Delays in diagnosis and treatment of pulmonary tuberculosis, and patient care-seeking pathways in China: a systematic review and meta-analysis

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Table of Contents

List of Tables

List of Figures

List of Appendices

Abbreviations and Acronyms

TB- Tuberculosis
PTB- Pulmonary Tuberculosis
EPTB- Extra-pulmonary Tuberculosis
CS- Chest symptomatic
DOTS- Directly Observed Treatment, Short-course
China CDC- Chinese Center for Disease Control and Prevention
NTP- National Tuberculosis Programme
CI- confidence interval
PD- Patient delay
HSD- Health system delay
DxD- Diagnostic delay
RxD- Treatment delay
TD- Total delay
HCP- Healthcare provider
SPP- Smear positive patients

Abstract (English)

BACKGROUND

Early diagnosis and treatment is a cornerstone of the effective control of tuberculosis (TB), both in China and elsewhere.

OBJECTIVES

To undertake a systematic review of the delay between the onset of TB symptoms and initiation of appropriate treatment, based on existing studies, and to summarize available information on patients' care-seeking behavior and the pathways to treatment in China.

METHODS

A systematic review and meta-analysis was performed. PubMed, EMBASE, the Web of Science and the China National Knowledge Infrastructure (CNKI) databases were searched to identify relevant studies. Study selection, data extraction and quality assessment were undertaken by two independent reviewers. The median length and interquartile range (IQR) of the median delays reported by the primary studies were summarized.

In addition, further estimates were made of the mean delay and variation of delay at an individual study level, based on known medians, sample sizes, and the IQR/range for each case. These results were used to pool the delay duration using a random effects mode. Finally, to meta-analyze care-seeking behaviors, a random effects model was deployed, using exact binomial likelihood. The review was reported according to the PRISMA standards. Subgroup analyses were conducted of data from different regions of China, urbanization level, and type of TB.

RESULTS

A total of 94 studies were included in the final analysis. The median of length of the reported patient delay was 18 days (IQR = 10 to 23 days) and the pooled mean was 18.4 days (95% CI = 11.8 to 25 days, I^2=0). The median length of diagnostic delay was 11 days (IQR = 5 to 24 days) with a pooled mean of 8.8 days (95% CI = 3.6 to 13.9 days, I^2=19.8%). The figures for the median and pooled mean of total delay were 55.5 days (IQR = 43.8 to 64.3 days) and 52.5 days respectively (95% CI = -6.5 to 111.4 days, I^2=0). There was significant variation identified in treatment patterns across China. The total patient delay in western China (85.2 days, 95% CI=23.8 to 146.7 days) was substantially longer than that in eastern China (17.4 days, 95% CI=10.4 to 24.4 days). Of the 64 studies that reported care-seeking behavior, 23 indicated that village clinics were used for initial health consultations and 36 indicated that general hospitals (county level and above)

were the initial contact points. Importantly, 82.7% of patients, who initially sought care in general hospitals, were referred directly to TB dispensaries (95% CI = 51.2 to 95.6%), whereas the percentage was only 14.3% among patients who initially sought care in village clinics (95% CI = 6.1 to 63.2%). Overall, people who initially sought care in village clinics had a more complex route to take, before ultimate referral to TB dispensaries, visiting more healthcare providers.

CONCLUSIONS

The findings highlight the significant patient delay experienced by patients in western China and the complex pathways to care that confront TB patients in rural areas. Additionally, this is one of the first meta-analyses of median outcomes in this area that also considers estimations of mean and variation. As such, the pooled results using estimated mean and variation provide a useful indication of the strengths and limitations of this methodological approach. This methodological approach will be useful in identifying areas for research in future.

Abstract (French)

CONTEXTE

Le diagnostic et le traitement précoces sont des éléments clés pour un contrôle efficace de la tuberculose (TB) en Chine ainsi que dans les autres régions du monde.

OBJECTIFS

Conduire une revue systématique du délai entre l'apparition des symptômes de TB et l'initiation du traitement recommandé (par des recherches récentes) et résumer l'information disponible sur le comportement des patients qui recherchent le soin pour TB ainsi que les voies qu'ils entreprennent à la recherche du traitement en Chine.

MÉTHODOLOGIE

Une revue systématique et une méta-analyse ont été conduites. