Advance Access & Delivery

Report & Analysis

Toward comprehensive global health care delivery: Addressing the double threat of tuberculosis and diabetes

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Acronyms

AA&D Advance Access & Delivery

BMI Body mass index

DALY Disability adjusted life years

DM Diabetes mellitus

DOTS Directly observed treatment, short-course

FBG Fasting blood glucose

GTT Glucose tolerance test

HIV Human immunodeficiency virus

IDF International Diabetes Federation

LTBI Latent TB infection

MDR-TB Multidrug-resistant tuberculosis

NCD Non-communicable disease

OGTT Oral glucose tolerance test

PHC Primary health care

QFT QuantiFER-ON-TB Gold

RBG Random blood glucose

RNTCP Revised National Tuberculosis Control Program of India

SEMDSA Society for Endocrinology, Metabolism, and Diabetes of South Africa

TB Tuberculosis

VDOT Video Directly Observed Therapy

WHO World Health Organization

XDR-TB Extensively drug-resistant tuberculosis

1 Introduction and Executive Summary

Across the world, limited progress is being made in the fight to reduce preventable deaths from both infectious and non-communicable diseases (NCDs). While there are many populations showing encouraging improvement in certain health outcomes, the fact remains that demographic shifts, economic drivers, population displacement, and rapid urbanization are threatening to reverse even the limited progress being made in crucial disease areas. Simultaneously, technological and medical advancements are failing to reach millions of people who need them, for tuberculosis (TB), diabetes mellitus (DM) and other diseases. It is self-evident that to address this situation meaningfully by providing high quality health care services, efforts will need to be sustained, flexible, yet carefully designed in local contexts to overcome the many barriers to care. It will also need to be a well-resourced effort both nationally and globally if rapid progress is to be made in building high quality health delivery systems that no longer fail the communities they are meant to serve.

When envisioning the principles of a health delivery platform designed to combat challenging diseases on a population level, an overarching concern is that health care systems are able to deliver a comprehensive health intervention to patients in the communities where they live and work, and not only in the hospital or clinic where space, wait times, and beds are increasingly at odds with the populations' needs. This type of delivery necessitates carefully supporting and capacitating health delivery platforms in the community, screening in a targeted but comprehensive manner, providing long term care in that system, or providing linkage to other quality care delivery options if preferred. These basic priorities are as valid for infectious diseases as they are for chronic diseases. However, as a practical matter, these priorities cannot and should not be applied to each disease area separately, with their own dedicated workforce and infrastructure; they must be done in a holistic, integrated fashion to strengthen the health system while improving services for each person in the community.[1] On a global level, with the enormous burden of both infectious diseases and, increasingly, NCDs, solutions must be designed to address multiple disease areas at once through comprehensive, patient centered care. These solutions must take advantage of the tried and true epidemic control strategies that the authors of this document organize into a "search – treat – prevent" framework that explores these program components at the patient, provider, and systems levels.

This document is a conceptual launching point (though many other similar points could also serve this purpose) and the authors hope that this work can be built upon and improved. For the purposes of this document, two disease areas in the top ten killers globally, TB and DM, were chosen to illustrate how even in a single overlapping and crucial area of global health care, the need for service integration, community-based solutions, inter-departmental and interdisciplinary cooperation, and quality improvement are pervasive and interconnected. Of the 9.6 million new people with active TB disease, approximately 1 million also had DM[2]. In a country like South Africa, TB and DM are the two leading

causes of death.[3] Although TB is now considered the largest infectious killer of adults worldwide, in many countries, chronic diseases, such as DM, chronic obstructive pulmonary disease, heart disease, certain oncological conditions, and disorders of mental health, contribute to higher burdens of morbidity and mortality. These diseases also lead to poor outcomes for other diseases in individual patients.[4] A comprehensive platform is needed to address these challenges in coordinated fashion, rather than in administrative, academic, and institutional isolation. Considering these two diseases together at length can illustrate some important points about the intersection of TB and DM, both within an individual patient and within health systems.

Four countries were chosen for this document that bear notably high burdens of these diseases and yet have very different public and private health system features: the Russian Federation, the Republic of Peru, the Republic of India, and the Republic of South Africa. In the South African and Indian settings, two cities (eThekwini/Durban and Chennai respectively) received particular focus within their national systems to illustrate the on-the-ground challenges and opportunities found there as programs are already undertaking initial work in this area to strengthen TB programs comprehensively. In the other two country sections, a more general systematic review and analysis were undertaken of TB and DM care delivery. To some degree in these countries, the diabetes care delivery infrastructure has been developed to an extent, but in most settings, it is weak or non-existent in the public sector. Some of the recommendations in this document are applicable to all four settings, but many site-specific challenges are also identified. All these countries have historically "vertical" TB care delivery programs, but are looking at how to move toward more comprehensive care delivery for TB and other disease-specific programs in an integrated fashion within their larger health care systems.

In all four sites, households where TB interventions are taking place are becoming the sites for testing how best to diagnose patients with co-morbidities that have a detrimental effect on curing TB, recovery and quality of life (e.g. DM, heart disease, etc.). Just as TB clusters around families and households, so do risk factors for DM. As these programs learn how to optimize diagnosis and care delivery for TB, the same is true for these other diseases. Discovering the optimal way to efficiently screen high-risk household members for DM should inform or provide the way for heart disease screening and other services. Indeed, in Russian rural areas and other areas with limited hospital access, this document notes that community-based programs that already interface most frequently with patients through integrated primary health care services (rather than TB or NCD clinics/specialists) may be initially best situated to deliver high quality, comprehensive care for TB and DM as well as other health challenges with the right reforms and investments. A common challenge is to find a way to design this sort of integrated multi-disease approach in urban settings, that while rich with hospital and clinical resources, in some cases are weaker in community health service outreach and place excessive burden on the patient to come to the clinics or health posts.

This is not the only common challenge these four countries face. They could all:

- Reduce the burden on the patient to overcome program deficiencies, by designing patient-centered approaches
- Improve the use of local, operational data to drive program improvement continuously
- Implement a biosocial systems model to complement the dominant biomedical approach
- Address discrimination against TB patients by health care providers in non-TB facilities including NCD clinics, address infection control concerns in these settings
- Consider the potential drug interactions that may take place while simultaneously being treated for TB and DM and be prepared to identify them
- Learn from and improve upon the experiences integrating disease programs for other linked epidemics like TB-HIV co-infection crisis that drive preventable death

By examining these two interlinked epidemics of TB and DM as an initial launch point for the broader conceptual exercise, the authors of this document encountered many potential areas for synergy and improvement. These include:

- Creation of interdisciplinary care and support teams with a focus on linkage to sustained quality care
- Finding efficiencies and mutually beneficial reforms through programmatic/resource overlap and coordination
- Providing supportive services like community health worker accompaniment, nutrition, patient education, transportation, and economic assistance programs
- Considering potentially beneficial synergies of simultaneous treatment—programs may eventually provide DM treatment in a way that is helpful for TB treatment (e.g. by using metformin, which appears potentially protective against tuberculosis)

In these settings, it is clear that care delivery improvements for one disease should systematically drive improved outcomes for other diseases, as they operate in an increasingly integrated care delivery programs. But this enormous task must begin somewhere specific in the programmatic landscape, with an eye on an ultimately health systems oriented approach. By looking first at the intersection of TB and DM in patients, providers, and health systems, and how each respond to this co-epidemic, this document is designed to provide a foundation for practical work in these settings, and for similar analysis in other areas of global health delivery science.

2 Republic of Peru: Thinking through integrated TB and DM care

2.1 Epidemiology of TB and DM in Peru

Peru accounts for 3.1% of the population of Latin America and the Caribbean, but has 11.6% of the region's tuberculosis (TB and 35.3% of MDR-TB cases.[5] In 2015, the national TB incidence rate was 87/100,000.[6] TB affects mostly adolescents and adults ages 15-54, with a slight increase in incidence rates again after 65 years of age. TB incidence rates decreased dramatically in the 1990s and have continued to decrease at much smaller rates since 2012. In Lima, treatment success rates have remained constant around 86%, but loss-to-follow-up rates increased from 8% to 10% between 2010 and 2013. In 2013, TB-HIV co-infection was 4%, whereas TB-DM co-morbidity was 6%, with 62% of TB patients screened for diabetes mellitus (DM).

In Peru, the highest disability adjusted life years (DALYs) among people between the ages of 45 and 59 is attributed to DM; among people of all ages, DM is 6th in DALYs.[7] Reports from the World Health Organization (2014),[8] PERUDIAB (2015),[9] and Health and Demographic Survey (2014),[10] estimate that Peru's DM prevalence among adults is approximately 7%, and only half of those cases have been diagnosed. Epidemiological data from 2012 among 3,000 DM patients in two hospitals in Lima showed that of the 90% of fasting blood glucose tests available, 65% were ≥130 mg/dL and of the 29% glycosylated hemoglobin test (HbA1c) results available, 67% showed levels ≥7%. Only 35% of these 3,000 patients have had one or more follow-up visits (beyond the initial diagnosis). The most common co-morbidities were arterial hypertension (11%), obesity (4%), thyroid disease (2%), and TB (1%). The International Diabetes Federation (IDF) estimates the average cost per DM patient at US$523.[11]

People who have DM are three times more likely to have TB.[12] In Peru, studies show that TB-DM co-infection is more common than previously thought,[13] and these patients have a higher risk of unsuccessful treatment outcomes compared to TB non-DM patients.[14] Among 225 TB patients enrolled in the TANDEM project, 9.3% had HbA1c ≥6.5%. From the group of patients 35 or older, 18% had HbA1c ≥6.5%. In addition to being aged 35 or older, obesity (body mass index [BMI] ≥30) was also associated with a higher risk of having DM.[15] Among patients with MDR-TB, prevalence is 6.3%; however, it increases to 29% among patients ages 44-54 and 31% for patients aged 55 years old and over.[16] MDR-TB and DM is also associated with higher body mass index (BMI) and higher death rates.

There is also a high prevalence of latent TB infection (LTBI) among DM patients in Peru. Using QuantiFER-ON-TB Gold (QFT) to test 173 DM patients, 49% had positive results, however the risk of LTBI becoming active TB among DM patients is still unknown.[17] Although TB-DM care management in TB units is complicated, point-of-care HbA1c and random blood glucose (RBG) offer strong diagnostic accuracy.[18] TB-DM management, particularly glucose control, remains one of the main barriers to coordinated TB-DM care in Peru.

Until recently, TB-DM patients at Hospital Dos de Mayo in Lima had to go to the endocrinologist's office in a separate section of the hospital for DM diagnosis, follow-ups, and nutritional counseling; this is the standard operating procedure in Peruvian hospitals. Yearlong efforts at this hospital to address this risky practice have resulted in some changes. While HbA1c is still not available in TB units, endocrinologists rotate to provide DM care at the TB unit once a week. Additionally, DM patients are regularly screened for TB symptoms in the DM unit, and an online system has been activated to monitor TB-DM cases. The constant barriers to TB-DM care integration reported were intra-unit communication and commitment to facilitate TB-DM patients care at the TB unit from the rotating endocrinologists.

2.2 Challenges for TB-DM management

During a DM training for Lima's TB unit providers in June 2016, nurses reported on the most significant challenges they face when trying to provide quality care for TB-DM patients. Their responses were recorded and discussed as a group with a TB-DM specialist. Information gathered during this discussion with providers, interviews with researchers and decision-makers, and visits to health care facilities were summarized into the system-, provider-, and patient-level challenges listed below:

System level: Interactions between the national TB and DM strategies

- No national guidelines for TB-DM care
- Poor integration of TB-DM care and management
- Lack of joint trainings and meetings for TB and DM staff
- Professionals (outside of TB unit) need TB sensitivity training
- Public health insurance does not cover glucometer or its test strips
- Scarcity of medical equipment and materials for DM (medication, glucometer, test strips, needles, insulin) in the TB units and laboratories

Provider level: Difficulties with specialist (endocrinologist) appointments

- Endocrinologists are scarce and only available at higher level facilities (hospitals)
- Nurses and physicians outside of the TB unit have limited knowledge about TB
- When patients visit specialists in hospitals, there is an increased risk for anyone in contact with them along their pathway to become around them infected with TB, including during waiting time in the hallways

Patient level: Barriers to TB-DM care

- Patients need staff to follow-up and educate them about DM
- Patients do not make it to their appointments with the specialists at hospitals for multiple reasons (e.g. inconvenience, forgetfulness, previous negative experience with non-TB staff)
- TB patients report discrimination when they attend appointments with endocrinologists
- TB patients are made to wait longer than other patients to see an endocrinologist

2.3 Recommendations for integrating TB-DM care in Peru

TB-DM co-morbidity has negative effects on TB treatment outcomes and interferes with DM care. In Peru, the incidence of TB-DM is growing without an integrated, patient-centered care delivery system. Thus, TB-DM patients face several barriers in detection and treatment at the system-, provider-, and patient-level. After assessing current care and consulting with stakeholders at various levels of care, six initial activities are recommended in Peru for how to integrate TB screening and community-based care with DM screening, diagnosis, and linkage to care:

- Team building for TB and DM providers
- TB-DM trainings for health care service providers
- Including a section on TB-DM in the national TB guidelines
- Facilitating patient-centered care for TB-DM patients
- Arranging for access to TB-DM care equipment and supplies
- Establishing a plan for monitoring and evaluation

2.3.1 TB-DM team building

The first step should be to create time and space for TB and DM care service providers to interact and develop solutions for an integrated TB-DM care agenda at the health system level. The first TB-DM conference took place in Peru May 19th, 2017. Stakeholders from the TB and DM fields attended, including researchers, physicians, specialists, nurses, and nurse technicians from Lima and other Peruvian provinces. This was an opportunity to disseminate the results from the research project TANDEM in Peru and other countries and provide a space for providers from TB and DM fields to interact and develop a strategy for the integration of TB and DM care.

This conference was the first of its kind, and should be followed-up with frequent opportunities for providers to engage in conversations about providing comprehensive TB-DM care. The objective of these encounters should be to identify barriers to integrated care and develop solutions that are acceptable, feasible, and sustainable for both teams. This type of team building should take place at the decision-making level (national TB programs and national DM program) as well as at the practice level within health care facilities (TB teams, specialists, researchers, patients, etc.). The ideas and plans produced during these meetings could be the foundation for local and national-level guidelines for integrated TB-DM care.

Team building in relation to TB-DM may need to include stakeholders beyond the national TB and DM programs. Mapping the key stakeholders and their relative influence will be essential to avoid bottlenecks in the processes that will integrate TB and DM care. Meetings with the appropriate stakeholders will also aid in gauging readiness for change and access to the political input required for success. One of the additional key stakeholders is the Ministry of Health's office of health promotion, Dirección General de Promoción de la Salud y Gestión Territorial, generates health policy and

promotes, disseminates public health messages, and builds strategic alliances that promote healthy living.

2.3.2 Health care service provider trainings

Within TB units, a crucial step at the provider-level is to develop the skills needed for integrating TB-DM care. Based on the most up-to-date scientific knowledge about TB-DM care, primary care physicians, nurses, and nurse technicians should be trained to provide basic DM care and education at health centers and hospitals, including nutrition counseling. These trainings should be scheduled at least yearly due to the high turnover rate in TB units.

As of May 2017, 168 health care service providers from health facilities in Lima Sur (southern Lima) have participated in online TB-DM training with support from the World Diabetes Foundation; the participating providers included physicians, nurses, and nurse technicians. This basic training included information of TB-DM epidemiology, diagnostics, treatment, and adverse drug reactions. Additionally, there has been one in-person TB-DM training for nurses working in health facilities in Lima in 2016. The online trainings have been scaled-up to provide basic information and refreshers to all TB-unit personnel. In-person training is also needed to enforce the online training and provide hands-on practice and discussions about barriers and possible solutions to integrate TB and DM care.

