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TITLE: Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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ABSTRACT

Introduction: Most sub-Saharan African countries endure a high burden of communicable diseases but also face a simultaneous rise of non-communicable illnesses. Interventions targeting particular epidemics are often executed within vertical programmes. We aim to develop a model that will strengthen health systems by shifting traditional vertical programmes to an adaptive diseases control approach through integrating communicable and non-communicable diseases diagnosis and management using the tuberculosis (TB) and diabetes mellitus (DM) dual epidemic as a case study.

Methods and analysis: This programme will use a mixed research design, with both qualitative and quantitative approaches. A prospective cohort design will be used in assessing integration of TB and DM services that will enable early diagnosis of dual TB/DM cases. Lastly, a stepped-wedge cluster randomized trial will assess the impact of introducing individualized TB/DM practices at the health care facility level. A blueprint for addressing communicable and non-communicable dual epidemics will be developed using several tools and techniques such as a collection of stakeholders' views and literature reviews, monitoring of key indicators in the TB/DM case study, and applying a system thinking approach to essential elements in the health service delivery.

Ethics and Dissemination: Ethical approval was granted by The National Research Health Ethical Committee with reference number NIMR/HQ/R.8a/Vol.IX/2988 and the implementation was endorsed by the President Office Regional Administration and Local Government Authority. The results will be proactively disseminated through peer-reviewed open access journals, policy briefs, various stakeholders, public engagement activities, conference presentations, and social media.

ARTICLE SUMMARY

Strengths and limitations of this study

- The study is conducted in pragmatic settings using a mixed study design to allow triangulation
- Considers all levels of service delivery while covering urban, semi-urban and rural settings
- The proposed ADEPT model outcome considers process and patient outcomes
- Lack of randomization of study settings or health facilities may introduce bias

INTRODUCTION

Tanzania like other sub-Saharan African countries endures a high burden of communicable diseases including multidrug resistant pathogens; but also a concurrent rise of non-communicable diseases (NCD) as populations urbanize, diets "westernize" and lifespans lengthen [1]. The health system is largely inflexible and during various period of disease epidemics, the health management teams operate in crisis-mode with limited capacity to plan for a long-term disease prevention [2]. Currently in Tanzania, planned interventions for several longstanding and socioeconomically draining epidemics like tuberculosis (TB) and diabetes mellitus (DM) and their associated comorbidities, are executed within disease specific or vertical programmes [3]. Vertical programmes operate in silos while in reality various communicable and NCDs and treatments can influence one another, and overlap in [4-7]populations of shared genetic backgrounds or environmental exposures, and in communities with similar socioeconomic conditions or behaviours. Vertical programmes can significantly constrain health care delivery, and represent a top-down approach that is rarely efficient or cost-effective, particularly when considering health challenges [8].

This sobering fact has been illuminated in different vertical programmes. In Tanzania, compendium of research studies uncovered a health systems gridlock for patients trying to

negotiate the road from diagnosis to treatment of TB[4-7]. There was a widespread underuse of the technologies mostly due to inadequate knowledge and skills on clinical application and interpretation of molecular diagnostics results. Likewise, there was not only a low response to the international consensus but also absence of linkage to care for patients presenting with TB but failing to be screened for DM and triaged to adequate DM services [9]. Similarly, in Tanzania DM services are centralized at the district and referral health facilities but also front-line health care providers were ill-prepared for DM management. Research studies conducted in different programmes to identify multimorbidity particularly the NCD have found a considerable client harbouring the burden of multiple diseases. The observed increasing prevalence of dual communicable and emerging non-communicable multimorbidity epidemics and the existing systemic bottlenecks suggest modification of models of health care delivery. We developed a model to strengthen health systems by shifting traditional vertical programmes to an adaptive diseases control approach through integrating communicable and NCDs. Henceforth, we describe the strategy to establish a contemporary **A**daptive **D**iseases control **E**xpert **P**rogramme in **T**anzania (Figure 1) (**ADEPT**), focusing on the TB/DM co-epidemic.

The dual TB and DM epidemic is ideal as a case for our ADEPT model because worldwide evidence shows a 3-fold increase of active TB in populations with DM compared to those without DM while the global prevalence of TB in DM populations ranges from 1% -14%[10 11]. In Tanzania, the effect was slightly higher and estimated at nearly 4-fold[12]. Indeed, stakeholders from The International Union Against Tuberculosis and Lung Disease and the World Diabetes Foundation outlined the historic Bali Initiative on TB and DM (endorsed by World Health Organization (WHO)), stating:

"▪That TB and DM represent two of the greatest global health challenges of our time, and their convergence globally represents a looming co-epidemic,

▪That this looming co-epidemic threatens progress against TB,

▪That, based on what we have learned from past co-epidemics, particularly TB-HIV, we must act

early and decisively to avoid large numbers of avoidable deaths" [13,14].

We understand this urgency all too well in Tanzania. Recently, we have observed an increase in the incidence of dual diagnosed patients with TB/DM epidemic ranging from 4% of all TB patients in rural areas to 17% in urban settings, resulting in a 5-fold increase of death compared to TB patients without DM [15,16]. Importantly, our research has determined that these deaths primarily occur *early*, in the first three months of TB treatment [15,16]. We now understand that this high and early mortality from TB/DM in Tanzania is due to both programmatic and biological factors [17]. For example, TB and DM services are not linked and these separated service lines lead to delayed interventions for both diseases [18]. Interestingly, targeted drug therapy of dual TB/DM disease may also open new ways of enhancing the effect of essential drugs against either disease[19]. Thus, data have suggested that the first-line anti-DM drug metformin could be a promising candidate for host-adjunctive anti-TB therapy, by reducing chronic inflammation and enhancing immune response[20].

Yet, other biological factors also contribute to poor TB/DM treatment outcomes including DM-related alterations in drug absorption and metabolism resulting in sub-therapeutic anti-TB drug serum concentrations, [21] and altered inflammatory/anti-inflammatory host immune defences. Furthermore, TB disease itself may worsen control of hyperglycaemia leading to uncontrolled DM [22]. In turn, patients with uncontrolled DM also have higher bacterial burdens of *M. tuberculosis* and more extensive lung disease, and therefore achieving anti-TB drug concentrations at the most optimal of levels may be even more important in patients with DM [23,24]. Yet, in our prior work in Tanzania, we found sub-therapeutic drug concentrations to occur in the majority of all TB patients [25,26]. While international standards mention therapeutic drug monitoring to guide TB/DM individualized dose adjustment[27], few programmes from TB-endemic settings have carried these recommendations forward[28]. Although the Tanzania Ministry of Health recognizes the challenge of the TB/DM epidemic, the vast majority of health facilities have

not been able to implement international standards of TB/DM care. Therefore, this research project will also take the opportunity to underpin implementation of the international standards for controlling the TB/DM in the health system and conduct applied research to answer critical scientific questions of direct patient benefit while simultaneously training the next generation of health systems scientists.

The overall study aim is to integrate TB/DM diagnosis and optimal management strategies in client-friendly clinics as part of an adaptive disease control framework to inform future best policies for integrating care of communicable and NCDs in Tanzania. The objectives are given below, and have been divided into the following;

I. Objective 1. Integrate TB, and DM services.

To study how early and accurate bidirectional screening of TB, including TB-HIV, and DM can be established in a client-friendly way while investigating how early and accurate treatment of dual TB/DM or TB-HIV/DM cases can be linked to specialized care and improve outcomes, and if feasible to sustain treatment at the primary health care level. Furthermore, investigation on how quality assurance for the laboratories serving TB/DM at the primary health care level can be established.

II. Objective 2. Deliver international standards of care for optimizing favourable outcomes.

To study how to apply diagnostic technologies such as WHO endorsed TB diagnostics for susceptibility testing, therapeutic drug monitoring for anti-TB medicine and HbA1c for monitoring of DM disease severity to deliver best practice for optimizing favourable dual TB/DM treatment outcomes Furthermore, to estimate the incidence and associated risk factors for treatment failure during dual TB/DM treatment, including the development of *M. tuberculosis* resistance, and whether the hypoglycaemic drug, metformin may have an adjunctive anti-TB effect.

III. Objective 3; Capacity building for training ADEPT health care workers and implementation & health system scientists

To study how short-course training to the front-line health care providers in best practices for dual TB/DM and other comorbidities at varying health system levels can be provided and be reflected in outcome of WP-1 and WP-2.

METHODS AND ANALYSIS

Conceptual framework of the ADEPT model

The ADEPT model pioneers the systems thinking methodology described by Swanson and colleagues to guide integrative changes in health practice, education, research and policy [29].

We proposed to introduce ADEPT first to the dual TB and DM epidemic as a case study of integrating communicable (TB) and non-communicable (DM) diseases [30 31] to engage currently siloed policy makers, researchers, and service providers [32]. The proposed ADEPT model is overarching by three principles with interdependent themes; transformational leadership, collaboration, and constant interactive learning. ADEPT will be evaluated using the logic framework developed by the WHO/US-Centre for Diseases Control and Prevention (US-CDC) (Figure 2) [33]. The design of input and output pillars reflect largely on the archetypical work

designed by Potters and Brought in 2004 for health system strengthening[34]. This includes a four-tier hierarchy with nine-interdependent elements as depicted in Figure 3.

Role, Structural and System capacity: ADEPT will mobilize physicians and nurse officers working at TB, DM, or general clinics at the regional level regardless of facility level. The team will serve as a Regional Technical Working Group (RTWG), and will be empowered to serve as mentors in the Region to support the health system to deliver best practices in patients with dual communicable and NCDs. The formed team will operate under the Regional Medical Officer (RMO), a newly formed structure that will also link with the National Technical Working Groups (NTWG) (Figure 1). RTWG under the leadership of RMO will conduct regular discussion with all stakeholders supporting the communicable and or NCDs intervention and associated co-morbidities. The discussion emanating from the meetings will guide local decision but also communicated to the Ministries; responsible for Health and Regional Administration and Local Government Authorities, and shared with responsible NTWG for prioritization (Figure 1).

The ADEPT consortium will meticulously and continuously explore gaps that will progressively evolve the system toward people-centred health system[35].

Staff and Personnel Training: ADEPT has collaborated with National Training Centres and hospitals/facilities that provide advanced/specialized care of patients in creating modules for training of the front-line healthcare providers (HCPs). Leadership and supervisory lines will be strengthened simultaneously with increasing accountability and establishment of a clinical audit programme. ADEPT has also created local technical working groups composed of senior front-line HCPs currently empowered with skills and knowledge for integrating and clinical management of communicable (TB) and non-communicable (DM) diseases[36]. The empowerment of HPCs has been facilitated by those training modules delivered as web-based or m-Health platforms for continuous professional development that has increased the reach to all HCPs that would otherwise not be possible due to limited funds. The designed modules

are not only adaptive to cover HCPs with different skills (for example, clinicians and nurses) but modules can be updated remotely should new processes need to be introduced. Importantly, the HCPs have endless access and updated alerts to their mobile numbers or emails prompting them to complete a new module.

Tools: Equipment and consumables for piloting the programme have been inventoried at participating facilities within the communities of study. Supplies for DM were frequently not available or inadequately stocked and these including glucometers, glucostrips, HbA1c devices, therapeutic drug monitoring supplies, recording and reporting. These tools were funded temporarily through the Danish International Development Agency. TB consumables, supplies and tools were procured through conventional channels.

Study design

This is a mixed research design; and applies both qualitative and quantitative approaches. Cross sectional design will be conducted for needs assessment and bidirectional screening while, prospective cohort designs will be deployed for and stepped wedged cluster non-randomized trial will be used in different work packages.

Study area

The research project will be conducted in three regions of Tanzania; Dar es Salaam, Iringa, and Kilimanjaro. Districts that will participate include Ilala and Kigamboni for Dar es Salaam, Iringa Municipal, Kilolo and Mufindi for Iringa, and Moshi Municipal, Same and Siha for Kilimanjaro.

Study outline

Objective 1 method: Integrate TB or TB/HIV and DM services

A prospective observational of the health system study will be conducted. It is recommended that at least 30 health facilities are needed for reliable and accurate results therefore each region will contribute at least 10 health facilities at various levels for integrating TB or TB/HIV and DM services [37]. The catchment area includes one- referral hospital, three district hospitals and at least

6 health centres/dispensaries. Integration will start stepwise from the referral (secondary or tertiary) hospitals levels towards primary health care clinics, i.e. the district hospitals followed by the health centres and dispensaries. Needs assessments have been carried to identify capacity of the health facility and decide whether the health facility will operate as a "one-stop shop" defined as TB and DM services provided at the same time using adjacent rooms, "partial integration" defined as health care providers swaps between clinics, or "remote integration" through cross referral of DM to TB services. Entries of TB/DM integration in TB services or TB/HIV services will be at the TB and DM clinics[38]. TB diagnosed cases will receive DM testing while at the DM clinics, presumed TB will be screened according to the standard national TB algorithm. An algorithm to identify cases with high potential for treatment failure including those with TB drug resistance and other DM co-morbidities will be identified and tabled for expert discussion. Participants will be managed according to the collaborative TB/DM services framework guideline [39] as follows;

Sub-objective 1.1. Method. Screening TB in DM patients

DM cases especially those with sub-optimal control as defined by HbA1c, will be screened for active TB. The algorithms for active TB case findings will be applied as described elsewhere[40 41].

