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Accelerating the End of TB:

Field Research from

Management Sciences for Health: 2008–2024

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Management Sciences *for* Health

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Management Sciences for Health (MSH)

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Dear Colleagues,

The Global tuberculosis report 2024 recently released by the World Health Organization (WHO) shows mixed progress in the fight against the disease. In 2023, nearly 8.2 million people were newly diagnosed with tuberculosis (TB), marking the highest number since 1995. Access to TB diagnosis and treatment has improved, but challenges remain. Additionally, limited access to rapid molecular diagnostic tests is an important barrier globally.

Although the number of TB-related deaths decreased in 2023, the estimated total of people falling ill with TB rose slightly, meaning the TB incidence and deaths are far from the UN's Sustainable Development Goals (SDGs) and End TB targets.

Despite some progress, TB remains one of the deadliest infectious diseases in the world, ranking among the top ten causes of death (replacing COVID-19).

TB Preventive Treatment (TPT) has achieved a record of 4.2 million people receiving TPT. Despite this progress, TPT coverage among contacts is still very low, at just 21% globally. In addition, drug-resistant strain TB (DR-TB) indicators are similar to previous years, with only 44% of people with RR/multidrug-resistant TB (MDR-TB) receiving treatment out of the estimated 400,000 who were sick. Chronic lack of resources for TB prevention and control worldwide contributes to the problem, with current funding reaching only 26% of the global target set by last year's UN High-level Meeting. Additionally, nearly 50% of people affected by TB and their families incur catastrophic costs related to TB care. The situation is even more dire for those with DR-TB, where an estimated 82% face catastrophic costs.

As a global community, we have the knowledge, tools, technologies, and treatments to end the TB epidemic. However the chronic lack of funding; huge catastrophic costs for people affected by TB and families; the combined threats of HIV and AIDS, diabetes, and other chronic diseases; the emergence of MDR-TB; increasing social conflicts and war with migration and displaced people; climate change; and pandemics have all affected the capacity of national health systems to offer basic TB services to the most vulnerable populations.

To address these phenomenal challenges and accelerate an end to TB, we must unify global and country level efforts and rethink current health systems. It is crucial that we reinforce primary health care; integrate health services such as diagnostic and laboratory platforms; and increase engagement of both public and private sectors, those affected by TB, local communities, and civil society organizations.

Bold policies—such as universal health coverage, political commitment at all levels of a health system (from health workers to national leadership), increased domestic and international financing support, strong social protection for patients and families, and research—are critical to stop TB.

For more than 22 years, Management Sciences for Health (MSH) has managed complex global TB projects in numerous countries. Our donors include the US Agency for International Development (USAID), US Centers

for Disease Control and Prevention (CDC), the Bill & Melinda Gates Foundation, the Global Fund, and numerous other organizations. Through our work, we have developed trusted partnerships with donors, government agencies (including ministries of health and national TB programs [NTPs] in Africa, Asia, Europe, and Latin America and the Caribbean), multilateral institutions, international partners, and the private sector.

Using a people-centered approach, we collaborate with local partners to develop health system solutions that address the needs of people affected by TB in several countries. We focus on strengthening national, regional, district, and local health managers and their institutions to provide high-quality health services, which is essential for enhancing the resilience and sustainability of health systems. Additionally, we have documented effective technical strategies, research findings, results, and lessons learned from our TB projects. We are committed to sharing these experiences, evidence, and insights with other stakeholders and implementers to support the ongoing efforts to end the TB epidemic.
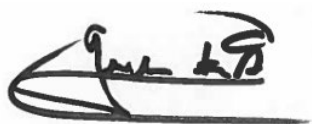
With this publication, we celebrate 17 years of TB research from MSH staff and local and international partners, as well as our donors, through the publication of more than 120 peer-reviewed articles in noted global public health and clinical scientific journals.

Our research and publications highlight MSH's technical approaches in the following technical areas:

- Quality directly observed treatment, short course (DOTS) implementation
- TB and COVID-19
- MDR-TB care and treatment
- TB contact investigation and TB preventive treatment
- e-TB Manager
- TB drug management and pharmacovigilance
- Capacity building and surveillance systems
- TB elimination
- TB in fragile states and volatile environments
- Urban DOTS and CB DOTS
- TB epidemiology, monitoring, and evaluation
- TB diagnostics, including GeneXpert implementation and digital X-ray
- Patient-centered care for vulnerable and special populations, including those with HIV and other diseases (e.g. Diabetes Mellitus)
- TB financing
- Stigma and discrimination
- Private sector engagement

I hope these collected articles will continue to provide insight to other partners and implementers and incentivize new generations of public health workers and experts to be involved in TB research on the frontline of the global fight against TB.

We are thankful for the deep collaboration of our respected colleagues: numerous MSH staff, international and national partners (ministries of health, NTPs, local nongovernmental organizations, and universities), and particularly the generous support provided by USAID.

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January 2008–July 2024

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PERSPECTIVES

Coronavirus Disease 2019 Diagnosis in Low- and Middle-Income Countries

The Big New Bully Disrupting TB and HIV Diagnostic Services

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Coronavirus disease 2019 (COVID-19) undermines control of other infectious diseases. Diagnostics are critical in health care. This opinion paper explores approaches for leveraging diagnostics for COVID-19 while retaining diagnostics for other infectious diseases, including tuberculosis (TB) and HIV. The authors reflect on experiences with GeneXpert technology for TB detection and opportunities for integration with other diseases. They also reflect on benefits and risks of integration. Placement of diagnostics in laboratory networks is largely nonintegrated and designated for specific diseases. Restricting the use of diagnostics leaves gaps in detection of TB, HIV, malaria, and COVID-19. Integrated laboratory systems can lead to more efficient testing while increasing access to critical diagnostics. However, the authors have observed that HIV diagnosis within the TB diagnostic network displaced TB diagnosis. Subsequently, COVID-19 disrupted both TB and HIV diagnosis. The World Health Organization recommended rapid molecular diagnostic networks for infectious diseases and there is a need for more investment to achieve diagnostic capacity for TB, HIV, COVID-19, and other emerging infectious diseases. Integrated laboratory systems require mapping laboratory networks, assessing needs for each infectious disease, and identifying resources. Otherwise, diagnostic capacity for one infectious disease may displace another. Further, not all aspects of optimal diagnostic networks fit all infectious diseases, but many efficiencies can be gained where integration is possible. *(J Mol Diagn 2022, 24: 289—293; https://doi.org/10.1016/j.jmoldx.2021.12.008)*

The roll-out of new technologies and the substantial growth in political and financial commitment by countries, regions, and bilateral and international donors (such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; President's Emergency Plan for AIDS Relief [PEPFAR]; and US Agency for International Development) and their global partners have facilitated a surge of global progress in health over the past 15 years.[1] Despite major progress in the global HIV and tuberculosis (TB) responses, these diseases continue to represent a public health burden in all regions, with inequitable coverage of diagnosis, prevention, and treatment.[2]

Globally, an estimated 10 million individuals fell ill with TB in 2019, a number that has been declining very slowly in recent years; although, in 2019, there was an estimated reduction of 1.2 million TB deaths among HIV-negative individuals.[3] Access to TB treatment has grown from 6 million in 2015 to 7.1 million in 2019, with increased access to TB preventive treatment as well, to 4.1 million.[4] New HIV infections among women aged 15 to 24 years fell by 25% between 2010 and 2018, and since 2010, AIDS-related mortality has declined by 33%.[5] Other diseases, such as hepatitis C and sexually transmitted diseases, have gained global prominence, with many low- and middle-income

countries (LMICs) beginning to implement services to reduce morbidity and mortality.

The coronavirus disease 2019 (COVID-19) pandemic has significantly disrupted health services due to cases over-burdening the health system or response measures that limit normal health program activities and care-seeking. As of October 14, 2021, there have been 239,007,759 confirmed cases of COVID-19, including 4,871,841 deaths, reported to the World Health Organization (WHO) globally, and 6,471,051,151 vaccine doses have been administered. The pandemic has undermined the progress made in the last decade in part because access to timely diagnostics for TB, HIV, and other opportunistic infections has been compromised; for example, to illustrate a few impacts of COVID-19, TB domestic resources have been diverted to COVID-19 response, affecting also staffing and facilities used to isolate COVID-19 cases. WHO has indicated that TB diagnosis has gone down 21% in 2020 compared with 2019 due to COVID, which translates into one-half million more deaths due to TB. If new strategies are not developed, implemented, and coordinated effectively at the global and national levels, long-term setbacks will result.[2–6] Effective interventions and services must be targeted to the most vulnerable individuals and populations—for example, pregnant women, young children, individuals living with HIV/AIDS or TB, the poor, and the elderly—while maintaining quality and efficiency in existing health programs.[6]

As countries make progress toward universal health care (UHC), diagnostics are a critical component of health benefits packages because most diseases or conditions cannot be managed without a clear diagnosis and laboratory tests for follow-up. COVID-19 exposes the need for a fundamental shift in service delivery models, including diagnostic integration and involvement of the private sector as highlighted in the last Lancet Commission report[7,8] (for a supplementary perspective, see https://www.statnews.com/2019/05/20/diagnostics-universal-health-coverage-succeed, last accessed December 8, 2020). The pandemic reveals that reality by exacerbating the gaps in detection of TB, HIV, and other opportunistic infections due, on one hand, to lack of laboratory capacity (eg, physical infrastructure and human resources) in some LMICs, even before the pandemic, and on the other hand, to mitigation strategies undertaken to respond to COVID-19.[7,8] These mitigation steps and shifting of resources have drastically reduced the capacity of health systems in LMICs to respond to other health issues because of overwhelmingly high demand for the care of patients with COVID-19 and interruptions within the supply chain.

Because the diagnostics have been built and funded specifically for certain diseases, the use of new advances that enable technology designed for one disease to detect other diseases is often not permitted. For example, GeneXpert, a technology that revolutionized TB molecular diagnostic testing and has a massive footprint in 145 LMICs, can now be used for HIV (viral load, early infant diagnosis) and COVID-19 testing through the recent release of the new Xpert Xpress SARS-CoV-2 cartridge (Cepheid, Sunnyvale, CA). However, financial and operational barriers generate concerns about how the utilization of this technology in weak laboratory systems and public health programs will undermine, for example, TB and HIV diagnostic capacity in some countries. Improper integration of technology may lead to suboptimal diagnosis and ultimately greater TB and HIV mortality. The newly introduced diagnostics need to be integrated in a phased, systematic manner, and optimized to meet program needs and targets for both existing diseases and new ones.[4–8]

Current Situation

Application of nucleic acid amplification tests (NAATs) has revolutionized rapid and accurate diagnostic testing for most pathogens for a decade. Automated batched or modular cartridge—based NAATs offer a combination of excellent sensitivity and specificity and reproducible, accurate test results, with minimal manipulation and decreased risk of cross-contamination, that has made PCR technology an appealing alternative to culture- or immunoassay-based testing for disease diagnosis. Although NAATs are more sensitive than most other tests for TB, culture remains the gold standard. However, culture can take months, whereas NAATs can be performed in less than 2 hours (http://www.stoptb.org/assets/documents/resources/wd/ERPD%20appr oved%20TB%20diagnostics%20info%20note.pdf?, last accessed January 25, 2022).[9–11] The opportunity for decentralization to lower levels of the health system makes NAATs an essential tool to implement the End TB Strategy and realize the UNAIDS 95-95-95 goals.[12]

For the past 10 years, the Xpert assay has represented the first major advance in TB diagnosis, allowing peripheral detection of rifampicin resistance, which enabled detection of drug-resistant TB and exponentially increased the numbers of cases treated. Additionally, the Xpert Ultra test increases the sensitivity of TB diagnosis in children, HIV-infected individuals, and paucibacillary and extrapulmonary TB; and since its endorsement by WHO, most countries have quickly started rolling out Xpert.[9–11] As of December 31, 2018, 10,562 GeneXpert machines (47,567 modules) had been procured across 136 of the 145 countries eligible for concessional prices (Cepheid, 2018; W. Van Gemert, unpublished data). However, existing GeneXpert technologies typically have low overall utilization, although this is site-dependent in several countries. Countries are not procuring enough cartridges to reach testing targets or fully utilize instruments due to algorithm constraints on implementation, weak specimen referral linkages to testing, and inadequate attention to maintenance and prompt repair.

High-throughput platforms, mostly at centralized levels, have been introduced on a massive scale for HIV early infant diagnosis, drug resistance detection, and viral load

monitoring for treatment response, with funding from the Global Fund, PEPFAR, and other agencies. The volume of viral load tests performed has increased significantly from the 15 million viral load tests conducted in 2017, and the number is projected to double to nearly 30 million by 2022. The UNAIDS 2020 report released during the COVID-19 pandemic showed that only 14 countries have achieved the 90-90-90 HIV treatment targets (90% of individuals living with HIV know their HIV status, of whom 90% are on antiretroviral treatment and of whom 90% are virally suppressed), including Eswatini, which has one of the highest HIV prevalence rates in the world. However, in many parts of the world, COVID-19 is colliding with the ongoing HIV epidemic.[6−8] A recent WHO HIV guideline recommends point-of-care diagnosis and monitoring as preferred over centralized laboratory testing because they significantly reduce turnaround time and result in saving lives.[10] Further, the WHO Health Assembly recommends integrated services; donors such as the Global Fund may reduce funding and expect further integration.

To control the spread of COVID-19, experts agree that an aggressive strategy of vaccination along with test, trace, and treatment is needed, combined with physical distancing measures and the use of masks. However, SARS-CoV-2 detection in some countries is limited by weak and uncoordinated laboratory systems, as well as insufficient laboratory equipment and test kits for PCR or access to rapid diagnostic tests. This insufficient capacity compels governments, for example, to restrict testing to individuals who meet specific narrow criteria.[13] Many efforts and partnerships to increase the response to COVID-19 in Africa and around the world have been launched, such as the Access to COVID-19 Tools Accelerator, which is coordinated by the Global Fund, WHO, UNICEF, and the Partnership to Accelerate COVID-19 Testing in Africa. However, after 19 months into the pandemic, lessons and progress in diagnostic pipelines are demonstrating the efficiency of antigen tests. The Global Fund is advocating for using antigen tests (3 USD, rather than GX for COVID-19 at 20 USD), and WHO is updating its antigen rapid diagnostic test guidance as well as preparing interim guidance on Recommendations for National SARS-CoV-2 Testing Strategies and Diagnostic Capacities.

Discussion

This paper aims to identify the best approach to using both existing and new technologies to address the COVID-19 pandemic and coexisting major public health challenges without jeopardizing the gains in diagnostic access for TB, HIV, and other opportunistic infections.

COVID-19 illustrates our common vulnerability to disease across borders, the public−private divide, and the limits of our fragmented approach to health.[2,11−13] A more coordinated, comprehensive, and integrated decentralization of services at the community level is urgently needed. In their paper, Pooran et al[11] make a case for value for money for point-of-care TB diagnostic services because such services reduce, not only death, but also economic loss in Africa. It also reduces transport costs to have testing performed more locally.

Governments and donors will need to revisit public health programs and systems in line with UHC in LMICs. Doing so will require a paradigm shift, with change management, task shifting, and bold policies. Centralized testing of patients for initial diagnosis should be shifted to the lowest administrative level possible (district), ideally at the point of care. Centralized laboratory staff will continue to have opportunities for leadership of the entire network, for example, quality assurance, introduction of new diagnostics, research, training, and mentoring.

The current diagnostic gaps in the HIV, TB, and COVID-19 response could be greatly mitigated by intensively investing in public health laboratory systems and optimizing use of existing technologies already introduced in many LMICs. However, many of the multiplex technologies are centralized in biosafety level 2 or 3 laboratories, due to high requirements for safety, human skills, resources, and alignment with vertical diagnostic programs.

The US Food and Drug Administration approved Xpert Xpress SARS-CoV-2 on March 21, 2020.[9,13] The test kit can deliver a COVID-19 diagnosis in 45 minutes. The machine can be placed in a biosafety level 1 or 2 laboratory or in mobile vehicles with similar safety requirements, making it ideal for community testing. This will reduce the costs of referral, from both the patient and health system perspectives. Other affordable point-of-care or near-patient multiplex platforms endorsed by WHO are available, such as TrueNat (Molbio Diagnostics, Goa, India) or TB loop-mediated isothermal amplification assay); and more platforms are in development or in clinical trials that can diagnose and monitor multiple diseases, including drug-resistant malaria [refer to: *https://www.devex.com/news/afterthe-pandemic-how-will-covid-19-transform-global-health-and-development-96936*, last accessed December 8, 2020; *http://www.stoptb.org/assets/documents/covid/Considerations%20for%20selection%20of%20SARS-CoV-2%20diagnostics.pdf*, last accessed December 8, 2020; *https://www.finddx.org/mal-fev/improved-malaria-rdts*, last accessed December 8, 2020].[14,15]

Multidisease molecular platforms [eg, Abbott's RealTime m2000sp and m-PIMA (Abbott, Abbott Park, IL); Cepheid's GeneXpert GX-4, -16, -48, and -80 modules; Hologic Panther, Roche COBAS AmpliPrep/COBAS TaqMan CAP/CTM 96; Roche cobas 4800/6800/8800 (Roche, Basel, Switzerland); Thermo Fisher's Applied Biosystems 7500 Fast Real-Time PCR system (Thermo Fisher, Waltham, MA); Becton Dickinson's BD MAX (Becton Dickinson, Franklin Lakes, NJ); and genesig Easy qPCR Detection Kit for nCoV-2019 (genesig, Chandler's Ford, UK)][6,7,10] have already been introduced for HIV, influenza,

hepatitis, and other diseases in many national reference laboratories and research institutes in LMICs. Additionally, the Food and Drug Administration has authorized—for emergency use—some of the test kits that can be accommodated by some of the platforms listed above for SARS-CoV-2.

Given these developments, the diagnostic pipeline for COVID-19 and other priority diseases is growing. Integrated technologies, such as next-generation sequencing, at peripheral levels might also be used for detection of drug resistance across diseases. Furthermore, treatment monitoring, such as viral load and bacterial load testing, might also be conducted using integrated platforms. Having well-functioning laboratory systems to detect multiple infectious diseases, their drug resistance patterns, and treatment responses at lower levels of the health system would enable a more equitable, human-centered approach, with increased access and decreased turn-around time, ultimately reducing morbidity and mortality from infectious disease, particularly TB and HIV.

Integration of diagnostic networks is at an early stage in LMICs. A few African, Asian, and Latin American countries have piloted diagnostic integration, mainly at selected central and intermediate laboratories; they include Cameroon (HIV and TB), Malawi (HIV and TB), Nigeria (hepatitis C and TB), Zimbabwe (HIV and TB), Brazil, the Caribbean countries, Democratic Republic of Congo, India, and Malaysia.[11] Best practices and lessons from these pilots are urgently needed to inform the development and scale-up of an integrated diagnostic laboratory network approach. This network will form the basis for a robust public health laboratory system in each country, with strong international and government collaboration, which will benefit all health programs, including reproductive health, maternal and child health, communicable diseases, emerging diseases, and cancer, in line with UHC.[7]

Several LMICs have already used GeneXpert technology to diagnose both TB and COVID-19,[8,14,16,17] but such integration has not been uniform across countries, revealing better approaches to follow in the future. The authors believe that no one size fits all, because countries vary in infrastructure, disease burden, and geographic peculiarities. Further, some countries have vector-borne diseases such as malaria and cholera that are relevant only in certain areas of the country. Nonetheless, many common links can be made across most LMICs to integrate their laboratory systems for infectious diseases and create a more resilient response on all tiers of their public health laboratory network, shifted closer and targeted to the communities that need them.

Recommendations

LMICs should take advantage of existing multiplex platforms, such as GeneXpert, high-throughput platform technologies, and laboratory networks, to introduce COVID-19 testing. These networks are already established and working well to make laboratory diagnostic services available in several countries. By integrating diagnostics for COVID-19 and other infectious diseases into a well-articulated laboratory system, we will gain efficiencies as well as move closer to UHC even during the COVID-19 pandemic. Introducing a vertical COVID-19 diagnostic service model would be expensive and inefficient in reaching the individuals who need the services—and it would not be sustainable.

Integrated, affordable multiplex technologies, particularly at the point of care, local and community levels, have the advantages of avoiding parallel diagnostic systems and duplication of activities such as referral and transport, equipment maintenance, human resource management, quality assurance, supply chain and quantification, and training—and duplication of the costs of those activities. In providing increased capacity and uptake for TB, HIV, COVID-19, and other existing or future opportunistic infections, integrated technologies offer better value for money and sustainability.

Innovative approaches to diagnostic integration can maximize investments while increasing access but require a strategic approach tailored to each country context based on mapping and optimizing the laboratory network, assessing the needs for detection capacity for each disease, and identifying the gaps so resources can be mobilized. Merely having the machines will not translate into great improvements. We must also strengthen:

- Political leadership to remove barriers to diagnostic integration, and roadmaps and strategic plans focused on increasing investment in diagnostic capacity in a holistic, coordinated way, with robust policies;
- Structures for supplies of consumables, maintenance, and sample transportation;
- Coordination and communication among disease control programs, including donors and the private sector;
- Technical assistance to ministries of health, local public health programs and institutions, and the private sector;
- Quality-assured, connected, and sustainable laboratory networks, led by a national public health laboratory or other governance body, to guarantee universal access to prevention, diagnostics, treatment, and care services; and
- Integrated laboratory information systems and dashboards to increase use of data and inform decision-making for patient management, program planning, and service delivery, while ensuring confidentiality.

Conclusion: Looking Ahead

Effective interventions and services will require transforming our way of diagnosing and treating individuals to enable countries to reach the End TB milestones and UNAIDS 95-95-95 goals, even while containing other diseases. If we do not act to mitigate the threat, COVID-19 will

lead to an upsurge in deaths from TB, HIV, and other opportunistic infections. If we take an integrated approach, leveraging the infrastructure and resources we have already invested in and moving swiftly to strengthen the health system as a whole, we can step up the fight against both COVID-19 and other diseases of major public health importance.

The authors call on all ministries of health, donors, implementers, partners, and supported countries to revisit their strategies by looking at all these opportunities. The authors recommend that donors focus investments in COVID-19 testing by taking advantage of existing platforms and infrastructures to maximize service coverage to save lives during the pandemic while serving as a benchmark to gauge progress toward implementing guidelines such as the WHO Essential Diagnostics List and investing in long-term UHC goals. This approach will cost far less than setting up parallel systems or centralizing testing in a few laboratories. This is a time to be bold and act fast.

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Author Contributions

A.U.N. wrote the manuscript; A.U.N., J.N.S., M.G. and P.G.S. wrote, reviewed, edited, and approved the final manuscript equally.

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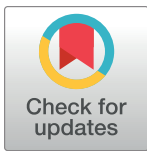
PLOS ONE

Poor treatment outcome and associated risk factors among patients with isoniazid mono-resistant tuberculosis: A systematic review and meta-analysis

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Abstract

Background

To date, isoniazid mono-resistant tuberculosis (TB) is becoming an emerging global public health problem. It is associated with poor treatment outcome. Different studies have assessed the treatment outcome of isoniazid mono-resistant TB cases, however, the findings are inconsistent and there is limited global comprehensive report. Thus, this study aimed to assess the poor treatment outcome and its associated risk factors among patients with isoniazid mono-resistant TB.

Methods

Studies that reported the treatment outcomes and associated factors among isoniazid mono-resistant TB were searched from electronic databases and other sources. We used Joana Briggs Institute critical appraisal tool to assess the study's quality. We assessed publication bias through visual inspection of the funnel plot and confirmed by Egger's regression test. We used STATA version 17 for statistical analysis.

Results

Among 347 studies identified from the whole search, data were extracted from 25 studies reported from 47 countries. The pooled successful and poor treatment outcomes were 78% (95%CI; 74%-83%) and 22% (95%CI; 17%-26%), respectively. Specifically, complete, cure, treatment failure, mortality, loss to follow-up and relapse rates were 34%(95%CI; 17%-52%), 62% (95%CI; 50%-73%), 5% (95%CI; 3%-7%), 6% (95%CI; 4%-8%), 12% (95%CI; 8%-17%), and 1.7% (95%CI; 0.4%-3.1%), respectively. Higher prevalence of pooled poor treatment outcome was found in the South East Asian Region (estimate; 40%, 95%C; 34%-45%), and African Region (estimate; 33%, 95%CI; 24%-42%). Previous TB treatment (OR;

1.74, 95%CI; 1.15–2.33), having cancer (OR; 3.53, 95%CI; 1.43–5.62), and being initially smear positive (OR; 1.26, 95%CI; 1.08–1.43) were associated with poor treatment outcome. While those patients who took rifampicin in the continuation phase (OR; 0.22, 95%CI; 0.04–0.41), had extrapulmonary TB (OR; 0.70, 95%CI; 0.55–0.85), and took second-line injectable drugs (OR; 0.54, 95%CI; 0.33–0.75) had reduced risk of poor treatment outcome.

Conclusion

Isoniazid mono-resistant TB patients had high poor treatment outcome. Thus, determination of isoniazid resistance pattern for all bacteriologically confirmed TB cases is critical for successful treatment outcome.

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Introduction

Tuberculosis (TB) is causing a huge public health impact being the second cause of mortality among infectious diseases. There were 9.9 million TB cases and more than 1.5 million deaths due to TB in 2020 [1]. The efforts for the prevention and control of TB becomes challenging due to the emergence of drug resistant TB mainly with respect to treatment outcome. Drug-resistant TB is associated with poor treatment outcome [1, 2]. Based on the 2021 global TB report, the global successful treatment outcome among drug susceptible and Multi-drug resistant TB (MDR-TB)/ Rifampicin resistant TB (RR-TB) cases were 86% and 59%, respectively [1]. Drug resistant TB have different categories including mono-resistant TB. When TB is caused by *Mycobacterium tuberculosis* strains which are resistant only to one anti-TB drug it is called mono-resistant TB and isoniazid mono-resistant TB is among the categories [1, 2].

The world health organization (WHO) through the END TB Strategic document recommends calls for the early TB diagnosis drug sensitivity testing (DST) [3]. The drug resistance pattern should be determined for all bacteriologically confirmed TB cases to put patients on the right treatment for successful treatment outcome and to prevent the emergence of additional drug-resistance. Even though, there are improvements in the recent years, this becomes difficult in many TB endemic low and middle-income countries having resource limitations. To date, due to the implementation of Xpert MTB/RIF assay many countries reported RR-TB to the WHO [1, 2]. In this assay, the resistance profile for the other potent anti-TB drug isoniazid is unknown that might have made the isoniazid mono-resistant TB cases to be less reported and be treated as drug susceptible TB [2]. However, about 11% of TB patients worldwide are estimated to have isoniazid resistant, rifampicin susceptible TB [2].

Studies conducted in different settings indicated that isoniazid mono-resistant TB is a problem in different countries [4–8]. The incidence of isoniazid mono-resistant TB is increasing and it is higher than RR-TB globally [9]. In addition, studies revealed that those isoniazid mono-resistant TB cases had higher rate of poor treatment outcome compared to the drug-susceptible TB cases [10–13]. There are studies that assessed the treatment outcome of isoniazid mono-resistant TB cases [4–7, 10–30], however, the findings are inconsistent. In addition, there is no comprehensive report at the global level. Thus, this study aimed to assess the poor treatment outcome and the associated risk factors among patients with isoniazid mono-resistant TB.

Methods

Protocol registration

The protocol for this study is registered on the international prospective register of systematic reviews (PROSPERO) with a registration number CRD42022372367.

Information source and search strategy

This study was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist [31] (**S1 Table**). Article searching was conducted systematically from the electronic databases including PubMed, CINAHL, Global Health, Global Health Medicus and Environment Index. In addition, our search extends to other grey literature sources such as Google and Google Scholar. The search was conducted up to 20 November 2022 for studies published in English language. Two authors (AA, EG) have conducted the article searching independently. The third author (ZWB) managed the inconsistencies arose between the two authors. The search was conducted using the keywords; isoniazid mono-resistant tuberculosis, treatment outcome and risk factors/determinants. The Boolean operators OR and AND were used accordingly. The search string for PubMed was ("Treatment Outcome"[MeSH Terms] OR (("poverty"[MeSH Terms] OR "poverty"[All Fields] OR "poor"[All Fields]) AND ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields])) OR ("Treatment Outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "Treatment Outcome"[All Fields])) AND (("isoniazid"[MeSH Terms] OR "isoniazid"[All Fields] OR "isoniazide"[All Fields]) AND "mono-resistant"[All Fields]) (**S2 Table**).

Study selection procedure

We have followed a step-wise approach to select the eligible studies. Primarily, all the studies identified from the whole search were exported to EndNote X8 citation manager, and we have removed the duplicates. In the next step, we have screened the articles by title and abstract. Then, full-text assessment was conducted for the remaining articles. Finally, we have included the articles that passed the full-text review in the final analysis. The article selection procedure was conducted by two independent authors (GD, GS) using pre-defined criteria that considered study subjects, study designs, quality, and outcome (**Fig 1**).

PICOS criteria

Participants: Isoniazid mono-resistant tuberculosis patients
    Intervention: Anti-TB treatment
    Comparator: Successful treatment outcome
    Outcome: Poor treatment outcome
    Study design: Observational studies.
    Study setting: Any setting in any country across the globe

Inclusion and exclusion criteria

Studies that reported either TB treatment outcome or risk factors of poor treatment outcome or both in patients with isoniazid mono-resistant TB were included in the study. There was no restriction on entering the study in terms of sample size. The exclusion criteria were review studies, and not differentiated the target population.
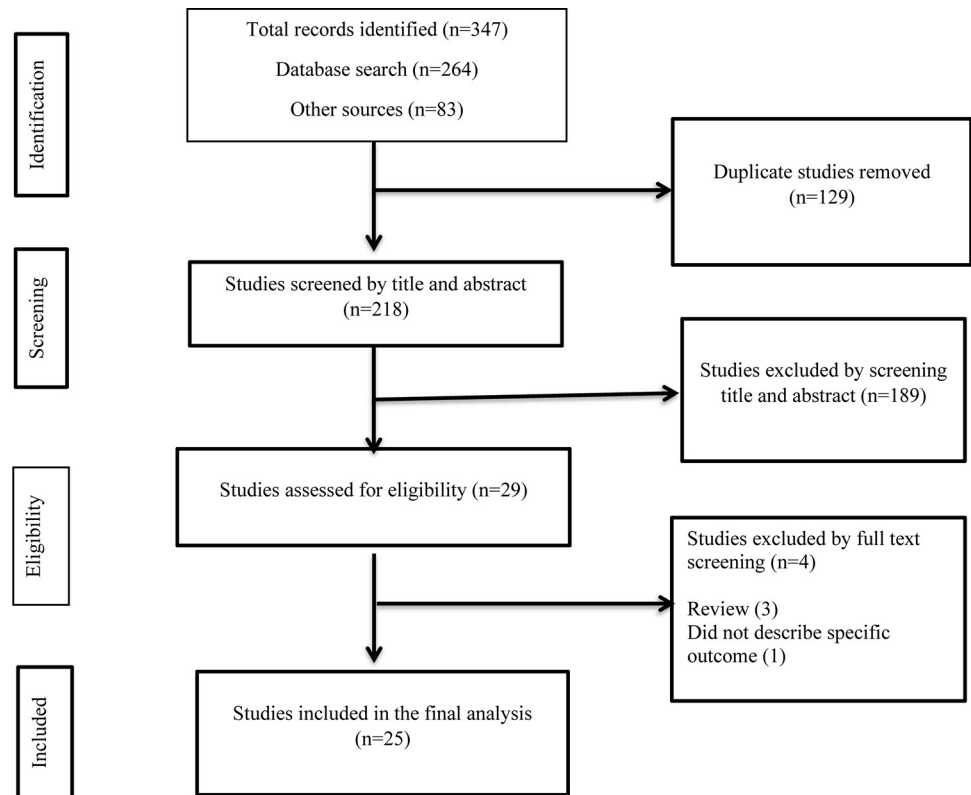
Fig 1. Flowchart describing the selection of studies for the systematic review and meta-analysis of poor treatment outcome and its associated factors among patients with isoniazid mono-resistant tuberculosis.

Data extraction

Data were extracted from the articles included in the final analysis using Microsoft Excel 2016 spreadsheet. The extracted data included; primary author name, publication year, country, data collection period, study design, data collection time (prospective vs retrospective), study setting/place, age of study participants, number of study participants, number having successful (completed, cured) and poor treatment outcomes (mortality, treatment failure, loss to follow-up), number of relapse in successfully treated cases, and factors associated with poor treatment outcomes. Data were extracted by two independent authors (AA, ZWB), and the third author (GD) managed the inconsistencies that arose between the two authors.

Risk of bias (quality) assessment of included studies

We have evaluated the methodological reputability and quality of the findings of the included studies using the Joanna Briggs Institute (JBI) critical appraisal tools for observational studies [32]. Two independent authors (GS, KE) conducted the quality assessment, and the third author (ZWB) resolved the inconsistencies. The checklist for cross-sectional, case control and cohort studies consists of 8, 10, and 11 indicators, respectively. Each indicator was equally scored and summed up to give 100%. The quality of the studies was scored to have high, medium and low quality if the overall quality score was >80%, 60–80% and <60%, respectively (S3 Table). The presence of publication bias was explored through visual evaluation of the funnel plot such that asymmetry of the funnel plot indicated the presence of publication bias.

Furthermore, we have conducted egger's regression test to confirm the presence of publication bias (P<0.05).

Outcomes

The primary outcome of this study was the treatment outcomes such as the successful and poor treatment outcomes along with different categories among patients with isoniazid mono-resistant tuberculosis. The secondary outcomes were the factors that associated with poor treatment outcomes in those patients.

Operational definition

The operational definition for isoniazid mono-resistant tuberculosis was based on the WHO definition. This type of tuberculosis is caused by *Mycobacterium tuberculosis* strains that are resistant to isoniazid but susceptible to rifampicin confirmed in vitro [33]. The definitions for the treatment outcomes is based on the WHO classification of TB treatment outcomes as described in the guideline [34].

Ethical approval and consent to participate

Since this study is based on a review of published articles, ethical approval is not mandatory. The protocol is registered on PROSPERO.

Data synthesis and statistical analysis

The pooled estimates of successful and poor treatment outcomes among patients with isoniazid mono-resistant TB was determined with its 95%CI by assuming the true effect size varies between studies. The pooled estimate for successful and poor treatment outcomes were determined as the ratio of numbers of isoniazid mono-resistant TB patients with successful and poor treatment outcomes to the total treated isoniazid mono-resistant TB patients, respectively. Besides, the pooled OR along with 95%CI was estimated for each factor to determine the factors associated with poor treatment outcomes. We have also performed a stratified analysis. We presented the data using the forest plot. The heterogeneity among the studies was assessed using the I^2 heterogeneity test and a value above 50% indicated the presence of substantial heterogeneity among studies [35, 36]. We have performed bi-variable and multi-variable meta-regression to assess the association of study year and sample size on poor treatment outcome. To assess the presence of publication bias, the funnel plot was inspected visually and Egger's regression test was conducted. For those parameters that had a publication bias (P<0.05) in the Egger's regression test [37, 38], we have performed a trim and fill analysis to adjust the publication bias. The statistical analysis was conducted using STATA version 17.

Results

Characteristics of included studies

From the whole search, we identified 347 studies and after removing 129 duplicates, 218 were screened by title and abstract. At this stage, 189 studies were excluded and the remaining 29 studies were screened by full text review. Finally, 25 studies were included in this study [4–7, 10–30]. These studies were reported from five continents and from all the six WHO regions. Accordingly, the most frequent number of studies were reported from Asia with 11 studies followed by North America (5 studies), Africa (4 studies), Europe (3 studies), and South America (2 studies). Per WHO regional classification, relatively higher number of studies were reported from the Region of Americas (AMR) with 7 studies. The frequencies of studies in the other

regions were; West Pacific Region (WPR) (5 studies), African Region (AFR) (4 studies), European Region (EUR) (4 studies), South Eastern Asian Region (SEAR) (3 studies), and Eastern Mediterranean Region (EMR) (2 studies). The studies were reported from 47 countries and a maximum of two studies were reported from a single country (South Africa, Taiwan, China, Portugal, USA, Canada, India, and Peru). A single study conducted in Europe comprises data collected from 31 countries [20] that made the number of countries included in the current systematic review and meta-analysis study to be 47 in number.

The studies were published from 2009 [15, 29] to 2022 [28]. The data collection period for most of the studies were after 2000 except two studies where the data collection period was from October 1992 to October 2005 for one study [15] and from 1995 to 2010 for the other study [11]. In the majority of the studies (88%, 22), data were collected retrospectively. The data in these studies were collected either from a health facility or from the national surveillance data registry database (**Table 1**).

Pooled treatment outcomes among isoniazid mono-resistant tuberculosis patients

In the current study, we extracted data to estimate the pooled prevalence of successful treatment outcome including cure rate and treatment completion rate, poor treatment outcome including death rate, treatment failure rate and loss to follow-up, relapse after successful treatment outcome, and factors associated with poor treatment outcome among patients with isoniazid mono-resistant tuberculosis.

Data were extracted from 24 and 23 studies to estimate the pooled prevalence of successful treatment outcome and poor treatment outcome, respectively. The largest sample size was 6796 in a study that comprises 31 European countries [20], while the smallest sample size was 9 in a study conducted in Saudi Arabia [21]. Among the studies, 11 studies had a sample size below 100 while the remaining studies had a sample size of 132 and above.

Based on data collected from 24 studies comprising 10, 698 isoniazid mono-resistant TB patients, 8606 had successful treatment outcome that gave a pooled estimate of 78% (95%CI; 74–83, I^2; 94.02%) (**Fig 2**). The symmetry of the funnel plot (**Fig 3**) and the statistical insignificance of the egger's regression test showed there is no publication bias (P = 0.080). Specifically, the pooled treatment completed and cured rate among isoniazid mono-resistant TB patients were 34% (95%CI; 17–52, I^2; 99.26%) (**S1 and S2** Figs) and 62% (95%CI; 50–73, I^2; 96.91%) (**S3 and S4** Figs), respectively. Based on the WHO regional classification, the pooled prevalence of successful treatment outcome from the highest to lowest pooled estimate were; AMR (estimate; 84%; 95%CI; 78–90, I^2; 87.66%), EUR (estimate; 84%; 95%CI; 77–91, I^2; 91.21%), WPR (estimate; 82%; 95%CI; 77–86, I^2; 64.67%), EMR (estimate; 75%; 95%CI; 44–106, I^2; 73.41%), AFR (estimate; 67%; 95%CI; 58–76, I^2; 74.28%), and SEAR (estimate; 62%; 95%CI; 56–69, I^2; 13.74%) (**Fig 2**) (**Table 2**).

The poor treatment outcome was estimated from 23 studies having 10,670 isoniazid mono-resistant TB patients. From these individuals, 2084 had poor treatment outcome that yield a pooled estimate of 22% (95%CI; 17–26, I^2; 94.08%) (**Fig 4**). The egger's regression test showed there is no publication bias (P = 0.107) (**Fig 5**). Specifically, the pooled treatment failure, mortality and loss to follow-up rates were 5% (95%CI; 3–7, I^2; 93.97%) (**S5 and S6** Figs), 6% (95% CI; 4–8, I^2; 88.73%) (**S7 and S9** Figs), and 12% (95%CI; 8–17, I^2; 96.58%) (**S9 and S10** Figs), respectively. Based on the WHO regional classification, the pooled prevalence of poor treatment outcome from the highest to lowest pooled estimate was; SEAR (estimate; 40%; 95%C; I34-45, I^2; 0.00%), AFR (estimate; 33%; 95%CI; 24–42, I^2; 74.28%), EMR (estimate; 25%; 95% CI; -0.06–56, I^2; 73.41%), WPR (estimate; 18%; 95%CI; 14–23, I^2; 64.63%), EUR (estimate;

Table 1. Characteristics of individual studies on the poor treatment outcome and associated risk factors among patients with isoniazid mono-resistant tuberculosis included in the current systematic review and meta-analysis.

Author year	Publication year	Country	Study period	Study design	Data collection time	Study setting	Age group	Sample size	Successful outcome		Poor outcome	
									N	%	N	%
Chien et al., 2014	2014	Taiwan	January 2004 to October 2011	Retrospective cohort study	Retrospectively	Four hospitals in northern, central, southern and eastern Taiwan	All age groups (Median age was 64 years)	395	328	83.04	67	16.96
Bachir et al., 2021	2021	France	January 1, 2016 to December 31, 2017	Multicenter case-control study	Retrospectively	University hospitals of Paris, Lille, Caen and Strasbourg	Median age was 35 years	97	75	77.32	22	22.68
Cattamanchi et al., 2009*	2009	USA	October 1992 to October 2005	Retrospective cohort study	Retrospectively	San Francisco Department of Public Health Tuberculosis Control Section	Median age was 47 years	137	-	-	-	-
Kwak et al., 2020	2020	South Korea	January 2005 to December 2018	Retrospective record review	Retrospectively	South Korean tertiary referral hospital	≥18 years	195	164	84.10	31	15.90
Binkhamis et al., 2021	2021	Saudi Arabia	May 2015 and April 2019	Cross-sectional analytical study	Retrospectively	King Khalid University Hospital	All age groups (range:1–90 years)	9	5	55.56	4	44.44
Murwira, et al., 2020	2020	Zimbabwe	March 2017 and December 2018	Retrospective cohort study	Retrospectively	National TB Reference Laboratory (NTBRL) in Bulawayo City and National TB programme	All age groups (Median age was 36 years, Interquartile range, was 29–45 years)	31	25	80.65	6	19.35
Chierakul et al., 2014	2014	Thailand	July 2009 and July 2011	Retrospective cohort study	Retrospectively	Siriraj Hospital	> 15 years	28	20	71.43	-	-
Jacobson et al., 2011	2011	South Africa	28 November 2000 to 28 May 2009	Retrospective cohort study	Retrospectively	22 clinics in the rural Cape Winelands East and Overberg Districts, Western Cape Province	All age groups (range:11–67 years)	151	101	66.89	50	33.11
Garcia et al., 2018	2018	Peru	January 2012 and December 2014	Cross-sectional study	Retrospectively	National registry of drug-resistant tuberculosis	All age groups	947	731	77.19	216	22.81
Karo et al., 2018	2018	31 European countries	2002 to 2014	Observational study	Retrospectively	European Surveillance System (TESSy)	All age groups (Median age was 41 years)	6796	5611	82.56	1185	17.44
Saldaña et al., 2016	2016	Mexico	1995 to 2010	Prospective cohort study	Prospectively	12 municipalities in the Orizaba Health Jurisdiction in Veracruz State	> 15 years	85	64	75.29	21	24.71
Villegas et al., 2016	2016	Peru	March 2010 to December 2011	Prospective cohort study	Prospectively	34 health facilities in a northern district of Lima	All age groups	82	63	76.83	19	23.17

(Continued)

Table 1. (Continued)

Author year	Publication year	Country	Study period	Study design	Data collection time	Study setting	Age group	Sample size	Successful outcome		Poor outcome	
									N	%	N	%
Edwards et al., 2020	2020	Canada	2007 to 2017	Retrospective cohort study	Retrospectively	One of three centralized comprehensive clinics in the province of Alberta	Median age was 37 years	98	90	91.84	8	8.16
Wang et al., 2014	2014	Taiwan	2006 January to 2007 December	Retrospective cohort study	Retrospectively	Chang Gung Memorial Hospital	All age groups	134	114	85.07	20	14.93
Sayfutdinov et al., 2021	2021	Uzbekistan	2017 to 2018	Retrospective cohort study	Retrospectively	Two regions of Uzbekistan (Fergana and Bukhara)	All age groups	132	105	79.55	27	20.45
der Heijden et al., 2017	2017	South Africa	2000 to 2012	Longitudinal study	Retrospectively	Prince Cyril Zulu Communicable Diseases Centre (PCZCDC)	All age groups (Median age was 34 years)	405	235	58.02	170	41.98
Romanowski et al., 2017	2017	Canada	2002 to 2014	Retrospective record review	Retrospectively	BC Centre for Disease Control (BCCDC)	All age groups (Median age was 46 years)	152	140	92.11	12	7.89
Santos et al., 2018	2018	Portugal	01 January 2008 to 31 December 2014	Retrospective record review	Retrospectively	National-Tuberculosis-Surveillance-System (SVIG-TB)	All age groups (Median age was 44 years)	232	210	90.52	22	9.48
Shao et al., 2020	2020	China	2013 to 2018	Retrospective cohort study	Retrospectively	Four national DR-TB surveillance sites of Jiangsu Province	All age groups (Median age was 48 years)	63	52	82.54	11	17.46
Kuaban et al., 2020	2020	Cameroon	January 2012 to March 2015	Retrospective record review	Retrospectively	In all the TB diagnostic and treatment centres (DTCs) in four regions of Cameroon namely the North West, South West, West, and Littoral regions	All age groups (range: 17–79 years)	45	32	71.11	13	28.89
Salindri et al., 2018	2018	USA	2009 to 2014	Retrospective cohort study	Retrospectively	Georgia State Electronic Notifiable Disease Surveillance System (SENDSS)	≥15 years	140	124	88.57	16	11.43
Nagar et al., 2022	2022	India	January 2019 to December 2020	Retrospective record review	Retrospectively	Ahmedabad city from Ni-kshay, an online web-based portal	≥18 years	243	144	59.26	99	40.74
Tabarsi et al., 2009	2009	Iran	2003 to 2005	Prospective cohort study	Prospectively	Masih Daneshvari Hospital	All age groups	42	37	88.10	5	11.90
Chunrong et al., 2020	2020	China	January 2016 to January 2019	Retrospective record review	Retrospectively	Shenzhen's drug-resistant TB project	All age groups (17–75 years)	144	102	70.83	42	29.17

(*Continued*)

Table 1. (Continued)

Author year	Publication year	Country	Study period	Study design	Data collection time	Study setting	Age group	Sample size	Successful outcome		Poor outcome	
									N	%	N	%
Garg et al., 2019	2019	India	January 1 to December 31, 2017	Retrospective record review	Retrospectively	At the nodal DRTB centre, Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh	All age groups	52	34	65.38	18	34.62

"-"; Not specifically indicated

* the study only indicated the treatment completion rate the total successful treatment outcome including the cured cases and the poor treatment outcome (failure, death and lost to follow-up) are not indicated in the study.

17%; 95%CI; 11–22, I^2; 85.06%), and AMR (estimate; 16%; 95%CI; 10–22, I^2; 87.75%) (**Fig 4**) (**Table 2**).

Pooled prevalence of relapse among successfully treated isoniazid mono-resistant tuberculosis patients

In this study, we have also assessed the relapse rate among isoniazid mono-resistant TB patients who had successful treatment outcome. We extracted data from eight studies comprising 970 successfully treated isoniazid mono-resistant TB cases. From these individuals, 28 developed relapse. The relapse period started from treatment completion and extends up to two years after treatment. Based on the random-effects model, the pooled prevalence of relapse among successfully treated isoniazid mono-resistant TB cases was 1.7% (95%CI; 0.4–3.1, I^2; 44.58%) (**Fig 6**).

Meta-regression

Besides, we have conducted a meta-regression analysis to assess the effect of sample size and publication year on the heterogeneity among studies that reported poor treatment outcome among isoniazid mono-resistant TB patients. The multivariable meta-regression model revealed that sample size (P = 0.713) and publication year (P = 0.464) did not significantly affected heterogeneity among studies (**Table 3**).

Risk factors of poor treatment outcome in isoniazid mono-resistant tuberculosis patients

In the current study, we assessed the risk factors associated with poor treatment outcome in isoniazid mono-resistant TB patients. We have performed the pooled estimate for the factors reported at least by two studies. We have estimated the pooled OR for 19 variables. The risk factors analyzed included demographic (sex, age group), smoking status, clinical factors such as having co-morbidities including diabetes, cancer, end-stage renal failure, and HIV, presence of cavity lesion in the chest radiograph, type of TB (extra-pulmonary vs pulmonary), initial smear status (smear positive vs smear negative), culture conversion after 2 months, drug-resistance level of isoniazid (high level vs low-level), and per taking different anti-TB drugs during
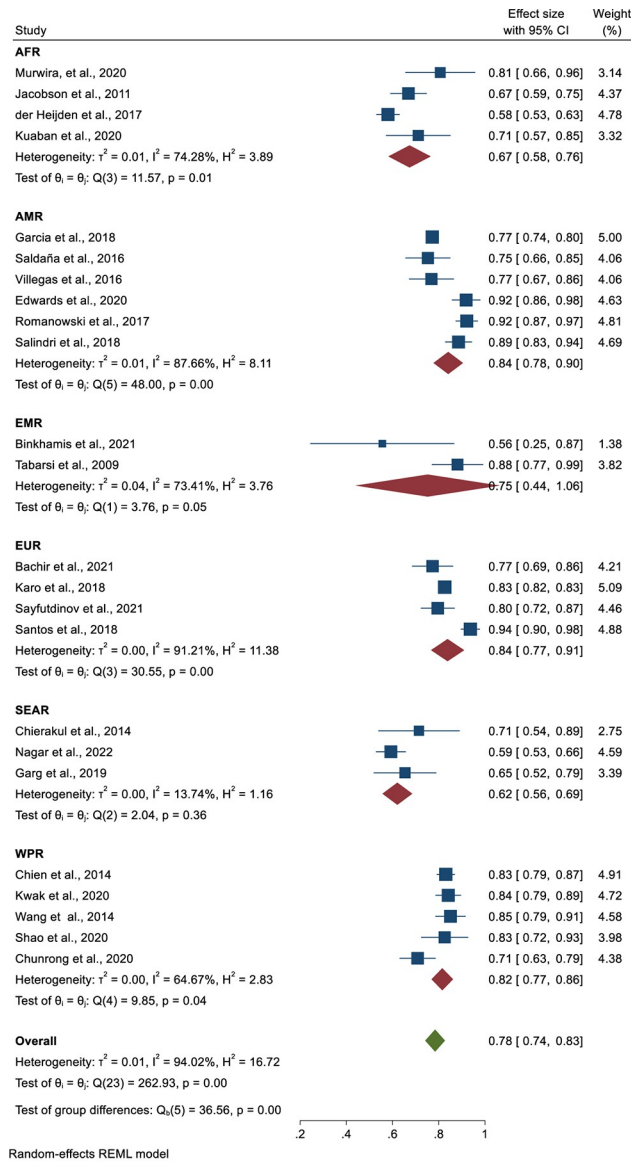
τ2; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared

heterogeneity statistic (variability between studies).

Fig 2. Forest plot for the pooled successful treatment outcome rate among patients with isoniazid mono-resistant tuberculosis.

https://doi.org/10.1371/journal.pone.0286194.g002

initiation phase isoniazid (INH), streptomycin (STR), fluoroquinolones (FLQ), second-line injectable drugs (SLIDs) and continuation phase (rifampicin (RIF), (pyrazinamide (PZA)).

Statistically significant association was found for previous TB history (pooled OR; 1.74; 95%CI; 1.15–2.33, I^2; 45.10%) (**Fig 7**), having cancer, (pooled OR; 3.53; 95%CI; 1.43–5.62, I^2; 0.00%) (**S11 Fig**), initially smear positive (pooled OR; 1.26, 95%CI; 1.08–1.43, I^2; 2.13%) (**Fig 8**), taking RIF in the continuation phase (pooled OR; 0.22, 95%CI; 0.04–0.41, I^2; 0.00%) (**S12 Fig**), having EPTB (pooled OR; 0.70, 95%CI; 0.55–0.85, I^2; 0.00%) (**S13 Fig**), and taking SLIDs (pooled OR; 0.54, 95%CI; 0.33–0.75, I^2; 0.00%) (**S14 Fig**). Accordingly, individuals with previous TB treatment history had 1.74 times the odds to had poor treatment outcome compared to
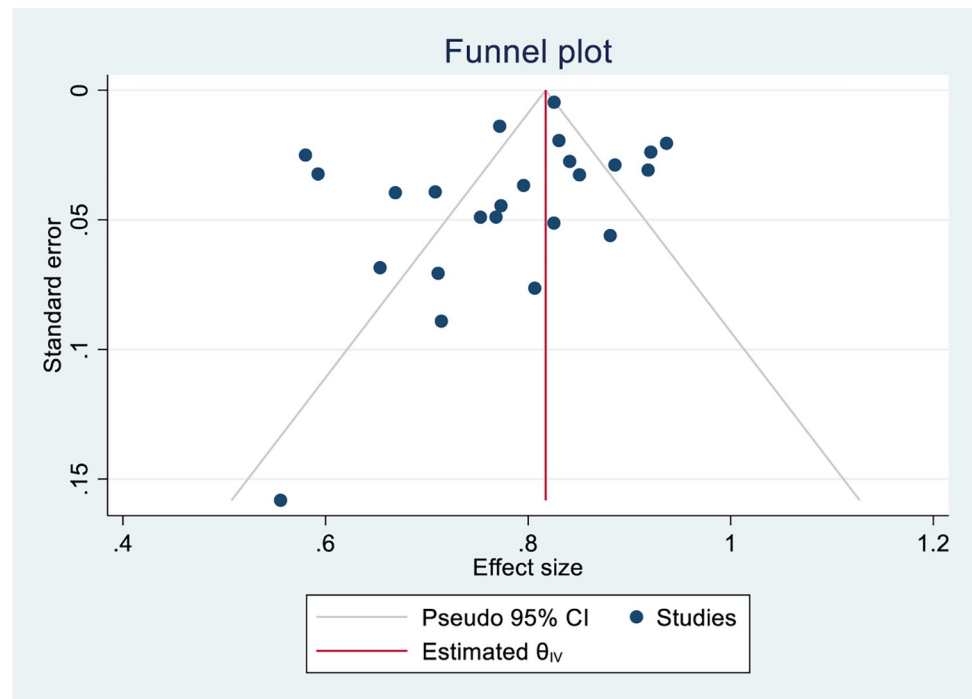
Fig 3. Funnel plot for the pooled successful treatment outcome rate among patients with isoniazid mono-resistant tuberculosis.

new patients. Those patients who had cancer had 3.53 times the odds to develop poor treatment outcome compared to the counterparts. In addition, those patients who were smear positive initially had 1.26 times the odds to develop poor treatment outcome compared to those having smear negative TB initially. Patients who took RIF in the continuation phase had 78% reduced risk to have poor treatment outcome compared to their counterparts. Furthermore, those who took SLIDs had 45% reduced risk to have poor treatment outcome compared to their counterparts. Besides, those patients with EPTB had 30% reduced risk of poor treatment outcomes compared to those who had pulmonary TB (**Table 2**).

Statistically significant association was not found for being male (pooled OR; 1.34, 95%CI; 0.90–1.77, I^2; 43.67%) (**S15 Fig**), older age (pooled OR; 0.97, 95%CI; 0.62–1,32, I^2;85.56%) (**S16 Fig**), being smoker (pooled OR; 95%CI; 0.89–4.20, I^2; 13.69%) (**S17 Fig**), having DM (pooled OR; 1.16, 95%CI; 0.70–1.63, I^2; 0.00%) (**S18 Fig**), having end-stage renal failure (pooled OR; 3.15, 95%CI; -0.07–6.38, I^2; 0.00%) (**S19 Fig**), being HIV positive (pooled OR; 2.26, 95%CI; 0.60–3.91, I^2; 43.47%) (**S20 Fig**), being high level INH resistance (pooled OR; 0.79, 5%CI; 0.36–1.21, I^2; 28.22%) (**S21 Fig**), taking INH in the initiation phase (pooled OR; 0.72, 95%CI; 0.33–1.11, I^2; 0.00%) (**S22 Fig**), taking STR in the initiation phase (pooled OR; 0.76, 95%CI; 0.15–1.37, I^2; 0.00%) (**S23 Fig**), taking FLQ in the initiation phase (pooled OR; 0.94, 95%CI; 0.48–1.39, I^2; 0.00%) (**S24 Fig**), taking PZA in the continuation phase (pooled OR; 0.87, 95%CI; 0.27–1.47, I^2; 0.00%) (**S25 Fig**), not culture converted after 2 months (pooled OR; 1.30, 95%CI; 0.59–2.00, I^2; 0.00%) (**S26 Fig**), and the presence cavity lesion in the chest radiograph (pooled OR; 1.23, 95%CI; 0.62–1.84, I^2; 0.00%) (**S27 Fig**) (**Table 2**).

Discussion

Based on the pooled estimates, about one fifth of isoniazid mono-resistant TB patients had poor treatment outcomes and different factors are associated with this. The study findings of
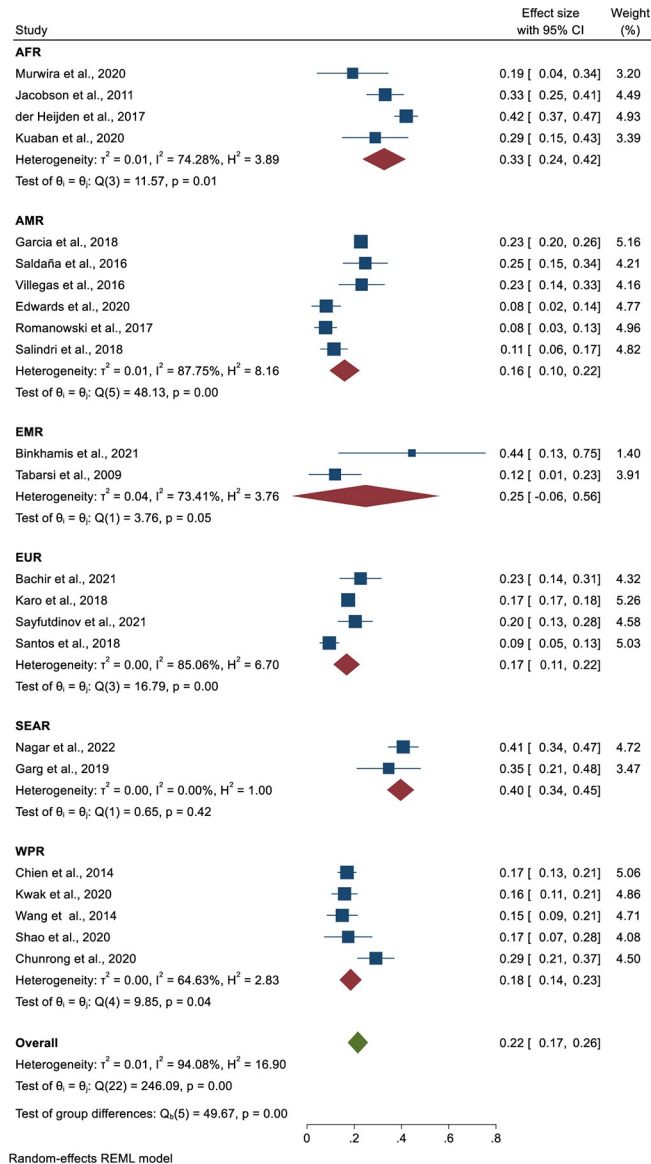
Table 2. The summary of the pooled on the poor treatment outcome and associated risk factors among patients with isoniazid mono-resistant tuberculosis per different categories.

Indicators	Number of studies	Pooled estimates	
		Estimate (prevalence/OR), 95%CI	Heterogeneity
			I^2
Successful treatment outcome			
Over all	24	78% (74–83)	94.02%
AFR	4	67% (58–76)	74.28%
AMR	6	84% (78–90)	87.66%
EMR	2	75% (44–106)	73.41%
EUR	4	84% (77–91)	91.21%
SEAR	3	62% (56–69)	13.74%
WPR	5	82% (77–86)	64.67%
Cure rate	15	62% (50–73)	96.91%
Complete rate	14	34% (17–52)	99.26%
Poor treatment outcome			
Over all	23	22% (17–26)	94.08%
AFR	4	33% (24–42)	74.28%
AMR	6	16%(10–22)	87.75%
EMR	2	25% (-6-56)	73.41%
EUR	4	17% (11–22)	85.06%
SEAR	2	40% (34–45)	0.00%
WPR	5	18% (14–23)	64.63%
Treatment failure	16	5% (3–7)	93.97%
Loss to follow-up	18	12% (8–17)	96.58%
Mortality	23	6% (4–8)	88.73%
Relapse after successful outcome	8	1.7% (0.4–3.1)	n33.58%
Risk factors of poor treatment outcome			
Previous anti-TB treatment	9	**1.74 (1.15–2.33)**	45.10%
Male sex	9	1.34 (0.90–1.77)	43.67%
Older age	9	0.97 (0.62, 1.32)	87.56%
Had HIV co-infection	6	2.26 (0.60–3.91)	43.47%
Smoking	2	2.54 (0.89–4.20)	13.69%
Had diabetes	3	1.16 (0.70–1.63)	0.00%
Had cancer	2	**3.53 (1.43–5.62)**	0.00%
Had end stage renal disease	2	3.15 (-0.07–6.38)	0.00%
Being smear positive initially	7	**1.26 (1.08–1.43)**	2.13%
Had high level INH resistance	6	0.79 (0.38–1.21)	28.22%
Took INH in the initiation phase	2	0.72(0.33–1.11)	0.00%
Took STR in the initiation phase	2	0.76 (0.15–1.37)	0.00%
Took FLQ in the initiation phase	3	0.94 (0.48–1.39)	0.00%
Took RIF in the continuation phase	2	**0.22 (0.04–0.41)**	0.00%
Took PZA in the continuation phase	2	0.87 (0.27–1.47)	0.005
Had extrapulmonary tuberculosis	4	**0.70 (0.55–0.85)**	0.00%
Not culture converted after 2 months of treatment	4	1.30 (0.59–2.00)	0.00%
Took SLIDs	2	**0.54 (0.33–0.75)**	0.00%
Had cavity lesion on the chest radiograph	3	1.23 (0.62–1.84)	0.00%

AFR; African region, AMR; Region of the Americas, EMR; Eastern Mediterranean Region, EUR; European Region, SEAR; South Eastern region, WPR; West Pacific Region, HIV; Human Immunodeficiency Virus, INH; Isoniazid, RIF; Rifampicin, STR; Streptomycin; FLQ; Fluoroquinolones, PZA; Pyrazinamide; SLIDs; Second Line Injectable Drugs, OR; Odds Ratio

Study	Effect size with 95% CI	Weight (%)
AFR		
Murwira et al., 2020	0.19 [0.04, 0.34]	3.20
Jacobson et al., 2011	0.33 [0.25, 0.41]	4.49
der Heijden et al., 2017	0.42 [0.37, 0.47]	4.93
Kuaban et al., 2020	0.29 [0.15, 0.43]	3.39
Heterogeneity: τ^2 = 0.01, I^2 = 74.28%, H^2 = 3.89	0.33 [0.24, 0.42]	
Test of $\theta_i = \theta_j$: Q(3) = 11.57, p = 0.01		
AMR		
Garcia et al., 2018	0.23 [0.20, 0.26]	5.16
Saldaña et al., 2016	0.25 [0.15, 0.34]	4.21
Villegas et al., 2016	0.23 [0.14, 0.33]	4.16
Edwards et al., 2020	0.08 [0.02, 0.14]	4.77
Romanowski et al., 2017	0.08 [0.03, 0.13]	4.96
Salindri et al., 2018	0.11 [0.06, 0.17]	4.82
Heterogeneity: τ^2 = 0.01, I^2 = 87.75%, H^2 = 8.16	0.16 [0.10, 0.22]	
Test of $\theta_i = \theta_j$: Q(5) = 48.13, p = 0.00		
EMR		
Binkhamis et al., 2021	0.44 [0.13, 0.75]	1.40
Tabarsi et al., 2009	0.12 [0.01, 0.23]	3.91
Heterogeneity: τ^2 = 0.04, I^2 = 73.41%, H^2 = 3.76	0.25 [-0.06, 0.56]	
Test of $\theta_i = \theta_j$: Q(1) = 3.76, p = 0.05		
EUR		
Bachir et al., 2021	0.23 [0.14, 0.31]	4.32
Karo et al., 2018	0.17 [0.17, 0.18]	5.26
Sayfutdinov et al., 2021	0.20 [0.13, 0.28]	4.58
Santos et al., 2018	0.09 [0.05, 0.13]	5.03
Heterogeneity: τ^2 = 0.00, I^2 = 85.06%, H^2 = 6.70	0.17 [0.11, 0.22]	
Test of $\theta_i = \theta_j$: Q(3) = 16.79, p = 0.00		
SEAR		
Nagar et al., 2022	0.41 [0.34, 0.47]	4.72
Garg et al., 2019	0.35 [0.21, 0.48]	3.47
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00	0.40 [0.34, 0.45]	
Test of $\theta_i = \theta_j$: Q(1) = 0.65, p = 0.42		
WPR		
Chien et al., 2014	0.17 [0.13, 0.21]	5.06
Kwak et al., 2020	0.16 [0.11, 0.21]	4.86
Wang et al., 2014	0.15 [0.09, 0.21]	4.71
Shao et al., 2020	0.17 [0.07, 0.28]	4.08
Chunrong et al., 2020	0.29 [0.21, 0.37]	4.50
Heterogeneity: τ^2 = 0.00, I^2 = 64.63%, H^2 = 2.83	0.18 [0.14, 0.23]	
Test of $\theta_i = \theta_j$: Q(4) = 9.85, p = 0.04		
Overall	0.22 [0.17, 0.26]	
Heterogeneity: τ^2 = 0.01, I^2 = 94.08%, H^2 = 16.90		
Test of $\theta_i = \theta_j$: Q(22) = 246.09, p = 0.00		
Test of group differences: $Q_b(5)$ = 49.67, p = 0.00		

0   .2   .4   .6   .8

Random-effects REML model

$\tau2$; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 4. Forest plot for the pooled poor treatment outcome rate among patients with isoniazid mono-resistant tuberculosis.

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this study revealed that the successful treatment rate among isoniazid mono-resistant TB patients was 79%. This finding is lower than the global average of the successful treatment outcome among drug-susceptible TB cases which was 85% and 86% for people newly enrolled on treatment in 2018 and in 2019, respectively [1, 2]. However, this is higher than MDR/RR-TB cases which was 59% based on the latest cohort [1], thus determining isoniazid resistant status for all bacteriologically confirmed TB cases may contribute for better treatment outcome and prevention of additional drug resistance. The successful treatment outcome among isoniazid mono-resistant TB cases had regional disparities, where better treatment success rate was
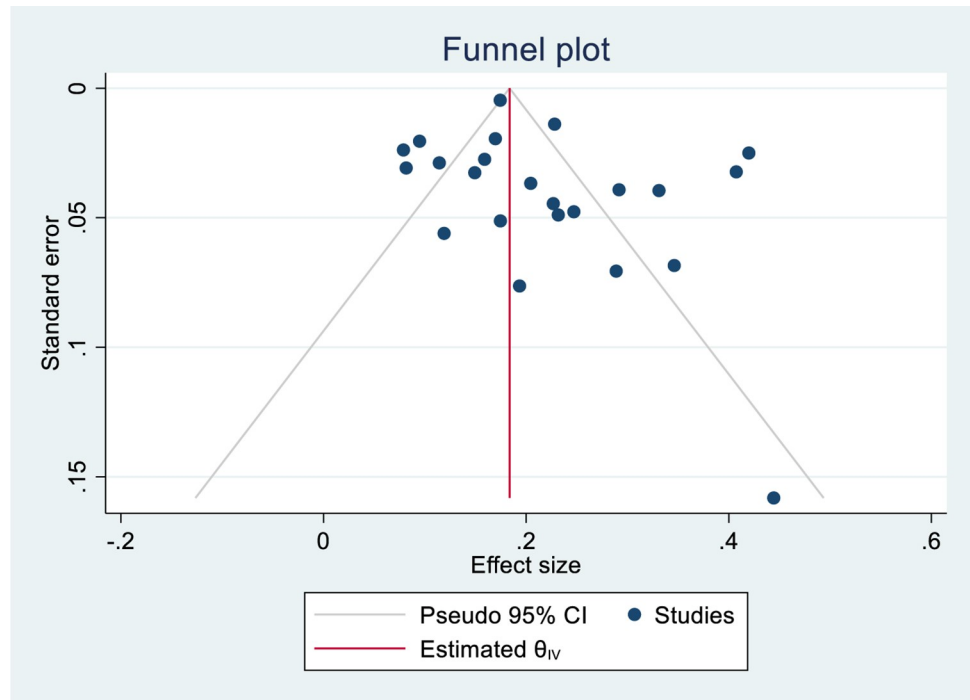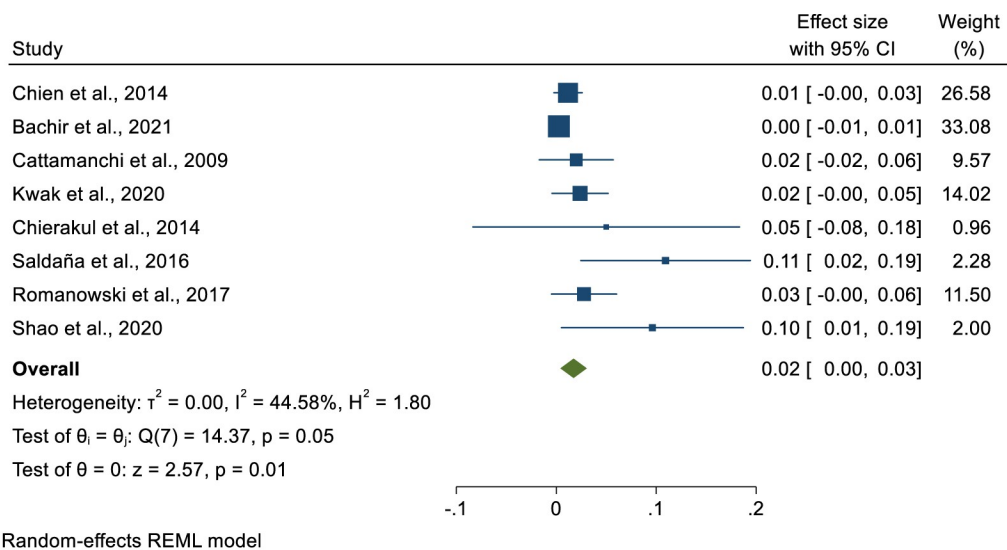
Fig 5. Funnel plot for the pooled poor treatment outcome rate among patients with isoniazid mono-resistant tuberculosis.

https://doi.org/10.1371/journal.pone.0286194.g005

$\tau 2$; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 6. Forest plot for the pooled relapse rate among successfully treated patients with isoniazid mono-resistant tuberculosis.

https://doi.org/10.1371/journal.pone.0286194.g006

Table 3. Meta-regression analysis of heterogeneity using sample size and publication year on poor treatment outcome.

Variable	Unadjusted model		Adjusted model	
	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value
Sample size	-5.76e-06 (-0.000035, 0.0000241)	0.719	-5.64e-06 (-0.0000357, 0.0000244)	0.713
Publication year	0.0051572 (-0.0085616, 0.0188759)	0.461	.0052476 (-0.0087989, 0.0192942)	0.464

https://doi.org/10.1371/journal.pone.0286194.t003

noted from AMR, EUR, and WPR having a successful treatment outcome above 80%, while lower treatment outcome was noted in AFR and SEAR having 71% and 62%, respectively. This revealed the importance of taking regional and country specific interventions.

The pooled poor treatment outcome among isoniazid-mono resistant TB patients estimated in this study is higher compared to drug-susceptible TB patients at the global level [1, 2]. Thus, determining isoniazid resistance level for all bacteriologically confirmed TB cases is important. In developing countries there is a gap in addressing the universal access to DST. Besides, most of the countries are using GeneXpert for the simultaneous detection of TB and rifampicin resistance. This test determines only the drug resistance pattern to rifampicin. Thus, the isoniazid resistance level may be underestimated and may be treated as drug susceptible TB. This might have resulted with poor treatment outcomes and increasing drug resistance [2]. Based on the sub-group analysis, higher poor treatment outcome is noted in the SEAR. Likewise, based on the 2020 global TB report, lower MDR/RR-TB treatment success rate was noted in SEAR [2].

We have estimated the pooled proportion of relapse among successfully treated isoniazid mono-resistant TB cases. The finding revealed that two percent of those patients had a relapse that extends up to two years after treatment completion. This relapse rate is relatively lower than the 3.7% relapse rate in a pooled estimate among patients enrolled on DOTs program
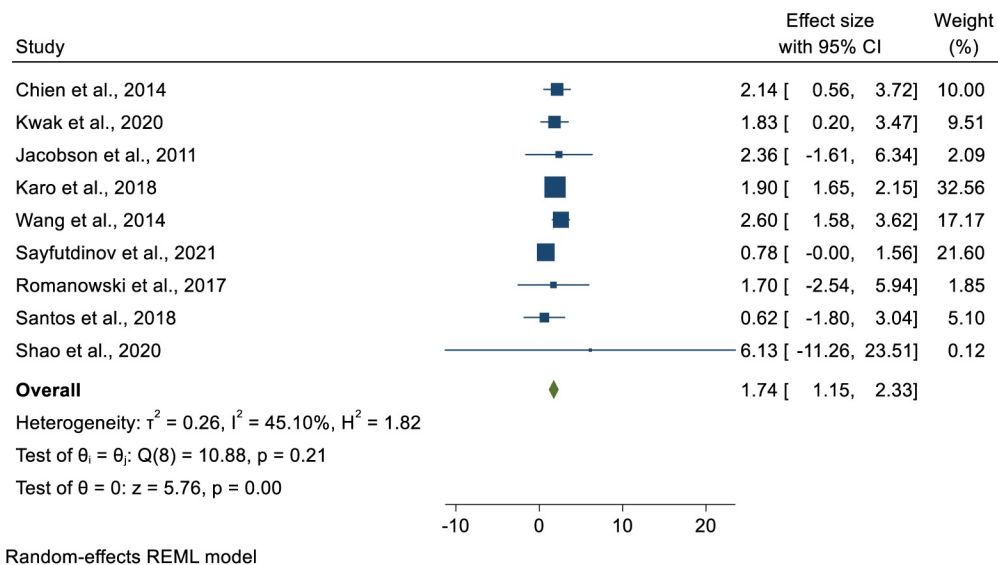
$\tau 2$; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 7. Forest plot for the association of previous TB treatment history with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
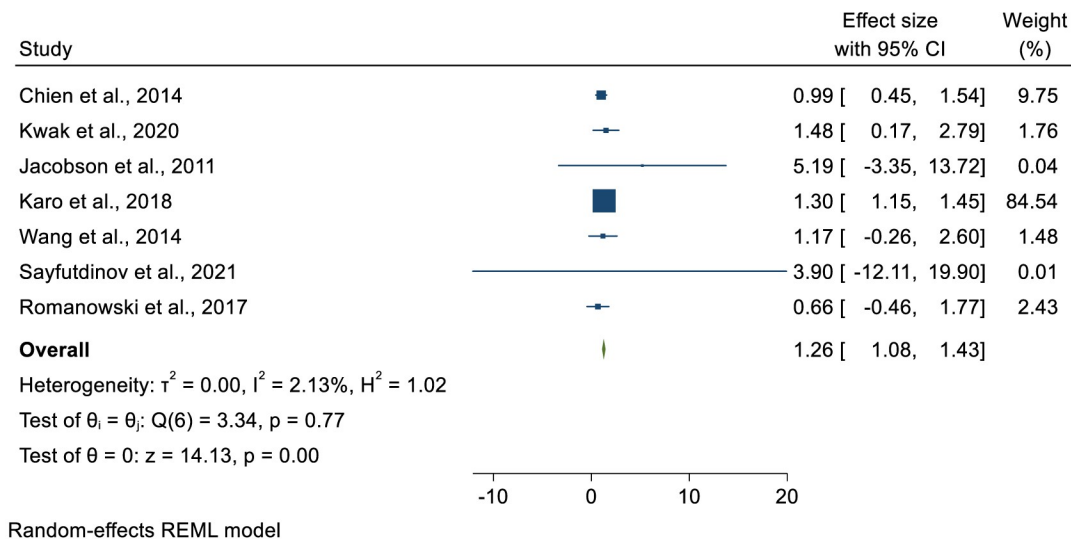
https://doi.org/10.1371/journal.pone.0286194.g007

Study		Effect size with 95% CI	Weight (%)
Chien et al., 2014		0.99 [0.45, 1.54]	9.75
Kwak et al., 2020		1.48 [0.17, 2.79]	1.76
Jacobson et al., 2011		5.19 [-3.35, 13.72]	0.04
Karo et al., 2018		1.30 [1.15, 1.45]	84.54
Wang et al., 2014		1.17 [-0.26, 2.60]	1.48
Sayfutdinov et al., 2021		3.90 [-12.11, 19.90]	0.01
Romanowski et al., 2017		0.66 [-0.46, 1.77]	2.43
Overall		1.26 [1.08, 1.43]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 2.13\%$, $H^2 = 1.02$			
Test of $\theta_i = \theta_j$: Q(6) = 3.34, p = 0.77			
Test of $\theta = 0$: z = 14.13, p = 0.00			

Random-effects REML model

$\tau 2$; Tau (between-study variance), I^2; I-squared heterogeneity statistic (variability between studies), H^2; H-squared heterogeneity statistic (variability between studies).

Fig 8. Forest plot for the association of being initially smear positive with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.

[39]. The pooled estimate in our study might be affected because the time of follow-up was different among the studies.

In the current study, we have conducted a pooled estimate to assess the factors associated with poor treatment outcome in isoniazid mono-resistant TB cases. The study findings revealed that, those patients who had a previous TB treatment history had 1.74 times the odds to develop poor treatment outcome compared to new cases. Association of previous TB treatment history for developing unsuccessful treatment outcome in TB patients for both drug-susceptible and drug-resistant TB was reported in different studies [40–44]. This risk factor is not specific to isoniazid mono-resistant TB, rather it is associated with unfavorable TB treatment outcome in general. The other identified risk factor is being smear positive initially. Initially smear positive patients had 1.26 times the odds to develop poor treatment outcome compared to smear negatives. Smear positive TB patients had higher bacterial load in their sputum reflecting the severity of the disease. Likewise, a global pooled estimate revealed that drug-resistant TB patients who were smear positive at the baseline had 1.58 times the risk to die [41]. Besides, those isoniazid mono-resistant TB cases who had cancer comorbid had 3.53 times the odds to had poor treatment outcome compared to the counter parts. Similarly, in a previous study it was reported that the 12-months all-cause mortality during TB in patients with malignancy was as high as 20.56% [45]. Thus, those patients with comorbid conditions should be critically followed during treatment.

The findings of this study also revealed that those patients who took rifampicin in the continuation phase had lower risk to develop poor treatment outcome. Including rifampicin for treatment of isoniazid-mono resistant TB cases is important to shorten the treatment duration. Our study also revealed that taking SLIDs lowered the risk of poor treatment outcome. However, in patients with confirmed rifampicin-susceptible and isoniazid-resistant TB, it is not recommended to add injectable agents to the treatment regimen [46]. In addition, compared to

PTB cases EPTB cases had 45% reduced risk to develop poor treatment outcome which needs further studies. It is difficult to document treatment cure in EPTB cases. In two studies conducted in Ethiopia, EPTB was reported as the risk factor for unsuccessful treatment outcome [47, 48].

Finally, the findings of this study should be interpreted by considering the limitations. The study findings of this study was based on a limited number of studies (24 studies) with small sample size for the majority that might affected the pooled estimates. In addition, in the majority of the primary studies data were collected retrospectively that might have introduced selection bias. Besides, there is high heterogeneity and publication bias was detected for some parameters that might affect the true estimates. However, we have performed a stratified analysis and we also performed a trim and fill analysis for those pooled estimates that had a publication bias that validated the findings of this study.

Conclusion

The findings of this study revealed that isoniazid mono-resistant TB patients had higher poor treatment outcome. The pooled estimates vary per geographical locations. Previous anti-TB treatment history, being smear positive initially, and having cancer were associated with poor treatment outcome in isoniazid mono-resistant TB patients. While, taking rifampicin in the continuation phase, taking SLIDs and having EPTB were associated with reduced risk of poor treatment outcome compared to their counter parts. Thus, determination of isoniazid resistance pattern for all bacteriological TB cases is critical to have successful treatment outcome.

Supporting information

S1 Table. Completed PRISMA 2009 checklist.
(DOCX)

S2 Table. Search engines.
(DOCX)

S3 Table. Quality assessment for the included studies in meta-analysis.
(DOCX)

S1 Fig. Forest plot for the complete rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S2 Fig. Funnel plot for the complete rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S3 Fig. Forest plot for the cure rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S4 Fig. Funnel plot for the cure rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S5 Fig. Forest plot for the treatment failure rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S6 Fig. Funnel plot for the treatment failure rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S7 Fig. Forest plot for the mortality rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S8 Fig. Funnel plot for the mortality rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S9 Fig. Forest plot for the lost to follow-up rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S10 Fig. Funnel plot for the lost to follow-up rate among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S11 Fig. Forest plot for the association of having cancer with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S12 Fig. Forest plot for the association of taking rifampicin in the continuation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S13 Fig. Forest plot for the association of having extrapulmonary tuberculosis with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S14 Fig. Forest plot for the association of taking second-line injectable drugs with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S15 Fig. Forest plot for the association of being male with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S16 Fig. Forest plot for the association of older age with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S17 Fig. Forest plot for the association of smoking with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S18 Fig. Forest plot for the association of having diabetes with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S19 Fig. Forest plot for the association of having end stage renal disease with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S20 Fig. Forest plot for the association of being HIV positive with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S21 Fig. Forest plot for the association of having high-level isoniazid resistance with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S22 Fig. Forest plot for the association of taking isoniazid in the initiation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S23 Fig. Forest plot for the association of taking streptomycin in the initiation phase with poor outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S24 Fig. Forest plot for the association of taking fluoroquinolones in the initiation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S25 Fig. Forest plot for the association of taking pyrazinamide in the continuation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S26 Fig. Forest plot for the association of not culture converted after 2 months' treatment of the initiation phase with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

S27 Fig. Forest plot for the association of having cavity during chest radiograph with poor treatment outcome among isoniazid mono-resistant tuberculosis patients.
(DOCX)

Acknowledgments

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The prevalence of latent tuberculosis infection in patients with chronic kidney disease: A systematic review and meta-analysis

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A R T I C L E I N F O

A B S T R A C T

Objective: To estimate the prevalence of latent tuberculosis infection (LTBI) in chronic kidney disease (CKD) patients.

Methods: This study was conducted following the PRISMA guidelines. We identified, 3694 studies from the whole search, and 59 studies were included. Each study's quality was assessed using JBI checklist. We employed STATA version 17 for statistical analysis. We assessed heterogeneity using I^2 heterogeneity test. Publication bias was assessed using funnel plot and Egger's test. We estimated the pooled LTBI prevalence in CKD patients along with 95%CI.

Results: The pooled prevalence of LTBI among CKD patients using data collected from 53 studies having 12,772 patients was 30.2% (95%CI; 25.5, 34.8). The pooled prevalence among pre-dialysis, hemodialysis, peritoneal dialysis, and renal transplanted patients was 17.8% (95%CI; 3.3, 32.4), 34.8% (95%CI; 29.1, 40.5), 25% (95%CI; 11, 38), and 16% (95%CI; 7, 25), respectively. The pooled prevalence of LTBI stratified by the laboratory screening methods was 25.3% (95%CI: 20.3–30.3) using TST, 28.0% (95%CI; 23.9–32.0) using QFT, and 32.6%, (95%CI: 23.7–41.5) using T-SPOT.

Conclusion: There is high prevalence of LTBI among CKD patients mainly in patients on dialysis. Thus, early diagnosis and treatment of LTBI in CKD patients should be performed to prevent active TB in CKD patients.

PROSPERO registration number: CRD42022372441.

1. Introduction

Tuberculosis (TB) continues to be a major public health issue across the globe. It is the second leading cause of mortality among

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Fig. 1. Flowchart describing the selection of studies for the systematic review and meta-analysis of latent tuberculosis prevalence among patients with chronic kidney disease.

infectious diseases next to COVID-19 [1]. Countries are committed to control and prevent TB by developing and adapting different strategies and measurable targets. The World Health Organization (WHO) developed the END-TB strategy that aims to reduce the incidence of TB to less than 10 per 100,000 populations by 2035 [2]. However, achieving this ambitious objective may be challenging unless a specific intervention approach that addresses the burden in a high-risk population is created and implemented. For example, specific groups of people, such as those with chronic kidney disease (CKD), are at a higher risk of contracting TB than the overall population, necessitating a focused intervention [3]. According to our recent global systematic review and meta-analysis, the incidence of TB in CKD patients was 3718/100,000 population [4]. A pooled estimate revealed that patients on dialysis had 3.6 times the risk to develop TB compared to the general population [5]. Currently, the incidence of CKD is rising in developing countries where TB is also endemic which may halt the TB prevention and control efforts to achieve the END-TB strategy [6].

Early detection and treatment of latent tuberculosis infection (LTBI) among groups of people with weakened immune systems, such as CKD patients, is critical for preventing the development of active TB. In addition, dialysis patients frequently travel to health facilities for medical care, which may increase the risk of infection with *Mycobacterium tuberculosis* [7]. When compared to healthy adults, these patients have a 10–25 fold increased chance of risk of reactivating LTBI [7]. The WHO recommends that persons undergoing dialysis or preparing for an organ transplant be tested and treated for LTBI [8]. There have been studies undertaken in different countries and settings to determine the prevalence of LTBI in CKD patients [7,9–23]. The prevalence of LTBI in CKD patients has been found to range from 6% [24,25] to 82% [23]. The systematic reviews were primarily concerned with comparing the performance of diagnostic tools for detecting of LTBI in dialysis patients [26–28]. However, there is limited data that reported the global, and regional prevalence of LTBI among CKD patients in general and across different categories. A global data that comprehensively assessed the burden of LTBI in CKD patients can be an essential input for policy development and guidance to boost the effort for TB prevention and control, as well to improve the quality of life for this population group. Thus, this study aimed to estimate the global pooled prevalence of LTBI among patients with CKD.

2. Methods

2.1. Protocol registration

The protocol for this systematic review and meta-analysis study is registered on the International Prospective Register of Systematic Reviews (PROSPERO) with a registration number CRD42022372441.

2.2. Article search strategy and selection procedure

This systematic review and meta-analysis study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. Two independent investigators (AA, ZWB) conducted article searching, and the third investigator (GD) resolved the inconsistencies. Both electronic databases and grey literature sources were searched for previously published studies that

reported LTBI among patients with any types of CKDs. We searched articles published in English language until November 21, 2022. PubMed, Global Index Medicus, Informit, Joanna Briggs Institute EBP Database (including OVID), and Global Health were among the electronic databases used. Whereas the grey literature sources were Google, and Google Scholar. The searching was carried out using the key terms in conjunction with the Boolean operators AND and OR. The keywords used in the current study includes; latent tuberculosis, chronic kidney disease patient, renal failure, dialysis, hemodialysis, peritoneal dialysis, renal-transplant, pre-renal transplant, and pre-dialysis. All of the articles identified during the entire search were exported to Endnote X8 citation manager. We have followed a stepwise approach to select the studies included in the final data-analysis. In the primary step, duplicates were removed and then the articles were screened by title and abstract. All the articles that passed the above stage were eligible for full-text screening and those that passed the full-text assessment were included in the final data analysis (Fig. 1) (Appendix).

2.3. PICOS criteria

Participants: Patients with chronic kidney disease.
Intervention: Not applicable.
Comparator: Not applicable.
Outcome: Latent TB infection.
Study design: Observational studies.
Study setting: Any setting in any country across the globe.

2.4. Inclusion and exclusion criteria

Studies that assessed prevalence of LTBI among different categories of CKD patients (pre-dialysis, hemodialysis, peritoneal dialysis, or renal transplanted) were included in the study. Review studies, incomplete studies and articles with different outcomes were excluded.

2.5. Data extraction

We extracted data from all studies included in the current systematic review and meta-analysis using the 2016 Microsoft Excel Spreadsheet. Two investigators (GS, EG) extracted data independently, and the inconsistencies were resolved through discussion and consensus was reached with the guidance of the third author (AA). The extracted data included; first author name, publication year, country, data collection period, study design, age group, type of CKD patients included, laboratory screening method, sample size, and number of patients who had LTBI. In addition to the above variables, the studies were categorized based on continent, WHO regional classification, and country TB burden category (Table 1).

2.6. Outcome

The primary outcome of this study was detection of LTBI among CKD patients with any category including pre-dialysis, hemo-dialysis, peritoneal dialysis, and renal transplant. The included studies used different laboratory screening methods alone or in combination for screening of LTBI in CDK patients; Tuberculin Skin Test (TST), QFT (QuantiFERON®-TB Gold), T-SPOT, and ELISPOT (enzyme-linked immunospot). The TST result was considered positive when the cut-off induration was $\geq$10 mm. From studies that employed a two-step TST, only the baseline results were taken to avoid a boosting phenomenon.

2.7. Quality assessment

Two independent investigators (AA, GS) assessed the quality and validity of individual studies included in this study using the Joanna Brigg's Institute critical appraisal tool [30]. The inconsistencies that arose between the two authors were resolved by the third investigator (ZWB). The JBI tool for prevalence study was used to assess the study's quality. Each question on the checklist was scored equally, and their total was calculated out of 100%. We classified the quality score as low, medium, and high quality when the score was <60%, 60–80%, and >80%, respectively.

2.8. Data synthesis and analysis

The data that were summarized in the 2016 Microsoft Excel Spreadsheet were exported to STATA version 17 for statistical analysis. The pooled prevalence of LTBI among CKD patients was estimated along with 95%CI. Sub-group analysis was performed based on CKD categories, LTBI laboratory screening methods, WHO regional classification, continent, country's income level, publication year, and TB burden category. We have presented the pooled estimates using forest plot. The presence of heterogeneity among studies was assessed using I^2 heterogeneity test where I^2 >50% was considered as the presence of substantial heterogeneity [31,32]. We have used the random-effect model considering the presence of substantial heterogeneity. We assessed the presence of publication bias through the visual inspection of the funnel plot and the statistical significance of the Egger's regression test (P < 0.05) [33,34]. A trim-and fill analysis was done to adjust the publication bias [35].

Table 1

Characteristics of individual studies on the prevalence of latent tuberculosis among patients with chronic kidney disease, included in the current systematic review and meta-analysis.

Author year	Country	Continent	TB burden category	Study period	Study design	Study group	Study setting	Age group	Diagnostic method
Wu et al., 2021	Taiwan	Asia	Not HBC	September 5, 2018 to September 5, 2019	Prospective study	HD	Kaohsiung Chang Gung Memorial Hospital	>18 years	QFT
Shu et al., 2015	Taiwan	Asia	Not HBC	January 2012 to June 2013	Cross-sectional	Patients undergoing dialysis, and those with severe CKD	National Taiwan University Hospital, a tertiary referral center, and its branches, regional teaching hospitals, and a local hemodialysis clinic.	≥20 years	QFT
Shu et al., 2012	Taiwan	Asia	Not HBC	March 2011 to February 2012	Cross-sectional	Dialysis	National Taiwan University Hospital, a tertiary referral center in northern Taiwan, and its branch in southern Taiwan.	≥20 years	QFT
Fonseca et al., 2013	Brazil	South America	HBC	December of 2008 to December of 2009	Cross-sectional	HD	Mineiro Institute of Nephrology	>18 years	TST
Gunluoglu et al., 2015	Turkey	Asia	Not HBC	September to November 2011	Cross-sectional	HD	Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital.	Mean age 62.2 years	TST and QFT
Passalent et al., 2007	Canada	North America	Not HBC	January 15 to April 15, 2005	Cross-sectional	HD	Toronto General Hospital site of the University Health Network	All	TST and T-SPOT
Ferreira et al., 2021	Brazil	South America	HBC	July to December 2018	Cross-sectional	HD	Clinical Hospital (HCFMRP-USP), of the Ribeirão Preto Nephrology Service (SENERP)	≥18 years	TST
Setyawati et al., 2021	Indonesia	Asia	HBC	May 2018	Cross-sectional	HD	Dr. Moewardi Surakarta Hospital	>18 years	TST and T-SPOT
Lee et al., 2010	Taiwan	Asia	Not HBC	October 2008	Cross-sectional	HD	Kaohsiung Veterans General Hospital	16.8–93.5 years	TST and QFT
Ahmadinejad et al., 2012	Iran	Asia	Not HBC	October 2009 to November 2010	Cross-sectional	Pre-transplantation	Tehran University of Medical Sciences.	16–65 years	TST and QFT
Sester et al., 2004	Germany	Europe	Not HBC	December 2001 to December 2002	Cross-sectional	HD	University of the Saarland	Mean age was 61.2 ± 15.2 years	TST
Al Jahdali et al., 2013	Saudi Arabia	Asia	Not HBC	August to December 2010	Cross-sectional	HD	KAMC-R	Mean age was 62.27 ± 11.79 years	TST and QFT
Kim et al., 2011	South Korea	Asia	Not HBC	June 2008 to December 2009	Cross-sectional	Transplant	University of Ulsan College of Medicine	>16 years	TST
Al Wakeel et al., 2015	Saudi Arabia	Asia	Not HBC	January 5, 2011 to March 31, 2013	Prospective study	Dialysis	King Khalid University Hospital, Security Forces Hospital and Lehbi Medical Center	≥18 years	TST and QFT
Lee et al., 2015	South Korea	Asia	Not HBC	–	Prospective study	Dialysis	Inje University Busan Paik hospital.	23–74 years	QFT
Ates et al., 2010	Turkey	Asia	Not HBC	15 February to July 15, 2008	Cross-sectional	HD	13 hemodialysis centers in five different cities	>15 years	TST
Chung et al., 2009	South Korea	Asia	Not HBC	1 March to April 30, 2008	Cross-sectional	HD	Gil Medical Centre, Gachon University of Medicine and Science	17–88 years	TST, QFT and T-SPOT
Shu et al., 2019	Taiwan	Asia	Not HBC	2014 to 2018	Cross-sectional	On pre transplantation and after transplantation	National Taiwan University Hospital,	≥20 years	QFT
Agarwal et al., 2015	India	Asia	HBC	May 2007 to August 2010	Cross-sectional	HD	All India Institute of Medical Sciences	18–88 years	TST and QFT

(continued on next page)

Table 1 (*continued*)

Author year	Country	Continent	TB burden category	Study period	Study design	Study group	Study setting	Age group	Diagnostic method
Sultan et al., 2016	Iraq	Asia	Not HBC	1st of April to December 15, 2014	Cross-sectional	HD	Baghdad teaching hospital	Mean age was 54.34 ± 15.25 years	TST
Hassen et al., 2013	Saudi Arabia	Asia	Not HBC	January 1 to May 30, 2009	Cross-sectional	HD	King Fahad specialist hospital in Dammam	≥18 years	TST and T-SPOT
Chagas et al., 2014	Brazil	South America	HBC	July 2011 to December 2013	Cross-sectional	HD	six existing dialysis services in Campo Grande, MS, Brazil	>18 years	TST
Romanowski., 2020	British Columbia, Canada	North America	Not HBC	January 1, 2012 to May 31, 2017	Retrospective cohort	Dialysis	British Columbia	≥18 years	IGRA (Not specified)
Hussein et al., 2017	Egypt	Africa	Not HBC	February to April 2016	Prospective study	HD	Sohag University Hospital	21–65 years	TST and QFT
Shankar et al., 2005	India	Asia	HBC	–	Prospective study	ESRD	Postgraduate Institute of Medical Education and Research Hospital, Chandigarh	18–60 years	TST
Triverio et al., 2009	Switzerland	Europe	Not HBC	–	Cross-sectional	HD	Geneva University Hospital	Mean age was 65 ± 15 years	TST, QFT and T-SPOT
Soysal et al., 2012	Turkey	Asia	Not HBC	May 2006 to May 2007	Prospective study	HD	Marmara University School of Medicine	19–84 years	TST and T-SPOT
Habesoglu et al., 2007	Turkey	Asia	Not HBC	–	Prospective study	HD	Adana Teaching and Training Hospital of Baskent University	Mean age was 50.0 ± 15.9 years	TST
Hoffmann et al., 2010	Switzerland	Europe	Not HBC	–	Prospective study	HD	Kantonsspital, St.Gallen	≥18 years	TST and QFT
Agarwal et al., 2010	India	Asia	HBC	May 2000 to May 2006	Prospective study	Transplant	All India Institute of Medical Sciences	14–60 years	TST
Lee et al., 2009	Taiwan	Asia	Not HBC	September 2005	Prospective study	HD	Kaohsiung Veterans General Hospital	34.4–77.7 years	TST, QFT and T-SPOT
Lin et al., 2020	Taiwan	Asia	Not HBC	March 1, 2017, to May 31, 2017	Cross-sectional	HD	Kaohsiung Medical University Hospital	≥20 years	QFT
Baek et al., 2019	South Korea	Asia	Not HBC	March 2017 to August 2019	Cross-sectional	Dialysis	Mediplex Sejong Hospital	All (mean age was 61.6 ± 12.6 years)	QFT
Bandiara et al., 2021	Indonesia	Asia	HBC	March to May 2020	Cross-sectional	HD	Dr. Hasan Sadikin Hospital	≥18 years	IGRA (Not specified)
Ogawa et al., 2021	Japan	Asia	Not HBC	–	Cross-sectional	HD	3 hospitals	62–79 years	QFT
SAYARLIOĞLU et al., 2011	Turkey	Asia	Not HBC	–	Cross-sectional	HD	Kahramanmaras State Hospital,	Mean age was 54.6 ± 14.9 years	TST and QFT
Carrazco-Ibarra et al., 2017	Mexico	North America	Not HBC	2011–2016	Retrospective cohort	Pre-transplantation	Hospital based study	–	TST
Seyhan et al., 2009	Turkey	Asia	Not HBC	November 2008 to December 2008	Cross-sectional	HD	Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital	Mean age was 56.2 ± 15.3 years	TST and QFT
Wauters et al., 2004	Belgium	Europe	Not HBC	September–October 2001	Cross-sectional	HD	University Hospital Gasthuisberg KU Leuven, Leuven and Virga Jesse Hospital, Hasselt	21–92 years	TST

Table 1 (*continued*)

Author year	Country	Continent	TB burden category	Study period	Study design	Study group	Study setting	Age group	Diagnostic method
Fang et al., 2002	Taiwan	Asia	Not HBC	June to July 1999	Cross-sectional	Dialysis	Kaoh siung Veterans General Hospital.	Mean age was 54.7 ± 17.3 years	TST
Winthrop et al., 2008	USA	North America	Not HBC	Oct-03	Cross-sectional	HD	Multisite study conducted by USA CDC	18–90 years	TST, QFT, and ELISPOT
Woeltje et al., 1998	USA	North America	Not HBC	June 1996 to August 1996	Cross-sectional	HD	Washington University School of Medicine, St Louis	19–91 years	TST
Smirnoff et al., 1998	USA	North America	Not HBC	1995	Cross-sectional	HD	The Mount Sinai Medical Center,	19–89 years	TST
Connel et al., 2010	United Kingdom	Europe	Not HBC	2008	Cross-sectional	CKD with different categories	Hammersmith Hospital	28–88 years	TST, QFT and T-SPOT
Cengiz et al., 2005	Turkey	Asia	Not HBC	–	Cross-sectional	HD	Ondokuz Mayıs University School of Medicine	Mean age was 49.9 ± 14.4 years	TST
Akcay et al., 2003	Turkey	Asia	Not HBC	January 1 to December 31, 1999	Cross-sectional	HD	Hacettepe University School of Medicine, Hemodialysis Unit	20–72 years	TST
Dogan et al., 2005	Turkey	Asia	Not HBC	June to December 2003	Prospective study	HD	Van (Yuzuncu Yil University Hospital, Yuksek Ihtisas Hospital) and the Mus State Hospital).	13–82 years	TST
Foster et al., 2016	Canada	North America	Not HBC	February 2008 to December 2008	Retrospective cohort	Dialysis	4 major hospital dialysis units in Winnipeg, Manitoba.	Mean age was 54.3 ± 14.7 years	TST
Khosroshahi et al., 2012	Iran	Asia	Not HBC	–	Cross-sectional	HD	two university hospitals in Tabriz	Mean age was 44.6 ± 15 years	TST
Altunoren et al., 2012	Turkey	Asia	Not HBC	–	Cross-sectional	Dialysis	Kahramanmaraş Sutcu Imam University	Mean age was 51.9 ± 15.5 years	TST
Edathodu et al., 2016	Saudi Arabia	Asia	Not HBC	August 2008 to May 2013	Prospective study	ESRD	King Faisal Specialist Hospital and Research Centre	≥14 years	TST and QFT
Maciel et al., 2018	Brazil	South America	HBC	January 2011 to July 2013	Cross-sectional	Transplant	Federal University of Minas Gerais Hospital das Clínicas	≥18 years	TST
Igari et al., 2019	Japan	Asia	Not HBC	April 2017 to March 2018	Cross-sectional	Transplant	National Hospital Organization Chiba-East Hospital	20–79	QFT and T-SPOT
Meinerz et al., 2021	Brazil	South America	HBC	April 4th, 2014 to Oct 31st, 2018, follow-up until Oct 31st, 2019	Prospective study	Transplant	Hospital based study	18–80 years	TST and QFT
Grant et al., 2012	Canada	South America	Not HBC	–	Cross-sectional	HD	Vancouver General Hospital	≥18 years	TST, QFT and T-SPOT
Chung et al., 2010	South Korea	Asia	Not HBC	February 1st to March 31st, 2009	Cross-sectional	HD	Gil Medical Center	18–81 years	TST, QFT and T-SPOT
Mohtashami et al., 2022	Iran	Asia	Not HBC	2018	Cross-sectional	HD	Khorramabad teaching hospitals.	>15 years	TST
Wang et al., 2020	Taiwan	Asia	Not HBC	2016–2019	Cross-sectional	HD	two tertiary-care medical centers	Mean age was 56.7 ± 11.2 years	QFT
Harris et al., 2016	Canada	North America	Not HBC	2007 to 2014	Cross-sectional	ESRD	British Columbia Centre for Disease Control	All	TST and IGRA (Not specified)

CKD; Chronic Kidney Disease, HD; Hemodialysis, HBC; High TB Burden Country, TST; Tuberculin Skin Test, QFT; QuantiFERON®-TB Gold, ELISPOT; enzyme-linked immunospot, "-"; Not described.
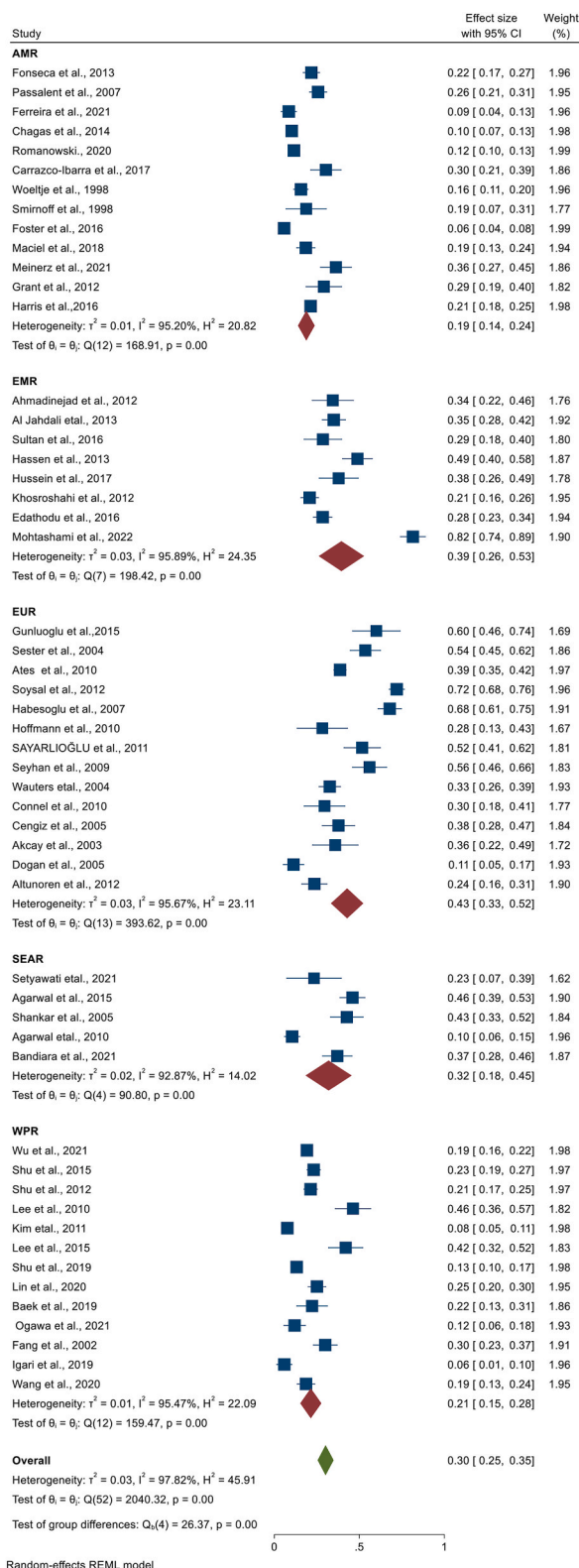
Fig. 2. Forest plot for the pooled prevalence of latent tuberculosis among patients with chronic kidney disease.
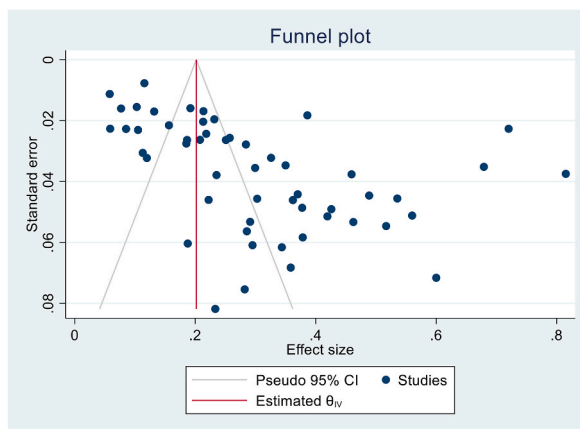
Fig. 3. Funnel plot for the pooled the pooled prevalence of latent tuberculosis among patients with chronic kidney disease.

