university of groningen

Personalised approaches to improve tuberculosis care

Cutting tuberculosis' many coats according to specific cloths

PhD thesis

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To my mother, Lia, and Nena

I am one of yours.

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Mann Tracht, un Gott Lacht

-old Yiddish saying

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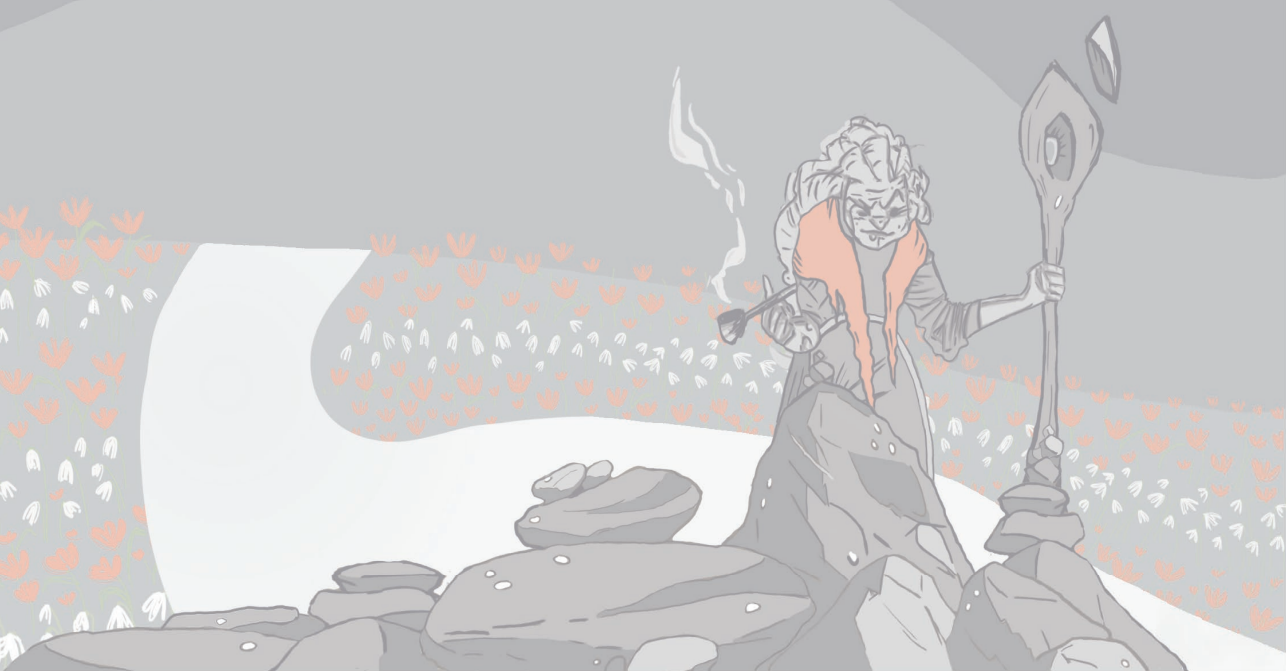
General Introduction and Outline of the Thesis



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General introduction

Tuberculosis

Multidrug resistant tuberculosis

Since bacteria responsible for TB, *Mycobacterium tuberculosis* (MTB), have been exposed to antimicrobial therapy, a new threat has emerged, in the form of resistant tuberculosis. MTB can have or acquire resistance genes, which is the reason even drug susceptible TB (DS-TB) is treated through a standard regimen of four antimicrobial drugs instead of one drug like many other bacterial infections. Resistance in MTB is classified as at least resistance to either rifampin or isoniazid, and includes mono-resistance, multi-drug resistance (MDR-TB), resistant to the two most important first line drugs, rifampin and isoniazid, and extensively-drug resistant TB (XDR-TB), characterised by resistance to multiple second line drugs. Either of these mutations mean that treatment can extend from its standard duration of six months to upwards of two years, significantly increasing life-long morbidity, mortality, and reduced treatment success rates. Thus, treatment success rates vary widely from as high as over 90%, to as low as 27% for XDR-TB with current treatment.

Epidemiology and transmission

One could consider MTB the quintessential opportunistic bacteria. An estimated fourth of the world population is infected with the latent form of MTB, which can survive in humans virtually a lifetime.

Active TB can be acquired, either through progression of the tuberculosis infection (TBI) or shortly after the transmission from an infected host, especially in a myriad of cases where the host immune system is impaired, including malnourishment, alcohol consumption, smoking, co-existing comorbidities, such as HIV, and even periods of high mental stress, found in at-risk groups such as impoverished or migrant populations [1–3]. Concerning the epidemiology of risk groups, malnourishment in its different forms has been formally linked to TB as early as the Second World War, when Cochrane, a physician and prisoner, was noting that TB incidence is higher

amongst the patients not receiving adequate amounts of food [4]. A systematic review has found an inverse relationship between BMI and TB incidence for the BMI range 18.5–30 kg/m2, with a 14% reduction in TB incidence for every unit increase in BMI. Furthermore, as another word for TB is "consumption", it stands to reason that TB will, in turn, exacerbate the caloric deficit and, in turn, malnourishment will increase the chance of having more severe forms of TB, and more treatment side-effects, especially hepatotoxicity [5]. At the same time, several analyses have observed a link between TB incidence and diabetes mellitus, which is associated with an up to threefold risk in developing TB [6]. Alcohol abuse and smoking independently increase the risk of acquiring TB infection (TBI) and TB disease [7], by causing immune susceptibility or depression, directly impairing host defence systems, and being directly linked to other risk factors for TB, including malnourishment, crowding, and poverty. When discussing comorbidities, TB is one of the main threats to patients living with HIV, as they are 16-27 times more likely to develop TB and TB is the main killer of HIV+ patients [8]. Concerning the recent COVID-19 pandemic, a viral infectious disease with airborne transmission also primarily affecting the lungs, it marked the advent of TB incidence indicators worsening, against the trend in past years of steady improvements. TB incidence in 2021 increased with 4.5% and the burden of DR-TB increased 3% between 2020 and 2021 [9].

High mental stress as a comorbidity includes diagnoses as clinical depression and, through immune system impairments, and socio-economic implications, can increase the likelihood of active TB disease [10].

These medical risk factors are associated in higher proportions in certain populations, including the impoverished, migrants, and prison populations.

Once progressed to the active form, in two thirds of cases [11], TB infects the lungs. Pulmonary TB is responsible for transmission of the disease. MTB is expelled from the lungs in aerosols, mostly due to the coughing patients present with. MTB does not survive for a prolonged time on surfaces, however it can live for up to six hours in air.

The rate of transmission of TB varies in reports, from a reproductive number of under

1 in the Netherlands to 4.3 in China in 2012. Transmission depends on several factors, such as host susceptibility, TB patient infectiousness, which, in turn depends on the clinical state of the individual, the procedures involved (for example cough-inducing procedures), and the radiological and microbiological status (cavity present on chest X-ray, positivity on smear microscopy and culture for MTB), environmental factors, and exposure parameters [12]. TBI can be acquired by breathing in air contaminated with MTB, favoured by certain conditions, such as crowding. Both acquiring TBI and progression to TB disease depend on internal host factors, such as immunity status and smoking.

The variability is also applicable to epidemiology, with the highest incidence rates, more than 100 per 100.000 population, being observed in sub-Saharan Africa and India. At the other end of the spectrum, low-incidence (under 10 cases per 100.000) and pre-elimination (under 10 cases per 100000) territories include Western Europe, Australia, Japan, and the US. Indeed, approximately 95% of TB cases occur in low and middle-income countries. A mathematical model estimated that ending extreme poverty resulted in a reduction in global incidence of TB of 33.4%. However, this model doesn't consider many complex aspects regarding TB management, particularly regarding differences between populations' cultures, healthcare systems, local disease contexts, governmental factors, and other societal factors [13]. Thus, local contexts must adapt differently to meet the global WHO goal of 90% reduction of TB incidence by 2035.

Tuberculosis clinical management

TB was one of the "big three" (along with HIV and malaria) diseases on which major efforts were dedicated by the WHO and its partners. These efforts coalesced in ensuring the standardised regimens for DS and DR-TB were implemented worldwide, with no new antibiotics being approved for TB between Rifampicin in the 1960s and Bedaquiline in the 2010s. In 1993, with the realisation of the threat posed by resistant strains of TB, the WHO declared it "a global emergency" and in 2001 the Stop TB Partnership was formed as a special branch dedicated to tackling TB.

TB treatment is cumbersome, even for DS-TB, both time-wise (lasting up to nine

months) and considering side effects, ranging from neuropathy to blindness. DR-TB is treated with multiple second line drugs, and, until 2018, when the global TB guidelines stopped recommending injectables (amikacin, kanamycin), close to 70% of patients would experience hearing loss. Newer regimens including bedaquiline, delamanid, and linezolid, improve once-outcomes of only half of multidrug resistant TB (MDR-TB) patients cured, to almost 70%, however, treatment for these forms of TB still lasts two years, leading to significant morbidity and mortality [14,15]. As an alternative to identifying newer medications, which can take 17 years to be regulatory-approved, repurposing existing medications is investigated in several trials. Shorter treatment regimens propose doubling or tripling dosages of existing TB drugs, a challenge considering the side effects reported at the usual posology.

One of the tools which can aid clinicians in medication choice and dosage is therapeutic drug monitoring (TDM) [16]. TDM is a set of techniques through which TB drugs can be measured in different body fluids, usually in blood to avoid over and under exposure. By taking measurements at different time points post drug administration a pharmacokinetic curve is obtained to ensure hitting the therapeutic window and avoiding inducing resistant strains by underdosing and drug toxicity by overdosing.

TDM implementation has several challenges to overcome before being widely used, chiefly its high costs and the unfamiliarity of the TB clinical world with the technique.

Current challenges in eradicating TB

The question asked time and again is how a curable, old-as-time, infectious disease is so difficult to eradicate?

First of all, MTB is an opportunistic bacterium. It takes advantage of the most vulnerable humans - living under the poverty line [17] and/or in high stress conditions [3], with food insecurity leading to malnourishment [18] or diabetes mellitus, abusing different substances, or with comorbidities such as HIV [19], and with mental health challenges impairing healthcare access, adherence, and medication response [20]. The usual targets for TBI live in resource-poor settings, where the latest diagnosis

and treatment options are not available and human and physical resources are sparse. Furthermore, the 30 countries accounting for almost 90% of yearly TB cases are vastly different, with unique socio-economical, cultural, medical settings, impeding the "one-glove-fits-all" approach [21].

Second of all, TB is a particular bacterium. It's hardy, capable of surviving and resisting even drug-aided immune systems, with its thick, lipid-rich wall making it harder to observe under a microscope and insulating it from classical mono-antimicrobial therapy [22]. Additionally, it befuddles the host immune system, through a host of immune evasion strategies that manipulate the phagosomal environment within host macrophages, modulate host cytokine response, and alter antigen-presenting mechanisms and T-cell responses, eventually leading it to nest in macrophages, form granulomas, and potentially infecting any organ in the body [23]. MTB is not only resilient, but also slow. With a doubling rate of 24 hours (compared to *E. coli* which doubles every 20 minutes), this phenomenon is in direct relation with its long lifespan, and it affects diagnosis and treatment lengths [24].

Therefore, even the basics of clinical care - diagnosis and treatment - are complicated simply by the nature of the bacteria itself. Diagnosis is further hindered by time and the subtle nature of symptoms. Making a timely diagnosis in an infectious disease is critical to curb its spread. TB manifests itself as a cough, lack of appetite, weight loss, and a slight fever, symptoms which are not alarming in themselves unless time has passed, during which the patient can be contagious [25].

The particularities of MTB also affect treatment, which, such as diagnosis, takes time. In turn, the complexity of the treatment implies higher risks of a patient developing side-effects such as drug toxicity or resistant bacteria or becoming lost to follow-up.

For these reasons, any strategy to eradicate TB should be made of a blend of medical interventions, combined with governmental, societal, and cultural interventions.

This type of complex thinking goes against the straightforward nature of medicine; however, more and more researchers, clinicians, and policy makers are changing their optics on this matter, a shift reflected in the WHO End TB Strategy.

The three pillars of the End TB Strategy which guide the eradication strategy for TB are "integrated, patient-centred TB care and prevention", "bold policies and supportive systems", and "intensified research and innovation" [26].

This PhD thesis approaches each pillar by trying to identify cost-effective, practical solutions which build upon existing research, use already available technologies, particularly digital health solutions, and can be implemented in a timely manner to obtain real-life results.

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Outline of the thesis

The thesis is organised on the three pillars of the End TB Strategy: integrated, patient-centred TB care and prevention - chapters 2-4; bold policies and supportive systems - chapters 5-6; intensified research and innovation - chapters 7-8. Chapter 9 focuses on future directions.

Integrated, patient-centred TB care and prevention

Chapter 2 aims to investigate one aspect of the first pillar of the End TB Strategy, integrated, patient-centred TB care, through patient-reported outcome measures (PROMs). The premise is that the burden of TB can be found not only in the treatment success indicator, but also by considering morbidity, in turn dependent on several under-investigated factors, such as quality of life. Healthcare-related quality of life has relatively recently become an integral part of healthcare systems analysis by proposing additional methods to quantify the short- and long-term impact of a disease on a patient's daily life, clinical and mental health, work capacity, and income. Several papers, including a systematic review indicate that the quality of life of TB patients could be impacted not only during treatment, but even after acquiring the status of "cured" [27,28]. This, in turn, could pose significant economic and medical challenges, especially in already burdened medical systems. Chapter 2 aims to understand the short term and long-term impact of DS- and DR-TB by investigating several aspects of potential TB impact, including the quality of life, work impairment, and disability during and after treatment by using standardised PROMs.

Chapter 3 aims to investigate therapeutic drug monitoring (TDM). TDM enables the clinician to have information about the actual TB drug concentrations mainly in plasma and make informed decisions in collaboration with the pharmacist about drug dosages which avoid underdosing or overdosing. Traditionally, antituberculosis drugs are given in mg per kg body weight, however, this approach has been proven to increase the risk of underdosing, which would, in turn, promote the emergence of drug-resistance, or overdosing, which increases the risks of treatment side effects. TDM could be especially useful for certain patient categories [29], including patients

with HIV+, diabetes mellitus, cirrhosis, gastro-intestinal impairment, or with slow-responding or resistant TB, and could potentially save costs by avoiding prolonging treatment, resistant forms, and drug toxicity. However, implementing the technique has been relatively costly until recently, when recent advancements in technology have offered potential cost-effective alternatives to TDM.

Chapter 3 aims to evaluate TDM's future potential in settings with higher TB burden, and resource-scarcity, where it has never been implemented before.

The population chosen for this study was from Romania and Ukraine, two countries relevant for European TB policies. Romania has the highest TB burden of all EU countries, accounting for a fourth of all EU TB cases [30]. Its immediate neighbour to the north, Ukraine, is a country in the top 30 WHO high TB burden countries, with 32 000 TB cases in 2020. Genetically, TB profiles are similar between countries [31], with the main difference being in the high burden of resistant TB (DR-TB) cases in Ukraine: 32.6% of all TB cases are DR-TB (incidence of 4117 cases in 2020) versus 5.8% in Romania (incidence of 430 in 2019) [32].

DS-TB success rates are comparable between countries, with 79.8% and 75.2%, for Romania and Ukraine respectively, compared to 76.5% of the WHO European region. Clinical management policies are similar, with both national TB guidelines recommending hospitalising most patients until culture negativity.

Chapter 3 will analyse which risk factors are associated with worse treatment outcomes in three clinical centres in the proposed countries.

Chapter 4, complementary to chapter 3, aims to describe the patient burden in three TB centres in Romania and Ukraine with a TDM indication following the current guidelines in order to estimate the opportunity of implementing TDM.

Bold policies and supportive systems

In the time before the industrial revolution, large-scale changes generally followed the top-down approach. A group of better informed and materially oriented elites affected most of the population. The willingness to challenge conventional wisdom

was rarely a common trait in past societies, but that all began to change first in the Era of Enlightenment and then, more profoundly and long lasting, by the industrial revolution. With the growing importance of scientific thought and, at the same time, with a wide shift toward democracy, the top-down attitude began to blend with a bottom-up approach. Modern policy making nowadays ideally blends these two methods of enacting change and considers multiple groups of persons in decision making. Policy should be developed by involving the people most affected by it (target population), the experts who will implement it (middle management), and the policymakers (stakeholders).

Chapter 5 will continue exploring the potential use of TDM, with a wider, global outlook, and with the final goal of deriving global consensus on the challenges and opportunities of this technique, and to potentially contribute to pillar 2 of the End TB Strategy, bold policies and supportive systems. The proposed research aims to establish the current global baseline for TDM use, identify key challenges in implementing it and inquire about future directions for TDM use in TB clinical care. An electronic questionnaire will be sent to TB clinical staff, pharmacists, laboratory staff, and stakeholders to collect data on different aspects of TDM usage in clinical care.

Chapter 6 will continue research within the second pillar of the End Tb Strategy, but with a different focus and scope. TBI can progress to active TB in different circumstances, with one of the at-risk populations for TBI progression to active TB, being recently arrived migrants.

The International Organisation for Migrants reports that overall, the estimated number of people living in a country other than their countries of birth in 2020 (281 million) is over three times the estimated number in 1970 [33]. Europe is a highly attractive space for both external and internal migrants as it facilitates internal migration by reducing the legislative red tape between member countries, and it offers safety, labour, and quality of life opportunities motivating migrants to relocate. 37.5 million people were born outside the EU (8.4% of all EU inhabitants) and 18.5 million people born in a different EU Member State from the one where they were resident (3.4%

of all EU inhabitants). Migrants have increased risk for TB through the risk of high exposure to TB, HIV, malnutrition, substance use, delayed diagnosis, low educational status, poor health-seeking behaviour, culture, stigma, and marginalisation. At the same time, there is not one European policy for TB in place, with countries deciding at a regional or national level who and how to screen for TB disease and latent TB infection (LTBI), how to fund TB programmes, and how to manage TB in their spaces.

Curbing TBI progression to active TB is one of the key areas low-incidence TB countries must achieve in order to eradicate TB. This is especially important for low-incidence territories, such as European countries, who receive migrants from high-incidence countries. We plan to distribute a survey concerning TBI programmes addressed to migrants to national level TB experts of the 32 countries within the EU/EEA + UK & Switzerland in order to understand views on policy and practice.

Intensified research and innovation

Chapter 7 and 8 following pillar 3 of the End TB Strategy (World Health Organization), on intensified research and innovation, focus on digital health, otherwise named eHealth or telemedicine, which implies the digital delivery of health services. Digital health is an appealing innovative subject to introduce to TB care for several reasons. First, the world has seen an explosion of available software and the hardware and network capabilities are constantly expanding, with approximately 60% of the world population having access to the Internet, including potentially TB patients. Especially for the patients who do not live adjacent to a TB medical facility or are mobile (e.g. migrants) access to digital communication platforms and follow-up could be useful. Secondly, digital health applications tend to be cost-effective, by saving transportation costs for patients and medical staff and reducing consultation times. Digital health can streamline communication between different medical specialties involved in TB diagnosis and treatment, ensure remote TB expertise in areas without a TB centre, and facilitate directly following treatment throughout, whilst maintaining relatively low start-up and maintenance costs.

In recent years, various types of digital health interventions have been implemented in TB clinical care already, from remote diagnosis aids to medication reminders, to

expert consultation and patient support.

In **Chapter 7** we plan to systematically evaluate the available research on implementing eHealth solutions in TB clinical care. This systematic review will use the "Recommendations on Digital Interventions for Health System Strengthening" WHO guideline to present outcomes. This framework proposes five domains to analyse digital health: effectiveness, acceptability, feasibility, resource use, and gender, rights, and equality.

In **Chapter 8** we aim to complete the image of eHealth implementation in TB clinical care by seeking to understand global perceptions on future eHealth use in TB, both from a patients and TB medical staff perspectives. Different countries have different socio-economic, cultural, and medical backgrounds, and thus have varied needs, advantages, and challenges, which this study proposes to explore. The goal is to complete the image of eHealth implementation in TB care which began in chapter two by having focus group interviews both with medical staff and TB patients, who comprise the potential user base of any TB-oriented app. Focus group interviews are particularly useful in this scenario, because they allow participants to have a fruitful conversation and use each other's experience to generate new ideas.

Chapter 9 provides a Discussion with Future Perspectives, and **Chapter 10** summarises the findings of this Thesis.

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N-ar fi rău să fie bine și în țara asta.

- Ion Creangă

2

Romanian Tuberculosis Patient Reported Outcome Measures: Tuberculosis has a Long Lasting Impact on Multiple Aspects of Participants' Wellbeing

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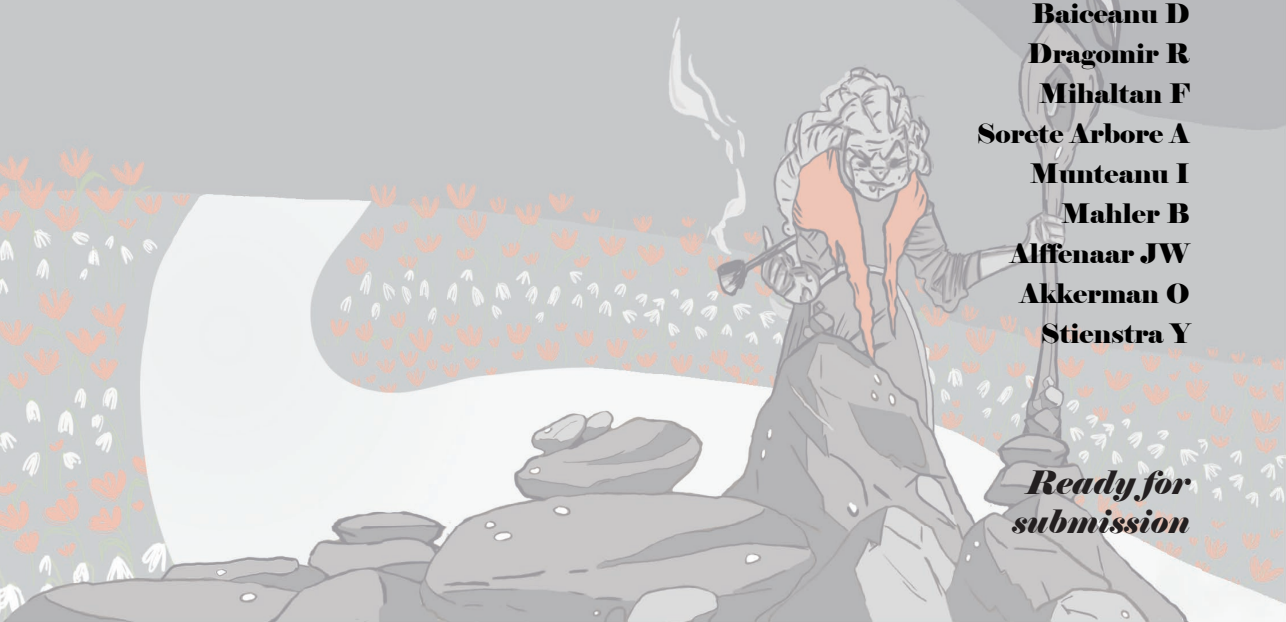

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2 Romanian Tuberculosis Patient Reported Outcome Measures: Tuberculosis has a Long Lasting Impact on Multiple Aspects of Participants' Well-being

Abstract

Background

Tuberculosis (TB) is responsible for significant morbidity and mortality. This study used four Patient Reported Outcome Measures (PROMS) to assess the status of persons affected by drug susceptible and drug resistant TB during their TB treatment or after treatment completion, in Romania, the highest TB burden country in the EU.

Methods

People affected by tuberculosis in two different regions in Romania were included during and after treatment, following a cross sectional design. PROMs used were Short Form-36 (SF-36), EuroQol Five Dimensions Five Levels (EQ-5D-5L), Work Productivity and Activity Impairment (WPAI), and the app-based audiometry screening tool uHear®. Descriptive statistics and relevant statistical tests were used to compare between groups and with the general Romanian population.

Results

Both drug susceptible and drug resistant TB patients experienced limitations due to TB, with drug resistant patients experiencing statistically significantly more pain and hearing loss. PROMs showed some improvement in the after-treatment group, however, compared to the general Romanian population for which data was available, all groups scored lower on all outcome measures.

Conclusion

PROMs offer the possibility of obtaining a more comprehensive view of patients' status by involving them directly in the medical process. This information could guide a rehabilitation strategy.

Introduction

Patients' perspectives have become increasingly recognised as important to medical management, as they can offer information about the burden of a disease beyond indicators such as incidence and mortality. The expanding use of patient-reported outcome measures (PROMs) has been a part of this shift. Initially developed for clinical trials, they have now been embedded in routine clinical settings for several domains, especially mental health [1]. PROMs consist of surveys collecting data regarding general wellbeing, symptoms, health-related quality of life, and functional status and are one of the possible patient follow-up tools.

Tuberculosis (TB), a primarily respiratory infectious disease caused by Mycobacterium tuberculosis, was not only responsible for 1.6 million deaths in 2021, but also has a significant impact on patients' lives [2]. The effects of the bacteria itself, combined with the complex, lengthy treatment, and post-treatment sequelae all contribute to a decrease in TB patients' quality of life, including effects on physical and emotional health, disability, and patients' financial wellbeing [3-5]. A recent systematic review found that after diagnosis of TB, nearly a quarter of patients had or developed mental health disorders. This percentage was higher than the percentage of patients reporting well-known disease effects such as respiratory impairment or treatment side effects, such as hearing loss [3]. On the economic plane, a study from India reported that nearly one third of patients on TB treatment had incurred catastrophic costs [4] and a study from Malawi showed that more TB patients were living in poverty one year after TB treatment completion [5]. Furthermore, several studies showed that patients with drug resistant TB (DR-TB) scored lower on quality-of-life indicators than those with DS-TB [6,7]. Treatment for this increasingly incident form of TB, can last up to two years and is more complex than drug susceptible TB (DS-TB) treatment.

Within the European Union/European Economic Area (EU/EEA), considered a low-incidence TB region, Romania accounts for 23.4% of total EU cases [8]. The 2019 European Commission report on Romania concluded that despite certain economic growth, inequality is increasing, and poverty remains high, with deepening regional disparities being amongst the highest in the EU. In this context, the healthcare

system has important challenges in offering medical accessibility and patient support [9]. PROMs are the outcomes of both the diseases and these challenges combined and can inform health care workers and policy makers on interventions potentially reducing disease impact.

Therefore, we studied differences in patient reported outcomes between drug susceptible and drug resistant TB patients in Romania. The secondary aim was to observe differences in PROMs between patients during TB treatment and patients after TB treatment completion.

Methods

Study participants

This is an observational, cross-sectional, multicentric study. Study participants were chosen from two main regions of Romania: the north-eastern region and the capital region, in south-Romania. The economic disparity between these two regions is the largest within Romania, 3.6 times the GDP. The study took place in TB centres and in field dispensaries, located in villages surrounding urban TB centres. Study sites were the Bisericani TB Expertise Centre (Piatra Neamt, Romania), the Iasi Regional Lung Hospital and TB Ambulatory (Iasi, Romania), and the Marius Nasta TB Institute and TB Ambulatory (Bucharest, Romania). Eligible participants were adults (>=18 years of age), capable and willing to provide consent, diagnosed with pulmonary TB, either on treatment or after with a maximum of five years post-treatment. Treatment end was defined as the last medication intake, as noted in the clinical chart. All eligible patients were approached either in person or via telephone (a maximum of two times) and invited to participate in the study, either in the hospital or in the rural ambulatory clinics.

Ethics

After being informed by an investigator about the study and having had time to think and ask questions, willing participants signed the informed consent form in their native language. The study was approved by each medical centre (METC 21064/

Iasi Regional Lung Hospital and TB Ambulatory (Iasi, Romania), 210/Bisericani TB Expertise Centre (Piatra Neamt, Romania), 10593/Marius Nasta TB Institute and TB Ambulatory (Bucharest, Romania), METC 2018 00981/University Medical Centrum Groningen (Groningen, the Netherlands).

Data collection

Patient data collection was performed using standardised forms. Data collection included general demographics, clinical data, two questionnaires regarding quality of life, a questionnaire regarding work and general financial status, and a self-administered hearing test.

The SF-36, consisting of a set of 36 plain-language scale questions, is one of the most widely used questionnaires to measure quality of life. Interpretation is based on grouping answers in eight domains: physical functioning, energy/fatigue, emotional well-being, physical and emotional limitations to work and daily life, bodily pain, energy/fatigue, and general health. The instrument has been used to measure the quality of life of patient populations with a specific disease, including tuberculosis [10,11], and has been validated and used previously to estimate quality of life of the general Romanian population [12]. The EQ-5D-5L, assesses quality of life through levels of impairment on different dimensions: mobility, self-care, daily activity, pain/discomfort, anxiety/depression and grouping results in health states (the best possible health state being 11111 and worse 55555). Additionally, this questionnaire contains a visual analogue scale for self-rated health. It has been used for tuberculosis outcomes [13] and it has been validated for the Romanian population [14,15].

The WPAI-GH is the most frequent tool used in health-related economic evaluations [16], and it has been used for several respiratory diseases [17]. It assesses work productivity and the impact of health on work and daily life with a recall period of one week [10] by asking questions regarding absenteeism (work lost) and the impact of health on work and daily life productivity. The WPAI referred to patients of employment age (under 65 for male and 61 for female for the Romanian population). Instrument scoring was performed using the official user manuals.

Audiometry was performed using the uHear app v.2.0.2, a validated software screening tool for loss of hearing [18]. Hardware equipment was maintained constant for all testing centres and it consisted in Marshall over ear headphones and an Iphone 4 SE. The app shows results for left and right ear, for 0.5kHz, 1KHz, 2kHz, 4kHz, 6kHz with 1 being "normal" and 5 being "profound hearing loss". Additionally, patients were asked pre-test if they perceived any subjective hearing loss.

Self-administered measures took 15-20 minutes to complete and the hearing test approximately 10 minutes.

For laboratory values, 48 IU/L for alanine transaminase (ALAT), 42 IU/L for aspartate transaminase (ASAT), and 1.35 mg/dL for men and 1.04 mg/dL for women for creatinine were considered normal upper limits.

Data analysis

Sample size was calculated based on the assumption that drug-susceptible (DS-TB) decreases overall quality of life by 10% measured by SF-36 results and drug-resistant (DR-TB) by 30%, with an enrolment ratio of 3:1, a power of 80% and a margin of error of 5%.

Comparisons of groups were performed through Chi square test, independent sample T tests or Mann-Whitney tests, as appropriate. Data analysis was performed using SPSS version 17.

Tuberculosis drug sensitivity data obtained either through classical antibiogram or Xpert MTB/RIF (GeneXpert, Cepheid) was used to classify patients as either DS-TB or DR-TB. The latter category was defined as any first line drug resistance or intolerance or a combination thereof and it included mono resistance to rifampicin or isoniazid, multi-drug resistance (MDR-TB), and (pre) extensive drug resistant TB (XDR-TB).

For the secondary research question, participants were grouped in during treatment (i.e. before the last medication intake) and after treatment (i.e. after the last medication intake) categories.

General participant characteristics are reported as such. Official registers were used for the income category and for cut-off points for the number of rooms per person [19].

SF-36 domain scores were obtained, with higher scores representing better outcomes (e.g. a participant experiences less pain at a score of 80 than at a score of 60). Median scores for each domain were compared between groups. Domain median and mean scores were further compared with their counterparts for the general Romanian population.

EQ-5D-5L results were dichotomised as participants with "no problems" and "problems" on each of the five dimensions and results were compared. The visual analogue scale results were compared as medians. Mean visual analogue scale results were used in the comparison with the general Romanian population as data on medians are not available.

The WPAI questionnaire was analysed for participants of employment age (under 65 for men and 63 for women). Results to question 1, referring to employment status, were compared as percentages of employed participants. Questions 2-4 refer to the amount of work hours lost due to health or other issues, with a recall period of one week. Results are reported in percentage of time lost from a maximum of 40-hour work week, the standard in Romania. Questions 5 and 6 are scales from 1 to 10 indicating the impact of healthcare status on work and other activities, respectively. Medians of results of questions 2-6 were compared.

Analysis of audiometry app results used the uHear manual interpretation [19,20], of averaging results for the 0.5kHz, 1KHz, 2kHz, 4kHz and considering anything over 40dB ("moderate loss") as abnormal. Hearing grades are presented as medians and abnormal hearing and subjective perception of abnormal hearing as percentages.

For categorical values, Chi-squared and or Fisher's exact test were used and for continuous values T-test and Mann-Whitney U test were used to compare groups, as appropriate, with significance set at $p<0.05$. Software used was IBM SPSS® v.27.

Results

Participant characteristics

A total of 201 DS-TB and 80 DR-TB were enrolled (Table 1), out of which 146 participants were receiving TB treatment. The median age was 45 years and 71% of the participants were male. Considering living conditions, including poverty indicators, the majority of patients lived in rural areas, and more than a third had their bathroom outdoors. The mean number of rooms per person in our study, 1.3 rooms per person was lower than the EU average of 1.6, but comparable with the Romanian mean of 1.1 [21]. A minority of patients presented with comorbidities: 3 (1%) with HIV, 12 (4%) with diabetes mellitus type 2, and 5 (2%) with cancer.

TB was diagnosed following the standard diagnostic routine. Almost all, 269 (96%), had a chest X-ray indicating TB, 208 (74%) had a positive sputum smear result, 222 (81%) had a positive culture result, with the rest of the patients being treated as TB based on clinical context. A majority, 222 (79%) were newly diagnosed with TB (177/201 (88%) of DS-TB and 45/80 (56%) of DR-TB), with the rest being retreatment cases.

Among the 80 patients with resistant TB, 4 (5%) had rifampicin mono-resistant TB, 5 (6%) had isoniazid mono-resistant TB, 50 (63%) had multidrug resistant TB, and 21 (26%) had extensively drug resistant TB (2019 definition). An injectable drug (amikacin or kanamycin) was used for 42 (15%) patients. Forty-three (15%) patients had elevated liver enzymes (either ALAT, ASAT, or both) and 8 (3%) had an elevated creatinine value in the course of their treatment.

Table 1: Participant characteristics

	DS-TB N=201	DR-TB N=80	Total N=281
Patient characteristics			
Male	139 (69%)	61 (76%)	199 (71%)
Age (years, median (IQR))	44 (31-55)	49 (40-57)	45 (33-57)
BMI (kg/m2, median IQR))	21 (20-24)	20 (18-24)	21 (19-24)
TB treatment phase			
During TB treatment	100 (50%)	46 (58%)	146
After TB treatment	101 (50%)	34 (42%)	135
Living conditions			
Urban	90 (45%)	36 (45%)	126 (45%)
Rural	109 (54%)	44 (55%)	153 (55%)
Homeless	2 (1%)	0	2 (.7%)
Outdoor Bathroom	83 (41%)	29 (35%)	112 (40%)
Education			
No education	2 (1%)	1 (1.3%)	3 (1%)
Under bachelor level	129 (64%)	57 (71%)	186 (66%)
Bachelor and above	70 (35%)	22 (28%)	92 (33%)
Lifestyle			
Current smokers	86 (43%)	41 (51%)	127 (45%)
Moderate or more alcohol intake*	28 (14%)	6 (8%)	34 (12%)

*defined as more than more than 8 drinks per week for women and 15 for men

SF-36

Seven of the eight SF-36 domains scores had no statistically significant differences between DS-TB and DR-TB groups. The only domain where groups' scores were statistically different was the “bodily pain” (p=0.029, Mann-Whitney U test, table 3). Compared to data available for the general Romanian population, DR-TB and during treatment groups scored lower on all domains, with the largest differences being noted in the “role of limitations” domains, both for physical health and emotional problems. These two domains included questions such as “during the past four weeks, have you had difficulty performing work or daily activities” and “during the

past four weeks, have you accomplished less than you would have liked". DS-TB and after treatment groups scored either similarly or slightly better median scores for several domains, including "emotional well-being" and "social functioning". For the "general health" domain, all groups scored lower medians and means (table 2, figure 1).

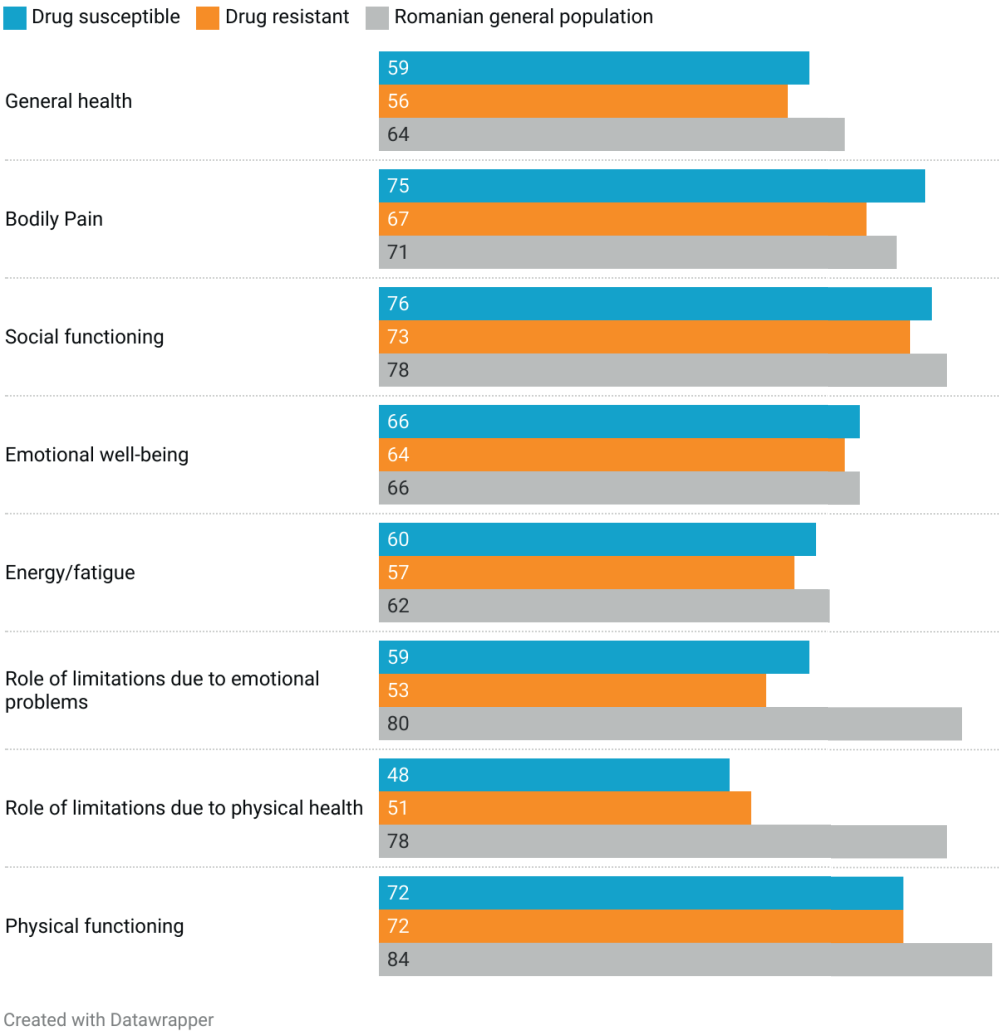

Figure 1: Mean of SF-36 domains for drug susceptible tuberculosis patients, drug resistant tuberculosis patients, and the general Romanian population. Higher scores represent better outcomes.

Domains with statistically significant differences depending on treatment stage were "role of limitations due to physical health" (25 (0-100) for patients during treatment and 75 (0-100) after treatment, p<.001), "role of limitations due to emotional problems" (33 (-100) for patients during treatment and 100 (0-100) after treatment, p=.001), and "social functioning" (75 (50-100) in patients during treatment and 88 (63-88) after treatment, p=.001).

Table 2: SF-36 domains scores comparisons between drug susceptible and drug-resistant TB patients and between patients during and after treatment completion. Higher scores represent better outcomes.

	DS-TB N=201	DR-TB N=80	During N=146	After N=135	Ro Pop1
Domain	**Median (IQR)**				
Physical functioning	85 (55-95)	75 (55-93)	75 (49-90)	90 (65-100)	95
Role of limitations due to physical health	50 (0-100)	50 (0-100)	25 (0-100)#	75 (0-100)#	100
Role of limitations due to emotional problems	100 (0-100)	67 (0-100)	33 (0-100)#	100 (0-100)#	100
Energy/fatigue	60 (40-80)	60 (40-70)	55 (40-76)	60 (45-80)	65
Emotional well-being	72 (52-80)	68 (52-76)	68 (52-80)	72 (56-80)	68
Social functioning	88 (62-100)	75 (50-100)	75 (50-100)#	88 (63-88)#	88
Bodily Pain	80 (56-100)*	68 (45-100)*	78 (45-100)	88 (55-88)	78
General health	60 (45-75)	55 (45-70)	60 (45-70)	60 (45-75)	65

*, - statistically significant differences between DS-TB and DR-TB;
#, - statistically significant differences between during and after treatment.
1 - General Romanian Population

EQ-5D-5L

There were several domains with differences in proportions of patients experiencing problems, however, the "pain" domain was the only one with statistically significant differences between DS-TB and DR-TB: 57% DS-TB reported not having any pain vs. 39% DR-TB, p=0.007 (Chi-Square test, table 3). Furthermore, the only statistically significant difference between patients during and after treatment is in the "mobility" domain.

Concerning the overall visual analogue scale, TB patients scored a mean of 74/100 (SD 22) and a median of 80 (60-90), with 35 (13%) reporting full health (100/100). The general Romanian population has a mean of 82.5 (SD 15.5) on the same scale and 52% reported full health.

Table 3: EQ-5D-5L domains comparisons between drug susceptible and drug-resistant TB patients and between patients during and after treatment completion

	DS-TB N=201	DR-TB N-80	During N=146	After N=135
Domain	**Number of participants experiencing problems, n (%)**			
Mobility	142 (71%)	49 (61%)	90 (62%)#	101 (75%)#
Self-care	180 (90%)	72 (90%)	132 (90%)	120 (89%)
Daily activity	147 (73%)	50 (63%)	101 (70%)	96 (71%)
Pain	114 (57%)*	31 (39%)*	75 (51%)	70 (52%)
Anxiety	110 (55%)	35 (44%)	70 (48%)	76 (56%)
EQ VAS (means, SD)	74 (SD 22)*	73 (SD 21)*	69 (SD 24)#	80 (SD 18)#

*, - statistically significant differences between DS-TB and DR-TB;
#, - statistically significant differences between during and after treatment.

Employment and WPAI

Of the total of 281 participants, 32 (11%) were of retirement age (65 for men and 63 for women) and were not included in the analysis. Approximately half of all patients earn less than the minimum wage in Romania. There were no statistically significant differences in the WPAI questionnaire between DS-TB and DR-TB, but there were differences between patients during and after treatment, with the latter category scoring better on all questions regarding work and daily activities. Patients during treatment lost all work hours as they were either hospitalised or on medical leave. For the same question, after treatment, patients reported missing no work hours (work hours missed during treatment 100 (0-100) vs. after treatment 0 (0-0), p<.001). At the same time, the after treatment group scored statistically significantly better on the domains pertaining to the impairment of TB on their work (impairment while working during treatment 50 (25-80) vs. after treatment 10 (0-45) p<.001, overall work impairment during treatment 100 (100-100) vs. after treatment 10 (0-80) p<.001) and

daily activities (during treatment 50 (10-70) vs. after treatment 20 (0-70),p=.003), but they still reported certain degrees of impairment (table 4).

Table 4: Employment and WPAI domains comparisons between drug susceptible and drug-resistant TB patients and between patients during and after treatment completion

	DS-TB N=179	DR-TB N=70	During N=129	After N=120
Item	**Number of participants, n (%)**			
Employed	82 (46%)	28 (40%)	53 (41%)	67 (48%)
Earning less than minimum wage	89 (50%)	38 (54%)	70 (54%)	57 (48%)
Less income after TB diagnosis	64 (36%)	21 (30%)	64 (44%)	57 (42%)
Domain	Median (IQR)			
Percent work hours missed due to health	100 (0-100)	0 (0-100)	100 (100-100)*	0 (0-0)*
Percent impairment while working due to health	50 (0-80)	20 (5-50)	50 (25-80)*	10 (0-45)*
Percent overall work impairment due to health	100 (0-100)	60 (10-100)	100 (100-100)*	10 (0-80)*
Percent daily activity impairment due to health	30 0-80)	25 (10-70)	50 (10-70)*	20 (0-70)*
*, ■ - statistically significant differences between during and after treatment.				

uHear Audiometry App results

Nine patients (7 DS-TB and 2 DR-TB) did not understand how to perform this test and were excluded from the analysis.

Hearing loss was statistically significantly worse for DR-TB across multiple hearing loss metrics, including patients' subjective perception, hearing test results through uHear, and if taking in account only high frequency hearing loss (table 5).

Subgroup analysis on different treatment schemes was performed. A total of 82 of 281 patients (28%) were on second line medication, out of which 41 (50%) were on injectable therapy (amikacin or kanamycin). Of these, 26 (63%) had a result indicating

on the uHear test compared to 83 (36%) of the participants without injectables in their treatment scheme (p=.002). Hearing loss for high frequencies (over 1Hz) was recorded by 29 (71%) of the group on injectable therapy versus 106 (46%) in the non-injectables group (p=.003, Chi Square test).

There were statistically significant differences in audiometry results between patients during and after treatment, with better scores noted in all parameters in the after-treatment group.

Table 5- Audiometry with uHear test results comparisons between drug susceptible and drug-resistant TB patients and between patients during and after treatment completion

	DS-TB N=194	DR-TB N=78	During N=129	After N=120
Item	**Number of participants, n (%)**			
Abnormal hearing right or left ear	69 (36%)*	42 (54%)*	65 (47%)#	42 (32%)#
Severe or profound hearing loss right or left (>80dB)	80 (41%)*	49 (63%)*	79 (60%)#	46 (35%)#
High frequency hearing loss right or left ear (for frequencies over 1 Hz)	93 (43%)*	52 (67%)*	80 (57%)#	56 (42%)#
	Median (IQR)			
Hearing grades right ear	2.4 (1-6)* (mild)	3.2 (1-6)* (moderate)	3 (2.2-3.8)# (moderate)	2.4 (2-3.3)# (mild)
Hearing grades left ear	2.6 (1-6)* (mild)	3 (1-5.4)* (moderate)	3 (2.2-3.8)# (moderate)	2.4 (2-3.3)# (mild)

*, - statistically significant differences between DS-TB and DR-TB;
#, - statistically significant differences between during and after treatment.

Discussion

This cross-sectional study investigated Romanian TB patients' reported outcome measures concerning general health, physical, social, and emotional well-being, and the impact the disease has had on their work and health through different instruments: three standardised questionnaires and app-based audiometry. The main statistically significant differences between DS-TB and DR-TB participants were in domains

pertaining to bodily pain and in the audiometry. Patients in the after-treatment group scored better on a majority of outcome measures, however, scored lower than the general Romanian population on all outcomes with comparisons available.

Our study population is aligned with other research indicating that socio-economic indicators and smoking are risk factors for TB. [23,24]. Compared with general Romanian population, more study participants lived in rural areas (55% vs. 46%) [25], more earned less than minimum wage (51% vs. 13%), and there was a higher proportion of active smokers (55% vs. 37% Romanian general population). Unemployment rates in our study population were almost ten times as high as the reported national unemployment rate for the same year (44% in our study vs. 5% Romania in 2019).

This research included two quality of life PROMs, the SF-36 and the EQ-5D-5L. Concerning both PROMs, there were no statistically significant differences between DS-TB and DR-TB patients except in the "pain" domains of both instruments. Joint pain is a reported side effect of second line TB drugs, including bedaquiline [26], however, other studies using the SF-36 found that pain was less significant in the MDR-TB group [27] than in the DS-TB group. At the same time, patients included in our study reported better quality of life outcomes than patients in other studies, especially concerning DR-TB [7,28-30]. As in our study, other research showed improvement in quality of life after the completion of TB treatment, especially visible on the EQ-5D-5L general health visual analogue scale. It is worth mentioning that other studies included patients only after a maximum one year post-treatment completion and our inclusion criteria expanded this time frame to up to five years. The domains with the lowest scores (i.e. the largest impact on participants' well-being) related to the limiting nature of the disease and emotional well-being. Concerning the latter, patients in the during and after treatment groups scored very similarly, suggesting there is little mental health improvement post-treatment. This has been indicated by other research, with experts calling for better mental support throughout and after TB [31].

The sample Romanian population which was used to compare results had a comparable age (for SF-36 mean age of 40 years, for EQ-5D-5L mean age of 48), but included more

female participants (for SF-36 and EQ-5D-5L there were 66% female participants). Compared to data available for the general Romanian population, TB patients scored lower especially in the domains pertaining to limitations due to physical health and emotional problems. This result matches other studies comparing quality of life with either control groups without TB or general populations [31].

Concerning employment, less than half of patients were employed, even after TB treatment completion. Another study performed in Malawi shows that employment was lowest at TB treatment completion, with 47% not being employed [5]. Furthermore, patients during treatment lost most of their working hours. For the patients in the intensive phase, this could be explained by the hospitalisation time. The Romanian TB guideline recommends hospitalisation for all pulmonary TB cases unless there is the possibility of direct observed therapy in isolation conditions [33]. A recent Global Tuberculosis Network review notes that globally hospitalisation times range between 20 and 60 days [34] for DS-TB and 50-180 days for DR-TB. However, 40% of S-TB and 25% of DR-TB patients were included after the intensive phases, which could indicate that TB impairs work productivity beyond hospitalisation time, during the course of the illness. After treatment, results indicate that the participants who are employed lose less time off work because of the disease, however, unemployment rates were high in all study groups, including the after-treatment group. Audiometry through the uHear app was a convenient method for patients to self-evaluate their hearing, with only a minority of participants not understanding the procedure. uHear app results confirm previous known facts regarding second-line treatment ototoxicity [35,36], with 30 out of the 41 (71%) patients who had aminoglycosides in their treatment scheme experiencing high frequency hearing loss. Whilst international guidelines from 2018 have removed aminoglycosides from the DR-TB treatment schemes and they are being phased out, it is notable that 36% of participants without an injectable drug also experience hearing loss [37] Hearing loss is the third cause of years lived with disability, after back pain and migraine. Hearing, therefore, may require extra attention in programmes supporting people affected by tuberculosis after treatment.

Considering TB follow-up, this study included several follow-up measures not included in current follow-up recommendations, but which would be useful for

appraising patient status. International guidelines recommend follow-up post-treatment, however, the Romanian strategy does not include such a chapter [38,39]. Clinicians demonstrated reluctance to implement PROMs in everyday practice as they feared, among other aspects, that it would add to the workload [40]. However, with the advent of the COVID-19 pandemic, and the high penetration of mobile technologies, digital follow-up could be a feasible, cost-effective future direction to pursue [41,42].

Strengths and limitations

This study is the first to investigate PROMs in the Romanian population, the highest TB burden country in the EU, accounting for a fourth of all TB cases in this region. Recruitment strategies aimed to ensure recruitment of a representative population sample of Romanian TB patients. Characteristics of the study population align with TB indicators for 2020 [7, 22]. Furthermore, this study consisted of several PROMs, offering a multi-dimensional view of patients' well-being and functional status. Employment and income may be under-reported in our results as participants can be reluctant to report untaxed income. Inclusion criteria were pulmonary TB as extrapulmonary TB potential participant pool would have been too small. We did not follow people affected by tuberculosis longitudinally, which would have allowed us to look for factors influencing well-being over the course of treatment.

Conclusion

Both DS- and DR-TB patients experience limitations due to TB, with PROMs showing partial recovery in the people affected by tuberculosis even after finishing treatment. The main differences between participants affected by DS-TB and DR-TB were in the measures studying pain and hearing loss. Compared to the general Romanian population, all groups scored lower on all domains for which data was available. PROMs offer the possibility of obtaining a more comprehensive view of patients' status, by involving them directly in the medical process. The possibility of follow-up through PROMs might be appealing to both clinicians and patients in high burden settings as part of digital health strategies.