Sub-objective 1.2. Method. Screening DM in TB patients

All TB cases irrespective of having "classical" symptoms (polyuria, polydipsia and polyphagia), cases will be screened with glucometer and Interpretation of results is as follows; if the random blood/serum glucose (RBG) ≤ 7.8 mmol/L or fasting blood glucose (FBG) ≤ 6.1 mmol/L without DM symptoms, blood or serum glucose will be considered normal. If the RBG is 7.8 – 11.0 mmol/L or FBG is 6.2 – 6.9 mmol/L, this will be considered as pre-DM. When RBG is ≥ 11mmol/L or FBG is ≥ 7.0 mmol/L this is DM. To exclude patients with transient hyperglycaemia due to cytokine stimulation (false DM diagnosis), Hb1Ac is used to confirm the diagnosis of DM in TB cases [22].

Individuals with pre-DM or DM will further be tested with HbA1c, and the interpretation of the results are as follows; HbA1c of ≤38 mmol/mol (≤ 5.6%); 39 < 48 mmol/mol (5.7% < 6.5%), and ≥ 48 mmol/mol (≥6.5%) will be reported and considered as normal, pre-DM and DM respectively[42]. TB cases with pre-DM will be re-evaluated in the mid-term of TB treatment and TB treatment completion to identify if the condition has resolved, or progressed or remained static; if pre-DM will have advanced to DM, patients will be treatment according to the DM guideline. The TB IPC practice that is applicable in HIV clinics will be applied[38].

Objective 2 methods: Deliver International Standards using diagnostics for optimizing outcomes

Health facilities effectively integrating dual TB/DM services will enter a next phase of delivering the best practice in dual TB/DM patients (Figure 4). The implementation design will study the best clinical practice of dual TB/DM services comprising of TB diagnostics including susceptibility testing, anti-TB therapeutic drug monitoring, and HbA1c for monitoring the DM and guide selection and combination of both anti-TB and anti-DM drugs. Under sequential roll out, or stepped wedge cluster trial design; facilities in each region integrating TB/DM services will be stepwise allocated; (referral hospitals>>district hospitals>>>health centres/dispensaries) to incorporate the best clinical practice package in dual TB/DM case treatment. Three centres from each region will be allocated to start the best practice of TB/DM package interventions concurrently. A new facility level will be subsequently allocated to implement the best practice TB/DM package in steps of 3 months (quarterly) intervals such that a complete coverage of 30 health facilities in WP1 will be obtained after 2 years and 9 months. In our previous observational study, we found 16% of TB/DM patients had unfavourable outcomes in Tanzania [16]. We assume that the best practice package will reduce the unfavourable event rate to 8 %. To achieve 90% power to detect this difference with a significance level of 5% with a non-compliance estimated at 8% [43], the adjusted minimum sample size of 970 TB/DM patients will be rigorously followed [44].

TB/DM or TB-HIV/DM individuals will provide baseline sputum for culture and drug susceptibility testing as well as smear microscopy. Patients will also test for HbA1c and renal function test to assess for severity of DM. Two weeks after starting anti-TB medication, blood will be collected for therapeutic drug monitoring of anti-TB drugs. Collection of blood will be through dry blood spot and transported to the Biotechnology Laboratory/Kilimanjaro Clinical Research Institute through Expedited Mail Services. The dry blood spot collection will be processed for testing the serum drug levels starting with rifampicin then isoniazid, and pyrazinamide using an assay validated according to international guidelines[45] Results will be communicated before day 21 of anti-TB treatment, and if needed the anti-TB dosage adjustment will be made. A TDM strategy suitable for fixed dose combination regimen will be applied. In summary, the therapeutic drug monitoring will be performed at week 2 of TB treatment, based on plasma concentrations results, the appropriate FDC tablets can be selected[46 47]. Serum drug exposure that differ at least 25% from target concentrations will be considered as clinically relevant [48]. Therefore, those below the target will be eligible for dose adjustment. Two weeks after dose adjustment, the drug concentrations will be confirmed[46]. In the continuation phase, the appropriate fixed drug combination of rifampicin and isoniazid can be selected, based on earlier measured drug concentrations. In addition, routine pharmaco-vigilance will complement the safety data of this strategy. TB/DM cases will have monthly mycobacteriological monitoring for detection of microbiological treatment failure. While DM monitoring will include the assessment of retinopathy, impaired wound healing (diabetic foot), and nephropathy[49 50]. HbA1c and renal function tests will also be followed at month 3 and 6 to enable further anti-DM regimen adjustment.

Objective 3 methods: Capacity building on training and applied research

Training of the frontline health care providers will follow the "*classical diffusions of innovation theory*" drawn by Dearing,2009 [51]. ADEPT will change the current passive delivery of

international standards of care into an active approach, and the training will be delivered in a step-down approach and will be implemented in phases;

- Phase 1- includes a self-learning package with assessment delivered through a web-based platform. The assessment will be shared to the ADEPT team prior to attending the next phase.
- Phase 2- Learners achieving > 80% of the web-based assessment will be invited to attend training of the trainer (ToT) workshop. Emphasis during this phase will be to expose individuals to acquire the principles, of the technology or innovations or intervention and conduct practical on dual TB/DM and associated co-morbidities including HIV-coinfection, malnutrition and non-communicable chronic lung diseases.
- Phase 3- ToT will receive package/materials to train frontline health service providers in their district. This will be the minimum package for providing dual TB and DM care with short modules and directives to the task to be conducted. ToT will deliver the training to the selected health facilities assigned to him/her.
- Phase 4- Competency of the ToT will combine assessment of best practice portfolio documented at their clinics, and also practice implemented by the trainers s/he empowered.

Medical education modules on TB/DM and associated comorbidities will be tailored to different roles and associated quality control questions for assessing the level of acquired skills for each type of health care provider (clinicians, nurses, pharmacist and laboratory staff). A minimum threshold of quality control pass will be included as one of the criteria to qualify the health facility to integrate TB/DM services. Other criteria will be sought from the health facility needs assessment tools, which will include availability, and operational infection prevention policy for

TB controls and equipment for DM diagnosis and prevention of complications. Knowledge comparison will be made pre and post training.

Data collection

Data collection will be done under routine patient care in clinics. Data management will follow and adhere to the Tanzania Code of Conduct for Research Integrity. Qualitative data will be summarized in qualitative case record forms while quantitative data will be available in the Multi-Schema Information Capture database, which is a customizable format current in use in Kilimanjaro, utilizing secure encryption services (www.mysql.com). Data collection, transfer, entry, validation, queries generation, audit, archival and ownership will be detailed in specific standard operational procedures as described elsewhere[52].

Data analysis plan on dual TB and DM

Outcome measures include;

Bidirectional screening and diagnosis of dual TB/DM disease

- Proportion of facilities capable of providing best practice of TB/DM services
- Proportion of laboratories supporting dual TB/DM services
- Proportion of health care providers trained in best practice on dual TB/DM services
- Proportion of registered TB patients screened for DM
- Proportion of diabetes patients screened for TB
- Proportion of registered TB patients identified with presumptive DM among patients and screened for DM and vice versa
- Proportion of registered TB patients tested for DM and vice versa.
- Proportion of registered TB patients diagnosed with DM and vice versa.
- Proportion of registered DM patients with TB referred to a TB clinic.
- Proportion of registered DM patients with TB started on TB treatment and vice versa.

Dual TB/DM treatment outcomes

TB treatment outcomes

- Proportion of TB/diabetes patients with favourable outcomes (cured, or treatment complete) or unfavourable outcomes (death, lost to follow-up, treatment failure)
- Proportion of TB/DM recurrence of TB one year after completion TB treatment as determined by sputum culture and advanced genomic technologies.
- Proportion of TB/DM acquiring DR-TB at the time of failure or TB recurrence
- Proportion of TB/DM patients with sub-optimal concentrations of first line anti-TB drugs at 2nd-week of treatment
- Proportion of TB/DM with abnormal HbA1c compared to the baseline
- Proportion of TB/DM patients with treatment adjustment

DM complications at baseline and at the end of TB treatment

- Proportion of TB/DM with hypertension, kidney dysfunction as estimated by the albuminuria/proteinuria, blood urea nitrogen and creatinine
- Proportional of TB/DM with neuropathy through assessment of bladder or erectile (male) dysfunction, sensorimotor neuropathy, orthostatic hypotension, sudomotor neuropathy, frequent non-infective diarrhoea or constipation
- Proportional of TB/DM with retinopathy as graded by severity (none, mild, moderate or severe)

We will assess the pathway of patients' experience and acceptability of dual TB/DM services [53].Likewise we will assess the feasibility and acceptability of all steps of ADEPT model as portrayed in Figure 2.

Conclusion

Health systems in most of sub-Saharan Africa are fragile despite facing an enormous burden of communicable diseases and NCDs. Unfortunately, resources are scare and therefore the

situation, as emblematic in the dual TB/DM epidemic in Tanzania, necessitates new thinking and an approach that will eventually build resilient health systems.[54] The proposed ADEPT model will challenge the status quo of the Tanzanian health system in addressing the existing systemic bottlenecks. Yet a key element of the ADEPT model is to create and nurture a learning system, teamwork, collective responsibilities, accountability, and leadership for a common favourable future. Consequently, front line HCPs and other locals will be empowered to innovate around health care delivery and changes that will be likely to have a long-term constructive effect[29].

ETHICS AND DISSEMINATION

This protocol has been approved at the local health research committee serving Kibong'oto Infectious Diseases Hospital and National Health Research Committee with reference numbers KNCHREC003 and NIMR/HQ/R.8a/Vol.IX/2988, respectively. Furthermore, the Ministries of Health and Regional Administrative & Local Government Authority have endorsed implementation of this protocol.

AUTHOR CONTRIBUTIONS

Each author has contributed significantly to and is willing to take public responsibility for one or more aspects of the protocol. All authors contributed to the design and provided critical revisions and approved the final version.

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DATA STATEMENT

The data sets that will be generated and analysed during the conduct of the study will be made available according to the available laws and regulations

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FIGURES LEGEND

Figure 1: This model will break the siloed policy makers, health providers and researchers and gradually transform the health system into a proactive self-organizing or self-repairing system. Essential elements (Performance, Instance Selection, Critique, and Learning), if operated effectively will form an adaptive learning system. The proposed TB/DM-ADEPT Model will interconnect all interactive elements through: (a) Setting a regular single platform for policy makers, researchers and service providers on TB/DM epidemic agenda (Learning element); (b) Implementing international standards of dual TB and DM care through integrative TB/DM collaborative services that will facilitate early diagnosis while providing individualized treatment of patients with dual TB/DM disease (Performance element); (c) Conduct TB/DM applied research in implementation and health system research science to determine how to deliver best practices that will enable a people-centred health system (Critique element); and (d) Train PhD and postdoctoral fellows to answer dual TB/DM health system challenges to strengthen applied research capacity and hands-on skills to create a critical mass of the next generation of scientists able to scale up TB/DM interventions and adapt to study other communicable/ non-communicable disease intersections (Instance Selection element).

Figure 2: Logic framework model for measuring outcomes and impact

Figure 3: Hierarchy of needs for strengthening the health system as described by Potter & Brough[34]

Figure 4: Introduction of integration of TB/DM services thereafter stepwise introduction of packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM case management at all levels of health facilities

COMPETING INTEREST STATEMENT:

None declared.

