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## Enhancing early tuberculosis detection in Kwazulu Natal An annotated bibliography

### TASK

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This annotated bibliography has been prepared for the Kwazulu-Natal Department of Health, as a first stage in further discussions towards a rapid evidence synthesis.

### COMMISSIONERS

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### SYNTHESIS TEAM

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### Rapid review requested

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*In Kwazulu-Natal, why is the detection of new TB cases decreasing annually, while there is still a high rate of HIV and there is a huge death rate related to TB?*

### Problem as identified by the knowledge user

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*Kwazulu-Natal has a high TB prevalence rate. Additionally, the province has a high rate of HIV. This leads to disability and a huge death rate related to TB. The Kwazulu-Natal Department of Health has implemented a number of interventions to actively identify persons who have early TB, so that they may be initiated onto treatment quickly, and early on in the active stage of their infection. However, these interventions are failing to identify persons who have early active TB infections.*

## Background

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KwaZulu-Natal has the one of the highest TB prevalence rates in South Africa, as well as high HIV prevalence and incidence rates. Thus, the TB/HIV co-infection rate is also high. One of the biggest factors contributing to complication and death from TB, is delayed diagnosis and treatment of the disease.

To better manage TB and reduce the morbidity and mortality caused by the disease, the Kwazulu-Natal Department of Health has put into place interventions that are aimed at finding early active TB, as a way of achieving timely diagnoses and treatment. While laboratory testing of sputum provides definitive diagnostic results, such testing is time consuming and costly, and cannot be conducted for everyone in the province. Thus the Kwazulu-Natal Department of Health has implemented risk assessment interventions, so as to identify those people who are likely to have early active TB, and therefore should have their sputum tested. These interventions include the use of lay/community health workers to conduct TB mass screening in communities, assessing every patient attending primary health care clinics, before they proceed to the consulting room. Furthermore, contact tracing is conducted for patients who test positive for TB. The risk assessment interview, conducted by lay/community health workers and facility health workers, consists of six questions associated with early active TB. When a patient answers yes to one of the risk assessment questions, their sputum is collected and sent to the national laboratory lab for testing. According to Ester Synman (Department of Health, Strategic Planner), this method has been validated. Furthermore, lay/community health workers and facility based health workers, have been trained in the proper conduct of the risk assessment interview, as well as how to correctly collect and handle sputum after this risk assessment. Yet despite these interventions, few cases of patients with early active TB are being found through the laboratory diagnostic tests. Thus the province continues to have low treatment rates (or few people with active TB on treatment), and high mortality due to TB as well as TB/HIV co-infections.

## State of the art series – Active case finding/screening

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Borgdorff, M. W., et al. (2013). "Active tuberculosis case finding: why, when and how? [Editorial]." *The International Journal of Tuberculosis and Lung Disease* **17**(3): 285-285.

Lönnroth, K., et al. (2013). "Systematic screening for active tuberculosis: rationale, definitions and key considerations [State of the art series. Active case finding/screening. Number 1 in the series]." *The International Journal of Tuberculosis and Lung Disease* **17**(3): 289-298.

The impact of current interventions to improve early detection of tuberculosis (TB) seems to have been saturated. Case detection trends have stagnated. TB incidence is falling in most settings worldwide, but the rate of decline is far lower than expected. There is growing evidence from national TB prevalence surveys and other research of a large pool of undetected TB in the community. Intensified efforts to further break down access barriers and scale up new and rapid diagnostic tools are likely to improve the situation. However, will these be enough? Or do we also need to reach out more towards people who do not actively seek care with well-recognisable TB symptoms? There have recently been calls to revisit TB screening, particularly in high-risk groups. The World Health Organization (WHO) recommends screening for TB in people with human immunodeficiency virus infection and in close TB contacts. Should

other risk groups also be screened systematically? Could mass, community-wide screening, which the WHO has discouraged over the past four decades, be of benefit in some situations? If so, what screening tools and approaches should be used? The WHO is in the process of seeking answers to these questions and developing guidelines on systematic screening for active TB. In this article, we present the rationale, definitions and key considerations underpinning this process.

Kranzer, K., et al. (2013). "The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review [State of the art series. Case finding/screening. Number 2 in the series]." The International Journal of Tuberculosis and Lung Disease **17**(4): 432-446.

**BACKGROUND:** Screening for tuberculosis (TB) disease aims to improve early TB case detection. The ultimate goal is to improve outcomes for people with TB and to reduce *Mycobacterium tuberculosis* transmission in the community through improved case detection, reduction in diagnostic delays and early treatment. Before screening programmes are recommended, evidence is needed of individual and/or community-level benefits.

**METHODS:** We conducted a systematic review of the literature to assess the evidence that screening for TB disease 1) initially increases the number of TB cases initiated on anti-tuberculosis treatment, 2) identifies cases earlier in the course of disease, 3) reduces mortality and morbidity, and 4) impacts on TB epidemiology.

**RESULTS:** A total of 28 798 publications were identified by the search strategy: 27 087 were excluded on initial screening and 1749 on full text review, leaving 62 publications that addressed at least one of the study questions. Screening increases the number of cases found in the short term. In many settings, more than half of the prevalent TB cases in the community remain undiagnosed. Screening tends to find cases earlier and with less severe disease, but this may be attributed to case-finding studies using more sensitive diagnostic methods than routine programmes. Treatment outcomes among people identified through screening are similar to outcomes among those identified through passive case finding. Current studies provide insufficient evidence to show that active screening for TB disease impacts on TB epidemiology.

**CONCLUSION:** Individual and community-level benefits from active screening for TB disease remain uncertain. So far, the benefits of earlier diagnosis on patient outcomes and transmission have not been established.

Zenner, D., et al. (2013). "Active case finding for tuberculosis among high-risk groups in low-incidence countries [State of the art series. Case finding/screening. Number 3 in the series]." The International Journal of Tuberculosis and Lung Disease **17**(5): 573-582.

In low-incidence countries, tuberculosis (TB) is now largely concentrated in high-risk groups such as migrants, homeless people, illicit drug users, alcoholics and prisoners. This has led to increased efforts to implement targeted active case finding for TB among specific populations. This review examines the evidence supporting active case finding in migrants and social risk groups, as well as the cost-effectiveness of interventions. While data from observational studies support active case finding in defined high-risk groups, further research to determine the effectiveness of specific tools and the cost-effectiveness of screening strategies is needed to inform evidence-based control methods in low-incidence countries. Inevitably, addressing TB in low-incidence countries will depend on effective disease control in high-burden countries.

Golub, J. E. and D. W. Dowdy (2013). "Screening for active tuberculosis: methodological challenges in implementation and evaluation [State of the art series. Active case finding/screening. Number 4 in the series]." The International Journal of Tuberculosis and Lung Disease **17**(6): 673-682.

series]." The International Journal of Tuberculosis and Lung Disease **17**(7): 856-865.

As active screening strategies for tuberculosis (TB) continue to rise globally, it has become increasingly important to consider the methodological challenges in designing and implementing these strategies. The key challenges associated with TB screening can be summarized in terms of four continua or spectra, namely those of 1) TB disease and diagnostic yield, 2) TB risk and resource availability, 3) TB screening strategies, and 4) outcomes and impact measurements of screening programs. In this review, we provide a discussion of these challenges to help guide development of TB screening strategies that will be effective in a given epidemiological setting.

Corbett, E. L. and P. MacPherson (2013). "Tuberculosis screening in high human immunodeficiency virus prevalence settings: turning promise into reality [State of the art series. Active case finding/screening. Number 5 in the series]." The International Journal of Tuberculosis and Lung Disease **17**(9): 1125-1138.

Twenty years of sky-high tuberculosis (TB) incidence rates and high TB mortality in high human immunodeficiency virus (HIV) prevalence countries have so far not been matched by the same magnitude or breadth of responses as seen in malaria or HIV programmes. Instead, recommendations have been narrowly focused on people presenting to health facilities for investigation of TB symptoms, or for HIV testing and care. However, despite the recent major investment and scale-up of TB and HIV services, undiagnosed TB remains highly prevalent at community level, implying that diagnosis of TB remains slow and incomplete. This maintains high transmission rates and exposes people living with HIV to high rates of morbidity and mortality.