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Chercher ce qui est vrai n'est pas ce qui est souhaitable.
-Albert Camus

2023

3

Treatment Outcomes of Drug Susceptible Tuberculosis Patients in Romania and Ukraine

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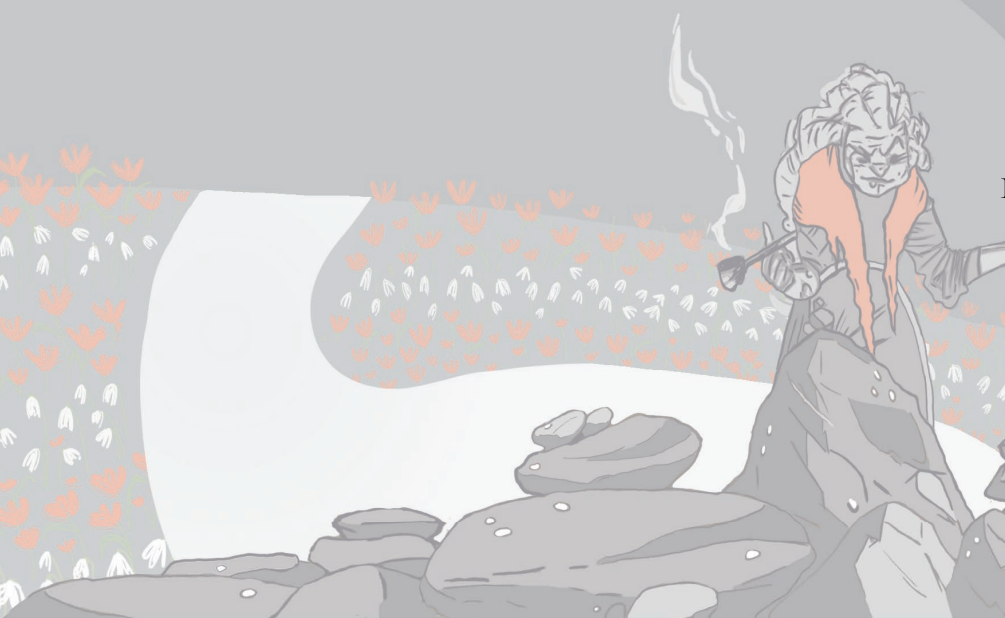

Submitted

Factors influencing drug susceptible tuberculosis outcomes in Romania and Ukraine

Abstract

Background

Tuberculosis (TB) remains one of the most globally impactful infectious diseases, still recording a mortality of 1.3 million in 2020. In Romania and Ukraine, two high burden countries in the context of the WHO European region, treatment is geared towards cure, however, this path is paved with significant negative aspects, from morbidity to loss to follow up.

Methods

A retrospective study was performed for drug susceptible TB patients hospitalised in three TB expertise centres in Romania and Ukraine using routinely collected data. Univariate logistic regression was followed by the development of logistic regression models for three outcomes: unfavourable outcomes, loss to follow up, and death.

Results

A total of 838 patients diagnosed with TB were eligible for inclusion. Median hospitalisation duration was 39 days (IQR 25-67) and median treatment length was 7 months (IQR 6-8). The combination of variables best predicting the outcomes differed. For the composite outcome of unfavourable treatment outcomes, being over 65 years of age, having chronic kidney disease, having at least one cavity present on chest X-Ray, being underweight, and having persistently abnormal laboratory parameters despite hospital interventions to improve them were included in the model.

Conclusion

Contextualising factors influencing TB outcomes in different settings can help developing tailor made interventions which can identify at-risk patients early in order to avoid unnecessary treatment effects.

Introduction

Tuberculosis (TB) remains one of the most globally impactful infectious diseases, still recording a mortality of 1.6 million in 2022 [1]. Ending TB starts with a better understanding of risk factors for incidence, prevalence, morbidity, and mortality. A systematic review on studies involving prediction models reported that the most common predictors for poor outcomes were age, sex, location of TB, body mass index, chest X-ray abnormalities, previous TB and HIV status [2]. The WHO recommends performing local research to tailor TB strategies for specific population needs as health care settings, socio-economic, and cultural settings differ [3].

The WHO TB European region has the fastest decline in TB incidence and mortality rates, and it is, overall, a low-incidence TB region. Yet, Romania and Ukraine still tackle large numbers of TB, with Romania having a fourth of all EU TB cases [4] and Ukraine being in the top 30 WHO high TB burden countries [5]. Both countries have healthcare policies geared towards TB treatment success. The success rates of 80% in drug susceptible TB in Romania and 75% in Ukraine compare to the overall success rate of 77% in the WHO European region [5-7]. However, the path to treatment success is being paved with significant morbidity, hospital admissions for all affected by TB, adverse events, and other unfavourable outcomes, such as loss to follow up (LTFU). As no prediction model for this setting was described [2] , this study aims to understand negative outcomes in drug susceptible TB patients in Romania and Ukraine.

Methods

Design

A retrospective multi-centre study was conducted on adult (>18 years) patients diagnosed with drug-susceptible TB (DS-TB) of any form and initiated treatment between 1st of January 2019 - 31st of December 2020. To be included, patients had to have had documented data including routine laboratory tests (renal and hepatic values) performed at least twice (once at diagnosis and once during follow up), and outcomes reported at the end of treatment.

Setting

The Bucharest Marius Nasta Institute, the Iasi Lung Hospital in Romania, and Chernivtsi TB Centre in Ukraine participated in this study. The study was approved by the ethics committee of each centre (Iași: 5483/2021, Bucharest: 10592/2019, Chernivtsi : 234/2021). The need for written informed consent was waived due to the retrospective nature of this study.

The Marius Nasta Institute in Bucharest is the regional TB centre for south Romania and also functions as the main centre of TB expertise in Romania. It services a blend of sensitive and resistant TB patients, mainly from the urban, higher income region of Bucharest (population of 1.83 million). The Iasi Lung Hospital is located in north-east Romania (population 3.83 million). Iasi is the second city in the country by population (500,668). The region has the lowest income in Romania, estimated to be 3.6 times lower than the Bucharest region and has a balanced rural-urban population (55.5% rural). Chernivtsi hospital treats patients from the Bukovyna region (population 901,632) in south Ukraine.

Data collection and storage

Data collection consisted of basic demographics, smoking and alcohol use, comorbidities, previous TB information, TB diagnosis, hospitalisation data (including laboratory parameters at treatment start and after 15-30 days of hospitalisation), and treatment outcomes (table 1). Patient data was codified and extracted from digital and paper medical records. Information for follow-up post-hospitalisation and TB outcomes was extracted from national TB registries using WHO definitions for treatment success, failure, lost to follow-up (LTFU), and death (Box 1) [8]. Extraction was cross verified by one other local investigator and the final dataset was also verified for incongruous data (IM). Data collection software used was Research Electronic Data Capture (REDCap) v11.0.3 and statistical analysis was performed in SPSS v.27.

Table 1 - Data collection

Category	Item
Basic demographics	Age, sex, rural/urban/homeless/prison
Lifestyle	Smoking (never, previous, current), alcohol use (never, light, moderate, frequent/binge)
Comorbidities	COPD, asthma, HIV, diabetes mellitus type 1 or 2, chronic kidney disease, cirrhosis of the liver, cardio-vascular (e.g. hypertension), gastro-intestinal (e.g. chronic ulcer)
Previous TB data	New case, relapse with previous TB over 2 years ago and under 2 years ago (rapid relapse)
TB diagnosis	Symptoms at presentation, sputum and culture results, chest X-ray description, drug susceptibility testing
Hospitalisation	Date of admission and discharge, adverse events reported, hepatic and renal values ((eGFR calculated with CKD-EPI) at baseline and during hospital stay (between day 15 and day 30); in case of abnormal baseline laboratory values, additional data collection was performed for their evolution: laboratory values returned to baseline; values improved during hospitalisation but never achieved baseline; persistently abnormal laboratory values despite clinical intervention.
TB outcomes	Month of culture conversion, total treatment duration, Treatment success, Unfavourable outcomes (death, loss to follow up, treatment failure)

Box 1: Definitions

New case - have never been treated for TB or have taken anti-TB drugs for less than 1 month

Retreatment - a patient who has undergone TB treatment in the past. Rapid relapse - a patient who has been treated for TB under 2 years ago

Slow response - s either smear positive pulmonary TB patients with sputum smear not decreasing adequately (4+ to 2+, 3+ to 1+, 2+/1+ to negativity) or not negative at the end of the intensive phase or no clinical improvement (no weight gain, no reduction in cough, persistent fever, worsening of chest X-Ray)

Treatment success:

- Cured - a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
- Treatment completed - TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Unfavourable outcomes:

- Treatment failed - TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
- Died - TB patient who dies for any reason before starting or during the course of treatment.
- Lost to follow-up - TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

Not evaluated - TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Data analysis

Descriptive statistics were used to characterise the study population. Age cut-off values were decided based on previous research. Univariate analysis was performed to determine the relationship of each independent variable with one of the outcomes: unfavourable outcomes (combined outcome of LTFU, treatment failure, and death), LTFU, and 6 months survival. For the latter, Cox proportional-hazards regression analysis was performed by analysing survival at the end of treatment and month of death. Multivariate logistic regression models for each outcome were developed by the stepwise approach. The first step was backward stepwise deletion, starting with a base model which included all variables under consideration and deleting collinear and least significant variables (threshold of $p<0.5$). The second step was adding back variables (threshold of $p<0.05$) until a final model with all variables being under the threshold of $p<0.2$ was obtained [9,10]. Each iteration was followed by a goodness of fit analysis. We evaluated the goodness-of-fit of the final models by using Hosmer-Lemeshow test and performance by the area under the receiver operating characteristic (ROC) curve. For Cox regression, proportional hazard assumptions were checked before fitting the model and using log-minus-log survival curve after fitting the model. Additionally, adjusted hazard ratios are presented for Cox regression models and adjusted odds ratios for logistic regression models, as well as 95% CIs.

Results

General characteristics

During the study period, a total of 838 TB patients were eligible for inclusion, 44% in both Iasi and Bucharest clinical sites, and 12% for Chernivtsi. Few patients (n=21) were excluded because they had missing hospitalisation data or were transferred out. Patients were predominantly adult males with 19.6% being over the age of 65 (Table 2).

Table 2 - Demographics and clinical features of sensitive TB patients admitted in 2019

Characteristic	Number	Percentage (%)	Median (IQR)
Age, y	838	100%	47 (35-61)
Sex	838	100%	
M	557	66.5%	
F	281	33.5%	
Body mass index	838	100%	21 (19-22.9)
Previous TB	838	100%	
New case	709	84.6%	
Previous TB > 2 yrs ago	99	11.8%	
Previous TB < 2 yrs ago	30	3.6%	
Smoking	761	90.8%	
Never	283	33.8%	
Former	78	9.3%	
Current	400	47.7%	
Alcohol consumption	655	78.2%	
Never	269	32.1%	
Light drinking	132	15.8%	
Moderate drinking	99	11.8%	
Heavy drinking	155	18.5%	
Number of comorbidities	838		1 (0-1)
TB Location	838	100%	
Pulmonary	606	72.3%	
Pleura	103	12.3%	
Other extrapulmonary	38	4.3%	
Lung and extrapulmonary	93	11.1%	
TB pulmonary X-ray	698	83.3%	
Unilateral	218	31.2%	
Bilateral	480	57.3%	
Direct microscopy of sputum	697	83.2%	
Positive	499	59.5%	
Negative	198	23.6%	
Culture result	690	82.3%	
Positive	639	92.6%	
Negative	51	6.1%	

Homelessness was reported in 1.3% of the patients and 19.1% of the patients were underweight, defined as having a BMI < 18.5kg/m2. Half of the patients included had at least one comorbidity at admission. The most frequently reported comorbidity was cardio-vascular (26.6%), followed by COPD (12.3%) and gastro-intestinal (12.3%), with a minority of the patients living with HIV (2.3%). Most (84.6%) were new TB patients. Chest X-ray descriptions predominantly describe infiltration (58.5%), followed by the presence of at least one cavity (43.2%). A majority of extrapulmonary locations of TB involved the pleura (75.8%), either alone or combined with pulmonary TB. A third of the patients (33.4%) were admitted for less than one month, with median days of hospitalisation being 39 (IQR 25-67). Patients were treated for a median of 7 months (IQR 6-8).

Outcomes

Treatment success was registered in 88.4% of patients (Table 3). In total, 11.3% patients had an unfavourable outcome. Treatment failure was reported in 0.5%, which precluded a statistical analysis performed for this outcome. 4.7% were LTFU and 6.2% died.

Table 3: Hospitalisation and outcomes

Characteristic	Number	Percentage (%)	Median (IQR)
Hospitalisation time, median days (IQR)	838	100%	39 (25-67)
Laboratory values	838	100%	
Abnormal laboratory values at baseline(1)	223	26.6%	
Abnormal laboratory values during hospitalisation	321	38.3%	
Follow up of laboratory parameters	248		
Abnormal values returned to baseline	174	70%	
Values improved, but never reached baseline	47	19%	
Persistently abnormal laboratory values	27	10.9%	
Clinical attitude to abnormal values	221		
No attitude	33	14.9%	
Supportive treatment(2)	83	37.6%	
Lowered dosages of TB medication	30	13.6%	
Paused TB drugs <= 7 days	20	9.0%	

Paused TB drugs > 7 days	31	14%	
Stopped/switched TB medication	24	16.7%	
Outcomes	838		
Treatment success	741	88.4%	
LTFU	39	4.7%	
Death	52	6.2%	1 (0-1)
Treatment failure	4	.5%	
Transfer	2	.2%	

Univariate analysis

Several variables demonstrated an association with one or more outcomes in the univariate analysis qualifying for inclusion in the model development. These included age over 65 years, homelessness, TB retreatment, the presence of cirrhosis of the liver or chronic kidney disease, being underweight (BMI<18.5kg/m2) or obese (BMI>30 kg/m2), having a microscopy result of sputum of at more than 9 bacilli/field (+++), having gastro-intestinal side effects during hospitalisation (e.g. nausea), and abnormal liver enzymes or renal function parameters. (Supplementary Material Table 1-3).

Multivariate analysis

Development of multivariate models to predict TB outcomes

The initial model for unfavourable outcomes included 23 variables. Variables were removed based on significance and through eliminating collinear variables, such as alcohol consumption, cirrhosis of the liver, and elevated liver enzymes at diagnosis or obesity and diabetes mellitus type 2. After backwards deletion, a set of four variables was obtained and, after adding back variables, the final model containing 5 variables was achieved. To obtain the final model, 64 iterations were performed. For LTFU, the initial model included 25 variables, which, after backwards deletion reduced to four and, after adding back variables and a total of 84 iterations, the final model contains five variables. The model for survival until the end of the treatment initially included 17 variables, which, after backward deletion, were reduced to 6, and, after a total of 55 iterations, the final model with seven variables was obtained.

Predictors included in models

The model for unfavourable outcomes (Goodness-of-fit Hosmer and Lemeshow test .962. sROC curve, area under de curve .773, 95% CI .681-.865) included five variables: being over 65 years of age, having chronic kidney disease as a comorbidity, having at least one cavity present on chest X-ray, being underweight, and having persistently abnormal laboratory parameters despite hospital interventions to improve them (table 4). The model for LTFU (Goodness-of-fit Hosmer and Lemeshow test 0.871, sROC area under the curve 0.860, 95% CI 0.800-0.921) included six variables: consuming alcohol, having COPD as a comorbidity, having had TB infection less than two years previous to the current admission, being obese, slow response to treatment, and sputum microscopy result of at least 2+ (table 5). The model for death included seven variables: being over 65 years of age, being male, having cirrhosis or chronic kidney disease as comorbidities, being underweight, having persistently abnormal laboratory parameters, and having slow response to treatment (table 6).

Table 4: Logistic regression for unfavourable outcomes

Unfavourable outcomes			**95% confidence interval**	
Variable	**P value**	**aOR**	**Lower**	**Upper**
Age >65 years	.157	2.024	.762	5.975
Chronic kidney disease	.002	11.529	2.432	54.659
Cavity present on chest X-ray	.196	1.785	.741	4.297
BMI <18.5 kg/m2	<.001	5.590	2.286	13.672
Persistently abnormal laboratory tests	.001	6.303	2.130	18.650

Goodness-of-fit Hosmer and Lemeshow test .962. sROC curve, area under de curve .773, 95% CI .681-.865; aOR - adjusted odds ratio

Table 5: Logistic regression for LTFU

LTFU			**95% confidence interval**	
Variable	**P value**	**aOR**	**Lower**	**Upper**
Alcohol consumption	.012	4.987	1.409	17.025
COPD	.017	3.705	1.264	10.864

Previous TB less than 2 years ago (rapid relapse)	<.001	14.478	3.375	56.113
BMI >30 kg/m2 (obesity)	<.001	17.165	3.843	76.660
Culture conversion at month two	.003	13.212	2.373	73.570
Ziehl-Nielsen sputum result of at least 2+	.013	4.455	1.371	14.477

Goodness-of-fit Hosmer and Lemeshow test .871. sROC area under the curve .860, 95% CI .800-.921 aOR - adjusted odds ratio

Table 6: Cox regression multivariate analysis - survival until end of treatment

			95% confidence interval	
Variable	**P value**	**aHR**	**Lower**	**Upper**
Age >65 yrs	<.001	5.727	3.002	10.925
Male	.030	2.219	1.079	4.564
Cirrhosis	.016	3.544	1.272	9.878
Chronic kidney disease	<.001	7.647	2.752	21.525
BMI <18.5 kg/m2 (underweight)	<.001	7.657	3.890	15.073
Persistent abnormal lab values	<.001	7.282	2.601	20.384
Slow responders	<.001	7.185	3.615	14.280

aHR - adjusted hazard ratio

Discussion

In this study, retrospective data regarding TB patients from three TB centres in Eastern Europe was analysed to develop multivariate models for the composite outcome of unfavourable treatment outcomes, and two of its components, namely death and loss to follow up. Variables included in the unfavourable outcomes model were being over 65 years of age, having chronic kidney disease, chest X-ray with at least one cavity, being underweight, and having persistently abnormal laboratory parameters despite hospital interventions to improve them. Four of these variables were found also in the death model and there is no overlap with the LTFU model.

Treatment success within our DS-TB population was higher than reported national indicators for 2019 (88.4% study treatment success vs. 79.8% RO and 75.2% UKR) [5]. Our study nevertheless included patients with DS-TB treated in TB expertise centres.

At the same time, this treatment success rate was achieved after hospitalising all affected by TB for a median of 39 days and almost eight months of treatment. A study investigating the success rates of extended therapy for DS-TB reports that for patients with a negative culture at month two there was 100% success rate after a median treatment duration of 275 days (nine months) and for culture positive patients (at month 2), the success rate was 74.5% [11]. However, global recommendations are shifting to shorter treatment regiments as research suggests they could obtain comparable success rates whilst minimising treatment impact [12] as studies prolonging treatment duration increases the chances of drug toxicity [13] and loss to follow up. Indeed, in our study, having culture conversion on time (before the end of the intensive phase of TB treatment) was a variable adding risk in the LTFU model, suggesting that patients feeling well might have a higher chance of TB treatment. At the same time, 15.5% of patients presented with at least one adverse effect during hospitalisation, ranging from mild allergic reactions to hospital infections with *Clostridium difficile*. Almost 40% of patients had abnormal liver enzymes and for 30% laboratory parameters did not normalise during hospitalisation. This information is routinely gathered during hospital stay, typically between day 14-30, to observe drug toxicity. Current strategies available in Romania and Ukraine to mitigate drug toxicity include supportive treatment, and pausing or removing drugs from the TB treatment scheme, however, if despite these measures the laboratory parameters do not improve, our models suggest it could be associated with unfavourable outcomes, including death. In these cases, therapeutic drug monitoring, a technique offering information about drug plasma concentrations, could be particularly useful, as it could more precisely guide treatment options [14].

Our model is comparable to earlier models [2] showing that age, sex, comorbidities, being underweight or malnourished, are predictors of unfavourable outcomes. Our population has, however, several particularities. For instance, opposite to most studies, which were performed in TB-HIV high burden areas, our study was performed in a TB population with a low HIV prevalence of 2.3% and therefore HIV infection and CD4 counts did not contribute to the model predicting unfavourable outcomes, as in other populations [15-18].

For the EU/EEA, previous models included gender (male), age, alcohol abuse, history of mental disorder, bilateral lung involvement, having anaemia, ≥1 significant comorbidity (Denmark, [19]) (Portugal, [15]). For the WHO European region, a retrospective study performed in Russia between 1993 and 2002 included sex, unemployment, being a retreatment case, alcohol abuse, severe TB form, residence, age), pulmonary TB (vs. extrapulmonary), prison history as predictors of negative outcomes. In our study, the composite outcome (unfavourable outcomes) had a larger proportion of death than LTFU, which could explain variables in common between unfavourable outcomes and death, and less with LTFU. As in the model developed in Russia, requiring retreatment was included in the LTFU model, but only if the previous TB infection had been less than two years previous, possibly indicating the cumbersome nature of actual TB treatment. Other studies performed in non-European settings note that risk for LTFU is increased for elderly, with low income and previous default (Iraq, [20]), or younger males, treated at primary health clinics in border or transit regions (Namibia, [21]). In our study, age was not included in the final multivariate model for LTFU as it was statistically insignificant both in univariate and in multivariate analyses.

Concerning weight, interestingly, being underweight, as reported in other models, was associated with unfavourable outcomes and death, but obesity was associated with LTFU.

Comparable to bilateral lung involvement, our study included having at least one cavity present on chest X-ray as one of the variables in the unfavourable outcomes model.

Differences of factors predicting unfavourable outcomes could arise from the specific particularities of our study centres, located in middle income countries with high TB burdens, highlighting the need to perform localised research in order to tailor clinical recommendations.

Strengths and limitations

Our retrospective study collected data introduced by clinicians in medical charts and the national TB register. We mitigated some of the impact of this limitation by

only including patients with chronicled follow up and ensuring that data collection is homogeneous via the REDCap electronic forms, as none of the clinical centres have a comprehensive electronic medical records system. This, in turn, could be considered a limitation, however, only 21 cases were not included based on missing data. Our large cohort is distinctive through its high TB burden in the European space, and with limited resources. Data included in the analysis is routinely collected in all TB centres, making the possibility of informing clinicians regarding at-risk cases facile. The stepwise approach used for model development is one of the most widely used in medical studies, however, it has inherent caveats. Last, but not least, this study collected data relevant for healthcare policy, such as hospitalisation and treatment duration for TB patients in these countries.

Conclusion

Our study demonstrated a different combination of routinely collected variables to best predict unfavourable outcomes, death, and loss to follow up for TB patients in Romania and Ukraine. The three different models highlight related factors which could contribute to a specific unfavourable outcome, and which might warrant careful clinical consideration.

These findings can assist clinicians identifying patients with an increased risk of an unfavourable outcome. The differences in the combination of variables best predicting unfavourable outcomes, LTFU and death, remind stakeholders to tailor interventions improving outcomes based on population targeted.

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Supplementary Material

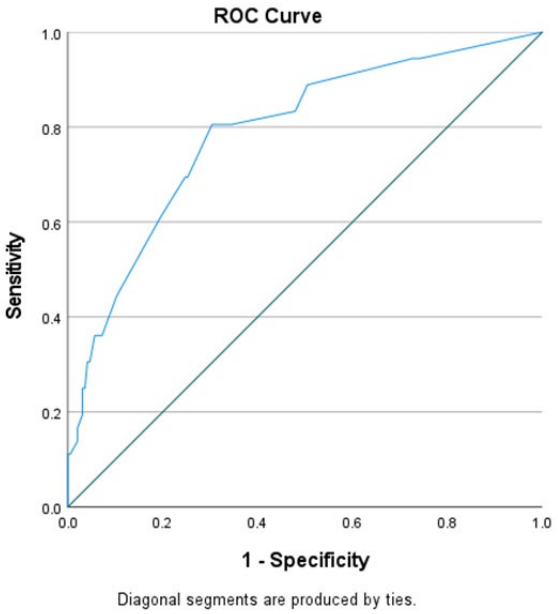
Supplementary Table: Univariate Analysis

	Unfavourable outcome				LTFU				Death			
Characteristics	Unfavourable Outcome N=101	No unfavourable outcome N=737	OR (95%CI)	P-value	LTFU N=42	Non-LTFU N=741	OR (95%CI)	P-value	Death N=46	No death N=756	HR (95%CI)	P-value
Age												
Under 35	14 (13.9%)	187 (25.4%)	1	-	11 (26.2%)	188 (25.4%)	1	-	1 (2.2%)	190 (25.1%)	1	-
35-under 65	55 (54.5%)	418 (56.7%)	1.75 (.95-3.24)	.07	24 (57.1%)	421 (56.8%)	.97 (.46-2.03)	.94	23 (50%)	429 (56.7%)	9.94 (1.34-73.59)	.025
Over 65	32 (31.7%)	132 (17.9%)	3.23 (1.66-6.30)	.001	7 (16.7%)	132 (17.8%)	.90 (.34-2.39)	.90	22 (47.8%)	137 (18.1%)	27.96 (3.77-207.43)	.001
Gender												
Male	72 (71.3%)	485 (65.8%)	1.29 (.81-2.03)	.28	28 (66.7%)	489 (66%)	1.03 (.53-1.99)	.92	34 (73.9%)	500 (66.1%)	1.43 (.74-2.77)	.29
Female	29 (28.7%)	252 (34.2%)	1	-	14 (33.3%)	252 (34%)	1	-	12 (26.1%)	256 (33.9%)	1	-
Living situation												
Urban	36 (35.6%)	304 (41.3%)	1	-	15 (35.7%)	306 (41.4%)	1	-	18 (39.1%)	311 (41.2%)	1	-
Rural	59 (58.4%)	427 (58%)	1.16 (.75-1.81)	.49	24 (57.1%)	429 (58%)	1.14 (.59-2.21)	.69	26 (56.5%)	438 (58%)	1.02 (.56-1.86)	.95
Homeless	6 (5.9%)	5 (0.7%)	10.13 (2.94-34.88)	<.001	3 (7%)	5 (0.7%)	12.24 (2.67-56.09)	.001	2 (4.3%)	6 (0.8%)	4.99	.03
Days hospitalisation												
<=30 days	50 (49.5%)	230 (31.2%)	1	-	15 (35.7%)	230 (31%)	1	-	32 (69.6%)	234 (31%)	1	-
>30 days	51 (50.5%)	507 (68.8%)	.46 (.30-.70)	<.001	27 (64.3%)	511 (69%)	.81 (.42-1.55)	.52	14 (30.4%)	522 (69%)	.21 (.11-.39)	<.001
Location of TB												
Pulmonary	76 (75.2%)	530 (71.9%)	1	-	31 (73.8%)	533 (71.9%)	1	-	34 (73.9%)	546 (72.2%)	1	-
Extrapulmonary	16 (15.8%)	123 (16.7%)	.91 (.51-1.61)	.74	9 (21.4%)	123 (16.6%)	1.26 (.58-2.71)	.55	6 (13%)	124 (16.4%)	.78 (.33-1.87)	.78
Combination	9 (8.9%)	84 (11.4%)	.75 (.36-1.55)	.43	2 (4.8%)	85 (11.5%)	.41 (.09-1.72)	.22	6 (13%)	86 (11.4%)	1.11 (.47-2.65)	.80
Previous TB												
New case	73 (72.3%)	636 (86.3%)	1	-	29 (69%)	639 (86.2%)	1		35 (76.1%)	648 (85.7%)	1	-
Prev TB over 2 years ago	17 (16.8%)	82 (11.1%)	1.80 (1.01-3.21)	.04	7 (16.7%)	83 (11.2%)	1.86 (0.78-4.38)	.16	8 (17.4%)	85 (11.2%)	1.70 (.79-3.67)	.17
Prev TB under 2 years ago	11 (10.9%)	19 (2.6%)	5.04 (2.31-11.01)	<.001	6 (14.3%)	19 (2.6%)	6.95 (2.59-18.73)	.00	3 (6.5%)	23 (3%)	2.29 (.70-7.44)	.17
Smoking												
Never	28 (30.8%)	255 (38.1%)			13 (34.2%)	256 (38%)	1		12 (30%)	261 (37.9%)	1	-

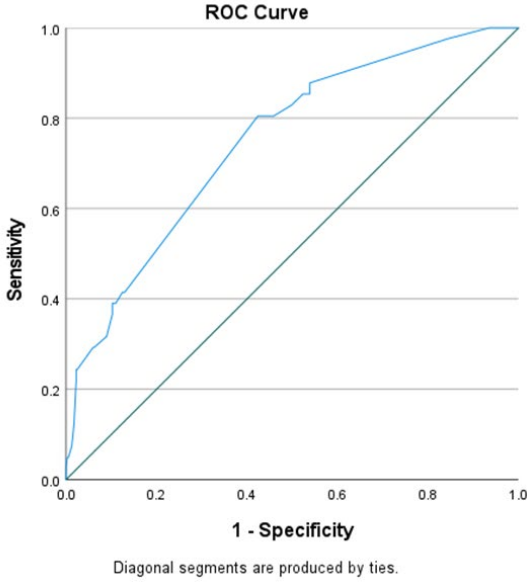
Characteristics	Unfavourable Outcome N=101	No unfavourable outcome N=737	OR (95%CI)	P-value	LTFU N=42	Non-LTFU N=741	OR (95%CI)	P-value	Death N=46	No death N=756	HR (95%CI)	P-value
Former	9 (9.9%)	69 (10.3%)	1.18 (.54-2.64)	.67	2 (5.3%)	69 (10.2%)	.57 (.13-2.59)	.47	5 (12.5%)	71 (10.3%)	1.50 (.53-4.27)	.44
Current	54 (59.3%)	346 (51.6%)	1.42 (.88-2.30)	.15	23 (60.5%)	349 (51.8%)	1.30 (.64-2.61)	.47	23 (57.5%)	356 (51.7%)	1.39 (.69-2.79)	.36
Alcohol												
Never	25 (28.7%)	244 (43%)	1	-	8 (22.9%)	244 (42.7%)	1		14 (34.1%)	250 (42.7%)	1	-
Light drinking	16 (18.4%)	116 (20.4%)	1.35 (.69-2.62)	.38	10 (28.6%)	116 (20.3%)	2.62 (1.01-6.83)	.047	4 (9.8%)	118 (20.1%)	.61 (.20-1.85)	.38
Moderate drinking	13 (14.9%)	86 (15.1%)	1.48 (.72-3.01)	.28	7 (20%)	87 (15.2%)	2.45 (.86-6.96)	.092	4 (9.8%)	90 (15.4%)	.80 (.26-2.43)	.80
Heavy drinking	33 (37.9%)	122 (21.5%)	2.64 (1.50-4.63)	.001	10 (28.6%)	124 (21.7%)	2.46 (.94-6.39)	.065	19 (46.3%)	128 (21.8%)	2.54 (1.28-5.07)	.008
Number of chronic conditions												
None	90 (89.1%)	702 (95.3%)	1	-	41 (97.6%)	706 (95.3%)	1	-	37 (80.4%)	720 (95.2%)	1	-
1-2	11 (10.9%)	35 (4.7%)	2.45 (1.20-4.99)	.01	1 (2.4%)	35 (4.7%)	.49 (0.67-3.68)	49	9 (19.6%)	36 (4.8%)	4.48 (2.16-9.29)	<.001
>= 3	0	0	-	-	0	0	-	-	0	0	-	-
PLHIV												
No	98 (97%)	721 (97.8%)			41 (97.6%)	725 (97.8%)	1	-	45 (97.8%)	739 (97.8%)	1	-
Yes	3 (3%)	16 (2.2%)	.73 (.21-2.53)	.61	1 (2.4%)	16 (2.2%)	.90 (.12-6.99)	.92	1 (2.2%)	17 (2.2%)	1.03 (.14-7.49)	.98
Cirrhosis												
No	95 (94.1%)	720 (97.7%)	1	-	41 (97.6%)	724 (97.7%)	1		41 (89.1%)	738 (97.6%)	1	-
Yes	6 (5.9%)	17 (2.3%)	.37 (.14-.97)	.61	1 (2.4%)	17 (2.3%)	.96 (.12-7.41)	.97	5 (10,9%)	18 (2.4%)	.22 (.09-.55)	.001
Diabetes mellitus												
No	98 (97%)	685 (92.9%)	1	-	42 (100%)	689 (93%)	1		43 (93.5%)	704 (93.1%)	1	-
Yes	3 (3%)	52 (7.1%)	2.48 (.76-8.09)	.13	0	52 (7%)	-		3 (6.5%)	52 (6.9%)	1.05 (.33-3.38)	.94
COPD												
No	85 (84.2%)	647 (87.8%)	1	-	32 (76.2%)	651 (87.9%)	1		85 (84.2%)	647 (87.8%)	1	-
Yes	16 (15.8%)	90 (12.2%)	.74 (.42-1.31)	.30	10 (23.8%)	90 (12.1%)	.44 (.21-.93)	.032	16 (15.8%)	90 (12.2%)	1.15 (.46-2.92)	.76
Asthma												
No	98 (97%)	728 (98.8%)	1	-	40 (95.2%)	732 (98.8%)	1	-	45 (97.8%)	745 (98.5%)	1	-
Yes	3 (3%)	9 (1.2%)	.40 (.11-1.52)	.18		9 (1.2%)	.25 (.05-1.17)	.079	1 (2.2%)	11 (1.5%)	.68 (.09-4.94)	.70
Cancer												
No	98 (97%)	709 (96.2%)	1	-	42 (100%)	713 (96.2%)	1	-	44 (95.7%)	727 (96.2%)	1	-

Characteristics	Unfavourable Outcome N=101	No unfavourable outcome N=737	OR (95%CI)	P-value	LTFU N=42	Non-LTFU N=741	OR (95%CI)	P-value	Death N=46	No death N=756	HR (95%CI)	P-value
Yes	3 (3%)	28 (3.8%)	1.29 (.39-4.32)	.68	0	28 (3.8%)	-	-	2 (4.3%)	29 (3.8%)	.89 (.22-3.66)	.87
Cardio-vascular												
No	66 (65.3%)	549 (74.5%)	1	-	29 (69%)	662 (74.5%)	1		27 (58.7%)	563 (74.5%)	1	-
Yes	35 (34.7%)	188 (25.5%)	.65 (.42-1.01)	.05	13 (31%)	189 (25.5%)	.76 (.39-1.50)	.43	19 (41.3%)	193 (25.5%)	.49 (.28-.89)	.02
No	86 (85.1%)	649 (88.1%)	1	-	39 (92.9%)	653 (88.1%)	1	-	36 (78.3%)	666 (88.1%)	1	-
Yes	15 (14.9%)	88 (11.9%)	.78 (.43-1.41)	.40	3 (7.1%)	88 (11.9%)	1.75 (.53-5.79)	.35	10 (21.7%)	90 (11.9%)	.49 (.25-1.00)	.05
Chronic Kidney Disease												
No	93 (92.1%)	727 (98.6%)	1	-	40 (95.2%)	731 (98.7%)	1	-	40 (87%)	746 (98.7%)	1	-
Yes	8 (7.9%)	10 (1.4%)	.16 (.06-.42)	<.001	2 (4.8%)	10 (1.3%)	.27 (.06-1.29)	.10	6 (13%)	10 (1.3%)	.12 (.05-.28)	<.001
BMI												
Normal weight	49 (48.5%)	532 (72.2%)	1	-	27 (64.3%)	535 (72.2%)	1	-	15 (32.6%)	540 (71.4%)	1	-
Underweight	38 (37.6%)	122 (16.6%)	3.38 (2.12-5.39)	<.001	8 (19%)	123 (16.6%)	1.29 (.57-2.90)	.54	26 (56.5%)	128 (16.9%)	6.69 (3.54-12.63)	<.001
Overweight	8 (7.9%)	64 (8.7%)	1.36 (.62-2.99)	.45	2 (4.8%)	64 (8.6%)	.61 (.14-2.67)	.52	4 (8.7%)	67 (8.9%)	2.11 (.70-6.37)	.18
Obese	6 (5.9%)	19 (2.6%)	3.42 (1.31-8.98)	.001	5 (11.9%)	19 (2.6%)	5.21 (1.81-15.02)	.002	1 (2.2%)	21 (2.8%)	1.72 (.23-13.04)	.59
TGO/ALAT Start (U/L)												
Normal (under 40 U/L)	74 (73.3%)	626 (84.9%)	1	-	35 (83.3%)	628 (84.8%)	1	-	32 (69.6%)	638 (84.4%)	1	-
<3x normal	20 (19.8%)	99 (13.4%)	1.71 (.99-2.92)	.05	5 (11.9%)	101 (13.6%)	.88 (.34-2.32)	.80	9 (19.6%)	106 (14%)	1.67 (.79-3.49)	.18
3x-10x normal	7 (6.9%)	11 (1.5%)	5.38 (2.02-14.31)	.001	2 (4.8%)	11 (1.5%)	3.26 (.69-15.29)	.13	5 (10.9%)	11 (1.5%)	7.73 (3.01-19.86)	<.001
>10x normal	0	1 (0.1%)	-	-	0	1 (0.1%)	-		0	1 (1.5%)	-	-
TGP/ASAT Start (U/L)												
Normal (under 56 U/L)	88 (87.1%)	679 (92.1%)	1	-	38 (90.5%)	683 (92.2%)	1	-	41 (89.1%)	694 (91.8%)	1	-
<3x normal	11 (10.9%)	52 (7.1%)	1.63 (.82-3.25)	.16	3 (7.1%)	52 (7%)	1.03 (.31-3.47)	.95	4 (8.7%)	56 (7.4%)	1.20 (.43-3.36)	.72

3x-10x normal	2 (2%)	6 (0.8%)	2.57 (.51-12.94)	.25	1 (2.4%)	6 (0.8%)	2.99 (.35-25.51)	.31	1 (2.2%)	6 (0.8%)	2.67 (.37-19.37)	.33
>10x normal	0	0	-	-	0	0	-	-	0	0	-	-
Characteristics	Unfavourable Outcome N=101	No unfavourable outcome N=737	OR (95%CI)	P-value	LTFU N=42	Non-LTFU N=741	OR (95%CI)	P-value	Death N=46	No death N=756	HR (95%CI)	P-value
TGO/ALAT Max Hosp (U/L)												
Normal (under 40 U/L)	63 (62.4%)	539 (73.2%)	1	-	31 (73.8%)	541 (73.1%)	1		27 (58.7%)	550 (72.8%)	1	-
<3x normal	25 (24.8%)	149 (20.2%)	1.44 (.87-2.36)	.15	7 (16.7%)	151 (20.4%)	.80 (.34-1.87)	.62	11 (23.9%)	155 (20.5%)	1.42 (.70-2.87)	.32
3x-10x normal	9 (8.9%)	39 (5.3%)	1.97 (.91-2.36)	.08	2 (4.8%)	39 (5.3%)	.89 (.20-3.87)	.88	7 (15.2%)	39 (5.2%)	3.47 (1.51-7.98)	.003
>10x normal	4 (4%)	9 (1.2%)	3.80 (1.13-12.71)	.03	2 (4.8%)	9 (1.2%)	3.88 (.80-18.72)	.09	1 (2.2%)	11 (1.5%)	1.85 (2.53-13.68)	.54
TGP/ASAT Max Hosp (U/L)												
Normal (under 56 U/L)	83 (82.8%)	610 (82.8%)	1	-	36 (87.8%)	614 (82.9%)	1	-	38 (82.6%)	624 (82.6%)	1	-
<3x normal	12 (12%)	94 (12.8%)	.94 (.49-1.79)	.85	2 (4.9%)	94 (12.7%)	.36 (.08-1.53)	.17	7 (15.2%)	97 (12.8%)	1.18 (.53-2.63)	.69
3x-10x normal	4 (4%)	29 (3.9%)	1.01 (.35-2.96)	.98	3 (7.3%)	29 (3.9%)	1.76 (.51-6.06)	.37	1 (2.2%)	29 (2.8%)	.58 (.08-4.19)	.58
>10x normal	1 (1%)	4 (0.5%)	1.84 (.20-16.64)	.59	0	4 (0.5%)	-	-	0	5 (0.7%)	-	-
eGFR Start (ml/min/1.73m2, CKD-EPI)												
Normal (over 60)	89 (88.1%)	692 (93.9%)	1	-	41 (87.6%)	696 (93.9%)	1	-	36 (78.3%)	710 (93.9%)	1	-
60-15	9 (8.9%)	43 (5.8%)	1.63 (.77-3.45)	.21	1 (2.4%)	43 (5.8%)	.39 (.05-2.93)	.36	7 (15.2%)	44 (5.8%)	3.04 (1.35-6.82)	.007
Under 15	3 (3%)	2 (0.3%)	11.66 (1.92-20.75)	.008	0	2 (0.3%)	-	-	3 (6.5%)	2 (0.3%)	14.68 (4.51-47.76)	<.001
eGFR Min Hosp (ml/min/1.73m2, CKD-EPI)												
Normal (over 60)	84 (83.2%)	685 (93.3%)	1	-	39 (92.9%)	689 (93.4%)	1	-	33 (71.7%)	703 (93.4%)	1	-
60-15	12 (11.9%)	45 (6.1%)	2.18 (1.11-4.28)	.02	3 (7.1%)	45 (6.1%)	1.18 (.35-3.95)	.79	8 (17.4%)	46 (6.1%)	3.57 (1.65-7.73)	.001
Under 15	5 (5%)	4 (.5%)	10.19 (2.69-38.70)	.001	0	4 (0.5%)	-	-	5 (10.9%)	4 (0.5%)	15.07 (5.87-38.73)	<.001



Supplementary Figure 1: SROC curve for Unfavourable Outcomes



Supplementary Figure 2 - SROC curve for Loss to Follow Up

Два чоботи – пара
- Ukrainian saying

2023

4

Therapeutic Drug Monitoring in Tuberculosis - Analysis of Opportunities in Romania and Ukraine

Margineanu I
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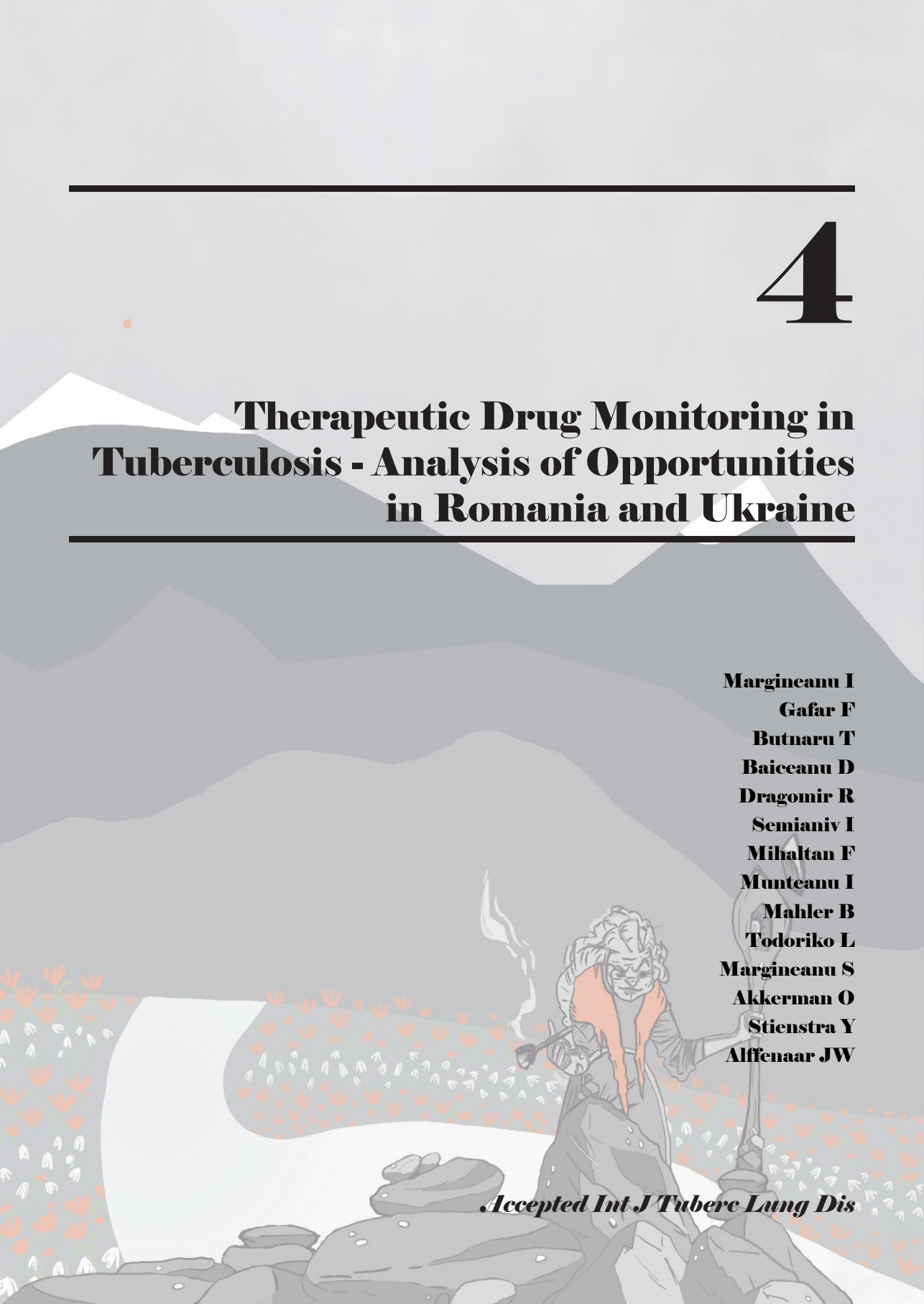

Accepted Int J Tuberc Lung Dis

Therapeutic drug monitoring in tuberculosis - analysis of opportunities in Romania and Ukraine

Summary

Introduction

Therapeutic drug monitoring (TDM) could improve tuberculosis (TB) treatment outcomes by avoiding drug toxicity or underdosing. In this study we describe the patient burden in three TB centres in Romania and Ukraine with a TDM indication following the current guidelines in order to estimate the opportunity of implementing TDM.

Methods

A retrospective multi-centre study was conducted in the Iasi Lung Hospital (Iasi, Romania), Bucharest Marius Nasta Institute (Bucharest, Romania) and Chernivtsi TB Centre (Chernivtsi, Ukraine) on adult hospitalised TB patients.

Results

A total of 927 participants were admitted, of which 37.8% had at least one indication for TDM, the most frequent being slow response to TB treatment (202/345, 58.6%). 55.5% had at least one cavity present on chest X-ray. Patients with TDM indication stayed in the hospital a median of 67 days and took on average two months more to reach a successful TB outcome.

Conclusion

TDM could be a valuable tool to improve management for selected TB patients. Waiting for culture results collected two months after start of treatment delays the decision whether to perform TDM. A randomised control trial should be performed in order to define TDM's precise role in TB therapy.

Introduction

Tuberculosis (TB) remains one of the most globally impactful infectious diseases, recording a mortality of 1.3 million in 2020. Global average treatment success rates are 86% for drug susceptible tuberculosis (DS-TB) and 59% for multidrug resistant tuberculosis (MDR-TB) [1].

Suboptimal treatment success rates have been linked to several factors either in relation with case severity or with the treatment in itself. In the former category, comorbidities (e.g. HIV or diabetes mellitus), differences in lifestyle (e.g. alcohol consumption, smoking), and in the severity of TB (e.g. the presence of cavities) can all complicate TB management. In the latter, the already complex and lengthy treatment can be further impaired by low or high drug exposures [2]. In this context, therapeutic drug monitoring (TDM) is a promising tool, which can aid clinical decision making by offering accurate measurements of drug concentrations allowing clinicians to make informed decisions on drug dosing [3]. Several global guidelines, including the World Health Organisation (WHO) guideline for drug resistant tuberculosis and the American Thoracic Society Guideline for TB as well as the Clinical Standards from the International Union Against Tuberculosis and Lung Disease recommend TDM for patients at risk of / or experiencing either drug toxicity, slow response to treatment, treatment failure or acquired resistance [4–7]. Patients at risk are considered those living with HIV, diagnosed with advanced kidney disease, diabetes mellitus or patients with drug resistant TB.

Romania has the highest TB burden within the European Union (EU), accounting for a fourth of all TB cases in the EU [8]. At the same time, Ukraine, bordering Romania to the north, is one of the top 30 countries with the highest TB burden, especially for MDR-TB [9]. Guidelines in both countries recommend admitting patients with TB disease at least for treatment initiation, optimally until culture negativity [10]. Owing to its high implementation costs and the lack of familiarity of clinicians and national stakeholders with this technique, TDM is currently not part of routine care in these settings. Furthermore, despite a large body of knowledge on the optimum plasma concentrations of TB drugs [11], there are information gaps concerning implementing

TDM in resource scarce settings, at the community level [3]. Future implementation of TDM strategies needs estimates of patients with a TDM indication as a basis for further cost-effectiveness studies.

In this study we describe the patient burden in three TB centres in Romania and Ukraine with a TDM indication following the current guidelines.

Methods

Design and setting

A retrospective multi-centre study was conducted in the Iasi Lung Hospital (Iasi, Romania), Bucharest Marius Nasta Institute (Bucharest, Romania) and Chernivtsi TB Centre (Chernivtsi, Ukraine).

The Iasi Lung Hospital is the regional TB centre for the north-eastern region. The Marius Nasta Institute is the national Romanian TB expertise centre. Chernivtsi TB Centre is the TB expertise centre in the Chernivetska Oblast, in south-western Ukraine. Inclusion criteria were hospitalised adult patients (aged >18 years), diagnosed with TB of any form, who initiated treatment between 1st of January 2019 - 31st of December 2020, and had both renal function and liver enzymes measured at least once during or at start of the treatment. Hospitalised TB patients in all centres have documented diagnosis data, HIV status known, and chronicled hospitalisation data. Other comorbidities were either documented (e.g. HbA1C for diabetes mellitus) or derived from medical history.

The study was approved by the ethics committee of each centre (5483/2021, Iasi, 10592/2019, Bucharest, 234/2021, Chernivtsi).

Data collection and storage

Patient and disease related data was extracted from medical records and captured in Research Electronic Data Capture (REDCap) v11.0.3, a secure web-based platform. Data extraction was verified by another investigator. Data collection mistakes were corrected and again verified by another investigator. After completion of data

collection IM performed a final random check of all data collection. Data collection included general demographics, smoking and alcohol consumption, and known comorbidities at the time of TB diagnosis. Diagnosis data included symptoms, chest X-ray interpretation, and results from direct microscopy of sputum and culture of sputum or other biological material. Baseline admission data included treatment schemes and hepatic and renal laboratory tests at baseline. Hospitalisation data recorded laboratory parameters, adverse events (AEs) noted, and management of hepatic or renal toxicity. TB treatment outcome was collected using WHO defined TB outcomes (time to culture conversion in month, total duration of treatment, treatment success, lost to follow up, death) [1].

For each patient indications for TDM were collected. TDM indications as listed in the guidelines [12,13] were: slow response to TB treatment (culture conversion beyond 2 months for DS-TB and 4 months for MDR-TB), severe gastro-intestinal abnormalities (severe gastroparesis, short bowel syndrome, chronic diarrhoea with malabsorption), impaired renal clearance (defined as glomerular filtration rate under 60 ml/min/1.73m2, CKD-EPI or acute kidney failure (drop in eGFR of at least 50%), comorbidities (HIV infection, diabetes mellitus type 2), and usage of second line TB medication. Descriptive statistics were used to characterise the data set and the programme used was IBM SPSS® v.27. All definitions of TB cases and outcomes follow the WHO framework (Health Organization).

Results

General Characteristics

Between 1st of January 2019 - 31st of December 2020 there were 927 TB patients admitted in all three centres. After excluding 19 patients based on lack of data on follow-up documents, 912 patients were included in the analysis, 378 in Iasi, 507 in Bucharest, and 154 in Chernivtsi. The median age was 47 (35-61), with 67.1% males, 58.1% living in rural environments, 48.1% current smokers and 60.8% currently consuming alcohol.

Considering comorbidities, the most frequently encountered were cardio-vascular

(e.g. hypertension, heart failure), in 28.3% of patients, followed by chronic obstructive pulmonary disease (COPD), 14.7% and diabetes mellitus, 6.4%. HIV was present in 2.3% of patients. A majority (838/912, 91.9%) had DS-TB, 20/912 (2.2%) were mono-resistant (R-TB), 18/912 (2%) MDR-TB and 36/912 (3.9%) (pre) extensive drug resistant (XDR-TB). A majority of RR-TB were in Ukraine (54 RR-TB in Ukraine versus 20 in Romania).