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- Interface between research and the performance
- Translate abstract recommendations of the critic into specific changes in the rules or parameters used by the performance element

Policy makers
[Learning element]

Tanzania Health System
[Performance element]

Addressing dual communicable and non-communicable diseases epidemic **[Blackboard]**

Research
[Critique element]

- National Technical Working Groups (NTWGs)
- Analyze the ability of the performance element
- Set specific recommendation

Can run in a stand alone mode without learning and may not need the other elements however, it will remain unresponsive to new challenges

Priority setting
[Instance selection element]

- Input to a model guiding to control its outputs
- Careful selection can improve reliability and efficiency of the model
- Need to be evaluated and rely upon an external critic to evaluate these instances

Ministry responsible for Regional Administration and Local Government Authorities

Ministry responsible for Health

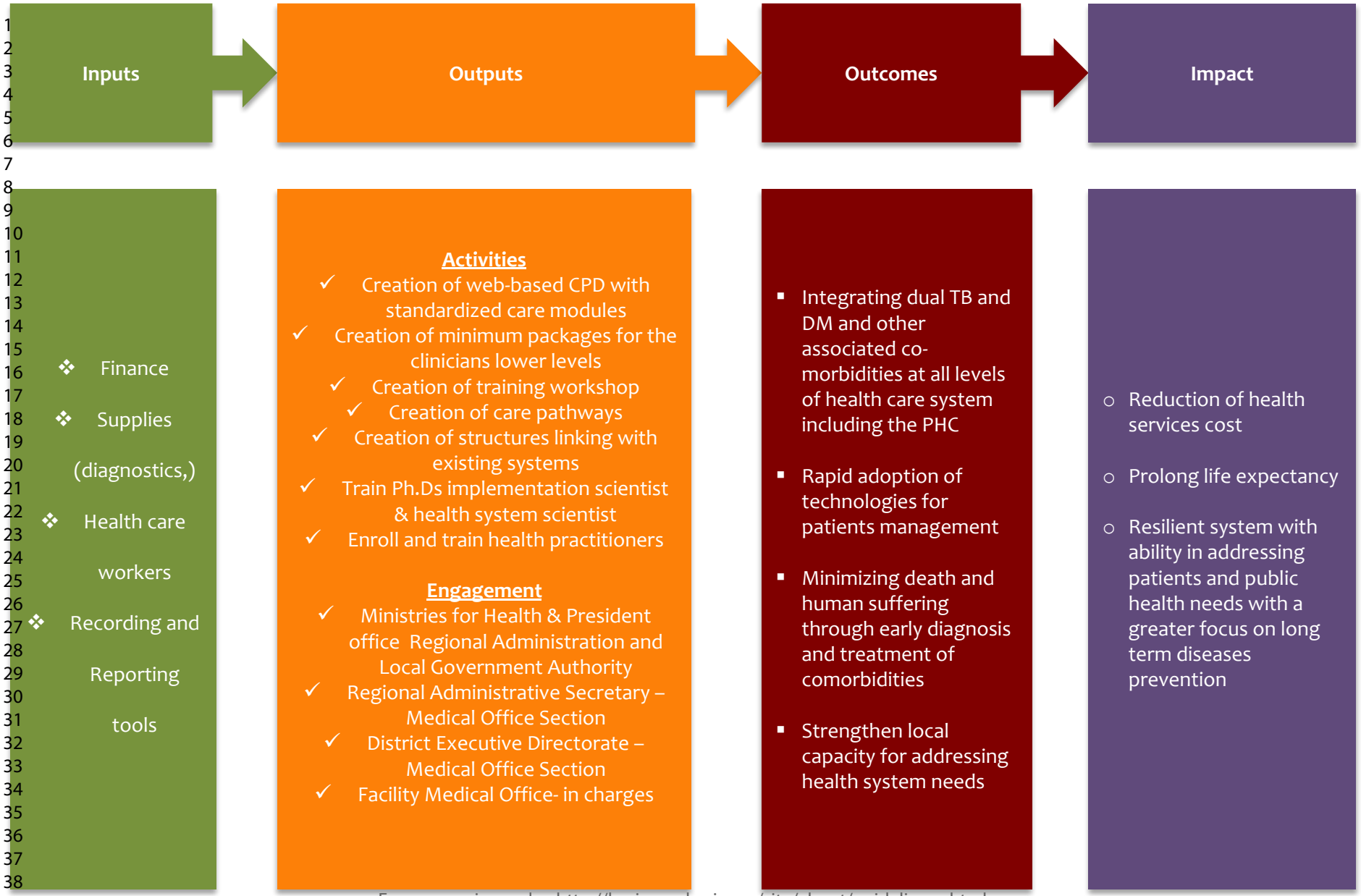
Regional Administrative Secretary/ RMO

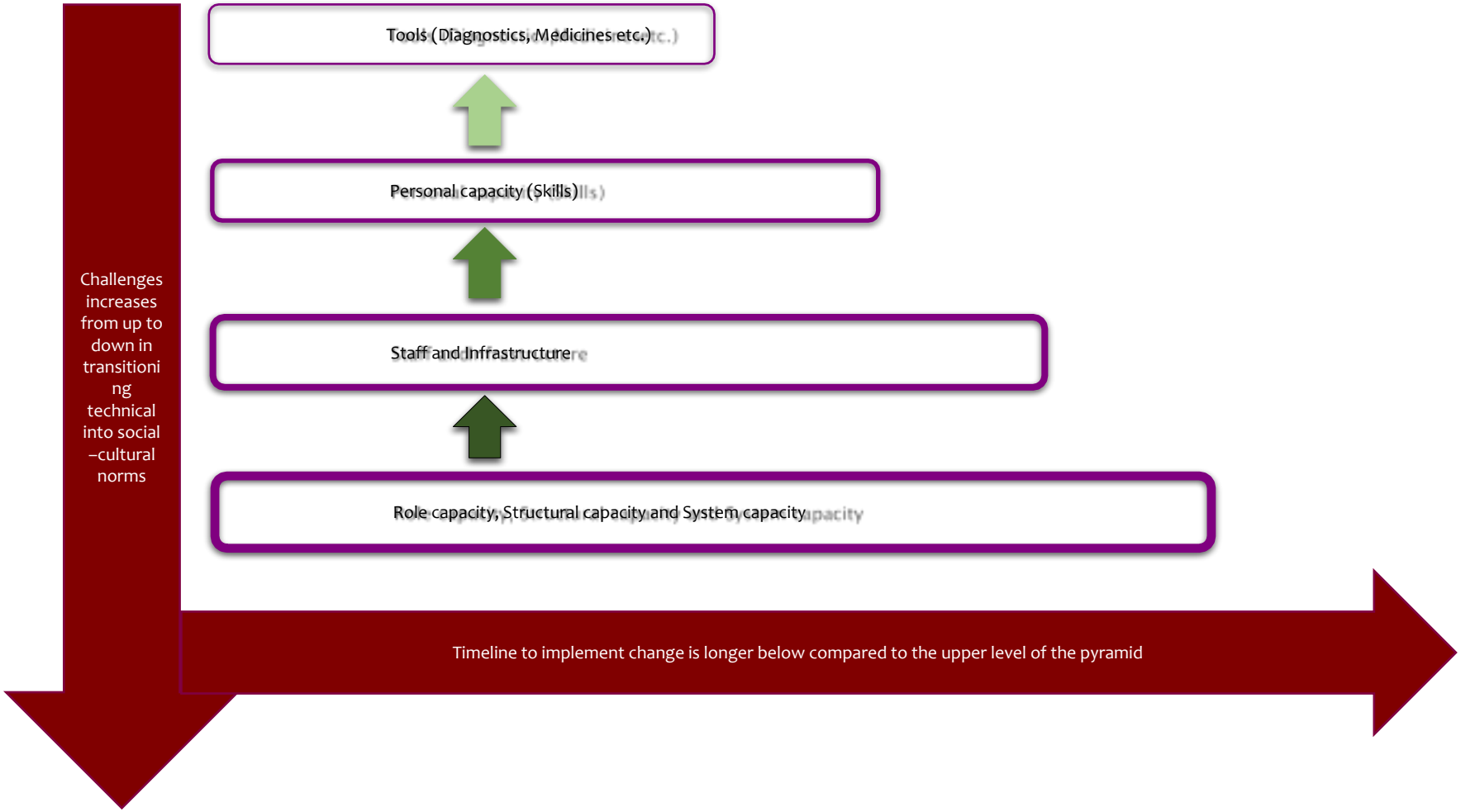
Regional Referral Hospital

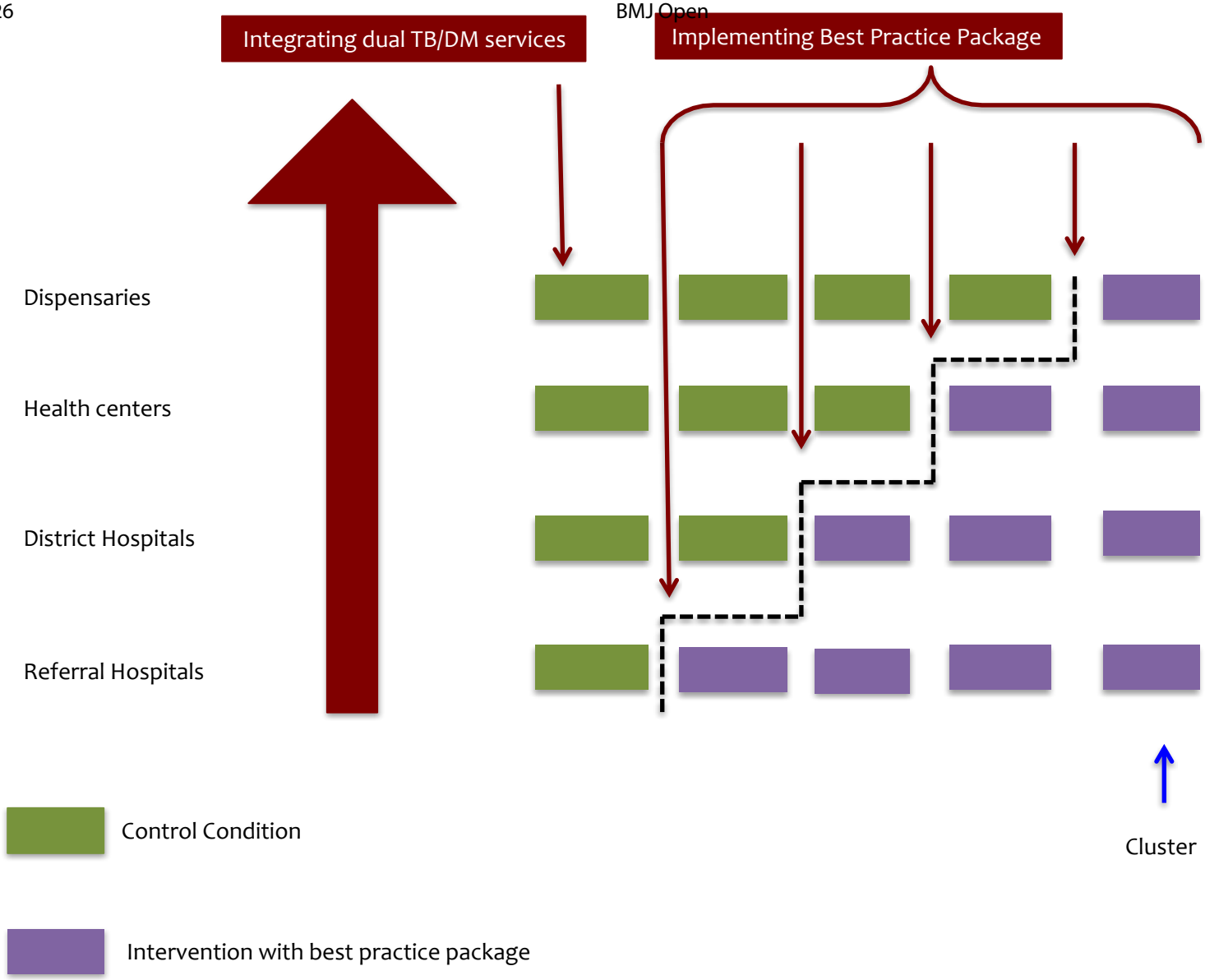
RTWG **[blackboard]**

Primary Health Care level

Other specialized health facilities, stakeholders, available in the region including research, training and private organization




Tools (Diagnostics, Medicines etc.)
Personal capacity (Skills)
Staff and Infrastructure
Role capacity, Structural capacity and System capacity
Challenges increases from up to down in transitioni ng technical into social –cultural norms
Timeline to implement change is longer below compared to the upper level of the pyramid


Integrating dual TB/DM services
Implementing Best Practice Package
Dispensaries
Health centers
District Hospitals
Referral Hospitals
Control Condition
Intervention with best practice package
Cluster

BMJ Open

Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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TITLE: Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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ABSTRACT

Introduction: Most sub-Saharan African countries endure a high burden of communicable diseases but also face a rise of non-communicable illnesses. Interventions targeting particular epidemics are often executed within vertical programmes. We aim to develop a model that will strengthen health systems by shifting traditional vertical programmes to an adaptive diseases management approach through integrating communicable and non-communicable diseases diagnosis and management using the tuberculosis (TB) and diabetes mellitus (DM) dual epidemic as a case study.

Methods and analysis: This programme will use a mixed research design, with both qualitative and quantitative approaches. Qualitative approach will explore patients with dual TB/DM experiences they encountered during health care seeking in health facilities and their perspectives centering on integration. A prospective cohort design will be used in assessing integration of TB and DM services to enable early diagnosis of dual TB/DM cases. Lastly, a stepped-wedge cluster randomized trial will assess the impact of introducing individualized TB/DM practices at the health care facility providing clinical management services level. A blueprint for addressing communicable and non-communicable dual epidemics will be developed using several tools and techniques such as a collection of stakeholders' views and literature reviews, monitoring of key indicators in the TB/DM case study, and applying a system thinking approach to essential elements in the health service delivery.

Ethics and Dissemination: Ethical approval was granted by The National Research Health Ethical Committee (reference number NIMR/HQ/R.8a/Vol.IX/2988) and the implementation was endorsed by the President Office Regional Administration and Local Government Authority. The results will be proactively disseminated through peer-reviewed open access journals, policy briefs, engagement with various stakeholders and community advisory boards, public engagement activities, conference presentations, and social media.