Table 2
The summary of the pooled prevalence of latent tuberculosis among chronic kidney disease patients per different categories.

Latent tuberculosis prevalence among patients with chronic kidney disease across different categories		Number of studies	Sample size	Number of LTBI cases	Pooled LTBI prevalence	
					Estimate, 95% CI	Heterogeneity I^2
Over all latent tuberculosis prevalence		53	12,772	3219	30% (26, 35)	97.82%
Per continent	Europe	4	451	170	36% (25, 48)	82.78%
	Asia	35	7273	2253	33% (27, 40)	97.57%
	North America	7	3662	536	18% (12, 24)	95.78%
	South America	6	1005	163	20% (12, 28)	93.50%
	Africa	1	74	28	38% (26, 49)	–
Per WHO regional classification	Region of Americas	13	4974	766	19% (14, 24)	95.20%
	European Region	8	1193	434	43% (33, 52)	95.67%
	East Mediterranean Region	14	2440	1113	39% (26, 53)	95.89%
	South East Asian Region	5	643	206	32% (18, 45)	92.87%
	West Pacific Region	13	3522	700	21% (15, 28)	95.47%
	African Region	–	–	–	–	–
Per publication year	1998–2010	17	2994	1008	34% (26, 42)	95.41%
	2011–2015	16	3647	1099	34% (25, 43)	97.65%
	2016–2022	20	6131	1112	24% (17, 31)	98.31%
Per high TB burden category	Included	10	1876	413	25% (16, 34)	95.81%
	Not included	43	10,896	2806	31% (26, 37)	98.02%
Per World Bank Group income classification of countries	Lower Middle Income	6	717	234	33% (21, 44)	90.82%
	Upper Middle Income	20	3839	1375	37% (28, 47)	97.89%
	High Income	27	8216	1610	24% (20, 29)	96.75%
Per laboratory diagnostic method	TST	47	8208	1966	25% (20, 30)	97.71%
	QFT	29	4821	1285	28% (24, 32)	90.83%
	T-SPOT	13	1412	595	33% (24, 42)	97.53%
	ELISPOT	1	97	27	–	–
Per chronic kidney disease categories	Pre-dialysis	3	432	61	18% (3, 32)	90.61%
	Hemodialysis	39	7534	2396	35% (29, 41)	96.87%
	Peritoneal dialysis	5	253	60	25% (11, 38)	83.48%
	Post-renal transplantation	6	1100	159	16% (7, 25)	94.26%

TST; Tuberculin Skin Test, QFT; QuantiFERON®-TB Gold, ELISPOT; enzyme-linked immunospot, WHO; World Health Organization, "-"; Not available.

3. Results

3.1. Study characteristics

From the whole search, 5316 studies were identified and 854 duplicates were removed. Title and abstract screening was conducted for the 4462 studies and 4388 were excluded. Then, the remaining 74 studies were assessed for full text and 59 studies were included in the final analysis. While the remaining 15 studies were excluded due to different reasons (review articles, incomplete studies, articles

Study	Effect size with 95% CI	Weight (%)
Fonseca et al., 2013	0.22 [0.17, 0.27]	2.21
Gunluoglu et al.,2015	0.36 [0.22, 0.51]	1.89
Passalent et al., 2007	0.13 [0.08, 0.18]	2.21
Ferreira et al., 2021	0.09 [0.04, 0.13]	2.22
Setyawati etal., 2021	0.20 [0.05, 0.35]	1.86
Lee et al., 2010	0.54 [0.42, 0.65]	2.02
Ahmadinejad et al., 2012	0.22 [0.11, 0.33]	2.04
Sester et al., 2004	0.54 [0.45, 0.62]	2.10
Al Jahdali etal., 2013	0.13 [0.08, 0.18]	2.21
Kim etal., 2011	0.08 [0.05, 0.11]	2.24
Al Wakeel et al., 2015	0.15 [0.11, 0.20]	2.21
Ates et al., 2010	0.39 [0.35, 0.42]	2.23
Chung et al., 2009	0.23 [0.16, 0.29]	2.17
Agarwal et al., 2015	0.17 [0.12, 0.23]	2.19
Sultan et al., 2016	0.29 [0.18, 0.40]	2.03
Hassen et al., 2013	0.19 [0.12, 0.26]	2.16
Chagas et al., 2014	0.10 [0.07, 0.13]	2.24
Hussein et al., 2017	0.14 [0.05, 0.22]	2.12
Shankar et al., 2005	0.43 [0.33, 0.52]	2.08
Triverio et al., 2009	0.19 [0.09, 0.30]	2.05
Soysal et al., 2012	0.53 [0.48, 0.58]	2.21
Habesoglu et al., 2007	0.68 [0.61, 0.75]	2.16
Hoffmann et al., 2010	0.09 [-0.02, 0.21]	2.01
Agarwal etal., 2010	0.10 [0.06, 0.15]	2.21
Lee etal., 2009	0.63 [0.45, 0.80]	1.78
SAYARLIOĞLU et al., 2011	0.31 [0.21, 0.41]	2.07
Carrazco-Ibarra et al., 2017	0.30 [0.21, 0.39]	2.10
Seyhan et al., 2009	0.34 [0.24, 0.44]	2.08
Wauters etal., 2004	0.33 [0.26, 0.39]	2.18
Fang et al., 2002	0.30 [0.23, 0.37]	2.16
Winthrop et al., 2008	0.26 [0.17, 0.35]	2.10
Woeltje et al., 1998	0.16 [0.11, 0.20]	2.22
Smirnoff et al., 1998	0.19 [0.07, 0.31]	2.00
Connel et al., 2010	0.08 [0.00, 0.16]	2.14
Cengiz et al., 2005	0.38 [0.28, 0.47]	2.09
Akcay et al., 2003	0.36 [0.22, 0.49]	1.94
Dogan et al., 2005	0.11 [0.05, 0.17]	2.18
Foster et al., 2016	0.06 [0.04, 0.08]	2.25
Khosroshahi et al., 2012	0.21 [0.16, 0.26]	2.20
Altunoren et al., 2012	0.24 [0.16, 0.31]	2.15
Edathodu et al., 2016	0.12 [0.08, 0.17]	2.22
Maciel et al., 2018	0.19 [0.13, 0.24]	2.20
Meinerz et al., 2021	0.18 [0.11, 0.25]	2.15
Grant et al., 2012	0.03 [-0.02, 0.07]	2.21
Chung et al., 2010	0.27 [0.17, 0.36]	2.10
Mohtashami et al., 2022	0.82 [0.74, 0.89]	2.15
Harris et al.,2016	0.03 [0.01, 0.04]	2.25
Overall	0.25 [0.20, 0.30]	

Heterogeneity: $\tau^2 = 0.03$, $I^2 = 97.71\%$, $H^2 = 43.69$

Test of $\theta_i = \theta_j$: Q(46) = 1725.69, p = 0.00

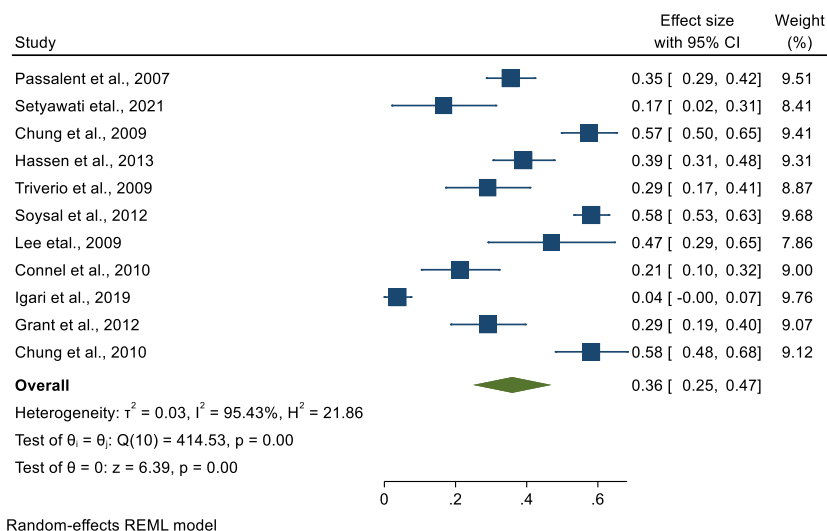Test of $\theta = 0$: z = 9.90, p = 0.00

Random-effects REML model

Fig. 4. Forest plot for the pooled prevalence of latent tuberculosis among patients with chronic kidney disease diagnosed using TST.

with different outcomes) (Fig. 1) (Appendix).

The studies were conducted in 18 countries from four continents. The highest number of studies were from Asia (39 studies) followed by North America (8 studies), South America (6 studies), and Europe (5 studies). The least number of study was from Africa with only one study conducted in Egypt. Based on the WHO regional classifications, the highest number of studies were from the West Pacific Region (WPR) with 16 studies followed by the European Region (EUR) (15 studies), the Region of Americans (AMR) (14 studies), Eastern Mediterranean Region (EMR) (9 studies), and South East Asian Region (SEAR) (5 studies). No study was reported from the WHO African Region (AFR). Specifically, the most frequent studies were from Turkeye (10 studies) followed by Taiwan (9 studies), South Korea (5 studies), Canada (5 studies), and Brazil (5 studies). The other studies were reported from Saudi Arabia, United States, India, Iran, Indonesia, Japan, Switzerland, Belgium, Egypt, Germany, Iraq, Mexico, and United Kingdom. Based on the World Bank income classification, 6, 20, and 27 studies were reported from lower middle income, upper middle income and high income countries, respectively.

Based on publication year, 22, 17, and 20 studies were published from 1998 to 2010, from 2011 to 2015 and from 2016 to 2022. Based on the 2021 global TB report, 10 studies were reported from high TB burden countries while the remaining 49 studies were reported from countries that were not included in the high TB burden country list. The majority of the studies (43 studies) were conducted using a cross-sectional study design **(Table 1)**.

Different laboratory diagnostic methods such as TST and IGRA (QFT, T-SPOT and ELISPOT) were used to detect LTBI in CKD patients. The IGRA method was used in 36 studies where QFT, T-SPOT, and ELISPOT were used in 29, 11 and 1 studies, respectively. However, the type of IGRA methods were not specified in three studies. Tuberculin skin test was used in 47 studies. These diagnostic methods were used alone or in different combinations **(Table 1)**.

3.2. Pooled prevalence of latent tuberculosis among patients with chronic kidney disease

We have extracted data from 59 studies, but the pooled prevalence of LTBI among CKD patients was determined by using 53 studies. In the remaining six studies, the studies used two or more laboratory screening methods and data was available for the specific method, but we were unable to get the overall LTBI prevalence in combination of the laboratory methods. The highest sample size was 1790 [13], while the lowest sample size was 30 [36]. The highest prevalence was 82% from Iran [23], and the lowest prevalence 6% from Canada [24] and from Japan [25]. When pooled together, 3219 CKD patients had LTBI from 12,772 patients. Based on the random effect model, the pooled prevalence of LTBI among CKD patients was estimated as 30.2% (95%CI; 25.5, 34.8, I^2; 97.82%) (Fig. 2). There was high heterogeneity among studies, and publication bias was revealed by funnel plot (Fig. 3) and Egger's regression test (P = 0.0006). However, after the trim-and-fill analysis, there was no change in the pooled estimate (Fig. 2) (Table 2).

Per continent, the highest pooled prevalence of LTBI among CKD patients was found in Europe (estimate; 36%, 95%CI; 25, 48, I^2; 82.78%) followed by Asia (estimate; 33%, 95%CI; 27, 40, I^2; 97.57%), South America (estimate; 20%, 95%CI; 12, 28, I^2; 93.50%), and North America (estimate; 18%, 95%CI; 12, 24, I^2; 95.78%). Since there is only one study from Africa conducted in Egypt with a prevalence of 38% (95% CI; 26, 49), we were unable to estimate the pooled prevalence. Per the WHO regional classification, the highest pooled estimate was found in EUR (estimate; 43%, 95%CI; 33, 52, I^2; 95.67%) followed by EMR (estimate; 39%, 95%CI; 26, 53, I^2; 95.89%), SEAR (estimate; 32%, 95%CI; 18, 45, I^2; 92.87%), WPR (estimate; 21%, 95%CI; 15, 28, I^2; 95.47%), and AMR (estimate; 19%, 95%CI; 14, 24, I^2; 95.20%) (Fig. 2). In addition, we have also performed a sub-group analysis based on publication year. The pooled prevalence of LTBI among CKD patients based on studies published from 1998 to 2010, from 2011 to 2015, and from 2016 to 2022, were 34% (95%CI; 26%, 42, I^2; 95.41%), 34% (95%CI; 25%, 43, I^2; 97.65%), and 24% (95%CI; 17%, 31, I^2; 98.31%), respectively. Besides, we performed a sub-group analysis considering classification of countries with TB burden category. Thus, the pooled prevalence of LTBI among CKD patients residing in high TB burden countries was 25% (95%CI; 16%, 34, I^2; 95.81%), while the pooled LTBI prevalence among CKD patients residing in the countries not included in the list of high TB burden countries was 31% (95%CI; 26%, 37, I^2; 98.02%). Furthermore, we have conducted a sub-group analysis based on the World Bank Group classification of countries by their income level. Accordingly, the pooled prevalence of LTBI was 24% **(95%CI; 20%, 29, I^2; 96.75%), 33% (95%CI; 21%, 44, I^2; 90.82%), and 37% (95%CI; 28%, 47, I^2; 97.89%) in CKD patients living in high income, lower middle income and upper middle income countries, respectively **(Table 2) (Appendix).**

3.3. Pooled prevalence of latent tuberculosis per laboratory diagnostic method

We have performed a sub-group analysis, using the laboratory diagnostic method used to detect LTBI in CKD patients. Accordingly, TST, QFT, T-SPOT, ELISPOT, and unspecified IGRA were used. Tuberculin skin test was used by 47 studies, where the highest prevalence was 82% [23] and the lowest prevalence was 3% [37,38]. A total of 8208 CKD patients were screened by TST and 1966 were found to have LTBI. Based on the random effect model, the pooled prevalence of LTBI among CKD patients screened by TST was 25.3% (95%CI; 20.3%, 30.3%, I^2; 97.71%) (Fig. 4). The Egger's regression test (P = 0.002) revealed the presence of publication bias **(Appendix)**. However, there is no change in the pooled prevalence after the trim and fill analysis. The QFT test was used in 29 studies where the largest and the smallest LTBI prevalence among CKD patients detected by QFT were 54% [39], and 6% [25], respectively. From 4821 CKD patients screened for LTBI using QFT, 1285 were found to have LTBI that gave a pooled prevalence of 28.0% (95%CI; 23.9, 32.0, I^2; 90.83%) (Fig. 5). The presence of publication bias was revealed by the asymmetry of the funnel plot and the statistical significance of the Egger's regression test (P = 0.0003) **(Appendix)**. After the trim and fill analysis, the pooled estimate became 25.4% (95%CI; 21.1%, 29.8%). The other laboratory method used to detect LTBI in CKD patients was T-SPOT that is used by 13 studies. Based on this method, the smallest and the highest LTBI prevalence was found to be 4% [25] and 58% [40], respectively. Among 1412 CKD
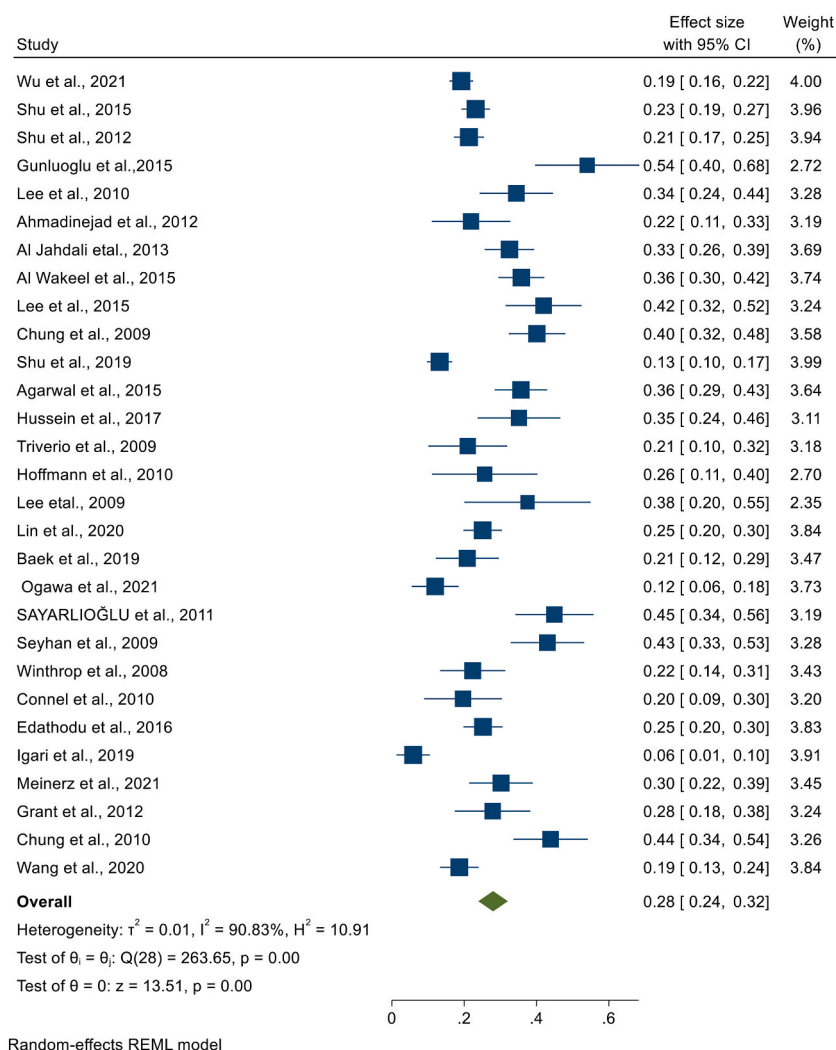
Fig. 5. Forest plot for the pooled prevalence of latent tuberculosis among patients with chronic kidney disease diagnosed using QFT.

patients screened for LTBI using T-SPOT, 595 patients were found to have LTBI. Based on the random effect model, the pooled prevalence of LTBI in CKD patients screened by T-SPOT was 32.6% (95% CI; 23.7, 41.5, I^2; 97.53%) (Fig. 6). Based on the Egger's regression test there is no publication bias (P = 0.306) **(Appendix).** Since there is only one study that used ELISPOT, it was difficult to estimate the pooled prevalence **(Table 2).**

3.4. Prevalence of latent tuberculosis across categories of chronic kidney disease

In this study, we have performed a sub-group analysis to estimate the pooled prevalence of LTBI based on the category of CKD such that pre-dialysis, hemodialysis, peritoneal dialysis and post-renal transplantation. Specifically, 39, 6, 5, and 3 studies assessed the prevalence of LTBI in hemodialysis, post-renal transplantation, peritoneal dialysis and pre-dialysis patients, respectively. Among 432 pre-dialysis patients, 61 were found to have LTBI that gave a pooled LTBI prevalence of 17.8% (95%CI; 3.3, 32.4, I^2; 90.61%) (Fig. 7). In hemodialysis patients, the smallest prevalence of LTBI was 9% [12], while the highest prevalence was 82% [23]. A total of 7534 hemodialysis patients were screened for LTBI and 2396 were found to have LTBI with a pooled LTBI prevalence of 34.8% (95%CI; 29.1, 40.5, I^2; 96.87%) (Fig. 8). The Egger's regression test was on the borderline (P = 0.049) that revealed the presence of publication bias. However, after the trim and fill analysis, there was no change in the pooled estimate. The third group of patients were those on peritoneal dialysis. We have estimated the pooled prevalence using four studies having 60 LTBI cases among 253 patients that gives a pooled prevalence of 25% (95%CI; 11, 38, I^2; 83.48%) (Fig. 9). The last group of CKD patients were those who had undergone renal transplantation. The pooled prevalence of LTBI among CKD patients who underwent transplantation was estimated using six studies that comprises 1100 renal transplanted patients. LTBI was detected in 159 patients that gave a pooled LTBI prevalence of 16% (95%CI; 7, 25, I^2; 94.26%) (Fig. 10) **(Table 2).**

Fig. 6. Forest plot for the pooled prevalence of latent tuberculosis among patients with chronic kidney disease diagnosed using TST.
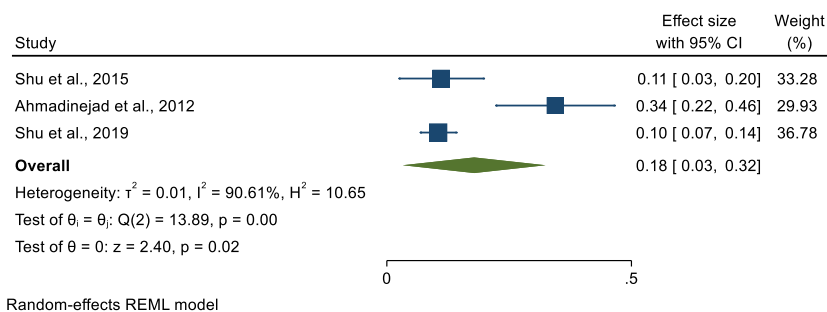
Fig. 7. Forest plot for the pooled prevalence of latent tuberculosis among pre-dialysis chronic kidney disease patients.

We conducted a meta-regression analysis to assess the effect of sample size and publication year on the heterogeneity among studies. The multivariate meta-regression model revealed that sample size (P = 0.064) and publication year (0.553) did not significantly predicted heterogeneity among studies. However, this model only explains 4.58% of the heterogeneity (Table 3).

4. Discussion

In this study, we estimated the pooled prevalence of latent tuberculosis among patients with chronic kidney disease based on data collected from 53 studies that included 12,772 CKD patients. The study findings indicated that nearly one-third of CKD patients had LTBI with regional disparities. In addition, we conducted a sub-group analysis to estimate the pooled prevalence of LTBI based on the type of CKD, the laboratory diagnostic methods, continent, WHO regional classification, country's income level, publication year, and TB burden classification.

This study revealed that, 30% of CKD patients had LTBI, which is higher compared to the prevalence in the general population, where one-fourth of the global population is infected with TB [1]. In addition, this pooled estimate exceeds the global pooled estimate obtained among the general population, which was less than 25% [41]. This higher LTBI prevalence among CKD patients indicated that this group of population are at higher risk to develop active TB. This was corroborated in our recent meta-analysis, in which 3718/100, 000 CKD patients got TB during their follow-up period, substantially above the TB incidence in the general population [4]. This emphasizes the necessity of early and active screening, testing and treatment of LTBI in CKD patients in order to strengthen active TB prevention and control, which can improve the quality of life in this population. The outcomes of this study can be used to develop future guidelines and guidance. According to the WHO regional classification of countries, the highest pooled estimate was found in EUR (43%), followed by EMR (39%), SEAR (32%), WPR (21%), and AMR (19%). In a previous global meta-analysis study the decreasing order of the pooled prevalence of LTBI among the general population stratified per WHO regional classification was SEAR, AFR, EMR, WPR, AMR and EUR. Since we did not get studies from the WHO African region, we were unable to find the estimate the pooled estimate.
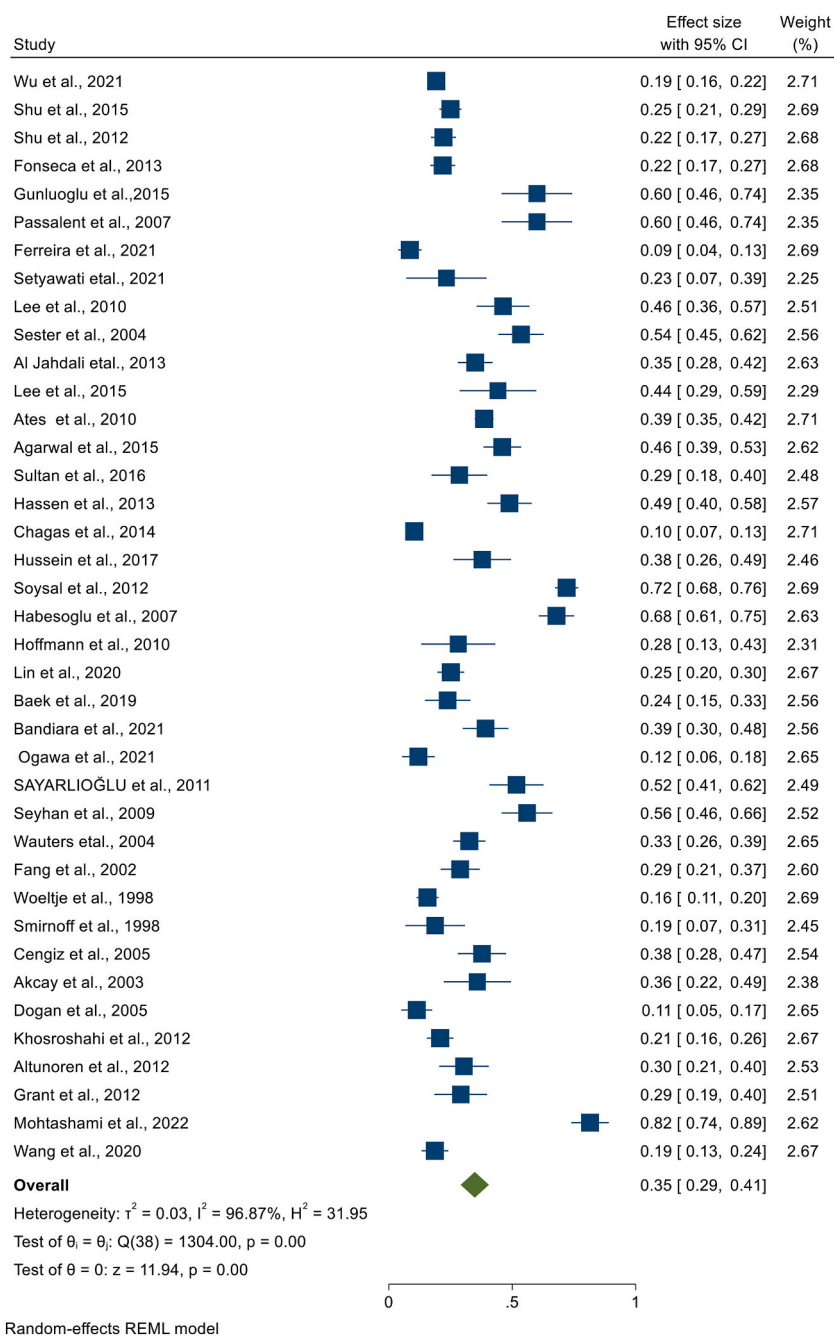
Fig. 8. Forest plot for the pooled prevalence of latent tuberculosis among hemodialysis patients.

We also conducted a sub-group analysis based on publication year, and the study findings revealed that the pooled estimate is lower in studies published after 2016 (24%) compared to studies published between 1998 and 2010 (34%), and between 2011 and 2015 (34%). A global study [42] similarly found a modest reduction in the prevalence of LTBI. In addition, we have also estimated the pooled prevalence based on country's TB burden classification. The findings revealed that countries not included in the high TB burden countries had a relatively greater prevalence than their counterparts did.

The current study found that dialysis patients in general and hemodialysis patients in particular, had higher LTBI prevalence as compared to pre-dialysis and post-renal transplanted patients. Dialysis patients, particularly those on hemodialysis, are at increased risk of contracting *Mycobacterium tuberculosis* through person-to-person transmission since they travel frequently and spend lengthy periods in health facilities.

Besides, we have performed a sub-group analysis based on the laboratory diagnostic method used to diagnose LTBI in CKD patients.
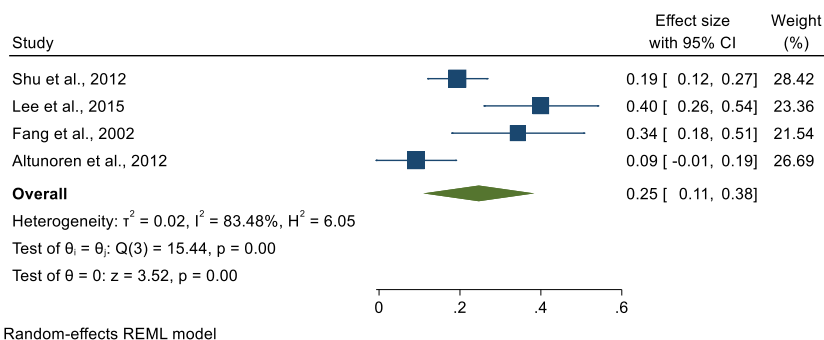
Fig. 9. Forest plot for the pooled prevalence of latent tuberculosis among peritoneal dialysis patients.
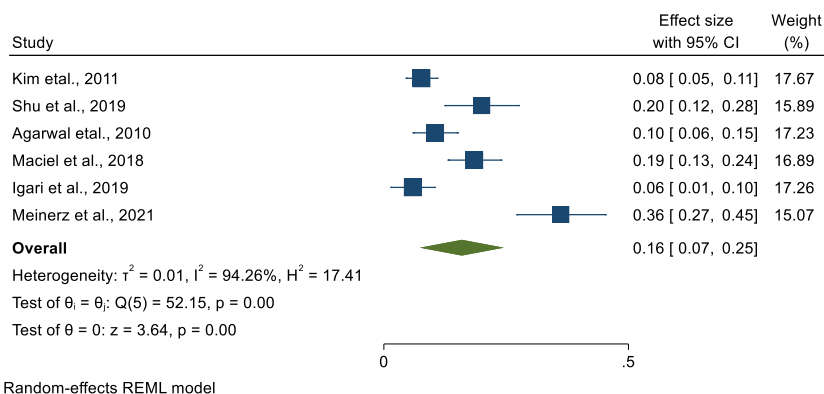
Fig. 10. Forest plot for the pooled prevalence of latent tuberculosis among patients who undergone renal transplantation.

Table 3
Meta-regression analysis of heterogeneity using sample size and publication year.

Variable	Unadjusted model		Adjusted model	
	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value
Sample size	−.0001712 (-.0003371 -5.31e-06)	0.043	−.0001609 (−.0003313 9.56e-06)	0.064
Publication year	−.0037576 (−.0114016, .0038865)	0.335	−.002313 (−.0099455 .0053196)	0.553

We found a relatively a higher pooled estimate in CKD patients diagnosed with IGRAs compared with TST. One possible reason might be the use of 10 mm cut-off in the TST. Likewise, this was reported by a previous global pooled estimate conducted in the general population [31].

In general, CKD patients suffer from multitude complications ranging from anemia, psychiatric diseases, cardiovascular complications, endocrine and metabolic abnormalities that needs to be given a focus to decrease high morbidity, mortality and poor quality of life [43–45].

Finally, the findings of this study should be interpreted by considering the following limitations. Primarily, under representation of CDKs from Africa in this review may have affected the global prevalence of LTBI in CDK patients. Second, the high heterogeneity among studies and the presence of publication bias may affect the true estimates. Lastly, since most of the original studies did not use specific cutoffs based on age and immunosuppression status of CKD patients, we did not perform analysis based on the specific cutoffs. However, we have performed stratified analysis that validated the current study findings.

5. Conclusion

This study identified higher prevalence of LTBI among CKD patients that needs attention of all concerned bodies to early detect and treat LTBI in this group of individual. There is disparities in the prevalence of LTBI per WHO regional classification, where CKD patients residing in the EUR, EMR and SEAR had relatively higher LTBI prevalence. In addition, dialysis patients mainly hemodialysis patients had higher LTBI prevalence compared to pre-dialysis and post-renal transplanted CKD patients. Besides, the prevalence of LTBI is higher in patients diagnosed with IGRA compared with those CKD patients diagnosed with TST. The findings in this study

indicate the need to give attention for the early diagnosis and treatment of LTBI in CKD patients. We recommended more studies from the African Region where TB is endemic and the prevalence of CKD is increasing.

Author contribution statement

Ayinalem Alemu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Zebenay Workneh Bitew: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Getu Diriba; Getachew Seid; Emebet Gashu: Performed the experiments.

Shewki Moga; Saro Abdella; Kirubel Eshetu; Getachew Tollera; Mesay Hailu Dangisso; Balako Gumi: Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e17181.

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Effectiveness of healthcare workers and volunteers training on improving tuberculosis case detection: A systematic review and meta-analysis

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Abstract

Introduction

Tuberculosis is the second most common infectious cause of death globally. Low TB case detection remains a major challenge to achieve the global End TB targets. This systematic review and meta-analysis aimed to determine whether training of health professionals and volunteers increase TB case detection.

Methods

We performed a systematic review and meta-analysis of randomized control trials and non-randomized control trials reporting on the effectiveness of health professionals and volunteers training on TB case detection. We searched PubMed, SCOPUS, Cochrane Library, and reference sections of included articles from inception through to 15 February 2021, for studies published in English. Study screening, data extraction, and bias assessments were performed independently by two reviewers with third and fourth reviewers participating to resolve conflicts. The risk of bias was assessed using the Joanna Briggs Institute (JBI) checklist. Meta-analyses were performed with a random effect model to estimate the effectiveness of training intervention on TB case detection.

Results

Of the 2015 unique records identified through our search strategies, 2007 records were excluded following the screening, leaving eight studies to be included in the final systematic review and meta-analysis. The results showed that providing training to health professionals and volunteers significantly increased TB case detection (RR: 1.60, 95% CI: 1.53, 1.66). There was not a significant degree of heterogeneity across the included study on the outcome of interest (I^2 = 0.00%, p = 0.667).

Conclusions

Providing training to healthcare workers and volunteers can increase TB case detection.

Data Availability: All relevant data are within the paper and its Supporting Information files.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: CD, Case detection; JBI, Joanna Briggs Institute; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MeSH, Medical Subject heading; RCT, randomized control trial; TB, Tuberculosis; WHO, World Health Organization

Introduction

Despite Tuberculosis (TB) is a preventable and treatable disease, it remains an important cause of death from an infectious agent [1], especially, TB, the second-deadliest infectious killer (after COVID-19), is caused by Mycobacterium tuberculosis, which primarily affects the lungs [2]. Based on the World Health Organization (WHO) report, approximately 10 million people who

developed TB in 2020. More than 4 million people have tuberculosis but have not been diagnosed or have not reported the disease to national authorities, which means 40% of all incident cases were not reported to the national tuberculosis program [2,3]. India (41%), Indonesia (14%), the Philippines (12%), and China (8%) were the countries that contributed the most to the global reduction in TB notifications between 2019 and 2020 [2].

Failure of TB case detection can increase the risk of death, severe illness, and transmission of TB in households and communities [4–7]. Previous studies showed that missed pulmonary TB cases can transmit the infection to 10–15 people per year, a major challenge to achieving the global End TB targets [8–10].

The reason for low TB case detection can be related to the healthcare system or patient-related factors. Lack of f adequate training of health professionals on the diagnosis and treatment of TB a common healthcare system factor affecting TB case detection [11–14]. Different interventions were designed to enhance TB case detection in the national TB programs. Most of the interventions designed to improve TB case detection were targeted to TB patients and the communities [15,16]. Extensive advocacy and awareness-raising activities have been implemented to educate people about TB diagnosis [1]. Patient education can be as simple as a booklet or as comprehensive as multiple session programs. However, this approach alone does not increase TB case detection. Additional measures, such as training of health professionals, health extension workers, and community volunteers might be required to increase TB case detection. While few studies have investigated the effects of providing training to health professionals and volunteers on TB case detection, the findings were inconsistent across studies [17–19]. To our knowledge, no systematic review has examined whether health professionals and volunteers training is an effective intervention to increase TB case detection. Therefore, this systematic review and meta-analysis aimed to determine whether training of health professional and volunteers increase TB case detection.

Materials and methods

Eligibility criteria

Studies were included if they were randomised controlled trials; non-randomised trials with at least a defined intervention and parallel control groups; quasi-experimental studies; controlled before-after studies with outcome measures before and after the intervention. The interventions were a provision of training to health professionals or any volunteers for at least three days. Potential comparators were usual care, or no intervention (i.e. no training). We excluded conference and meeting abstracts, and non-English language articles, animal studies and those that had insufficient information on the main outcome of interest. The outcome of interest was the TB case detection rate. Our research eligibility in the PICO (Population, Intervention, Comparator, Outcome) format is included in (Table 1).

Study	Study design	Country	Target population	Diagnostic approach	Total sample	Intervention group		Control group		Outcomes
						PIG	CIG	PCG	CCG	
Fairall LR et al. 2005 [17]	Cluster RCT	South Africa	Adults	Sputum smear microscopy two times	1782	892	57	890	34	Sputum screening for tuberculosis was higher among. Patients in the intervention arm but not significantly. During the three months of the study period, 57 new cases of tuberculosis were diagnosed in intervention clinics compared with 34 in control clinics.
Ayles et al. 2013 [18]	Cluster RCT	South Africa	Adults	Sputum smear microscopy and culture	962655	447228	1730	515427	236	The prevalence of culture confirmed pulmonary tuberculosis in adults was increased.
Datiko DG and Lindtjorn B, 2009 [19]	Cluster RCT	Ethiopia	All ages	Sputum smear microscopy	296611	178138	230	118673	88	The mean CDR was higher in intervention kebeles.
Talukder K et al. 2012[12]	Cluster RCT	Bangladesh	Child	Keith Edwards TB score was used as a diagnostic test	3460	1577	175	1883	150	TB notification rates increased significantly more in the intervention (from 3.8% to 12%) than in the control centers. Sputum smear-negative TB was a significant increase in the number of children diagnosed with sputum smear-negative pulmonary TB in the intervention centers.
Shargie EB et al. 2006 [16]	Cluster RCT	Ethiopia	All ages	Sputum smear microscopy	54405	18950	24	33455	33	All forms of TB notification rate was 125 (159/127 607) in intervention and 98 (221/225 284) in the control groups.
Datiko DG et al.2017 [29]	Non-RCT	Ethiopia	All ages	Sputum smear microscopy	6700000	3500000	27918	1200000	5483	All forms of TB increased from 102 to 177 per 100 000 population in the intervention group.
Joshi B et al. 2015 [13]	Non-RCT	Nepal	Child	Sputum smear microscopy, chest X-ray, and tuberculin skin test	2211909	1489425	360	722484	113	The proportion of all TB cases, the intervention districts showed a significant increase in childhood TB between Years 1 and 2 (from 3.9% to 5.0%), while the control districts showed no significant difference (from 4.2% to 4.9%).
Reddy KK et al.2016	Non-RCT	India	All ages		11784	7823	658	3961	255	Smear positive case detection was increased.
Oshi DC et al. 2016 [11]	Non-RCT	Nigeria	Child	Sputum smear microscopy, Keith Edwards's child tuberculosis scores	25,258,888	14742185	1067	10516765	683	Tuberculosis cases in the intervention areas were increased as compared with the control groups.

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Table 1. The characteristics of the studies included in the systematic review and meta-analysis.
https://doi.org/10.1371/journal.pone.0271825.t001

Search strategy, information sources and selection criteria

We conducted an electronic medical literature search on PubMed, Cochrane Library, and Scopus databases for relevant randomized controlled trials describing training as an intervention to increase TB case detection, published from the date of each database inception to 15 February 2021. The review was performed according to the standard procedures of the Cochrane Collaboration [20]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to report the review [21]. The protocol was registered in PROSPERO with registration number CRD42021284106. A comprehensive search strategy was developed using the search terms and medical subject headings [22]. The complete PubMed search strategy is provided in the (S1 File). Reference lists of included papers were screened for additional relevant articles using forward and backward citation search. Corresponding authors were contacted by email in some instances when additional information was required. Key terms were used to search a library database (S1 Table).

Study selection

All studies identified through the search strategies were imported into EndNote version 7 for screening. After removing duplicate articles, screening of papers by title and abstract were carried out independently by two researchers (DA and GD). Screening of full-text papers was also carried out by the same two researchers for inclusion based on pre-defined eligibility criteria.

Disagreement on the inclusion or exclusion of selected papers was resolved through discussion and consensus with co-authors (MBS, EWM, TAD, and FAG).

Data extraction

Data were extracted from included studies using Microsoft Excel 2016 spreadsheet (Microsoft, Redmond, Washington, USA) by two researchers (DA, GD,). The spreadsheet was checked and refined before extraction began. Data extracted from each study included: name of the first author, year of publication, study design, place of study, type of participant, type of intervention (comparison groups and sample size of each group), outcomes (case detection rate), and the key findings. Information on the duration of implementation, frequency of interventions, site of intervention, and the number of interventions were also extracted.

Outcome measurement

The primary outcome was TB case detection, expressed by the proportion of all new cases of TB with a confirmed diagnosis.

Quality assessment

The quality of the included studies was independently assessed by two investigators (DA and EWM) using Joanna Briggs Institute (JBI). The JBI checklist is designed to assess 13 components of RCT study design including randomization method, allocation concealment, baseline characteristics, patient blinding, therapist blinding, observer blinding, co-intervention control, compliance, attrition rate, end-point assessment time point, intention to treat analysis, the same outcome measurement way and reliable outcome measurement [23]. The authors considered low risk of bias 'Yes' either the study protocol is available and all of the studies' pre-specified outcomes that are of interest in the review have been reported in the pre-specified way or the study protocol is not available but it is clear that the published reports include all of the study's pre-specified outcomes and all expected outcomes that are of interest in the review. Authors considered high risk of bias 'No' if any of the following is fulfilled: Not all of the study's pre-specified primary outcomes have been reported, one or more primary outcomes is reported using measurements analysis methods or subsets of the data that were not pre-specified, one or more reported primary outcomes were not pre-specified, one or more outcomes of interest in the review are reported incompletely, the study report fails to include results for a key outcome that would be expected to have been reported for such a study. Authors considered unclear if there is insufficient information to permit judgment of 'Yes' or 'No'.

Other sources of bias such as recruitment bias were considered as "No" if bias is detected due to problems not covered elsewhere and "Yes" if no other bias is detected. Blinding was classified as "Yes" if steps were taken to ensure that those recording the main outcome of the study were blind to the assigned interventions, and "No" if this was not the case, or if there was no description of the method for assessing the adequacy of the randomization procedure. Completeness of follow-up was assessed as "Yes" if steps to the handling of incomplete outcome data were complete and unlikely to have produced bias or "No" if the attrition amount or handling of incomplete outcome data was not maintained.

The instrument or tool used to assess the risk of bias, rigor, or study quality was reported along with some summary estimate of the quality of primary studies in the included research synthesis [24]. Therefore, the quality of each study was assessed based on JBI quality assessment criteria (S2 Table).

Data analysis

Meta-analysis with a random effect model was performed to calculate relative risk (RR) with 95% confidence intervals [25]. Heterogeneity between studies was assessed by the index of heterogeneity squared (I^2) statistics with 95% CI. The I^2 statistic measures the proportion of observed variance between trials that is not due to chance (rather due to real differences across studies populations and interventions). The I^2 value less than 30% was interpreted as low evidence of heterogeneity, between 30% and 60% was moderate heterogeneity and I^2 more than 60% was interpreted as evidence of substantial heterogeneity [26]. Meta-regression was used to explore whether study characteristics explained heterogeneity. Publication bias was assessed qualitatively by visual inspection of funnel plots and quantitatively by Egger's test. Sensitivity analysis was also conducted based on the quality and characteristics of the studies. The data analysis was performed by Stata version 16. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

Results

Study selection

Of 4052 studies obtained from the database search, 2037 articles were excluded due to duplications. After removing duplicates, 2015 articles were screened by titles and abstracts and 1946 articles were excluded which resulted in 69 potential articles for full-text review. After a full-text review, 9 studies met the eligibility criteria and were included in the final analysis (Fig 1).
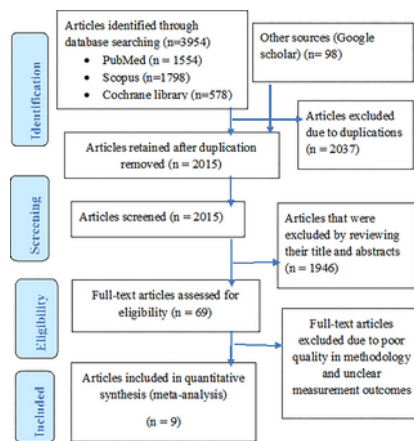
Fig 1. PRISMA flow chart of study selection.
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Study characteristics

Table 1 summarizes the characteristics of the included studies. Studies were conducted in five different countries. All the studies were from African and Asian continents. The population groups were children (under the age of 15) for three studies [29–31], adults for two studies [27,28], and both adults and children for four studies [18,19,29,30]. Interventional trials were included in this analysis. Five of the studies were cluster RCTs, whereas the other four were non–RCTs.

In all studies, the training provided for health workers and volunteers were focused on symptoms, diagnostic and screening methods, and treatment of TB cases. The duration of the intervention varied from 3 months [27] to 54 months [28,29]. Sputum smear microscopic and gene Xpert were used to diagnose TB (Table 1).

Most of the studies included in this study used instructor-led training, demonstration, hands-on training, group-based training, job training, and technology-based training (text message), but the method used by the three studies [19,28,31] is not clear. As a result, it is difficult to determine which training method is more effective in identifying TB case detection.

Effectiveness of healthcare workers and volunteers training on improving TB case detection

Nine interventional studies were included to investigate whether the intervention group had an effective improvement in TB case detection rate as compared to the control arms. Seven out of nine selected studies were effective to improve the case detection while the other two studies showed that the interventions had not improved the case detection rate. The overall pooled effect size estimate showed that healthcare workers and volunteers training was significantly improved TB case detection (RR: 1.60, 95% CI: 1.53, 1.66) (Fig 2). In addition, sensitivity analysis showed that there was no single study that affects the overall effect of the intervention (Fig 3).
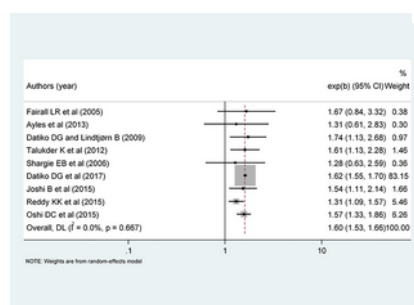
Fig 2. Forest plot of the effect size of training on tuberculosis case detection in TB high burden settings.
https://doi.org/10.1371/journal.pone.0271825.g002
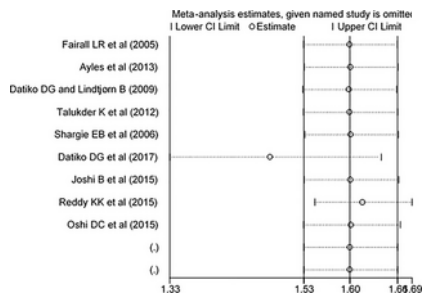
Fig 3. Sensitivity test on effect of training on tuberculosis case detection.
https://doi.org/10.1371/journal.pone.0271825.g003

Heterogeneity and publication bias

There was no a significant degree of heterogeneity across the included study on the outcome of interest (I^2 = 0.00%, p=0.667) (Fig 2). Neither the funnel plot (Fig 4) nor the egger tests showed evidence of significant publication bias (P = 0.244).
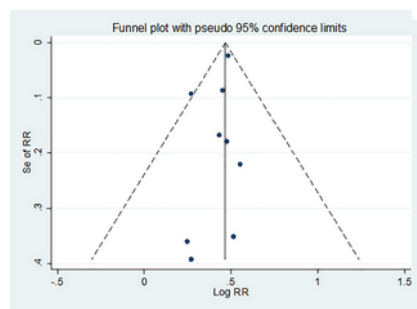
Fig 4. Funnel plot analysis of publication bias.
https://doi.org/10.1371/journal.pone.0271825.g004

Risks of bias assessment

The risk of bias assessment showed that seven studies had a low risk of bias for random sequence generation and adequate allocation concealment. A blind outcome assessment was reported from only one study (28). In all studies, there was no relevant outcome reporting bias observed. Also, there was no reporting in attrition and selective reporting bias (Table 2).

Table 2. Risk bias assessment using JBI checklist.
https://doi.org/10.1371/journal.pone.0271825.t002

Discussion

This is the first systematic review and meta-analysis that quantified the effectiveness of providing training for healthcare workers and volunteers on TB case detection. Our findings showed that providing training to healthcare workers and community volunteers significantly increased TB case detection. This is an important finding suggesting the need to scaling-up training to improve case detection and to achieve the global End TB targets [25,34,35].

Community healthcare workers being more familiar with the community and trusted by the community were involved in the intervention. Providing training to community volunteers may improve their knowledge of TB and they can refer suspected cases to TB programs. A previous study found that community-based case detection approach helps to empower patients to deal with their

problems [36]. Providing training to health professionals may also be useful for the proper diagnosis and treatment of TB patients [31,32]. Although different training approaches were used their effectiveness in increasing TB case detection were not significantly differ [18,29,31–33].

The World Health Organization (WHO) has a target to end TB by 2035 [37]. The findings from this systematic review provide important evidence that may contribute to achieve this ambitious target. This systematic review revealed that providing effective training to health professionals and community workers can improve TB case detection. It has therefore had a great impact on TB case findings by implementing educational training for healthcare providers and community volunteers. This systematic review and meta-analysis have also implications for health staff and researchers by increasing their knowledge on the effectiveness of training intervention on TB cases detection. Although many people with TB infection remain undiagnosed and had a lack of care [38], our study showed that the implementation of training packages considerably effective approach to case detection and helps to reduce unnecessary delays in diagnosis and received care. The implementation of interventions and using accurate diagnostic tests may improve TB case notification. Therefore, the findings of this study could in turn be implemented into practice.

