SUMMARY INFORMATION

Title: Identifying and addressing mental and physical multimorbidity in people with TB. Countries: Pakistan, Sudan & Tanzania Duration: 18 months Amount requested: £200K Seed-funding activities: Reviews, secondary data analysis, network development and capacity-building.

PROJECT DESCRIPTION

We focus on multimorbidity (including non-communicable diseases, mental disorders and chronic communicable diseases in people with TB ('TB multimorbidity'). Primary research question: How can we improve life expectancy and quality of life in people with TB multimorbidity?

Study design

We will conduct interlinking research, networking and capacity-building activities to: (i) define multimorbidity clusters that contribute the highest disease burden in people with TB, (ii) identify interventions to prevent, screen and manage non-communicable diseases (NCD), mental disorders and chronic communicable diseases (CCD), which can be integrated within TB programmes for patients in these clusters and (iii) build a network and strengthen capacity to plan a future research programme on TB multimorbidity. We will undertake 4 workstreams (WS):

WS1: Review of published literature and analysis of World Health Survey data to estimate prevalence, patterns, risk factors and disease burden associated with TB multimorbidity (months 0-10).

WS2: Review to identify candidate interventions to prevent, screen and treat the cluster(s) of diseases, which contribute most to TB multimorbidity disease burden (months 10-15).

WS3: Establish a global TB Multimorbidity Network (months 0-6 months), agree priority TB multimorbidity clusters (months 10-11) and collate an inventory of candidate interventions for a TB multimorbidity 'package' to be developed and evaluated in future work (15-18 months).

WS4: Build capacity in research, leadership, finance, governance and policy. (0-18 months)

To secure **community, patient and public involvement**, a **community panel** will be setup in one country in the first instance, meeting 3-monthly to advise on our plans and support dissemination.

For this preliminary work, we focus on three countries, Pakistan, Sudan and Tanzania that have a high TB disease burden, well-developed TB programmes, and contrasting levels of HIV, NCDs and health risk behaviours; and where the applicants have established collaborations with TB, HIV, mental health and NCD programmes.

We acknowledge this is an ambitious proposal, but these existing collaborations and our previous work undertaking related literature reviews,[1] secondary data analyses,[2] building networks and capacity in South Asia[3] and Africa,[4] mean that we can be confident about delivering it.

Outputs from this seed-funding work (evidence on clusters/interventions, a global TB Multimorbidity Network and strengthened capacity) will inform a **future research programme (**and associated capacity-building), to develop and evaluate a TB multimorbidity intervention package.

WS1: Systematic literature review and secondary data analysis (disease clusters)

Purpose: To estimate the prevalence, patterns and impact of NCD, mental illness and CCD multimorbidity in people with TB, including identifying clusters of diseases that contribute most to disease burden and their modifiable risk factors in low- and middle-income countries (LMIC).
Methods: We will do this by 1) evidence syntheses and 2) secondary data analysis.

1a) We will **conduct a meta-review**, identifying all previous systematic reviews and meta-analyses that have investigated *individual chronic conditions* in people with TB (reporting in accordance with PRISMA). The quality of systematic reviews will be summarised with the AMSTAR tool.
1b) We will **undertake a systematic review** of observational studies that have investigated *TB multimorbidity,* in accordance with MOOSE guidelines. For both reviews, major databases will be searched from inception for studies reporting on the prevalence, incidence or comparison of chronic conditions in people with TB, and control populations. We will extract data on the prevalence, incidence, risk and burden of chronic conditions in people with TB and controls, where possible identifying differences by gender and socio-economic group. For the meta-review, data will be summarised in an evidence map, to identify current knowledge of chronic conditions in TB and gaps in the evidence. For the systematic review of observational studies, if sufficiently homogeneous, we will conduct a meta-analysis calculating the pooled prevalence, incidence and comparative risk of

multimorbidity in people with TB and versus controls. Data on the burden, impact on quality of life and other outcomes from TB multimorbidity will be summarised in a narrative synthesis.

