Improving Tuberculosis Case Finding in Indonesia

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CHAPTER 1

General Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. The most frequent clinical manifestation of the disease is pulmonary TB, but it can affect any part of the body (extra-pulmonary TB), including the skin, lymph nodes, spine, joints, genitourinary tract, nervous system, and gastrointestinal tract.[1]

TB is an old disease. It existed in ancient Egypt; historical records show that pathological signs of TB were present in a mummy dating back to 2400 BC.[2] An effective treatment for TB only became available in the 1940s, when the first anti-TB drug streptomycin was discovered.[3]

The use of anti-TB drugs, together with improved socio-economic conditions and systematic control of TB in many Western countries, led to a firm belief in the 1980s that TB had been conquered and that priority status was no longer justified for the disease.[4,5] However, the emerging HIV epidemic in Africa in the latter half of the 1980s caused a second wave TB epidemic that increased at an alarming speed due to TB-HIV co-infection. Multi-drug resistant TB (MDR-TB) concurrently emerged in several countries due to poorly organized TB services.[3] As a result, the World Health Organization (WHO) declared TB a global emergency in 1993,[6,7] which boosted international efforts to curb the TB epidemic. WHO and the International Union against Tuberculosis and Lung Diseases (IUATLD) introduced the direct observed treatment short course therapy (DOTS) strategy.[8] The Stop TB Partnership was established in 2000 as a global movement to accelerate social and political action aimed at stopping TB.[9] Reduction of the TB burden has also been part of the Millennium Development Goals (MDGs) that aim to halt and reverse the incidence of TB by 2015. A substantial amount of international funding has been secured and channeled through the Global Fund initiative since 2002. However, despite all of these efforts, TB remains a major global health threat and a leading cause of death from curable infectious disease worldwide, especially in Africa and Asia.[9] As the country with the fifth highest TB burden, Indonesia had an estimated 430,000 new cases in 2009, with an estimated mortality of 62,000.[10] TB was the second leading cause of death in Indonesia in 2009.[11]

1.1 | TB EPIDEMIOLOGY

M. tuberculosis was first described as the causative agent of TB by Robert Koch in 1882. It is a bacillus with an acid/alcohol fast staining property and a unique cell wall structure that provides a lipid barrier responsible for the bacteria's virulence, growth rate, development of resistance to antibiotics, and host defense mechanisms. The bacilli have a slow growing rate, are capable of intracellular multiplication, and are resistant to harsh physio-chemical environments, in which they can remain dormant as a latent infection.[12]

A person with pulmonary TB can transmit TB bacilli through small airborne droplets, called droplet nuclei, when the person sneezes, coughs, sings, or talks. The infectious droplet nuclei can remain airborne for hours after expectoration.[13] After being inhaled by a non-infected person, the infectious droplets have to overcome the physical defense of the respiratory tract. When the bacilli pass this defense system and reach the alveoli in the lungs, they are taken up by macrophages, initiating a chain reaction of cell-mediated immune response.[8,12] In a person with a good immune response, the bacilli can be contained in necrotic lesions, which undergo fibrosis and calcification, resulting in latent infection.[12] In a less immune competent person, the infection can progress to active TB, in which a lung cavity is formed, breaking into the bronchi as the necrosis reaction expands. When this reaction occurs, the host becomes an infectious individual with smear-positive sputum upon microscopic examination. Approximately 50-80% of all smear-positive TB patients will die in the absence of treatment.[14]

An estimated 5-10% of infected persons develop active TB during their lifetime.[12] The risk of active TB increases to 15% annually among TB-infected HIV-positive patients in the absence of anti-retroviral treatment.[15] The risk also increases under conditions that compromise the host immune system, e.g., malnutrition, extensive corticosteroid therapy, diabetes mellitus, or cancer chemotherapy.[8] The risk of extra-pulmonary TB is approximately 20% in immune-competent individuals, but the risk is higher among HIV-positive TB patients.[8,9] The more common forms of extra-pulmonary TB include pleural effusion, lymphadenopathy, pericarditis, and involvement of the spine, bones and joints, central nervous system (meningitis or cerebral tuberculoma), or gastrointestinal system.[8] Another fatal form of extra-pulmonary TB is disseminated or miliary TB. The bacilli spread throughout the body via the blood, leading to multi-organ involvement.[12] The clinical manifestation of pulmonary involvement is a miliary, rather than infiltrate, pattern. Mortality is high despite chemotherapy and may be related to delays in diagnosis and underlying medical conditions.[8]

In countries in which the TB transmission rate is high or stable for many years, the incident cases are highest among young adults due to recent infection or re-infection. As the rate of transmission falls, new TB cases shift to older age groups and are mostly due to re-activation of a latent infection.[16] TB occurs more frequently among males in many countries, possibly due

to the fact that females have less access to health facilities, but it may also reflect the underlying epidemiological differences between males and females with regard to infection exposure and susceptibility to disease.[17]

The WHO estimates that one-third of the world population has been infected with *M. tuberculosis*. Globally, 14 million TB cases were reported in 2009, approximately 9.4 million of which were new TB cases. Among HIV-negative individuals, 1.3 million deaths were caused by TB.[10] More TB cases exist today than at any other time in history,[5] and the absolute number of cases continues to increase slightly from year to year. Most cases occur in Asia and Africa (55% and 30%, respectively). Approximately 50% of the new cases were in the five highest burden countries: India, China, Nigeria, South Africa, and Indonesia.[10] The case detection rate (CDR), defined as all cases detected out of the estimated incident cases, was 63% in 2009 and is equivalent to 5.8 million notified TB cases.[10]

In 2009, an estimated 12% (1.1 million) of TB patients globally were co-infected with HIV. Countries in sub-Saharan Africa have the highest co-infection rate at approximately 37% of TB cases. Approximately 80% of TB-HIV co-infections were in the African region. The number of TB deaths among new TB patients with an HIV-positive status was estimated to be 0.4 million in 2009.[10]

The number of MDR-TB, which is defined as TB cases with resistance to two anti-TB drugs (isoniazid and rifampicin),[18,19] was estimated at 440,000 cases in 2008. Currently, 27 countries (including 15 countries in Eastern Europe) are considered as having a high MDR-TB burden.[10] The more advanced form of anti-TB drug resistance is referred to as extensive drug-resistant TB (XDR-TB), defined as resistance to isoniazid, rifampicin, and fluoroquinolone, a second line injectable anti-TB drug. This condition is virtually untreatable with currently available anti-TB drugs. A study in South Africa found that 70% of XDR cases die within 30 days of sputum collection for culture examination, and the death rate increases to 98% in 7 months.[20] By July 2010, 58 countries and territories had reported at least one case of XDR-TB.[10] The true scale of the MDR/XDR TB problem, however, remains uncertain. A lack of laboratory capacity to identify drug-resistant TB hinders many countries from reporting such cases.[10]

1.2 | TB CONTROL

The framework for TB control is based on the epidemiological model of the natural history of the disease (Figure 1.1).[22] Case management has always been the focus of TB control because it reduces the risk of death, restores health, and prevents further transmission.[21,22] Most intervention technologies used in TB control today are based on technologies used in the 19th

and 20th centuries, such as sputum smear microscopy examination, the tuberculin skin test (TST), BCG vaccine, and most TB drugs.

TB diagnostics

In many high burden countries, microscopic examination of sputum, a technique that was used by Robert Koch when he discovered *M. tuberculosis*, is the only available TB diagnostic test. The method is cheap, fast, and highly specific, but sensitivity is low, especially among HIV-positive individuals.[23,24] Culture of TB bacilli in Löwenstein-Jensen (LJ) media is currently the gold standard for TB diagnosis, but it takes 6-8 weeks, which limits the usefulness of culture as a first line diagnostic test.[21] To diagnose TB infection, Koch introduced a technique to inoculate antigens produced from killed tubercle bacilli, called the tuberculin skin test (TST).[13] The test is performed by intradermally injecting purified protein derivative (PPD) containing five tuberculin units; a positive result is demonstrated by induration at the site of injection after 48 to 72 hours.[12] The test is essential for understanding the dynamics of tuberculosis epidemics in the community, but the sensitivity and specificity are influenced by cross-reaction with environmental mycobacteria and previous BCG vaccination.[12,13]

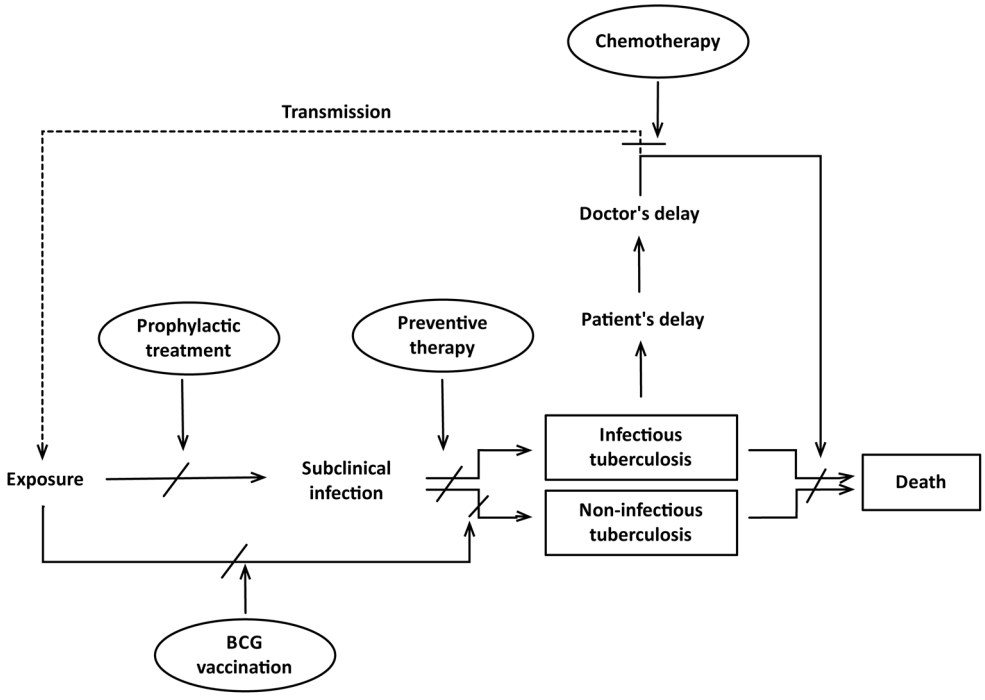

Figure 1.1 | The framework of TB control based on the epidemiological model of the natural history of TB.[22]

Through the Foundation for Innovative New Diagnostics (FIND), the WHO supports the development of new TB diagnostic tests using modern technologies. Sputum processing, fluorescence microscopy, and a light emitting diode (LED) lighting source are improvements to existing microscopic examination.[23,25,26] A liquid culture system that detects the CO_2 production or O_2 consumption of the bacilli has been developed to reduce the time needed in conventional culture methods.[23,27] A new nucleic acid amplification test (NAAT) based TB diagnostic termed MTB/RIF was recently endorsed by the WHO.[28] The NAAT test provides sensitivity comparable to culture but leads to results in less than 2 hours. The test can also be used to detect multi-drug resistance.[29] Furthermore, the test performs better than other conventional tests in terms of safety, contamination, and ease of use.[28] Interferon gamma release assays (IGRAs) are an attractive alternative to TST as a diagnostic test for latent infection; it has higher specificity than TST and is not affected by BCG vaccination.[30] Despite the progress in diagnostic technology, researchers are still challenged to explore specific biomarkers to develop a simple, inexpensive point of care test for TB.[31] A point of care test, which is defined as a simple and rapid test that can be applied easily in a primary health care setting without extensive technical support, would markedly reduce diagnostic delay and improve disease outcomes.

TB drugs

The WHO currently endorses a 6 to 8-month short course regimen with a fixed dose combination (FDC). Treatment is divided into two phases: an initial phase for 2 months followed by a continuation phase of 4 months. Only a limited number of anti-TB drugs are available today. WHO lists five essential drugs as first line anti-TB drugs against *M. tuberculosis*: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S)). The preferred regimen is isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) three times a week during the initial phase, followed by isoniazid and rifampicin (HR) daily or three times a week during the continuation phase.[32,33] The alternative regimen is isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) daily during the initial phase, followed by isoniazid and ethambutol (HE) daily for 6 months. The current WHO policy is to phase out this alternative regimen due to a lack of evidence regarding a difference in the failure or relapse rate between daily and three times weekly regimens.[32,33] Isoniazid is the drug of choice for prophylactic or preventive therapy. Evidence suggests that isoniazid preventive therapy (IPT) combined with highly active anti-retroviral (HAART) treatment provides a 76% to 89% reduction in TB risk among HIV-infected individuals in countries with a high TB burden.[34,35] The effect of isoniazid as a prophylactic or preventive therapy on tuberculosis incidence may be due to the treatment of early, subclinical *M. tuberculosis* infection. Isoniazid has been reported to improve the host immune response, which may provide long-term protection.[36]

TB vaccines

No effective vaccine yet exists to prevent adult pulmonary TB. Bacille Calmette-Guerin (BCG) vaccine, which was introduced in 1921, is the only available TB vaccine. The vaccine provides good protection against miliary and meningeal TB early in life, but it does not offer protection against adult pulmonary TB. New TB vaccines are on the horizon, with approximately 10 vaccine candidates currently in the clinical trial stage. These vaccine candidates aim at replacing BCG or enhancing BCG-induced immunity.[37]

TB global strategy

The MDGs for TB control are to halt and begin to reverse the incidence of TB by 2015.[38] The Stop TB Partnership has set two additional targets: to halve TB prevalence and death rates by 2015 compared to the levels in 1990, and elimination of TB by 2050.[9,38] To achieve these goals, the WHO has endorsed the DOTS strategy, which was launched in 1994 following the announcement of TB as a global emergency. DOTS has also become a brand name for a policy package with five pillars[3,38]:

1. Political commitment,
2. Quality-assured sputum microscopy,
3. Uninterrupted supply of anti-TB drugs,
4. Standardized short-course chemotherapy for all TB cases under directly observed treatment (DOT),
5. Recording and reporting system.

The DOTS strategy was well accepted internationally. The World Bank considered this strategy the most cost-effective intervention in health. As a result, international organizations, countries, and donors support this strategy. The TB control program has gained global momentum, and 119 countries had adopted the DOTS strategy in their national TB control programs by 1998. To achieve the MDG target in 2015, the WHO, in the Global Plan to Stop TB 2001-2005, called for program expansion to meet the immediate target of 70% CDR among the estimated infectious cases, and successfully treat 85% of the detected cases. The CDR increased markedly from 35% in 1995 to 57% in 2005. The rate stabilized at around 60% in 2008, but still has not met the target of 70% CDR.[10,39] With the increase in TB-HIV co-infection and MDR-TB, and to accelerate the case detection rate, the Global Plan to Stop TB 2006-2015 addresses the challenge of TB-HIV co-infection and MDR-TB activities. Case detection was also intensified through the involvement of all health care providers using a public-private mix approach, and by integrating TB case detection into a broader respiratory case management strategy, the 'Practical Approach to Lung Health' (PAL) approach (WHO 2006). The Global Plan also addressed the need for strengthening the health system. Evidence indicates that a strong health system is a prerequisite for reaching

the MDGs [40-42], and there is a growing consensus that the health system in many developing countries is too fragile and fragmented to deliver the volume and quality of services needed.[41]

1.3 | CARE-SEEKING BEHAVIOR

The care-seeking behavior of patients with disease is crucial for many control programs. The fact that people do not engage in an expected health behavior has been discussed and documented frequently.[43] Several concepts and theories exist about such behavior in psychology (e.g., theory of planned behavior, reasoned action, and health belief model),[43,44,45] sociology (sick role and illness behavior), and anthropology (temporal model of stages in medical care).[46] One thing is certain, care-seeking behavior involves complex inter-relating factors, which differ from one context to another.

Care-seeking behavior also plays a critical role in TB control program and is considered one priority area in the operational research of TB programs,[47] particularly because TB control program use passive case detection. Styblo, who developed the foundation for the DOTS strategy, argued that a patient with TB symptoms is usually ill enough to seek treatment.[48] Furthermore, active case detection is not considered cost effective.[49] However, various studies have shown that a high proportion of TB patients go to private health providers.[50-52] Private health providers correlate with several unsuccessful consultations involving several providers, increasing the risk of longer diagnostic delay.[52-57] A longer diagnostic delay is associated with increased disease severity, increased risk of further transmission, and poor prognosis of disease outcome.[58-60]

Diagnostic delay is defined as the duration between the reported onset of TB symptoms and the time of TB diagnosis. It consists of two components: patient delay and health system delay. Patient delay is usually defined as the duration between the reported onset of TB symptoms and first contact with health care providers, particularly medical health providers. Health system delay is usually defined as the delay from the first contact with medical health providers to diagnosis or initiation of anti-TB treatment. Some consider health system delay as provider or doctor delay or health services delay and use the terms interchangeably.[3,61]

1.4 | TB CONTROL IN INDONESIA

Historically, TB control in Indonesia can be traced back to the pre-independence era, before 1945. The first national TB control program was initiated in 1969.[62] From 1972 to 1995 the TB control program was implemented at the primary health care level on an ambulatory basis.

After a successful implementation of the pilot DOTS strategy in three provinces, the Indonesia Ministry of Health adopted and started to scale up the DOTS strategy nationally in 1995. From 1995 to 2000, national guidelines for TB control applying the DOTS strategy were implemented in health centers. Starting in 2000, the TB program in Indonesia accelerated DOTS implementation nationwide and started to involve public and private hospitals as a part of a public-private mix (PPM) policy. Since 2003, the PPM strategy was scaled up nationwide. During seven years of implementation, 563 of 1478 hospitals were involved in the TB control program, with an average of 80 hospitals per year.[63]

As a result of this systematic effort, TB prevalence reduced three-fold over a period of 25 years (from 317/100,000 to 104/100,000 in 2004).[64] The 70% CDR target was met nationally in 2006. Treatment successes above 85% were maintained from 2000 onwards.[65] However, much effort is still needed. Indonesia has different epidemiological settings and health system performance varies across the country. In 2004, a national TB prevalence survey showed marked geographical differences in prevalence between Java/Bali and the eastern part of Indonesia (59/100,000 versus 189/100,000, respectively).[64] Clustered TB cases, which may indicate barriers to health care access, were also found in eastern Indonesia.

Though Indonesia was initially considered as a country with a low prevalence of HIV with a concentrated epidemic, the prevalence of HIV has increased at an alarming speed over the past few years. The estimated HIV prevalence was 0.1% in 2001 and doubled to 0.2% in 2007.[66] The estimated number of people living with HIV increased dramatically from 93,000 in 2001 to 270,000 in 2007.[66] The prevalence among risk groups is highest among injecting drug users (IDUs), prisoners, transvestites, partners of IDUs, and sex workers, with a prevalence of 26.8%, 12.0%, 11.8%, 8.9%, and 3.6%, respectively.[67] The number of AIDS cases has increased 15-times in 10 years.[68] TB was reported as the leading opportunistic infection among hospitalized AIDS patients.[69] Thus, there is growing concern for the threat of a dual epidemic in Indonesia.

Nationally, the TB control program is managed by the Directorate General (DG) of Disease Control and Environmental Health. However, the program also involves the DG of Medical Care, which is responsible for medical services in hospitals and clinics, and the DG of Community Health, which is responsible for services in primary health centers. Operationally, TB services are managed at the district level. Each district health office appoints a district TB manager, who is responsible for the treatment register, regular reports, coordination between various facilities, and TB drug supply. TB services are mainly provided in primary health centers. In districts that have implemented PPM, some hospitals and/or private practitioners provide DOTS services. At the provincial level, DOTS teams have been established that provides technical support to district TB control programs in addition to monitoring.

1.5 | INDONESIA'S HEALTH SYSTEM MODEL

A health system is defined as all organizations, people, and actions whose primary intent is to promote, restore, or maintain health. This includes efforts to influence determinants of health as well as more direct health improving activities. Thus, a health system is more than the pyramid of publicly owned facilities that deliver personal health services.[70]

In Indonesia, the public health system is organized as a tiered system. Referral hospitals are available at district, provincial, and central levels. Primary medical services and many public health interventions (including TB control) are provided through community/primary health centers. At least one health center is located in every subdistrict, with two to three sub health centers depending on the size of the coverage area and/or population. At the village level there are village midwife clinics and integrated health posts.[71]

Parallel with the public health system is the rapidly growing, but not systematically regulated, group of private health providers. The private providers consist of private practitioners (e.g., physicians, midwives, nurses), private clinics, and private hospitals. Approximately 75% of public health workers are also part-time private practitioners, and 51% of hospitals in Indonesia are private hospitals.[72] Roughly 60% of the population seeks medical care in the private sector.[73] Furthermore, alternative health providers are available, such as providers of traditional and alternative medicine, which are predominantly not registered at the health offices and, therefore, unregulated.

To identify determinants of the performance of the TB control program, we utilized a health system model developed by Erasmus MC and the WHO as a theoretical framework for our studies. The model is a compartmental model that describes pulmonary TB patients' care-seeking behavior and the steps in the health system until detection and treatment (Figure 1.2). The model starts with all symptomatic TB cases in the population (i.e. all smear-positive patients), and a subpopulation of smear-negative patients with symptoms serious enough to potentially prompt them to seek health care. Some of the patients will never seek care, but most of them will seek care and eventually be diagnosed either in DOTS or (private) non-DOTS services. The model was adjusted to the Indonesian context and is presented in detail in Chapter 2 of this thesis.

1.6 | OBJECTIVES AND RESEARCH QUESTIONS

The overall objective of this thesis is to identify ways to improve TB case detection in Indonesia, focusing on two major issues in the TB control program: 1) the interaction of TB patients or individuals suspected to have TB with the health system providing TB services, and 2) new challenges in the Indonesia TB control program, particularly the emerging HIV epidemic.

The specific research questions of the thesis are as follows:

1. What are the patterns of care-seeking behavior among TB suspects in Indonesia?
2. How effective is the performance of the health system providing DOTS services?
3. Which improvement would benefit the performance of TB program the most?
4. How will the HIV epidemic impact the TB program in Indonesia?

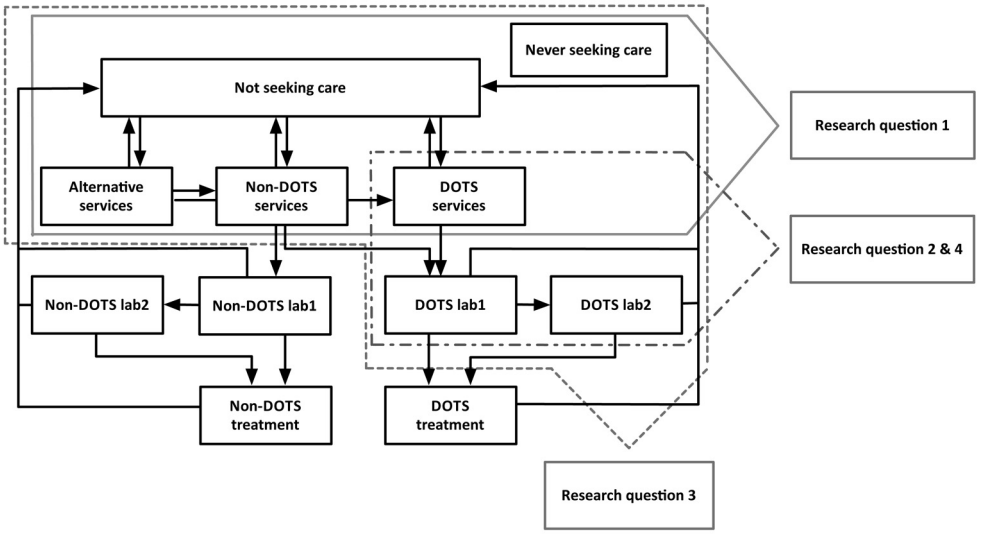

Figure 1.2 | Health system model for TB control in Indonesia and the associated research questions in the thesis.

1.7 | STUDY SETTING: JOGJAKARTA PROVINCE

Jogjakarta province is located in the central part of Java Island, Indonesia. Indonesia is the largest archipelago in the world. The country has a total population of 237 million and is the fourth most populous country in the world. Over half of the total population lives on Java Island, with a population density of more than 1,300 per km^2 in some areas.

Jogjakarta province consists of one urban, one suburban, and three rural districts, has 3.5 million inhabitants, and covers an area of 3,185 km^2. The average population density is 1,099 per km^2. The province has a relatively well-functioning health system, with primary care consisting of approximately 2000 private practitioners and 117 public community health centers staffed with doctors, midwives, and nurses. This first-level network is backed up by nine public and 24 private hospitals.

The province has a relatively well-established TB control program with the lowest estimated incidence rate of smear-positive TB in Indonesia, at 63/100,000 population in 2004. The 117 public health centers are the backbone of the national tuberculosis control program's DOTS services in Jogjakarta. Since 2000, hospitals have been involved in the TB program as part of the PPM policy in Indonesia through the Hospital DOTS Linkage (HDL) project initiative.[74] The initiative was a pilot project to develop a model for hospital involvement in the TB program in Indonesia. Five lung clinics and 24 hospitals were involved and connected to the existing health centers network to improve TB case management. As a result, the number of notified new TB cases in the TB program increased three-fold from 22/100,000 in 2000 to 70/100,000 in 2004.[74] Following the successful implementation of the pilot project, the PPM project management was subsequently integrated into the provincial health office's TB control program in 2006. The involvement of small-scale private providers was also piloted in 2004 by engaging private practitioners to refer individuals suspected to have TB to DOTS facilities for a diagnostic work-up.[75]

Our studies were conducted from 2006 to 2010. The studies in Chapters 2, 7, and 8 were conducted from 2006 to 2007. Studies in Chapters 3 and 5 were conducted from 2007 to 2008. The study in Chapter 4 was conducted in 2009, and the study in Chapter 6 was conducted from 2009 to 2010.

1.8 | THESIS STRUCTURE

This thesis consists of seven scientific papers. The first paper (Chapter 2) provides the theoretical framework of the thesis. The framework is based on a mathematical model of TB and the health system developed at the Department of Public Health of Erasmus MC in collaboration with the WHO. Chapters 3 and 4 answer the first research question; Chapter 3 explores the determinants of patient delay in health facilities using the theory of planned behavior (TPB), whereas Chapter 4 describes the pattern of care-seeking behavior among TB suspects in the community. Chapters 5 and 6 answer the second research question; Chapter 5 describes the interaction between TB patients and the health system during their care-seeking process prior to TB diagnosis, and Chapter 6 describes TB diagnostic performance at DOTS facilities. Chapters 3-6 also answer the third research question. In particular, Chapters 7 and 8 discuss the impact of the HIV epidemic on the TB control program in Indonesia. Chapter 7 describes the burden of HIV-positive cases among TB patients and the use of voluntary HIV counseling and testing (VCT) among TB patients. Chapter 8 discusses the acceptance and barriers of introducing HIV testing in the TB control program. Table 1.1 provides a summary of the methodology used in each chapter.

This thesis concludes with a general discussion of the findings in Chapter 9, their policy implications, and recommendations for improving TB case detection in Indonesia.

Table 1.1 | Summary of the methodology used in each chapter.

Chapter	Design	Population and sample	Data sources	Outcomes
Chapter 2	Mathematical model	(Hypothetical) TB patients in the community	Panel of experts Secondary data from TB surveillance report	Model validation Exploring the impact of potential case finding strategies
Chapter 3	Cross sectional study	TB suspect patients (n=194) at 5 lung clinics in Jogjakarta province	Interview with TB suspects	Patient delay in health facilities
Chapter 4	Cross sectional study	Individuals with TB symptoms (n=746) in the population Jogjakarta province	Interview with TB suspects	Care seeking pattern of TB suspects in the community
Chapter 5	Cross sectional study	Newly diagnosed TB patients (n=275) from 89 DOTS facilities in Jogjakarta province	Interview with TB patients	TB diagnostic delay
Chapter 6	Clinical audit	All TB suspects (n=724) registered in 18 health centers and 2 lung clinics in Jogjakarta municipality	TB register in health centers and lung clinics	TB diagnostic performance at DOTS facilities
Chapter 7	Cross sectional study	Newly diagnosed TB patients (n=989) from 88 DOTS facilities in Jogjakarta province	Database of HIV test results Interview with TB patients	HIV prevalence among TB cases Uptake of VCT
Chapter 8	Qualitative study	TB patients (n=33) recruited in the HIV prevalence study, medical doctors, TB nurses, and TB program managers	In depth interview with TB patients, medical doctors and program managers Focus group discussion with nurses	HIV testing acceptance and perceived barriers among TB patients, health providers and program managers

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CHAPTER 2

How to optimize tuberculosis case finding: explorations for Indonesia with a health system model

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SUMMARY

Background: A mathematical model was designed to explore the impact of three strategies for better tuberculosis case finding. Strategies included: (1) reducing the number of tuberculosis patients who do not seek care; (2) reducing patient delay; and (3) engaging non-DOTS providers in the referral of tuberculosis suspects to DOTS services in the Indonesian health system context. The impact of these strategies on tuberculosis mortality and treatment outcome was estimated using a mathematical model of the Indonesian health system.

Methods: The model consists of multiple compartments representing logical movement of a respiratory symptomatic (tuberculosis suspect) through the health system, including patient and health system delays. Main outputs of the model are tuberculosis death rate and treatment outcome (i.e. full or partial cure). We quantified the model parameters using a two round Delphi survey with five Indonesian tuberculosis experts.

Results: The model validation shows that four critical model outputs (average duration of symptom onset to treatment, detection rate, cure rate, and death rate) were reasonably close to existing available data, erring towards more optimistic outcomes than are actually reported. The model predicted that an intervention to reduce the proportion of tuberculosis patients who never seek care would have the biggest impact on tuberculosis death prevention, while an intervention resulting in more referrals of tuberculosis suspects to DOTS facilities would yield higher cure rates. This finding is similar for situations where the alternative sector is a more important health resource, such as in most other parts of Indonesia.

Conclusion: We used mathematical modeling to explore the impact of Indonesian health system interventions on tuberculosis treatment outcome and deaths. Because detailed data were not available regarding the current Indonesian population, we relied on expert opinion to quantify the parameters. The fact that the model output showed similar results to epidemiological data suggests that the experts had an accurate understanding of this subject, thereby reassuring the quality of our predictions. The model highlighted the potential effectiveness of active case finding of tuberculosis patients with limited access to DOTS facilities in the developing country setting.

2.1 | BACKGROUND

Tuberculosis (TB) is one of the world's leading causes of death and disease. Despite the development and availability of effective treatment for several decades, TB still results in 1.6 million deaths per year.[1] Reducing the burden of global TB disease is a part of broader developmental frameworks such as the Millennium Development Goals (MDG). The MDG clearly state that prevalence and mortality rate of TB should be addressed with a goal towards increase in case detection rate (CDR) and treatment success rate within DOTS (Direct Observed Treatment, Short course) strategy. The importance of intensified case finding was acknowledged by the Second Ad Hoc Committee on the Tuberculosis Epidemic, who recognized that DOTS alone was incapable of reducing morbidity and mortality in TB patients.[2]

Indonesia is ranked third in the world for tuberculosis burden [1]. Following the nation-wide introduction of DOTS in 1995, the country's National TB Control Program (NTP) has successfully reached the international targets for case detection (>70%) and treatment success (>85%).[1] However, much work remains to be done to ensure these achievements contribute to the TB-related MDG of cutting the prevalence and death rate in half by 2015. The Stop TB Partnership has recommended a six-point strategy to reach these goals. The strategy components are: (1) quality DOTS expansion and enhancement; (2) addressing TB/HIV, multi-drug resistant TB (MDR-TB), and other challenges; (3) health system strengthening; (4) broader engagement of all care providers; (5) empowering communities; and (6) promoting research.[3] This recommendation addresses the importance of intensified efforts towards case finding. The Indonesian NTP has accordingly adopted this strategy into its 2006-2010 strategic framework.[4] Thus the current challenge for the NTP is determining how to best allocate limited resources across the six-point strategy. Clearly, with limited resources, there is a need to rationally set priorities.

In an effort to determine the most efficacious method of case finding, we developed a mathematical model of the health system through which TB patients seek care. We explored the potential use of this model to optimize TB case finding in the Indonesian health system context, by comparing three possible case finding intervention strategies: (1) reducing the number of TB patients who do not seek care; (2) reducing patients' delay in seeking treatment; and (3) engaging non-DOTS providers in the referral of TB suspects to DOTS services. Applying an innovative method, the parameters in the model are quantified by an adjusted Delphi approach using expert knowledge.

2.2 | METHODS

Model structure

We developed a compartmental model that describes a TB patients' care seeking behavior and the health system performance of both DOTS and non-DOTS services (e.g. private physicians, nurses, and midwives) in Indonesia. The model was developed with ModelMaker™ version 3.0.3. The model mimics the journey of pulmonary TB patients beginning with the onset of symptoms and follows their care seeking behavior through the health system (Figure 2.1). Our model population is applicable to all symptomatic TB cases; all smear positive patients, and a subpopulation of smear negative patients with symptoms serious enough to potentially prompt them to seek health care.

There are 11 compartments within the model. Each compartment represents a situation that TB patients encounter during care seeking after the onset of TB clinical symptoms. The model begins with symptomatic TB patients in the population not yet seeking health care *(Not seeking care)*. A proportion of TB patients will never be identified because they never seek help *(Never seeking),* or prematurely drop out of the health care system before being identified as a TB case. However, the majority of patients will eventually be diagnosed and cured after proper chemotherapy.

TB patients may choose three different types of health care providers: *Alternative, Non-DOTS,* and *DOTS services*; however, adequate (not necessarily standardized) infrastructure for TB diagnosis and treatment can only be accessed through *DOTS* and *Non-DOTS service* providers. The *Alternative services* concern all health providers that do not practice modern western medicine, such as traditional healers and spiritualist. *Alternative services* also include self-medication, both using traditional or modern (over the counter) medicine. We assume that patients can move directly from the *Alternative services* to either *DOTS* or *Non-DOTS services*, while patients in *DOTS* or *Non-DOTS services* need to move back to *Not seeking care* before possibly moving to another sector. If patients do not drop out, they will eventually be identified as TB suspects and referred for diagnostic testing *(DOTS lab1* or *Non-DOTS lab1)*.

Several potential outcomes may result from the diagnostic process. Following diagnostic testing, patients may be (i) identified as TB positive (i.e. true positive diagnosis) and referred for treatment *(DOTS treatment* and *Non-DOTS treatment)*, (ii) identified as TB negative (i.e. false negative diagnosis) but require additional testing, or (iii) identified as TB negative with a move back to the *Not seeking care* compartment, i.e. drop-out. TB patients who are referred for a second diagnostic test *(DOTS lab2* and *Non-DOTS lab2)* may follow one of the following courses: (i) diagnosed as TB positive and recommended for treatment, (ii) diagnosed as TB negative and exit the health system, or (iii) fail to complete testing and drop out of the system.

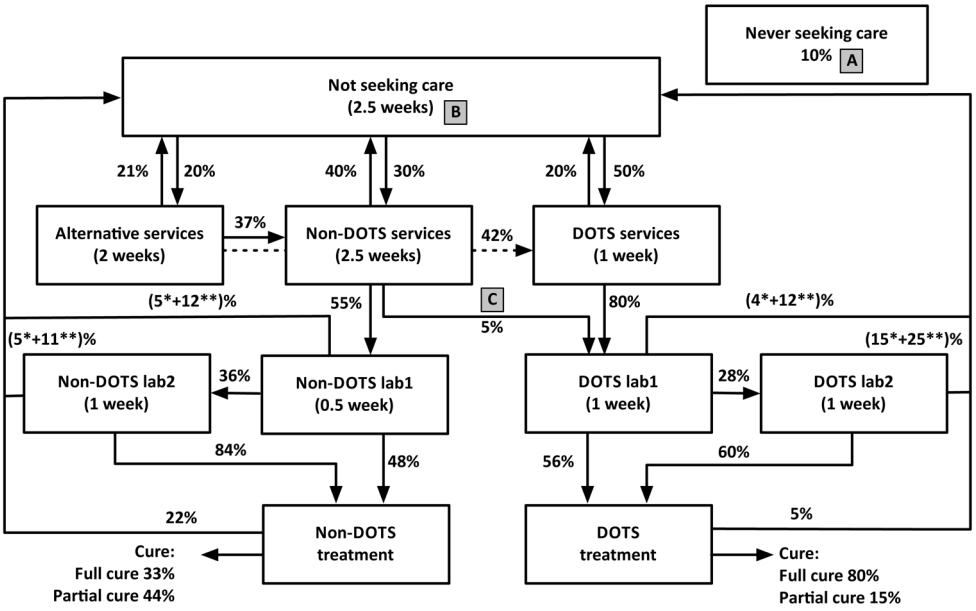

Figure 2.1 | Basic structure of the health system compartmental model, and corresponding parameters as quantified through expert consultation. Boxes represent compartments, i.e. stages of the care seeking process. Arrows represent the flow (transition) of individuals between compartments. These individuals are TB suspects/respiratory symptomatics, who are defined as patients with pulmonary TB symptoms serious enough to trigger them to seek health care. TB diagnosis and treatment is not available in the alternative health sector. In DOTS services, the first laboratory examination (*DOTS lab1*) is smear microscopy and the second examination (*DOTS lab2*) is chest X ray, while in Non-DOTS services the situation is vice versa. Parameters are durations and proportions. Durations are defined as the average full duration of being in a certain compartment, thus not including dropout. Proportions concern fractions of TB patients moving into the next compartments. Main outcomes of the model are TB death, cure, and spontaneous recovery. A; B; C are the intervention strategies simulated in this model (see text and Table 3). * Negative test result; ** drop out during diagnostic process. The dotted arrow represents a direct flow from *Alternative* to *DOTS services*.

The two final compartments, *DOTS treatment* and *Non-DOTS treatment* are stages where TB patients receive treatment. Some of the referred patients will not receive treatment and drop out of the system. However most patients will be cured or partially cured. Partially cured means TB patients have received treatment for some period of time, but have failed to complete the full course of therapy; thus they are at risk of relapse.

Durations and proportions are parameters of the model that may vary based on strategic intervention or changes in patient behavior. Durations are defined as the average full duration of being in certain compartment; these values do not include the duration of patients who drop out from the compartment. Proportions concern the fractions of TB patients moving into the next compartments. All durations are reported in weeks. The duration and proportions per compartment were translated into transition rates (i.e. number/week) of TB patients moving to adjacent compartments.

Other parameters included in the model are TB death rate and spontaneous recovery rate for TB patients not receiving treatment. Using the Berg study data from the pre-treatment era,[5] we estimated that the TB death and recovery rate are approximately 0.3 and 0.2 per year, respectively. These rates correspond to a cumulative TB death and recovery of 40% and 29% after two years, or 73% and 26% after 10 years, respectively, in the absence of effective treatment.

The main outcomes of the model are death, spontaneous cure, and partial or full cure after treatment. Additional outcomes are the average duration of the care seeking process i.e. duration before treatment, the case detection and cure rate, and TB death rate.

Parameter quantification process

Parameter quantification was conducted through a two round modified Delphi survey. Due to the poor response rate when using questionnaires, as suggested in the standard Delphi guideline, we instead conducted direct interviews with all participants. Ten experts were identified, and five of these agreed to participate. The experts were selected based on their experience related to the Indonesian TB control program and/or patients care seeking behavior. We made appointments to meet the experts individually for each round. During each individual encounter we posed several questions displayed as a Word file on a laptop computer. Responses were entered directly into the file. We reviewed the answers with the expert before we saved the file as their final response for that round.