2.3.3 TB-DM in national TB guidelines

The formalization of an integrated TB-DM model for the health system is essential for planning, monitoring, and evaluating TB-DM care, including spaces for TB and DM teams to strategize and train together. The next recommendation is to develop a TB-DM chapter to include in the national TB guidelines that is acceptable, feasible, and sustainable for TB as well as DM health care service providers. Adding a section or chapter in the national DM guidelines on TB-DM care is recommended as well, if appropriate. These chapters should apply the most effective strategies available to date in the scientific literature and be developed in collaboration with the national TB and DM program teams, and Direccion General de Promocion de la Salud (DGPS).

TB-DM providers' team building and joint trainings, in addition to scientific evidence, will serve as the basis for the chapters on integrated TB-DM care. The chapters of this training could include flow charts, protocols, list of medications and adverse reactions, and indicators for monitoring and evaluation. Additionally, educational materials targeting patients should be distributed for TB-DM patients and those at high risk of this co-morbidity. A first draft for such educational materials has been developed by the World Diabetes Foundation in collaboration with the Universidad Peruana Cayetano Heredia. This effort surged from the study "Linkage between Tuberculosis and Diabetes – WDF 15-1224", and is a patient-centered and context-specific patient guide to TB-DM that that could be widely disseminated.

2.3.4 Facilitate TB-DM care for patients (patient-centered care)

While it should go without saying, when technical, financial, and human resources are scarce and communication with the patient or potential patient is weak, it is important to consider strengthening the health system rather than insisting a patient is at fault. A shift to patient-centered care is recommended by facilitating DM care within TB units and addressing patient-level barriers by understanding how they make decisions, where they live and work, and their own clinical situation. This can be accomplished through training primary care physicians, nurses, and nurse technicians in basic TB-DM care, as described above, and integrating TB units into part of a comprehensive-care service site for both diseases. TB patients in Peru should be screened for DM and receive basic TB-DM care within the TB units, consulting as needed with an endocrinologist.

Following the conclusions drawn from the TANDEM project, TB patients should be screened for DM with the HbA1c test if their blood sugar levels are high, if they are aged >35 years old, or if they are obese. Once the TB team is trained, follow-ups, including nutrition counseling services, for TB-DM could be delivered at the health center level, instead of only at hospitals. Eventually, these health service networks should reach the homes of patients to provide easily accessible comprehensive care. Health education on DM should also be provided by the TB teams at the health centers, with appropriate educational materials. The health center's nutritionist or someone at the TB unit could be trained to provide nutritional counseling to TB-DM patients. Nutrition is a particularly important subject since the nutritional recommendations given to a non-DM TB patient could worsen the condition of a TB-DM patient.

2.3.5 Equipment for TB-DM care

Currently, TB units do not have access to HbA1c tests, glucometers, test strips, or educational materials for TB-DM in Peru. These are costly but necessary tools to integrate the diagnosis and care processes for TB-DM patients. In Peru, the public health insurance system provides TB treatment (diagnosis, treatment, doctor visits) with very minimum out-of-pockets costs to patients. Unfortunately, it does not cover glucometers or test strips for anyone due to costs, and TB units are not equipped or permitted to use HbA1c tests for DM diagnosis. Thus, TB-DM patients who receive TB care at health centers must travel to a hospital for diagnosis and follow-ups with endocrinologists, wait for extended periods of time, experience discrimination, and expose hospital staff and patients to TB if they are symptomatic.

To overcome these system-level barriers to integrated TB-DM care, the national TB program and national DM program (chronic diseases) must work together to pressure the public health insurance system for coverage of HbA1c tests, glucometers, and test strips and access to these supplies at health centers. The approximate costs for glucometers and a month supply of test strips are 100 Peruvian soles (US$30) and 80 soles (US$24), respectively. To explore a cheaper alternative for both the national comprehensive health plan (Seguro Integral de Salud) and national employee health plan, a program

could compare the cost-effectiveness of providing one glucometer per TB-DM patient versus one per TB unit, where TB-DM patients could at least control their blood sugar once per day, when they take their TB medications. A strong collaboration between TB and DM programs, and the Ministry of Health's office of health promotion will be key to making a sustainable policy change that could solve the unmet demand for equipment and supplies needed for an integrated TB-DM care model.

2.3.6 Monitoring and evaluation

The effects of the above recommendations should be monitored and evaluated to ensure that patients are benefiting from the integrated TB-DM services and that resources are used efficiently. Monitoring and evaluation is a step that is neglected during the process of research or project implementation. TB-DM care integration is a new initiative in Peru, an opportunity to provide quality, comprehensive TB-DM care to patients who previously faced several barriers in their care. A well-designed monitoring and evaluation plan will serve to make continuous, sustainable improvements to TB-DM care integration and to replicate these efforts in other countries with a high TB-DM co-morbidity burden.

Unfortunately, due to recent epidemiological shifts, the TB-DM field has limited scientific evidence to support logistical, programmatic, and clinical decisions. The monitoring and evaluation process will be an opportunity to reevaluate the recommendations above, establish new strategic objectives, gather data for future decisions, and establish a research agenda. For example, a study showed that the prevalence of LTBI among DM patients in Lima was 49%, however whether this figure can be extrapolated, the probability that an DM patient with LTBI will develop active TB, and whether chemoprophylaxis among DM patients is effective at preventing TB are unknown. With this information, programs could determine TB risk among DM patients, and draft screening protocols and programmatic flowcharts as needed.

3 Republic of South Africa: Search-Treat-Prevent framework for addressing DM in eThekwini, KwaZulu Natal

3.1 Burden of TB and DM in South Africa

South Africa has one of highest incidence of tuberculosis (TB) in the world at 834 cases per 100,000 population[19] and the International Diabetes Federation estimates that there are 2.3 million adults with diabetes mellitus (DM) in South Africa, leading to nearly 80,000 DM deaths annually.[20] It is the leading cause of death in the country for women, and 5th leading cause for men[21]. Despite the significance of this epidemic, there are few successful efforts to date to systematically link patients to care in the communities where they live and work on a population level despite the many relative strengths of the health system. In South Africa, TB and DM are the top two causes of mortality at 7.2% and 5.4% of all deaths, respectively.[22] Both diseases are complicated, require long-term management, and have the potential to create further complications and substantial economic duress on patients and their families, as they particularly affect the productive years.[23,24] The substantial burden of TB and DM on the population requires a comprehensive and ambitious response through integrated, patient-centered health systems. This report provides an overview of the challenges to managing DM at various levels and provides general recommendations utilizing comprehensive search-treat-prevent framework to address eThekwini, KwaZulu Natal (KZN)'s TB burden (which is consistently in the top 3 provincial rates in the country) and DM care simultaneously. The search-treat-prevent approach draws on a comprehensive set of established epidemic control strategies utilized and refined to improve care delivery and treatment support for TB patients and their contacts in several settings around the world, with evidence for this approach summarized in a special series in the Lancet entitled *How to Eliminate Tuberculosis*.[25]

KZN accounts for 17.7% of total deaths in the country. Located on the eastern region facing the Indian Ocean, KZN is comprised of 10.3 million people, with a sizable portion of the population identifying as Asian/Indian South Africans. The national prevalence of DM is 9.2% whereas the KZN's prevalence of DM is 12.5%. However, when accounting for the undiagnosed percentage of diabetic patients, Sahadew et al[26] estimated a prevalence of 34.1%. KZN's large population of Indian descent, known to have higher rates of diabetes, which may contribute to the higher than average rates in KZN as compared with the rest of the country. Unsurprisingly, eThekwini-Durban, KZN's largest municipality, had the highest rates of DM and the study also reported that 50% of all new cases were identified in the municipality itself. Among Black South Africans living in eThekwini, the prevalence ranged from 11.9-13.1%, depending on the test that was used.[27]

In 2014, The Lancet reviewed the state of TB and DM co-morbidities, specifically focusing on policies and programs. The review highlighted need for improved integration of care and prevention in

traditionally “vertical” disease-specific services, the adequate provision and quality of nutrition associated with TB and DM, and bold policies and support systems coupled with operations research to establish best practices. These recommendations are critical in South Africa, where 8% of TB cases are associated with DM, the third highest incidence of TB associated with DM after India and China.[28]

3.2 Leveraging the re-engineering of the primary health care system

To address the TB and DM epidemics, integrated, comprehensive, and patient-centered approaches must be the focus of health systems. Researchers have looked closely at patient experience in the health system, with some striking examples of single-patient experiences. One rigorous study of a single patient showed that for 58% of her MDR-TB treatment duration, she was receiving clearly inadequate care[29].

In 2011, South Africa began to move towards a primary health care model, which includes three streams: ward-based outreach teams, school service strengthening, and clinical specialist teams in each district. This model serves as an important step towards effective delivery of services around TB and DM, however, effective and quality coverage as well as meaningful linkage to care continues to have its challenges

In partnership with a wide range of stakeholders, the KZN Department of Health developed a “90% diagnosed-90% treated-90% adherence” strategy (90-90-90) for both hypertension and DM. Responding to the increasing burden of non-communicable disease burdens in the province and district, the KZN Department of Health has set ambitious targets against these diseases. The actual performance compared to targets is not known at this time, but based on author field interviews, progress is only beginning. Both the municipality and the province have been part of focused discussions around the design and implementation of an ambitious, citywide strategy to eliminate TB in an integrated, comprehensive fashion within government guidelines but supplemented in a comprehensive fashion.

On the national and provincial level, additional stakeholders that are vital to guiding policy and practice include the South African Medical Research Council, the International Diabetes Federation and the Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMDSA). These stakeholders provide policy expertise, develop guidelines, support programs, increase advocacy, and contribute funds for diabetes management. SEMDSA, for example, writes the country’s guidelines on management and care, while Medtronic, currently funds a US$17 million project around community based to expand care and management of DM. Additional support for exploring how to provide optimal DM care is provided by private sector care provider associations, pharmaceutical companies and their associated foundations, and others.

3.3 Learning from TB-HIV co-infection -- systems challenges

As South Africa has begun to move towards a more patient-centered approach of primary care as evidenced by the recent reengineering of their primary health care centers, there are many lessons that can be can be learned from the innovative ways that diseases such as HIV and TB have been monitored and addressed across the country to date. While steps have been taken to build capacity and strengthen the existing network of primary health care providers across the 764 primary health care centers in KZN, there remain many challenges to ensure that care is both comprehensive and accessible for patients and their families. With a high-density catchment population of roughly 13,687 per primary health care center, it is important that future efforts to address the TB and diabetes partner closely with the 19 community health centers (CHCs) and over 170 mobile clinics that are located in the province. As a large proportion of those at risk for TB and DM in KZN are unemployed and living in various degrees of informal housing across the area, there are many opportunities to learn what will be required to fully embed care delivery and support programs within the existing programs offered by the one metro municipality of eThekwini and 10 district municipalities. Specifically, lesson from TB-HIV co-management programs are instructive. Loveday et. al. of the patient journey study found that the systems level challenges for the patient that received notably poor care with MDR-TB and HIV co-infection were many, and included:

- Drug shortages and stock outs for months at a time
- Expensive or inadequate laboratory services
- Unhelpful monitoring and evaluation systems
- Provider deviating from required treatment guidelines
- Inadequate integration of TB and HIV services[30]

These broad challenges and others related to the temporal length and shifting nature of DM treatment should be expected to manifest in many different ways as the city attempts to tackle TB and DM together. This is a policy and practical space where few resources have been devoted by national or foreign aid funding channels compared to HIV and even TB programs.

While pharmaceutical shortages may be mitigated by the simplicity and affordability of DM drugs, particularly for oral use, other consumables are needed and will require significant management and procurement expertise to successfully provide to patients as needed. To assess the rough costs of these needs per 500 patients, interviews on-site were conducted to understand the human resources needed to support ongoing screening, and link patients and their families to care at existing community clinics and PHCs in urban settings in KZN.

The following spreadsheet outlines certain programmatic costs necessary for appropriate diabetes testing and treatment (including HbA1C, blood glucose tests, generic government-procured insulin, and oral medications), necessary self-monitoring tools (glucometer, test strips, and supplies). This table takes into account the main operational and clinical components of sound diabetes screening, linkage to care, and patient support, but recognizes that each patients' treatment journey may look different and a tailored treatment plan will be necessary which may include expenses not captured by this table.

Approximate treatment and consumable costs, RSA 2017		
Consumable/other expenses	**Itemized cost (South African Rand)**	**Itemized cost (US$)**
HBA1C tests	R198.66	US$ 15.50 USD
Test kits (gloves, vacutainer, phlebotomy consumables)	R30.27	US$2.36
Generic insulin (3ML pen)	R250	US$19.28
Glucometers	R416.81 pack of 50	US$32.57
Test strips	R198.00 pack of 50	US$15.50
Metformin or generic (Glucophage)	R258 pack of 30 (500mg) tablets	US$19.85

US$1= 12.96 South African Rand, all conversions are rounded to nearest dollar value.

Table SA.1 Approximate treatment and consumable costs, RSA 2017 [31]

Interviewees also suggested an estimated additive (additional state or non-profit complementary support for a Department of Health public health program) to find, link to care, and manage approximately 1000 patients per year would require a project manager, clinical nurse coordinator, a dozen community screeners and facility screeners each in this setting, as well as dedicated data management and endocrinologists' time.

3.4 Recommendations for Systems-, Provider-, and Patient-level interventions against DM

As KZN approaches the strengthening of response to both TB and DM, multiple challenges currently exist across systems, providers, and beneficiaries/patients. These challenges are not always specific to diabetes in KZN but management of these challenges can have a positive impact in reducing the burden of DM on patients. In summary:

Systems-level

- Large numbers of people living with diabetes are undiagnosed and where diagnosed, are subject to lack of program follow up
- Data collection and management regarding DM patients are weak, where collected systematically it does not seem to drive quality improvement
- Limited capacity to teach and integrate self-management techniques among patients, a critical factor in addressing DM at the population level

Provider-level

- Lack of standardized screening practices across primary health care providers in public sector, despite some standardized documents in draft form
- Lack of training and effective linkage to care services both within disease services and across services, again despite existing management standards and guidelines
- Lack of comprehensive (onsite or referred) nutrition, physical activity, and DM management programs for patients in the public and private sectors
- No systematic or efficient linkage to navigate as a patient between public and private sectors; many patients begin care in one but transition to care in another public or private network, often leading to loss of relevant information

Patient-level

- Very limited active linkages to screening or care for DM patients; largely passive system for patients despite promising reforms and guidelines
- Not informed by health service providers as to where or how to access mandated public health services other than local primary health center when available
- Limited or in some cases non-existent awareness about DM and related health challenges and their impacts on health
- Low level of knowledge among active patients regarding treatment regimens with little support offered for patients or their family members to ask questions regarding side effect management, drug-drug interaction, etc.
- No systematically implemented nutritional programs for patients with DM and other co-morbidities

3.5 Summary recommendations for improved service delivery in South Africa using search-treat-prevent approach

Based on the nine challenges identified, there are nine recommendations that were associated with the challenges to inform the broader development of patient-centered but ultimately systems-oriented programming in KZN. These recommendations have been divided into the search, treat, and prevent activities across systems, providers, and individual level interventions. Table SA2 provides an overview of the recommendations:

	Search	Treat	Prevent
Systems	Improve detection of undiagnosed and defaulter cases, including linkage to care	Improve data collection and management	Improve access to self-monitoring capacity
Providers	Strengthen primary health care center screening through operational research	Increase integrated care providers by strengthening clinical capacity where diagnosed	Ensure availability of counseling and education on-site
Beneficiaries / Patients	Increase awareness about diabetes and its complications	Increase awareness of medication management	Improve nutritional access

Table SA.2 Recommendations for Applying Search-Treat-Prevent Strategy to DM

3.5.1 Search recommendations

3.5.1.1 Systems: improve detection of undiagnosed and patients who discontinued treatment, and link to care

The International Diabetes Federation estimates that three quarters of cases of DM are undiagnosed in Africa, the largest proportion of any region. The health system in South Africa must invest in ensuring screening of risk factors and identification of cases as a clear priority for addressing the DM burden, utilizing the appropriate risk assessment tools to maximize the efficiency and targeted nature of such population-level screening. Opportunities exist to leverage the primary health care system re-engineering to improve diagnosis, specifically using ward-based outreach teams and the primary health care centers and community health care centers. According to interviewees, the ward-based outreach teams were initially focused on maternal and child health-related outcomes, so do not universally cover the population, though their mandate is growing and in flux according to expert interviews as the integrated national health initiative proceeds. These ward-based teams should be sufficiently trained in integrated care for diseases such as TB and DM or pre-diabetes as well as a special focus on linkage to care and maintenance of quality care. Examples such as the Western Cape's 2017 Community Health Worker Guide provide practical guidance for community health workers on screening and supporting the treatment and management of chronic conditions, as well as when and how to connect the patients to appropriate health facilities.