2) We will **conduct a secondary analysis of World Health Survey** (WHS) data on TB and nine long-term conditions across the 43 LMIC to investigate prevalence of TB multimorbidity and clustering of conditions, comparing these to general population controls and exploring differences by gender and socio-economic status. Data from the WHS are representative and open access.

In the three study countries, Pakistan, Sudan and Tanzania, we will also **scope out other potential sources of data** on the epidemiology of TB multimorbidity that could potentially be used in a future programme to identify disease clusters and estimate their prevalence, associations and impact, and for case finding in a trial. To identify data sources, we will ask experts including Bureaux of Statistics, WHO Country Offices and experts in our TB Multimorbidity Network. We will collect information on: data collection methods; access (permissions, costs); quality assurance; coverage (geographical/ population); inclusion of key demographic and health variables; and dates and frequency of updating. In our preparatory work, we have identified a few potentially useful datasets including healthcare databases, national surveys and observational studies. In Pakistan, these include diabetes measures for 80,000 patients with TB and the Khyber Pakhtunkhwa Integrated Population Survey of 22,000 individuals, which includes a wide range of CD, NCD and risk factor variables in addition to TB. Other potential sources include routine data on patients with multi-drug resistant TB including data on mental illness. In Sudan, Epi-Lab have access to several datasets including data from the Comprehensive Lung Health Project and Triage Plus,[5] covering chronic respiratory conditions, HIV and tobacco use in people with TB.

Outputs: Reviews and WHS analysis will provide a complete evidence map of knowledge of NCD, mental disorder and CCD prevalence, incidence, disease clusters, risk factors, burden and outcomes in people with TB and identify knowledge gaps. Exploration of other datasets may provide additional help in defining target clusters. Findings will inform the subsequent programme and direct the focus into key areas where there is the greatest TB multimorbidity burden.

WS2: Structured literature review (interventions)

Background: Interventions to address individual conditions comorbid with TB are described in the literature. Moreover, initiatives such as the 'WHO Package of Essential NCD interventions,'[6] WHO Mental Health GAP Action Programme (mhGAP)[7] and 'Disease Control Priorities 3'[8] describe evidence-based interventions to prevent, screen and manage common chronic conditions in low-resource settings (although not specifically for TB).

Purpose: To identify contents and modes of delivery and effectiveness of interventions to prevent, screen and treat chronic disease clusters in people with TB to inform the design of a 'TB multimorbidity intervention package'.

Methods: An Expert Reference Group, selected from the TB Multimorbidity Network (see WS3), will review outputs from WS1 and agree one or more priority clusters that contribute the greatest burden, considering feasibility of intervening and potential for impact. We will then undertake a structured review[9] of experimental and quasi-experimental studies, reviews and guidance describing and evaluating interventions aimed at improving outcomes in people with TB and these clusters of chronic conditions. We will search major databases and extract data on participants, settings, interventions, controls, outcomes and potential sources of biases. Intervention details and evidence of effectiveness and implementation will be summarised in a narrative synthesis, including information about modes of delivery and resources and health systems requirements.

Outputs: An inventory of candidate interventions for the TB multimorbidity care package, and information relevant to their integration and implementation in TB services. From this, a shortlist of interventions and their configuration will be agreed through an iterative process involving option appraisals and expert consensus development by the TB Multimorbidity Network (see WS3).

WS3: Building a TB Multimorbidity Network

We will establish a new TB Multimorbidity Network, bringing together members of existing networks and collaborations related to mental and physical multimorbidity, lung health and NCD (IMPACT https://www.york.ac.uk/healthsciences/research/mental-health/projects/impact/; IMPALA https://www.lstmed.ac.uk/impala; ASTRA https://www.york.ac.uk/healthsciences/research/public-health/projects/astra/) and those working on specific comorbidities such as TB and diabetes e.g. International Union against TB and Lung Diseases (The UNION).[10]

Purpose: Supporting development and delivery of research, dissemination, implementation and capacity-building activities during seed-funding and the future programme. The network will serve as a platform for future research partnerships and a vehicle for improving services and addressing TB multimorbidity knowledge gaps.