During the initial round, participants were first asked to give their view on the basic assumptions of the model structure, in particular the assumptions that some of the patients never seek care, that drop-outs move back to the *Not seeking care* compartment, and the specific diagnostic process sequence. Thereafter they were asked to provide initial estimates for all durations and proportions in the model. In the second round, the mean, median, and extreme responses were presented and participants were invited to revise their estimates given the initial round results. For our analysis we used the reported median of proportions and durations from the second round.

The experts were asked to consider the context of Jogjakarta province, which is located in the central part of Java Island. The province consists of a mix of urban, semi urban, and rural districts. It has a relatively well-established TB control program according to Indonesian standards. It has

a TB incidence of 63/100,000, which is the lowest incidence rate in Indonesia.[6] Furthermore, several new TB control interventions, such as public-private hospital involvement, have been piloted in this province with positive outcomes.[7]

DOTS services in Indonesia are mainly based in public health centers. However, current NTP policy is to involve hospitals (both public and private) as part of the "engaging all care providers" strategy. In Jogjakarta province, the hospital DOTS linkage had been implemented for five years and reached its maturity prior to conduction of this study. Thus, we can safely assume that the diagnosis procedures and treatment in DOTS hospitals are to a large extent identical to the health centers.

Model explorations and data validation

Initially, we ran the model to validate the quantifications derived from the experts and verify that they resulted in meaningful predictions. To this end, we used the model to simulate a cohort of symptomatic TB patients and predict in which compartments they would ultimately be located. The following four typical TB program indicators were compared with actual data: duration before treatment, case detection rate, cure rate, and TB death rate. Duration before treatment is the average duration of time from initial location within the *Not seeking care* compartment to the point before entering the *DOTS treatment* compartment for all symptomatic TB cases ultimately ending in the *DOTS treatment* compartment. Case detection is the proportion of a full cohort of symptomatic TB cases starting in *Not* or *Never seeking care* that eventually move to *DOTS treatment* via *DOTS lab1*. Cure rate is the proportion of all symptomatic TB cases in the *DOTS treatment* compartment that are ultimately cured. TB death rate is the proportion of a full cohort of symptomatic TB cases starting in *Not* or *Never seeking care* that die over time due to TB.

For model validation, we compared these four typical TB program indicators with actual data from the national or provincial TB program.

- The duration before treatment was derived from the latest Indonesian TB prevalence survey in 2004.[6]
- In the model, case detection rate was defined as all TB patients (smear positive and smear negative) detected in both DOTS and Non-DOTS services. However, since the existing information available from the Indonesian TB program only includes smear positive TB cases detected in DOTS services, we compared the smear positives detected in *DOTS lab1* in our model output with the proportion of smear positive detected within the WHO estimated number of total TB cases and the proportion of smear positive detected within the WHO estimated number of smear positive cases. If we assume that symptomatic cases consist of all smear positive cases and between 10%-40% of smear negative TB cases, using the WHO estimated incidence rate of all cases (239/100,000) and the estimated smear positive

incidence (108/100,000) for Indonesia,[8] the estimated incidence for all symptomatic cases is between 121 and 160 per 100,000 population. Using the estimated smear positive incidence for Jogjakarta province (63/100,000),[6] this translates to an estimated incidence of all symptomatic cases in this province of 71-94/100,000 population. Given the population size of Jogjakarta of 3.44 million in 2005,[9] this leads to 2,400-3,200 symptomatic cases in Jogjakarta. Using the notified number of 1,240 smear positive TB cases reported in Jogjakarta province in 2005,[9] this leads to 39% to 52% of all symptomatic TB cases detected in the DOTS services in Jogjakarta.

– The cure rate is the proportion of new smear positive TB patients cured after treatment received within DOTS services. The reported number of patients cured in the Jogjakarta province TB program surveillance system was 1053 of a total of 1300 TB patients treated in DOTS facilities in Jogjakarta province in 2005.[9] This represents a cure rate of 81%.
– TB observed death rate is estimated from the 2005 WHO-reported TB mortality rate of Indonesia, 41/100,000.[8] We adjusted this value to exclude extra-pulmonary TB cases by assuming that the pulmonary TB death rate is 80% of the WHO figure. Furthermore, we assume that the Jogjakarta figure is 60% of the national pulmonary TB death. This lower death rate is based on the general health indicators of Jogjakarta province, which are better than those of Indonesia as a whole. Although the crude mortality rate is slightly higher (7.8 compared to 6.6/100,000), the life expectancy at birth and maternal mortality rate are considerably better in Jogjakarta. Moreover, the health system performance in Jogjakarta is far better than in Indonesia in general; TB is one of the top ten causes of death nationally, while this was not the case in Jogjakarta province. Based on these calculations, the pulmonary TB death rate in Jogjakarta province should be 20/100,000. Given the population size of 3.44 million, we arrive at approximately 700 pulmonary TB deaths in Jogjakarta per year. This means that the 'observed' TB death is between 22%-29% in 2005.

These model outcomes were used as the baseline situation to be compared with three strategies to improve TB case finding. The strategies are as follows: strategy (A) is to reduce the proportion of TB patients who never seek care (*Never seeking care* compartment) by 50%; the second strategy (B) is to reduce patients' delay (reduce duration in *Not seeking care* compartment by 50%); the third strategy (C) is to refer all TB suspect patients from non-DOTS services to DOTS services (i.e. from *Non-DOTS services* to *DOTS lab1* compartment).

We also considered a different scenario in which a greater proportion of TB patients remain in the *Alternative services* sector. In this model, we assumed that 20% of the TB patients that would have gone to the *DOTS* and *Non-DOTS* compartment now move to the *Alternative services* compartment. Also in this model, patients cannot move directly from the Alternative sector to other sectors, but first need to return to the *Not seeking care* compartment. This scenario

reflects the health system situation of Indonesian settings outside Java-Bali, where the number of health care facilities (both public and private) is less, and TB patients face greater geographical challenges.

Sensitivity analysis

A univariate sensitivity analysis was performed to assess how the main results (proportions death and partially cured) change with different model assumptions. To this end we multiplied the baseline values of the transition rates of patients going out of each compartment by 2/3 and 3/2, one rate at a time, and ran the model again. The change in outcomes gives an indication of the sensitivity of the model to the assumed parameter values. By varying transition rates, rather than the expert-derived proportions, all proportions moving out of particular compartments still add up to 100%.

2.3 | RESULTS

Parameter quantification

All experts (Table 2.1) agreed that the model structure and diagnostic process sequence provided an adequate representation of reality for TB patients and the TB control program in Indonesia. The medians of the expert derived average durations and proportions are reported in Figure 2.1. In general, the experts suggested that most of the TB patients (90%) seek treatment, with an average duration of 2.5 weeks after their first symptoms before entering the healthcare system. Fifty percent of those seeking treatment go to *DOTS services* and 20% to *Alternative services* as their first health service preference. The experts also acknowledged that *DOTS services* have a better capacity to diagnose and treat TB patients, with a lower drop out rate during treatment and a higher cure rate, compared to *non-DOTS services*. The experts reported a slightly longer duration until treatment for the Non-DOTS sector compared to the DOTS sector. In particular, the assumed duration prior to TB suspicion was 1.5 weeks longer, whereas this was only partly counterbalanced by a 0.5-week shorter duration until diagnosis by the first lab. Furthermore, there were no considerable differences in the experts' estimated parameter values (i.e. durations and proportions) between the first and second Delphi round (data not shown).

Model simulation

Figure 2.2 shows a baseline cohort of TB patients during their care seeking process. Most of the patients are cured after treatment. Only a small fraction of TB patients, mainly those who never seek treatment, remain as a source of infection after 100 weeks (approximately 2 years). The

model also demonstrates that only a negligible proportion of TB patients stay in the *Alternative services* sector, compared to the *DOTS* or *Non-DOTS services*.

Table 2.1 | Characteristics of the expert panel

Expert 1:	TB project manager with a vast experience in developing public-private mix among hospitals (TB Hospital DOTS Linkage/HDL) in Jogjakarta province since 2000-2005.
Expert 2:	Microbiologist who works at the university and as laboratory technical consultant for the TB control program. The expert is also involved in the laboratory capacity strengthening, as a part of the TB Hospital DOTS Linkage project in Jogjakarta. Member of national TB laboratory working group, has recent experience with the study of TB patients' care seeking behavior in this province.
Expert 3:	Urban district TB control program manager with recent experience of conducting a TB patients care seeking behavior study in Jogjakarta province.
Expert 4:	Former rural district TB-control program manager who has health promotion expertise and vast experience in health seeking behavior interventions.
Expert 5:	Medical doctor who was head of a public health center in Jogjakarta during the daytime and a private practitioner in the evening. As the head of the health center the expert has experience in involving private practitioners in the health center catchment area.

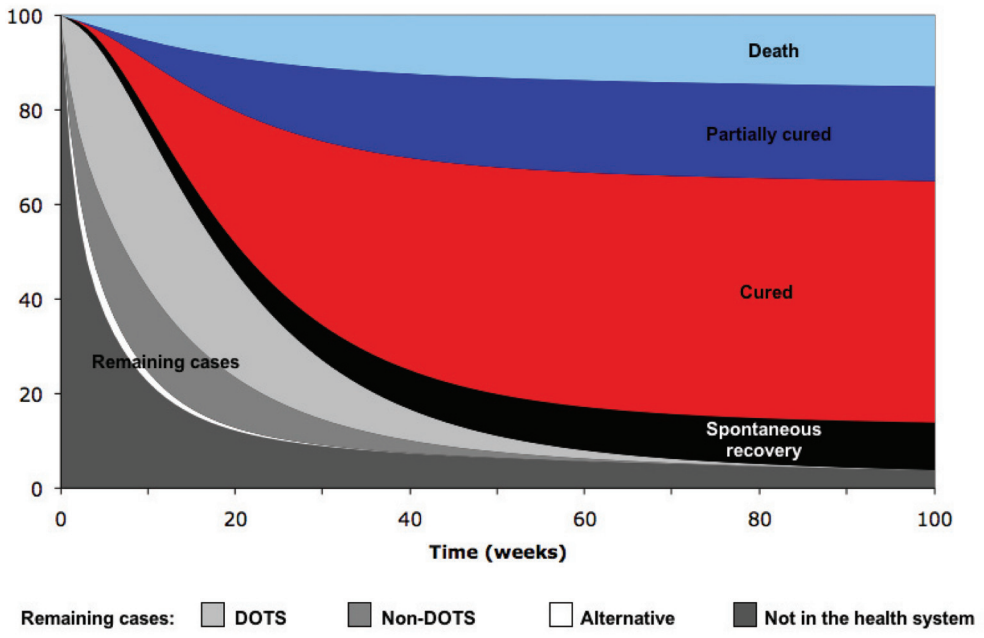

Figure 2.2 | Cumulative outcome of the care seeking process of TB patients' cohort, starting in *Not seeking care* (90%) and *Never seeking care* (10%) compartments.

It is reassuring that the Delphi survey quantifications correspond with an average total duration before treatment of 9.3 weeks. This is in agreement with findings from a recent Indonesia national TB prevalence survey, which reported a mean of 10.3 weeks (Table 2.2). Other critical model outputs are also similar to the existing data. The model prediction for the proportion of smear positive TB patients through DOTS services is within the range of the existing TB case finding data, and the predicted cure rate is slightly less than that found in the data. However, the predicted mortality rate in the model is lower than the estimated range of TB death in Jogjakarta province. As a whole, all model predictions are reasonably close to the reported data, but to some degree overly optimistic.

Table 2.2 | Comparison of model output with available data

	Existing data	Model output
Mean duration from the first TB symptoms to treatment (weeks)	10.3 [a]	9.3
Proportion (%) of all TB-cases detected as smear positive through DOTS services	39 - 52 [b]	48.0
Proportion (%) of TB patients in the DOTS services eventually cured	81.0 [c]	72.3
Proportion (%) of all TB cases that eventually die	22 - 29 [d]	16.6

Model output and data concern symptomatic pulmonary TB cases; both smear positive and part of smear negatives, with symptoms serious enough to potentially prompt them to seek health care.
[a] based on an Indonesian TB prevalence survey in 2004 [7].
[b] based on smear positive cases detected in Jogjakarta province TB program, assuming that all smear positive and between 10%-40% smear negative TB cases are symptomatic.
[c] the reported cure rate from Jogjakarta provincial TB program in 2005 [9].
[d] based on the WHO estimated death rate for Indonesia as a whole, after correction for 20% extra-pulmonary TB and a 40% lower death rate in Jogjakarta Province [1].

If we consider an alternative situation in which 20% of patients move to the alternative sector, instead of to the *DOTS* and *Non-DOTS services*, the average total duration before treatment would be 12 weeks (not shown). Also for this scenario, most of the TB patients are cured; however a larger proportion of TB cases would die and the cure rate would be lower than in the previous situation (Table 2.3).

Table 2.3 illustrates the outcomes of different possible case finding strategies simulated in the model. Strategy A, which is to reduce the number of TB patients who never seek care, is more effective in preventing deaths than strategy B and C. However, strategy C, involving private providers in the referral of TB patients to DOTS facility, leads to a substantially higher proportion

of fully cured patients among those receiving treatment. These findings are similar for the scenario with a higher rate of patients initially entering the alternative health sector.

Table 2.3 | Predicted effect of three interventions (A, B, C) on a cohort of TB patients (%)

Scenario	Model outcome	No intervention	With intervention		
			A	B	C
Baseline [a]	Death	16.6	14.2	15.5	16.5
	Partially cured	19.6	20.7	20.1	11.5
	Cured	52.8	55.7	54.1	61.0
	Spontaneous recovery	11.1	9.5	10.3	11.0
More important alternative health sector [b]	Death	18.1	15.8	16.6	18.0
	Partially cured	18.5	19.6	19.2	11.1
	Cured	51.2	54.1	53.1	58.9
	Spontaneous recovery	12.1	10.5	11.1	12.0

A: strategy to reduce the proportion of TB patients who never seek care (Never seeking compartment) by 50%;
B: strategy to reduce patients' delay (i.e. reduce duration in Not seeking care compartment) by 50%;
C: strategy to refer all TB suspect patients from non-DOTS services to DOTS services (from Non-DOTS services to DOTS lab1 compartment).
[a]: Simulation using experts estimated parameters
[b]: Simulation using adjusted parameters in the alternative health sector, i.e. if 20% of the flow of TB patients to the DOTS and Non-DOTS services compartments now move to the Alternative services compartment (i.e. the proportion of TB patients move from Not seeking care compartment to Alternative, Non-DOTS, and DOTS services compartments are 36%, 24%, and 40% respectively), and patients cannot go directly to the DOTS and Non-DOTS services.

Figure 2.3 shows the results of sensitivity analysis. It is clear that changing the model parameters has only a limited impact on outcomes. TB death varied maximally from 15.9 to 17.2 (baseline value of 16.6), while the proportion partially cured varied from 17.9 to 21.7 (baseline value of 19.6). The transition rate from *Not seeking care* to *Non-DOTS services* has the strongest influence on the proportion partially cured. A higher flow to *Non-DOTS services* leads to more patients partially cured, and the proportion TB death slightly decreases as well. The flow from *Not seeking care* to *DOTS services* has by far the biggest influence on TB death, and illustrates that assuming a higher rate of patients going to the *DOTS services* corresponds with a decreased death rate. The proportion partially cured decreases to a comparable degree. Dropout rates (i.e. moving back to *Not seeking care*) show a modest but consistent pattern: a higher rate of dropping out from the

non-DOTS compartments of the model always leads to more TB death and less partially cured, whereas dropping out from the DOTS compartments always leads to both more TB death and more partially cured.

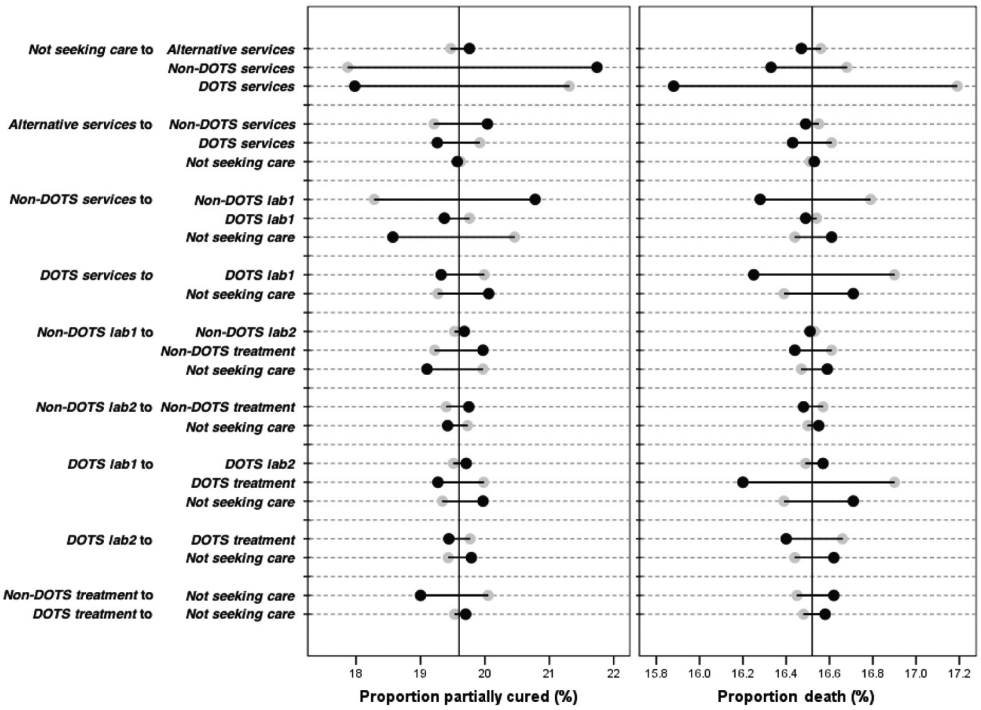

Figure 2.3 | Sensitivity analysis: impact of changes of the transition rates between the different model compartments on the predicted percentage of partially cured and TB-related death. Grey dots represent the results using a transition rate of 2/3 times the baseline value, and black dots represent the results using a transition rate of 3/2 times the baseline value. The two vertical black lines represent the respective baseline outcomes.

2.4 | DISCUSSION

This mathematical model guided by parameter values based on expert opinion is a novel approach to study the role of health systems in TB control. Findings from the model simulation suggest that some critical outputs of the model are reasonably close to the existing data, although they tended to be somewhat optimistic. Model explorations show that increasing care-seeking behavior may

have a considerable impact on preventing TB death. Additionally, referral of suspected TB cases to DOTS facilities will increase treatment success and prevent partial cure. This finding is similar to a situation with more patients initially entering the alternative health sector. Furthermore, sensitivity analysis revealed that the model predictions are not very sensitive to the assumed parameter values, with the health care seeking rates having the biggest impact.

As the TB control program relies on passive case finding, success is determined by patients' care seeking behavior and health system performance. Previous studies examining TB case finding mainly focus on either the care-seeking behavior of TB patients,[10-14] or the health system determinants.[7,15-17] In the 1970s, Piot developed a model of the TB treatment-seeking process, which included both patient and health system determinants.[18] Two recent studies have addressed the interaction between TB patients and health system through modeling; however these studies focused more on the diagnostic process rather than case finding strategies.[19,20] Our study contributes to the body of knowledge by combining all factors related to TB control into one coherent framework using mathematical modeling. This model takes into account the various types of existing health services, the duration and pattern of care seeking behavior, and TB patient outcome (i.e. death, partial/full cure, and spontaneous recovery).

Our model does not account for the complexities present in the natural history of TB infection, but considers a simple constant risk of death or spontaneous recovery while being in the health system. Including progression and regression of the disease through different stages of severity would allow prediction of the impact of early case detection. Relapse after treatment failure or incomplete cure, MDR-TB, and HIV co-infection will have a different impact on the progression and risk of death in individual TB cases. A more complex model has been designed that considers these factors.[21] Our model also does not include TB transmission. In reality, earlier and better treatment of TB patients will to some extent lower the transmission rate and thereby result in fewer secondary cases in the population. Our predictions on prevented TB deaths are therefore underestimations.

It is difficult to estimate the number of TB patients existing outside government run health services in Indonesia and other developing countries. Consensus methods, such as Delphi, are likely the only means to obtain quantitative information.[22,23] Despite the fact that most of the Delphi studies are not designed to be statistically significant and the ideal panel size has not been identified,[22] most studies involve large numbers of participants.[22-26] Therefore, our expert estimated parameters should be interpreted with caution. Still, our results show that the critical outcomes of our model are reasonably close to the existing data, which supports the validity of the parameters (Table 2.2). It is notable that outcomes of our model are consistently – but to different degrees – more optimistic than epidemiological data. We realize that we could not do a formal statistical validation of the model, since the 'observed' data themselves are partly based on model predictions (by WHO) and additional assumptions.

Because health system characteristics and TB patients' care seeking behavior differs in different regions, our study results may not be directly generalizable to other settings. However, the model can be adapted to others settings provided parameter values are regionally specific.

At present, there is a recognized global urgency to improve TB case detection.[27] The Second Ad Hoc Committee on the Tuberculosis Epidemic also acknowledged that a high DOTS treatment rate alone was incapable of reducing morbidity and mortality, without additional intensified case finding.[2] Heller *et al.* used modeling simulation and suggested a similar result.[28] There are several different strategies for increasing case finding, such as active case finding (ACF), enhanced case finding (ECF),[29] and expanded passive case finding via increased interaction with private sectors.[30] The difference between ACF and ECF is the level of direct interaction with the target population. ACF is often more labor intensive, involving face-to-face contact and immediate onsite evaluation. ECF educates the population about the symptoms of TB through publicity and education, and encourages self-presentation to medical services.[29] Studies also show that implementation strategies of ACF (radiography screening or symptom based screening,[31] tuberculin screening,[32] and contact tracing [33-35]), ECF (health education, community involvement,[29] or outreach program [36]), and case finding in the public and private sector outside of DOTS program (via involvement of private practitioners in suspected TB case referral,[37] diagnosis and treatment [30,38]) can be feasible and effectively improve TB case finding.

Three strategies are hypothesized to potentially improve TB detection and cure rates. Strategy A can be implemented through symptom-based household contact screening as conducted in Northern Lima, Peru.[35] An example of intervention to achieve strategy B is the community outreach program in rural Southern Ethiopia,[36] where a TB campaign was conducted prior to a monthly outreach visit to communities. Strategy C is exemplified by the involvement of private providers, such as informal village doctors in Bangladesh, to refer TB suspects to DOTS facilities.[37] All these interventions lead to substantial improvement in TB case finding. However, the feasibility of actually adopting the suggested intervention strategies in Jogjakarta province remains to be seen. For example, to refer all TB suspect patients to DOTS facilities (strategy C) requires involvement of all private providers. In reality, this may be impractical and difficult to achieve. The feasibility and acceptability of an intervention is to a large extent setting-specific. Any intervention program should be assessed after consultation with local experts. Still, explorations with the model can at least demonstrate the most promising control options with regard to their expected effectiveness.

Effectiveness of a disease intervention is commonly measured by averted disease burden in terms of disability adjusted life years (DALY). In TB, 86% of healthy life lost can be attributed to premature death, while only 14% is due to illness.[30] The model shows that reducing the number of never seeking care TB patients will have the greatest impact on mortality, and will

thus result in the greatest improvement in DALY. Further, Borgdorff *et al.* suggested that ACF would only have limited impact on mortality if the intervention detects patients who would otherwise have been detected through self-reporting.[39] Thus challenges remain in targeting specific high-risk TB sub-groups, e.g. prison inmates, HIV patients, and urban slums dwellers, who have limited access to health services and are less likely to seek care on their own.

The potential effectiveness of implementation strategies should also be judged against the potential costs for implementing such strategies. This is a particularly important consideration in resource-constrained settings such as Indonesia. In these settings, cheaper, albeit less effective, interventions may be a more pragmatic option. Several economic evaluation studies have assessed the cost effectiveness of different TB control strategies, mainly related to DOTS. However, only a limited number of economic evaluations on case finding strategies are available, mainly in the setting of developed countries.[30,32,40,41] Further, no economic evaluation has been published on community based case finding or interventions to refer TB suspects from private providers to DOTS facilities. A study in Dar es Salaam suggests that an active case finding strategy may cost less than $276 US per case treated (1996 exchange rate), in a situation where household cost is the main component of cost for tuberculosis management.[42] The Indonesia NTP's marginal costs of a case successfully treated for 2004-2005 is approximately US $450.[1,43] This suggests that the ACF strategy in high-risk populations with limited access to DOTS facilities could potentially be considered cost-effective in the Indonesian context. Notwithstanding, formal cost effectiveness analysis comparing ACF, community based case finding, and intervention to refer TB suspects from private providers to DOTS facilities (which is beyond the scope of this study) clearly needs to be carried out before ACF can be advocated as a priority policy option. Results of an economic study of an intervention to refer TB suspects from private providers to DOTS facilities in Jogjakarta province is undergoing evaluation at the time of writing and is expected to shed more light on this issue.

Our model development process has demonstrated significant gaps in knowledge. In general there is little data about the TB diagnosis and treatment process and the outcome in non-DOTS services. Also, little is known about TB patients who never seek care and TB patients who enter the alternative services sector. Another knowledge gap exists regarding the sensitivity of health services in identifying TB suspects. Further, there are limited evidences of cost effectiveness of TB case finding implementation strategies. Thus, further studies are needed to provide such evidence.

2.5 | CONCLUSION

We used mathematical modeling to explore the impact of Indonesian health system interventions on tuberculosis treatment outcome and deaths. We relied on expert opinion to quantify the parameters. The fact that the model output showed similar results to epidemiological data suggests that the experts had an accurate understanding of this subject, thereby reassuring the quality of our predictions. The model highlighted the potential effectiveness of active case finding of tuberculosis patients with limited access to DOTS facilities in the developing country setting.

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CHAPTER 3

Patient delay determinants for patients with suspected tuberculosis in Jogjakarta province, Indonesia

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ABSTRACT

Objectives: Indonesia has a high incidence of tuberculosis (TB), despite the successful introduction of the Directly Observed Treatment Short course strategy (DOTS-strategy). DOTS depends on passive case finding. It is therefore important to identify determinants of patient delay and reasons for visiting a DOTS healthcare provider when seeking care. The aim of this study was to assess these determinants in TB suspects (coughing for at least two weeks).

Methods: Cross-sectional data were gathered with a structured questionnaire in which psychosocial determinants were based on an extended version of the Theory of Planned Behavior (TPB). The study was conducted in five governmental lung clinics of Jogjakarta province. In total 194 TB suspects that registered at the lung clinics were interviewed.

Results: The median patient delay was 14 days (range 0-145). Ordinal regression analyses showed that visiting a private healthcare provider when first seeking healthcare, reporting travel distance/travel time as reason for choosing a certain healthcare provider when first seeking healthcare, discussing the symptoms with family, a reported short travel time, but no factors of TPB, were significantly associated with a shorter patient delay. An important factor negatively associated with visiting a DOTS clinic was the reported travel time.

Conclusion: Accessibility of the healthcare provider was the main determinant of patient delay, but the role of psychosocial factors cannot be fully excluded. Urban and suburban areas have relatively good access to (private) healthcare, hence the short delay. Thus, future studies should be focused on extending the DOTS strategy to the private sector.

3.1 | INTRODUCTION

Indonesia has a high incidence of tuberculosis (TB); it ranks the fifth highest among all countries in terms of the prevalence of TB .[1] To control the TB epidemic, the World Health Organization (WHO) has recommended the Directly Observed Treatment Short course strategy (DOTS-strategy). The implementation of this strategy started in 1995 and in 2007 there was a population coverage of 100% in Indonesia with a case detection rate of 51% of all new TB cases.[2] The main clinical elements of the DOTS strategy are free diagnosis, free treatment, and supervised treatment.[3] The global targets set by the WHO for 2015 are to have halted and begin to reverse the incidence of TB by 2015 and to halve TB prevalence and mortality rates compared with a baseline of 1990. In Indonesia the mortality rate has, as of 2006, decreased by 50% compared to 1990; however, the prevalence rate was decreased by 32% in 2009 and the incidence rate is basically constant since 1990.[1]

The DOTS strategy depends on passive case finding; thus, an important factor in the successful diagnosis and treatment of TB is the healthcare seeking behavior of individuals suspected of having TB. According to the TB/HIV clinical manual, a TB suspect is defined as someone with a cough that has lasted for at least two weeks.[4] A long delay in diagnosis is associated with increased transmission of TB.[5] To improve the control of TB, it is very important to understand the determinants of patient delay – defined as the time between onset of symptoms and the first visit to a healthcare provider – and the reasons for first visiting a DOTS healthcare provider.

A limited number of studies has reported on healthcare seeking behavior in the Indonesian context. A qualitative study performed in Jogjakarta province suggested that income and the advice of household members had the strongest influence on seeking healthcare.[6] Another qualitative study by Watkins and Plant identified additional determinants of seeking healthcare, including knowledge and awareness of TB, availability of the healthcare provider, cost, and stigmatisation.[7] Other studies have shown that age, gender, education, and place of residence were determinants of seeking healthcare in patients with TB.[8-10] However, to date, all studies on determinants of patient delay of patients suspected of TB in the Indonesian population were qualitative; no quantitative studies have assessed the relative importance of various factors, including social cognitive factors, in determining healthcare seeking and patient delay.

Insight in psychosocial determinants of patient delay and visiting a DOTS clinic is important as these determinants can be used as change targets in health promotion programs. We deployed an extended version of the Theory of Planned Behavior (TPB) as a theoretical framework for assessing the psychosocial determinants of patient delay.[11] The Theory of Planned Behavior (TPB) is a social cognitive model that proposes that the intention to perform a certain behavior is a direct proxy of action and that this intention is determined by: (1) the attitude toward the behavior, (2) the subjective norm, or the perceived social pressure associated with performing

the behavior, and (3) the perceived behavioral control, or the extent to which the patient thinks he/she is capable of performing the behavior.[11] To enhance the prediction of human behavior we extended the model wit the following factors; perceived vulnerability for TB, the perceived severity of TB, knowledge of TB, perceived severity of symptoms and perceived stigmatisation of TB. A detailed description of the extended version of the TPB is given in Appendix 2.

The aim of our study was to assess the (psychosocial) determinants of patient delay for patients that presented at one of the five governmental lung clinics (with a cough that had lasted more than two weeks) in Jogjakarta province, Central Java – with a focus on psychosocial determinants. Moreover, we assessed which of these determinants was associated with visiting a DOTS healthcare provider when first seeking healthcare.

3.2 | MATERIALS AND METHODS

Design and study population

A cross-sectional study was conducted by interviewing TB suspects with a structured questionnaire. The study was conducted in all five lung clinics (all governmental) in Jogjakarta province during the second quarter of 2008. The DOTS strategy has been implemented in these five lung clinics, and in all healthcare centers (117 in total) and 18 public and private hospitals. Details about the study setting can be found in Appendix 1. Patients were eligible for inclusion when coughing lasted for at least two weeks. Patients were excluded from the study when they reported coughing for more than 6 months (i.e., to reduce recall bias), when it was not possible to interview the patient (i.e., due to not being able to speak the Indonesian language, severe illness, unconsciousness, severe psychiatric disease, severe intellectual impairment, and hearing loss), or when the patient was under 15 years old. The targeted sample size was 200 patients, based on the rule of thumb of a minimum of 15 patients per predictor with an estimated model consisting of 10 predictors. The number of patients included in each lung clinic was weighted based on the number of patients diagnosed with TB in each clinic in the second quarter of 2007. Consecutive sampling was used to include the patients in the study upon registration at the lung clinic. All patients provided informed and signed consent to participate in the study. Due to cultural norms – as it is inappropriate to ask further questions after the patient refused to participate – no basic socio-demographic data and reasons for refusal could be collected on patients who refused to participate. Approximately 15% of the patients refused to participate in the study.

The study was approved by the Ethical Committee of Research in Medical Health of the Faculty of Medicine of Gadjah Mada University, Indonesia.

Questionnaire

The questionnaire was developed in English, translated into the Indonesian language, and then translated back into English to check the translation. It included socio-demographic data, questions to asses patient delay – measured in days from onset of coughing until first visit to a healthcare provider – and healthcare seeking behavior and the items of the extended version of the TPB. The socio-economic status was mainly based on property (see Appendix 3 for more detail). Based on the cumulative score (range 0-46), we classified the patients as either lower (score <18) or upper class (score >18) using a median split as this gave the best correlation with patient delay. The items of the extended version of the TPB were mainly derived from a study by Watkins and Plant conducted on Bali.[7] The TPB items were assessed with questions based on a 5-point scale. The questions were posed to the patients by asking them to consider what they would do if they started coughing again. Thus, patients were asked about their current considerations; they were not asked to recall the considerations made when they first visited a healthcare provider during the current episode of coughing. A detailed outline of the questionnaire is shown in Appendix 3.

To assess the internal consistency of the direct measures of the extended version of the TPB, Cronbach's alpha was calculated (Table 3.1).[12]

Data collection

Four trained interviewers performed the interviews in the Indonesian language. After obtaining informed consent, the patient was interviewed in a quiet room where confidentiality could be guaranteed. For patients 15-18 years old, parental consent was also obtained. To assess questions related to an event in the past (e.g., the beginning of the cough), the patient was shown a calendar that indicated important holidays and events of the year. Patients received a small non-financial incentive for participating in the study.

Data analyses

The data were double entered in Epi Info software, version 3.4.3 (CDC, http://www.cdc.gov/epiinfo/). Analyses were performed with SPSS (version 16.0 for Microsoft Windows).

Patient delay was not normally distributed, the Shapiro-Wilk test showed a p-value <.0001; therefore, patient delay was categorised into five categories with approximately equal numbers of patients per category. The determinants of patient delay were analysed with ordinal regression, which takes into account the order of the categories of the dependent variable. Ordinal regression assumes that the effect of the independent variables is the same across the different categories of the dependent variable. The test of parallel lines showed a p-value >.05, reflecting that use of ordinal regression was justified.[13] Logistic regression was used to identify factors that determined the choice of visiting a DOTS clinic when first seeking healthcare. For both outcome measures (patient delay and first visit being a DOTS clinic), univariate analysis was

conducted to estimate the crude effects of the factors. Unless otherwise indicated, factors of the extended version of the TPB were analysed continuously. Variables with a p-value <.20 were then selected for the multivariate analyses. A likelihood ratio backward selection procedure was used to select the variables for the model; variables with a p-value < .10 were maintained. Based on the multivariate analyses, adjusted odds ratio's were presented for the variables maintained in the model.

3.3 | RESULTS

Patient characteristics

From the end of April to the end of June 2008, 194 patients who had been coughing for over two weeks were interviewed. The interviews lasted on average 45 minutes to an hour. For fifty-six patients (29%), this interview represented their first time seeking healthcare. Patients had sought healthcare a median of two times and a maximum of nine times. Eighty-eight patients (45%) visited a private healthcare provider when first seeking healthcare. The mean patient age was 39 years old (14.1 SD, range 16-77) and 104 (54%) patients were male. On a scale of 0-46, the mean SES score was 21 (5.1 SD, range 9-38), which correspondents with middle class. More details on patient characteristics can be found in Appendix 1.

Determinants of patient delay

The median patient delay was 14 days (range 0-146), with a mean of 19.1 days (1.52 SD). Patients that visited a public healthcare provider when first seeking healthcare had a median patient delay of 17 days (range 0-146); patients that visited a private healthcare provider had a median patient delay of 7 days (range 0-112). The patients generally had high intentions, favourable attitudes, subjective norms in favour of visiting a healthcare provider, and positive perceived behavioral control, with mean scores above 3.5 (Table 3.1). This means that patients had the intention to seek healthcare for coughing and perceived no barriers to perform this behavior. The direct measures were considered good by the Cronbach's alpha scores.

Univariate analyses showed that the factors in the extended version of the TPB (direct and indirect measures) were not significantly associated with patient delay (Table 3.2). Patients that reported many symptoms (5-10) had a shorter patient delay compared to those that reported few (1-4) symptoms. The factors marital status, occupation, residence (urban/rural), highest education, SES score, the use of self-medication, the use of traditional medicine, visiting a traditional healer, or the serious symptom of haemoptysis were significantly associated with patient delay.

Table 3.1 | Descriptive statistics of the factors included in the extended version of the Theory of Planned Behavior. N=194 patients with a cough that lasted at least two weeks

	Mean (range)[a]	Cronbach's Alpha[b]
Intention	4.2 (1-5)	-- [c]
Attitude	4.2 (1-5)	0.89
Subjective norm	4.1 (1-5)	0.90
Perceived behavioral control	3.7 (1-5)	0.86
Knowledge score	9.1 (0-15)	-- [d]
Perceived severity of symptoms	3.2 (1-5)	0.81
Perceived severity of TB	2.0 (1-5)	0.80
Perceived vulnerability of TB	2.4 (1-5)	0.96
Perceived stigma	2.1 (1-5)	0.64

[a] A score below 3 is not in favour of the seeking healthcare for coughing, a score of 3 indicates a neutral position, and a score >3 is in favour of seeking healthcare for coughing.
[b] The Cronbach's alpha is a measure of the internal consistency of questions that measure the same factor, and it indicates the validity of the measurement of that factor. Cronbach's alpha ranges from 0 to 1, where an alpha > 0.60 was considered satisfactory, and an alpha > 0.80 was considered good.
[c] Not applicable because only one question was asked.
[d] Not applicable because the factor measured different aspects of the knowledge of TB, which do not need to be internally consistent with each other.

The independent variables for the multivariate analysis included gender, symptoms discussed with others, first healthcare provider visited, reason for choosing that particular healthcare provider, and travel time. Males had longer patient delays than females, but this effect was not significant in the multivariate analysis. Patients that visited a private healthcare provider during first healthcare visit had a significant shorter patient delay compared to patients visiting a public healthcare provider. Compared to discussing symptoms with a spouse, discussing symptoms with other family members was negatively associated with patient delay, resulting in shorter delay. In contrast, discussing symptoms with non-family members resulted in more delay (positive association). Among the reasons given for choosing a certain healthcare provider, mentioning travel distance and travel time as reason for visiting a particular health care provider was significantly associated with a shorter patient delay compared to mentioning quality of service. A travel time longer than 14 min was associated with a longer patient delay (p=.054).