One specific focus of outreach should be on individuals who start on medication, but may not continue due to various barriers. Rates of treatment default from DM care, at 1.8% in 2014 in KZN have been strongly associated with amputations.[32] When patients discontinue treatment and such traumatic procedures are possibilities, the burden to respond falls upon the program rather than patient to outline the risks and likely ramifications of treatment or non-treatment of a patient's disease. Programming should ensure strategic focus on immediately supporting patients who are not being adequately served by their DM programs, while programmatic improvements are considered and

implemented. Additionally, other community, household, and facility-based screening efforts can and should fully integrate co-morbidities, such as TB. Such integrated services delivered by health workers in the households, via primary health care and community health care clinics, and outreach teams should streamline the patient's engagement with the health system to ensure more efficient service provision, limiting barriers such as transportation and time meeting with multiple providers.

3.5.1.2 Providers: strengthen primary health care center screening through operational research.

The public sector plays a crucial role in the detection of DM patients, identifying over 38% of all cases.[33] It is therefore critical to have strong primary health care providers in the public sector implementing effective screening strategies, especially those in clinics. At this moment, clinics are especially important in provision of care and coordination of ward-based services and linkage to reference hospital systems. In fact, clinics provide initiation of 63%-80% of pharmaceutical therapy in KZN.[34] Therefore, multi-disciplinary team of providers in clinics should use carefully designed effective screening methods, utilizing the new, existing guidelines for the community health care workers and other tools that should continuously improved over time. Risk factors screening standards for primary health care centers are provided in the Adult Primary Care Guidelines for South Africa. They include family history of DM, BMI and waist circumference, hypertension diagnosis, and then moving quickly to doing a finger prick test. Screening is targeted to individuals 40 years old or older. However, further operational research is needed to identify implementation gaps after screening, in capacity of the health system to link to appropriate care and manage of treatment.

3.5.1.3 Individuals: increase awareness about diabetes and potential complications

To effectively identify cases of DM, care demand-side interventions such as raising awareness among the public is one consideration. The high rates of undiagnosed individuals with DM requires social marketing campaigns and advocacy to promote patient-initiated screening and efforts to date in this category are occasional and ad-hoc. While there are yearly public events to raise awareness of the disease, more information should be provided detailing specific awareness of risk factors, and identifying channels to refer family members or acquaintances to screening and care. Once in the program, improved education initiatives can also improve patient retention by showing how default from DM therapy management is associated with higher rates of amputation and mortality. Though trends demonstrate decrease in defaulter rates between 2013 and 2014 according to Pillay et al,[35] opportunities exist to engage with patients through mobile application or SMS, ensuring connection to health care services.

3.5.2 Treat recommendations

3.5.2.1 Systems: Improve data collection and management

As most individuals are diagnosed in the clinic-based settings, strengthening data collection and management will improve tracking of DM patients and their outcomes as well as the effectiveness of

the KZN DM strategy. According to KZN's Department of Health's 90-90-90 strategy, the province identified a prevalence of 9.6%, with a higher prevalence among older adults aged 45 years old and older. Yet, their actual rates of identified diagnosis and treatment are far below targets. Using clinic-specific data quality analysis to strengthen specific regions' care may help reduce burden among especially vulnerable regions or clinics. Additionally, Pillay et al.[36] found decreases in the number of patients on treatment between 2010 to 2014, in contradiction to global trends. Thus, at a systems level, the health system should ensure that clinics and hospitals have high quality data collection and management, which is responsive to the needs of the population as well as at the clinic level.

Pillay et al.[37] found that comprehensive data sheets, and their complimentary computer programs, were components of an effective intervention in improving DM care in a resource-limited clinic through standardization of DM management by providers. This intervention also included retraining clinicians according to South African guidelines and ensuring the provision of a multi-disciplinary team of providers. Ultimately, a "data for action" approach is required that prioritizes not only effective data collection but the timely, programmatically focused utilization of that data to drive improvements in the program and quality of care delivered. The District Health Information System that collects patient information in the public health care sector in KZN does not have the current capacity to systematically link to other registries of DM patients in KZN for patient transfer or management, though it does aggregate by facility in a de-identified fashion for research and quality improvement purposes. This is an opportunity to build a population-health database for patients with DM alone, as well as TB-DM patients. This would only be true provided that any new technological addition to the health information systems in KZN are tailored to speak directly to the existing electronic and paper records-keeping system.

3.5.2.2 Providers: Increase integrated care by strengthening clinical capacity where diagnosed.

The 2017 SEMDSA guidelines for South Africa reviewed research identifying that evidence suggests the need for improvement in adequate standards of care at all levels. Managing care is further compounded by the complex needs required for DM, including multiple potential complications. An intervention by Pillay et al.[38] retrained clinicians on the ophthalmological, electrocardiograph, serological, and podiatric examinations, and nurses on blood pressures, weight, height and circumference measurements, and urine dipstick readings. This intervention contributed to the improvement of clinical practices as well as glycemic control in both type 1 and type 2 DM. All intervention trainings followed existing SEMDSA guidelines in a resource-limited setting in KZN.

Other studies have shown that simpler interventions such as point-of-care hemoglobin testing for DM are significantly associated with improvements in glycemic control over time, while reducing treatment delays in clinic.[39] However, these studies did not specifically review co-morbidities. A study by Mcebula et al.[40] suggested the need for laboratory testing, rather than point of care HbA1c testing, among patients with TB, such as primary TB clinics. Integrated care therefore will require ensuring understanding differences in managing other chronic conditions.

Management of DM can be further complicated in regions with high co-morbidities, especially in countries with highly specialized health practitioners. During scoping study conducted by AA&D in 2016, providers at one hospital reported differences in management of DM care among patients. MDR-TB patients from hospitals were transported to DM specialists in other locations for treatment and/or support by some physicians, whereas other physicians choose to manage the DM care along with TB and MDR-TB care. Physicians also reported interviews that the TB patients face significant stigma in these settings by providers. Integrated care services are required in MDR hospital settings for TB patients, and non-TB clinical settings require awareness building and education around TB management and infection control.

3.5.2.3 Patients: Increase awareness of medication management

During initial meetings in KZN in 2017, the authors of this report briefly engaged with patients, and these conversations with patients in DM care in KZN demonstrated varying awareness of each prescription medications they were consuming. Patient knowledge and even basic awareness of medication management and the importance of adherence to care is a critical factor.

Other programming efforts must also be considered for self-monitoring DM care, which require a combination of systems level efforts and patient education. Access to glucometers for effective and consistent self-management of DM is limited. Evidence from interventions suggests glucometers may be helpful for self-monitoring to help patients make informed decisions for health seeking behavior with intensive education on the use and associated actions.[41] However, the costs can be prohibitive; as media reports have suggested that the KZN government only provides 1 box of 50 test strips to insulin users per month.[42] Regardless of program performance at this moment, what is urgently needed is new operational research programs to show how these services, consumables and awareness programs can be provided in a timely, efficient, and integrated fashion.

3.5.3 Prevent recommendations

3.5.3.1 Systems: Improve access to self-monitoring capacity

In moving towards patient-centered models of care, the 2017 SEMDSA guidelines outline the DM self-management and support recommendations. These guidelines state that patients receive adequate support that includes structured education at diagnosis and repeated intervals; by trained and certified educators delivering evidenced based DM self-management education support. This has been attempted; for example, in their comprehensive intervention in resource-limited clinic, Pillay et al.[43] included an endocrinologist, podiatrist, dietician, ophthalmologist, diabetic nurse educator, and general practitioners. The DM nurse educator was available during every visit for patient engagement, providing intensive education. There are clear limits to how much burden can be placed on patients to fully understand their disease and therefore manage it appropriately; ultimately this is a supportive recommendation to maximize the impact of an improved comprehensive DM program that is linked to the integrated health system.

3.5.3.2 Providers: Ensure availability of counseling and education on-site

Improving nutrition and physical activity is an important component for effective management of DM. According to expert informational interviews, access to dieticians, part of the complete package of the multidisciplinary team needed to effectively prevent and manage DM, is limited to only the worst DM cases in the country and is therefore reactive in nature. In terms of expert availability, the majority of dietitians work in the private sector while many patients access care in the public sector.[44] The only public sector organization of DM educators connected with the government is The Diabetes Education Society of South Africa (affiliated with SEMDSA), which should assist in identifying potential for incentives for engagement across both private and public sectors, and in increasing the supply of multidisciplinary teams needed to manage DM care.

3.5.3.3 Patients: Improve nutritional access

Quality nutritional access is another critical component required for the management, treatment and prevention of DM, pre-diabetes, heart disease, and TB. Those diagnosed with TB should have access to nutritional packages in South Africa, yet population coverage and adequate caloric coverage is incomplete, according to health provider interviews. Additional publicly provided disability support should also be available to TB patients, however, beneficiaries face barriers in accessing these provisions. With co-morbidities, such as DM, nutrition is doubly important. Improved access to adequate and healthy nutrition is critical to management and treatment of both diseases and to prevention of further complications associated with diseases.

4 The Russian Federation: Integrated TB and DM Program Review and Recommendations

Numerous epidemiological studies have broadly explored the relationship between diabetes (DM) and tuberculosis (TB) and the nature of their interaction with respect to co-morbidity. The effect of DM on TB has long been a concern of clinicians and investigators, but this has been somewhat neglected with the emergence of appropriate treatment for both diseases.[45] In recent decades, with the increasing prevalence of TB, now the leading infectious global killer of adults, particularly difficult to treat MDR-TB, and a surge in diabetes cases in the world, the relationship is reemerging as a significant public health problem that must be further explored clinically and programmatically in terms of health care delivery. Careful planning and collaboration are necessary to reduce the dual burden of DM and TB. This section summarizes the evidence and recommendations in the policy guidelines for collaborative TB and DM services; it reviews existing information and discusses the issues that would be helpful for determining research and program priorities in the Russian Federation.

Although infection with human immunodeficiency virus (HIV) is considered as the most potent risk factor for TB, the high prevalence of DM in the world and its effect on TB burden is greater than HIV infection in many studies.[46] The definite pathophysiological mechanism of the effect of DM as a predisposing risk factor for TB is unknown. Some hypotheses are suggested: depressed cellular immunity, dysfunction of alveolar macrophages, low levels of interferon gamma, pulmonary microangiopathy, and micronutrient deficiency.[47,48]

4.1 Epidemiology of TB and DM in Russia: Co-epidemics Abound

According to WHO estimates for Russia in 2014, TB incidence was 84 (76–93) per 100,000 population and TB prevalence was 109 (49–192) per 100,000 population. According to the Russian official data in 2015, TB incidence was 57.7 per 100,000 population and varied from 38 (Central Federal District) to 98 (Siberian Federal District) and 102 (Far Eastern Federal District).[49] According to WHO estimates for Russia, in 2014 the MDR-TB burden was 19% (14–25) in new cases and 49% (40–59) in retreatment cases.[50] According to Russian official data, MDR-TB prevalence increased from 24.8 per 100,000 population in 2014 to 25.5 per 100,000 population in 2015. The proportion of patients with MDR-TB among patients with active pulmonary TB increased from 43.6% to 47.5%. It was concluded that the TB epidemic in Russia has appeared to stabilize with a trend toward improvement (Figure R1)[51]:

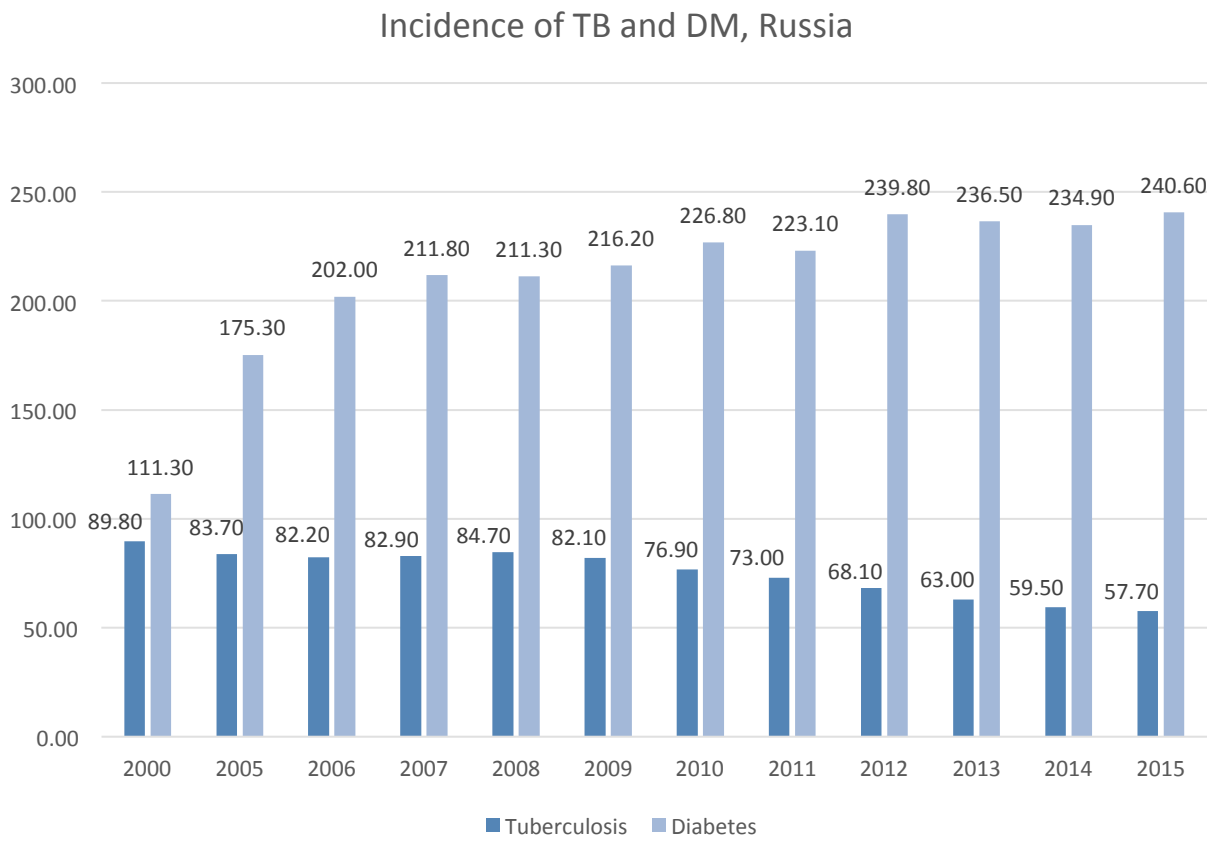

Figure R.1 Incidence for TB and DM, Russian Federation[52]

In the future, it should be noted that the epidemiological process will be adversely affected by the HIV co-epidemic due to an increasing number of patients with advanced HIV infection, and patients with MDR-TB and XDR-TB. Also, aging, changes in life style, and socioeconomic factors have led to an increased prevalence of DM, particularly, type 2 DM. According to official reports in the Russian Federation for 2015, the number of registered patients with DM was 4,418,305. The number of patients increased by 5.6% from the previous year (2014; 4,184,582 registered patients and between 2013 and 2015, the number increased by 23% (from 825,868 individuals in 2013).[53] Notably, pulmonary TB is the one of the most frequent complications of DM and due to a rising prevalence of DM, the relative contribution of DM to the TB epidemic will increase.[54,55]

Depending on the time of occurrence of DM and TB, patients can be divided into three groups:

- Patients diagnosed with both diseases simultaneously or within a very short period of time (interval of 1-2 months)
- DM patients diagnosed with TB, with severe or minor symptoms
- TB patients diagnosed with DM with varying severity of symptoms, including the so-called impaired glucose tolerance and "asymptomatic" diabetes.