Core members will also serve as an Expert Reference Group (ERG) to help develop consensus on priority clusters and candidate interventions in this seed-funding work, and to identify data sources for secondary analysis, participate in intervention package design and advise on important outcomes and countries to include in a future programme. Membership will comprise our mental health, NCD and TB programme partners in South Asia and Africa, and will be interdisciplinary, including policymakers, managers, academics, clinicians and patient, public and community groups. The membership will be expanded via networking at conferences, and through an open invitation to groups with synergistic interests (via our GACD, GCRF and NIHR Global Health links).

Activities: We will hold an initiation meeting to agree programme plans and Network Terms of Reference, and two follow-up meetings (one via teleconference) over 18 months. The ERG will review outputs from WS1 and WS2 to develop consensus on the target disease cluster(s) and interventions for the TB multimorbidity package. Managed by an administrator, we will set up a Google group and shared folder, website and twitter handle. Members will co-produce a 6-monthly newsletter to share news of programme activities, events and outputs. To enhance sustainability, we will embed Network activities with those of our NIHR/GCRF groups, encouraging early career researchers to participate in (and lead) networking activities, contributing to building their capacity. We will also seek funding e.g. GCRF Impact Development awards to support Network activities.

Outputs: Success indicators will be a diverse membership (geography, sector, discipline), established ERG, website and social media usage metrics, newsletters/ meetings held as planned, joint funding applications and co-authored publications.

WS4: Building capacity

Purpose: Following the principles of the Essence Framework,[11] our capacity-building activities will address assessed individual and organisational capacity gaps, harnessing our assets (both the research team's and TB Multimorbidity Network's) in order to: position LMIC investigators to lead the future research programme and promote engagement between academics and policymakers.

Activities: We will strengthen research, research leadership and finance governance capabilities through a mix of experiential learning and training. Early career researchers will be supervised and assigned a mentor to help develop skills (through participation in WS 1-3) in literature review, meta-analysis, academic writing and publication. Research leadership capacity will be strengthened through mentoring and a bespoke leadership training programme for Co-Is. We will support LMIC partner organisations to meet the African Academy of Sciences Good Financial Grants Practice standards for management of research funds, with a baseline self-assessment, followed by tailored support to achieve standards and provide assurance required to act as a grantee (Silver tier). York's Research Grants and Contracts (RGC) office has a wealth of expertise and will share their policies and procedures. Participation in the TB Multimorbidity Network will help develop networking skills. Finally, we will set up a **'Research-Policy Forum'** in each country, innovative in bringing together researchers and policymakers responsible for different sectors of mental and physical health to support joint policymaking across sectors.

Outputs: Strengthened capacity in research, research leadership, finance governance, networking and evidence-based policymaking, evidenced by changes in capacity metrics by 18 months.

Future programme

Work completed with this seed-funding will help refine our plans for a future programme. Following the MRC framework for complex interventions, we will develop and evaluate an integrated package of care designed to prevent, detect and treat multimorbidity, and improve outcomes (including TB outcomes) in people with TB. We will also investigate the outcomes of TB multimorbidity by exploiting existing datasets (where possible) and/or in a cohort study in 3-4 LMICs chosen to reflect diversity in TB multimorbidity clusters and health systems. Further growth of capacity in research, research leadership and research governance will also be integrated within the programme.

IMPACT AND IMPORTANCE

Multimorbidity, a norm in patients with chronic diseases,[12] is largely neglected in traditional, typically single-disease focused health services and programmes.[13] The need to address multimorbidity through effective, integrated and scalable healthcare interventions is well documented.[14] Our

proposal focuses on multimorbidity in patients where one of these chronic conditions is TB because:[15] (a) the **adverse interactions** between TB and many other chronic conditions enhance vulnerability at the individual, and sustain these epidemics at the population level, and (b) the **synergies** between chronic infections such as TB and other CCD (e.g. HIV, hepatitis) NCD (e.g. diabetes, lung disease, depression) demand effective integrated models to prevent, screen and treat these conditions. The likely high disease burden due to these adverse interactions and the potential health gains through these synergies makes patients with TB multimorbidity a high priority.