Table 3.2 | Ordinal regression of determinants of patient delay in individuals that sought health care for a cough that lasted >2 weeks in lung clinics in Jogjakarta province, Indonesia

Variable	N	Mean patient delay (days)	Crude OR* (95% CI)	p-value	Adjusted OR* (95%CI)	p-value
Intention score [a, b]						
Low	161	18.6	1	--		
High	33	21.3	1.14 (0.59-2.20)	0.71		
Attitude [a]	194	19.1	1.67 (0.92-3.00)	0.10		
Subjective norm [a]	194	19.1	0.73 (0.34-1.55)	0.41		
Perceived behavioral control [a, b]						
Low	79	22.7	1	--		
High	115	16.6	0.80 (0.48-1.33)	0.39		
Perceived severity of symptoms [a]	194	19.1	1.12 (0.83-1.50)	0.45		
Perceived severity of TB [a, b]						
Low	41	21.7	1	--		
High	153	18.4	0.85 (0.46-1.56)	0.60		
Perceived vulnerability for TB [a, b]						
Low	94	18.2	1	--		
High	100	20.0	1.19 (0.72-1.94)	0.51		
Perceived stigma [b]						
Low	103	21.4	1	--		
High	91	16.5	1,29 (0,78-2,13)	0.31		
Knowledge score	194	19.1	1.11 (0.95-1.28)	0.19		
Age (decades)	194	19.1	1.11 (0.93-1.32)	0.27		
Gender						
Female	90	13.9	1	--	1	--
Male	104	23.6	2.39 (1.42-3.97)	0.001	1.58 (0.92-2.71)	0.10
Occupation						
Others	87	18.1	1	--		
Private sector	107	19.9	1.16 (0.70-1.91)	0.56		
Residence						
Rural	57	20.5	1	--		
Urban	137	17.2	0.75 (0.43-1.30)	0.30		
Highest education				0.28		
Elementary school or lower	50	21.7	1	--		
Junior High school	37	13.5	0.62 (0.29-1.32)	0.22		
Senior High school	68	22.0	1.15 (0.60-2.19)	0.67		
University	39	15.9	0.69 (0.33-1.46)	0.34		

Variable	N	Mean patient delay (days)	Crude OR* (95% CI)	p-value	Adjusted OR* (95%CI)	p-value
Socio economic status						
Lower class	55	21.5	1	--		
Upper class	139	18.1	0.84 (0.48-1.45)	0.52		
Number of symptoms						
1-4	85	15.4	1	--		
5-10	109	22.0	1.57 (0.94-2.59)	0.083		
Discussed symptoms with				<0.001		<0.001
Spouse	123	19.1	1	--	1	--
Other family members	47	14.2	0.45 (0.25-0.83)	0.011	0.44 (0.23-0.85)	0.014
Non-family members [c]	24	28.5	3.00 (1.35-6.68)	0.007	2.70 (1.19-6.16)	0.018
First HP* visited [d]						
Public system	106	23.6	1	--	1	--
Private sector	88	13.7	0.30 (0.18-0.51)	<0.001	0.51 (0.29-0.90)	0.020
Reasons for visiting that particular HP				<0.001		<0.001
Quality of service	82	24.0	1	--	1	--
Travel distance/travel time	75	11.7	0.22 (0.12-0.40)	<0.001	0.35 (0.18-0.67)	<0.001
Other	37	23.2	0.70 (0.35-1.41)	0.32	0.78 (0.38-1.61)	0.35
Travel time to first HP				<0.001		0.054
0-14 min.	69	12.0	1	--	1	--
15-29 min.	74	20.4	2.77 (1.52-5.05)	0.001	2.17 (1.17-4.04)	0.014
30 > min.	51	26.8	5.75 (2.92-11.4)	<0.001	2.61 (1.18-5.74)	0.017

**OR = odds ratio; CI = confidence interval; HP = healthcare provider.*

[a] Factors are coded in such a way that a high score is theoretically in favour of the behavior.

[b] Based on a median split of the continuous variable.

[c] Includes two patients who did not discuss their symptoms at all.

[d] The lung clinics, healthcare centers, and governmental hospitals were categorised as public systems.

Determinants of visiting a DOTS clinic when first seeking healthcare

Of the 194 patients included in the study, 110 (57%) visited a DOTS healthcare provider when first seeking healthcare. The majority of DOTS healthcare providers consisted of lung clinics (55%) and healthcare centers (34%). A tendency to visit a DOTS healthcare provider was associated with the quality of service as reason to choose a certain healthcare provider (p=.078, Table 3.3). The number of reported symptoms was not significantly associated with visiting a DOTS clinic. Other factors that were not associated with visiting a DOTS healthcare provider when first seeking healthcare included; age, use of self-medication, and use of traditional medicine. Having senior high school as highest education seems to be significant, but the factor highest education as a whole was not significant (p=0.18) and could not be kept in the multivariate analyses.

Table 3.3 | Logistic regression of determinants for visiting a DOTS clinic as the first healthcare provider by patients with a cough that lasted > 2 weeks, who visited a lung clinic in Jogjakarta province, Indonesia.

Variable	n / N (%) [a]	Crude OR* (95% CI)	p-value	Adjusted OR* (95%CI)	p-value
Intention score [b]	110 / 188 (59)	0.57 (0.27- 1.18)	0.128		
Attitude [b, c]					
Low	70 / 109 (64)	1	--		
High	40 / 79 (51)	0.57 (0.32-1.03)	0.063		
Subjective norm [b, c]					
Low	93 / 146 (64)	1	--		
High	17 / 42 (40)	0.39 (0.19-0.78)	0.008	0.25 (0.10-0.59)	0.002
Perceived behavioral control [b]	110 / 188 (59)	0.77 (0.48-1.25)	0.29		
Perceived severity of symptoms [b]	110 / 188 (59)	0.73 (0.51-1.03)	0.072	0.57 (0.38-0.85)	0.006
Knowledge score			0.70		
Low	21 / 37 (57)	1	--		
Average	71 / 117 (61)	1.18 (0.56-2.49)	0.67		
High	18 / 34 (53)	0.86 (0.34-2.19)	0.75		
Gender					
Female	47 / 88 (53)	1	--		
Male	63 / 100 (63)	1.49 (0.83-2.66)	0.18		
Highest education			0.18		
Elementary school or lower	24 / 49 (49)	1	--		
Junior High school	21 / 35 (60)	1.56 (0.65-3.76)	0.32		
Senior High school	45 / 66 (68)	2.23 (1.04-4.79)	0.039		
University	20 / 38 (53)	1.16 (0.50-2.70)	0.74		
Main occupation					
Others	41 / 84 (49)	1	--	1	--
Private sector	69 / 104 (66)	2.07 (1.15-3.73)	0.016	2.77 (1.38-5.53)	0.004
Residence					
Rural	29 / 54 (54)	1	--		
Urban	81 / 134 (60)	1.32 (0.70-2.49)	0.40		
Socio economic status score (continuous)	110 / 188 (59)	0.98 (0.92-1.03)	0.42		
Total number of symptoms	110 / 188 (59)	0.90 (0.78-1.05)	0.17		
Discussed symptoms with others			0.16		
Spouse	72 / 120 (60)	1	--		
Other family members	21 / 44 (48)	0.61 (0.30-1.22)	0.16		
Non-family members [d]	17 / 24 (71)	1.62 (0.62-4.20)	0.32		

Variable	n / N (%) [a]	Crude OR* (95% CI)	p-value	Adjusted OR* (95%CI)	p-value
Reasons for visiting that particular HP			0.078		
Travel distance/travel time	35 / 72 (49)	1	--		
Quality of service	54 / 81 (67)	2.11 (1.10-4.06)	0.025		
Other	21 / 35 (60)	1.59 (0.70-3.60)	0.27		
Travel time to first HP (hr)	110 / 188 (59)	15.0 (4.1-54.7)	<0.001	29.0 (6.4-132)	<0.001

**OR = odds ratio; CI = confidence interval; HP = healthcare provider.*
[a] n = number of patients that visited a DOTS HP; N = total number of patients in this category.
[b] Factors are coded such that a high score is theoretically in favour of the behavior.
[c] Based on a median split of the continuous variable.
[d] Includes two patients who did not discuss their symptoms at all.

Multivariate analyses showed a significantly lower chance of visiting a DOTS healthcare provider when first seeking healthcare among those reporting a positive subjective norm and perceiving their symptoms as serious. Patients visiting a DOTS clinic were significantly more often employed in the private sector and reported a significant longer travel time. We also tested what effect patient delay would have on visiting a DOTS clinic by including it in the multivariate analysis. Patient delay was significantly and positively associated with visiting a DOTS healthcare provider when first seeking healthcare. Patient delay only minimally changed the effects of the other determinants.

3.4 | DISCUSSION

The aim of our study was to assess the determinants of patient delay of patients suspected of TB (defined as a patient with a cough for at least two weeks) presenting at a lung clinic in Jogjakarta province, Central Java. This study was the first to apply a theoretical framework to an investigation of patient delay determinants in TB. The median patient delay was 14 days, range 0-145. A shorter patient delay was significantly associated with choosing a private healthcare provider when first seeking healthcare, reporting travel distance/travel time as reason for choosing a certain healthcare provider when first seeking healthcare, discussing the symptoms with family, and a short travel time to the first healthcare provider. The extended version of the TPB did not appear to offer a further explanation of patient delay. Visiting a DOTS clinic when first seeking healthcare was determined by a positive subjective norm towards seeking healthcare for coughing, perceiving their symptoms as severe, employment in the private sector, and a longer travel time to the first visited healthcare provider.

Some limitations were inherent to our study design. First, patients who did not visit one of the lung clinics were not interviewed, including those that did not seek healthcare; this probably resulted in an underestimation of patient delay. Also, patients with TB that visited a lung clinic with a cough that lasted less than two weeks were not interviewed; which in turn could have resulted in an overestimation of patient delay. Second, the patients were asked about their beliefs regarding visiting a healthcare provider after they had performed this behavior. Had the patients been asked to recall their past beliefs regarding visiting a healthcare provider, there answers might have got altered by their current beliefs. Besides that, it is easier for a patient to state his current beliefs instead of recalling past beliefs. Therefore, we assumed that the current beliefs, although they may have been altered by performing the behavior, still express the differences in beliefs associated with differences in patient delay. However, as the TPB assumes that a certain level of intention is needed before the patient performs the behavior, these differences in beliefs and intentions might have faded away in the process of healthcare seeking. To avoid these inherent limitations, an alternative study design would be to identify patients suspected of TB at the household level. However, that would have required investigating a prohibitively large population in order to include an equivalent number of patients with a cough that lasted at least two weeks. In this study we were unable to directly determine reasons why people delayed. When patients where asked for reasons why they delayed, most of them stated it was because of the symptoms were not severe. The high rate of this answer while perceived severity of symptoms was not associated with the delay suggests that this might be a social desirable answer. These limitations may partly explain why this study did not identify any of the TPB factors as determinants of patient delay with the included number of patients.

In this study, the median patient delay was relatively short (14 days) compared to other studies conducted in both developing and developed countries that reported a median delay of over 20 days.[14-22] The relatively short patient delay found in this study may be due to the fact that the majority of the included patients lived in urban areas with an extended network of healthcare providers.[9,23-25] Thus, our study population had good access to healthcare. Therefore, the generalisability of our study may be restricted to urban and sub-urban areas with a relatively accessible healthcare system.

The finding that discussing the symptoms with family was associated with shorter patient delay compared to discussing the symptoms to non-family members confirmed the suggestion by Watkins and Plant and Rintiswati *et al.* that the opinions of people next to the patients have an important influence on their healthcare seeking behavior.[6,7] Studies conducted in Botswana,[26] South Africa,[16] and Malawi[27] also found a positive relationship between advice from others and healthcare seeking behavior, but they did not analyse the association with patient delay.[16,26,27] The positive influence of the advice of family members on healthcare seeking behavior highlights the need for population-wide education programs to inform both

the high risk population and their social environment on adequate healthcare seeking behavior for coughing more than 2 weeks. We found that choosing a public healthcare provider when first seeking healthcare was associated with a significantly longer patient delay. This finding was also reported in a study on TB conducted in South India.[14] A study conducted in Malawi also found that the distance to a healthcare provider and the quality of service were the main reasons for choosing a particular healthcare provider when first seeking healthcare, but that study did not analyse the effect on patient delay.[27] Other studies conducted in Ethiopia and South India also found that travel time or distance were significant determinants of patient delay.[14,21] These results suggested that availability, particularly of public healthcare providers, should be the primary concern of policy makers.

It is difficult to explain the finding that working in the private sector was significantly associated with a higher probability of choosing a DOTS clinic when first seeking healthcare. A possible explanation could be that people working in the private sector had higher incomes, which enabled access to better transportation and reduced the issue of distance to the clinic. Another explanation could be that people in the private sector were more likely to work in shifts; thus, they were more likely to be free for morning visits to a DOTS healthcare provider, which were only open during the morning hours. Other studies found an association between distance and choosing a DOTS healthcare provider in general, but those studies did not analyse the association between distance and visiting a non-DOTS healthcare provider.[18,21] A qualitative study conducted in Vietnam investigated specific reasons for choosing a private healthcare provider versus a healthcare provider connected to the National TB Program (NTP).[28] They found that patients perceived that the NTP provided good healthcare, but other qualitative aspects were considered negative (e.g. DOTS treatment regimes and longer waiting times). That might also have been the case in our study. We found that patients were more likely to visit a DOTS clinic when quality of service was their reason for choosing their first healthcare provider; however, those patients exhibited a significantly longer patient delay. This suggests that patients who valued quality of service above other characteristics in the healthcare provider experienced barriers to visiting the healthcare provider of their choice. One important barrier to visiting a DOTS healthcare provider seems to be the travel time as people visiting a DOTS healthcare provider when first seeking healthcare had a significant longer travel time. Therefore, to improve the utilization of the DOTS healthcare providers, the focus should be on improving accessibility. A positive subjective norm towards seeking healthcare for coughing was negatively associated with visiting a DOTS health care provider during first healthcare seeking action. It suggests that important others give the patients the advice to visit a non-DOTS healthcare provider as first healthcare visit. This finding further highlights the need not to target the high-risk population only but also the people that are important to them, especially family members.

Another major finding of our study was that none of the factors of the extended version of the TPB was significantly associated with patient delay. This suggested that these factors were not relevant to the control of TB. Nevertheless, the role of psychosocial factors cannot be fully excluded, because we found that discussing the symptoms with others and the reasons of patients for choosing their first healthcare provider were important determinants of patient delay. Thus, conclusions about the importance of psychosocial factors in determining patient delay must await future studies that identify patients with suspected TB at the household level, before they visit a healthcare provider.

Patients that visited a private healthcare provider when first seeking healthcare had a patient delay sufficiently short to obviate the necessity of further decreasing the delay. In fact, a shorter delay may be counterproductive in the control of TB, because the difficulty in recognising the early symptoms of TB could result in a longer system delay.[4] Early treatment of symptoms without a proper diagnosis could lead to inappropriate antibiotic use, an increased delay in the diagnosis of TB and unnecessary utilization of the healthcare system. However, the public system had a considerably longer patient delay. Because most public healthcare providers are DOTS healthcare providers, this indicated that the DOTS healthcare system lacked accessibility. The best way to address this would be to increase the density of public and DOTS healthcare providers, because the travel time to the healthcare provider was also an important determinant of patient delay. However, given the popularity of private healthcare providers and their high density in Jogjakarta province,[29] it might be more effective to extend the DOTS strategy to the private sector. This was also suggested in a study that used a mathematical model to estimate the impact of different strategies on tuberculosis mortality and treatment outcome.[30] Although Ahmad *et al.* concluded that actively finding cases would provide the best outcomes,[30] that strategy may be less cost effective than other strategies, including involvement of the private sector in the DOTS strategy. Mahendradhata *et al.* conducted a study to evaluate the incremental cost-effectiveness of such an initiative in Jogjakarta province where private practitioners were engaged to refer patient suspected of TB to an healthcare center for DOTS-treatment.[29] They concluded that this strategy could be cost-effective given a well functioning DOTS program. Nevertheless, extending the DOTS strategy to the private sector would involve some difficulty. Some characteristics of the DOTS programs (e.g., supervised treatment) may conflict with characteristics of private healthcare providers (e.g., flexibility and privacy). Also, the broad variety of types of private healthcare providers poses a challenge for successfully extending the DOTS strategy to the private sector. Despite these challenges, some initiatives are currently being implemented to involve the private sector in TB control. The results of our study support the usefulness of these efforts. Yet some considerations need to be made. A recent study conducted in Jogjakarta province showed that visiting a DOTS healthcare provider during first healthcare

visit did not result in a shorter diagnostic delay suggested that the focus first need to be on strengthening the health system and improving diagnostic quality within DOTS services.[31]

We conclude that accessibility of the healthcare provider was the primary determinant of patient delay, and that psychosocial factors were not significant determinants of this delay. Given the short reported patient delay when a private healthcare provider was chosen in first seeking healthcare, we recommend that the major concern of policymakers should be improving the utilization of DOTS healthcare providers, particularly in the private sector.

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Appendix 1 | Setting of the study performed in Yogyakarta province, Indonesia, to identify patient delay determinants for patients with suspected tuberculosis and additional patient characteristics

Setting

Yogyakarta Province is a densely populated province in Central Java that is well developed compared to other parts of Indonesia. Of the 3.2 million inhabitants, approximately 44% live in rural areas.[1] The healthcare system consists of an extended network of healthcare providers including public, private, and traditional healthcare providers. The DOTS strategy is widely implemented in the governmental health system, and recently, the private sector has also gotten involved.[1] Part of the public system includes five governmental (first line) clinics specialised in the treatment of lung diseases. These specialised services are established in urban and suburban areas, and they are visited by patients from Yogyakarta province and the surrounding provinces, including both urban and rural areas. The services of the lung clinics are only available during the morning hours.

Additional patient characteristics

Most of the included patients (166, 86%) reported three or less healthcare seeking action or before. Of the included patients, 151 (78%) were from two lung clinics located in the city of Yogyakarta. The other 43 patients (22%) were interviewed in one of the other three clinics located in the suburban and rural areas of Yogyakarta province. A total of 137 patients (71%) resided in an urban area and 20 patients (10%) resided outside Yogyakarta province. The patients were rather well educated, only 4 (2%) patients had not attended any school, and 39 patients (20%) had a university degree. Half of the patients had used self-medication, 62 (32%) had tried traditional medicines, and 13 (7%) reported visiting a traditional healer when seeking healthcare. None of the latter 13 patients had visited a traditional healer the first time they had sought healthcare.

One third of the patients (60, 31%) visited a lung clinic when first seeking healthcare; 52 patients visited a private doctor (27%); and 37 visited a healthcare center (19%). The other patients visited a private clinic (14, 7%), a midwife or nurse (13, 7%), or a hospital (17, 9%). One patient visited a hospital in Japan.

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Appendix 2 | Conceptual framework for the extended version of the Theory of Planned Behavior for identifying patient delay determinants for patients with suspected tuberculosis in Yogyakarta province, Indonesia

The Theory of Planned Behavior (TPB) is a social cognitive model used to identify beliefs and cognitions that underlie the intention to perform a certain behavior. The model assumes that the intention to perform a certain behavior is a direct proxy of the behavior and that this intention is determined by three major factors: (1) a favourable or unfavourable *attitude* of the patient toward the behavior, (2) the *subjective norm*, a measure of the social pressure associated with performing the behavior, which is perceived by the patient, and (3) the *perceived behavioral control*, or the extent to which the patient thinks he/she is capable of performing the behavior. Each of these three factors can be measured directly and indirectly. For example, the attitude of an individual toward the behavior can be measured directly by asking the individual whether he/she perceives the behavior to be pleasant, good, beneficial etc. and indirectly by measuring the patient's *behavioral beliefs*. However, individual beliefs do not have equal importance in influencing the behavior; thus, each belief should be weighted according to the *outcome evaluation* of that belief. In the same way, the subjective norm can be assessed indirectly by assessing the patient's perception of what important other people think about the behavior (*normative beliefs*), weighted by the patient's motivation to comply with the wishes of these important others (*motivation to comply*). Perceived behavioral control is composed of the patient's beliefs about the presence of certain barriers (*control belief strength*), weighted by the patient's perception of being able to control those barriers (*control belief power*).

Despite the extensive body of literature on the determinants of patient delay in patients with TB and those with suspected TB,[1,2] no studies could be identified that have applied a theoretical framework to investigate the perceptions and cognitions that underlie patient delay. Several studies have emphasized the use of the TPB as a theoretical framework for explaining patient delay for other diseases.[3,4] One study applied the TPB to explain variations in help-seeking intentions for symptoms of breast cancer.[5] Their work suggested that attitude and perceived behavioral control were significantly higher in subjects who intended to seek healthcare promptly compared to potential delayers. Compton and Esterberg performed a pilot study to examine associations between the three central constructs of the TPB and treatment delay for a first episode of non-affective psychosis.[6] Although that study focused on treatment delay, rather than patient delay, and they interviewed relatives, rather than the patients, the study design was similar to the present study. They found that perceived behavioral control and a perceived stigma were significantly inversely associated with treatment delay. Those studies suggested that the TPB could be applied as a theoretical framework for describing patient delay in general.

Although the TPB has not been applied before in the context of TB, the literature has suggested that the factors of the TPB may be able to explain variations in patient delay for patients with suspected TB. Some studies have suggested that beliefs about getting healthcare had an effect on the healthcare seeking behavior of patients with TB and suspected TB. Watkins and Plant, and Rintiswati *et al.* pointed out the influence of important other people on healthcare seeking behavior, and also mentioned several external constraints that may influence healthcare seeking behavior.[7,8]

To enhance the prediction of human behavior, the TPB can be extended with measures specifically associated with patient delay. Based on a review of the literature, we extended the model with two factors from the Health Belief Model (HBM); the *perceived vulnerability for TB*, or the perceived chances of acquiring TB, and the *perceived severity of TB*, or the perceived seriousness and consequences of TB.[9-11] The TPB was further extended with the *knowledge of TB,*[7,12-14] *perceived severity of symptoms,*[7,9,15] and *perceived stigmatisation of TB*.[7,16]

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Appendix 3 | Outline of the questionnaire for identifying patient delay determinants for patients with suspected tuberculosis in Yogyakarta province, Indonesia

The questionnaire included socio-demographic data (name, age, residence, civil status, religion, education, and primary occupation). The socio-economic status (SES) was estimated by assessing home ownership, home building materials, drinking water and energy sources, and property (car, motorcycle, bicycle, cable TV, DVD player, non-cable TV, VCD player, radio, air conditioner, washing machine, or refrigerator). These items were scored according to their economic value. Based on the cumulative score (range 0-46), we classified the patients as either lower (score < 18) or upper class (score >18). Patient residences were categorised as urban or rural, based on data from the national government.[1] The duration of patient delay (in days) was measured by asking the patient when the symptoms started and the date of the first healthcare visit. Additional questions assessed other symptoms (in addition to coughing) that prompted the first decision to seek healthcare, use of self-medication, use of traditional medicine, the type of healthcare provider first visited, and the reasons for visiting that particular healthcare provider at that particular time. Other information was obtained concerning the visit, including the travelling time and distance to the first health care provider and the costs (in Indonesian Rupiah) expended in making the first healthcare visit.

The items of the extended version of the TPB were mainly derived from a study by Watkins and Plant conducted in Bali, which explored the healthcare seeking behavior of patients with TB and suspected TB.[2] We also searched the literature to identify other potential factors for determining patient delay. The behavior we were interested in studying was a visit to a healthcare provider to get treatment for coughing. The TPB items were assessed with questions based on a 5-point scale. The questions were posed to the patients by asking them to consider what they would do if they started coughing again. Thus, patients were asked about their current considerations; they were not asked to recall the considerations made when they first visited a healthcare provider during the current episode of coughing.

Factor (number of itmes[1])	Example	Scale
Intention (1)	The next time you start coughing, you will make plans to visit a healthcare provider to get healthcare	1. strongly disagree 2. disagree 3. not disagree, not agree 4. agree 5. strongly agree
Attitude (7)	For you, visiting a healthcare provider to get healthcare when you start coughing is: – harmful-beneficial – good-bad – unpleasant-pleasant	1. very harmful 2. harmful 3. not harmful, not beneficial 4. beneficial 5. very beneficial
Behavioral beliefs (6)[2]	If you visit a healthcare provider to get healthcare when you start coughing: – you will get the correct diagnosis – the coughing will be cured	1. very unlikely 2. unlikely 3. neither unlikely, nor likely 4. likely 5. very likely
Outcome evaluation (6)[2]	– Getting the correct diagnose is *[…]*[3] – Getting the coughing cured is *[…]*[3]	1. extreme undesirable 2. undesirable 3. neither undesirable or desirable 4. desirable 5. extreme desirable
Subjective norm (6)	– You are expected to visit a healthcare provider to get healthcare when you start coughing – If you visit a healthcare provider to get health-care when you start coughing, you will be supported by most people who have influence on you	1. strongly disagree 2. disagree 3. neither agree or disagree 4. agree 5. strongly agree
Normative beliefs (6)[4]	– Your parents/family would approve of your visit to a healthcare provider to get healthcare when you start coughing Your parents/family will visit a healthcare provider to get healthcare when they start coughing	1. strongly approve 2. approve 3. neither approve or disapprove 4. disapprove 5. strongly disapprove 1. completely true 2. true 3. neither true or false 4. false 5. completely false
Motivation to comply (6)[4]	– What your parents/family think you should do is important to you – Doing what your parents/family do is important to you	1. not at all 2. a bit 3. average 4. much 5. very much
Perceived behavioral control (6)	Imagine that you started coughing again. You want to go to a healthcare provider to get healthcare for coughing but: – you do not have enough money for visiting the healthcare provider. How confident are you that you can visit the healthcare provider? – you find out that the additional costs for travelling and food are very high. In this situation, you feel yourself *[…]*[2] to visit the healthcare provider	1. very unconfident 2. unconfident 3. neither confident or unconfident 4. confident 5. very confident 1. very able 2. able 3. neither able, nor unable 4. unable 5. very unable

Factor (number of itmes[1])	Example	Scale
Control beliefs strength (5) [4]	When you visit a healthcare provider to get healthcare when you start coughing: – you expect it will be time consuming – you expect it will be easy to get to the health facility	1. strongly disagree 2. disagree 3. neither agree or disagree 4. agree 5. strongly agree
Control beliefs power (5) [4]	– When it is time consuming to visit a healthcare provider it is *[…]* [2] that you will visit a healthcare provider to get healthcare when you start coughing – When it is easy to get to the healthcare provider it will be *[…]* [2] that you will visit a healthcare provider to get healthcare when you start coughing	1. much less likely 2. less likely 3. the same chance 4. more likely 5. much more likely
Knowledge score (15) [6]	– TB can be caused by smoking – TB can be transmitted by food – Coughing is a symptom of TB	1. true 2. false 3. don't know
Perceived severity of symptoms (3)	When you visited a healthcare provider for the first time during this period of coughing to get healthcare for coughing: – your symptoms were life threatening – your symptoms were serious	1. strongly agree 2. agree 3. neither agree or disagree 4. disagree 5. strongly disagree
Perceived severity of TB (3)	– Tuberculosis is a life threatening disease – Tuberculosis might lead to death if left untreated	1. strongly agree 2. agree 3. neither agree or disagree 4. disagree 5. strongly disagree
Perceived vulnerability for TB (3)	– Your chances of getting TB are – You think that your risk of getting diagnosed with TB is	1. very low 2. low 3. average 4. high 5. very high 1. very unlikely 2. unlikely 3. average 4. likely 5. very likely
Perceived stigma (8)	Imagine that you are diagnosed with TB; what do people in the community think about you: – People in the community think that you are dirty – People in the community think that you will not be allowed to work	1. strongly disagree 2. disagree 3. neither agree or disagree 4. agree 5. strongly agree

[1] Number of questions asked to assess factor.

[2] These factors are indirect measures of attitude.

[3] The patients were asked to finish the sentence with the option that was most applicable to their situation.

[4] These factors are indirect measures of subjective norm.

[5] These factors are indirect measures of perceived behavioral control.

[6] The knowledge questions covered the subject's knowledge of the causes of TB, ways of transmitting TB, curability of TB, and symptoms of TB.

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CHAPTER 4

Care seeking behavior among individuals with tuberculosis symptoms in Jogjakarta province, Indonesia: a community-based study

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Submitted

SUMMARY

Background: Care seeking behavior of individuals with symptoms of tuberculosis (TB) is a critical factor in early detection and treatment. Thorough understanding of determinants of the care seeking process will help TB program managers to improve TB case finding. The objective of this study is to assess determinants of care seeking behavior in individuals with TB symptoms at the population level.

Methods: A cross sectional survey was conducted. Adult individuals with cough longer than two weeks were interviewed. Data on sociodemographics, TB status, onset of TB symptoms, TB knowledge , type of health facility visited, and duration of each visit were collected.

Results: In total, 746 respondents were interviewed. Approximately 10% of TB suspects had not yet sought care. Of those who had sought care, less than half presented directly to medical health care providers. Female gender and multiple symptoms were associated with care seeking action. The median duration of patient delay was 17 days. Male gender and unemployment were associated with longer delay in presentation.

Conclusions: The patient delay of individuals with TB symptoms in Jogjakarta province is relatively short. Efforts need to be focused on encouraging TB suspected individuals to seek appropriate services through health education and quality improvement of health providers.

4.1 | INTRODUCTION

Early detection and treatment are crucial determinants of successful tuberculosis (TB) control. Reducing diagnostic delay shortens the infectious period and improves treatment outcome, which will lead to a significant reduction in transmission of TB in the community.[1,2] As TB control programs rely on passive case finding, care-seeking behavior of TB patients is a critical factor for early diagnosis.

Many similar studies on care seeking behavior among TB patients have been conducted. [3-5] These reports found that patient delay, often defined as a duration from the onset of TB symptoms to the first visit to a health care provider, is on average longer than 4 weeks in many developing countries; this is considered an acceptable duration of diagnostic delay for smear-positive TB cases.[6] However, these were mostly facility based studies at TB control program-affiliated health facilities. Therefore the results may underestimate patient delay, as many TB cases in developing countries are diagnosed and treated by private health providers.[7] Also, some patients are likely never diagnosed, and are thus missing entirely. Despite evidence suggesting a significant contribution of patient delay to overall diagnostic delay,[3-5] only a limited number of studies have explored determinants of patient delay or the decision to initiate care-seeking action at the community level.[8-13] While the time dependent nature of patient delay is variable, the above mentioned studies did not take this attribute into consideration when exploring determinants of patient delay.

Several studies on care seeking behavior of TB patients were conducted in Indonesia.[14-16] However, these studies were all performed at TB control program-affiliated health facilities, thus suffer from the same limitations as many previous health facility-based studies on TB patients' care seeking behavior. Our study aims to explore the determinants of care seeking behavior of individuals with TB symptoms at the population level. We also quantify the magnitude of patient delay and its determinants. To this end, we did a cross sectional survey in the community among individuals with TB symptoms.

4.2 | METHODS

Study setting

Jogjakarta province is located in the central part of Java Island and has five districts. The population is approximately 3.5 million, with 44% living in rural areas. The demographic composition is predominantly adult, with 51% being 25-59 years old and 13% over 59 years old. [17] The province has a well functioning health system consisting of approximately 2000 private practitioners, 117 health centers, 9 public hospitals, and 24 private hospitals. It has a relatively

well-established TB control program, implemented using the World Health Organization (WHO) endorsed Direct Observed Treatment Short-course (DOTS) strategy. The backbone of the local TB program is a network of all 117 health centers, 18 public and private hospitals, and 5 lung clinics. The estimated TB incidence in the province in 2004 is 63/100 000.[18]

Data collection

We conducted a cross sectional survey using a modified WHO/Expanded Program on Immunization (WHO/EPI) rapid survey.[19,20] We selected three districts: Jogjakarta, Sleman, and Bantul to represent urban, suburban, and rural areas, respectively. Fifty communities (clusters) were randomly selected with probability proportionate to population size. In each cluster the first household to be visited was randomly selected. The nearest household from the first selected household was the next visited, and so on until 15 eligible respondents were recruited. Inclusion criteria were age 15 years or above, persistent cough for more than two weeks, and willingness to participate. Exclusion criteria were reported chronic respiratory problems (asthma, chronic obstructive pulmonary disease), not understanding the survey procedure or questions, or refusal to participate.

Seven interviewers were trained to perform data collection. Interviews were conducted in the Indonesian language. A field manager reviewed the results daily for validity of respondents' responses. A re-interview was conducted if considered necessary. Patients were interviewed using a structured quantitative questionnaire.

The questionnaire consisted of questions on socio-demographics, TB status, onset of TB symptoms, knowledge of TB (cause, symptoms, transmission, and treatment), number and type of health facilities utilized, duration between symptom onset to the first care seeking action, and subsequent visits prior to the interview. Perceived accessibility (accessible distance, flexibility of service time, ease of transportation), affordability (price of service and transportation), service quality (good reputation, provider hospitality, strong medicine), and the role of significant others (families, neighbours, and friends) in determining the first health facility utilized were also recorded.

We defined patient delay as duration between reported onset of the symptom to the reported first medical health care provider visit, which was not necessarily the first care seeking action.[21] Medical health care providers consisted of private practitioners, health centers, hospitals, and lung clinics, while alternative health providers consisted of traditional medicine practitioners and local kiosks or pharmacies that sell over the counter (OTC) drugs. The alternative health providers do not have access to TB diagnostic facilities, thus visiting these providers will not lead to a confirmed TB diagnosis.

The interview results were double entered by research assistants and the two resulting files compared to evaluate for typing errors, missing data, and inconsistencies before analysis.

Statistical analysis

Data were analysed using SPSS for Windows version 16. Logistic regression was used to analyse the determinants of suspected TB patients who initiated care-seeking action versus not initiating action. Second, it was used for those visiting medical health care providers among suspected TB patients starting the care seeking process versus visiting alternative health providers. Cox proportional hazard model (survival analysis) was used to analyse determinants of patient delay. We assumed that patients who had not yet visited a medical health care provider might later on visit one. Therefore, we took the duration of care seeking process or illness of these individuals into consideration in the survival analysis as right censored at the point of interview. Factors were first tested univariately. Factors with P values <0.20 were included in the multivariate model and entered using the backward LR method. Factors with P values <0.05 were maintained in the final model. Duration of patient delay was presented as median with inter-quartile range (IQR). The median of patient delay was calculated using the Kaplan-Meier survival method.

Ethical consideration

Prior to recruitment, written consent was obtained from all respondents or their guardian in case of respondents aged 15-18 years. Respondents were recommended to have a sputum smear examination at the nearest health center following the interview process. The study received ethical approval from the ethical committee of the Faculty of Medicine, Gadjah Mada University.

4.3 | RESULTS

Of those individuals who were identified as having symptoms suspected for TB, all agreed to participate. A total of 746 individuals with cough for more than two weeks were interviewed (Table 4.1). Approximately 62% of respondents were female, 44.5% were sixty years old and older, 70.1% were married, and 67.3% had an elementary or lower education level. More than one-third of respondents were unskilled labourers, 20.1% were self-employed, 9.2% unemployed, and 26.1% were housewives. The majority of respondents were not poor and lived either in rural or suburban areas. Of the 746 respondents, 11.3% (n=84) were not (yet) seeking care, 40.7% (n=304) went directly to medical health care providers, mostly at health centers, and 48% (n=358) went directly to alternative health providers, mostly procuring OTC at drug stores or local kiosks.

Table 4.2 shows the determinants of care seeking action. Being female and having multiple symptoms were the only factors associated with seeking care (OR 2.90, 95% CI 1.78-4.72 and OR 1.43, 95% CI 1.16-1.75, respectively). Interestingly, educational status and knowledge about TB did not correlate with the decision to seek care. Of those who did not seek care (n=84), 62% reported mild symptoms, and 19% reported the financial burden as the main reason for not

seeking care. No individuals expressed stigmatization as the reason for not seeking care (data not shown).

Table 4.1 | Socio demographic characteristics of the study population and the first care seeking action

Variable	n (%)
Total	746 (100)
Sex	
Male	283 (37.9)
Female	463 (62.1)
Age group	
15-29 years	126 (16.9)
30-44 years	51 (6.8)
45-59 years	230 (30.8)
60-74 years	237 (31.8)
>74 years	102 (13.7)
Marital status	
Not married	45 (6.0)
Married	523 (70.1)
Divorced/widowed	178 (23.9)
Educational status	
No education	232 (31.1)
Primary school	270 (36.2)
Junior high school	101 (13.5)
High school	116 (15.5)
College/university	26 (3.5)
Missing	1 (0.1)
Employment status	
Unemployed	69 (9.2)
Student	12 (1.6)
Housewife	195 (26.1)
Retired	18 (2.4)
Unskilled labor	267 (35.8)
Self employed/business owner	150 (20.1)
Other	35 (4.7)
Socio-economic status	
Poor	159 (21.3)
Not poor	587 (78.7)

Variable	n (%)
District	
Urban	177 (23.7)
Semi urban	286 (38.3)
Rural	283 (37.9)
First care seeking action	
Medical health providers	
Private doctor/paramedic/clinic	139 (18.6)
Health center	148 (19.8)
Hospital/Lung clinics	17 (2.3)
Alternative health providers	
Pharmacy	50 (6.7)
Drug store/local kiosk	234 (31.4)
Traditional medicine	74(9.9)
No action	84 (11.3)

Of those who sought care (n=662), 45.9% (n=304) utilized medical health care providers as the first care seeking action (Table 4.3). Older age (OR 1.38, 95% CI 1.23-1.56), employment status, and perceived good quality of health care providers (OR 4.72, 95% CI 3.12-7.14) were significantly associated with direct visit to medical health care providers, while recommendation from significant others (OR 0.59, 95% CI 0.37-0.94) was significantly associated with visiting alternative health providers as the first care seeking action. Marital, education, socioeconomic, urban-rural status, and knowledge of TB were not associated with first care seeking action being with medical health care providers.

Of those who sought care (n=662), only 55.0% (n=410) eventually visited medical health care providers at the time of interview (Table 4.4). The median duration of patient delay was 17 days; the lower limit of the IQR was 7 days. The upper limit was unknown, as approximately 45% of the respondents had not yet visited medical health providers at the time of interview and were right censored. Many of these cases were censored above the median value (Figure 4.1), but most had initiated their care seeking process with alternative providers. Being male (HR 0.66, 95% CI 0.51-0.86), a student (HR 0.28, 95% CI 0.09-0.93), and self-employed (HR 0.60, 96% CI 0.39-0.92) were significantly associated with longer patient delay. The median duration of patient delay among males was considerably longer than females (52 versus 14 days, respectively). Having good knowledge of TB did not lead to shorter patient delay. Age, marital status, education, socioeconomic status, and urban-rural status also did not correlate with duration of patient delay.

Table 4.2 | Determinant of TB suspect individuals who initiated care-seeking process after the onset of TB symptoms. N denotes TB suspect individuals and n represents TB suspects who initiated care-seeking action. Missing data is reported but not included in the statistical analysis.

Variable	n/N	%	Univariate			Multivariate (Backward LR)		
			OR	95% CI	p	OR	95% CI	p
All	662/746	88.7						
Sex								
Male	235/283	83.0	1					
Female	427/463	92.2	2.42	1.53-3.84	<0.001	2.90	1.78-4.72	<0.001
Age group (years)					0.051			
15-29	110/126	87.3	1					
30-44	47/51	92.2	1.71	0.54-5.39	0.36			
45-59	211/230	91.7	1.62	0.80-3.27	0.18			
60-74	212/237	89.5	1.23	0.63-2.41	0.54			
>74	82/102	80.4	0.60	0.30-1.22	0.16			
Marital status					0.39			
Not married	40/45	88.9	0.92	0.35-2.43	0.85			
Divorced/widowed	153/178	86.0	0.71	0.42-1.17	0.17			
Married	469/523	89.7	1					
Educational status					0.19			
No education	198/232	85.3	1					
Primary school	243/270	90.0	1.55	0.90-2.65	0.11			
Junior high school	89/101	88.1	1.27	0.63-2.58	0.50			
High school	109/116	94.0	2.70	1.15-6.23	0.023			
College/university	23/26	88.5	1.32	0.38-4.63	0.67			
Missing	0/1	0.0						

Variable	n/N	%	Univariate			Multivariate (Backward LR)		
			OR	95% CI	p	OR	95% CI	p
Employment status					0.008			
Unemployed	55/69	79.7	1					
Student	9/12	75.0	0.76	0.18-3.20	0.71			
Housewife	186/195	95.4	5.30	2.16-12.81	<0.001			
Retired	15/18	83.3	1.27	0.32-5.02	0.73			
Unskilled labor/ farmer	231/267	86.5	1.63	0.82-3.24	0.16			
Self employed	136/150	90.7	2.47	1.11-5.53	0.027			
Other*	30/35	85.7	1.53	0.50-4.70	0.46			
Socio-economic status								
Poor	137/159	86.2	1					
Non poor	525/587	89.4	1.36	0.81-2.30	0.25			
Urban-rural status					0.064			
Urban	165/177	93.2	1.75	0.88-3.50	0.11			
Sub-urban	246/286	86.0	0.78	0.48-1.29	0.34			
Rural	251/283	88.7	1					
# of symptoms°								
1	86/105	81.9						
2	184/214	86.0						
3	183/203	90.1						
>3	209/224	93.3						
# of symptoms (continuous)			1.37	1.13-1.66	0.002	1.43	1.16-1.75	0.001
TB Knowledge					0.080			
Good	184/206	89.3	1.36	0.79-2.35	0.26			
Average	202/219	92.32	1.94	1.08-3.48	0.027			
Low	276/321	86.0	1					

**Other: Military/Police/Civil servant/Professionals/Private sector employees*
°Symptom including: cough, cough with sputum, cough with blood, fever, shortness of breath, chest pain, weight lost

Table 4.3 | Determinant of TB suspect individuals who selected medical health providers (private practitioners, health centers, hospitals, lung clinics) as their first care seeking action. N denotes TB suspect who initiated care-seeking action and n represents TB suspects who visited medical health providers as their first care seeking action.