The most common cases are patients diagnosed with both conditions at the same time, and who have developed DM relatively recently (within one year). The number of TB patients with long-term DM is significantly lower. For such patients, TB has most often been diagnosed in the presence of moderate or severe metabolic syndrome (uncontrolled DM). For example, at the Moscow City Endocrinology Dispensary, it has been found that the rate of TB in patients with severe, moderate, and mild forms of DM were 5.6%, 2%, and 0.9%, respectively.[56] Several small epidemiological studies have been conducted in Russia at the regional level. For example, in Tomsk, 6.5% of TB patients at the local TB service have had diabetes.[57] In Chechnya, a study found that 10% of TB patients had co-morbidity.[58]

According to the official recommendations of the Russian Ministry of Health, registered DM patients have to be screened with a chest X-rays at the time of DM diagnosis and once a year thereafter (Figure R2):

Figure R.2 TB screening among patients with DM

Any DM patient with suspicious symptoms such as cough for more than 2-3 weeks, weight loss, fever, or an abnormal imaging study is supposed to be investigated for presence of active TB. Screening is

recommended, especially in people with uncontrolled DM and children with DM who have had recent TB exposure.

If Tuberculosis is diagnosed in a diabetic patient during the annual check-up, he/she is referred for TB treatment into the regional TB service. In this case, diabetes management is a mutual responsibility of both services.

Currently, prophylactic treatment for TB contacts with DM (i.e., LTBI cases) is not implemented because there is not enough evidence for Russian policymakers on the advantages of TB prophylaxis among DM patients. One study was conducted in Germany in the 1950s, evaluated post-treatment prophylaxis with isoniazid for 6-24 months after completion of a full course of treatment for active TB in patients with DM; recurrence rates were lower in the intervention group.[59] In a second study conducted in Russia in the 1960s, administration of an analogue of isoniazid for in patients with DM lowered the incidence of TB compared to controls by 2-3 fold.[60] Both studies were problematic due to the absence of randomization and the lack of details regarding the interventions. Therefore, the true effectiveness of chemoprophylaxis in patients with DM remains unknown without randomized controlled trial data. For Russian policy makers, there is not sufficient evidence to support any preventive therapy for patients with DM who have TB infection. However, preventive therapy may be considered in the Russian context for people with DM who have close TB contacts.[61]

All TB patients receive fasting blood glucose and urine glucose testing as part of the initial diagnostic assessment in the following institutional settings (Figure R3):

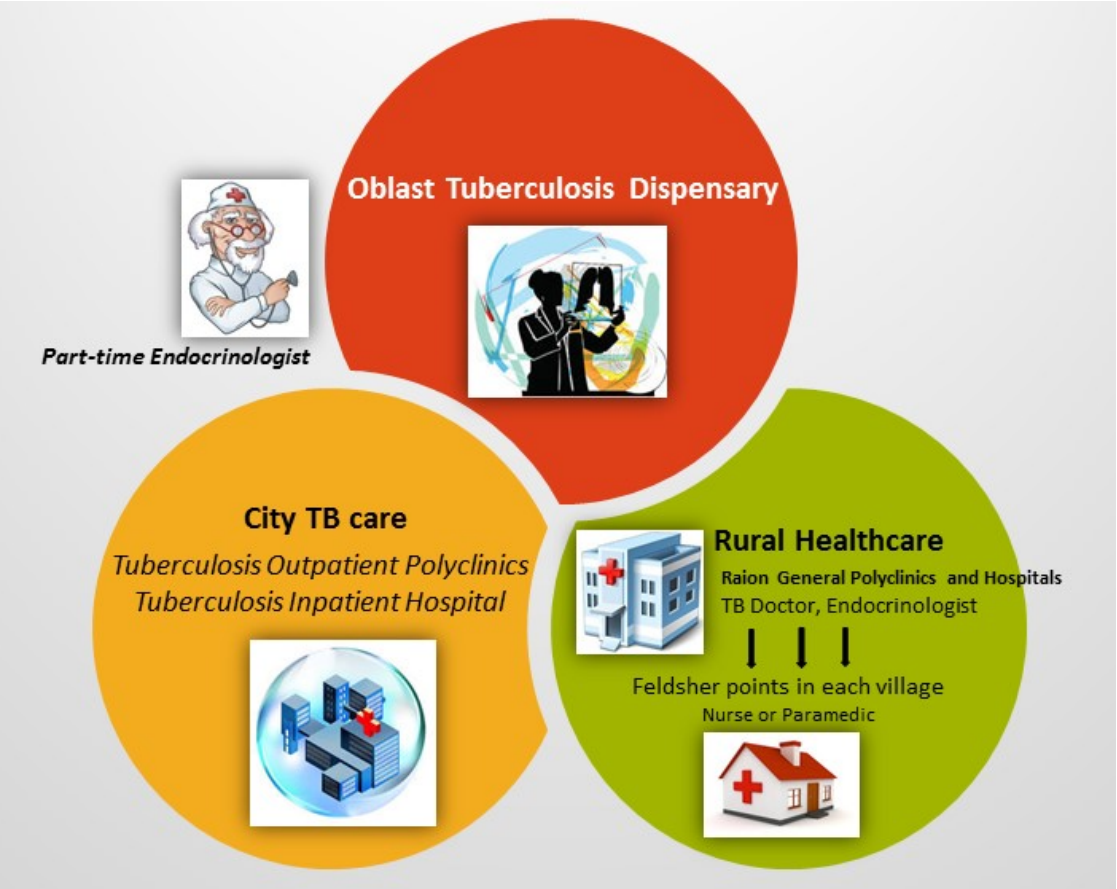

Figure R.3 Screening for DM among patients with TB

If the results indicate, patients are scheduled for an endocrinology consultation, as reported below for other sites as well. In each regional TB dispensary, there is a part-time endocrinologist or, more often, a consultant. The specialist may request further diagnostic testing, such as RBG, 2-hour postprandial glucose (2hPG), HbA1c (if available), and glucose tolerance test (GTT). For TB patients with the existing diagnosis of DM, the endocrinologist evaluates them at the TB treatment initiation point to assess possible interactions between DM and TB medications. Further, consultations are scheduled as part of the patient treatment monitoring individual plan.[62]

In Russia, if DM is newly diagnosed in a TB patient, he/she must finish TB treatment first. Only after TB treatment completion, the patient will be referred to the endocrinology service and registered as a DM patient. In this case, DM management is a responsibility of an endocrinology specialist at the TB service.

The authors' conversations with active Russian TB specialist physicians reveal a lack of knowledge about TB-DM co-morbidity clinical management between both TB and endocrinology specialists.

4.2 Existing Models for DOTS delivery in TB services

The WHO's End TB Strategy promotes service integration for the management of TB/HIV and other co-morbidities. The internationally recommended directly observed treatment, short-course (DOTS) strategy for TB control has been seen by some researchers and policy makers as highly efficient due to its standardized approach, but by design DOTS does not cover all the programmatic requirements of an effective, comprehensive TB program. If implemented well, continuous supervision of treatment adherence and patient support in DOTS[63] also provides an important opportunity for integrated health education and clinical management of patients suffering from TB-DM co-morbidity if proper supportive services are in place. In Russia, patients diagnosed with DM starting TB treatment receive consultation with an endocrinology specialist for confirmation of diagnosis and advice concerning medications, diet, and physical exercise. The patients then continue their TB treatment as inpatients or outpatients. After the patients have completed the full course of anti-TB treatment, they are sent back to the endocrinology clinic for follow-up to detect TB relapse. The same system could be adopted for DM patients who are diagnosed with TB at the DM clinic. This shows that the existing well-functioning TB control program can be adopted to integrate DM care, through:

- In-patient facilities (e.g., TB hospital)
- Models of TB outpatient care
- TB dispensary polyclinics
- TB dispensary day hospital
- TB dispensary home-based care ("hospital-at-home")
- TB dispensary patient-centered accompaniment
- TB dispensary video-DOTS
- Home care
- Primary care clinics (in distant city districts and rural areas)

4.3 Recommendations

In Russia, where official screening programs and basic management algorithms are already in place, the majority of the work required will involve sustained coordination and collaboration between DM and TB clinical services by initiating more innovative means of collaboration, as well as putting in place an effective referral system. Implementing the recommendations will likely be most straightforward in settings where TB and DM services are being offered through primary health care services, such as rural areas. This may have important ramifications for the future of integrated, comprehensive programs in Russia and other countries as the connective tissue offered by primary care programs will ultimately benefit any multi-disease effort when properly utilized. The following activities are

recommendations reached following a thorough examination of the programmatic and policy components in place in Russia.

4.3.1 Collaborative activities between TB and DM services

Establish mechanisms for collaboration:

- Set up means of coordinating DM and TB activities (designated physician or liaison working at both sites as a TB-DM coordinator)
- Conduct surveillance of TB disease prevalence among persons with DM
- Conduct surveillance of DM prevalence in TB patients
- Conduct monitoring and evaluation of collaborative DM and TB activities

Detect and manage TB in DM patients:

- Intensify detection of TB disease and TB infection among persons with DM, with annual scheduled screening for DM patients after TB exposure.
- Ensure TB infection control in health-care settings where DM is managed
- Ensure high-quality TB treatment and management in DM patients, including where needed preventive therapy for high risk groups

Detect and manage DM in TB patients:

- Screen TB patients for DM systematically
- Ensure regular DM consultations by endocrinology specialists as part of TB service
- Ensure high-quality DM management among TB patients

4.3.2 Operational research suggestions

Screening and prevention:

- Determine the best tools and strategies for screening and diagnosing DM among people with TB, and vice versa
- Establish whether people with DM should be screened for TB infection and treated if found, treated; the effectiveness of TB preventive therapy needs to be established through a randomized controlled trial

Case management:

- Identify the benefit and program issues related to more intensified DM monitoring and treatment in TB patients
- Identify models of health service delivery that can best contribute to the integration and sustainability of care for people with TB-DM within vertical delivered clinical services
- Establish how to leverage the DOTS approach already implemented and further supported by government programs for DM prevention, diagnosis and care

Monitoring and evaluation:

- Determine current and projected future rates of TB-DM at the national and regional levels

- Introduce joint indicators for the monitoring and evaluation of TB-DM efforts at oblast, regional, state or national levels

4.3.3 Policy implementation

On the national level, officials should support coordination mechanisms for TB and DM regional services. TB Research Institutes in Moscow, Saint Petersburg, and Novosibirsk, as well as the Federal Endocrinology Research Center in Moscow should develop a cooperative TB-DM research agenda, including the potential research agenda detailed above.

4.3.4 Program implementation

The Chief TB Specialist and Chief Endocrinology Specialist of the Russian Ministry of Health are responsible for overseeing the implementation of the collaborative program, including assessing the cost of implementation. At the regional levels, management of both clinical services should make resources available and develop guidance to include TB-DM activities, ideally with space being allowed for civil society collaboration to innovate in care delivery, coordination, and incentives to reach care points where needed.

4.3.5 Health service delivery: DOTS-based TB-DM patient education, monitoring, and management

An integrated co-management approach presents itself as an optimal solution for patients with TB-DM. During the initial phase of TB treatment, there is strict supervision and support, which includes many interactions with health care staff that provide opportunities for integrated health education and integrated clinical management (Figure R4)[64]:

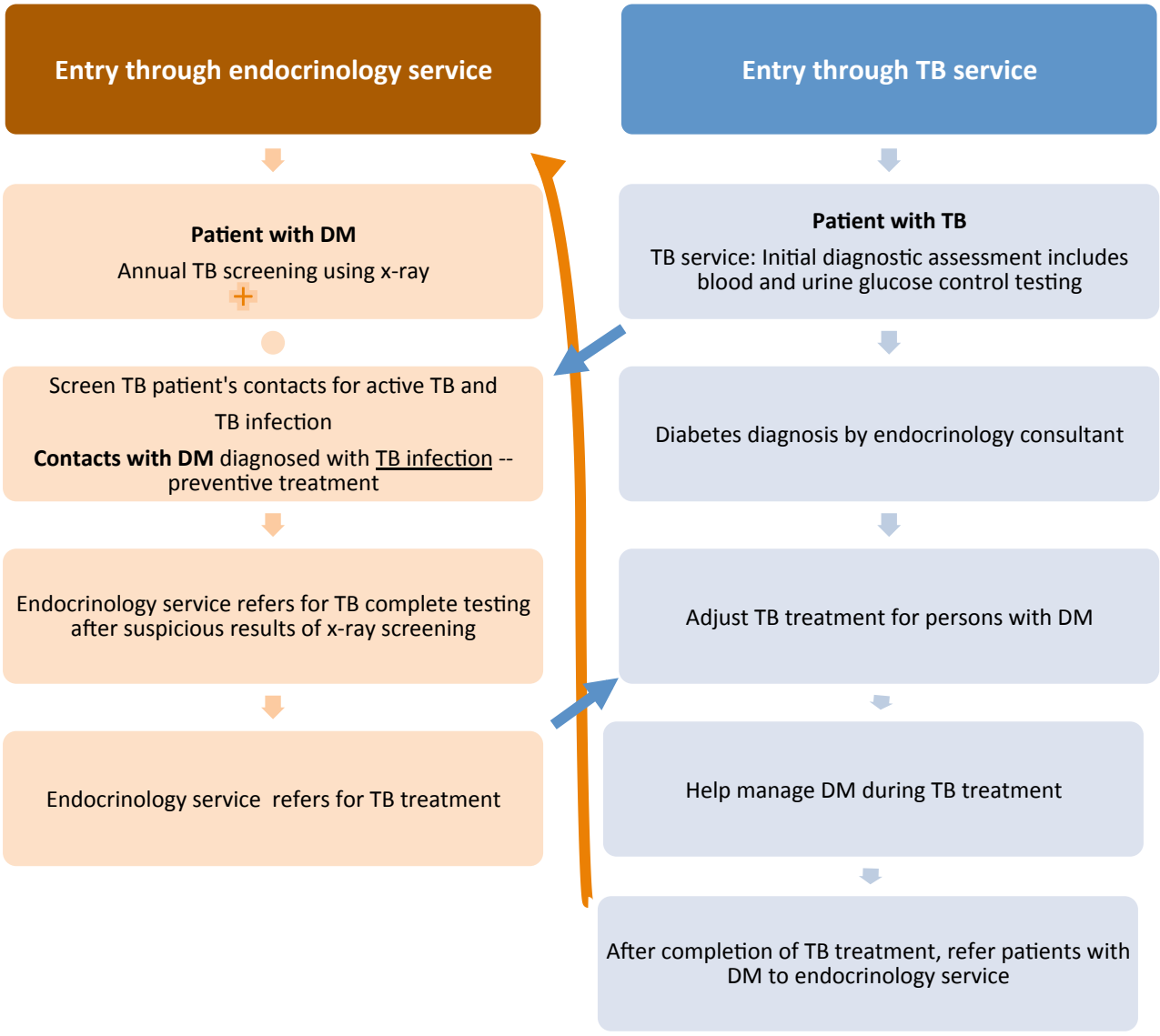

Figure R.4 Entry through TB and endocrinology services

In the TB service, patients with DM are referred to an endocrinologist for diagnostic confirmation and advice about diet, exercise, and medications, and have their DM managed during the course of TB treatment. Once TB treatment is complete, patients should be by regulation referred permanently to the DM clinic, with vigilant follow-up to identify recurrent TB. A similar approach could be adopted for persons with DM who are diagnosed with TB, with the management of co-morbidity being centered at the TB clinic during the entire length of TB treatment. This would require discussion, education, training, and resources directed at the TB clinics but, as with HIV-associated TB, this would be better for the patient, who would be considered programmatically as one person with two diseases. There are still uncertainties about the optimum treatment strategies in patients with co-morbidity in the implementation science literature. Extended TB treatment in DM patients is used in some places,

which has been the subject of some recent published research. However, the evidence for extending treatment beyond 6 months is weak; no randomized controlled trials have assessed whether extended or otherwise changed treatment regimens are more effective than standardized regimens. It would seem sensible in those with co-morbidity to treat DM with diet, lifestyle modifications, metformin and insulin, as those last two medications have little interaction with TB drugs. Finally, little is known about facility-based TB transmission in DM clinics.

