treat TB

Technology, Research, Education, and
Technical Assistance for Tuberculosis

Technology, Research, Education, and Technical Assistance for Tuberculosis (TREAT TB)

Description of Research Outputs
2009 - 2014

The Union

International Union Against
Tuberculosis and Lung Disease
Health solutions for the poor

Contents

Introduction

The Technology, Research, Education and Technical Assistance for TB (TREAT TB) began in October 2008 when the U.S. Agency for International Development (USAID) and the International Union Against Tuberculosis and Lung Disease signed a five year cooperative agreement that aimed to contribute to new knowledge through field evaluations of diagnostic tools, clinical trials of priority research questions, and targeted operational research benefitting global, regional and country TB control efforts.

In the five years of TREAT TB activity, The Union and its partners widely engaged both public and private institutions as well as ministries of health (MOHs) who were uniquely positioned to plan and implement research activities. The Union used its active involvement in the working groups and task forces of the Stop TB Partnership, its strong country and regional networks, and its regional and country offices as platforms from which to coordinate activities.

The pages that follow describe the activities and outputs of research implemented through the TREAT TB initiative.

This report is made possible by the generous support of the American people through the United States Agency for International Development (USAID). The contents are the responsibility of The Union and do not necessarily reflect the views of USAID or the United States Government.

Overview of TREAT TB Initiative

Since its launch in October 2008, the Technology, Research, Education and Technical Assistance for TB (TREAT TB) initiative aimed to build a successful research partnership model to facilitate changes in international standards and practices in ways that serve country needs. The initiative had four key outputs:

Output 1: The Evidence base for optimal diagnosis of tuberculosis strengthened

TREAT TB began just as several promising new diagnostic tools emerged. While many of these new tools were recommended by the WHO, most of the research presented to WHO guideline committees focused on the clinical accuracy of these new tools with limited information on laboratory infrastructure requirements and other needs. Because the performance of diagnostic tools may vary in different epidemiological settings or within patient risk groups, TREAT TB organized research projects that would help country-level stakeholders to decide whether a tool is suited for their particular context and what infrastructure is needed for its implementation and scale-up. These activities included:

Systematic Reviews:

Name of Research Project	Findings	Method of Dissemination
Microcolony culture techniques for tuberculosis diagnosis: a systematic review.	This study found MODS and TLA to be accurate tools for active tuberculosis but did not find sufficient evidence to make conclusions on the test's impact on patient outcomes.	Publication: Leung E, Minion J, Benedetti A, Pai M, and Menzies D. Microcolony culture techniques for tuberculosis diagnosis: a systematic review. Int J Tuberc Lung Dis 2012; 16(1): 16-27.
Diagnosing Tuberculosis with Urine Lipoarabinomannan: Systematic Review and Meta-Analysis.	This systematic review evaluated the performance of the LAM urine assay as a diagnostic test for tuberculosis. Although many TB experts have high hopes for this test, the review found its performance highly variable and its sensitivity suboptimal for routine clinical use.	Publication: J. Minion, E. Leung, E. Talbot, K. Dheda, M. Pai, and D. Menzies. Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis. Eur Respir J:00257-2011.
Interferon-gamma release assays and childhood tuberculosis:	This assessment of interferon-gamma release assays (IGRAs) and the tuberculin skin test (TST) in the diagnosis of tuberculosis	Publication: Mandalakas A, Detjen A, Hesseling A, Benedetti A and Menzies D. Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis. Int J Tuberc Lung Dis 2011; 15(8): 1018-1032.

systematic review and meta-analysis.	(TB) infection and disease in children, found that TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of the disease in children and called for a rigorous, standardized approach to evaluate TB diagnostic tests in children.	
How Methodologic Differences Affect Results of Economic Analyses: A Systematic Review of Interferon Gamma Release Assays for the Diagnosis of LTBI.	This study was a systematic review of methodologic aspects of CEA that evaluate Interferon Gamma Release Assays (IGRA) for the detection of Latent Tuberculosis Infection (LTBI), in order to understand how differences affect study results. The authors found that more guidance is needed to help scientists, clinicians and program managers accurately interpret the results of these assays.	Publication: Oxlade O, Pinto M, Trajman A, and Menzies D. How Methodologic Differences Affect Results of Economic Analyses: A Systematic Review of Interferon Gamma Release Assays for the Diagnosis of LTBI. PloS One 2013; 10.1371. URL: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0056044
A systematic review of the assessment of the feasibility of implementation of diagnostic tests in low and middle income countries.	Forthcoming in 2015.	Forthcoming in 2015.

PROVE IT studies:

Name of Research Project	Findings	Method of Dissemination
Beyond accuracy: creating a comprehensive evidence base for TB diagnostic tools.	In December 2010, the Liverpool School of Tropical Medicine (LSTM) led by Dr. Gillian Mann and TREAT TB partners and staff published this description of the Impact Assessment Framework (IAF). The IAF was later used to develop the protocols for the PROVE IT studies in Brazil, Russia, and South Africa.	Publication: Mann G, Squire SB, Bissell K, Eliseev P, Du Toit E, Hesseling A, Nicol M, Detjen A, Kritski A. Beyond accuracy: creating a comprehensive evidence base for TB diagnostic tools. Int J Tuberc Lung Dis. 2010 Dec;14(12):1518-24.
A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus Line Probe Assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town.	This study provided information on how to optimize the implementation of new diagnostic tools, including the magnitude and nature of the inputs required to implement molecular tests as part of diagnostic algorithms in routine health services as well as the range of benefits for patients and their clinical management.	Publication: Naidoo P, du Toit E, Dunbar R, Lombard C, Caldwell J, et al. (2014) A Comparison of Multidrug-Resistant Tuberculosis Treatment Commencement Times in MDRTBPlus Line Probe Assay and Xpert® MTB/RIF-Based Algorithms in a Routine Operational Setting in Cape Town. PLoS ONE 9(7): e103328.
Outcomes from Patients with Presumed Drug Resistant Tuberculosis in five reference centers in Brazil.	The findings from this study revealed that improved identification of presumed DR-TB cases is urgently needed at primary and secondary level, along with improvements in the flow of patients and/or clinical samples to referral centers. At referral level, the standardization of clinical and laboratory procedures should also be reviewed to provide a more appropriate case management model for improving quality of care and control of TB.	Pending Publication.
Evaluation of the impact of Line Probe Assay on time to treatment initiation for MDR TB patients in Archangelsk region of Russia.	This study found that using Line Probe Assays to diagnose MDR-TB resulted in patients receiving the correct treatment earlier. The most significant reduction was observed among sputum	Pending Publication.

