
7. Crabtree-Ramirez B, Jenkins CA, Shepherd BE, Jayathilake K, Veloso VG, Carriquiry G, Gotuzzo E, Cortes CP, Padgett D, McGowan C, Sierra-Madero J, Koenig S, Pape JW, Sterling TR; CCASAnet Region of IeDEA. Tuberculosis treatment intermittency in the continuation phase and mortality in HIV-positive persons receiving antiretroviral therapy. BMC Infect Dis. 2022 Apr 5;22(1):341. doi: 10.1186/s12879-022-07330-5. PMID: 35382770; PMCID: PMC8985331.
8. Arriaga MB, Araújo-Pereira M, Barreto-Duarte B, Sales C, Miguez-Pinto JP, Nogueira EB, Nogueira BMF, Rocha MS, Souza AB, Benjamin A, de Oliveira JG, Moreira ASR, Queiroz ATL, Rodrigues MMS, Spener-Gomes R, Figueiredo MC, Durovni B, Cavalcante S, Lapa-E-Silva JR, Kristki AL, Cordeiro-Santos M, Sterling TR, Rolla VC, Andrade BB; RePORT-Brazil consortium. Prevalence and Clinical Profiling of Dysglycemia and HIV Infection in Persons With Pulmonary Tuberculosis in Brazil. Front Med (Lausanne). 2022 Jan 21;8:804173. doi: 10.3389/fmed.2021.804173. PMID: 35127760; PMCID: PMC8814308.
9. Pietersen E, Anderson K, van der Heijden YF. Public health and hospital-based nursing intersection: Case study of drug-resistant tuberculosis patients. Public Health Nurs. 2022 Jan;39(1):170-179. doi: 10.1111/phn.13042. Epub 2022 Jan 6. PMID: 34990027; PMCID: PMC8766955.
10. Haas DW, Abdelwahab MT, van Beek SW, Baker P, Maartens G, Bradford Y, Ritchie MD, Wasserman S, Meintjes G, Beeri K, Gandhi NR, Svensson EM, Denti P, Brust JCM. Pharmacogenetics of Between-Individual Variability in Plasma Clearance of Bedaquiline and Clofazimine in South Africa. J Infect Dis. 2022 Jan 29:jiac024. doi: 10.1093/infdis/jiac024. Epub ahead of print. PMID: 35091749.
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12. Costa AG, Carvalho BKS, Araújo-Pereira M, Ibiapina HNS, Spener-Gomes R, Souza AB, Gomes-Silva A, Andrade AMS, Silva EC, Arriaga MB, Benjamin A, Rocha MS, Moreira ASR, Oliveira JG, Figueiredo MC, Turner MM, Durovni B, Cavalcante S, Kritski AL, Rolla VC, Sterling TR, Andrade BB, Cordeiro-Santos M; RePORT-Brazil Consortium. Lessons Learned from Implementation of an Interferon Gamma Release Assay to Screen for Latent Tuberculosis Infection in a Large Multicenter Observational Cohort Study in Brazil. Microbiol Spectr. 2021 Dec 22;9(3):e0116321. doi: 10.1128/Spectrum.01163-21. Epub 2021 Dec 1. PMID: 34851140; PMCID: PMC8635161
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16. van der Heijden YF, Zhang B, Chougnet CA, Huaman MA. Cytomegalovirus Infection Is Associated With Increased Prevalence of Latent Tuberculosis Infection. Open Forum Infect Dis. 2021 Oct 23;8(11):ofab539. doi: 10.1093/ofid/ofab539. PMID: 35198641; PMCID: PMC8855520.
17. Radtke KK, Ernest JP, Zhang N, Ammerman NC, Nuermberger E, Belknap R, Boyd R, Sterling TR, Savic RM. Comparative Efficacy of Rifapentine Alone and in Combination with Isoniazid for Latent Tuberculosis Infection: a Translational Pharmacokinetic-Pharmacodynamic Modeling Study. Antimicrob Agents Chemother. 2021 Nov 17;65(12):e0170521. doi: 10.1128/AAC.01705-21. Epub 2021 Oct 4. PMID: 34606336; PMCID: PMC8597776
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Rocinha is the largest favela in Rio de Janeiro.

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