Trained health workers and community volunteers were the keys to detecting TB cases in the community and primary health care settings and trained community volunteers were crucial to conduct household contact screening in detecting cases and refer cases to nearby TB diagnostic centers [33]. The finding of this systematic review supported the importance of providing educational training to improve the TB case detection rate.

Our review had several limitations. We have included articles published in English only. Most studies included in our study used a sputum smear microscope as a main diagnostic method for TB that mainly identifies positive pulmonary TB, and this type of diagnostic approach has limited ability to identify true positive cases. This evidence is substantiated with another report that conventional tests like microscopic examination have low accurate TB diagnosis as compared to Xpert [39]. Possibly, many people with TB infection are still undetected in resource-limited and TB high burden countries [40]. Study related characteristics were not explored using a meta-regression due to low number of available studies. Some studies show that the training method used is not clear, so it is difficult to know which training method is more effective to increase case detection. We find this to be one of the limitations of the study.

Conclusions

This systematic review and meta-analysis found that the TB case detection rate can be improved by providing training for healthcare workers and volunteers. Therefore, strengthened educational training interventions should be encouraged to improve TB case detections and to ultimately achieve the End-TB targets.

Supporting information

S1 File. PubMed advanced search terms.
https://doi.org/10.1371/journal.pone.0271825.s001
(DOCX)

S1 Table. Search key terms.
https://doi.org/10.1371/journal.pone.0271825.s002
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S2 Table. Data collection and risk assessment for RCTs and non-RCTs studies.
https://doi.org/10.1371/journal.pone.0271825.s003
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BMJ Open

Prevalence and incidence of symptomatic pulmonary tuberculosis based on repeated population screening in a district in Ethiopia: a prospective cohort study

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ABSTRACT

Objective In Ethiopia, one-third of the estimated tuberculosis cases are not detected or reported. Incidence estimates are inaccurate and rarely measured directly. Assessing the 'real' incidence under programme conditions is useful to understand the situation. This study aimed to measure the prevalence and incidence of symptomatic pulmonary tuberculosis (PTB) during 1 year in the adult population of Dale in Ethiopia.

Design A prospective population-based cohort study.

Setting Every household in Dale was visited three times at 4-month intervals.

Participants Individuals aged ≥15 years.

Outcome measures Microscopy smear positive PTB (PTB s+), bacteriologically confirmed PTB (PTB b+) by microscopy, GeneXpert, or culture and clinically diagnosed PTB (PTB c+).

Results Among 136 181 individuals, 2052 had presumptive TB (persistent cough for 14 days or more with or without *haemoptysis, weight loss, fever, night sweats, chest pain or difficulty breathing*), in the first round of household visits including 93 with PTB s+, 98 with PTB b+ and 24 with PTB c+; adding those with PTB who were already on treatment, the total number of PTB was 201, and the prevalence was 147 (95% CI: 127 to 168)/100 000 population. Out of all patients with PTB, the proportion detected by symptom screening was in PTB s+ 65%, PTB b+ 67% and PTB c+44%. During 96 388 person-years follow-up, 1909 had presumptive TB, 320 had PTB and the total incidence of PTB was 332 (95% CI: 297 to 370)/100 000 person-years, while the incidence of PTB s+, PTB b+ and PTB c+ was 230 (95% CI: 201 to 262), 263 (95% CI: 232 to 297) and 68 (95% CI: 53 to 86)/100 000 person-years, respectively.

Conclusion The prevalence of symptomatic sputum smear-positive TB was still high, only one-third of prevalent PTB cases notified and the incidence rate highest in the age group 25–34 years, indicating ongoing transmission. Finding missing people with TB through repeated symptom screening can contribute to reducing transmission.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study included a large sample and worked closely with the national tuberculosis programme and the community structures that contributed to its sustainability.

⇒ We report not only the prevalence but also the incidence of symptomatic pulmonary tuberculosis during 1 year, which is often not reported elsewhere.

⇒ The study screened a very high proportion of households in the district, giving an accurate measure of the burden of tuberculosis, where the probability of missing people with tuberculosis is small.

⇒ Tuberculosis cases notified were chosen the year before the study because we could not separate the patients identified by the screening from those who attended the health services themselves.

⇒ Only symptomatic patients with tuberculosis were reported, and it is known that many patients are more or less asymptomatic.

BACKGROUND

Tuberculosis (TB) is an infectious disease transmitted by mycobacterial droplets from coughing patients. The global End TB strategy aims to reduce the sources of infection by curing infected individuals with effective anti-TB drugs and has helped reduce the incidence of TB worldwide. The estimated global incidence of TB has recently decreased by 9% from 2015 to 2019, but still 11% less than the End TB targets set for 2020. The incidence of TB is unevenly distributed globally with the highest estimated TB incidence rate in Africa, at 226/100 000 population in 2019. However, the TB incidence rate in Africa declined by 16% from 2015 to 2019, which is greater than the average global decline but still not fast enough to reach the Sustainable Development Goal milestones.[1–4] Ethiopia achieved the first milestone of End TB with a 31% decrease in the estimated incidence rate from 2015 to 2020 (192 to 132/100 000 population).

The national X-ray-based TB survey in Ethiopia in 2010 reported *prevalence* estimates of

108 per 100 000 population for smear-positive pulmonary tuberculosis (PTB s+) and 277/100 000 population for bacteriologically confirmed pulmonary tuberculosis (PTB b+).[5] Only two studies have investigated the pulmonary TB (PTB) *incidence,* both *based on screening of respiratory symptoms.* A study in a central district of Ethiopia in 2013 reported that the incidence of PTB s+ was 214/100 000 person-years and that of PTB b+ was 232/100 000 person-years,[6] while a study in the northern part of the country in 2011 reported that the incidence of PTB s+ was 311/100 000 person-years.[7] However, notifications in the country indicate that one-third of TB cases are still undetected, and more than half of them are in those aged 15–34 years old. Hence, the true incidence of TB is unknown and under-researched because generating these estimates requires massive resources.[8 9]

Therefore, locally available data using the existing health system may help to understand the epidemiology of the disease as well as to validate national estimates, since these are not accurate in areas with disparities in health outcomes and programme implementation. The 'missed' or 'diagnosed late' individuals are important sources of TB transmission.[5 10] Repeated assessment of subnational population-level incidence and prevalence patterns may help the programme quantify the impact of the control efforts to support local decision-making.[10–12]

Dale district was part of a community-based project with active TB case-finding implemented in 2010.[13] The study initially showed high notification rates in the district, which gradually decreased over time (215/100 000 in 2011 to 66/100 000 in 2015). It is not clear to what extent the decline reflects a real decline in TB incidence or is the result of going back to the routine health service delivery strategy without a systematic screening of the community. The impact has therefore not been sufficiently described and documented. Hence, this study aimed to measure the prevalence and incidence of symptomatic PTB through repeated population-based screening in the adult population of the Dale district in southern Ethiopia.

METHODS
Study design and population
This was a population-based prospective cohort study including repeated symptom screening in three consecutive rounds of household visits, from October 2016 to September 2017, in Dale district of southern Ethiopia. The target population was everyone who resided in the 36 administrative units (*kebeles*) in the district. The population data were obtained from the district health offices and each *kebele*. A persistent cough for 14 days or more with or without *haemoptysis, weight loss, fever, night sweats, chest pain or difficulty breathing* was taken as a sign of presumptive TB. Individuals with presumptive TB were enrolled after informed consent, and the population ≥15 years are included in this report. The total population denominator for the population aged ≥15 years was 136 181, based on official data from the Central Statistics Agency

in Ethiopia.[14] The coverage of households screened is based on the number of households visited over the number of households registered at each time point. The prevalence of PTB was calculated by dividing the number of patients diagnosed during the first round of visits by the population covered. The incidence rate was calculated by dividing the number of patients with PTB identified during the follow-up period (ie, in the second and third rounds of household visits) by person-years of observation-time. We used the strengthening of the Reporting of Observational Studies in Epidemiology cohort reporting guidelines (online supplemental file 1).[15]

Study setting
The Dale district is a densely populated rural community with 10 health centres, 2 clinics and 36 health posts; TB care follows the End TB strategy.[16] Since 2010, the non-governmental organisation REACH Ethiopia has been developing an innovative model using close-to-community providers, including in the Dale district, contributing to community TB care implementation in Ethiopia.[6 13] Microscopy, but not GeneXpert nor X-ray examination, can be performed at health centres. The primary test for PTB diagnosis is sputum smear microscopy, which is cost-efficient and accessible, but has low sensitivity.[17–19] The only GeneXpert equipment in the area is located outside of Dale district in the town administration of Yirgalem.

Patient and public involvement
No patients were involved in setting the research question or the outcomes, the conduct, interpretation, writing or dissemination of the results. The study was conducted in close collaboration with the Dale district National TB and Leprosy Programme (NTLP). They were informed about the study in advance and were actively involved throughout the design and implementation and in dissemination of the results. The project team organised consultative meetings with participants from regional, zonal and woreda level organisations, non-governmental organisations and religious institutions throughout the full study period. Village-women were included as representatives for the population in Dale.

Data collection
As a first step of the screening, trained female health extension workers (HEWs) familiar with the village went door-to-door, asking if any household member had respiratory symptoms compatible with TB, including those not at home during the survey. HEWs are well-established and trusted by the communities. Those identified with symptoms were carefully followed and asked to come to the health post for a test. This also applied to household members not at home at the time of the visit. Health personnel offered to come to the home to collect sputum for persons having difficulties in reaching the health facilities.
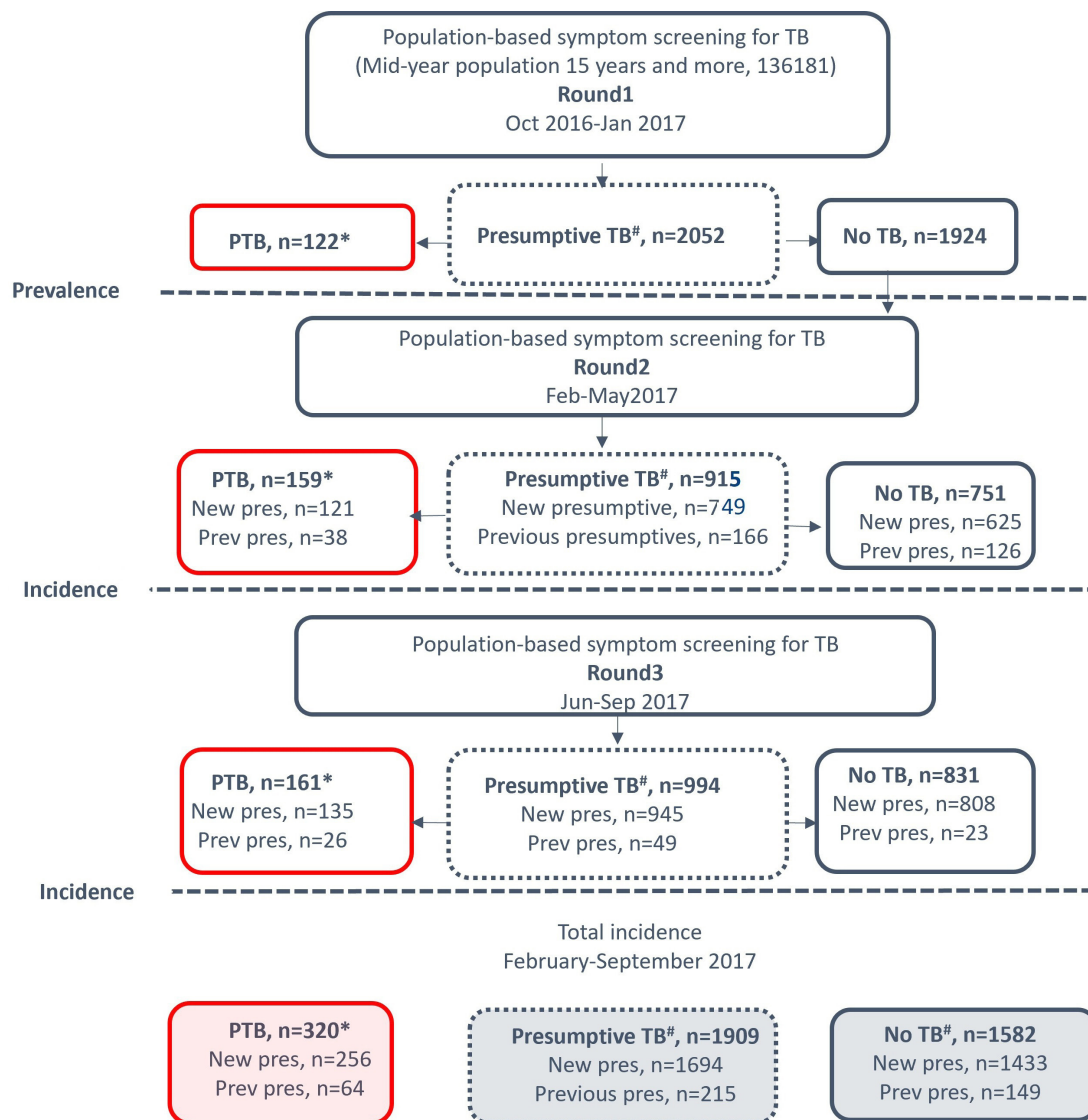
Figure 1 Study flow chart showing three rounds of household screening for TB in Dale district, 2016–2017. PTB, pulmonary TB; TB, tuberculosis. PTB: pulmonary tuberculosis. New pres: first episode of presumptive TB. Prev presumptive: the participant has been identified with presumptive TB in a previous round of household visits and enrolment dates were minimum 30 days apart. ‡Population denominator, estimates from Central Statistics Agency (CSA) in Ethiopia (estimated from a population census of 2007); Some patients had more than one episode.

Pretested semi-structured questionnaires were used to identify individuals with respiratory symptoms compatible with PTB and to collect clinical, demographic and socio-economic data (online supplemental file 2). Individuals identified with presumptive TB were asked to come to the health post to provide sputum. The sputum samples were collected and transported to the health centre for smear microscopy. Once identified by the study, participants received care, free of charge, as in the routine TB programme. If individuals were diagnosed with TB, they were treated according to the NTLP guidelines.[20] For patients diagnosed with drug-resistant TB, second-line drugs and follow-up were available at the nearby Yirgalem Hospital that initiates drug resistance TB treatment—free of charge. Individuals diagnosed with other diseases were referred for treatment. To ensure the quality of the laboratory, 50% of the slides were randomly selected

from participating catchment facilities and retested at the regional laboratory. Smear-positive samples were further validated by GeneXpert. Those already on TB treatment at the time of the survey were not included in the screening data of new incident cases. However, aggregate surveillance data from the NTLP on the number of patients already on TB treatment were added to those detected by screening in the prevalence calculation to facilitate comparison with other studies. Aggregated notification data were obtained from the NTLP from 2011 to 2018. Quarterly TB data were used to track those notified with PTB s+ or PTB c+ before, during, and after the study period to evaluate the impact of interventions on routine TB notification. The project ensured that all patients with TB identified through the project were registered in the TB register.[21]

Table 1 Results of three rounds of testing individuals with presumptive tuberculosis in Dale, 2016–2017

Household visits		Presumptive TB episodes*, n	PTB, n	PTB b+, n	PTB c+, n	% presumptive PTB with PTB		
						PTB[1]	PTB b+[1]	PTB c+[1]
Round 1	New presumptive; only tested once	1729	76	71	5	4	4	0.3
	New presumptive; TB with a repeat test	323	46	27	19	14	8	5.9
	New presumptive; all†	2052	122	98	24	6	5	1.2
Round 2	New presumptive; only tested once	630	72	71	1	11	11	0.2
	New presumptive; TB with a repeat test	119	49	19	30	41	16	25.2
	New presumptive; all†	753	121	90	31	16	12	4.1
	Previous presumptive	166	38	19	19	23	11	11.4
	Total	919	159	109	50	17	12	5.4
Round 3	New presumptive; only tested once	900	121	119	2	13	13	0.2
	New presumptive; TB with a repeat test	45	14	11	3	31	24	6.7
	New presumptive; all†	945	135	130	5	14	14	0.5
	Previous presumptive	49	26	15	11	53	31	22.4
	Total	994	161	145	16	16	15	1.6
Rounds 1+2+3	New presumptive	3746	378	318	60	10	8	2.0
	Previous presumptive	215	64	34	30	30	16	14.0

*The number of episodes is higher than the number of individuals as some were identified more than once.
†New presumptive all means only tested once plus repeat tests within the same round.
PTB[1], PTB means the proportion of presumptive TB cases with a positive bacteriological test result plus clinically diagnosed PTB; PTB, pulmonary TB; PTB b+, bacteriologically confirmed PTB; PTB c+, clinically diagnosed; TB, tuberculosis.

Operational definitions

As mentioned above, the term 'presumptive TB' was used to define individuals who had respiratory symptoms compatible with TB.[22] 'New presumptive' *was used the first time an individual was identified in the study as having symptoms of TB.* Those with presumptive TB who tested negative for TB were included in the denominator for the consecutive rounds. If they were identified as having presumptive TB in a consecutive round of household visits (more than 30 days apart), they were classified as 'previous presumptive with a new episode'. *PTB s+ was defined as at least one positive result by smear microscopy. PTB b+ included having at least one positive result by smear microscopy, GeneXpert or culture. PTB c+ was based on a clinical decision to start anti-TB treatment in those with persistent symptoms and negative bacteriological results; this diagnosis was usually (if not always) also supported by radiological findings. PTB b+ and PTB c+ both indicated a diagnosis of PTB. The* 'screening prevalence' *of PTB was calculated based on individuals identified with PTB in the first round (October 2016 to January 2017) of household visits divided by the total adult population (per 100 000 population). The* 'total prevalence' *also included patients who were already on TB treatment at the time of the first screening round. The incidence was calculated based on the number of individuals newly identified with PTB in the second (February to May 2017) and third (June to September 2017) rounds of household visits divided by the person-years observation time (per 100 000 person-years). Person-years were calculated from the date of enrolment for screening or the end of follow-up on 31 September 2017, for all study participants.* 'Notification' *is based on TB register.*

Diagnosis

For diagnosis, two spot sputum samples were collected according to standard procedures. Sputum smear-positive samples were sent for confirmation of diagnosis by GeneXpert at Yirgalem Hospital and by culture at the Armauer Hansen Research Institute in Addis Ababa. The use of GeneXpert for all samples was not feasible at the time of the study and was mainly limited to validation for smear-positive (drug-resistant TB diagnosis). In addition, smear-negative samples from HIV positive persons and persistent coughers still symptomatic after a course of broad-spectrum antibiotic were sent for analysis by GeneXpert and cultured in line with NTLP guidelines. Data on TB diagnosis, treatment and treatment outcome

were obtained from the TB register in the health centre. It was not possible to disentangle those identified through the household screening from those who approached the health centre on their own initiative. Individuals with chest X-ray abnormalities[23] were transferred to Yirgalem Hospital for clinical diagnosis of TB.

Data quality and analysis

Data were entered into Excel (Microsoft Office Proofing Tool 2016, Microsoft Corporation). The data quality was assessed by frequency distributions, cross-tabulations and double-entry of a 10% random sample of the data. The difference between the first and second data entries was 0.1%, and no systematic errors were detected. Stata V.14 and OpenEpi[24] were used for analyses.

RESULTS

Population-based symptom screening

The coverage of households screened was high, ranging from 96% to 98% in the three rounds of household visits, (online supplemental file 3). Figure 1 shows a flow chart of the population in the three rounds of household screening. During the study-period, 3746 out of 136181 persons in the screened target population were identified with presumptive TB. Of these, 442 persons were diagnosed with PTB. In total 352 cases had PTB b+; among them 263 were positive by smear microscopy, GeneXpert and culture, and 52 were positive by smear microscopy only, 34 were positive by GeneXpert only and 3 were positive by culture only. Of the 90 PTB c+ cases, 72 had the GeneXpert test (71 negatives and 1 error test), and none had culture tests. Chest X-ray was taken of 142 persistent coughers who needed further examination after broad spectrum antibiotic treatment; 86 had findings suggestive of PTB, 55 had normal and one unclear X-ray finding.

Table 1 shows results of three rounds of testing individuals with presumptive TB. The number of individuals presumed to have PTB was highest in the first round and halved in the two following rounds. The proportions of PTB cases among individuals with presumptive TB were 6%, 17% and 16% across the three rounds; the proportions of individuals with PTB b+ were 5%, 12% and 15%, respectively; and the proportions of PTB c+ were 5%, 10% and 13%, respectively. The proportion of PTB among individuals with presumptive TB who completed a course of broad-spectrum antibiotics and returned for another test was higher in the second and third rounds (14%, 41% and 31% for rounds 1, 2 and 3, respectively). Seventeen TB cases with symptoms of PTB were eventually diagnosed with extrapulmonary TB but not PTB, and excluded from the study (online supplemental table 1). Four individuals were identified with rifampicin resistance among 263 PTB b+ cases with rifampicin resistance test results. Women had a significantly higher prevalence and incidence of presumptive TB, a lower proportion with PTB b+ cases and a lower prevalence and incidence of PTB than men.

Prevalence of symptomatic PTB

Table 2 shows the total prevalence of PTB in the study area in first round of visits. Among the population of 136 181, 2052 had presumptive TB, 93 were diagnosed with PTB s+, 98 with PTB b+ and 24 with PTB c+. The total number of patients with PTB detected by symptom screening was 122; adding 49 PTB b+ (all of them PTB s+) and 30 PTB c+ patients who were already on TB treatment at the first round, the total number of PTB cases was 201, and the prevalence rate of PTB was 147 (95% CI: 127 to 168)/100 000 population. In those detected by screening, the prevalence rates of PTB b+ and PTB

Table 2 Total prevalence and percentage detected with pulmonary tuberculosis in the first round of visits in Dale, October 2016 to January 2017

Covariate	Number of PTB during screening		Number of PTB before screening		Total prevalence of PTB		% detected by screening	
	PTB b+	PTB c+	PTB b+	PTB c+	PTB b+ per 100 000 (95% CI)	PTB c+ per 100 000 (95% CI)	PTB b+	PTB c+
Total	98	24	49	30	108 (90 to 125)	39 (29 to 50)	67	44
Age in years								
15–24	27	7	23	5	100 (76 to 132)	24 (13 to 41)	54	58
25–34	31	7	15	6	135 (100 to 179)	38 (21 to 64)	67	54
35–44	26	2	4	2	126 (86 to 177)	17 (5 to 40)	87	50
45–54	7	4	4	5	82 (43 to 143)	67 (33 to 123)	64	44
55+	7	4	3	12	65 (33 to 116)	104 (61 to 166)	70	25
Sex								
Male	56	15	27	17	122 (98 to 151)	47 (33 to 66)	67	47
Female	42	9	22	13	93 (72 to 118)	32 (21 to 48)	66	41

n, number; PTB, pulmonary TB; PTB b+, bacteriologically confirmed PTB; PTB c+, clinically diagnosed PTB; TB, tuberculosis.

c+ were 72 (95% CI: 57 to 86) and 17 (95% CI: 10 to 24)/100 000 population, respectively. The prevalence rate of PTB s+ was 68 (95% CI: 54 to 82)/100 000 population from screening and 104 (95% CI: 87 to 121)/100 000 population including patients already on treatment. The percentages of patients detected by screening were as follows: PTB s+, 65%; PTB b+, 67%; and PTB c+, 44%. Among both PTB b+ and PTB c+ patients detected, only one out of three had been identified by the health system (online supplemental tables 2–6).

Incidence of symptomatic PTB

The overall observation time was 96 388 person-years, with 1909 individuals identified with presumptive TB, 254 with PTB b+ (including 222 smear-positive) and 66 with PTB c+ (table 3). The total number of PTB cases

Table 3 Incidence of presumptive and pulmonary tuberculosis in the adult population in Dale, February to September 2017

Visits	Covariate	Presumptive TB Episode per 100 000	PTB incidence PTB[1] per 100 000 (95% CI)	PTB b+ per 100 000 (95% CI)	PTB c+ per 100 000 (95% CI)	Proportion of presumptive TB with PTB (%) PTB[1]	PTB b+	PTB c+
Round 2	Total	1920 (1798–2047)	333 (284 to 388)	228 (188 to 274)	104 (78 to 137)	17	12	5
	Age in years							
	15–24	1034 (891–1194)	281 (210 to 369)	212 (151 to 289)	68 (37 to 117)	27	21	7
	25–34	1750 (1524–2000)	429 (322 to 559)	336 (244 to 453)	92 (48 to 160)	25	19	5
	35–44	2065 (1773–2392)	324 (218 to 465)	228 (141 to 350)	96 (44 to 182)	16	11	5
	45–54	3096 (2652–3595)	298 (176 to 474)	130 (257 to 258)	167 (82 to 308)	10	4	5
	55+	4039 (3493–4647)	342 (202 to 543)	106 (39 to 236)	235 (123 to 408)	8	3	6
	Sex							
	Male	1697 (1537–1869)	337 (269 to 418)	223 (169 to 290)	114 (76 to 163)	20	13	7
	Female	2140 (1960–2331)	329 (262 to 408)	233 (178 to 303)	96 (62 to 141)	15	11	4
Round 3	Total	2040 (1916–2170)	330 (282 to 384)	297 (252 to 349)	32 (194 to 522)	16	15	2
	Age in years							
	15–24	895 (763–1043)	322 (246 to 415)	305 (232 to 396)	17 (4 to 46)	36	34	2
	25–34	2126 (1878–2399)	521 (403 to 662)	455 (346 to 587)	66 (30 to 125)	25	21	3
	35–44	2222 (1923–2556)	187 (110 to 297)	152 (84 to 253)	35 (9 to 95)	8	7	2
	45–54	3617 (3142–4144)	180 (91 to 320)	162 (78 to 297)	18 (1 to 89)	5	4	0.50
	55+	3856 (3334–4438)	307 (178 to 496)	287 (163 to 470)	20 (10 to 100)	8	7	1
	Sex							
	Male	1757 (1595–1930)	319 (253 to 396)	294 (231 to 369)	25 (10 to 52)	18	17	1
	Female	2318 (2134–2516)	341 (274 to 420)	300 (238 to 375)	40 (20 to 72)	15	13	2
Round 2+3	Overall	1981 (1893–2071)	332 (297 to 370)	263 (232 to 297)	68 (53 to 86)	18	14	4
	Age in years							
	15–24	964 (865–1071)	302 (248 to 364)	259 (210 to 317)	43 (25 to 69)	32	27	5
	25–34	1940 (1769–2122)	475 (394 to 569)	396 (322 to 482)	79 (49 to 121)	25	21	4
	35–44	2145 (1932–2374)	254 (186 to 340)	189 (132 to 264)	65 (34 to 113)	12	9	3
	45–54	3361 (3031–3719)	238 (159 to 344)	146 (86 to 234)	91 (46 to 160)	7	4	3
	55+	3946 (3562–4359)	324 (224 to 454)	198 (123 to 304)	125 (68 to 213)	8	5	3
	Sex							
	Male	1727 (1612–1848)	328 (279 to 382)	259 (216 to 308)	69 (48 to 95)	19	15	4
	Female	2230 (2100–2366)	336 (287 to 391)	268 (224 to 317)	67 (47 to 94)	15	12	3

PTB, pulmonary TB; PTB[1], PTB means the proportion of presumptive TB cases with a positive bacteriological test result plus clinically diagnosed PTB; PTB b+, bacteriologically confirmed PTB; PTB c+, clinically diagnosed.

A

B
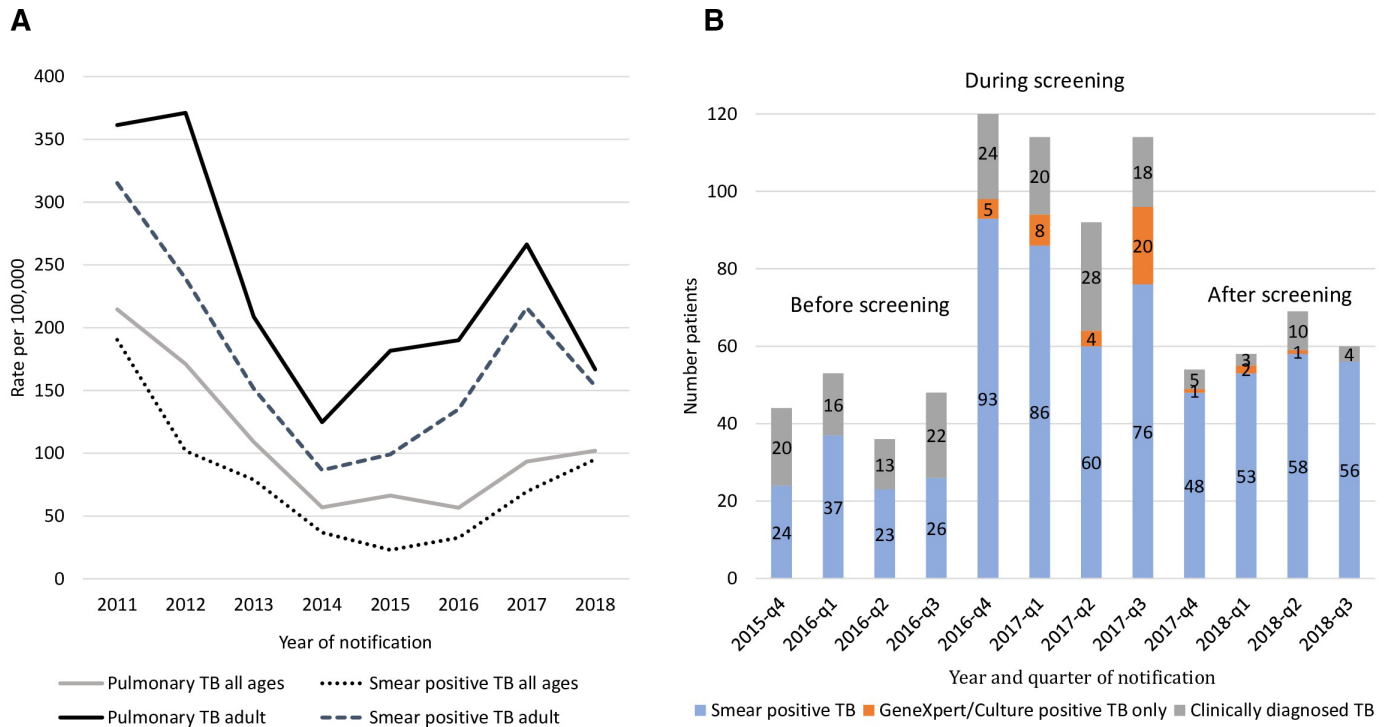
Figure 2 Case notification of patients with pulmonary TB in Dale district (A) rate per 100 000 population by category 2011–2018, and (B) absolute number of patients before, during and after screening from quarter 4 2015 to quarter 3 2018 (source National TB and Leprosy Programme). TB, tuberculosis.

was 320. The incidence of PTB was 332 (95% CI: 297 to 370)/100 000 person-years; the incidence rates of PTB s+, PTB b+ and PTB c+ were 230 (95% CI: 201 to 262), 263 (95% CI: 232 to 297) and 68 (95% CI: 53 to 86)/100 000 person-years, respectively (online supplemental table 7). The incidence rates of PTB s+ and PTB b+ were highest among 25–34 years old (online supplemental table 8).

PTB rate ratio comparison by sex
We estimated the ratios of the notification rate to the total prevalence rate (including cases already on TB treatment in the first round of the survey) as well as to the incidence rates for PTB b+, PTB c+ and PTB s+. The prevalence-to-notification rate ratios for PTB s+ were 1.28:1 for all adults, 1.2:1 for men and 1.4:1 for women. The ratios of the prevalence rate to the incidence rate were 0.45:1 for all adults, 0.52:1 for men and 0.40:1 for women. The ratios of the notification rate to the incidence rate of PTB b+ were 0.35:1 for all adults, 0.42:1 for men and 0.28:1 for women (online supplemental table 9).

PTB notification trend by year
Figure 2 shows (A) case notification rate 2011–2018 (B) and the number of patients before (four-quarters), during and after screening. The PTB s+ notification rates were 81 (95% CI: 66 to 96), 231 (95% CI: 206 to 257) and 150 (95% CI: 130 to 170)/100 000 population, respectively. The notification rates increased threefold during the project year and then decreased after the project but were higher than before the project. The notification rates had wide ranges between catchment areas,

particularly before the start of the current project (online supplemental tables 10–12).

DISCUSSION
This systematic symptom-based population-based TB screening in a district of Ethiopia found a point prevalence of smear-positive TB of 104/100 000 population, twice the level found in Ethiopia's 2010 national prevalence survey using smear-microscopy among symptomatic (58/100 000), where half of the cases were identified not by symptoms but by X-ray screening alone.[5] Only one-third of individuals with TB were detected by the routine NTLP services. The incidence of PTB was 332/100 000 person-years, highest among those with persistent symptoms and in those aged 25–34 years old. Higher TB rates in young people in a community indicates high transmission, since with falling rates the median age of patients with TB increases as the infected population becomes older.[2 25 26]

Our study showed a prevalence similar to that found in a 2013 local symptom-based survey from central Ethiopia, with a PTB s+ prevalence rate of 109 (67–150)/100 000 population,[6] while other symptom-based studies reported a higher prevalence of PTB s+: 169/100 000 population in northern Ethiopia in 2011,[27] 139/100 000 population in southern Ethiopia in 2016[28] and 78–174/100 000 population in other studies from different rural areas in Ethiopia, demonstrating how the disease burden varies across the country.[12 29–31] Compared with our data from

Ethiopia, a systematic review of national TB prevalence surveys (including X-ray and not based on symptoms) in Africa has revealed a higher prevalence of PTB s+ in Kenya (230/100 000) and Uganda (174/100 000), but a comparable prevalence in Ghana (111/100 000) and a lower prevalence in Gambia (90/100 000) and Rwanda (74/100 000). The difference in prevalence rates across studies could be due to differences in methods, year of study and location. Studies based on smear microscopy alone had lower prevalence rates than studies using the more sensitive tools GeneXpert and culture.[27 28 32]

In the current study, two out of three individuals with PTB s+ remained undetected in the communities, which is in agreement with a systematic review in Ethiopia showing a point prevalence of undiagnosed PTB s+ of 79 (56–113)/100 000, with an active-to-passive case finding ratio of 2.3:1,[32] which is also comparable to our prevalence of 72 (57–86)/100 000 population. Similarly, two individuals out of five with PTB c+ remained undetected. PTB c+ contributed 20–36% to the total prevalence and incidence of PTB in our study; 44% of PTB c+cases were detected by screening. In general, all PTB c+ diagnoses were based on chest X-ray. Overall, active TB case finding increases TB detection through community engagement with HEWs, thereby improving community awareness and access to TB treatment.[33 34] A lower prevalence of HIV and TB-HIV co-infections in the region[35] may have contributed to a lower prevalence of TB compared with the other studies. TB mainly affects women due to socio-economic disadvantages and domestic responsibilities. Women accounted for only 44% of the nationally notified cases in 2020 in Ethiopia, and such trends persisted for several years.[11] The prevalence of PTB was not statistically different by sex in this study.

The incidence of PTB s+ was 230 (201–262)/100 000 person-years, which is similar to the most recent report based on symptom screening, 214 (163–263)/100 000 person-years for PTB s+ central Ethiopia in 2013, but lower than 311 (240–382)/100 000 person-years in northern Ethiopia in 2011.[6 7] The age group 25–34 years had the highest incidence of PTB s+ cases, with no difference by sex; this may indicate heightened recent community transmission.

Individuals with presumptive TB for more than one round of screening (previous presumptive) were more likely to have PTB b+ (16%) than a new presumptive TB case (8%).[36] Similar trends were seen in a study in Guinea-Bissau, where smear-negative chronic coughers had a 5% higher smear-positivity rate after a month than new presumptive TB cases.[37] As expected, this study found more cases of PTB with a longer follow-up of chronic coughers after negative results than those initially identified with presumptive TB, thus emphasising the need to reach this population with feasible interventions and follow-up that can improve the identification of more TB cases.[37 38]

Our study allowed us to directly calculate the prevalence-to-incidence ratio. In an ideal world where the duration of the TB disease episode is not much more than 6 months (from disease onset to rapid start and completion of treatment) the ratio should be close to 0.5. In our study, of those with PTB s+, the ratio was 0.45:1 overall; 0.52:1 in men and 0.4:1 in women. These findings with a low ratio are likely due to the systematic and repeated screening with high coverage. Our prevalence-to-incidence ratio was lower than the study from another region of Ethiopia that reported rate ratio of 0.6:1.[6]

In prevalence surveys, the true incidence is normally unknown, and notification rates are used to estimate the incidence while taking into consideration underdiagnoses and under-reporting. The prevalence-to-notification rate ratio in PTB s+ cases in our study was 1.28:1, consistent with the finding that only one-third of patients with TB were detected and notified; therefore, showing that they had TB for a long time before diagnosis. In national surveys, the prevalence-to-notification rate ratios in PTB s+ patients have been reported to be 1.19:1 in Ethiopia, 0.62:1 in Gambia and 5.8:1 in Nigeria.[39]

The notification rate increased threefold during the intervention year, indicating that the decline of TB notifications since the previous intervention did not only reflect decline in TB incidence but also less case-finding activities. The decreasing incidence is a function of early detection and effective treatment of infectious cases. In our study, it may be too early to see that the reduced transmission leads to lower TB incidence. Besides, we may have missed TB cases during our initial screening since we only included symptomatic persons and mainly confirmed the diagnosis using smear-positive microscopy. Although some smear-negative patients were started on treatment as clinical cases, others could be identified as smear-positive during subsequent rounds of screening. This delay may have resulted in continued transmission and persistently high incidence.

This study had two main strengths. First, the project worked in close collaboration with the NTLP, and very few people declined to participate. Due to the large study population, the data provide precise estimates of the prevalence and incidence of PTB. Second, the engagement of existing health systems and community structures increased the community involvement, thus contributing to its sustainability. Challenges include that only symptomatic patients with TB were reported, and it is known that many patients are more or less asymptomatic.[40 41] However, since the same screening method is used in three rounds of visits, we are able to compare prevalence and incidence and assess changes over time. Individuals who did not participate in the first round of household visits, either because they were unavailable at the time of the visit or they did not come for sputum testing, may have been diagnosed with PTB in the second round (ie, prevalent but counted as incident cases). This may have overestimated the incidence. However, the number should be low because the coverage of households screened was high and screening-questions included household members who were not at home at the time of

the visit. We cannot rule out that there was some drop-off in the referral process of presumptive TB and sample collection, but none were reported as lost to follow-up and the proportion was probably very low. Finally, since the patients detected by screening could not be separated from those who attended health services by themselves, the year before the study was chosen as 'notification'.

From a public health perspective, in this study, two-thirds of symptomatic individuals with smear-positive PTB were undetected and transmitting TB in the community. Why individuals with symptoms of the deadly disease in a setting with reasonably accessible health services do not seek treatment is a major question. Increasing access by lowering the cost of care (patients should not have travel and other-related expenses to seek care), better diagnostic tools and addressing the impact of stigma are important factors to consider. Based on the study results, community screening for respiratory symptoms at intervals (every 3–4 months) may improve case findings and reduce delay in TB diagnosis in the community.

CONCLUSIONS

The prevalence rate of symptomatic sputum microscopy-positive TB was still high and similar to the magnitude found in the district at the start of a previous project and only one-third of PTB cases were notified. The incidence rate was highest in the age group 25–34 years. These findings indicate low TB case finding in the community and ongoing transmission of PTB. Cost-effective interventions implemented under routine programme conditions that engage the existing health system structures are needed to find the missing people with TB, decrease transmission and contribute to a sustained decline in the incidence of TB in a society.

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Effect of multicomponent interventions on tuberculosis notification in mining and pastoralist districts of Oromia region in Ethiopia: a longitudinal quasi-experimental study

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ABSTRACT

Objective To demonstrate the impact of interventions on tuberculosis (TB) case detection in mining and pastoralist districts in southeastern Ethiopia over a 10-year period.

Design Longitudinal quasi-experimental study.

Setting Health centres and hospitals in six mining districts implemented interventions and seven nearby districts functioned as controls.

Participants Data from the national District Health Information System (DHIS-2) were used for this study; therefore, people did not participate in this study.

Interventions Directed at training, active case finding and improving treatment outcomes.

Primary and secondary outcome measures Primarily, trends in TB case notification and percentage of bacteriologically confirmed TB—as collected by DHIS-2—between pre-intervention (2012–2015) and post-intervention (2016–2021) were analysed. Secondarily, post-intervention was split into early post-intervention (2016–2018) and late post-intervention (2019–2021) to also study the long-term effects of the intervention.

Results For all forms of TB, case notification significantly increased between pre-intervention and early post-intervention (incidence rate ratio (IRR): 1.21, 95% CI: 1.13, 1.31; p<0.001) and significantly decreased between pre-intervention/early post-intervention and late post-intervention (IRR: 0.82, 95% CI: 0.76, 0.89; p<0.001 and IRR: 0.67, 95% CI: 0.62, 0.73; p<0.001). For bacteriologically confirmed cases, we found a significant decrease between pre-intervention/early post-intervention and late post-intervention (IRR: 0.88, 95% CI: 0.81, 0.97; p<0.001 and IRR: 0.81, 95% CI: 0.74, 0.89; p<0.001). The percentage of bacteriologically confirmed cases was significantly lower in the intervention districts during pre-intervention (B: −14.24 percentage points, 95% CI: −19.27, −9.21) and early post-intervention (B: −7.78, 95% CI: −15.46, −0.010; p=0.047). From early post-intervention to late post-intervention, we found a significant increase (B: 9.12, 95% CI: 0.92 to 17.33; p=0.032).

Conclusions The decrease in TB notifications in intervention districts during late post-intervention is possibly due to a decline in actual TB burden as a result

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Trends in case notification over a longer period of time (10 years) have not been studied often.
⇒ The use of case notification data from control districts enabled us to analyse the effect of interventions.
⇒ Use of difference-in-differences analyses confirmed the impact of the interventions.
⇒ The parallel outcome assumption criteria were not met for the difference-in-differences analyses.
⇒ The quasi-experimental design did not enable us to control the implemented interventions.

of the interventions. The unabated increase in case notification in control districts may be due to continued TB transmission in the community.

INTRODUCTION

Tuberculosis (TB) continues to be among the leading causes of infectious morbidity and mortality, claiming the lives of 1.6 million people in 2022.[1] Moreover, the health system misses nearly one-third of the estimated number of patients, and <90% of those detected are successfully treated. Reasons for missing people along the care cascade include limited access to healthcare services, underdeveloped health reporting systems, insufficient human resources, and poor linkages between private providers and national TB programmes.[2] The COVID-19 pandemic led to disruptions in TB care services, further constraining case detection efforts.[3] To achieve the End TB Strategy goals of '95% reduction in TB deaths' and '90% reduction in TB incidence', strengthening the detection and treatment of TB is crucial.[4] High-impact and sustainable interventions that

can be implemented across high TB burden settings are urgently needed.[2]

Ethiopia is 1 of the 30 high TB and HIV-associated TB burden countries, with an incidence of 119 per 100 000 people in 2020.[1] In 2019, 29.3% of TB cases were not notified to the national TB programme.[5] Oromia region has 37% of Ethiopia's TB cases, with high rates in its southeastern zones of Guji and Borena.[6 7]

Guji and Borena zones are home to some of Ethiopia's major traditional mines. Several studies showed that TB is more prevalent among miners than in the general population.[7–9] This high prevalence is due to unhealthy working and living conditions, such as exposure to silica dust, crowded environments with insufficient ventilation, and excessive alcohol and tobacco use. The flourishing sex industry at mining sites induces the risk of sexually transmitted infections, such as HIV, which in turn increases the risk of active TB.[10] In general, HIV is one factor that contributes to the occurrence of TB in Ethiopia.[11] Additionally, many miners are also migrants and are associated with even more risk factors, including limited access to TB diagnosis and treatment. Moreover, their migration might enable TB transmission to the general population.[7 12] Furthermore, mining shafts are often located in hard-to-reach rural areas where access to care, and thus diagnosis and treatment of TB, are challenging.[13] Because the mining industry is one of the largest employers of men in sub-Saharan Africa and miners face multiple risk factors for TB, mining populations are important targets for TB case finding and treatment outcome interventions,[12] especially in Ethiopia where the number of TB cases is disproportionately high.

Pastoralists comprise about 12% of the Ethiopian population. They live in drought areas and often face food scarcity and stress, which are risk factors for TB.[14] Access to healthcare is problematic due to long distances to health facilities.[15] Hence, disease control activities, including TB diagnosis and treatment, are often delayed. Improving diagnostic and treatment services tailored to pastoralists' needs should be prioritised.[14 15]

Several interventions, including active case finding, have been implemented in other high burden settings.[16–18] For interventions implemented for a period of 1–2 years, an increase in case notification is expected. Yet, in the long term, a decline in TB prevalence and incidence is an expected result of these interventions.[19] A few studies from Africa and Asia show the long-term impact of different active case finding strategies.[20 21] In Zimbabwe, for example, six rounds of mobile van-based active case finding over a period of 3 years were associated with a 41% reduction in TB prevalence.[20] A modelling study from Pakistan suggested a sustained reduction in TB prevalence and incidence after 5 years of communication-oriented active case finding.[21] However, there is no clear guidance on the cut-off point when programmes should set a decline in the case notification rate (CNR) as an indicator of intervention success. Therefore, national and subnational programmes use an increase in the CNR as

the best indicator of success in programme performance without regard to the duration of past and ongoing interventions. Context-specific target setting is rarely done due to a lack of local data and knowledge on how prior interventions can lead to declining prevalence and incidence.

The mining and pastoralist populations described in this study form an important target group for CNR improvement. The availability of intervention data over a relatively long span of time also makes it suitable for comparing the short-term and long-term impacts of the interventions. Data are scarce on the effectiveness of such interventions among mining and pastoralist populations. Our objective was to demonstrate the impact of multifaceted interventions on case detection in mining and pastoralist districts in southeastern Ethiopia.

METHODS
Study design
This study has a longitudinal quasi-experimental design embedded within an ongoing comprehensive TB programme. We categorised districts that received intensive programme support as intervention districts and those that received regular support as control districts. For the aim of this study, districts were monitored over a period of 10 years.

Study setting
Persistently high numbers of TB incidence in Guji and Borena zones in the Oromia region in Ethiopia and the presence of at-risk groups (miners, migrant workers and pastoralist communities) triggered designing this project. Six mining woredas (districts) were pinpointed to implement the multifaceted interventions, and seven nearby districts were selected as control districts for this study. Figure 1 and table 2 show the location and demographics of the selected woredas, respectively.

Patient and public involvement
None.

Interventions
Following the initial site visit (February–July 2015), a series of actions and interventions were designed (August–October 2015) and implemented (November 2015–June 2016) under technical assistance from three successive US Agency for International Development-funded projects: HEAL TB, Challenge TB and Eliminate TB (figure 2).[22–24] See table 1 for a detailed description of implemented interventions.

Data sources and analysis
We used TB case notification data (all forms (AFs) of TB and bacteriologically confirmed (BC) TB) from the national District Health Information System (DHIS-2) in this study for 2012–2021. With the use of DHIS-2 data, no identifiable patient data were used. We analysed trends in TB case notification, CNR and percentage of BC TB cases over time and between intervention and control
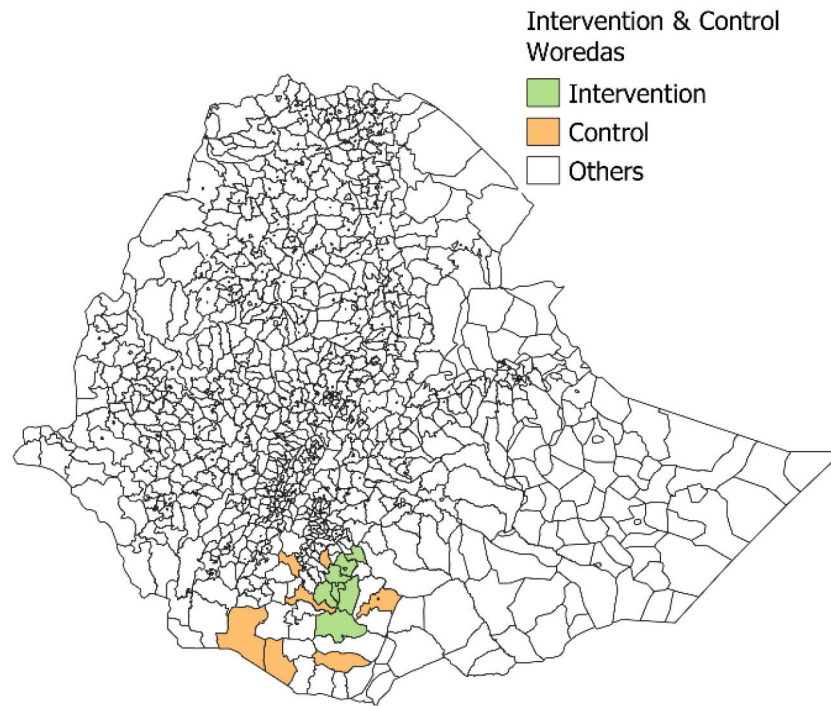
**Figure 1** Map of Ethiopia with selected intervention and control woredas.

districts. We computed CNR per 100 000 population and the percentage of BC TB cases.

We used line graphs to describe and visualise differences between control and intervention districts in trends of cases notified, CNR and percentage of BC TB cases over the 10 years of follow-up. To study whether differences and patterns found in the graphs are statistically significant, we performed a difference-in-differences (DID) analysis using a Poisson regression technique. The DID method has origins in John Snow's cholera study in 1855, but it is currently more widely used in social sciences research.[25] This technique is suitable for making a combination of before–after and treatment–control comparisons. Moreover, it allows data use on a group level rather than on an individual level, which is necessary in this study. DID analysis allowed us to estimate the effect of the interventions on the people living in intervention districts. The technique controls for unobservable time and group characteristics that confound the effect of the treatment on the outcome.[26]

We used the number of TB notifications as the dependent count variable (AFs of TB and BC TB separately). As predictor variables, we used district (0=control, 1=intervention) and time. To assess changes over time, we

dichotomised the follow-up period into pre-intervention (2012–2015) and post-intervention (2016–2021). Additionally, to analyse the impact of interventions in both the short and long term, we categorised time into three periods: pre-intervention (2012–2015), early post-intervention (2016–2018) and late post-intervention (2019–2021).

We performed Poisson regression analyses and used the exponential estimates of the beta values as measures of effect, described as incidence rate ratios (IRRs). We described the results as IRRs with its 95% CI, and a p value of <0.05 was considered statistically significant. We used interaction terms to analyse how the effect (difference between control and intervention districts) found at baseline (pre-intervention) changed over time; significance was determined at p<0.05. The control districts and pre-intervention time were used as reference categories. Yet, we changed the time reference category once to early post-intervention in DID with categorised time to assess the difference between early-post intervention and late post-intervention. Subsequently, we analysed trends in the percentage of BC TB cases out of AFs of TB cases between intervention and control districts and over time. We treated the percentage of BC TB cases out of AFs
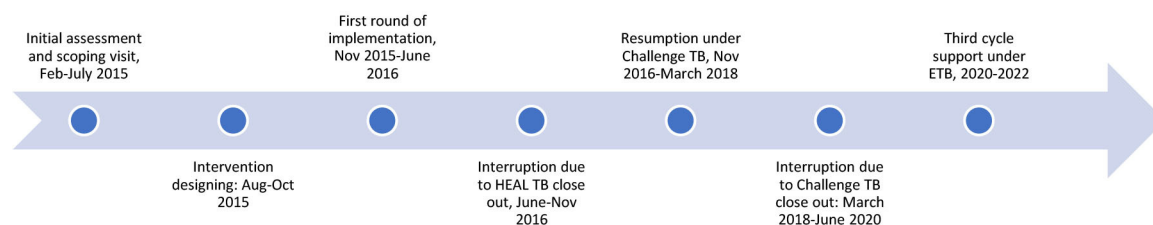
Figure 2 Timeline of intervention implementation. ETB, Eliminate TB; TB, tuberculosis.