More than a third of patients had at least one indication for TDM (345/912, 37.8%) of which 244/345 (70.7%) patients had only one indication for TDM, 65 (18.8%) had two, and 36 had three or more (10.4%). The most frequently observed indication for TDM was slow response to TB treatment (202/345, 58.6%), followed by administration of second line medication (including for DS-TB intolerant to one of the first line drugs) (92/345, 26.1%). Of the 92 participants, 72 (97.3%) were DR-TB (figure 1).

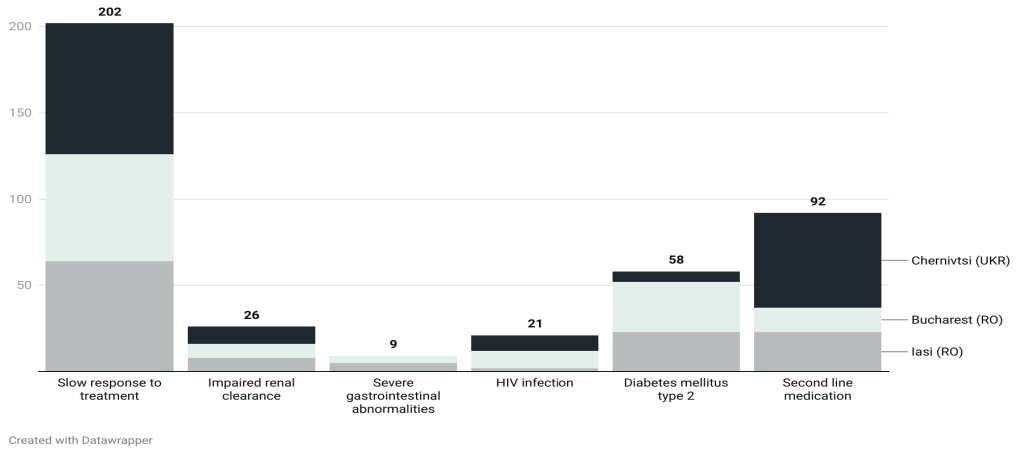

Figure 1: Guideline-driven TDM indications

Description of the population with TDM indication

The three clinical sites were different in their proportion of patients with TDM indication, with Chernivtsi, Ukraine, having 125 patients with TDM indication out of 154 (81%), and the sites in Romania having 29.4% and 28.7% for Iasi and Bucharest respectively. Sex, age, or living situation (rural, urban, homeless) were comparable between groups. Most (82%) were new TB patients, with the remainder being relapse cases. A majority had pulmonary TB (79.4%), with 9% presenting with a combination

of lung and pleural TB. Concerning pulmonary TB diagnosis, 59.1% had bilateral involvement of the lungs, and 55.5% had at least one cavity present on pulmonary chest X-ray. 26.4% had sputum with >9 bacili/field (+++) and 35.4% had culture result of >100 colonies (statistically significant more than the group without TDM indication) (table 1).

Table 1 - Characteristics of patients with TDM indication

Characteristic	Patients with TDM indication N=345	
	N	Percent
Study site		
Iasi	111	29.4%
Bucharest	109	28.7%
Chernivtsi	125	81.2%
Demographics		
Age (years) (median, IQR)	48	37-60
Male	232	67.2%
BMI (Kg/m2) (median, IQR)	20.8	18.8-22.9
Living conditions		
Urban	130	37.7%
Rural	208	59.1%
Homeless	9	2.6%
Lifestyle		
Current smoker	175	51%
Former smoker	39	11.3%
Currently consuming alcohol	187	65.8%
Comorbidities		
Asthma	0	
COPD	70	20.3%
Cancer	7	2%
Cardio-vascular	136	39.4%
Gastro-intestinal (including chronic gastritis, ulcer)	72	20.9%
Cirrhosis of the liver	8	2.3%

Chronic kidney disease	12	3.5%
Number of comorbidities (mean, SD)	1.16	0.99
TB characteristics		
New case	283	82%
Rapid relapse (previous TB under 2 years ago)	16	4.6%
Number of symptoms at initial presentation (median, IQR)	4	2-5.5
Anatomical site		
Lung	274	79.4%
Pleural TB without lung involvement	14	4.1%
Lung and extrapulmonary	31	9%
Extrapulmonary other than pleura	26	7.5%
Chest X-Ray		
Pulmonary TB with both lungs involved	246	71.3%
At least one cavity present	191	55.5%
Fibrosis present	38	11%
Sputum		
Negative	55	15.9%
Paucibacillar	35	10.1%
+ (10-99 bacilli/100 fields)	46	13.3%
++(1-9 bacilli/field)	89	25.8%
+++(>9 bacilli/field)	91	26.4%
Culture		
Negative	12	3.5%
1-9 colonies	57	16.5%
10-100 colonies	126	36.5%
> 100 colonies	122	35.4%

Patients with TDM indication stayed in the hospital a median of 67 days (33.5-98), in contrast with patients without a TDM indication who stayed a median of 25 days (23-64). Increased liver enzymes were observed in 31.9% of the patients with TDM indication, with 7.3% having a >5 times elevation in ASAT. For eGFR, 19.4% had abnormal eGFR during hospitalisation, with 2.3% having acute kidney injury (defined by a decrease in eGFR of >50%). The time recorded for the abnormal values -either hepatic or renal- to improve and/or normalise was a median of 33 days (19-60), and

17.6% of patients with abnormal values did not record a significant improvement despite clinical measures taken, including supportive measures and medication alteration.

Side effects were reported in 24.6% of patients with TDM indication, the most frequent being gastro-intestinal (e.g. nausea) in 7.8% of cases, and 2% presenting a severe allergic reaction.

Clinical measures taken to improve laboratory parameters or mitigate side effects included supportive treatment (3.5%), lowered dosages of TB drugs (4.4%), pausing TB medication for more than 7 days (4.6%). The clinical decision to stop and/or switch TB medication was made for 15.4% of patients with TDM indication (versus for 0.7% in patients without TDM indication). The most frequently involved drugs were pyrazinamide, which was replaced for a fluoroquinolone, either levofloxacin or ofloxacin (8/25), with the rest of the cases some other first line medications being switched for a fluoroquinolone, and in five cases for a combination including an injectable drug (amikacin or kanamycin).

Concerning WHO TB outcomes, patients with TDM indication achieved treatment success in 86.6% and 88% in patients without TDM indication. Death was recorded in 5.7% of patients with TDM indication and 6.7% in patients without TDM indication. Treatment duration was a median of two months more for patients with TDM indication (8 months, IQR 6-10 versus 6 months, IQR 6-8) (Table 2)

Table 2: TB Treatment outcomes of participants without and with guideline TDM indication

Characteristics	Participants without TDM indication, N=567	Participants with TDM indication, N=345
Treatment duration, months (IQR)	6 (6-8)	8 (6-10)
Treatment success	497 (88%)	298 (86.6%)
Treatment failure	3 (0.6%)	1 (0.3%)
Death	36 (6.7%)	18 (5.7%)
Lost to follow up	29 (5.5%)	27 (8.3%)

Discussion

In this retrospective study of TDM opportunities in three centres in Romania and Ukraine in which TDM is not routinely performed, more than a third of the included patients with TB disease would have an indication for TDM if that strategy would be implemented, most commonly based on a slow response to treatment.

There were differences in the percentage of patients with TDM indication per centre: in Ukraine, 81.2% of hospitalised patients within the year 2019 had indication for TDM, whereas in Romania 29.4% and 28.7%. This reflects for example differences in admitted patients, with Ukraine having a majority of the RR-TB population. Additionally, it could reflect on differences of the base population of admission, where Ukraine has lower income than Romania and more RR-TB cases. In a system with fewer resources, the decision to treat in ambulatory regime is possibly made in more cases, despite national guidelines recommendations. The proportion of patients who achieved treatment success was comparable to patients without TDM indications but the treatment duration was longer, a fact in relation to guidelines recommending prolonging treatment based on delayed culture conversion.

This study demonstrates that more than a thief of patients (37.8%) were eligible for TDM according to the guidelines. Although the study sites were located in middle-income countries, another study with a similar methodology performed in Australia, showed a similar proportion of patients (35%) were eligible for TDM [14]. We speculate that this would indicate that roughly the same large proportion of patients would be eligible for TDM regardless of setting. This comes with potential challenges when considering the opportunity of implementing TDM.

In our study, guideline TDM indicators inherently selected clinically worse patients. This is concurrent with current knowledge that patients with comorbidities and/or more TB presentations are at higher risk of suboptimal treatment outcome or developing adverse drug related events. More than half (58.6%) of patients in our study were included on the basis of slow response to treatment, compared to only 9% in the previously mentioned Australian study, in which patients were more often

selected based on comorbidities (e.g. diabetes mellitus). Factors influencing time to culture conversion in HIV-negative DS-TB patients include the presence of diabetes mellitus and extensive disease, smoking, and alcohol consumption [15]. For MDR-TB patients, one study has concluded that the main risk factors for delayed culture conversion are high smear grade, smoking, alcohol consumption, and ofloxacin resistance [16]. In our study, patients with TDM indication were more frequently consuming alcohol, had more comorbidities, and tended to have more severe disease, with higher smear grade and culture results, bilateral lung involvement, and more of them having cavitary disease. However, as culture conversion depends on various clinical parameters, it should not be used alone to predict TB treatment effectiveness [17]. Furthermore, in an international survey TB experts responded that only 7% of those who perform TDM use slow response to treatment as a criterion to initiate TDM [18].

Guidelines recommend performing TDM if second-line drugs are present in the treatment scheme, regardless of resistance. Indeed, out of 92 patients who received second line medication [20], had DS-TB and were treated with either a fluoroquinolone and/or an injectable drug. The evidence seems to indicate that fluoroquinolones might be underdosed in patients with DR-TB [2] and, additionally, for DS-TB patients, rifampicin could affect moxifloxacin drug concentrations [21]. TDM could aid clinicians in both these cases. More robust studies are needed to clarify the benefit of TDM for fluoroquinolones in DS-TB [22].

Patients with TDM indication were hospitalised for a median duration of more than two months while patients without TDM indications were discharged after 35 days. The national TB guidelines of Romania and Ukraine recommend hospitalisation until at least microscopy of sputum is negative, preferably until culture negativity [23]. This means that patients with more severe disease, comorbidities, and side effects remain in hospital longer due to their condition. As mentioned earlier this mirrors the TDM indications. At the same time, despite TB outcomes according to the WHO not being statistically significantly different between groups, patients with TDM indication stayed on treatment for a median of two months more than patients without TDM indication, indicating that to achieve the same outcomes, more effort

and resources had to be involved. Taking in consideration estimates of additional hospitalisation costs per patient calculated on extended admission in Romania (4363 EUR) and Ukraine (1109 EUR) 2425 there is a potential economic benefit in addition to clinical benefit associated with treatment optimization of these hospitalised patients [19,20]. Implementing TDM can be associated with high costs, both considering dedicated machinery, (e.g. High-performance liquid chromatography, HPLC) and its consumables (assays) and trained personnel in its use. Willingness to implement TDM would be facilitated by additional evidence on cost-effectiveness. Evaluation of the impact of TDM should include strategies to identify patient categories and to collect and analyse data easily, e.g. by dried blood spots, saliva sampling or optimising use of HPLC tools. Depending on the approach of TDM e.g. dried blood spot and saliva sampling and prioritisation of specific patients, TDM could be a cost-effective intervention, especially in TB hospitals in university centres, which could have access to a HPLC machine from other departments. This would help to overcome one of the most important barriers to implementing TDM which is the perceived large costs associated with the technique [18]. Robust economic studies based on randomised clinical trials evaluating TDM are needed to clarify the cost effectiveness of implementing TDM, especially in lower income countries with high TB burdens.

Strengths & Limitations

This is a large-scale retrospective study in three centres relevant to the European region as Romania has one fourth of the TB cases in EU/EEA and Ukraine has fifth-highest number of confirmed cases of extensively drug-resistant TB in the world. Despite the retrospective nature of this study performed where TDM is not yet routinely implemented, data suggests potential benefits in implementing TDM in these settings based on the number of patients with a TDM indication, and that the decision to implement TDM should be considered on a centre by centre basis.

Conclusion

This study, performed in a high TB burden setting showed that more than a third of the TB patients are eligible for TDM according to current guidelines, most of them being included on the basis of slow response to treatment. In this context, waiting

for culture results collected two months after start of treatment delays the decision whether to perform TDM An alternative approach is to perform TDM after 1 or 2 weeks of treatment for those with risk factors for suboptimal drug exposure 5, for example the presence of cavities which would impair drug effectiveness due to lower penetration in the cavities, however, this decision should be mindful of existing resources. The decision to implement TDM in a certain setting should take into account patient profile, cost-effectiveness, potential benefits, and thus would warrant a randomised controlled trial to investigate further the potential TDM opportunities in low resource settings.

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Goedkoop is duurkoop
- old Dutch saying

2023

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Practices of Therapeutic Drug Monitoring in Tuberculosis: an International Survey

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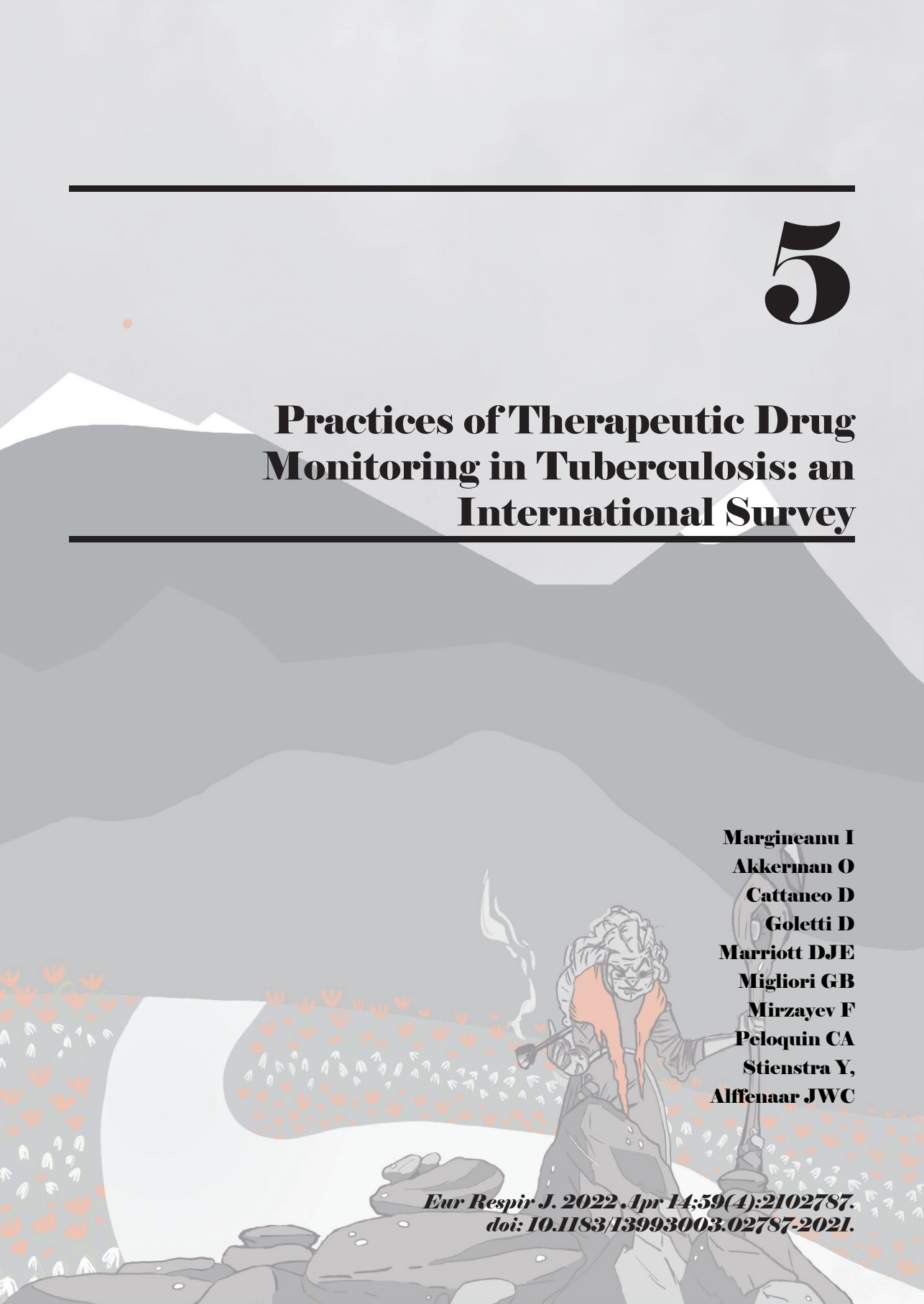

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Practices of therapeutic drug monitoring in tuberculosis: an international survey

Tuberculosis (TB), is still one of the top 10 causes of death in low and lower-middle income countries [1]. TB's long and complex treatment, side-effects, and development of resistant bacteria compromise treatment success. To improve treatment outcomes, therapeutic drug monitoring (TDM) has been included in TB treatment guidelines [2–4] to be considered for specific situations in which there is documented or expected poor response to treatment, drug toxicity, or a lower drug concentration. Several strategies for implementation of TDM for programmatic use have been proposed to overcome barriers to widespread use of TDM [5,6], including more accessible techniques such as dried-blood spot analysis or saliva and urine testing, [7] but uptake in programmatic care is still limited [8].

To understand current use and barriers and facilitators to implementing TDM in TB management we performed an electronic survey which can be found at this webpage: https://is.gd/TDMSurvey

The survey consisted of six sections asking participants if and how TDM is used in their setting. Several questions had multiple-choice answers. The survey was piloted by three of the co-authors (GB, DG, CP) and it took on average 15 minutes to complete. The survey was built in RedCap Systems and distributed through the Global Tuberculosis Network (160 email addresses), the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (638 email addresses), and the Global Drug-resistant TB Initiative members (400 email addresses).

Responses were received from 86 participants, spanning 46 countries across all seven continents (figure 1).

Participants worked as clinicians (19; 22%), pharmacists (31; 36%), researchers (34; 40%), and public health staff (8; 9%). Half worked as academic professionals (43; 50%). By type of medical facility, most participants worked in an university hospital (36; 42%), followed by tuberculosis expert centre (22; 26%), general hospital (18; 21%),

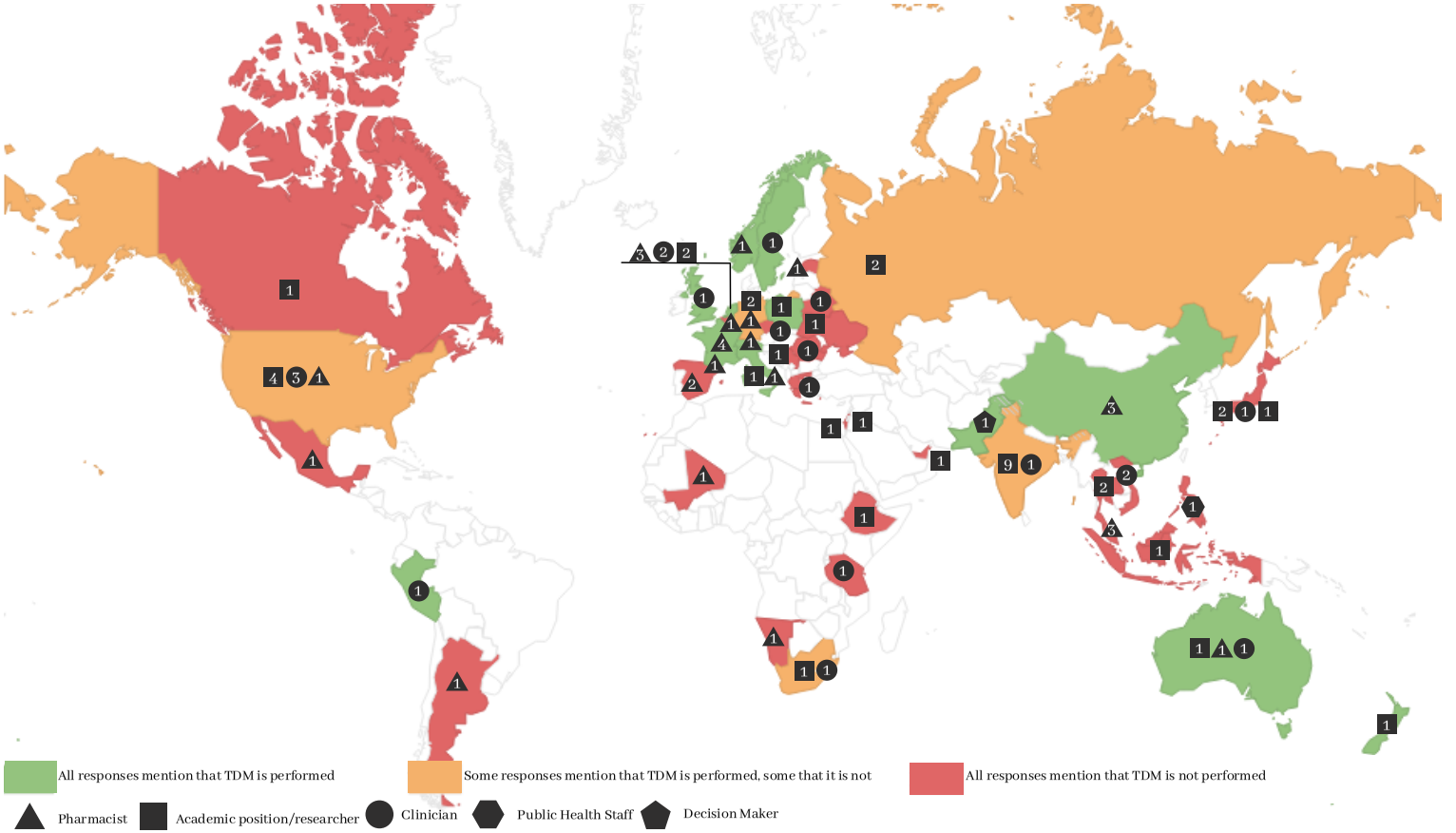

Figure 1: Survey responses

private hospital (9; 10%), infectious diseases centre (8; 9%), outpatient clinic (6; 7%), with several working in more than one facility (12; 13.9%). A majority answered on behalf of their institution only (60; 70%), with 11 (13%) and 15 (17%) responding for region and country respectively.

TDM was performed by 43 out of the total of 86 survey participants (50%), within a total of 18 countries. Those who undertook TDM, indicated the following reasons for initiation: gastro-intestinal abnormalities were the most common indication (24/43; 56%), followed by chronic kidney disease, cirrhosis, and HIV+ (22/43; 51%), acute kidney injury (20/43; 47%), diabetes mellitus (19/43; 44%), pregnancy (18/43; 42%), malnutrition (17/43; 40%), and age < 18 (9/43; 21%). Two participants mentioned that all patients were eligible for TDM and one included "COVID-19" as a comorbidity.

Approximately half of all participants reported performing TDM for all TB patients irrespective of drug susceptibility (18/43; 42%), followed by performing TDM if resistant to rifampicin +/- other first line agents (7/43; 16%), MDR-TB (3/43; 7%), XDR-TB (1/43; 2%), or applying additional criteria such as slow-response or rapid relapse (3/43; 7%) or other, undisclosed criteria (11/43; 26%).

Considering drugs for which TDM is performed, 12/43 (28%) performed TDM on all first line drugs and 27/43 (63%) performed on at least rifampicin. The second most frequent drug class analysed was aminoglycosides (17; 40%), followed by linezolid (16/43; 37%), fluoroquinolones (12/43; 27%), carbapenems (11/43; 26%), bedaquiline and cycloserine (9/43; 21%).

TDM was most often performed in pharmacology laboratories (21/43; 49%), followed by university laboratories (7/43; 16%), microbiology (4/43; 9%), public health institutions (4/43; 9%), private laboratories (4/43; 9%), chemistry laboratories (3/43; 7%). Sampling strategies varied, with 13 (30%) performing peak and trough concentrations, sampling at different time points for each drug (12/43; 28%), and collecting a full pharmacokinetic curve (6/43; 14%). The samples most often utilised for TDM were plasma and serum (20/43; 47%), with a few participants reporting they performed TDM on dried blood spot samples (3/43; 7%), saliva or cerebro-spinal fluid (2/43; 5%). More than half of responses (24; 56%) indicated that drug assays were

validated according to FDA, CLSI or EMA guidelines.

Participants indicated that TDM results were received in under five days in 15(35%), in five-ten days (9/43; 21%), or more than 10 days (3/43; 7%) and that they would use TDM results as advice for dose adjustment (25/43; 58%), changing the drug (12/43; 28%), or change in route of administration (11/43; 26%).

Participants utilised a variety of guidelines to perform TDM: national guidelines (10/43; 23%), specific articles (9/43; 21%), international guidelines (8/43; 19%), facility guidelines (5/43; 12%).

TDM was most often paid for by public healthcare or health insurance (21/43; 49%). Alternative sources of funding were TB-specific research grants (6/43; 14%), hospital funds (6/43; 14%) or the patients themselves (5/43; 12%).

The following responses arose from questions open to all 86 participants, regardless of whether or not they performed TDM. Concerning costs, approximately half the participants considered TDM to be cost-effective (39/86; 45%), with some (8/86; 9%) stating it depended on several factors, such as long term dosing, length of hospital stay, and choosing the right patients for TDM. A minority considered TDM not cost-effective (8/86; 9%) and the rest responded that they do not know the answer to this question (31/86; 36%). Furthermore, participants would predominantly spend a maximum of 20 euros (14/86; 16%) or 10 euros (14/86; 16%) per assay, with some reporting they would go up to 50 euros (5/86; 6%) or even 100 euros (5/86; 6%).

Participants reported the main barriers to TDM usage to be a lack of knowledge among the medical staff (32/86; 37%), followed by lack of funding and lack of guideline usage (30/86; 35%), no political/governmental will (17/86; 20%), TDM implementation costs were too high (11/86; 13%), and TDM implementation too complicated (6/86; 7%). One participant specifically mentioned that “many clinicians don’t necessarily agree with TDM”, and another explained that the workload is very high as it is, without introducing a new technique.

Participants indicated training efforts should focus on clinical/laboratory staff (29/86;

34%), then educate stakeholders (26/86; 30%), and finally, hospital administrators (18/86; 22%).

The present study is the first to investigate TDM use in TB through a worldwide survey.

Our survey showed that progress in TDM is being made, with half of the survey participants using TDM. Cheaper and easy to use assays [9–11], clinical guidelines [2–4] and laboratory quality control standards [12] are all increasing in availability. However, the main challenge is a lack of widespread information about TDM, with progress being recognised by participants who look towards guidelines and research when performing TDM.

Half of our responders work in an academic field, indicating that responses arrived from experts already using or interested in using the technique. One potential limiting factor is that even through choosing dissemination networks relevant to the field, we might not have captured a representative sample of the target population of potential TDM users.

Responses to our survey indicate that there is concern surrounding cost-effectiveness and the resources available in different settings to implement TDM. Robust research in diverse settings is needed through high quality studies which investigate and can better inform stakeholders of the potential long-term cost-savings TDM can provide [13].

The electronic survey is open for further data collection and, if you would like to contribute towards further research in this field, you are invited to complete it: https://is.gd/TDMSurvey

Acknowledgements

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I'm not foreign
No, I'm just human
-Sister Bliss & Rollo

6

Country-Specific Approaches to Latent Tuberculosis Screening Targeting Migrants in EU/EEA Countries:

A Survey of National Experts, September 2019 to February 2020

Margineanu I
Rustage K
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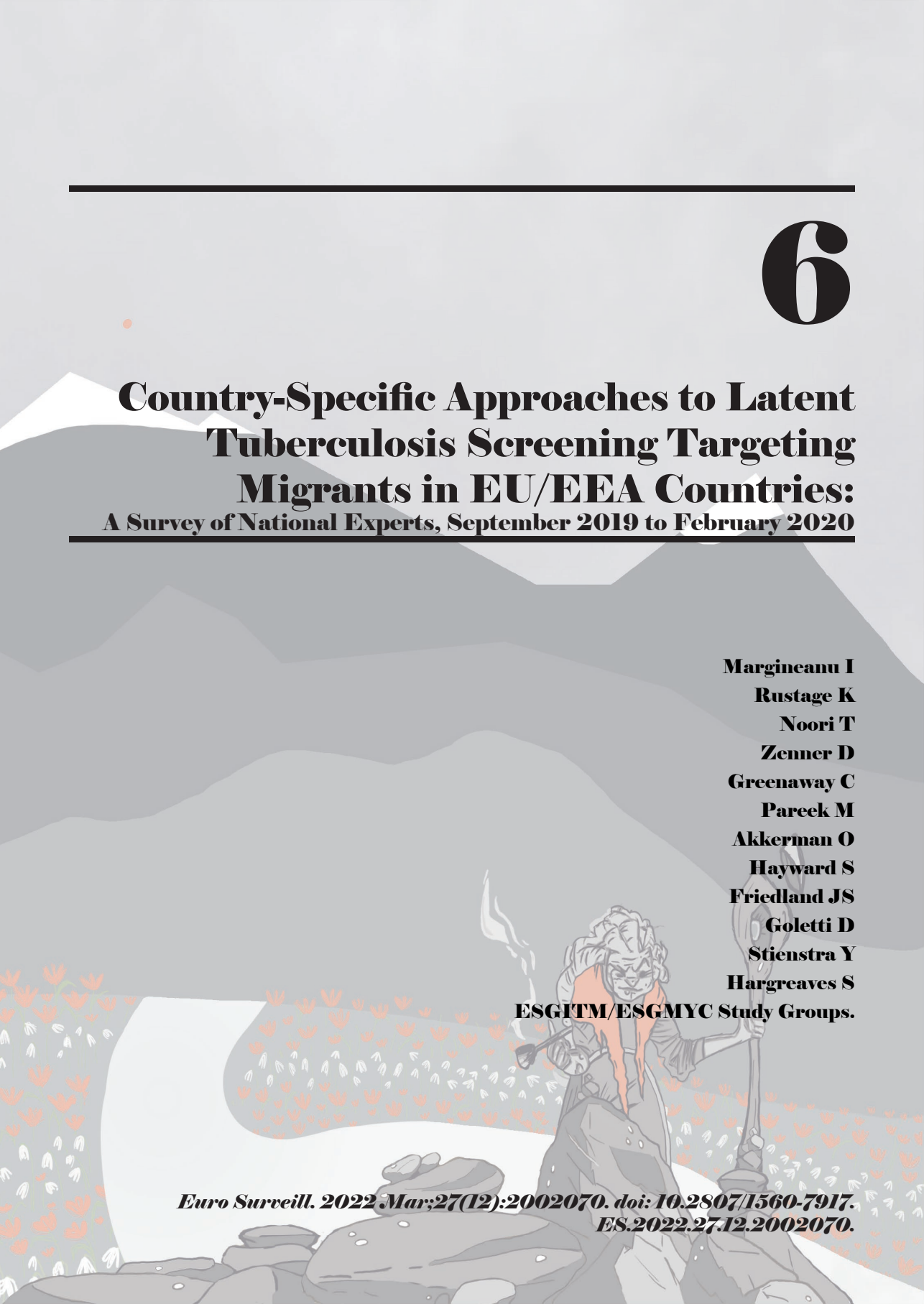
Friedland JS
Goletti D
Stienstra Y
Hargreaves S
ESGITM/ESGMYC Study Groups.



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Country-specific approaches to latent tuberculosis screening targeting migrants to EU/EEA countries: a survey of national experts, September 2019 to February 2020

Abstract

Background

Migrants to low TB incidence countries in the EU/EEA are an at-risk group for LTBI and are increasingly included in LTBI screening programmes. We investigated current approaches and implementation of LTBI screening in recently arrived migrants in the EU/EEA and Switzerland.

Methods

At least one TB expert working at a national level from each EU/EEA country and Switzerland completed an electronic questionnaire. We used descriptive analyses to calculate percentages, and framework analysis to synthesise free-text responses.

Results

Experts from 32 countries were approached (response rate 94%). 15 experts reported that their country has an LTBI screening programme targeting migrants; five reported plans to implement one in the near future; 10 reported having no programme. LTBI screening is addressed predominantly to asylum seekers (n=12) and refugees (n=11). Most (n=12) countries use 'country of origin' as the main eligibility criteria. Countries took similar approaches to diagnosis and treatment, with divergent approaches for follow-up. Six experts reported that migrants experience higher rates of drop-out compared to non-migrant groups for several reasons. Most experts (73%) called for a renewed focus on expanding efforts to screen for LTBI in migrants arriving in low-incidence countries.

Conclusion

Our data highlight a range of approaches to LTBI screening in migrants across EU/EEA. Experts are calling for a renewed focus on expanding and strengthening efforts to meaningfully include migrants in these programmes if we are to meet regional and global elimination targets for TB.

Introduction

Recent estimates place the current global latent tuberculosis infection (LTBI) prevalence at 1.3 billion people (roughly a fourth of the world population) [1–3]. There is likely a 5-15% rate of LTBI infections progressing to active disease, but this could be higher for at-risk groups [4,5], which includes migrants.

Recently arrived migrants (defined as foreign born individuals) moving from high incidence tuberculosis (TB) areas are thought to be an at-risk group for latent tuberculosis infection (LTBI) and potentially progression to active disease, particularly within the first 5 years of arrival [6,7]. Across the European Union (EU)/European Economic Area (EEA) countries, the majority of active TB cases in migrants are considered to be due to reactivation of LTBI infection acquired in their country of origin, with migrant populations facing a disproportionate burden of active disease [6,7].

Guidance from the European Centre for Disease Prevention and Control (ECDC) [8] recommends offering LTBI screening to all migrants from high-burden TB countries on arrival to low-incidence countries, and the World Health Organization (WHO) [6] have published guidelines in this area, yet it is not clear to what extent existing guidelines are followed [9] and the specific approaches taken by EU/EEA countries to screening and treat recently arrived migrants for LTBI, with an urgent need to explore lessons learned and share best practice [10,11].

One recent systematic review highlighted that in countries that focus efforts on identifying LTBI positive migrants on arrival, only 54% of migrants with a positive LTBI test complete treatment [4], raising questions around how successful these programmes are in including migrant patients and engaging them in the screening and treatment pathway. Evolving treatment options, including shorter treatment regimens, could dramatically improve delivery of LTBI programmes in at-risk groups. Particular efforts [12] are also now being made to engage under-served, and diverse groups, including migrants in personalised and culturally tailored TB treatment schemes, which are equally applicable to LTBI programmes, and could improve treatment outcomes particularly when combined with newer treatment options.

Current research indicates the effectiveness and cost-effectiveness of LTBI screening and treatment is limited but could be improved through strengthening care cascades and tailored screening to specific groups [10,13,14], yet it is unclear to what extent EU/EEA countries are adapting services to specifically respond to the needs of migrants, and numerous questions around optimal approaches remain [15].

We therefore did an electronic questionnaire survey, approaching national TB experts from all EU/EEA countries and Switzerland, exploring current approaches to LTBI screening in recently arrived migrants and perspectives around policy and practice across the Region.

Methods

Approach to questionnaire development

We developed an electronic questionnaire survey containing structured and open-ended questions around country specific LTBI screening policies for recently arrived migrants in the EU/EEA and Switzerland. Switzerland was included because the country has been hosting large numbers of refugees since 2015. This approach of engaging national experts has been successfully used previously [16]. For survey development we sought expert input from members of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Travellers and Migrants (ESGITM) and Study Group for Mycobacterial Infections (ESGMYC). The questionnaire was designed to take 15 minutes to complete and comprised five sections dealing with different aspects of LTBI management: Current approach, policies, and practice for LTBI screening in recently arrived migrants, approaches to diagnosis, treatment, and follow-up, and innovations and next steps in delivery of LTBI screening to migrants. The survey contained open-ended questions to gain broader perspectives from across the region on the future of LTBI policies and practice.

For the purposes of this research, we defined recently arrived migrants as a “foreign-born person, in the host country for <10 years”, a refugee as an individual “granted asylum in the host country” and an asylum seeker as “awaiting a decision on their

asylum application in the host country". Definitions were presented at the beginning of the questionnaire (Supplement 1).

The questionnaire was piloted with two TB experts and their input was used to refine and improve the final questionnaire. These experts were excluded from the analysis.

The questionnaire was written in English and translated upon request.

Approach and data analysis

We approached experts in all 32 EU/EEA countries and Switzerland. We drew on the expertise of members of the ESGITM and ESGMYC network to support us in identifying key TB/LTBI experts in each country and to identify the expert either responsible or with direct knowledge of the current national TB/LTBI programme. If the expert initially approached was not directly involved in the national TB/LTBI programme, we identified the correct expert either through consultation with other existing experts within the country or by performing digital searches through PubMed to identify country-specific TB/LTBI publications and approached senior and first authors and through official National Websites. We aimed to identify one expert per country working at the national level within the field of tuberculosis, for example within the Ministry of Health, a Public Health Institution, a National Tuberculosis Programmes or equivalent. Contact was made via email and with telephone follow-up calls where needed. Experts were contacted between September 2019 and February 2020, and for those who agreed to take part a questionnaire survey was sent via email. A first reminder was sent after 10 days, and subsequent reminders each consecutive week where needed. Experts were asked to complete the electronic form and email it back to us.

The 32 countries from which we approached experts were: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom.

Data were extracted from the completed questionnaires by one researcher (IM) in Microsoft Excel, and the process was duplicated by a second researcher (KR). Descriptive analysis was performed to calculate percentages and proportions. A framework analysis was conducted to synthesise free-text responses to the open-ended questions. Data on TB incidences of countries were extracted from WHO figures [17]. Raw data is kept on a secure server located in the Rijksuniversiteit Groningen/ University Medical Centrum Groningen. The study meets all the Universities GDPR requirements. No identifiable data is contained in any published materials.

Results

Survey response

30 of 32 (94%) approached experts completed the questionnaire. We were unable to ascertain a response from Hungary. Germany's expert reported back that policies for LTBI differed between the 16 different states within the federation and declined to participate because it was not possible to respond in a coherent way as having a "national" approach. Romania's expert requested to have the survey translated into Romanian, which was done.

For included surveys, three of the experts (10%) were working directly for Ministries of Health, 18 (60%) were affiliated with National Tuberculosis Programmes or Institutes, and nine (30%) were working within National Public Health or Communicable Diseases Institutions. Detailed information on the expert group and their expertise can be found in Supplement 2.

Implementation of LTBI screening programmes including migrants

Fifteen of 30 (50%) experts reported offering screening for recently arrived migrants for LTBI, with five having plans to implement LTBI screening in migrants in the future. Ten reported not having screening programmes for LTBI addressing migrants (Figure 1).

Among the 10 experts that reported not performing LTBI screening for recently arrived migrants, there were divergent responses in terms of the utility of screening and future directions. Seven of these 10 experts did not report any intention to

expand screening, citing that there were too few migrants in the country to make it worthwhile, and a lack of evidence of cost effectiveness (a comment from one expert from a country with TB incidence of 8.4 per 100,000 cases). Other experts in countries not performing screening programmes, criticised a lack of clear international recommendation for LTBI screening. One expert reported that they had a high incidence of active TB (44 per 100.000 cases), and were instead focused on this. Three experts said they were enthusiastic about future LTBI screening in migrants but requested more data on effectiveness and emphasised the need to convince governmental bodies of the utility of LTBI screening.

Current approaches to LTBI screening in migrants

The majority, 12 of 15 (80%) experts in countries with LTBI programmes reported including asylum seekers and/or refugees. Nine (60%) reported including also undocumented migrants; eight (53%) students; seven (46%) labour migrants. Six (40%) experts report screening all these different categories of migrants (Figure 2A).

Experts in nine of 15 (60%) countries reported that LTBI screening in recently arrived migrants is performed after settlement; seven (47%) of 15 report performing screening at the time of arrival (two experts reported performing screening at the time of arrival and after settlement) with one (7%) expert reporting that LTBI screening was done in migrants additionally before arrival through pre-departure screening programmes. Eight (53%) experts report screening recently arrived migrants through either primary care or tertiary facilities (e.g. specialised TB centres), six (40%) report screening within refugee camps, and five (33%) in specialist migrant centres or HIV centres.

Nine of 15 (60%) experts reported screening on the basis of age, of which six reported focusing solely on migrants under 18 years of age, one screening the 19-35 years category, and the remaining two experts reported including all migrants under 36 years of age. Further, ten experts (67%) reported including migrants who are contacts of active TB cases and eight experts (53%) reported including migrants based on comorbidities, with all eight including HIV+ patients and persons on immunosuppressive treatment (figure 2B).

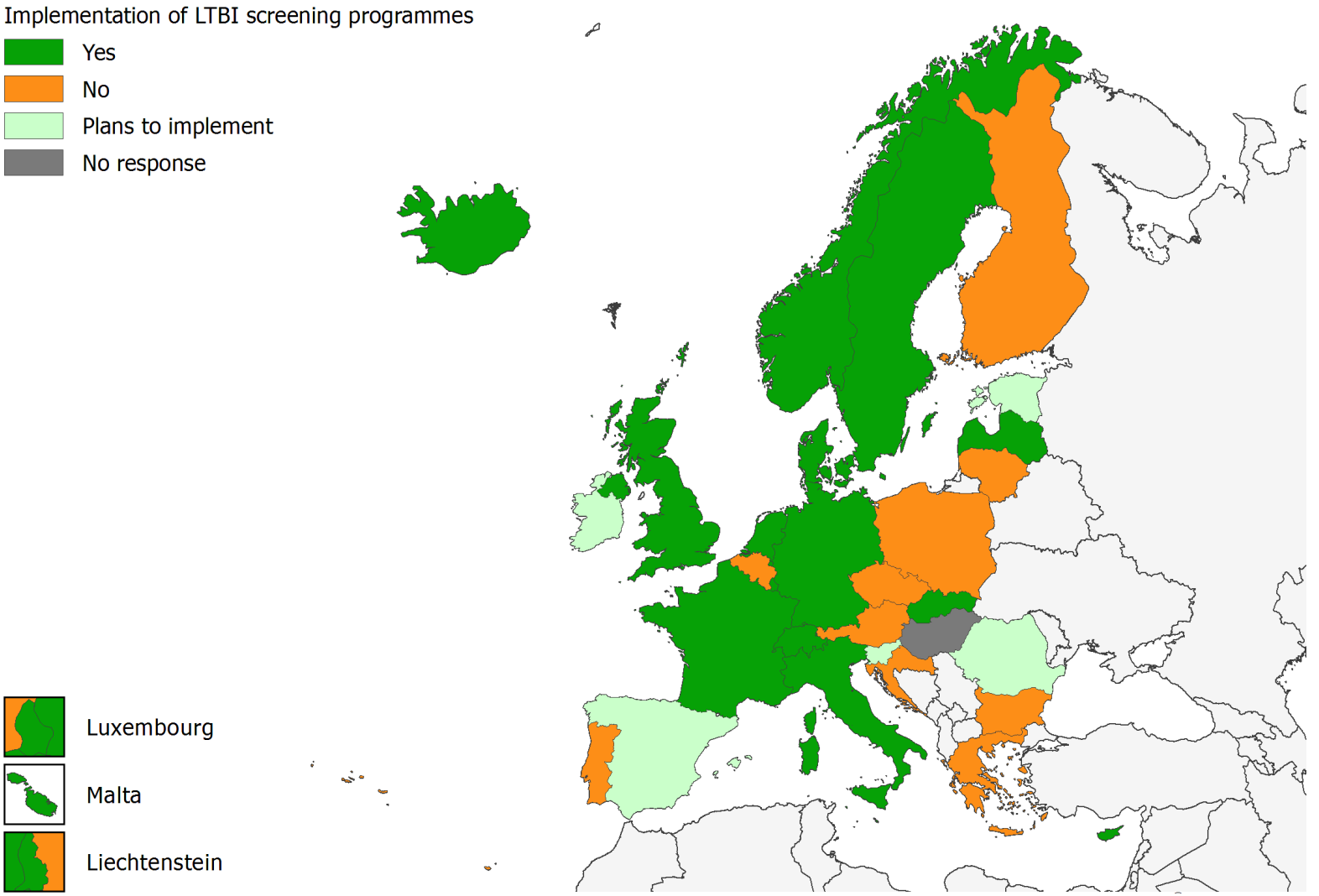

Figure 1: Implementation of LTBI screening programmes across the Eu/EEA+Switzerland

Twelve of 15 (80%) experts reported screening based on migrants' country of origin, ten (67%) taking into consideration TB incidence within the originating country, and two (13%) basing screening on defined geographical areas such as Africa, Asia, and the Middle East. The threshold for defining high incidence countries of origin for presenting migrants varied between countries. We found that participating countries used a range of definitions for a high-burden country ranging from 40 cases per 100,000 to 200 cases per 100,000 (figure 2B).

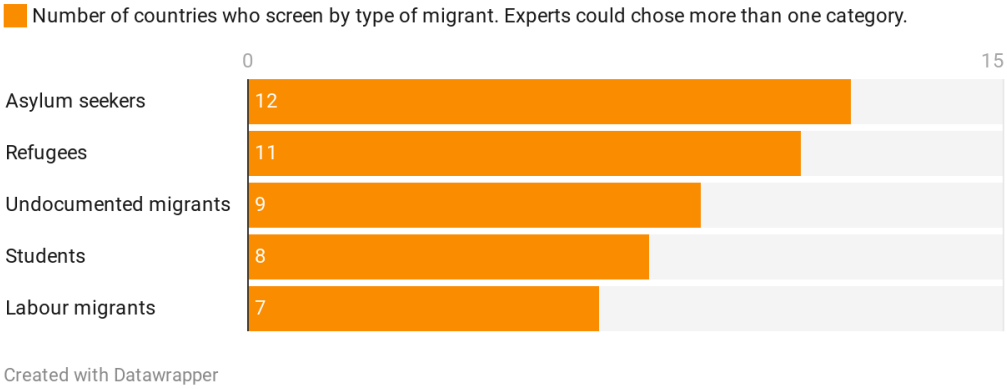

Figure 2A: Number of countries who screen by type of migrant

Diagnosis, treatment, and follow-up approaches

Thirteen of 15 (86%) experts who reported existing LTBI screening programmes including migrants reported using either tuberculin skin-test (TST) and/or interferon gamma release assays (IGRAs) to screen for LTBI and ten of 15 (67%) reported using an X-Ray in the diagnostic work-up. Diagnostic procedures differed by country and the approach was dependent on several factors, including the presence of BCG scar (2 experts), age (5 experts) or area of work (visa migrants or migrants working in healthcare facilities, 2 experts).

In terms of treatment approach, ten of 15 (67%) reported offering treatment to all migrants diagnosed with LTBI within their country, with two (13%) only offering treatment to younger adults (under 40 years and under 35 years). All experts reported that their countries followed at least one of the recommended regimens: Rifampicin and Isoniazid (3 months), Rifampicin (4 months), or Isoniazid (6 or 9 months). Seven

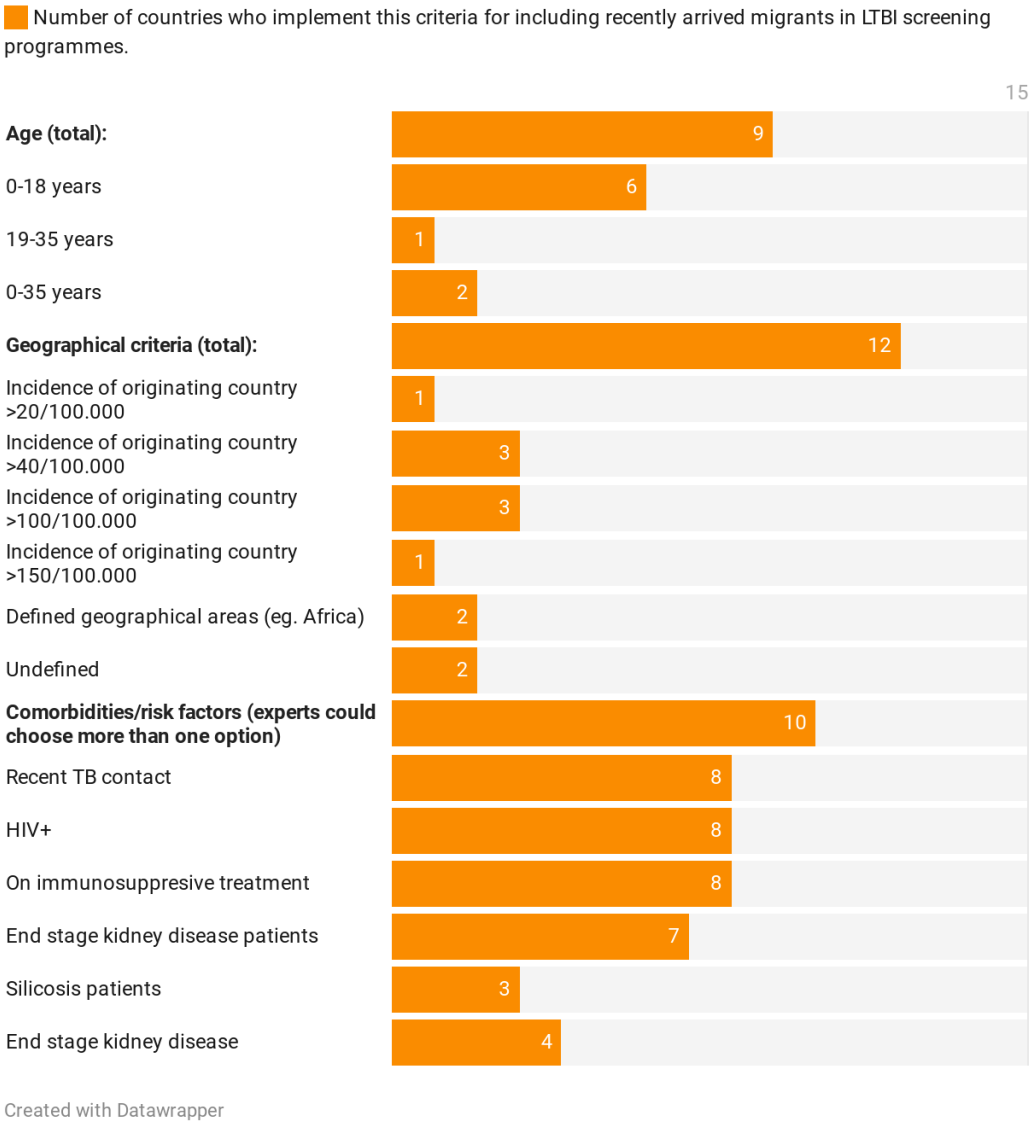

Figure 2B: Number of countries who screen by type of migrant

of 15 (46%) reported having the shortest treatment as the first option. One expert noted that Rifampicin is expensive in their local context and thus the Isoniazid-based longer regimen is preferred.

Duration and frequency of follow-up varied across countries. Fourteen of 15 (93%) experts reported that systems were in place to follow up migrant patients, with all performing liver enzyme tests to evaluate the potential liver toxicity of the drugs.

However, they reported variations in time-frames for follow-up, with six (40%) reporting monthly follow-up visits, one (7%) reporting performing at week two, then at one month and one (7%) at week two-four-eight. Twenty-four month follow up was performed in two (13%) countries. Seven (47%) offer counselling and/or peer-based support during treatment and follow-up.

Of the 15 experts who reported performing LTBI screening in recently arrived migrants, 12 (80%) offer all LTBI screening and treatment free of charge. Of the three who reported not offering it free of charge, one (7%) reported offering it free for migrants lacking social security, one (7%) only if the migrants are under 18 years of age, and one (7%) reported that only the treatment element is free of charge.

Migrant drop out in LTBI screening programmes and current challenges

Six of 15 (40%) experts reported that migrants experience higher rates of drop-out in their view compared to the non-migrant population. Five (33%) reported no differences in dropout rates and four (26%) reported that the situation was unclear or they were unaware of any differences. Most experts, eight of 15 (53%) reported that adherence to treatment for LTBI was the biggest challenge, whilst three experts (20%) noted that engaging migrants in screening is difficult, with a range of other factors identified (Figure 3). Reasons mentioned for dropout were migrants' lack of motivation and language barriers (8; 53%), relocation (7; 46%), competing priorities of the migrants (5; 33%) (Figure 3).

Views of experts on existing guidelines and current practice

Fourteen of 15 (93%) experts reported that their country used the national guideline on who to screen, eight used WHO guidelines, and six used ECDC guidelines.