More intensive use of TB screening, with broader definitions of target populations, expanded indications for screening both inside and outside of health facilities, and appropriate selection of new diagnostic tools, offers the prospect of rapidly improving population-level control of TB. Diagnostic accuracy of suitable (high throughput) algorithms remains the major barrier to realising this goal.

In the present study, we review the evidence available to guide expanded TB screening in HIV-prevalent settings, ideally through combined TB-HIV interventions that provide screening for both TB and HIV, and maximise entry to HIV and TB care and prevention. Ideally, we would systematically test, treat and prevent TB and HIV comprehensively, offering both TB and HIV screening to all health facility attendees, TB households and all adults in the highest risk communities. However, we are still held back by inadequate diagnostics, financing and paucity of population-impact data. Relevant contemporary research showing the high need for potential gains, and pitfalls from expanded and intensified TB screening in high HIV prevalence settings are discussed in this review.

Uplekar, M., et al. (2013). "Programmatic approaches to screening for active tuberculosis [State of the art series. Active case finding/screening. Number 6 in the series]." The International Journal of Tuberculosis and Lung Disease **17**(10): 1248-1256.

Passive case finding, the detection of tuberculosis (TB) cases among persons presenting to health facilities with symptoms suggestive of TB, has remained the principal public health approach for TB diagnosis. While this approach, in combination with improved treatment, has led to substantial global progress, the overall epidemiological impact has been inadequate. Stagnating case notifications and sluggish decline in incidence prompt the pursuit of a more active approach to TB case detection. Screening among contacts of TB patients and people living with human immunodeficiency virus infection, long recommended, needs scaling up. Screening in other risk groups may also be considered, depending on the epidemiological situation. The

World Health Organization (WHO) has recently produced recommendations on systematic screening for active TB, which set out principles and provide guidance on the prioritisation of risk groups for screening and choice of screening and diagnostic algorithms. With a view to help translate WHO recommendations into practice, this concluding article of the State of the Art series discusses programmatic approaches. Published literature is scanty. However, considerable field experience exists to draw important lessons. Cautioning against a hasty pursuit of active case finding, the article stresses that programmatic implementation of TB screening requires a systematic approach. Important considerations should include setting clear goals and objectives based on a thorough assessment of the situation; considering the place of TB screening in the overall approach to enhancing TB detection; identifying and prioritising risk groups; choosing appropriate screening and diagnostic algorithms; and pursuing setting-specific implementation strategies with engagement of relevant partners, due attention to ethical considerations and built-in monitoring and evaluation.

## Systematic and literature reviews on tuberculosis detection

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Cheon, S. A., et al. (2016). "Recent tuberculosis diagnosis toward the end TB strategy." Journal of Microbiological Methods **123**(Supplement C): 51-61.

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis*. Despite global TB eradication efforts, it is still a global public health concern, especially in low- and middle-income countries. Most of the active TB infections are curable with early diagnosis and appropriate treatment, but drug-resistant TB is difficult and expensive to treat in immunocompetent as well as immunocompromised individuals. Thus, rapid, economic, and accurate point-of-care tools for TB diagnosis are required urgently. This review describes the history of *M. tuberculosis* detection methods up to date and the recent advances using nanotechnology for point-of-care testing of TB diagnosis.

Fox, G. J., et al. (2011). "Active case finding in contacts of people with tuberculosis." Cochrane Database of Systematic Reviews(9).

**BACKGROUND:** Tuberculosis is a major global health challenge that is caused by a bacteria which is spread by airborne droplets. Mostly patients are identified in high-burden countries when they visit health care facilities ('passive case finding'). Contacts of tuberculosis patients are a high-risk group for developing the disease. Actively screening contacts of people with confirmed tuberculosis may improve case detection rates and control of the disease.

**Objectives:** This study aims to compare whether active case finding among contacts of people with confirmed tuberculosis increases case detection compared to usual practice.

**SEARCH METHODS:** In April 2011 we searched CENTRAL (The Cochrane Library 2011, Issue 2), MEDLINE, EMBASE, LILACS and mRCT. We also checked article reference lists, the International Journal of Tuberculosis and Lung Disease and contacted relevant researchers and organizations. **Selection criteria:** Randomized and quasi-randomized trials of active case finding to detect tuberculosis disease among close and casual contacts of patients with microbiologically proven pulmonary tuberculosis (by sputum smear and/or culture).