The bidirectional adverse interactions between TB and NCD (including mental illnesses) and other CCD are life-limiting. Chronic conditions and their risk factors have a substantial influence on the TB epidemic in high-burden countries.[16] Diabetes increases the risk of developing active TB three-fold; in countries with high burden of both TB and diabetes (e.g. India), almost half of all people with TB may have diabetes or pre-diabetes.[17] Patients with TB and diabetes are less likely to respond to treatment and are at higher risk of multi-drug resistant TB.[18] The global diabetes epidemic impedes achievement of Global End TB Targets; better diabetes prevention and control could avert more than a million TB deaths in 13 high-burden countries by 2035.[19] Mental disorders and TB share many common determinants and risk factors;[20][21] 1 in 4 people with TB has depression, adversely affecting adherence to treatment and recovery.[2] Other examples of TB and NCD multimorbidity include a higher risk of TB in chronic kidney disease[22] and TB being a risk factor for developing and progressing chronic lung[23] and cardiovascular diseases.[24] Almost 1 in 6 people with TB also has HIV infection; HIV increases the risk of acquiring TB by 20- to 40-fold.[25] Presence of TB worsens HIV outcomes.[26] The epidemic increases in HIV/AIDS between 1990-2005 led to a five-fold increase in TB incidence in sub-Saharan Africa.[15]

The links between TB and other CCDs and NCDs offer opportunities to investigate integrated and efficient approaches to prevent, screen and manage multimorbidities in high-TB burden countries.[15] Our focus on TB programmes (a typically vertical approach) in high burden countries will allow us to examine how they can be adapted to address multimorbidity (overlooked in the past) without sacrificing recent gains. TB programmes are also a good 'proving ground' to develop and test approaches to multimorbidity because: (a) they engage with individuals over a sustained period offering numerous opportunities to prevent, screen and manage other conditions or modifiable risk factors; (b) their (relatively) strong and well-resourced infrastructure can provide a platform for (what will inevitably be) complex interventions to address multimorbidity; (c) there is wide recognition of need and strong global and national policy support to address TB multimorbidity (e.g. WHO's '*End TB Strategy,*' Stop TB Partnership's '*The Paradigm Shift: Global Plan to End TB 2016-2020*' and the '*Global Fund Support for Co-infections and Co-morbidities*'[27]), and (d) there are existing frameworks for integration,[28] approaches (case-detection activities)[29] and effective interventions.[30][6][7]

We therefore, aim to investigate how to improve outcomes in TB multimorbidity in a targeted, integrated and cost-effective manner in high TB burden countries. Not only may this improve outcomes in individual patients with chronic conditions (including TB)[29] but also halt the bidirectional fuelling between CCD and NCD epidemics at a population level. Overall, our proposed work has the potential to improve health, mortality and also provide economic benefits- improving productivity, and reducing poverty and healthcare costs.

RESEARCH TEAM

Strength of the team: Our interdisciplinary team brings together the research and clinical expertise, as well as in-depth country and health systems knowledge required to conduct this and the planned longer-term programme. A strength is our close alignment with the IMPACT Group - a NIHR-funded global health Group on Mental and Physical Multimorbidity - and our links with a range of networks across Asia and Africa which span chronic communicable, non-communicable and mental health conditions. **N Siddiqi** (joint-PI), the co-director of IMPACT has expertise in mental and physical multimorbidity and is CI of several NIHR-funded studies on diabetes and mental Illness. She offers an in-depth understanding of the needs of those with mental and physical ill-health. **Elsey** (joint PI) has led several large studies on MDR TB and mental health (DFID), urban health (GCRF), TB and tobacco (EUH2020); her expertise includes intervention development and systematic reviews. The joint PIs' have complementary backgrounds (liaison psychiatry/public health), methodological expertise (quantitative and trials/mixed and participatory methods) and global South networks.