	positive patients, who started treatment for MDR-TB 26.5 days earlier than patients who were diagnosed without LPAs.	

Virtual Implementation:

Name of Research Project	Findings	Method of Dissemination
A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools.	In Years 2 and 3, TREAT TB partners at the Liverpool School of Tropical Medicine (LSTM), National Taiwan University, and Harvard University School of Public Health designed a novel modelling approach that links transmission modelling with operational modelling. They published a paper describing describing how this model could be used to support the selection and implementation of new diagnostic tools for tuberculosis.	• Publication: Lin H-H, Langley I, Mwenda R, Doulla B, Egwaga S, Millington K, Mann G, Murray M, Squire SB, and Cohen T. A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. Int J Tuberc Lung Dis 2011; 15(8):996-1004.

• Brochure

• Symposium |
| PROVE IT & Virtual Implementation | Forthcoming in 2015 | Forthcoming in 2015. |
| The impact of new tuberculosis diagnostics on transmission: why context matters. Bulletin of the World Health Organization. 90(10):739-747A. 2012. | The results of this model-based quantitative analysis found that novel diagnostic tests can have substantial population-level impact on tuberculosis epidemics, but only in certain contexts or in combination with interventions geared towards promoting earlier health-care seeking after symptom onset to reduce the length of the infectious period. | Publication: Lin HH, Dowdy D, Dye C, Murray M, Cohen T. The impact of new tuberculosis diagnostics on transmission: why context matters. Bulletin of the World Health Organization. 90(10):739-747A. 2012. http://www.who.int/bulletin/volumes/90/10/11-101436/en/ |

Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions.	The research team concluded that a health system modelling approach using a discrete-event simulation (DES) tool can provide information to help policy makers understand context-specific impacts in resource-constrained settings and make decisions on TB diagnostic tools. The DES can, and where possible should, be linked to a disease transmission component to enhance predictions and to provide outputs on important factors such as TB incidence which will in turn impact health system and patient outcomes.	Publication: Langley I, Doulla B, Lin HH, Millington K, Squire B. Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions. Health Care Managex Sci. 15(3):239-53. 2012.
Assessing the patient, health system, and population impacts of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach.	This study identified three strategies as cost-effective in Tanzania. These three strategies included: 1) the full scale-up of Xpert; 2) same-day use of LED fluorescence microscopy; and 3) targeted use of Xpert for diagnosis of presumptive TB cases with HIV infection.	Publication: Langley I, MSc; Lin H-H, MD; Egwaga S, MD; Doulla B MSc; Ku C-C, BS; Murray M, MD; Cohen, T MD; Squire SB, MD

(Forthcoming in late 2014.) |
| Operational modelling to guide implementation and scale-up of diagnostic tests within the health system: exploring opportunities for parasitic disease diagnostics based on example application for tuberculosis. | This study demonstrated how the technique of operational modelling applied in the developing world to support decisions on diagnostics for tuberculosis could provide useful insights to support implementation of appropriate diagnostic innovations for parasitic diseases. | Langley I, Adams E, Doulla B, Squire SB. Operational modelling to guide implementation and scale-up of diagnostic tests within the health system: exploring opportunities for parasitic disease diagnostics based on example application for tuberculosis. Parasitology, 2014. http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=9305289 |

Output 2: Patient management practices improved for MDR-TB, TB-HIV co-infection and other priority areas via results of clinical trials and operational research

TREAT TB's STREAM Trial aimed to address an urgent need for shortened and effective treatment for multidrug-resistant tuberculosis. The objective of the trial is to determine whether a standardised nine month MDR-TB treatment regimen used effectively in one country under study conditions resulting in excellent treatment outcomes can be used with minimal modification in additional, different settings with comparable success. The trial will provide important evidence to inform MDR-TB treatment recommendations from global technical agencies, including WHO and The Union.

Output 3: High priority research undertaken to address operational barriers to optimal program performance

With decades of experience in treating tuberculosis in limited-resource settings, The Union understood that operational barriers, including a shortage of health workers, lack of follow-up mechanisms, and limited access to medicine among others, often hindered the performance of health programs. Because the challenges faced by each program are unique, TREAT TB commissioned several research projects that identified key bottlenecks affecting the work of their national or regional tuberculosis program.