ARTICLE SUMMARY

Strengths and limitations of this study

- The study is conducted in pragmatic settings using a mixed study design to allow triangulation
- Considers service delivery at varying health facilities levels while covering urban, semi-urban and rural settings
- The proposed ADEPT model outcome considers process and patient-centered outcomes
- Lack of randomization of study settings or health facilities may introduce bias

INTRODUCTION

Tanzania like other sub-Saharan African countries endures a high burden of communicable infections including multidrug resistant pathogens; but also a concurrent rise of non-communicable diseases (NCD) as populations urbanize, diets "westernize" and lifespans lengthen [1]. The health system is largely inflexible and during various periods of disease epidemics, the health management teams operate in crisis-mode with limited capacity to plan for long-term disease prevention [2]. Currently in Tanzania, planned interventions for several longstanding and socioeconomically draining epidemics like tuberculosis (TB) and diabetes mellitus (DM) and their associated comorbidities, are executed within disease specific or vertical programmes [3]. Vertical programmes operate in silos while in reality various communicable and NCDs and treatments can influence one another, and overlap in populations of shared genetic backgrounds or environmental exposures, and in communities with similar socioeconomic determinants of health. Vertical programmes can significantly constrain health care delivery, and represent a top-down approach that is rarely efficient or cost-effective, particularly when considering prevailing regional health challenges [4].

This sobering fact has been illuminated in recent study of different vertical programmes in

Tanzania. We recently completed a compendium of research studies that uncovered a health system gridlock for patients trying to negotiate the road from diagnosis to treatment of TB[5-8]. There was a widespread underuse of the technologies mostly due to inadequate dissemination of healthcare provider knowledge and skills on clinical application and interpretation of molecular diagnostics despite clear patient preference for onsite rapid results and moving assays to meet patients where they were at along the care continuum [9]. Likewise, there was not only minimal resources to implement international consensus diagnostics, but also an absence of linkage to care for patients presenting with TB and with need to triage to adequate DM services [10]. Similarly, in Tanzania DM services are centralized at the district and referral health facilities but also front-line health care providers were ill-prepared for DM management[11]. Research studies conducted in different programmes to identify multi-morbidity, particularly the NCDs, have found a considerable burden of people harbouring multiple common diseases[12]. The observed increasing prevalence of dual communicable and emerging non-communicable multimorbidity epidemics and the existing systemic bottlenecks suggest the urgent need for modification of models of health care delivery. We developed a model to strengthen health systems by shifting traditional vertical programmes to a patient-centred adaptive diseases control approach through integrating communicable and NCDs. Henceforth, we describe the strategy to establish a contemporary **A**daptive **D**iseases control **E**xpert **P**rogramme in **T**anzania (Figure 1) (**ADEPT**), focusing on the TB/DM co-epidemic.

The dual TB/DM epidemic is ideal as a case for our ADEPT model because worldwide evidence shows a 3-fold increase of active TB in populations with DM compared to those without DM, while the global prevalence of TB in DM populations ranges from 1% -14%[13,14]. In Tanzania, the effect was slightly higher and estimated at nearly 4-fold increase of active TB in DM population[15]. Indeed, stakeholders from The International Union Against Tuberculosis and Lung Disease and the World Diabetes Foundation outlined the historic Bali Initiative on TB and DM (endorsed by

World Health Organization (WHO)), stating:

"▪That TB and DM represent two of the greatest global health challenges of our time, and their convergence globally represents a looming co-epidemic,

▪That this looming co-epidemic threatens progress against TB,

▪That, based on what we have learned from past co-epidemics, particularly TB-HIV, we must act early and decisively to avoid large numbers of avoidable deaths" [16,17].

We understand this urgency all too well in Tanzania. Recently, we have observed an increase in the incidence of dual diagnosed patients with TB/DM ranging from 4% of all TB patients in rural areas to 17% in urban settings, resulting in a 5-fold increase of death compared to TB patients without DM [18,19]. Importantly, our research has determined that these deaths primarily occur early, in the first three months of TB treatment [18,19]. We now understand that this high and early mortality from TB/DM in Tanzania is due to both programmatic and biological factors [20]. For example, TB and DM services are not linked and these separated service lines lead to delayed interventions for both diseases [21]. Interestingly, targeted drug therapy of dual TB/DM disease may also open new ways of enhancing the effect of essential drugs against either disease[22]. Thus, data have suggested that the first-line anti-DM drug metformin could be a promising candidate for host-adjunctive anti-TB therapy, by reducing chronic inflammation and enhancing immune response[23].

Yet, other biological factors also contribute to poor TB/DM treatment outcomes including DM-related alterations in drug absorption and metabolism resulting in sub-therapeutic anti-TB drug serum concentrations, [24] and altered inflammatory/anti-inflammatory host immune defences. Furthermore, TB disease itself may worsen control of hyperglycaemia leading to uncontrolled DM [25]. In turn, patients with uncontrolled DM also have higher bacterial burdens of *M. tuberculosis* and more extensive lung disease, and therefore achieving anti-TB drug concentrations at the most optimal of levels may be even more important in patients with DM

[26,27]. Yet, in our prior work in Tanzania, we found sub-therapeutic drug concentrations to occur in the majority of all TB patients [28,29]. While international standards mention therapeutic drug monitoring to guide TB/DM individualized dose adjustment[30], few programmes from TB-endemic settings have carried these recommendations forward[31]. Although the Tanzania Ministry of Health recognizes the challenge of the TB/DM epidemic, the vast majority of health facilities have not been able to implement international standards of TB/DM care. Therefore, this research project will also take the opportunity to underpin implementation of the international standards for controlling the TB/DM in the health system and conduct applied research to answer critical scientific questions of direct patient benefit while simultaneously training the next generation of health systems scientists.

The overall aims of developing an ADEPT model is to strengthen the health systems by shifting traditional vertical programmes to a patient-centred adaptive diseases control approach through integrating communicable and non-communicable diseases using the TB and DM dual epidemic as a case study in Tanzania. Integration of the TB/DM diagnosis and optimal management strategies will be conducted in client-friendly clinical space near to patient's entry into the health systems, as part of an adaptive disease control framework to inform future best policies for integrating care of communicable and NCDs in Tanzania.

Overview of the ADEPT Model

The ADEPT model has three components considered as vital to re-orient the health system to address dual communicable and NCDs. Each component is described as follows;

I. **A Step-wise Training approach: The objective is to improve knowledge, skills and resource acquisition for the frontline health care providers to integrate communicable and NCDs at varying health system levels.**

This model follows the "classical diffusions of innovation theory" described elsewhere [32] and organised on-job training in two clusters that will stepwise deliver a logically related set of internationals standards of patients with communicable and NCDs. The first cluster consisting of mentors that train to integrate communicable and non-communicable diseases. The potential mentors will be selected by the health managers at the respective health facilities, preferably working in either a general clinic or TB or DM clinic but also a minimum of undergraduate training. This cluster will also then serve as subsequent mentors. The initial training is through the e-learning methodology and pre-defined proceeding criterion (score > 80% of the online training) to the next phase which is a face-to-face workshop. The aim of the workshop is to expose individuals to acquire hands-on skills and conduct practical exercises related to clinical services focusing on algorithms of management or nursing care and new endorsed technologies. The second cluster will receive training and mentorship from the first cluster. The first cluster receives package/materials to train the second cluster working at the same level or at primary health care facilities.

II. Adaptive service delivery. The objective is to integrate communicable and NCDs at varying health system levels

Clinics delivering communicable or NCDs at varying levels of health facilities will receive training using a step-wise model. Considerations of infection prevention control will guide a service delivery approach while considering patient-centred recommendations. The first clinic will be applicable to clients with TB with or without other co-morbidities. Recognizing individuals with non-communicable lung diseases (CLDs) presenting with features akin of TB, a separate clinic may need to be organized. For the TB and CLD clinics, although potentially operating separately, it is important to maintain the link of these clinics as an important component of practical approach of lung health. The third clinic will encompass all non-TB-non-CLD with or without other

comorbidities including HIV, DM, and Hypertension. A multimorbidity team within a health facility will facilitate mechanisms for screening communicable and NCDs.

III. Learning system model: The objective is to create a platform for reviewing data and information generated during implementation, and create a 'self-repairing' mechanism

The mentors or first cluster of trainees will have regular meetings at the Regional Medical Officer with attendance of District Medical Officers and different programme coordinators; including TB & Leprosy, NCDs, HIV, Malaria and Neglected Tropical Diseases. The meeting will review the clinical audit and quality improvement reports from health facilities focusing on health service delivery and identify the gaps for actions. Likewise, the coordinators will share on the expected national targets in their local context. The meeting report will be submitted to the higher authorities responsible for health. Currently the report will be submitted to the Ministry of Health Community Development Gender Elderly and Children and the President Office Regional Administration and Local Government Authority. The report will be included in the respective national technical working groups (TWG) for incorporation in the general provision of technical direction and advice. The relay mechanisms from the TWG to regions will also be established.

ADEPT Model Research Questions Component

Implementation research

1. What patients did with dual TB and DM experience and what were their perspectives on services they received in the health facilities?
2. What is/are the most effective approach/es to de-implement health facility practices that do not support effective integration of proposed service delivery model using TB and DM as a case study?

3. What is the best approach to deliver on-job training and facilitate delivery of integration of TB and DM in a patient-centred approach?
4. What is the feasibility, acceptability and fidelity of the implemented designed models?
5. Where is the best place in the HCS system to implement (or initiate) integration of TB and DM?

Operational research in TB and DM

1. How many additional dual TB and DM patients will be identified during bi-directional screening of TB and DM services who would otherwise not have been identified?
2. What are the treatment outcomes of patients with dual TB and DM with or without HIV compared to other patients without DM?
3. What are the effects of therapeutic drug monitoring on dose adjustment and subsequently on treatment outcomes?

METHODS AND ANALYSIS FOR ADEPT MODEL

Conceptual framework of the ADEPT model

The ADEPT model pioneers the systems thinking methodology described by Swanson and colleagues to guide integrative changes in health practice, education, research and policy [33]. We proposed to introduce ADEPT first to the dual TB/DM epidemic as a case study of integrating communicable and non-communicable diseases [34,35] to engage currently siloed policy makers, researchers, and service providers [36]. The proposed ADEPT model is supported by three principles with interdependent themes; transformational leadership, collaboration, and a constant interactive learning process prompting to self-repairing mechanisms. ADEPT will be evaluated using the logic framework developed by the WHO/US-Center for Diseases Control and Prevention (US-CDC) (Figure 2) [37]. The design of input and output pillars reflect largely on the archetypical work designed by Potters and Brought in 2004 for health system strengthening[38]. This includes a four-tier hierarchy with nine-interdependent elements as depicted in Figure 3.

Role, Structural and System capacity: ADEPT will mobilize physicians and nurse officers working at TB, DM, or general clinics at the regional level regardless of the facility level. The team will serve as a Regional Technical Working Group (RTWG), and will be empowered to serve as mentors in the Region to support the health system to deliver best practices in patients with dual communicable and NCDs. The formed team will operate under the Regional Medical Officer (RMO), a newly formed structure that will also link with the National Technical Working Groups (NTWG) (Figure 1). RTWG under the leadership of RMO will conduct regular discussion with all stakeholders supporting the communicable and or NCDs intervention and associated co-morbidities. The discussion emanating from the meetings will guide local decision but will also be communicated to the Ministries responsible for Health and Regional Administration and Local Government Authorities, and shared with responsible NTWG for prioritization (Figure 1).

The ADEPT consortium will meticulously and continuously explore gaps that will progressively evolve the system toward people-centred health system[39].

Staff and Personnel Training: ADEPT has collaborated with National Training Centres and hospitals/facilities that provide advanced/specialized care of patients in creating modules for training of the front-line healthcare providers (HCPs). Leadership and supervisory lines will be strengthened simultaneously with increasing accountability and establishment of a clinical audit programme. ADEPT has also created local technical working groups composed of senior front-line HCPs currently empowered with skills and knowledge for integrating and clinical management of communicable (TB) and non-communicable (DM) diseases[11]. The empowerment of HPCs has been facilitated by those training modules delivered as web-based or m-Health platforms for continuous professional development that has increased the reach to all HCPs that would otherwise not be possible due to limited funds. The designed modules are not only adaptive to cover HCPs with different skills (for example, clinicians and nurses) but modules can be updated remotely should new processes need to be introduced for instance

emerging epidemics like COVID-19. Importantly, the HCPs have endless access and updated alerts to their mobile numbers or emails prompting them to complete a new module.

Tools: Equipment and consumables for piloting the programme have been inventoried at participating facilities within the communities of study. Supplies for DM were frequently not available or inadequately stocked and these including glucometers, glucostrips, HbA1c devices, therapeutic drug monitoring supplies, recording and reporting. These tools were funded temporarily through the Danish International Development Agency, subsequently health facilities will take over. TB consumables, supplies and tools were procured through conventional channels including the cost sharing and implementing partners.