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Table 1 Key study interventions, coordination and management

Intervention districts	Control districts
A. Key interventions	A. Key interventions
1. Action plan: set and endorsed by senior management at regional health bureau level	1. Action plan: district-level TB and other communicable diseases management
2. Six-day training: provided for newly deployed health extension workers (HEWs)[1 21]	2. Training: quota-based training for health extension training every 3–5 years
3. Gap-filling training: provided for existing HEWs	3. No such service
4. One Xpert machine: placed at a health centre to serve all districts	4. Patient referral: for Xpert service in nearby districts
5. Training on slide fixing and transportation: provided to 146 health workers from non-diagnostic health centres	5. No such service—patient referral applied
6. 29 motor bikes: provided to the woredas	6. One motor bike for all district health services
7. Billboard messages (in local language) on TB prevention: prepared and placed at five major market sites	7. No such service
8. Sensitisation workshop: conducted on Xpert utilisation, childhood TB and infection control; recording provided to TB focal persons from all woredas	8. No such service
9. Basic comprehensive TB/HIV training: provided to health workers in TB clinics	9. Basic TB/HIV training once a year
10. Other supportive actions: supported zonal review meetings, one-on-one review meetings and supervision	10. Participate in regional cluster review meeting
B. Coordination and programme management	B. Coordination and programme management
1. Coordination and programme management a. Supporting and capacitating woreda health offices and health facilities in overall planning, coordination, implementation, and monitoring and evaluation	1. No such service
2. Community mobilisation and sensitisation a. Providing health education at mining shafts for mine workers and at schools b. Social mobilisation at gatherings: selection and training of active TB volunteers, supporting women health development armies and supporting catchment area meetings c. Distributing leaflets/brochures with messages on TB prevention and control	2. Occasional health education on TB by HEWs or community volunteers
3. Improving diagnostic capacity a. Slide fixing and referral, integrated refresher training and comprehensive TB/HIV training b. Strengthening sample transportation from mining shafts to diagnostic centres	3. Postal service engaged in specimen transportation
4. Active case finding a. TB screening of mine workers at mining shafts b. TB screening at houses/tents c. Strengthening facility and community-level case findings: strengthening outpatient department screening at facilities within the mining woredas and strengthening community presumptive TB identification and referral d. Strengthening and conducting retrospective and prospective contact investigation at both the facility and community levels e. Selecting, training and engaging active community TB volunteers in presumptive identification and referral f. Strengthening the referral linkage between health centres and health posts	4. Active case finding a. Facility-based TB screening b. Routine or prospective contact screening c. HEW-led referral linkage between health posts and health facilities
5. Treatment and adherence support packages a. Ensuring strict Directly Observed Therapy Shortcourse (DOTS) provision is in place at health posts and health centres through supportive supervision/mentorship b. Selecting, training and supervising volunteer TB treatment supporters c. Retrieval of absentees, treatment interrupters and patients who are lost to follow-up	5. DOTS: mainly at health centres by health providers
6. Strengthening monitoring and evaluation a. Supporting improvement of data quality through on-site verification and checking b. Regular supportive supervision and quarterly review meetings c. Organising and preparing monthly progress reports	6. Supportive supervision and review meetings twice a year
TB, tuberculosis.	

Table 2 Information on the intervention and control districts

Zones	Name of woreda	Population in 2018	Public health facilities			Total
			Hospital	Health centre	Health post	
Intervention districts						
Guji*	Adolla Redde	195 101	1	5	28	34
	Gerja	67 065	0	4	20	24
	Odo Shakiso	130 630	0	5	31	36
	Saba-Boru	177 139	1	5	11	17
West Guji	Melkasoda	79 996	1	4	12	17
Borena	Arero	44 733	1	2	18	21
Total		694 664	4	25	120	149
Control districts						
Guji*	Uraga	152 828	1	5	33	39
	Liben	83 695	0	3	17	20
West Guji	Dugda Dawa	115 947	0	3	11	14
	Gelana	94 508	0	3	29	32
Borena	Teltele	78 367	1	4	24	29
	Dhas	21 649	0	4	8	12
	Dillo	27 057	0	3	10	13
Total		458 104	2	25	132	159

*This woreda has recently been divided into two (Saba-Boru and Aga Woyu); the information is the sum of the two.

of TB as a continuous dependent variable and district and time as predictor variables, as specified above. We performed a linear regression analysis and used beta values (including 95% CI) as measures of effect. We also used interaction terms between time and interventions to study differences over time. Statistical significance was set at p<0.05. All analyses were performed in STATA V.17.0.

RESULTS

Background information on the intervention and control districts participating in this study is provided in table 2.

Trends in number of cases notified
AFs of TB

In the intervention districts, the number of AFs of TB cases notified increased during the pre-intervention period, from 1076 cases in 2012 to 1276 cases in 2015 (+19%). This increase continued through the early post-intervention period with 1554 cases in 2018 (+22%) but declined to 1179 in 2021 (−24%). In the control districts, a steady decline was seen in the number of cases reported between 2012 and 2017 (−46%). It reached a nadir in 2017 (432 cases), after which it steadily increased, reaching a peak of 897 cases in 2021 (+108%). Figure 3A shows trends in the number of notified AFs of TB cases in the intervention and control districts.

When analysing differences in cases notified between intervention and control districts with dichotomised intervention time, we found an IRR of 1.92 (95% CI: 1.84, 2.02). The rate ratio for case notification was 1.92 times higher in the intervention districts than in the control districts before the intervention was implemented. This baseline effect did not change statistically significant in the period after the interventions were implemented (IRR: 0.99, 95% CI: 0.93, 1.05) (see table 3).

The DID analysis with categorised intervention time also showed an IRR of 1.92 (95% CI: 1.84, 2.02) for notification within intervention districts compared with control in the pre-intervention period. This effect increased statistically significant by a factor of 1.21 (95% CI: 1.13, 1.31) during the early post-intervention period. The rate ratio for notification was 2.34 (1.92×1.21) times higher in intervention than in control districts. The baseline effect of 1.92 decreased statistically significant by a factor of 0.82 (95% CI: 0.76, 0.88) during the late post-intervention period. The rate ratio for notification was 1.57 (1.92×0.82) times higher in the intervention districts than in the control districts. When changing the time reference category to the early post-intervention period, the difference in rate ratio for notification between the intervention and control districts decreased from early post-intervention to late post-intervention by a factor of 0.67 (95% CI: 0.62, 0.73). Thus, the pattern seen in figure 3A is confirmed to be statistically significant (p<0.05).
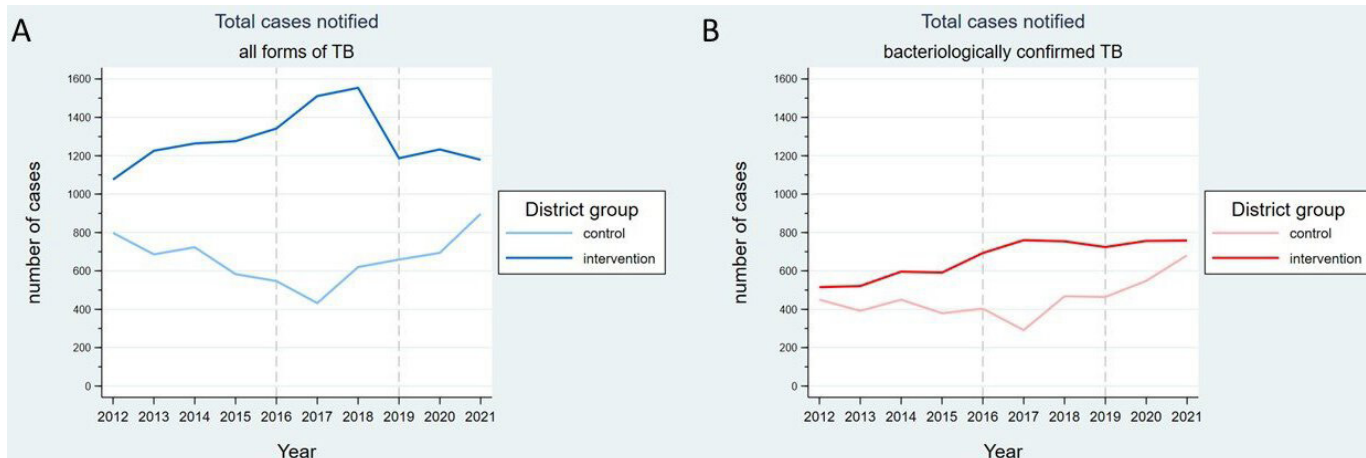
Figure 3 Visualisation of time trends in number of cases notified for (A) all forms of TB and (B) bacteriologically confirmed TB. The two lines in the figures represent the trends in case notification in the control (lighter colour) and intervention (darker colour) districts. The dashed lines in the figures represent the different intervention periods: pre-intervention (2012–2015), early post-intervention (2016–2018) and late post-intervention (2019–2021). TB, tuberculosis.

Bacteriologically confirmed TB

Similarly, the number of BC cases of TB in the intervention districts increased during the pre-intervention period from 515 cases in 2012 to 591 cases in 2015 (+15%). This increase continued through the early post-intervention period with 754 cases in 2018 (+28%), thereafter the number of cases notified stayed almost stable until 2021 (+0.5%). In contrast, the number of cases reported between 2012 and 2017 decreased in the control districts, reaching a nadir of 291 cases in 2017 (−35%). Afterwards, the number of cases notified increased steadily, reaching a peak in 2021 (+134%). Figure 3B shows trends in the number of notified BC TB cases in the intervention and control districts.

When analysing differences in cases notified between the intervention and control districts with dichotomised intervention time, we found an IRR of 1.47 (95% CI: 1.38,

1.57). The rate ratio for notification was 1.47 times higher in the intervention districts than in the control districts before the intervention was implemented. This effect did not change significantly in the period after the intervention was implemented (IRR 0.96, 95% CI: 0.89, 1.04), as shown in table 4.

The DID analysis with categorised treatment time also showed an IRR of 1.47 (95% CI: 1.38, 1.57) for BC TB notification in the pre-intervention period. The effect changed by a factor of 1.05 (95% CI: 0.99, 1.20) during the early post-intervention period, but this difference was not statistically significant. Yet, the effect of 1.47 changed by a factor of 0.88 (95% CI: 0.81, 0.97) from the pre-intervention to late post-intervention period. The rate ratio for notification was 1.29 (1.47×0.88) times higher in intervention districts than in control districts during the late post-intervention period, which was a

Table 3 Results of DID Poisson regression analyses for case notification of all forms of TB

	IRR	95% CI	SE	P value
DID model 1: analysis with dichotomised time				
Intervention districts	1.92	1.84, 2.02	0.046	<0.001
Post-intervention period	1.00	0.95, 1.05	0.025	0.989
Intervention districts×post-intervention period	0.99	0.93, 1.05	0.030	0.672
DID model 2: analysis with categorised time				
Intervention districts	1.92	1.84, 2.02	0.046	<0.001
Early post-intervention period	0.86	0.81, 0.92	0.027	<0.001
Late post-intervention period	1.13	1.07, 1.19	0.032	<0.001
Intervention districts×early post-intervention period	1.21	1.13, 1.31	0.046	<0.001
Intervention districts×late post-intervention period	0.82	0.76, 0.89	0.029	<0.001
Intervention districts×late post-intervention* period	0.67	0.62, 0.73	0.027	<0.001

Reference category: control (district group), pre-intervention (time).
*Time reference group changed to early post-intervention.
DID, difference-in-differences; IRR, incidence rate ratio; TB, tuberculosis.

Table 4 Results of DID Poisson regression analyses for case notification of bacteriologically confirmed TB

	IRR	95% CI	SE	P value
DID model 1: analysis with dichotomised time				
Intervention districts	1.47	1.38, 1.57	0.048	<0.001
Post-intervention period	1.24	1.17, 1.31	0.038	<0.001
Intervention districts×post-intervention period	0.96	0.89, 1.04	0.039	0.360
DID model 2: analysis with categorised time				
Intervention districts	1.47	1.38, 1.57	0.048	<0.001
Early post-intervention period	1.05	0.97, 1.13	0.040	0.240
Late post-intervention period	1.42	1.32, 1.52	0.049	<0.001
Intervention districts×early post-intervention period	1.09	0.99, 1.20	0.053	0.076
Intervention districts×late post-intervention period	0.88	0.81, 0.97	0.040	0.006
Intervention districts×late post-intervention* period	0.81	0.74, 0.89	0.039	<0.001

Reference category: control (district group), pre-intervention (time).
*Time reference group changed to early post-intervention.
DID, difference-in-differences; IRR, incidence rate ratio; TB, tuberculosis.

significant decrease from the pre-intervention period. When changing the time reference category to early post-intervention, the difference in rate ratio for notification between the intervention and control districts decreased significantly between the early post-intervention and late post-intervention periods by a factor of 0.81 (95% CI: 0.74 to 0.89) (see table 4).

Trends in CNR
During the study period (2012–2021), the CNR for AFs of TB was higher in the intervention districts than in the control districts (figure 4A). When analysing the lines for control and intervention districts over time separately, we see different time patterns. For the intervention districts, we see an increase in CNR followed by a decrease, whereas we see a decrease followed by an increase in the control districts. CNR of intervention districts increased throughout the pre-intervention and early

post-intervention periods: from 200.1 cases per 100 000 in 2012 to 223.7 cases per 100 000 in 2018 (+12%). Afterwards, it declined to 184.9 per 100 000 in 2021 (–17%). In control districts, CNR decreased from 131.7 per 100 000 in 2012 to 76.5 per 100 000 in 2017 (–42%), and from 2017 onwards, it reversed, reaching a peak of 144.2 per 100 000 in 2021 (+88%).

Figure 4B shows that during the study period, the CNR for BC TB was higher in the intervention districts than in the control districts. When analysing the lines for control and intervention districts over time separately, we see a more parallel time pattern compared with CNR for AFs of TB. In the intervention districts, the CNR of BC TB showed an overall increasing trend, but CNR between 2 consecutive years fluctuated. From 2012 to 2021, we saw an increase of 24%, but in the control districts, we saw a fluctuating decline in CNR until a drop in 2017 (51.6 per
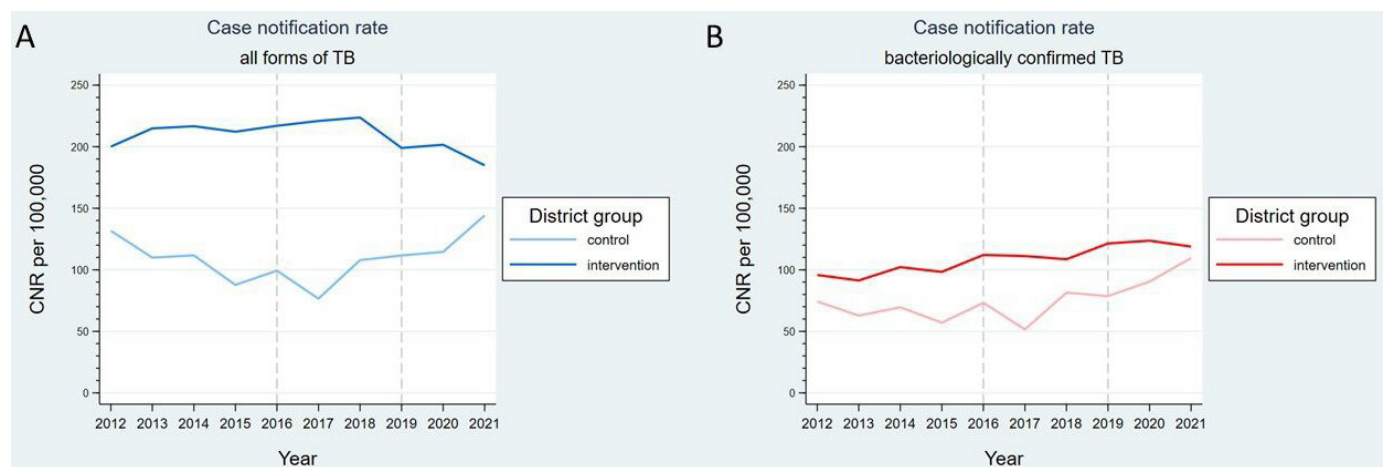
Figure 4 Visualisations of time trends in case notification rate (CNR) of (A) all forms of TB and (B) bacteriologically confirmed TB. The two lines in the figures represent the trends in case notification in the control (lighter colour) and intervention (darker colour) districts. The dashed lines in the figures represent the different intervention periods: pre-intervention (2012–2015), early post-intervention (2016–2018) and late post-intervention (2019–2021). TB, tuberculosis.
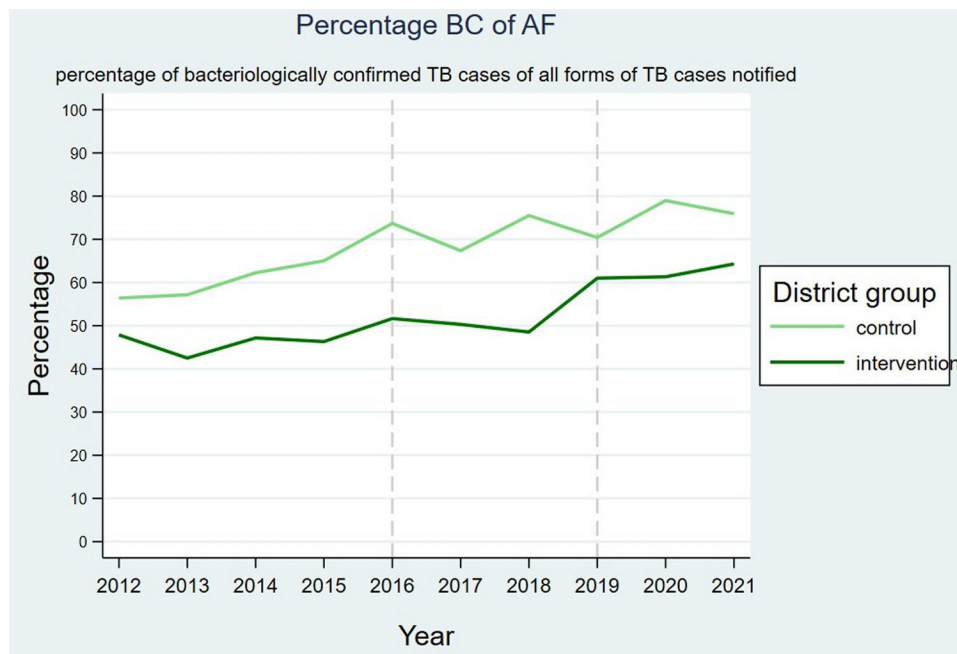
Figure 5 Visualisation of time trends in percentage of bacteriologically confirmed (BC) TB cases out of all forms (AFs) of TB cases. The two lines in the figure represent the trends in case notification in the control (lighter colour) and intervention (darker colour) districts. The dashed lines in the figures represent the different intervention periods: pre-intervention (2012–2015), early post-intervention (2016–2018) and late post-intervention (2019–2021). TB, tuberculosis.

100 000 people, −31%). CNR then increased to a peak in 2021 (+112%).

Both control groups (AFs of TB and BC TB) showed a decline in CNR during the pre-intervention period and 1 year after, with a nadir in 2017 (figure 4A,B). In contrast, the intervention districts showed an increase in CNR at the beginning without a drop in 2017. CNR for AFs of TB in the intervention groups declined from 2018 onwards, while CNR for BC TB increased. This could suggest that more people were accurately diagnosed over time in the intervention zones.

Trends in percentage of BC TB out of AFs of TB

Figure 5 shows the percentage of BC cases out of AFs of TB notified. The percentage is always higher in the control districts than in the intervention districts. However, the dark green line (reflecting the intervention group) shows a stable increase over time, while the lighter green line fluctuates.

The DID analysis with dichotomised intervention time shows a significant difference of −14.24 percentage points (95% CI: −21.58, −6.89) for the intervention districts compared with the control districts during the pre-intervention period. This baseline effect did not change significantly in the period after the intervention was implemented (B: −3.22, 95% CI: −12.7, 6.26). See table 5 for the results of the DID analysis.

When analysing the percentage of BC cases out of AFs of TB over the three time periods, we found that the intervention districts had a statistically significantly lower percentage at baseline (pre-intervention) than the control districts (B: −14.24, 95% CI: −19.27, −9.21). This

difference got bigger during the early post-intervention period: −7.78 (95% CI: −15.46, −0.010) to −14.24+−7.78=−22.02. During the late post-intervention period, the difference in percentages between control and intervention districts decreased but not significantly. When comparing the late post-intervention with the early post-intervention period, we saw an increase of 9.12 percentage points (95% CI: 0.92, 17.33), which is significant. Table 5 shows the results of the DID analysis of the percentage of BC TB cases out of AFs of TB.

DISCUSSION

In this study, we found significant differences between intervention and control districts over time in the number of notified TB cases and percentage of BC TB cases. There was a significant increase in the number of notified AFs of TB cases in the intervention districts from the pre-intervention to the early post-intervention period, while it reached a nadir in control districts over the same period. During the late post-intervention period, these trends were reversed significantly. The number of notified BC TB cases in intervention districts increased during the early post-intervention period; however, this was not significant. During the late post-intervention period, we saw a significant decrease in BC TB and AFs of TB notifications in intervention districts compared with control districts. Furthermore, the comparison of CNR showed a similar pattern, and the proportion of BC TB cases out of AFs of TB increased steadily over time in both control and intervention districts, although it was always significantly lower in intervention districts.

Table 5 Results of DID linear regression analyses on the percentage of all forms of TB notified that are bacteriologically confirmed

	B	95% CI	SE	P value
DID model 1: analysis with dichotomised time				
Intervention districts	−14.24	−21.58, 6.89	3.466	<0.001
Post-intervention period	13.44	6.73, 20.14	3.163	<0.001
Intervention districts×post-intervention period	−3.22	−12.7, 6.26	4.474	0.482
DID model 2: analysis with categorised time				
Intervention districts	−14.24	−19.27, 9.21	2.344	<0.001
Early post-intervention period	11.98	6.55, 17.41	2.531	<0.001
Late post-intervention period	14.90	9.47, 20.33	2.531	<0.001
Intervention districts×early post-intervention period	−7.78	−15.46, 0.010	3.58	0.047
Intervention districts×late post-intervention period	1.34	−6.34, 9.02	3.58	0.713
Intervention districts×late post-intervention* period	9.12	0.92, 17.33	3.83	0.032

Reference category: control (district group), pre-intervention (time).
*Time reference group changed to early post-intervention.
DID, difference-in-differences; TB, tuberculosis.

These findings highlight the importance of careful analysis of post-intervention outcomes before drawing conclusions on the impact of interventions. Traditionally, increase in notifications is taken as a positive impact, which may be true for the immediate post-intervention period. However, even when there is a decline in cases or no change at all, it could still be a positive impact. In 2017, for example, the decline in the number of AFs of TB notified cases was significantly higher in the control districts, and for BC TB, this difference was close to significant (p=0.076). This appears to be linked to the major political instability (leadership transition) that affected Ethiopia at that time. These numbers suggest that the intervention improved the resilience of the health system in certain districts. In the future, resilience of TB programmes in projects and research should get more attention.

Another striking finding in this study is the unabated increase in case notification (AFs of TB and BC TB) in the control districts after the 2017 dip. In the absence of any significant investment in case finding, the increase in case notification is unlikely to be a measure of success. Rather, this could be an indicator of unchecked disease transmission due to late diagnosis, poor infection control practices, or inaccurate recording and reporting.[27] This shows that contextual analysis might be needed to rate TB management progress.

The increase in the number of notified cases shortly after intervention implementation was as expected, since multiple studies showed comparable findings in the past. In Nigeria, a multifaceted active case finding approach, similar to this study, was used in a low-resource setting. This led to a 112.9% increase in case finding during implementation compared with baseline.[28] A study in Nepal on active case finding placed GeneXpert machines throughout intervention districts, among other interventions. In these intervention districts, 29% more TB cases were found than in control zones.[29] A previous study in southern Ethiopia focused on community-based interventions that led to an increase in case notification from 64 per 100 000 at baseline to 127 per 100 000 during implementation.[30]

Analysing the effect of interventions on the long term is more challenging. Our study found a significant decrease in AFs of TB and BC TB cases notified in the intervention districts during the late post-intervention period compared with both the pre-intervention and early post-intervention periods. Meanwhile, case notification in control districts increased during the early and late post-intervention periods; this could mean that the actual prevalence was dropping in intervention districts compared with control districts. This decrease could be due to COVID-19 measures. However, TB notifications did not drop in control districts and not for BC TB only; therefore, we think it reflects an actual decrease in case notifications. A study in Vietnam found a similar pattern: during the fourth year after implementation, a decline in prevalence was seen.[31] Furthermore, the steady increase we found in case notification of BC TB and the proportion of BC TB cases could suggest that diagnosis is done more accurately in intervention districts over time than in control districts, where we saw a fluctuating pattern. A recent systematic review of interventions found that active case finding might increase TB notifications in high-risk populations.[32]

The study has both strengths and limitations. In the DID analysis, three key assumptions should be fulfilled: stable unit treatment value assumption (outcomes are equal for patients in control and intervention districts

and treatment that is given is the same for all in control and all in intervention districts); intervention is unrelated to outcome at baseline (allocation of intervention was not determined by outcome); and control/intervention have parallel trends in outcome. In this study, the latter assumption is violated, as we see a different pattern in notification in the years before the intervention was implemented. Since the other assumptions were met, the DID analysis was the best available rigorous statistical method and allowed us to do statistical analysis on top of descriptive analysis. This adds value to the research field. Since most district coordinators are qualified at the postgraduate level, they are trained (or could be trained) to conduct analyses like these to evaluate subnational programme performance. Moreover, DID allows us to interpret results intuitively and use group-level data, and it could provide causal relationships. This study focused on two risk groups in Ethiopia: miners and pastoralists. Those two populations are likely to face challenges when it comes to seeking healthcare.[8][33] Multiple studies suggest that proper TB diagnosis and treatment of pastoralists and miners require service expansion, adaptation of TB programmes to the specific context of pastoralist and miner communities, and decentralisation management.[33][34] The one-size-fits-all approach regarding TB diagnosis and treatment hampers timely and accurate TB care for pastoralists and probably miners as well.[35] This study considered the characteristics of both populations when designing suitable and sustainable interventions and support actions that can be scaled up in similar settings.

A weakness of this study was the disruption of intervention intensity due to the transition between projects. The decline in the number of notified cases between 2018 and 2020, for example, could be due to less technical support rather than actual decline. We did not have control over what was implemented in the control districts.

Conclusions

This study gives fresh perspective about the way TB case finding efforts should be evaluated at the subnational level in settings with a dual burden of risk factors. Our analysis shows that after about 4 years of intensive case finding efforts, the number of reported cases tends to decline. This provides an important clue about when national TB programmes should start adjusting their case notification targets after well-supported interventions have been in place. The multifaceted interventions in mining and pastoralist areas of Ethiopia have a clear impact on TB case notification and burden. We recommend that these interventions be scaled up to other settings, and the results should be further evaluated on a broader scale. DID analysis could be used by national programmes to measure both the short-term and long-term effects of interventions.

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Epidemiology of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis

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A R T I C L E I N F O

A B S T R A C T

Objectives: To estimate the pooled proportion of extensively drug-resistant tuberculosis (XDR-TB) and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) in patients with multidrug-resistant TB (MDR-TB).

Methods: We systematically searched articles from electronic databases: MEDLINE (PubMed), ScienceDirect, and Google Scholar. We also searched gray literature from the different literature sources main outcome of the review was either XDR-TB or pre-XDR-TB in patients with MDR-TB. We used the random-effects model, considering the substantial heterogeneity among studies. Heterogeneity was assessed by subgroup analyses. STATA version 14 was used for analysis.

Results: A total of 64 studies that reported on 12,711 patients with MDR-TB from 22 countries were retrieved. The pooled proportion of pre-XDR-TB was 26% (95% confidence interval [CI]: 22-31%), whereas XDR-TB in MDR-TB cases was 9% (95% CI: 7-11%) in patients treated for MDR-TB. The pooled proportion of resistance to fluoroquinolones was 27% (95% CI: 22-33%) and second-line injectable drugs was 11% (95% CI: 9-13%). Whereas the pooled resistance proportions to bedaquiline, clofazimine, delamanid, and linezolid were 5% (95% CI: 1-8%), 4% (95% CI: 0-10%), 5% (95% CI: 2-8%), and 4% (95% CI: 2-10%), respectively.

Conclusion: The burden of pre-XDR-TB and XDR-TB in MDR-TB were considerable. The high burdens of pre-XDR-TB and XDR-TB in patients treated for MDR-TB suggests the need to strengthen TB programs and drug resistance surveillance.

Introduction

The rise of drug-resistant (DR) bacterial infections is becoming a major public health concern worldwide. It threatens global tuberculosis (TB) control programs and makes TB diagnosis and treatment challenging. In the past 20 years, DR-TB has spread across the world and continued to be a challenge to global TB control efforts [1]. A recent estimate indicated 465,000 incident cases of multidrug resistance/rifampicin (RIF) resistance (MDR/RR-TB) occurred worldwide [2]. In addition, an estimated 3.6% of new TB cases and 18% of previously treated TB cases have developed MDR-TB in 2021 [3]. Moreover, on average, 6.2% of XDR-TB was esti-

mated in 2019 among patients treated for MDR-TB [2]. Prolonged duration required for the treatment, low cure rates, and the cost of drugs and toxicity make DR-TB treatment the most costly challenge [4].

Migration, housing conditions, poverty, and the emergence of other diseases, such as HIV and diabetes, are the factors fueled the burden of MDR/XDR-TB [5,6]. Furthermore, low laboratory diagnosis capabilities that delay DR-TB diagnosis and limited access to second-line MDR-TB treatment are associated with the transmission of resistant strains. Therefore, to stop the emergency of DR-TB strain, the best strategy is evidence-based diagnosis and treatment [7].

Before 2021, XDR-TB was defined as a disease caused by *Mycobacterium tuberculosis* with resistance to at least isoniazid (INH) and RIF (MDR-TB), with further resistance to any fluoroquinolones (FQs) and a second-line injectable drug (SLID) (kanamycin, amikacin, or capreomycin). Pre-XDR-TB is defined as TB with resistance to INH, RIF, and either an FQ or a second-line injectable agent but not both [4]. Based on new experimental and observational data, the World Health Organization (WHO) recently updated its guidelines, in which the late-generation FQs (levofloxacin and moxifloxacin) and WHO group A drugs (linezolid and bedaquiline) are recommended for the treatment of MDR-TB. In this guideline, XDR-TB is defined as an infection with MDR *M. tuberculosis* that is resistant to any FQs and at least one of the group A drugs. The most effective use of group A drugs to improve MDR-TB treatment requires appropriate drug susceptibility testing results [8].

The DR-TB treatment method has been updated in 2022. This document includes two new recommendations. The first regimen is the use of bedaquiline, pretomanid, linezolid, and moxifloxacin regimen for 6 months. This regimen is composed of bedaquiline, pretomanid, linezolid, and moxifloxacin and given to patients with MDR/RR-TB. However, patients with MDR/RR-TB with FQs additional resistance (pre-XDR-TB) should be treated for 9 months with all oral regimens. The consolidated guidelines includes the existing recommendations in the treatment regimens for INH-resistant TB with longer all oral regimens, monitoring of treatment response, timing of antiretroviral therapy in MDR/RR-TB for the patients infected with HIV, and the use of surgery for patients receiving MDR-TB treatment [8].

Several review studies have attempted to pool the proportion of MDR-TB cases. However, there are few review studies that attempted to estimate the pooled proportion of pre-XDR-TB and XDR-TB. Thus, we aimed to determine the pooled proportion of pre-XDR-TB and XDR-TB among patients diagnosed with MDR-TB from published primary studies.

Methods

Protocol registration

To prevent duplicates, the review study databases were searched for similar systematic reviews before this review commenced. The protocol of this systematic review and meta-analysis was registered in International Prospective Register of Systematic Reviews at the University of York database and obtained registration number PROSPERO ID: CRD42022343112.

Databases and search strategy

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines for reporting systematic reviews and meta-analyses [9,10]. We estimated the pooled proportion of pre-XDR-TB and XDR-TB in patients with MDR-TB for global occurrence. We conducted systematic searches of the following electronic databases: MEDLINE (PubMed), ScienceDirect, and Google Scholar, until July 20, 2022 for articles published in English, without limiting the year of publication. Studies that reported pre-XDR-TB and XDR-TB globally were included in the analysis. We used search terms: "(extensively drug-resistant tuberculosis OR XDR-TB) AND (pre-extensively drug-resistant tuberculosis OR Pre-XDR-TB) AND (drug-resistant tuberculosis OR DR-TB) AND (second-line drug resistance)" for the PubMed database search in both free text and medical subject heading.

Inclusion and exclusion criteria

We included cross-sectional studies that reported the proportion of either pre-XDR or XDR-TB among patients diagnosed with MDR-TB. However, we excluded studies that compared or validated the diagnostic methods for the detection of DR-TB and treatment outcomes. In addition, we excluded case studies, editorials, author comments, commentaries, general evaluations, and professional opinions to avoid duplicates.

Study selection

To identify potential studies, two authors (GD and BY) independently searched the electronic databases. Two reviewers (GD and DFG) independently screened the full-text papers to choose relevant articles based on the inclusion criteria. Differences between the two reviewers were resolved through discussion between the two authors (GD and DFG).

PICOS criteria

- Participants: patients with MDR-TB with pre-XDR-TB and XDR-TB.
- Intervention: not applicable.
- Comparator: not applicable.
- Outcome: pre-XDR-TB and XDR-TB among patients with MDR-TB.
- Study design: observational studies.
- Study setting: any setting in any country worldwide.

Definition of terms

Based on a previous 2021 definition, pre-XDR-TB and XDR-TB were defined as:

- Pre-XDR-TB was defined as TB with resistance to INH and RIF and either an FQ or a second-line injectables.
- XDR-TB referred to MDR-TB that is resistant to INH and rifampin plus any fluoroquinolone and at least one of the three SLIDs.
- New TB case is defined as a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB drugs for less than a month.
- Previously treated TB case refers to a patient who has received anti-TB drugs in the past for a month or longer.

Data extraction

We extracted the data in a standard prepared Microsoft Excel sheet. Two authors (GD and BY) independently extracted the data from the selected primary studies. Data were extracted on the variables: first author name; year of publication; study period; study area (country); study design; a number of MDR-TB; a number of XDR-TB; a number of pre-XDR-TB; FLQ resistance; SLIDs resistance, new drugs resistance Bedaquiline (BDQ), Clofazimine (CFZ), Delamanid (DLM), and Linezolid (LZD), and previous treatment history.
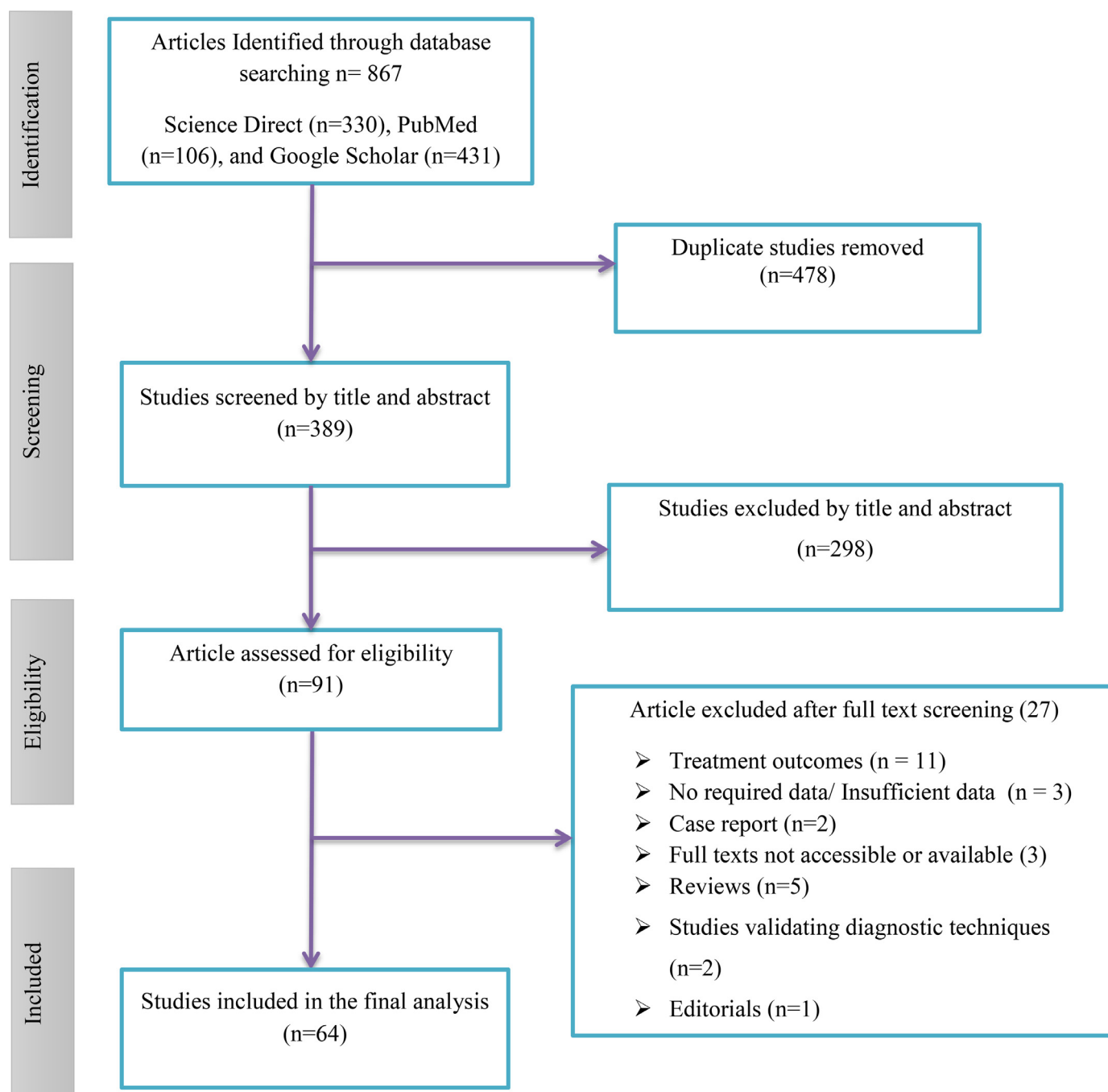
Figure 1. Flowchart describing the selection of studies for the systematic review and meta-analysis of extensively drug-resistant-TB and pre- extensively drug-resistant-TB TB in globally. TB, tuberculosis.

Discrepancies between the two authors' on data records were resolved by consensus.

Risk of bias assessment and quality assessment

Two authors (GD and AA) evaluated the quality of the selected studies independently and in cases of inconsistencies a third reviewer (BY) was involved. We used Newcastle-Ottawa scale adapted for cross-sectional studies to assess the quality of the included studies. Newcastle-Ottawa scale rates the likelihood of bias in three domains of observational studies. These are the (1) selection of participants, (2) comparability, and (3) outcomes. For each numbered item in the selection and outcome categories, a study

receives up to one point, and for comparability, a study may receive up to two points [11]. For low-, moderate-, and high-quality studies, the corresponding scores of 0-3, 4-6, and 7-9 were given, respectively. We used the *I*-squared statistic (I^2) to assess the heterogeneity in the reported proportion. $I^2 \geq 50\%$ was used to indicate the presence of heterogeneity [12]. Moreover, a funnel plot was used to examine the possibility of publication bias.

Statistical analysis

We used the random-effects model to pool the proportion of pre-XDR-TB and XDR-TB and their 95% confidence interval (CI). The pooled proportion of pre-XDR-TB and XDR-TB in patients with

Table 1

Characteristics of the individual studies on XDR-TB and pre-XDR-TB among DR-TB patients in globally included in the current systematic review and meta-analysis.

First author, year	Study design	Country	WHO regions	Study period	MDR-TB	XDR-TB	Pre-XDR-TB	XDR-TB New	XDR-TB Previous treated	Pre- XDR-TB New	Pre- XDR-TB Previous treated	FQs resistance	SLIDs resistance
Adwani et al. [14]	cross-sectional	India	SEAR	2014	227	11	127	11	0	127	0	127	19
Agonafir et al. [15]	cross-sectional	Ethiopia	AFR	2005-2006	46	2	0	0	2	0	0	2	0
Araujo et al. [75]	cross-sectional	Brazil	AMR	2013-2019	33	2	3	1	1	1	2	5	2
Elion Assiana et al. [16]	cross-sectional	Congo	AFR	2018-2019	9	1	1	NR	NR	NR	NR	2	1
Banerjee et al. [17]	cross-sectional	California	AMR	1993-2006	424	18	77	NR	NR	NR	NR	NR	NR
Bedru et al. [18]	cross-sectional	Ethiopia	AFR	2017-2018	30	3	1	1	2	0	1	NR	NR
Calver et al. [19]	cross-sectional	South Africa	AFR	2003-2005	77	5	26	NR	NR	NR	NR	NR	NR
Chen et al. [20]	cross-sectional	China	WPR	2014 -2015	51	0	24	0	0	10	14	24	0
Cheng et al. [21]	cross-sectional	Cambodia	WPR	2012- 2017	118	3	16	NR	NR	NR	NR	15	5
Dagne et al. [20]	cross-sectional	Ethiopia	AFR	2019	99	1	8	NR	NR	NR	NR	7	3
Dala et al. [21]	cross-sectional	India	SEAR	2005-2013	340	33	193	NR	NR	NR	NR	179	41
Daniel et al. [24]	cross-sectional	Nigeria	AFR	2007-2011	50	0	10	0	10	0	10	8	NR
Diriba et al. [25]	cross-sectional	Ethiopia	AFR	2019	14	0	3	0	0	2	1	2	1
Ennassiri et al. [26]	cross-sectional	Morocco	EMR	2015	155	4	18	NR	NR	NR	NR	16	6
Gadhav et al. [27]	cross-sectional	India	SEAR	2019	700	23	143	NR	NR	NR	NR	106	58
Gallo et al. [28]	cross-sectional	Brazil	AMR	2011-2013	313	32	60	6	26	1	47	59	33
He et al. [29]	cross-sectional	China	WPR	2015	102	9	30	NR	NR	NR	NR	24	6
Jabbar et al. [30]	cross-sectional	Pakistan	EMR	2016-2017	62	5	0	NR	NR	NR	NR	5	5
Jain et al. [31]	retrospective	India	SEAR	2007-2009	130	11	55	NR	NR	NR	NR	36	19
Jaksuwan et al. [32]	cross-sectional	Thailand	SEAR	2005-2012	24	1	9	NR	NR	NR	NR	NR	NR
James et al. [33]	cross-sectional	India	SEAR	2003 -2007	103	45	0	NR	NR	NR	NR	NR	NR
Javaid et al. [34]	cross-sectional	Pakistan	EMR	2011-2012	132	2	65	NR	NR	NR	NR	67	5
Kozińska et al. [5]	cross-sectional	Poland	EUR	2000-2009	297	36	19	NR	NR	NR	NR	NR	NR
Kumar et al. [35]	cross-sectional	India	SEAR	2014-2016	173	3	33	1	2	5	28	NR	NR
Kuo et al. [36]	cross-sectional	Taiwan	WPR	2011-2015	63	4	0	NR	NR	0	0	4	4
Lai et al. [37]	cross-sectional	Taiwan	WPR	2000-2006	150	10	0	1	9	NR	NR	6	4
Lee et al. [38]	cross-sectional	South Korea	WPR	2011-2017	85	9	29	NR	NR	NR	NR	32	15
Lee et al. [39]	cross-sectional	Korea	WPR	2006-2013	145	55	0	27	28	0	0	43	12
Macedo et al. [40]	cross-sectional	Portugal	EUR	2008-2010	50	12	0	NR	NR	NR	NR	NR	NR
Madukaji et al. [41]	cross-sectional	Nigeria	AFR	2018-2019	101	12	16	NR	NR	NR	NR	5	12
Matsui et al. [42]	cross-sectional	Brazil	AMR	2016-2017	92	5	11	1	4	5	6	NR	NR
Mbuh et al. [43]	cross-sectional	Cameroon	AFR	2016-2017	75	1	2	0	1	0	2	NR	NR
Misra et al. [44]	cohort study	India	SEAR	2017-2019	62	48	11	NR	NR	NR	NR	48	11

Table 1 (*continued*)

First author, year	Study design	Country	WHO regions	Study period	MDR-TB	XDR-TB	Pre-XDR-TB	XDR-TB New	XDR-TB Previous treated	Pre- XDR-TB New	Pre- XDR-TB Previous treated	FQs resistance	SLIDs resistance
Mohan et al. [45]	cross-sectional	India	SEAR	2012	87	3	0	NR	NR	NR	NR	NR	NR
Mok et al. [46]	cross-sectional	Korea	WPR	2010-2014	378	47	78	20	27	37	41	96	68
Momen et al. [47]	cross-sectional	Morocco	EMR	2015-2018	200	5	48	2	3	5	42	27	25
Namburete et al. [48]	cross-sectional	Mozambique	AFR	2014–2015	25	0	6	0	0	NR	NR	6	0
Nguyen et al. [49]	cross-sectional	Vietnamese	WPR	2011	91	5	15	2	3	8	7	15	5
Noor et al. [50]	cross-sectional	Bangladesh	SEAR	2011-2012	59	2	9	0	2	0	9	7	2
Park et al. [51]	retrospective	Korea	WPR	2008	2,472	749	0	313	436	0	0	NR	NR
Poudel et al. [52]	cross-sectional	Nepal	SEAR	2007-2010	109	13	43	NR	NR	NR	NR	NR	NR
Qi et al. [53]	cross-sectional	China	WPR	2009-2011	249	31	77	10	21	NR	NR	89	41
Ramachandran et al. [54]	cross-sectional	India	SEAR	2005	216	7	0	0	7	NR	NR	52	10
Riccardi et al. [55]	retrospective	Italy	EUR	2000-2015	370	0	83	0	0	NR	NR	NR	NR
Salvato et al. [56]	cross-sectional	Brazil	AMR	2013-2014	87	4	8	NR	NR	NR	NR	NR	NR
Sethi et al. [57]	cross-sectional	India	SEAR	2018	687	59	265	6	53	103	192	295	70
Sharma et al. [58]	retrospective	India	SEAR	2003	211	5	25		5	NR	NR	21	14
Sharma et al. [59]	cross-sectional	India	SEAR	2014-2016	49	1	9	NR	NR	NR	NR	NR	NR
Shibabaw et al. [60]	cross-sectional	Ethiopia	AFR	2016-2018	176	1	10	1	0	1	9	NR	NR
Singhal et al. [61]	cross-sectional	India	SEAR	2012-2013	87	10	43	NR	NR	NR	NR	41	16
Tasnim et al. [62]	cross-sectional	Bangladesh	SEAR	2016-2017	68	4	11	1	3	3	8	9	2
Tuladhar et al. [63]	cross-sectional	Nepal	SEAR	2015	57	1	29	NR	NR	NR	NR	21	8
Ullah et al. [64]	retrospective	Pakistan	EMR	2019-2020	180	8	62	NR	NR	NR	NR	62	8
Vashakidze et al. [65]	cross-sectional	Georgia	EUR	2005-2007	261	33	96	6	27	NR	NR	75	54
Wang et al. [66]	cross-sectional	china	WPR	2008-2012	206	41	90	NR	NR	NR	NR	90	35
Wang et al. [67]	cross-sectional	china	WPR	2020	391	28	94	NR	NR	NR	NR	68	NR
Welekidan et al. [68]	cross-sectional	Ethiopia	AFR	2018-2019	38	0	2	NR	NR	NR	2	2	0
Xu et al. [69]	cross-sectional	China	WPR	2015-2018	17	0	9	NR	NR	1	8	9	NR
Yang et al. [70]	cross-sectional	China	WPR	2008-2009	239	29	138	14	15	64	74	134	77
Yang et al. [71]	cross-sectional	Korea	WPR	2017	420	9	17	NR	NR	NR	NR	NR	NR
Yao et al. [13]	cross-sectional	China	WPR	2018-2019	425	29	282	NR	NR	NR	NR	311	171
Yuan et al. [72]	cross-sectional	China	WPR	2010-2011	77	16	26	NR	NR	NR	NR	16	13
Yuan et al. [73]	cross-sectional	China	WPR	2010-2011	159	13	0	3	10	NR	NR	NR	NR
Zheng et al. [74]	cross-sectional	China	WPR	2014-2016	88	9	44	NR	NR	NR	NR	34	11

AFR, African region; AMR, region of the Americas; DR-TB, drug-resistant tuberculosis; EMR, Eastern Mediterranean eegion; EUR, European region; FQs, fluoroquinolone; MDR-TB, multidrug-resistant tuberculosis; SEAR, South-East Asian region; SLID, second-line injectable drug; WPR, Western Pacific region; XDR-TB, extensively drug-resistant tuberculosis.
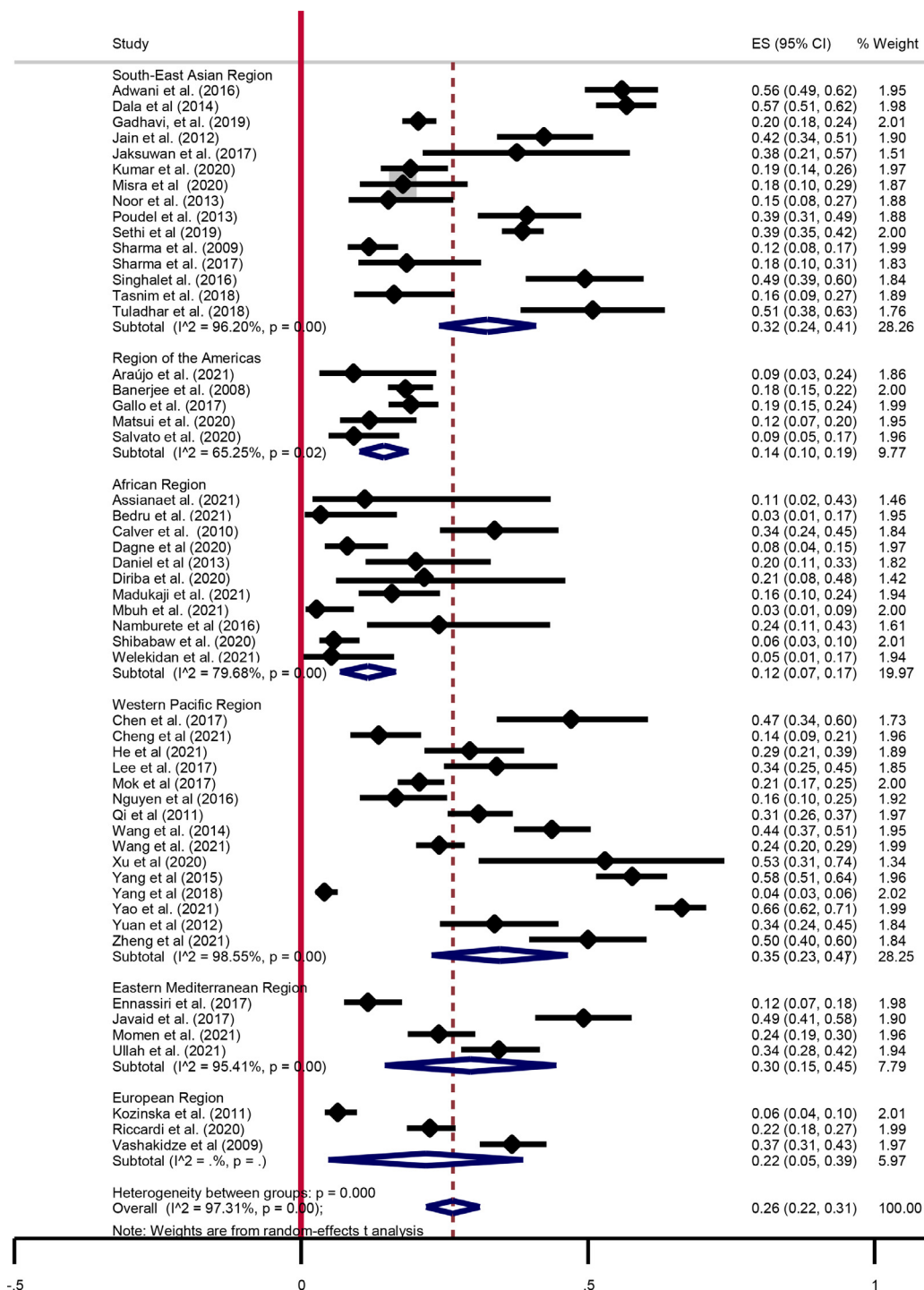
Figure 2. Summary of pooled estimates of pre-extensively drug-resistant-tuberculosis among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size. New diagnosed cases Previously treated diagnosed cases.