Name of Research Project	Findings	Method of Dissemination
High Prevalence of Tuberculosis and Serious Bloodstream Infections in Ambulatory Individuals Presenting for Antiretroviral Therapy in Malawi.	This two-year prospective cohort study that determined the prevalence of undiagnosed TB infection among patients receiving anti-retroviral treatment in Lilongwe, Malawi. This study found 1/5 of the patients in this cohort had a serious, but undiagnosed illness and 10% had tuberculosis.	Publication: Bedell RA, Anderson STB, van Lettow M, Åkesson A, Corbett EL, et al. (2012) High Prevalence of Tuberculosis and Serious Bloodstream Infections in Ambulatory Individuals Presenting for Antiretroviral Therapy in Malawi. PLoS ONE 7(6): e39347. doi:10.1371/journal.pone.0039347
Retreatment Tuberculosis Cases Categorised as "Other": Are They Properly Managed?	This study examined the catergorisation of retreatment patients in Malawi found that treatment success was low and revealed an urgent need for improvement in the recording, diagnosis, and management of retreatment patients.	Tweya H, Kanyerere H, Ben-Smith A, Kwanjana J, Jahn A, et al. (2011) Retreatment Tuberculosis Cases Categorised as ''Other'': Are They Properly Managed? PLoS ONE 6(12): e28034. doi:10.1371/journal.pone.0028034
Source of Previous Treatment for Retreatment TB Cases Registered under the National TB Control Programme.	The study confirmed that nearly half of the retreatment cases registered with the national programme were most recently treated outside the programme setting. The authors concluded that improved efforts to treat and support patients seeking	Publication: Sachdeva K, Srinath S, Dewan P, Nair S, Reddy R, Kundu D, Chadha S.S., Madhugiri A, Parmar M, Chauhan L.S. Source of Previous Treatment for Retreatment TB Cases Registered under the National TB Control

	services from private providers were urgently needed.	Programme PLoS ONE 6(7): doi:10.1371/journal.pone.0022061
Tuberculosis 'Retreatment Others': Profile and Treatment Outcomes in the State of Andhra Pradesh.	The aim of this study was to document the demographic and disease characteristics and treatment outcomes of TB cases classified as 'retreatment other' and compare their treatment outcomes with those of smear-positive retreatment cases. The researchers found that patients classified as 'retreatment other' were predominantly patients with sputum smear-negative TB and had significantly better outcomes than smear-positive retreatment patients.	Srinath S, Sharath B, Santosha K, Chadha S.S., Roopa S, Chander K, Wares F, Chauhan L.S., Wilson N.C., Harries A.D. Tuberculosis 'Retreatment Others': Profile and Treatment Outcomes in the State of Andhra Pradesh. Int J Tuberc Lung Dis 2011, 15(1): 105-109.
Tuberculosis Retreatment: A Topic Whose Time Has Come.	This editorial described the increasing for retreatment services for patients unsuccessfully treated with traditional regimens and described TREAT TB's work to facilitate further research on this important topic.	Rusen I.D. Tuberculosis Retreatment: A Topic Whose Time Has Come (PDF 103 KB). Int J Tuberc Lung Dis 2009; 13(10): 1192.

TREAT TB partners and staff also generated awareness about the need for and importance of operational research by writing articles and editorials in widely read global health journals. Please see the table below for a list of some of these publications.

Title	Author	Publication
The Union and Médecins Sans Frontières approach to operational research.	Tony Harries, I.D. Rusen, Anne Detjen and others.	Harries A, Rusen ID, Reid T, Detjen A, Berger S, Bissell K, Hinderaker S, Edginton M, Fussell M, Fujiwara P, Zachariah R. The Union and Médecins Sans Frontières approach to operational research. Int J Tuberc Lung Dis 2011; 15(2):144-54.
Operational Research on Operational Research.	I.D. Rusen	Rusen, ID. Operational research on operational research: much more to be learned. Int J Tuberc Lung Dis 2011; 15(11):1421.

Output 4: Assistance to USAID missions and local partners to define and address priority research needs

Locally relevant operational research is a high priority for national TB programs, but many countries have been unable to fully incorporate operational research into program activities due to limitations in both local capacity and available technical assistance. In partnership with USAID missions in South Africa and India, TREAT TB worked with local partners to create a national cadre of health professionals and scientists with strong skills in operational research.

Project	Country	Number Trained	Number of Publications	Links
Operational Research Assistance Project (ORAP)	South Africa	103	11 manuscripts (8 of those are published, 3 are pending publication) 12 presentations 20 posters	J. C. Heunis, N. G. Kigozi, S. van der Merwe, P. Chikobvu, N. Beyers. Sex-related trends in non-conversion of new smear-positive tuberculosis patients in the Free State, South Africa. PHA 2014; 4(1): 66–7. URL: http://www.ingentaconnect.com/content/iuatld/pha/2014/00000004/00000001/art00016 S.A. Schulz, H.R. Draper, P. Naidoo. A comparative study of tuberculosis patients initiated on ART and receiving different models of TB-HIV care. IJTLD 2013: Volume 17, Number 12. URL: http://www.ncbi.nlm.nih.gov/pubmed/24200268 M. Osman, A. C. Hesseling, N. Beyers, D. A. Enarson, D. Rusen, C. Lombard, S. S. van Wyk. Routine programmatic delivery of isoniazid preventive therapy to children in Cape Town, South Africa. PHA 2013; 3(3): 199–203. URL: http://www.ingentaconnect.com/content/iuatld/pha/2013/00000003/00000003/art00004 A. Bekker, A. L. Slogrove, H. S. Schaaf, K. Du Preez, A. C. Hesseling. Determinants of tuberculosis treatment completion among newborns in a high-burden setting IJTLD 2014; Volume 18, Number 3. URL: http://www.ingentaconnect.com/content/iuatld/ijtld/2014/00000018/00000003/art00017?crawler=true M. M. Claassens, E. Jacobs, E. Cyster, K. Jennings, A. James, R. Dunbar, D. A. Enarson, M. W. Borgdorff, N. Beyers. Tuberculosis cases missed in primary health care

| | | | | facilities should we redefine case finding? IJTLD 2014; Volume 17, Number 5. URL: http://www.ingentaconnect.com/content/iuatld/ijtld/2013/00000017/00000005/art00009?crawler=true

Kaplan R, Caldwell J, Bekker L-G, Jennings K, Lombard C, Enarson DA, Wood R, Beyers N. Integration of TB and ART services fails to improve TB treatment outcomes: Comparison of ART/TB primary healthcare services in Cape Town, South Africa SAMJ, Vol. 104, No. 3 March 2014. URL: http://www.ncbi.nlm.nih.gov/pubmed/24897825