METHODS AND ANALYSIS FOR TB AND DM

Study design

This is a mixed research design and applies both qualitative and quantitative approaches. A cross sectional design will be conducted for needs assessment and bidirectional screening and bidirectional screening of TB and DM while a prospective cohort design will be deployed for assessing the treatment outcomes of patients with dual TB/DM. A stepped wedged cluster non-randomized trial design will be for assessing effect of therapeutic drug monitoring for dose adjustment and subsequent treatment outcome of patients with dual TB/DM. Stepped-wedged methodology is a design that is preferably used when implementation and research go hand in hand, especially with complex medical procedures this is a preferred approach.

A stepped wedge cluster randomised trial design is the most robust design that is logistically feasible whilst providing the level of evidence of efficacy and effectiveness to support further implementation in health care[40,41]. This design helps to minimise ethical issues related to withholding the optimized care in a traditional individual randomized trial design and can be considered of low or negligible risk.

Study area

The research project will be conducted in three regions of Tanzania; Dar es Salaam, Iringa, and Kilimanjaro. Districts that will participate include Ilala and Kigamboni for Dar es Salaam, Iringa Municipal, Kilolo and Mufindi for Iringa, and Moshi Municipal, Same and Siha for Kilimanjaro. We selected areas to affiliate with the workplaces of the current consortium's Tanzanian expertise and to reflect representative population types. Dar es Salaam is largely a metropolitan while Iringa and Kilimanjaro selected areas cover rural (Kilolo and Siha), semi-urban (Mufindi and Same) and urban settings (Iringa Municipal and Moshi Municipal). According to the National TB survey of 2012, the TB prevalence is high in Dar es Salaam and in rural settings[42]. The burden of DM is 9% in Tanzania but is more common in urban settings[43].

Study outline

Objective 1 method: Integrate TB or TB/HIV and DM services

A prospective cohort study of the health system will be conducted to observe the effect of the step-down approach and integration of services. It is recommended that at least 30 health facilities are needed for reliable and accurate results therefore each region will contribute at least 10 health facilities at various levels for integrating TB or TB/HIV and DM services [44]. The catchment area includes one- referral hospital, three district hospitals and at least 6 health centres/dispensaries. Integration will start stepwise from the referral (secondary or tertiary) hospitals levels; corresponding with the stepwise training model towards primary health care clinics, i.e. the district hospitals followed by the health centres and dispensaries. Needs assessments have been carried to identify capacity of the health facility and decide whether the health facility will operate as a "one-stop shop" defined as TB and DM services provided at the same time using adjacent rooms, "partial integration" defined as health care providers swaps between clinics, or "remote integration" through cross referral of DM to TB services. Entries of TB/DM integration in TB services or TB/HIV services will be at the TB and DM clinics [45]. People

diagnosed with TB diagnosed will receive DM testing while at the DM clinics, presumed TB will be screened according to the standard national TB algorithm. An algorithm to identify people with active TB and high potential for treatment failure, including those with TB drug resistance and other DM co-morbidities, will be identified and tabled for expert discussion of additional support mechanisms that can be mobilized. Participants will be managed according to the collaborative TB/DM services framework guideline [46] as follows;

Sub-objective 1.1. Method. Screening TB in DM patients

People with DM, especially those with sub-optimal control as defined by HbA1c, will be screened for active TB. The algorithms for active TB will be applied as described elsewhere[47 48].

Sub-objective 1.2. Method. Screening DM in TB patients

All people with active TB irrespective of having "classical" symptoms (polyuria, polydipsia and polyphagia) will be screened with glucometer and interpretation of results is as follows; if the random blood/serum glucose (RBG) ≤ 7.8 mmol/L or fasting blood glucose (FBG) ≤ 6.1 mmol/L without DM symptoms, blood or serum glucose will be considered normal. If the RBG is 7.8 – 11.0 mmol/L or FBG is 6.2 – 6.9 mmol/L, this will be considered as pre-DM. When RBG is ≥ 11mmol/L or FBG is ≥ 7.0 mmol/L this is DM[49]. To exclude patients with transient hyperglycaemia due to cytokine stimulation (false DM diagnosis), Hb1Ac will be performed in follow-up [25]. Individuals with pre-DM or DM further tested with HbA1c, interpretation of the results will be as follows; HbA1c of ≤38 mmol/mol (≤ 5.6%); 39 < 48 mmol/mol (5.7% < 6.5%), and ≥ 48 mmol/mol (≥6.5%) will be reported and considered as normal, pre-DM and DM respectively[50]. People with active TB and pre-DM will be re-evaluated in the mid-term of TB treatment and TB treatment completion to identify if the condition has resolved, progressed, or remained static; if pre-DM will have advanced to DM, patients will be treated according to the DM guideline. The TB Infection Prevention Control practice that is applicable in HIV clinics will be applied[45].

Objective 2 methods: Determine effect of diagnostics (HbA1c and therapeutic drug monitoring) for regimen and dosage selection for optimizing treatment outcomes of patients with dual TB/DM

Health facilities effectively integrating dual TB/DM services will enter a next phase of using therapeutic drug monitoring for personalized dose adjustment to optimize dual TB/DM patient management (Figure 4). The implementation study design will describe the outcomes of patients with dual TB/DM tested with diagnostics comprising of susceptibility testing, anti-TB therapeutic drug monitoring, and HbA1c for monitoring the DM and guide selection and combination of both anti-TB and anti-DM drugs. The stepped wedge trial design will be used for assessing the effect of therapeutic drug monitoring will have 3-phases: pre-enrolment phases where prior to implementation of all facilities will serve as controls; roll-out period when health facilities cross-over from control to active implementing the therapeutic drug monitoring (TDM); post-rollout when all selected health facilities will be implementing TDM.

Health facilities in each region integrating TB/DM services will be allocated; to incorporate the therapeutic drug monitoring in optimizing anti-TB drug dosages. In our previous observational study, we found 16% of TB/DM patients had unfavourable outcomes in Tanzania [19]. We assume that the therapeutic drug monitoring will reduce the unfavourable event rate to 8 %. To achieve 90% power to detect this difference with a significance level of 5% with a non-compliance estimated at 8% [51], the adjusted minimum sample size of 970 TB/DM patients will be rigorously followed [52]. TB/DM or TB-HIV/DM individuals will provide baseline sputum for culture and drug susceptibility testing as well as smear microscopy. Patients will also test for HbA1c and renal function test to assess for severity of DM. Two weeks after starting anti-TB medication, blood will be collected for therapeutic drug monitoring of anti-TB drugs. Collection of blood will be through dry blood spot and transported to the Biotechnology Laboratory/Kilimanjaro Clinical Research Institute through Expedited Mail Services. The dry blood spot collection will be

processed for testing the serum drug levels starting first with rifampicin using an assay validated according to international guidelines[53] Results will be communicated before day 21 of anti-TB treatment, and if needed the anti-TB dosage adjustment will be made. A TDM strategy suitable for a fixed dose combination regimen will be applied. In summary, the therapeutic drug monitoring will be performed at week 2 of TB treatment, and based on plasma concentrations results, the appropriate FDC tablets can be selected[54,55]. Serum drug exposure that differs by at least 25% from target concentrations will be considered as clinically relevant [56]. Therefore, those below the target will be eligible for dose adjustment. Two weeks after dose adjustment, the new drug concentrations will be assayed and determined if having met target[54]. In the continuation phase, the appropriate fixed drug combination of rifampicin and isoniazid can be selected, based on earlier measured drug concentrations. In addition, routine pharmaco-vigilance will complement the safety data of this strategy. TB/DM cases will have monthly mycobacteriological monitoring for detection of microbiological treatment failure. While DM monitoring will include the assessment of retinopathy, impaired wound healing (diabetic foot), and nephropathy[57,58]. HbA1c and renal function tests will also be followed at month 3 and 6 to enable further anti-DM regimen adjustment.

Objective 3 methods: Capacity building on training and applied research

Training of the frontline health care providers will follow the "*classical diffusions of innovation theory*" drawn by Dearing (2009) **[REF].** ADEPT will change the current passive delivery of international standards of care into an active approach, and the training will be delivered in a step-wise approach and will be implemented in phases;

- Phase 1- includes a self-learning package for TB and DM and associated comorbidities contents with assessment delivered through a web-based platform. The assessment will be shared to the ADEPT team prior to attending the next phase.

- Phase 2- Learners achieving > 80% of the web-based assessment will be invited to attend training of the trainer (ToT) workshop. Emphasis during this phase will be to expose individuals to acquire the principles, of the technology or innovations or intervention and conduct practical on dual TB/DM and associated co-morbidities including HIV-coinfection, malnutrition and non-communicable chronic lung diseases.
- Phase 3- ToT will receive package/materials to train frontline health service providers in their district. This will be the minimum package for providing dual TB and DM care with short modules and directives to the task to be conducted. ToT will deliver the training to the selected health facilities assigned to him/her.
- Phase 4- Competency of the ToT will combine assessment of best practice portfolio documented at their clinics, and also practice implemented by the trainers s/he empowered.

Medical education modules on TB/DM and associated comorbidities will be tailored to different roles and associated quality control questions for assessing the level of acquired skills for each type of health care provider (clinicians, nurses, pharmacist and laboratory staff). A minimum threshold of quality control pass will be included as one of the criteria to qualify the health facility to integrate TB/DM services. Other criteria will be sought from the health facility needs assessment tools, which will include availability, and operational infection prevention policy for TB controls and equipment for DM diagnosis and prevention of complications. Knowledge comparison will be made pre- and post-training.

Data collection

Data collection will be done under routine patient care in clinics. Data management will follow and adhere to the Tanzania Code of Conduct for Research Integrity. Qualitative data will be summarized in qualitative case record forms while quantitative data will be available in the Multi-Schema Information Capture database, which is a customizable format current in use in

Kilimanjaro, utilizing secure encryption services (www.mysql.com). Data collection, transfer, entry, validation, queries generation, audit, archival and ownership will be detailed in specific standard operational procedures as described elsewhere[59].

Data analysis plan on dual TB and DM

Outcome measures include;

Bidirectional screening and diagnosis of dual TB/DM disease

- Proportion of health facilities capable of providing best practice of TB/DM services at varying levels
- Proportion of laboratories supporting dual TB/DM services
- Proportion of health care providers trained in best practice on dual TB/DM services
- Proportion of registered TB patients screened for DM
- Proportion of diabetes patients screened for TB
- Proportion of registered TB patients identified with presumptive DM among patients and screened for DM and vice versa
- Proportion of registered TB patients tested for DM and vice versa.
- Proportion of registered TB patients diagnosed with DM and vice versa.
- Proportion of registered DM patients with TB referred to a TB clinic.
- Proportion of registered DM patients with TB started on TB treatment and vice versa.

Dual TB/DM treatment outcomes

TB treatment outcomes

- Proportion of TB/diabetes patients with favourable outcomes (cured, or treatment complete) or unfavourable outcomes (death, lost to follow-up, treatment failure)
- Proportion of TB/DM recurrence of TB one year after completion TB treatment as determined by sputum culture and advanced genomic technologies.

- Proportion of TB/DM acquiring DR-TB at the time of failure or TB recurrence
- Proportion of TB/DM patients with sub-optimal concentrations of first line anti-TB drugs at 2nd-week of treatment
- Proportion of TB/DM with abnormal HbA1c compared to the baseline
- Proportion of TB/DM patients with treatment adjustment

DM complications at baseline and at the end of TB treatment

- Proportion of TB/DM with hypertension, kidney dysfunction as estimated by the albuminuria/proteinuria, blood urea nitrogen and creatinine
- Proportional of TB/DM with neuropathy through assessment of bladder or erectile (male) dysfunction, sensorimotor neuropathy, orthostatic hypotension, sudomotor neuropathy, frequent non-infective diarrhoea or constipation
- Proportional of TB/DM with retinopathy as graded by severity (none, mild, moderate or severe)

We will assess the pathway of patients' experience and acceptability of dual TB/DM services [60].Likewise we will assess the feasibility and acceptability of all steps of ADEPT model as portrayed in Figure 2.

PATIENT AND PUBLIC INVOLVEMENT

Development of this protocol was informed by series of research studies that included one study that examined patients experience of health services in the health facilities[9]. Findings from the described research objectives will be shared with patients' organizations subsequently contribute in shaping the agenda of effective integration of communicable and non-communicable diseases

ETHICS AND DISSEMINATION

This protocol has been approved at the local health research committee serving Kibong'oto Infectious Diseases Hospital and National Health Research Committee with reference numbers

KNCHREC003 and NIMR/HQ/R.8a/Vol.IX/2988, respectively. Furthermore, the Ministries of Health and Regional Administrative & Local Government Authority have endorsed implementation of this protocol.

AUTHOR CONTRIBUTIONS

SGM, DLC, KR and ICB conceptualized and designed the model and proposal.TL, SH, JWA and MSB contributed in the design of the concept particularly in TB/DM research component including Mycobacteriology, TDM and mHealth respectively. DLC obtained the funding for the ADEPT project from the Ministry of Foreign Affairs of Denmark. SGM lead the implementation of the protocol in Tanzania while KR, and MSB lead implementation of the stepwise model. NEN co-lead the implementation in Iringa. BTM co-lead implementation of the TDM in Tanzania together with SH and JWA. All authors provided technical inputs in the proposal. SGM wrote the manuscript with input from all the authors. All authors have approved the final version and agreed to be accountable for all aspects of the work related to accuracy and integrity.

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DATA STATEMENT

The data sets that will be generated and analysed during the conduct of the study will be made available according to the available laws and regulations

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FIGURES LEGEND

Figure 1: This model will break the siloed policy makers, health providers and researchers and gradually transform the health system into a proactive self-organizing or self-repairing system. Essential elements (Performance, Instance Selection, Critique, and Learning), if operated effectively will form an adaptive learning system. The proposed TB/DM-ADEPT Model will interconnect all interactive elements through: (a) Setting a regular single platform for policy makers, researchers and service providers on TB/DM epidemic agenda (Learning element); (b) Implementing international standards of dual TB and DM care through integrative TB/DM collaborative services that will facilitate early diagnosis while providing individualized treatment of patients with dual TB/DM disease (Performance element); (c) Conduct TB/DM applied research in implementation and health system research science to determine how to deliver best practices that will enable a people-centred health system (Critique element); and (d) Train PhD and postdoctoral fellows to answer dual TB/DM health system challenges to strengthen applied research capacity and hands-on skills to create a critical mass of the next generation of scientists able to scale up TB/DM interventions and adapt to study other communicable/ non-communicable disease intersections (Instance Selection element).

Figure 2: Logic framework model for measuring outcomes and impact

Figure 3: Hierarchy of needs for strengthening the health system as described by Potter & Brough[34]

Figure 4: Introduction of integration of TB/DM services thereafter stepwise introduction of packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM case management at all levels of health facilities

COMPETING INTEREST STATEMENT:

None declared.

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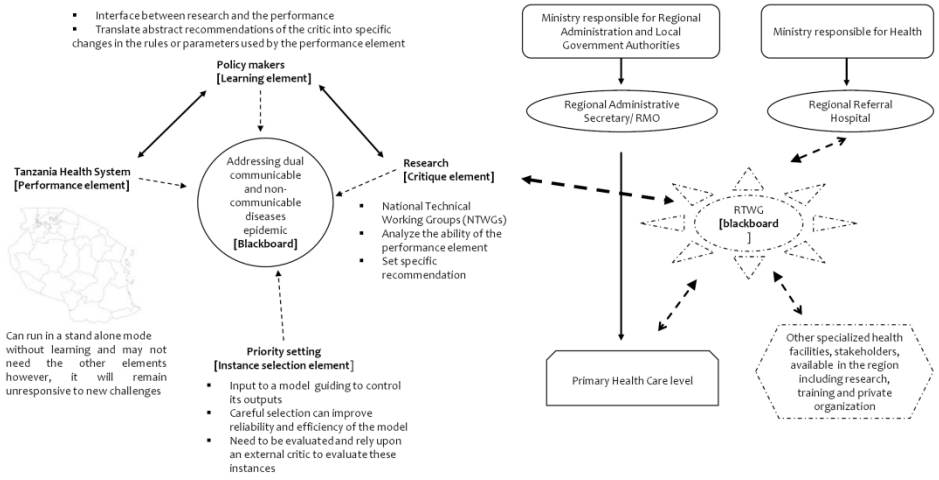

Figure 1: This model will break the siloed policy makers, health providers and researchers and gradually transform the health system into a proactive self-organizing or self-repairing system. Essential elements (Performance, Instance Selection, Critique, and Learning), if operated effectively will form an adaptive learning system. The proposed TB/DM-ADEPT Model will interconnect all interactive elements through: (a) Setting a regular single platform for policy makers, researchers and service providers on TB/DM epidemic agenda (Learning element); (b) Implementing international standards of dual TB and DM care through integrative TB/DM collaborative services that will facilitate early diagnosis while providing individualized treatment of patients with dual TB/DM disease (Performance element); (c) Conduct TB/DM applied research in implementation and health system research science to determine how to deliver best practices that will enable a people-centred health system (Critique element); and (d) Train PhD and postdoctoral fellows to answer dual TB/DM health system challenges to strengthen applied research capacity and hands-on skills to create a critical mass of the next generation of scientists able to scale up TB/DM interventions and adapt to study other communicable/ non-communicable disease intersections (Instance Selection element).

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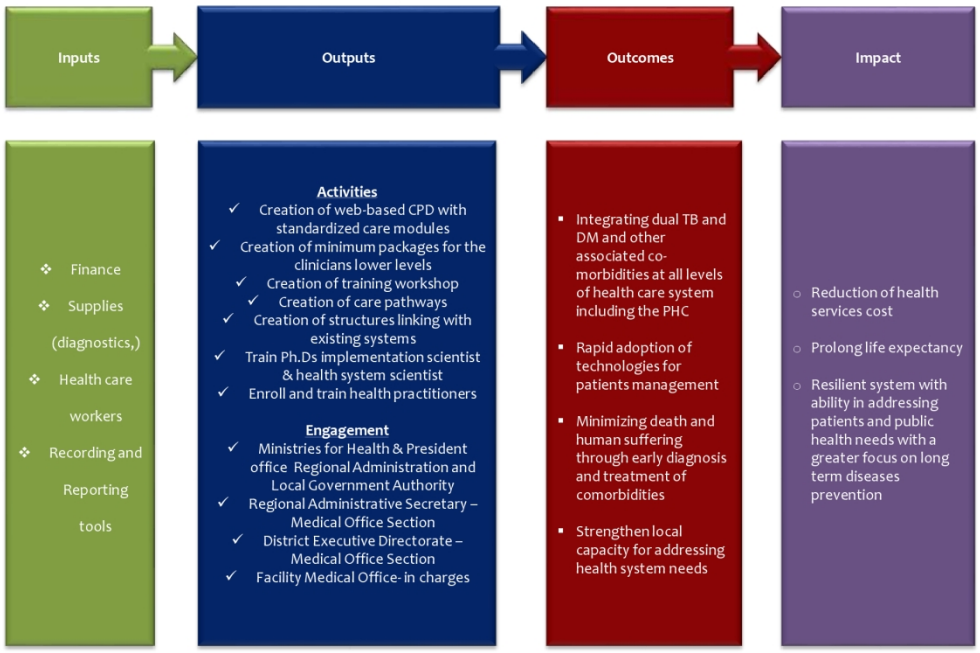

Logic framework model for measuring outcomes and impact

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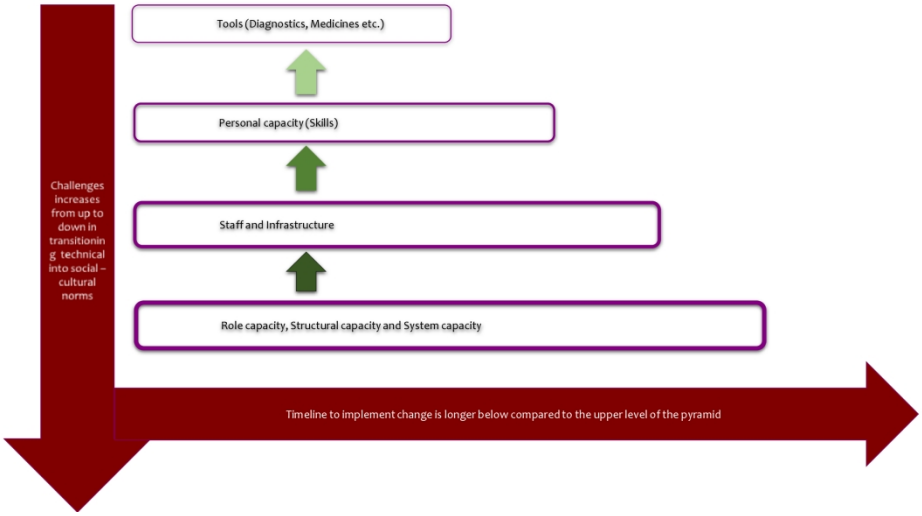

Hierarchy of needs for strengthening the health system as described by Potter & Brough34

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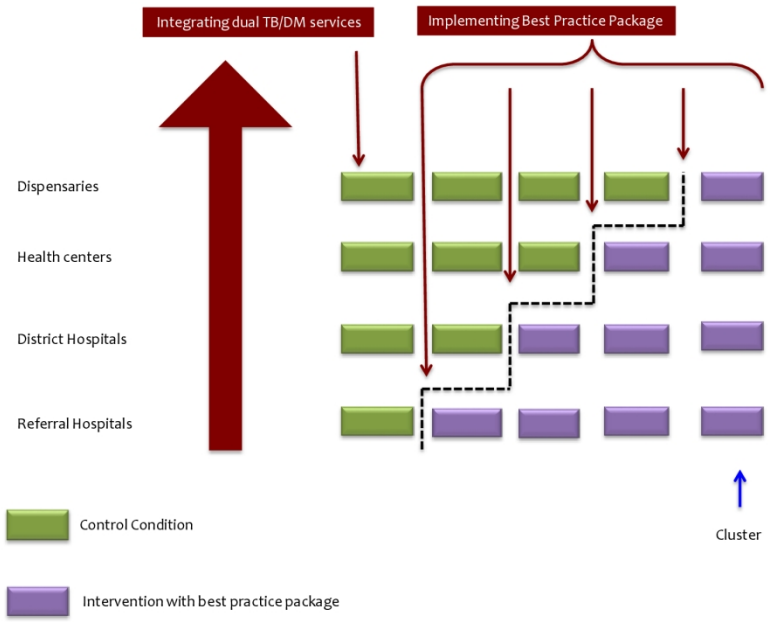

Introduction of integration of TB/DM services thereafter stepwise introduction of packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM case management at all levels of health facilities

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BMJ Open

Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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TITLE: Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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Adaptive diseases intervention programme, Communicable and non-communicable dual epidemics, tuberculosis and diabetes dual epidemic, health systems, implementation science

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ABSTRACT

Introduction: Most sub-Saharan African countries endure a high burden of communicable infections but also face a rise of non-communicable diseases (NCDs). Interventions targeting particular epidemics are often executed within vertical programmes. We establish an **A**daptive **D**iseases control **E**xpert **P**rogramme in **T**anzania (ADEPT) model with three domains; step-wise training approach, integration of communicable and NCDs and a learning system and. The model aims to shift traditional vertical programmes to an adaptive diseases management approach through integrating communicable and NCDs using the tuberculosis (TB) and diabetes mellitus (DM) dual epidemic as a case study. We aim to describe the ADEPT protocol with underpinned implementation and operational research on TB/DM.

Methods and analysis: The model implement a collaborative TB and DM services protocol as endorsed by the World Health Organization in Tanzania. Evaluation of the process and outcomes will follow the logic framework. A mixed research design with both qualitative and quantitative approaches will be used in applied research action. Anticipated implementation research outcomes include at the health facilities level for organizing TB/DM services, pathways of TB/DM patients seeking care in different health facilities, factors in service delivery that need de-implementation, and the ADEPT model implementation feasibility, acceptability and fidelity. Expected operational research outcomes include additional identified patients with dual TB/DM, the prevalence of comorbidities like hypertension in TB/DM patients and final treatment outcomes of TB/DM including treatment related complications. Findings will inform the future policies and practices for integrating communicable and NCDs services.

Ethics and Dissemination: Ethical approval was granted by The National Research Health Ethical Committee (Ref-No. NIMR/HQ/R.8a/Vol.IX/2988) and the implementation endorsed by the Government authorities. Findings will be proactively disseminated through multiple mechanisms

including peer-reviewed journals, and engagement with various stakeholders' example in conferences and social media.

ARTICLE SUMMARY

Strengths and limitations of this study

- The ADEPT model implementation underpins pragmatic research using a mixed study design to allow triangulation
- Considers service delivery at varying health facilities levels while covering urban, semi-urban and rural settings
- The proposed ADEPT model outcome considers process and patient-centered outcomes
- Lack of randomization of study settings or health facilities may introduce bias

INTRODUCTION

Tanzania like other sub-Saharan African countries endures a high burden of communicable infections including multidrug resistant pathogens; but also a concurrent rise of non-communicable diseases (NCD) as populations urbanize, diets "westernize" and lifespans lengthen [1]. The health system is largely inflexible and during various periods of disease epidemics, the health management teams operate in crisis-mode with limited capacity to plan for long-term disease prevention [2]. Currently in Tanzania, planned interventions for several longstanding and socioeconomically draining infectious diseases epidemics like tuberculosis (TB) or human immunodeficiency virus (HIV), are executed within disease specific or vertical programmes [3]. Vertical programmes operate in silos while in reality various communicable and NCDs and treatments can influence one another, and overlap in populations of shared genetic backgrounds or environmental exposures, and in communities with similar socioeconomic determinants of health. Furthermore, vertical programmes significantly constrain health care delivery, and are rarely efficient or cost-effective, particularly when considering prevailing regional health challenges [4]. This sobering fact has been illuminated in Tanzanian research

studies that uncovered a health system gridlock largely contributed by limited resources and skills-training for front-line health care providers, and weak linkage to other health services with the subsequent effect of underuse of technologies [5-10].