MDR-TB was estimated using the "metaprop" command in STATA 14 (STATA Corporation, College Station, TX, USA). The estimates of pre-XDR-TB and XDR-TB pooled proportion were compared descriptively by the WHO regional categories and patient TB treatment history.

Results

Study selection

A total of 867 records were retrieved from the electronic and gray literature search and imported to EndNote reference manager.

Of the total retrieved record, 389 remained after the duplicates were removed; Of 389 records, 298 were excluded by reviewing the title and abstract for population, intervention, and outcome difference with the current review. A total of 91 original articles were retrieved and fully articles were reviewed, and 27 were removed based on exclusion criteria. Finally, total of 64 articles were included in this review [5,13–75] (Figure 1).

Characteristics of the studies included in the review

Detailed characteristics of included studies are depicted in Table 1. The included studies were reported from 22
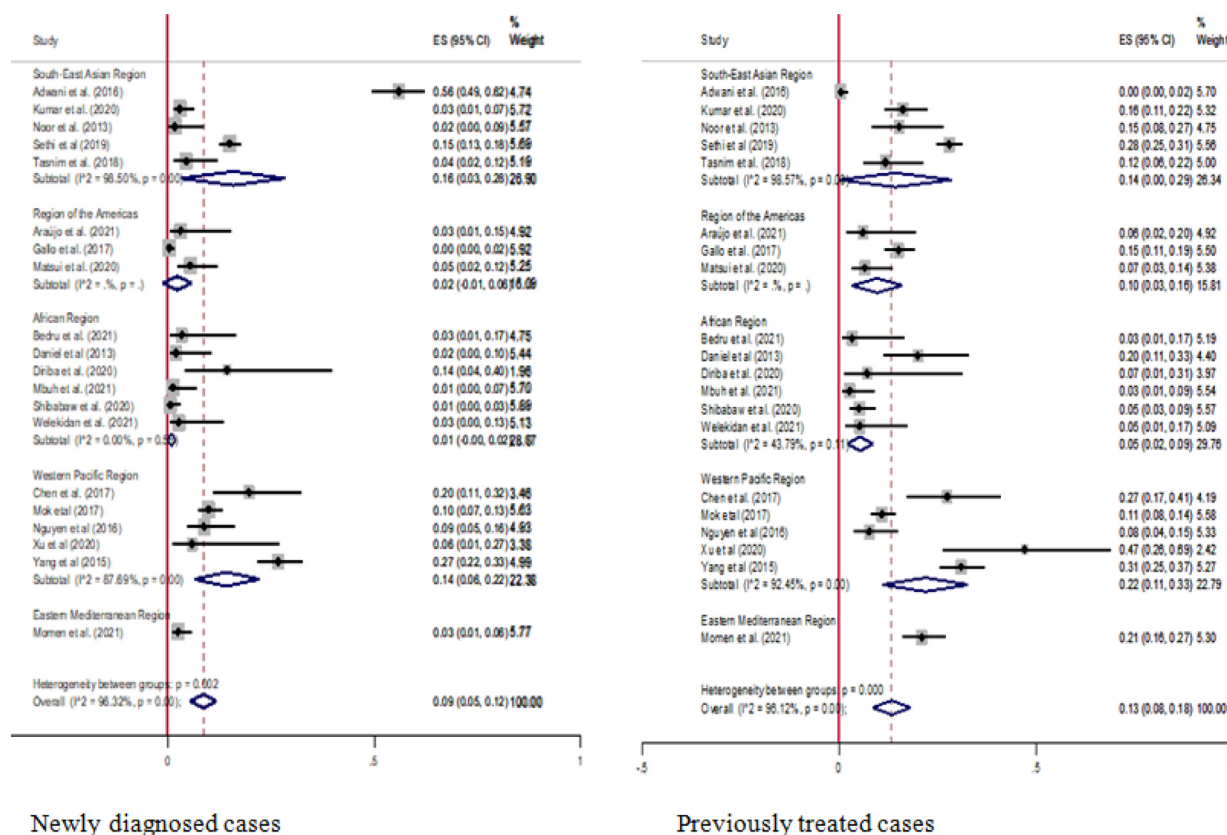
Figure 3. Pooled estimates of pre-extensively drug-resistant-tuberculosis among new and previous treated multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

countries across the WHO regions. A total of 13 studies were reported from in India [14,23,27,31,33,35,44,45,54,57–59,61] and 11 from China [13,20,29,53,66,67,69,70,72–74]. A total of 20 studies were reported from the Western Pacific [13,20,21,29,36–39,46,49,51,53,66,67,69–74] and 18 from South-East Asian regions [14,23,27,31–33,35,44,45,50,52,54,57–59,61–63]. A total of 12 studies reported from African region [15,16,18,19,22,24,25,41,43,48,60,68]. The remaining 14 studies were reported from the Eastern Mediterranean, Americas, and European regions [5,17,26,28,30,34,40,42,47,55,56,64,65,75].

The data were extracted from 64 studies involving a total of 12,711 patients with MDR-TB who were treated from 2003 to 2020, with publication years ranging from 2008 to 2021. The sample size of MDR-TB in the included studies varied from nine [16] to 2472 [51]. Among the 64 studies, 53 reported pre-XDR cases, whereas 57 reported XDR-TB cases.

Pooled proportion of pre-XDR-TB

The pooled proportion of pre-XDR-TB among MDR-TB cases was 26% (95% CI: 22-31; $I^2 = 97.31\%$). China had the highest proportion of pre-XDR-TB (66%) [13] and Ethiopia the lowest (3%) [18]. In the Western Pacific, South-East Asian, Eastern Mediterranean, European, Americas, and African regions, the pooled proportions of pre-XDR-TB were 35% (95% CI: 23-47, $I^2 = 98.55\%$), 32% (95% CI: 24-41; $I^2 = 96.2\%$), 30% (95% CI: 15-45; $I^2 = 95.41\%$), 22% (95% CI: 5-39), 14% (95% CI: 10-19; $I^2 = 65.25\%$), and 12% (95% CI: 7-17; $I^2 = 79.68\%$), respectively (Figure 2).

In the current study, we also performed a subgroup analysis based on the treatment history of patients with MDR-TB (newly diagnosed and previously treated cases). In the newly diagnosed group, the data were extracted from 23 studies, with the sample

sizes ranging from 14 [25] to 687 [57]. A study in China had the highest proportion of pre-XDR-TB (27%) [70], whereas Ethiopia and Cameroon had the lowest (1%) [43,60]. The pooled proportion of pre-XDR-TB among newly diagnosed MDR-TB cases was 9% (95% CI: 5-12; $I^2 = 96.32\%$). In the previously treated group, the data were extracted from 19 studies with sample sizes ranging from 14 [25] to 687 [57]. Similarly, the highest proportion of pre-XDR-TB (47%) was reported in China (69), whereas Ethiopia and Cameroon had the lowest (3%) [18,43]. The pooled proportion estimate of pre-XDR-TB proportion was 13% (95% CI: 8-18; $I^2 = 96.12\%$) (Figure 3).

Pooled proportion of XDR-TB

The proportion of XDR-TB was reported in all WHO regions. The estimated pooled proportion of XDR-TB among patients with MDR-TB was 9% (95% CI: 7-11; $I^2 = 95.98\%$). The highest proportion of XDR-TB was reported in India (77%) [44] and the lowest in Ethiopia [60] and Cameron (1%) [43]. The pooled proportions of XDR-TB in the Western Pacific, South-East Asian, Americas, African, and Eastern Mediterranean regions were 12% (95% CI: 7-17; $I^2 = 19.62\%$), 10% (95% CI: 6-13; $I^2 = 94.54\%$), 6% (95% CI: 3-9; $I^2 = 57.54\%$), and 3% (95% CI: 1-5; $I^2 = 65.68\%$), 3% (95% CI: 1-4; $I^2 = 19.62\%$), respectively (Figure 4).

In the current study, we performed a subgroup analysis based on the treatment history of patients with MDR-TB (newly diagnosed and previously treated cases). In the newly diagnosed group, the data were extracted from 23 studies with a sample size ranges from nine [16] to 2472 [51]. Whereas the data was extracted from 25 studies, with sample sizes ranging from 33 [75] to 2472 [51], on previously treated patients. The pooled estimates of XDR-TB among newly diagnosed patients with MDR-TB were 3% (95% CI:
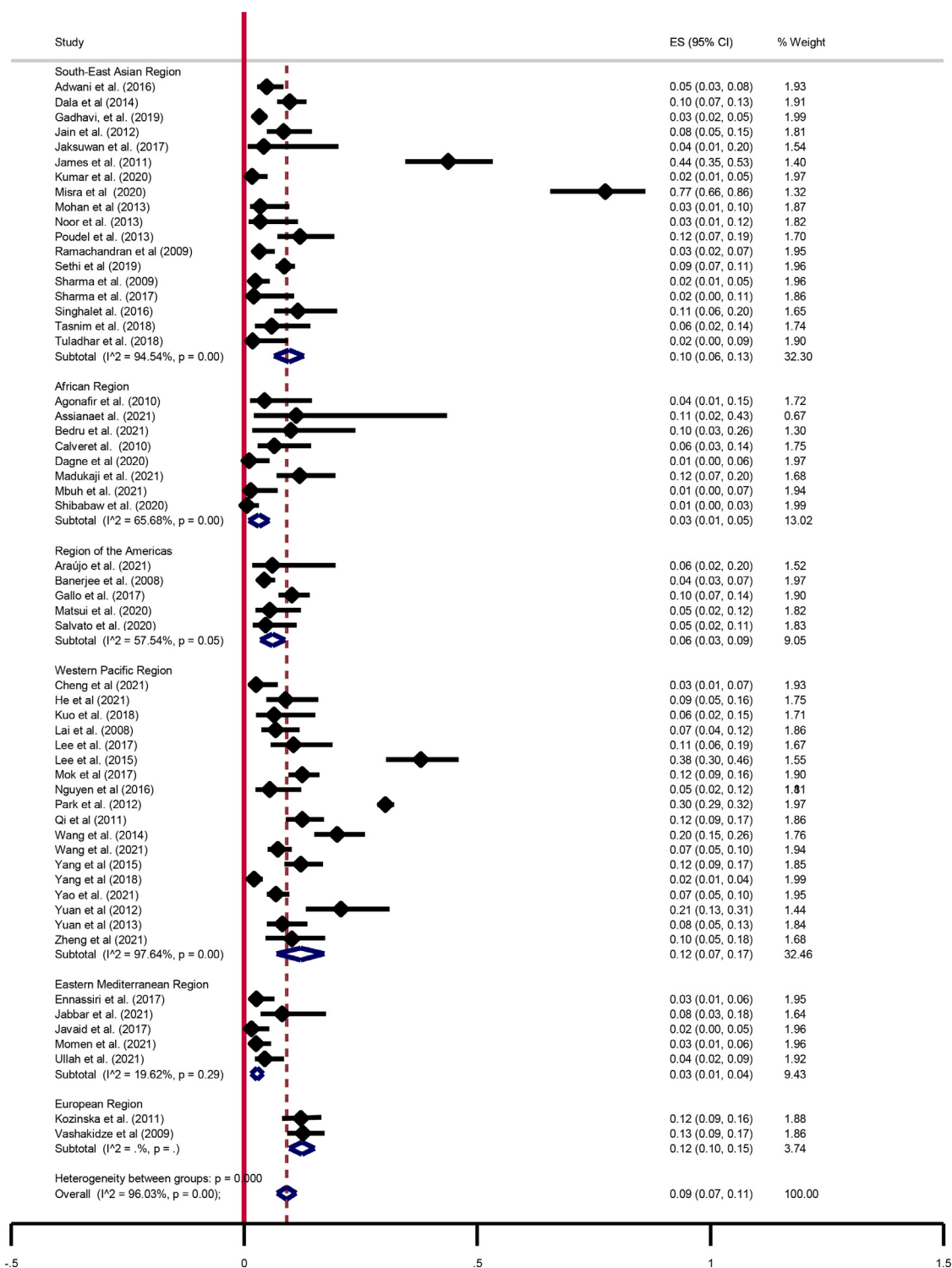
Figure 4. Pooled estimates of extensively drug-resistant-tuberculosis among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

2-5; I^2 = 93.58%) and 6% (95% CI: 4-8; I^2 = 95.62%) among previously treated patients (Figure 5).

Pooled proportion estimates of FQs, SLID, and new drugs (BDQ, CFZ, DLM, and LZD)

In this study, we estimated the pooled proportion of resistance to FQs, SLIDs, and new drugs among patients with MDR-TB. The highest proportion of FQs resistance was 77% [44], whereas the lowest proportion was 4% [15,37]. Furthermore, the highest proportion of SLIDs resistance was 40% [13], whereas the lowest proportion was 3% [50,62]. The overall pooled proportion of FQs resistance among MDR-TB cases were 27% (95% CI: 22-33; I^2 = 97.53%) and 11% (95% CI: 9-13; I^2 = 91.31%) SLIDs resistance (Figure 6).

In this study, we performed a subgroup analysis to estimate the pooled new drug resistance among patients with MDR-TB. The pooled proportion of new drugs resistance was estimated from five studies for BDQ and LZD, four studies for DLM, and three stud-
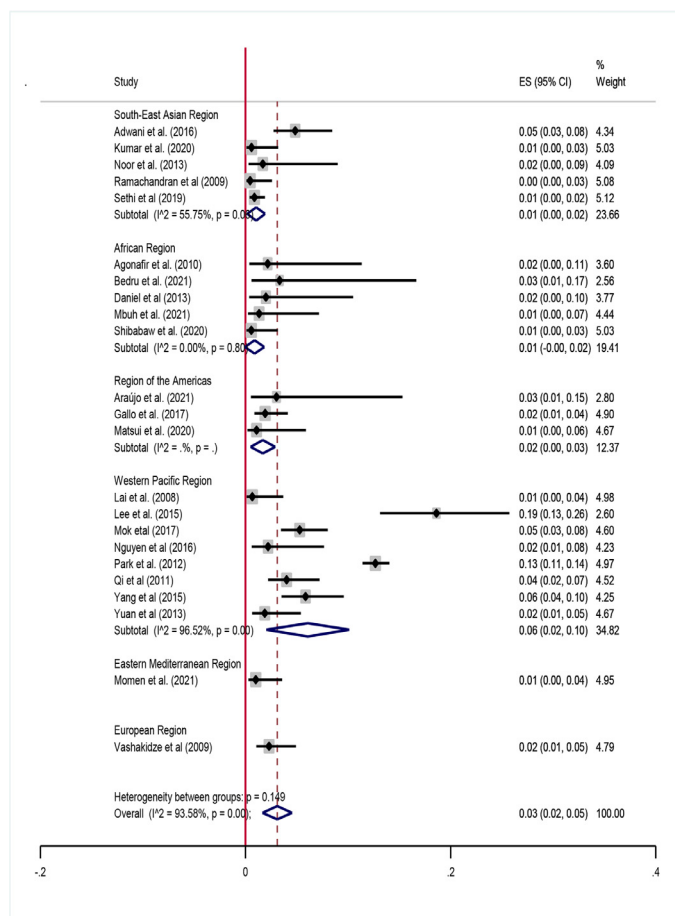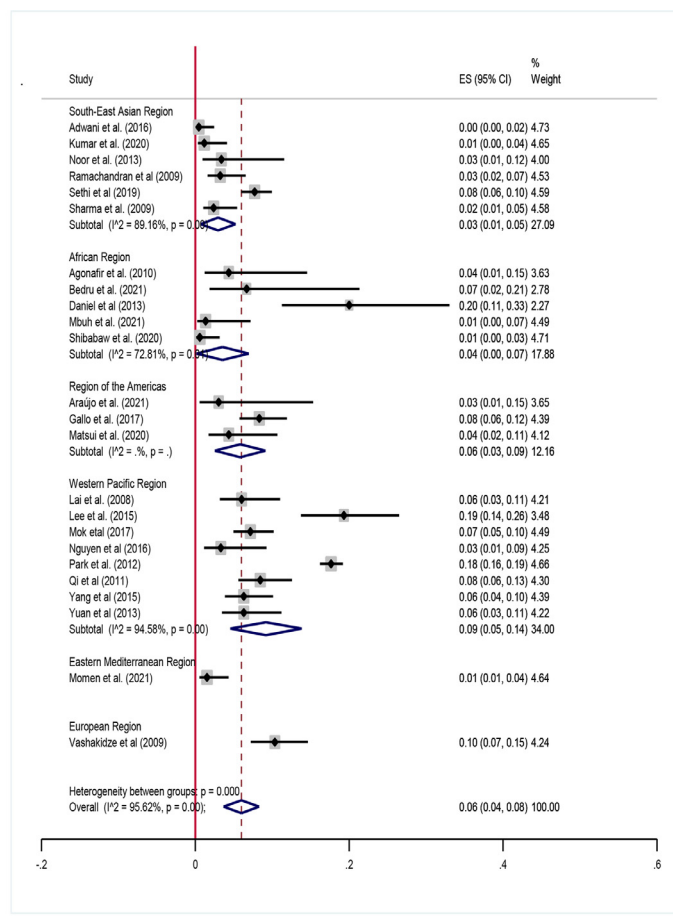
New diagnosed cases   Previously treated diagnosed cases

Figure 5. Pooled estimates of extensively drug-resistant-tuberculosis among new and previous treated multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

ies for CFZ [13,29,67,71,74]. The sample size of the included studies ranged from 88 [74] to 425 [13]. The pooled proportion of resistance to new drugs among patients with MDR-TB was 5% (95% CI: 1-8; $I^2 = 90.84\%$) for BDQ, 4% (95% CI: 0-10; $I^2 = 84.27\%$) for CFZ, 5% (95% CI: 2-8; $I^2 = 80.80\%$) for DLM, and 4% (95% CI: 2-10; $I^2 = 67.39\%$) for LZD (Figure 7).

Publication bias

We assessed the publication bias using funnel plots with the effect size and their standard errors. Visual inspection showed that the presence of publication bias was observed for the majority of the estimation of pre-XDR-TB, with fewer studies clustered at the tip of the funnel and the others distributed to the right and left corners of the funnel. The funnel plot for XDR-TB patients was relatively symmetrical, with only few studies visible in the right corners (Figure 8).

Discussion

This systematic review and meta-analysis estimated the pooled proportion of pre-XDR and XDR-TB among patients diagnosed with MDR-TB from the study reported worldwide. The pooled proportions of XDR-TB among new patients with MDR-TB were 3% and 6% in previously treated patients. The pooled proportions of pre-XDR-TB among new patients with MDR-TB were 9% and 13% among

previously treated patients. The overall pooled proportion of pre-XDR was 26%, whereas the proportion of XDR-TB was 9% among patients diagnosed with MDR-TB. The pooled proportion of FQs resistance was 27% and the proportion of SLIDs resistance was 11%. A considerable proportion of resistance to new drugs BDQ (5%), CFZ (4%), DLM (5%), and LZD (4%) were also reported worldwide.

In the current review, the pooled proportion of XDR-TB was 9%. This is relatively higher than the proportion reported by the WHO global TB report in 2019, in which the proportion of XDR-TB was 6.2% [4]. This substantial difference could be due to the fact that the current meta-analysis was based on the findings from published clinical studies that reported data from diverse patient populations in various settings. The data, therefore, effectively entails regional influences and different epidemiological factors contribute to drug resistance and do not involve selective sampling of patients. Moreover, the proportion reported in the current review might reflect the status of suspected isolates referred for resistance testing rather than the might actual prevalence that estimated from representative participates. In contrast, the proportion given by WHO is based on the estimation from the TB program report, which could lead to underestimation, whereas the current review is based on the primary studies reported by independent researchers worldwide, which could be more representative. The results of the current review findings were relatively similar to the 2018 WHO global TB report, in which the proportion of XDR-TB was 8.5% [76].
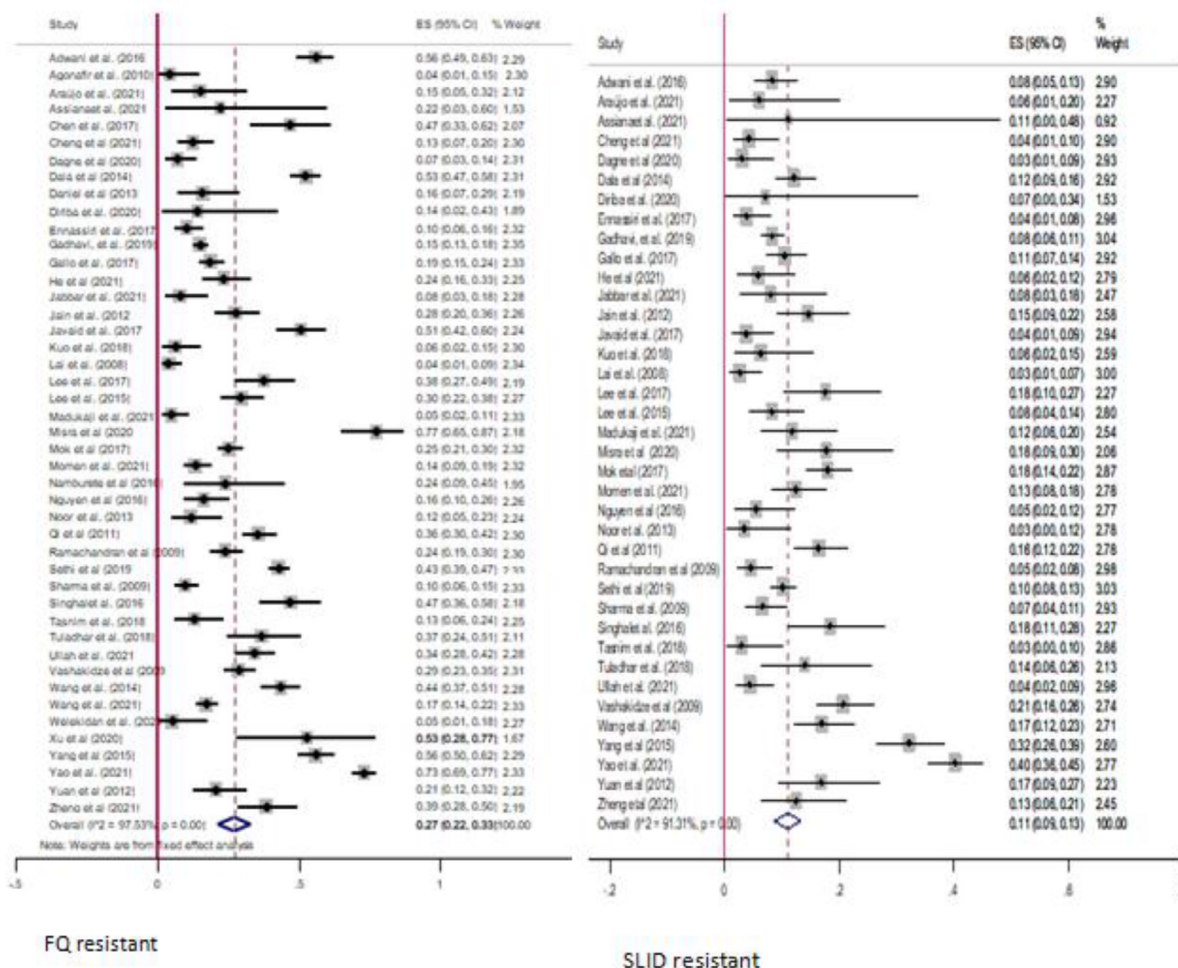
Figure 6. Summary of pooled estimates of FQs resistance and SLIDs resistance among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size; FQs, fluoroquinolone; SLID, second-line injectable drug.

The proportion of XDR-TB among newly diagnosed patients with MDR-TB was 3% and 6% in previously treated patients. The combined proportion of pre-XDR-TB patients among the newly diagnosed patients with MDR-TB was 9% and 13% in the previously treated patients. The WHO estimate showed that 25,038 cases of pre-XDR-TB or XDR-TB were detected worldwide in 2022 [3]. However, there is limited information on the burden of pre-XDR-TB and XDR-TB among MDR-TB cases based on their previous treatment history.

The findings of the current study showed that more than a quarter of patients with MDR-TB had pre-XDR-TB with the majority were resistant to FQs. The pooled proportion of pre-XDR-TB in the current review is higher than the WHO estimate of 2021 [77]. The study results show that the proportion of pre-XDR-TB is higher and strains remains a major global public health concern in the area of antimicrobial resistance.

Based on the subgroup analysis, there are differences in the proportion of pre-XDR and XDR-TB in the WHO-defined regions of the world. The Western Pacific and South-East Asian regions have the highest rates of pre-XDR-TB and XDR-TB proportion. These regions should primarily examine the major risk factors for the high rates of DR-TB and intensify their efforts to address factors associated with high prevalence of DR-TB. The Beijing family is highly prevalent in these two regions and could be among the factors associated with the high proportion of DR-TB in the region [61]. The higher proportion of pre-XDR and XDR-TB might be due to the

considerable variation in the coverage of high MDR/RR-TB burden countries and the high burden of the Beijing family.

The current review determined the proportion of FQs resistance cases. The pooled proportion of FQs resistance among MDR-TB cases was 27%. This finding is higher than the estimate of WHO in 2019, in which the proportion of FQs was 20.8% [4]. This difference is most likely due to the fact that majority of the included publications being from countries with high proportion of DR-TB. In addition, the possible reasons behind the high proportion of FQs are access and indiscriminate use of some of the commonly available FQ antibiotics for the treatment of various infection diseases [78]. Furthermore, the pooled proportion of SLID resistance among patients with MDR-TB was found to be 11%. The proportion of FQs resistance was equal to resistance to SLID proportion. This might be due to the fact that injectable drugs are less frequently used than FQs to treat common infections.

WHO has updated the MDR-TB treatment recommendations, in which injectable drugs are replaced by new drugs (BDQ, CFZ, DLM, and LZD). The update is required because the SLIDs are associated with an increase in deaths, treatment failures, relapses, and severe side effects, including permanent hearing loss [79]. Despite the limited evidence on new drugs, five published studies were included in the current review. In the current review, the proportion of resistance to new drugs (BDQ, CFZ, DLM, and LZD) among patients with MDR-TB was considerable. The occurrence of drug resistance among these four new anti-TB drugs was highlighted by
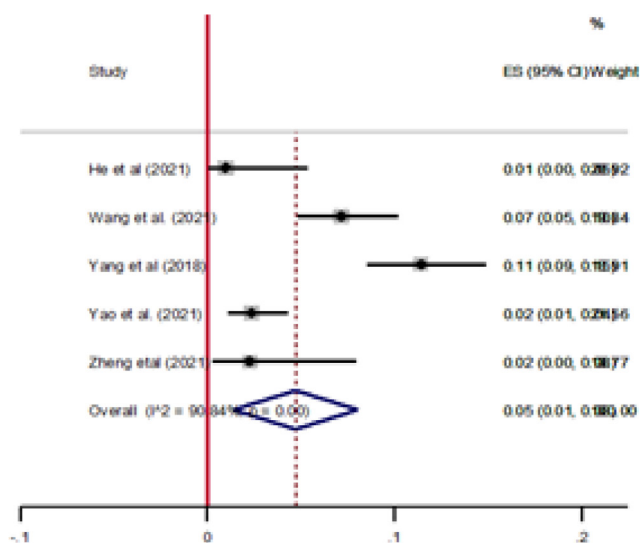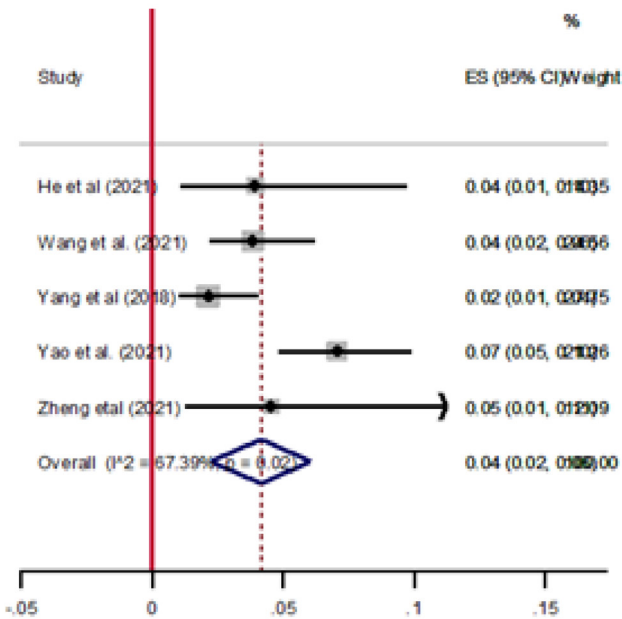
Forest plot for pooled prevalence rate of Bedaquiline
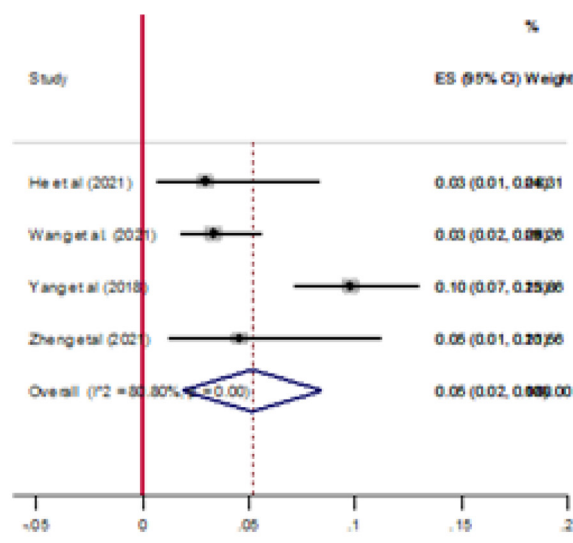
Forest plot for pooled prevalence rate of Delamanid
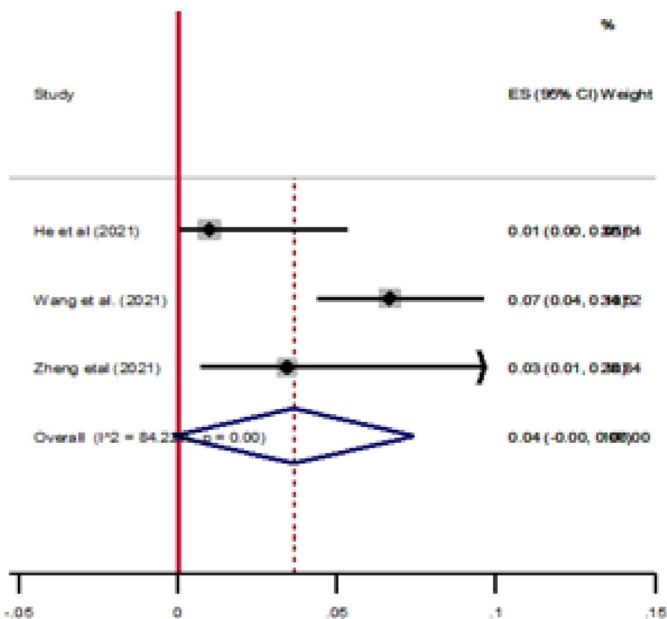
Forest plot for pooled prevalence rate of Clofazimine

Forest plot for pooled prevalence rate of Linezolid

Figure 7. Summary of the pooled prevalence of new drug resistance among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

the relatively higher proportion of resistance to BDQ and DLM. The introduction of new drugs may represent a new era in the care of patients with DR-TB by minimizing the toxicity associated with injectable drugs, reducing the spread of disease, reducing mortality rates, and improving successful treatment outcomes [31]. However, our findings revealed that 4-5% of patients with MDR-TB developed resistance to new drugs. Our findings imply that appropriate strategies are required to reduce resistance acquired during treatment.

Our review has several strengths. We used a random-effects model to address the problem of heterogeneity on the effect sizes between the included studies. In addition, we conducted a subgroup analysis using previous TB treatment history to determine the potential sources of heterogeneity. Although we cannot exclude

the risk of publication bias, we used a sensitive search strategy and included a large number of studies. Moreover, we included a large number of studies that published from different parts of the world, which increases the generalizability of our findings. The current review study has some limitations. We included the studies that were published in English only, which could induce publication bias. In addition, the majority of the included studies were reported from the Western Pacific and South-East Asian regions, which could have overestimated the proportion of pre-XDR-TB and XDR-TB in this region and might have induced variation in the coverage of high MDR/RR-TB burden among the countries. Moreover, we did not evaluate the effect of HIV and other factors that could have predicted the proportion of pre-XDR-TB and XDR-TB due to the lack of data on potential predictors from the included stud-
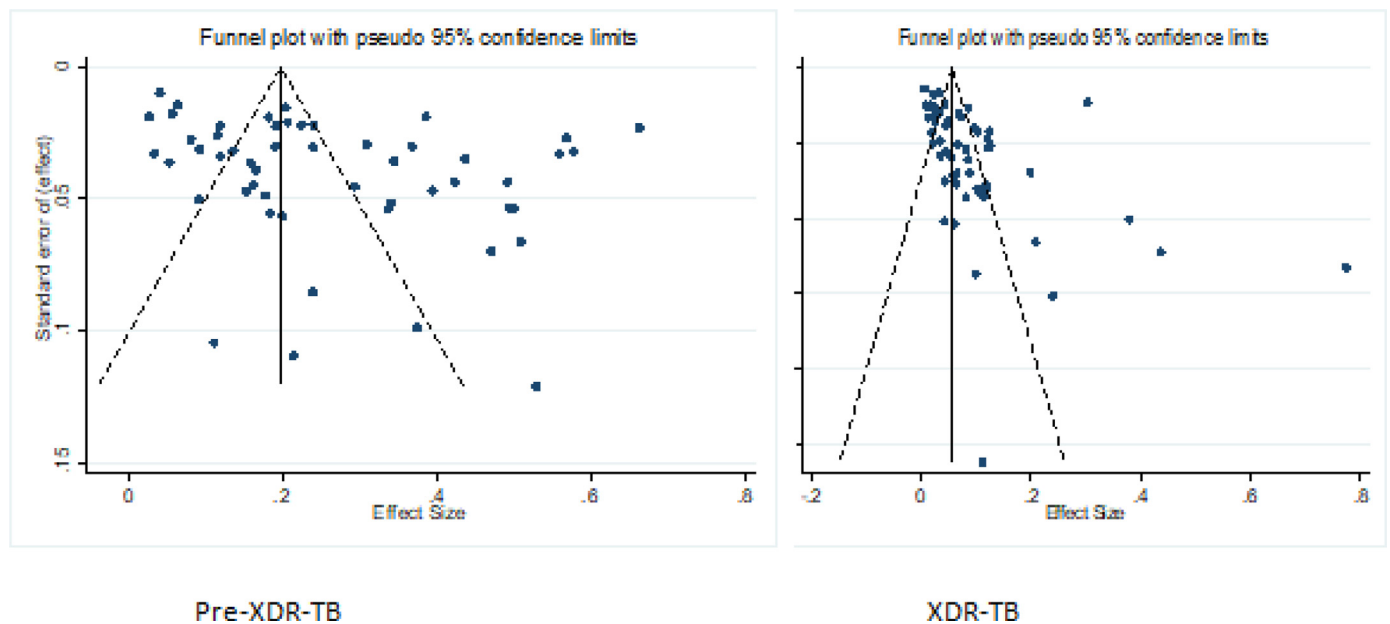
Figure 8. Funnel plots analyzing publication bias among studies evaluated for pre-XDR-TB and XDR-TB. XDR-TB, extensively drug-resistant-tuberculosis

ies. Despite these limitations listed previously, the current study results would not be affected by these limitations.

Conclusion

The current review study showed the presence of a higher proportion of pre-XDR-TB and XDR-TB than the WHO estimates. The highest proportions of pre-XDR-TB and XDR-TB were observed in the Western Pacific and South-East Asian regions. A considerable proportion of resistance to new drugs was also observed. Programmatic interventions are required to reduce the occurrence of pre-XDR-TB and XDR-TB. Countries should implement robust passive or active surveillance of DR-TB to understand the current burden of resistance to second-line and newly introduced drugs.

Declaration of competing interests

The authors have no competing interests to declare.

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Ethical approval and consent to participate

Not applicable.

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Author contributions

GD conceptualized, designed, and drafted the manuscript. GD, AA, BY, HHT, HM, DFG, KE, and AK: article searching, data extraction, and quality assessment. GD, AA, DFG, and BY: data analysis of the manuscript. AA, HHT, AK, SM, SA, GT, and MHD: writing, review, and editing of the final manuscript. All authors read, reviewed, and approved the final manuscript.

Availability of data and materials

All relevant data are available from the corresponding author upon request.

Consent for publication

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.04.392.

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The Contribution of Private Health Facilities to the Urban Tuberculosis Program of Afghanistan

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ABSTRACT

SETTING: Although the prevalence of tuberculosis (TB) is generally higher in urban areas than in rural areas, coordination between the private and public sectors for TB control is weak.

OBJECTIVE: To share experience from an urban DOTS program in five cities of Afghanistan.

DESIGN: An urban DOTS project was designed in 2009 in Kabul, Afghanistan, and later expanded to Kandahar, Jalalabad, Herat, Mazari-i-Sharif, and Paul-i-Khomri cities.

RESULTS: In total, 57 public health facilities and 49 private facilities provided DOTS services in the five cities from 2015 to 2018. A total of 28,542 (10.6%) adults (aged $\geq$ 15) screened were diagnosed with TB (all forms). The private sector contributed 5,618 (19.7%) of those. Positivity rates among presumptive TB cases in public facilities were 18.9%, 12.5%, 14.4%, and 4.8% in 2015, 2016, 2017, and 2018, respectively. In private facilities, positivity rates were 25.8%, 39.5%, and 27.4 % in 2016, 2017, and 2018, respectively.

CONCLUSION: The private sector's contribution to case detection was very high and the TB positivity rate among people screened in the private sector was high, which could be due to more selective screening rather than all health facility visitors done by public health facilities.

INTRODUCTION

With rapid urbanization of the world, we expect population health to improve overall because people will have better access to health services and infrastructure. However, other factors, including overcrowding, proliferation of slums, and lack of access to health services because of cost or cultural factors, aggravate TB transmission in cities [1]. In one European study, the rate of TB in cities was two times higher than the national notification rates [2]. In many countries, the urban TB burden is much higher than the rural one; for example, in Bangladesh the prevalence of TB in urban areas was 334 per 100,000 population, while it was 274 per 100,000 in rural areas [3]. In the same national survey of TB in Bangladesh, the TB death rate was higher in urban areas, at 8.5% versus 4% in rural areas [3]. In a Kenyan national prevalence survey, the urban TB prevalence rate was 760 per 100,000 population, while rural TB prevalence was 453 per 100,000 [4]. In Pakistan, the reverse is true: prevalence of TB in rural areas was 471 per 100,000 population, while it was 309 per 100,000 in urban areas [5]. A study comparing multidrug-resistant TB isolates in rural India and Mumbai city found that 51% of isolates from Mumbai residents were multidrug-resistant, while the proportion was only 2% in patients who lived in a nearby rural region. The authors posit that Mumbai has become a hot spot for MDR-TB because private-sector practitioners, a major source of health care in the city, are not regulated and do not follow the nationally approved regimens for treatment of TB [6]. In a South African study, cases of extremely drug-resistant TB(X-DR TB) were clustered in poor neighborhoods, characterized by lower educational attainment (12% vs. 9%), higher unemployment (29% vs. 20%), and a lower proportion of homes with flush toilets (36.4% vs. 68.9%) [7].

In Afghanistan the incidence of TB was estimated at 189 per 100,000 in 2017, a level that has remained the same for the past 17 years, while the case notification rate increased from 103.7 per 100,000 in 2008 to 131.3 per 100,000 in 2017 [8]. The case notification rate varies by province, from as low as 46 per 100,000 in Panjshir Province to 300.2 per 100,000 population in Kunar Province (WHO database, 2017), but no disaggregated data for urban and rural areas exist for Afghanistan. In Kabul, a TB project performance report reported that case notification increased from 59 per 100,000 in 2009 to 125 per 100,000 population in 2015 [9].

We analyzed the data collected in the routine health information system for five cities, excluding Kabul, to show the increase in case notification and treatment outcomes.

STUDY POPULATION, DESIGN, AND METHODS

Settings

In 2017 we published an analysis of six years of experience in Kabul with urban DOTS [9], a successful approach that was expanded to five other cities of Afghanistan with a combined population of 1.9 million: Kandahar, Jalalabad, Herat, Mazari-i-Sharif, and Paul-i-Khomri [10]. In 2015, 35 (42%) of 83 public health facilities were providing DOTS services, and 18 (18.3%) of 98 private health facilities were DOTS centers (National TB Program [NTP], surveillance database, 2015).

The DOTS Expansion Approaches

We also published information about the approaches we used for DOTS expansion in 2017 [9], so this article briefly summarizes them. Two types of health care providers serve urban areas: the public sector managed and funded by the government, and the private for-profit sector. TB diagnosis and treatment services are free even in the private sector, except for the consultation fee for the first visit of a client to a private health facility. The Ministry of Public Health recognized some of the private health facilities as DOTS centers, based on criteria such as existence of a laboratory and outpatient department (OPD), and advised clients to use those facilities, as well as public-sector health facilities, to obtain TB prevention and care services.

A baseline assessments of both the public and private health facilities at the beginning of the expansion was done with the objective of assessing human resources, and diagnostics capacities, as well facilities space adequacy to give TB services. Based on the findings, training as given to health workers on the national comprehensive TB care and prevention guideline, and standard

operating procedures, reagents for diagnostics, drugs, and other supplies supplied. Provincial or NTP program officers supervised and mentored both the private and public DOTS centers quarterly.

Data Collection and Analysis

The data we used were collected in Excel using the routine NTP recording and reporting forms and reported quarterly to the provincial offices and the NTP. Although TB services were provided in urban areas, clients came from both rural and urban areas. In our analysis we included patients aged 15 years and above. Data were entered in Excel and analyzed manually. Proportions, rates, and ratios were used to analyze the secondary data.

Ethical Statement

We used only routine program data for this analysis, and we solicited approval from the NTP to publish the data. The research was implemented in close collaboration with the NTP, which reviewed and approved the manuscript for publication.

RESULTS

In total 181 health facilities had DOTS capacity as per the nationals standard, and we were able to engage 106 (58.5%) of them as DOTS centers. The number of DOTS centers in the private sector grew from 18 in 2015 to 57 in 2018. Of the total of 3,581,079 OPD visitors over the age of 15 years old, the majority of patients (2,960,718 [(89.6%)]), visited public health facilities. The number of people seeking care in public health facilities increased from 502,112 in 2015 to 862,191 in 2018. The same trend of increase in patient load, from 65,547 in 2015 to 107,868 in 2018, was also observed in private health facilities. The striking difference between the public and private health facilities was that the private health facilities did not screen all OPD visitors except those whose major complaints coincided with sign and symptoms of TB. Of all screened OPD visitors (unfortunately the number screened was not recorded), 268,677 were reported to be presumptive TB cases and 28,542 (10.5%) were diagnosed with TB (all forms). The positivity rates for the public health facilities were 18.2%, 12.2%, 13.9%, and 4.5% in 2015, 2016, 2017, and 2018, respectively. In the private sector, the positivity rates were higher, at 25.1%, 38.1%, and 26.2 % in 2016, 2017, and 2018 respectively (Table 1).

Out of 28,542 TB cases (all forms) diagnosed in the public and private health facilities in the four years, 10,156 (35.5%) were bacteriologically confirmed. There was a large difference in the proportion of bacteriologically confirmed TB cases between the public and private health facilities. In the public sector, 8,891 (38.1%) cases were bacteriologically confirmed TB, while the proportion was 1,265 (22.5%) in the private health facilities. Clinically diagnosed TB (11,822 [41.4%]) and extrapulmonary TB (6,564 [23.0%]) constituted the majority of the TB diagnoses in both public and private DOTS centers.

Treatment success rates also improved, from 81% in 2015 to 86% in 2018. The treatment success rate was not different between the public and private health facilities: it was 81% in 2015 and increased to 85% in 2018 in the public sector, and it rose from 82% in 2016 to 85% in 2018 in the private health facilities.

DISCUSSION

Based on the experience gained in Kabul, the NTP and Challenge TB together expanded the urban DOTS program to five more cities, which resulted in increasing case notification of all forms of TB from 5,520 in 2015 to 7,988 in 2018. Many of the changes came from private-sector engagement. In 2015 only 329 cases were notified by the private sector. This number reached 2,093 in 2018—an almost 536% increase, while the increase in public health facilities was only 30%. The increases can be explained by the expansion of TB DOTS to the private sector and the capacity-building efforts in the public sector. The TB positivity rate out of all presumptive TB cases has decreased from 18.9% in 2015 to 4.8% ($p < 0.05$) in 2018 in the public health facilities. In the private sector, the all forms of TB positivity rate was 25.8%, 39.5%, and 27.4% in 2016, 2017, and 2018 respectively. Because all visitors in the OPD are screened for TB in the public health facilities, the positivity rate is low in the public sector.

In an evaluation of passive and active case-finding approaches in health facilities of Afghanistan, the rate of TB (all forms) diagnosed was 0.3% in the first year and 0.5% in the second year [11], which is a little lower than our findings in the public sector. The NTP should decide if blanket TB screening in OPDs is effective in Afghanistan, from a time and cost perspective, as compared to targeted screening of contacts and people from high-risk groups.

We saw also a difference in the proportions of extrapulmonary TB and bacteriologically confirmed TB diagnoses between the public and private centers. Of all forms of TB diagnosed, 8,891 (38.8%) were bacteriologically confirmed in the public centers, while only 5,618 (22.5%) were bacteriologically confirmed in the private sector ($P < 0.05$). The proportion of

bacteriologically confirmed cases was lower than the proportion reported in 2017, which was 61% of pulmonary TB cases [8]. One possible reason for the discrepancy in the proportion of bacteriologically confirmed cases between the reported national proportion and the proportion in the five cities in this study could be that the capacity to diagnose non-pulmonary presumptive TB is low in peripheral health centers, and cases are referred to secondary and tertiary hospitals in the cities. As a result, most of the referred cases diagnoses would be either extrapulmonary TB or smear-negative clinically diagnosed pulmonary TB cases.

The private sector is usually attracted to TB diagnosis because patients can pay for registration and investigations, and it is in the interest of the private sector to provide comprehensive clinical services to retain clients who have the ability to pay. The challenge comes in administering daily DOT and following up with patients, which are free services. In Afghanistan the treatment success rate in the private sector is equivalent to the rate in the public sector, which was 85% in 2018. In Kenya the private-sector treatment success rate ranged from 74% to 85% in a four-year report, and the reason for such a high rate was that the patients seen in the private sector can pay for registration and diagnostic tests, while the government provides drugs free of charge [12]. We recommend research on incentives for the private sector to provide free TB prevention and care services in Afghanistan.

CONCLUSIONS

We found that the private-sector contribution to case detection in Afghanistan was high and the treatment success rate was also high and equivalent to that of the public sector. Although the contribution is high, what we do not know is that what factors motivate private practitioners to give full or partial free services to patients. Studying these factors will help to include more private health facilities, including those at the lower level, such as pharmacies, in TB screening.

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AUTHORS' CONTRIBUTIONS

Designed the study and led the research: : A. Hammim, M.K. Seddiq, S.M Sayedi, K.M. Rashidi, G.Q. Qader, L. Manzoor, M. Melese, P. G. Suarez. All others participated in the data analysis and writing. All authors have approved the manuscript for submission.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Table 1. Screening for TB and TB cases diagnosed in public and private health facilities, 2014-2019

Year	2015		2016		2017		2018		Total
Indicator	**Public**	**Private**	**Public**	**Private**	**Public**	**Private**	**Public**	**Private**	**Total**
Total number of Health facilities (HFs) with DOTS capacity	67	71	70	83	83	90	83	98	181
Number (%) of HFs that were DOTS centers	35	18	38	37	42	45	49	57	106
Number of patients ≥15 years who visited OPDs	502,112	65,547	792,000	73,036	804,415	94,765	862,191	107,868	3,301,934
Total number of presumptive TB cases identified	27,444	NA	41,278	4,511	39,921	5,134	142,761	7,628	268,677
Total number of all forms of TB patients diagnosed	5,191 (18.9)	329	5,196 (12.5)	1,166 (25.8)	5,757 (14.4)	2,030 (39.5)	6,780 (4.7)	2,093 (27.4)	28,542 (10.6)
Number (%) bacteriologically confirmed TB patients	1,918 (36.9)	50 (15.2)	2,037 (39.2)	310 (26.6)	2,222 (38.6)	401 (19.7)	2,714 (40.0)	504 (24.1)	10,156 (35.5)
Treatment success rate	81	NA	82	83	85	84	85	85	NA

IMPACT FACTOR 2.8

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Article

Uptake and Completion of Tuberculosis Preventive Treatment Using 12-Dose, Weekly Isoniazid–Rifapentine Regimen in Bangladesh: A Community-Based Implementation Study

Md. Toufiq Rahman, Farzana Hossain, Rupali Sisir Banu, Md. Shamiul Islam, Shamsher Alam, Abu Jamil Faisel, Hamid Salim, Oscar Cordon, Pedro Suarez, Hamidah Hussain et al.

MDPI

Article

Uptake and Completion of Tuberculosis Preventive Treatment Using 12-Dose, Weekly Isoniazid–Rifapentine Regimen in Bangladesh: A Community-Based Implementation Study

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Abstract: Background: The United Nations high-level meeting (UNHLM) pledged to enroll 30 million in tuberculosis preventive treatment (TPT) by 2022, necessitating TPT expansion to all at tuberculosis (TB) risk. We assessed the uptake and completion of a 12-dose, weekly isoniazid–rifapentine (3HP) TPT regimen. Methods: Between February 2018 and March 2019 in Dhaka, community-based TPT using 3HP targeted household contacts of 883 confirmed drug-sensitive pulmonary TB patients. Adhering to World Health Organization guidelines, contacts underwent active TB screening before TPT initiation. Results: Of 3193 contacts who were advised health facility visits for screening, 67% (*n* = 2149) complied. Among these, 1804 (84%) received chest X-rays. Active TB was diagnosed in 39 (2%) contacts; they commenced TB treatment. Over 97% of 1216 contacts began TPT, with completion rates higher among females, those with more education and income, non-slum residents, and those without 3HP-related adverse events. Adverse events, mainly mild, occurred in 5% of participants. Conclusions: The 3HP regimen, with its short duration, self-administered option, and minimal side effects, achieved satisfactory completion rates. A community-focused TPT approach is feasible, scalable nationally, and aligns with UNHLM targets.