Marx FM, Dunbar R, Enarson DA, Beyers N. The rate of sputum smear-positive tuberculosis after treatment default in a high-burden setting: a retrospective cohort study. PLoS One. 2012;7(9):e45724. Epub 2012/10/11. URL: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0045724

Marx FM. Sputum smear-positive tuberculosis among previously treated individuals in the Western Cape Province, South Africa. SACEMA Quarterly. Epub 2013/3/18. URL: http://sacemaquarterly.com/tuberculosis/sputum-smear-positive-tuberculosis-among-previously-treated-individuals-in-the-western-cape-province-south-africa.html |
|---|---|---|---|---|
| National Operational Research Assistance Project | India | 12 | Research Ongoing | Forthcoming in 2015. |
| Virtual Training | Multiple | 4 | Research Ongoing | Forthcoming in 2015. |

In addition to direct training, TREAT TB also developed a range of resources the professionals interested in learning more about operational research could access independently. These included:

Resource	Method of Dissemination	Usage rate
Online Introduction to the Impact Assessment Framework and Policy Transfer Analysis (E-tool).	• TREAT TB website • World Conference on Lung Health	Accessed by more than 300 health professionals worldwide.
Operational Research to Improve Health Services: A Guide to Proposal Development (Guidebook).	• Online • Face-to-face training courses • World Conference on Lung Health	4100 copies of the English-language publication and 800 copies of the Spanish-language were distributed at Union courses and conferences Downloaded 4285 times since 2011.
A Guide to Country Level Implementation and Programme Support (Guidebook).	• Online • Face-to-face training courses • World Conference on Lung Health	700 hardcopies distributed at Union courses and conferences Downloaded more than 2600 times since 2011.
Operational Research E-tool .	• Online • Face-to-face training courses	Accessed by more than 500 TREAT TB website viewers as of July 2014. Distributed on DVD to 50 health professionals based in Ethiopia.

Key Projects

Malawi: Prevalence of TB and Other Serious Infections among Patients Receiving Anti-Retroviral Treatment

In 2008, AIDS was the leading cause of death in Malawi. To curb the mortality rate, the Government of Malawi launched an initiative to provide ARVs to all patients that needed these medicines, but mortality among patients accessing ARVs remained high, particularly for those with unexplained weight loss, fever, and chronic diarrhea. Although these symptoms are signs of tuberculosis (TB) infection, the diagnostic tool commonly available to clinicians in Malawi at that time – smear microscopy – has low sensitivity for HIV-positive patients.

Through TREAT TB, a consortium of partners[1] gathered evidence that policy-makers could use to improve the diagnosis of TB. Beginning in January 2010, these partners implemented a study that sought to determine the prevalence of undiagnosed TB and blood stream infections among patients who initiate antiretroviral treatment (ART) with unexplained weight loss and/or fever. During the implementation phase of the study, the research team enrolled 469 patients in a prospective observational cohort study from Zomba Central Hospital and Thyolo District Hospital in southern Malawi.

The study's results show that approximately one-third of the patients were diagnosed with a serious pathogen due to the additional tests conducted by the TREAT TB study team. With approximately 25% of the study population found to have active TB (117 possible, probable and confirmed cases out the 469 patients enrolled in the study), the researchers also confirmed that undiagnosed TB was the most common causes of chronic fever and/or weight loss among smear-negative, HIV-positive patients on ARV treatment. After this initial publication, a research team led by Dr. Richard Bedell published a second article that documented the persistently high death toll among patients with chronic, non-specific TB symptoms. This article, "Six-month mortality among HIV-infected Adults Presenting for Antiretroviral Therapy with Unexplained Weight Loss, Chronic Fever or Diarrhea in Malawi," found that diagnostic and treatment delay for TB was strongly associated with the risk of death.

After the findings of this research project were published, Dignitas International continued to work in partnership with the Ministry of Health in Malawi to identify additional research topics that may improve the diagnosis and treatment of TB among persons living with HIV and to facilitate TB-HIV

---

[1] This consortium included Dignitas International, Médecins Sans Frontières, the Malawi Liverpool Wellcome Trust Clinical Research Programme, the UN-WHO Special Programme for Research and Training in Tropical Diseases (TDR), The Union, the Malawi National Tuberculosis Control Programme and the Malawi HIV/AIDS Department in the Ministry of Health.

treatment integration. In addition to ongoing participation in the Ministry of Health's TB-HIV working group, Dignitas International organized a research prioritization workshop for national stakeholders in March 2013. This workshop resulted in the development of four additional research proposals as well as two technical recommendations for the Ministry of Health. One of these studies, on TB-HIV integration of services in Malawi is in press, and another major study, on the use of urine-LAM and Xpert MTB/Rif for the diagnosis of TB in severely immunocompromised HIV-infected TB suspects, has been funded and will commence in late 2014.

Global Consultation on Retreatment and Operational Research

Existing treatment regimens fail to cure more than one million patients suffering from tuberculosis every year.[2] These patients then require what is called "retreatment ", a course of medicine that uses second-line drugs. Without research informing guidelines on the use of these drugs, the chance of increasing drug resistance and treating patients with ineffective medicines was high.

To help produce the needed research on retreatment regimens, TREAT TB convened the Global Consultation on Retreatment Regimens in June 2009. During this meeting, TREAT TB staff and partners shared information on existing retreatment regimens, produced a detailed agenda listing the priority research questions, and prepared to conduct three research projects on the most urgent questions related to retreatment .

The studies conducted with TREAT TB support examined how retreatment cases were managed in Malawi and India and began with the project, "Retreatment Tuberculosis Cases Categorised as 'Other': Are They Properly Managed?" This was the first study from a routine TB programme setting in sub-Saharan Africa to explore the characteristics and treatment outcomes in previously-treated adult TB patients registered as 'other'. This study found that more than half of the retreatment cases classified as 'other' were treated with first-line drugs even though Malawi national TB guidelines mandate treatment with second-line drugs for such patients. Not surprisingly, the overall treatment success for patients classified as 'other' was low.

The second study, "Source of Previous Treatment for Retreatment TB Cases Registered under the National TB Control Programme, India" found that nearly half of the retreatment cases registered with the national programme were treated in the private sector.

The last study, "Tuberculosis 'retreatment others': profile and treatment outcomes in the state of Andhra Pradesh," found such cases were predominantly sputum smear-negative after reviewing more than a thousand patient records.   This study aimed to serve as the starting point from which the RNTCP could begin to evaluate retreatment cases in India.

The official research agenda on retreatment regimens was published in 2009 and released ahead of the 2009 World Conference on Lung Health in Cancun, Mexico. The findings of TREAT TB-funded studies were later published in peer-reviewed, scientific journals and shared with government and other stakeholders. The findings of the studies conducted in India provided were useful for partners because they demonstrated that TB control efforts should prioritize patients who obtain health services in the private sector by confirming that the majority of retreatment cases received treatment from sources outside the national tuberculosis programme. These studies also showed that the majority of patients who were previously treated in private sector were cured after being re-treated under the auspices RNTCP. Similarly, the study conducted in Malawi provided helpful recommendations to the National Ministry of Health on ways to improve TB diagnosis activities.

---

[2] http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000427

Policy Relevant Outcomes from Validating Evidence on Impact (PROVE IT)

When TREAT TB began, its staff and partners understood that there is a clear need to expand evaluations of new diagnostic tools for TB to gather evidence beyond conventional accuracy data (i.e., sensitivity and specificity). To test the performance of two recently recommended new diagnostic tools, Line Probe Assays (LPA) and Xpert MTB/RIF, TREAT TB partners conducted the Policy Relevant Outcomes from Validating Evidence on ImpacT (PROVE IT) from 2010 through 2013 in Russia, South Africa, and Brazil. An Impact Assessment Framework (IAF), which enabled the comprehensive assessment of a new tool as part of a diagnostic algorithm and within the context of the health system, guided the study design, data collection procedures, and analysis for pragmatic evaluations at each site.

The research team began by developing a generic PROVE IT study protocol that addressed different layers of the IAF. To assess effectiveness, PROVE IT measured the impact of implementing a either LPA or Xpert into diagnostic algorithms on 'time from sputum collection to initiation of multidrug-resistant (MDR) treatment'. Equity issues were addressed by collecting data on patient costs incurred during the diagnostic process. Health system requirements were identified by collecting health system expenses, such as laboratory costs, implementation and maintenance, and training. The generic protocol was then tailored to fit each of the study sites, which were at different stages of the selection or implementation process of Line Probe Assays (LPA) and/or Xpert MTB/RIF.

A qualitative policy transfer analysis was designed to study the process from decision-making stage to implementation to policy change and scale-up of a new tool. Each country team conducted qualitative interviews with policy makers, health care managers and workers.

In all three sites, the study focused on the magnitude and range of benefits for patients and their care and the inputs required to implement molecular diagnostics as part of a TB diagnostic algorithm in a routine operational setting. The evaluation was undertaken from both a health system and a patient perspective.

PROVE IT in Cape Town, South Africa

The Desmond Tutu TB Centre led by Dr Pren Naidoo conducted the PROVE IT study in Cape Town, South Africa. In 2008, the South Africa Health Department implemented Hain-MDRTBPlus LPA as a replacement for conventional drug sensitivity tests for high MDR-risk cases and started to implement Xpert MTB/RIF in 2011, replacing smear microscopy for all TB suspects. The PROVE IT South Africa research team followed this implementation process in a routine setting, comparing the LPA-based 'Targeted' algorithm to the Xpert-based 'Universal' algorithm primary healthcare clinics. Both tests were performed in a centralised laboratory of the National Health Laboratory System (NHLS) receiving specimens by courier services. Results were faxed and sent back to the clinics by courier, and standardized treatment for MDR-TB patients is initiated at a TB hospital or at clinics.

PROVE IT in Brazil

With Dr Afrânio Kritski as primary investigator, REDE-TB conducted the study in multiple sites throughout Brazil. According to local law, new technologies have to be evaluated under field conditions in the country before implementation in the public health system, including a health economic evaluation. During the time the PROVE IT study was being implemented, the Hain/MTBDRplus (LPA), XpertMTB/RIF and MGIT960 had been commercialized in Brazil, but not incorporated in the public health system for the diagnosis of TB or MDR-TB. The study team developed a pragmatic, cluster randomized cross-over design in five study sites in four provinces of Brazil to assess Xpert, LPA and MGIT for the diagnosis of MDR-TB. The study was performed at referral centers, where patients with presumed DR/MDR TB are seen and initiated on treatment. The different diagnostic tests were placed at the laboratories of these sites. In addition to 'time to treatment', smear and culture conversion after two and six months of treatment were added as outcome measures.

PROVE IT in Arkhangelsk Region, Russia

Under the direction of Prof Andrey Maryandyshev and Dr Platon Eliseev, the Northern State Medical University and the Arkhangelsk Regional Anti-Tuberculosis Dispensary conducted the PROVE IT study in Russia. The laboratory of the Arkhangelsk Clinical Anti TB Dispensary (ACAD) implemented Hain/MTBDRplus LPA for all TB suspects in late 2009, and PROVE IT aimed to assess its impact on MDR diagnosis and treatment in both the civil as well as the penitentiary system. Liquid (MGIT) and solid culture (Löwenstein Jensen, LJ) systems remained in place throughout the duration of the study, which chose a concurrent (LPA versus MGIT) combined with a historical comparison (LPA versus LJ). Diagnostic and patient pathways differ between smear positive and smear negative patients, but MDR treatment for all is initiated only at the hospital level. The prison health system operates almost completely independent, and TB diagnosis and DST are based on LJ. With the implementation of LPA additional specimens are sent to ACAD for a more rapid diagnosis.