Eight experts (53%) reported a number of effective ways of engaging migrants better in LTBI screening programmes. Responses ranged from building greater awareness amongst migrants about LTBI screening through leaflets and educational campaigns to translating materials in migrants' languages. In addition, delivering educational campaigns for medical staff, government officials, or the general public

about the importance of LTBI screening in migrants was deemed an important approach, alongside using technology to increase efficiency and dissemination and better tailoring of screening programmes specifically for migrants.

22 out of all (30) experts surveyed (73%) reported that we should expand efforts to screen for LTBI, especially for migrants coming from high-incidence countries into low-incidence countries, with all of 22 of the opinion that screening should be performed at the point of entry or holding level. 10 (33%) stated that a focus should also be given to screening within the community, and 2 (7%) after relocation. Going

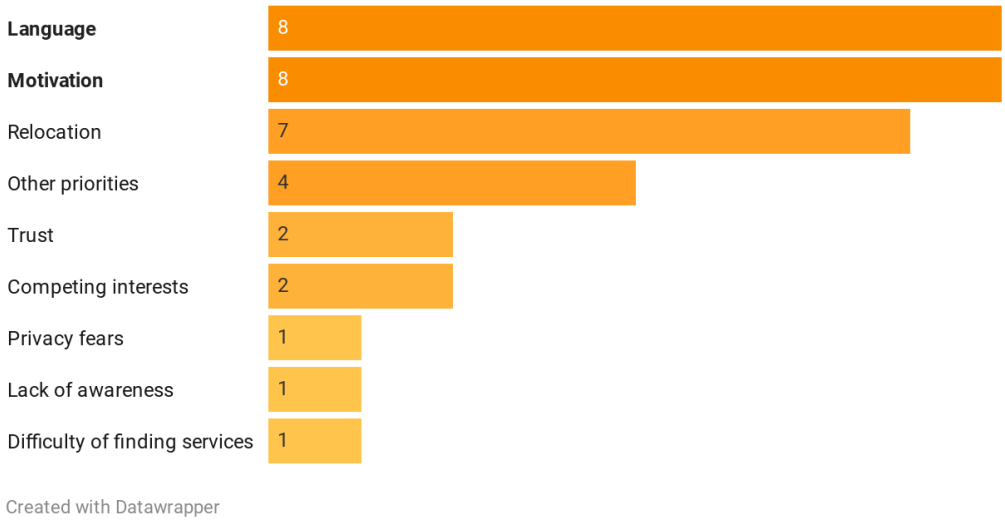

Figure 3: Reasons for migrants' dropout identified by experts

forward, experts highlighted a range of key priorities for strengthening the design and delivery of LTBI programmes including migrants in EU/EEA countries (Figure 4). The free-text responses highlight the expert's opinion that it is important to expand current programmes to include all types of migrants, to invest in LTBI programmes for migrants and to use technological tools and equipment to streamline this process.

Discussion

Half of reporting countries in the EU/EEA and Switzerland (15 of 30) are now operating an LTBI screening programme targeting migrants specifically, according to our survey, with five reporting plans to implement one in the near future. The

majority of experts called for a renewed focus on expanding efforts to screen for LTBI in migrants entering low-incidence countries. Screening programmes include mainly asylum seekers and refugees, with a focus on younger migrants (<36 years), addressing migrants after settlement in a range of settings. Most countries use country of origin as the main screening criteria, yet thresholds used by different European countries to define a high burden TB country of origin varied (from 40 cases per 100,000 to 200 cases per 100,000; or broad categories of Asia, Africa, Middle East), and by age-groups. Countries took similar approaches to diagnosis but used one of three different recommended treatment regimens, with divergent approaches to follow-up. Six country experts reported that migrants experience higher rates of drop-out compared to other groups for a range of reasons, suggesting that LTBI programmes may need to be strengthened to improve effectiveness and cost-effectiveness. Our data highlight a range of approaches to LTBI screening in migrants across EU/EEA countries and suggest that greater clarity and further evidence are needed around what constitutes an effective and cost-effective approach if we are to reduce the

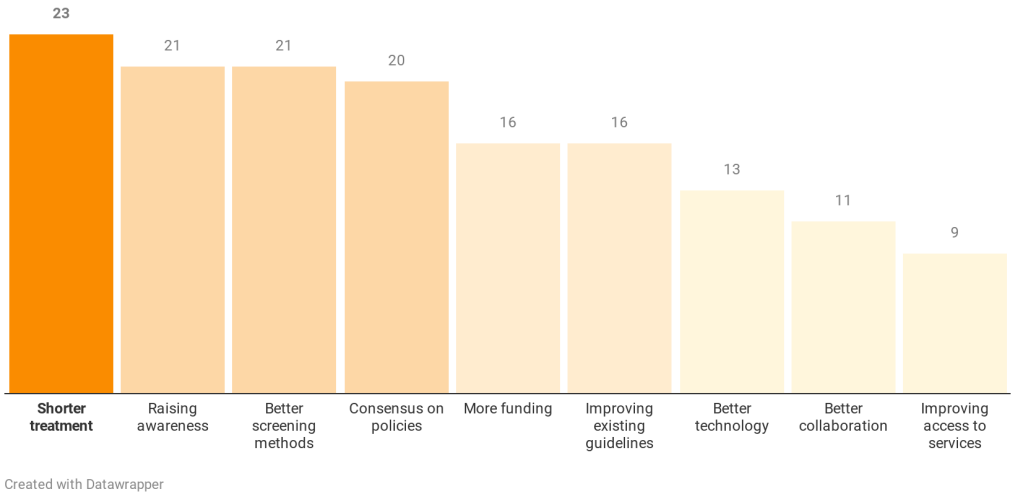

Figure 4: Priorities for LTBI screening according to experts

number of active TB cases and meet regional and global elimination targets.

This work builds on previous research and discourse around approaches to migrant LTBI screening. Kunst et al [18], in a 2017 systematic review of past data and recent surveillance data from certain EU/EEA countries on active TB and LTBI reported that countries use different definitions for coverage and yield of screening for active TB and LTBI and different screening strategies and settings, calling for a European platform for multi-country data collection and analysis, sharing of countries' policies and practices, and harmonisation of migrant screening strategies. This work also builds on similar findings from a previous study in which national-level European TB experts focusing on LTBI and active TB in refugees specifically, in which 19 out of 38 experts reported systematic screening in-country for LTBI in migrants who were refugees. Our study is broader and encompasses a focus on a wider group of migrants [19].

In our study, for example, we report a range of thresholds being adopted across EU/EEA countries for screening based on country of origin, but in many cases the rationale supporting the screening approach used remains unclear. Pareek et al [7] reported that screening for latent infection can be implemented cost-effectively with the two most cost-effective strategies reported to be to screen individuals from countries with a tuberculosis incidence of more than 250 cases per 100 000 (incremental cost-effectiveness ratio [ICER] was £17 956 [£1=US$1·60] per prevented case of tuberculosis) and a strategy of screening migrants from countries with more than 150 cases per 100 000 (including immigrants from the Indian subcontinent), which identified 92% of infected immigrants and prevented an additional 29 cases of active TB. The present study suggests that the approach of including mainly or exclusively migrant groups such as asylum seekers and refugees may need to be reconsidered. In our survey most countries reported including asylum seekers and refugees; however, this group of migrants form only a small subset of the total migrant population within EU/EEA countries from high-burden countries [20]. Furthermore, the top countries from which migrants arrive in the EU/EEA are high-incidence TB countries, the proportion of TB among migrants has increased from 10% in 2000 to 25% in 2010, and the main reported reason for active TB amongst migrants in the EU is reactivation of LTBI, suggesting that inclusion of a wider group of migrants is likely warranted [8,21].

Literature has shown that treatment adherence depends on multiple factors in migrants [4], which is supported by our study. Experts reported their view that migrants may experience higher rates of drop out than other groups, with reasons given in our survey including lack of motivation, competing interests, and language barriers. It is unclear to what extent divergent approaches to screening location and timing of screening after arrival may also play a key part. Guidelines [8,23] highlight the need for educational programmes and patient-centred LTBI management, and to ensure treatment is free of charge to migrants. Encouragingly, most countries in our survey reported not charging migrants for screening and treatment for LTBI.

Experts called for an expansion and strengthening of LTBI programmes addressed to migrants. This could include encompassing a wider range of migrants, a broader age spectrum, offering migrants tailored advice (including translating materials that address migrant-specific needs) and support, and combining LTBI screening with other diseases and service delivery models – i.e. vaccination, and other infectious diseases screening programmes that address migrants. Migrants face many barriers to accessing healthcare and a range of socio-economic, linguistic and cultural factors need to be considered. To improve such programmes will be critical to identify community-based approaches that engage migrants in the design and delivery of interventions. Data are needed to show the effectiveness and cost-effectiveness of these programmes to support governments in decision-making around the utility of such screening approaches.

A limitation of our study is that we asked nation-wide experts to reflect on current policies and practice, which implies we might have missed some local efforts which have not yet been implemented on a nation-wide level, and we are aware that experts may have differing views and knowledge levels. Considerable efforts were made to identify the correct respondent for each country, to mitigate against this and to identify the expert either responsible or with direct knowledge of the current national TB/LTBI programme. If the expert initially approached was not directly involved in the national TB/LTBI programme, we identified the correct expert either through consultation with other existing experts within the country or by performing digital searches and contacting the appropriate expert.

Conclusions

This survey provides policy makers and planners on the current state of play with respect to LTBI screening approaches in EU/EEA countries. This could inform national and local decision-making to strengthen and develop these programmes and improve health outcomes in migrant populations across the EU/EEA and Switzerland as we move towards TB elimination targets [18]. Providing migrants with preventive health services, including migrants residing in high-income countries in the EU/EEA, is a core component of the universal health coverage agenda within the context of the 2030 Agenda for Sustainable Development and its associated Goals [15].

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Conflict of interest

The authors report no conflict of interest.

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Supplementary material

Supplement 1 - Survey

This supplementary material is hosted by Eurosurveillance as supporting information alongside the article "Country-specific approaches to latent tuberculosis screening targeting migrants to EU/EEA countries: a survey of national experts, 2020", on behalf of the authors, who remain responsible for the accuracy and appropriateness of the content. The same standards for ethics, copyright, attributions and permissions as for the article apply. Supplements are not edited by Eurosurveillance and the journal is not responsible for the maintenance of any links or email addresses provided therein.

ESGITM and ESGMYC survey of policy and practice for latent tuberculosis infection (LTBI) screening in migrant populations across Europe

We would value your input into a short survey to explore how EU/EEA countries approach LTBI screening in recently arrived migrants, on behalf of the ESCMID Study Group for Infections in Travellers and Migrants (ESGITM) and the ESCMID Study Group for Mycobacterial Infections (ESGMYC).

For the purposes of this survey, definitions are:

- Recently arrived migrant: Foreign-born, in the host country for <10 years
- Refugee: Granted asylum in the host country
- Asylum seeker: Awaiting a decision on their asylum application in host country

After completing the questionnaire, please return this form to: ismargineanu@gmail.com
Name: Click here to enter text.Email: Click here to enter text. Field of expertise: Click here to enter text.
Position: Click here to enter text.
Country of employment: Choose an item.
Section 1: Current screening approach in recently arrived migrants

Do you perform latent tuberculosis infection (LTBI) screening in your country for any population group?
Yes.
No
Do you target recently arrived migrants for LTBI screening in your country?
Yes. If Yes, please proceed to section 2.
No, but there are plans to perform LTBI screening for recently arrived migrants in the near future. Please shortly describe these plans whilst keeping in mind Sections 2-4: Click here to enter text.
No. Could you briefly explain the reasons for the current situation: Click here to enter text. If No, please proceed to section 5.

Section 2: Current LTBI screening approach in recently arrived migrants

Is LTBI screening mandatory for all recently arrived migrants?
Yes
No
Which categories of migrants do you screen for LTBI? [Select all that apply]

▯ All recently arrived foreign born nationals

▯Students

▯ Highly skilled labour migrants

▯Low-skilled labour migrants

▯Temporary workers

▯Refugees

▯Asylum seekers

▯Undocumented migrants

▯ Migrants who arrive through specific visa schemes, please define: Click here to enter text.

▯Other, please specify: Click here to enter text.

▯ LTBI screening performed based on other criteria rather than category of migrant

If you screen on the basis of migrant country of origin what are your specific criteria? [Select all that apply]

Burden of TB criterion:

▯Migrants from high burden countries. Please define a high burden country: Click here to enter text. per 100.000 population

▯Migrants from medium burden countries. Please define a high burden country: Click here to enter text. per 100.000 population

▯Migrants from low burden countries. Please define a high burden country: Click here to enter text. per 100.000 population

▯Other definition regarding burden: Click here to enter text.

▯Burden of TB in country of origin in not a criterion.

Geographical region criterion:

▯Migrants originating from the following geographical regions or countries (name all which apply): Click here to enter text.

▯Geographical region of TB not a criterion.

If you screen on the basis of age, what are the specific age groups you target? [Select all that apply]
▯0-18 years ▯ 19-35 years ▯36-65 years ▯≥66 years ▯Age not a criterion.

If you screen based on comorbidities/other criteria, which specific comorbidities in recently arrived migrant groups do you target? [Select all that apply]

▯HIV infection

▯any Immunosuppressive treatment
▯ only TNF-alpha inhibitors

▯Pulmonary fibrosis

▯End stage kidney disease

▯ Diabetes Mellitus

▯ Silicosis

▯Recent known contacts of infectious TB cases

▯Transplant

▯Other, please specify: Click here to enter text.

When is LTBI screening performed in recently arrived migrants? [Select all that apply]
▯Before arrival
▯On arrival
▯After some time during settlement phase
▯Other, please specify: Click here to enter text.
If you have selected more than one option, please explain what percentage and which types of migrants (if applicable) are screened at different time points: Click here to enter text.

Where is LTBI screening performed? [Select all that apply]

- ▯ In refugee camps
- ▯In holding centres (reception centres, detention centres)
- ▯Within HIV services
- ▯ Within antenatal services
- ▯In primary care
- ▯In specialist (tertiary) care
- ▯In specialist migrant health centres
- ▯As part of a pre-entry assessment
- ▯Through the visa programme
- ▯At the workplace or school
- ▯In other medical facilities
- ▯Other, please specify: Click here to enter text.

Section 3: Diagnosis and management approaches to LTBI

What are the screening methods you use in your LTBI screening for recently arrived migrants? [Select all that apply]

- ▯History suggestive for TB exposure
- ▯TST ▯IGRA QuantiFERON ▯IGRA T-SPOT
- ▯X-Ray (modifications suggesting previous/healed TB)
- ▯Other, please specify: Click here to enter text.

Do these screening methods differ based on certain criteria? [Select all that apply]

- ▯Yes, based on age. In what way? Click here to enter text.
- ▯Yes, based on country of origin. In what way? Click here to enter text.
- ▯Yes, based on type/context of migrant. In what way? Click here to enter text.
- ▯Yes, based on other criteria. Please specify: Click here to enter text.
- ▯ yes, based on the history/evidence of scar of BCG-vaccination

If you detect LTBI in a migrant, what is the approach taken?

- ▯All migrants with positive LTBI test are offered preventive therapy
- ▯Some migrants with positive LTBI testing undergo preventive therapy. Please state who specifically: Click here to enter text.
- ▯ Some migrants with positive LTBI testing are followed and observed. Please state who specifically: Click here to enter text. Please state how long they are observed: Click here to enter text.
- ▯No migrants with positive LTBI testing are offered preventive therapy

Which preventive therapy regime would you chose for eligible persons?

First choice: Drug Choose an item. for Click here to enter text. months
Second choice: Drug Choose an item. for Click here to enter text. months
Third choice: Drug Choose an item. for Click here to enter text. months

- ▯Other, please specify: Click here to enter text.

If you have mentioned more than one choice for preventive therapy, how do you choose between the different preventive therapy treatment approaches? Click here to enter text.

Do you monitor a recently arrived migrant who began preventive therapy?

- ▯Yes, all recently arrived migrants are followed-up, for Click here to enter text. months
- ▯Yes, only in specific cases: Click here to enter text., for Click here to enter text. months
- ▯No

Do you keep a record of all recently arrived migrants who have been screened, treated, or followed-up for LTBI?

- ▯Yes, for all recently arrived migrants
- ▯Yes, for some recently arrived migrants
- ▯No, we do not keep records

In those eligible to preventive therapy, before starting the therapy [Select all that apply]:

- ▯ Liver tests are performed (i.e. transaminases, bilirubine)
- ▯ Tests for HCV and HBV are performed (HCV-Ab, HBsAg/HBsAb)?

In those undergoing preventive therapy, during therapy:

- ▯ Drug toxicity is monitored by liver tests (i.e. transaminases, bilirubine). Please describe the

monitoring scheme: Click here to enter text.

IS the screening procedure and preventive therapy free of charge?:

▫ Yes

▫ No

▫Some aspects are free of charge: Click here to enter text.

In your country, do migrants experience higher rates of drop out compared to the host populations undergoing LTBI screening and treatment?

▫Yes (proceed to question 16)

▫No (proceed to section 4, question 18)

If Yes at question 19: in your opinion, on a national level, what key problems do migrant face with LTBI screening, treatment, or follow-up? [Select all that apply]

▫Engaging them in LTBI screening

▫Returning for their screening results

▫Initiating preventive therapy when they test positive for LTBI.

▫Adhering to preventive therapy

In your national screening programmes:

▫What percentage of migrants refuse treatment per annum Click here to enter text.

▫What percentage of migrants are lost to follow-up per annum Click here to enter text.

If yes at question 19, in your opinion what are the key issues that migrants face that make it more difficult for them to complete LTBI screening, treatment, or follow-up? [Select all that apply]

▫ relocation and housing issues

▫ trust issues with service providers

▫privacy fears

▫language barriers

▫other competing priorities

▫lack of motivation

▫high bureaucracy related to accessing screening

▫other reasons, please specify: Click here to enter text.

Section 4: Guidelines and practice

Are there specific national, regional, or international guidelines that you follow in your country for LTBI screening in recently arrived migrants?

▫Yes (proceed to question 23)

Please choose all that apply: ▫National guideline ▫ ECDC ▫ CDC ▫ IOM ▫WHO ▫Other, please specify: Click here to enter text.

▫No (proceed to question 25)

On a scale from 1 to 10 with 1 being "not at all important" and 10 being "very important", how important are the guidelines you are using in your clinical decision-making process regarding LTBI screening in recently arrived migrants?

Choose an item: Choose an item.

Are you satisfied with the guidelines available in guiding your approach to LTBI screening in recently arrived migrants?

▫Yes

▫No: please explain why Click here to enter text.

Section 5: Next steps in delivery of LTBI screening to migrant populations

Are you aware of any innovative approaches in your country to raise awareness of LTBI screening (e.g. educational campaigns, leaflets on arrival, outreach programmes) or ensure capturing and adherence of migrants in LTBI screening? Please describe them briefly here: Click here to enter text.

In your opinion, is it the right approach to expand LTBI screening programmes across the EU/EEA targeting recently arrived migrants?

▫Yes, short description of reasons: Click here to enter text.

▫No, short description of reasons: Click here to enter text.

In your opinion, at what stage in the migration process should LTBI screening be offered?
▯Pre-entry, in the countries of origin
▯At the point of entry
▯At the holding level (reception centres, refugee camps, detention centres)
▯Within the community after arrival e.g., primary care
▯By employers/schools before or after arrival
▯Once residence status has been gained (e.g. granted asylum)
▯Other, please specify: Click here to enter text.

In your view, what needs to change in terms of current approaches to LTBI screening programmes targeting recently arrived migrants in your country? Click here to enter text.

Please state if you believe any of these steps would be a priority to improving LTBI screening approaches targeting recently arrived migrants:

Step	Priority	
Developing migrant specific LTBI guidelines	▯	▯
More regional/national funding for LTBI screening in migrants across EU/EEA region	▯	▯
Finding a better consensus on which specific recently arrived migrants should be targeted for LTBI screening on or after arrival	▯	▯
Better collaboration with the originating countries of dominant migrant groups to the EU/EEA	▯	▯
Improved awareness raising/education amongst migrant populations about the benefits of screening and treatment for LTBI	▯	▯
Investing in newer/better methods of LTBI screening	▯	▯
Improving access to existing/current LTBI screening methods		
Adopting/promoting shorter treatment options	▯	▯
Investing in newer technology or software to aid in the LTBI screening and management process	▯	▯
Other, please specify: Click here to enter text.		

On behalf of the ESGITM/ESGMYC we would like to thank you for completing this questionnaire.
University Medical Centrum Groningen (Ioana Margineanu, Ymkje Stienstra)

St George's University of London
MARIE CURIE ALUMNI
Pronkjewail
Istituto Nazionale per le Malattie Infettive IRCCS L. Spallanzani
ESCMID MANAGING I PROMOTING

Supplement 2: Institutions of participating experts

This supplementary material is hosted by Eurosurveillance as supporting information alongside the article "Country-specific approaches to latent tuberculosis screening targeting migrants to EU/EEA countries: a survey of national experts, 2020", on behalf of the authors, who remain responsible for the accuracy and appropriateness of the content. The same standards for ethics, copyright, attributions and permissions as for the article apply. Supplements are not edited by Eurosurveillance and the journal is not responsible for the maintenance of any links or email addresses provided therein.

Country	Institution	Area of Expertise
Austria	Ministry of Health	Public Health/Infectious Diseases
Belgium	National Tuberculosis Association	Public Health/Respiratory Diseases
Bulgaria	National Tuberculosis Programme	Public Health/Tuberculosis in Children
Croatia	National Public Health Institute	Public Health/Epidemiology
Cyprus	National Public Health Institute	Infectious Diseases/ Tuberculosis
Czech Republic	National Tuberculosis Programme	Epidemiology/Tuberculosis
Denmark	Infectious Diseases Surveillance Unit	Infectious Diseases/ Tuberculosis
Estonia	National Tuberculosis Programme	Multi drug resistant tuberculosis
Finland	National Tuberculosis Programme	Tuberculosis Epidemiology/ Surveillance/Control
France	National Tuberculosis Prevention Network	Tuberculosis
Greece	National Tuberculosis Hospital	Multi drug resistant tuberculosis
Iceland	National Tuberculosis Programme	Respiratory Diseases
Ireland	National Public Health Institute	Public Health
Italy	Ministry of Health, National Public Health Institute	Tuberculosis
Latvia	National Public Health Institute	Public Health
Lithuania	Ministry of Health	Respiratory Diseases
Luxembourg	National Infectious Diseases Control Unit	Infectious Diseases
Malta	National Infectious Diseases Control Unit	Infectious Diseases, Migrant Health
Netherlands	National Tuberculosis Programme	Public Health, Infectious Diseases
Norway	National Tuberculosis Programme	Respiratory Diseases
Poland	National Tuberculosis Programme	Microbiology
Portugal	National Tuberculosis Programme	Respiratory Diseases

Romania	National Tuberculosis Programme	Respiratory Diseases
Slovakia	National Tuberculosis Programme	Respiratory Diseases
Slovenia	National Tuberculosis Programme	Internal Medicine/Tuberculosis
Spain	National Tuberculosis Programme	Tuberculosis
Sweden	National Public Health Institute	Epidemiology, tuberculosis
Switzerland	National Tuberculosis Programme	Tuberculosis, Asylum seekers
Lichtenstein	National Tuberculosis Programme	Tuberculosis, Asylum seekers
United Kingdom	National Tuberculosis Programme	Tuberculosis

Ubi concordia, ibi victoria.
- Latin proverb

2023

7

Patients and Medical Staff Attitudes Toward the Future Inclusion of eHealth in Tuberculosis Management

Perspectives From Six Countries Evaluated Using a Qualitative Framework

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Patients and Medical Staff Attitudes Towards the Future Inclusion of eHealth in Tuberculosis Management: Perspectives from Six Countries Evaluated using a Qualitative Framework

Summary

Background

Digitally delivering healthcare services (eHealth) is very attractive for tuberculosis (TB) management, as this disease has a complex diagnosis, lengthy management, and involves multiple medical and non-medical specialists. Especially in low and middle income countries, eHealth could potentially offer cost-effective solutions to bridge financial, social, time and distance challenges.

Objectives

To understand what would make eHealth globally applicable and to gain insight into different TB situations, opportunities, and challenges.

Methods

We performed focus group interviews with TB experts and patients from six different countries on four different continents. The focus group interviews followed the theory of planned behaviour framework in order to offer structured recommendations for a versatile eHealth solution. The focus group interviews were preceded by a general demographic and technology usage questionnaire. Questionnaire results were analysed using basic statistics in Microsoft Excel. Focus group interview data was analysed using ATLAS.ti V.8 by assigning codes to quotations and grouping codes into the five domains within the framework.

Results

A total of 29 patients and 32 medical staff members were included in our study. All medical staff had used the Internet whereas nine (31%) of patients had never been online.

The codes with the most quotations were information in relation to eHealth (144 quotations) and communication (67 quotations). The consensus amongst all participants, from all countries is that there are important communication and information gaps which could be bridged by an eHealth application. Participants from different countries also highlighted different challenges, such as a majority of asylum seeker patients or lack of infrastructure which could be addressed by building an eHealth app.

Conclusion

Within the six countries interviewed there is high enthusiasm towards eHealth in TB. A potential app could first target information and communication gaps in tuberculosis, with additional modules aimed at setting-specific challenges.

Introduction

The continuous growth of Internet and smart technologies' availability have modified many aspects of life, including healthcare delivery. With more than half the world's population online [1], delivering health related services digitally has never been more appealing or accessible, with the electronic health (eHealth) market expected growth estimated at 22% by 2024 [2].

Tuberculosis (TB) is one the deadliest infectious diseases worldwide, with an estimated number of 1.5 million deaths yearly. The more resistant forms of TB, like multidrug resistant or extensively drug resistant pose a new threat, with treatment success rates between 50-60% globally. TB diagnosis is complex, its treatment is lengthy, and it requires close collaboration of different medical and non-medical experts, together with the patients, to ensure TB management is adequately performed, especially in challenging settings, such as patients living in remote locations or constrained by socio-economic factors.

Studies piloting various types of eHealth technologies and conducted around the world have evaluated multiple areas where eHealth could aid tuberculosis. From improving communication amongst medical staff [5] and with the patients [6], to reducing costs [7], and improving treatment indicators, especially in situations where patients were travelling [8] or in hard to reach regions [9], eHealth seems to be a promising field of research and an useful, cost-efficient, and acceptable improvement for tuberculosis.

On the other hand, multiple studies and reports, including a consumer report from the European Union [10] have observed that there are certain difficulties when implementing eHealth, such as lack of acceptance, unfavourable regulations, and insufficient funding [11]. The progress of eHealth in lower income countries is limited by lack of know-how, funding, technology and communications ability [12].

Taking into consideration the particular nature of tuberculosis and the population differences, together with the potential benefits and challenges of eHealth, tailored research would aid in creating useful, tailor-made eHealth apps. This idea

is recommended in multiple studies, including a recent review of smartphone applications [13]. Market research, defined as an "organised effort to gather information about target markets" [14], is an important component of any business strategy which aims to create a new product. In order to make sure a product is useful, acceptable, qualitative, market research is performed in order to understand the needs and preferences of the market. One of the frameworks which can be used to conduct market research is the theory of planned behaviour [15] which links psychological intent to three determinants: attitude towards behaviour, subjective norm, and perceived behavioural control. This theory attempts to explain behavioural intentions and has been previously used in numerous studies to investigate and explain intention and possible adoption rate of new interventions [16,17].

This study aims to identify potential users' perceptions about eHealth use in tuberculosis. We used the theory of planned behaviour framework to interview both TB experts and TB patients in six diverse countries from four different continents, in order to form recommendations for a well received, usable, comprehensive and efficient tuberculosis eHealth application.

Methods

Participants

Adult (over 18 years of age) participants from Romania, Greece, Netherlands, Indonesia, Ghana, and Venezuela were approached in the collaborating clinics and invited to participate through face-to-face conversations. Two participant groups per country were interviewed, one comprising of actual or former tuberculosis patients and one of the TB medical staff experts. Experts had to have worked in a TB clinic on a daily basis for at least three years. Participants were recruited through purposive sampling, by investigators visiting different medical facilities specialised in tuberculosis care. The target of participants was 2-6 per focus group as all the participants were highly involved with the topic of TB and a discussion in larger groups are not recommended [18].

Study design

The study was performed in two parts. The first phase comprised of a short questionnaire intended to collect demographic data and basic Internet and mobile usage statistics by asking the experience, in years and the number of hours per day spent using the Internet and smartphones, and a numbered scale on which participants ordered activities performed in order of frequency (with 5 being most frequent- and 1 less frequent). Activities were defined as "communication" (e.g. whatsapp, facebook messenger), "social media" (e.g. facebook, instagram), "utilities" (e.g. banking, weather), "work", games, and "health/medical".

The second part comprised of the semi-structured focus group interviews. Questions were designed to repeatedly ask the same subject in different ways, in order to achieve data saturation, irrespective of time needed. In order to adhere to qualitative reporting standards, the COREQ checklist was used [19].

In order to minimise the risk of bias, the researcher conducting the interviews had no previous history with either patients or the medical staff involved and conducted the interviews in a private room, with a homogeneous group, patients separated from medical staff. The interviews were conducted in the participants' native tongues or in a language they felt comfortable in, transcribed verbatim and translated by a native speaker with proficiency in English.

Framework

In order to develop a globally acceptable application, which can be used in different settings, interviews targeted diverse countries, with different cultures, socio-economic status, and tuberculosis populations. Thus, six different countries, Romania, Ghana, Indonesia, Greece, the Netherlands, and Venezuela were chosen with respect to have a mix of geography, socio-economic status, healthcare systems and tuberculosis profiles (table S1).

The focus groups followed a semi-structured framework based on the theory of planned behaviour (table 1). This psychological theory proposes that intention –in

our case, use of eHealth - has a number of determinants. The original work describes three main determinants and these were used in order not only to stay true to the framework, but also to guide interviews in a simple, efficient manner. The first is the attitude towards the behaviour, defined by the strength of the attitude and the evaluation of the outcome, favourable or unfavourable. The second is the subjective norm, or beliefs about the normative expectations of others, the perceived social pressure to perform or preclude from the behaviour. The last is the perceived ease or difficulty of performing the behaviour and is based on past experience as well as anticipated factors which might facilitate or impede a specific behaviour [15]. The last domain, "preferred features" was added to further stratify user preferences.

Ethics

The study was approved by the ethics committee of the initiating institute, the University Medical Centrum Groningen (METc 2017/448) and the medical facilities of each country participating in the study. All focus group participants signed informed consent expressing their volition to participate in the study.

Data collection and analysis

A thematic approach using ATLAS.ti software V.8 was used to analyse the transcripts by one investigator (IM) and reviewed by the supervisory authors. After identifying major themes in response to the questions asked and the theory of planned behaviour framework, the transcriptions were indexed using topic coding (table S2). Codes were assigned to phrases addressing an issue in the positive or negative (e.g. "Maybe if we use an app, [the process] would be made simpler" versus "[eHealth] would give us double the job") and were assigned whenever a quote was repeated by other participants in the focus group but not by the same participant. For clarification purposes, see definitions in text box S1. 100% of the coding was performed by two independent authors (IM, CL). Conflicts were resolved by discussions between the two coders, with the aid of one of the supervisors (YS).

Descriptive statistics were used to present quantitative results. Medians and interquartile ranges were used to present Internet and mobile experience. Codes

were reported as a total and, per domain and theme as proportions of the total.

Table 1 – Interview structure based on the theory of planned behaviour

Domain	Question
Attitude Toward Behaviour	Q1: Which problems/challenges in TB management could be solvable by an eHealth solution?
	Q1 follow-up: If you would have to prioritise, which would be the biggest challenge?
Subjective Norm	Q2 (two-part): How do you think the medical staff / patients here would react to the implementation of an eHealth solution?
	Q2 follow up: What do you think will be the biggest problem/motivator to accept and use eHealth?
Perceived ease/difficulty towards behaviour	Q3: Do you use technology regularly to assist with your work/patient life (for admitted patients)?
	Q3 follow-up A: Do you think the implementation of various software solutions have made your life (work/patient) easier or harder?
	Q3 follow-up B: Why?
	Q3 follow-up C: What could be done to a new eHealth app to make it really useful?
	Q4: Do you think implementing eHealth in your daily lives will be easy or difficult?
	Q4 follow-up A: Why?
	Q4 follow-up B: What would make it easier or harder to implement?
Preferred features	Q5: Name five features or things you would likely use most in an eHealth app.
	Q5 follow-up: Which one do you feel you need most? Which process of tuberculosis management would be most suitable to be streamlined through eHealth?

Results

General Questionnaire Results

A total of 29 patients and 32 medical staff members responded to the questionnaire and participated in the focus group. Four patients were former TB patients and had finished their treatment within six months of the interview, with the majority being current patients. Age ranged between 23 and 63 for patients and 30 and 60 for medical staff. Gender distribution was mostly male amongst patients (n=20 males, 68%) and mostly female (n=26 females, 81%) amongst medical staff. 19 patients (65%) and 22 medical staff (68%) lived in urban environments. Education levels were lower in patients groups than in the medical staff group: the highest level of education amongst patients was bachelor and amongst medical staff doctorate (PhD).

General Internet and mobile Internet usage was almost half within the patients group compared to the medical staff (figure 1): average years of experience using the Internet 6.1, [1-16] person-years versus 13.9 [5-35] person-years. All medical staff had used the Internet whereas 9 out of the total 29 patients (31%) had never been online. Concerning mobile phone usage, staff median experience was 7.4 [0.3-15] person-years versus 3.4 [0-10] person-years for patients. 13 patients (44%) have never used mobile data and 10 (34%) have never used a smartphone. Out of all patients' groups, the least tech savvy were the Romanians and the most were from Venezuela. From the medical staff groups, Ghana had the worst experience with the Internet and mobile, and the Netherlands the best. Internet and mobile usage in hours per day were lower for the low and middle-income countries than for the high income countries, but this correlation was observed only in the patients groups and not in the experts groups.

The 20 patients who use the Internet responded mostly employ it for communication (median 4/6), followed by social media (median 4/6), utilities (median 3/6), medical/health (median 2/6), work and games (median 1/6). For smartphones, the 18 patients ordered the categories the same, but with more patients using messenger (median 4.5/6) and less using for social media and utility (median 3/6).

The 32 staff members use the Internet mostly for communication and work (median

5/6), and the least use for games (median 1/5). Medical staff use smartphones also mostly for communication (median 5/6), followed by social media and work (4/6).

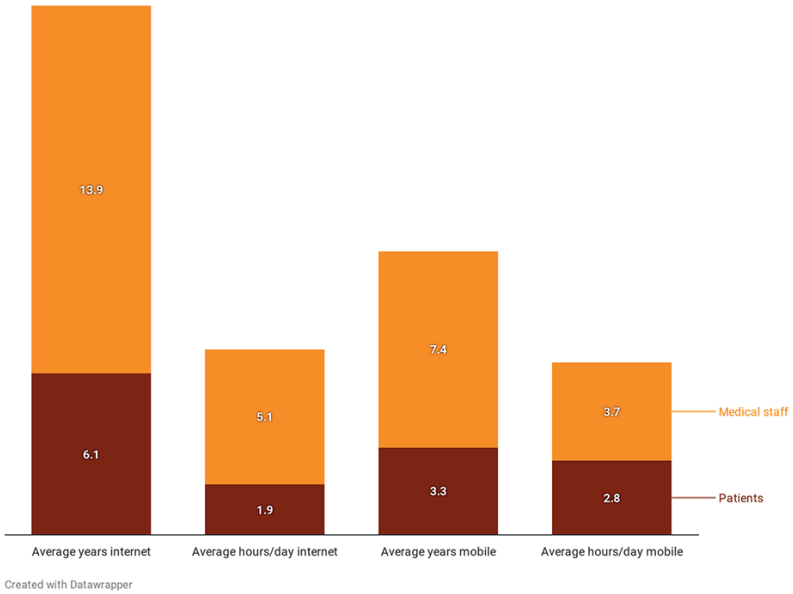

Figure 1 – Internet and mobile experience for the two participant groups

Focus group interviews – general results

The final yield was 13 focus group interviews, two per country; with 2 focus groups conducted with Dutch medical staff as the tuberculosis clinic and at the Municipal Health Center Groningen (a type of outpatient clinic) are geographically separated. The final duration of each interview ranged between 25 and 45 minutes.

By domain, "attitude towards behaviour" contained the most quotes, with "preferred features" containing the least (figure 2). By far the most discussed topic was the potential of eHealth to improve information and/or education concerning tuberculosis amongst patients, the public, and even medical staff (n=144 quotes). The countries which mentioned this aspect the most were Venezuela (55 quotes) and the Netherlands (31 quotes).

A summary of the most frequent themes/codes and example quotations can be found in table S3.

Thematic and Code Analysis

"Attitude Towards Behaviour" domain contained five codes, with a total yield of 339 quotations out of the total 911 quotations (37.2%), most of all domains (figure 5). Even though experience varied between patients and medical staff, both groups overwhelmingly explained that their outlook concerning implementing eHealth in tuberculosis is positive (n=292 quotes, 86.1%), with most expected impact in the information and communication fields.

Figure 2 – Quotes per domain

» Interviewer: W*hat would be the first priority when implementing an eHealth solution?*

Education. –Medical Staff, Romania «

FCG participant 1: Actually there is already a program for TB managing. It has been running actually, but not everyone used it. [referring to an electronic database for medical staff]. FCG participant 2: ***Maybe if using an app, [it] would make it simpler.***– Medical Staff, Indonesia «

Participants also offered examples of specific ways in which eHealth can improve tuberculosis management.

» ***It's important to really explain that the disease is treatable and to know more about this disease and to say that people can survive.*** – Patient, Venezuela «

Participants felt that speed, convenience, flexibility, and the ability to communicate and obtain information over long distances were very important factors contributing to a positive outcome.

»***And also the plain fact that they wouldn't have to come to the hospital could be a***

motive [to adopt an eHealth app] - Medical Staff, Greece «

Although the expected outcome is mostly positive, some challenges have been identified, such as a need for personal contact. Interestingly, within the same focus group, one person believed an app would enhance contact and others did not:

»Participant no.1: ***The fault is the lack of contact in DOT and an app could do that.*** Participant no.2: ***Yes, but nothing can replace the live contact.*** - Medical Staff, the Netherlands «

Furthermore, patients mentioned a need for trustworthy sources of information, and some medical staff were concerned about patients intruding on their personal time if the app were to be on their personal phones or of doubling the workload (traditional system and eHealth).

"Subjective Norm" domain contained six codes with a total of 208 quotations (22.8% of total quotations). All groups felt there is a certain degree of pressure to perform the behaviour as they felt the status quo should be improved and they thought eHealth could be a useful tool for such improvement. Participants described gaps especially in communication and information access which would encourage them to use a trusted eHealth app.

» ***There needs to be more explanations about what you can do, more explanations about the multiple versions of TB. We don't know about that you can have it in your bones, people don't know about adverse reactions, we don't know about these things.*** - Patient, the Netherlands «

»***Sometimes it [the Internet search] will not give you a straight answer. Sometimes it will lead you to further look***. - Patient, Ghana «

Concerning the particular usage of eHealth in tuberculosis and the perceived subjective norm concerning the general public, patients spoke about stigma and how eHealth, through education, could solve such problems.

»***For example, I feel a lot of rejection every time, people changed a lot when they found I***

am TB positive, they don't even say hello directly to me, but from afar and this rejection is due to the lack of knowledge, education. –Patient, Venezuela «

Participants believed either that eHealth would be easy to implement or that it is possible, but that ease of implementation will depend on certain factors, most frequently, technology savviness.

»***If I could use technology, I would use it. But now I am afraid I would make mistakes whilst using it because I would get confused.*** -Patient, Greece «

»***Our Tb patients are not there yet. We don't really have university professors with TB.*** -Medical Staff, Romania «

Participants also mentioned a lack of resources as possible impediments to eHealth implementation. Lower income countries tended to mention more often a lack of physical resources, such as electricity, network coverage or hardware (computers, phones), whereas higher income countries were worried about the lack of human resources needed to manage a potential extra burden of eHealth.

»***They [the patients] get their phones stolen, or all sorts of cables can be robbed.*** - Medical staff, Venezuela «

»***The [clinic] does not have the manpower to see everyone, they [clinic staff] go [to see patients] maybe once every two months.*** - Medical Staff, Netherlands «

"Perceived Ease or Difficulty Towards Behaviour" contained nine codes and a total of 203 quotations (22.2% of total quotations). A minority of participants expressed they don't think they could implement a new app, quoting reasons such as illiteracy or lack of time. Most either said they would have no problems integrating a new app within their digital routines or that they would require the app to check certain boxes which would facilitate adoption (e.g. have a simple interface, contain a training module, see below)perform a specific function to facilitate adoption.

»***We are always open to new technology which could help us improve even more.*** - Medical Staff, Greece «

» Interviewer: *how do you think you'd react to a new app in your lives?* «

»***Easy, easy*** [raised voice, altogether] - Patients, Venezuela «

» ***And if you have too many apps, like we already do, to have another one, it could be time consuming. We wouldn't want to be overloaded.*** - Medical staff, the Netherlands «

Participants identified steps which are mandatory to perform in order to have an easy to use app, such as privacy or localising the app. «

»***Privacy, that's what I would consider first. There shouldn't be any breaches because otherwise it wouldn't succeed so no one should have access to data.*** - Patient, Greece«

Facilitators concerning implementation, such as financial incentives in the form of extra staff or equipment or offering the app for free were also identified, especially since some participants expressly mentioned the financial difficulties some patients are in.

» ***I believe if the app could be in every language and the devices would be provided people would be very grateful, so it won't also be useful, but they would be more compliant.*** -Medical staff, Greece «

» ***Then the cost. It should be free.*** - Patient, Ghana «

Some participants expressed a desire to be trained in how to use the app or for a demo module to be presented as they believe this would facilitate quick adoption.

» ***Some of us will need someone to teach us.*** - Patient, Romania «

Concerning the app itself, participants believed ease of use would be furthered by a simple and friendly user interface, by adding a community building module, either for the patients or for medical staff, adding a training module, and using videos to transmit information.

» ***It should be simple, with not many things, because it would demotivate me.*** - Medical staff, the Netherlands «

» ***It can also even have people who are also being successfully treated, people like that communicating, all that being put into the app so that when the person goes, person knows from the beginning how the treatment goes, and after treatment what to expect.*** - Medical staff, Ghana «

"Preferred Features" contained seven codes with a total of 161 quotations (17.6% out of total quotations). Concerning information media, most participants expressed a preference for video, followed by images and text and would like a gamification component, such as quizzes to enhance the user experience.

» ***I think film would be nice. When you read you can put it away.*** - Medical Staff, the Netherlands «

» ***Or maybe a countdown, how far you are and how much you have left and then patients know what to eat. For them to see how easy it is and to stimulate them to continue.*** - Medical Staff, the Netherlands «

Participants would rather use the app for treatment (n=38) than for diagnosis (n=17) or prevention (n=19), and they would want a notification or reminding system implemented to encourage treatment adherence and follow-up.

» ***Patients can use an application to schedule visits to health facilities, start treatment, when should do sputum test, do monthly check up. Things that they usually do here, but it will be paperless/electronically.***

Then all these [digital] notes can be brought everywhere, I mean paper note can be lost, can be damaged. - Medical staff, Indonesia «

» ***Through this media/app patients can be educated and we can reinforce prevention.*** - Medical staff, Venezuela «

Discussion

Principal findings

Using a health behaviour framework for market research [20], this study explored

attitudes towards eHealth implementation in tuberculosis. Semi-structured focus group interviews were performed worldwide with medical staff and patients to better understand key motivators, challenges, facilitators and user preferences for implementing new eHealth solutions. A number of important insights have been gathered, as has a prioritisation of features to be implemented, which can be used when planning new eHealth apps for tuberculosis. Overall, both patients and TB experts have expressed enthusiasm at the potential of eHealth, with an overwhelming consensus that the first domains where it could be useful are information and communication.

"Attitude towards eHealth" domain presents encouraging results, with 229 out of 339 (67%) codes expressing a positive expectation about eHealth capabilities. Overwhelmingly participants felt there is a lack of knowledge about tuberculosis amongst patients, the general public, and even amongst medical practitioners. These findings are mirrored by a systematic review which concluded that within 14 non-European countries there is a lack of knowledge amongst medical practitioners concerning national or internal TB guidelines [21] and by multiple studies identifying knowledge gaps amongst patients [22–24]. Furthermore, a recent review highlighted that many apps offer inaccurate information [25]. Participants expect that an eHealth solution would be used to educate, to provide accurate, secure, and friendly information.

"Subjective norm" describes the most important pressure to adopt eHealth as the lack of information and communication, felt across the board. Participants described a lack of clear, open communication channels both between patients and medical staff and between different specialties involved in TB management. Multiple studies have linked lack of patient-medical staff relationships to poorer outcomes in tuberculosis [26–28], or concluded that communication methods should be tailored, [29] and/or have called to improving collaborations between medical staff involved in TB care [30]. Participants in our study would not only welcome online TB-related communities, but also believe that communication could be improved through an app and that, in itself, would improve tuberculosis management and the stigma felt at the moment. On the other hand, a challenge identified was the need for human, personal contact,

identified especially by a minority of Dutch participants (two).

Concerning "perceived ease or difficulty of use", most participants felt they could implement a new app easily, though some participants mentioned a fear that a new app would be time consuming.

One important factor which could influence adoption was identified as technology savviness, linked to age and experience with use, however, some participants felt that training could bridge this gap. Indeed, one study using video directly observed therapy noted that "Older participants in particular enjoyed learning to use a smartphone" [31]. A facilitator mentioned by some participants is localisation, translating the app in the local language. A minority of participants quoted illiteracy as a barrier to regular app use.

On a local level, interviewees from countries with a resource paucity, such as Venezuela or Greece, expressed a need for extra human or physical resources. Most participants agreed that an app should be free. Interestingly, concerning technology accessibility, opinions varied widely, from "even if they are illiterate they use the Internet, google, even if they can't write their own signature, they can go online" to "they probably have 1 smartphone per family and they don't use the Internet all the time".

From a development perspective, the only truly mandatory feature to be implemented would be privacy/security, as this was a concern expressed in multiple interviews, both my expert and patients. A recent systematic review performed by the authors [manuscript submitted] highlighted that within seven studies which quantified this aspect, there were zero privacy breaches for a pooled 71 patients.

Participants mentioned other features, such as a treatment module, with asynchronous video-therapy and reminders, and a diagnosis module, with an emphasis on self-diagnosing education in order to hasten hospital visits. Participants also expressed a desire to have a gamification component and believed video would best facilitate app adoption. Table S4 summarised recommendations when developing a new eHealth app for tuberculosis.

Comparison with Prior Work

There are few studies exploring user attitudes for eHealth for tuberculosis. A study from Mozambique [32] which explored text messaging found, as our study did, that messaging should be used for reminders and motivational texts in order to increase retention and that the main obstacle would be privacy assurance. Another study [33] involving focus group interviews with medical staff for a COPD telerehabilitation app found that education and skill training are "highly essential" to support successful implementation. A study from Saudi Arabia [34] showed that perceived usefulness and perceived ease are significant factors to performing the behaviour, results corroborated with our study.

Furthermore, a recent systematic review performed by the main authors revealed that already implemented eHealth apps focused rarely on education, despite it being one of the two major needs felt by the participants within the focus groups.

This study offers a more diverse perspective on eHealth use in tuberculosis, by conducting interviews in six countries on four different continents, in order to gain a more global perspective for a potential app which could be universally applicable.

Limitations

Purposive sampling was used which might have selected participants already more open to new technology. Furthermore, individual interviews might have elicited different results as they have less risk of bias and are more in-depth. The theory of planned behaviour is a useful tool to gauge decision-making with the caveat that it does not take in account socio-economic, religious, gender-based factors.

Strengths

This study was conducted in six different settings, offering a better understanding of how populations across the globe might decide concerning adopting eHealth in tuberculosis management. TB patients and TB experts were approached, thus covering the potential user base for future eHealth solutions. The theory of planned behaviour is a simple, elegant way to conduct focus group interviews and to understand decision-

making processes. Two independent authors coded the interviews, thus limiting bias.

Conclusion

This study used focus group interviews performed in six countries in order to gauge perceptions about eHealth usage in tuberculosis management and to draw recommendations for further implementation.

All six countries' participants are enthusiastic about eHealth and most users expect a potential app to be helpful. There is a global need to improve information access and communication and participants feel that eHealth could help bridge this gap.

Most themes resounded in all countries interviewed, but there are certain particularities, such as a large proportion of asylum seekers or lack of infrastructure or training, which should be addressed when trying to implement eHealth in specific settings.

Despite individual preferences, the global sentiment is that eHealth is a promising field of research which will be well received and with the potential to enhance multiple aspects of tuberculosis care, with an emphasis on the need to communicate and to educate.

Author roles

Ioana Margineanu (MD, PhDc, Female) & Ymkje Stienstra (MD, Prof, Female) initiated and designed the study.

Ioana Margineanu coordinated the interviews, translated the Romanian interview, translated (with the help of a translator) the Netherlands interview, participated in interview transcription, coded the interviews (independently) and wrote the full text and created the figures.

Christina Louka (MD, PhDc, Female) conducted and translated the Greece interview, participated in interview transcription, coded the interviews (independently), reviewed full text and figures.

Maria Vicenti-Gonzales (PhD, Female) conducted and translated the Venezuela interview, participated in interview transcription, reviewed full text and figures.

Morita Saktiawati (MD, PhD, Female) conducted and translated the Indonesia interview, participated in interview transcription, reviewed full text and figures.

Johannes Schierle (MA, Male) and Kabiru M Abass (MD, PhDc, Male) conducted and translated the Ghana interview, participated in interview transcription, reviewed full text and figures.

Onno Akkerman (MD, PhD, Male), Jan-Willem Alffenaar (Prof, Male), Adelita V. Ranchor (Prof, Female), Ymkje Stienstra supervised all stages of the study process and reviewed full text and figures.

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Supplementary Material

Text Box S1 – Definitions

- Domain – one of the main four code groups used, e.g. "Subjective Norm".
  - Code – topic of conversation. Can be supportive or against a certain common idea, e.g. "eHealth would be time efficient" and "eHealth would make us work doubly" both belong to the same code
    - Theme – within a ctode, a positive OR a negative attitude towards a code, e.g. "eHealth would be time efficient" and "eHealth would make us work doubly" are two opposing themes within the same code
      - Quote – direct quote from a focus group participant.

Table S1 - Country profiles

Country	Income	TB Incidence	TB particularity	Continent
Romania	Medium	74: 100.000	Within the EU, Romania has still very high TB incidence which accounts for 23.1% of EU TB. MDR and XDR numbers have increased in recent years.	Europe
Greece	High	4.5: 100.000	Greece is a low incidence country which has received additional TB cases through migration. The financial crisis complicated TB management.	Europe
Netherlands	High	5.2: 100.000	The Netherlands has successful treatment outcomes in TB because of a standardised national response. They are a low-incidence country where most TB cases are discovered within foreign-born nationals.	Europe
Indonesia	Lower-middle	391: 100.00	TB is under notified and 1 out of 2 treatment plans are inappropriate thus resistant TB is a major issue.	Asia
Ghana	Lower-middle	156: 100.000	Ghana is struggling with a lack of resources to tackle TB and a large number of HIV+ persons. HIV+ amongst TB patients varies between different geographical regions in Ghana, ranging between 9.4% and 33.4%.	Africa
Venezuela	Low	33: 100.000	With advent of the financial crisis, Venezuela, a country which used to have low incidence, how has seen a resurgence of TB cases. Lack of resources impedes TB management.	South America

Table S2 – Coding

Domain	Codes
Attitude Toward Behaviour	communication – eHealth
	eHealth – speed
	eHealth – would/wouldn't help in TB
	information/education – eHealth
	my own experience with tech
Subjective Norm	communication – status quo
	how will others react to eHealth in TB
	information – status quo
	local environment
	other's experience with tech
	stigma/isolation
Perceived ease/difficulty towards behaviour	community building/testimonials
	I can/I can't implement eHealth
	localisation
	money/devices
	privacy/Confidentiality
	repeatability
	user interface/simplicity
	training
	videos
Preferred features	screening/prevention
	diagnosis
	treatment
	reminders
	gamification
	media preference
	anything else

Table S3 - Themes/Codes Ordered by Frequency

Domain: Attitude Towards Outcome What do I expect to happen when implementing an eHealth app? What do I expect it will be useful for?	
Code: Information/education in relation to eHealth, n=144	
Key themes	Examples
eHealth would help for information or education, especially in this particular ways/settings, n=96	"The app should send to people what could happen to them." FG3 "There needs to be more explanations about what you can do." FG4 "It's important to really explain that the disease is treatable and to know more about this disease and to say that people can survive." FG7 "So educative sessions which are really up to date because to address the ignorance from the patients. Topics like transmission and ways of transmission." FG8 "I think that it would probably give people who are not even health workers a broad view about the whole condition. Because if you are there to know about the symptoms and the presentation from the app then you easily know that, I should probably be thinking of this very condition and therefore need to go to the hospital for check-up." FG13
Information/Education should be the first priority when designing an app, n=40	"Education. Mentality changes with social interaction." FG6 "Mainly focused on education." FG8 "Yea. For more information." FG12
There are some challenges/ I am sceptical about certain aspects concerning using eHealth to inform, n=8	"No, because people are prejudiced and I don't think this would help because it might scare them more to read about that stuff" FG1 "One of the challenges would be that the app is known as trustworthy, so we can know the app is related to the formal sources, so with the ministry of health." FG7
Code: Communication in relation to eHealth, n=67	
Key themes	Examples
eHealth can be used for specific types/settings of communication, n=17	"Video if they relocate, for example in another country." FG9 "The app should contain a system where each person can create their own user and be able to contact the experts for medical doctors in rural areas or resident doctors who want to contact the experts… through this app this should be possible" FG8 "And the also you can include the management of the symptoms of the condition aside from using the medication and the treatment, I mean management that is convenient at home." FG13
eHealth can facilitate patient - doctor communication, n=20	"Yes that [using an app for communication] would be perfect because if I cannot communicate with my doctor, I will go only and I will find all this different information and I don't know which is correct and wrong" FG1 "But you have to find a way to reach and communicate with as many patients as possible." FG2 "I also think that application's purposes are just sharing knowledge and information. Only for consultation, and not giving prescription or medicine." FG10 "Interviewer: Of all these things, which is most important to you? Which is number 1? FG Participant: That there is a specialist [at the other end of the app]."FG12

There are certain obstacles in using eHealth for communication, n=11	"But you can't do that with an app, obtain the homely contact." FG3 "So the more difficult thing is the globalisation of the app to enable the communication between peers and doctors like inside one country and between countries, this would be the most difficult." FG8 "If they couldn't reach us with our personal phone then we would use the app." FG2
eHealth can facilitate doctor-doctor communication, n=11	"How the report[s] can be done with discipline and in order… because [they] involve many parties like the 5th floor staffs, doctors, pharmacist. In order to create a more integrated system for the health providers." FG11 "So to start contacting other peers, other specialists, to build up the information which will be managed among medical personnel and to also contact people and specialists from other countries." FG8
eHealth will make communication easier, n=9	"And if [in our country] it would be working as it should it could enhance our quality of life in terms of communication." FG8 "Automatically the application can be accessed and used from anywhere." FG11 "Yes, I would love it. Here, we talk all the time. I think it would be very useful." FG5
Code: My own experience with technology, n=58	
Key themes	Examples
Based on my experience with technology, I will probably use an app/ have little difficulty adopting a new app/ I won't feel pressured or afraid to use a new app, n=40	"My opinion is that the Internet is this century's best discovery." FG6 "It's so easy." FG9 "Well apps are designed for easy use, I don't think I had an app I did not know how to use…" FG9 "Yes apps and technology make our lives easier for example with bank transfers to purchase things I think it's important." FG7
Based on my experience, I will find it difficult to adopt a new app/ I am afraid to use technology/ Technology makes me feel uncomfortable, n=18	"The best example is when the power goes out. You feel a complete lack of control. It's the same with computers." FG6 "I am illiterate so I wouldn't be able to use the app." FG1 "No [the Internet is indeed not secure] because for example people use Internet to gossip and u can explore the private life of others" FG11
Code: eHealth would/would not help in TB, n=42	
Key themes	Examples
An app would help in TB management, n=33	"I will support health application development. Please publish it as soon as possible." FG10 "Yes of course it would make it easier." FG1 "But it would help a lot with adherence." FG2 "And we would have more freedom." FG9
An app would not help in TB management, n=10	"There are problems are so complex that they can't be solved by eHealth." FG9 "Make it harder, giving us the double job." FG11
Code: eHealth would be faster, n=28	
Key themes	Examples
An app would be faster, n=21	"Regarding the studies, so now I don't have to buy a guide, a printed guide, because I can download it from the Internet, I save time, yes, I save a lot of time." FG7 "We get results faster, like about lab tests, or about our disease." FG5

An app would be faster especially in regards to travel/ distance, n=6	"Yes because it would also help the people who live far away." FG1 "I think it would ease. My home is far away, so if I come here I still need to queue, it will waste my time. If it is clear when is my turn, I can use my time for other things." FG5
Domain: Subjective norm How will others react? What are the societal/community norms concerning eHealth?	
Code: How will other people (the other group) react to an eHealth solution, n=52	
Key themes	Examples
There will be challenges/ implementing the app will depend on certain factors, n=23	"Simpler for the younger people, harder for the older." FG9 "Mentality [will be a problem]. Scepticism before anything new. Something new we're forced to do." FG6 "If you were formed in a compute era, everything will be easier. We have examples here in our hospital, some people get it very quickly, some people not so much, because they don't have the training, the experience with it." FG6
eHealth will be easily accepted, n=15	"They will like it." FG7 "I believe the staff will be open to this app because the workload will be easier to deal with." FG1
Code: Communication – status quo, n=39	
Key themes	Examples
Communication needs to be improved within our job/ community, n=31	"And we don't have a connection with labs. Results come on the post. We also don't have connection with the hospitals." FG3 "People should tell us more things to our face. But also they should tell us the positive sides, not only the negatives. You know, one hot, one cold." FG5 "And that is important time for the patient…if we had a rapid connection, we can have a communication with resistant tb specialist quicker and not waste the time of the patient." FG8
We have no problems communicating n=6	"We have never used Internet to get In touch with doctors." FG1
Challenges in using an app to improve communication, n=2	"Ok, trust in patient is very important and you have to have it, but you can't always be sure, he can always spit [the pills], you never know." FG3
Code: Challenges to implementing eHealth within the local environment, n=38	
Key themes	Examples
Infrastructure challenges: lack of network, physical, human resources, n=20	"They get their phones stolen, or all sorts of cables can be robbed." FG8 "The [clinic] does not have the manpower to see everyone, they go maybe once every two months, with this, you could see if someone has gained or lost weight." FG9 "To add to that, I think that the use of data is one thing you should be looking at. It could be made in such a way that you download it as a one time download and probably there could be an update when necessary."FG13
Patient-related challenges, n=7	"Right now we have mainly illiterate asylum seekers, no [nationals]" FG2 "Oh, this [an app with video-DOTS] would be great. But patients go work the fields, when would they do that?" FG6
Medical staff-related challenges, n=7	"I think the doctors don't know about TB." FG4 "They worked slowly though it was Emergency Room." FG10

Other challenges, n=3	"There is no political willpower." FG6
No challenges perceived, n=1	"Most of our patients are happy with the treatment and department." FG2
Code: Information status quo, n=31	
Key themes	Examples
Information is not accurate/ not enough, n=23	"And also there is a huge lack of knowledge because for example I did the test I got the result with a positive cross and because I didn't know what that medians I didn't go to the hospital immediately." FG7 "It's sad to say but nowadays there is also a lot of ignorance among medical personnel related to the treatment of patients, especially those medical doctors who don't work in public health." FG8 "Well, sometimes you are searching for something for example in the Internet, the websites that you researching, sometimes it delays. Sometimes the fault is from the website. Sometimes the delay is from the network. So if it is made easier for where we can find more information for TB." FG12
Information flow is imperfect, n=8	"Information is good, but then there is too much information, you have to digest it. We have patients coming in, I know what I have. Let me test you versus the Internet." FG6 "What I know is what I've been doing in this project with asylum seekers and immigrants in [country], [...] and from my experience is that there is a big difference between healthcare regulations in other countries and it's hard for this group of people to obtain accurate and fast information." FG3
Code: Stigma and TB, n=28	
Key themes	Examples
I felt stigmatised, n=27	"People will say it to your face: <<move aside, TB-infected person!>>" FG5 "It's enough to be a TB case in a school and everyone feels the stigma. It's horrible." FG6 "For example I feel a lot of rejection every time, people changed a lot when they found I am TB positive, they don't even say hello directly to me, but from afar and this rejection is due to the lack of knowledge, education." FG7 "I can say that maybe you go to any community with such a disease, some people will be afraid and think that you may infect them with the disease without knowing that I have taken the drugs for some time."FG12
I don't feel TB is a stigmatising disease, n=1	FG participant: "But we never had a problem with fear of transmitting it to people." Interviewer: "But other people were afraid?" FG Participant: "No, we never had such problems." FG1
Code: Other's experience with tech, n=20 (Patients about medical staff and vice versa)	
Key themes	Examples
I don't think there will be problems in implementing a new eHealth app for the "other" group, n=12	"I don't think using an app will be a problem...even if they are illiterate they use smartphones...even if they illiterate they use the Internet, google, even if they can't write their own signature, they can go online." FG2 "Yea, health application will be suitable for young people, since they stick to their gadgets." FG10 "[People] You are aware that this thing [mobile apps] is happening and I have been seeing it on social media." FG13

I think there will be problems in implementing a new eHealth app for the "other" group, n=8	"Our Tb patients are not there yet. We don't really have university professors with TB." FG6 "For example the people who don't have resources they probably have 1 smartphone per family and they don't use Internet all the time." FG7
Domain: Perceived ease/difficulty towards behaviour Can I implement eHealth? Would it be easy or difficult? What would make implementation easier or more difficult?	
Code: I can/can't use a new eHealth app, n=37	
Key themes	Examples
I think I am capable of using eHealth in my work/daily life, n=15	Interviewer: "How do you think adoption of a new app would be for you?" FG participants: "Easy, easy." [raised voice, altogether] FG7 "I don't think it's going to be much of a problem." FG13
I am capable of using eHealth, if some conditions are met, n=16	"It [the eHealth app] has to have more things to be usable or I use my regular things." FG3 "And the time to learn it and the time you have to spend at work if you have your own patients there." FG9 "Patient: I don't think it will be a problem for me because it has become part of me. I have been using it. It is just a matter of maybe, for example upgrading an app, whether to access it." FG12
I don't think I am capable of using eHealth, n=6	"I am illiterate so I wouldn't be able to use the app." FG1 "And if you have too many apps, like we already do, to have another one, it could be time consuming. We wouldn't want to be overloaded." FG9
Code: Financial challenges/incentives, n=34	
Key themes	Examples
In order to be able to implement an app, we need physical and human resources, n=16	"We could give them the actual devices, like a smartphone." FG2 "In my office I don't have a go-to PC, nor a printer… the PC has a poor memory…so we then have to take the work home or go to another place to be able to do our job." FG8
The app should be free, n=7	"If it's free then we would definitely use it." FG6
There are some challenges concerning financial situations, n=8	"We have a lot of immigrants and even [natives to the country] people, but homeless, with a lot of comorbidities, some even without a phone, but I think that for some it's difficult to buy and use a phone…" FG9 "They [the patients] are poor." FG6 "We don't have money to buy credits, for the bundle and network." FG12
The app will be cost-effective, n=3	"But it is cost effective long term." FG2
Code: Community building features would help implement eHealth in TB, n=31	
Key themes	Examples

A community building module for patients would/would not help in implementing eHealth, n=21	"For example testimonials & interviews where people show they got treated & improved so they show the disease can be curable." FG7 "Maybe new TB patients would benefit from old TB patients, how's the food, what the nurses can do for you." FG4 FG Participant no. 1: "Here, we talk all the time. I think it would be very useful." Interviewer: "What would you talk about?" FG Participant no.2: "Ha, what and when was your last drink?" [laughter] FG Participant no.1: "Pills, vodka, he, I finished treatment." FG Participant no.3: "This is a good way to establish relationships." FG5
An expert community would help in implementing eHealth, n=10	"So to start contacting other peers, other specialists, to build up te information which will be managed among medical personnel and to also contact people and specialists from other countries." FG8 "..and it would be good to work closer together because things would be easier." FG3
Code: Privacy would ease behaviour, n=18	
Key themes	Examples
Making sure the app is confidential should be a top priority/ would help in implementing eHealth, n=14	"Privacy, that's what I would consider first. There shouldn't be any breaches because otherwise it wouldn't succeed so no one should have access to data." FG2 "The web page should be secure – we need Internet security." FG8
I don't care/ Confidentiality shouldn't be a big problem, n=4	"I would not care to show my identity as a TB patient to show that TB patients can survive." FG7 "But it might not a problem as this is an app. We already had experience with [other apps], we have our own account, so only us who can see it." FG11
Code: Videos would ease behaviour, n=18	
Key themes	Examples
Educational videos would help eHealth adoption, n=12	"But if there are videos… about how I should feel every week…first week this, second week [it would be useful]." FG4
Video-DOT would help eHealth adoption, n=6	FG participant no. 1: "…and DOT with video, and to call them to meetings." FG participant no. 2: "Real-time DOT?" FG participant no. 3: "But maybe you could watch the videos in your own time and the patient would be ok." FG participant no. 2: "Yeah you could walk and watch in between things." FG3
Code: Training would ease behaviour, n=17	
Key themes	Examples
Training would facilitate app implementation	"Training of the medical staff and the people who will actually administrate it." FG2 "I think some education and orientation for users must be done, first there should be a socialization, then educate how to use the apps. Then make the e-manual." FG10 "We would need a training module. For everyone." FG6
Code: Localisation would ease behaviour, n=16	
Key themes	Examples

Translation would help/should be a priority	"You get to work with different nationalities and every nationality has different backgrounds, so we need an app in different languages." FG3 "And the language will be a problem, it has to be translated." FG9
Domain: Preferred Features What features or modules would I like the app to have?	
Code: Treatment module, n=45	
Key themes	Examples
eHealth would help with appointments/ follow-up, n=12	"and for making an appointment through mail or video" FG3
eHealth would help with adherence/ video – DOTs, n=13	"It [eHealth] would help a lot with adherence." FG2 "and DOT with video" FG3
eHealth would enable patients to have control over their own treatment through a dedicated log-in profile system, n=11	"You can check your treatment so anyone with a phone can make use of this app." FG7 "Yes, medical service through application. It also can be made separately, for doctor and patients." FG10
eHealth could help us monitor side effects, n=9	"To monitor, we can monitor the patients easier, wherever they are" FG11 "So possible reactions as well as side effects of the medication should be looked out for." FG13
Code: Media preference, n=38	
Key themes	Examples
Video, n=18	"I think film would be nice. When you read you can put it away."FG4 "Educational videos." FG8
Images, n=12	"Maybe some photos of the TST." FG3
Text, n=8	"Text like in the language of the patient, yes!" FG3 "A message would be great. SMS."FG6
Audio, n=5	"Audio would be best." FG4
Code: Reminders, n=29	
Key themes	Examples
A useful/the most useful feature in an app would be a reminder function, especially for treatment, n=24, or for appointments n=5	"You need to make an app which tracks the pill box at the same time with an sms with a video. Though it's still hard to be sure that he swallows his pills. Patients are very inventive." FG6 "I say that the moment you receive the positive test they should alert you." FG7 "Maybe reminders for contacts or for pills – and to also tell you that." FG9
Code: User interface (UI), n=29	
Key themes	Examples

UI should be simple/easy to use, n=14	"It should be simple, with not many things, because it would demotivate me." FG9 "But the application should be made as simple as possible." FG11 "It depends on how the app is presented. I mean if I am trying to open this app and it says do this, open this site, do that, enter this, it becomes too complicated. But if the app itself is very simple to use, you open it and you are there: symptoms, you click there, complications, they are here, treatment model here, then it makes it simple. So I think it is how the app itself is presented to the people. If it is made simpler to use for everybody then it wouldn't be a problem." FG13
UI should be friendly, n=5	"You have to be very positive, not to scare them." FG3 "No one wants to leave their comfort zone." FG6
UI – other recommendations, n=10	"I think the design and options are important, and i think that the app could be a different way to work and think." FG3 "Something striking, something that catches the attention." FG8 "And something to help him make contact with you like a button with information about how to contact us." FG9
Code: Prevention, n=22	
Key themes	Examples
I would like an eHealth app to be used for educating for screening/prevention, n=17	"Through this media/app patients can be educated and we can reinforce prevention." FG8 "And also diagnostically because people don't recognise the symptoms and if they were informed it would be easier." FG2
I would like an eHealth app to be used for prevention, n=6	"I think the first one [feature to be implemented] should be prevention." FG7
Code: Diagnosis, n=19	
Key themes	Examples
I would like a diagnosis feature in the app, n=17	"So the patients can also have the tools to self-diagnose." FG8 "[I would like] monthly lab results." FG8 "But also implement that the TB test should be the first exam done to diagnose." FG7
An app could never contain a diagnosis feature, n=2	"But in no case it can replace the diagnostics of TB." FG2
Code: Gamification, n=16	
Key themes	Examples
Gamification would be a preferred feature, n=10	"Or maybe a countdown, how far you are and how much you have left and then patients know what to eat. For them to see how easy it is and to stimulate them to continue." FG3 "For example for younger, we need maybe little games." FG9
Within gamification, I think a quiz would be a useful module, n=6	"Maybe some quizzes. This would be great. Anonymous, of course." FG6
Code: Miscellaneous, n=10	
Key themes	Examples

Miscellaneous features or ideas which would improve eHealth app or adoption	"Also if this could be known through the media and then it would get good feedback from the media and so it would be easier to implement because it would lead to actual awareness so more people would know about it and we could do it" FG2 "So, maybe psychological counselling? Morale is very low." FG5 "Can you make it in offline mode first? Because not everyone has a good Internet connection or data package. So, after download and we do not have Internet connection we can still access the apps, can you do that?" FG10
Code: Repeatability, n=3	
Key themes	Examples
Repeatability is a preferred feature	"You keep saying it, but you can replay a video online." FG3

Table S4 - Recommendations when developing a new eHealth app for tuberculosis

Type	Recommendations
General	Target the app for education, followed by communication, treatment, prevention, diagnosis.
	Identify a multi-disciplinary team which can create a universally usable app, but recruit local members to advise, tailor-make, and translate.
	Create a concept revolving around modules or build separate apps (e.g. for medical staff and for patients).
App related	Make sure the app is private and secure.
	Focus on a simple and friendly user interface, with a preference offered to images/icons and less to text.
	Create training and educational videos.
	Offer the app for free.
Implementation	Find local tech leaders which can learn the app quickly and facilitate dissemination and further education.
	Preferably, offer devices for at least the most disadvantaged members of the target populace.
	If designing a medical staff app, discuss with administrators so that the app decreases the workload and doesn't simply add to it.
	Have an active tech support.
Modules	Education module, preferably with a gamification component.
	Communication component either for: ● medical staff (results, expert forum) ● patients (testimonials, community) ● medical staff-patients (side effects, questions, appointments)
	Treatment module: calendar, video-DOT, reminders.

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eHealth in TB Clinical Management: a Systematic Review and Meta-Analysis

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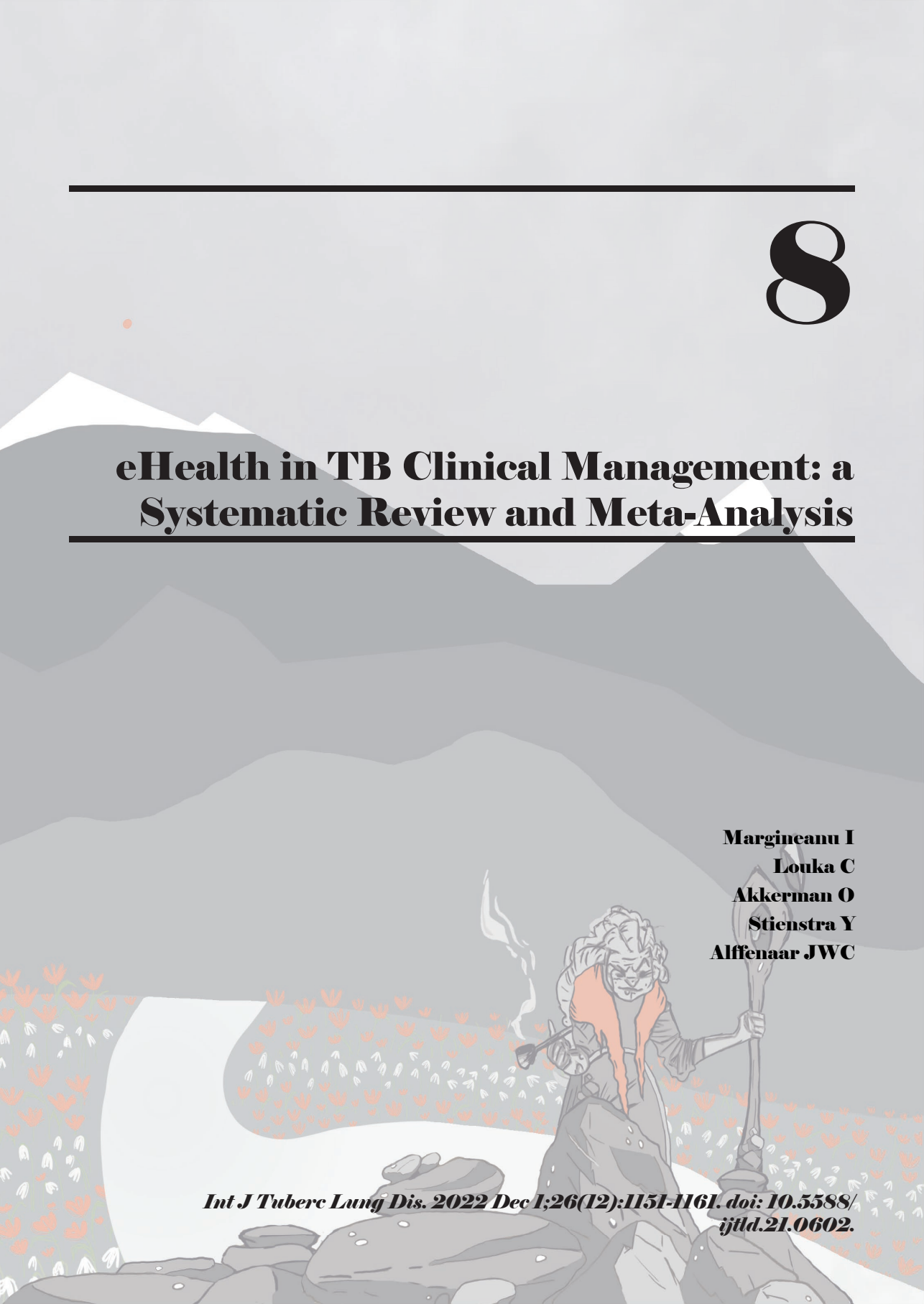

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eHealth in Tuberculosis Clinical Management: a Systematic Review and Meta-Analysis

Abstract

Background

The constant expansion of Internet and mobile technologies has created new opportunities in the field of eHealth, or the digital delivery of healthcare services. Tuberculosis (TB) is an attractive field for eHealth implementation. This systematic review and meta-analysis aims to examine eHealth and its impact on TB clinical management in order to formulate recommendations for further development.

Methods

A systematic search was performed according to the PRISMA framework, in PubMed and Embase, until April 2021. Screening, extraction, and quality assessment were performed by two independent researchers. Included studies had evaluated an Internet and/or mobile-based eHealth intervention, with an impact on TB clinical management. Outcomes were organised following the five domains described in the WHO "Recommendations on Digital Interventions for Health System Strengthening" guideline.

Results

Search strategy yielded 3873 studies and 89 full-texts were included. eHealth tended to enhance screening, diagnosis, and treatment indicators, whilst being cost-effective and acceptable to users. The main challenges concern hardware malfunction and software misuse.

Conclusion

This study offers a broad overview of the innovative field of eHealth applications in TB. Different studies implementing eHealth solutions consistently reported on benefits, but also on specific challenges. eHealth is a promising field of research and could enhance clinical management of TB.

Introduction

In the past 25 years, the growing availability of Internet-based technologies has shifted the global landscape [1]. In 2021, 60% of the world's population has Internet access, 2 billion of which are in low- income countries, steadily closing the gap in Internet and cellular access [2].

The medical world has begun to take advantage of these technologies by employing more and more Internet and mobile solutions which expand, assist or enhance medical activities, a field known as digital health or electronic health (eHealth)[3]. The WHO has recently published the "Global Strategy on Digital Health 2020-2025" report, highlighting the requirements for successful implementation of digital health, and encouraging development of this field in a sustainable, equitable, transparent manner [4].

Emerging technologies are especially attractive for tuberculosis (TB), as they could provide cost-efficient, practical, innovative solutions [5–7] for an infectious disease which primarily affects low and lower income countries [8]. However, as with every relatively new research field, interventions have been experimental, employing different technologies, study designs, and covering multiple aspects of TB management.

The field of eHealth in TB is gaining traction, recognised by the End-TB strategy [9] specifically includes the "use of innovative information and communication technologies for health", encouraging further development on eHealth. Furthermore, the recent guideline "Recommendations on Digital Interventions for Health System Strengthening" [10] comes to address some of these issues regarding heterogeneity by offering a framework to organise, inform, and guide stakeholders and policy-makers about the role of eHealth interventions in healthcare delivery.

Efforts to organise the field of eHealth in TB and to provide recommendations for future development are underway, however recent reviews have either been narrative [11], or focused on certain aspects of TB care [12]. This systematic review addresses multiple calls to organise this new field, including from the European Commission,

and especially in the present global context [13,14] and aims to offer a "birds-eye" view on implemented eHealth interventions in TB care to understand their application, opportunities, and challenges in order to provide recommendations for future development of eHealth in TB care.

Methods

A research protocol was developed according to the referred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework and registered on the International prospective register of systematic reviews (PROSPERO registration number CRD42018115440).

A systematic literature search was performed in PubMed and EMBASE with a final check in April 2021.

eHealth interventions were defined as any solution which employed Internet and/or mobile devices, deployed in a clinical medical setting. Two authors (IM, CL) independently screened all papers' titles and abstracts. Unresolved conflicts were resolved by a third reviewer (JWC). Software used for screening and quality evaluation was Covidence, for data extraction Microsoft Excel 2013, and for meta-analysis RevMan 5.4.

Search queries

Known synonyms and word clouds for "eHealth" were used in the search query. Full search query can be found in the Supplementary Material.

Study selection

Inclusion criteria: usage of Internet and/or mobile technologies, implementation analysis, user base with at least one of TB current or former patients, TB contacts, medical staff involved in TB clinical care (nurses, physicians, para-medical staff), comparison present. Studies were included regardless of language written, basic demographics, or type of study. Papers excluded were grey literature, any type of reviews, policy papers, books. For the studies without full text access, the original

authors were contacted.

Outcome measures

Outcome measures were grouped following the WHO "Recommendations on digital interventions for health system strengthening" evidence-to-decision framework [10], which generated the five main domains under which all outcomes were nested. Effectiveness included diagnosis and treatment indicators, such as adherence and cure rates. Acceptability referred to outcomes pertaining to user perceptions of the intervention, such as acceptability and user satisfaction with the intervention. Feasibility covered challenges and facilitators for the interventions. Resource use pertained to cost-effectiveness. Gender, rights, equality focused on privacy and patient support.

Data extraction and quality assessment

Data extraction included first author, year of publication, country, type of study, type of intervention, the PICO criteria (population, intervention, comparison, outcome), and GRADE criteria for quality assessment [15]. Two authors (IM, CL) independently performed data extraction and quality assessment, where outcomes were graded by taking in consideration the overall quality of the studies included, based on the GRADE quality of evidence criteria [16]. Publication bias was analysed by using funnel plots and on an individual study basis by evaluating the publications themselves.

Data Synthesis and Analysis

Meta-analysis was performed on studies with studies with similar populations and outcome measures and different analyses were performed depending on outcome: studies reporting dichotomous data were analysed using the random effects odds ratio Mantel-Haenzel method, 95% confidence interval; this model was chosen based on the assumption that there might be other factors influencing the outcome beyond the intervention itself; studies reporting continuous data were analysed using inverse variance random effects and expressed in mean difference, 95% confidence interval; studies reporting diagnosis accuracy were included in a diagnosis accuracy review

and described as a forest plot (including specificity and sensitivity of each diagnosis method included) and a summary receiver operating characteristics (SROC) plot. All outcomes not in meta-analysis were reported as a narrative synthesis. An excel file was compiled using all studies' data, based on outcomes. All costs were harmonised in euro, for 2021 by using an inflation calculator [17] and the current exchange rate.

Role of the funding source: none.

Results

General results

Search queries resulted in 3873 studies eligible for screening, out of which 89 were included in our review (figure 1). Only six full texts (1.48%) warranted the additional opinion of a third reviewer. One study was not written in English [18] and it was translated using the authors' research network.

Out of the 89 studies, 17 were randomised controlled trials, seven cluster-randomised controlled trials, 21 non-randomised controlled trials, and 44 used a "before and after" design. By country of implementation, the largest proportion of studies were performed in the United States of America (n=12), followed by South Africa (n=11).

There has been an increase in the number of studies performed as the years progressed, with a maximum of four studies published per year before 2015 to 18 studies in 2020 and, at the same time, an increase in the quality of studies: before the year 2015 there were seven (cluster-)RCTs (22%) and after there were 17 out of 57 (30%). By the GRADE criteria for quality of evidence, 35 (39%) had very low, 32 (36%) low, seven (8%) moderate, and 15 (17%) high. There was no clear publication bias identified as funnel plots indicate differences in results and there have been negative results published across studies. Of the 89 studies, 86 (93.3%) report no conflict of interest and three studies report authors setting up small academic companies to collect royalties from their proposed interventions. [19–21] A majority of studies analysed a maximum of three WHO domains, with only five reporting outcomes on all five domains (figure 2).

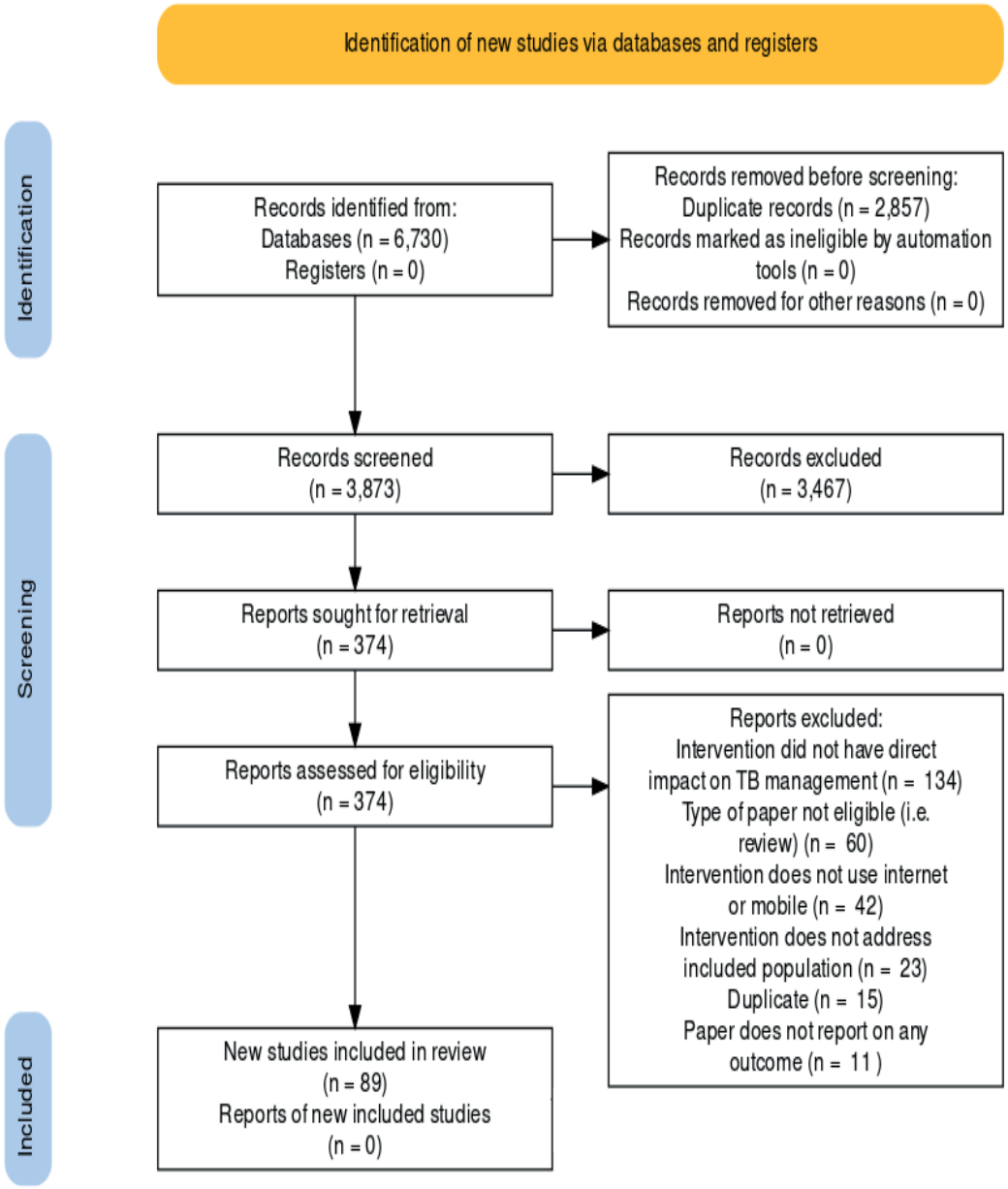

Figure 1: PRISMA

Effectiveness domain

eHealth tended to enhance diagnosis procedures at each step of the diagnosis cascade. Through eHealth, TB diagnoses could be made where there was a lack of expertise, with one study mentioning a remote panel of experts helped avoid "22

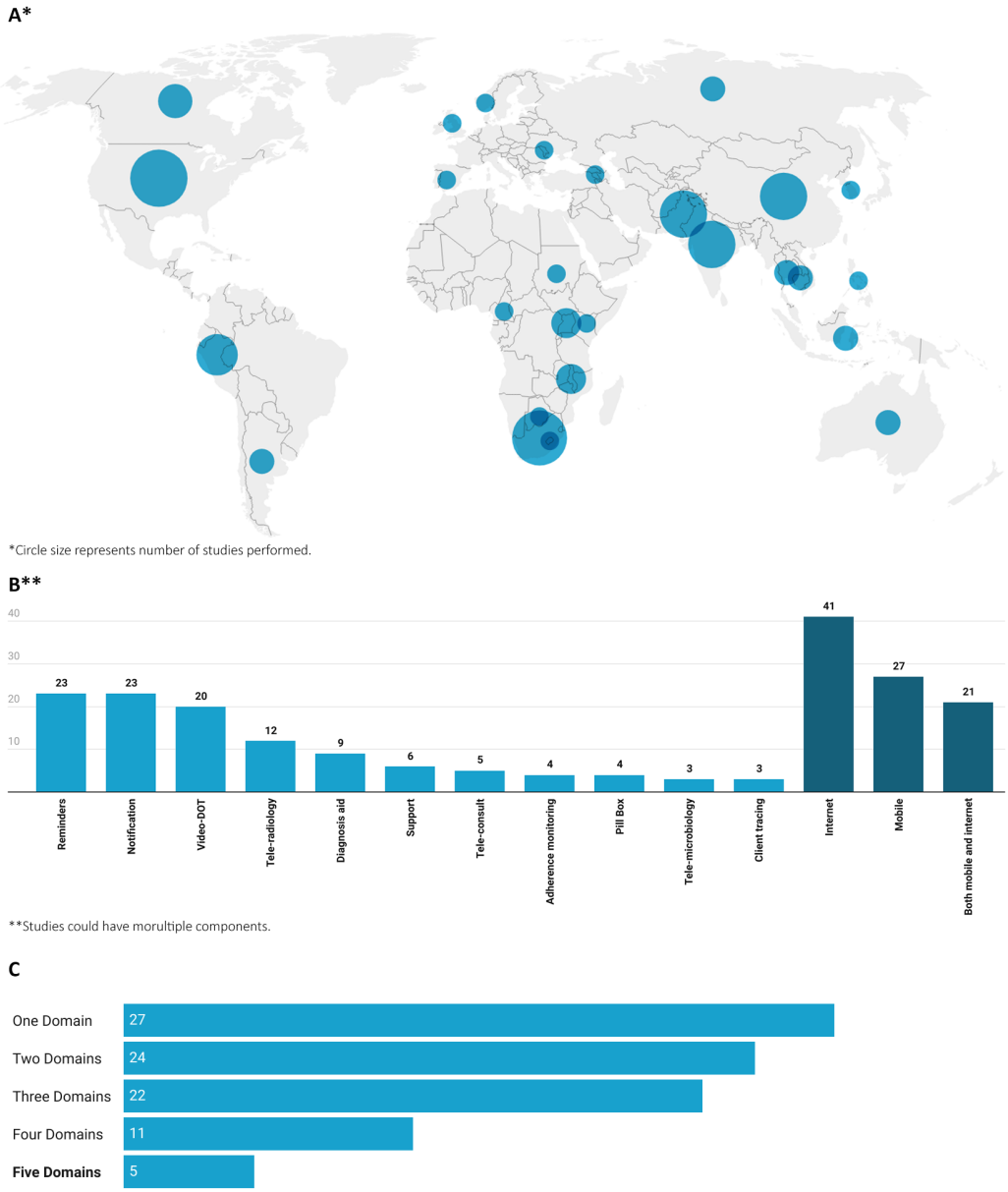

Figure 2: Study characteristics. 2A - Geographic location. 2B - Types of interventions. 2C - Number of domains reported on.

wrong treatment schemes" [22]. Secondly, meta-analysis indicated that eHealth increased the likelihood of a person to be correctly referred, resulting in a higher chance of initiating treatment in a timely manner (table 1), with one study observing

that the intervention increased the number of microbiological samples correctly referred 275 fold (from 9 to 2479) [23].

In recent years, the most robust analyses concerning diagnosis have focused on artificial intelligence/machine learning programmes dedicated to radiology and meta-analysis suggests that these supersede standard of care (figure 3, figure Supplementary 1). Two studies not only compared automated diagnosis aids to genomic tests, but also to physicians and concluded that the interventions superseded standard of care. Studies mention several caveats, such as the fact that automated TB scoring will depend on cut-off points and that diagnosis accuracy might be lower for certain diagnoses such as "hilar adenopathy" and "consolidation" [24].

Concerning treatment indicators (table 1, figure Supplementary 2, figure Supplementary 3), digital health tended to perform better, meta-analysis indicating that the odds ratio of a patient completing treatment within the eHealth group was higher than standard of care and that patients in the eHealth group had overall a higher observable fraction. Furthermore, meta-analysis reports on a higher cure rate for the eHealth group. Two studies analysing the same app, 99DOTS, report generally worse outcomes, explained by the misuse of the app by both patients and medical providers alike, attributed to a lack of training and dissemination.

eHealth introduction reduced error rates in medical charts and in laboratory results compared to standard of care, such as incorrect bacteriological results or medication doses. Various studies also noted additional benefits of eHealth interventions such as "less paperwork", "automatic response to frequent questions", "viewing all patient information on one page", "less nurses exposed to TB", "increased reporting of side effects".

Acceptability Domain

Overall, users were satisfied with the interventions, measured either qualitatively or quantitatively. Satisfaction scores were higher in intervention groups and most participants would prefer or would recommend the interventions (figure 4). Similarly, most users perceived the interventions as useful.

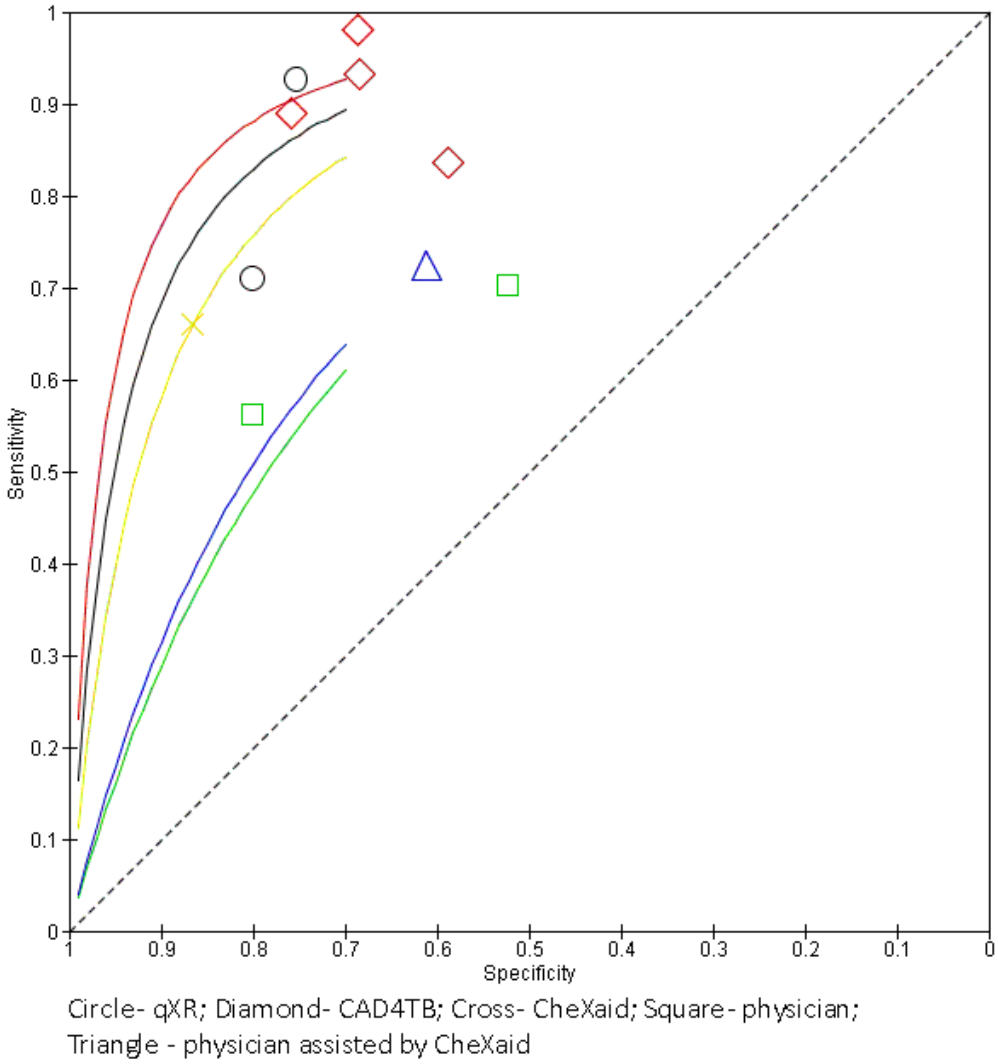

Figure 3: SROC Plot of automated X-ray diagnosis aids and standard of care

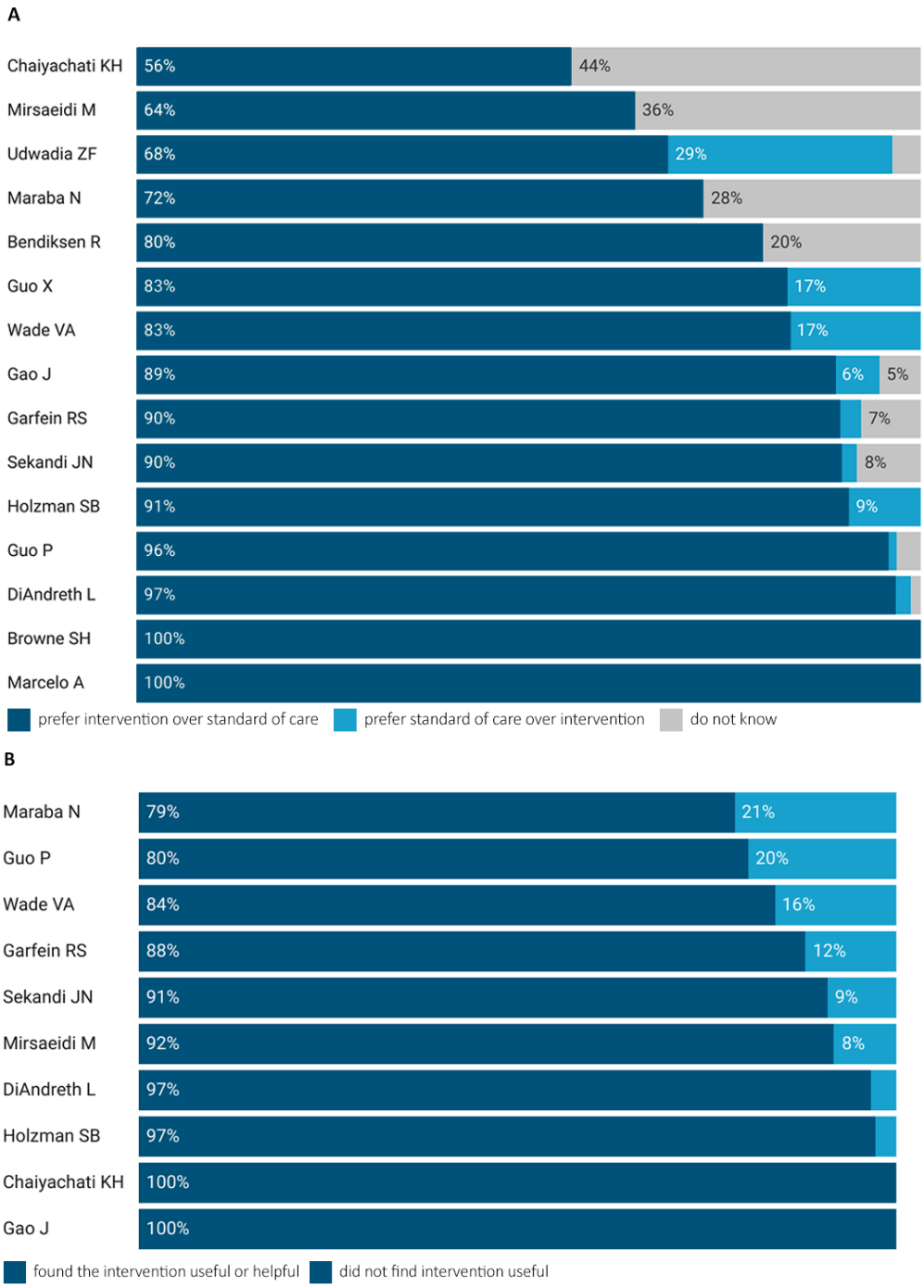

Figure 4: Users who prefer interventions and who find interventions useful. A - Percentage of participants who prefer interventions over standard of care. B - Percentage of particiants who found interventions useful

Feasibility Domain

Four main types of challenges were reported by studies: hardware, software, network/electricity and user-base. Hardware availability was reported as an issue in a minority of cases, with most users experiencing malfunction or battery drain. Software issues were easier to solve, with one study mentioning that there were "1.13 technical issues a month, which the medical staff could fix themselves" [25] and another that "use improved with experience" [26]. Network interruptions and limited Internet bandwidth caused several studies to report issues with data transmission, however, out of 17 studies reporting on these issues, 15 were before 2020.

The most important user-related challenge is not understanding how the intervention works, with one study mentioning that "problems were resolved in 77.6%-91.8% of cases" through training. In one study with automated SMS reminders, 28% of users did not always understand the message due to technical language.

Resource Use Domain

None of the included studies concluded that eHealth interventions are more costly than standard of care, all reporting various degrees of savings, depending on local economy and the travel time, translated in work hours saved, and resources it would take to reach the patients (figure 5).

Interventions also saved time, the most notable differences being in communicating between different medical specialties, particularly in the cases where results and consultations would be performed via postal services. Additionally, interventions saved time for direct observed therapy, as noted also by the meta-analysis results by reducing travel and consultation time, which, in turn, led some studies to report on medical facilities being able to consult more patients per unit of time.

Studies mentioned that patients felt "cared for by staff", "80.9% family supporters reported that phone calls helped them feel confident that the disease was under control". Concerning privacy, intervention users generally believed the intervention was more confidential than standard of care and, indeed, there were zero reported

breaches throughout the studies.