Variable	n/N	%	Univariate			Multivariate (Backward LR)		
			OR	95% CI	p	OR	95% CI	p
All	304/662	45.9						
Sex								
Male	98/235	41.7	1					
Female	206/427	48.2	1.30	0.94-1.80	0.11			
Age group (years)								
15-29	33/110	30.0						
30-44	19/47	40.4						
45-59	89/211	42.2						
60-74	106/212	50.0						
>74	57/82	69.5						
Age (continuous in 10 years)			1.32	1.20-1.47	<0.001	1.38	1.23-1.56	<0.001
Marital status					0.051			
Not married	14/40	35.0	0.68	0.34-1.33	0.26			
Divorced/widowed	82/153	53.6	1.45	1.01-2.10	0.047			
Married	208/469	44.3	1					
Educational status					0.069			
No education	108/198	54.5	1					
Primary school	105/243	43.2	0.63	0.44-0.93	0.018			
Junior high school	36/89	40.4	0.57	0.34-0.94	0.028			
High school	46/109	42.2	0.61	0.38-0.98	0.039			
College/university	9/23	39.1	0.54	0.22-1.30	0.17			
Employment status					<0.001			0.044
Unemployed	31/55	56.4	1			1		
Student	2/9	22.2	0.22	0.04-1.16	0.08	0.88	0.15-5.21	0.89
Housewife	105/186	56.5	1.00	0.55-1.84	0.99	1.28	0.66-2.48	0.47
Retired	9/15	60.0	1.16	0.36-3.71	0.80	1.12	0.33-3.88	0.86

Variable	n/N	%	Univariate			Multivariate (Backward LR)		
			OR	95% CI	p	OR	95% CI	p
Employment status *(continued)*					<0.001			0.044
Unskilled labor/ farmer	102/231	44.2	0.61	0.34-1.11	0.11	0.78	0.41-1.49	0.46
Self employed	45/136	33.1	0.38	0.20-0.73	0.003	0.54	0.27-1.09	0.09
Other	10/30	33.3	0.39	0.15-0.98	0.045	0.66	0.23-1.89	0.44
Socio-economic status								
Poor	61/137	44.5	1					
Non poor	243/525	46.3	1.07	0.74-1.57	0.71			
Urban-rural status					0.70			
Urban	72/165	43.6	0.85	0.57-1.25	0.40			
Sub-urban	112/246	45.5	0.91	0.64-1.30	0.61			
Rural	120/251	47.8	1					
TB Knowledge					0.24			
Good	76/184	41.3	0.72	0.50-1.06	0.09			
Average	92/202	45.5	0.86	0.60-1.24	0.43			
Low	136/276	49.3	1					
Perceived accessibility of the selected health provider								
Yes	163/368	44.3	1					
No	141/292	48.3	1.17	0.86-1.60	0.31			
Perceived affordability of the selected health provider								
Yes	114/287	39.7	1					
No	190/373	50.9	1.58	1.15-2.15	0.004			
Perceived quality of the selected health provider								
Yes	117/162	72.2	4.31	2.92-6.36	<0.001	4.72	3.12-7.14	<0.001
No	187/497	37.6	1			1		
Significant others recommendation								
Yes	41/108	38.0	0.67	0.44-1.03	0.066	0.59	0.37-0.94	0.027
No	263/552	47.6	1			1		

**Other: Military/Police/Civil servant/Professionals/Private sector employees*

Table 4.4 | Result of Cox regression analysis of the determinants of the patient delay up to the first visit to medical health providers. N denotes TB suspects involved in the study, n represents the number TB suspects' who eventually visited medical health provider.

Variable	n/N	% of censored cases	Median (in days)	Univariate			Multivariate (Backward LR)		
				OR	95% CI	p	HR	95% CI	p
All	410/746	45.0	17.0						
Sex									
Male	129/283	54.4	52.0	0.64	0.52-0.79	<0.001	0.66	0.51-0.86	0.002
Female	281/463	39.3	14.0	1			1		
Age group (years)						0.49			
15-29	58/126	54.0	30.0	1					
30-44	28/51	45.1	14.0	1.25	0.80-1.97	0.33			
45-59	127/230	44.8	14.0	1.32	0.97-1.80	0.08			
60-74	137/237	42.2	16.0	1.28	0.94-1.74	0.12			
>74	60/102	41.2	14.0	1.30	0.90-1.86	0.16			
Marital status						0.14			
Not married	18/45	60.0	NA	0.64	0.39-1.02	0.06			
Divorced/widowed	104/178	41.6	14.0	1.06	0.84-1.32	0.64			
Married	288/523	44.9	16.0	1					
Educational status						0.92			
No education	135/232	41.8	14.0	1					
Primary school	144/270	46.7	17.0	0.90	0.71-1.14	0.40			
Junior high school	52/101	48.5	21.0	0.93	0.67-1.28	0.65			
High school	68/116	43.1	17.0	0.96	0.71-1.28	0.77			
College/university	13/26	50.0	14.0	0.84	0.47-1.48	0.54			
Missing	0/1								
Employment status						<0.001			0.005
Unemployed	39/69	43.5	20.0	1			1		
Student	3/12	75.0	NA	0.37	0.11-1.20	0.096	0.28	0.09-0.93	0.037
Housewife	136/195	30.3	10.0	1.42	0.99-2.03	0.055	0.98	0.64-1.49	0.91
Retired	13/18	27.8	14.0	1.47	0.79-2.76	0.23	1.17	0.61-2.24	0.63
Unskilled labor/ farmer	135/267	49.4	23.0	0.87	0.61-1.25	0.45	0.73	0.50-1.06	0.10
Self employed	67/150	55.3	38.0	0.77	0.52-1.15	0.20	0.60	0.39-0.92	0.020
Other*	17/35	51.4	82.0	0.83	0.47-1.47	0.53	0.76	0.43-1.34	0.34

Variable	n/N	% of censored cases	Median (in days)	Univariate			Multivariate (Backward LR)		
				OR	95% CI	p	HR	95% CI	p
Socio-economic status									
Poor	83/169	47.8	28.0	0.88	0.69-1.12	0.29			
Non poor	327/587	44.3	16.0	1					
Urban-rural status						0.46			
Urban	100/177	43.5	14.0	1.03	0.80-1.33	0.80			
Sub-urban	150/286	47.6	21.0	0.89	0.72-1.12	0.32			
Rural	160/283	43.5	14.0	1					
TB Knowledge						0.55			
Good	108/206	47.6	21.0	1.03	0.81-1.31	0.83			
Average	127/219	42.0	14.0	1.14	0.88-1.47	0.32			
Low	175/321	45.5	20.0	1					

**Other: Military/Police/Civil servant/Professionals/Private sector employees*

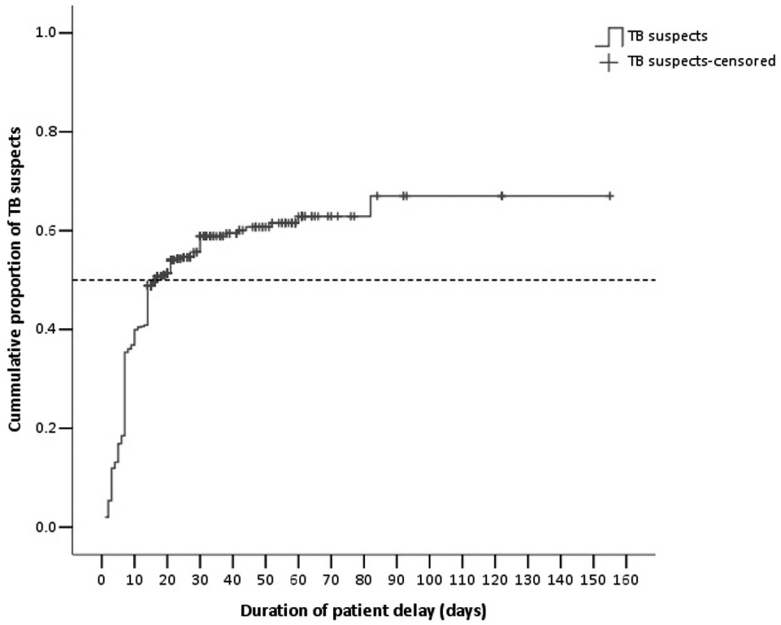

Figure 4.1 | The cumulative distribution of TB suspects and the duration of patient delay (first visit to medical health providers) in days. TB suspects who had not yet visited medical health providers at the time of interview were right censored. Dotted line is the median of the patient delay (17 days).

4.4 | DISCUSSION

In the present study, 11.3% of individuals with TB symptoms did not seek medical care. Of those who sought care, 46.0% went directly to the medical health care providers and only 55.0% had visited medical health care providers at the time of interview. Female gender and have multiple symptoms were associated with care seeking action. Older age and having a good perceived quality of service were the determinants of directly visiting medical health care providers. Male gender, being self-employed, and being a student were determinants associated with longer patient delay. The median duration of patient delay was 17 days. Many of the analyzed socio-demographic determinants did not correlate with care-seeking action, direct visit to medical health care providers, or patient delay. Interestingly, even high educational status and knowledge about TB did not correlate with any part of the care seeking process.

This is one of only a few studies on care seeking behavior of individuals with TB symptoms at the community level. This is the first study to analyze the real life situation, where some TB suspects had not (yet) sought care or visited medical health care providers, into consideration in the analysis of duration and determinants of patient delay. Our study has some limitations. First of all, the WHO/EPI rapid survey method, despite being widely adopted to assess different aspects of health seeking behavior,[22] has intrinsic shortcomings. In particular we did not use a formal household register as a sampling frame but rather generated an ad hoc sampling frame as detailed elsewhere.[19] In the case of non-response, call back is not usually conducted, which may lead to selection bias; for example, many young adult males might not be available during data collection process due to their role as the primary breadwinner for the household. However we tried to revisit the household if the reported individual with symptoms was not available during our visit. Studies suggested that if conducted properly, the rapid survey provides accurate results.[20,22] However, our findings should be interpreted cautiously in stratified analysis, especially when geographical accessibility leads to selection bias.[22] It is fortunate that our study population was easily accessible using available transportation modes. Second, our study was based on reported historical events, which are vulnerable to recall bias. To minimize this bias we only recruited individuals with symptoms present for 6 months or less before the time of interview. Third, we collected self-reported data, which is vulnerable to social desirability bias. This may explain the zero non-response rates, in which only motivated individuals reported their symptoms and were willing to be interviewed. Furthermore, in this Javanese setting, where social harmony is the norm,[23] concealing actual situations may be culturally preferable and refusing to participate may be considered impolite. Despite the abovementioned limitations, we have tried to minimize potential bias where possible and to obtain an adequate sample size; we believe that the study is still largely valid.

The proportion of TB suspects who did not take any action (11.2%) was quite low, and comparable to previous studies in Vietnam.[8,9] Studies in India and Philippines found a markedly higher rate of non-action ranging from 23% to 43%. The proportion of TB suspects who went directly to medical health care providers (46.0%) was lower than in studies from India (88.0%-94.0%) but higher than the rate in the Philippines (25.4%).[10-13,24,25] Contrary to the current study, our previous analysis found that approximately 70% of patients with suspected TB first visited medical health care providers.[15] However, the latter was a facility based study and may suffer from self selection bias, i.e. most patients diagnosed in TB facilities were individuals who proceed directly to medical health care providers when they become ill. The current study, therefore, gives a more accurate estimation of the average TB patients' first care seeking action.

Care seeking behavior involves many complex interrelating factors, such as socio-demographic and economic issues, psychosocial variables, and perceived quality and accessibility of health care providers, which are mostly context specific. Therefore, studies exploring the same factors may have different findings when performed in different populations. We found female gender to be associated with care seeking, as reported in studies from Vietnam.[8,9] However, studies in Ethiopia and India found no correlation between gender and care seeking.[10-13] A systematic review of care seeking behavior studies of different illnesses also found mixed results.[26] Having multiple symptoms was also associated with care seeking. The number of symptoms may reflect the severity of the disease. Many studies suggest that the reason for not seeking care was mostly due to a low perceived severity of symptoms.[9-13,27]

Of those who sought care, older age, employment status, perceived good quality of service, and significant others were associated with first utilization of medical health providers. Similar studies in Ethiopia, Vietnam, and India found no association between age and health provider preference.[9-13] One possible explanation for our study finding is that older people perceive their illness to be more sever and require more immediate medical care than younger persons. Studies in Africa and Indonesia also found a relationship between advice from significant others and care seeking action.[28-30,14] One other study also found perceived quality of service as a determinant for selecting a medical health care provider at the first visit.[28]

We found that the median duration of patient delay was relatively short (17 days) compared to many previous studies in developing countries.[3-5] Furthermore, these studies were mostly conducted at TB-affiliated facilities, thus creating selection bias and likely underestimating the delay. However our finding shows a high proportion of individuals were censored (45%), suggesting that a considerable proportion of suspected TB patients may have a very long patient delay. We also found that men had a considerable longer delay than women. This is in agreement with a study from South Africa,[31] while many studies showed no significant association. [5,13,32,33] However, a systematic review of studies evaluating different diseases suggests that men are usually less likely than women to seek help from health professionals.[26] Being self-

employed was also associated with longer patient delay. This may be due to the fact that self-employed individuals work in informal sectors and earn their income on a daily basis. Thus, they waited until symptoms were significant before pursuing care.

Previous studies suggest that a lower level of education and lack of TB knowledge would be associated with longer patient delay,[3,5] Our study, on the contrary, found that knowledge of TB did not correlate with care seeking or patient delay. As cough is a very prevalent illness in these areas, which may be attributed to the high prevalence of smoking in Indonesia (46.8% among adult males in 2008),[34] one possible explanation is that even people with proper knowledge of TB may expect their symptom to be due to a less-threatening illness.

We found a relatively short patient delay, no association between TB knowledge and patient delay, and only gender and employment status as significantly correlating with longer delay. Thus improving general TB awareness does not seem to be an adequate strategy. In fact, a shorter patient delay can be counterproductive, as the early symptoms of TB may be difficult to recognize, which could result in a longer health system delay. However, with only 55.0% of suspected TB patients having visiting medical health care providers, results should be analyzed with caution. Our findings, however, show that only 11.3% of patients with suspected TB did not (yet) seek care, and approximately 33% had visited alternative health providers but not formal medical health care providers. Therefore, the challenge remains in determining how to modify the care-seeking behavior of suspected TB patients who used and remained under treatment from alternative health providers to switch to medical health care providers. Furthermore, our previous model simulations suggest that reducing the duration of patient delay and the proportion of TB patients visiting alternative health providers has a promising impact on preventing TB death and increasing cure rates in this setting.[35]

The absence of a significant perceived barrier to accessing health care providers and recommendation from significant others were the main reason for selecting health care providers. Thus program managers need to develop strategies and social marketing campaigns to promote the DOTS (direct observed treatment, short course) strategy branding in the community, with the primary message of benefits associated with early TB diagnosis, along with free and high quality TB diagnosis and treatment in TB-affiliated facilities. Specific media channels or strategies need to be developed in order to reach male audiences.

Additional health system strengthening strategies are needed, especially to improve the diagnostic capacity of health facilities providing DOTS services. This is important, as our previous study suggested that diagnostic delay in this province may be associated with quality of service in DOTS facilities.[15] Furthermore our current study found that TB suspects considered a good quality of service as an important factor for selecting medical health care providers.

We conclude that patient delay among TB suspects in Jogjakarta province is relatively short. Many socio-demographic determinants and knowledge of TB do not correlate with care seeking behavior or duration of patient delay. Effort needs to be focused on modifying the care-seeking behavior of suspected TB patients who stay with alternative health services through specific health promotion strategies together with improving quality of services among medical health care workers providing TB services.

4.5 | ACKNOWLEDGEMENT

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CHAPTER 5

Diagnostic delay among tuberculosis patients in Jogjakarta Province, Indonesia is related to the quality of services in DOTS facilities

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SUMMARY

Objectives: Understanding determinants of care seeking pattern and diagnostic delay among TB patients diagnosed at DOTS facilities in Jogjakarta, Indonesia.

Methods: We conducted a cross sectional survey among newly diagnosed TB patients in 89 DOTS facilities. We reconstructed their history of care seeking through retrospective interviews. Data regarding socio-demographics determinants, onset of TB symptoms, type of health facilities visited, duration of each care seeking action were recorded.

Results: In total 253 TB patients were included in the study. The median duration of patients' delay was 1 week and the total duration of diagnostic delay was 5.4 weeks. The median number of visits was 4. Many of the patients' socio-demographic determinants did not associate with the care seeking patterns, and no socio-demographic determinants were associated with the duration of diagnostic delay. More than 60% of TB patients started their care seeking processes outside DOTS facilities, however the number of visits in DOTS facilities was higher during overall care seeking process. Surprisingly, patient's immediate visits to a DOTS facility did not correspond to shorter diagnostic delay.

Conclusion: Diagnostic delay in Jogjakarta province was not associated with patients' socio demographic factors, but mainly related with the existing health system providing DOTS services. This suggests that strengthening health system and improving diagnostic quality within DOTS services is now a more rationale strategy than expanding the TB program to engage more providers.

5.1 | INTRODUCTION

Indonesia has the fifth largest number of new tuberculosis (TB) cases worldwide.[1] The Indonesia National TB Program (NTP) adopted the WHO direct observed treatment short course (DOTS) strategy in 1995 and met the global target in 2006.[1] However a considerable proportion of TB patients obtain care from health providers outside NTP. This is due to inadequate DOTS facilities coverage and because many health providers (e.g. hospitals and private practitioners) are not linked to the TB program.[2,3] As a consequence, TB patients may not be treated or not treated early enough in accordance to the international standards of TB care (ISTC).

An effective TB control program requires early diagnosis and immediate treatment. Diagnostic delay is strongly associated with a longer duration of infectiousness, increases severity of the disease, higher need for hospitalization and poor prognosis of disease outcome.[4-7] Both field studies and mathematical modelling suggest that reducing diagnostic delay contributes to the reduction in incidence, mortality rates and disease transmission in the community.[8,9]

Systematic reviews on diagnostic delay studies of TB patients showed that many similar studies had been conducted both in developed and developing countries.[7,10] However, most of these studies focussed on the determinants of patients, health system, or total duration of diagnostic delays. Few studies explored the pathways of the care-seeking process of TB patients in the health systems,[11-13] with no information regarding the determinants of patients' individual movements through different health care services during their care-seeking process. Understanding the care-seeking pattern will help program managers to identify the weak links in the diagnostic process.

In this study, we explored the pathways and determinants of the care-seeking behavior of confirmed TB patients during their diagnostic process in Jogjakarta province, Indonesia. We also assessed the magnitude of diagnostic delay, and explored the associations with previous care-seeking actions. To this end, we interviewed newly diagnosed TB patients in DOTS facilities and recorded their care-seeking process from the onset of symptoms to the time of diagnosis.

5.2 | METHODS

Study setting and population

The study was conducted in Jogjakarta Province, central Java, which has 3.2 million inhabitants, covers an area of 3185 km^2, and has two urban and three rural districts. The province's primary care consists of about 2000 private practices and 117 public community health centers. Both are staffed with doctors, midwives and nurses. This first-level network is backed up by 9 public and 24 private hospitals.

The provincial TB control program relies on a network of all primary health centers, five lung clinics and 18 public and private hospitals. This network is established to ensure that TB patients have access to a good system of monitoring and quality assurance for both diagnosis processes and treatment outcome.

Data collection

Our study was part of a TB program economic evaluation study in Indonesia.[14] The study received ethical approval from the ethical committee of the Faculty of Medicine, Gadjah Mada University and an endorsement from the NTP manager. We included one urban (Jogjakarta municipality) and two rural areas (Kulonprogo and Gunung Kidul districts) in the study. Patients were recruited from all 89 DOTS facilities (public health center, hospital and lung clinic) in these areas. Between November 2006 and February 2007, consecutive new TB patients (smear positive and negative) aged 15 years or older, who consented to participate in the study, were recruited. All patients recruited in the economic evaluation study in Jogjakarta province were included in our study. The sample size was adequate to reach precision of 5% at the 95% confidence level for an expected frequency of 60% TB patients starting their care-seeking process outside DOTS providers. Upon receiving the patient's consent, a TB worker arranged an interview schedule. The interview was conducted in the patient's house or a health facility depending on the patient's preference. Four interviewers were trained to perform data collection. Interviews were conducted in the Indonesian language. A field manager reviewed the results daily for validity of respondents' responses. A re-interview was conducted if considered necessary.

Patients were interviewed using a structured quantitative questionnaire. They were asked about socio-demographics (age, sex, occupation, marital status, socio-economic level), onset of TB symptoms, number and type of health facilities visited during the care-seeking process, time from onset of symptoms to the first care-seeking action (patient delay), and time from consecutive visits to health facilities to TB diagnosis. Provider delay was defined as the cumulative time from the first health provider visit until TB diagnosis. The total duration of diagnostic delay was the sum of patient delay and provider delay. Socio-economic status of individuals was measured by the status of their households.[14-16]

We constructed a full retrospective history of TB patients' care-seeking process from the onset of symptoms to the moment of diagnosis in DOTS facilities. Each care-seeking action, such as visit to health facility, buy over the counter (OTC) or traditional (herbal) medicine was recorded as one visit. We divided the type of care providers into three categories i.e. Alternative, Non-DOTS and DOTS services. The Alternative services consisted of all non-modern western medicine health providers (e.g. traditional healers) and self-medication, both using traditional or modern OTC medicine.[17] Non-DOTS services consisted of modern health facilities outside the TB program (e.g. private practitioners and hospitals); DOTS services consisted of all health providers involved

in the TB program. DOTS status was based on the current list of facilities involved in TB program in the Jogjakarta Province. If a patient visited a health facility outside Jogjakarta Province, facility involvement was verified through contacting the local TB program officer. If the status could not be verified, we considered the facility as Non-DOTS. This only happened in two cases.

The interview results were double-entered and the two resulting files compared to check for typing errors, missing data, and inconsistencies before analysis.

Statistical analysis

Data were analysed using spss for Windows version 16. We used different regression models to explore the association between various factors with three types of outcomes. A Cox proportional hazard model (survival analysis) was used to assess determinants of duration of diagnostic delay, whereas Poisson regression was used to analyse number of visits. Logistic regression was used to analyse the dichotomous outcome of movement from a particular type of health services to DOTS services or an alternative type. Logistic regression was also used to analyse the proportion of visits to the DOTS services resulting in diagnosis as a TB case. The unit of analysis of the first and second regression models was the individual patient, whilst the unit of analysis in the logistic regression models was a patient visit. Factors were first tested univariately. Factors with $P<0.20$ were maintained in the final multivariate model. Duration of patient delay, diagnostic delay and number of visits are presented as median with inter-quartile range (IQR).

5.3 | RESULTS

A total of 837 new TB patients were registered during the study period. Of those who were registered, 275 patients were interviewed; 56% were males. 74% were 15-54 years old, 56% lived in urban settings, 59% were diagnosed in hospitals or lung clinics, and 65% had sputum smear positive pulmonary TB. No significant differences were found in terms of gender, age group, type of diagnostic facilities and type of TB cases between the TB patients who were recruited and those who were only registered. Only TB patients in urban areas were significantly overrepresented (66% vs. 56%). Of the 275 respondents, 22 extra-pulmonary TB were excluded as they had significantly longer diagnostic delay suggesting a different pattern of care-seeking behavior.

Figure 5.1 shows that slightly more patients (n=96) first visited DOTS services than Non-DOTS (n=79) or Alternative services (n=78). Afterwards, TB patients often repeatedly visited the same type of health services or moved to other services. Most TB patients went through different types of health services before they were eventually diagnosed. However, most of the patients' movement happened in the DOTS services. Furthermore, movements to DOTS services occurred

more often than movement from DOTS to other services. It is noteworthy that repeated visits within the same type of health services were not necessarily visits to the same health care providers (e.g. the same health centers, or hospitals) and the subsequent visits can be attributed to both provider and self-referral.

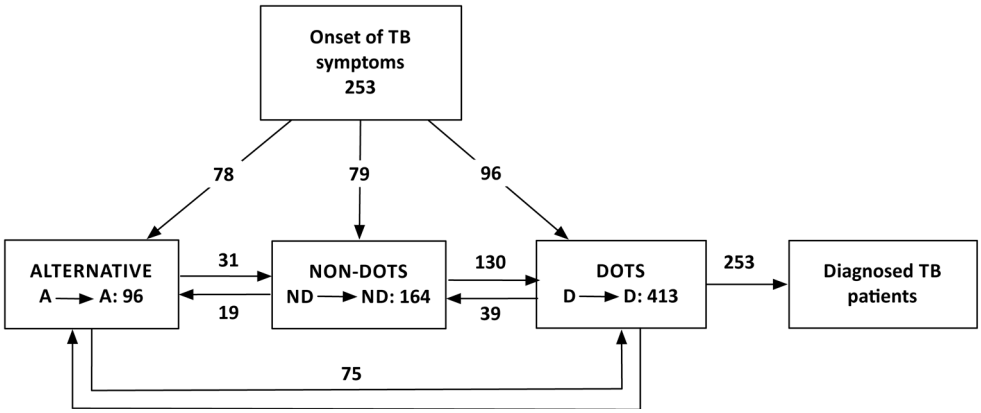

Figure 5.1 | Pattern of TB patients' care seeking process from the time they started seeking care to diagnosis in DOTS facilities. Arrows represent all patients' movements. The first movement of a patient was the first care seeking action after the onset of TB symptoms. The second movement was the movement from the health facility service visited on the first care seeking action to a health facility service visited in the second care seeking action, and so on. These movements continued until TB diagnosis was eventually obtained. The movements occurred within the same type of health service (arrows within boxes) or between different types of health services (arrows between boxes). Most individual patients had multiple visits within and between different health services.

The minimum number of health facility visits before TB diagnosis was one (n=4); the maximum, 17 (n=1). All visits of the latter patient were to DOTS facilities (data not shown). The median number of visits before diagnosis was 4 (IQR 3-6). The median patient delay was 1.0 week (IQR 0.4-2.0 weeks). The distribution of the duration of diagnostic delay was highly skewed, with a median of 5.4 weeks (IQR 2.8-11.5 weeks). Table 5.1 shows the basic demographic characteristics of the study population and the association of these characteristics with diagnostic delay and number of visits. Poor socioeconomic status was associated with a shorter diagnostic delay (HR 1.31, 95% CI 1.01-1.71). However, this factor was not associated with number of patients' visits.

Durations of diagnostic delays were similar between patients who first visited DOTS services and those who visited Alternative or Non-DOTS services, even though TB patients who first visited DOTS services had significantly fewer visits than TB patients who were in Alternative or Non-DOTS services.

There were no significant differences between patients who first visited DOTS and those who used other type of health facilities in term of sex, age, marriage, education, employment and socioeconomic status (Table 5.2). TB patients who lived in urban area were more likely to visit DOTS services than those who lived in rural areas (OR 2.01, 95% CI 1.15-3.50).

Table 5.3 shows that of all movements from Alternative services, 37% (n=75) were to DOTS services. TB patients with poor socio economic status, living in urban areas and with longer duration of symptoms were more likely to move from Alternative to DOTS services (OR 3.46, 95% CI 1.68-7.14; OR 2.28, 95% CI 1.12-4.63 and OR 1.07, 95% CI 1.03-1.11 respectively). TB patients with high school education were less likely to move from Alternative to DOTS services (OR 0.25, 95% CI 0.08–0.74). Movement from Non-DOTS to DOTS services was more common (42%) (Table 5.4). TB patients from urban areas and with a longer duration of symptoms were more likely to move from Non-DOTS to DOTS services (OR 1.79, 95% CI 1.12-2.85 and OR 1.05, 95% CI 1.02-1.09 respectively).

Table 5.5 shows how often visit of the TB patients to the DOTS services resulted in diagnosis (i.e. 253 times, once for every patient) or in a subsequent health care visit. Socio-demographic variables did not play a significant role in determining whether patients were diagnosed or not when visiting the DOTS services. Only patients with more previous visits (OR 2.22, 95% CI 1.77-2.77) were more likely to be diagnosed whilst in DOTS services.

Table 5.1 | Result of Cox regression analysis of the total duration and Poisson regression of the total number of visits during the diagnosis process from reported onset of symptoms to TB diagnosis.

Variable	n	Mean total duration of diagnostic delay (in weeks)	Univariate			Mean of total number of visits	Univariate		
			Hazard ratio	95% CI	P		B	95% CI	P
All	253	9.65				3.97			
Sex									
Male	153	9.92	1	-	-	3.78	0		
Female	100	9.24	1.07	0.83-1.38	0.61	3.97	0.05	-0.08-0.18	0.46
Age group					0.43				
15-24years	54	10.49	0.96	0.66-1.39	0.82	3.81	-0.01	-0.19-0.18	0.95
25-34 years	55	9.18	0.99	0.69-1.43	0.98	3.56	-0.07	-0.26-0.12	0.44
35-44 years	39	12.39	0.71	0.48-1.07	0.10	4.15	0.08	-0.12-0.28	0.44
45-54 years	43	8.38	1.05	0.71-1.56	0.79	4.05	0.05	-0.14-0.25	0.60
>54 years	62	8.50	1	-	-	3.84	0		
Marital status									
Not Married	73	11.23	0.88	0.67-1.15	0.35	3.78	-0.03	-0.17-0.11	0.69
Married	180	9.01	1	-	-	3.89	0		
Educational status					0.44				
No Education	20	9.22	0.82	0.47-1.41	0.47	4.00	0.03	-025-0.30	0.85
Primary school	59	8.84	0.80	0.53-1.21	0.29	3.47	-0.11	-0.33-0.10	0.29
Junior high school	43	9.14	0.82	0.53-1.27	0.37	3.79	-0.03	-0.25-0.20	0.81
High school	93	11.42	0.69	0.47-1.01	0.06	4.09	0.05	-0.14-0.24	0.62
College/university	38	7.40	1	-	-	3.89	0		

Variable	n	Mean total duration of diagnostic delay (in weeks)	Univariate			Mean of total number of visits	Univariate		
			Hazard ratio	95% CI	P		B	95% CI	P
Employment status					0.82				
Unemployed	110	10.35	1	-	-	3.87	0		
Farmer/unskilled labor	63	8.33	1.15	0.84-1.56	0.39	4.05	0.04	-0.11-0.20	0.58
Skilled labor/Self employed	69	9.15	0.14	0.77-1.68	0.51	3.70	-0.05	-0.20-0.11	0.55
Other‡	10	14.19	1.04	0.73-1.48	0.81	3.70	-0.05	-0.38-0.29	0.79
Socio-economic status									
Poor	93	7.43	1.31	1.01-1.71	0.042*	3.69	-0.07	-0.20-0.06	0.30
Not poor	160	10.95	1	-	-	3.96	0		
Urban-rural status									
Urban	163	9.30	1	-	-	3.60	0		
Rural	90	10.28	0.88	0.68-1.14	0.33	4.33	0.19	0.06-0.32	0.004
First visit at:					0.55				
Alternative	78	10.41	0.87	0.64-1.18	0.36	4.29	0.36	0.20-0.52	0.000**
Non-DOTS	79	8.48	1.01	0.75-1.38	0.93	4.47	0.40	0.24-0.55	0.000
DOTS	96	10.00	1	-		3.00	0		

‡Other: Military/Police/Civil servant/Professionals

**Only socio-economic status remained in multivariate analysis*

***History of first visit was the only factor significant in the multivariate analysis (B= 0.36 95% CI. 0.20 – 0.52 p=0.000)*

Table 5.2 | Determinants of TB patients who went to DOTS services as their first care seeking action. N denotes TB patients, and n represents first seeking action in DOTS services. Missing data is reported but not included in the statistical analysis.

Variable	n/N	%	Univariate		
			OR	95% CI	P
All	96/253	37.9			
Sex					
Male	60/153	39.2	1	-	-
Female	36/100	36.0	0.87	0.52-1.47	0.61
Age group (years)					0.23
15-24	16/54	29.6	0.88	0.40-1.95	0.76
25-34	21/55	38.2	1.30	0.61-2.78	0.50
35-44	19/39	48.7	2.00	0.88-4.55	0.10
45-54	20/43	46.5	1.83	0.82-4.07	0.14
>54	20/62	32.3	1	-	-
Marital status					
Not married	25/73	34.2	0.80	0.45-1.41	0.44
Married	71/180	39.4	1	-	-
Educational status					0.77
No education	8/20	40.0	1.02	0.34-3.09	0.97
Primary school	18/59	30.5	0.67	0.29-1.58	0.36
Junior high school	17/43	39.5	1.00	0.41-2.45	1.00
High school	38/93	40.9	1.06	0.49-2.29	0.88
College/university	15/38	39.5	1	-	-
Employment status					0.94
Unemployed	41/110	37.3	1	-	-
Farmer/Unskilled labor	26/63	41.3	1.18	0.63-2.23	0.60
Skilled labor/Self employed	25/69	36.2	0.96	0.51-1.79	0.89
Other‡	4/10	40.0	1.12	0.30-4.21	0.87
Missing	0/1	0.0			
Socio-economic status					
Poor	30/93	32.3	0.68	0.40-1.16	0.16
Not poor	66/ 160	41.3	1	-	-
Urban-rural status					
Urban	71/163	43.6	2.01	1.15-3.50	0.014*
Rural	25/90	27.8	1	-	-

‡*Other: Military/Police/Civil servant/Professionals*

** Only urban and rural status remained in multivariate analysis*

Table 5.3 | Determinants of TB patients moved to DOTS services, when they were in Alternative services. N denotes number of visit in Alternative health services and n represents number of next visit to DOTS services. Missing data is reported but not included in the statistical analysis.

Variable	n/N	%	Univariate			Multivariate (Backward LR)		
			OR	95% CI	p	OR	95% CI	p
All	75/202	37.1						
Sex								
Male	43/122	35.2	1	-	-			
Female	32/80	40.0	1.23	0.69-2.19	0.49			
Age group (years)					0.09			
15-24	23/48	47.9	1.40	0.63-3.16	0.41			
25-34	10/36	27.8	0.59	0.23-1.49	0.26			
35-44	12/25	48.0	1.41	0.53-3.74	0.49			
45-54	11/45	24.4	0.49	0.20-1.21	0.12			
>54	19/48	39.6	1	-	-			
Marital status								
Not married	26/70	37.1	1.00	0.55-1.82	1.00			
Married	49/132	37.1	1	-	-			
Educational status					0.036			0.017
No education	7/18	38.9	0.42	0.12-1.56	0.20	0.59	0.13-2.63	0.49
Primary school	16/34	47.1	0.59	0.19-1.82	0.36	1.02	0.30-3.51	0.97
Junior high school	20/51	39.2	0.43	0.15-1.24	0.12	0.53	0.17-1.64	0.27
High school	20/79	25.3	0.23	0.08-0.63	0.005	0.25	0.08-0.74	0.013
College/university	12/20	60.0	1	-	-	1		
Employment status					0.64			
Unemployed	32/82	39.0	1	-	-			
Farmer/Unskilled labor	19/51	37.3	0.93	0.45-1.91	0.84			
Skilled labor/Self employed	21/57	36.8	0.91	0.45-1.83	0.79			
Other‡	2/11	18.2	0.35	0.07-1.71	0.19			
Missing	1/1	100.0						
Socio-economic status								
Poor	30/58	51.7	2.36	1.26-4.40	0.007	3.46	1.68-7.14	0.001
Not poor	45/144	31.3	1	-	-	1		
Urban-rural status								
Urban	51/121	42.1	1.73	0.95-3.15	0.072	2.28	1.12-4.63	0.023
Rural	24/81	29.6	1	-		1		

Table 5.3 | *Continued*

Variable	n/N	%	Univariate			Multivariate (Backward LR)		
			OR	95% CI	p	OR	95% CI	p
Number of previous visits								
0-2	49/119	41.2						
3-5	18/52	34.6						
>5	8/31	25.8						
Number of previous visits (continuous)			0.95	0.84-1.07	0.38			
Duration of symptoms								
0-3 weeks	23/80	28.8						
4-7 weeks	18/51	35.3						
8-11 weeks	15/35	42.9						
12-15 weeks	6/12	50.0						
≥16 weeks	13/24	54.2						
Duration of symptoms continuous (in weeks)			1.04	1.00-1.07	0.040	1.07	1.03-1.11	0.001

[‡]*Other: Military/Police/Civil servant/Professionals*

Table 5.4 | Determinants of TB patients moved to DOTS services, when they were in Non-DOTS services. N denotes number of visit in Non-DOTS services, and n represents number of next visit to DOTS services.

Variable	n/N	%	Univariate			Multivariate (Backward LR)		
			OR	95% CI	P	OR	95% CI	p
All	130/313	41.5						
Sex								
Male	75/182	41.2	1	-	-			
Female	55/131	42.0	1.03	0.66-1.63	0.90			
Age group (years)					0.60			
15-24	26/60	43.3	1.07	0.54-3.10	0.85			
25-34	32/66	48.5	1.31	0.68-2.53	0.42			
35-44	21/56	37.5	0.84	0.42-1.69	0.62			
45-54	18/52	34.6	0.74	0.36-1.52	0.41			
>54	33/79	41.8	1	-	-			
Marital status								
Not married	34/81	42.0	0.58	0.22-1.52	0.27			
Married	96/232	41.4	1	-	-			

Variable	n/N	%	Univariate			Multivariate (Backward LR)		
			OR	95% CI	P	OR	95% CI	p
Educational status					0.19			
No education	9/29	31.0	0.55	0.20-1.47	0.23			
Primary school	34/70	48.6	1.14	0.53-2.46	0.73			
Junior high school	14/48	29.2	0.50	0.21-1.19	0.12			
High school	54/124	43.5	0.93	0.46-1.89	0.85			
College/university	19/42	45.2	1	-	-			
Employment status					0.063			
Unemployed	61/149	40.9	1	-	-			
Farmer/Unskilled labor	32/96	33.3	0.72	0.42-1.23	0.23			
Skilled labor/Self employed	31/56	55.4	1.79	0.96-3.33	0.066			
Other[‡]	6/12	50.0	1.44	0.44-4.68	0.54			
Socio-economic status								
Poor	49/127	38.6	0.81	0.51-1.29	0.38			
Not poor	81/186	43.5	1	-	-			
Urban-rural status								
Urban	71/150	47.3	1.58	1.01-2.49	0.046	1.79	1.12-2.85	0.015
Rural	59/163	36.2	1	-	-	1		
Number of previous visits								
0-2	61/155	39.4	1.15					
3-5	50/117	42.7	1.33					
>5	19/41	46.3	1					
Number of previous visits			1.06	0.96-1.19	0.22			
Duration of symptoms								
0-3 weeks	48/122	39.3	1					
4-7 weeks	36/93	38.7	0.97					
8-11 weeks	17/51	33.3	0.77					
12-15 weeks	12/24	50.0	1.54					
≥16 weeks	17/23	73.9	4.37					
Duration of symptoms continuous (in weeks)			1.05	1.01-1.08	0.007	1.05	1.02-1.09	0.003

[‡]*Other: Military/Police/Civil servant/Professionals*

Table 5.5 | Determinants of TB patients eventually diagnosed, when they were in DOTS services. N denotes number of visit in DOTS services, and n represents number of TB patients diagnosed in DOTS services.

Variable	n/N	%	Univariate		
			OR	95% CI	P
All	253/714	34.2			
Sex					
Male	153/428	35.7	1	-	-
Female	100/286	35.0	0.83	0.71-1.32	0.97
Age group (years)					0.96
15-24	54/152	35.5	0.99	0.63-1.56	0.95
25-34	55/149	36.9	1.05	0.66-1.65	0.84
35-44	39/120	32.5	0.86	0.53-1.41	0.56
45-54	43/120	35.8	1.00	0.62-1.63	1.00
>54	62/173	35.8	1	-	-
Marital status					
Not married	73/198	36.9	1.09	0.78-1.53	0.62
Married	180/516	34.9	1	-	-
Educational status					0.61
No education	20/53	37.7	1.37	0.70-2.69	0.36
Primary school	59/160	36.9	1.32	0.80-2.18	0.27
Junior high school	43/107	40.2	1.52	0.88-2.62	0.13
High school	93/270	34.4	1.19	0.75-1.87	0.46
College/university	38/124	30.6	1	-	-
Employment status					0.73
Unemployed	110/305	36.1	1	-	-
Farmer/Unskilled labor	63/171	36.8	1.03	0.70-1.53	0.87
Skilled labor/Self employed	69/211	32.7	0.86	0.60-1.25	0.34
Other‡	10/24	41.7	1.27	0.54-2.95	0.58
Missing	1/3	33.3			
Socio-economic status					
Poor	93/251	37.1	1.09	0.59-2.03	0.78
Not poor	160/463	34.6	1	-	-
Urban-rural status					
Urban	163/478	34.1	1	-	-
Rural	90/236	38.1	1.19	0.86-1.65	0.29

Variable	n/N	%	Univariate		
			OR	95% CI	P
Number of previous visits					
0-2	35/228	15.4			
3-5	142/329	43.2			
>5	76/157	48.4			
Number of previous visits (continuous)			2.22	1.77-2.77	0.000*
Duration of symptoms (in weeks)					
0-3	85/252	33.7			
4-7	69/197	35.0			
8-11	39/104	37.5			
12-15	22/56	39.3			
>16	38/105	36.2			
Duration of symptoms continuous (in weeks)			1.00	0.99-1.02	0.69

‡Other: Military/Police/Civil servant/Professionals
**Only number of previous visits remained in multivariate analysis*

5.3 | DISCUSSION

Our study suggests that more than 60% of the patients started their care-seeking process outside DOTS service providers. The median of patients' delay was 1.0 week, the median of diagnostic delay and number of visits before diagnosis was 5.4 weeks and four visits. Many of the patients' socio-demographic determinants were not associated with the care-seeking pattern or the duration of diagnostic delay, and no socio-demographic determinants were associated with the number of patient visits. More than 60% of TB patients started their care-seeking processes outside DOTS facilities, but the number of visits in DOTS facilities was larger during the overall care-seeking process. Surprisingly, a patient's immediate visit to a DOTS facility did not correspond to shorter diagnostic delay.

Our study has three important limitations. Firstly, it was based on reported historical events, which is vulnerable to recall bias. To minimize this bias we only recruited newly diagnosed TB patients. Secondly, we only interviewed patients who were diagnosed at DOTS facilities. This may give an underestimation of the duration of diagnostic delay, as experiences of TB patients diagnosed at facilities outside the DOTS services were not taken into account. To minimize these limitations required a prospective follow up study of TB suspect identified in the community until diagnosis either in DOTS or Non-DOTS services. However, identifying TB suspects without

providing access to proper diagnostic facilities would raise ethical questions, whilst providing access would interfere with the normal care-seeking behavior in their natural environment. Thirdly, measurement of the possible determinants in this study was limited to socio-demographic variables, whilst other studies showed that the determinants of diagnostic delay are more complex than merely socio-demographic characteristics, such as provider's service quality and personal beliefs.[7,10] This limitation may explain partly why we found only few significant results in our study.

We found that the patients' delay in our study (1 week) is shorter than in other studies in high endemic countries (between 2 and 9 weeks),[18-23] but it is similar to patients' delay reported in Italy, New Zealand and Taiwan.[24-26] The reported total diagnostic delay in our study (5.4 weeks) is also relatively short compared to other studies in high endemic countries (8–19 weeks).[4,18-23,27] However it is comparable to studies in Japan and United States,[29,30] which reported durations of 6 and 5 weeks consecutively. This duration is close to the considered an acceptable duration for diagnostic delay of smear-positive TB cases of 4 weeks.[31] Jogjakarta is one of the provinces in Indonesia with a strong TB control program and a well-established health system. The NTP had piloted several TB intervention strategies in this province.[14,32] Furthermore, several national media campaigns have been launched to increase awareness about the TB program in Indonesia. These factors may explain the short patient delay and diagnostic delay found in this study. Surprisingly, many of the socio-demographic determinants in our study were not associated with diagnostic delay. In many other settings, being female,[20,21,30,33] old age,[4,21,26,28,34-36,39] low education level,[26,30,34-38] being single [22,39] and low occupational status [4,40] were associated with longer diagnostic delay.

Low socio-economic status was correlated with shorter duration of diagnostic delay. This finding contrasted with other studies, whereby low socio-economic status is a risk for a longer duration delay.[4,18,19,21,35,41-45] Interestingly, the number of visits was similar between poor and non-poor TB patients. This suggests that the clinical presentation may be more severe in poor patients, so that they seek care earlier than the higher socio economic group. It is known that faster TB progression is related to poor nutritional status.

Our study showed a short patient delay, a longer provider delay, a majority visits in DOTS facilities and only a greater number of visits associated with TB diagnosis. This indicates problem of early detection among health workers in DOTS facilities. Many; studies show that first care-seeking with private providers correlates with several unsuccessful consultations, involving several providers, and thus a high risk of longer diagnostic delay.[19,21,33,37,44,46] Our study, however, found similar durations between TB patients who first visited DOTS providers compared to those who first visited private or alternative providers. This is consistent with a previous study in the same setting.[47] Although the average number of visits was significantly smaller for patient who first visited DOTS facilities, this difference (3 vs. 4.5 visits) is negligible for

the practice of TB control. Interestingly, patients in urban areas were more likely to immediately visit DOTS facilities, which indicate better access to DOTS facilities in urban areas, as more DOTS providers are available (i.e. hospitals and lung clinics). However, patients in urban areas were not diagnosed faster, thus it amplifies the problem of diagnostic delay in DOTS services.

Starting immediately with visiting DOTS facilities does not necessarily correlate with shorter duration of diagnostic delay in Jogjakarta. One possible explanation is that many TB patients may have shopped around for care at various health facilities before a diagnosis of TB was made. Rintiswati *et al.* suggested that many of the TB patients in this province were 'shopaholics'.[48] Another explanation may be the expansion of DOTS in this province. In Jogjakarta, public and private hospitals were involved in the TB program since 2000 as part of public private mix (PPM) policy in Indonesia.[32] A hospital TB case load study in Java suggested that not every hospital involved in the TB program integrated the National TB program guideline into their services, and that there were complex but weak links within hospital's different outpatients units with TB unit.[49] Thus many outpatients with TB symptoms in the hospitals involved in a DOTS program do not have access to proper TB diagnostic procedures and treatments. At health center level, TB diagnosis is poorly performed. Sakundarno *et al.* found that only 14% of sputum samples collected at health centers were of a good quality, and only 24% of TB suspects reported that how to produce sputum samples had been explained to them by health providers.[50] Another study reported that only 55% of lab technicians correctly identified all positive sputum smear slides, whilst only 40% of nurses at health centers had proper knowledge of TB causes.[51]

As many TB patients in developing countries seek care from private providers, advocacy on engaging all providers in TB control is increasing.[52] In the current Stop TB Strategy, WHO endorses the engagement of all providers based on the PPM approach.[38] This is expected to improve case detection, minimize diagnostic delay and therefore improve treatment outcomes. However, as previously mentioned, our study showed that first contact with DOTS providers did not necessarily reduce diagnostic delay, even though the majority of patients visits before diagnosis were to DOTS services. Thus, in a situation where PPM activities have been established, as in Jogjakarta Province, the more extensive network of DOTS providers may become part of the problem. Probandari *et al.* highlighted that approximately 50% of TB patients treated in DOTS affiliated hospitals were not recorded in the hospital TB DOTS register, suggesting that treatment was not in line with the ISTC guideline.[49]

We conclude that diagnostic delay in Jogjakarta province was not associated with patients' socio demographic factors, but mainly related with the existing health system providing DOTS services. This suggests that strengthening the health system and improving diagnostic quality within DOTS services is now a more rational strategy than expanding the TB program to engage more providers.

5.5 | ACKNOWLEDGEMENTS

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CHAPTER 6

Diagnostic work-up and loss of tuberculosis suspects in Jogjakarta, Indonesia

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Submitted.

SUMMARY

Background: Early and accurate diagnosis of pulmonary tuberculosis (TB) is critical for successful TB control. To assist the diagnosis of smear-negative pulmonary TB, WHO recommended the use of diagnostic algorithm. Our study aims to evaluate the implementation of the national tuberculosis program diagnostic algorithm in routine health cares setting in Jogjakarta, Indonesia.
Methods: We prospectively documented the diagnostic work-up of all new tuberculosis suspects until a diagnosis was reached. We used clinical audit forms to record chronologically each step. Data on patients' gender, age, symptoms, type, dates and results of examinations, and final diagnosis were collected.
Results: 754 tuberculosis suspects were recorded. 43.5% of the tuberculosis suspects were lost during the diagnostic work-up in the health centers against 0% in lung clinics. Of those who completed diagnostic work-ups, 51.1% and 100.0% of TB suspects were diagnosed without following the national tuberculosis diagnostic algorithm in health centers and lung clinics respectively. However, the work-up in the latter was generally conforming to international standard for tuberculosis care (ISTC). The diagnostic delays were significantly longer in health centers compared to lung clinics.
Conclusions: There is a need to revise the national TB algorithm and to differentiate it according to level of care. The high rate of patients lost in health centers need to be addressed through implementing patient tracing and better program supervision.

6.1 | INTRODUCTION

Early and accurate diagnosis of pulmonary tuberculosis (TB) is critical for better treatment outcome and reduction of transmission.[1,2] TB diagnosis gold standard is bacilli culture in Löwenstein-Jensen (LJ) media, but it is difficult to provide in many resource poor setting countries. Moreover, LJ culture takes 6-8 weeks, which limits the usefulness of culture as first line diagnostic test. Rapid cultures in liquid media provide faster result but are more expensive and prone to contamination.[3] Therefore, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) endorse sputum smear microscopy examination, with at least, one sputum smear-positive for diagnosis of smear-positive TB.[4,5] For TB suspected patients, with negative sputum results, the diagnostic criteria for smear-negative pulmonary TB encompasses at least two negative smear sputum specimens, radiographic abnormalities consistent with active pulmonary TB, no response to a course of broad-spectrum antibiotics, HIV status and a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy. [4]

WHO recommended the use of diagnostic algorithms to diagnose smear-negative pulmonary TB,[6] and many TB high endemic countries have adopted the algorithm approach.[7] But the effectiveness of the diagnostic algorithms is influenced by local factors such as HIV prevalence, the adoption of the algorithm at frontline health care services and the adherence of local clinicians to the algorithm.[8] Several studies have evaluated diagnostic algorithms, mainly focusing on performance of the algorithm in diagnosing smear-negative TB among HIV patients[8,9] or in specific setting.[10-13] However, studies that evaluate the implementation and adherence to such algorithm in routine settings are lacking but would help program managers to identify and correct possible weaknesses in the diagnostic process. This study evaluated the implementation of the national TB diagnostic algorithm in routine health care setting in Indonesia.

6.2 | METHODS

Study setting

Jogjakarta municipality is an urban area with approximately half a million population. The TB control program in Jogyakarta municipality relies on a network of 18 public health centers, 2 lung clinics and 9 public and private hospitals. The health centers consist of 4 microscopy health centers (MHC), capable of performing smear microscopy and 14 satellite health centers (SHC) that collect sputum specimens from TB suspects, prepare smear slides and subsequently send the slides to the MHC for microscopy reading. The lung clinics have smear microscopy, chest radiography and VCT services. TB incidence in Jogyakarta municipality is estimated at 63/100,000[14] and HIV

prevalence among TB patients is estimated at 1.9%.[15] The TB diagnosis network is supported by an external quality assurance mechanism through quarterly cross-checks by the Provincial Health Laboratory, with technical assistance from the Microbiology Laboratory, Faculty of Medicine, Gadjah Mada University (FM GMU).

Data collection and analysis

The study took place from November 2009 until May 2010 in the all public health centers and lung clinics in Jogjakarta municipality.

All TB suspects registered at health centers and lung clinics were included. The definition of TB suspect from the NTP guideline was employed, in which patient with symptom of cough for more than two weeks is considered as TB suspect.[16] Their diagnostic work-ups, defined as clinical and laboratory examinations received, were prospectively documented. The diagnostic work-up was started from the time a patient was considered as TB suspect, to the time when diagnosis was obtained. A clinical audit form to record chronologically, step-by-step, the diagnostic work-up was developed and tested prior to data collection. Data on patients' gender, age, symptoms, type, dates, sequence and results of examinations, and final diagnosis were collected. Patients who did not return to their previous health facility and complete their diagnostic work-up, were considered lost and not traced back. A trained nurse filled in the audit form in each facility. A field coordinator conducted monthly supervision visit to check the completeness of data collected and to crosscheck with the patients' clinical file and laboratory register.

We compared the actual diagnostic work-up with the national TB diagnostic algorithm (Figure 1-solid lines and boxes). All cases that did not match the standardized pathways were categorized as other pathways (Figure1-dotted lines and boxes).

All data were double entered into a database checked for typing errors, missing data, and inconsistencies. Data were analyzed using SPSS for Windows version 16. Logistic regression was used to analyze factors associated with patient lost, positivity of TB diagnosis among suspects who completed the diagnosis work-up, and smear positivity of TB cases. Factors were first tested univariately. Factors with $P<0.20$ were maintained using backward LR approach in the multivariate model. Chi square was used to assess the background characteristics of patients visited lung clinics and health centers. A median based test was used to assess differences in diagnostic delay between lung clinics, MHC and SHC.

Ethical clearance was obtained from the ethical committee of FM GMU, Indonesia and the ethics committee of the University of Antwerp, Belgium.

6.3 | RESULTS

Seven hundred twenty four (724) patients were registered as TB suspects during the study. The majority, 76.5% (n=554) attended health centers and 23.5% (n=170) attended lung clinics (Figure 6.2). The gender and age distribution of patients consulting at health centers and lung clinics was similar (data not shown). Of patients who consulted health centers, 43.5% (n=241) were lost, while none was lost in lung clinics. Of patients that completed diagnostic work-up, the adherence to the national TB diagnostic algorithm was 0.0% in lung clinics, and 48.9% (n=153) in health centers.

Figure 6.1 shows a summary of the diagnostic pathways in lung clinics and health centers. Most of the patients (n=502, 69.7%) started their diagnostic work-up with sputum smear microscopic examination, but only 21.1% (n=153) followed thereafter the standardized algorithm and completed diagnostic work-up.

One hundred thirty six of 461 (29.5%) suspects who first received sputum smear examinations but had negative results followed later non-standardized pathways (second dashed line on the right of Figure 6.1), with 22.6% (n=104) were diagnosed as non-TB because were clinically better. Approximately 30% (n=218) of patients did not follow the national algorithm from the start of diagnostic work-ups. They started their diagnostic work-up with chest radiography, antibiotics trial, or a combination of these procedures with sputum smear microscopy. It is of note that all TB suspects, who were not lost to follow up, received a sputum smear microscopy examination at one or the other point during their diagnostic work-up.

Patients were lost at every level of the diagnostic work-up (Figure 6.1) and this already occurred at a very early stages. The highest frequency of lost occurred, however after a negative 1st set of sputum smears: in 44% (n=204) of the 461 smear-negative patients. Patient lost was similar in males and females, but varied slightly among different age group (Table 6.1). Patient lost was significantly higher in SHC compared to MHC (OR 2.06, 95% CI 1.41-3.02, p<0.001).

Of those TB suspects who completed their diagnosis process, gender and type of health facility were associated with TB diagnosis. Only older age was associated with TB diagnosis (OR 0.75, 95% CI 0.66-0.86, p<001). There were no significant differences between patients who were diagnosed as TB smear-positive and TB smear-negative in terms of gender, age group and type of health facility where they were diagnosed, only sputum smear as the first examination was associated with TB smear positivity (OR 2.93, 95% CI 1.10-7.77), p<0.03) (data not shown).

The median duration of diagnostic delay for smear-positive, excluding the patients that dropped out, was 1 day in lung clinics and 4 days in MHC and 7.5 days in SHC. The median delay until diagnosis for smear-negative TB and non-TB case was also longer in the SHC compared to the delay in both MHC and lung clinics. The median tests showed that there were significantly longer duration of diagnostic delays in satellite, MHC compare to lung clinics among smear-positive, smear-negative and non-TB patients (Table 6.2).

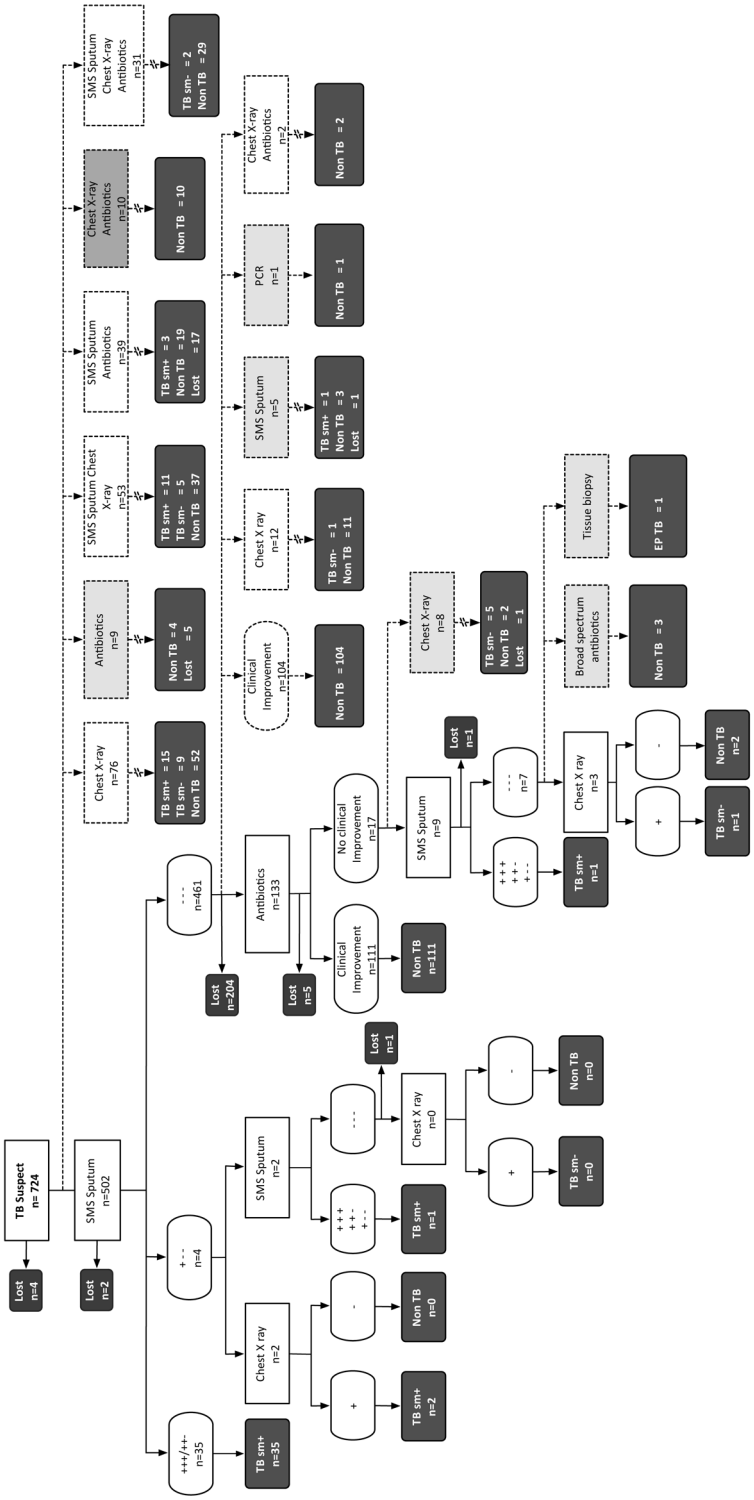

Figure 6.1 | Pathway of diagnostic work-up of TB suspected patients in lung clinics and health centers. The solid line arrows and boxes represent diagnostic work-ups that follow the standardized national TB diagnostic algorithm. The dashed line arrows and boxes represent diagnostic work-up that did not follow the standardized algorithm. Light grey boxes represent pathways that only occurred in health centers. Dark grey box represents pathways that only occurred in lung clinics. Broken arrows represent different diagnostic examination, which are not shown in the graph. All patients who completed diagnostic work-up received sputum smear examination at a certain point during their diagnostic work-up. TB: tuberculosis, EP TB: Extra-pulmonary TB, TB sm+: smear-positive tuberculosis, TB sm-: smear-negative tuberculosis.

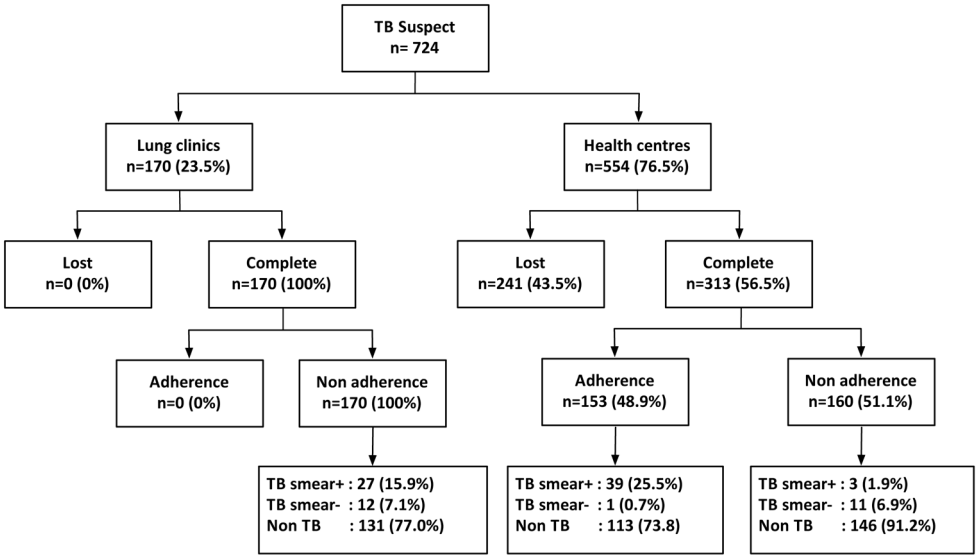

Figure 6.2 | Adherence to the national TB diagnostic algorithm and outcomes of diagnostic work-ups in lung clinics and health centers.

Table 6.1 | Determinants of patient lost among 554 TB suspects in health centers in Jogjakarta municipality.

Variable	n/N	%	Univariate		
			OR	95% CI	P
All	241/554	43.3			
First step work-up					
Sputum smears microscopy	215/497	43.3	1		
Others [†]	22/53	41.5	0.93	0.52-1.65	0.81
Nothing[±]	4/4	100.0			
Sex					
Male	115/262	43.9	1.03	0.74-1.44	0.86
Female	126/292	43.2	1		
Age group (years)					0.10
18-25	28/81	34.6	0.70	0.39-126	0.23
26-35	40/88	45.5	1.10	0.62-1.94	0.74
36-45	47/89	52.8	1.48	0.84-2.59	0.18
46-55	45/92	48.9	1.26	0.72-2.21	0.41
56-65	34/95	35.8	0.74	0.42-1.29	0.29
>65	47/109	43.1	1		
Type of health facility					
MHC	53/168	31.5	1		
SHC	188/386	48.7	2.06	1.41-3.02	<0.001*

[†] Chest X-ray, antibiotics or combination of X-ray, antibiotics with/without sputum smears
[±]Suspects who were directly lost before any examination performed. Not included in the statistical analysis.
**Only type of health facility remained in multivariate analysis.*

Table 6.2 | Duration of diagnostic delay (in days) according to the diagnostic outcome for TB suspects who completed the diagnostic work-up

	Lung clinics		MHC		SHC		P value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
TB smear-positive	27	1 (1-1)	16	4 (2-7)	26	7.5 (5 – 12)	<0.001
TB negative	12	2 (1-4)	4	10 (5-88)	8	13.5 (5 – 14)	0.006
Non-TB	131	2 (1-4)	95	8 (5-15)	164	11 (8 – 11)	<0.001

IQR= inter-quartile range

6.4 | DISCUSSION

This is one of a few studies, focusing on the process of diagnostic work-up in DOTS facilities. Our study found that all diagnosis work-ups in lung clinics and 51% in health centers did not comply to the standardized national algorithm. There were no patient losts in lung clinics, however 43.5% of patients lost was found in health centers. We also found longer duration of diagnostic delay in health centers compared to lung clinics.

Some limitations of our study need to be taken into account. First, we limited ourselves to the lung clinics and health centers, therefore TB diagnostic work-ups at DOTS affiliated hospitals were not documented. However, the hospitals diagnostic infrastructure and technical capacity are similar to the lung clinics, thus we expect the variation of diagnostic pathways in these hospitals are comparable to lung clinics. Second, patients lost were not traced back, but this reflects the actual performance of the health services. Third, culture examination was not performed; since we did not aim to evaluate the effectiveness of the diagnostic algorithm.

Non-adherence to the standardized diagnostic algorithm was high. One important reason was a non-TB diagnosis among patients with a negative first series of sputum smear result and showing clinical improvement. It is a reasonable clinical decision, however the existing algorithm does not accommodate this option. If it is considered acceptable, the non-adherence in the health centers drops to 18.2% (n=57). Other studies in Ethiopia, and India also showed a high rate of non-adherence.[17-19] While, different types of non-adherence exists e.g. sequence of examinations, inadequate examination or absence of recommended examination.[17-19] We found that sequence of examinations was the main reason for non-adherence. Most patients in lung clinics in particular, received multiple examinations at the first consultation, due to the availability of chest radiography. Also specialized chest doctors are more likely to rely on their clinical judgment than on the diagnostic algorithm.

Patients lost in health centers were surprisingly high. A study in Pakistan found lower proportion of patient lost (13%).[20] We found that gender did not correlate with default rate, while a study conducted by Khan *et al.* found that male defaulted more frequently than female.[20] Patient lost in SHC was twice higher than in MHC. Several studies suggested that quality of services is a common reason for defaulting before initiating treatment.[20-22] One possible explanation in our study could be the substantial longer duration of diagnostic work-up in SHC. Another possibility is inadequate information provided to the patients in SHC. A study in similar setting in Java indicated that only 20% of the nurses in health centers provided adequate information on providing sputum sample to TB suspects.[23] As patients were not traced, we did not know if they felt better or consulted other health services. For the latter cases, as the subsequent consultations were all self-referral, we, therefore, did not consider that as part of the TB diagnostic work-ups under the study. There is also a possibility of self-selection i.e. patients with minor symptoms went to the SHC while more severe patients might prefer to go to the MHC or lung clinics, and the latter may also be more motivated to adhere to health providers' orders.

The diagnostic delays are significantly longer in SHC and MHC compared to lung clinics. This depends most probably on the diagnostic capacity available, which influence the timing of different examinations prescribed. All facilities and skills required to perform smear-negative TB diagnosis are readily available in lung clinics, while SHC need to send the sputum smears to the referral MHC and wait for the reporting back of the results. Also in case of prescription of chest radiography by the health centers, most patients need to be referred to higher-level hospitals or lung clinics, which causes further delay. Furthermore, lung clinics tend to perform multiple examinations at the same contact. Although this practice is not in line with the national diagnostic algorithm, it significantly reduced the duration of diagnostic work-up.

All diagnosis at the lung clinics were made without complying with the national diagnostic algorithm, but this considerably reduced the delay to diagnosis and prevented patients lost. Getahun *et al.* have argued that the health service delay introduced by applying TB diagnostic algorithm in a linear fashion could be life threatening particularly among HIV positive patients, as it needs 11-34 days to establish the diagnosis of smear-negative pulmonary TB under the most optimistic scenarios.[7] The Stop TB Partnership endorsed an international standard of tuberculosis care (ISTC) since 2006. The ISTC acknowledges many situations in which the level of care can, and should, go beyond what is specified in the ISTC.[24] While the standardized diagnostic algorithms are developed to improve TB diagnosis sensibility and specificity among health providers within TB control program, the purpose of the ISTC is to provide guidelines, which are more suitable for all practitioners and allows some degree of flexibility. The standard 2 and 4 of the ISTC recommend that all patients suspected of having pulmonary TB and all person with chest radiographic findings suggestive of tuberculosis should have sputum specimens submitted for microbiological examination. The ISTC also acknowledges the fact that no single

provider commonly follows the steps in the TB diagnostic algorithm in a sequential fashion. The algorithm should, therefore, be viewed as presenting an approach to diagnosis that incorporates the main components of, and a framework for, the diagnostic evaluation. Furthermore the approach outlined in the algorithm may be quite costly to the patient and deter her/him from continuing with the diagnostic evaluation. Therefore the ISTC recommends that application of such an algorithm must be done in a flexible manner.[25] Our study found that all TB patients who completed diagnostic work-up, both in lung clinics and health centers, received sputum examination at certain point during their diagnostic work-up, thus still conforming to the ISTC recommendations. Considering the diagnostic capacity of lung clinics, applying ISTC is more suitable than following the standardized national TB diagnostic algorithm. A recent study also suggests that the performance of the WHO based diagnostic algorithm for HIV negative TB suspects is far from optimal.[12] Another study among HIV positive patients also suggests that chest radiography is the best next step after sputum examination as the best first step.[9] Clearly, the Indonesia national TB program (NTP) needs to reevaluate the current diagnostic algorithm and current policy, taking into account possible scenarios at different levels of care, new evidences and recent international policy recommendations.

Futhermore, the high rate of patients lost in health centers needs special attention. Improving service quality through better communication with patients may be the answer. However Khan *et al.* reported that even when patients were counseled, this did not reduce patients lost rate during diagnostic work-up.[20] Faster diagnostic technology may be a better answer. WHO has recently endorsed a new rapid molecular test for TB diagnosis following a successful evaluation in low-income countries field setting.[26,27] The test provides a sensitivity comparable to culture, but with results in less than 2 hours. However, considerable resources need to be invested and much time will elapse before this new method will be generally implemented in Indonesian. Therefore, improving quality of service, implementing patients tracing, offer a diversified national algorithm and ensure better program supervision may be the best option for the moment.

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CHAPTER 7

VCT uptake and HIV prevalence among TB patients in Jogjakarta, Indonesia

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SUMMARY

Introduction: We aimed to establish HIV prevalence and uptake of unlinked anonymous testing and Voluntary Counselling and Testing (VCT) among tuberculosis (TB) patients in Jogjakarta, Indonesia.

Method: We introduced unlinked anonymous HIV testing for TB patients attending DOTS services between April and December 2006. Patients were additionally offered VCT services.

Results: Out of 1269 TB patients who were offered unlinked anonymous testing, 989 (77.9%; 95% CI 75.6-80.1%) accepted. HIV prevalence was 1.9% (95% CI 1.6-2.2%). HIV infections were less frequently diagnosed among TB patients who attended public health center (OR 0.15; 95% CI 0.03-0.70) rather than public hospital. They were more frequent in TB patients with a university education background (OR 5.16; 95% CI 1.01-26.63) and a history of HIV testing (OR 57.87; 95% CI 9.42-355.62). Of the 989 patients who accepted unlinked anonymous testing, only 133 (13.4%; 95%CI 11.5-15.7) expressed interest in VCT. Of these, 52 (39.1%; 95% CI 31.2-47.6) attended VCT. Interest was higher among students (OR 2.35; 95% CI 1.24-4.46) and those offered VCT by public health centers (OR 8.02; 95% CI 5.11-12.60).

Conclusion: The HIV prevalence in Jogjakarta is higher than expected and needs to be monitored cautiously. Unlinked anonymous HIV testing is well accepted and can be implemented with modest additional efforts. Before adopting the WHO recommendation for linked confidential testing, access to VCT services should be improved.

7.1 | INTRODUCTION

Indonesia's National TB Control Program (NTP) has achieved the international targets for case detection (>70%) and treatment success rate (>85%) in 2006.[1] However, recent trends suggest the potential for a dual TB-HIV epidemic. The number of reported AIDS cases in Indonesia has increased 15 fold over the past ten years.[2] Patients with TB-HIV co-infection are reported from hospitals and jails in several provinces. Furthermore, TB is one of the leading opportunistic infections among hospitalized AIDS patients.[3]

The World Health Organization (WHO) recommends HIV testing among TB patients as a key component of the health sector's response to the intersecting TB and HIV epidemics. HIV testing among TB patients can serve as a pillar for integrated surveillance that is much needed to monitor the dual epidemic trend and to enable the development of sound prevention strategies. [4] Moreover, it can facilitate referral for appropriate care, support and treatment for TB patients with HIV infections.[5]

In view of the high HIV infection rates in some settings and the improved prospects for HIV/AIDS treatment, an ethical debate has emerged surrounding HIV testing among TB patients, particularly with regard to unlinked anonymous or "blinded" methods.[4] This led to linked confidential testing through an 'opt in' approach, which has been offered in centers designated for voluntary counselling and testing (VCT).[6] Recently however, WHO encouraged adoption of provider-initiated linked confidential testing and counselling (PITC).[7] In contrast to VCT, PITC is based on an 'opt out' approach in which the clinician initiates counselling when an individual is seeking medical care with signs or symptoms compatible with HIV infection.[6]

Ultimately, decisions about whether and how to implement HIV testing in TB patients, particularly in countries with low-level and concentrated epidemics like Indonesia, should be guided by an assessment of the local epidemiological context and the feasibility of alternative testing strategies. This study aimed to determine the HIV prevalence among TB patients in the different types of health facilities in Jogjakarta, Indonesia, and to assess the feasibility of unlinked anonymous HIV testing for routine surveillance and 'opt-in' linked confidential HIV testing as an entry point for integrated TB-HIV care.

7.2 | METHOD

Study context

Jogjakarta province is located in the central part of Java Island, has 3.2 million inhabitants and covers an area of 3185 square km. The province's primary care offer consists of some 650 private practices and 117 public community health centers staffed with doctors, midwives and nurses.

This first-level network is backed up by 9 public and 24 private hospitals. The provincial TB control strategy involves all 117 public health centers, 5 chest clinics and 18 hospitals (public and private), linking them for monitoring of diagnosis and treatment outcomes as well as quality assurance for smear microscopy.[8]

The province is currently facing a concentrated HIV epidemic, with 92 AIDS cases (2.3 per 100.000 population) reported as of 2006.[2] The HIV prevalence among the general adult population in Jogjakarta is estimated at 0.15-2.0%,[9] though much higher among high-risk groups: clients of commercial sex workers (0.69-1.19%); commercial sex workers (3.6-7.4%); prisoners (3.7-8.0%); and injecting drug users (29.0-52.9%).[2] HIV surveillance in the province is mainly based on routine reporting of AIDS cases by hospitals and on annual seroprevalence surveys among risk groups. Voluntary Counselling and Testing (VCT) services have been established in four hospitals and one non-governmental organization clinic in Jogjakarta municipality. These services are provided free of charge and can be reached from the surrounding districts within 45 minutes by public transport.

Study design

We piloted unlinked anonymous HIV testing among TB patients attending Directly Observed Treatment, Short-course (DOTS) services in Jogjakarta province and additionally facilitated linked confidential testing. The protocol was developed iteratively in consultation with key stakeholders and informed mainly by the WHO guideline on TB-HIV surveillance.[4]

A minimum sample size of 916 was required based on the following assumptions: the WHO estimate of percentage of HIV infection in TB cases in Indonesia (0.6%), a desired precision of 0.05% (with α= 5.0%), and an additional to anticipate 5% poor quality blood specimens.[10] Out of five districts in the province, we selected three districts, which well represented urban, semi-urban and rural settings. Within the three districts, we involved all 88 DOTS facilities: 68 health centers, 16 hospitals, and 4 chest clinics. We weighted the minimum sample size for each facility type to reflect their contributions per district to TB case finding in 2005.

Between April and December 2006, consecutive new TB patients (smear positive, smear negative, extrapulmonary) and relapses, aged 15 and above, who gave informed consent were recruited into the study until the required sample size was reached. The TB case definitions of the NTP guideline were employed.[11] The guideline prescribes diagnosis of smear positive pulmonary TB on the basis of: (1) at least two positive results out of three consecutive sputum samples; or (2) one positive result out of three consecutive sputum samples complemented by chest X-ray indicative of TB. Smear negative pulmonary TB has to be diagnosed based on: (1) negative results from all three consecutive sputum samples; (2) chest X-ray indicative of TB; (3) no clinical improvement after empirical non-TB antibiotic treatment; and (4) physician's

judgment. Persons who were too ill to be counselled or unable to comprehend the procedure were excluded.

Eligible TB patients were recruited during their initial treatment visit and recorded in the TB register to avoid double enrollment. Specifically trained health workers offered TB patients unlinked anonymous HIV testing and additionally the freely available hospital-based VCT services. Their interactions were guided by the content of a brochure covering basic knowledge of HIV transmission and the importance of HIV testing that was subsequently offered to the patient. Access to antiretroviral treatment, as a possible benefit of VCT, was to be explicitly mentioned. If the patient expressed interest in visiting the VCT services, the health worker made an appointment with the testing center and provided a referral slip as well as a modest incentive to cover two return trips to the VCT centers with public transport.

Blood samples were transported from the TB facilities to the provincial laboratory. HIV was assessed in the provincial laboratory using Entebe HIV dipstick (Hepatika Laboratories, Indonesia) and Determine HIV1/2 (Abbot Laboratories, Germany), according to a WHO standard algorithm already in use for annual HIV serosurveys in the province.[12] The provincial laboratory re-tested all positive and 10% of the negative HIV tests with Vironostika HIV Uniform II Antigen Ag/Ab (Biomerieux, France).

The health workers who offered HIV testing also administered on site a short questionnaire (available from the corresponding author), which was designed for this study, but with future adoption for routine recording and reporting in mind. The questionnaire identified the health facility type, and collected information on district, age, gender, education, occupation, marital status of the patients, type and duration of TB symptom and history of HIV testing. All data were double entered and checked for inconsistencies before analysis. Analysis was conducted using SPSS 15.0. (SPSS Inc, Chicago, IL, USA). In univariate analysis, differences between proportions were tested with Chi-square or Fisher Exact test. Logistic regression analysis was performed to identify independent determinants for a positive HIV test and for interest in VCT.

Ethical considerations

Prior to recruitment, informed consent was obtained from all respondents or their guardian in case of patients aged 15 to 18 years. Whether or not a patient consented to participate did not influence the standard of care he/she received. Respondents were encouraged, but never forced to consult VCT centers. The Jogjakarta provincial health office had sufficient supply of Highly Active Antiretroviral Treatment (HAART) regiments, which were freely available to patients taking up VCT. Patient's anonymity was protected by applying unique codes in place of personal identifiers on the data collection forms.