While clearly showing the advantages of rapid diagnostic tools, PROVE IT also revealed the importance of optimizing the diagnostic pathways into which these tools are integrated to reduce both health system but also patient delays. Publications on the different aspects of PROVE IT, treatment initiation, health system and patient costs, and policy transfer analysis are being finalized by the country teams and will be published in 2014 and 2015.

Evaluation of Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis (STREAM)

Multidrug-resistant tuberculosis (MDR-TB) is one of the gravest challenges facing the global health community today. While drug-sensitive TB can usually be cured easily and cheaply within six months, currently available regimens for MDR-TB are painful, expensive, and require at least two years of treatment to achieve any success. Consequently, hundreds of thousands of MDR-TB patients do not have access to the long, expensive treatment while those who do access the treatment often fare poorly.

The TREAT TB project coordination team worked with the Medical Research Council-Clinical Trials Unit (MRC-CTU) at the University College London to design a clinical trial that could determine if a standardized nine-month regimen that was confirmed to be highly successful among patients in Bangladesh, could cure patients in other geographic regions. Since 2012, the STREAM research team at MRC-CTU has been implementing the STREAM Trial at several sites in South Africa, Viet Nam, and Ethiopia. In 2014, Mongolia joined the trial. The study treatment provides moxifloxacin, clofazimine, ethambutol, and pyrazinamide for nine months (40 weeks) and kanamycin, isoniazid, and prothionamide given during the first four months (16 weeks) only. Dosage is based on the individual patient's weight.

Between 2012 and 2014, close to four hundred patients were enrolled in Stage I of the STREAM Trial at the four study sites and randomly assigned to receive either the nine-month STREAM regimen or the locally used WHO standardized treatment. The findings of this study may provide the global health community with a treatment for MDR-TB that is affordable, accessible, and effective.

In parallel to the clinical assessment, TREAT TB has also partnered with the Liverpool School of Tropical Medicine to conduct a cost-effectiveness evaluation of the STREAM regimen which will identify both the costs and cost-savings for patients and health systems. The financial burden of MDR-TB has been linked with poor adherence and may have long-term implications for the financial security of patients and their families, particularly among the highly disadvantaged groups who form a large proportion of TB patients. Shorter treatment regimens, like STREAM, have the potential to reduce the burden of MDR-TB on patients and health systems but actual impact depends on multiple factors. The Liverpool team will assess this impact by identifying and measuring resources used in staff time, consumables, and fixed assets. With patient consent, data on socioeconomic status, education, employment, housing, and costs of food, transport, and medications. Data are collected by interviewing patients and appropriate personnel and from records held by funders and healthcare providers.

The success of the Stage I of the STREAM Trial enabled the team to expand the study to include two other regimens utilizing the newly licensed drug, bedaquiline - a shorter, six-month regimen and an all-oral regimen. Stage II of the STREAM Trial will begin in 2015. The results of Stage II may provide health professionals with a treatment for MDR-TB that does not require the use of an injectable medicine – one of the most sought after goals in global TB control today.

Virtual Implementation

A number of new tools with the potential to improve the diagnosis of tuberculosis had been introduced and recommended by the World Health Organization (WHO) between 2007 and 2010. Policy-makers in countries affected by the global tuberculosis epidemic had to decide which of these new tools are best suited for their epidemiological and health system requirements. Because many of the countries affected by the epidemic have limited resources, these policy-makers also had to determine which tool or combination of tools would reduce transmission in the most cost-effective way. However, it is too expensive, time-consuming, and disruptive for the health system to test the performance of all new tools in the real world.

Virtual implementation provided a way for policy-makers to obtain the information they needed to make accurate predictions on the new tools' requirements for use and overall impact. Virtual implementation uses an integrated model that estimates the cost-effectiveness of different diagnostic options and compares outcomes from the patient, health system, and population perspective. TREAT TB partners from the Liverpool School of Tropical Medicine (LSTM), the National Taiwan University, and the Harvard School of Public Health/Brigham and Women's Hospital piloted virtual implementation in Tanzania.

With an incidence rate of 165 per 100,000 people, tuberculosis is a serious public health problem in Tanzania.[3] Designing the model to represent the operational and epidemiological context of Tanzania, the virtual implementation team worked in partnership with National TB and Leprosy Programme (NTLP) of Tanzania to assess the impact of improved microscopy and Xpert MTB/RIF when scaled up nationally. The NTLP provided the necessary data and inputs to the model, which identified three cost-effective strategies for the implementation of these new diagnostic tools. Since the initial pilot, the NTLP expanded the use of virtual training in Tanzania by training staff on how to use the model and installing the model in individual district sites.

The information and findings gained from the pilot in Tanzania also informed research and policymaking in other countries. Researchers in Ethiopia are developing ways to use virtual implementation on decision related to the roll-out of Xpert MTB/RIF in Addis Ababa. Aside from its use for TB-related tools and interventions, virtual implementation is also being considered to answer questions related to other diseases.

---

[3] STOP TB Partnership. Tanzania Country Profile. (2012 Data). URL: http://www.stoptb.org/countries/tbdata.asp

Country-based Operational Research Assistance Programmes

Locally relevant operational research is a high priority for national TB programs. The inclusion of "enabling and promoting research" as one of the components of the expanded Stop TB Strategy has reinforced the vital role of research in successful TB control efforts. Yet many countries have been unable to fully incorporate operational research into program activities due, in part, to limitations in both local capacity and available technical assistance.