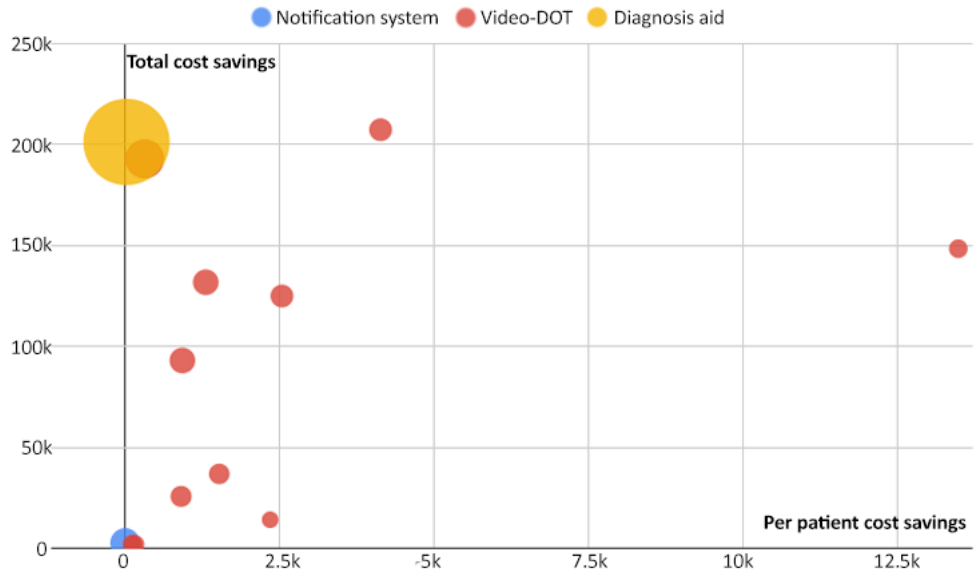

Figure 5: Cost-savings of medical facilities

Table 1: Summary of outcomes

Outcome **Quality of evidence**	**Outcome Summary**
Domain: Effectiveness	
Referrals **Moderate**	Meta-analysis, random effects, favours intervention: odds ratio for a person to be correctly referred in intervention vs. standard of care: 4.38 [2.35-8.19, 95% confidence interval], Tau^2 0.79, I^2=97%. Total events in intervention: 5405/919090. Total events in control: 2517/1217270. 8 studies, [43–50]
Diagnosis performance **Moderate**	Meta-analysis, diagnosis accuracy, sROC analysis, radiology automated diagnosis tools tend to outperform standard of care (physician) (figure 3). Diagnosis of TB established through sputum culture or Gene X-pert. Total number of patients: 17925. 5 studies, [19,51–54]
Diagnosis **Narrative outcomes**	Tele-radiology [55–59], tele-microscopy [60,61] with human experts aiding the diagnosis: concordance of 74.7%-100% with standard of care. Automated radiology [24,62] and TST readers [29] accuracy depend on cut-off points, ranging from 20% to 95%. Automated TB diagnosis aids have sensitivity of 66.67% and 89% [30,63]
Adherence: patients **Moderate**	Meta-analysis, odds ratio, random effects, favours intervention: odds ratio for a person to complete TB treatment in intervention vs. standard of care: 1.79 [1.33-2.40, 95% confidence interval], Tau^2 0.35, I^2=85%, Z=3.89. Total events in intervention: 3400/5414. Total events in control: 4177/6824. 27 studies, [5,21,32,33,35,38,45,64–83]
Adherence: fraction of observed doses (FEDO) **Moderate**	Meta-analysis, mean difference, favours intervention: patients in intervention groups had a higher observable fraction with 10.86% than standard of care [0.75-20.97, 95% confidence interval] Tau^2 200, I^2=99%, Z=2.11. Total patients in intervention: 681. Total patients in control: 704. 8 studies, [5,18,21,37,67,83–85]
Adherence: fraction of observed doses (FEDO) **Narrative outcomes**	FEDO reported as the same between groups by one study [86], better in intervention groups in seven studies [5,37,76,87,88], and worse in intervention by one study (underutilised app because of the reported errors) [34]
Cure rate **Moderate**	Meta-analysis, odds ratio, random effects, favours intervention: odds ratio for patients in intervention groups to be cured 1.45 [1.08-1.94, 95% confidence interval] vs. standard of care, Tau^2 0.09, I^2=68%, Z=2.49. Total events in intervention: 1249/2259. Total events in control: 1248/2633. 8 studies, [33,34,38,73,74,79,81,89]
Cure rate **Narrative outcomes**	Cure rate was lower in intervention (11% vs. 30%, the app was misused by patients and health providers alike) [35]
Sputum conversion **Narrative outcomes**	Patients in intervention groups had faster sputum conversion by 16 days in one study [25], more patients had sputum conversion at 2 months in three studies [45,78,90]. One study reported that less non-MDR patients in intervention sputum converted at 2 months [90]
Error rate **Low**	There were between 10% and 97% less errors in intervention vs. standard of care (paper forms), 4 studies, [22,38,91,92]

Intervention additional benefits **Narrative outcomes**	In order of frequency: flexibility (4), improved communication (4), convenience (3), the possibility of individualising the intervention (2), less medical staff exposed to active cases (1), improvement of the knowledge base (1). 13 studies, [22,30,37,66,67,70,76,85–87,93–95]
Domain: Acceptability	
User satisfaction **Low**	Between 61% and 100% of the participants would recommend the intervention. 15 studies, [7,18,21,26,37,49,57,71,81,83,84,94,96–98]
	Users in intervention groups scored higher on satisfaction scores: 99.5% vs. 99.2%, 100% vs. 70%; 92% vs. 88%. 90.3%, 3 studies, [25,85,89]
	Narrative: "Satisfaction in intervention groups 3.29 higher than control"[87], "high satisfaction in intervention group" [57,72,86], "overall, satisfaction was higher in intervention than in control" [70], 3 studies, [70,86,87]
Intervention perceived usefulness **Low**	Between 79% and 100% found intervention useful, 10 studies, [20,21,32,71,73,75,81,82,95–97]
	More users in intervention groups found the intervention useful, 2 studies, 96% vs. 56.6%, 80% vs. 32%. [71,81] Medical staff agreed intervention was useful, 1 study, [99]
	Usefulness scores: 7.5/10 and 7.7/10. 2 studies, [32,92]
Domain: Feasibility	
Hardware challenges **Narrative outcomes**	Most frequent hardware challenges: broken equipment or dead batteries, 7 studies, [68,72,75,76,88,94,97]; shared phones: 4 studies; stolen phone: 2 studies, [75,100]
Software challenges **Low**	Software-related incidents, up to 10% (0.7-8%) of missed videos or messages, 9 studies, [18,20,26,33,59,68,76,97,101,102] Software challenges: Messages not sent, 2 studies [46,103] consults not being performed, 1 study (initially 25%, dropped to 8% after learning curve) [47] "system freeze", "software quirks", "server down" [18,20,26,33,59,68,76,97,101,102]
Network/electricity challenges **Very low**	Network-related issues: interruptions between 2 days and 8 weeks, "lower adherence correlated with poor network coverage", "slow Internet", 17 studies, [20,30,32,37,50,59,72,75,76,85,86,88,92,94,97,103,104]
	Reports on electricity outages causing issues, "for several participants", 4 studies, [66,75,88,97]
User base specific challenges narrative **Very low**	Lack of comprehension/training about the intervention, 10 studies, [20,34,66,68,75,76,88,93,97]. Not knowing phone number, 4 studies, [47,50,75,100]. Preference for face-to-face contact, 5 studies, [33,35,46,60,80,86]. Scheduling conflicts and forgetfulness, 4 studies, [18,76,85,94]. Other user challenges, "more interest in computers than in the intervention", "no trickle-down effect", 3 studies, [21,22,91]

Domain: Resource use	
Cost-saving **Low**	Medical facilities saved costs, between 13.5 and 13495.7 EUR per patient in travel and personnel costs, 10 studies [5,7,20,62,65,84,85,102,105,106] Patients saved costs, between 1.5 EUR and 75 EUR in travel costs, 4 studie, [71,81,87,106]. Costs saving, other: the break-even point would be 2.9–5.5 years [101], "if one is willing to pay $2, the probability of cost-effectiveness rises to almost 90%" [37], costs per session associated with live-VDOT (6.54 EUR), recorded-VDOT (5.35 EUR), clinic-DOT (8.46 EUR) and field-DOT (19.83 EUR) [106].
Mileage-saving **Low**	Saved 2368 km and 454.93 km per patient. 2 studies, [85,103] Interventions are especially useful where travel would be a necessity, 7 studies, [7,21,22,32,39,76,94]
Capacity-saving **Low**	Interventions allowed medical facilities to increase their capacity ("see more patients"): between 100% and 208%, 6 studies, [39,43,44,50,76,102]
Time-saving **Moderate**	Meta-analysis, mean difference, favours intervention: intervention consults and observed doses were faster with a mean difference of 11.25 minutes [8.57–13.92], 95% confidence interval] than standard of care, Tau^2 14.28, I^2=99%, Z=8.24. Total patients in intervention: 2042. Total patients in control: 3139, 5 studies, [5,18,81,92,106]
Time-saving **Narrative outcomes**	Saved time, 2.93–3.1 minutes saved per sample [101], between 19.7 minutes and 3.24 hours saved per consult, [71,86,87,102], less visits per patient were required in intervention: from 38,160 to 4604 (decrease of 87.9%) [99]. Intervention was 7x slower (small field of view in tele-microscopy) [60], 13 studies, [22,23,25,26,38,39,44,57,59,70,107,108]
Domain: Gender, equality, rights	
Education **Very low**	Increase knowledge scores of 12%, 21%, 2 studies, [75,96]. No difference in knowledge scores, 3 studies [30,64,73]
Patient support **Narrative outcomes**	Patients felt "cared for by staff", 2 studies, [32,80], "80.9% family supporters reported that phone calls helped them feel confident that the disease was under control"[89], 1 study mentioned no difference in support levels between intervention and control [82]
Privacy **Low**	2%–27% of users worried about privacy breaches. 3 studies, [26,37,71]
	56.6%–100% users felt the intervention was better at protecting their privacy than control, 12 studies, [7,18,20,21,30,49,70,71,84–86,101]
	There were zero privacy breaches for 819 participants (vs. one privacy breach in one study in the control group), 8 studies, [21,26,32,49,66,75,90,95]

Discussion

This systematic review evaluated eHealth applicability for TB prevention and treatment following the framework of the "Recommendations on digital interventions for health system strengthening" and aggregated data from 89 clinical trials. As the years progressed, the research body grew, the field became more established and, therefore, studies became more rigorous. This phenomenon was observed by another

systematic review [12].

Overall, interventions tended to be non-inferior or perform slightly better regarding diagnosis and treatment indicators. An earlier systematic review investigated the role of mobile phones in HIV/TB management and demonstrated a positive effect on medication adherence [27] while another systematic review found no difference in adherence [28]. Unsurprisingly, effectiveness of interventions depends on the setting and level of care in which they are tested.

Concerning diagnosis, results suggest that tele-medicine is feasible to implement in current practice, especially for locations lacking TB expertise. Other diagnosis apps, such as the automated TST reader, can be used only with the aid of skilled medical personnel [29]. Important to note is that medical chart error rate dropped in all studies which quantified it, and additional benefits, such as reduced workloads, were mentioned as early as 1999 [30]: "Electronic information resources eliminated bulky manuals and charts. Nurses also reported greater empowerment."

The benefits felt by the users were reflected in the acceptability domain, where a majority of users found interventions useful and more satisfactory than standard of care. This could be especially relevant in the current context of the COVID-19 pandemic, which has decreased potential and current patient's healthcare access, leading to a decrease in TB detection and a loss of adherence [31]. One included study specifically included XDR patients in danger of losing medication and consultations during the COVID-19 crisis in India and conclude that "while inexpensive and expedient, telemedicine may risk compromising the quality of care associated with a physical examination; however, in times of COVID 19, this is a trade-off we may have to accept." However, if we analyse HCW and patient user preference for face-to-face contact under the "acceptability" domain, we note that there is a minority of studies with users citing this preference.

Implementing eHealth is not without its challenges, also mentioned by an analysis on the landscape and research priorities in eHealth [11]. Overall, impactful hardware issues happened primarily in Low and Middle-income countries, besides dead phone batteries which happened everywhere. Stolen, broken, shared, or not having a phone

were noted in six low-income countries (LIC) and 11 middle-income countries (MIC). The same distribution was observed for network failures, with only six studies being in HIC out of 17. Electricity outages all happened in LIC or MIC.

User-related challenges were reported by most studies and were the most diverse, ranging from users not knowing their own phone number [32,33] to "the requesting physician appeared to take more interest in computers than in the medical diagnosis" [22]. Regarding the user base, multiple studies note that successful implementation is dependent on the user's tech savviness and, barring that, their education. The best example of this cautionary tale is the 99DOTS app, where multiple studies note that its misuse and underuse because of a lack of training lead to inefficiencies in its implementation [34,35].

The domain where eHealth shined was cost-effectiveness. Introduction of medication monitors and VOT are expected to lead to substantial cost savings [36]. This forecast is supported by the results presented in the resource use domain, with interventions saving costs per patient. This is especially because of travel time and costs for either the patient or the medical staff, but also because via the Internet, consultations tended to be more efficient, with one nurse noting "it was easier to finish videophone visits, as the patients did not try to prolong calls by offering a cup of tea or social interaction" [37]. Furthermore, interventions also streamlined sample and result transport and communication to the extent of one study noting that before eHealth implementation "because of the delay, patients as well as his or her physicians often forgot that they had ever performed a culture" [38]. Lastly, eHealth tended to make better use of human resources, with one study specifically mentioning that the capacity of medical facilities increased, "without a reduction in the volume of [control] encounters" [39].

Concerning privacy, a minority of patients included mentioned to be worried about privacy breaches and a majority consider digital health to be safer than controls. One study noted that whilst 58% of medical staff worried about unintentional disclosure of private files, 87% of patients were not worried at all about confidentiality breaches. Within the studies included, there were zero reported privacy breaches (versus one

in a control group). It appears that if professionals approach eHealth in TB care with the same rigour they approach any other professional medical data, the users can trust the capabilities to keep their data confidential.

Last but not least, as TB is stigmatising, lonely disease [40], it is important to highlight the studies which reported that patients "no longer felt isolated" [41], "were happy when receiving motivational texts" [42], and felt "cared for by staff" [32]. However, no studies reported on gender, sexual, or race inequalities.

Overall, it is important to note that whilst eHealth was at least non-inferior concerning effectiveness, users trusted and were satisfied with the interventions and, if accounting for potential challenges, eHealth implementation is cost-effective. eHealth interventions could be especially relevant in the current context.

Strengths

This systematic review organises a broad body of evidence and offers an overview of the five WHO domains for analysing eHealth. The focus of this review is clinical care and by analysing the interplay between the five domains, it can offer advice on the challenges to be accounted for before implementing eHealth and the potential benefits especially pertaining to user perception, patient data safety and cost-effectiveness.

Limitations

As eHealth is a relatively new field, earlier studies tended to have as a comparison group a historical cohort or the same cohort. Similarly, methods to analyse eHealth impact have evolved, from simple interviews to offering standardised questionnaires and performing economic analysis. However, only five studies analyse all WHO domains. Grey literature was not accessed as the cursory search revealed that it tended to skim on outcome reporting. Quality of evidence varies, with the best evidence in the effectiveness domain and the least in the gender, equality, rights domain.

Conclusion

The general trend is that eHealth adoption in TB is growing and that eHealth interventions fulfil the five WHO domains goals. Interventions tended to add value to standard of care, measured by "hard" indicators of effectiveness and resource use, but also by "soft" indicators of acceptability. eHealth interventions are especially useful if considering the necessity of travel and in settings with a lack of resources and expertise. However, infrastructure, experience, and training are needed to ensure that eHealth is effective, but as the global trend is towards using more and more technology in everyday life, users will become savvier, health interventions will become more readily available, and evidence more robust and reliable.

Author contributions

IM performed protocol development, search query creation, title and abstract screening, full text screening, data extraction, quality assessment, wrote the full text and created figures.

CL assisted in protocol development, search query creation, performed fully title and abstract screening, full text screening, data extraction, quality assessment, and reviewed the full text and the appendix.

JWA, YS, OA supervised and assisted all phases of study development and reviewed the drafts (table Supplementary 1).

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Supplementary material

Search strings

Pubmed search

("Telemedicine"[Mesh] OR "Distance Counseling"[Mesh] OR "Internet"[Mesh] OR "Mobile Applications"[Mesh] OR "Cell Phone"[Mesh] OR "Electronic Mail"[Mesh] OR e-health[tiab] OR ehealth[tiab] OR m-health[tiab] OR mhealth[tiab] OR telemedicine[tiab] OR app[tiab] OR apps[tiab] OR mobile[tiab] OR phone*[tiab] OR smartphone[tiab] OR tablet[tiab] OR tablets[tiab] OR web-based[tiab] OR webbased[tiab] OR online[tiab] OR Internet[tiab] OR e-therap*[tiab] OR e-program*[tiab] OR software[tiab] OR sms[tiab] OR text messaging[tiab] OR email[tiab] OR e-mail[tiab])

AND

("Tuberculosis"[Mesh] OR tuberculosis[tiab])

Embase search

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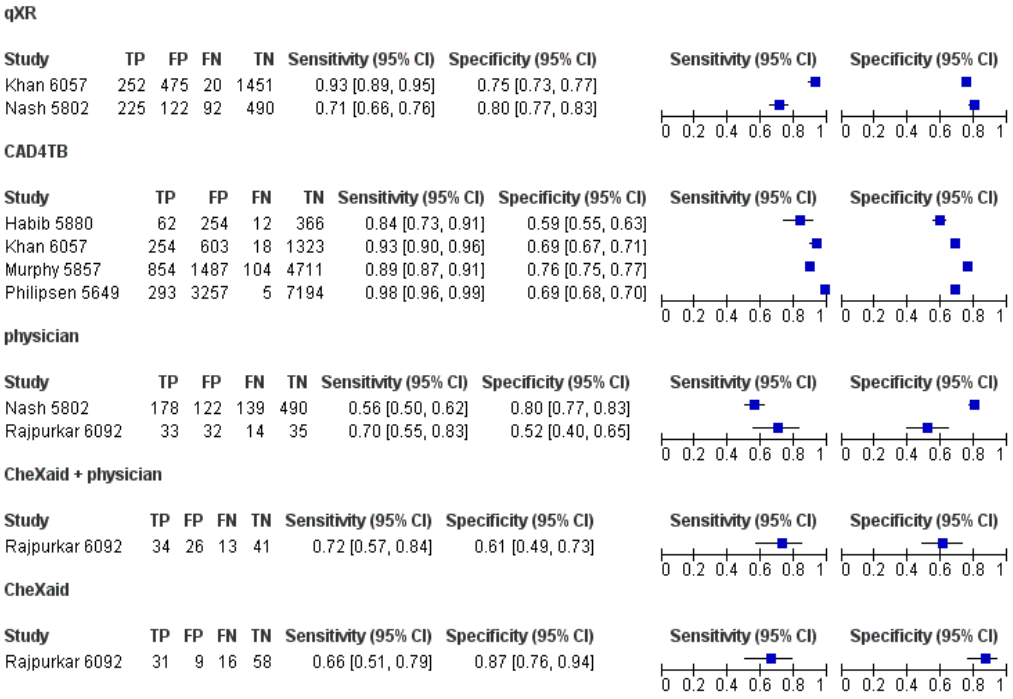

Figure Supplementary 1: Meta-analysis on diagnosis accuracy, forest plots

TP - true positive; FP - false positive; FN - false negative; TN - true negative

8

Comparison of different imaging artificial intelligence algorithms. TB diagnosis confirmation obtained with sputum cultures (Khan 6057, Nash 5802), Xpert MTB/RIF (Habib 5880, Murphy 5857, Philipsen 5649), or both (Rajpurkar 6092). Meta-analysis used was diagnosis test accuracy, which analyses different diagnosis tests true and false positives and true and false negatives in order to obtain an overall sensitivity and specificity. Because of the inherent heterogeneity of such studies, a random effects model is usually chosen. Forest plots graphically illustrate the data presented, giving an estimation of the distance from the value of 1, and a visual representation of the confidence intervals the different studies reported.

Fig. S2-A: Forrest plot of "Diagnosis yield" outcome

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Chadha, 2017	127	194	67	194	12.1%	3.59 [2.36, 5.46]
Choun, 2017	108	109	1213	1948	5.6%	65.44 [9.12, 469.80]
Davis, 2019	7	471	5	448	8.9%	1.34 [0.42, 4.24]
DiAndreth L	127	174	19	226	11.5%	29.44 [16.54, 52.41]
Khan, 2012	3140	915767	496	1213226	12.8%	8.41 [7.65, 9.25]
Long, 2015 (1)	497	623	126	200	12.3%	2.32 [1.64, 3.28]
Long, 2015 (2)	503	669	241	362	12.5%	1.52 [1.15, 2.01]
Wagstaff, 2019	331	405	78	101	11.7%	1.32 [0.78, 2.24]
Wang, 2009	565	678	272	565	12.5%	5.39 [4.15, 6.99]
Total (95% CI)		**919090**		**1217270**	**100.0%**	**4.38 [2.35, 8.19]**
Total events	5405		2517			

Heterogeneity: Tau² = 0.79; Chi² = 251.94, df = 8 (P < 0.00001); I² = 97%
Test for overall effect: Z = 4.63 (P < 0.00001)

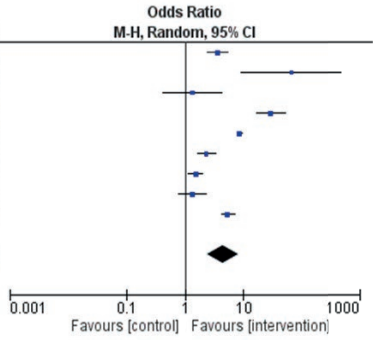

Fig. S2-B: Forrest plot of "Treatment adherence" outcome

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Ali, 2019	69	74	69	74	2.9%	1.00 [0.28, 3.61]
Bassett, 2016	75	194	89	212	5.7%	0.87 [0.59, 1.30]
Belknap, 2017	240	315	237	321	5.8%	1.13 [0.79, 1.62]
Browne, 2019	32	41	0	20	0.9%	140.26 [7.74, 2541.64]
Chen 2020	53	80	98	160	5.2%	1.24 [0.71, 2.18]
Chuck, 2016	47	49	260	267	2.2%	0.63 [0.13, 3.14]
Das Gupta, 2020	184	222	104	111	4.2%	0.33 [0.14, 0.76]
Fang, 2017	154	160	165	190	3.9%	3.89 [1.55, 9.74]
Faroqui, 2017	49	74	49	74	4.7%	1.00 [0.51, 1.98]
Guo P, 2020	202	203	198	202	1.4%	4.08 [0.45, 36.83]
Guo X, 2020	148	235	7	158	4.3%	36.70 [16.44, 81.89]
Hermans, 2017	128	183	224	302	5.7%	0.81 [0.54, 1.22]
Hirsch-Moverman, 2017	163	183	132	166	5.0%	2.10 [1.15, 3.82]
Holzman, 2018	10	28	4	28	2.8%	3.33 [0.90, 12.36]
Holzschuh, 2017	15	15	12	12		Not estimable
Iribarren, 2013	17	18	17	19	1.1%	2.00 [0.17, 24.19]
Johnston, 2018	117	153	148	183	5.3%	0.77 [0.45, 1.30]
Khachadourian, 2929	187	187	172	198	0.9%	57.61 [3.48, 952.55]
Kumboyono, 2017	42	45	36	45	2.6%	3.50 [0.88, 13.92]
Lam, 2018	44	50	196	302	4.0%	3.97 [1.64, 9.61]
Lee, 2011	62	91	210	366	5.4%	1.59 [0.98, 2.59]
Long, 2015 (1)	150	150	656	691	0.9%	16.28 [0.99, 266.83]
Mohammed 2016	332	1104	325	1093	6.2%	1.02 [0.85, 1.22]
Ratchakit-Nedsuwan, 2020	39	40	37	40	1.3%	3.16 [0.31, 31.78]
Story, 2019	78	122	35	114	5.2%	4.00 [2.32, 6.89]
Thekkur P, 2019	510	870	443	961	6.2%	1.66 [1.38, 1.99]
Yoeli, 2019	285	569	254	535	6.1%	1.11 [0.88, 1.41]
Total (95% CI)		**5455**		**6844**	**100.0%**	**1.79 [1.33, 2.40]**
Total events	3432		4177			

Heterogeneity: Tau² = 0.35; Chi² = 168.47, df = 25 (P < 0.00001); I² = 85%
Test for overall effect: Z = 3.89 (P < 0.0001)

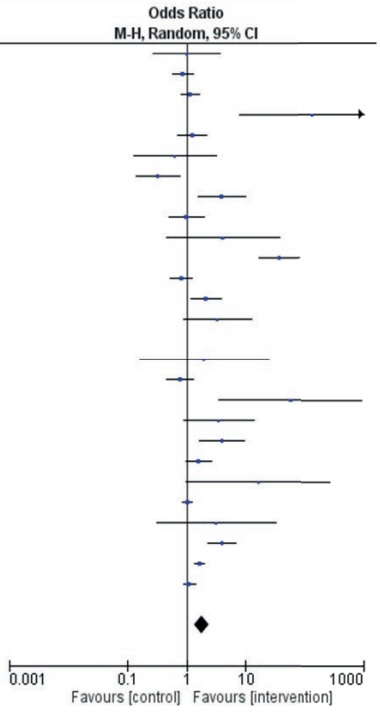

Fig. S2-C: Forrest plot of "FEDO" outcome

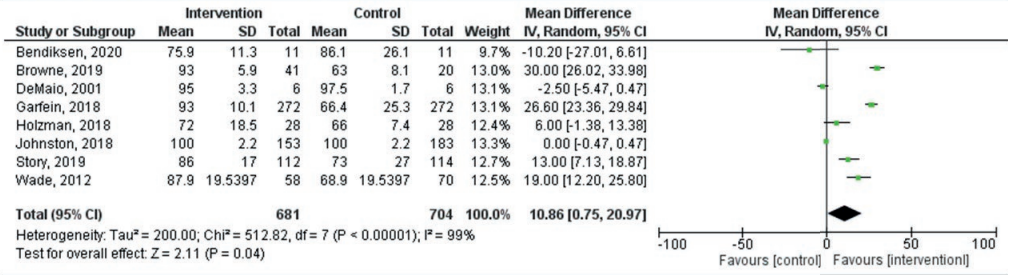

Fig. S2-D: Forrest plot of "Cure rate" outcome

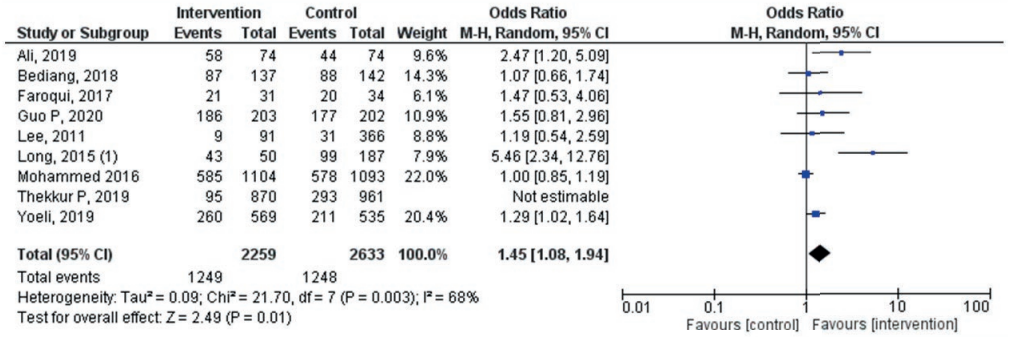

Fig. S2-E: Forrest plot of "TIme saving" outcome

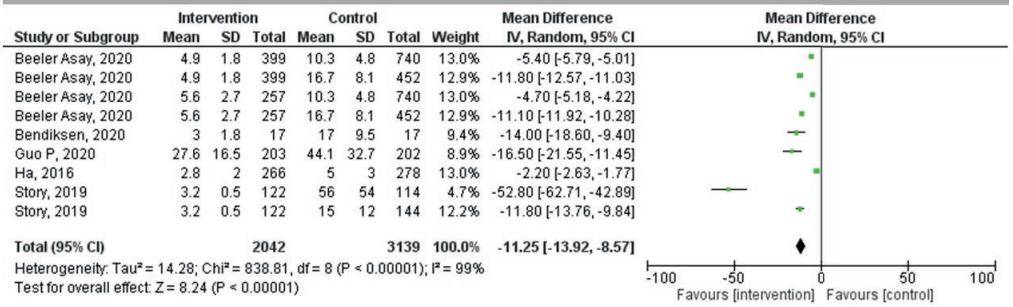

Figure Supplementary 2: Meta-analysis, forest plots

I^2 values >= 50% indicate study heterogeneity is high, hence random effects model was chosen as per recommendations. Forest plots show a tendency favouring interventions. For S2-A an event was defined as a person being correctly referred for TB diagnosis. For S2-B an event was defined as a patient reported as completed TB treatment. For S2-C, the number of reported missed doses and the number of patients in the study were analysed in order to calculate the mean difference of missed reported doses between groups. For S2-D, an event was defined as a patient reported as cured within a study. For S2-E the time (in minutes) necessary to conduct a consultation or administer a dose of observed medication was input in the meta-analysis in order to analyse the mean difference of time spent between intervention and standard of care groups.

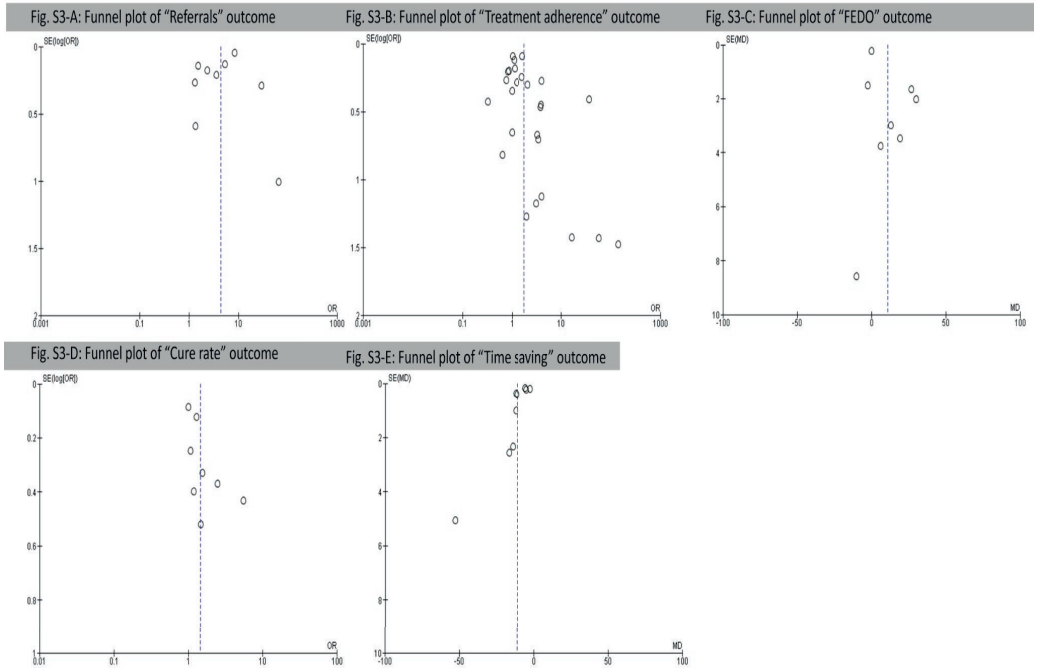

Figure Supplementary 3: Meta-analysis, funnel plots

Funnel plots were used to visually analyse the possibility of publication bias. Funnel plots are especially useful when meta-analysis contains smaller studies as they tend to show larger effect sizes and greater variability. The X-axis represents effect estimates and the Y-axis study precision (study size). Funnel plots were analysed visually for symmetry and potential sources of bias for outliers were taken into consideration. When results were corroborated with the meta-analysis, the sources of bias were better explained by study designs rather than by publication bias. Within all studies, a majority were of smaller scale, and within them, negative results were published and included in the funnel plots, thus, overall, the authors considered that there is a relatively small chance for publication bias.

Table Supplementary1: Summary of study characteristics

TB = tuberculosis; RCT = randomised control trial; CRCT = cluster randomised control trial; NRCT = non-randomised control trial; BAS = before and after study; SMS = short messaging system. PLHIV - people living with HIV

First author	Country	Year	Population (P) Intervention (I) Comparison (C)	Type GRADE	Summary of Outcomes
Z.F. Udwadia	India	2021	P: TB patients, 28 I: Tele-consults, notifications C: Standard of care, same cohort	BAS 1	68% of patients preferred the convenience of intervention; 27% of patients preferred control; 5% of patients had no specific preference.
J. Hodges	Russia	2021	P: TB PLHIV patients, 60 I: Notifications, support C: Standard of care, historical cohort	BAS 1	Lower mortality by 6 months in the intervention subset (1 death, not attributed to HIV or TB) compared with the pre-intervention cohort (10 deaths, 7 attributed to HIV, p = 0.02). Exposure to the intervention was associated with a decreased likelihood of developing the composite outcome (adjusted odds ratio = 0.33, p = 0.029). Retention of care scale indicators high in intervention.
S.H. Chen	China	2020	P: TB patients, 80 intervention, 160 control I: Video-DOT C: Standard of care	NRCT 2	Adherence intervention 66.60% vs. control 61.42% (p = 0.001). Satisfaction with location arrangement (p < 0.001), ensuring treatment adherence (p = 0.027) were higher in intervention. Satisfaction with privacy issues (p = 0.005) were superior in the intervention group.
J.N. Sekandi	Uganda	2020	P: TB patients, 50 I: Video-DOT C: Standard of care, same cohort	BAS 1	82.2% of expected videos were received. The median fraction of expected doses observed was 85%. 98% were satisfied and 88% found the intervention easy to use. Phone malfunction, dead batteries, app errors, network and electricity disruptions accounted for lost videos.
P. Rajpurkar	South Africa	2020	P: Prospective TB patients, 114 I: Automated diagnosis based on radiology and clinical parameters (CheXaid) C: Standard of care, same cohort	BAS 2	The stand-alone algorithm: mean accuracy of 0.79 (95% CI 0.77, 0.82) vs. physicians: mean assisted accuracy of 0.65 (95% CI 0.60, 0.70). The stand-alone algorithm had a sensitivity of 0.67 (95% CI 0.62, 0.73) and specificity of 0.87 (95% CI 0.85, 0.90).
L. DiAndreth	South Africa	2020	P: Prospective TB/HIV+ patients, intervention 226; control 174; Survey respondents: 159 I: Diagnosis notification system via SMS/calls C: Standard of Care	NRCT 2	Viewed their test results within 7 days of their enrollment: intervention (73.0%) vs. control 8.6% (p < 0.001); likelihood to return to clinic: intervention 20.0% vs. control 8.6% (p=0.02). 95% felt their information was more protected and confidential when delivered via phone than by the clinic; 96.9% wanted to receive other health information on their phone; 96.9% preferred intervention. No participant reported intervention causing accidental disclosures or instances where others saw their laboratory results without permission.
F.A. Khan	Pakistan	2020	P: Prospective TB patients, 2198 I: Radiology diagnosis aid (qXRv2 & CAD4TBv6) C: Standard of care, same cohort	BAS 2	qXRv2, overall sensitivity was 0·93 (95% CI 0·89–0·95) and specificity was 0·75 (0·73–0·77). CAD4TBv6 sensitivity (0·93, 0·90–0·96) had specificity 0·69 (0·67–0·71).
G.R. Beeler Asay	USA	2020	P: TB patients, intervention 103; control 122; Sessions: intervention 173; control 170 I: Video-DOT synchronous and asynchronous C: Standard of care, historical cohort	BAS 2	Live Video-DOT time 4.86 minutes (95% CI = 3.77,6.26) vs. recorded Video-DOT 5.62 (95% CI = 4.06,7.77) vs. clinic DOT 10.27 (95% CI = 7.51, 14.04) vs. field DOT 10.13 (95% CI = 7.89, 3.01) + travel time 16.67 minutes (95% CI = 12.08, 22.99). Costs per session are lower in Video-DOT than DOT groups for healthcare and lower in Video-DOT also for patients.

P. Guo	China	2020	P: TB patients, intervention 203, control 202; Survey respondents Intervention 199, Control 196 I: Video-DOT asynchronous C: Standard of care	RCT 4	Cured: intervention 186 (91.6%) vs. control 177 (87.6%); lost to follow up intervention 1 (0.5%) vs. control 4 (2.0%) (not statistically significant). Average time per dose observed intervention 16.5 min vs. control 44.1 DOT (including travel time), p < 0.01. Costs intervention Y-- 34.3 (4.41 EUR) vs. control Y-- 71.6 (9.21 EUR), p < 0.01. Survey responses: "convenient & comfortable" intervention 191 [96.0%] vs. control 111 [56.6%], p < 0.001, "would recommend the method to other patients" intervention 191 [96.0%] vs. control 113 [57.7%], p < 0.001.
L. Ravenscroft	Rep. of Moldova	2020	P: TB patients, intervention: 85, control 90 I: Video-DOT, asynchronous C: Standard of care	RCT 4	Failure to adhere: control 5.24 days/14 days vs. intervention 1.29 days/14 days, (95% CI 3.35–4.67 days, p<0.01). Intervention saved an average of 58 h (95% CI 48–68 h; p<0.01) and an average EUR 25 over the course of the 4-month study period (self-reported). Cumulative log-odds increment in satisfaction of being in the intervention treatment group is 3.29 (95% CI 1.66–4.92; p<0.01). Treatment success not statistically different. Intervention patients are 11% more likely to report side-effects.
X. Guo	China	2020	P: TB patients, intervention 235; control 158; Survey respondents: intervention 235; control 131; Medical staff 66 I: Video-DOT synchronous, reminders C: Standard of care	NRCT 2	≥95% of doses observed: intervention 63.0% (148/235) vs. control: 4.4% (7/158) (P<.001). 5 patients in the intervention group failed to send a video for at least three consecutive days and were advised to transfer to control, but all of them requested to be allowed to remain on intervention. The median estimated total time spent traveling over 6 months: control 60 hours vs. intervention 12 hours. Estimated total transportation costs: control intervention ¥720 vs. control ¥96 (difference of 25 EUR) Patients satisfied: intervention 191/235 (81%) vs. control 53/131 (40%). Felt there was no violation in privacy: intervention 133/235 (57%), control 85/131 (65%). Most medical staff preferred intervention.
F. Madhani	Pakistan	2020	P: Prospective TB patients: 127 062 I: Radiology diagnosis aid (CAD4TB) C: Standard of care, same cohort	BAS 2	Prevalence of Xpert positivity was lowest (0.7%) in the under 50 category (CAD4TB score), and rose to 23.5% in the over 90 category overall, and the trend was similar in both hospital and community settings.
D. Das Gupta	India	2020	P: TB patients, intervention 222, control 111; Medical staff: 8 I: SMS and phone reminders C: Standard of care	NRCT 1	Treatment completion: intervention group A: 93/111 (84%), group B: 91/111 (82%), control: 104/111(93%) (not significant). Reminder cues contributed to an increase in their self-motivation, the interviewed patients also indicated feeling that they had received personal care, with someone always there to remind them to take their medicine on a regular basis.
V. Khachadourian	Armenia	2020	P: TB patients, intervention 187; control 198 I: Counselling; SMS and phone reminders C: Standard of care	cRCT 3	Adherence: intervention 100% vs. Control 87.3% patients. Intervention 78.4% reported that the text messages were helpful in reminding them to take their drugs; 66.2% to visit the clinic weekly; 10% would have taken the drugs regardless of those reminders. 80.9% of family supporters reported that phone calls helped them feel confident that the disease was under control.
S.S. Habib	Pakistan	2020	P: Diabetes mellitus potential TB patients: 694 I: Radiology diagnosis aid (CAD4TB) C: Standard of care, same cohort	BAS 2	Intervention cut-offs (automated score) of 50 and 90 yielded sensitivities of 90.5% and 48.7% respectively. Potential TB cases missed and Xpert testing yield were the lowest at the cut-off of 50 and highest at 90.
K. Murphy	Pakistan	2020	P: X-Rays: 5565; compared to experts: 500 I: Radiology diagnosis aid (CAD4TB) C: Standard of care, cohort	BAS 2	With sensitivity set at 90% the system can achieve 76% specificity. The performance of CAD4TB v6 is very similar to expert observers, particularly at high sensitivities, and no observer is seen to perform significantly better (above the 95% confidence interval) than CAD4TB v6 at any operating point. Cost savings per TB case detected at 0.95 sensitivity is 36.18 EUR.
R. Ratchakit-Nedsuwan	Thailand	2020	P: TB patients initial, intervention 50, control 50; month 6, intervention 40, control 40; focus group 8 I: Pill box, reminders, calls C: Standard of care	RCT 4	>80% of doses: control 37/40 vs. intervention 39/40, hazard ratio 3.2 (0.2–170.2). Treatment success: control 39/41 vs. intervention 36/40 (no significant difference). Most of the participants reported positive feedback regarding the core functions of the intervention. Half of the participants experienced lack of or a poor mobile network signal and fast battery draining. A few participants commented about the size and weight of the device, too-small instruction font size on the lid, an inaudible alarm volume when placing it on another floor of the house, and concern about small children's reactions.

M. Nash	India	2020	P: X-Rays, intervention 317; control 612 I: Radiology diagnosis aid (qXR) C: Standard of care, same cohort	NRCT 2	For the general classification of an X-Ray as 'abnormal', intervention AUC of 0.87 (95% CI: 0.84, 0.91). The lowest AUC achieved by intervention, 0.75 (95% CI 0.70, 0.80) and 0.76 (95% CI: 0.73, 0.79), were for detection of 'hilar lymphadenopathy' and 'consolidation', respectively. For detecting abnormalities 'cavity,' 'fibrosis,' 'pleural effusion', 'opacity' and 'blunted costophrenic angle', intervention achieved AUC ranging from 0.84 to 0.94. The highest AUC achieved by qXR, 0.94 (95% CI: 0.91, 0.96), was for detection of 'cardiomegaly'.
R. Bendiksen	Norway	2020	P: TB patients: 17; Medical staff: 17 I: Video-DOT, synchronous C: Standard of care, same cohort	BAS 1	Compliance with medication intake: intervention 89.8% vs. control 95.4%. The median time spent by medical staff: control 17 (2–40) minutes vs. intervention 3 (1–8) minutes. Medical staff opinions about frequency of practical problems in intervention: 5 "never", 7 "rarely", 5 "often". Technical problems (8.9%, 268 out of 3,023 days during the intervention) were the most common single reason why intervention was not performed. Patients' opinion about confidentiality 11 "better in intervention", 6 "I do not know". 14 out of 17 patients preferred intervention, and 15 would recommend intervention to others.14 out of 17 medical staff preferred intervention and all wanted I to be continued for new patients.
A. Prabhu	India	2020	P: TB-PLHIV patients 72; Medical staff 21 I: Pill box with phone number for adherence C: Standard of care, same cohort	BAS 1	Average adherence:intervention 27% vs. treatment card 99% in the TB treatment card ($p < 0.0001$). Treatment completion 49 of 72 (68%), death 15 (21%), loss to follow up 3 (4%). Primary issue was missed calls not being registered (app error). Medical staff challenge was Lack of communication between medical staff. Patient challenges: lack of motivation, confusion regarding procedures, not owning a mobile phone or sharing.
E. Yoeli	Kenya	2019	P: TB patients: Intervention 569, Control 535 I: SMS and calls for adherence. Gamification element. C: Standard of care	RCT 3	Unsuccessful treatment outcomes: intervention 24 patients (4.2%) vs. control 70 patients (13.1%) (P<0.001).
S.B. Holzman	India	2019	P: TB patients, 25; survey respondents, 22 I: Video-DOT, asynchronous, SMS reminders C: Standard of care, same cohort	BAS 1	Median adherence on vDOT was 74% (IQR 62%-84%). After including verbally verified doses (following unverifiable or incomplete videos), the median verifiable fraction was 86% (IQR 74%-98%). A total of 91% (20/22) of surveyed patients described intervention as easy to use. 91% (20/22) found text message reminders helpful. The majority felt intervention would be more convenient (20/22, 91%) and preferred (20/22, 91%) over in-person DOT. 82% (18/22) felt intervention would preserve patient privacy over in-person DOT, 18% (4/22) disagreed.
N. Wang	China	2019	P: TB patients, 169 (15 switched to standard of care); Medical staff, 9 I: Pill Box C: Standard of care, historical cohort	BAS 1	Median adherence rate (average percentage of doses taken) was 99.3% (83.4% - 100.0%). Factors increasing the likelihood of patients switching back to standard of care: migrants vs. local persons, retreatment vs. new TB cases, over 65 years of age. Medical staff agreed intervention was useful. 8/9 considered the intervention to be a moderate increase in their workloads. Number of visits in standard of care 38,160 vs. intervention 4604 (decrease of 87.9%).
C.K. Lam	USA	2019	P: DOT Sessions: 38 035, clinic DOT: 12002; field DOT: 15483; live VDOT: 7185; asynchronous VDOT: 3365 I: Video-DOT synchronous and asynchronous C: Standard of care, historical cohort	BAS 2	Total cost per session (labor + non-labor): I live-VDOT 6.54, I recorded-VDOT 5.35, C clinic-DOT 8.46, C field-DOT 19.83. Total annual DOT cost (247 working days): I live-VDOT 46 927, I recorded-VDOT 18 463, C clinic-DOT 102, C field-DOT 494 308 521. Increasing I in the future would reduce costs.
J.E. Farley	South Africa	2019	P: Prospective TB patients 6341; Resistant- TB patients: 41 I: Notification system for medical staff and patients C: Standard of care, historical cohort	BAS 1	Intervention time from diagnosis to linkage to care: 10h.41 mins. Time from linkage to care to treatment initiation: 2 days. 11h.31 min; total 3 days, 21 h, 17 min vs. control 10 -22 days. Intervention 5 (12%) lost to follow-up vs. control 30%.
R.H.H.M. Philipsen		2019	P: X-Rays: 10 755 of which 200 were used with independent expert I: Radiology diagnosis aid (CAD4TB) C: Standard of care, same cohort	BAS 2	Using a threshold of 60, the software had a sensitivity of 0.98 and a specificity of 0.69. For the random 200, the physician had a sensitivity of 0.82 (95%CI 0.74–0.89) and specificity of 0.87 (95%CI 0.81–0.96) vs. software: same specificity and not statistically different slightly higher sensitivity (0.83, 95%CI 0.72–0.94; P ¼ 0.739).

S.H. Browne	South Africa	2019	P: TB patients intervention 41, control 21 I: Ingested medication monitor C: Standard of care	RCT 4	Intent-to-treat (ITT) analysis within the RCT showed intervention confirmed 93% versus 63% control (p < 0.001) of daily doses prescribed. 100% of participants preferred using intervention.
A.O.A. Ali	Sudan	2019	P: TB Patients: Intervention 74; control: 74 I: Reminder SMS and calls during treatment. C: Standard of care	NRCT 2	Default rate: Intervention 6.8%; 5 out of 74 vs. control: 10.8%; 8 out of 74 (P-value 0.563; OR: 1.673, 95% C.I. 0.521- 5.374). Cure rate Intervention 58 /74 (78.4.0%) vs. control: 44 (59.5) of the 74 (P-value 0.020; OR: 2,472, 95% CI:1.133 – 5.434). At the end of treatment, the knowledge in the intervention group was better than in the control group. Intervention rated as "useful": 72(97.3%) and "not useful" 2 (2.7%).
S. Palupi	Indonesia	2019	P: TB samples: Intervention 2479, Control 9 I: notification system C: Standard of care	BAS 1	Specimen referral went up from 9 cases referred for rapid molecular testing (RMT) in sept 2017 to 2479 in sept 2018 (after intervention). Notification of results "within a minute".
J. L. Davis	Uganda	2019	P: TB Patients Intervention 190; Control 213; TB Contacts Intervention 471; Control 448 I: SMS reminders, notification system C: Standard of care	RCT 3	SMS delivered to 95 (50%) of the intervention arm (programming error). Yield of contact investigation Intervention 7/471, 1.5% vs. control 5/448, 1.1%(OR 1.34, 95% CI 0.42–4.24, p=0.62). <20% of SMSs achieved their full effects. Barriers to intervention: sharing phones, broken phones, inability to read text messages, lack of familiarity with or attentiveness to SMS, preference for in-person disclosure of results.
S. Moayedi-Nia	Canada	2019	P: Tuberculin skin tests: 64 photos of administration, 72 photos of induration; Medical staff: 6 I: Automated photo analysis of TST on mobile phone app C: Standard of care, same cohort	BAS 2	TST induration, proportion of "correct on first reading": 0-4mm intervention 95% vs. control 83%, 5-9mm, intervention 20% vs. control 33%, 10-14mm intervention 77% vs. control 67%, >=15mm intervention 92% vs. control 91%.
P. Thekkur	India	2019	P: TB PLHIV+ Patients, intervention 870, control 961 I: Phone call reminders and automated answer after medication administration C: Standard of care	NRCT 1	Successful intervention 605 (69.5) vs. control 736 (76.6) <p 0.001. Poor implementation of intervention meant that treatment was mostly unsupervised. Treatment completed intervention 510/870 (58.6%) vs. control 443/961 (46.1%) p < 0.001. Challenges: not owning a mobile phone, not knowing how to use, lack of motivation, app-related challenges, preference for human interaction, staff related issues.
A. Story	UK	2019	P: TB Patients: Intervention 114, Control 112 I: Video-DOT asynchronous C: Standard of care	RCT 4	≥80% scheduled observations successfully completed during the first 2 months: 70% I vs. 31% C (adjusted odds ratio [OR] 5·48, 95% CI 3·10–9·68; p<0·0001). Average staff time per dose observed was C 56 min community based observed therapy; C 15 min for clinic-based observed therapy, and 3·2 min I. The costs C £5700 per patient vs. I £1645 per patient.
A. Wagstaff	South Africa	2019	P: Potential TB patients: intervention group A163, group B 155, control 97 I: SMS reminders C: Standard of care	RCT 4	Returned to collect TB diagnosis results: 78/101 C vs. 331/405 I. HIV patients were more responsive to the SMS. Non-delivery of the message excluded 15% of initial I participants and human error 5%.
K. Schwab	Malawi	2018	P: Potential TB cases: 181 examinations, in-depth analysis 108,1629 images; Medical staff: 11 I: Tele-ultrasound C: Standard of care, same cohort	BAS 1	General labelling of images as abnormal: intervention 96 (6%) vs. control 85 (5%) as abnormal, revealing an overall agreement of 98%. Pericardial effusion: 99.1%, periportal LAD 98.1%, para-aortic LAD 98.1%, left pleural effusion 99.1%, right pleural effusion 95.4%, ascites 99.1%, liver lesions 99.1%, splenic lesions 99.1%, other abnormalities 93.5%, any abnormality 97.8% Clinicians identified 92% of abnormalities seen by the expert reader.

R. S. Garfein	USA	2018	P: TB Patients Intervention 274; Control 159 I: Video-DOT, asynchronous C: Standard of care, historical cohort	BAS 2	Fraction of expected doses observed (FEDO): 93% intervention vs. 66.4% control. FEDO increased with longer use of intervention, higher annual income, and decreased with marihuana use in the past 6 months, poor network connection, taking medications away from home. Intervention was 6-46% cheaper than observed therapy (range $3,031–$3,911 versus range $3,212–$5,788) mostly due to personnel costs. 90% would choose intervention. Most believed I was more confidential than control.
C. K. Lam	USA	2018	P: LTBI Patients Intervention 50, Control 302 I: Video-DOT, synchronous C: Standard of care, historical cohort, same cohort	BAS 2	205 issues, of which: health department related 29, patient equipment 43, patient knowledge 3. Technical issues did not prevent continuation of observation sessions. Completed treatment intervention 44 (88.0%) vs. control 196 (64.9%).
N. Maraba	South Africa	2018	P: TB patients, intervention 319, control 457; TB patients Interviewed: 14; Medical staff: 7 interviewed I: notification system C: Standard of care, same cohort	BAS 1	Proportion of results available within 48 hours: I 96.8% vs. C 68.6% (p <0.001). Proportion of treatment within 28 days I 28/33 (84.8%) vs. C 30/44 (68.2%), (p = 0.08). In-depth interviews showed that providers easily integrated the intervention application into routine TB investigation and patients positively received the delivery of results via text message. Time from sputum collection to TB treatment initiation 4 days control vs. to 3 days, not statistically significant.
S. B. Holzman	USA	2018	P: TB patients: 28 I: VDOT asynchronous C: Standard of care, same cohort	BAS 1	Adherence: I 94% vs. C 98%, P = .17). Total treatment doses observed: I 72% vs. C 66%, P = .03. Staff, patients: cited increased treatment flexibility, convenience, and patient privacy in I. Cost analysis estimates savings with I of $1391 per patient for a standard 6-month treatment course.
G.Bediang	Cameroon	2018	P: TB patients, intervention 137, control 142 I: SMS reminders C: Standard of care	RCT 3	At 6 months: cure rate 87 (63.5%) in I vs. 88 (62%) in C (OR = 1.06 [0.65, 1.73]; p = 0.791). Satisfaction general management: 99.5 I and 99.2% C (p = 0.41)." Support provided for adherence to drug prescriptions - 99.6% of satisfaction in I vs. 99.1% in C (MD: 0.5% [− 0.2, 1.2]; p = 0.1).
J. C. Johnston	Canada	2018	P: LTBI patients, intervention 170, control 188 I: SMS reminders C: Standard of Care	RCT 4	Intention-to-treat analysis, proportion of participants completing LTBI therapy: 79.4% I and 81.9% C, (RR 0.97, 95% CI 0.88–1.07; p=0.550). Results were similar for pre-specified secondary endpoints, including time-to-completion of LTBI therapy, completion of >90% of prescribed LTBI doses and health-related quality of life.
R. Belknap	USA, Spain, Hong Kong, South Africa	2018	P: TB patients, intervention 315, control 321 I: SMS reminders C: Standard of Care	RCT 3	Treatment completion: 76.4% (CI, 71.3% - 80.8%) intervention vs. 74.0% (CI, 68.9% - 78.6%) control.
T. Buchman	USA	2017	P: TB patients, intervention 24, control 94 I: Video-DOT synchronous C: Standard of care, same cohort	BAS 1	Total mileage savings and time were $9,929.07 and 614 hours.
J. Gao	China Canada	2018	P: Participants, intervention 193, control 134 I: Educational video C: Standard of care, same cohort	BAS 2	Viewing the video was associated with a 1.04 (95% CI 0.85–1.26) or a 21% increase in a knowledge score. Of 193 viewers who completed the survey, 84% rated the TB video as "somewhat/very helpful", and 89% might recommend the video to others."
Y. Hirsch-Moverman	Lesotho	2017	P: TB PLHIV+ patients, intervention 183, control 166; Interviewees, patients 30, medical staff: 30 I: SMS and phone call reminders C: Standard of care	CRCT 2	41.9% stated that intervention increased adherence; 89.1% in I vs. 79.5% in control. Facilitators: cues for medication & appointments, access to telephone; choice in selecting time & frequency of intervention. Challenges: lack of previous phone usage, coded messages were confusing, electricity, technical. Satisfaction: medical staff expressed support; patients were appreciative.