It is essential that clinicians who treat patients for TB and/or diabetes should be trained on TB and DM screening and management protocols. They should educate patients (in Russia called "School of Patient" initiatives) about risks and provide referrals to services as appropriate. Regional health administration, medical academic institutions, and NGOs should develop a TB-DM standard training course similar to TB/HIV trainings.

Clinicians should consider different models of ambulatory care management for both conditions, such as day hospital, hospital-at-home, and patient-center accompaniment proven successful for TB and MDR-TB. However, in all these cases, a spectrum of accompaniment for patient adherence to treatment should be considered. Some TB-DM patients may be served better with video DOTS (VDOT). This option provides flexibility, cost-effectiveness, and is a culturally competent alternative to DOTS for TB patients in many regions in Russia. Establishing video DOTS for management of dual treatment and monitoring appears to be a feasible, ethical, and culturally suitable option according to interviews.

Anticipated problems include providing TB-DM patients with medications and testing supply. For patients with diabetes registered at the endocrinology service, the cost of drugs, glucometers, and testing strips is an issue. The average cost per type 2 DM patient for basic hypoglycemic therapy is about US$126 or 7500 Russian Rubles per year. The state subsidizes medicines and provides patients with Russian-made glucometers and 720 test strips, enough for two tests per day for a year, but there are some notable problems with this system. The Russia-made glucometer is subject to the perception among patients of not being of high quality, as it is frequently difficult and painful to get enough blood for a sample. It is also considered by some experts to be inaccurate and many patients prefer to buy imported, expensive testing equipment, creating an economic burden on many patients. All DM drugs are available in Russia; one study in Moscow showed that 80% of type 2 DM patients were prescribed oral hypoglycemic medications, 20% received insulin, and just 1.5% of people were using diet alone to control their condition.[65]

TB patients diagnosed with DM during TB treatment are not registered in the endocrinology system and they are not included into the current annual budgets and regional procurement plans. It is possible that regional TB services could buy some DM medications (depending on financial situations), but TB patients, many of whom are socially and economically deprived, have to buy all testing equipment and consumables themselves. Table R1 below provides a summary of programmatic issues related to the treatment and care of patients with both TB and DM:

Program issue	Intervention	Considerations
Extended length of TB treatment	Currently minimum of 6 months for drug susceptible TB and 20 months for DR-TB	For TB-DM patients, it is usual to have increased rates of treatment failure and recurrent TB – consideration for extended treatment; this should be evaluated through clinical study. Reasons for increased failure and recurrent TB are not known and include more extensive TB disease, altered DM immune response, and reduced concentrations of TB drugs.
Reduced drug plasma concentrations	DM medications might increase hepatic metabolism reducing TB drugs plasma concentrations and making dose adjustments difficult.	Weight-adjusted doses of anti-TB drugs might be needed, although this is difficult to implement in routine programmatic practice. Associated antiretroviral therapy for HIV-infected TB patients may incur additional interactions
Adherence to medication	Adherence could be compromised by symptoms of both diseases (high pill counts, side effects of drugs).	Appropriate patient education ("School of Patient" practices). Consider different models of ambulatory care management (Day Hospital, Hospital-at-Home, Patient-Center Accompaniment ("Sputnik"), Video-DOTS).
TB infection control	Potential high risk of TB transmission if infection control inadequate.	It is possible that recurrent disease may result from unintentional exposure to undiagnosed TB in DM clinics. More information needed about the role of DM clinics in facilitating transmission of *Mycobacterium tuberculosis.*
Lifestyle modifications	Monitoring glucose levels daily (self-testing) is an essential part of managing diabetes. Getting patients to quit smoking and reduce alcohol consumption. Dietary advice Exercise	Patient training is necessary to monitor blood glucose levels; provide patients with testing devices. TB service must provide patients with diabetes medications. Smoking and alcohol are both risk factors for TB and compromise healthy outcomes in NCDs such as DM. The classic dietary advice for controlling DM and TB may be conflicting: calorie restriction to lose weight (DM) vs. high protein, high calorie intake to gain weight (TB). Health care workers will require specific guidance to deal with this. It can also be confusing for patients, who will require proper counseling. DM patients should have daily physical activity; when they also have TB, this may be practically difficult due to the physical condition of the patient. As the condition of the patient improves, gradual increase in exercise should be introduced.

Table R.1. Programmatic issues related to the treatment and care of patients with both TB and DM

Improved understanding of the bidirectional relationship of the two TB and DM is necessary for proper planning and collaboration to reduce the dual burden. DM is fueling the spread of TB in Russia, largely because DM rates are increasing, and studies suggest that DM increases the risk of TB disease, as addressed earlier in this report. DM is also more difficult to manage in people who have TB and the inverse is also true. Successfully addressing TB-DM requires a coordinated response to both diseases at all levels of the health system, from the design and implementation of national policies to the management of disease control programs to the delivery of services to individual patients. These recommendations would not require establishing a new health care division or mobilizing an excessive amount of money. They are practical and actionable steps, based on evidence compiled to date that can be implemented through ongoing Russian health care delivery programs and allocated funding. However, policymakers, public officials, health program managers, and clinicians must recognize that the approaching co-epidemic of TB-DM is a serious commitment for not only the public sector but civil society, patients, and the communities in which they live, as a first step to more integrated care across the health care system for these and other diseases.

5 Republic of India: Strengthening the Nexus between TB and DM treatment Programs

5.1 Epidemiology of TB and DM in India

According to the WHO 2016 Global TB Report, India accounts for 27% of the global burden of TB incidence and 34% of global TB deaths. In 2015, while the updated estimate of TB incidence (including both new and relapse TB cases per year) for India was 2.8 million cases (Figure I1), only 1.7 million TB incidences were diagnosed and notified. This means that approximately 1.1 million presumptive patients were outstanding based on this estimate.[66]

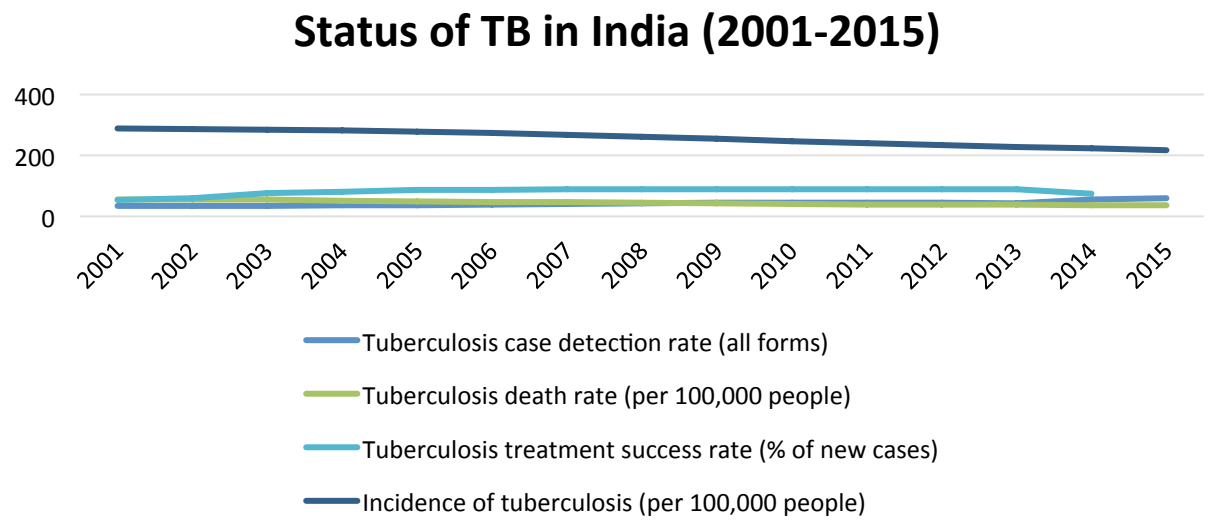

Figure I.1 TB analysis for India 2001-2015[67]

Per 100,000 population, India's TB prevalence is close to 211 cases, while mortality is 19 deaths. In 2015, nearly 478,000 people died from TB, making it one of the leading causes of death in India. While these incidence estimates provide an initial scale of the disease burden, the full picture of the TB burden will be known only upon the completion of a rigorous national TB prevalence survey, which is scheduled in 2017-18.

The Indian National Health Policy of 2017 recognizes the impact of TB among other diseases on India and it also highlights the causal links between health outcomes and social determinants of health[68].

India has a population of 1.3 billion, of which more than 60 million[69] people have DM or are at risk of developing it, making it second only to China[70] in terms of the number of adults living with DM. The prevalence of diabetes in 2013 in India was 9.1%, only slightly higher than the world average of 8.3%. Interestingly, while the DM rate increased by around 45% globally between 1990 and 2013, it jumped

by a massive 122.5% in India in the same period.[71,72] In 2015, over 900,000 million deaths were attributed directly or indirectly to DM in India.[73] DM is fast becoming a widespread epidemic in India[74]; there are many reasons for this rapid increase in DM among Indians including rapid urbanization and its associated lifestyle changes, socioeconomic factors, poor nutrition and genetic predisposition.[75] Approximately 11% of the urban population[76] and 3% of the rural population above the age of 15 years have diabetes.

While national level data reveals the high prevalence of DM, like TB, there is substantial variation in the disease burden across the country that needs to be systematically analyzed. A representative study of three large cities in South Asia (Chennai, New Delhi and Karachi) showed that "one in every five adults had DM and two out of every five adults had pre-diabetes."[77] By 2035, India's population is expected to increase to 1.5 billion and number of cases of DM is expected to increase by 1.8 fold to 109 million; estimates suggest that DM will be responsible for close to 2 million deaths.[78]

Despite these large numbers of people with DM in India, few people are aware of DM and its implications. The Chennai Urban Rural Epidemiology Study stated that only approximately 25% of the Indian population is aware of DM. Furthermore, understanding the implications of DM and is additional risks was even lower. For example, in one study only 11.9% of study participants recognized that obesity and lack of physical activity increased the risk of DM.[79] In addition to the lack of understanding of DM, its treatment and associated complications make it a challenging medical condition. Several factors such as sociocultural aspects, limited qualified facilities for DM care, poor monitoring, and poor linking of patients to lifestyle change, among others, add to these challenges.

Epidemiological studies in India have investigated the correlation between DM and TB and found increased prevalence of active TB among people with DM.[80] A study from Jaipur, Rajasthan, reported, "diabetes is one of the factors leading to relapse of TB cases."[81] In addition to negatively affecting treatment outcomes (as also found in global studies cited previously), DM in the Indian setting also compounds the severe economic burden on TB patients.[82] Many of those affected with DM and TB continue to be undiagnosed or are unaware that they have one or both of these diseases, resulting in significant underreporting. Sometimes this occurs because of the number of TB and DM patients seeking care in private sector first, whereas national figures primarily rely on public sector data.

5.2 Economic burden of TB and DM in India

Due to its high and ever-increasing prevalence, there is broad agreement that DM is a grave threat to public health in India. In addition to yielding poor health outcomes, DM in India also contributes to direct and indirect costs to patients and their families. Data from studies and wage information from Western India evince that DM alone can cause a per capita burden of 9.6% of a "semi-skilled" worker's annual wages.[83] Thus in India, DM patients with limited financial resources spend a major proportion of their earnings on DM management[84].

A detailed literature review to identify the economic burden of DM in India found that the past studies are fragmented and mainly focus on the cost to individuals but not on the health systems and the country in general.[85] Factors such as physician's opportunity cost, development of additional medical complications and loss of productivity create additional burden on the health systems of a country. A World Economic Forum report on economic implications of non-communicable diseases (NCDs) in India estimates that "India stands to lose $4.58 trillion USD before 2030 due to NCDs."[86] Of this, DM accounts for $0.15 trillion USD or 3.2% [87]of the total. With increasing disease burden, the economic cost of DM highlights the urgent need for the health care organizations and planning bodies to prioritize local health policies and projects to prevent and manage of DM and its complications.[88]

Given the minimum wage in Tamil Nadu, the costs of treating TB and DM for patients and their families is significant at between 10% to 12% of wages, [89] contributing to the economically fragile situations which many at risk already face. Because of the combined economic burden of TB and DM, vulnerable populations are more likely to fall into the poverty trap[90] and it is estimated that in India more than 63 million persons were pushed to poverty due to health care costs every year.[91] This burden of double disease is more than a medical issue, so it is imperative that any intervention should be designed and implemented to ease out the economic burden on patients.

5.3 Current status of TB and DM care in India

The context of TB care and prevention in India is changing rapidly due to epidemiological and demographic transitions. Increases in NCDs such as DM and hypertension are changing the different risk factors associated with TB.[92] In addition, there exists plurality in health care providers and care delivery platforms that includes various traditional forms of treatment. This multiplicity in providers means that some patients may or may not get the correct timely treatment,[93] resulting in worsening of symptoms and outcomes. Logistically, it also makes it harder to track patients' prognosis as they move from one health care system to another. The challenge before the Indian health services at the state, city, and national levels are to address these issues without building unnecessarily "vertical" additional program for TB care, which can be avoided by integrating TB screening, care, and prevention into health systems that meet patients where they live and work, rather than requiring life-changing burdens in terms of financial resources and time away from other pursuits.

The Revised National Tuberculosis Control Program (RNTCP) is the state-run TB control initiative of the Government of India with the stated goal of decreasing TB-related mortality and morbidity. Launched in 1997, the program is based on the mid-1990s WHO-recommended DOTS strategy, which RNTCP expanded across the country in a phased manner and has built upon in various ways.[94] The National Institute for Research in Tuberculosis is an internationally recognized institution in TB research that plays a central role in TB research and elimination program in India. The focused approach to TB research and treatment through the national TB control program has resulted in a modest decline of the rate of incidence over the last several years.

However, this rate of change is very small and is complicated by various prevalence surveys and city-specific TB outbreaks, including a sharp rise in MDR-TB in certain urban centers. Though national-level data for incidence suggests progress, the latest plan for TB elimination in India ambitiously calls for "reducing TB incidence from 217 per 100,000 in 2015 to 142 by 2020 and 44 by 2025 and reducing mortality per 100,000 population from 32 in year to 15 by 2020 and 3 per 100,000 by 2025."[95] It is with this aim that in March 2017, the Government of India launched the National Strategic Plan for Elimination of Tuberculosis by 2025. This plan focuses on a comprehensive approach to TB elimination and has set an ambitious goal of "achieving a rapid decline in burden of TB, morbidity and mortality while working towards elimination of TB by 2025" using a "Detect-Treat-Prevent-Build" approach. However, India spends significantly less on health expenditure, at 1.4% of gross domestic product GDP[96] than most other countries in the world, and it spends less on health care than Brazil, Russia, or China. It is estimated that executing the plan between 2017-2025 will cost nearly US$2.5 billion, posing a huge challenge to operationalizing the plan because it is more than the 2012–2017 planned budget.[97]

Though there is a robust national public structure to detect and treat TB, patients often initially seek care through the private sector. TB patients may go to a retail pharmacist in their community or other informal/traditional medical providers to seek treatment before seeking care from a qualified provider for TB treatment.[98] [99] TB patients, particularly from low-income groups or with those with limited access to resources, face long and difficult pathways to reach health facilities that provide the appropriate care. Compared to their male counterparts, women take even longer to begin treatment according to these studies. Thus, informal pathways to care need to be taken into account in the cascade of TB care and treatment. Refer to Annex 3 for the extensive set of stakeholders including those outside of the public health programs and Annex 5 for example of patient pathways across the various health care systems.

TB control efforts in India are currently in transition. There have recently been significant public statements and generally increasing political engagement in the development of the plan for TB elimination, and the RNTCP has rolled out a new electronic data management system, E-NIKSHAY, which is likely to improve notification of cases that are being treated in private sector. Implementation of new public-private partnerships in major Indian cities is expected to increase case detection, improve quality of private-sector care, and better capture data on private-sector treatment outcomes.[100]

Currently, the Indian national program on DM falls under the National Program for Prevention and Control of Cancer, Diabetes and Cardiovascular Disease and Stroke (NPCDCS).

Summary objectives of NPCDCS, Adapted
-Opportunistically screen at all levels in the health care delivery system from sub-center and above for early detection of diabetes, hypertension and common cancers. Outreach camps are also envisaged. -Promote healthy living through behavior change with involvement of the community, civil society, community based organizations, media etc. -Prevent and control of chronic non-communicable diseases (NCDs) especially, cancer, diabetes, cardiovascular diseases (CVDs) and stroke. -Build capacity at various levels of health care prevention, early diagnosis, treatment, information, education and communication (IEC)/behavior change communication (BCC), operational research and rehabilitation. -Provide support for development of a database of non-communicable diseases NCDs through a surveillance system and monitor non-communicable disease NCD morbidity and mortality and risk factors ***Source: TB-Diabetes Joint Framework 2017, Government of India***

Box I.1 Summary objectives of NPCDCS, Adapted by Authors

Unlike for TB, the government of India does not have a publicly financed, standalone national DM prevention and control program, which can be both a significant barrier to resource commitment in the short term, but a concurrent opportunity for strategic, integrated engagement at health service level in a given state or city in the medium and long term.

Regardless of these future possibilities, the private sector is very active and is often the first point for seeking treatment for people with DM today. A study in a small town in Tamil Nadu showed that around 85% of DM care is sought in the private sector.[101] Thus any programmatic intervention for DM treatment and management should include the private sector and work collaboratively in a comprehensive manner with linkage to high quality care as he primary goal. However, the general experience in India to date is that competing priorities of the public and private sectors can often lead to coordination challenges, rather than yielding multi-institutional, geographically focused health coalitions. This delineation of stakeholders and providers also extends to TB and DM; programs for TB and DM have been historically implemented independently in India. Each has its own budget streams, targets, implementation plan, frameworks, and monitoring mechanisms. High costs create barriers to accessing care and adhering to treatments for both diseases, especially for the poorest patients. Key observations from previous experiences at least initially tackling the diseases together include human resource constraints, patient flow issues, screening and referral issues, and recording and reporting issues.

Key observations from previous experiences integrating TB-DM in India	
Issue	**Adapted issues from Lonnroth, Bhojani and Trop Med Int Health Working Group**
Human Resources Constraints	- Need for dedicated staff assigned for the comorbid conditions as they may be trained in only one of the two ailments. - Recording and reporting of patient records manually can lead to additional work for the staff.
Multiple providers, Screening and referral constraints	- 'Informal providers' (IP) and traditional care providers may not refer the patients to other more appropriate physicians/care providers until the care of the patient is complicated or difficult to manage. This delay in referral can worsen symptoms and be a costly burden on patient and health sector. - There is no/little standard protocol for treatment in many health care facilities. - Multiple providers are involved in care for patients with diabetes could make treatment seem more complex for the patients.
Patient Flow and data management constraints	- As diabetes patients are likely to visit clinics a few times each quarter, it may result in double counting in denominators and result in errors analysis and quality improvement. - Collection of sputum samples on different days causes inconvenience to patients and can result in loss to follow up.
Recording and Reporting constraints	- Lack of electronic filing system: manual or paper-based cards used for patient records can make frequent retrieval of data for monitoring, verification and reporting difficult. In some cases even paper-based records may not be maintained properly. - Deficits in the design and format: some of the templates may not capture those who already had TB at the time of screening for diabetes. The reverse may also be true.
High costs of care	- Create barriers to access care and adherence to treatments for both diseases, especially for the poorest patients.

Table I.1 Key Observations integrating TB-DM care in India[102]

5.4 Recommended opportunities to strengthen the joint TB-DM care framework

5.4.1 Joint framework between NPCDCS and RNTCP as a starting point

The government of India has in fact developed a joint collaborative framework to systemically respond to the double burden of TB and DM, by interfacing between the NPCDCS and RNTCP. It aims to guide national programs, health personnel, and other stakeholders working in the area of prevention and control of TB and/or DM. The broad objectives of the program are to:

- Implement early screening of DM among TB patients and vice-versa
- Strengthen the referral mechanism across NPCDCS and RNTCP

- Strengthen management of TB and/or DM patients in general
- Establish surveillance and monitoring mechanism for collaborative framework

The framework calls for intensified TB case finding in the NCD clinics. Those with identified symptoms will be referred to RNTCP facilities for diagnosis and treatment. Patients referred from NCD clinic will be referred back after the patient is on TB treatment. Similarly, TB patients being treated under the RNTCP program will be screened for DM. If the random blood glucose value is greater than 140mg/dL or more, the patient will be referred to NCD clinic for investigation and treatment of DM. As per the framework, the staff from the RNTCP and NCPDS will meet on a monthly basis to monitor progress of this joint approach and report on the progress. The indicators for monitoring have been listed (adapted by authors) as follows:

1 Indicators for monitoring under the RNTCP program		
Indicators	**Numerator**	**Denominator**
1.1 Proportion of registered patients screened for diabetes	# of TB patients screened for diabetes	# of TB patients registered
1.2 Proportion of screened TB patients with Diabetes	# of TB patients diagnosed with diabetes	# of TB patients screened for diabetes
1.3 Proportion of TB patients diagnosed with diabetes and linked with diabetes-care services	# of TB patients diagnosed with diabetes linked with NCD clinic	# of TB patients screened for diabetes
2 Indicators for monitoring under the NCPDS program		
2.1 Proportion of patients at NCD clinic screened for TB symptoms	# of patients at NCD screened for TB symptoms	Total # of patients registered at NCD clinic
2.2 Proportion of patients at NCD clinic tested positive for TB symptoms and diagnosed for TB	# of confirmed TB patients found among NCD patients (found to be positive for Tb symptoms)	Total # of patients at NCD clinic suspected for TB (screened for TB symptoms and found to be positive)
2.3 Proportion of identified TB patients at NCD clinic confirmed with TB and initiated on anti-TB treatment	# of TB patients diagnosed and confirmed at NCD clinic who are on ATT treatment	Number of TB patients identified among attendees at NCD clinic

Table I.2 Indicators for monitoring under the RNTCP program, as stated
Source: National Framework for Joint Approach to TB-Diabetes 2017

The framework is a first-level acknowledgment of the co-morbidity and provides for cross referrals of the patient between the two programs to enable diagnosis and treatment. However, the framework does not detail the actual process of managing effective collaboration between the two national programs. As shown in this report's Annex (the adapted Joint Activities flowchart), there is no single agency that has unitary responsibility, so accountability and responsibility are shared at best and elusive at worst. There remains the risk of losing patients along the cascade of care who may choose to

go to the informal or private sector throughout the process. Incentivizing staff and informal sector stakeholders for referrals and follow up of patients across the two public programs could be an effective approach. To ensure that a patient is well supported throughout their joint treatment journey, it will be crucial that providers from both the TB and NCD clinics interact on a regular basis to coordinate care across disease areas. Currently, in a city like Chennai, Tamil Nadu, the services are often accessed by patients as follows:

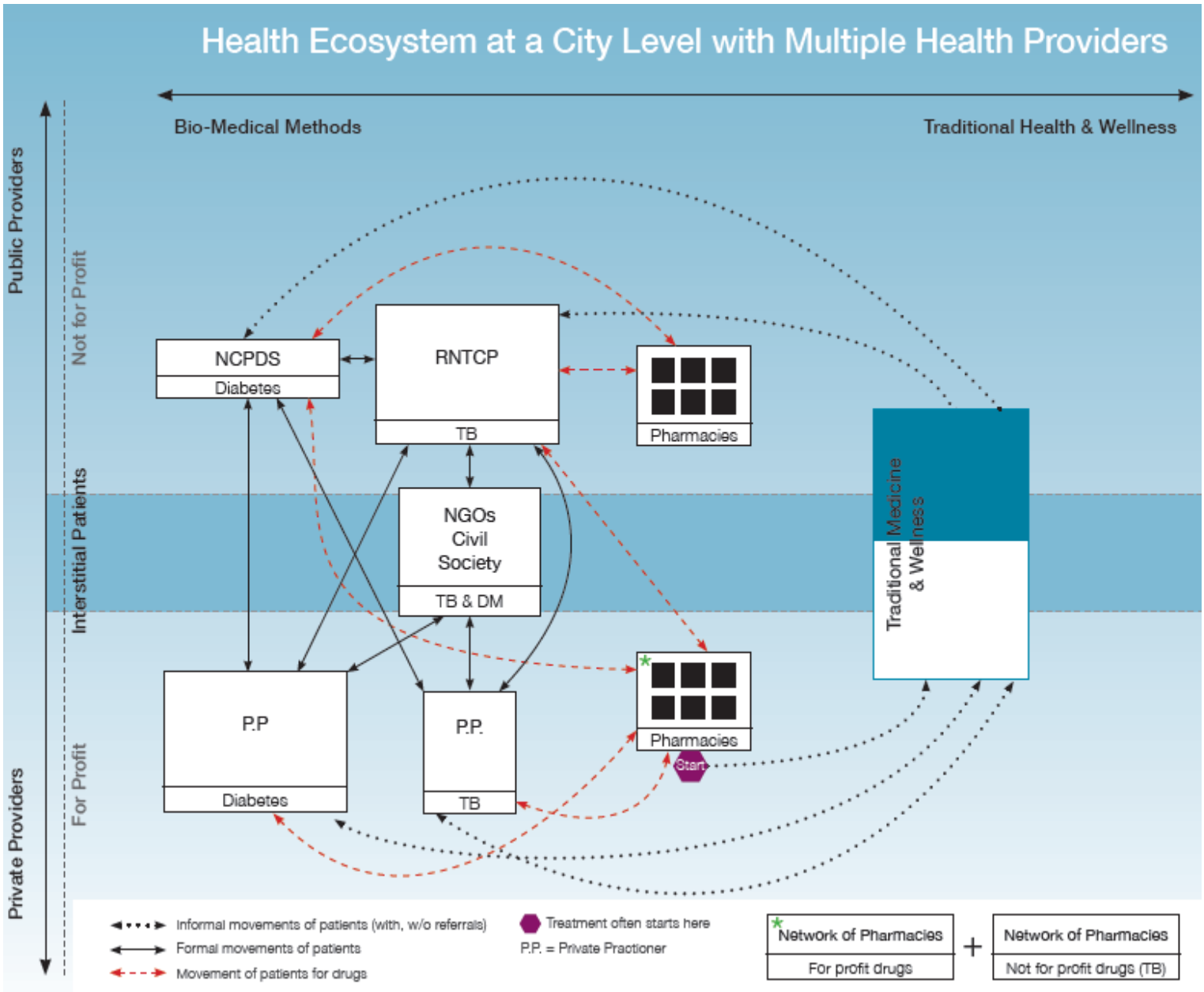

Figure I.3: Health ecosystems for TB and DM at a city level (India, example from Chennai)

5.4.2 Initial overarching recommendations for patient-centered programs

There are clearly important and urgent opportunities to further improve the integration of TB and DM programs by strengthening the coordination between services, and working with various health providers in the health eco-system. By shifting from an institution-based program to patient-centric approach, the potential integrative interventions are many. Specifically, programs should consider

- Searching for patients using convenient bidirectional screening for TB and DM that subsequently (but urgently) integrates screening for other NCDs to take advantage of the present health workers
- Providing comprehensive treatment linkage for co-morbid TB and DM (or link to quality private care if patient prefers), as well as eventually other NCDs like heart disease and some cancers
- Preventing active TB and worsening DM, in terms of preventive care post-exposure management for high-risk groups for TB, and avoiding progressing from pre-diabetes to DM through self-management and accompaniment

Throughout, constant quality improvement and improved monitoring systems will provide helpful informational feedback to the programs both in public and private sector that are implementing these priorities. Costs should not only be a consideration for the implementing program but explicitly for the patient; studies have shown in India how diabetes ranks among the top four causes of catastrophic health spending (an event seen in almost half of the surveyed households) as recently as last year.[103]

Approximate Treatment and consumable costs		
Consumable/other expenses	**Itemized cost (INR)**	**Itemized cost (USD)**
HBA1C tests	INR 500	$ 8 USD
Test kits (gloves, vacutainer, phlebotomy consumables)	INR 300-600 (depending on the brand and quantity)	$5-10 USD
Generic insulin (3ML pen)	INR 400-1000	$ 7-16 USD
Glucometers	INR 1700	$ 26 USD
Cooler bags	INR 1200	$18 USD
Ice packs	INR 200	$ 19 USD
Test strips	INR 16- 24 per strip (800-1200 for 50 strips, depending on the supplier and quantity)	0.25 – 0.37 USD
Metformin or generic (Glucophage)	INR 1.5 per tablet (15 per strip of 10 tablets)	$ 0.02 USD

Table I.3 Approximate Treatment and consumable costs Republic of India
$1USD= Rs. 65 INR, all conversions are rounded to nearest dollar value.

Interviews also suggested additive support to the public health system through non-profits or new agencies to support roughly 1000 new patients initially for TB-DM work would require a project

manager, clinical director, expert nurses, roughly 12 health promoters/community health workers, as well as database management and endocrinologists' time.

For example in an Indian city like Chennai, within the public programs for TB and DM, TB patients in the public sector (and some private sector civil society providers) with suspected or confirmed DM should be referred to an NCD clinic. A site-specific referral and feedback mechanism will need to be developed to enable information for the exchange of information. Good cooperation and collaboration will need to be developed between the two sets of staff teams, taking into account the published literature on the topic in the Indian context, but also the specific policy and institutional landscape for providers in Chennai or wherever the program resides.