TREAT TB sought to help partners overcome these limitations by implementing high-impact training initiatives that would create a cadre of professionals well-versed in operational research. With support from the USAID mission in Pretoria, TREAT TB partnered with the Desmond Tutu TB Centre at Stellenbosch University to prioritize operational research as an integral component of the National TB Control Program through the Operational Research Assistance Project (ORAP). By implementing the ORAP initiative, the Desmond Tutu TB Centre aimed to strengthen the capacity of South African professionals at national, provincial, and local levels to conduct operational research independently. Through ORAP, a series of academic institution-government health programme partnerships were established as the basis for a programme of operational research development and implementation.

The specific activities undertaken during ORAP included research protocol development workshops, mentoring to refine research protocols, support for implementation of operational research, and support for data analysis, report writing, and publication of research findings. From 2010 through 2013, more than a hundred participants from health services and academic institutions in South Africa have participated in the project. Aside from several journal articles that covered a range of topics in TB control[4], ORAP also resulted in the publication of *Operational Research to Improve Health Services: A Guide for Proposal Development*. This manual has not only been used in South Africa, but was also incorporated into OR courses in Ethiopia through TB CARE.

In 2012, the ORAP program was launched in India with support from the USAID mission in New Delhi. The aim of this project was to facilitate the review of national OR priorities and develop a cadre of talented professionals with the skills to conduct this type of research. In 2013, the local TREAT TB team and the Government of India released a report that systematically analyzed 20 years of published Operational Research studies in India. This report, *Operational Research in India for TB Care and Control: Continuity and Change*, was the first of its kind in India and is now available for free download online.[5]

From September 2011 through October 2014, the TREAT TB operational research assistance program in India trained two cohorts from a wide spectrum of backgrounds ranging from medical colleges, public health graduate programmes to working national programme managers. Since 2013, the Indian OR Course has been endorsed as an accredited course by the WHO's SORT-IT initiative, deepening the credibility of an already well-regarded training initiative. Currently, 11 peer-reviewed papers have already been published in peer-reviewed journals such as *PLoS One*, *International Journal of Tuberculosis*

---

[4] http://sun025.sun.ac.za/portal/page/portal/Health_Sciences/English/Centres/dttc/Archive/Archive_2011
[5] http://www.axshya-theunion.org/images/documents/or-tb-care-control.pdf

and Lung Disease and *Public Health Action* from the first cohort of participants. Another ten papers from the second cohort will be submitted for publication in late 2014 and 2015.

Virtual Learning Programme for Operational Research

Operational research offers an effective way to ensure quality health services and practices. Operational research plays a key role in generating evidence needed to inform stakeholders about important public health issues and also contribute to policy change. As a result, operational research skills are vitally important for public health practitioners and researchers.

But the demands of clinicians and other health professionals sometimes prevent them from travelling to operational research training programmes abroad. Web-based learning has proven to be an effective way to resolve the obstacles that prevent much needed health professionals from participating in traditional operational research courses. To the meet the new for online training in operational research, The Union launched the TREAT TB Virtual Learning Programme for Operational Research in May 2013. The programme is scheduled to run through December 2014.

Like The Union's face-to-face training initiatives, the TREAT TB "Virtual Learning Programme for Operational Research" aimed to enable clinicians and other health professionals who previously were unfamiliar with this type of research to conduct an operational research study and generate evidence that relates directly to goals set forth by their local national tuberculosis programmes.

The training sessions emphasized the successful development and execution of a research protocol. Participants were supported by a facilitator/mentor who provided guidance and input throughout the learning programme. The Virtual Learning Programme has three stages: the preparation or "pre-work" phase; the online classroom phase; and post-class phase. Utilizing different stages enables the team to deliver some content during the online synchronous sessions while giving the participants the freedom to complete other material outside of the virtual classroom.

The pre-work phase included two self-directed e-courses and some introductory reading. During the online classroom phase, a series of lectures (see table below) were given in synchronous format. These sessions were interspersed with webinar content, as well as additional interactive, non-synchronous activities. During the post-class phase, the participants implemented their research protocols with support from TREAT TB, the facilitators, and the assigned mentors. Examples of the assistance provided to programme participants include: guidance on completing the ethics review process; project planning and budgeting; research publication and dissemination of findings.

Virtual Training Lectures

Lecture	Facilitator	Type
What is OR? Defining your research question; Protocol format	I.D. Rusen	synchronous
Study design; Determinants and outcomes; Study variables	Donald Enarson	synchronous
Sampling methods; Confounding and bias	Chen-Yuan Chiang	synchronous
Working with existing data, basic analysis and the research plan	Mareli Claassens	synchronous
Advanced analysis	Chen-Yuan Chiang	synchronous
Manuscript writing and presentation skills	I.D. Rusen	synchronous

Below is the list of projects that the virtual training participants implemented as a result of this programme. The results of these studies were presented during the 45th World Conference on Lung Health in Barcelona, Spain in October 2014.

"Early Anti-retroviral therapy initiation of MDR-TB and HIV co-infected patients in Swaziland"

This retrospective cohort study sought to determine if the initiation of antiretroviral treatment (ART) in the first eight weeks of treatment for multidrug-resistant tuberculosis (MDR-TB) is associated with treatment success among MDR-TB/HIV co-infected patients in a TB hospital in Swaziland. Once the data analysis is complete, this study will describe the ART initiation among MDR-TB patients, determine the treatment outcomes of MDR-TB/HIV co-infected patients and determine the association between initiation of ART in the first eight weeks and DR-TB treatment success.

"Pulmonary TB contact tracing in a priority municipality for disease control in Brazil"
Controlling TB spread in the community requires public health practitioners to identify TB latent among contacts of TB pulmonary patients. In some areas of Brazil, TB control has been decentralized to Primary Health Care (PHC). Because these contact tracing actions are influenced by operational challenges, it is important to evaluate the effectiveness of TB contact tracing efforts within PHC facilities. As a result, this research sought to evaluate how TB contact tracing efforts conducted in PHC facilities can help identify strategies and innovative policies for improving TB control in Brazil.