J. Strymish	USA	2017	P: Prospective LTBI Patients, intervention 285 (39 LTBI), control 195 I: Tele-consultation C: Standard of care	NRCT 1	Intervention is faster: 0.6 days (SD 3.6) vs. 16.5 days (SD 12.4) P < .0; Intervention expands volume of consults without reducing the number of time per consults: 285 intervention vs. 195 control. Intervention is most useful for patients who need to travel long distances to reach the clinic.
R. J. Farooqi	Pakistan	2017	P: TB patients, intervention 74, control 74 I: SMS reminders C: Standard of care	RCT 2	Outcomes were not significantly different: 21 cured in intervention vs. 20 in control.
S.M. Hermans	Uganda	2017	P: TB PLHIV+ patients: Intervention 171, Control 274 I: SMS and phone call reminders C: Standard of care, historical cohort	NRCT 1	Composite outcome 8 weeks of treatment & end of treatment: not significantly different. Increase: 6/8 test questions baseline to 7/8 test questions. 165 (96%) rated intervention as helpful or very helpful; 92% intervention was helpful. 0 breaches of confidentiality. 28% did not understand the message, 26% unable to use phone for a mean duration of 14 (IQR 5-28) days; Main challenges: network, provider, system did not recognise reply; human-related issues.
K. Choun	Cambodia	2017	P: TB patients, 106 I: Phone reminders, mobile app C: Standard of care, historical cohort	BAS 2	Intervention 103 (97%) contacted & placed/continued on TB treatment vs. control 31-81%. Facilitators: patients not traced directly were traced through health facilities.
S. Chadha	India	2017	P: Medical staff, intervention 30, control139; Potential TB cases, intervention 1056, control 552; TB patients diagnosed, intervention 127, control 67; Diagnosed on day 1, intervention 99, control 59 I: Notification system C: Standard of care	NRCT 2	The number of TB patients diagnosed on day 1 (day of referral) was 158/194 (82%); 99/194 (51%) were referred by intervention. The number of diagnosed TB patients started on treatment on day 1 was 80/194 (41%); 48/80 (60%) were referred by intervention. The remaining patients were started on treatment within 7 days of diagnosis. The number of patients who received observed therapy: 60 from intervention and 39 from control.
X.H. Fang	China	2017	P: TB patients Intervention 160; Control 190 I: SMS reminders C: Standard of care	CRCT 3	Re-examined sputum 2 months intervention 96.88% vs. control 87.89%, p=0.002, 6 months Intervention 88.13% vs. control 69.47%, p=0.001. Completed the treatment intervention 154 (96.25%) vs. control 165 (86.84%), p=0.002.
E. L. Holzschuh	USA	2017	P: TB patients: Intervention 15, Control 12 I: Video-DOT asynchronous C: Standard of care, same cohort	NRCT 1	14 completed treatment; 1 interrupted - adverse event. $2,066 saved in km. Advantageous in case of travel, family relocation.
I. Prieto-Egido	Spain	2016	P: TB Diagnosis Samples: 70 sputum and 20 bronchial aspirate I: Tele-microbiology C: Standard of care, same cohort	BAS 1	100% concordance between intervention and control. Intervention took 7x longer than control - field of vision 10x smaller; remote interaction could be a challenge.
C.Chuck	USA	2016	P: TB patients, intervention 49, control 267 I: Video-DOT synchronous C: Standard of care, same cohort	BAS 2	Completed treatment: intervention 47 (96%) vs. control 260/267 (97%). Issues reported by 54 patients, 276 were technical problems, 49 were patient-related challenges such as patients forgetting their appointment, having schedule conflicts, or patient being out of camera view; and 21 were due to smartphone misuse. Facilitators: travel, weather, twice capacity.
S. Mohammed	Pakistan	2016	P: TB patients, intervention 1104, control 1093 I: SMS reminders, support, confirmation text from patients C: Standard of care	RCT 3	Challenges: system failure, administrative, GPRS outage, participants opting out/dying, not knowing their phone number/not sharing; response rates fell in time: 48% in the first two weeks to 24% (eight-month regimen) and 20% (six-month regimen) in the last two weeks. No significant impact on treatment success.

Y. P. Ha	Botswana	2016	P: Medical staff: 2; TB contacts, intervention 89, control 113 TB I: Notification system C: Standard of care	NRCT	Control 5.0 min per contact (IQR 4.0–8.0) vs. intervention 2.8 min per contact (IQR: 1.7–4.4), (p < .001); 12/113 (10.6%) contacts had ≥1 missing or illogical values vs. 0 in intervention. Intervention proved to be faster, with less errors. Overall rating 2.1/7.0, system usefulness 1.6/7.0, information quality 2.6/7.0, interface quality 2.3/7.0 (lower scores are better). Challenges: network, system (server).
I. V. Bassett	South Africa	2016	P: TB patients, intervention 187, control 198 I: Counselling, SMS and phone reminders C: Standard of care	RCT 4	Proportion of patients completing treatment: 39% intervention vs. 42% control; RR 0.93, 95% CI: 0.80 to 1.08).
R. Long	Canada	2015	P: TB patients, intervention 150, control 691 I: Virtual clinic C: Standard of care, same cohort	BAS 2	6 treatment outcome indicators both groups similar. Followed to three smears negative intervention > control (93% I vs. 55% C, p = 0.0001); end-of-initial phase sputum culture and chest radiograph, intervention > control (78% C vs. 50% I, p = 0.01; 68% C vs. 52% I, p = 0.05, respectively); proportion of TB cases treated with observed therapy intervention > control (100.0% I vs. 95.0% C, p = 0.004). 3 indicators, one related to case management, one related to treatment outcome and one related to contact management, intervention > control; on 3 indicators, two related to case management and one related to contact management, control > intervention.
X. Liu	China	2015	P: TB patients, intervention 1008 text msg; 997 medication monitor; 1064 combined; control 1104 I: Pill Box, SMS reminders, Medication box reminder C: Standard of care	CRCT 4	Measure = at least 20% of doses missed: 29.9% control vs. 27.3% in intervention (adjusted mean ratio 0.94, 95% CI 0.71, 1.24). Intervention lower loss to follow-up and occurrence of poor treatment outcome than control. Challenges: minor problems 56.5% intervention & 27.3% combined arm: "These problems included incorrect usage of the phone by the patient (42.0%), network failure (21.1%), and no money on the phone account (14.9%). Problems with the medication monitor or phone were resolved in 88.7% of occurrences."
Kumboyono	Indonesia	2015	P: TB patients, intervention 45, control 45 I: SMS reminders, support C: Standard of Care	NRCT 1	Treatment compliance intervention 93.3% vs. control 80% P=0.059. Awareness not significantly different (Fishers exact).
S. J. Iribarren	Argentina	2015	P: TB patients, intervention 19, control 18 I: SMS reminders, confirmation text from patients C: Standard of care	RCT 2	Medical staff all agreed that intervention beneficial; Advantage for "rural or semi-rural settings where access to health care was challenging". Challenges: network, Internet, electricity, travelling, mobile phone provider; different problems with automated software.
M. Mirsaeidi	USA	2015	P: TB patients, 11 I: Video-DOT C: Standard of care	BAS 1	7 (88%) of the patients interviewed thought it was an improvement & would recommend. Intervention saved 13495.7 EUR per patient, in travel time and operational costs.
N. Lorent	Cambodia	2014	P: Medical staff: 37; Potential TB cases 315.874 screened, 12.201 with TB symptoms; TB patients 10.301 I: Notification system C: Standard of care, historical cohort	BAS 1	Median of 3 days vs. 7-10 days faster time to obtain lab results after implementing the intervention.
T.R. Schulz	Australia	2014	P: 119 patients of which 49 LTBI I: Tele-consultation C: Standard of care, historical cohort	BAS 1	Nearly 500 km of travel and 127 kg of CO(2) production was avoided per consultation. Technical issues were faced in 25% of consultations, most frequently sound problems and connections dropping out. A bandwidth of at least 512 kbps and latency of no more than 300 ms is required.

S. J. Iribarren	Argentina	2013	P: TB patients, intervention 19, control 18 I: SMS reminders, confirmation text from patients C: Standard of care	RCT 2	Helpfulness Intervention 9/12, all components equally helpful. Patients felt "cared by staff". Treatment completion: 34/37 (92%) total, 17/18 I; 17/19 C.
J. A. Blaya	Peru	2013	P: Health centers intervention 29, control 49; TB patients: intervention 890, control 781 I: Notification system C: Standard of care	CRCT 4	Receive results: drug susceptibility tests (DST) median 11 intervention vs. 17 control days, p,0.001 and culture 5 intervention vs. 8 control days, p,0.001; faster culture conversion: 16 days sooner intervention, 20% less than control (p = 0.047); treatment turnaround time did not differ significantly 88 v. 77 days, p = 0.28.
K.H. Chaiyachati	South Africa	2013	P: TB patients, 4, Medical staff, 5 I: Notification system C: Standard of care, historical cohort	BAS 1	Intervention improved communication & collaboration, nurses felt more included; improved workflow. Satisfaction was high among medical staff. One phone malfunctioned, repaired within one week. Programme was periodically freezing. There were no network issues. Medical staff were sometimes forgetting to use intervention. Travel was saved.
M. A. Gassanov	Canada	2012	P: TB patients 13 I: Video-DOT, synchronous C: Standard of care, same cohort	BAS 1	Treatment compliance same (~ 98%); Average duration of I = 10 min vs. 36 min C; Advantages: high flexibility, privacy. Disadvantages: interpersonal connection, few patients had technical issues - individual network.
V. A. Wade	Australia	2012	P: TB patients, intervention 58, control 70; TB Patients Interviewed: 12; Medical staff: 18 I: Video-DOT synchronous C: Standard of care	NRCT 1	Intervention significantly reduced the percentage of missed observation episodes; non-adherence the same in intervention & control; felt it increases adherence; Benefits: flexibility, convenience; good relationship with nurses; nurses said it's faster; cohesion of medical staff team. 10/12 very satisfied, 2 mixed feelings. Average of 2 days was lost from the Intervention technical, network, electricity, hardware; 1 would prefer control because privacy, but impractical. "If one is willing to pay $2, the probability of cost-effectiveness rises to almost 90%".
R. M. Coulborn	Malawi	2012	P: X-Rays, 159 I: Tele-radiology C: Standard of care, same cohort	BAS 1	70.9% intervention (radiologist using eHealth) coincided with at least 1 diagnosis in control (clinical staff). Intervention management initially proposed by control 36 patients (23.5%); some had tuberculosis and others had other pulmonary ailments. 2 (1.3%) diagnosed by intervention, missed in control. 1 misdiagnosis of TB corrected by intervention, I averted inappropriate treatment in 16 patients (10.5%).
A. J. Khan	Pakistan	2012	P: Potential TB cases: 469 896 individuals screened, suspected: 7463 I: Mobile app for TB screening C: Standard of care, historical cohort	NRCT 1	Notification of adult pulmonary tuberculosis increased 3.77 times (415 vs. 1576) and childhood pulmonary tuberculosis by 7.32 times (28 vs. 205). This was a 2·21 times increase (95% CI 1·93–2·53; p=0.000) relative to the change in the control area, where the number decreased by 9%. Facilitated by: community laypeople and financial incentives.
P. Kunawararak	Thailand	2011	P: TB patients non-MDR intervention 30; control 30; MDR-TB intervention 19, control 19 I: Phone call reminder C: Standard of care	NRCT 1	MDR: Sputum conversion rate at 1 mo 90% intervention vs. 20% control (p<0.001); non MDR: I 37% I and 52% control (p=0.221); MDR and non MDR success rates 100% intervention vs. control MDR 73.7% (p=0.0001), non MDR-TB 96.7% (p=0.047). Accidental reveal of disease in control group. Opinion: increased patient communication, awareness, confidentiality.
T.C. Chen	Taiwan/ China	2011	P: TB patients, intervention 127, control 96 I: Notification system, reminders C: Standard of care	NRCT 2	Laboratory delay 3 control vs. 1 intervention days (P<.001), response delay 0 control vs. 0 intervention (P<.045), interval from admission to transfer to the isolation room 8.5 control vs. 3 intervention days (P <.001). Proportion of patients transferred to isolation within 1 day increased significantly. No significant difference in the total number of medical staff exposed to each active TB patient in control vs. intervention, but reported number of nurses exposed per patient with active TB who stayed in the general ward was significantly less during the intervention phase (P<.039).
A. Marcelo	Pakistan	2011	P: TB patients, 88 I: Tele-radiology C: Standard of care, same cohort	BAS 1	Agreement in 71 cases (80.6%) and disagreement in 17 cases (19.38%) between intervention and control. Average delay in waiting for results, less with 34.6 hours (range 9 minutes to 289.2 hours) after intervention. The average delay at the rural site (59.15 hours) was more than for the urban site (15.9 hours). Culture results: intervention 32.4% positive vs. control 27.6% positive. 2-month clinical follow-up: better improvement in symptoms and weight of the patients diagnosed in control vs. intervention. Medical staff showed satisfaction with the quality of images, were at complete ease in making diagnostic decisions, and never requested repeat Xrays.

J. A. Blaya	Peru	2011	P: Medical staff intervention 891, control 780; Smear Microscopy Intervention 1623, control 1348; Culture intervention 4203, control 2130 I: Notification system C: Standard of care	CRCT 4	Faster to receive results: drug susceptibility tests (DST) median 9 vs. 16 days, p<0.001 and culture results 4 vs. 8 days, p<0.001; peripheral health centres, communication times for DST (median 22 I vs. 19 C days, p<0.30) and culture (10 intervention vs. 9 control days, p¼0.10) results, same proportion of 'late' DSTs (p<0.57) compared with the control. Intervention does not "trickle down" to peripheral health centres.
J. E. Lee	Korea	2010	P: TB patients, intervention 163, control 441 I: Notification system C: Standard of care, historical cohort	BAS 1	Initiation of treatment 86.3% control vs. 94.5% intervention (P<0.05); delay 22.9 control days vs. 5.6 intervention days; completion 57.4% control vs. 68.1% intervention (P<0.01); interruption of treatment not significantly changed proportion of cured not significantly changed 8.5% control vs. 9.9% intervention, (P=0.67); success rate (cure rate + completion rate) was significantly increased (OR: 0.54, Intervention 0.32-0.93, P=0.03).
J. A. Blaya	Peru	2010	P: Medical staff: N/A; Samples: Smear Microscopy Intervention 709, Control 561; Culture Intervention 697; Control 498 I: Notification system C: Standard of care	CRCT 4	Intervention had 82% fewer errors than control for DST (2.1% vs. 11.9%, P < 0.001). For cultures, intervention had 87% fewer (2.0% vs. 15.1%, P < 0.001); missing paper results the same; users found results in the intervention that they did not have in control.
N. Mahmud	Malawi	2010	P: TB patients, intervention 200, control 100; Medical staff: 75 I: notification system C: Standard of care, historical cohort	BAS 1	Net savings $2,750/6 months; total of 648 hours transport time for TB coordinator; 500 hours saved for nurse; doubled number of patients seen (100 -> 200); 2.11% technical problems.
L. Wang	China	2009	P: TB patients: 817 reported by hospital; 565 referred; 189 traced out of 229 needed tracing I: TB patient tracing and notifications via phone calls C: Standard of care, historical cohort	NRCT 2	Reported TB 42.5% control vs. 95.3% intervention (P < 0.001); referred 48.1% control vs. 83.3% intervention (P < 0.001); arrived at the medical facility 59.3% control vs. 83.2% intervention (P < 0.001); arriving at the medical facility □3 days after reporting 38.4% control vs. 66.2% intervention (P < 0.001); 71.7% increase in patients seen at the target hospitals. This is higher than the 25.8% increase in patients initially seen outside the target hospitals (P <0.001).
M. Zimic	Peru	2008	P: Microbiology samples: *Mycobacterium tuberculosis*: 50, Atypical Mycobacteria 20, Culture negative: 5 I: tele-microscopy with mobile phone C: Standard of care, same cohort	BAS 2	98.7% concordance 74/75 (1 atypical mycobacteria). The single discrepancy corresponded to an atypical mycobacterium that was misclassified as a contaminant after mobile phone transmission.
J. A. Blaya	Peru	2008	P: Microscopy samples: Culture Intervention 1871, Control: 1679; Smear Microscopy intervention 2081, Control 1686 I: Notification system C: Standard of care	RCT 4	Time spent collecting & processing: 54% (5.45 to 2.52 min) for smear microscopy and by 66% (4.72 to 1.62 min) for cultures; Collection time: microscopy (1.36–2.11 min) and cultures (1.04–1.15 min) more vs. control; Processing: intervention required 90% less time for smear microscopy (4.09–0.41 min) and 87% less for cultures (3.68–0.47 min) vs. control. Monetary break even point is 5.5 yrs. Satisfaction: mean 5/5 intervention vs. mean 3.5/5 control. 1.13 /month technical problems staff could fix themselves.
B. Dwolatzky	South Africa	2006	P: TB patients, 20 I: Patient tracing & notifications using PDA/GPS C: Standard of care, same cohort	BAS 1	Less crowded community 9/10 located homes on photograph; crowded community 6/10 located homes; both places with GPS 10/10 located homes.

S. B. Uldal	Russia	2005	P: TB patients: 47; Medical staff: 5 experts I: Tele-consult C: Standard of care, same cohort	BAS 1	Consensus >90%; 7 no difference in treatment; 22 wrong treatment avoided; 8 (17%) intervention revealed incorrect completion of local TB statistics; 1 wk-1mo saved for 24/47 (51%) cases; 1 case <1wk; 20 cases no change; faster in 37 cases; 30 (64%) saved trip to main city. In 10 cases (21%), the panel considered that the personnel increased their knowledge about a disease. 9 (19%), the panel considered that the requesting physician appeared to take more interest in computers than in the medical diagnosis.
S. B. Bavdekar	India	2005	P: Prospective TB Patients 200 (out of which 6 TB) I: Internet-based diagnosis aid C: Standard of care, same cohort	BAS 1	Tuberculosis: 6 cases, 4 matched by the diagnosis aid.
S. S. Choi	Peru	2004	P: Medical staff 7; TB patients: Intervention 95 (before) +102 (after), Control 92 (before) +81 (after) I: notification system, reminders C: Standard of care	NRCT 1	Medical record errors rates: error/patients intervention 17.4% December to 3.1% April (P=0.0075) vs. control 8.6% December to 6.9% April (P=0.66). The nurses enjoyed working with the new system because it simplified workflow.
J. DeMaio	USA	2001	P: TB patients, 6 I: Video-DOT synchronous C: Standard of care, same cohort	BAS 1	Adherence 97.5% on control & 95% on intervention. Up to 98% without technical problems. 16 doses of intervention missed: 6 not at home, 9 network (28k modem speed). Average satisfaction scores, 8.8 intervention and 8.4 control. Overall satisfaction intervention 9.2. Savings in travel expenses of $2870 and personnel expenses of $7993. A total of 8830 miles of travel saved. Quick (2–5 min), flexibility in scheduling.
P. Corr	South Africa	2000	P: intervention 27 prospective TB X-Rays (1 TB diagnosis), control 100 I: Tele-radiology via email C: Standard of care, same cohort	BAS 1	96 diagnostic quality (96%) in controlC vs. 23 (85%) in intervention; good correlation of diagnosis remote - centre 90 cases (94%) for control and 23 out of 27 images and a normal appearance in the other four images for intervention.
G. Hripcsak	USA	1999	P: Medical staff: 8; TB patients: 43 I: Diagnosis aid C: Standard of care, same cohort	BAS 1	Positive pred value 0.96 (0.89–0.99); sensitivity of 0.89 (95% CI 0.75–0.96); Benefits: less paperwork, knowledge; nurse empowerment. Connection dropped from time to time. Some nurses complained the device was heavy. Patients trusted the privacy of the intervention.
P. Corr	South Africa	1997	P: TB patients 100; X-Rays: 75 I: Tele-radiology app and phone C: Standard of care, same cohort	BAS 1	Altered management: detection of pulmonary tuberculosis (10 patients (5%)) and miliary tuberculosis (2 patients). Undiagnosed spinal tuberculosis was detected in 3 patients. Allowed same day reporting. Issues encountered with transmission and phone network.

Table S2. PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5, S1

Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	S6-S16
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	5, S5

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- Vulcan greeting

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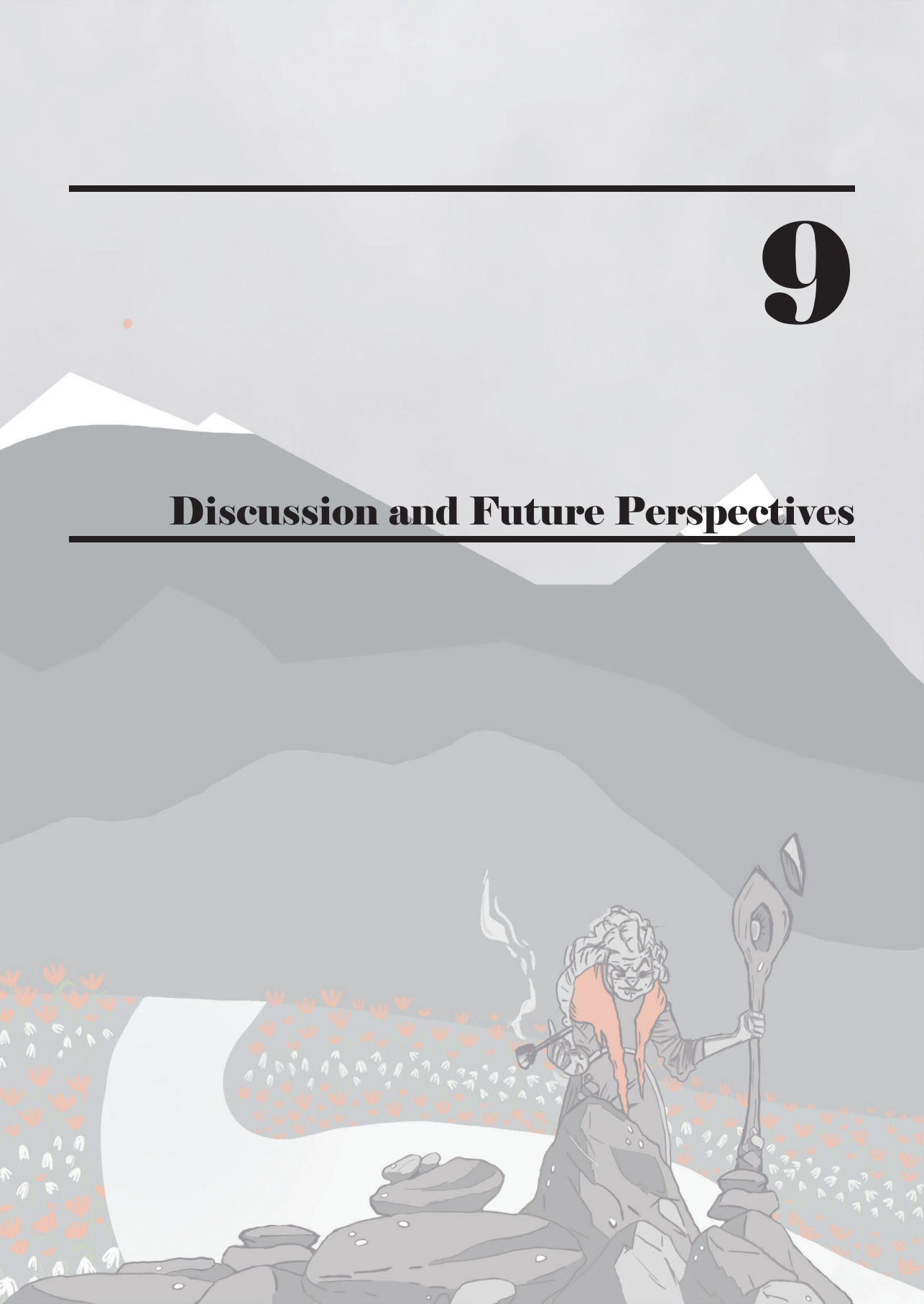
Discussion and Future Perspectives



Discussion and future perspectives

In the near 75 years since the first drug-driven cured TB cases were reported in the 1950s, the four drugs comprising the standard drug susceptible (DS) TB regimen were developed, implemented, and the complementary directly observed therapy (DOT) was recommended to prevent non-compliance. At the same time, epidemiological strides have also been made, with countries around the globe using better tools and more rigorous procedures to identify and prevent TB infection (TBI). However, the progress to eradicating TB has not been without challenges, including the rise of resistant forms (DR-TB), and its coexistence with several other infectious diseases, including HIV and COVID-19.

In this thesis we discuss TB clinical care in a contextualised manner and propose practical directions for future expansion.

Integrated, patient-centred TB care and prevention

This thesis approached this pillar of the World Health Organisation (WHO) End TB Strategy in two main ways: by studying results of patient reported outcome measures, thus involving patients in clinical care, and by understanding the population better in order to implement personalised medicine techniques, including therapeutic drug monitoring (TDM).

Patient centred care through patient reported outcome measures

The 1982 Making Health Care Decisions: A Report on the Ethical and Legal Implications of Informed Consent in the Patient-Practitioner Relationship was published and it is widely considered to be the documentary origin of shared decision making in healthcare [1]. Today, patient involvement in medical reasoning takes different forms, from patient involvement in drug development [2], to advancements in the notions of informed consent to include ideas of "active, shared decision making" [1].

Chapter 2 involved actual and former Romanian TB patients, both by DS-TB and DR-TB, by aiming to understand what their needs are, beyond purely epidemiological

outcomes such as mortality. The study used patient reported outcome measures (PROMs), comprising of standardised questionnaires participants performed themselves, in order to better understand the multiple impacts of TB on patients' lives, such as quality of life, mental health, work impairment, and disability, in order to tailor future interventions to better serve specific patients' needs. Results presented in chapter 2, based on comparing PROMs between DS-TB and DR-TB, during and after TB treatment, indicate that all groups report various degrees of impact on quality of life as a consequence of the disease, with the highest impact being felt by DR-TB patients during their treatment. The largest self-reported challenges within the groups pertain to the limiting nature of the disease, either for daily or work activities. Concerning the latter, patients are out of work at least during the intensive phase as the Romanian national TB guideline [3] recommends hospitalisation for all pulmonary TB cases unless there is the possibility of DOT in isolation conditions, which occurs in a minority of cases. This is comparable to global trends as a recent Global Tuberculosis Network review notes that globally hospitalisation times range between 20 and 60 days for DS-TB and 50-180 days for DR-TB [4]. At the same time, despite employed former TB patients reporting no loss in work hours, 52% were still unemployed after TB treatment end. Indeed, former TB patients reported better outcome measures than in-treatment patients on a plethora of quality of life domains. However, all groups tended to score lower than data availabe for the general Romanian population, with the caveat that our TB population consisted of two thirds men and the general Romanian population for which data was available consisted of two thirds women.

Last, but not least, this study included an app based screening audiometry which revealed that even in the case of patients not on ototoxic treatment, a third suffer from hearing loss. Surpassed only by migraine and back pain, hearing loss is the third cause of years lived with disability worldwide. Results indicate that it would be worth performing this test even with the advent of ototoxic TB drugs being phased out and shorter DR-TB being introduced worldwide.

A recent systematic review, found that the "force of mortality" for TB survivors is 2.91 (95% CI 2·21–3·84) times higher than in those who had never had tuberculosis

[5]. However, the focus of the medical world has been on shortening diagnosis and treatment times, by using new diagnosis techniques [6], introducing new TB drugs and shortening treatment length [7]. Whereas all these measures are important for TB disease control and managing potential drug toxicity, Chapter 2 emphasises the negative impact TB has on multiple facets during and after treatment and uses tools patients could use themselves to report disease evolution. Clinicians have been reluctant to implement PROMs as they feared, among other things, the potential time consumption [8]. The standardised tests used in this study took 30 minutes to complete, and, in context of the increase in usage of mobile technology, especially post COVID-19, PROMs could be a feasible alternative to perform follow-up without the need for patients or clinicians to travel. Especially for high burden, low resource settings, PROMs could be a cost-effective, acceptable alternative to classical follow-up, and at the same time could paint a more comprehensive picture of a TB patients' status during and after treatment.

Patient centred care through personalised medicine

International guidelines recommend tailored TB treatment to specific patient populations and to individual patients [9]. In order to understand the specific context within Romania and Ukraine, **Chapter 3** presents a retrospective study investigating DS-TB outcomes, conducted in three TB expertise centres. Univariate analysis was followed by the development of multivariate models for three TB outcomes: unfavourable treatment outcome, death, and loss to follow up (LTFU).

DS-TB success rates in our study were better than the reported national averages for Romania and Ukraine, and those, in turn, are better than the WHO European Region reported averages [10]. However, these success rates were achieved after a mean of 50 days of hospitalisation and eight months of DS-TB treatment. A study investigating the success rates of extended therapy for DS-TB reports that for patients with a negative culture at month two there was 100% success rate after a median treatment duration of 275 days (nine months) and for culture positive patients, the success rate was 74.5% [11]. One of the current goals for TB management is to shorten treatment duration in order to decrease the risk of loss to follow up and drug toxicity

- in our study, 85% of the population presented with at least one side effect during hospitalisation. However, in order to avoid the "one glove fit all" approach, Chapter 3 aimed to understand the contextualised road to treatment success.

The model for unfavourable outcomes developed in Chapter 3 is comparable with other similar models [12]. Common variables with other studies include being over 65 years of age, being underweight, or having more severe TB disease, in our study evidenced by the presence of at least one cavity on thoracic X-ray. There were, at the same time, differences specific for the studied population. For instance, our population has low HIV rates and thus that was not a variable included in our study, opposed to other research performed in high HIV prevalence areas. Interestingly, obesity and on time culture conversion were variable used in the LTFU model, but not in unfavourable outcomes or death, indicating that patients who are clinically less at risk for side effects could be more at risk of renouncing treatment.

Our study included all variables routinely gathered in TB patients in Romania and Ukraine, including the paraclinical follow-up performed after treatment initiation. Liver enzymes and kidney function tests are taken mandatorily after two weeks-one month of treatment and results indicate that if elevated values do not improve, despite available clinical measures, it could be an indicator for worse TB outcomes. Unfortunately, in Romania and Ukraine the only measures available include supportive treatment or altering the treatment scheme through pausing or removing one or more TB drugs. A personalised medicine technique, such as TDM, could assist in clinical decision-making to avoid drug toxicity and, through selective pressure, facilitating the emergence of resistant *Mycobacterium tuberculosis* strains.

Chapter 3 highlighted several risk factors for unfavourable TB outcomes and the potential interplay between them in the specific context of Romania and Ukraine. Using routinely collected data, clinicians could, in the future, be informed automatically about the risk of a certain patient, in the same manner as other automated risk scores [13] such as the Framingham score for cardio-vascular risk or the CURB-65 pneumonia severity index. Furthermore, this chapter highlights that future personalised medicine interventions, including targeting at-risk patients for lifestyle

modifications and introducing techniques such as TDM for clinical management could improve patient outcomes from a multifaceted perspective.

Regarding the aforementioned personalised medicine technique, **Chapter 4** aimed to better understand the potential of TDM implementation in Romania and Ukraine by analysing all admitted TB cases in three TB expertise centres for the duration of one calendar year. Patients were analysed for TDM eligibility following international guidelines. The most used criteria for TDM inclusion was slow response to treatment, followed by the administration of second line medication. 38% of patients were eligible for TDM, with notable differences in the percentage of patients with TDM indication per centre: in Ukraine, 81.2% of hospitalised patients within the year 2019 had at least an indication for TDM, whereas in Romania 29.4% and 28.7%. This reflects differences in the pool of TB population, with Ukraine having 10 times more DR-TB cases than Romania. Overall results match another similar study performed in a high-income country, Australia, where 35% of patients were TDM eligible [14]. The TDM-eligible population had higher smear and culture grades, more often bilateral lung involvement and cavitary disease. These results would indicate that using diagnosis criteria such as chest X-Ray, smear, and culture results might be comparable with the culture conversion criteria which takes at least two months to materialise. Keeping in mind that the intensive phase of DS-TB is two months and that the new treatment recommendations for DR-TB include a six month regimen, TDM might be best utilised at the beginning of treatment. The population which would have been selected following guideline criteria for TDM had comparable TB outcomes according to the WHO to the population not eligible for TDM. The contrasts were found in hospitalisation time, overall treatment duration and the presence of side effects (25% of TDM eligible vs 13% of TDM ineligible) and evidence of treatment toxicity (kidney injury TDM eligible 2.3% vs TDM ineligible 0.2%).

Chapters 3 and 4 highlight that, despite treatment success rates being at least acceptable by international standards, the road to these outcomes is paved with significant morbidity, which is a burden for the patients themselves and for the medical system, which has to involve more resources to achieve treatment success. Taken in concordance with results presented in Chapter 2, the effects of TB disease

and its treatment are visible not only short term, during treatment, but also long-term, even five years after treatment completion.

These findings should incentivise medical staff and stakeholders alike to plan for interventions beyond TB medication and managing its side effects. Involving patients in their own care, tackling comorbidities, and socio-economic particularities, implementing interventions which could elevate long term physical and mental post-TB rehabilitation could all be potentially cost-effective avenues of further research.

Concerning aiding clinicians in choosing at-risk patients, a calculating tool, could be useful to quickly triage patients more prone for complicated management. Furthermore, TDM could be a useful technique to aid clinical decision-making, especially in higher burden settings such as Romania and Ukraine. Regarding TDM, before implementing this technique in a new setting, an analysis should be made balancing its benefits to its potential challenges.

Bold policies and supportive systems

This pillar of the WHO End TB strategy suggests, among other items, to strive to achieve a universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control.

Towards better policy concerning therapeutic drug monitoring

Concerning the rational use of medicine, introducing TDM, a technique which could offer detailed information about drug concentrations, could aid in adjusting TB treatment schemes in order to avoid drug toxicity and acquired resistance [15]. However, introducing this technique in clinical settings with no experience with it could present several challenges. In order to spend time and resources to introduce a new technique, stakeholders must be convinced that it is worth the investment.

Chapter 5 explored opinions of TB experts worldwide, who have experience using TDM in their clinical practice and who have not implemented this technique alike. A digital questionnaire was distributed using several international networks to TB

clinicians and clinical pharmacists, with several questions pertaining to the current practices in TDM use, the perceived benefits and challenges to using and/or implementing this technique.

Findings show that, despite TDM being recommended by the WHO and the American Thoracic Society (ATS) TB guidelines, it was used by only half of the respondents. Participants who did not use TDM were overall enthusiastic about introducing TDM in TB clinical care, however, they also indicated that introducing TDM would involve not only the financial advance in equipment and assays, but especially training medical and paramedical staff in its use. Considering that TDM would be most useful in TB endemic areas, where theoretically the cost-benefit would be optimum, this should be investigated by a robust clinical trial [15]. Future research should focus on offering a roadmap for TDM implementation, especially in resource scarce, high TB incidence settings, and an emphasis placed on involving patients in the decision-making process of drug dosages, risk assessment, and choice of therapy. A prospective trial with the main aim of comparing treatment outcomes could have three arms, one in which TB clinicians are informed about at-risk patients, one in which TDM is performed and they are also informed about blood drug levels, and a control arm, in which standard of care is followed. Gathering feed-back from clinicians and laboratory staff about the process would comprise the usability component. An economic analysis on the amount of resources invested versus treatment duration and hospital measures to avoid and mitigate side effects could be then performed. Finally, using PROMs to enhance classical TB indicators such as mortality could be used to understand the impact of these interventions.

Towards TB policy concerning recently arrived migrants

Chapter 6 investigated European-wide policies concerning TBI for recently arrived migrants by approaching all national TB programme managers or equivalent in 32 EU/EEA + Switzerland + UK. Within this space, only half of countries have a policy in place to screen recently arrived migrants for TBI. Procedures to screen for TB are similar amongst the countries which perform them, with differences noted in the type of migrant screened and the timing (a majority, 60%, perform TBI screening after

settlement). Current challenges in TBI screening identified by programme managers were migrants' lack of motivation, language barriers, and relocation.

There was consensus amongst all study participants regarding several factors, including the need for a European-wide guideline for approaching TB, especially for mobile populations. Europe is an active space for labour migration, both from outside Europe and within EU/EEA bounds, however, only half of the countries who do perform TBI screening include labour migrants. In the context of the war in Ukraine, which displaced an estimate of 5 million refugees from a country on the top 10 highest burden TB countries worldwide into several countries without a national TBI screening programme (Romania, Hungary, Czech Republic, Germany) [16] it is imperative that a unified policy is agreed upon and implemented at a European level.

Intensified research and innovation

The year 1995 is most agreed upon as starting the age of the Internet, with the 2000s marking the advent of social media and the full immersion in the digital age. In 2022, five billion people had access to the Internet. The medical community, despite being slow on the uptake, has not ignored this technology entirely, with digital health, or the digital delivery of healthcare services, becoming an item on the agenda of every major medical organisation. TB is an especially attractive target for digital health implementation.

Chapter 7 explores how digital health can be employed in TB clinical care, through a systematic review and meta-analysis. The 89 studies included in the final analysis present results from various Internet based technologies, used in different points of TB care. Concerning diagnosis, digital health interventions offered access to TB experts in areas without such expertise available, and offered the possibility of automating parts of TB screening procedures, such as TST or chest X-ray reading. Regarding treatment, digital health provided cost-effective alternatives to the standard of care DOTs strategy and to in-person consultations in situations where travelling is a burden for the population, such as resource-poor settings, remote areas, or for mobile populations. Studies included in the analysis also reported high acceptability rates across their results, for patients and medical providers alike. The challenges

to implementing digital health identified within the included studies mirror the challenges with any new technology, as mentioned in Chapter 5. Access to adequate equipment (hardware and software), and, especially, the need to adequately train the user base (both medical professionals and patients) in the use of digital tools were the most frequent caveats mentioned. Overall, digital health interventions added value to standard of care, being especially useful when the necessity of travel intersects lack of resources or a lack of possibility of traveling, such as in resource scarce, mobile population, or in the advent of a (new) pandemic. Evidence across the included studies, was, however, low, and more robust studies are needed to investigate the multiple domains of TB care where digital health could be implemented.

Chapter 8 investigated worldwide perceptions regarding digital health implementation by performing focus group interviews with medical staff and TB patients. The consensus amongst all participants, from all six countries involved, is that there are important communication and information gaps which could be bridged by a digital health tool. Overwhelmingly participants felt there is a lack of knowledge about tuberculosis amongst patients, the general public, and even amongst medical practitioners. These findings are mirrored in several studies [17–19]. Regarding communication, participants in our study believed that it could be improved via an app by either facilitating medical access or creating online TB communities. Lessons should be learned from the forceful online push of COVID-19 towards digital spaces. Various healthcare settings and multiple worldwide TB associations are encouraging implementation of digital health in the forms of forums, chatbots to answer basic queries and monitoring systems to enhance standard of care [20]. At the same time, digital health faces some important challenges. Privacy is one main aspect to consider, especially taking into account several reported security breaches and ransomware attacks of medical facilities, or large data leaks from insurance providers. Several solutions could exist, from ensuring no identifiable data is stored on global servers, or using newer security solutions, such as blockchain. Research suggests that within the digital health pilots studied there were no security breaches and that patients felt their data was more secure digitally than on paper forms, which are also vulnerable to data breaches.

A second challenge to overcome is reluctance and inexperience with using digital technologies by medical staff, researchers, and patients alike. This knowledge gap will inevitably be closing as more and more people become acquainted with software, and as digital technologies gain larger acceptance, however, ensuring adequate training and educating patients and medical staff about how to use the proposed digital solution is an important step to ensure its success.

Last, but not least, policies and practices, reflecting different socio-economic, cultural, governmental, political realities, differ worldwide. The path to a widely accepted and used digital health solution, as it was with the standardised treatment, must ensure consistency, but also adaptability to local realities and needs.

The future of TB in ever-changing contexts

TB has witnessed changes in humanity for 40,000 years. More recently, contexts regarding the bacteria itself, the location of the humans it targets, concomitant medical and non-medical events have posed additional challenges to eradicating TB - but, at the same time our understanding of the disease itself and the available tools to tackle it have also changed.

The future should ensure that the medical world takes advantage of newer technologies, and, starting from a point of consensus and stability, creates solutions which can have widespread use, but which can be adapted quickly to local contexts and ever-changing circumstances.

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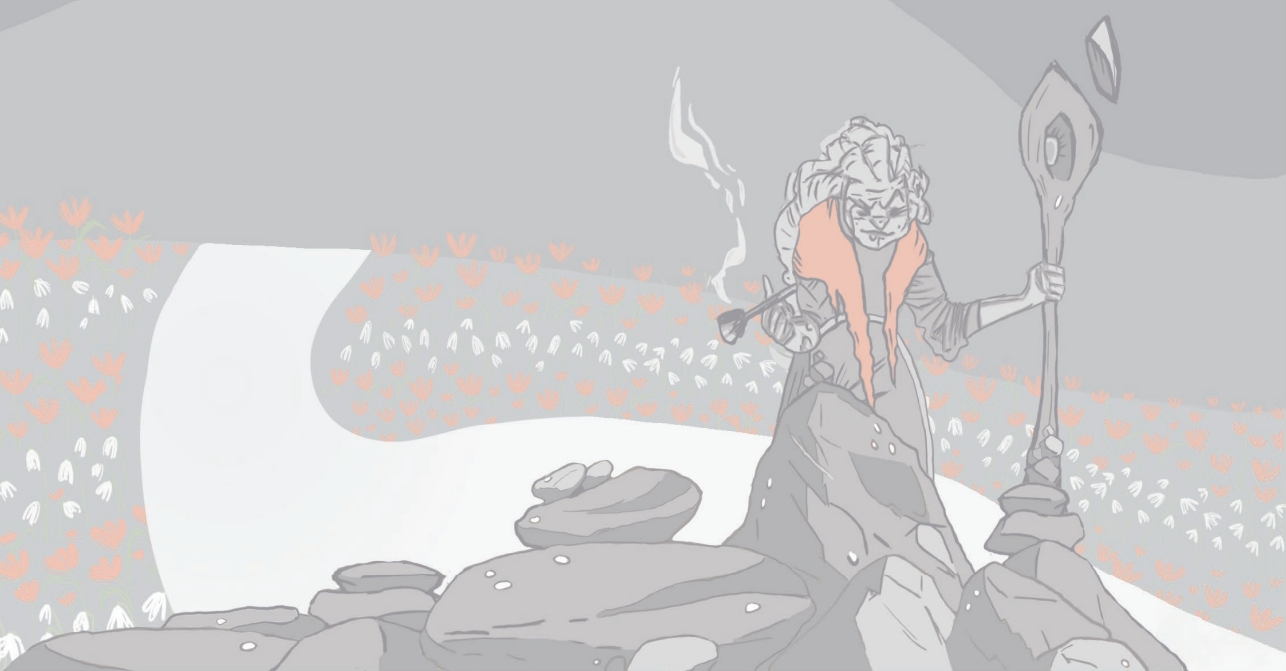
If I had more time, I would have written a shorter letter.
- Mark Twain

10

Summary. Samenvatting. Sumar.



Summary

In this thesis, we discussed personalised approches to tuberculosis (TB) care in high burden settings by performing different types of research in different settings. The thesis follows the three guiding pillars of the World Health Organisation End TB strategy: integrated, patient-centered TB care and prevention, bold policies and supportive systems, and intensified care and innovation.

The first pillar, integrated, patient-centered TB care and prevention was approached in chapters 2-4.

In chapter 2 we evaluated patients suffering from drug susceptible (DS-TB) and drug resistant (DR-TB) TB, who were either during TB treatment or at a maximum of five years post treatment through a series of patient reported outcome measures (PROMs). PROM have been used previously for other pathologies to evaluate the physical and mental status of patients by enabling them to self-evaluate their currrent healthstatus and wellbeing. The PROMs used in this study included three standardised questionnaires and one app-based screening audiometry. The questionnaires included quality of life and work impairment assesssments. Results indicate that all groups of patients suffer from disability, in different degrees, with the least favorable outcomes being reported in the DR-TB during treatment group. The largest self-reported challenges within the groups pertain to the limiting nature of the disease, either for daily or work activities. Concerning the latter, 52% of all patients were unemployment, even after TB treatment had ended. Despite better outcomes reported in the group of participants included after TB treatmend end, all groups had lower scores in quality of life than the general Romanian population. Chapter 2 emphasises the negative impact TB has on multiple facets of patients' wellbeing and uses tools patients could use themselves to report disease evolution. Clinicians have been reluctant to implement PROMs as they feared, among other things, the potential time consumption. The standardised tests used in this study took 30 minutes to complete, and, in context of the increase in usage of mobile technology, PROMs could be a feasible alternative to perform follow-up without the need for patients or clinicians to travel. Especially for high burden, low resource

settings, PROMs could be a cost-effective, acceptable alternative to classical follow-up, and at the same time could paint a more comprehensive picture of a TB patients' status during and after treatment.

Chapter 3 presents a retrospective study investigating DS-TB outcomes was conducted in three TB expertise centres in Romania and Ukraine, two neighboring high burden TB countries in Europe. Univariate analysis was followed by the development of multivariate models for three TB outcomes: unfavourable treatment outcome, death, and loss to follow up (LTFU). DS-TB success rates in our study were better than the reported national averages for Romania and Ukraine, and those, in turn, are better than the WHO European Region reported averages. However, these success rates were achieved after a mean of 50 days of hospitalisation and eight months of DS-TB treatment. One of the current goals for TB management is to shorten treatment duration in order to decrease the risk of loss to follow up and drug toxicity - in our study, 85% of the population presented with at least one side effect during hospitalisation. Contexualising patient population in specific settings is one of the recommendations of the WHO. The models developed for our population are comparable with other models previously developed, but have several differences, for instance the absence of HIV from a majority of the patients included and thus from the models developed. Our study included all variables routinely gathered in TB patients in Romania and Ukraine, including the paraclinical follow-up performed after treatment initiation. Liver enzymes and kidney function tests are taken mandatorily after two weeks-one month of treatment and results indicate that if elevated values do not improve, despite available clinical measures, it could be an indicator for worse TB outcomes. Unfortunately, in Romania and Ukraine the only measures available include supportive treatment or altering the treatment scheme through pausing or removing one or more TB drugs. A personalised medicine technique, such as therapeutic dug monitoring (TDM), could assist in clinical decision-making to avoid drug toxicity and selecting resistant strains of *Mycobacterium tuberculosis*.

In order to better understand the population which would best benefit from TDM,

Chapter 4 analysed all admitted TB cases in three TB expertise centres for the duration of one calendar year. TDM eligibility was based on international guidelines. 38% of patients were eligible for TDM, with the most used criteria for TDM inclusion was slow response to treatment, followed by the administration of second line medication. The TDM-eligible population had higher smear and culture grades, more often bilateral lung involvement and cavitary disease. These results would indicate that using diagnosis criteria such as chest X-Ray, smear, and culture results might be comparable with the culture conversion criteria which takes at least two months to materialise. The TDM eligible population, despite having comparable TB treatment outcomes with the non-eligible population, had a longer overall treatment duration and more frequent side effects (25% of TDM eligible vs 13% of TDM ineligible).

The chapters nested under this pillar suggest that involving patients in their own care, tackling medical and socio-economic particularities, and implementing personalised medicine interventions could all be potentially cost-effective and beneficial avenues of further research.

The second pillar, bold policies and supportie systems, was the basis of chapters 5-6.

Chapter 5 continued the TDM avenue by exploring TDM in present and future use through collecting worldwide expert opinions. 86 TB experts, either TB clinicians or clinical pharmacists, responded to a digital questionnaire with several questions pertaining to the current practices in TDM use, the perceived benefits and challenges to implementing this technique. TDM was used by only half of the respondents. Participants who did not use TDM were overall enthusiastic about introducing TDM in TB clinical care, however, they also indicated that introducing TDM would involve not only the financial advance in equipment and assays, but especially training medical and paramedical staff in its use. Future research should focus on offering a roadmap for TDM implementation, especially in resource scarce, high TB incidence settings, and an emphasis placed on involving patients in the decision-making process of drug dosages, risk assessment, and choice of therapy.

Chapter 6 investigated European-wide policies concerning TB infection (TBI) for recently arrived migrants by approaching all national TB programme managers or

equivalent in 32 EU/EEA + Switzerland + UK. Within this space, only half of countries have a policy in place to screen recently arrived migrants for TBI. TBI screening is addressed predominantly to asylum seekers and refugees. Countries took similar approaches to diagnosis and treatment, with divergent approaches for follow-up. Current challenges in TBI screening identified by programme managers were migrants' lack of motivation, language barriers, and relocation. There was consensus amongst all study participants regarding several factors, including the need for a European-wide guideline for approaching TB, especially for mobile populations. Europe is an active space for labour migration, both from outside Europe and within EU/EEA bounds, however, only half of the countries who do perform TBI screening include labour migrants. Chapter 6 highlights a range of approaches to TBI screening in migrants across EU/EEA and consensus regardng expanding and strengthening efforts to meaningfully include migrants in screening programmes.

The third pillar, intensified research and innovation, was approached in Chapters 7 and 8.

Chapter 7 explored how digital health can be employed in TB clinical care, through a systematic review and meta-analysis. The 89 studies included in the final analysis present results from various Internet based technologies, used in different points of TB care. Concerning diagnosis, digital health interventions offered access to TB experts in areas without such expertise available, and offered the possibility of automating parts of TB screening procedures, such as TST or chest X-ray reading. Regarding treatment, digital health provided cost-effective alternatives to the standard of care DOTs strategy and to in-person consultations in situations where travelling is a burden for the population, such as resource-poor settings, remote areas, or for mobile populations. Studies included in the analysis also reported high acceptability rates across their results, for patients and medical providers alike. The challenges to implementing digital health identified were access to adequate equipment and, the need to adequately train the user base. Evidence across the included studies, was, however, low, and more robust studies are needed to investigate the multiple domains of TB care where digital health could be implemented.

Chapter 8 investigated worldwide perceptions regarding digital health implementation by performing focus group interviews with medical staff and TB patients. The consensus amongst all participants, from all six countries involved, is that there are important communication and information gaps which could be bridged by a digital health tool. Overwhelmingly participants felt there is a lack of knowledge about tuberculosis amongst patients, the general public, and even amongst medical practitioners. Regarding communication, participants in our study believed that it could be improved via an app by either facilitating medical access or creating online TB communities, although some participants would prefer a hybrid system as they value in person consultations. Participants also identified several challenges, from the need to ensure patient privacy, to a resilience to change and a lack of failiarity of potential users with medical apps. The path to a widely accepted and used digital health solution, as it was with the standardised treatment, must ensure consistency, but also adaptability to local realities and needs.

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Samenvatting

In dit proefschrift beschreven we gepersonaliseerde benaderingen van tuberculose (TBC)-zorg in omgevingen met een hoge belasting, door verschillende soorten onderzoek in verschillende omgevingen uit te voeren. Het proefschrift volgt de drie leidende pijlers van de 'End TB'-strategie van de Wereldgezondheidsorganisatie: geïntegreerde, patiëntgerichte TBC-zorg en -preventie, gedurfd beleid en ondersteunende systemen , en geïntensiveerde zorg en innovatie.

De eerste pijler werd beschreven in hoofdstukken 2-4: geïntegreerde, patiëntgerichte TBC-zorg en -preventie.

In hoofdstuk 2 evalueerden we patiënten die leden aan medicijngevoelige (drug-sensitive TBC, DS-TBC) en medicijnresistente (drug-resistant TBC, DR-TBC) TBC, die ofwel tijdens de TBC-behandeling ofwel maximaal vijf jaar na de behandeling waren, door middel van een reeks door de patiënt gerapporteerde uitkomstmaten (patient-reported outcome measures, PROM's). PROM is eerder gebruikt voor andere pathologieën, om de fysieke en mentale status van patiënten te evalueren door hen in staat te stellen zelf hun huidige gezondheidsstatus en welzijn te evalueren. De PROM's die in deze studie werden gebruikt, omvatten drie gestandaardiseerde vragenlijsten en één app-gebaseerde screeningaudiometrie. De vragenlijsten omvatten beoordelingen van de kwaliteit van leven en werkbeperkingen. De resultaten geven aan dat alle groepen patiënten in verschillende mate last hebben van handicaps, waarbij de minst gunstige uitkomsten worden gerapporteerd in de DR-TBC groep tijdens de behandeling. De grootste zelfgerapporteerde uitdagingen binnen de groepen hebben betrekking op de beperkende aard van de ziekte, zowel voor dagelijkse als voor werkactiviteiten. Wat dat laatste betreft, was 52% van alle patiënten werkloos, zelfs nadat de TBC-behandeling was beëindigd. Ondanks betere resultaten die werden gerapporteerd in de groep deelnemers die was opgenomen na het einde van de TBC-behandeling, scoorden alle groepen lager op kwaliteit van leven dan de algemene Roemeense bevolking. Hoofdstuk 2 benadrukt de negatieve impact die TBC heeft op meerdere facetten van het welzijn van patiënten en gebruikt hulpmiddelen die patiënten zelf kunnen gebruiken om de voortgang van de ziekte te

rapporteren. Clinici waren terughoudend om PROM's te implementeren, onder meer omdat ze bang waren voor het mogelijke tijdsverbruik. De gestandaardiseerde tests die in dit onderzoek werden gebruikt, namen 30 minuten in beslag en, in de context van het toenemende gebruik van mobiele technologie, zouden PROM's een haalbaar alternatief kunnen zijn om follow-up uit te voeren zonder dat patiënten of clinici hoeven te reizen. Vooral voor instellingen met een hoge belasting en weinig middelen zouden PROM's een kosteneffectief, acceptabel alternatief kunnen zijn voor klassieke follow-up, en tegelijkertijd een volledigere beeld kunnen schetsen van de status van TBC-patiënten tijdens en na de behandeling.

Hoofdstuk 3 presenteert een retrospectief onderzoek naar de uitkomsten van DS-TBC, uitgevoerd in drie TBC-expertisecentra ¬¬¬¬¬in Roemenië en Oekraïne, twee naburige landen met een hoge TBC-ziektelast in Europa. Univariate analyse werd gevolgd door de ontwikkeling van multivariate modellen voor drie TBC-uitkomsten: ongunstig behandelresultaat, overlijden en verlies voor follow-up (loss to follow up, LTFU). DS-TBC-succespercentages in ons onderzoek waren beter dan de gerapporteerde nationale gemiddelden voor Roemenië en Oekraïne, en die zijn op hun beurt beter dan de gerapporteerde gemiddelden van de Europese regio van de WHO. Deze succespercentages werden echter bereikt na gemiddeld 50 dagen ziekenhuisopname en acht maanden DS-TBC-behandeling. Een van de huidige doelen voor de behandeling van tuberculose is het verkorten van de behandelingsduur om het risico op verlies voor follow-up en medicijntoxiciteit te verminderen - in onze studie kreeg 85% van de populatie ten minste één bijwerking tijdens ziekenhuisopname. Het contextualiseren van de patiëntenpopulatie in specifieke settings is een van de aanbevelingen van de WHO. De voor onze populatie ontwikkelde modellen zijn vergelijkbaar met andere eerder ontwikkelde modellen, maar er zijn een aantal verschillen, bijvoorbeeld de afwezigheid van hiv bij een meerderheid van de meegenomen patiënten en dus ook bij de ontwikkelde modellen. Onze studie omvatte alle variabelen die routinematig worden verzameld bij TBC-patiënten in Roemenië en Oekraïne, inclusief de paraklinische follow-up die wordt uitgevoerd na de start van de behandeling. Leverenzymen en nierfunctietesten worden verplicht uitgevoerd na twee weken tot een maand behandeling en de resultaten geven aan dat als verhoogde

waarden niet verbeteren, ondanks beschikbare klinische maatregelen, dit een indicator kan zijn voor slechtere TBC-uitkomsten. Helaas zijn in Roemenië en Oekraïne de enige beschikbare maatregelen ondersteunende behandeling of het wijzigen van het behandelschema door een of meer TBC-medicijnen te onderbreken of te schrappen. Een gepersonaliseerde medicijntechniek, zoals therapeutic drug monitoring (TDM), zou kunnen helpen bij de klinische besluitvorming om medicijntoxiciteit te voorkomen en resistente stammen van Mycobacterium tuberculosis te selecteren.

Om beter inzicht te krijgen in de populatie die het meeste baat zou hebben bij TDM, analyseerde hoofdstuk 4 alle opgenomen TBC-gevallen in drie TBC-expertisecentra gedurende een kalenderjaar. De geschiktheid voor TDM was gebaseerd op internationale richtlijnen. 38% van de patiënten kwam in aanmerking voor TDM, waarbij de meest gebruikte criteria voor TDM-inclusie een trage respons op de behandeling waren, gevolgd door de toediening van tweedelijnsmedicatie. De TDM-geschikte populatie had hogere uitstrijk- en kweekgraden, vaker bilaterale longbetrokkenheid en cavitaire ziekte. Deze resultaten zouden erop wijzen dat het gebruik van diagnosecriteria zoals thoraxfoto's, uitstrijkjes en kweekresultaten vergelijkbaar zou kunnen zijn met de kweekconversiecriteria, die ten minste twee maanden in beslag nemen. De populatie die in aanmerking kwam voor TDM had, ondanks vergelijkbare TBC-behandelingsresultaten met de populatie die niet in aanmerking kwampopulatie, een langere totale behandelingsduur en frequentere bijwerkingen (25% van de TDM-in aanmerking komende versus 13% van de TDM niet-geschikt).

De hoofdstukken die onder deze pijler vallen, suggereren dat het betrekken van patiënten bij hun eigen zorg, het aanpakken van medische en sociaal-economische bijzonderheden en het implementeren van gepersonaliseerde medische interventies allemaal mogelijk kosteneffectieve en nuttige wegen kunnen zijn voor verder onderzoek.

De tweede pijler, gedurfd beleid en ondersteunende systemen, vormde de basis van de hoofdstukken 5-6.

Hoofdstuk 5 zette de TDM-route voort door TDM te verkennen in huidig en

toekomstig gebruik door wereldwijde expertmeningen te verzamelen. 86 TBC-experts, TBC-medici of klinisch apothekers beantwoordden een digitale vragenlijst met verschillende vragen over de huidige praktijk van het gebruik van TDM, de ervaren voordelen en uitdagingen bij het implementeren van deze techniek. TDM werd door slechts de helft van de respondenten gebruikt. Deelnemers die geen TDM gebruikten, waren over het algemeen enthousiast over de introductie van TDM in de klinische zorg voor TBC. Ze gaven echter ook aan dat de introductie van TDM niet alleen een financiële vooruitgang in apparatuur en assays met zich mee zou brengen, maar vooral ook het trainen van medisch en paramedisch personeel in het gebruik ervan. Toekomstig onderzoek moet zich richten op het aanbieden van een routekaart voor TDM-implementatie, met name in omgevingen met schaarse middelen en een hoge incidentie van tuberculose, en de nadruk moet worden gelegd op het betrekken van patiënten bij het besluitvormingsproces over medicijndoseringen, risicobeoordeling en therapiekeuze.

Hoofdstuk 6 onderzocht Europees beleid met betrekking tot TBC-infectie (TBI) voor recent aangekomen migranten door alle nationale TBC-programmamanagers of gelijkwaardig in 32 EU/EER + Zwitserland + VK te benaderen. Binnen deze ruimte heeft slechts de helft van de landen een beleid om recent aangekomen migranten te screenen op TBI. TBI-screening richt zich met name op asielzoekers en vluchtelingen. Landen hanteerden vergelijkbare benaderingen voor diagnose en behandeling, met uiteenlopende benaderingen voor de follow-up. Huidige uitdagingen bij TBI-screening die door programmamanagers werden geïdentificeerd, waren het gebrek aan motivatie van migranten, taalbarrières en verhuizing. Er was consensus onder alle studiedeelnemers over verschillende factoren, waaronder de behoefte aan een Europese richtlijn voor de aanpak van tuberculose, met name voor mobiele populaties. Europa is een actieve ruimte voor arbeidsmigratie, zowel van buiten Europa als binnen EU/EER-grenzen, maar slechts in de helft van de landen die TBI-screening uitvoeren worden arbeidsmigranten meegenomen. Hoofdstuk 6 belicht een reeks benaderingen van TBI-screening bij migranten in de EU/EER en consensus over het uitbreiden en versterken van inspanningen om migranten op zinvolle wijze op te nemen in screeningprogramma's.

De derde pijler, intensivering van onderzoek en innovatie, is in de hoofdstukken 7 en 8 aan de orde gekomen.

Hoofdstuk 7 onderzocht hoe digitale gezondheidszorg kan worden ingezet in de klinische zorg voor TBC, door middel van een systematische review en meta-analyse. De 89 onderzoeken die in de uiteindelijke analyse zijn opgenomen, presenteren de resultaten van verschillende op Internet gebaseerde technologieën die op verschillende plaatsen in de TBC-zorg worden gebruikt. Wat de diagnose betreft, boden digitale gezondheidsinterventies toegang tot TBC-experts op gebieden waar dergelijke expertise niet beschikbaar was, en boden ze de mogelijkheid om delen van TBC-screeningprocedures te automatiseren, zoals TST of het lezen van thoraxfoto's. Wat de behandeling betreft, bood digitale gezondheidszorg kosteneffectieve alternatieven voor de DOT-strategie voor standaardzorg en voor persoonlijke consulten in situaties waarin reizen een last is voor de bevolking, zoals in omgevingen met weinig middelen, afgelegen gebieden of voor mobiele bevolkingsgroepen. Studies die in de analyse zijn opgenomen, rapporteerden ook hoge acceptatiepercentages voor hun resultaten, zowel voor patiënten als voor medische zorgverleners. De geïdentificeerde uitdagingen bij het implementeren van digitale gezondheid waren toegang tot geschikte apparatuur en de noodzaak om het gebruikersbestand adequaat te trainen. Het bewijs in de opgenomen studies was echter laag en er zijn meer robuuste studies nodig om de verschillende domeinen van TBC-zorg te onderzoeken waar digitale gezondheidszorg zou kunnen worden geïmplementeerd.

Hoofdstuk 8 onderzocht wereldwijde percepties met betrekking tot de implementatie van digitale gezondheidszorg door middel van focusgroepinterviews met medisch personeel en TBC-patiënten. De consensus onder alle deelnemers, uit alle zes betrokken landen, is dat er belangrijke communicatie- en informatielacunes zijn die kunnen worden overbrugd door een digitale gezondheidstool. De meerderheid van de deelnemers vond dat er een gebrek aan kennis over tuberculose is bij patiënten, het grote publiek en zelfs bij artsen. Wat betreft de communicatie, waren de deelnemers aan ons onderzoek van mening dat deze via een app zou kunnen worden verbeterd, door medische toegang te vergemakkelijken of door online TBC-gemeenschappen te creëren, hoewel sommige deelnemers de voorkeur zouden geven aan een hybride

systeem omdat ze persoonlijke consulten waarderen. Deelnemers identificeerden ook verschillende uitdagingen, van de noodzaak om de privacy van de patiënt te waarborgen, tot de veerkracht om te veranderen en een gebrek aan bekendheid van potentiële gebruikers met medische apps. De weg naar een algemeen aanvaarde en gebruikte digitale gezondheidsoplossing, zoals bij de gestandaardiseerde behandeling, moet zorgen voor consistentie, maar ook voor aanpassing aan de lokale realiteit en behoeften.

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Sumar

În această teză, am discutat abordări personalizate în tratamentul tuberculozei (TB), în special în contexte epidemiologice cu incidență mare de TB. Teza de doctorat este structurată urmărind cei trei piloni ai strategiei Organizației Mondiale a Sănătății (OMS) STOP TB: *îngrijire și prevenție integrate, centrate pe pacient, politici îndrăznețe și sisteme de susținere și îngrijire și inovare intensificată.*

Primul pilon, *îngrijirea și prevenirea TB integrate, centrate pe pacient*, a fost abordat în capitolele 2-4.

În capitolul 2 am evaluat pacienți care suferă de TB susceptibilă la medicamente (TB-DS) și rezistentă la medicamente (TB-DR), care au fost fie în timpul tratamentului TB, fie la maximum cinci ani după tratament, printr-o serie de măsuri raportate de pacient (PROM-uri). PROM-urile au fost utilizate anterior pentru alte patologii pentru a evalua starea fizică și psihică a pacienților, permițându-le să-și auto-evalueze starea lor actuală de sănătate și bunăstare. PROM-urile utilizate în acest studiu au inclus trei chestionare standardizate și o audiometrie de screening bazată pe o aplicație instalată pe telefonul mobil. Chestionarele au inclus evaluări ale calității vieții și ale deficiențelor la locul de muncă. Rezultatele indică faptul că toate grupurile de pacienți suferă de dizabilitate, în grade diferite, cele mai puțin favorabile rezultate fiind raportate de către pacienți care suferă de DR-TB în timpul tratamentului. Cele mai mari provocări auto-raportate de către pacienții incluși în studiu se referă la natura limitativă a bolii, fie pentru activitățile zilnice, fie pentru activitățile de muncă. În ceea ce privește acestea din urmă, 52% dintre toți pacienții erau șomeri, chiar și după ce tratamentul TB încetase. În ciuda rezultatelor mai bune raportate în grupul de participanți incluși după terminarea tratamentului TB, toate grupurile au avut scoruri mai mici în calitatea vieții decât populația generală din România. Capitolul 2 subliniază impactul negativ pe care TB îl are asupra multiplelor fațete ale bunăstării pacienților și utilizează instrumente pe care pacienții le-ar putea folosi pentru a raporta evoluția bolii. Clinicienii au fost reticenți în a implementa PROM, deoarece se temeau, printre altele, de consumul potențial de timp. Testele standardizate utilizate în acest studiu au durat 30 de minute pentru a fi finalizate și, în contextul

creșterii utilizării tehnologiei mobile, PROM-urile ar putea fi o alternativă fezabilă pentru a efectua urmărirea pacienților fără a fi nevoie ca pacienții sau clinicienii să se deplaseze în acest scop. PROM-urile ar putea fi o alternativă rentabilă și acceptabilă la standardul clinic actual, mai ales în contextele epidemiologice cu incidență mare de TB și cu resurse umane și materiale puține. În același timp, PROM-urile ar putea descrie o imagine mai cuprinzătoare a stării pacienților cu TB.

Capitolul 3 prezintă un studiu retrospectiv care a investigat rezultatele tratamentului pentru DS-TB. Acest studiu a fost realizat în trei centre de expertiză TB din România și Ucraina, două țări europene vecine cu important context epidemiologic pentru TB. Analiza logistică univariată a fost urmată de dezvoltarea unor modele multivariate pentru trei rezultate ale tratamentului pentru TB: rezultat nefavorabil al tratamentului, deces și pierderea din urmărire. Ratele de succes DS-TB în studiul nostru au fost mai bune decât mediile naționale raportate pentru România și Ucraina, iar acestea, la rândul lor, sunt mai bune decât mediile raportate în Regiunea Europeană a OMS. Cu toate acestea, aceste rate de succes au fost atinse după o medie de 50 de zile de spitalizare și opt luni de tratament DS-TB. Unul dintre obiectivele actuale pentru managementul tuberculozei este scurtarea duratei tratamentului pentru a scădea riscul de pierdere din urmărire și toxicitatea medicamentului - în studiul nostru, 85% din populație a prezentat cel puțin un efect secundar în timpul spitalizării. Contextualizarea populației de pacienți în anumite situații este una dintre recomandările OMS. Modelele dezvoltate pentru populația noastră sunt comparabile cu alte modele dezvoltate anterior, dar au mai multe diferențe, de exemplu absența HIV de la majoritatea pacienților incluși și deci din modelele dezvoltate. Studiul nostru a inclus toate variabilele colectate în mod obișnuit la pacienții cu TB din România și Ucraina, inclusiv urmărirea paraclinică efectuată după inițierea tratamentului. Testele enzimelor hepatice și ale funcției renale sunt efectuate în mod obligatoriu după două săptămâni-o lună de tratament, iar rezultatele indică faptul că dacă valorile crescute nu se îmbunătățesc, în ciuda măsurilor clinice disponibile, ar putea fi un indicator al rezultatelor mai slabe ale tratamentului tuberculozei. Din păcate, în România și Ucraina singurele măsuri disponibile includ tratamentul de susținere sau modificarea schemei de tratament prin întreruperea sau eliminarea unuia sau

mai multor medicamente antituberculoase. O tehnică de medicină personalizată, cum ar fi monitorizarea terapeutică a medicamentelor în sânge (TDM), ar putea ajuta la luarea deciziilor clinice pentru a evita toxicitatea medicamentului și la selectarea tulpinilor rezistente de *Mycobacterium tuberculosis*.

Pentru a înțelege mai bine populația care ar beneficia cel mai bine de TDM, Capitolul 4 a analizat toate cazurile de TB admise în trei centre de expertiză TB pe durata unui an calendaristic. Eligibilitatea TDM s-a bazat pe liniile directoare internaționale. 38% dintre pacienți au fost eligibili pentru TDM, criteriul cel mai utilizat pentru includerea TDM fiind răspunsul lent la tratament, urmat de administrarea de medicamente de linia a doua. Populația eligibilă pentru TDM a avut scoruri mai mari la frotiul direct din spută și la cultura sputei și a avut mai des implicare pulmonară bilaterală și boală cavitară pe radiografia toracică. Aceste rezultate ar indica faptul că utilizarea criteriilor de diagnostic, cum ar fi radiografia toracică, frotiul și rezultatele culturii ar putea fi comparabile cu criteriile de conversie a culturii, care durează cel puțin două luni pentru a se materializa. Populația eligibilă pentru TDM, în ciuda faptului că a avut rezultate comparabile ale tratamentului TB cu populația neeligibilă, a avut o durată generală mai lungă a tratamentului și efecte secundare mai frecvente (25% din TDM eligibile față de 13% din TDM neeligibile).

Capitolele încadrate în acest pilon sugerează că implicarea pacienților în propria îngrijire, abordarea particularităților medicale și socio-economice și implementarea intervențiilor medicale personalizate ar putea fi toate căi potențial rentabile și benefice de cercetare ulterioară.

Al doilea pilon, *politici îndrăznețe și sisteme de sprijin*, a stat la baza capitolelor 5-6.

Capitolul 5 a continuat investigarea oportunităților TDM prin colectarea opiniilor experților din întreaga lume despre utilizarea prezentă și viitoare a TDM. 86 de experți în TB, fie medici, farmaciști clinici, încadrați sau nu în sistemul universitar, au răspuns la un chestionar digital cu multipe întrebări referitoare la practicile curente în utilizarea TDM și beneficiile și provocările percepute pentru implementarea acestei tehnici. TDM este folosit doar de jumătate dintre respondenți. Participanții care nu au folosit TDM au fost în general entuziasmați de ideea introducerii TDM

în îngrijirea clinică a pacienților cu TB, totuși, ei au indicat că acest lucru ar implica nu numai creșterea finanțelor disponibile pentru echipamente și teste, ci mai ales instruirea personalului medical și paramedical în utilizarea acestei tehnici noi. Cercetările viitoare ar trebui să se concentreze pe oferirea unei foi de parcurs pentru implementarea TDM, în special în mediile cu resurse limitate, cu incidență ridicată a TB și punând accentul pe implicarea pacienților în procesul de luare a deciziilor privind dozarea medicamentelor, evaluarea riscurilor și alegerea terapiei.

Capitolul 6 a investigat politicile actuale la nivel european privind infecția cu TB (TBI) pentru migranții recent sosiți, abordând toți managerii naționali de programe TB sau echivalent din 32 de țări din UE/SEE + Elveția + Regatul Unit. În acest spațiu, doar jumătate dintre țări au o politică în vigoare pentru a verifica migranții recent sosiți pentru TBI. Screeningul TBI se adresează în principal solicitanților de azil și refugiaților. Politicile naționale privind acest screening sunt similare respectiv la diagnostic și tratament, dar au abordări divergente în legătură cu urmărirea pacienților. Provocările actuale în depistarea TBI identificate de managerii de program au fost lipsa de motivație a migranților, barierele lingvistice și relocarea. A existat consens în rândul tuturor participanților în studiu cu privire la mai mulți factori, inclusiv necesitatea unui ghid la nivel european pentru abordarea tuberculozei, în special pentru populațiile mobile. Europa este un spațiu activ pentru migrația forței de muncă, atât din afara Europei, cât și în limitele UE/SEE, cu toate acestea, doar jumătate dintre țările care efectuează depistarea TBI includ migranți de muncă. Capitolul 6 evidențiază o serie de abordări ale screening-ului TBI la migranți în UE/SEE și un consens cu privire la extinderea și consolidarea eforturilor de includere semnificativă a migranților în programele de screening.

Al treilea pilon, *cercetarea intensificată și inovarea*, a fost abordat în capitolele 7 și 8.

Capitolul 7 a explorat modul în care sănătatea digitală poate fi folosită în îngrijirea clinică a TB, printr-o revizuire sistematică a literaturii și o meta-analiză. Cele 89 de studii incluse în analiza finală prezintă rezultate deduse din implementarea diverselor tehnologii bazate pe Internet, utilizate în diferite momente ale îngrijirii TB. În ceea ce privește diagnosticul, intervențiile de sănătate digitală au oferit acces medicilor la

experți TB acolo unde această expertiză lipsea și au oferit posibilitatea automatizării părților procedurilor de depistare a TB, cum ar fi TST sau radiografia toracică digitală. În ceea ce privește tratamentul, sănătatea digitală a oferit alternative rentabile la strategia de observare directă a terapiei (DOT), care este momentan standardul de îngrijire medicală. Consultațiile de telemedicină sunt, de asemenea, o alternativă pentru situațiile în care călătoriile reprezentau o povară pentru populație. Studiile incluse în analiză au raportat, de asemenea, rate ridicate de acceptabilitate pentru tehnologiile testate, atât din partea pacienților, cât și din partea furnizorilor de servicii medicale. Provocările pentru implementarea sănătății digitale identificate în acest studiu au fost accesul la echipamente adecvate și nevoia de a instrui suficient baza de utilizatori. Puterea dovezilor din studiile incluse a fost, totuși, scăzută și sunt necesare studii mai solide pentru a investiga multiplele domenii ale îngrijirii TB în care ar putea fi implementată sănătatea digitală.

Capitolul 8 a investigat percepțiile la nivel mondial cu privire la implementarea sănătății digitale prin realizarea de interviuri de tip „focus-grup" cu personalul medical implicat în îngrijirea TB și pacienți suferind de TB. Consensul participanților în studiu, din toate cele șase țări implicate, este că există lacune importante de comunicare și informare care ar putea fi depășite printr-un instrument digital de sănătate. În mare parte, participanții au simțit că există o lipsă de cunoștințe despre tuberculoză în rândul pacienților, publicului larg și chiar în rândul medicilor. În ceea ce privește comunicarea, participanții la studiul nostru au considerat că aceasta ar putea fi îmbunătățită prin intermediul unei aplicații, fie prin facilitarea accesului medical, fie prin crearea de comunități online de tuberculoză, deși unii participanți ar prefera un sistem hibrid, deoarece apreciază consultațiile personale. Participanții au identificat, de asemenea, mai multe provocări, de la necesitatea de a asigura confidențialitatea pacientului, până la reziliența la schimbare și o lipsă de experiență a potențialilor utilizatori cu aplicații medicale. Drumul către o soluție de sănătate digitală larg acceptată și utilizată, așa cum a fost și cu tratamentul standardizat, trebuie să asigure consistență, dar și adaptabilitate la realitățile și nevoile locale.

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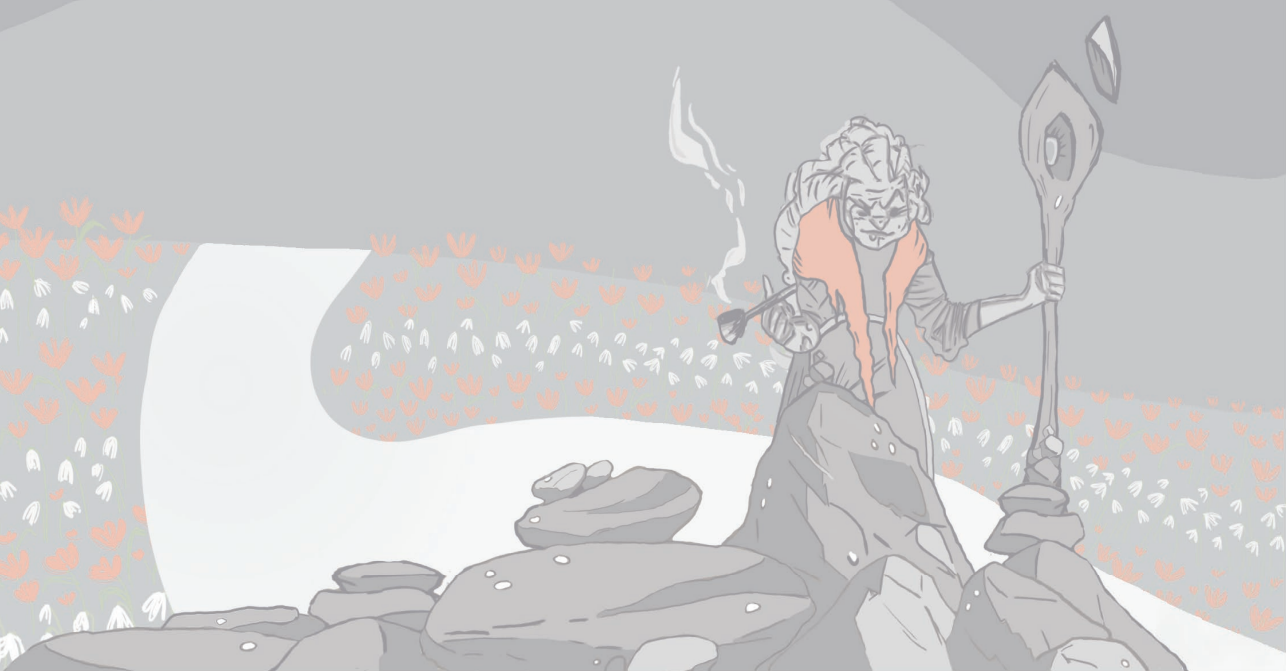
Oh, what a long, strange trip it's been
- The Grateful Dead

11

Acknowledgements & Stories



Acknowledgements

Oh, what a long, strange trip it's been is both a lyric from the Grateful Dead song *Truckin'*, but also a rather difficult achievement to obtain in *World of Warcraft*, an online game which took a rather big chunk of my time. It's difficult because it's a composite achievement requiring the player to perform many different tasks spread throughout a calendar year. I mention it not only to set the stage for myself being a giant nerd (my pun game is real), but also because it's one of the most international, varied achievements in the game. So, sit awhile and listen. Queue music.

The Goliards, Carmina Burana manuscript, O fortuna, arranged by Carl Orff, played by Therion.

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Within the whirling wheel of working on this PhD, there were three grounding pillars, **my supervisors.**

Jan-Willem is one of the few people who does not give me social anxiety when I send a text because he is so prompt in his replies. Frankly, I do not know how he does it. I have failed him many times in delivering deadlines, remembering appointments, being fully awake at our 12 AM online meetings, and he has kept his calm, collected, understanding, humorous, and hyper-efficient manner throughout. The backgrounds of our meetings were indeed, weird. Between Kasabian blaring during a rainy festival, many nights when I left my friends in one room and I rushed in another, sickness, moving houses, floods, and fires, the memories of our interaction blur into one 1 AM submission. This PhD could not have happened without the rock that is Jan-Willem and I could not have asked for a better mentor.

Ymkje arrived on a plane in Romania to visit me on the day my grandfather died. That week blurred in a whirlwind, rushing between a conference I helped organise, hospitals we did research in, and the funeral home. The memory which remains, however, is of the board games we played. The second vivid memory I have of our time together was learning over lunch that I would have the opportunity to become

project manager right before my bike got taken away by Gemeente Groningen for being "annoyingly parked". The point being that Ymkje has a very magical knack for being there at the perfect time. Even though we sometimes have different research styles, I was blessed to have a second supervisor who was passionate, funny, and who gave me more chances than maybe I deserved.

I met *Onno* in Romania, when "our" TB team met the Dutch TB team and we chuckled of how the TB world attracts "a kind of people". I felt I knew Onno even before I knew Onno. He came in as a supervisor later, and worked as a balancing board between two (sometimes) rather opposite senior researchers. Clinically, medically, I am closest to him and he understood questions and nuances that would have been missed otherwise. Within the strange research family unit we became, Onno would be something of a big brother.

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...and my work grandparents would be Traian and Tjip.

I applied for this grant after a fortuitous meeting between two very similar professors. They're both Gandalf-type nerds who use social media as a bulletin board for their infinitive wisdom and random facts. They both lived very interesting lives worth listening to over a nice glass of something. Both their pairs of eyes swivel with curiosity in their head, making them ask themselves and the world a thousand questions per minute. Even in their old(er) age, people have to keep up.

The story of *Traian* becoming my mentor is intricately linked with the universe wishing me to research TB. I met him first when I was in high-school and I worked at a conference he was presiding over. At 15 or so I had to step in and do simultaneous translation for the welcoming address, from Romanian to English, for the invited speakers. The main speech was about TB not being a sexy disease (true). Later, in medical school, he was my respiratory medicine professor, and for my exam I presented the case of a dear friend of mine who had had TB. Even later, in my first year of internship, I was looking for a PhD supervisor who actually wanted to do research (the Romanian educational system is splendid). It took me about six months

to convince him I am not a "nepo baby". We never managed to do a PhD together. Politics was against both of us. But he saw much earlier than I did that I need to get out of the country. We tried in several directions until one day he called me out of the blue, as he very often did, to invite me for a beer with a (mainly) Dutch TB team. Which is where I met...

Tjip. The world is indeed a village. You meet people and you instantly click, even beyond generations, and cultures, and opinions. I remember vividly sitting at that table, nervously enjoying a beer with this TB titan, hearing "we should do something together" with my skeptical Romanian mind going "yeah, I've heard this before". But look, we did. I can hardly believe it. Please, don't stop putting birds on facebook, the world needs more of them.

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I have always found myself working slightly between the lines and slightly outside the boxes. Of course, this liminality has been filled with other humans. So the next section comprises **my extended work family.**

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In the Netherlands my foremost department was *Clinical Pharmacy and Pharmacology*. It was the first place I listened to Dutch in a professional environment, which spurred my curiosity for the language. And, despite me being more out than in, I could not have asked for a better department to begin my journey in the Netherlands.

My other departments, Medical Microbiology, Internal Medicine, Lung Science - have all been places where I met people just as or even more passionate about the field they were in. Within these I'd like to place special thanks to *John*, Pronkjewail's spirit animal, for the humour, kindness, and interesting conversations, and to *Banhu*, for spinning beautiful tales which made me fall in love with microbiology.

Continuing with the adults in the room, *Dominik, Deliana, Shikha, Zohar, and Chris*. You cannot imagine how much it means to me that I can be myself within the context of a work relationship. Thank you, thank you, thank you. **Sally,** I have learned so much

from you working under your tutelage. **GB**, please never stop typing three worded replies, they are truly the best.

Christina, my work sister. Thank you for everything. Especially thank you for pork and mushrooms, the best working table in the world, and calling me out when I was a b*&^h. You're the first person I met when we began this journey and one of the closest work relationships I've ever had.

Marjolein, thank you for being a better student than I deserved. *Hayley, Leo, Nilima.* Hayley, you are a ray of sunshine in an iridescent bubble. Leo, I love your dry humour, talking games, complaining about things, and all the weird stuff you brought home, including but not limited to the worse rum on planet Earth, a ball, a boat. Nilima, you are a work inspiration, but, please, don't forget to have some fun too. I loved bouncing around ideas with you guys about how to approach work and the work environment, our board game nights, and learning how (and how not to) share a house in between a home and a knock knock joke. **Marina**, thank you for giving me work shelter in your home. I miss playing games with you, drinking fancy cocktails, and your mom's cooking. **Pepe**, the monitor you gave me saved my life and learning about arancini changed my life. **Nilay**, you are an oasis of calm and composure I can only aspire to. **Paola**, let's shoe shop again, it was a very fun 30 minutes. **AG**, don't stop being most likely to succeed. **Rita**, I still wonder when we'll grab that coffee. **Arezoo**, the way you follow your dreams is an inspiration. **Usma, Chris, Mafalda, Federica**, I know we've interacted less, but I have learned things from you nonetheless and I thank you for it.

Alina, Carolin, Steffie, Xuelai, Shaomin- I never thought six women could have such a productive work relationship. Our year in GOPHER was truly magical. I have learned so much about integrating different perspectives, working with different people of different cultures, and getting things done. To all the lovely people of the GSMS, **Rob, Rod, Frits, Rita, Johanna, Tiago, Matthijs, Nadka, Jeroen, Torben, Ivan, Vasilena**, and, of course, our spirit animal, **Sandra**. I hope, despite my poor humour, that I did right by you guys. I know I had a lot of fun doing stuff and growing the council with you.

Andrea, we have had similar life journeys and share common goals and ideals and I miss our lively Latin nerdy talks.

And, just when I thought my work family could not extend even more, here I am, in a new job. **Karin**, you are one of the best bosses I've ever encountered. **Johann** and **Gerd**, our meetings feel like coffee time. And to the extended work environment - I have the sense I will make weirdly enduring friendships.

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In Romania,

Adriana, my work cool great aunt. You helped make the impossible possible. You are tough, because you had to be, but somehow you never quite lost your kindness, your gentleness, your quintessential femininity. I loved our talks and you aided me through some very frustrating hurdles and for all those moments and more, I will be eternally grateful. **Lili,** we have a weird connection as you've known me literally my whole life. It was a pleasure visiting all those villages with you, even though we started very early and the roads were very bumpy. **Marcela, Maria, Violeta**, and all the other lovely ladies (and one man) of the Iasi TB Dispensary, thank you for all the hard unpaid work you did do make these studies possible. *Andrei* ("my" Onno), you're one of the guys who I can always rely on to get s*&t done. From managing to make a ruin a relatively habitable hospital, to removing the tears of frustration from my eyes, you were there to get things over the finish line. **Radu**, maybe, just maybe, might be the right person to make that hospital great again. And, even if in real life you'll always have your differences, at least in my acknowledgments, you'll be in the same paragraph as Cristian. **Cristian**, it was an absolute delight working with you. Your flavour of crazy is lovely, no matter what others might think. Don't change. **Mărioara**, you were my first attending in the lung hospital and, even now, you're one of the coolest doctors I know and one of the loveliest humans I've had the privilege of meeting. Simona, thank you for helping with some weird late night questions when I was working the hospital archive. And on that note, thank you **Rodica** and **Viorel**. Rodica, you've known me forever, and you were one of the only people who noticed how defeated I felt by the witch of Pneumo Iasi. Viorel, I had so much fun in the archive, thank you for trying to organise the unorganisable. **Bogdan** and **Cristina**. Well, there would be a lot to say but I will just say this: you are too kind for this world. **Zitta** and **Carmen**, you are one

terrible duo. I will forever miss angrily discussing autumn leaves, receiving coffee in the morning, and all the staff of the triage room. It was truly the best hospital time I ever had. **Ioana, Beatrice, Florin**, thank you for making research in Bucharest possible. I hope we can do it again soon. **Teodora, Dragos** and, later, **Raluca**. I am very lucky to have ran into you guys, willing and able to do all the fieldwork in very tricky conditions. I appreciate and I understand all the hard work and patience that went into these studies. **Marius, Beatrice, Ioana, Florin,** thank you for facilitating research in Romania, without your dedication several papers could not have been accomplished. And to all the folks who mentored me along the way, and/or from whom I drew valuable lessons, **Cristi, Ioana, Laurentiu, Ovidiu,** thanks for all the fish. **Petru**, thank you for Sound of Science, it was one of the first real outlets for my impulse to do science communication.

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And beyond,

In Ukraine, I'd like to thank **Igor** and **Liliana**, for helping do some really tricky research papers and always being available for questions, even from a bunker. I would like to thank **Maria** for doing some kick ass interviews in Venezuela and for becoming a good friend in the process. Thank you, **Morita**, for doing the same for Indonesia.

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Growing up, I never really had a large family. My little nucleus did leave me with one important lesson: **you can chose.** You can chose your family and, in doing so, ensure bonds more unbreakable than blood.

Alexandra, and Iolanda, my foremost kidney people. Alexandra, *Polanda*, you are my brain. Iolanda, you are my heart. I love you. And I really wish I could say more without crying of joy for having you in my life for so long, so far, and through so much.

Raluca, dear, adventure is calling. Thank you for Sandman and the best road trips. Let's goddamn go in another one, now I can finally drive you and take your wrong directions. PS. You can do it.

Ana **and** *Jorj.* My home away from home. Everything is a little bit more bearable when I am sitting two meters away from a glass of wine, a good conversation, and, occasionally, some trashy TV. I don't think I could have made it as well without Ana coming back home out of boredom and Jorj managing to say exactly the right thing at the right time. And to the extended pandemic home of DET. **Debu**, shot!, *Andi,* thank you for the bear hugs. *Luiza,* your smile and your steadfastness warm my heart. **Mihai** & **Laura**, you're an adorable couple of lovely humans. And also to recently added **Chester, Ovidiu, Geo, Robert, Alice, Mica, Mihai**, I am oh so very happy to have come home one day and found it filled with the laughter and (viking) love you brought into it.

FRI/WoW boyz2men, Andrei, Slopa, Tudor, 57, Hyp -and I'll add Berna in here for really good measure- you guys are ones I like to argue with the most. You've always challenged me to be better, to know more, and to critically appraise the world. *Andrei*, our relationship cannot be explained. Suffice to say I have learned more about love from you than from most other people. *Slopa*, thank you for walking me out and bringing me home. *Tudor*, we are like a Thaddius fight, one misstep and we find ourselves on the wrong polarity. Still one of my favorite bosses. 57, thank you for all the late nights, giggles, and music. *Berna*, never stop never stopping making fun of me. **Hyp**, thank you for the pictures and the random encounters. PS. **Vexor & Avq**, playing with you guys has been an honour.

Iriiiiiiiiiiiishhhh! *Cezara*, *Nicole*, *Ana*, *Kitty*, *Cristina*[Cristina], *Raluca* , *Diana, Madalina*. I have to thank Cezara for bringing me to your metaphorical bosoms. I adore how different we are. I adore how we get along effortlessly, without pressure or constraints. I love the care, the honest to god care we have for one another. All the little things you do are magic, and all our conversations, via text or live, make me feel like I am never away from you. Your presence in my life, through good and bad, and at all odd hours, enriches me.

And speaking of boys. *Patras*, you're my favorite stalker. *Emma*, you are the single lady I can only aspire to be, voices and all. *Laura,* I would have not gotten here without you. *Bogdan*, stop talking, it only gets worse. *Leo*, keep cooking and answering unrequited

questions. *Madalin,* get the music going. **Silviu**, stop choosing bad habits for fun. *Florin,* for the love of God, settle on a thing to smoke. Speaking of, **Manu, Misu, Luparu,** it's always great to see you play together. **Gabi,** go create without modesty. *Dan,* that bar you like, is truly horrible, change it. *Alex*, stop remembering things from a thousand years ago like a girl. *Mihai,* don't forget about the one our grandmas set you up to be with. I'm unbearable, I know.

Teo & Serj, maybe we will manage to play some games soon. **Teona & Adi**, I am grateful for all the episodes I had you in my life. **Teo & Cristi**, let's get together soon, when everyone is functional. *Adriana & Daniel*, you were the best roommate and guild master anyone could have ever wanted.

Roxana, Lavinia, Delia, Adi, Stefan, Zazi, Lisandra, Danut, Silvia, Olivia, Oana, Cristian, Ovidiu (x2), Nicoleta, Radu, Costin, Flori - going through med school and beyond with you guys has been truly amazing. And I'd like to especially pause and say special thanks to *Roxana* and *Lavinia,* who always taught me how to be a better human and *Ovidiu,* my work brother from another mother.

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There is some sort of magic in Groningen. The magic of finding people. These are them, the ones I found here.

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Lengthy-board-games-that-take-an-inordinate-amount-of-time-but-bring-us-together-group. *Laurent*, my brother from another mother. If I'd start listing the things I am thankful for in you, it would be like listing the things I like about myself (and none of the bad). But, most of all, I am thankful for something I will never achieve, your emotional stability. *Renate*, my friend with the giant brain and even bigger heart, thank you for the privilege of allowing me to walk through your doors and unlock all these secret levels you have. *Nick*, you are an excellent trip buddy and I love having your steadfast presence in my life. *Alex,* love of my life, my moon and stars. Thank you for a lot but mostly thank you for the laughter. *Mike & Alba*, I am truly, truly, happy to

have welcomed you in our little family.

Astro (-adjacent) peoples. *Alka*, we are working now together so thank you for the cover. You are one of the people I clicked instantly and I will forever be attracted by your inner glow, warm and strong. You can do anything you damn well please. And speaking of really getting to know people through blood, sweat, but mostly tears, *Fernanda,* you're one of the people who will always understand me a bit better than I do myself. And *Bogdan,* it will be ok. You're awesome. Never forget that. *Alle,* you will eternally and in perpetuity, lose. *Vagelis,* your kindness is a beacon and a benchmark we should all follow. *Marina*, yet another fun Greek I adore for your wits, grace, and debates. *Andrea,* you have one of the best smiles I have ever seen on a boy. *Pranav*, you're one of the coolest basic b. nerds I know. *Katya & Enrico,* I love the fact that you are able to not only have opinions, but, more importantly, to change them. *Olmo*, I will forever appreciate your bravery and sense of play. *Willie,* don't stop putting all our cooking skills to shame. *Dani*, don't stop fighting the good fight. The *Saturday Coffee Group*, **Jonas, Julia, Maxime, Hyoyin, Anne,** you have made the pandemic that much more bearable. **Yasmina & Emiel**, you're too cute for words. **Nika, Simon, Teymoor, Lorraine, Dani, Eduardo, Bram,** and all the rest I have forgotten because I am a horrible human being, you have all brought food for thought with every interaction we had.

The tribe of Liminoid (-adjacent). *Alle & Adri,* I met you together and I am very happy you are finally so. *Hannes*, one of these days the seesaw will find its center, I know it. *Olga & JuanPe* you are the embodiment of #couplegoals, brilliant as individuals, water together. *Kasper & Sylvia*, I always find an oasis of calm and having things together when I meet you. *Luca,* thank you for all the (meta)physical food. *Leo & Inez*, I feel enriched by every (new) interaction we have. You good people. *Can*, I feel we will always find ourselves wherever help is needed, sharing meaningful glances. *Olivia, Annemiek, Danielle, Serena*, you are such fun, complex humans, spending time with you never ceases to entertain & warm the cockles of my heart. *Juan, Daniel, Saber, George*, you make me feel safe and cared for. And to S**imone, Jasha, Cyrus, Sander, Trekken, Leoni, Lars, Chris, Stefania, Igor, Sari, Dikkie, Dennis, Agatha, Philippe, Angelo, Serena, Andrei** and all the others who have enjoyed a late night early morning

together - it's always an absolute pleasure.

To **Jean Maxim**, thank you for allowing me to preach in (sometimes) comedic ways on the grand stage of Groningen. And to all the new found friends - Alin, Michiel, Eric, Valerio, Annelies, Michael et.al. - I stand up with and to, thank you, thank you, thank you, for being my kind of people.

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Boris. I have grown so much. It has been a strange, strange year, where I wrote to you more words than any of us can count. You can doubt many things, but never doubt the love I have for you.

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To the fencing peoples. *Martijn & Alexa*, you are wonderful and it's been lovely to see you grow. Thank you for saving me from a storm. My board, *Meine, Jeffrey, Charlotte,* it was an absolute delight. *Gijs* (and Martijn) thank you for the best ethically wrong debates. *Jesse, Alexa, Bram, Meine*, thank you for sharing my love of sabre. And to our trainers, *JJ and Rink*, you're the best we could have hoped for and more. And to the rest of the guys, including but not limited to Michiel, Sophia, Jorn, Stefano, sharing a hall with you from time to time has brought great joy and some pains in my life.

∞

To all the ones I have lost. Ozzy, you were an amazing cat/dog and you are still dearly missed. Father, I understand and thus, forgive you. Ligia, wherever you are, I know you're looking down with care. Tudor, the quintessential one who got away, I will never forget high tea, low pizza, and dramedies. Irina, ah the things we do for love.

Grandma, the best moments of my life, when I am happiest, I remember being flown around the home, you dragging me on a carpet, like I saw in Aladdin. You brought the best stories in my life, 1001 Arabian Nights, folk Romanian stories, Mulan, and an understanding of chemistry, which still define me to this day.

Nena, I miss you most days. I want to call you every time I am in pain and every time

I am healed, every time something happens to me, so basically ten times a day on a daily basis. I remember you every time I dance and every time I am funny and every time I make an unlikely friend. Every fibre of my being is made of you and the lessons you've taught me.

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To the ones I have forgotten, I am sure you'll make me sorry.

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To **F.C.D. Aria** & **C.L.F. Nix** who one day maybe will learn to read.

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Mother. I trust no one in this world completely, not even myself. Humans dissapoint. You are not human. You are the only being I truly trust. Te iubesc.

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The Story of Baba Dochia

There are many variations on several legends surrounding Baba Dochia. This is mine.

Once upon a time, there was a Roman emperor, Traian, who fell in love with a Dacian princess, Dochia. See, the Dacians were the ancient peoples inhabiting the land which would become Romania - after being conquered by the Romans. So, of course Dochia did not welcome the romantic advances of her soon to be subduer. But he persisted and persisted and, in desperation, Dochia asked for the help of their god, Zalmoxes. So Zalmoxes told her she can find refuge on a sacred mountain. In some stories, she turns to stone so she can be impenetrable to any unwanted attention. In other, she eventually thaws enough to the advancements of one person to have a son (or maybe it's a virgin birth, who knows). She raises alone her son, who becomes the Romanian god of love, *Dragobete*. His name probably comes from the old Slavic root *drag(u)*, which also gives us the word for love, *dragoste*. The day of Dragobete, the equivalent of Valentine's day but with less social pressure and much more ritual, is celebrated on February 24th.

So Dragobete, the son of Dochia, who by now was old enough to receive the adage *Baba*, "meaning old lady", "grandmother", or even "hag", falls in love with a girl. And Baba Dochia hates this girl. She thinks she's not good enough, she despises the fact that she'll lose her only son - so, to "test" her, she sends her to wash a dirty, sooty, black skein of fleece. And no matter how much she tries, this girl cannot make the fleece clean again. So, in her desperation, she asks the help of the god of spring, or little March, *Mărțișor*. The place we get the name for March and the planet Mars, is the Roman god *Marte*. Unlike his Greek counterpart, Marte was revered in very war like Roman culture, especially as a bringer of peace through war and a bringer of the new year and agrarian prosperity through sacrifice and the shedding of blood. So *Mărțișor* gives some of his blood to this girl, which turns the skein of fleece white. This is why on the first of March in Romania we give each other ribbons of red and white - to symbolise the beginning of a new year and the fact that most things in life - love, friendship, happiness - come with sacrifice.

Coming back to our story, when Baba Dochia sees the white fleece, she goes into a murderous rage and, for the first time in many, many, many years, she decides to descend the mountain to face this girl.

As she descends from the cold, cold mountain, she gets warmer and warmer and starts shedding her coats. Step after step, coat after coat, she thaws with the spring that welcomes her. But spring in Romania is tricky, and there is always one. last. frost. When that last bout of frozen air hits her, she freezes, and turns to stone. Between the first and eights of March Romanians chose a day and if the weather is good, their whole year will be good and if not, not.

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I like this story for many reasons. Baba Dochia's many coats are like the many layers of *Mycobacterium tuberculosis* cell wall. What we do with so many drugs is strip away the layers in order to kill the bacteria. If the drugs are not in the right combination, and not in the right dosage, and not the correct length of time, we won't manage to kill it and, just like young Baba Dochia, the bacterium will find refuge in some remote corner of our body, and lay there, dormant and threatening.

Tuberculosis is, also like this story, very old. And, also like this story, and good stories in general, it transcends borders and creeds - you see, the microbiological world has no boundaries and no biases when it comes to communicating and this is how we get resistant bacteria. This story's core remained the same - a steady companion of the history of my country, much like tuberculosis itself as a steady companion of humanity, but it has elements from peoples communicating with each other, just as the bacteria do as well, just much more efficiently than humans do.

The story also has a lot of mythological tropes surrounding feminism. Women have often fallen into monstrosity for daring to say no to a man (Lilith), betraying each other (Medusa, Circe) or exuding strong feelings (Durga's anger giving birth to Kali the destroyer). Why these tropes are relevant to my PhD is twofold. For once, the glass ceiling is a very real thing to which academia is, unfortunately, not immune. And whilst it would be easy to say it's made entirely by patriarchal men, I have learned the

hard way that sometimes the biggest obstacles in the way of women succeeding are other women. Moving forward, it might be wise to listen to some of these cautionary tales - lest we, and, by extension, progress, turn to stone.

The story also has several elements of wit, perseverance, and aid found throughout Romanian folklore. Knowing who to ask for help, finding a friend (or a god) willing to sacrifice for you without asking anything in exchange, being willing to go the extra mile for the greater good, and getting creative with solutions, are all elements I hope I hint throughout my research that I believe are essential to curing this time-old disease.

I realised partway through the cover creative process that a *Sin City* vibe might be appropriate for the cover. Tuberculosis has tended to be more romanticised than other diseases, but it still a bloody, disabling, brutal disease so a marriage between a storybook style and the (neo) noir style of Frank Miller seemed very appropriate.

But, there is hope. The road might be long and winding, but there is spring at the end of it. Blood will turn to flowers. The monster will turn to stone. If we don't give up, we might just have less people suffering less from tuberculosis.

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(non)Fictional Character Bio

Ioana was born in Iași, Romania, on a day her mother could remember, the 5th of May 1988. Ioana comes from a long line of humans who had an unfortunate combination of characteristics: curiosity, common sense, and critical thinking.

Growing up, in Ioana's case, this combination was mostly unfortunate for her teachers and class mates. Ioana loved to learn, anything and everything, and hated uninspiring teachers and bullies.

At age 11 she was enticed into child labour by her mother, who had just started a company organising medical events. There, Ioana learned how to wear a skirt, solve very varied problems, and the fact that physicians are not beyond petty theft.

At age 14 Ioana was dissecting her first onion when she had the realisation she wishes to do something in life sciences. Her mentor was a 1.5 m redhead with a penchant for Marlyn Manson. "I don't like the drugs" was playing in the background. At age 16-17 Ioana translated live a speech about tuberculosis. The universe was talking to her without her knowledge.

Ioana decided on medical school in her hometown with the initial intent of becoming either a forensic doctor or a pediatrician. The first option fell because she realised she might not want the local mafia to threaten her family and the second option fell because she realised she could not handle (other) children's families. In the end, a combination of good mentors and a curiosity for everything led Ioana to train in internal medicine. She eventually found her second home in the Lung Hospital and, within it, an affinity for tuberculosis. There was something about a disease directly and indirectly bullying the people it affects which spoke to Ioana's lifelong ethos.

Ioana has always been lucky with mentors -and in general with attracting interesting, kind, lovely people- and with fortunate events. So when her most important mentor met his brother from another mother, it created the perfect circumstance for Ioana to leave her home country and do research in the Netherlands.

Ioana's curiosity has led her to do many different things - to the point where it is now increasingly difficult to describe the full range of skills and abilities on a CV.

Philosophically speaking, Ioana is very good at organising people and things. She likes finding ways that different people with different personalities, backgrounds, and skill sets can work together, make each other shine, and improve an existing status quo. She has also at least dabbled in so many things that she can have a good overview of a situation and her mind automatically goes to imagining ways processes can be improved upon. Ioana has always held the belief that if people understood "more things better" they would end up making kinder choices so she also loves being a part of knowledge transfer.

Practically speaking, Ioana has done graphics design, photography, web design, SEO, copywriting, translating, writing, and editing in English and Romanian, event organising, been part of several boards of her peers, designed pub quizzes, treasure hunts, (co) owned an escape room and team building small company, performed all manner of research activities, presented at various conferences, taught various things from physiology to public speaking, became project manager and now is employed in a graduate school, and, somewhere along the way, became a board certified internal medicine physician. In her spare time, she plays video games and board games, travels, plays various sports, does stand up comedy, and consumes culture, from music to books to museums and art installations with a firm tendency towards fantastical storytelling.

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Patient reported outcomes of drug susceptible and drug resistant tuberculosis patients in Romania

Margineanu I, Butnaru T, Lam M, Baiceanu D, Dragomir R, Mihaltan F, Sorete Arbore A, Munteanu I, Mahler B, Alffenaar JW, Akkerman O, Stienstra Y

Submitted

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Margineanu I, Gafar F, Butnaru T, Baiceanu D, Dragomir R, Semianiv I, Mihaltan F, Munteanu I, Mahler B, Todoriko L, Margineanu S, Stienstra Y, Alffenaar JC, Akkerman O

The International Journal of Tuberculosis and Lung Disease

Submitted

Therapeutic drug monitoring in tuberculosis - analysis of opportunities in Romania and Ukraine

Margineanu I, Gafar F, Butnaru T, Baiceanu D, Dragomir R, Semianiv I, Mihaltan F Munteanu I, Mahler B, Todoriko L, Margineanu S, Akkerman O, Stienstra Y, Alffenaar JC

The International Journal of Tuberculosis and Lung Disease

Accepted

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