**Data collection and analysis:** Two authors independently assessed eligibility and the methodological quality of the trials that were extracted using a search method that was outlined

previously.

**MAIN RESULTS:** No trials met the inclusion criteria for this review. One RCT did test the effect of active case finding in contacts, but the intervention in that trial also included screening for, and treatment of, LTBI in contacts; and the separate effect of active case finding could not be estimated. **Authors' conclusions:** There are currently insufficient data from randomized controlled trials or quasi-randomized controlled trials to evaluate the effect of active case finding for tuberculosis among contacts of patients with confirmed disease. While observational studies show that contacts have a higher risk of developing tuberculosis than the general population, further research is needed to determine whether active case finding among contacts significantly increases case detection rates.

McNerney, R., et al. (2015). "New tuberculosis diagnostics and rollout." *Int J Infect Dis* **32**(Supplement C): 81-86.

Early detection and effective treatment are crucial for tuberculosis control, but global case detection rates remain low. The diagnosis of paediatric and extrapulmonary disease is problematic and there are, as yet, no rapid screening tests to assist active case finding in the community. Progress has been made in clinic-based detection tools with the introduction of Xpert MTB/RIF, a nucleic acid amplification test that combines sample processing and analysis in a single instrument to provide a diagnostic result and detection of resistance to rifampicin in under 2h. Enthusiasm for Xpert MTB/RIF has been high and global rollout has been facilitated by donor agencies. However, concerns remain about access and sustainability due to the high cost and infrastructure requirements. Although more sensitive than smear microscopy, early studies suggest the impact of the new test on case detection rates and patient survival has been limited. Alternative technologies are being developed, including non-sputum-based tests to assist the detection of extrapulmonary disease. Evaluation studies are needed to provide evidence of the impact of the new technologies on patient outcomes. This will enable appropriate placement of new diagnostic products in the healthcare system to support the control and eventual eradication of tuberculosis disease.

Musa, B. M., et al. (2014). "Systematic review and metanalysis on community based interventions in tuberculosis care in developing countries." *Niger J Med* **23**(2): 103-117.

**Note:** Full text for this article has not been found. May not exist.

**BACKGROUND:** We aimed to evaluate the effectiveness of Lay Health Workers (LHW) in increasing case detection rate and treatment success outcome of Tuberculosis cases  
**METHODS:** PUBMED,; Google scholar, African Journal Online (AJOL) and other search engines were systematically searched, for literature from 2000 to 2012 for studies that are either: [randomized/cluster randomized/non randomized or prospective cohort study]; assessing lay Health care worker participation in tuberculosis (TB) treatment, using the key words (LHW, TB and treatment). Studies were pooled using a random effect model. Of the thirteen studies that fulfilled the inclusion criteria for systemic review, only five were heterogeneous enough for a meta-analysis.

**RESULTS:** There was a marginal effectiveness of LHW involvement in TB treatment success rate, RR 1.09 Confidence Interval. [0.98-1.21]. There was no publication bias; with {p = 0.135 for Eggar's weighed regression analysis}. Restrictive analysis showed a marginally higher summary relative risk in rural based studies RR 1.12, C.I. [1.01-1.24]; compared to urban studies RR 1.01, C.I. [0.91-1.13].

**CONCLUSION:** The use of Lay Health care workers is associated with a marginal benefit in

improving TB treatment success compared to standard facility based TB care. Larger studies are needed to properly prove its superiority.

Yan, L., et al. (2016). "Systematic review: Comparison of Xpert MTB/RIF, LAMP and SAT methods for the diagnosis of pulmonary tuberculosis." *Tuberculosis* **96**(Supplement C): 75-86.