"Factors associated with unsuccessful treatment outcomes of MDR-TB patients in Tamil Nadu state, India"
This cross-sectional study that assessed the treatment outcomes and identified the risk factors associated with unsuccessful treatment outcomes such as death, failure, and default in patients with MDR-TB in a high HIV-prevalence setting of Tamil Nadu State in India. The overall objectives of this study were to evaluate the demographic, clinical characteristics and MDR-TB treatment services associated with unsuccessful treatment outcomes for MDR-TB patients in Tamil Nadu. This study involved the

review of the records of more than 200 patients who received treatment for MDR-TB in Tamil Nadu between 1 January 2009 and 30 June 2011 under the Revised National Tuberculosis Control Program (RNTCP). The results of this study will be used to help strengthen MDR-TB control efforts in India.

"Which combination of the six tuberculosis screening questions predicts sputum smear with the highest accuracy?"

This study aimed to determine the minimum set of questions required to rule in or rule out tuberculosis infection by sputum smear microscopy using data from a community-based TB case finding project. The findings from this project are expected to help inform future TB case detection efforts implemented in rural community settings.

TREAT TB Case Studies

EnCompass LLC conducted case studies of TREAT TB's work in Brazil and the Virtual Implementation project. These case studies gathered qualitative data from in-depth interviews with key stakeholders and other research methods to provide contextual meaning to the quantitative data collected during these projects. The findings of the case studies provided a deeper understanding of the processes behind research design, implementation, and integration of findings into policy.

A Multidisciplinary Health Partnership in Brazil

The first case study sought to determine how the TREAT TB initiative affected the development of its local partner in Brazil, Rede-TB, as a leading TB research institution. Rede-TB is a non-governmental organization founded in 2001 to promote clinical and operational research related to TB and develop a TB control research capacity in Brazil. Consisting of more than 160 members from 47 institutions, Rede-TB provided a network through which organizations dedicated to the development and validation of new drugs, vaccines, diagnostic tools, and control strategies could work together. When the PROVE-IT study began, TB was a critical public health problem in Brazil, which 83,000 new cases annually and ranked third on the list of the 22 countries with heavy TB burdens.

Between 2010 and 2013, Rede-TB implemented the PROVE IT study in Brazil independently and incorporated community advisory boards (CABs) as an essential component of the study. In the beginning of the study, the research team encountered challenges related to a lack of interest from patients and low levels of provider support. Because the CABS were made up of activists from vulnerable communities, health workers from the facilities participating in the study, and former TB patients, they were able to increase enrolment into the study by explaining the research aims to current patients and health providers in communities disproportionately affected by TB. PROVE IT was a multidisciplinary study that required the diverse members of the network to train and work together. The case study found that this experience created strong professional ties among physicians, nurses, administrators, and laboratory technicians – many of whom had never interacted before. Aside from facilitating the implementation of the PROVE IT study, these professional partnerships led to improved TB diagnostic services, increased surveillance for MDR-TB, and better identification of possible TB cases.

Virtual Implementation Up-Close

The second case study aimed to identify synergies that promote or inhibit TB research processes. Through its partnership with the modelers at Liverpool School of Tropical Medicine, Harvard University and the National University of Taiwan, TREAT TB aimed to create a tool to assist policy-makers to make more rational decisions about choosing diagnostic tests. Early on in the project, the team realized that traditional transmission modeling would not provide the answers policy-makers needed. Many of the biggest challenges to the successful use of new diagnostic tests in limited-resource settings, such as refrigeration and transportation, mirrored those familiar to supply chain modelers in the corporate sector. Therefore, the team expanded to include a private sector modeling expert.

Over the next several months, the team was able to compliment each other's strengths and create a model that combined aspects of health systems and transmission modeling. They then applied this model to real-world situations in Tanzania in 2011. The results were useful to the National TB program in Tanzania, who are now using this model to guide their decisions related to the roll out of Xpert MTB/RIF. Aside from its contribution to TB control, the virtual implementation project produced several important lessons for future collaborations. First, face-to-face contact was crucial to building successful working relationships. Although the team communicated via email and Skype often, they found that good personal interactions at real-time meetings were a precondition to building an effective professional partnership. Second, it is important to invest the time needed to agree on clear goals. While the process to develop the virtual implementation approach took time to create, this time was needed to develop a valuable resource. Third, additional time is needed to allow for the partners to reach a common ground. Finally, multidisciplinary partnerships work when every member of the team recognizes the unique but synergistic role they each have to fulfill.

Summary

Although the type of research undertaken varied greatly, from a clinical trial of a shortened MDR-TB regimen to systematic reviews of the published scientific literature, the research undertaken through the TREAT TB Initiative aimed to address gaps in research related to global TB control and ensure results were relevant to programme needs.

Many of the key projects described in this report addressed challenges in the diagnosis of tuberculosis. Other projects underlined the importance of involving the local community in both TB interventions and research designed to improve TB diagnosis and treatment. The Union and its partners hope that these findings will inform future policies and practices in countries with heavy TB burdens and the priorities of major donors.

TREAT TB has also illustrated the challenges and rewards of implementing research in limited-resource settings. Those who participated in the initiative will continue to publish and present their experiences to help others learn from the actions taken during first five years of TREAT TB.

List of TREAT TB Partners

1. Brigham & Women's Hospital/Harvard School of Public Health

2. Desmond Tutu TB Centre, South Africa

3. Dignitas International

4. EnCompass LLC

5. Liverpool School of Tropical Medicine

6. McGill University

7. Medical Research Council - Clinical Trials Unit at University College London

8. National Tuberculosis Institute, India

9. Northern State Medical University (NSMU), Arkhangelsk, Russia

10. Rede-TB, Brazil

11. Institute of Tropical Medicine

12. World Health Organization