Keywords: TB preventive treatment; UNHLM; End TB; TPT; 3HP; Bangladesh

1. Introduction

Tuberculosis (TB) infection (TBI) is an important reservoir of TB disease, and it is important to treat individuals with TBI to break the chain of transmission and prevent the further spread of the disease in the community [1]. It is estimated that over one-fourth of the world's population is infected with *Mycobacterium tuberculosis*, the bacteria responsible for TB disease [2]. If TB infection remains untreated, 5–10% of individuals with TBI develop active TB in their lifetime, with 50% developing the active disease within two years after infection [3,4]. A study by Dye et al. showed that to meet World Health Organization (WHO) End TB targets, TBI treatment will need to be incorporated into TB programs, as merely treating the active disease will not result in a significant reduction in the burden

given the large number of individuals infected with TB. These individuals with TBI will continue to give rise to TB cases because of reactivation [5]. The WHO recommends that TB preventive treatment (TPT) should be prioritized for contacts of TB patients [6]. Thus, the prevention of new TB infections and their progression to active TB disease is critical to reducing the burden of the disease and resulting deaths, as well as to achieving the United Nations high-level meeting (UNHLM) on TB and End TB Strategy targets for 2022 and 2030/2035.

TB remains a major public health concern in Bangladesh, with an estimated 360,000 people who developed TB and 44,000 died from TB in 2020 in the country [7]. The country's annual report on TB shows that, although TB case detection and notification in Bangladesh is increasing steadily (approximately 5% annually), the estimated TB incidence has remained static—between 225/100,000 and 221/100,000 since 2001 [8]. The current National Tuberculosis Control Program (NTP) in Bangladesh focuses heavily on detecting new TB cases and treating these new patients with a limited focus on TPT. Children younger than five years and people living with human immunodeficiency virus (HIV) are prioritized for isoniazid preventive treatment (IPT) with a daily dose for six months. Although the NTP and partners have been implementing IPT among children of <5 years for years, the coverage is only 51% among all eligible children, with a completion rate of around 75% [7]. In Bangladesh, the implementation of TPT strategies is hindered by limited resources that affect healthcare capacity and cultural barriers such as health literacy that affect the public perception of TPT and adherence to it. Global evidence also suggests that the acceptance and completion rates of IPT are often low (30–64%) because of the long duration of treatment [9], and implementation of TPT is challenging. The current initiatives are not enough to achieve a significant reduction in TB infection in line with the UNHLM and End TB targets for TPT.

The recent WHO guideline recommends several shorter regimens, which can minimize the burden on both patients and health systems. One of the recommended TPT regimens is a once-weekly dose of rifapentine and isoniazid for three months (3HP). This regimen has comparable adverse events and better treatment completion rates [10–17]. The experience with this regimen in low-resource programmatic settings is lacking, but given once-weekly dosing and higher completion rates, as observed in other trials, it is expected to improve adherence and address the operational challenges associated with IPT. At present, there are no data available in Bangladesh on the eligibility, initiation, and completion of TPT for child contacts and the feasibility of TPT for other household (HH) contacts. Understanding this implementation feasibility can potentially inform the effective development of future TPT programs and thus warrants comprehensive programmatic research. The current study was conducted to assess the uptake and completion of the 3HP regimen and better understand the programmatic challenges with the intervention delivery, uptake, and completion of the 3HP regimen for TPT.

2. Materials and Methods

2.1. Ethical Approval

Ethical approval for the study was obtained from the Bangladesh Medical Research Council (Registration Number 127 14 06 2018). Written informed consent for participation was obtained by project staff prior to enrollment into the study from adults and from guardians/parents of children. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. All participants enrolled in this study received free services, including costs for investigation and TPT with 3HP.

2.2. Study Design and Location

A community-based implementation study was conducted under routine programmatic settings in Dhaka (South City Corporation Zones 3, 4, and 5), Bangladesh, between February 2018 and March 2019 to assess the uptake and completion of TPT with 3HP. The

design of this study and the intervention packages were supported by a prior qualitative study on the barriers to and facilitators of existing IPT program in Bangladesh [18].

2.3. Study Population

The study population comprised the HH contacts of bacteriologically confirmed (B+) pulmonary-drug-susceptible TB (DS-TB) patients (index patients) enrolled for TB treatment at all 12 NTP-linked treatment facilities in the selected areas during the study period.

2.4. Inclusion and Exclusion Criteria

All HH contacts of index DS-TB patients were considered eligible if (i) both the index DS-TB patients and their families lived in our selected study sites and (ii) the individual was aged over two years. The HH contacts were excluded from the study for the following reasons: (i) they were already receiving TB disease treatment or IPT at the time of the HH contact investigation; (ii) they were women who were pregnant or planning pregnancy during the study period; (iii) the HH contact was under two years of age, as rifapentine is not recommended for this age group. Pregnant women were excluded given the limited safety data on the 3HP regimen during pregnancy. This precaution, reflecting ethical considerations and the need to mitigate unknown fetal health risks, aligns with the principle of safeguarding participant safety in clinical research, especially in populations with insufficiently studied treatment effects.

2.5. Identification of HH Contacts for TPT

Field Supervisors (FSs) who had prior experience working with TB were recruited by the study and received training on the study implementation process. The FSs extracted the contact details of the index TB patients from the treatment registers and interviewed each index patient over the phone to enumerate the HH contacts. They encouraged the index patient to bring their HH contacts to the nearest health facility for contact screening and clinical evaluation. Once HH contacts arrived at the facility, Treatment Counselors (TCs) counseled the index TB patients and the HH contacts on the risk of developing TB and the importance of TPT. Then, the TCs conducted verbal screening for the presence of TB symptoms, and a physician conducted a clinical assessment. Based on the advice of the physician, free chest X-rays (CXRs) were offered to all contacts to rule out TB disease as per the NTP protocol. Rapid molecular tests (if sputum was available) were performed for the contacts with abnormal CXRs to detect active TB disease. When active TB disease was confirmed, the project field staff connected the patient with an NTP-linked TB treatment facility for treatment initiation. Those HH contacts considered not to have active TB disease were counseled by the treatment counselor and invited to initiate TPT with a 3HP regimen. For HH contacts with self-reported previous episode(s) of TB, the NTP records were reviewed to verify previous treatment and outcome history. If the individual had not completed TB treatment, was not declared cured/had not completed treatment, or did not have documented proof, he or she was referred to the TB treatment facility for further evaluation before being fully eligible for TPT.

In instances where the HH contacts did not come for evaluation or were reluctant to come within one week of the initial phone call, the TCs made at least three reminder phone calls, and then, community health workers (CHWs) from the NTP visited the HHs within three weeks to talk with the contacts face-to-face and motivated them to go for evaluation.

2.6. Initiation of TPT with 3HP

The HH contacts who were willing to participate and met the inclusion criteria were considered eligible. The eligible HH contacts took the recommended first dose of the TPT in front of the physician within seven days of the initial evaluation. The 3HP regimen was used among eligible contacts >2 years old and as a self-administered treatment procedure by the participants with support from the project team and the CHWs [11,12].

2.7. Treatment Support and Monitoring of Adverse Events

A trained CHW (acting as a treatment supporter) from a local non-governmental organization (NGO) visited the participant at home bi-weekly to follow up on treatment progress and to assess any adverse drug reactions. The treatment adherence was assessed through self-reported pill intake by the HH contacts over the phone and reconfirmed by pill count and reviewing the household diaries of CHWs during follow-up household visits. The treatment completion was defined as completing at least 11 doses of 3HP within 3 months. The TCs called the HH contacts on TPT every two weeks during the treatment period. In addition, the FSs visited all HHs monthly, quantified adherence, asked about adverse events, and recorded the results. If either CHWs or FSs identified a possible adverse event, they immediately communicated with the physician and referred the participant to the hospital for clinical evaluation if needed. Contacts on 3HP visited the health facility every month for follow-up evaluation by the physician. Enablers (USD 36 per month) to promote treatment adherence were provided to CHWs, and travel and investigation costs were reimbursed to the participating families. The HH contacts could also self-report any adverse events to the CHWs or to the project physician, which were recorded on a standardized open-ended adverse event reporting tool. The reported adverse events were immediately assessed, graded, and managed by the physicians. In cases of drop-out from the TPT, the CHWs explored the reason for discontinuation and recorded the reasons.

2.8. Data Analysis

All data were analyzed using the Statistical Package for Social Sciences, version 24 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to report the data. The data involving continuous variables (age, schooling, income, etc.) were analyzed using a rank-sum test, and the results are presented as the median value plus the minimum and maximum values. Sex, residence, occupation, comorbidity, etc., variables are presented as frequency and percentage. The cumulative probability of an HH contact completing all stages of the TB preventive care cascade was assessed in all eligible participants, and the proportion of HH contacts completing 3HP was assessed among all those who initiated the regimen. Univariate logistic regression analysis was used to analyze the relationships between various factors and the subjects' completion of TPT, and the results were calculated as an odds ratio (OR) and its 95% confidence interval (95% CI). A multivariable non-conditional logistic regression analysis was then performed on univariate variables that were statistically significant, with the criteria for inclusion being a p-value ≤ 0.050.

3. Results

3.1. Demographic and Clinical Characteristics

During the study period, 3193 HH contacts of 883 index TB patients were enumerated and counseled to visit health facilities for evaluation. Of 3193 HH contacts, 67% ($n = 2149$) showed up at the health facilities and were verbally screened, of whom 54% ($n = 1167$) were female, and the mean age of the contacts was 21.2 years (Standard Deviation (SD) $\pm$ 17.5). Of the 1216 contacts initiated into TPT, the mean age was 27.4 (SD $\pm$ 23.8), and 56% ($n = 675$) were female. Diabetes was the predominant comorbidity among contacts. It was observed that most of the contacts needed two phone calls from the project team to get them to the facilities for evaluation (Table 1).

Table 1. Socio-demographic characteristics of the household contacts of index TB patients who were verbally screened (*n* = 2149) and initiated TB preventive treatment (*n* = 1216) using the 3HP regimen.

Variables	Household Contacts Verbally Screened (*n* = 2149)	Household Contacts Who Initiated TPT with 3HP (*n* = 1216)
Age—mean age (± SD)	21.2 (±17.5)	27.4 (±23.8)
<5	65 (3.0%)	40 (3.3%)
5–<15	484 (22.5%)	272 (22.4%)
15 and above	1600 (74.5%)	904 (74.3%)
Female	1178 (54.8%)	675 (56.0%)
Schooling in year		
No schooling	323 (15.0%)	146 (12.0%)
1–5 years	726 (33.8%)	383 (31.5%)
6–10 years	710 (33.0%)	345 (28.4%)
10+ years	390 (18.1%)	342 (28.1%)
Household income/month in BDT (mean ± SD) *	14,532 ± 9853	15,251 ± 10,235
≤5000	14 (0.7%)	7 (0.5%)
5001–10,000	321 (14.9%)	165 (13.6%)
10,001–20,000+	1814 (84.4%)	1044 (85.9%)
Original residence		
Permanent resident of Dhaka	677 (31.5%)	398 (32.7%)
Tenant (rural-to-urban migrant)	1472 (68.5%)	818 (67.3%)
Current dwelling status		
Living in slums	1027 (47.8%)	589 (48.4%)
Non-slum households	1122 (52.2%)	627 (51.6%)
Occupation		
Student and dependent child	543 (25.3%)	361 (29.7%)
Day labor/garments/factory work	605 (28.2%)	234 (19.2%)
Self-employed and business	359 (16.7%)	138 (11.3%)
Public/private service	246 (11.4%)	132 (10.9%)
Homemaker	380 (19.9%)	341 (28.0%)
Unemployed	16 (0.7%)	10 (0.8%)
Current or past smoker	892 (41.4%)	483 (39.7%)
Comorbidity		
No comorbidity	1372 (68.5%)	1194 (98.2%)
Diabetes mellitus	95 (4.4%)	16 (1.3%)
Hypertension	409 (19.0%)	04 (0.3%)
Asthma	14 (0.7%)	01 (0.1%)
Thyroid dysfunction	159 (7.4%)	01 (0.1%)
Experienced any adverse events	NA	65 (5.3%)

* USD 1 = BDT 110.

3.2. Evaluation, Initiation, and Completion of TPT among HH Contacts

Of the 2149 contacts who visited the health facilities and were verbally screened, 1804 contacts (84%) completed an evaluation with CXRs. Among CXRs performed, 39 (2%) contacts were found to have active TB (abnormal CXR and molecular test), and 92 (5%) were below two years and initiated on IPT. The remaining 1673 (93%) eligible contacts were invited to enroll on TPT with the 3HP regimen. Of those eligible, 1216 (73%) initiated the 3HP regimen, 97% (*n* = 1175) of whom completed the regimen (Figure 1). The TPT completion among adults was 99.8%, and in females, 99.9%. The cumulative probability of completing all steps of the TB prevention cascade was 63% among the study population.

Among the HH contacts who did not complete the treatment, 78% (*n* = 32) dropped out between 2 and 5 weeks after the treatment initiation. The most common reason for noncompletion of TPT was a refusal to continue treatment due to side effects or fear of side effects (*n* = 32; 78%). Furthermore, 14.6% (*n* = 6) migrated to a different area where 3HP intervention was not available. Only a small proportion (*n* = 3; 7.3%) was advised by a doctor to stop treatment because of unusual events experienced during TPT (Table 2).
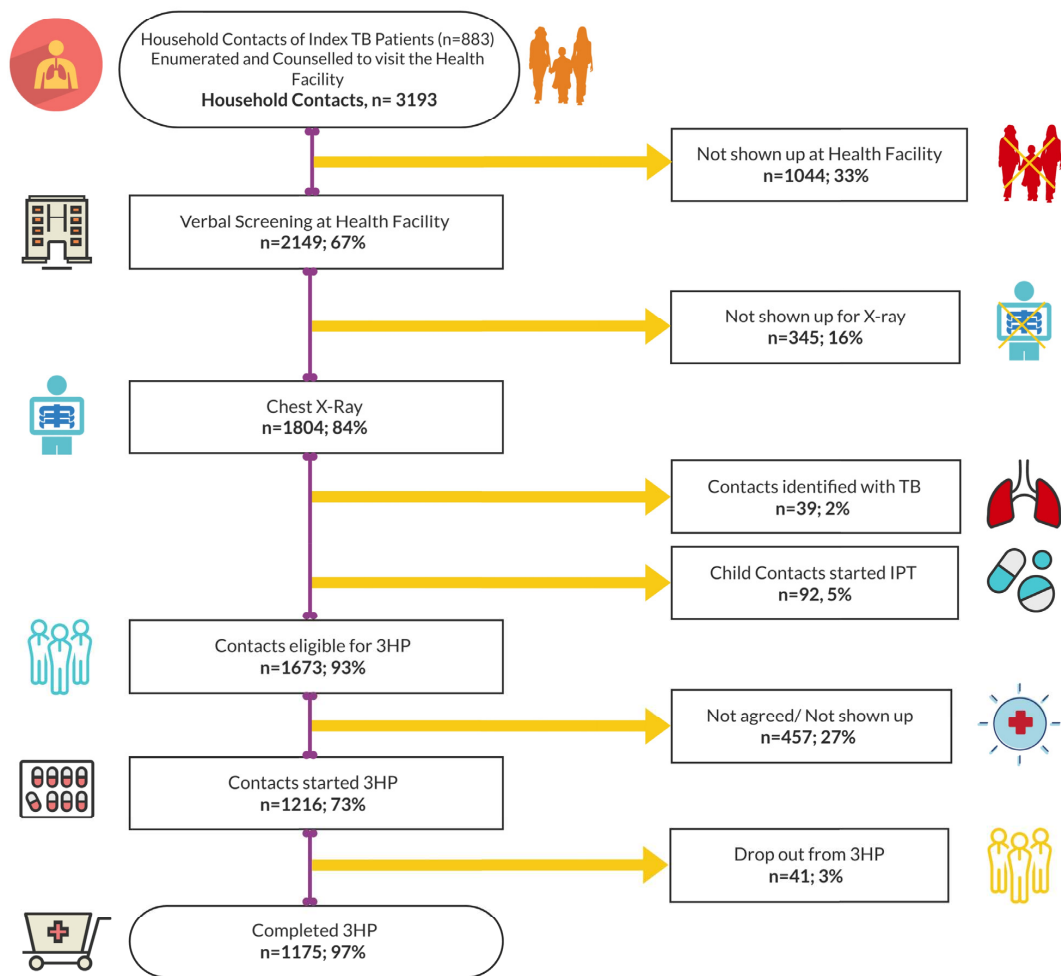
Figure 1. TPT enrollment and completion cascade with 3HP, February 2018–March 2019.

Table 2. Number and percentage of household contacts with adverse events after any 3HP dose by type and grade (*n* = 65).

Experienced Adverse Events after Any 3HP Dose by Type *	Frequency ** with Grading ***			
	Not Graded	Grade 1	Grade 2	Grades 3, 4, and 5
Gastrointestinal—nausea/vomiting	-	20 (1.64%)	01 (0.08%)	-
Neurological symptoms	-	01 (0.08%)	-	-
Muscle pain	-	02 (0.16%)	-	-
Hepatotoxicity	-	00 (0.00%)	-	-
Flu-like symptoms	-	10 (0.82%)	01 (0.08%)	-
Dermal—itching/skin rash	01 (0.08%)	09 (0.74%)	-	-
Respiratory symptoms	-	02 (0.16%)	-	-
Fatigue	-	07 (0.58%)	-	-
Headache	-	06 (0.49%)	-	-
Other symptoms ‡	-	05 (0.41%)	-	-
Total experiencing adverse events	01 (0.08%)	62 (5.09%)	02 (0.16%)	00 (0.00%)

* Includes all adverse events reported by the participants deemed to be "related" or "possibly related" to 3HP medication by the project physician. ** Number of participants experiencing an adverse event of a certain severity with one or more doses where each participant is counted only once at the highest level of severity for that type, and the percentages are taken out of the total number of patients on TPT. *** Grade 1 = mild—discomfort noticed but no disruption of normal daily activity; Grade 2 = moderate—discomfort sufficient to reduce or affect daily activity; Grade 3 = severe—inability to work or perform a normal daily activity; Grade 4 = life-threatening or disabling—represents an immediate threat to life; Grade 5 = death—death related to an adverse event. ‡ Other related or possibly related adverse events included dizziness, insomnia, increased blood pressure, and gynecologic symptoms (spotting) (all Grade 1).

3.3. Reported Adverse Events

During the TPT, 5.3% (*n* = 65) of HH contacts on TPT experienced adverse events. However, no major adverse events were observed, nor were any hospitalizations required. Most of the adverse events were Grade 1, and symptomatic management alone resolved the presenting issues (Table 2). The majority of adverse events were reported in subjects aged 15 years and older (*n* = 51; 4.2%) and among females (*n* = 35; 2.9%). Of the three contacts who stopped TPT as per the suggestion of the physician, one was hypertensive and had poor adherence to antihypertensive medications, and two female patients had gynecologic symptoms (spotting).

3.4. Factors Associated with TPT Completion with the 3HP Regimen

Table 3 presents bivariate and multivariable logistic regression models examining the association between TPT completion with 3HP and demographic characteristics and clinical factors. The multivariable model reveals that TPT completion was higher in contacts aged 15 years or more (OR 1.5; 95% CI 1.1–2.0; *p* 0.043); female contacts (OR 1.7; 95% CI 1.3–2.1; *p* 0.009); contacts with higher education (OR 1.4; 95% CI 1.1–1.9; *p* 0.044); contacts with high HH income (OR 1.5; 95% CI 1.0–2.1; *p* 0.047); contacts those with no comorbidities (OR 1.7; 95% CI 1.1–2.2; *p* 0.046); and those who did not experience any adverse events while on the 3HP regimen (OR 1.6; 95% CI 1.2–2.1; *p* 0.009).

Table 3. Bivariate and multivariable logistic regression examining the association between TPT completion with 3HP and demographic characteristics and clinical factors.

Variables	Bivariate Model		Multivariable Model *	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Current age (r = age < 15 years)	2.1 (1.8–2.4)	0.004	1.5 (1.1–2.0)	0.043
Female (r = male)	2.5 (1.7–2.8)	0.002	1.7 (1.3–2.1)	0.009
Schooling in year (r = 0)	2.2 (1.7–2.5)	0.004	1.4 (1.1–1.9)	0.044
Monthly household income > BDT 10,000 (r = ≤ BDT 10,000) [a]	1.7 (1.3–2.1)	0.005	1.5 (1.0–2.1)	0.047
Permeant urban resident (r = rural-to-urban migrant with temporary settlement)	1.2 (0.8–2.3)	0.098	NA	
Lives in non-slum household (r = lives in slum)	1.6 (1.3–2.1)	0.049	1.1 (0.7–2.4)	0.088
Occupation: non-manual work (r = manual work)	1.1 (0.7–2.7)	0.106	NA	
No comorbidities (r = have had any comorbidities)	2.3 (1.8–2.5)	0.008	1.7 (1.1–2.2)	0.046
Experienced no adverse events (r = experienced any adverse events)	1.8 (1.3–2.4)	0.003	1.6 (1.2–2.1)	0.009
Intervention Approaches				
Reminder phone calls + treatment counseling (r = reminder phone calls only for the next dose schedule)	2.7 (2.1–3.2)	0.002	1.9 (1.5–2.4)	0.007
Reminder phone calls + treatment counseling + follow-up home visit by health workers (r = reminder phone calls only)	3.2 (2.7–3.6)	0.001	2.1 (1.5–2.7)	0.005

* The multivariable model only included the variables that were found to be statistically significant in the bivariate model, with the criteria for inclusion being a *p*-value ≤ 0.050; [a] USD 1 = BDT 105; r = reference category; OR, odds ratio; CI, confidence interval.

The multivariable logistic regression model identified the significant independent predictors of TPT completion with the 3HP regimen. Female sex, higher schooling, higher income, older age, contacts with no comorbidities, and contacts who did not experience any adverse events while on a 3HP regimen were all found to be independent predictors of TPT completion with a 3HP regimen.

3.5. Intervention Approaches

We used multiple intervention approaches for contact investigation and TPT enrollment during treatment. They included phone calls only, phone calls plus counseling, and phone calls plus counseling plus home visits. Among those who attended the health facility (*n* = 2149), 88% (*n* = 1890) came based on the phone calls made to the index patients by the project staff; 9.1% (*n* = 196) came based on phone calls plus counseling; and the remaining 2.9% (*n* = 63) came as a result of the combined efforts of phone calls, counseling, and HH visits. Further, during the treatment, reminder phone calls to inform subjects about the next dose schedule, phone-based and/or face-to-face treatment counseling, and follow-up home visits by the project staff and NGO CHWs were all found to be associated with the completion of the 3HP regimen (Table 3).

4. Discussion

This is the first population-based study in Bangladesh that has assessed the implementation feasibility of TPT under routine programmatic settings with a 12-dose, weekly 3HP regimen among the HH contacts of DS-TB patients. The use of 3HP for the treatment of TBI was found to be feasible and well accepted. Consistent with the findings of other studies, we found that a weekly 3HP regimen has higher treatment completion rates (97.3%) compared with under-five children in the ongoing IPT program (74.6%) in Bangladesh, with fewer adverse events, and the results were similar across subgroups of people without HIV [19–21].

Several other studies that included shorter TPT regimens have shown a better completion rate compared with longer regimens [11,12,22]. The treatment completion rates in this study were also higher than in other large randomized controlled studies, phase 4 studies, and other cohort studies conducted among adults and children in developed and developing country settings [11,12,22–32]. A recent prospective cohort study conducted on children and adolescents in Pakistan using a 1HP regimen reported a 94% completion rate [33].

In Bangladesh, the national TB program provides IPT to children aged under five years who are contacts of B+ TB patients, and there is no provision of TPT for adult contacts. The majority (about 62%) of the HH contacts who were enrolled for the TPT in our study were adults, and treatment completion rates among the adults were also as high as children. Our study generated solid evidence that it is possible to implement TPT among adult populations through the existing routine TB program in Bangladesh. We observed that a higher percentage of our study population (56%) were female, and TPT completion was significantly higher among the female participants. This result will help in shaping the healthcare-seeking behavior of female HH contacts.

We noted a low frequency (5.3%) of adverse events with 3HP among the study participants, mostly of mild severity, and they were comparable with previous studies [22,24,34–36]. A recent systematic review including data from 23 randomized and 55 non-randomized studies also reported a similar low frequency of adverse events with 3HP compared with INH monotherapy [36]. The low adverse events observed in our study might also be attributed to the low drop-out and high treatment completion rates among the contacts who initiated the TPT with 3HP.

The project's field activities were carried out by its project field staff and NGO CHWs alongside their regular community health interventions. The data indicated that intervention approaches resulted in a high level of TPT enrollment, adherence to treatment, and TPT completion. The possible explanations for this high participation and completion rate may be related to the use of multiple approaches like counseling, phone calls only, phone calls plus counseling, and phone calls plus counseling plus home visits. During the treatment period, we also used reminder phone calls to inform subjects about the next dose schedule, phone-based and face-to-face treatment support and counseling, and follow-up home visits—all of these may have had cumulative effects on the outcomes and helped the participants to make informed decisions to adhere to and complete the TPT. Moreover,

the CHWs used in this study were involved in community mobilization, and they were well accepted and trusted by the community, which created an enabling environment for the target community [37]. The study demonstrated that it is feasible to implement a TPT intervention utilizing ongoing TB program infrastructure and the facilities of the government and NGOs in a resource-limited setting.

The prevention of active TB disease with TPT is a critical component of the WHO's End TB Strategy. This study proved that a convenient and easy-to-administer TPT regimen should be considered to achieve END TB and UNHLM targets. Considering the high completion rate of this TPT, the abundant care in managing HH contacts (evaluation and enrollment to TPT) and the interventions used to support the TPT can be adopted by the national program. However, the NTP should also consider critical issues with the programmatic scale-up of TPT, including policy considerations, ruling out active TB, diagnostic tests and evaluation, the time to start treatment, safety, uninterrupted drug supplies, treatment adherence monitoring, recording, reporting, etc., before adopting a countrywide TPT imitative. Utilizing CXR as an initial diagnostic tool is also critical given its heightened sensitivity, even though our study did not achieve complete coverage. This experience underscores the importance of advocating for CXR usage in early TB detection, particularly in identifying subclinical or asymptomatic patients.

One of the limitations of this study was that it only implemented TPT in the urban settings of Dhaka, and it is essential to recognize that the experience may differ in rural areas. This may not represent the entire country and limits the generalizability of our results. Specifically, healthcare infrastructure, community dynamics, and patient behaviors may vary in rural settings. However, considering that urban TB is the most challenging aspect of TB control efforts and the presence of extensive community programs (the Sasthya Sebika model) in the rural areas of Bangladesh [38], we believe this study will help in formulating appropriately targeted measures and future TPT programs in Bangladesh. Future research efforts should aim to assess the feasibility and implementation of TPT programs in rural areas considering the specific challenges and opportunities posed by these contexts. The study also did not have a true comparative group for the HH contacts for whom TPT was initiated using 3HP. Future research should aim to explore the effectiveness of the 3HP regimen across various demographic groups and settings. Additionally, comparative studies between the 3HP regimen and the standard 6-month IPT regimen would provide valuable insights into the relative benefits of these approaches. Furthermore, investigations into the long-term outcomes and cost-effectiveness of the 3HP regimen would be beneficial for informing policy decisions and optimizing TB prevention strategies. Further, the study did not use any test to confirm the presence of TBI. The Interferon-Gamma Release Assay is not used in this country, so the tuberculin skin test (TST) was the only test we could use. However, mass, population-wide TBI testing was not feasible considering the high TB burden setting, and the TST is inconclusive. The absence of TBI confirmation in our study could potentially result in some misclassification of TBI status, and this may impact the generalizability of our results to settings with routine TBI testing. In such settings, the decision to initiate TPT might be guided by a combination of clinical evaluation, TBI test results, and individual risk factors. Therefore, the applicability of our findings to areas with robust TBI testing should be made with an awareness of this limitation.

5. Conclusions

In this community-based implementation study, TPT using 3HP was found to have a high completion rate. The convenient weekly regimen of 3HP, the shorter treatment duration, and minimal adverse events resulted in higher treatment adherence among those who were enrolled in this study. The study findings exhibited a strong case for considering the integration of the 3HP regimen into the national TB control program in Bangladesh. The study demonstrated that the identification of potential HH contacts for TPT in urban areas and high treatment completion could be achieved through a well-designed, community-based program using the existing program structure and involving

appropriately trained CHWs. Targeted awareness creation, counseling, rigorous follow-up, and a self-administered TPT option also contributed to achieving higher TPT adherence.

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SHORT COMMUNICATION

Descriptors of multidrug-resistant TB deaths in Ethiopia

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Deaths related to multidrug-resistant TB among patients who had received a second-line anti-TB drugs in Ethiopia were analysed. Respectively 38/704 (5.4%) and 44/995 (4.4%) deaths were identified in two cohorts (2015 and 2022). In the 2015 cohort, severe malnutrition was less prevalent, previous treatment rates were three times higher, hypokalaemia was more frequent, and the use of the Xpert® MTB/RIF assay, respiratory failure and severe anaemia/pancytopenia were less common than in the 2022 cohort. We observed that there were variations in adverse events when different treatment regimens were used over different time periods. To ensure proper patient care, correct guidance must be consistently implemented.

Drug-resistant TB (DR-TB) remains a critical concern for public health. According to 2019 data from Ethiopia, an estimated 1.1% of the new TB cases and 7.5% of those who had previously undergone TB treatment among the reported TB cases were found to have rifampicin-resistant TB (RR-TB).[1,2] In 2020, Ethiopia was removed from the list of 30 countries with a high burden of rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB).[2]

COVID-19 pandemic has reversed years of progress in providing essential TB services, including the reduced numbers of TB notifications, access to TB diagnostics tests, enrolment for effective treatments and provision of quality services.[1] The overall number of TB deaths have also increased due to reduced access to TB diagnosis and treatment because of the pandemic.[1] This may have also had adverse consequences for DR-TB mortality. Improving patient-centred care delivery to DR-TB patients by implementing regular clinical analysis of unfavourable outcomes, specifically, DR-TB-related deaths helps to identify common cause of deaths that could guide the development of targeted interventions and provide practical recommendations to healthcare workers (HCWs) in the field.

METHODS

Study area, period, population, and data collection procedure

A hospital-based review was conducted in selected high-load RR/MDR-TB treatment initiating centres (TICs). We analysed RR/MDR-TB patient charts and registers using structured checklists to describe the case fatality of RR/MDR-TB, the distribution and magnitude of clinical parameters related to RR/MDR-TB deaths. Data were collected from June 2012 to June 2015 (the 2015 cohort) from Amhara and Oromia Regions; and from July 2020 to June 2022 (the 2022 cohort) from the Oromia, Amhara, Addis Ababa, South Nation and Nationalities and Peoples (SNNP) Regions to compare relevant variables related to TB deaths. Sociodemographic variables (age, sex), HIV status, previous TB treatment and comorbid diseases were some of the variables included in the analysis. All deaths in selected treatment centres were line-listed and their charts were reviewed to get the necessary information.

We conducted descriptive statistical analyses. This review was carried out after obtaining approval for the extraction of the secondary data from the regional ethical clearance committee.

ASPECTS OF INTEREST

Sociodemographic and clinical characteristics

In the 2015 cohort of patients, a total of 38 MDR/RR-TB deaths out of a total of 704 RR/MDR-TB patients were documented in Oromia and Amhara Regions of the country. In the 2022 cohort of patients, a total of 44 MDR/RR-TB deaths out of a total of 995 RR/MDR-TB patients were registered and reviewed from Addis Ababa, SNNP, Oromia and Amhara. RR/MDR-TB-related death rates were 5.4% in the 2015 cohort and 4.4% in 2022 cohort. In the 2022 cohort, more than 93% of patients had severe form of disease at the time of diagnosis, which may have contributed to early death. Compared to the 2022 cohort, severe malnutrition was less prevalent (odds ratio [OR] 0.24, 95% confidence interval [CI] 0.93–0.63), history of previous treatment was three times higher (OR 2.77, 95% CI 1.05–7.24), electrolyte imbalance (hypokalaemia) was more frequent (28% vs. 3%, Fisher's Exact test, $P = 0.001$), and Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) testing (37% vs. 95%, $P < 0.001$), respiratory failure (3% vs. 29%, Fisher's Exact test, $P = 0.013$) and severe anaemia/pancytopenia were less common (3% vs. 35%, Fisher's Exact test, $P = 0.003$) in the 2015 cohort. Early death (within 2 months of treatment initiation) and other factors such as comorbidities (HIV and diabetes mellitus) in the two cohorts were similar (Table). In the 2022 cohort, 41/44 (93%) of patients who died had severe forms of TB (mainly disseminated TB, miliary TB and extensive bilateral lung disease) at the time of diagnosis (Figure).

In the 2015 cohort, the standard long treatment regimen that included injectables was the predominant treatment regimen, with over 95% of patients receiving it in all TICs across the country. In the 2022

TABLE Sociodemographic and clinical data among RR/MDR-TB patients who died during the review period in 2015 and 2022

Variables	2015 (n = 38) n (%)	2022 (n = 44) n (%)	OR (95% CI)	P value
Male sex	16 (43)	25 (57)	0.58 (0.24–1.39)	0.224
Mean age, years	37.1	38.7		
Severe malnutrition	8 (39)	23 (51)	0.24 (0.93–0.63)	0.004*
Early death, less than 2 months	31 (80)	40 (93)	—	0.331
HIV-positive	10 (30.3)	12 (27.9)	0.98 (0.36–2.60)	0.980
DM	3 (14)	4 (15)	—	1.000
Confirmed using Xpert MTB/Rif	14 (37)	42 (95)	—	<0.001*
Confirmed using culture/LPA	21 (60)	2 (5)	—	—
Missed	3	0		
Previous treatment history	32 (84)	26 (61)	2.77 (1.05–7.24)	0.038*
Home death	23 (42.4)	20 (45.5)	1.84 (0.77–4.41)	0.173
Adverse events	30 (66)	31 (70.4)	1.57 (0.58–4.24)	0.379
Hypokalaemia	11 (28)	1 (3)	—	0.001*
Renal failure/ uraemia	4 (13)	2 (6)	—	0.424
Refractory vomiting/severe dyspepsia	5 (17)	2 (6)	—	0.255
Hepatitis	3 (10)	1 (3)	—	0.354
Severe anaemia/ pancytopenia	1 (3)	11 (35)	—	0.003*
Psychosis	2 (7)	4 (13)	—	0.671
Respiratory failure	1 (3)	9 (29)	—	0.013*
Congestive heart failure	1 (3)	1 (3)	—	1.000

*Statistically significant.
RR/MDR-TB = rifampicin-resistant/multidrug-resistant TB; OR = odds ratio; CI = confidence interval; DM = diabetes mellitus; LPA = line-probe assay.
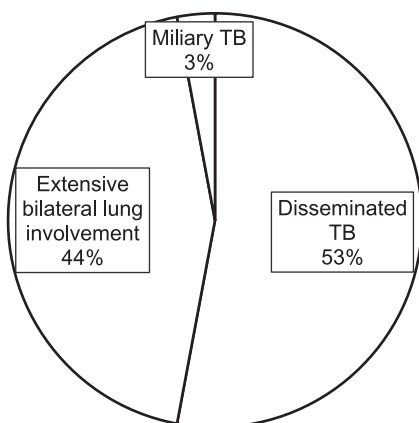
FIGURE RR/MDR-TB disease severity status in 2022 cohort (n = 44). RR/MDR-TB = rifampicin-resistant/multidrug-resistant TB.

cohort, the all-oral bedaquiline (BDQ) and linezolid (LZD) containing longer treatment regimens were administered to 57% of patients, followed by the short, all-oral, BDQ-containing regimen (23%). The remainder (16%) were on individualised regimens. Only 5% of patients were on injectable-containing treatment regimens. RR/MDR-TB patients were managed in line with Ethiopian national guideline recommendations for the management of RR/MDR-TB.[2]

DISCUSSION

Our review indicates that RR/MDR-TB-related mortality is more prevalent in patients with malnutrition, which has been worsening over time. Malnutrition was observed in individuals with severe disease and typically manifested within the initial months of presentation during the study periods. Almost all patients had severe forms of the disease at the time of diagnosis, which may have contributed to early death. Although the use of molecular diagnostic testing (GeneXpert) has increased, the rate of early deaths remained similar in the two cohorts. Risk factors such as previous treatment and comorbidities like malnutrition, diabetes mellitus and HIV/AIDS, were frequent in both cohorts, which is in concordance with other studies.[3–6] We identified variations in adverse events, including the shift from an injectable-based regimen with notable electrolyte imbalances in the 2015 cohort to an all-oral BDQ and LZD-based regimen with a significant occurrence of severe anaemia/pancytopenia in the more recent 2022 cohort. These variations in adverse events are consistent with reports from other countries.[7,8]

CONCLUSION

This hospital-based TB mortality review showed severe malnutrition was more prevalent among patients who died of RR/MDR-TB. The persistence of early deaths underscores the need for additional prospective studies to gain a clearer understanding of the underlying causes of these fatalities. Patients experienced adverse events while on treatment, and these varied according to regimen type and the presence of risk factors like severe malnutrition and a history of previous treatment. We strongly recommend adjunctive nutritional care, including therapeutic feeding, for all DR-TB patients as standard of care. We also recommend the use of emergency care management services for RR/MDR-TB patients to prevent early death. Similarly, patients experiencing adverse events including drug toxicities, those with comorbid conditions and risk factors should be managed in consultation with senior experts based on guidelines and global recommendations. We also recommend implementing community awareness programmes that promote psychosocial support and encourage early healthcare-seeking behaviour.

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Les décès liés à la TB multirésistante chez les patients ayant reçu des médicaments antituberculeux de seconde ligne en Éthiopie ont été analysés. Respectivement 38/704 (5,4%) et 44/995 (4,4%) décès ont été identifiés dans deux cohortes (2015 et 2022). Dans la cohorte 2015, la malnutrition sévère était moins fréquente, les taux de traitement antérieur étaient trois fois plus élevés, l'hypokaliémie était plus fréquente, et l'utilisation du test Xpert® MTB/RIF, l'insuffisance respiratoire et l'anémie/pancytopénie sévère étaient moins fréquentes que dans la cohorte 2022. Nous avons observé des variations dans les effets indésirables lorsque différents schémas thérapeutiques étaient utilisés sur différentes périodes. Pour garantir des soins adéquats aux patients, des consignes appropriées doivent être appliquées de manière régulière.

TB-related catastrophic costs and associated factors for patients in Ethiopia

Dear Editor,

TB predominately affects the disadvantaged and the most vulnerable communities in precarious socioeconomic situations, with vicious cycles of poverty and disease.[1] Despite the widespread adoption of 'free TB care' policies, TB-affected households still face prohibitive direct medical costs.[2] TB illness is often compounded by high out-of-pocket (OOP) spending for direct costs (i.e., costs for diagnosis, treatment, transportation, and temporary accommodations when visiting health facilities) and indirect costs incurred due to the income foregone when looking for and receiving treatment or lost employment due to disability, stigma or discrimination.[1] Catastrophic cost, defined as an OOP spending of more than 20% of a household's annual income, forces many patients and their families to cut down on their daily necessities.[1,3,4] TB services are exempted in Ethiopia, and yet the proportion of TB patients facing TB-related catastrophic costs has been estimated at 40%.[5] The COVID-19 pandemic and associated economic crisis (alongside the ongoing conflict), could have further exacerbated the TB catastrophic cost. Nevertheless, nationally representative TB patient cost surveys have not been conducted. This study aimed thus to determine the magnitude and main drivers of costs incurred by TB patients and their households.

We conducted a health facility-based cross-sectional survey from November 2020 to February 2021 in 19 study zones in four regions in Ethiopia: Oromia, Amhara, Sidama, and Southern Nations, Nationalities and Peoples (SNNP). An estimated 80,481,771 people reside in these regions, representing 80% of the national population in 2020[6] and contributing to 54% of the national TB burden.[7] One-third of the public health facilities that provide TB treatment were randomly selected from all the districts within the study zones. The participants were selected randomly among patients receiving treatment during the study period, one from low TB load health facilities (<100 TB patients per year) and two from high TB load health facilities (<100 TB patients per year). TB patients who were receiving TB treatment in the sampled health facilities for at least 14 days, regardless of age and type of TB, were considered for inclusion in the study. The WHO generic TB cost survey questionnaire[8] was customized to the local context and translated into three local languages (Amharic, Oromiffa and Sidama). Data were collected from patients or their parents/guardians while attending their TB treatment follow-up visits.

The analysis included basic descriptive statistics to present sociodemographic factors and the extent of catastrophic costs. The average spending during the continuation phase was used to estimate the cost for the whole TB treatment period and of patients in the initiation phase. Catastrophic costs were determined by giving a binary value for whether patients incurred catastrophic costs or not. Bivariate and multivariate analyses were applied to assess the factors associated with TB patients' catastrophic costs. All variables with a P-value of less than 0.05 in the bivariate analysis were entered into the multivariable regression. We obtained support letters and permission from each study region's ethical review committee. Oral consent was obtained prior to the interview of TB patients. Assent was obtained from the parent or guardian for children under 14 years of age.

A total of 433 TB patients participated: 56% were male, the mean age was 33.6 (male: 35.8 and female: 30.8), the median age was 30 (male 33 and female 28), 59.4% had attended school grades 1–12, and 39.3% were farmers. One average, a TB patient incurred a total of USD715.5 for TB-related costs: with 87.8% and 12.2% direct and indirect costs (income lost related to time lost), respectively. Direct costs attributed to non-medical (food, drink, and accommodations) (55.5%), transport (20.7%) and medical cost for TB treatment (11.6%). Of the 433 study participants, 66.1% experienced catastrophic costs related to TB diagnosis and treatment when using a threshold of more than 20% of their annual income. Additionally, 39% faced catastrophic costs at a higher threshold of more than 30% of their annual income. Compared with TB patients from Amhara, Sidama TB patients were 71% less likely to face TB-related catastrophic costs (adjusted odds ratio [aOR] 0.29, 95% confidence interval [CI] 0.11–0.76). Farmers were 74% (aOR 0.26, 95% CI 0.11–0.62) more likely than government employees and 66% (aOR 0.34, 95% CI 0.18–0.61) more likely than the self-employed to experience catastrophic costs. TB patients with directly observed treatment (DOT) at home were 61% less likely to experience catastrophic costs than those who attended DOT at a health facility (aOR 0.39, 95% CI 0.24–0.65). TB patients with at least one family member on TB treatment were 93% more likely to experience catastrophic costs than those with no family member on TB treatment (aOR 1.93, 95% CI 1.10–3.42; Table).

Our findings indicated approximately two-thirds of TB patients and their families experienced TB-related

Table. TB-related costs, catastrophic costs (>20% of household annual income), and bivariate and multivariable analysis based on the sociodemographic characteristics of TB patients (n = 433).

A) Sociodemographic characteristics of TB patients

Variables	Not catastrophic n (%)	Catastrophic n (%)	Bivariate analysis cOR (95% CI)	Multivariable analysis aOR (95% CI)
Region				
Amhara	43 (40)	64 (60)	1	
Oromia	76 (47.8)	83 (52.2)	0.73 (0.45–1.21)	0.65 (0.39–1.09)
Sidama	15 (65.2)	9 (34.8)	0.36 (0.14–0.92)	0.29 (0.11–0.76*)
SNNP	79 (55.2)	64 (44.8)	0.54 (0.33–0.90)	0.61 (0.36–1.04)
Sex				
Female	66 (34.4)	126 (65.6)	1	
Male	81 (33.6)	160 (66.4)	1.03 (0.70–1.54)	
Age, years				
<15	6 (40)	9 (60)	1	
15–24	35 (23.5)	76 (68.5)	1.45 (0.48–4.38)	
25–49	78 (32.6)	161 (67.4)	1.38 (0.47–4.00)	
>49	28 (41.2)	40 (58.8)	0.95 (0.30–2.98)	
Education				
Illiterate	49 (35.5)	89 (64.5)	0.86 (0.57–1.35)	
≤Grade 12	84 (32.6)	174 (67.4)	1	
>Grade 12	14 (37.8)	23 (62.2)	0.77 (0.38–1.61)	
Occupation				
Farmer	48 (28.6)	122 (71.8)	1	
Government employment	20 (45.5)	24 (54.6)	0.47 (0.24–0.93)	0.29 (0.1–0.66*)
Self-employed	50 (44.3)	63 (55.8)	0.5 (0.30–0.82)	0.44 (0.20–0.68*)
Unemployed	29 (27.4)	77 (72.6)	1.04 (0.61–1.80)	0.73 (0.39–1.40)
Treating health facility				
Private facility	53 (47.3)	59 (52.7)	1	
Public health center	31 (52.5)	28 (47.5)	0.52 (0.14–1.92)	
DOT support provider				
Health facility	77 (30)	170 (70)	1	
Self or home-based	70 (39.6)	107 (60.4)	0.44 (0.28–0.69)	0.39 (0.24–065*)

B) TB-related direct and indirect costs

	Direct costs (USD)			Indirect costs (USD)	
	Transport costs	Drink, food and accommodation	Medical cost of TB treatment	Income lost related to time lost	Total costs (USD)
Cost in number	148.1	397.1	83.0	87.3	715.5
Proportion of total cost, %	20.7	55.5	11.6	12.2	100

* Statistically significant.
cOR = crude odds ratio; CI = confidence interval; aOR = adjusted OR; SNNP = Southern Nations, Nationalities and Peoples; DOT = directly observed therapy; USD = US dollar.

catastrophic costs. This is higher than the 2014 estimate of 58% across all low- and middle-income countries,[9] 43% of global estimates,[10] and 40% from Ethiopia[5] and other African[9] and Asian countries.[3] This is despite the exempted cost of TB services in Ethiopia, with direct costs contributing the highest share. The prohibitively high direct non-medical costs, and medical costs representing less than 20%, have been reported by many studies conducted in Ethiopia[11] and other African countries[12] and systematic reviews.[9] Therefore, the policy in Ethiopia may consider implementing a 'TB patients' exemption' rather than a 'TB service exemption'. Receiving TB DOT at home is associated with a lower likelihood of experiencing catastrophic costs, which may be due to the reduced costs for transportation, food and accommodation associated with at-home treatment with fewer visits to health facilities.[13] Further decentralization of DOT services near the patient, through self

or home-based DOT, may reduce catastrophic costs. The higher financial impact of TB on farmers has repercussions often extending beyond the patient to the family and caregivers. Farmers often reside in rural areas, requiring them to overcome many barriers to adhere to DOT, such as travelling long distances to facilities.[2] The regional differences in catastrophic costs are mainly due to differences in the type of TB: the Sidama region has a higher number of bacteriologically confirmed TB cases, whereas Ahmara has higher extrapulmonary TB.[14] The diagnostic and treatment service for extrapulmonary TB is usually delayed, expensive and requires a longer period of treatment.[15]

In conclusion, the high burden of catastrophic costs necessitates a decentralization of TB diagnosis and treatment services, the scaling up of community and home-based DOT, and the need to establish a community support system to help with nutrition and transportation costs.

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KEY WORDS: tuberculosis; decentralized healthcare; DOT; directly observed treatment; out-of-pocket expenses

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TB-related catastrophic costs in Ethiopia

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OBJECTIVES: To measure the progress towards reducing TB-related catastrophic costs in 19 zones of Amhara, Oromia, SNNP (Southern Nations and Nationalities, and Peoples) and Sidama Regions of Ethiopia.

METHODS: A baseline survey was conducted in randomly selected health facilities from all districts within the 19 zones from November 2020 to February 2021. Interventions targeting the major drivers of catastrophic costs identified in the baseline survey, such as installation of 126 GeneXpert and 13 Truenat machines, securing connectivity of 372 GeneXpert, establishing alternative specimen referral systems, and capacity-building of health workers, were implemented. A follow-up survey was conducted from October to December 2022. The WHO generic tool was used to collect data based on probability proportional to size. Data were entered into STATA software, and the proportion of catastrophic costs was calculated and compared between the two surveys.

RESULTS: A total of 433 and 397 patients participated in the baseline and follow-up surveys, respectively. The proportion of catastrophic costs reduced from 64.7% to 43.8% ($P < 0.0001$). The share of direct non-medical costs decreased from 76.2% to 19.2%, while medical and indirect costs increased from 11.6% and 12.3% to 30.4% and 52.4 %.

CONCLUSION: The proportion of households facing TB-related catastrophic costs has significantly reduced over the 2-year period. However, it remains unacceptably high and varies among regions. Further reducing the catastrophic costs requires multisectoral response, reviewing the TB service exemption policy, further decentralisation and improving the quality of TB services.

TB is one of the top infectious disease killers worldwide, and the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) poses a significant challenge to global health. TB causes significant productivity losses due to illness, disability, and premature death, leading to economic hardship for patients and their families.[1]

Particularly in low-income settings where access to affordable healthcare is limited, the costs associated with diagnosis and treatment of TB force many households to cut down on necessities such as food, clothing, and children's education or they decide not to use services simply because they cannot afford them, which in turn contribute to poor health outcomes and increase the risk of disease transmission.[2,3] Particularly, the poor and vulnerable segments of society are pushed into a vicious cycle of ill health and poverty.[4]

The WHO report indicates that, globally, approximately 50% of TB patients and their families faced catastrophic costs in 2022, defined as direct medical expenditures, direct non-medical expenditures, and indirect costs (e.g., income losses) that total more than 20% of household income.[5] The average income loss due to TB illness can be equivalent to more than one year's income,[6] and even more among MDR-TB patients and their households.[7]

Ethiopia has made significant progress in extending healthcare services to rural and disadvantaged urban areas, with over 94% of the population now having access to primary healthcare.[8] TB diagnosis and treatment has been integrated within the primary healthcare settings to enable early detection and prompt initiation of treatment and is offered free of charge at all public health facilities.[9] TB confirmatory diagnosis services such as Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) and X-rays for clinical diagnosis have been expanded to diagnostics in more than 350 hospitals and high TB burden health centres, while advanced diagnosis such as liquid and solid culture and whole genome sequencing are also available at regional and zonal levels. Community-based TB care, engaging community health workers and volunteers, has also been initiated to enhance TB case identification, treatment adherence, and monitoring, especially in remote and underserved areas.

Consequently, the incidence of TB has decreased from 421/100,000 people in 2000 to 119/100,000 people in 2022. Despite this significant decline, Ethiopia remains among the 30 countries with a high burden of TB, with over 145,000 people contracting the disease and more than 19,000 deaths attributed to TB. Additionally, the WHO estimates that approximately 30% of TB cases go undetected by the healthcare system.[10] While a national study on the TB catastrophic cost survey has not been conducted, a smaller-scale study focusing solely on direct costs and another meta-analysis study suggested that 40% and 51% of TB patients face catastrophic costs.[11,12] These studies also showed that private facility diagnosis, drug-resistant TB, TB-HIV co-infection, hospitalisation, household income, and diagnosis delays were the major factors associated with catastrophic costs.[11–13]

Ethiopia has adopted the WHO End TB strategy,[14] which achieves 'Zero TB-related catastrophic costs' by 2025.[15] The Management Sciences for Health, through the USAID Eliminate TB Project, provides support for national TB control efforts in Amhara, Oromia, Southern Nations, Nationalities, and Peoples (SNNP), and Sidama Regions. Therefore, this study seeks to

assess the advancement in reducing catastrophic costs within the framework of the project, serving as valuable information for policymakers at all levels to make evidence-based decisions.