The study protocol was approved by the ethical review committee of the Faculty of Medicine, Gadjah Mada University and endorsed by the relevant Indonesian health authorities.

7.3 | RESULTS

In total, 1681 TB patients were registered by the participating DOTS services in the study districts (Figure 7.1). Among these, 1269 (75.5%) were invited to participate in the study. The remaining 412 (24.5%) were not invited due to exclusion criteria (26.5%), time constraints within the facility (35.2%), and other reasons (38.3%). The predominant 'other' reason concerned the challenging conditions imposed by the severe earthquake that struck the study area in May 2006. 989 of the 1269 (77.9%; 95% CI 75.6-80.1%) invited patients accepted unlinked anonymous testing and were all tested. There were no significant differences between those that accepted or not in terms of gender, age and district. A significant difference in acceptance rates was only observed with regard to the type of health facility where patients were recruited, with lower acceptance rates in hospitals compared with public heath centers ($p<0.001$).

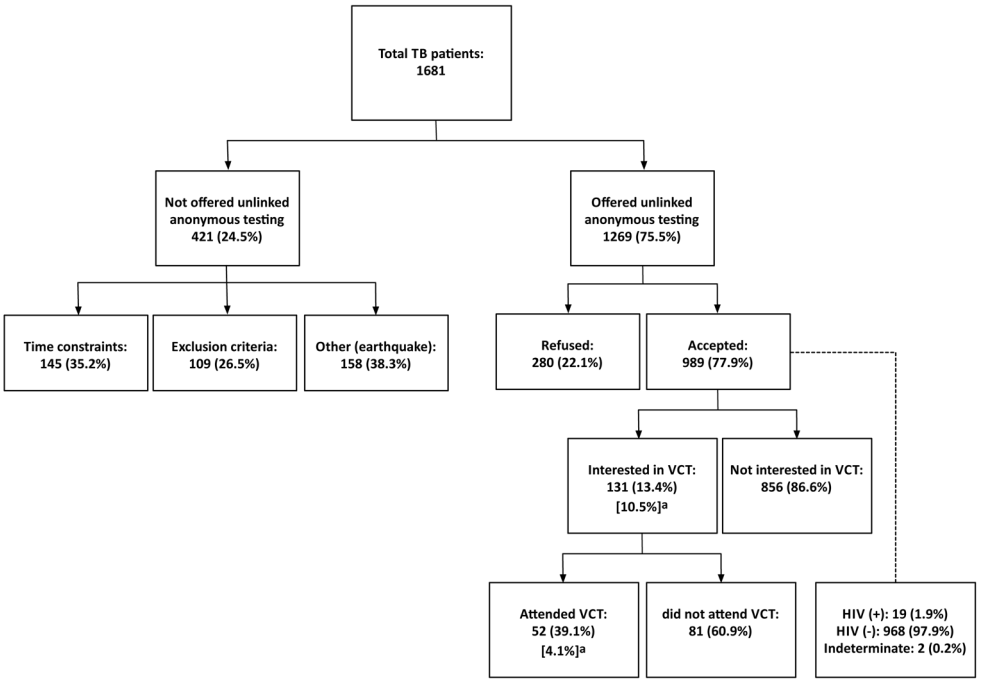

Figure 7.1 | Acceptability of unlinked anonymous HIV testing and voluntary counselling and testing (VCT) among tuberculosis patients in Jogjakarta province, Indonesia in 2006. [a] Denominator = 1269 (offered unlinked anonymous testing).

HIV prevalence among all tested TB patients was 1.9% (95% CI 1.6-2.2%). There were no significant differences between TB patients who were HIV positive and those who were HIV negative in terms of district, gender, age, occupation, marital/relationship status and TB patient categories (Table 7.1). The proportion of HIV positive TB patients were lower in health centers (OR 0.15; 95% CI 0.03-0.70) or chest clinics (OR 0.19; 95% CI 0.05-0.82) than in public hospitals. It was higher in TB patients with University level education background (OR 5.16; 95% CI 1.01-26.63). HIV infections were also more frequently diagnosed in TB patients with a history of HIV testing (OR 57.87; 95% CI 9.42-355.62).

Table 7.1 | Characteristics of TB patients and HIV test result in Jogjakarta province, Indonesia in 2006 (N=987)*

Variable	Total	HIV positive n (%)	Univariate		Multivariate	
			OR	95% CI	OR	95% CI
All	987	19 (1.9)	-	-	-	-
District						
Sleman	309	9 (2.9)	1		1	
Jogjakarta	532	9 (1.7)	0.57	(0.23-1.46)	1.07	(0.30-3.77)
Bantul	146	1 (0.7)	0.23	(0.03-1.83)	0.94	(0.10-9.04)
Health facility where TB patient was diagnosed						
Public hospital	232	11 (4.7)	1		1	
Private hospital	69	1 (1.4)	0.30	(0.04-2.33)	0.20	(0.19-2.15)
Health center	360	3 (0.8)	0.17	(0.05-0.61)	0.15	(0.03-0.70)
Chest clinic	322	4 (1.2)	0.25	(0.08-0.80)	0.19	(0.05-0.82)
Sex						
Male	596	13 (2.2)	1		1	
Female	390	6 (1.5)	0.70	(0.26-1.86)	0.52	(0.13-2.05)
Age group						
15-24 years	222	6 (2.7)	1		1	
25-34 years	249	7 (2.8)	1.04	(0.34-3.13)	0.93	(0.21-4.06)
35-44 years	147	4 (2.7)	1.03	(0.29-3.69)	1.21	(0.20-7.12)
>44 years	367	2 (0.5)	0.20	(0.03-1.09)	0.20	(0.23-1.59)
Education level						
No education, elementary or junior high school	471	4 (0.8)	1		1	
High school	370	8 (2.2)	2.58	(0.77-8.64)	2.86	(0.72-11.40)
University	146	7 (4.8)	5.88	(1.70-20.4)	5.16	(1.01-26.63)

Table 7.1 | *Continued*

Variable	Total	HIV positive n (%)	Univariate		Multivariate	
			OR	95% CI	OR	95% CI
Occupation						
Unemployed/informal	527	10 (1.9)	1			
Student	117	4 (3.4)	1.83	(0.56-5.94)	0.36	(0.06-2.36)
Employed	203	2 (1.0)	0.51	(0.11-2.37)	0.25	(0.05-1.37)
Housewife	140	3 (2.1)	1.13	(0.30-4.17)	2.17	(0.36-13.20)
Married/in relationship						
No	302	8 (2.6)	1		1	
Yes	682	11 (1.6)	0.60	(0.24-1.51)	1.51	(0.34-6.66)
History of HIV testing						
No	962	15 (1.6)	1		1	
Yes	8	4 (50.0)	63.1	(14.4-276.5)	57.87	(9.42-355.62)
Patient category 1						
Relapse/failure	54	1 (1.9)	1		1	
New/intensive phase	932	18 (1.9)	1.04	(0.14-7.97)	1.08	(0.09-13.04)
Patient category 2						
Pulmonary smear positive	606	10 (1.7)	1		1	
Pulmonary smear negative/ Extrapulmonary	380	9 (2.4)	1.45	(0.54-3.89)	0.74	(0.90-13.04)

**Patients with indeterminate HIV test results and with missing values excluded*

Only 133 (13.4%; 95% CI 11.5-15.7%) of the 989 patients who accepted unlinked anonymous HIV testing expressed interest to attend VCT. Eventually, only 52 (4.1%; 95% CI 3.1-5.3%) of the 1269 patients who were offered unlinked anonymous testing actually attended VCT (Figure 7.1). Between the three patient groups (those who expressed no interest for VCT; those who expressed interest but did not attend VCT; and those who attended VCT), there were no significant differences observed in terms of district, sex, education, history of HIV testing and patient categories (Table 7.2). TB patients were more interested for VCT if they were students (OR 2.35; 95% CI 1.24-4.46) or aged between 15-44 years old (OR 1.88; 95%CI 1.13-3.13) (Table 7.3). They were also more interested if they had been offered the service by a public health center (OR 8.02; 95% CI 5.11-12.60).

Table 7.2 | Characteristics of TB patients and response to VCT offer in Jogjakarta province, Indonesia in 2006 (N=989)

Variable	Total	Response (%)			P value
		Attended VCT (n= 52)	Interested but did not attend VCT (n= 81)	Not interested in VCT (n=856)	
All	989	-	-	-	-
District					0.31
Sleman	309	6.8	7.1	86.1	
Jogjakarta	533	4.5	7.9	87.6	
Bantul	147	4.8	11.6	83.7	
Health facility offering VCT to TB patient					<0.001
Public hospital	228	3.1	3.5	93.4	
Private hospital	65	6.2	4.6	89.2	
Health center	365	9.9	16.4	73.7	
Chest clinic	331	1.5	3.0	95.5	
Sex					0.53
Male	598	5.9	8.4	85.8	
Female	390	4.4	7.7	87.9	
Age group					0.05
15-24 years	222	6.3	12.2	81.5	
25-34 years	250	6.0	8.4	85.6	
35-44 years	147	3.4	9.5	87.1	
>44 years	368	4.9	4.9	90.2	
Education					0.19
No education, elementary or junior high school	473	4.6	6.6	88.8	
High school	370	5.7	8.6	85.7	
University	146	6.2	12.3	81.5	
Occupation					0.02
Unemployed/informal	528	4.9	8.0	87.1	
Student	117	8.5	14.5	76.9	
Employed	204	4.4	8.8	86.8	
Housewife	140	5.0	2.9	92.1	
Married/in relationship					0.04
No	302	5.3	11.6	83.1	
Yes	684	5.3	6.7	88.0	

Table 7.2 | *Continued*

Variable	Total	Response (%)			P value
		Attended VCT (n= 52)	Interested but did not attend VCT (n= 81)	Not interested in VCT (n=856)	
History of HIV testing					0.56
No	964	5.1	8.2	86.7	
Yes	8	12.5	12.5	75.0	
Patient category 1					0.40
Relapse/failure	54	9.3	7.4	83.3	
New/intensive phase	934	5.0	8.2	86.7	
Sex					0.94
Pulmonary smear positive	606	5.4	8.3	86.3	
Pulmonary smear negative/ Extrapulmonary	382	5.0	8.1	86.9	

Table 7.3 | Determinants of VCT interest among TB patients in Jogjakarta province, Indonesia in 2006 (N=989)

Variable	N (%interested for VCT)	Univariate		Multivariate	
		OR	95% CI	OR	95% CI
District					
Sleman	309 (13.9)	1		1	
Jogjakarta	533 (12.4)	0.87	(0.58-1.32)	1.24	(0.69-2.23)
Bantul	147 (16.3)	1.21	(0.70-2.01)	1.70	(0.97-2.99)
Health facility offering VCT to TB patients					
Chest clinic/public hospital/ private hospital	624 (5.9)	1		1	
Health center	365 (26.3)	5.66	(3.77-8.50)	8.02	(5.11-12.60)
Sex					
Male	598 (14.2)	1		1	
Female	390 (12.1)	0.83	(0.57-1.21)	0.70	(0.46-1.06)
Age group					
>44 years	340 (9.4)	1		1	
15-44 years	647 (15.5)	1.76	(1.15-2.68)	1.88	(1.13-3.13)
Education level					
No education, elementary school or junior high school	473 (11.2)	1		1	
High school or University	516 (15.5)	1.45	(1.00-2.11)	1.40	(0.90-2.17)

Variable	N (%interested for VCT)	Univariate		Multivariate	
		OR	95% CI	OR	95% CI
Occupation					
Employed/unemployed/ housewife	872 (12.2)	1		1	
Student	117 (23.1)	2.17	(1.35-3.49)	2.350	(1.24-4.46)
Married/in relationship					
No	302 (16.9)	1		1	
Yes	684 (12.0)	0.67	(0.46-0.98)	1.35	(0.79-2.29)

7.4 | DISCUSSION

This is one of the rare TB-HIV co-infection prevalence studies carried out in a setting with a low prevalence -or concentrated epidemic- of HIV. Our study is also the first to document TB patients' interest in VCT in such a setting and to establish the acceptability of unlinked anonymous HIV testing in Indonesia.

We limited our study population to those attending DOTS TB services, as these services detected 73% of TB cases in 2006.[1] While one could expect differences between DOTS patients and those TB patients managed in non-DOTS services in terms of socio-economic status, most of the TB suspects attending non-DOTS services in the study area are eventually being referred to DOTS services.[13] Some of the TB patients attending DOTS services were not invited to participate due to operational reasons and of those invited, some refused. However, a comparison of tested and not tested patients shows no differences in patient profile.

The acceptance rate of unlinked anonymous HIV testing among our TB patients is high (77.9%). There exist no comparable data on unlinked anonymous testing uptake among TB patients as other studies utilized VCT as entry point.[14-18] Studies in another target population, women attending antenatal clinics in Uganda,[19] observed on the one hand a low uptake of unlinked anonymous testing (27%) and on the other hand a high uptake of VCT (73%). In settings where HIV is generalized, one can expect more demand for VCT services than for unlinked testings that does not lead to any direct individual benefit. Moreover, many other differences across settings such as coverage and effectiveness of VCT campaigns, service quality and accessibility, and availability of HAART can influence uptake. Notwithstanding, our findings support the use of an unlinked anonymous HIV surveillance strategy among TB patients in Indonesia, where HIV has not gained high visibility. It could be introduced with relatively modest additional inputs: one day of training for health workers, specimen collection kits and linkage to the provincial laboratory. This should be accompanied by promotion for VCT in the now existing centers, which raises issues that will be discussed further on.

Due to methodological differences our prevalence result may not be directly comparable to results from other studies. Furthermore, HIV testing in TB suspects, rather than in TB cases, would possibly return higher HIV prevalence rates. The difference could be marked in generalized HIV setting where the diagnosis of TB is a challenge,[20] but it is probably negligible in Jogjakarta. At any rate, our data suggests that HIV prevalence among TB patients in Jogjakarta is significantly higher than the national (0.14-0.18%) and provincial (0.15-0.20%) estimates for the general adult population.[9,21] The prevalence we found in TB patients is close to HIV prevalence in risk populations such as commercial sex workers and injecting drug users, which is between 2.42-5.44% in the province.[9] It is also considerably higher than the estimated HIV prevalence of 0.6% among all new adult TB patients in Indonesia.[22] This implies that the magnitude of co-infection in other Indonesian provinces with concentrated HIV epidemics could also be substantially higher than the national average. This further implies that TB patients in Jogjakarta and similar settings in Indonesia should be considered as an important target group for HIV care and prevention.

Potential risk factors for HIV infection in TB patients that could easily and reliably be assessed were investigated, but in the interpretation one has to take into account possible (residual) confounding and endogenicity. Few were found to be significant. This might however reflect the study's lack of power to detect moderate differences at the subgroup level. HIV prevalence was slightly higher among those aged 15-44 years in our study population, but this was not statistically significant. A study in Ukraine did not identify age as a risk factor,[16] while others did.[14,18,23] In our study, the proportion of female TB patients infected with HIV is slightly lower than the male TB patients. This however was also not statistically significant. Other TB-HIV co-infection studies have reported no association,[14,16,24] or that HIV infection was significantly more frequent in males,[18,23] or in women.[17] We also observed a higher HIV prevalence among TB patients with higher education levels. This is in line with the study conducted by Van der Werf *et al.* in Eritrea.[24] The above sometimes-contrasting findings between studies indicate that the importance of demographic characteristics as risk factors for HIV infection in TB patients is largely context bound and related to the dynamics of the local HIV epidemiology.

We find no significant difference in HIV rates between smear positive and smear negative TB patients. Studies in India documented that HIV prevalence was higher among smear positive patients.[14,18] These conflicting results could be attributed to the difficulty of diagnosing smear negative TB, particularly in HIV patients.[25] HIV infection is most often found among TB patients with a history of previous HIV testing in our study. This comes as no surprise, as those who had been interested in being tested in the past probably considered themselves at risk. HIV is also more often diagnosed among TB patients attending public hospitals. This indicates that public referral hospitals in major Indonesian towns could be a strategic entry point for integrated TB-HIV care and surveillance.

Interest in VCT is very low in Jogjakarta. Studies in settings with generalized HIV epidemic reported much higher rates.[15-17] Only Jerene *et al*. in Ethiopia reported individual determinants of VCT interest in TB patients.[17] While some other studies were conducted in other sub-populations, mainly pregnant women, better education;[19,26] self perceived risk;[17,19] marital status;[26] and history of VCT utilization[26] were reported as predictors. We observe higher interest among TB patients who were students or young. This suggests that introduction of VCT testing strategy would be more fruitful if targeted to TB patients with these characteristics.

TB patients offered VCT in a public health center were notably much more likely to be interested. This points to the importance of structural conditions for effective VCT. As health centers tend to see fewer TB patients than other facilities, health center workers have more time to communicate on VCT services. The importance of structural factors for VCT interest was also noted in other studies on TB patients.[15,17] There is a need to ensure supportive conditions, particularly in hospitals, to move forward with integrated TB-HIV surveillance and care.

Finally, referral to VCT services in our study was organized in four central hospitals located in Jogjakarta municipality. Patients interested in VCT were offered incentives for transport. However, this may not have offset the opportunity costs (e.g. being away from work) when travelling to VCT, waiting for the counsellor, undertaking the counselling and testing process and returning for the results the next day. All this poses barriers to attendance. It has, in particular, been shown that providing the result on the same day increases VCT uptake among clients of a sexually transmitted disease clinic and an AIDS information center.[27,28] A strong effect of VCT location on uptake was also observed in studies among groups other than TB patients.[29-31] Expansion of VCT sites into the decentralized DOTS services or establishing mobile VCT units to visit DOTS services may therefore provide substantial leverage.

7.5 | CONCLUSIONS

The HIV prevalence among TB patients in Jogjakarta, Indonesia is higher than expected and there is a clear need to cautiously monitor the trend of co-infection in this and other provinces. We have demonstrated that acceptability of unlinked anonymous HIV testing among TB patients is high, and that such surveillance schemes can be implemented in low prevalence settings without much additional effort. However, if Indonesian health authorities want to adopt the current WHO recommendation for linked confidential testing, they must first boost acceptance for this strategy among TB patients. This requires improving access and ensuring availability of time, skills and facilities for VCT services. Taking into account the available resources, such a large undertaking should initially be targeted at students diagnosed in referral hospitals and prioritize provinces with a more advanced HIV epidemic. Likewise, Ministries of Health in other countries

with emerging TB-HIV epidemics should not delay introduction of HIV testing among TB patients, after thoughtfully considering the appropriate testing modalities.

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7.8 | ETHICAL APPROVAL

The study protocol was approved by the ethical review committee of the Faculty of Medicine, Gadjah Mada University, Indonesia and endorsed by the Expert Committee of the National TB Control Program, Republic of Indonesia.

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CHAPTER 8

Barriers for introducing HIV testing among tuberculosis patients in Jogjakarta, Indonesia: a qualitative study

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ABSTRACT

Background: HIV and HIV-TB co-infection are slowly increasing in Indonesia. WHO recommends HIV testing among TB patients as a key response to the dual HIV-TB epidemic. Concerns over potential negative impacts to TB control and lack of operational clarity have hindered progress. We investigated the barriers and opportunities for introducing HIV testing perceived by TB patients and providers in Jogjakarta, Indonesia.

Methods: We offered Voluntary Counselling and Testing (VCT) to TB patients in parallel to a HIV prevalence survey. We conducted in-depth interviews with 33 TB patients, 3 specialist physicians and 3 disease control managers. We also conducted 4 Focus Group Discussions (FGDs) with nurses. All interviews and FGDs were recorded and data analysis was supported by the QSR N6® software.

Results: Patients' and providers' knowledge regarding HIV was poor. The main barriers perceived by patients were: burden for accessing VCT and fear of knowing the test results. Stigma caused concerns among providers, but did not play much role in patients' attitude towards VCT. The main barriers perceived by providers were communication, patients feeling offended, stigmatization and additional burden.

Conclusion: Introduction of HIV testing among TB patients in Indonesia should be accompanied by patient and provider education as well as providing conditions for effective communication.

8.1 | INTRODUCTION

Indonesia is critical to the global tuberculosis (TB) control efforts and increasingly important in the global HIV control efforts. The country ranks third in the world for TB burden.[1] The number of reported AIDS cases has increased by 15 fold in the past ten years.[2] The rapid increase of new HIV infections in Indonesia makes the epidemic one of the fastest growing in Asia, even though the aggregate national prevalence is as low as 0.16%.[3] By the end of 2007, there were 296 Voluntary Counselling and Testing (VCT) clinics throughout Indonesia, in addition to 153 hospitals which provide free antiretroviral treatment.[3] Patients with HIV-TB co-infection are appearing in hospitals and jails across several provinces and TB is a leading opportunistic infection among AIDS patients.[4] These trends suggest a potential of a dual HIV-TB epidemic, which many other developing countries, particularly in Sub-Saharan Africa are already facing.

WHO Interim Policy on HIV-TB recommends HIV testing among TB patients as an entry point for integrated HIV-TB care and surveillance.[5] However, scaling-up of this policy has been lagging.[6] Concerns over stigmatization which may generate TB patients unwillingness to use HIV associated services (with potential negative impact on TB case detection) and lack of detailed operational guidelines are among the important barriers.[6,7]

Additionally, there is an ethical debate surrounding HIV testing among TB patients, particularly with regard to the unlinked anonymous testing method, in view of the improved prospects for HIV/AIDS treatment.[8] This led to linked confidential testing through an 'opt in' approach, which has been offered in Voluntary Counselling and Testing (VCT) centers.[9] More recently, WHO encouraged the adoption of provider-initiated linked confidential testing and counselling (PITC).[10] In contrast to VCT, PITC is based on an 'opt out' approach in which the clinician initiates counselling when an individual is seeking medical care with signs or symptoms compatible with HIV infection.[9]

Ultimately, decisions about how to implement HIV testing in TB patients, should be guided by an understanding of issues surrounding HIV testing among TB patients from the local stakeholders' perspectives.[11] Studies on groups other than TB patients suggest that knowledge, fear and access may constitute important barriers to HIV testing.[12-14] This study aimed to shed light on the issue through investigating the barriers for introducing HIV testing perceived by TB patients and providers in Jogjakarta, Indonesia.

8.2 | METHOD

Study context

Jogjakarta province is located in the central part of Java island. It is divided into five districts, has 3.2 million inhabitants and covers an area of 3,185 square km. The province's primary care network consists of around 650 private practices and 117 public community health centers staffed with doctors, midwives and nurses. These first line services are backed up by 9 public hospitals and 24 private hospitals. The backbone of NTP's DOTS (Directly Observed Treatment, Short-course) program in Jogjakarta province comprises a network of the 117 public health centers, 5 chest clinics and 18 public and private hospitals.

HIV prevalence among the general adult population in Jogjakarta province is 0.15-2.0%.[15] It is much higher among high-risk groups, e.g. sex workers [4.6 (3.6-6.4)%]; injecting drug users [39.3(29.0-52.7%)]. VCT services have been established in four hospitals and one NGO clinic. The standard procedure in these VCT services, in accordance to WHO guidelines for settings with HIV prevalence ≤10%,[16] requires three HIV tests (two rapid and one Enzyme Immunoassays test). Patients would have to return the next day to obtain all three test results. These VCT services are free of charge for all, including TB patients, through financial support from the Global Fund to fight AIDS, TB and Malaria.

Study design

The study was conducted in parallel to a HIV prevalence survey among TB patients carried out between April and December 2006. The survey targeted TB patients attending all (88) public and private DOTS services in three out of five districts in the province. TB patients in participating health facilities were offered unlinked anonymous HIV testing for survey purpose and additionally free services of four hospital-based VCT centers. Nurses provided patients with standardized information on HIV and VCT services aided by a brochure which was subsequently given to the patient. If the patient expressed interest, nurses made an appointment with a VCT center and provided an incentive to cover transport expenses to the center. Out of 1269 TB patients whom were offered unlinked anonymous testing during the survey, 989 (77.9%) accepted.[17] The HIV prevalence was 1.9% (95% CI 1.6-2.2%).[17] Out of these 989 patients, 133 (13.4%) expressed interest in VCT but only 52 (39.1%) subsequently attended VCT.

The patients were asked whether they would be willing to be recruited for follow up in-depth interviews. We grouped the patients who accepted into four groups: (1) patients who refused unlinked anonymous testing and expressed no interest in VCT; (2) patients who accepted unlinked anonymous testing and expressed no interest in VCT; (3) patients who expressed interest, but did not attend VCT; and (4) patients who attended VCT. Among 1269 patients offered unlinked anonymous testing and VCT service during the parallel survey, 764 accepted to be interviewed.

Figure 8.1 presents the distribution of these consenting patients by the 4 patient categories. We aimed to purposively sample eight patients within each group, keeping in mind the type of health facility attended and additionally age, gender, education and urban/rural residency. Appointments were made by nurses for the in-depth interviews of selected patients.

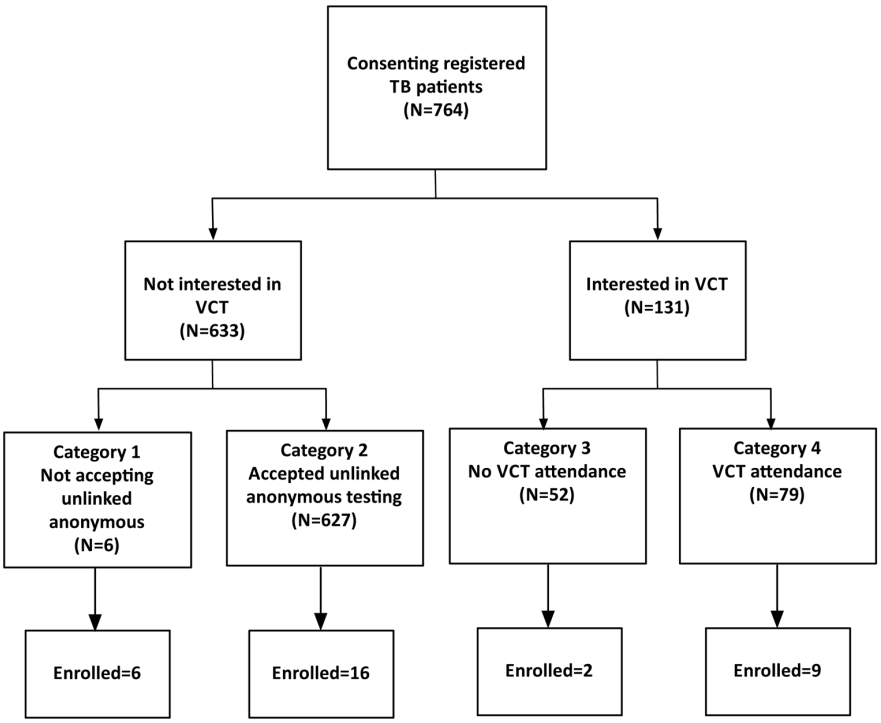

Figure 8.1 | Patient flow.

We interviewed 33 patients: 6 patients for group 1; 16 patients for group 2; 2 patients for group 3; and 9 patients for group 4. We faced difficulties recruiting patients for group 3 because the interview was perceived as a blaming attempt since they had received an incentive to cover transport to VCT, but had not attended. The large number of patients in group 2 was due to the need to increase the number of interviews to make up for the limited information collected from the first 8 respondents related to their very poor knowledge about HIV/AIDS. Patients were interviewed on the basis of an in-depth interview guide on why they were interested or not interested in VCT and probed for factors that hinder or support VCT uptake, e.g. knowledge, attitudes, information given by health providers regarding VCT.

Barriers preventing DOTS services providers to offer VCT services were also explored. We investigated nurses' perceptions through four Focus-Group Discussions (FGDs) sampling the different health facility types: (1) urban health centers; (2) rural health centers; (3) private hospitals; and (4) public hospitals and chest clinics. Within each group, we purposively selected nurses who were most involved in the offering HIV testing among TB patients and represented facilities with variation of patients' interest rate toward HIV testing. Each group consisted of eight to nine nurses. We finally carried out three in-depth interviews with all the specialist physicians providing DOTS services in public and private hospitals and with the three district disease control managers.

The in-depth interviews and FGDs were conducted by the first and second author.

Data analysis

We recorded and fully transcribed all in-depth interviews and FGDs. Data analysis was supported using the QSR N6® software (QSR International Pty. Ltd., Melbourne, Australia, 2002). The analysis was inductive which implies that categories of analysis were not imposed *a priori* on the data but are identified through the analysis process [18]. Transcripts imported into the software database were scrutinized to identify emerging and recurrent themes and a codebook was progressively established and structured. Text units were coded systematically. Coding frequency permitted to identify key issues and trends regarding perceptions of patients and providers about barriers to HIV testing.

Ethical issues

We safeguarded confidentiality of patients' serostatus by unlinking HIV test results from our patients' identities. Informed consent was obtained from all respondents prior to data collection. All collected data were kept anonymous. Ethical approval for the qualitative data collection and the HIV-TB prevalence survey was given by the ethical review committee of the Faculty of Medicine, Gadjah Mada University, Indonesia.

8.3 | RESULTS

Patients' characteristics

Table 8.1 presents the characteristics of the interviewed patients' for the four categories. There were slightly more males then females among the patients. In general, they were predominantly aged between 20-40 years old, married, had secondary education and were offered VCT services by a public care provider. The groups' characteristics were in general similar with the exception of group 1 having slightly more old patients and group 4 having more patients attending public health facilities.

Table 8.1 | Characteristics of enrolled TB patients

Patients' Characteristics	Patients' category*				Total N (%)
	Group 1 N (%)	Group 2 N (%)	Group 3 N (%)	Group 4 N (%)	
Gender					
Male	4 (66.7)	8 (50.0)	1 (50.0)	5 (55.6)	18 (54.5)
Female	2 (33.3)	8 (50.0)	1 (50.0)	4 (44.4)	15 (45.5)
Age group					
15-19 years old	0 (0.0)	0 (0.0)	1 (50.0)	1 (11.1)	2 (6.1)
20-29 years old	2 (33.3)	9 (56.3)	1 (50.0)	4 (44.4)	16 (48.5)
30-39 years old	0 (0.0)	8 (31.3)	0 (0.0)	1 (11.1)	6 (18.2)
40-49 years old	0 (0.0)	2 (12.5)	0 (0.0)	3 (33.3)	5 (15.2)
>49 years old	4 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.1)
Education					
Primary	1 (16.7)	2 (12.5)	0 (0.0)	2 (22.2)	5 (15.2)
Secondary	3 (50.0)	11 (68.8)	0 (0.0)	4 (44.4)	18 (54.5)
Tertiary	2 (33.3)	3 (18.8)	2 (100.0)	3 (33.3)	10 (30.3)
Married					
Yes	4 (66.7)	11 (68.8)	1 (50.0)	5 (55.6)	21 (63.6)
No	2 (33.3)	5 (31.3)	1 (50.0)	4 (44.4)	12 (36.4)
Health facility type					
Public	3 (50.0)	11 (68.8)	2 (100.0)	8 (88.9)	24 (72.7)
Private	3 (50.0)	5 (31.3)	0 (0.0)	1 (11.1)	9 (27.3)
TOTAL	6 (100.0)	16 (100.0)	2 (100.0)	9 (100.0)	33 (100.0

**Patients category:*
Group 1. Not accepting unlinked anonymous and not interested for VCT
Group 2. Accepted unlinked anonymous but not interested for VCT
Group 3. Accepted unlinked anonymous, expressed interest but did not attended VCT
Group 4. Accepted unlinked anonymous and attended VCT

Factors influencing patients' interests in VCT

Many of our respondents (22) were not interested to attend VCT regardless of gender, age, education and marital status. Most patients (24) had no negative feeling towards the HIV test offer, though some (9) clearly felt offended:

> "Frankly, that time I was offended. From the beginning, it was already explained that HIV is transmitted by this and that, not all drug users get it, also not all 'others' [risk groups] get it. And then all the sudden they offered me HIV test?" *23-year-old, male, university student, attended VCT*

Knowledge of many respondents (11) on HIV was poor, ranging from those who had never heard of HIV to those who knew little. Patients with limited knowledge were less interested in VCT:

> "The problem is I don't even know what HF [HIV] is. Is it a new disease? I am just a layperson, so I don't know. It was my son who replied. [I told him] you should respond because you are the one who can answer." *52 year-old, male, employee, not interested in VCT*

> "Well what can I say? That HIV is not scary. It's just another disease. It can be cured." *29-year-old, female, employee, not interested in VCT*

Misconceptions regarding transmission of HIV/AIDS were common:

> "You can get infected through having a [sexual] relationship or through drugs or through smoking cigarettes, that's all I know. I heard it before from stories, you know, on TV." *26-year-old, male, unemployed, attended VCT*

> "I would imagine, that people who get infected by HIV are those who keep changing partners. If one doesn't change partners and does not use illegal drugs, then probably [he/she] can't get infected." *45-year-old, male, construction worker, attended VCT*

Table 8.2 summarizes the relations between main patients' perceptions and VCT interest. Many patients (16) did not report to perceive themselves at risk, or simply did not know enough to attribute risk (10):

> "It's just for a test. It's not because one gets TB that one will get HIV. I've never done anything [wrong]. So I don't mind and I am also looking for a new experience. I am confident that the result will be non-reactive. No worries whatsoever. I am sure, Insya Allah [God's willing], as the doctor already know, that I won't get it. I imagine if one gets it. Oh my God!" *37-year-old, male, employee, attended VCT*

"I mean usually those who get HIV are those who like to go out at night, they like to…well, like commercial sex workers, they're like that, so they must get it. I never go out at night. I hardly leave my house. How can I get HIV?" *29-year-old, female, employee, attended VCT*

Table 8.2 | Patients' perceptions and interest for VCT

Patient's perception		**Interested for VCT**
At risk of being infected	Yes	majority
	No	minority
VCT entails benefits	Yes	roughly half
	No	small minority
HIV patients are stigmatized	Yes	roughly half
	No	minority
Fear of knowing test result	Yes	small minority
	No	vast majority
Access to VCT is a burden	Yes	minority
	No	vast minority

A few patients (7) accepted that they could be at risk and were interested in VCT:

"I've never done anything wrong [risky], or had a [sexual] relationship with someone with HIV. I've never received blood transfusion, never. I don't believe I can get HIV but, there's a possibility I get it because of TB, they say that can make you get infected easily." *45-year-old, male, construction worker, attended VCT*

"No, I was already told [by the health worker] that from …from the lungs it can lead to HIV. So I already knew beforehand." *24-year-old, female, self-employed, attended VCT*

Nearly half of the patients (16) perceived a certain benefit of HIV testing, regardless of whether they reported to perceive themselves at risk or not. Many of these (9) expressed interest towards VCT:

"Well, to be able to know [whether I get] AIDS or …HIV. I was not surprised [to be offered HIV testing]. I wanted to be examined to see if I had other diseases." *26-year-old, male, unemployed, attended VCT*

Some patients (10) perceived some stigmatization towards people living with HIV in the society. Others (8) did not perceive stigmatization, while the remaining participants (15) had no opinion. Most of those who perceived stigmatization (6) however were interested in VCT:

> "[They are] afraid to get infected, yes. Also afraid of … what else…Well, it's a shameful and horrible disease. It's terrifying. So I would be afraid to be isolated, to be treated as someone infectious, as someone who has a pathetic disease. If I can, I will just avoid such disease." *29-year-old, female, attended VCT*

> "Well, the problem is AIDS is... Well, it is a shameful disease. I don't know… The problem is most people who get AIDS are those who do wrong things. People where I live, if they know, they will avoid you immediately." *17-year-old, female, student, attended VCT*

Some patients (5) feared knowing the HIV test result and were not interested in VCT, or initially expressed interest, but eventually changed their mind:

> "Why did it go that far? Saying HIV was like this and that. That made me scared. It's about psychology, I am sure I don't have HIV, but I am not mentally ready. It's enough that I got TB. If for instance I had to be tested for something like that [HIV], it could make things more complicated with so many problems…Oohhh!" *23-year-old, male, student, not interested in VCT*

> "If they take my blood again, then they will test it, then if it turns out that I have that disease, it's like being struck on the head, it's a mental burden. What I am afraid of is that there is no cure yet, you die because of HIV. So if there's no treatment you will just die." *23-year-old male, student, initially expressed interest, but did not attend VCT*

A number of patients (8) also perceived burden for accessing and utilizing VCT. Most of these (6) were not interested in VCT.