K Siddiqi, an expert in tobacco and lung health and trials in LMIC, will link the TB Multimorbidity Network with several global networks: respiratory diseases (Global Health Respiratory Network - a

meta-network of nine NIHR-funded Groups and Units in Asia and Africa); NCD (Global Alliance for Chronic Diseases); TB (EU-funded TB and Tobacco consortium in S Asia) and tobacco (ASTRA - NIHR-funded global health Group in S Asia and TCCP - GCRF-funded capacity building programme in Asia and Africa). **Stubbs** has extensive expertise in evidence synthesis and analysis of large data with a focus on mental and physical comorbidities (including TB) and global health.

Our proposal is also supported by IMPALA, the NIHR-funded Unit addressing TB and lung health, which brings together partners from nine African countries (two are co-Is: EPILab in Sudan led by **ElSony** and NIMR Mbeya Medical Research Centre in Tanzania led by **Ntinginya**. CoIs **Tolhurst** and **Egere** (LSTM) in the IMPALA hub will help encourage other African partners to join the Network and future research.

The team in Pakistan includes Co-I **ul-Haq** (KMU); he brings detailed knowledge of multi-morbidities in Pakistan and has led large-scale research programmes working closely with the public and private health sectors. As the ex-director of WHO EMRO, **S Siddiqi** (AKU) has extensive experience in health systems and policy work in the region. He will link the TB Multimorbidities Network to his extensive contacts in WHO. **Fatima**, the Director of Research within Pakistan's National TB programme is well placed to ensure the TB multimorbidity package can be delivered within TB services. She has worked closely with K Siddiqi and Elsey and was successful in taking research findings into policy. As the head of TB section in the UNION, she will help address TB multimorbidity at the highest level. **Nizami** is the Director, WHO collaborating centre for mental health and Institute of Psychiatry in Rawalpindi. With his extensive service, policy and academic links, he is well placed to advise on and help deliver the proposed research activities and help extend the Network's national and regional (South Asian) influence. Host organisation: The University of York has well-established finance, due-diligence, research governance and administrative systems and is experienced in supporting multi-disciplinary and multi-country research programmes. The York Trials Unit (YTU) has conducted many trials in LMICs and has sound procedures to support partners to implement high quality trials. **Torgerson's** (YTU Director) early engagement will guide information gathering and ensure that future plans to evaluate effectiveness are appropriate. Equitable partnerships and team working: An underlying principle of our project is developing and maintaining equitable partnership. We will do this through transparent management structures, joint decision-making, shared leadership, regular communications and partners' control over their own resources. Members of the applicant team have a track record of working together effectively within several consortiums e.g. IMPACT, ARISE and TB & Tobacco.

PROJECT PARTNERS

As members of a TB Multimorbidity Network, our partners will share their expertise, knowledge and collaborations to support the programme. Partners represent diverse constituencies: countries /regions, Govt. and NGO sectors, health services/programmes, clinical specialities and disciplines.

The **UNION** (Yan Lin, Senior Advisor and TB/diabetes expert) will use his global office holders and members to advocate for and help deliver the TB multimorbidity programme and join the ERG.

The **NIHR IMPALA** Unit, with 20 TB and lung health organisations in 9 African countries, will share knowledge and expertise and contacts and host one of the Network meetings.

Common Management Unit, TB, HIV/AIDS, malaria, Pakistan (Achakzai, HIV Programme Manager), will be on the ERG, help explore datasets and contribute knowledge on HIV-related disease clustering. **National Diabetes Task Force** and **Pakistan Endocrine Society** and **Pakistan Psychiatric Society** (Aamir and Mukhtar) will bring links with national NCD and mental health professional bodies to support the Network. **ARK Foundation (**Huque, Director) and **HERD International,** (Baral, Director), two leading NGOs in TB control will explore scope for extending this work in Bangladesh and Nepal respectively. **Centre for Injury Prevention Research, Bangladesh (**Saidur, Director) will contribute NCD expertise within the Network as ERG member.

Global Public Health Division, Public Health England (Walker, Consultant) will bring expertise on mental health and TB and PHE support.

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