5.4.3 Working with various health providers in the larger health "eco-system"

As seen above, multiple types of health care providers exist in the Indian health ecosystem. These include public, private, formal, qualified, and informal providers. Some of these are also traditional healers and other forms of treatment:

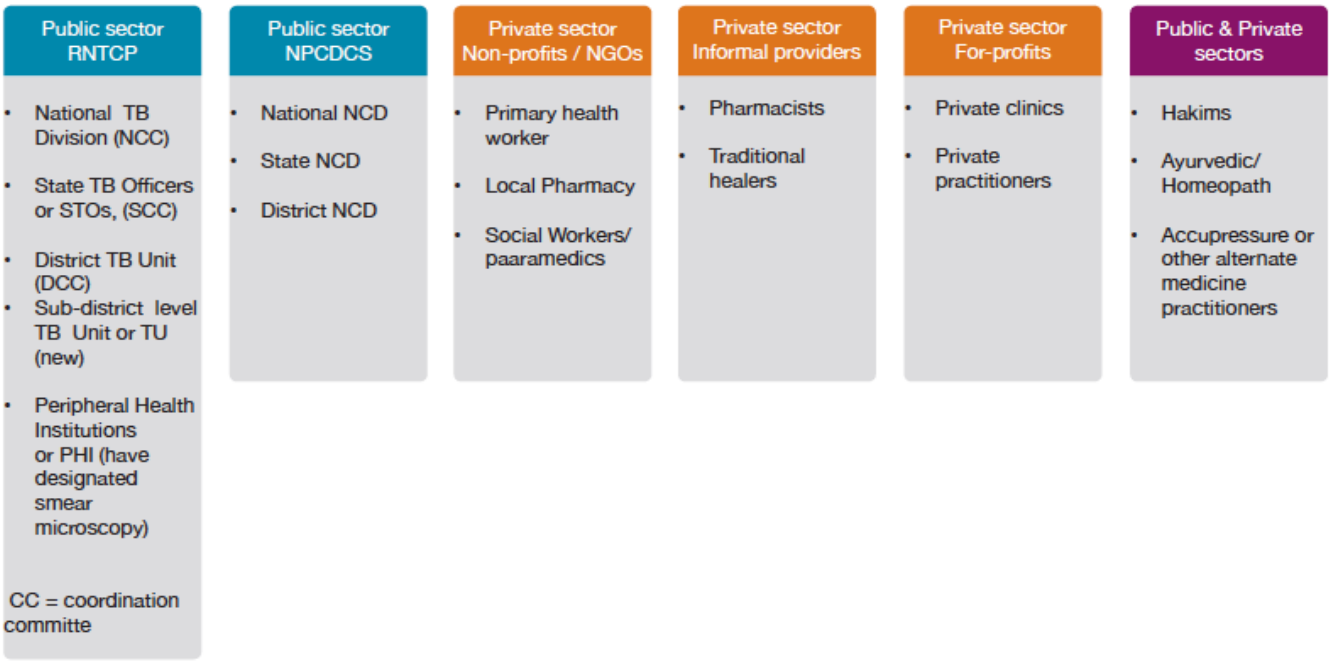

Figure I.4: TB and DM Stakeholder Chart (Chennai example)

A patient may go to one or more providers before seeking non-traditional formal biomedical care either in the private or public health care setting. Sometimes by the time this transition happens, the patient's condition has worsened and they have advanced forms of symptoms (e.g., coughing blood or unstable glycemic levels). The joint framework does not capture the movement of patients between the public, private, formal, and informal health systems across the various health care touch points.

See Annex 3 for the stakeholder chart and Annex 4 for the flowchart explaining the flow of patients between NCDs and RNTCP network.

5.4.4 Shift from institution-based program to patient-centric approach

Given the challenges present for DM patients and their families during a period of active TB disease, a patient-centric, comprehensive approach is necessary to maximize treatment outcomes for both TB and DM. Before a strategy is determined, stakeholder analysis will be necessary to understand the role of different actors in the health care chain. See Annex 3 for the stakeholder chart. Annex 4 outlines the flow of patients between public NCDs and TB networks as identified by the Joint Framework. Given that different stakeholder groups can impact outcomes, the joint framework must focus on all stakeholders across the formal, informal, public, and private sectors. This process needs to be made easy for the patient and should include active follow-up from both NCD and TB staff. Otherwise there is risk that patient will not continue both of treatments simultaneously, resulting in poor glycemic and/or TB control.

Although this joint framework seems to take into account co-morbid conditions, the risks of loss of contact and follow-up with co-morbid patients remains. Retaining two disparate systems with poor linkages also means that patient data is maintained separately, complicating record keeping for providers on both ends. Separate sets of patient data may even contribute to undesirable drug-drug interactions. Coordination of treatment and data sharing may not be done electronically and in real time due to infrastructural limitations in India, thereby resulting in patients receiving treatment regimens that may not work well together.

5.4.5 Comprehensive integration and potential interventions

5.4.5.1 Search: bidirectional screening for TB and DM

Coordination of combined screening and diagnosis of infectious and non-communicable diseases should be emphasized, both in health-care sites as well as at the community level.[104, 105] As discussed previously, several studies suggest that bidirectional screening of TB and DM can mitigate the risks of co-morbidity and poor treatment outcomes. This approach is also important to realizing synergistic gains across disease areas writ large, and, if implemented in the community as well as clinics, it may serve as a potentially efficient operational example for other multi-disease efforts in India.

Smear microscopy has been used as the standard diagnostic test for TB diagnosis in high-burden countries including India for decades. While it is seen as economical, it only detects only half of all TB cases and imposes serious time commitment. If this is the only test performed, it may result in patients being put directly put onto a standardized first-line regimen without any testing for drug resistance of the TB strain. Chest x-ray plays a prominent role in any successful comprehensive TB elimination program around the world, and even in India is equally economical with one x-ray costing roughly the cost of required two smear tests (US$5-7) and reliable test for diagnosis of TB. Integration of tools that

use more reliable technology, such as GeneXpert, and could result in timely detection of rifampicin-resistant cases is also paving the way for correct treatment in cities and rural areas across India. While there are efforts to incorporate these recent technologies into the national TB program, programmatic barriers such as usage restrictions based on geography or type of program need to be removed and to make screening and diagnosis more effective. Based on field experience at the various project sites, active case finding of the patient's contacts to rule out TB transmission is strongly recommended in addition to testing symptomatic patients. Treatment of LTBI, while challenging in resource constrained settings, is nonetheless highly effective in treating presumptive TB cases based on their high-risk status, and a is a key component in any historical example of a TB program that has removed the disease as a public health threat.

Similarly, newer reliable testing tools such as Hb1AC for DM could be introduced into the detection algorithm where applicable, in addition to the fasting blood glucose and oral glucose tolerance test methods. Since this is comparatively a more expensive test, vouchers for testing could be provided to those with high levels of glucose who may need more consistent monitoring of glycemic levels.

As discussed in the previous section, DM patients often seek treatment through informal care providers such as traditional healers or local pharmacists or even through non-medical professionals who are often family friends. In order to strengthen the program, private and informal health care providers could be appropriately trained to play critical roles through the care cascade, for example through formal or informal efforts to diagnose TB, including extra-pulmonary TB, as has been explored in Bangladesh.[106] This could be done in groups or through an informal partner system where public health facilities could train the informal providers based in particular hotspots. In the case of DM, it would also be useful to have periodic training programs for the many various types of private providers or some subsection of these, to ensure use of standard best practices for testing, diagnosis, and treatment. This knowledge base is especially important in cases of known or potential TB-DM co-morbidity. Many patients may first seek informal providers, such as their local pharmacists or the traditional care providers, who may not refer the patients to other more appropriate physicians or formal care providers until the condition of the patient is unmanageable. Delayed referral imposes a more severe and costly burden on patients and health sector as a whole. Thus referral systems should include incentives for timely and appropriate referrals.

It is fairly straightforward to screen TB patients for DM at the peripheral health center level and testing for DM is largely considered acceptable among TB patients.[107] This can help with timely DM case detection and treatment, and indirectly lead to better TB treatment outcomes.[108] Though screening tools for DM are reliable, testing methods vary. One option would be to train staff in the use of glucometers, subsequently followed by blood tests. While HbA1c is the global gold standard test for diagnosis of DM, it is not available to a large section of Indian population.[109] As an alternative, many Indian physicians will test based on random blood sugar or FBG levels. The American Diabetes Association recommends that the FBG test be repeated before making a diagnosis of DM.[110,111]

Glucometers are a cost-effective method to test and monitor glucose levels; they can be used at home and community settings, and administered by patients themselves or by community health workers. However, it is essential to ensure that expired strips are not used for the testing.[112] A combination of these tests could be used for reliable method of detection on a case-by-case basis.

Systematic screening for TB in people with DM could improve early detection in settings with a high TB burden.[113] Based on symptoms and/or patient demographics (those that are contacts or are in high-risk groups) DM patients could be screened for TB through an improved screening and diagnosis algorithm including chest X-ray, GeneXpert, and smear microscopy in accordance with local guidelines.

5.4.5.2 Treat: concurrent and comprehensive treatment for co-morbidity of TB and DM

A comprehensive treatment program would include diagnosis, prescribing appropriate drugs, information on the side effects and support on nutrition intake for each of the treatment regimen, with additional patient support provided as necessary. Training for practitioners is critical. One example from South India showed a positive impact of training on treatment adherence. Even a simple one-day training program on DM for health care providers, including physicians involved in TB care, could lead to significant improvements in screening and management of co-morbid DM. This could also increase awareness of DM among TB patients, enabling compliance with screening and care for DM.[114] Shifting responsibility from senior health-care workers, such as physicians, and toward nurses, community health workers, and peer support networks among DM patients in low-resource sites is effective in the management of DM and cardiovascular risk.[115]

Minimizing the effort required for patients by linking quality treatment and support for these co-morbidities could help with the retention of patients and their families throughout screening, follow-up, referral, and treatment support. Such linkages require working with both public and private providers to develop systems of tracking patients as they may move from one system to other during the course of treatment. Reducing the hurdles needed to access each level of treatment for both TB and DM must go one step beyond the Joint Framework, requiring simplified follow-up for providers working in both programs to facilitate adherence.

Efforts must be made to ensure that the treatment of co-morbid conditions are done from a patient-centric approach by proactively minimizing the hurdles at each level of treatment across TB and DM programs. The joint collaborative framework details a referral process for patients being simultaneously treated for TB and DM through the RNTCP and NCPCDS programs, respectively. However, there is a clear need to further simplify the follow-up across these programs to facilitate adherence and consistent follow-up.

5.4.5.3 Preventing TB and DM

Prevention is an essential part of the management and treatment of both TB and DM. A DM prevention program must focus on physical activity, consuming a healthy and nutritious diet, and

avoiding alcohol and smoking. RNTCP and NCD facilities alike should provide DM education for patients and their families in each visit to reinforce the importance of these lifestyle aspects. TB prevention should address issues of poor nutrition, overcrowding, indoors air pollution, and poor living conditions. Risk surveys for populations vulnerable to both TB and DM should be undertaken in order to develop protocol for effective cross screening and testing. Lastly, it is imperative that advocacy and outreach play a part in the prevention of both these diseases. A comprehensive approach to addressing TB and DM along improvements in ventilation and air quality may be helpful in promoting the overall environment in which these people live and work.

5.4.5.4 Translating research into policy

As the interactions in the human body between TB and DM are increasingly well understood, so is the need for effective and collective interventions that cross-institutional and departmental lines. A multi-institutional collaboration with further, pilot-level testing, operational research and subsequent scale-up, and randomized control trials where applicable and appropriate can strengthen the existing policy and programming where TB and DM intersect.[116] In particular, population-level operational research initiatives will enable policy makers to identify existing gaps in the existing health structures and enable possible corrective action.[117]

The national plans and Joint Framework are important first steps to allow time and direction for these different policymaking bodies to interact. They highlight the need to intervene in a comprehensive manner by strategically working towards screening, treatment, prevention, and building enabling environments through a joint framework. Conceptually, while the NPCDCS program includes DM into its objectives through the NCD work, there is an urgent need for local coalitions including the public and private sector to further build active and seamless links to the plan for TB elimination and other infectious co-morbidities, even as a focused national DM intervention program helps to address other prevailing chronic diseases more squarely within NPCDCS' mandate.[118]

While targets for such national level country plans are focused on bringing down the incidence and prevalence rates, there may not be enough incentives at either the national and subnational levels (city, district, state) to actively search for new cases after the administrative target rate is reached for a given health worker. Previous efforts on TB in regions such as Tomsk (Russia) and New York City (USA)[119] demonstrate that when concentrated efforts towards comprehensive case finding programs are implemented, the number of cases notified initially increases before decreasing. These early upward trends indicated that active detection strategies had been effective. Thus national plan and Joint Framework on TB-DM could incorporate mechanisms that incentivize capturing the actual diseases burden and place the increases in incidence in a context that is not punitive for project managers in terms of their perceived performance.

5.5 Recommendations and ways forward in integrating TB and DM care in India

The development of the Joint Framework demonstrates at least a general high-level commitment to move this joint approach forward. However, at an operational level, quick analysis leads the reader to the conclusion that the framework, if implemented in any specific program, would need to be more collaborative and responsive to the unique health system parameters and local patients' needs. Developing a system that accounts for patients' movements between diverse set of health care providers and supports them through their health pathways will help in monitoring progress and treatment outcomes. Lifestyle changes in exercise, nutrition and diet, and monetary or insurance support will further spur progress in terms of treatment outcomes and the impact of these diseases on the community. Iterations of the framework should be based on implementation and monitoring using an evidence-based, bottom-up approach. While a centrally developed plan is helpful to coordinate countrywide efforts, garner funding, and provide a conduit to share best practices, the plan should initially stimulate local autonomy to deliver results for patients, their families, and health systems based on the authors' experience. This will help local government, state providers, patient care organizations, and grassroots agencies to leverage the on-the-ground situation and local conditions into results.

Moving forward, further recommendations for building a comprehensive program of integrated TB-DM care include:

- Consolidating data from various national and regional studies
- Implementing a comprehensive approach that enables seamless migration for patients
- Increasing advocacy and lifestyle counseling
- Reducing patients' economic burden and increasing access to health care
- Stakeholder coordination and management (Figure I.5 below)

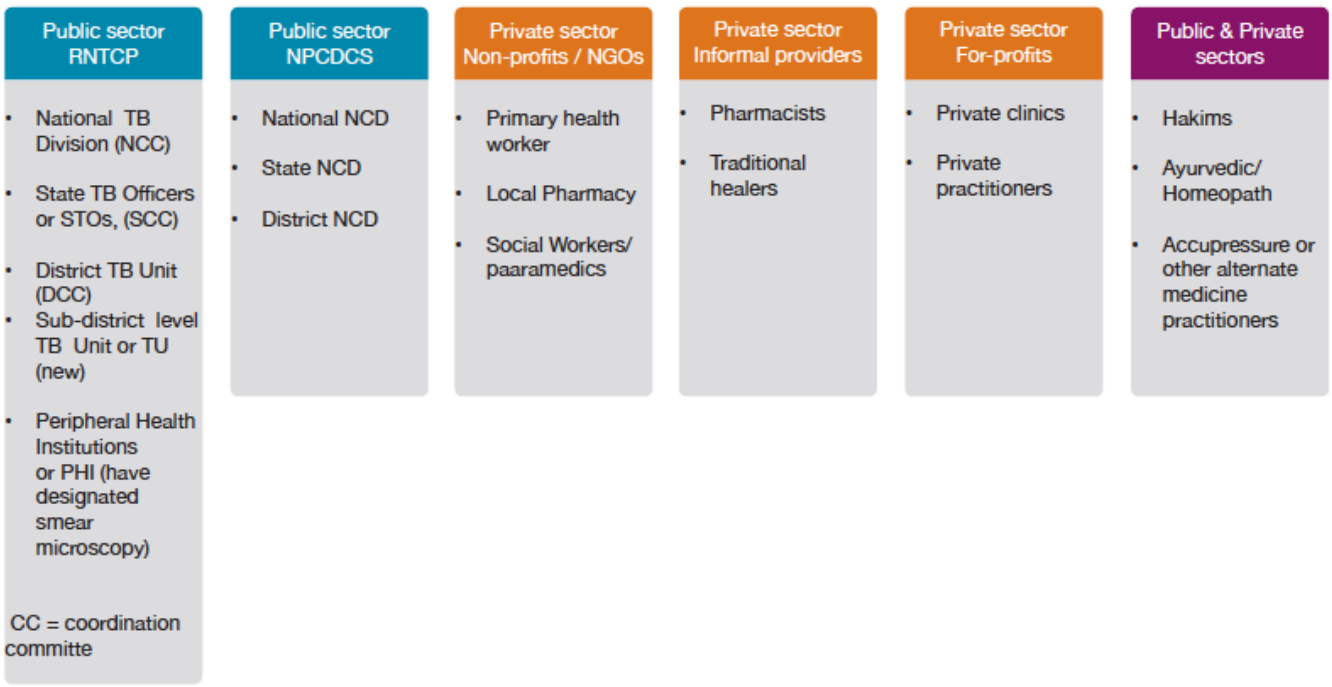

Figure I.5: TB and DM stakeholder coordination and management chart

5.5.1 Consolidating data from various national and regional studies

Though national prevalence numbers for both TB and DM provide an estimate of the burden of the two diseases, there are substantial variations at the local or regional level. For example, cities including Chennai and New Delhi have excessive burden of DM. Likewise, at the city level there are hotspots with a higher incidence rate of TB. There are some fragmented studies on the economic burden of DM and TB in India, but they are confined to specific areas of some states and mainly focus on the cost to individuals, but not on the health systems and the country as a whole[120]. Incorporating operational research in the active projects will test assumptions and highlight gaps in the understanding of disease burden and its economic impact.

5.5.2 Implementing a comprehensive approach that enables seamless migration for patients

A comprehensive epidemic control model includes early screening and disease detection, treatment linkage, support through treatment, and prevention activities to "turn off the tap" of disease. For both TB and DM, community-based screening can help diagnose patients in the initial stages. Active case finding and timely treatment mitigate high costs incurred when the TB and/or DM are diagnosed at a later stage, while improving treatment outcomes.

While vertical intervention programs for TB and DM benefit patients with one of the two diseases, for co-morbid conditions, proposed interventions should minimize physical and administrative movement of patients across the two health care programs that are often based out of two different health care centers. When necessary, the experience of navigating between TB and DM care should be seamless for both patients and health care providers. Screening and management of TB and DM can be jointly coordinated and require education, clinical care, and consultations, especially immediately following the diagnosis.[121] Patients often move from private to public care providers and vice-versa. Coordination between the different health programs, including those in the private and informal sector, will need further strengthening. Providers practicing alternate and non-formal methods of treatment should encourage patients to follow reliable testing and treatment protocols.

A responsive system also includes paraprofessionals, friends and family members of the patients, informal providers, and non-profits that assist the patient to adhere to the treatment of TB and DM. This enables treatment adherence and reduces loss to follow-up. This collaboration of public interest oriented organizations helps patients link up to appropriate health services. For example, in Chennai, when patients are referred to REACH (an NGO working towards TB treatment and elimination) their staff can help to link patients to high-level TB and DM care through their public-private mix centers and the organization's network of pharmacies and community health workers.

While a vertical intervention program for DM will help in getting the necessary focus, past experience suggests that vertical programs have limited sustainability and scope. Further, such programs if

designed and implemented in isolation, may negatively affect non-targeted populations and could increase fragmentation service delivery fragmentation.

5.5.3 Expanding lifestyle counseling, diabetes treatment advocacy, and differentiated messaging

Lifestyle counseling should be a critical component in the treatment of DM, hypertension, and TB. Currently, there are limited links to lifestyle counseling among most private sector providers. Patients from every segment will benefit from the non-profit entity that promotes a healthy lifestyle.

5.5.4 Reducing patients' economic burdens and increasing access to health care

Because patients face significant economic burdens, intervention programs should be designed and implemented to easing the economic burden on patients. Strategies include providing care closer to where they live and work, providing free or subsidized screening, diagnosis, and the follow-up treatment options. Additional support to patients could include counseling for treatment and nutrition, monetary allowance against loss of productive work to support their families, providing meal services or meals at discounted prices while on treatment, and covering the cost of transportation to clinics and pharmacies. Additionally, improving access to universal health care or some other form of health insurance can help reduce this economic burden, for example by coordinating with the national insurance policy to supplement patients' treatment, diagnostics, and medicines. Similarly, for TB, such an insurance program could help pay for x-rays and GeneXpert testing, thereby reducing barriers to screening and treatment. Multi-institutional collective action mechanisms that include market forces in their considerations can also help in improving access to affordable medicines and improve supply chain management and procurement. Given that medicines constitute a sizable proportion of private costs, competition among multiple firms, combined with improved forecasting and quantification methods can increase competition to bring costs down[122]. Careful monitoring of access and quality of care among vulnerable and target populations is necessary to ensure that no segment of patients is left behind in a challenging context like an urban Indian setting.

6 Pharmacological considerations for the treatment of TB and DM

Treating DM and TB in individuals affected by both diseases is an urgent priority globally, but also individually given the poor outcomes that each disease can lead to for the other. The currently available literature on drug-drug interactions describes a number of pharmacokinetic (PK) interactions that must be take into consideration when simultaneously treating TB and DM and highlights the need for more research as health systems tackle this double threat. Clinical guidelines at the national and international level, when available, need to integrate new learnings and knowledge about these medications when taken by the patients. The absorption, distribution, metabolism, and elimination of TB and DM therapies can be impacted through a variety of mechanisms, possible affecting clinical outcomes for both diseases. Any population-level programs should have clinical practice working groups that can assess dose adjustment for these mostly generic medicines taken by patients and feed that synthesized information into the authoritative national guideline working groups and private practitioners.

6.1 TB medications on DM therapy

Cytochrome (CYP) P450 is a family of isozymes responsible for the biotransformation of many drugs and is an important determinant of drug metabolism in the body. The CYP450 family comprises multiple different isozymes, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP2E1, and CYP3A4.[123] In general, induction of CYP isozymes results in higher rates of metabolism and inhibition of CYP isozymes results in lower rates of metabolism. Pharmacological management of TB and DM is influenced by drug-drug interactions between TB and DM medications involving the CYP450 isozymes, often impacting the metabolism of the medications.

Among first-line TB medications, rifampin has been the best studied and has the largest number of PK drug-drug interactions with DM medications. Rifampin is a strong inducer of CYP3A4 and also induces CYP2C8, CYP2C9, CYP2C19, and to some extent, CYP1A2.[124] A number of DM medications are substrates of these CYP isozymes (Table P1) and the metabolism of these medications can be moderately to substantially impacted when co-administered with rifampin. Sulfonylureas have shown reductions in concentrations of 39%, 18%, and 34% for glyburide, glipizide, and glimepiride, respectively.[125,126] Meglitinides have shown reductions in concentrations of 24% and 57% for nateglinide and rapaglinide, respectively.[127,128] Thiazolidinediones, also known as glitazones, show reductions in concentrations of 54-64% and 54% for rosiglitazone and pioglitazone, respectively.[129,130,131] Dipeptidyl peptidase 4 inhibitors, a class of oral antidiabetic medications commonly used in adjunct to other antidiabetic medications, have shown reductions in the concentration of saxagliptan by 53-76%.[132,133,134]

Isoniazid, another first line TB medication, is an inhibitor of multiple CYP isozymes, including CYP2C9, CYP2E1, and CYP3A4. Although there are no recently published PK studies available on its impact with DM medications, case reports and animal studies describe incidences of hypoglycemia when isoniazid is co-administered with sulfonylureas or insulin.[135,136,137]

Drug-drug interaction studies of second line TB medications involve varied cellular mechanisms and there is little research describing details of these interactions. In vitro PK studies performed on bedaquiline have shown little to no inducing or inhibiting impact on CYP450 isozymes, however its metabolite, M2, shows inhibitory action on CYP3A4, 2B6, 2D6, and 2C19.[138] A review of pharmacological considerations for bedaquiline and delamanid reported that both medications are highly bound to plasma proteins, and therefore, may compete with insulin and other oral DM medications, affecting free drug concentrations in the body.[139] Although the PK profiles of bedaquiline and delamanid indicate potential for interaction with DM medications, there are no direct studies of these interactions in the literature. Flouroquinolones have been described to cause dysglycemias, particularly in patients with DM, however, agents within the antibiotic class exhibit this effect at varying degrees.[140] The exact mechanisms of this interaction are not fully known and although literature on the clinical impact of this effect is available for DM patients,[141,142,143,144] no research of this interaction among TB-DM patients was found. Para-aminosalycilic acid is part of a case report from 1980 indicating a possible drug interaction with metformin,[145] however, no current studies describe this potential interaction in any further detail. Lastly, rifabutin, a relative to rifampin, is a strong CYP3A4 inducer but PK studies show its effects are not as potent as rifampin.[146,147] Despite the more favorable PK profile of rifabutin, no PK studies on its effects with DM medications were available.

Rifapentine, another second line medication in the family of rifamycins, is used for the treatment of both active and latent TB infection (LTBI). When combined with isoniazid, rifapentine has shown to be valuable in the treatment of LTBI.[148] Additionally, inhaled routes of administration are being explored for more effective non-invasive therapy[149] and its once to twice weekly dosing makes it a good candidate for improving medication adherence. Rifapentine, however, is also a potent inducer of CYP3A4, CYP2C9, and CYP2C8. Drug interaction studies with bedaquiline, a CYP3A4 substrate, caused a 3.96 fold increase in bedaquiline elimination and as much as a 75% decrease in expected drug concentrations.[150,151] Although no drug-drug interaction studies of rifapentine with DM medications were found, the PK profile of rifapentine would suggest that it may also reduce drug serum concentrations of oral DM medications that are substrates of CYP3A4, CYP2C9 and CYP2C8.

6.2 DM disease and medications on TB therapy

DM impacts the body in multiple ways and also affects all aspects of PK, including the absorption, distribution, metabolism, and elimination of TB medications.[152,153,154,155] Due to these changes, some literature shows DM patients treated for TB are at risk of having reduced concentrations of isoniazid and rifampin by as much as 50%.[156,157] The reduced concentrations of first line TB medications may

result in reduced treatment efficacy, resulting in prolonged culture positivity or the development of resistance.

Metformin, a gold standard for the treatment of type 2 DM, is not metabolized by the liver, and therefore is not impacted by drug interactions with TB medications that affect CYP isozymes. Recent literature has begun to show possible protective effects of metformin on the development of TB. Marupuru et al revealed that metformin, given to patients with DM, exhibit a 3.9 fold protective effect against TB (OR = 0.256, 0.16-0.40), irrespective of the dose.[158] Metformin promotes the formation of anti-inflammatory M2 macrophages and T-regulatory and CD8 memory T cells and studies show it is able to inhibit the intracellular growth of mycobacteria as well as enhance the efficacy of TB medications, possibly leading to better TB treatment outcomes.[159,160] A retrospective study showed 3.6% of DM patients taking metformin had decreased time to microbiological conversion.[35,161] These effects, as well as its wide use for DM therapy and lack of drug interactions with TB medications, make metformin an attractive candidate for host directed therapy for TB (Table P1)[162]:

DM medication class	CYP Substrate
Sulfonylureas	CYP2C9
Meglitinides	CYP2C8, CYP2C9, CYP3A4
Thiazolidinediones	CYP2C8, CYP2C9, CYP3A4
Dipeptidyl peptidase 4 inhibitors	CYP3A4*
*** CYP3A4 plays minor roles in the metabolism of sitagliptan and linagliptan.** [163,164]	

Table P1: DM Medications and CYP substrates involved in their metabolism.

6.3 Research priorities for pharmacological management of TB and DM

Based on current literature, there are four recommendations for research priorities that may aid in advancement of pharmacological management of TB and DM.

6.3.1 Further research evaluating the clinical impact of TB and DM drug interactions and optimal medication management of patients with TB and DM.

Although in vitro and in vivo PK studies are expanding knowledge on drug-drug interactions, there is still limited knowledge on the clinical significance of these interactions. Many of the PK studies on drug-drug interactions are conducted in vitro or on a small group of healthy subjects, and in some studies, reductions in drug concentrations did not directly correlate to observed effects as there was no statistically significant impact on glucose levels of patients despite decreased drug concentrations.[165,166,167] Clinical outcomes can also be affected by concomitant disease states, different patient factors, and varied target goals of therapy, all which must be taken into consideration in further

studies. Additional research on the impact of drug-drug interactions on clinical outcomes will aid in better understanding where and if changes in therapy should be made.

If changes in therapy are warranted, studies on optimal dosing for oral DM medications and first line TB medications in patients who have both diseases could provide guidance for more effective medication therapy management. Insulin has been shown to cost between 61-75% of the per capita income in select countries of Africa and its high cost and accessibility is a huge barrier to expanding care in low and middle-income countries.[168] Research is needed to better understand how optimal dosing of oral medications works towards alleviating the economic burden of insulin use. Additionally, a better understanding of optimal dosing strategies for TB and DM medications can aid in the development of much needed national or international treatment guidelines.

6.3.2 Strengthening of PK studies and clinical outcome studies among second line TB medications in patients with DM.

There is minimal literature available on the potential interactions of many second-line TB medications with DM medications. A better understanding of possible drug interactions between second-line medications with both oral and injectable DM medications will be important in advancing care of patients with drug-resistant TB. Additionally, further studies exploring drug-drug interactions of oral and inhaled rifapentine with DM medications will provide better understanding of how its use for treating LTBI may affect DM therapy.

6.3.3 Further studies exploring the role of metformin in TB therapy.

The current research on the role of metformin as an option for host directed therapy shows its potential benefits in patients who have TB and DM. In addition to further studies on its impact in improving clinical outcomes for patients who have both diseases, studies exploring its role in only TB patients would be useful in better understanding its place in therapy.

6.3.4 Pharmacoeconomic studies on the impact of drug-drug interactions.

Reducing unnecessary health care costs in resource-constrained settings should remain a priority. Equally important to understanding the clinical impact of drug-drug interactions is the costs they are incurring to patients and the health system. Sub-optimal treatment of TB prolongs therapy with medications that already cause multiple adverse effects and sub-optimal therapy for DM allows for development of micro and macrovascular complications, which require further care and could worsen TB outcomes. The costs for this additional care could be avoided with advancements in medication therapy management.

7 Conclusion

The considerable set of challenges outlined in this document are the cumulative result of the intersecting TB and DM epidemics, nurtured and intensified by global socio-economic and demographic drivers, and diverging institutional priorities. National economic considerations and the level of public health care provision by the governments in these four countries will also determine how much progress can be attained in this challenging and rapidly changing time against these epidemics.

The many other associated infectious and non-communicable co-morbidities, from smoking, obesity, heart disease to HIV, are also not the subject of any in-depth review in this document but will continue to play critical roles in determining whether, and how, cities like Chennai and eThekwini, the four focus countries more generally, and the many global public health organizations are able to tackle this twin epidemic. These challenges are analyzed in this document by focusing on the roughly 1 million people who are newly affected by both active TB disease and DM, two top ten killers of adults worldwide.

Beyond this focus, each of these diseases presents its own set of daunting challenges that similarly requires new tools, innovative strategic framing, and a rigorously applied synthesis of health systems thinking paired with an increased focus on the actual experience of each individual patient. By applying the many varied resources at the hands of global, national, municipal, and local entities, these challenges can an must be overcome.

8 Endnotes

[All references available upon request to lead author via shared drive. Please include name, insitutional affiliation [if applicable], and email in any correspondance]

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