> "The process would become too cumbersome. When I think about it, it will just make the process longer and complicated. My intention to seek treatment was just to get my coughs cured." *25-year-old, male, self-employed, not interested in VCT*

> "Well, at that time I thought, if they can do it at that moment, I wouldn't mind. I thought it would take too much time. [I asked] how I would know the result. [They said] if I wanted to know I have to go there. How can I manage the time?" *51-year-old, male, employee, not interested in VCT*

Nurses' perceptions

Table 8.3 depicts the distribution of main issues perceived by nurses across different type of health facilities. Most nurses considered their knowledge of HIV-TB insufficient:

> "At the least, the lab technician, TB worker, nurse and doctor should know about the HIV issue comprehensively. Sometimes we go for training and bring home materials, but we don't really read them. There are patients who really need information on what is the relevance, goals. Yesterday there were two like that. At the end I had to read, I had to open the reference for them. The problem is we ourselves do not understand HIV comprehensively." *Female, nurse, rural health center*

Table 8.3 | Nurses' perceptions of barriers to introduce HIV testing among TB patients*

Perception	Health centers		Hospitals and chest clinics	
	Rural	Urban	Public	Private
'Hard' patients	-	-	+	++
Additional burden	+/-	+/-	++	++
Patients offended	-	-	++	++
Stigmatization	+	+/-	+++	++
Lack of facility	+	+++	+/-	+
Communication difficulty	+/-	+/-	++	+++

** "+++" = critical; "++" = very important; "+" = "important"; "+/-" = less important; "-" = negligible*

Nurses especially in the hospitals perceived that there are patients difficult to deal with, for instance skeptical highly educated patients. Nurses in hospitals also more frequently perceived offended patients as an issue:

> "Once we had a patient who was a high school teacher. We discussed how TB is the leading opportunistic infection for HIV. At the end it became confusing because the theory was not clear. At the end she refused. So how can we deal with patients who are highly educated?" *Female, nurse, rural health center*

> "Even though we have explained this and that…but in the end it doesn't seem to suffice. We really are not effective." *Female, nurse, public hospital*

> "The majority reacts negatively [to the offer]. Patients feel they have never done any wrongdoings. Patients feel they could not get it. Especially the VIPs [Very Important Person – Patients in first class wards]. All the VIPs refused." *Female, nurse, private hospital*

Lack of facilities was an issue perceived by nurses of all types of structures:

> "The room is still mixed [with other patients]. So, if possible, a separate room, which would be better to give patient education. It's inconvenient for us to do it when there are other patients around." *Male, nurse, public hospital*

> "We don't have a special room. Our place until now is semi-permanent, so mixed Maybe it wasn't convenient to offer the test to the patients under such condition." *Female, nurse, rural health center*

Nurses at all facilities perceived some burden due to having to offer an HIV test, particularly with limited time available:

> "We don't have enough staff, for our lung clinic. It's just me and one assistant. If there are many patients we really don't have time, really too overwhelmed to offer [HIV testing]. We have more time in the morning. Those patients who accepted the offer are usually those who come in the morning." *Female, nurse, private hospital*

Nurses in hospitals particularly perceived difficulties in communication, mainly when it comes to patients who are 'hard' to deal with:

> "If they have detailed questions we have difficulty in explaining in details. We can handle general questions, but university students ask a lot of questions which are beyond our knowledge." *Female, nurse, private hospital*

Stigmatization of people living with HIV/AIDS within the community was perceived to be a barrier, particularly in hospitals*:*

> "They had fear, what if they turn out to be [HIV] positive? What would happen when they have to face the community. Some of them are community leaders." *Female, nurse, private hospital*

Strikingly, a few nurses' comments suggested that some nurses stigmatize people living with HIV:

> "We're also worried, what if nurses get it too? It will [then] become very risky for [HIV-negative] patients. We need to isolate them if we can identify them, but until now we don't know who is positive and who is not. Even if it's [just] gonorrhoea and somebody [staff] knows, everyone [staffs' behavior] becomes different." *Female, nurse, public hospital*

Perceptions of decision makers: specialists and disease control managers

Both specialists and disease control managers perceived patient-provider communication and stigmatization as important barriers to VCT uptake:

> "Yes, I've observed that some health workers really can't talk, they can't communicate. Really, it's not that they don't want to do it, but they simply don't have the capacity to do it. So we can't do anything, because they are all we got." *Female, disease control manager, urban district*

> "What I liked about the program [introducing HIV testing among TB patients] was that the TB patients got more attention. There was a demand to the health worker to be able to communicate better. We basically have nurses and doctors who can communicate well, but the majority have limited communication skills and it's not just a matter of education, it's also about personality." *Male, disease control manager, rural district*

Specialists seemed to be more optimistic, giving more emphasis on the managerial challenges than on the operational:

> "The most important thing is that this is integrated at the top level. If this is still under two different national programs then it will be difficult for policy making. If it's integrated at the top level, [we] at the frontline just have to implement. But if at the top there are still two heads, what can we do? It's a sensitive issue, but that's the reality." *Male, senior lung specialist, public chest clinic and private hospital*

> "The management system needs to be repaired. If we're integrating TB and HIV, the management becomes more [crucial]. Especially that we're involving two different national programs together. The financing, the organization…" *Male, junior lung specialist, teaching hospital and private hospital*

They also perceived much less additional burden:

> "I don't feel any [significant] additional burden. As far as I've observed, care delivery was not disrupted. Of course there were some additional things [tasks], but not so much." *Male, senior lung specialist, public chest clinic and private hospital*

However, specialists strongly perceived lack of knowledge on HIV to be a major hindrance to introduce testing, including among colleagues:

> "Even in this hospital, other specialists don't really know [about HIV]. Internal medicine and dermatovenereology [specialists] know quite a bit, but others still ask a lot of questions. They only know it superficially." *Male, internist, private and teaching hospital*

But both district control managers and specialists were not concerned with potential harms to the TB control program's performance:

> "No, I am not worried, the patients were not obliged to be tested … and I've observed no reduction of case reporting so far. Our patients were not running away." *Female, disease control manager, urban district*

8.4 | DISCUSSION

Previous studies examining the motivations and deterrents to HIV testing have been carried out mainly among groups other than TB patients, i.e.: pregnant women;[14,19] drug users; [12,20] poor population;[21] and multiple risk groups.[13,22] Our study contributes to the evolving body of evidence on specific factors that influence introduction of HIV testing among TB patients. This study is limited by qualitative research boundaries. Issues perceived by patients and providers were identified. Although trends emerge, the respective influence of each issue was not quantified. This could be documented through a quantitative survey building on our findings, which points out the key issues to be taken into account. We have focused on contrasts between patients who expressed and did not express interest for VCT because only two patients who expressed interest but did not attend could be interviewed (group 3) and because we interviewed more patients who did not express interest but accepted unlinked anonymous (group 2). This means our findings can be interpreted in terms of VCT uptake rather than interest. Although our findings are context bound, generalization can be considered to other provinces in Indonesia with similar socio-economic, HIV-TB epidemiology and health system characteristics. Some specific findings may hold in similar settings in other countries.

Knowledge

Knowledge of TB patients on HIV and its transmission was strikingly poor with considerable misconceptions, particularly regarding transmission routes. Pregnant women in Hong Kong and China reportedly also had inadequate knowledge regarding HIV transmission.[14,23] Poor knowledge of HIV among the general population in the US and pregnant women in Hong Kong is associated with poor uptake of HIV testing.[14,22] In addition, our findings suggest that knowledge of providers regarding HIV and HIV-TB is also insufficient. A similar lack of knowledge particularly regarding HIV testing among physicians was documented in India.[24,25] The need for professional education to precede VCT programs has also been further affirmed by a study among health workers in China.[23]

Stigmatization

Our data suggests that stigmatization of HIV is present in the Indonesian society. HIV/AIDS has been one of the most stigmatized diseases of the last 20 years.[26] HIV-associated stigma has remained a barrier to testing among pregnant women in China.[23] Perceived stigmatization among mineworkers in South Africa and urban inhabitants in Mali reportedly also deterred them from HIV testing.[27,28] Stigmatization was also considered to be an important barrier to HIV testing by nurses in our study. Our findings further show that there are even nurses who also stigmatize HIV patients. This is similar to the findings from China in which 30% of health workers would not treat HIV patients.[23] However, our data suggests that stigmatization did not play much role on patients VCT interest. Most likely this is because HIV/AIDS in our setting is not yet a widespread disease with high visibility. Other factors outweigh stigmatization when it comes to interest in VCT, e.g. a clear indication of the risk for HIV infection, as effectively communicated by the care provider, coupled with patients' concerns for their personal well-being.

Perceived benefit and risk

Perceived benefit and risk showed considerable influence on VCT interest among our TB patients. Mineworkers in South Africa perceive HIV testing to be more acceptable if antiretroviral therapy (ARVs) become more available.[27] Rates of HIV testing tend to increase as perceived benefits increase. However, the most worrying HIV testing barrier is that people do not perceive themselves at risk.[29] The main stated reason for refusal of HIV screening among TB patients in Tamilnadu, India was 'no risk behavior'.[30] Some drug users in the US indeed did not test for HIV as they had not perceived themselves at risk.[12] Perception of not being at risk persists as a barrier to testing in the US, despite self-report of high-risk behaviors.[13] We likewise encountered a similar tendency among our TB patients.

Fear of knowing the test result

Our findings indicate that fear of knowing test result plays a role in VCT interest. Such fear has also been documented as a barrier among risk populations in the US.[13] A survey among Indonesian drug users in Bali province documented that the most important reason for avoiding HIV testing (55% respondents) was fear of positive results.[20] A qualitative study carried out more recently in the same risk population affirmed the importance of fear of knowing the test result as a barrier.[31]

Perceived burden for utilizing VCT

In addition to transportation, our patients still had to spend considerable time waiting for the counselor to see them, undergo the counseling process, have their blood taken, return home and come back again the next day for the result. The length of the process, linked to the perception

of not being at risk, was enough to deter most patients. Our TB patients were offered transport incentives, but this did not help much. Other studies have documented similar observations. Some Indonesian drug users refused testing because of the long wait and complicated procedures.[20] Accessibility of the VCT centers has been shown to motivate TB patients in India to undergo testing for HIV.[30] Drug users in the US decided to test because the site was immediately available and they need not travel far.[12]

Communication

A main barrier from the providers' side was related to communication. Providers attributed this problem to difficulties to communicate on HIV issues, lack of time and adequate facilities. The disease control managers stated that health workers hardly communicate with patients and that some health workers did not have proper communication skills. Patient-provider communication around HIV in resource-constrained setting seemingly falls short of best-practice standard.[25]

Our findings additionally revealed that communication was influenced by characteristics of the patient, provider and healthcare facility conditions. The worst case scenario occurs when a skeptical highly educated patient comes into contact with a nurse worker with poor communication skills in an overburdened hospital. This highlights the need for creating the material conditions in the health services which make it easier for health workers to interact with patients. Indonesia's health services were designed to cope with acute diseases and the existing service delivery model is clearly not conducive to effective VCT. HIV/AIDS is a complex chronic condition requiring long-term involvement, patient-centered approaches and patient-provider communication starting from the point of HIV testing offer.

The magnitude of communication problems identified in this study was not evenly distributed across health facility types and was more prominent in hospitals especially private. These hospitals are overloaded with patients. They also see more patients who are challenging to deal with. All of these issues have to be managed under conditions of limited time, staff and facilities.

8.5 | CONCLUSIONS

TB patients evidently experienced multiple barriers that can deter them for HIV testing. The study highlighted that patients' and providers' knowledge regarding HIV was inadequate in our setting. The main barriers to HIV testing identified were: fear, burden to access VCT and communication problems. Stigma exists in society and caused concerns among providers, but did not seem to play much role in patients' interest in VCT.

If the Ministry of Health intends to move forward with linked confidential HIV testing among TB patients through VCT, provider's and patient's knowledge need to be improved simultaneously, the general healthcare system strengthened by providing the necessary conditions for effective communication and patient-provider interaction and offering VCT at potential DOTS services that can provide results on the same day. The potential acceptability of the alternative PITC model would be worth to explore further. However, it would clearly require even more demanding pre-conditions and thus should be reserved for settings with more advanced HIV epidemic. In any case, efforts to understand and overcome specific local barriers must accompany efforts to introduce HIV testing among TB patients.

8.6 | COMPETING INTERESTS

The authors declare that they have no competing interests in the subject matter.

8.7 | ACKNOWLEDGEMENTS

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CHAPTER 9

General Discussion

This chapter discusses the main findings of the studies in contrast with the current literature and answers the research questions. The policy implications of the studies are also highlighted.

9.1 | ANSWERS TO THE RESEARCH QUESTIONS

1. What are the patterns of care-seeking behavior among TB suspects in Indonesia?

Our studies focused on four elements of the care-seeking process, namely: 1) quantifying the number of TB suspects who did not (yet) seek care (Chapter 4); 2) evaluating the determinants of any care-seeking action (Chapter 4); 3) evaluating the pattern of first care-seeking actions and its determinants (Chapters 3 and 4); and 4) evaluating patient delay and its determinants (Chapters 3 and 4). We found that approximately 11% of TB suspects did not (yet) seek care. Being female and having multiple symptoms was significantly associated with any care-seeking action. Of those who sought care, 46% went directly to medical health providers. Being older and perceiving good quality of service were the determinants of directly visiting medical health providers, but recommendations from significant others was associated with a direct visit to alternative providers. Only 55% of TB suspects had visited medical health providers at the time of the study. The median patient delay in our studies was approximately 2 weeks. The extended version of the Theory of Planned Behavior (TPB) did not offer an explanation as to why some TB suspects had longer patient delay. Being male, self-employed, or a student were determinants of long patient delay. Visiting private providers and discussing symptoms with a spouse were associated with shorter patient delay. Interestingly, TB knowledge was not associated with any part of the care-seeking process (Chapters 3 and 4).

Care seeking by TB suspects is critical for the early detection of TB cases. However, care-seeking behavior involves many complex inter-relating factors, e.g., socio-demographic, economic, and psychosocial factors. It also involves perceived quality and the accessibility of health care providers, which are primarily context specific. Therefore, significant determinants may differ from one study setting to another.[1] We found that gender is significantly associated with care-seeking actions, whereas studies in India and Ethiopia have suggested otherwise.[2-5] We confirmed that significant others play an important role in determining care-seeking behavior, which was previously found in studies of TB patients in Africa and Indonesia.[6-9] Previous studies suggested that the perceived quality of services is a determinant for selecting a medical health care provider at the first visit.[10,11]

We found that patient delay was relatively short compared to many previous studies in developing countries.[1,12,13] We also found that being male, a student, or self-employed were determinants of a significantly longer delay. A systematic review of studies of different diseases also suggested that men usually are less likely than women to seek the help of health

professionals.[14] Though other studies have suggested that TB knowledge is associated with patient delay,[1,13] our study suggested otherwise. One possible explanation is that, because cough is a very prevalent illness in these areas, even people with proper knowledge of TB may expect their symptoms to be due to a non-threatening illness and not TB.

2. How effective is the performance of the health system providing DOTS services?

In our assessment, we took five elements of health system performance into account: 1) diagnostic delay and its determinants (Chapter 5); 2) interaction of TB patients with the health system during the care-seeking process prior to TB diagnosis (Chapter 5); 3) adherence to the national TB diagnostic guidelines (Chapter 6); 4) patient loss during diagnostic work-up (Chapter 6); and 5) duration of diagnostic work-up in DOTS facilities (Chapter 6)

We found that the median diagnostic delay for TB patients who were diagnosed at DOTS facilities was 5.4 weeks. Our study suggested that more than 60% of the TB patients started their care-seeking actions in alternative and private non-DOTS health sectors. However, the number of patient visits to DOTS health providers was highest during the overall care-seeking process. Moreover, whether patients immediately visited a DOTS facility did not correspond with a shorter diagnostic delay. We also assessed the diagnostic work-up at two types of DOTS health facilities: health centers and lung clinics. We found that 43.5% of TB suspects were lost during diagnostic work-up at health centers, but none in lung clinics. None of the TB suspects in lung clinics and 49% in health centers were diagnosed according to the national TB diagnostic algorithm. We also found a significantly longer duration for diagnostic work-up in health centers compared to lung clinics. All TB suspects who completed diagnostic work-ups underwent sputum smear microscopic examination at some point during their diagnostic work-up.

Our study in Chapter 5 indicated the problem of early detection by health workers in DOTS facilities. Many studies show that starting care-seeking by visiting private providers correlates with multiple unsuccessful consultations, involving multiple providers, and results in a high risk of longer diagnostic delay.[15-18] However, we found that first visiting private providers is not associated with longer diagnostic delay. Even patients in urban areas, who have better access to DOTS facilities, were not diagnosed faster. One possible explanation is that many TB patients may have shopped around for care at various health facilities before a diagnosis of TB was made.[9] Another explanation may be the broader network of DOTS health providers after the expansion of hospital DOTS, in which more than 80% of hospitals in the province are involved, through the HDL project since 2000.[19] A hospital TB case load study in Java suggested that not all hospitals involved in the TB program integrated the national TB program guidelines into their services, and that there are weak links between different outpatient units and the TB unit within a hospital. This study also identified that approximately 19% to 53% of all TB cases managed in the hospitals do not receive standardized diagnosis and treatment.[20]

At the health center level, our study showed that TB diagnosis was not adequately performed (Chapter 6). Many patients were lost during diagnostic work-up without any trace-back effort. A study in Pakistan suggested that 5.2% of patients lost during diagnostic work-up are smear-positive cases and, therefore, at high risk of spreading infection.[21] The findings from our recent study also indicate that patients were not traced back because there is no clear policy for patient tracing when sputum results are negative; thus, the TB program managers mainly focus on finding smear-positive TB patients (data not yet published).

In addition, many health workers at health centers and lung clinics do not adhere to the national diagnostic algorithm, but their actions may be clinically justified. For instance, a non-TB diagnosis for patients with a negative first series of sputum smears who show clinical improvement. This option is not available as a diagnosis end-point in the current diagnostic algorithm. The non-adherence to the national diagnostic algorithm in lung clinics significantly reduced diagnostic delay compared to health centers and prevented patient loss. A recent study also suggested that the performance of the WHO-based diagnostic algorithm for HIV-negative TB suspects is far from optimal.[22] Another study among HIV-positive patients suggested that chest radiography is the best next step after sputum examination.[23] Most importantly, however, is that the non-adherence in both types of facilities is still in accordance with the international standard for tuberculosis care (ISTC) for TB diagnosis.

3. Which improvement would benefit the performance of the TB program the most?

In the first research question, we identified relatively favorable care-seeking behavior by individuals suspected of having TB. We measured a short patient delay, with a small proportion of TB suspects not (yet) seeking care and many TB suspects going directly to medical health providers. The findings also indicated perceived good quality of service and recommendation from a significant other as significant determinants for selecting particular health providers. In the second research question, we demonstrated inadequate performance of the health system providing DOTS services in TB diagnosis. There were more visits to DOTS providers compared to non-DOTS or alternative providers during the entire care-seeking process, and a high proportion of patients were lost during diagnostic work-up in DOTS facilities. These findings demonstrate a clear need to strengthen the health system providing DOTS services. Interventions that focus on improving community awareness and TB patient care-seeking behavior may be an additional, but not necessarily essential, component of intervention strategies. Steen *et al*. argued that when the diagnostic delay is primarily related to health services and not the patient's knowledge and understanding of TB, as demonstrated in our studies, interventions directed at patients will not be useful.[6] Therefore, interventions that focus on strengthening the health system that provides DOTS services is likely to be more beneficial than community-based interventions that focus on modifying the care seeking behavior of TB suspects.

The performance of the health system can be improved several ways. Our studies identified critical points for improved TB case detection: 1) improving the quality of services at DOTS facilities; 2) implementing patient tracing among patients who are lost during diagnostic work-up; 3) evaluating the current diagnostic algorithm and offering a diversified national algorithm that takes into account possible scenarios at different levels of care; and 4) ensuring better program supervision.

The 2006-2015 and 2011-2015 Global Plan to Stop TB recommends engaging all care providers as a strategy to improve the detection of TB cases. However, we argue that expanding DOTS services to involve more private providers may not be the best option in this setting. We found no significant difference in diagnostic delay between those who first visited private providers compared to DOTS providers. Furthermore, involving private providers may put additional stress on the existing health system, which already has difficulty maintaining adequate program performance. A bigger network of providers also requires additional resources to be effectively maintained. A previous study that evaluated the process of a PPM partnership between hospitals and the TB control program in Jogjakarta province suggested that the governance and partnership between hospitals involved in the HDL project and provincial TB control program declined after the project was integrated into the routine TB control program due to lack of leadership, low personnel retention, and financing problems.[24]

Our findings in Chapter 3 suggest the usefulness of involving private providers/practitioners given the popularity of private providers and their extensive availability in Jogjakarta province. Our model simulation (Chapter 2) also demonstrated that an intervention that enables private providers to refer more TB suspects to DOTS facilities will have greater treatment success and prevent incomplete treatment, which is a major risk factor for MDR-TB.[25] An economic study that evaluated program interventions targeted at private practitioners in 2004 revealed that involving private practitioners could be cost effective.[26] However, Mahendradhata found that the actual caseload per private health provider is notably low. Thus, despite the potential impact of further expanding DOTS services through private provider involvement, this intervention will only marginally impact TB case detection.[27] I will further discuss the implications of our study findings on the TB control program in Indonesia in section 9.2.

4. How will the HIV epidemic impact the TB program in Indonesia?

To assess the impact of the HIV epidemic on the TB program, we quantified the prevalence of HIV infection among TB patients. Then, we assessed the level of TB patient participation in different HIV testing strategies and its determinants. Finally, we assessed the acceptance of HIV testing among users and providers and identified barriers and enablers for introducing a HIV testing service into TB programs.

We found that the HIV prevalence among TB patients (1.9%) is three times higher than previously estimated by WHO/UNAIDS.[28] This finding indicates that the burden of TB-HIV co-infection might have more serious consequences to the TB program than previously expected. Because the burden of HIV among TB patients is considered low by WHO standards,[29] the impact of the HIV epidemic on the TB program is still limited. However, efforts are needed to set up a HIV surveillance system in the TB program to monitor the HIV trend among TB patients closely, so that a timely and appropriate response can be ensured. The challenge is to select the appropriate HIV testing and surveillance strategy that is acceptable to both TB patients and health providers.

Our study in Chapter 7 demonstrated that HIV testing is widely accepted among TB patients, particularly when an unlinked anonymous testing strategy in which all identifying patient data is omitted was employed. However, when patients were offered free access to VCT clinics, our studies found a disappointingly low participation rate (4.1%). Perceived additional burden was the main reason for not visiting VCT centers, even when a transport incentive was provided. Previous studies also suggested that the limited number and spatial coverage of existing VCT centers in developing countries hampers the acceptability of such services.[30,31] Introduction of HIV testing in a hospital setting requires special consideration, particularly because hospitals have a high TB caseload and some of the hospitals also provide VCT services. A one-day test result and closer location of the test have been shown to increase VCT uptake.[32-35] However, our findings suggest that structural barriers (e.g., adequate private rooms for consultation, number of personnel, and communication skills) exist in hospitals, preventing effective HIV testing services. Thus, interventions to minimize the existing barriers need to be in place. In addition, the internal referral mechanism, which is currently weak in hospitals,[20] needs to be strengthened.

Overall, our study has demonstrated that, with modest efforts, TB-HIV surveillance can be performed in a low HIV prevalence and resource poor setting such as Indonesia. However, without adequate preparation and careful planning, the introduction of HIV testing into the TB program may add an additional burden to the health system that provides DOTS, which is already having difficulty maintaining adequate performance.

9.2 | FURTHER IMPLICATIONS OF THE FINDINGS

Generalizability to Indonesia as a whole

Our studies may not be fully applicable to the wider context of the TB control program in Indonesia, as Jogjakarta has a different epidemiological situation in terms of TB and HIV incidence and prevalence. Wide variations exist in the health system characteristics and socio-economic context across the country, which are relatively favorable for Jogjakarta province. To

this end, our findings may best be generalized to a limited number of other Indonesian areas with a similar setting: a relatively well functioning health system with a mix of public and private health providers, no particular geographical barriers to health service access, a population with relatively good socio-economic and demographic status, and a concentrated HIV epidemic, such as in Java and Bali islands. In the future, the study findings may become more relevant for Indonesia as a whole, when the general situation in the country improves. This would also apply to other similar low and middle-income countries with a high TB burden in Asia.

Other aspects also hinder the generalization of our study findings to a broader health system context. First, our studies focus on the performance of frontline health providers, but the health system structure is more complex. The WHO health system framework defined health systems as building blocks of government stewardship, financing, human resource management, pharmaceutical management, service financing, and delivering services. These building blocks have four core functions, i.e. stewardship, creating resources, financing, and delivering services.[36] Our studies focus mainly on the function of delivering the services of the health system. The stewardship, resources creation, and financing functions of the health system in the TB program in this setting have been studied elsewhere.[20,26,37,38] These studies generally suggest that PPM intervention can be cost effective but requires a specific processes and context in which the processes of the public-private partnership are not adequately managed. Secondly, data on health system performance were only gathered in DOTS services. Despite the fact that private non-DOTS providers detect and treat TB patients, gathering data on their performance was difficult due to a strong attitude among private health providers regarding patient privacy. Our effort to collect data from private non-DOTS providers during the study in Chapter 5 only resulted in interviews with five TB patients. However, many studies have suggested that the performance of non-DOTS service providers in general is worse than DOTS service providers.[8,10,15,18]

Strengthening vs. expanding DOTS services: A trade-off between equity and quality?

Our studies demonstrate that there is a clear need to continuously strengthen the health system providing DOTS, even after the successful implementation of a PPM intervention. Our studies confirm previous studies that demonstrated that the health system in Jogjakarta province has had difficulties maintaining effective performance after the hospital DOTS linkage (HDL) project was phased out.[20,37] Our study findings suggest that the problem of detecting TB cases early lies in the more extensive, but not optimally managed, network of DOTS health providers. Thus, a critical question is whether equitable access to the TB service justifies reduced quality.

The Global Plan to Stop TB 2006-2015 endorsed a six-point strategy to achieve the TB related MDGs: 1) pursue high-quality DOTS expansion and enhancement; 2) address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations; 3) contribute to health system strengthening;

4) engage all care providers; 5) empower people with TB and communities through partnerships; and 6) enable and promote research.[39,40] This recommendation addresses the importance of intensified efforts towards case detection, which has been translated into expanding DOTS strategies to different (both state and non-state owned) health providers through PPM approaches. Clearly, the current global strategy recognizes the importance of both the accessibility and quality of DOTS services.

The WHO policy on the PPM strategy is based on recognizing that the targeted service coverage cannot be achieved by replicating existing models for service delivery or focusing only on the public sector.[41,42] An increasing number of countries has implemented PPM activities, from 13 in 2003 to 58 in 2008, and was supported by the Global Fund. Care providers involved in PPM vary by region depending on the preferred health provider used by TB patients as the first point of care, e.g., semi-formal village doctors in Bangladesh, private practitioners in India and Indonesia, private hospitals in China and Indonesia, pharmacies in Cambodia, and prisons in many countries in Eastern Europe.[43] Studies have also demonstrated that different models of PPM intervention strategies could be cost effective.[26,38,44,45] However, the cost effectiveness of a PPM model is not universally applicable and is context-specific to the setting in which it is implemented.[38] Furthermore, the overall PPM contribution to the new TB notification rate varies, and in many countries the contribution is less than 20% of all notifications.[43] Most importantly, under which conditions the scaling-up of PPM DOTS is more cost effective than strengthening the existing DOTS services is still unclear.[46]

The PPM interventions, like many other global initiatives, are implemented primarily through external international financial and technical assistance. For good project performance, a new ad hoc or parallel system is created, as the existing system is considered to have little or no capacity, or is already overburdened with the existing workload. The new system is staffed with highly skilled professionals who work efficiently over the implementation period on a temporary basis. As a result, at the end of the project, the NTPs and technical agencies are able to demonstrate strong program performance upon project evaluation. After a transition period, the new intervention is integrated into the routine TB control program and the operational, managerial, and leadership responsibilities of the project are shifted to provincial or district TB program managers and their staffs. The routine TB officers, though having acquired new skills during the implementation of the project, may not be as resourceful and efficient as the professional staff hired during the implementation period. Coupled with a lack of financial capacity and the high staff turnover at the district and provincial levels, the quality of the newly developed system cannot be sustained and may deteriorate.

Ensuring the quality and consistency of health interventions when delivered on a large scale can be challenging.[42] We agree with Mahendradhata and Probandari that health system strengthening should place strong emphasis on building the capacity of local health offices

to be capable of their governance and leadership roles in the local health system.[24,46] This is also one of the key messages of health system strengthening endorsed by the WHO.[47] Governance is commonly weak in public-private partnerships,[24,48] which the Indonesia NTP needs to seriously take into account when further scaling up PPM interventions nationwide. Instead of rapidly scaling up PPM interventions in order to achieve international, donor driven objectives at the expense of poor quality services, the NTP should carefully reconsider their current implementation strategy. Furthermore, instead of using a 'one fits all' policy for PPM implementation, the NTP should take into account the complexities of intervention at different local health system levels. Intervention complexity is defined as the quality and quantity of non-financial resources required to implement and sustain an intervention, which consists of four dimensions: the intervention itself; delivery characteristics; requirement for government capacity; and usage characteristics.[42,49] Private providers consist of different institutions with different ownership statuses, missions, organizational structures, and complexities. In terms of delivery, interventions differ in their requirements regarding facilities, human resources, and other operational issues. Furthermore, demands on the government vary, with some interventions requiring more extensive government engagement in policy, service delivery, and regulation. Usage characteristics are related to the existing demand, which can be measured from the care-seeking behavior of the TB patients. Understanding intervention complexities helps in the identification of resource constraints and strategies to overcome challenges to successful implementation.[42]

The WHO has developed guidelines for performing national assessments and offers an implementation tool for PPM interventions.[50,51] These guidelines provide a systematic, stepwise approach for national assessments, planning, and implementation of PPM activities. In our view, these guidelines do not offer enough tools to assess the governance and leadership capacity of the existing health system or to plan, implement, and monitor necessary measures for building or improving the existing capacity. In order to take these guidelines one step further, there is a clear need to adapt the international perspective of the guidelines into the local perspective of the provincial and district health system contexts. There is also a clear need to evaluate the implementation of PPM activities systematically using scientifically sound evaluation methods. The WHO PPM guidelines indeed offer a toolkit for monitoring and evaluation, but do not provide methods for evaluation beyond routine monitoring and evaluation using surveillance data. A routine surveillance system can be a valuable resource for monitoring the implementation process and immediate program output. However, a more robust research method is needed to assess the intermediate or long-term health impact of the interventions, as we have demonstrated in our studies (Chapters 5 and 6). Therefore, the NTP should allocate a reasonable portion of the budget for systematic and rigorous evaluation studies.

Integrating HIV surveillance into TB programs: How to implement

Our study demonstrated that HIV testing, particularly the unlinked anonymous method, is well accepted by TB patients and TB health providers. With the increasing rate of HIV prevalence in Indonesia, there is a clear need to introduce HIV testing into the TB program nationwide, particularly for cautious monitoring of the trend of co-infection, in order to have an adequate and timely response to create public awareness, build political will, mobilize resources, and integrate service delivery when needed.

Routine HIV testing is the ideal policy option. It would provide HIV-positive TB patients access to proper care, support, and treatment (CST). Routine HIV testing together with proper CST not only improves the quality of the surveillance system, but also significantly increases both the survival rate and the quality of life of co-infected patients. However, setting up and running such services requires an investment of considerable resources to train personnel and set-up and run the services. Unfortunately, many resource poor countries do not have the necessary resources at their disposal. Also, not every DOTS facility (particularly in health centers) has a large enough TB caseload for routine HIV testing to be cost effective. Referring TB patients to a nearby VCT clinic for HIV testing may be an option, but at the expense of introducing access barriers, as demonstrated in our study.

The more rational option would be to set up periodic surveys or sentinel surveillance. Sentinel surveillance is defined as a system by which "specific sites and population groups are selected, a predetermined number of persons are routinely tested, and testing is performed in a regular and consistent way".[52] Sentinel surveillance usually applies an unlinked anonymous HIV testing method to leftover blood specimens that were collected for other purposes and stripped of all identifying markers, with no informed consent required.[52] However, this would not apply to TB patients because no blood specimen is collected for diagnostic purposes. In this situation, the WHO recommends an unlinked anonymous or linked test in which the specimen is coded and can be linked to a personal identifier, with informed consent and free access to VCT.[53] A reasonable improvement for both the surveillance system and CST of HIV positive cases would be to select hospitals and lung clinics, due to their high TB case loads, with well functioning TB and VCT services as sentinel sites and to offer linked confidential tests to all TB patients.

In a setting with high TB-HIV caseload, as in the Papua provinces, integrating TB-HIV cases under one roof should be considered. The rationale for an integrated service is that TB patients have immediate VCT services, accelerated access to ART, reduced incidence of TB and opportunistic infection among co-infected persons, early TB diagnosis for co-infected persons, and improved cure rates among TB patients. Such a service would facilitate integrated management of co-infected persons and streamline the resources needed.[54] Additionally, good infection control measures need to be in place, particularly in facilities that provide integrated TB-HIV to prevent TB transmission between TB-HIV co-infected persons and HIV-positive individuals without TB.

These efforts are in line with the WHO's three recommendations for TB-HIV collaboration, particularly to prevent further transmission of TB among HIV patients: intensified case detection; isoniazid preventive therapy (IPT); and infection control (IC).[55] In the long run, collaborative efforts need to be integrated not only at the frontline health providers, but also at every level of TB and HIV control programs.

Health system research: Beyond randomized control trials and cost effectiveness studies

Though all health interventions have some degree of complexity, the health system intervention is often considered a relatively complex intervention.[56,57] In the field of service delivery, interventions can be considered particularly complex because they are delivered across different levels of service providers, delivered in a new setting, or when new tasks are performed by the staff or current tasks are performed in a new context.[58] Two main methods are used to evaluate such interventions: 1) a randomized controlled trial to evaluate the efficacy and effectiveness of the intervention or 2) economic evaluation to assess the cost effectiveness of the intervention. Though the randomized controlled trial is the gold standard for evaluating interventions, some have argued the appropriateness of this method for evaluating complex interventions because this approach does not provide information on why and how the interventions work.[56,57] A cost-effectiveness study also has limitations in evaluating complex interventions. Most cost-effectiveness studies are primarily used for evaluating clinical interventions, e.g., new drugs, surgery or screening, or for generalized application using aggregate data, whereas the outcomes of health system interventions, such as PPM interventions, are context specific and depend on private provider characteristics, stakeholder interactions, and the management of the intervention.[38]

Assessment of such complex interventions should therefore shift from the randomized controlled trial to systems thinking and prospective evaluation with plausibility rather than probability design.[59] Systems thinking allows the evaluation of the process and the context of the intervention to be an integral part of the evaluation of its effects.[56] Research questions should shift from 'whether PPM works', to 'how, why, in what circumstances, for whom, and to what extent' PPM works.[58] The same thinking also applies to evaluation of the cost-effectiveness of an intervention. Many studies have shown that PPM interventions are cost-effective, but we need to shift the questions to 'in which context is the intervention cost-effective' and 'how can the cost-effectiveness be improved'.[38]

9.3 | CONCLUSIONS AND RECOMMENDATIONS

Conclusions

- The care-seeking behavior of TB suspects in Jogjakarta province of Indonesia is relatively favorable.
- The health system providing DOTS services in Jogjakarta province of Indonesia has difficulty maintaining effective performance in diagnosing TB cases.
- Strengthening the health system providing DOTS is likely to be more effective than modifying the care seeking behavior of TB suspects.
- The HIV epidemic in Indonesia still has a limited impact on the TB program, but the trend of HIV-TB co-infection needs to be monitored cautiously for a timely and appropriate response.

Recommendations

- To improve TB case detection in Indonesia, interventions should focus on strengthening the health system providing DOTS.
- The trend of the HIV epidemic among TB patients in Indonesia needs to be monitored cautiously for a timely and appropriate response.
- Adapt the WHO guidelines for the PPM assessment and implementation activities into local provincial and district system contexts in order to determine the right PPM strategies for different provinces and districts.

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Summary

The objective of this thesis is to identify ways to improve tuberculosis case finding in Indonesia. To achieve the objective, this thesis focuses on two major issues in TB control: 1) the interaction of TB patients and individuals suspected to have TB with the health system providing TB services and 2) the impact of the emerging HIV epidemic on the national TB control program. This thesis consists of 9 chapters, with 7 scientific papers (Chapters 2-8), general introduction (Chapter 1) and discussion (Chapter 9).

In **Chapter 1**, we give a general introduction to TB epidemiology, natural history, diagnosis, and treatment, and the WHO recommended DOTS strategy as the global TB control strategy. We also introduce the care seeking behavior theories and concepts and its importance to TB control. The Indonesian health system structure, the national TB control program, and the health system model that we use as a theoretical framework are also discussed. The studies were conducted in Jogjakarta province, in central part of Java Island, Indonesia, with 117 public health centers, 24 hospitals, and 5 lung clinics as the backbone of the TB program in this province.

In this thesis, we address the following research questions:

1. What are the patterns of care seeking behavior among TB suspects in Indonesia?
2. How effective is the performance of the health system providing DOTS services?
3. Which improvement would benefit the performance of TB program the most?
4. How will the HIV epidemic impact the TB program in Indonesia?

In **Chapter 2**, we provide the theoretical framework of the interaction between TB patients and health system. The framework is based on a mathematical model of TB and health system developed by Erasmus MC. The model was adjusted to reflect the health system in Indonesian context, in which alternative sector, private providers (Non-DOTS) and public providers (DOTS) co-exist. The model mimics the journey of pulmonary TB patients through the health system, beginning with the onset of symptoms, followed by care seeking behavior. We used experts' opinions to quantify model parameters, followed by a model simulations exercise to describe the performance of the current TB control program in Indonesia. We subsequently explored the impact of potential case finding strategies. The model shows the potential effectiveness of active case finding strategy in settings where access to DOTS facilities is limited.

Chapters 3 and 4 discuss the care seeking behavior of TB suspects both in health facilities and in community settings. Patient delay and its determinants are explored. **Chapter 3** aims to explore determinants of TB suspects' care seeking behavior, using the theory of planned behavior (TPB) as a theoretical framework. A structured questionnaire, which consists of questions regarding socio-demographics data, patient delay, health care seeking behavior and an extended version of

TPB, was developed. In total 194 TB suspect patients at 5 lung clinics in Jogjakarta province were interviewed. We found that the patient delay was relatively short (14 days), with accessibility of the healthcare provider being the main determinant of patient delay. The extended version of TPB did not associate with patient delay, but the role of psychosocial factors cannot be fully excluded.

Chapter 4 describes the pattern of care seeking behavior of individuals with TB symptoms in the community. We quantify the proportion of TB suspects who did not seek care and explore the determinants of care seeking actions. We further assess the determinants of patient delay in the community. We did a population based cross-sectional survey. We interviewed adult individuals with cough longer than two weeks. Data on socio-demographics, TB status, onset of TB symptoms, TB knowledge, types of health facilities visited, and duration of each visit were collected. In total 746 individuals with TB symptoms in three urban, sub-urban and rural districts of Jogjakarta province were interviewed. We found that approximately 10% of TB suspects had not yet sought care. Of those who had sought care, less than half presented directly to medical health care providers. Female gender and multiple symptoms were associated with any care seeking action. Of those who sought care, 46% went directly to medical health providers. Being older and perceiving good quality of service were the determinants of directly visiting medical health providers, but recommendation from significant others was associated with a direct visit to alternative providers. The median duration of patient delay (17 days) was relatively short. Male gender and unemployment were associated with longer delay in presentation.

Chapters 5 and 6 explore the performance of the health system in providing TB services in Indonesia. **Chapter 5** describes the interaction between TB patients and health system during their diagnostic process. Determinants of patients' movement, diagnostic delay, number of visits and TB diagnosis are explored. A cross-sectional survey among newly diagnosed TB patients was conducted at 89 DOTS facilities in Jogjakarta province. We reconstructed the history of 253 TB patients care seeking processes through retrospective interviews. We found that the total duration of diagnostic delay was 5.4 weeks. The median number of visits was 4. Many of the patients' socio-demographic determinants did not associate with the care seeking patterns, and no socio-demographic determinants were associated with longer diagnostic delay. More than 60% of TB patients started their care seeking processes outside DOTS facilities, but the number of visits in DOTS facilities was higher during the overall care seeking process. Surprisingly, immediately visiting a DOTS facility did not correspond with shorter diagnostic delay. The diagnostic delay in Jogjakarta province was, therefore, mainly related with the existing health system providing DOTS services.

Chapter 6 describes the TB diagnostic performance at DOTS facilities. The study focuses on adherence to the existing standardized national TB diagnostic guideline, determinants of lost

during diagnostic work-up, TB diagnosis and quantification of the duration of diagnostic work-ups of TB suspects. We prospectively documented the diagnostic work-up of new tuberculosis suspects until a diagnosis was reached. We used clinical audit forms to record each step chronologically. Data on patients' gender, age, symptoms, types, dates and results of examinations, and the final diagnosis were collected. In all 43.5% of the tuberculosis suspects were lost during the diagnostic work-up in health centers but none in lung clinics. None of the TB suspects in lung clinics and 49% in health centers were diagnosed according to the national TB diagnostic algorithm. We also found a significantly longer duration for diagnostic work-up in health centers compared to lung clinics. All TB suspects who completed diagnostic work-ups underwent sputum smear microscopic examination at some point during their diagnostic work-up, suggesting that these practices are still agree with the international standard for tuberculosis care (ISTC).

Chapters 7 and 8 discuss the current and future challenges of the TB control program in Indonesia, particularly with the alarming increase of the number of HIV cases in Indonesia. In **Chapter 7**, we describe the burden and socio-demographic characteristics of HIV positive cases among TB patients, and the up-take of voluntary HIV counseling and testing (VCT) among TB patients. We introduced unlinked anonymous HIV testing for newly diagnosed TB patients attending DOTS services and patients were additionally offered VCT services. As many as 987 TB patients, participated in the survey. We found that the HIV prevalence was 1.9%. HIV infections were less frequently diagnosed among TB patients who attended a public health center rather than a public hospital, and HIV was more common in TB patients with a university education background and a history of HIV testing. We found that only 13.4% patients who accepted unlinked anonymous testing expressed interest in VCT. Of these only 39% (n=52) attended VCT. Interest was higher among students and those offered VCT by public health centers.