Likewise, the prevalence of dual communicable and NCD epidemics is increasing, yet communicable clinics are unprepared to deal with dual services [11, 12]. For instance, the prevalence of DM ranged 4 – 17 % and hypertension ranged 7 – 25 % in people leaving with HIV attending clinics in Tanzania cities, while, in other settings within Tanzania, the prevalence of DM ranged 4 – 5% and hypertension ranged 22 – 30% [13, 14]. Likewise, the incidence of dual diagnosed patients with TB/DM ranges from 4% of all TB patients in rural areas to 17% in urban settings. [15, 16]. Evidence has shown that TB/DM death is 5-fold higher compared to TB patients without DM and that death primarily occurred early, in the first three months of TB treatment [15, 16]. This high and early mortality from TB/DM in Tanzania is due to both programmatic and biological factors [17]. The TB and DM services are not linked and these separated service lines lead to delayed interventions for both diseases [18]. Biological factors contributing to poor TB/DM treatment outcomes includes DM-related alterations in drug absorption and metabolism resulting in sub-therapeutic anti-TB drug serum concentrations, altered inflammatory/anti-inflammatory host immune defences and worsened control of hyperglycaemia leading to uncontrolled DM [19] [20]

The existing systemic bottlenecks hinder optimal service delivery particularly in individuals with dual communicable and NCDs, thus suggesting the urgent need for modification of models of health care delivery. We developed a model to strengthen health systems by shifting traditional vertical programmes to a patient-centred adaptive diseases control approach through integrating communicable and NCDs. The model intention is to integrate technologies and innovations to personalize treatment and increase impact on quality care through novel strategies while facilitating the interruption of the cycle of transmission, and mortality in

communities.

Henceforth, we describe the strategy to establish a contemporary **A**daptive **D**iseases control **E**xpert **P**rogramme in **T**anzania (**ADEPT**). The ADEPT model is likely to pioneer the systems thinking methodology described by Swanson and colleagues to guide integrative changes in the health system [21], and it includes three interdependent domains; (i) step-wise training approach for knowledge and skills improvement of the frontline health care providers, (ii) adaptive service delivery through integration of communicable and NCD and (iii) continuous learning and integration of dual communicable and NCD (Figure 1).

The objective of this protocol is to describe the implementation of ADEPT model using the TB and DM dual epidemic as a case study in Tanzania with underpinned applied research questions (both operational and implementation research) to answer critical scientific questions of direct patient and public benefit. The protocol will generate evidence that will subsequently inform the forthcoming best policies for integrating care of communicable and NCDs in the country.

Overview of the ADEPT Model

The ADEPT model has three components considered as vital to re-orient the health system to efficiently address dual communicable and NCDs. Each component is described as follows;

I. **A Step-wise Training approach: The objective is to improve knowledge, skills-training and resource acquisition for the frontline health care providers to integrate communicable and NCDs at varying health system levels.**

This approach follows the "classical diffusions of innovation theory" described elsewhere [22] and organised on-job training in two clusters that will stepwise deliver a logically related set of internationals standards of patients with communicable and NCDs. The first cluster consisting of mentors that train to integrate communicable and non-communicable diseases. The potential mentors will be selected by the health managers at the respective health facilities, preferably

working in either a general clinic or TB or DM clinic. This cluster will also then serve as subsequent mentors. The initial training is through the e-learning methodology and pre-defined proceeding criterion (score > 80% of the online training) to the next phase which is a face-to-face workshop. The aim of the workshop is to expose individuals to acquire hands-on skills and conduct practical exercises related to clinical services focusing on algorithms of management or nursing care and new endorsed technologies. The second cluster will receive training and mentorship from the first cluster. The first cluster receives package/materials to train the second cluster working at the same level or at primary health care facilities.

II. Adaptive service delivery. The objective is to integrate communicable and NCDs at varying health system levels

Clinics delivering communicable or NCDs at varying levels of health facilities will receive training using a step-wise model. Considerations of infection prevention control will guide a service delivery approach while considering patient-centred recommendations. The first clinic will be applicable to clients with TB with or without other co-morbidities. Recognizing individuals with non-communicable lung diseases (CLDs) such as chronic obstructive pulmonary diseases presenting with features akin of TB, a separate clinic may need to be organized. For the TB and CLD clinics, although potentially operating separately, it is important to maintain the link of these clinics as an important component of practical approach of lung health. The third clinic will encompass all non-TB-non-CLD with or without other comorbidities including HIV, DM, and Hypertension. A multimorbidity team within a health facility will facilitate mechanisms for screening communicable and NCDs.

III. Learning system: The objective is to create a platform for reviewing data and information generated during implementation, and create a 'self-repairing' mechanism

The mentors or first cluster of trainees will have regular meetings at the Regional Medical Officer with attendance of District Medical Officers and different programme coordinators; including TB & Leprosy, NCDs, HIV, Malaria and Neglected Tropical Diseases. The meeting will review the clinical audit and quality improvement reports from health facilities focusing on health service delivery and identify the gaps for actions. Likewise, the coordinators will share on the expected national targets in their local context. The meeting report will be submitted to the higher authorities responsible for health. Currently the report will be submitted to the Ministry of Health Community Development Gender Elderly and Children and the President Office Regional Administration and Local Government Authority. The report will be included in the respective national technical working groups (TWG) for incorporation in the general provision of technical direction and advice. The relay mechanisms from the TWG to regions will also be established.

ADEPT Model Research Questions Component

The proposed research questions focus on integration of TB and DM services. The proposed questions cover the scope of implementation and operational research sciences.

Implementation research

1. Where is the best place in the HCS system to implement (or initiate) integration of TB and DM?
2. What is the best approach to deliver on-job training and facilitate delivery of integration of TB and DM in a patient-centred approach?
3. What did patients with dual TB and DM experience and what were their perspectives on services they received in the health facilities?
4. What is/are the most effective approach/es to *de*-implement health facility practices that do not support effective integration of proposed service delivery model using TB and DM as a case study?

5. What is the feasibility, acceptability and fidelity of the implemented designed models on TB/DM?
6. What are the effects of therapeutic drug monitoring on personalized dose adjustment and subsequently on treatment outcomes?

Operational research in TB and DM

1. How many additional dual TB and DM patients will be identified during bi-directional screening of TB and DM services who would otherwise not have been identified?
2. What are the treatment outcomes of patients with dual TB and DM with or without HIV compared to other patients without DM?

METHODS AND ANALYSIS FOR ADEPT MODEL

The protocol deploys the International Union Against Tuberculosis and Lung Disease and the World Diabetes Foundation outlined Bali Initiative on TB and DM collaborative services that was endorsed by World Health Organization (WHO) [23, 24]. The model will be evaluated using the logic framework developed by the WHO/US-Center for Diseases Control and Prevention (US-CDC) (Figure 2) [25]. The design of input and output pillars reflect largely on the archetypical work designed by Potters and Brought in 2004 for health system strengthening [26]. This includes a four-tier hierarchy with nine-interdependent elements as depicted in Figure 3.

Staff and Personnel Training: The ADEPT consortium collaborates with the National Training Centres and hospitals/facilities that provide advanced/specialized care of patients for executing the stepwise training approach on TB/DM and associated co-morbidites. Training includes modules delivered as web-based or m-Health platforms, covering different skills (for example, clinicians and nurses) and can be updated remotely should new processes need to be introduced. Health care providers will have endless access and updated alerts to their mobile numbers or emails prompting them to complete a new module.

Role, Structural and System capacity: Mentors spawned in the step-wise training approach form a team under the Regional Medical Officer (RMO). Together with implementing partners or stakeholders will conduct regular review on TB/DM services. The clinical audit programme is built-in to increase accountability but also as a one of the learning system components [12]. The goal is to guide local decision but will also be communicated to the Ministries responsible for Health and Regional Administration and Local Government Authorities.

Tools: Supplies for DM were frequently not available or inadequately stocked and these including glucometers, glucostrips, HbA1c devices, therapeutic drug monitoring supplies, recording and reporting. These tools were funded temporarily through the Danish International Development Agency, subsequently health facilities will take over. TB consumables, supplies and tools were procured through conventional channels.

METHODS AND ANALYSIS FOR TB AND DM RESEARCH

Study design

(i) Set of Implementation research questions

A set of implementation research questions will deploy a mixed research design, both qualitative and quantitative approaches. A cross sectional design will be conducted for the needs assessment to identify where to provide clinical management of dual TB/DM and exploring the patient's perspective and experience on dual TB/DM services using in-dept interviews of patients with TB/DM. A prospective cohort design will be deployed to identify factors hindering appropriate integration, feasibility, acceptability and fidelity.

A stepped wedged cluster non-randomized trial design will be for assessing effect of therapeutic drug monitoring for dose adjustment and subsequent treatment outcome of patients with dual TB/DM. Stepped-wedged methodology is a design that is preferably used when implementation and research go hand in hand, especially with complex medical procedures this is a preferred approach. A stepped wedge cluster randomised trial design is the most robust design that is

logistically feasible whilst providing the level of evidence of efficacy and effectiveness to support further implementation in health care[27, 28]. This design helps to minimise ethical issues related to withholding the optimized care in a traditional individual randomized trial design and can be considered of low or negligible risk.

(ii) Set of operational research question

Cross sectional and prospective cohort design will be conducted through reviewing patients' registries that receive bidirectional screening and treatment outcomes of dual TB/DM respectively.

Study area

The research project will be conducted in three regions of Tanzania; Dar es Salaam, Iringa, and Kilimanjaro. Districts that will participate include Ilala and Kigamboni for Dar es Salaam, Iringa Municipal, Kilolo and Mufindi for Iringa, and Moshi Municipal, Same and Siha for Kilimanjaro. We selected areas to affiliate with the workplaces of the current consortium's Tanzanian expertise and to reflect representative population types. Dar es Salaam is largely a metropolitan while Iringa and Kilimanjaro selected areas cover rural (Kilolo and Siha), semi-urban (Mufindi and Same) and urban settings (Iringa Municipal and Moshi Municipal). According to the National TB survey of 2012, the TB prevalence is high in Dar es Salaam and in rural settings[29]. The burden of DM is 9% in Tanzania but is more common in urban settings[30].

Study outline: Set of the implementation Research Objectives

At least 30 health facilities are needed for reliable and accurate results therefore each region will contribute at least 10 health facilities at various levels for integrating TB or TB/HIV and DM services [31]. The catchment area includes one- referral hospital, three district hospitals and at least 6 health centres/dispensaries. Using the WHO service availability and readiness assessment, the identified capacity of the health facility will guide decisions on whether the health facility will operate as a "one-stop shop" defined as TB and DM services provided at the same time using

adjacent rooms, "partial integration" defined as health care providers swaps between clinics, or "remote integration" through cross referral of DM to TB services. Operational infection prevention policy for TB controls and equipment for monitoring DM to prevent complications are vital for decision. Entries of TB/DM integration in TB services or TB/HIV services will be at the TB and DM clinics [32].

In the step-wise training approach, the online course will have a pre- and post-courses assessment using the standard questions. Knowledge comparison will be made pre- and post-training. During integration of dual TB/DM, patients receiving services for at least 3 months will be invited for interview using a guide. Discussion will focus on identifying the pathway the patients have experienced or encountered of receiving dual TB/DM services. Patients will be asked to provide suggestions on pathways and service provision.

Information collected from the need's assessment and in-depth interview of participants' pathways of care will identify practices that need to be de-implemented. Discussion with the health managers and responsible authorities will be conducted to reinforce *de*-implementation of those practices. Pilot of clinical audit focused on de-implementing those practices will complement the processes.

Health facilities effectively integrating dual TB/DM services will enter a next phase of using therapeutic drug monitoring for personalized dose adjustment to optimize dual TB/DM patient management (Figure 4). The implementation study design will describe the outcomes of patients with dual TB/DM tested with diagnostics comprising of susceptibility testing, anti-TB therapeutic drug monitoring, and HbA1c for monitoring the DM and guide selection and combination of both anti-TB and anti-DM drugs. The stepped wedge trial design will be used for assessing the effect of therapeutic drug monitoring will have 3-phases: pre-enrolment phases where prior to implementation of all facilities will serve as controls; roll-out period when health facilities cross-

over from control to active implementing the therapeutic drug monitoring; post-rollout when all selected health facilities will be implementing therapeutic drug monitoring.