Summary Technological advances in nucleic acid amplification have led to breakthroughs in the early detection of PTB compared to traditional sputum smear tests. The sensitivity and specificity of loop-mediated isothermal amplification (LAMP), simultaneous amplification testing (SAT), and Xpert MTB/RIF for the diagnosis of pulmonary tuberculosis were evaluated. A critical review of previous studies of LAMP, SAT, and Xpert MTB/RIF for the diagnosis of pulmonary tuberculosis that used laboratory culturing as the reference method was carried out together with a meta-analysis. In 25 previous studies, the pooled sensitivity and specificity of the diagnosis of tuberculosis were 93% and 94% for LAMP, 96% and 88% for SAT, and 89% and 98% for Xpert MTB/RIF. The I<sup>2</sup> values for the pooled data were >80%, indicating significant heterogeneity. In the smear-positive subgroup analysis of LAMP, the sensitivity increased from 93% to 98% (I<sup>2</sup> = 2.6%), and specificity was 68% (I<sup>2</sup> = 38.4%). In the HIV-infected subgroup analysis of Xpert MTB/RIF, the pooled sensitivity and specificity were 79% (I<sup>2</sup> = 72.9%) and 99% (I<sup>2</sup> = 64.4%). In the HIV-negative subgroup analysis for Xpert MTB/RIF, the pooled sensitivity and specificity were 72% (I<sup>2</sup> = 49.6%) and 99% (I<sup>2</sup> = 64.5%). LAMP, SAT and Xpert MTB/RIF had comparably high levels of sensitivity and specificity for the diagnosis of tuberculosis. The diagnostic sensitivity and specificity of three methods were similar, with LAMP being highly sensitive for the diagnosis of smear-positive PTB. The cost effectiveness of LAMP and SAT make them particularly suitable tests for diagnosing PTB in developing countries.

## Relevant South African studies

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McCarthy, K. M., et al. (2016). "Implementation and Operational Research: What Happens After a Negative Test for Tuberculosis? Evaluating Adherence to TB Diagnostic Algorithms in South African Primary Health Clinics." *JAIDS Journal of Acquired Immune Deficiency Syndromes* **71**(5): e119-e126.

INTRODUCTION AND BACKGROUND: Diagnostic tests for tuberculosis (TB) using sputum have suboptimal sensitivity among HIV-positive persons. We assessed health care worker adherence to TB diagnostic algorithms after negative sputum test results.

METHODS: The XTEND (Xpert for TB—Evaluating a New Diagnostic) trial compared outcomes among people tested for TB in primary care clinics using Xpert MTB/RIF vs. smear microscopy as the initial test. We analyzed data from XTEND participants who were HIV positive or HIV status unknown, whose initial sputum Xpert MTB/RIF or microscopy result was negative. If chest radiography, sputum culture, or hospital referral took place, the algorithm for TB diagnosis was considered followed. Analysis of intervention (Xpert MTB/RIF) effect on algorithm adherence used methods for cluster-randomized trials with small number of clusters.

RESULTS: Among 4037 XTEND participants with initial negative test results, 2155 (53%) reported being or testing HIV positive and 540 (14%) had unknown HIV status. Among 2155 HIV-positive participants [684 (32%) male, mean age 37 years (range, 18–79 years)], there was evidence of algorithm adherence among 515 (24%). Adherence was less likely among persons tested initially with Xpert MTB/RIF vs. smear [14% (142/1031) vs. 32% (364/1122), adjusted risk ratio 0.34 (95%

CI: 0.17 to 0.65)] and for participants with unknown vs. positive HIV status [59/540 (11%) vs. 507/2155 (24%)].

**CONCLUSIONS:** We observed poorer adherence to TB diagnostic algorithms among HIV-positive persons tested initially with Xpert MTB/RIF vs. microscopy. Poor adherence to TB diagnostic algorithms and incomplete coverage of HIV testing represents a missed opportunity to diagnose TB and HIV, and may contribute to TB mortality.

Mohr, E., et al. (2017). "Missed opportunities for earlier diagnosis of rifampicin-resistant tuberculosis despite access to Xpert(R) MTB/RIF." *Int J Tuberc Lung Dis* **21**(10): 1100-1105.

**OBJECTIVE:** To assess the proportion of rifampicin-resistant tuberculosis (RR-TB) patients with potential earlier RR-TB diagnoses in Khayelitsha, South Africa.