METHODS

Study setting and design
We conducted health facility-based cross-sectional TB cost surveys at two different points in 19 zones of Amhara, Oromia, SNNP, and Sidama Regions of Ethiopia, where the project is functioning. Based on projections from the 2007 Census, these zones constitute an estimated 42,806,707 people in 2022,[16] and more than 1,050 public health centres, 58 hospitals, and 26 private health facilities provide TB diagnosis and treatment services. The is health centres serve as the first point of contact for TB diagnosis and treatment, where they collect samples from presumptive cases, transport them to the nearest diagnostic sites, or refer patients for clinical diagnosis. They also initiate DOTS for confirmed TB cases, provide adherence support, and monitor treatment outcomes using sputum smear microscopy. Assuming a TB incidence rate of 132 cases per 100,000 population and a case detection rate of 70%, during the baseline survey, we anticipate approximately 19,638 TB patients per 6 months. distributed among the health facilities, and 2–4 patients visit the health facility for follow-up or medication collection each month.

As part of the project, we conducted a baseline survey from November 2020 to February 2021 to understand the extent and factors associated with TB-related catastrophic costs. After implementing various interventions, a follow-up survey was conducted from October to December 2022.

Intervention
Various interventions targeting the major drivers of catastrophic cost and improving access to diagnostic and treatment services have been implemented. This included installing an additional 126 GeneXpert machines and 13 Truenat (Molbio Diagnostics, Verna, India) machines and ensuring the connectivity of 372 GeneXpert machines. In addition, an alternative specimen referral system was established that enabled remote health facilities to transport TB specimens to diagnostic centres using non-healthcare workers, thereby ensuring continuous service while healthcare workers focus on their duties. In addition, enhanced support was provided to further decentralise TB DOTS services to health posts and the community level, particularly for those in remote areas. This was crucial for reducing the time and financial costs of long-distance travel and improving treatment outcomes.

Furthermore, several capacity-building training sessions and supportive supervision programmes were conducted to improve the quality of TB diagnosis and treatment and ensure a consistent supply of drugs and supplies. Overall, these interventions not only enhance access to and quality of TB diagnosis and treatment services but also reduce the need for long-distance travel and multiple healthcare visits before diagnosis. They also reduce the time and expenses associated with patient referrals for diagnosis and travel to health centres for DOT services.

Sampling method
The sample size was determined using the single point calculation formula, 41% catastrophic costs,[2] and an absolute precision of 4%. This yielded, with an additional 10 % contingency, a sample of 460 patients and 424 patients in the baseline and follow-up surveys, respectively. Consequently, one-third of the health facilities providing DOTs were selected from each district using the rule of thumb, and the estimated sample size was distributed proportionally across all health facilities.

The data collection involved customising the WHO generic TB cost survey,[1] which was previously used in Vietnam[17] and China,[18] adopted to local language and context. The project staff, who were also trained on the questionnaire, data collection approach, and ethical considerations, collected the data via a paper-based questionnaire while patients visited the health facility for follow-up or to collect their drugs. The average household annual income and direct and indirect costs incurred (operational definition in Table 1) in the intensive and continuous phases of treatment were collected on the basis of patient response.

Data management, validation, and analysis
The data were entered into STATA software (Stata, College Station, TX, USA) by clerks who received a 1-day orientation, and double entry was performed for every twentieth questionnaire to ensure data quality. Based on the WHO protocol,[19] we calculated the total medical costs, total travel costs, total food costs, total accommodation costs, and total income lost for the particular episode phase the patient is in, and the cost for other phases was estimated from similar patients (matched by type of TB and facility) interviewed in the other phases of illness. Then, we calculated the total cost of each patient during the DOTS period, and if the total costs, net of transfers and reimbursements, exceeded 20% of the total annual household's pre-TB income, they were considered catastrophic. We used a binary response model to identify the factors most significantly associated with catastrophic costs, using a χ^2 test with two-tailed $P < 0.05$ considered to be the threshold for statistical significance. In addition, the proportion and mean difference of the direct and indirect costs in the two surveys were compared, and $P < 0.05$ were used to determine the level of significance difference.

Ethical considerations
We obtained support letters and permission from each study region's ethical review committee. Oral consent was obtained before the interview of patients with TB. Consent was obtained from the parent or guardian of children under 14 years of age.

RESULTS

Data were collected from 433 (94.1%) TB patients from 342 health facilities in the baseline survey and from 397 (90.2%) TB patients in 300 health facilities in the follow-up survey. Despite the slight difference in the number of patients with TB between the two surveys, the demographic and socioeconomic characteristics of the study participants were similar (Table 2). The average annual income of patients with TB in the baseline and follow-up surveys was US$715.50 and US$690.10, respectively. The number of patients enrolled from public hospitals was 74 (16.8%) during the baseline survey and 93 (23.4%) in the follow-up survey (Z-score 2.4, $P = 0.02$; Table 2).

Costs faced by patients with TB during baseline and follow-up surveys
The mean medical and non-medical costs were US$117.90 and US$213.00 at baseline and declined to US$41.80 and US$50.40 at follow-up ($P < 0.0001$). The mean indirect cost slightly increased from US$41.20 at baseline to US$45.70 at follow-up; however, this increase was not statistically significant (Table 3).

Proportion of the catastrophic cost
In the baseline survey, 64.7% of TB patients faced catastrophic costs, which decreased to 43.8% in the follow-up surveys ($P <$

TABLE 1. Definitions of indirect, direct, and catastrophic costs.

Type of cost	Elements included in cost type	Methods used to calculate costs
Direct medical costs	Cost of consultations, laboratory tests, and other medical procedures	Sum of all medical costs net of any reimbursements
Direct non-medical costs	• Transportation costs • Cost of accommodations, food, nutritional supplements • Hourly wage lost due to time loss, visiting health facilities for diagnosis and DOT, or a visit to pick up TB drugs	Sum of direct non-medical and direct medical costs net of any reimbursements
Indirect costs	• Lost productivity or wage due to illness	Sum of the reported product or wages during the TB episode, as reported by an individual

DOT = directly observed therapy.

TABLE 2. Summary of demographic and socioeconomic characteristics of TB patients at baseline and follow-up surveys.

		TB cost survey		
		Baseline survey (n = 433) n (%)	Follow-up survey (n = 397) n (%)	
Variables				P-value
Regions	Oromia	159 (36.8)	161 (40.6)	0.52
	Amhara	107 (24.8)	87 (21.9)	
	Sidama	24 (5.3)	40 (10.1)	
	SNNP	143 (33.1)	109 (27.5)	
Sex	Female	192 (44.3)	171 (43.0)	0.43
	Male	241 (55.7)	226 (57.0)	
Age, years	<15	15 (3.5)	16 (4.1)	0.73
	15–24	111 (25.6)	101 (25.5)	
	25–49	239 (55.2)	225 (56.7)	
	>49	68 (15.7)	54 (13.7)	
Educational status	Illiterate	138 (31.9)	130 (32.8)	0.62
	Grade 1–12	257 (59.4)	231 (58.3)	
	College/university	38 (8.8)	36 (9.0)	
Treating health facilities	Private facility	14 (3.2)	6 (1.5)	0.08
	Public health centre	345 (80.0)	298 (75.1)	0.08
	Public hospital	74 (16.8)	93 (23.4)	0.02
Treatment phase	Intensive	121 (30.0)	134 (33.8)	0.72
	Continuation	312 (70.0)	263 (66.2)	

SNNP = Southern Nations, Nationalities, and Peoples.

TABLE 3. Mean medical, non-medical, and indirect costs of the two surveys (US$).

Type of cost	Baseline	Follow-up	Z-score	P-value
Average annual household income	715.5	690.1	4.63	0.732
Mean medical cost	117.9	41.8	4.86	< 0.0001
Mean non-medical cost	213.0	50.4	8.38	< 0.0001
Mean indirect cost	41.2	45.7	1.83	0.76
Mean total cost	372.1	137.8	7.10	<0.001

*Exchange rate of US$1 = ETB44.3 for the baseline and US$1 = ETB52.8 for the follow-up survey. ETB = Ethiopian birr.

0.001). Significant reduction in the proportion of households experiencing TB-related catastrophic costs was observed in the Amhara, Oromia, and SNNP Regions ($P < 0.05$), but no change was observed in Sidama Region (Table 4). The share of direct non-medical cost reduced by 57.6 percentage points (from 76.2% to 18.6%) between the two surveys, while the share of direct medical cost and indirect costs increased by 18.4 and 39.2 percentage points (Table 5).

DISCUSSION

The proportion of households experiencing TB-related catastrophic costs showed a 21.0 % point reduction in the follow-up surveys conducted after 2 years of implementing the interventions. This is expected given the wide range of interventions implemented following the baseline survey in the regions. Despite this encouraging achievement, the current proportion of catastrophic costs (44%) in

TABLE 4.   Proportion of patients who incurred TB-related catastrophic costs in the baseline survey and the follow-up survey, by region.

	Participants		Catastrophic cost		Difference, %	
Region	Baseline *n*	Follow-up *n*	Baseline *n* (%)	Follow-up *n* (%)	*Z*-score	*P*-value
Amhara	107	87	89 (83.2)	51 (58.6)	3.8	<0.0001
Oromia	159	161	108 (67.9)	65 (40.4)	4.9	<0.0001
Sidama	24	40	14 (58.3)	20 (50.0)	1.2	0.26
SNNP	143	109	69 (48.3)	38 (34.8)	1.3	0.02
Total	433	397	280 (64.7)	174 (43.8)	6.2	<0.000 1

SNNP = Southern Nations, Nationalities, and Peoples.

TABLE 5.   Proportion of the different costs categories in the two TB cost surveys.

Type of cost	Baseline %	Follow-up %	*Z*-score	*P*-value
Direct medical cost	11.6	30.0	8.6	<0.0001
Direct non-medical cost	76.2	18.6	21.8	<0.0001
Indirect cost	12.2	51.4	16.0	<0.0001

the four regions is unacceptably high. This implies addressing the determinants of catastrophic cost; therefore, achieving the national target 'zero catastrophic cost by 2025' might require a commitment of high-level leadership and coordinated multisectoral actions.

The major reduction was related to direct non-medical costs, including transport and food and drink costs. This could be mainly associated with the additional TB diagnostic equipment allocated in health facilities nearest to the community, improvement of the sample transportation system by non-health workers, rather than patient referral for diagnosis, as well as decentralisation of TB treatment follow-up to health posts—all of which reduce the frequency and distance to visit health facilities.

In contrast, while the mean cost shows a slight reduction, the share of medical and indirect costs, out of the total cost, shows an increase in the follow-up survey. This could be due to the significant reduction in direct non-medical costs. However, inflation in the costs of transport, accommodation, and food items, which we did not consider in the calculation, could also contribute to the difference. It also indicates that patients are still visiting many health facilities before diagnosis and continue to experience delays, implying the need to improve the quality of TB diagnosis and treatment.

However, given the interventions implemented, continuing high out-of-pocket (OOP) spending to receive medical care is concerning. This is mainly because of the policy that exempts 'TB diagnosis and treatment' only, but the costs incurred before diagnosis, when patients must visit different health institutes before TB disease confirmation,[20] diagnosis of extrapulmonary TB, and diagnosis and treatment for illness other than TB, developed due to TB disease or side effects of TB drugs, are not covered by the exemption policy.[21]

The proportion of catastrophic events has shown a significant reduction in all regions, except in Sidama Region. However, there remains a wide difference among regions, despite the same health system and policy. The Amhara Region has higher TB-related catastrophic costs. This could be due to the higher proportion of extrapulmonary TB (EPTB) cases in the region.[3] EPTB is known to have a delay in diagnosis[4] and is not exempted in Ethiopia,[21] which contributes to higher OOPs.

Limitations

The two TB catastrophic surveys in Ethiopia were undertaken when the country was in two different contexts, and factors such as the COVID-19 epidemic and the conflict in northern Ethiopia and the Oromia Region could affect the estimation of catastrophic cost. In addition, the surveys were conducted mainly in rural agrarian regions, excluding cities and pastoral regions, indicating caution for generalizability. The effect of inflation rate, which is not considered in the calculations, is another limitation that could affect the estimation.

CONCLUSIONS

Although there was a 21% reduction between the two surveys over the 2 years, the proportion of households experiencing TB and TB-related catastrophic costs remains unacceptably high. The health sector should consider revising the policy 'TB services exemption', to 'TB patient exemption', to cover the costs of diagnosis and treatment for illnesses other than TB, including pre-diagnosis costs and diagnosis of EPTB, as well as further decentralisation of improving access to and quality of TB diagnosis and treatment services. Undertaking future studies in Ethiopia, including a national TB cost survey, by applying a stronger prospective cohort study design with all relevant determinants is essential to understand the detailed factors associated with catastrophic cost in the country.

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OBJECTIFS : Mesurer les progrès accomplis dans la réduction des coûts catastrophiques liés à la TB dans 19 zones des régions d'Amhara, d'Oromia, de SNNP (Région des nations, nationalités et peuples du Sud) et de Sidama en Éthiopie.

MÉTHODES : Une enquête de base a été menée dans des établissements de santé sélectionnés au hasard dans tous les districts des 19 zones de novembre 2020 à février 2021. Des interventions ciblant les principaux facteurs de coûts catastrophiques identifiés dans l'enquête de référence, telles que l'installation de 126 machines GeneXpert et 13 Truenat, la sécurisation de la connectivité de 372 GeneXpert, la mise en place de systèmes alternatifs d'orientation des échantillons et le renforcement des capacités des agents de santé, ont été mises en œuvre. Une enquête de suivi a été menée d'octobre à décembre 2022. L'outil générique de l'OMS a été utilisé pour recueillir des données fondées sur une probabilité proportionnelle à la taille. Les données ont été saisies dans le logiciel STATA, et la proportion des coûts catastrophiques a été calculée et comparée entre les deux enquêtes.

RÉSULTATS : Au total, 433 et 397 patients ont participé respectivement à l'enquête de base et à l'enquête de suivi. La proportion des coûts catastrophiques est passée de 64,7% à 43,8% ($P < 0,0001$). La part des coûts non médicaux directs a diminué, passant de 76,2% à 19,2%, tandis que les coûts médicaux et indirects sont passés de 11,6% et 12,3% à 30,4% et 52,4%.

CONCLUSION : La proportion de ménages confrontés à des coûts catastrophiques liés à la tuberculose a considérablement diminué au cours de la période de 2 ans. Cependant, il reste inacceptable et varie selon les régions. Pour réduire davantage les coûts catastrophiques, il faut une réponse multisectorielle, une révision de la politique d'exemption des services de lutte contre la TB, une décentralisation plus poussée et une amélioration de la qualité des services de lutte contre la TB.

ORIGINAL RESEARCH

Survival Rate and Predictors of Mortality Among TB-HIV Co-Infected Patients During Tuberculosis Treatment at Public Health Facilities in Bahir Dar City, Northwest Ethiopia

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Background: Tuberculosis and human immunodeficiency virus co-infection pose a major public health concern, particularly in developing countries. The survival and predictors of mortality were not sufficiently studied among TB-HIV co-infected patients in Ethiopia.

Objective: This study aimed to investigate the survival rate and predictors of mortality among TB-HIV co-infected patients during TB treatment at public health facilities in Bahir Dar, Northwest Ethiopia.

Methods: A retrospective follow-up study was conducted among 401 TB-HIV co-infected patients who were treated for tuberculosis between July 2018 and June 2022 at public health facilities in Bahir Dar city, Ethiopia. Data were collected using a structured checklist from patient charts. Data entry and analysis were done using EpiData 3.1 and Stata version 15, respectively. A Cox proportional Hazard regression model was used to identify predictors of mortality. Predictors with P < 0.05 in the multivariable regression were considered statistically significant.

Results: Among the 401 TB-HIV co-infected patients, 59 (14.7%) died during the follow-up period. Predictors like lower BMI (AHR = 3.00, 95% CI = 1.44, 6.28), extrapulmonary TB infection (AHR = 3.30, 95% CI = 1.50, 7.29), presence of opportunistic infection (AHR = 5.07, 95% CI = 2.55, 10.08), functional status (bedridden: AHR = 4.49, 95% CI = 1.63, 12.33), and adherence to TB treatment (fair = AHR = 2.74, 95% CI = 1.41, 7.20, and poor = AHR = 3.75, 95% CI = 1.52, 9.23) were associated with mortality.

Conclusion: Mortality among TB and HIV coinfected people was high at public health facilities in Bahir Dar city. This result suggested that in order to increase patient survival, it would be necessary to enhance nutritional status, increase adherence to TB treatment, and prevent opportunistic infections.

Keywords: TB, HIV, mortality, predictors, retrospective, survival, Ethiopia

Introduction

Tuberculosis (TB) and the Human Immunodeficiency Virus (HIV) are among the leading public health problems globally. Tuberculosis is one of the most common illnesses and causes of death among people living with HIV (PLWHIV). HIV positive individuals have a 20–30 times greater risk of contracting TB than HIV negative individuals due to lowered immunity. Reports also indicated that PLWHIV are more likely to develop active TB than HIV negative.[1,2] The global TB report 2021 stated that out of ten million people infected with TB, 8% were PLHIV. The proportion of TB episodes coinfected with HIV was highest in the African region, exceeding 50% in parts of Southern Africa.[2]

TB and HIV form a lethal combination, each speeding the other's progress. As a result, individuals with co-infections of TB and HIV have a significant risk of increased mortality. Without proper treatment, 60% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.[3] Globally, 1.6 million people died from TB and 1 million from HIV in 2017 and accounting for one in every 300,000 deaths from both diseases.[1] Most recently, about one-third of all AIDS-related deaths worldwide are caused by TB, which is the leading cause of death among HIV-positive individuals. An estimated 167,000 people died from TB-HIV coinfection in 2022.[3] The syndromic interaction between TB and HIV has played a ruinous role, with Africans bearing a disproportionate share of the burden. In 2019, people in Africa accounted for 73% of TB-HIV co-infection cases and 81% of all TB-HIV deaths. At the country level, South Africa and Nigeria rank among the worst affected in sub-Saharan Africa and globally for both diseases.[4,5] In addition to TB disease, PLHIV bears a high burden of drug-resistant TB strains; thus, if diagnosis is delayed, there is an increased risk of mortality from multidrug-resistant and extensively drug-resistant TB in this population.[6]

With an estimated TB incidence rate of 164 per 100,000 people and 112 cases per 100,000 TB cases among PLWHIV, Ethiopia is one of the twenty nations in the world with the highest burdens of TB and TB-HIV.[7,8] According to a nationwide retrospective cohort study, 9% of HIV patients receiving treatment also had TB.[9] About 13% of all new TB cases are also HIV coinfected. Moreover, Ethiopia is one of the high TB-HIV and multidrug resistant TB (MDR TB) burden countries. Among TB patients with known HIV status, about 11% were HIV co-infected.[10] According to the global report, 3600 people in Ethiopia who had TB and HIV co-infections died while receiving TB treatment in 2017 alone.[11] Despite the availability of free ART and anti-TB medications in the country, the survival rate for those with TB and HIV co-infection has not increased.[12,13]

Studies conducted worldwide indicated that the survival of TB-HIV infected patients was determined by different predictors. Socio-demographic and personal factors like age, sex, residency, education, occupation and body mass index play a key role in predicting the mortality of people co-infected with HIV and TB in countries around the world.[14–18] Studies showed that patients with TB-HIV without ART tend to have poorer TB outcomes compared to those who are on ART, and TB infection with late presentation and HIV diagnosis are further risk factors for unsuccessful TB treatment outcomes among patients with TB-HIV.[19,20] Previous research has also shown a significant correlation between TB-HIV-related mortalities and baseline CD4 cell count, WHO clinical stage, use of co-trimoxazole preventive therapy, the presence of opportunistic infections and baseline functional level.[9,21,22] Although, co-infection with TB and HIV is bidirectional and a dual public health burden worldwide, TB-HIV co-infected patients have not received enough attention.[23,24]

A few studies conducted in Ethiopia found that factors such as ART status, baseline CD4 cell count, baseline functional level, WHO clinical stage, cotrimoxazole preventive therapy, type of TB diagnosis, and coexistence of other opportunistic infections (OIs) were predictive of survival among TB-HIV co-infected patients.[21,25] However, previous studies are not sufficient to estimate the survival status of the patients. In addition, the results of earlier studies may no longer be applicable to use as an intervention tool to improve patient survival because there are recurring or ongoing changes in the characteristics of the diseases, in the ART and TB treatment regimens, in population migration, and in the drug resistance of the disease. As a result, up-to-date studies are required that take all these changes into consideration. Therefore, this study was conducted to identify the survival status and predictors of mortality among TB-HIV-coinfected patients who were on TB treatment between 2018 and 2022 at public health facilities in Bahir Dar City.

Methods and Materials
Study Setting and Period
This study was conducted at public health facilities located in Bahir Dar City by reviewing medical records of patients recorded from July 2018 to June 2022. Bahir Dar is the capital city of Amhara Regional State, which is located 560 km northwest of Addis Ababa, the capital of Ethiopia. There are eleven HCs and three public hospitals administered by the Bahir Dar city health department. These facilities are expected to serve about 422,580 people around Bahir Dar and other nearby areas.

Study Design: An institution-based retrospective follow-up study was conducted among TB-HIV co-infected patients treated at public health facilities in Bahir Dar city.

Source and Study Populations

The source population was all TB-HIV-coinfected patients being treated for TB at public health facilities in Bahir Dar city, while the study population was all TB-HIV-coinfected patients being treated for TB at public health facilities in Bahir Dar city from July 2018 to June 2022.

Inclusion and Exclusion Criteria

All TB-HIV co-infected patients who were treated for TB at public health facilities in Bahir Dar city from July 2018 to June 2022 were included. And those patient charts that lacked complete disease documentation, an incomplete base line, and follow-up data were excluded from the study.

Study Variables
Dependent Variable

The dependent variable for this study was survival time to death of TB-HIV co-infected patients from the time of initiation of TB treatment to end of follow-up period.

Independent Variables

Socio demographic factors: age, sex, marital status, educational status, occupation, residence.
Clinical characteristics: WHO clinical stage, CD4 count/mm^3, hemoglobin level, nutritional status (Weight, Height), site of TB, functional status, comorbidities (DM, HTN, Asthma) and opportunistic infection (OI).
Treatment-related factors: TB regimen, ART regimen, adherence to TB and HIV, and CPT.

Operational Definition

Survival time: The time in days between diagnosis of TB-HIV co-infection and occurrence of outcome (event or censored).
Time to death: The time from TB-HIV co-infection to the occurrence of the event (death) during the follow-up period.
Events: The event of this study is death of a TB-HIV co-infected patients.
Censored: Represents patients lost to follow-up, treatment completed, recovered and treatment failure.
Loss to follow-up: A TB-HIV co-infected patient whose treatment was interrupted for 2 consecutive months or more.
Transferred out: Those TB-HIV patients who were transferred-out to another health facilities for TB treatment.
Adherence: A patient was following the recommended course of treatment by taking all prescribed medications and coming for scheduled exams and tests.

Sampling Techniques and Procedures

All patients co-infected with TB and HIV who were registered and receiving follow-up care from July 2018 to June 2022 were included in the current study. During the study period, a total of 2675 HIV-positive clients and 3192 TB patients were notified. Among these patients, 472 were TB-HIV co-infected. Each TB-HIV co-infection patient in the cohort was retrospectively studied, starting from the initiation of TB treatment to the occurrence of the outcome (event or censored) or the end of the follow-up period. Seventy-one charts were rejected due to incompleteness, and 401 TB-HIV-coinfected patients who were treated during the study period were included in the study.

Data Collection Methods and Procedures

The data were collected using a structured checklist prepared in English. The data extraction tool was adapted from existing studies and adopted from patients' charts, registrations, and ART and TB intake forms. The tool consisted of predictors related to socio-demographic characteristics, clinical characteristics of the patient, laboratory investigations, treatment, and adherence to treatment. Four nurses who have training in ART and TB participated in the data collection process.

Data Quality Assurance

Prior to actual work, data collectors and supervisors were given a one-day orientation on data collection tools. During orientation, emphasis was given on the purpose of the study, how to use data extraction tools and their content, and how to address possible problems. In each facility, a card room porter was recruited for card delivery from the card room. The principal investigator and the supervisors closely monitored the whole data collection process on a regular basis. The collected data were cleaned before the analysis.

Data Processing and Analysis

Data were entered using EpiData version 3.1 and analyzed using STATA version 15. Before analysis, the data were cleaned and checked for consistency by using simple frequencies and cross tabulation; re-categorization of categorical variables and categorization of continuous variables was done to make it suitable for analysis. Descriptive statistics were used to present the demographic and background clinical characteristics of the patients. The Kaplan–Meier survival curve was used to estimate the median survival time and cumulative probability of survival, while the Log rank test was used to assess overall survival differences between group predictors. Cox proportional hazard regression analysis was used to identify the potential predictors of mortality. Multicollinearity between predictors was checked. A bivariable Cox-proportional hazard regression model was fitted for each explanatory variable, and those variables having a p-value ≤0.25 were selected for multivariable analysis. The adjusted hazard ratio (AHR) with 95% confidence intervals was computed, and statistical significance was declared at $p < 0.05$. Finally, results were presented using tables, graphs, and text.

Results

Socio-Demographic Characteristics

The data used for this study was obtained from the medical records of 401 TB-HIV-coinfected patients. The median age of the patient was 35, with an interquartile range of 13 years (28 to 41). Slightly more than half, 227 (56.6%) were male in sex, and most, 340 (84.79%) of them were urban regarding their residency. A total of 164 (40.9%) individuals were married, and nearly one-third (30.43%) of participants had no formal education (Table 1).

Table 1 Socio-Demographic Characteristics of TB-HIV Co-Infected Patients at PHFs in Bahir Dar City, Northwest Ethiopia, August 2023 (n = 401)

Variables	Category	Frequency	Percent
Age	<15	15	3.74
	15–24	38	9.48
	25–34	147	36.66
	35–44	126	31.42
	≥45	75	18.70
Sex	Male	227	56.61
	Female	174	43.39
Residence	Urban	340	84.79
	Rural	61	15.21

(*Continued*)

Table 1 (Continued).

Variables	Category	Frequency	Percent
Educational level	No formal education	122	30.43
	Primary	111	27.68
	Secondary	110	27.43
	Diploma and above	58	14.46
Occupation	Employed (private and govt)	103	25.68
	Farmer	104	25.94
	Merchant	49	12.22
	Not working (student)	46	11.47
	Daily laborer	82	20.45
	Others	17	4.24
Marital status	Currently married	164	40.90
	Single	123	30.67
	Divorced	77	19.20
	Widowed	37	9.23

Background Clinical Characteristics

The findings of this study showed that among participants majority, 358 (89.28%) were in advanced WHO stages (stage III and IV). In addition, 20 (4.99%), 10 (2.49%) and 24 (5.99%) had asthma, diabetic mellitus, and hypertension, respectively. Among individuals who have one or more comorbidities 23 (42.59%) died during the follow-up period. Regarding the functional status of participants, 291 (72.57%), 96 (23.94%), and 14 (3.49%) were working, ambulatory, and bedridden, respectively. More than half (55.86%) of patients were diagnosed with pulmonary TB, while the rest, 177 (44.14%), were extra-pulmonary. Among 83 (20.7%) patients who had opportunistic infections, 38 (45.78%) died during the follow-up period. In addition, from 97 (24.19%) patients with a CD4 count <200 cells/mm^3, 17 (17.5%) died during the TB treatment period. Of the study's participants, 168 (41.90%) had their ART treatment regimen changed after enrolling, and 25 (14.88%) of them passed away while receiving TB treatment. Among those patients who were co-infected, 19 (4.74%) and 20 (4.99%) exhibited poor adherence to ART and TB treatment, respectively. There were 283 (70.57%) patients who received cotrimoxazole preventive therapy, of whom 7.77% died during TB treatment and the follow-up period (Table 2).

Mortality and Survival Status of TB-HIV Co-infected Patients

Among the 401 patients who were included in this study, there were 310 (73.3%) treatment successes, 59 (14.7%) deaths, 18 (4.5%) did not get evaluated, 8 (2.0%) lost follow-ups, and 6 (1.5%) treatment failures. High mortality in TB and HIV co-infected patients was observed in the earlier months of the treatment period. Twelve (27%), twenty-two (64%), and fifty-four (95%) of deaths among co-infected patients occurred in the second, third, and sixth-months following anti-TB treatment initiation, respectively. The incidence rate of mortality among TB-HIV coinfected patients was 7.47 per 10,000-person day (95%: CI = 5.79, 9.64) or 242 per 10,000-person month. The survival rates were also 96%, 90%, and 85% at 2, 3, and 6 months, respectively, after the initiation of TB treatment.

Table 2 Base Line Clinical Characteristics of TB and HIV Co-Infected Patients During TB Treatment at PHFs in Bahir Dar City, Northwest Ethiopia, August 2023 (n = 401)

Variable	Category	Frequency	Percentage
WHO clinical stage	I	24	5.98
	II	19	4.74
	III	180	44.89
	IV	178	44.39
Body Mass Index	<18.5	161	40.15
	18.5–24.5	191	47.63
	>24.5	49	12.22
Site of tuberculosis	Pulmonary	224	55.86
	Extra Pulmonary	177	44.14
History of opportunistic infection	Yes	83	20.70
	No	318	79.30
Functional status	Working	291	72.57
	Ambulance	96	23.94
	Bedridden	14	3.49
CD4 count	<200	97	24.19
	>200	304	75.81
Hemoglobin level	Abnormal	144	35.91
	Normal	257	64.09
Regimen change	Yes	168	41.90
	No	233	58.10
ART Adherence	Good	354	88.28
	Fair	28	6.98
	Poor	19	4.74
Tuberculosis Adherence	Good	332	82.79
	Fair	33	8.23
	Poor	36	8.98
CPT	Started	283	70.57
	Not started	118	29.43

Abbreviations: CD4, clusters of differentiation 4; ART, antiretroviral therapy; OI opportunistic infection, CPT, co-trimoxazole preventives therapy.

Overall Survival and Survival Comparison Between Group Predictors

The Kaplan–Meier technique was employed to plot the survival graph. Even though there was no abrupt decline, the Kaplan–Meier survival curve showed that overall survival was gradually declining until about three months (the 200 days) of the follow-up period. However, in the subsequent follow-up period, the graph flattened out, showing nearly

constant survival time until the end of the follow-up period (Figure 1). The Log rank test and the KM graphical curve were used to evaluate survival differences for categorical predictors. Therefore, a separate Kaplan–Meier graph was drawn for each predictor. Accordingly, there were differences in the survival times for predictors such as the site of the TB, the presence of OI, the body mass index, the patient's functional level, TB adherence, status of DM, CD4 count, and CPT. For other group predictors such as sex, residency, or age, there were, however, no clear differences in survival time.

Predictors of Mortality Among TB-HIV Coinfected Patients

In this study, the Cox proportional hazard analysis was used to identify significant predictors of mortality. Variables that meet the basic requirements of the Cox proportional hazard assumptions and that had a p-value of ≤0.25 in the bi-variable Cox proportional analysis were included in the final model. Accordingly, marital status, the presence of asthma, the presence of DM, BMI, WHO clinical stages, sites of TB, the presence of OI, the functional status of the patients, adherence to the ART treatment, adherence to TB treatment, and cotrimoxazole preventive therapy were variables fitted into the final model. In multi-variable Cox-Proportional Hazard model, BMI, the site of TB infection, the presence of OI, functional status of the patient, and adherence to TB treatment were remain significant predictors of mortality.

Patients who had a BMI of lower than normal were 3.00 times higher risks of dying as a compared to those who had normal BMI (AHR = 3.00, 95% CI = 1.44, 6.28). Patients with Extrapulmonary TB had 3.30 times more risk of death than patients with pulmonary TB (AHR = 3.30, 95% CI = 1.49, 7.29). The risk of dying was 5.07 times higher for those patients with OIs as compared to their counterparts (AHR = 5.07; 95% CI = 2.55, 10.09). Bedridden patients had a mortality risk that was 4.49 times higher than those with working functional status (AHR = 4.49; 95% CI = 1.63, 12.33). Furthermore, this study found that patients who had fair and poor adherence to their TB treatment had 2.74 times (AHR = 2.74, 95% CI = 1.41, 7.20) and 3.75 times (AHR = 3.75, 95% CI, 1.52, 9.23) a higher risk of dying during TB treatment compared to patients who had good adherence to their treatment, respectively (Table 3).
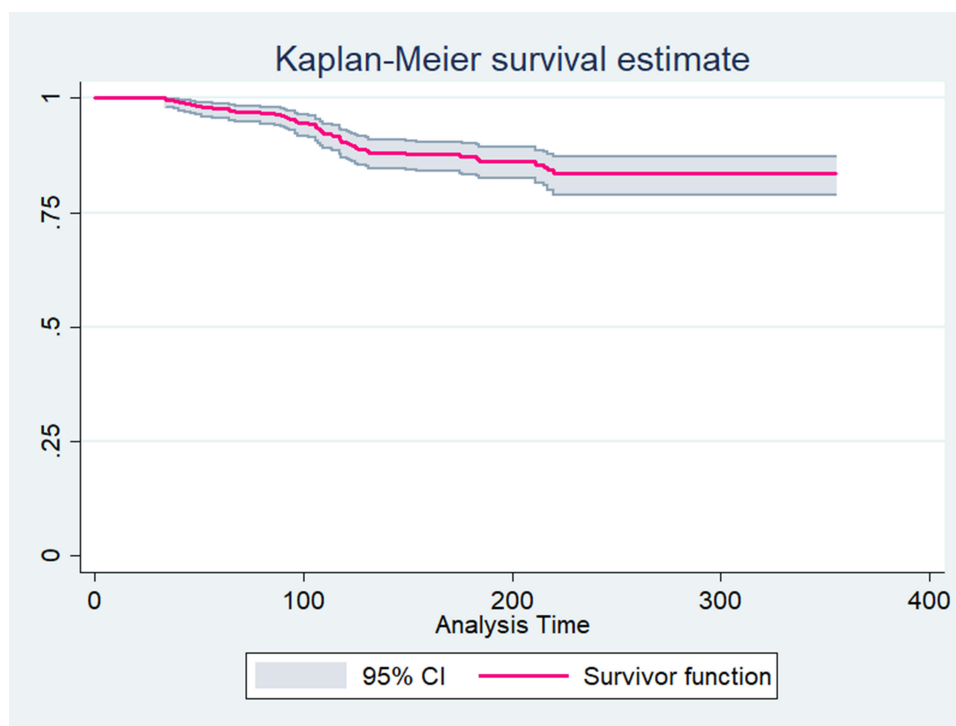
Figure 1 Overall Kaplan-Meier survival probability curve among TB-HIV coinfected patients, during TB treatment at PHFs in Bahir Dar City, Northwest Ethiopia, August 2023 (n = 401).

Table 3 Multivariable Cox Regression Analysis Among TB-HIV Co-Infected Patients Being Treated for TB at PHFs in Bahir Dar City, Northwest Ethiopia, August 2023 (n = 401)

Variables	Category	Outcome			CHR 95% CI	AHR (95% CI)	P-value
		Censored	Event	Total			
Asthma	No	333 (87.40)	48 (12.60)	381(100)	I	I	0.37
	Yes	9 (45.00)	11 (55.00)	20 (100)	4.82 (2.50, 9.29)	1.49 (0.63, 3.60)	
Diabetics	No	335 (85.68)	56 (14.32)	391(100)	I	I	0.38
	Yes	7 (70.00)	3 (30.00)	10 (100)	2.26 (0.71, 7.22)	1.53 (0.48, 6.51)	
BMI	<18.5	130 (80.75)	31 (19.25)	161 (100)	I	3.00 (1.44, 6.28)	
	18.5–24.5	177 (92.67)	14 (7.33)	191 (100)		I	0.01*
	>24.5	35 (71.43)	14 (28.57)	49 (100)	1.44 (0.76, 2.71)	0.56 (0.98, 5.66)	0.66
WHO stage	I	23 (95.83)	1 (4.17)	24 (100)	I	I	
	II	16 (84.21)	3 (15.79)	19 (100)	0.24 (0.025, 2.30)	7.84 (0.75, 8.50)	0.09
	III	159(88.33)	21 (11.67)	180 (100)	0.68 (0.20, 2.27)	2.82 (0.34, 23.53)	0.34
	IV	144(80.90)	34 (19.10)	178 (100)	1.14 (0.35, 3.71)	1.77 (0.21, 14.63)	0.60
OI	No	297 (93.40)	21 (6.60)	318(100)	I	I	<0.001*
	Yes	45 (54.22)	38 (45.78)	83 (100)	9.48 (5.55, 16.20)	5.07 (2.55, 10.08)	
Functional Status	Working	250(85.91)	41 (14.09)	291(100)	I	I	
	Ambulance	85 (88.54)	11 (11.46)	96 (100)	1.22 (0.63, 2.38)	0.52 (0.25, 1.09)	0.08
	Bedridden	7 (50.00)	7 (50.00)	14 (100)	5.66 (2.19, 14.63)	4.49 (1.63, 12.33)	0.004*
Adherence (ART)	Good	326 (92.09)	28 (7.91)	354 (100)	I	I	
	Fair	9(32.14)	19 (67.86)	28 (100)	0.08 (0.45, 0.15)	0.98 (0.72, 4.90)	0.20
	Poor	7 (36.84)	12 (63.16)	19 (100)	0.81 (0.39, 1.67)	1.30 (0.44, 3.83)	0.06
Adherence (TB)	Good	308 (92.8)	24 (7.2)	333 (100)	I	I	
	Fair	15 (45.5)	18 (54.5)	33(100)	0.05 (0.03, 0.10)	2.74 (1.41, 7.20)	0.04*
	Poor	19(52.8)	17(47.2)	36(100)	1.11 (0.57, 2.16)	3.75 (1.52, 9.23)	0.004*
Marital status	Married	154 (93.90)	10 (6.10)	164 (100)	I	I	
	Single	106 (86.18)	17 (13.82)	123 (100)	2.42 (1.11, 5.29)	1.37 (0.55, 3.37)	0.50
	Divorced	61 (79.22)	16 (20.78)	77 (100)	3.72 (1.69, 8.20)	1.10 (0.39, 3.08)	0.85
	Widowed	21 (56.76)	16 (43.24)	37 (100)	8.29 (3.76, 18.27)	1.31 (0.49, 3.44)	0.59
CPT	No started	81 (68.64)	37 (31.36)	118 (100)	I		0.21
	Started	261(92.23)	22 (7.77)	283 (100)	0.22 (0.13, 0.38)	0.68 (0.29, 1.31)	
Site of TB	Pulmonary	210 (93.75)	14 (6.25)	224 (100)	I	I	0.003*
	Extra Pulmonary	132 (74.58)	45 (25.42)	177 (100)	(2.46, 8.16)	3.30(1.50, 7.29)	

Note: *Indicated significant predictors with a p-value of <0.05.
Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CPT, co-trimoxazole preventive therapy; OI, opportunistic infection; TB, tuberculosis.

Discussion

This study was conducted to determine the survival time and predictors of mortality among TB-HIV co-infected patients during tuberculosis treatment at public health facilities in Bahir Dar. The finding indicated that the median follow-up period was 212 days with a minimum and maximum days of 34 and 355 days.

This study revealed that the cumulative incidence of mortality was 14.7% (95% CI = 11.4%, 18.6%) among TB-HIV co-infected patients during TB treatment and follow-up period. The finding was consistent with a study in Myanmar, 13.7%[26] and Ethiopian studies reported from, Somali, 11.1%[27] and Bahir Dar, 18%.[28] But it was lower than studies in Almaty, Kazakhstan 27.4%,[29] Metu Karl Hospital 20.9%,[30] Mizan Tepi University Hospital 21.8%,[31] and Mekelle, 23.0%.[24] However, this finding significantly higher than the study conducted in Harar town 7.7%.[32] The overall incidence rate was 2.42 per 100 person months (95% CI = 1.88, 3.12), which was higher than studies conducted in

Metu Karl Referral Hospital and Mizan Tepi teaching Hospital which reported 1.21 per 100 person month and 0.52 per 100 person month, respectively.[4,30] However, the finding was lower than a study conducted in Bahir Dar[28] which reported 4.1 per 100 Person-Month. The differences might be having been due to differences in the study's design and period, differences in the quality of care in the treatment center and changes in the treatment protocol.

TB-HIV co-infected patients whose BMI was lower than normal (BMI < 18.5 kg/m2) had more than three times higher risk of death as compared to those with normal BMI. The finding was in line with a study in Lesotho[18] and an Ethiopian study conducted in Mekelle.[33] The possible justification might be that those with a lower BMI are supposed to suffer from malnutrition, which is one of the causes of immunocompromising diseases that result in death.

Site of TB was also a predictor of mortality, and hence, Extra Pulmonary TB (EPTB) had 3.3 times more risk of mortality than pulmonary TB. The finding was consistent with studies conducted in Ethiopia, Mekelle[24] and Bahir Dar.[28] Possible justification for the similarities might be that EPTB cases have a greater chance of being disseminated to different body organs, which may result in treatment failure, and, finally lead to multi-drug resistance and mortality.[24] Unlikely, the result of this study were different from a study conducted in Ambo Referral Hospital, Ethiopia, indicated PTB patients were 2.3 times more likely to die than EPTB.[21] The differences might be due to differences in study period, setting and design of the study.

Those patients with opportunistic infections had 5.07 times higher risk of dying compared with those without opportunistic infections. The finding was consistent with other studies conducted in Botswana[34] and Cameron[35] and at teaching hospitals in Harar Ethiopia.[32] The possible reason could be that those patients with opportunistic infection less likely to resist TB and recover from their illness.

The functional status of the patient was another predictor of mortality among TB-HIV coinfected patients. Those bed ridden patients were 4.49 times more at risk of death compared to those with working status. The finding was in line with studies conducted at Mizan Tepi, Bahir Dar, Metu Karl and Jimma Referral hospitals.[4,28,30,36] This might be because bedridden patients have a worse prognosis for health because of a relentless immunity-lowering cycle, which can result in patients contracting opportunistic infections and dying.[30]

According to this study, participants with poor adherence to TB treatment had 3.75 times an increased risk of mortality as compared to good adherence. This agreed with a study done in Mizan-Tepi southwest Ethiopia.[31] The similarities could be those people who were unable to take TB drugs adherently had come up with many problems such as treatment failure, a resistant strain which resulted in death of their outcome.

Limitations of the Study

The data were extracted from secondary sources, and as a result, some important variables related to behavioral factors like smoking, drug use, and others like income were missed, which might be potential predictors of mortality in TB-HIV co-infected patients.

Conclusion

The findings of this study indicated that there was high mortality among TB-HIV coinfected patients during the follow-up period, and specifically, low survival was observed in the earlier months of initiation of TB treatment. Since the number of deaths was significantly high, efforts must be made to reduce it. Low BMI (<18 gm/m2) at baseline, presence of OI, EPTB, bedridden functional status, and inability to adhere to anti-TB treatment were independent predictors affecting the survival of TB-HIV co-infected patients. Therefore, to increase the survival of the patient, health care providers in the study area should work to improve the nutrition status of the patient, improve their adherence, and prevent and treat opportunistic infections.

Abbreviations

AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; BMI, body mass index; CD4, cluster differentiation-4; EPTB, extra pulmonary TB; HIV, human immunodeficiency virus; OI, opportunistic infection; PHFs, public health facilities; TB, tuberculosis; WHO, World Health Organization.

Data Sharing Statement

The corresponding author will provide the datasets used and/or analyzed for this study upon reasonable request.

Ethics Approval

The study was conducted after getting ethical clearance from the Amhara Public Health Institute research directorate ethical review committee. The study utilized the five-year secondary data collected retrospectively from individual patient medical records. Therefore, the ethical committee approved that there was no patient consent as there was no direct patient contact during data collection, provided that the data would be used only for the sole purpose of the study. The letter of cooperation written by the ethical committee on January 27, 2023, with a reference number of 1888/APHI, was presented to each health facility in Bahir Dar city. The research committee in each health facility gave a grant to conduct the research in their respective facilities. Confidentiality of the information was secured throughout the study by excluding names and patient medical record numbers on the data extraction form, and the data were used only for the proposed study. This study adhered to the Declaration of Helsinki's ethical standards.

Author Contributions

All authors made a significant contribution to this work, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests in this work.

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# A survey of the effectiveness of centralized consilia in providing advice on drug-resistant TB

Dear Editor,
Annually, approximately 410,000 people globally acquire multidrug-resistant TB (MDR-TB) and rifampicin-resistant TB (RR-TB).[1] However, in 2021, only 161,746 people were enrolled in MDR/RR-TB treatment, with most of the enrollees being adults.[2] The biggest barrier to care is failure to diagnose drug-resistant TB (DR-TB), but once it is diagnosed, access to treatment and lack of provider experience are important additional barriers.[1] To expand treatment capacity, centralized hubs of expertise have been set up in many countries to provide either advice and/or direction in selecting treatment regimens and monitoring for tolerability and effectiveness. However, centralization of care may also be a barrier to prompt treatment initiation, especially when centralized decision-making is required before drugs are released. These systems, called 'consilia', evolved when MDR/RR-TB treatment was first introduced, and control was prioritized over access.[3] Currently, WHO provides guidelines on the duration and composition of treatment, but consilia may still be important in some settings for translating these guidelines into individual patient decisions.[4] In 2000, the first forum for advice on MDR/RR-TB treatment, the 'Green Light Committee (GLC)' was created to improve access to quality-assured second-line anti-TB drugs.[3] In 2014, because many care providers had limited experience in devising and monitoring treatment for DR-TB, WHO recommended that MDR-TB and extensively drug-resistant TB (XDR-TB) case management be overseen by centralized teams at regional levels. These are meant to help with the discussion of difficult cases and serve as the 'gateway to accessing second-line drugs and/or the new drugs'.[4] A typical TB consilium is made up of clinicians, public health officers, microbiologists, pharmacologists and other relevant roles. Although consilia aim to improve care for MDR-TB and XDR TB, there are both advantages and disadvantages. Advantages include the ability to receive expert advice, collaboration amongst TB experts, peer quality assurance and potential teaching opportunities. Disadvantages include a slower response rate (potentially leading to delays in initiating treatment) and a limited number of cases that can be discussed.[5] RESIST-TB and the Union's DR-TB Working Group sought to examine the role of centralized decision-making as perceived by its users and to determine how it might be improved. We therefore performed a survey examining MDR/RR-TB decision-making and recommendations within different countries.

A questionnaire with 17 questions was sent by e-mail to approximately 1,500 members of the Tuberculosis Section of the International Union Against Tuberculosis and Lung Disease (The Union) – see Supplementary Data for the questionnaire. Members of The Union were also encouraged to share the survey with non-members. The survey was open from March to June 2023. We excluded responses that answered which country they were responding from but did not complete any subsequent questions. Responses were stratified by country. In addition, we grouped the 38 free-response recommendations by categories based on keywords to gain insight into needs and potential improvements in MDR/RR-TB care support.

We received 175 survey responses from 46 countries, but 70 respondents did not initiate the questionnaire, leaving 105 responses from 46 countries for analysis. Of the 46 countries, 13 (28%) were in the WHO African region, 5 (11%) in the Eastern Mediterranean, 11 (24%) in the European, 6 (13%) in the Americas, 2 (4%) in Southeast Asian and 9 (20%) in the Western Pacific. Of the 46 countries represented in this analysis, 38 (84.4%) had a consilium (or several consilia) that gave advice on MDR/RR-TB treatment regimens and 8 (21.1%) did not. Of the 38 countries with a consilium, 29 (76.3%) had circumstances requiring their advice, whereas 9 (23.7%) did not. Of these 29 countries, 8 were in Africa, 3 in the Eastern Mediterranean, 7 in Europe, 4 in the Americas, 2 in Southeast Asia and 5 in the Western Pacific. There was variability in the circumstances in which consilium advice was required (Figure). Of the consilia in the 29 countries where advice was mandatory, 23 (79%), provided advice within 2 weeks, 4 (14%) within 2–3 weeks and 2 (7%) in four or more weeks. In the open response field, our respondents observed that consilia were often understaffed and lacked adequate financial and social support for patients. They also identified challenges that may have been outside the remit of the consilium that adversely affected patient treatment decisions, such as lack of drug availability and limited access to second-line susceptibility testing. Specifically, in 27% of the countries, respondents identified the lack of access to susceptibility testing for drugs used in MDR/RR-TB treatment as an important barrier. In addition, lack of access to bedaquiline, pretomanid and or delamanid was cited in 12%, and the high cost of treatment to the patient was cited in 7%.

These results show substantial variability in the circumstances where consilium input must be sought (per local TB Program guidelines) and considerable

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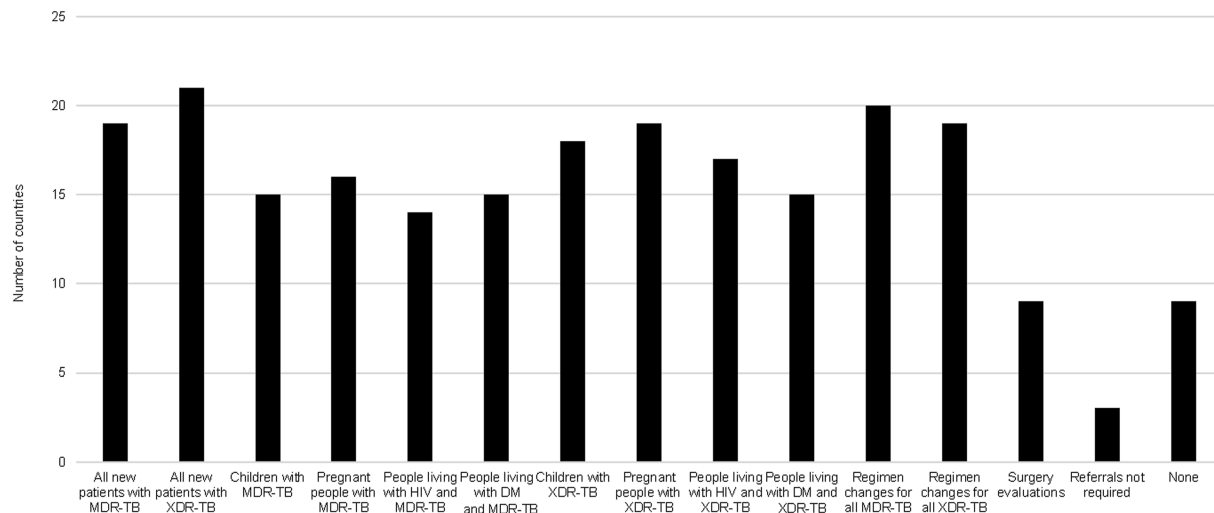
Figure.   Circumstances when advice from consilium must be sought according to national guidelines. MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB; DM = diabetes mellitus.

differences in the time taken to respond with treatment advice. The results of our survey on consilia are similar to challenges reported in the literature: other studies have reported that shortages of expert staff to manage high caseloads can slow response times;[5] and a French consilium (comprised of a small number of experts) also noted average response time of one month.[6,7] In comparison, the European Respiratory Society/WHO consilium (comprised of 54 experts) reported an average response time of 48 hours, and five other countries (four of them in Europe) reported responses in 1–5 days.[7] The French consilium saw an increase in the availability of the new drugs over time, whereas access and availability remain challenging in the countries responding to our survey. In countries with small numbers of patients with MDR/RR-TB and where clinical expertise is limited, consilia can function to ensure quality of care. An alternative is to set up special treatment centers rather than overseeing inexperienced clinicians treating occasional patients. In countries where the burden is substantial, consilia may need to focus on training providers of MDR/RR-TB care so they can function without oversight. Moreover, where there are substantial numbers of children with MDR/RR-TB, there may be a need for specialized support.

These results demonstrate a substantial degree of variability between countries and the need to improve responsiveness for treatment guidance. The availability of Group A second-line drugs and susceptibility testing to these drugs continues to be suboptimal.[8] The functions of consilia may need to be more closely matched to the local conditions to reflect the levels of MDR/RR-TB in the population.

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