TB/DM or TB-HIV/DM individuals will provide baseline sputum for culture and drug susceptibility testing as well as smear microscopy. Patients will also test for HbA1c and renal function test to assess for severity of DM. Two weeks after starting anti-TB medication, blood will be collected for therapeutic drug monitoring of anti-TB drugs. Collection of blood will be through dry blood spot and transported to the Biotechnology Laboratory/Kilimanjaro Clinical Research Institute through Expedited Mail Services. The dry blood spot collection will be processed for testing the serum drug levels starting first with rifampicin using an assay validated according to international guidelines[33] Results will be communicated before day 21 of anti-TB treatment, and if needed the anti-TB dosage adjustment will be made. A TDM strategy suitable for a fixed dose combination regimen will be applied. In summary, the therapeutic drug monitoring will be performed at week 2 of TB treatment, and based on plasma concentrations results, the appropriate FDC tablets can be selected[34, 35]. Serum drug exposure that differs by at least 25% from target concentrations will be considered as clinically relevant [36]. Therefore, those below the target will be eligible for dose adjustment. Two weeks after dose adjustment, the new drug concentrations will be assayed and determined if having met target [34]. In the continuation phase, the appropriate fixed drug combination of rifampicin and isoniazid can be selected, based on earlier measured drug concentrations. In addition, routine pharmaco-vigilance will complement the safety data of this strategy. TB/DM cases will have monthly mycobacteriological monitoring for detection of microbiological treatment failure. While DM monitoring will include the assessment of retinopathy, impaired wound healing (diabetic foot), and nephropathy [37, 38]. HbA1c and renal function tests will also be followed at month 3 and 6 to enable further anti-DM regimen adjustment.

Key elements of the ADEPT model (step-wise training approach, integration of communicable & NCDs and learning system) will be assessed for the coverage to estimate feasibility, acceptability of different stakeholders on various stages of the model. Adherence of different algorithms and steps described will be assessed and estimate the fidelity.

The data collection and analysis will be summarized in qualitative case record forms while quantitative data will be available in the Multi-Schema Information Capture database, which is a customizable format current in use in Kilimanjaro, utilizing secure encryption services (www.mysql.com). Data collection, transfer, entry, validation, queries generation, audit, archival and ownership will be detailed in specific standard operational procedures as described elsewhere[39]. Outcome measures include

- Proportion of health facilities capable of providing dual TB/DM bidirectional screening with or without clinical management at varying levels
- Pathway of patients' experience and acceptability of dual TB/DM services [40]
- Effect of stepwise training on integration of dual TB/DM services at varying levels
- Systemic factors hindering optimal integration of TB/DM services at varying levels
- The ADEPT model implementation feasibility, acceptability of health care providers & health managers and fidelity focusing on proportion of registered TB patients screened for DM and vice versa as portrayed in Figure 2.
- Treatment outcomes of patients with TB/DM adjusted for dosages with results from TDM compared to those without TDM

Study outline: Set of the Operation Research Objective

People with DM, especially those with sub-optimal control as defined by HbA1c, will be screened for active TB. The algorithms for active TB will be applied as described elsewhere[41] [42].

All people with active TB irrespective of having "classical" symptoms (polyuria, polydipsia and

polyphagia) will be screened with glucometer and interpretation of results is as follows; if the random blood/serum glucose (RBG) ≤ 7.8 mmol/L or fasting blood glucose (FBG) ≤ 6.1 mmol/L without DM symptoms, blood or serum glucose will be considered normal. If the RBG is 7.8 – 11.0 mmol/L or FBG is 6.2 – 6.9 mmol/L, this will be considered as pre-DM. When RBG is ≥ 11mmol/L or FBG is ≥ 7.0 mmol/L this is DM[43]. To exclude patients with transient hyperglycaemia due to cytokine stimulation (false DM diagnosis), Hb1Ac will be performed in follow-up [19]**.** Individuals with pre-DM or DM further tested with HbA1c, interpretation of the results will be as follows; HbA1c of ≤38 mmol/mol (≤ 5.6%); 39 < 48 mmol/mol (5.7% < 6.5%), and ≥ 48 mmol/mol (≥6.5%) will be reported and considered as normal, pre-DM and DM respectively[44]. People with active TB and pre-DM will be re-evaluated in the mid-term of TB treatment and TB treatment completion to identify if the condition has resolved, progressed, or remained static; if pre-DM will have advanced to DM, patients will be treated according to the DM guideline. The TB Infection Prevention Control practice that is applicable in HIV clinics will be applied[32].

An algorithm to identify people with active TB and high potential for treatment failure, including those with TB drug resistance and other DM co-morbidities, will be identified and tabled for expert discussion of additional support mechanisms that can be mobilized. Participants will be managed according to the collaborative TB/DM services framework guideline [45].

The data collection will be done under routine patient care in clinics. The outcome measures include;

- Incremental value of bidirectional screening in diagnosis of patients with dual TB/DM
- Proportion of TB/diabetes patients with favourable outcomes (cured, or treatment complete) or unfavourable outcomes (death, lost to follow-up, treatment failure)
- Proportion of TB/DM with additional comorbidities such as hypertension, kidney dysfunction, and retinopathy

PATIENT AND PUBLIC INVOLVEMENT

Development of this protocol was informed by a series of research studies that included one study that examined patients' experience of health services in the health facilities [9]. Findings from the described research objectives will be shared with patients' organizations for further refinement before subsequently contributing in shaping the agenda of effective integration of communicable and non-communicable diseases for policy makers.

ETHICS AND DISSEMINATION

This protocol has been approved at the local health research committee serving Kibong'oto Infectious Diseases Hospital and National Health Research Committee with reference numbers KNCHREC003 and NIMR/HQ/R.8a/Vol.IX/2988, respectively. Furthermore, the Ministries of Health and Regional Administrative & Local Government Authority have endorsed implementation of this protocol.

AUTHOR CONTRIBUTIONS

SGM, DLC, KR and ICB conceptualized and designed the model and proposal.TL, SH, JWA and MSB contributed in the design of the concept particularly in TB/DM research component. DLC obtained the funding for the ADEPT project from the Ministry of Foreign Affairs of Denmark. SGM lead the implementation of the protocol in Tanzania while KR, and MSB lead implementation of the stepwise model. NEN co-lead the implementation in Iringa. BTM co-lead implementation of the TDM in Tanzania together with SH and JWA. All authors provided technical inputs in the proposal. SGM wrote the manuscript with input from all the authors. All authors have approved the final version and agreed to be accountable for all aspects of the work related to accuracy and integrity.

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DATA STATEMENT

The data sets that will be generated and analysed during the conduct of the study will be made available according to the available laws and regulations

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FIGURES LEGEND

Figure 1: The ADEPT model includes three essential domains. The performance domain is identified as integration of communicable and non-communicable diseases. For effective delivery of adaptive service, the performance domain requires support by the second and third domains called a stepwise training approach and learning systems. The stepwise training approach will ensure the frontline health care providers acquire knowledge and skills necessary for integrating communicable and NCDs. The learning system domain should be continuously operating by including processes like implementation research and clinical audits which serves as a system lens to continuously inform the operation of the performance domain. Information flow including clinical guidelines and new practices will go through the stepwise training approach. The three functioning domains create an adaptive service delivery model for the health system.

Figure 2: Logic framework model for measuring outcomes and impact

Figure 3: Hierarchy of needs for strengthening the health system as described by Potter & Brough[34]

Figure 4: Introduction of integration of TB/DM services thereafter stepwise introduction of packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM case management at all levels of health facilities

COMPETING INTEREST STATEMENT:

None declared.

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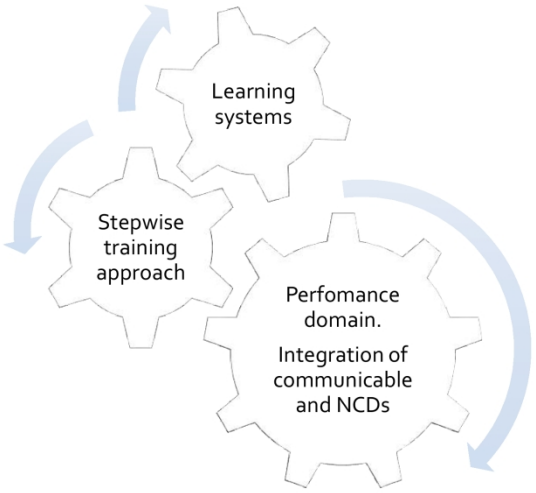

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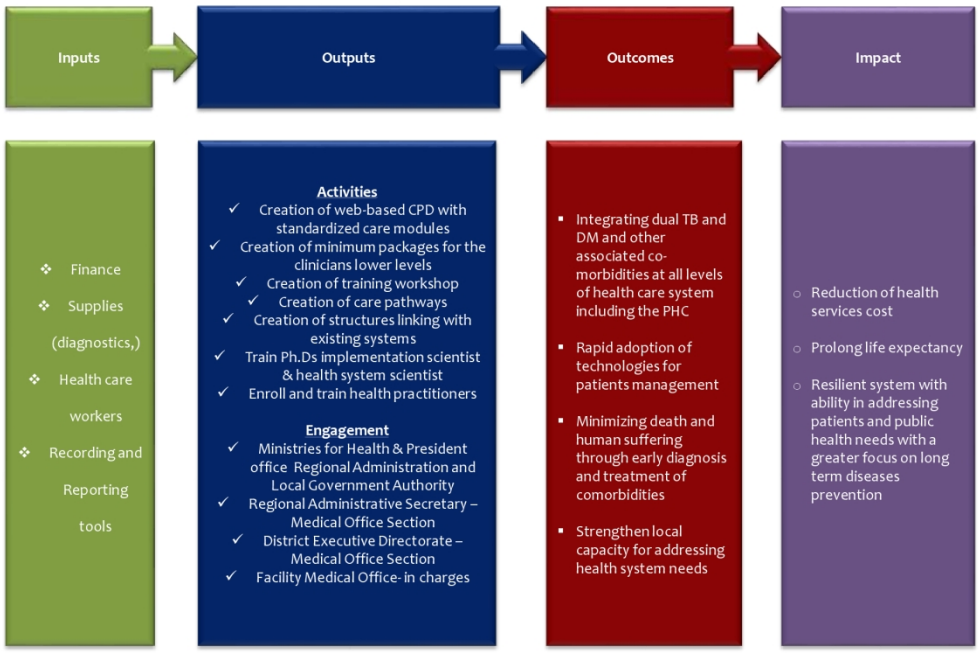

Logic framework model for measuring outcomes and impact

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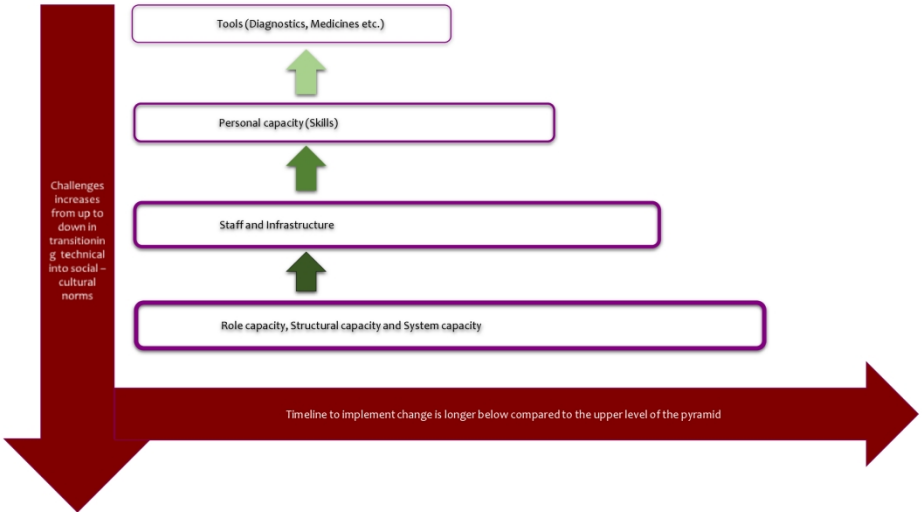

Hierarchy of needs for strengthening the health system as described by Potter & Brough34

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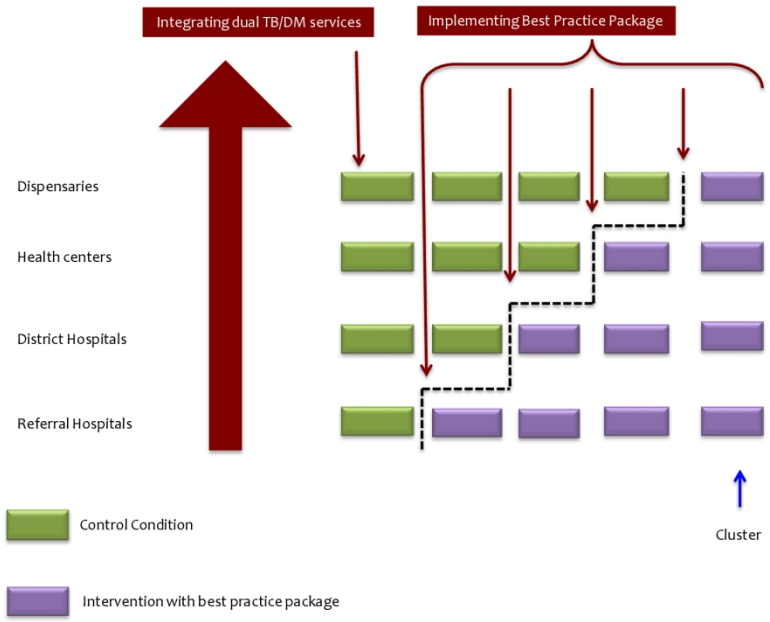

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