**DESIGN:** We conducted a retrospective analysis among RR-TB patients diagnosed from 2012 to 2014. Patients were considered to have missed opportunities for earlier diagnosis if 1) they were incorrectly screened according to the Western Cape diagnostic algorithm; 2) the first specimen was not tested using Xpert(R) MTB/RIF; 3) no specimen was ever tested; or 4) the initial Xpert test showed a negative result, but no subsequent specimen was sent for follow-up testing in human immunodeficiency virus-positive patients.

**RESULTS:** Among 543 patients, 386 (71%) were diagnosed with Xpert and 112 (21%) had had at least one presentation at a health care facility within the 6 months before the presentation at which RR-TB was diagnosed. Overall, 95/543 (18%) patients were screened incorrectly at some point: 48 at diagnostic presentation only, 38 at previous presentation only, and 9 at both previous and diagnostic presentations.

**CONCLUSIONS:** These data show that a significant proportion of RR-TB patients might have been diagnosed earlier, and suggest that case detection could be improved if diagnostic algorithms were followed more closely. Further training and monitoring is required to ensure the greatest benefit from universal Xpert implementation.

Podewils, L. J., et al. (2015). "Completeness and Reliability of the Republic of South Africa National Tuberculosis (TB) Surveillance System." *BMC Public Health* **15**(1): 765.

**BACKGROUND:** Accurate surveillance data are paramount to effective TB control. The Republic of South Africa's National TB Control Program (NTP) has conducted TB surveillance since 1995 and adopted the Electronic TB Register (ETR) in 2005. This evaluation aimed to determine the completeness and reliability of data in the Republic of South Africa's TB Surveillance System.

**METHODS:** Three of nine provinces, three subdistricts per province, and 54 health facilities were selected by stratified random sampling. At each facility, 30 (or all if <30) patients diagnosed in Quarter 1 2009 were randomly selected for review. Patient information was evaluated across two paper and four electronic sources. Completeness of program indicators between paper and electronic sources was compared with chi-square tests. The kappa statistic was used to evaluate agreement of values.

**RESULTS:** Over one-third (33.7 %) of all persons with presumptive TB recorded as smear positive in the TB Suspect Register did not have any records documenting notification, treatment, or management for TB disease. Of 1339 persons with a record as a TB patient at the facility, 1077 (80 %) were recorded in all data sources. Over 98 % of records contained complete age and sex data. Completeness varied for HIV status (53-86 %;  $p < 0.001$ ) and DOT during the intensive phase of treatment (17-54 %;  $p < 0.001$ ). Agreement for sex was excellent across sources (kappa 0.94); moderate for patient type (0.78), treatment regimen (0.79), treatment outcome (0.71); and poor for HIV status (0.33).



**CONCLUSIONS:** The current evaluation revealed that one-third of persons diagnosed with TB disease may not have been notified of their disease or initiated on treatment ('initial defaulters'). The ETR is not capturing all TB patients. Further, among patients with a TB record, completeness and reliability of information in the TB Surveillance System is inconsistent across data sources. Actions are urgently needed to ensure that all diagnosed patients are treated and managed and improve the integrity of surveillance information.

## Additional study that may be of interest

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Mauch, V., et al. (2013). "Free tuberculosis diagnosis and treatment are not enough: patient cost evidence from three continents." The International Journal of Tuberculosis and Lung Disease **17**(3): 381-387.

**SETTING:** The National Tuberculosis Programs of Ghana, Viet Nam and the Dominican Republic.  
**OBJECTIVE:** To assess the direct and indirect costs of tuberculosis (TB) diagnosis and treatment for patients and households.

**DESIGN:** Each country translated and adapted a structured questionnaire, the Tool to Estimate Patients' Costs. A random sample of new adult patients treated for at least 1 month was interviewed in all three countries.

**RESULTS:** Across the countries, 27-70% of patients stopped working and experienced reduced income, 5-37% sold property and 17-47% borrowed money due to TB. Hospitalisation costs (US\$42-118) and additional food items formed the largest part of direct costs during treatment. Average total patient costs (US\$538-1268) were equivalent to approximately 1 year of individual income.

**CONCLUSION:** We observed similar patterns and challenges of TB-related costs for patients across the three countries. We advocate for global, united action for TB patients to be included under social protection schemes and for national TB programmes to improve equitable access to care.

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