Chapter 8 further discusses the challenges of introducing HIV testing within the Indonesia TB control program. We explored the acceptance and perceived barriers of having HIV testing among TB patients, health providers, and TB program managers. All TB patients who were tested for HIV infection in Chapter 7 were offered VCT services. To access the acceptance and perceived barriers of having HIV testing, we conducted in-depth interviews with 33 TB patients, 3 specialist physicians and 3 disease control managers. We also conducted 4 focus Group Discussions with nurses. We found that patients' and providers' knowledge regarding HIV was poor. The main barriers perceived by patients were: burden for accessing VCT and fear of knowing the test results. Stigma caused concerns among providers, but did not play much role in patients' attitude towards VCT. The main barriers perceived by providers were communication, patients feeling offended, stigmatization and additional burden.

In **Chapter 9**, we provide and discuss answers to the research questions. We also discuss the implications of study findings to the TB control program in Indonesia, particularly the need to continuously strengthen the health system in providing DOTS services and the best way to

integrate HIV testing into the national TB control program. At the end of the chapter, we arrive at the following conclusions and recommendations:

CONCLUSIONS

- The care-seeking behavior of TB suspects in Jogjakarta province of Indonesia is relatively favorable.
- The health system providing DOTS services in Jogjakarta province of Indonesia has difficulty maintaining effective performance in diagnosing TB cases.
- Strengthening the health system providing DOTS is likely to be more effective than modifying the care seeking behavior of TB suspects.
- The HIV epidemic in Indonesia still has a limited impact on the TB program, but the trend of HIV-TB co-infection needs to be monitored cautiously for a timely and appropriate response.

RECOMMENDATIONS

- To improve TB case detection in Indonesia, interventions should focus on strengthening the health system providing DOTS.
- The trend of the HIV epidemic among TB patients in Indonesia needs to be monitored cautiously for a timely and appropriate response.
- Adapt the WHO guidelines for the PPM assessment and implementation activities into local provincial and district system contexts in order to determine the right PPM strategies for different provinces and districts.

Samenvatting

De doelstelling van dit proefschrift is manieren te vinden om de opsporing van tuberculose gevallen in Indonesië te verbeteren. Daartoe richt dit proefschrift zich op twee belangrijke kwesties bij tbc-bestrijding: 1) de interactie van tbc-patiënten en mensen met verdenking op tbc met dat deel van de gezondheidszorg dat tbc-diensten levert en 2) de impact van de opkomende hiv-epidemie op het nationale tbc-bestrijdingsprogramma. Dit proefschrift heeft negen hoofdstukken: zeven wetenschappelijke artikelen (hoofdstukken 2-8), die vooraf worden gegaan door een algemene inleiding (hoofdstuk 1) en worden gevolgd door een afsluitende beschouwing (hoofdstuk 9).

In **hoofdstuk 1** geven we een algemene inleiding in de epidemiologie, het natuurlijke beloop, de diagnostiek en de behandeling van tbc, en bespreken we de DOTS-strategie, die door de WHO wordt aanbevolen als mondiale strategie voor tbc-bestrijding. Tevens introduceren we de theorieën en concepten op het gebied van hulpzoekgedrag en het belang hiervan voor tbc-beheersing. Ten slotte worden ook het Indonesische gezondheidszorgstelsel en het nationale tbc-beheersingsprogramma besproken, alsmede het gezondheidssysteem model
dat we als theoretisch kader gebruiken. De studies zijn uitgevoerd in de provincie Jogjakarta in centraal Java, Indonesië, waar 117 openbare gezondheidscentra, 24 ziekenhuizen en 5 longklinieken de ruggengraat van het provinciale tbc-programma vormen.

In dit proefschrift hebben we de volgende onderzoeksvragen gesteld:

1. Welke patronen van hulpzoekgedrag worden in Indonesië aangetroffen bij mensen met verdenking op tbc?
2. Hoe effectief is het gezondheidszorgsysteem bij de verstrekking van DOTS-diensten?
3. Welke verbetering zou het grootste positieve effect op het tbc-programma hebben?
4. Hoe zal de hiv-epidemie van invloed zijn op het tbc-programma in Indonesië?

In **hoofdstuk 2** introduceren we het theoretische kader voor het onderzoek naar de interactie tussen tbc-patiënten en het gezondheidszorgsysteem. Het kader is gebaseerd op een door Erasmus MC ontwikkeld wiskundig model voor tbc en gezondheidszorgsystemen. Het model is zodanig ingericht dat het een weergave is van het Indonesische gezondheidszorgsysteem, waarin de alternatieve sector, particuliere zorgaanbieders (non-DOTS) en openbare zorgaanbieders (DOTS) naast elkaar bestaan. Het model simuleert het traject dat patiënten met long-tbc volgen door het gezondheidszorgsysteem, vanaf de eerste symptomen, gevolgd door hulpzoekgedrag. We hebben de inzichten van deskundigen gebruikt om de parameters van het model te kwantificeren, waarna we een simulatie hebben uitgevoerd om het functioneren van het huidige tbc-beheersingsprogramma in Indonesië te beschrijven. Vervolgens hebben we de effecten onderzocht van enkele mogelijke strategieën voor opsoring vantbc-gevallen. Het model toont de

mogelijke effectiviteit van actieve opsporingsstrategieën in omgevingen met beperkte toegang tot DOTS-voorzieningen.

Hoofdstukken 3 en 4 gaan over het hulpzoekgedrag van mensen met tbc-verdenking in zowel gezondheidszorgvoorzieningen als hun gemeenschappen. Er wordt gekeken naar vertraging in hulpzoekgedrag bij patiënten en de determinanten hiervan. In **hoofdstuk 3** worden de determinanten van het hulpzoekgedrag van mensen met verdenking op tbc verkend, waarbij de theorie van gepland gedrag (TPB) als theoretisch kader wordt gebruikt. Er is een gestructureerde vragenlijst ontwikkeld, met vragen die betrekking hebben op socio-demografische omstandigheden, hulpzoekgedrag en vertraging in hulpzoek gedrag bij de patiënten een uitgebreide versie van TPB. In totaal zijn 194 patiënten met verdenking op tbc in 5 longklinieken in de provincie Jogjakarta ondervraagd. We zagen daarbij dat de gemiddelde patiëntvertraging relatief kort was (14 dagen), waarbij de toegankelijkheid van de gezondheidszorgaanbieder de belangrijkste determinant van patiëntvertraging was. De uitgebreide TPB-versie vertoonde geen verband met patiëntvertraging, maar de rol van psychosociale factoren kan niet geheel worden uitgesloten.

Hoofdstuk 4 gaat in op het patroon van hulpzoekgedrag van mensen met tbc-symptomen in hun gemeenschap. We kwantificeren welk percentage van mensen met verdenking op tbc geen hulp zocht en verkennen de determinanten van hulpzoekgedrag. We gaan nader in op de determinanten van patiëntvertraging in de gemeenschap. We hebben een populatiegebaseerd cross-sectioneel onderzoek uitgevoerd. We hebben daartoe volwassenen ondervraagd die langer dan twee weken hoestklachten hadden. Er zijn gegevens verzameld over socio-demografische omstandigheden, tbc-status, aanvang van tbc-symptomen, kennis over tbc, soorten bezochte gezondheidszorgvoorzieningen, en duur van de verschillende bezoeken. In totaal zijn interviews afgenomen bij 746 mensen met tbc-symptomen in drie stedelijke, voorstedelijke en rurale gebieden van de provincie Jogjakarta. We stelden vast dat circa 11% van de mensen met verdenking op tbc nog geen hulp had gezocht. Van hen die al wel hulp hadden gezocht, was 46% direct naar medische zorgaanbieders gegaan. De vrouwelijke sekse en meervoudige symptomen waren positief geassocieerd met elke vorm van hulpzoekgedrag. Ouder zijn en het gevoel hebben dat de geleverde zorg van goede kwaliteit is, waren de determinanten voor het direct bezoeken van medische zorgaanbieders, maar aanbevelingen van belangrijke anderen in de directe omgeving was positief geassocieerd met een direct bezoek aan alternatieve aanbieders. De mediaan van de patiëntvertraging was 17 dagen, waarmee deze relatief kort was. De mannelijke sekse en werkloosheid waren positief geassocieerd met een grotere vertraging bij het zich aanmelden.

In de hoofdstukken 5 en 6 wordt onderzocht hoe de gezondheidszorg in Indonesië functioneert bij het verlenen van tbc-diensten. **Hoofdstuk 5** beschrijft de interactie tussen tbc-patiënten en de gezondheidszorgtijdens hun diagnostische proces. De determinanten van de bewegingen van patiënten binnen de gezondheidszorg, diagnostische vertraging, het

aantal bezoeken en de tbc-diagnose worden onderzocht. Er is bij 89 DOTS-voorzieningen in de provincie Jogjakarta een cross-sectioneel onderzoek uitgevoerd onder patiënten bij wie nog maar kort daarvoor tbc was vastgesteld. We hebben met behulp van retrospectieve interviews de hulpzoekgeschiedenis van 253 tbc-patiënten gereconstrueerd. De totale duur van de diagnostische vertraging bleek gemiddeld 5,4 weken te bedragen. De mediaan van het aantal bezoeken was 4. Veel van de socio-demografische determinanten van de patiënten vertoonden geen verband met de hulpzoekpatronen, en geen ervan bleek geassocieerd met een langere diagnostische vertraging. Voor ruim 60% van de tbc-patiënten begon het hulpzoekproces buiten DOTS-voorzieningen, maar het aantal bezoeken aan DOTS-voorzieningen was hoger tijdens het totale hulpzoekproces. Verrassenderwijs bleek het onmiddellijk bezoeken van een DOTS-voorziening niet te corresponderen met een kortere diagnostische vertraging. De diagnostische vertraging in de provincie Jogjakarta hield derhalve vooral verband met de verlening van DOTS-diensten binnen het gezondheidszorgsysteem.

Hoofdstuk 6 beschrijft de prestaties van DOTS-voorzieningen op het gebied van tbc-diagnostiek. Het onderzoek is gericht op naleving van de bestaande gestandaardiseerde nationale richtlijn voor tbc-diagnostiek, determinanten van verlies bij diagnostische *work-up*, tbc-diagnose en kwantificatie van de duur van diagnostische workups van mensen met verdenking op tbc. We hebben de diagnostische workup van nieuwe tuberculose-verdenkingen bijgehouden en gedocumenteerd totdat er een diagnose was gesteld. We hebben klinische auditformulieren gebruikt om alle stappen chronologisch vast te leggen. Hiermee werden gegevens over de sekse, leeftijd en symptomen van de patiënt, alsmede de soorten, data en resultaten van onderzoeken, en de uiteindelijke diagnose verzameld. Alles bij elkaar werd in gezondheidscentra tijdens de diagnostische workups 43,5% van de mensen met verdenking op tuberculose verloren, maar niemand in longklinieken. Van de mensen met tbc-verdenking werd in de longklinieken niemand en in de gezondheidscentra 49% gediagnosticeerd volgens het nationale algoritme voor tbc-diagnostiek. We hebben ook vastgesteld dat de diagnostische workups in de gezondheidscentra significant meer tijd in beslag namen dan in de longklinieken. Bij alle mensen met tbc-verdenking voor wie de volledige diagnostische workup werd uitgevoerd, is tijdens de workup op enig moment een microscopische speekseltest uitgevoerd, hetgeen erop duidt dat deze praktijk nog in overeenstemming is met de ISTC (International Standard for Tuberculosis Care).

Hoofdstukken 7 en 8 gaan over de huidige en toekomstige uitdagingen voor het tbc-bestrijdingsprogramma in Indonesië, met name tegen de achtergrond van de alarmerende toename van het aantal hiv-besmettingen in het land. In **hoofdstuk 7** beschrijven we het aandeel en de socio-demografische kenmerken van de hiv-positieve gevallen onder de tbc-patiënten, en de mate waarin tbc-patiënten vrijwillig kiezen voor hiv-counseling en -tests (VCT). We hebben anonieme hiv-tests voor pas gediagnosticeerde tbc-patiënten die gebruikmaken van DOTS-diensten geïntroduceerd, en de patiënten kregen ook nog VCT aangeboden. Aan dit onderzoek

werd door maar liefst 987 tbc-patiënten deelgenomen. We hebben een hiv-prevalentie van 1,9% vastgesteld. Er werden minder vaak hiv-infecties aangetroffen bij tbc-patiënten in een openbaar gezondheidscentrum dan in een openbaar ziekenhuis, en hiv kwam meer voor bij tbc-patiënten met een academische opleiding en die zich al eerder op hiv hadden laten testen. We stelden vast dat slechts 13,4% van de patiënten die instemden met een anonieme test belangstelling had voor VCT. Van hen heeft slechts 39% (n=52) zich daadwerkelijk voor VCT gemeld. De belangstelling was groter onder studenten en hen die VCT kregen aangeboden door openbare gezondheidscentra.

Hoofdstuk 8 behandelt verder de uitdagingen die gepaard gaan met de introductie van hiv-tests in het Indonesische tbc-bestrijdingsprogramma. We hebben gekeken naar de acceptatie van en de ervaren obstakels voor het uitvoeren van hiv-tests onder tbc-patiënten, zorgaanbieders, en tbc-programmamanagers. Alle tbc-patiënten bij wie in hoofdstuk 7 werd getest op hiv-besmetting kregen VCT aangeboden. Om de acceptatie van en de ervaren obstakels voor het uitvoeren van hiv-tests te kunnen inschatten, hebben we uitgebreide interviews afgenomen bij 33 tbc-patiënten, drie specialisten en drie ziektebeheersingsmanagers. Bovendien hebben we hier vier uit verpleegkundigen bestaande focusgroepen over laten praten. We hebben vastgesteld dat het kennisniveau over hiv bij zowel patiënten als zorgaanbieders laag was. De belangrijkste obstakels zoals ervaren door de patiënten waren: belemmering bij de toegang tot VCT en angst om de uitslag van de test te weten te komen. De mogelijkheid van stigmatisering speelde wel een rol voor de zorgaanbieders, maar niet zozeer voor de patiënten bij hun houding ten opzichte van VCT. De belangrijkste obstakels zoals ervaren door de zorgaanbieders waren communicatie, het risico dat patiënten zich beledigd zouden voelen, stigmatisering en de extra last**.**

In **hoofdstuk 9** geven we antwoorden op de onderzoeksvragen en bespreken we deze. We bespreken tevens de implicaties van de onderzoeksresultaten voor het tbc-bestrijdingsprogramma in Indonesië, met name de noodzaak om het gezondheidszorgsysteem te blijven versterken op het gebied van DOTS-diensten en de beste manier om hiv-tests te integreren in het nationale tbc-bestrijdingsprogramma. Aan het eind van het hoofdstuk komen we uit op de volgende conclusies en aanbevelingen:

CONCLUSIES

- Het hulpzoekgedrag van mensen met verdenking op tbc in de Indonesische provincie Jogjakarta is relatief gunstig.
- Het gezondheidszorgsysteem dat DOTS-diensten in de provincie Jogjakarta levert ondervindt problemen bij het op effectieve wijze diagnosticeren van tbc-gevallen.
- Het zal waarschijnlijk effectiever zijn het zorgstelsel dat DOTS levert te versterken dan om te proberen het hulpzoekgedrag van mensen met verdenking op tbc te veranderen.
- De hiv-epidemie in Indonesië heeft vooralsnog een beperkte impact op het tbc-programma, maar de ontwikkeling van gelijktijdige hiv- en tbc-besmettingen moet zorgvuldig worden gevolgd zodat er tijdig met passende maatregelen kan worden gereageerd.

AANBEVELINGEN

- Om in Indonesië tot een betere detectie van tbc-gevallen te komen is het verstandig interventies te richten op versterking van het zorgstelsel dat DOTS-diensten aanbiedt.
- De ontwikkeling van de hiv-epidemie onder tbc-patiënten in Indonesië moet zorgvuldig worden gevolgd, zodat er tijdig met passende maatregelen kan worden gereageerd.
- Pas de WHO-richtlijnen voor PPM-beoordelings- en implementatieactiviteiten aan aan de situaties in de betreffende provincies en districten om zo de juiste PPM-strategieën voor de verschillende provincies en districten vast te kunnen stellen.

Ringkasan

Disertasi ini bertujuan untuk mengidentifikasi cara untuk meningkatkan penemuan kasus Tuberkulosis (TB) di Indonesia. Untuk mencapai tujuan tersebut, disertasi ini memfokuskan pada dua isu utama dalam pengendalian penyakit TB, yaitu: 1) interaksi antara pasien dan suspek TB dengan sistem kesehatan yang menyediakan layanan pengobatan TB, serta 2) dampak munculnya epidemi HIV terhadap program pengendalian program TB di Indonesia. Disertasi ini terdiri dari 9 bab, yang meliputi pendahuluan (bab 1), tujuh publikasi penelitian (bab 2-8) dan diskusi umum (bab 9).

Bab 1 berisi gambaran umum tentang epidemiologi, riwayat alamiah penyakit, diagnosis dan pengobatan TB, serta strategi DOTS yang direkomendasi WHO sebagai strategi global pengendalian TB. Bab ini juga mengenalkan teori dan konsep perilaku mencari pengobatan dan kepentingannya dalam pengendalian TB. Gambaran sistem kesehatan dan program pengendalian penyakit TB di Indonesia beserta model sistem kesehatan yang digunakan sebagai kerangka teoritis penelitian juga dibahas. Seluruh penelitian yang digunakan dalam disertasi ini dilakukan di propinsi Daerah Istimewa Yogyakarta (DIY), Indonesia. Propinsi ini mempunyai fasilitas layanan kesehatan sejumlah 117 Puskesmas, 24 rumah sakit dan 5 BP4 sebagai ujung tombak dari program pengendalian TB di wilayah tersebut.

Pertanyaan penelitian yang diajukan dalam disertasi ini adalah sebagai berikut:

1. Bagaimana pola perilaku pencarian pengobatan suspek TB di Indonesia?
2. Bagaimana efektivitas kinerja sistem kesehatan di dalam memberikan layanan TB berbasis DOTS?
3. Intervensi-intervensi apakah yang memiliki daya ungkit tertinggi untuk memperbaiki kinerja program pengendalian TB?
4. Bagaimana pengaruh munculnya epidemi HIV terhadap program TB di Indonesia?

Kerangka teoritis interaksi antara pasien TB dengan sistem kesehatan disajikan pada **bab 2**. Kerangka ini didasarkan atas model matematis sistem kesehatan dan pengendalian TB yang dikembangkan oleh Erasmus MC. Model tersebut disesuaikan dengan konteks sistem kesehatan di Indonesia, yang mempunyai tiga jenis penyelenggara layanan kesehatan, yaitu: fasilitas kesehatan pemerintah (DOTS), swasta (Non-DOTS) dan alternatif. Model matematis tersebut mencerminkan perjalanan pasien TB sejak munculnya gejala TB hingga mencari pengobatan di dalam suatu sistem kesehatan. Opini ahli digunakan untuk mengidentifikasi parameter-parameter perilaku mencari pengobatan, yang ditindaklanjuti dengan simulasi model untuk mendeskripsikan kinerja program pengendalian TB di Indonesia dan mengeksplorasi dampak berbagai strategi potensial dalam penemuan kasus. Simulasi model menunjukkan potensi

efektivitas penemuan penderita TB secara aktif pada situasi dimana penderita TB mempunyai keterbatasan akses terhadap fasilitas layanan kesehatan.

Bab 3 dan 4 mendiskusikan perilaku suspek TB dalam mencari pengobatan, baik di fasilitas layanan kesehatan maupun di komunitas. Kedua bab ini mengekplorasi keterlambatan pasien dan faktor-faktor yang mempengaruhinya. **Bab 3** bertujuan untuk mengekplorasi determinan perilaku suspek TB dalam mencari pengobatan dengan menggunakan kerangka teori perilaku terencana (*the theory of planned behavior* – TPB). Kami mewawancarai 194 suspek TB yang berkunjung ke lima BP4 di propinsi DIY dengan menggunakan kuesioner terstruktur. Kuesioner tersebut berisi pertanyaan-pertanyaan mengenai data sosiodemografi, keterlambatan pasien, perilaku pencarian layanan kesehatan dan modifikasi teori perilaku terencana (TPB). Hasil penelitian menunjukkan bahwa keterlambatan pasien relatif singkat (14 hari), dengan determinan utama berupa kemudahan akses terhadap fasilitas layanan kesehatan. Penelitian ini juga menunjukkan bahwa modifikasi TPB tidak berhubungan dengan keterlambatan pasien, meskipun tidak dapat mengesampingkan peran faktor-faktor psikososial dalam menjelaskan keterlambatan pasien.

Bab 4 menggambarkan pola perilaku suspek TB dalam pencarian pengobatan di komunitas. Survei potong lintang dilakukan untuk mengetahui proporsi suspek TB yang tidak mencari pengobatan dan mengeksplorasi determinan-determinan perilaku mencari pengobatan. Kami mewawancarai 746 suspek TB di komunitas di tiga kabupaten yang merepresentasikan wilayah urban, sub-urban dan pedesaan di propinsi DIY. Wawancara dilakukan untuk mengumpulkan data sosiodemografi, status TB, waktu mulainya gejala TB, pengetahuan tentang TB, jenis fasilitas kesehatan yang dikunjungi, dan durasi yang diperlukan untuk setiap kunjungan. Penelitian ini menemukan bahwa 11% suspek TB yang diwawancarai belum pernah mencari pengobatan. Dari suspek TB yang telah berobat, 46% diantaranya langsung mengunjungi layanan kesehatan modern (dokter, perawat, puskesmas dan rumah sakit) setelah gejala timbul. Usia yang lebih tua dan persepsi tentang mutu layanan yang baik, merupakan determinan untuk langsung menggunakan layanan kesehatan medis, sedangkan saran dari orang terdekat berhubungan dengan penggunaan fasilitas kesehatan alternatif setelah gejala timbul. Median durasi keterlambatan pasien relatif singkat (17 hari). Jenis kelamin laki-laki dan pengangguran merupakan determinan bagi peningkatan durasi keterlambatan pasien.

Bab 5 dan 6 mengeksplorasi kinerja sistem kesehatan dalam memberikan layanan TB di Indonesia. **Bab 5** mendiskusikan interaksi antara pasien TB dan sistem kesehatan selama proses penegakan diagnosis, meliputi eksplorasi determinan pergerakan pasien dalam sistem kesehatan, keterlambatan diagnosis, dan jumlah kunjungan pasien sebelum penegakan diagnosis TB. Untuk mencapai tujuan tersebut, dilakukan survei potong lintang pada pasien TB baru yang didiagnosis di 89 fasilitas DOTS di propinsi DIY. Kami merekonstuksi secara retrospektif proses pencarian pengobatan pada 253 pasien TB hingga proses penegakan diagnosis. Penelitian ini menemukan bahwa durasi keterlambatan diagnosis adalah 5,4 minggu, dengan median jumlah kunjungan ke

fasilitas kesehatan sebanyak empat kali. Determinan sosiodemografi pasien banyak yang tidak berhubungan dengan durasi keterlambatan diagnosis. Lebih dari 60% pasien TB memulai proses pencarian pengobatan di luar fasilitas DOTS, akan tetapi jumlah kunjungan di berbagai fasilitas DOTS lebih tinggi dibandingkan fasilitas Non-DOTS selama proses pencarian pengobatan. Di luar dugaan, kunjungan langsung ke fasilitas DOTS setelah gejala timbul ternyata tidak berhubungan dengan waktu diagnosis yang lebih pendek. Dengan demikian, disimpulkan bahwa keterlambatan diagnosis pasien TB di propinsi DIY terkait dengan sistem kesehatan yang tidak adekuat dalam memberikan layanan DOTS.

Bab 6 mendeskripsikan kinerja fasilitas DOTS dalam mendiagnosis TB. Penelitian ini memusatkan pada kepatuhan penyedia layanan kesehatan terhadap pedoman nasional untuk diagnosis TB, determinan tidak kembalinya suspek TB ke fasilitas kesehatan untuk menyelesaikan proses diagnosis, dan kuantifikasi durasi proses diagnosis pada suspek TB. Secara prospektif, proses diagnosis TB didokumentasi sejak seorang pasien dinyatakan sebagai suspek TB hingga diagnosis ditegakkan. Penelitian ini menggunakan formulir audit klinis untuk merekam jenis-jenis pemeriksaan yang dilakukan selama proses diagnosis TB secara berurutan. Kami mengumpulkan data tentang jenis kelamin penderita, umur, gejala-gejala TB, jenis, tanggal dan hasil setiap pemeriksaan diagnosis, serta hasil akhir diagnosis. Hasil penelitian menunjukkan bahwa 43,5% suspek TB di Puskesmas hilang selama proses diagnosis, sebaliknya tidak ada seorangpun suspek TB yang hilang di BP4. Seluruh suspek TB di BP4 dan 49% suspek TB di Puskesmas tidak didiagnosis sesuai dengan algoritma standard diagnosis TB yang diterbitkan oleh Sub-direktorat TB, Kementerian Kesehatan. Waktu yang diperlukan untuk proses diagnosis di Puskesmas secara statistik lebih lama dibandingkan dengan di BP4. Seluruh suspek TB yang menyelesaikan proses pemeriksaan diagnosis menjalani pemeriksaan mikroskopis dahak pada suatu waktu tertentu selama proses diagnosis dilakukan. Praktek ini sejalan dengan rekomendasi *International Standard for Tuberculosis Care* (ISTC).

Bab 7 dan 8 membahas tantangan program TB, terutama dengan semakin meningkatnya jumlah penderita HIV di Indonesia. **Bab 7** menggambarkan beban dan karakteristik sosio-demografi pasien TB-HIV, dan minat pasien TB untuk melakukan tes HIV dengan metode *voluntary counseling and testing* (VCT). Kami melakukan serosurvei HIV pada pasien TB baru yang didiagnosis, dengan menggunakan metode *unlinked anonymous*. Pasien yang setuju untuk berpartisipasi dalam survei tersebut ditawari untuk melakukan VCT apabila ingin mengetahui status HIVnya. Sebanyak 987 pasien baru TB berpartisipasi dalam survei tersebut dan prevalensi HIV ditemukan sebesar 1,9%. Infeksi HIV lebih jarang ditemukan pada pasien TB yang berkunjung ke Puskesmas bila dibandingkan dengan yang mengunjungi rumah sakit pemerintah. Infeksi HIV juga lebih sering ditemukan pada pasien TB dengan latar belakang pendidikan setingkat perguruan tinggi dan riwayat testing HIV sebelumnya. Penelitian ini juga menunjukkan bahwa 13,4% dari pasien yang berpartisipasi dalam penelitian tertarik untuk melakukan VCT. Diantara mereka yang

tertarik untuk VCT, hanya 39% (n=52) yang datang ke fasilitas VCT. Ketertarikan untuk melakukan VCT lebih banyak ditemukan pada kelompok pelajar dan pasien yang berkunjung ke Puskesmas.

Bab 8 lebih lanjut mendiskusikan tentang tantangan untuk memperkenalkan layanan tes HIV di dalam program TB. Bab ini mengeksplorasi penerimaan dan persepsi tentang hambatan untuk memberikan layanan tes HIV bagi pasien TB. Pengumpulan data dilakukan melalui wawancara mendalam kepada 33 pasien TB, tiga dokter spesialis, dan tiga wasor TB. Selain itu, dilakukan pula empat diskusi kelompok terarah dengan perawat yang menjadi petugas TB di Puskesmas dan rumah sakit. Hasil penelitian menunjukkan bahwa masih terdapat banyak miskonsepsi tentang HIV di kalangan petugas kesehatan dan pasien TB. Hambatan utama yang dirasakan oleh pasien TB antara lain: beban tambahan untuk mengunjungi layanan VCT dan kekhawatiran tentang hasil tes. Meskipun stigma menjadi perhatian utama pada petugas kesehatan, akan tetapi hal ini tidak terlalu diperhatikan dalam sikap pasien terhadap VCT. Hambatan utama yang dirasakan oleh petugas kesehatan adalah hambatan komunikasi, kekhawatiran bila menyinggung perasaan pasien, stigmatisasi dan tambahan beban kerja.

Bab terakhir (**bab 9**) mengulas keseluruhan hasil penelitan dan mendiskusikan jawaban atas pertanyaan-pertanyaan penelitian. Bab ini lebih lanjut membahas mengenai implikasi hasil penelitian terhadap program pengendalian TB di Indonesia, khususnya mengenai perlunya penguatan sistem kesehatan secara berkesinambungan dan cara terbaik untuk mengintegrasikan layanan tes HIV ke dalam program TB nasional. Bab ini ditutup dengan kesimpulan dan rekomendasi sebagai berikut:

KESIMPULAN

- Perilaku mencari pengobatan diantara suspek TB di propinsi DIY Indonesia relatif baik.
- Sistem kesehatan yang menyediakan layanan DOTS di propinsi DIY Indonesia tidak mampu mempertahankan kinerja yang efektif untuk mendiagnosis kasus-kasus TB.
- Perbaikan sistem kesehatan yang memberikan layanan DOTS akan memberikan daya ungkit yang lebih efektif terhadap kinerja program TB dibandingkan dengan intervensi yang dilakukan untuk mempengaruhi perilaku suspek TB dalam mencari layanan kesehatan.
- Dampak epidemi HIV di Indonesia terhadap program TB masih terbatas, akan tetapi tren peningkatan kasus koinfeksi TB-HIV harus dimonitor secara hati-hati.

REKOMENDASI

- Untuk memperbaiki penemuan kasus TB di Indonesia, intervensi sebaiknya difokuskan pada penguatan sistem kesehatan yang memberikan layanan DOTS.
- Tren peningkatan kasus TB-HIV harus dimonitor secara hati-hati agar dapat melakukan respon yang memadai dan tepat waktu.
- Melakukan adaptasi pedoman WHO mengenai penilaian kebutuhan dan implementasi strategi PPM agar sesuai dengan kebutuhan dan konteks sistem kesehatan di tingkat propinsi dan kabupaten.

Abbreviations

ACF : Active Case Finding
AIDS : Acquired Immune Deficiency Syndrome
BCG : Bacille Calmette-Guerin
CDR : Case Detection Rate
CI : Confidence Interval
CST : Care Support and Treatment
DALY : Disability Adjusted Life Years
DG : Directorate General
DOTS : Direct Observe Treatment Short-course
ECF : Enhanced Case Finding
FDC : Fixed Dose Combination
FGD : Focus Group Discussion
FIND : Foundation for Innovative New Diagnostics
FM GMU : Faculty of Medicine, Gadjah Mada University
HAART : Highly Active Anti-retroviral Therapy
HBM : Health Belief Model
HDL : Hospital DOTS Linkage
HIV : Human Immunodeficiency Virus
HR : Hazard Ratio
IDUs : Injecting Drug Users
IGRAs : Interferon Gamma Release Assays
IPT : Isoniazid Preventive Therapy
IQR : Inter-quartile Range
ISTC : International Standard Tuberculosis Care
IUATLD : International Union Against Lung Diseases
LED : Light Emitting Diode
LJ media : Löwenstein-Jensen Media
MDGs : Millennium Development Goals
MDR-TB : Multi Drug-resistant Tuberculosis
MHC : Microscopy Health Center
NAAT : Nucleic Acid Amplification Test
NTP : National TB Control Program
OR : Odds Ratio
OTC drugs : Over the Counter Drugs
PAL : Practical Approach To Lung Health

PITC : Provider-initiated Testing and Counseling
PPD : Purified Protein Derivative
PPM : Public-Private Mix
SES : Socio-economic Status
SHC : Satellite Health Center
TB : Tuberculosis
TPB : Theory of Planned Behavior
TST : Tuberculin Skin Test
UNAIDS : The Joint United Nations Program on HIV/AIDS
VCT : Voluntary Counseling and Testing
WHO : World Health Organization
WHO/EPI : World Health Organization/Expanded Program on Immunization
XDR-TB : Extensive Drug-resistant Tuberculosis

Acknowledgement

I began this journey with a naivety, even ignorance, of the TB problem in Indonesia. Despite the fact that one of my relatives died because of TB during my medical training and that Indonesia is ranked third as country with the highest number of TB cases globally, I felt that TB was a distant reality. Then, I was being fascinated with conflict and displacement issues, which was a major public health problem back in the early 2000's. However, a request from my previous dean Prof. Hardyanto Soebono and my mentor the late dr. Haryanto Supardi in 2004 to join a newly initiated collaborative project on TB-HIV training and research that lead to this PhD, changed my course of life. I began to see the human face of TB as we were more involved with the local and national TB control program and especially when I learnt that my sister was diagnosed with TB a few years later. Throughout my PhD endeavor, I have depended upon many individuals, groups and institutions, without whom it would not have been possible to finish this thesis. I wish to thank everyone who has played an important role throughout my journey.

Naturally I begin with my mentors. I am indebted to my promotor Prof. Jan Hendrik Richardus for your indispensable wise counseling, unconditional trust and thoughtful guidance. Your calmness has always comforted me. Thank you for trusting me and taking the risk as guarantor to reserve a time slot for my defense, even when my thesis was not yet finalized. Intellectually, I am deeply indebted to my mentor, and co-promoter Sake J de Vlas. Your role in shaping my PhD studies into coherent outcomes was incalculable. Through your sharp and critical comments, obsession for details and perfection, combined with Dutch hospitality, you managed to walk me through the complexities of PhD studies. I value your mentorship over the past years and the great times you provided me every time your family hosted me at your place.

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When I started to think of the design of my thesis cover, I turned my self to friends both offline and online. I give my huge appreciation to Sathya Buana (an online friend), who voluntarily offered his assistance and provided me with simple, yet artistic cover design. I could not thank enough for your effort. You are my guardian angel.

My sincere gratitude for all families and friends who made us feel at home in Rotterdam. In particular Bang Syam and his family for providing me with a place I can call home, since the first time I arrived in Rotterdam. I thank you for your endless and unconditional support, sharing your extraordinary life story and most of all, for being my best friend. I thank families of Oom Abdulah Eskak, Oom Sugijono, Jono Subagyo and many others Javanese Suriname families in Rotterdam for sharing their life, love and laughter with my family.

To my extended family in Indonesia, particularly my mother, my sisters and my in laws; thank you for always keeping your faith in me. Thank you for your unconditional love and support and reminding me that there is a place called home in Jogjakarta. Special appreciation goes to my sister Kirana, who gave me a reality check that TB can contract anybody, even my closest family.

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Last but not least, I thank you God…

Curriculum Vitae

Riris Andono Ahmad was born in Banyumas, Indonesia, on 5 May 1972. He graduated as medical doctor from Gadjah Mada University, Indonesia, in 2000. Prior to his medical degree, he received a master training in Epidemiology and Public Health from Umea University, Sweden, in 1999. He joined the Department of Public Health, Gadjah Mada University, Indonesia, in 2000. In 2002 he worked with WHO Indonesia as a national consultant for an emergency and humanitarian project in North Molluca, where he coordinated the post conflict WHO project on health system strengthening, communicable disease control and emergency preparedness. In 2003, he worked as a part-time consultant for an USAID funded project on an integrated malaria surveillance system in Indonesia. Following the collaboration between GMU, Erasmus MC and ITM Antwerp on a TB-HIV research project from 2004-2007, he focused his research interest on tuberculosis and HIV. Through this project, he worked closely with the national TB program (NTP). He was actively involved in several studies on TB and TB-HIV operational research in Indonesia funded by the NTP, WHO and KNCV. He was also involved in the development of the 2006-2010 Strategic Plan for Tuberculosis Control in Indonesia and the Indonesia Global Fund proposal in 2008. Starting in 2009 he was involved in providing lectures in the Tuberculosis Public Private Mix Course, and a course coordinator for the TB Operational Research Course, as part of international courses offered by the TBCTA Regional Training Center (Retrac) Asia, Faculty of Medicine, Gadjah Mada University, Indonesia.

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: Riris Andono Ahmad	PhD period: 2009-2011
Erasmus MC Department: Public Health	Promotor(s): Jan Hendrik Richardus
Research School: NIHES	Supervisor: Sake Jan de Vlas

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
– Survival Analysis for Clinicians	2010	1.4
– Conceptual foundation of epidemiologic study design	2010	0.7
– Causal inference	2010	0.7
– History of epidemiologic ideas	2010	0.7
– Advances in epidemiologic study design	2010	0.4
– Principles of Epidemiologic Data-analysis	2011	0.7
– Courses for the quantitative researcher	2011	1.4
– Bayesian Statistics	2011	1.1
– Diagnostic Research	2011	0.7
– Planning and Evaluation of Screening	2011	1.4
Specific courses (e.g. Research school, Medical Training)		
– IUATLD International Tuberculosis Course	2009	120 hours
Seminars and workshops		
– Regional meeting of national TB programme managers, WHO/SEARO, New Delhi, India.	2010	32 hours
– Workshop on development of standardized curriculum for Implementation/Operational Research, WHO, Geneva, Switzerland.	2010	32 hours
– Workshop on development of good health research practice course module, WHO, Geneva, Switzerland.	2010	32 hours

Presentations		
– Oral presentation entitled: Improving the national TB control program in Indonesia: explorations with a health systems model. Presented at the 5th European Congress on Tropical Medicine and International Health, Amsterdam, The Netherlands	2007	15 hours
– Poster presentation entitled: Economic evaluation of PPM-DOTS in Indonesia. Presented at the 39th World Conference for Lung Health, Cape Town, South Africa.	2008	8 hours
– Oral presentation entitled: Confirmed TB patients care seeking behavior and diagnostic delay in Jogjakarta Province, Indonesia. Presented at the World Federation Public Health Association Congress, Istanbul, Turkey.	2009	15 hours
– Oral presentation entitled: Implementation of TB diagnostic process algorithm in Puskesmas, in Jogjakarta Municipality. Presented at National Tuberculosis Parade conference, Bandung, Indonesia	2010	10 hours
– Poster presentation entitled: The diagnostic process of TB suspect in Jogjakarta, Indonesia: from algorithm to reality. Presented at the 39th World Conference for Lung Health, November 2010, Berlin, Germany.	2010	20 hours
– Oral presentation entitled: TB regional training center (ReTraC), FM GMU. Presented at the 42nd World Conference for Lung Health, Lille, France.	2011	10 hours

(Inter)national conferences		
– 39th World Conference for Lung Health, Cape Town, South Africa	2008	40 hours
– World Federation Public Health Association Congress, Istanbul, Turkey	2009	42 hours
– National Tuberculosis Parade conference, Bandung, Indonesia	2010	12 hours
– NTVG symposium, Utrecht, The Netherlands	2010	8 hours
– 41st World Conference for Lung Health, Berlin, Germany	2010	40 hours
– 42nd World Conference for Lung Health, Lille, France	2011	40 hours
Other	2011	8 hours
2. Teaching		
	Year	**Workload (Hours/ECTS)**
Lecturing		
– Lecture of Epidemiology course for medical students, Faculty of Medicine, Gadjah Mada University (FM GMU), Indonesia	2009	4 hours
– Lecture of Epidemiology course for master student in Tropical Health program, FM GMU, Indonesia	2009	20 hours
– Lecture on Tuberculosis Public Private Mix Course, TBCTA Regional Training Center (Retrac) Asia, FM GMU, Indonesia.	2019	12 hours
– Lecture on Course of Tuberculosis Operational Research Course, TBCTA Regional Training Center (Retrac) Asia, FM GMU, Indonesia.	2010	16 hours
– Lecture on introduction of mathematical modeling in International Health course, Erasmus MC	2011	8 hours
Supervising Master's theses		
– Supervising master thesis at GMU Master of Public Health Program (2 students)	2009	20 hours
Other		
– Course coordinator of the Epidemiology course for Master program in Tropical Health, FM GMU	2009	20 hours
– Course coordinator of the International Course on Tuberculosis Operational Research, TBCTA Regional Training Center (Retrac) Asia, Faculty of Medicine, Gadjah Mada University, Indonesia.	2010	40 hours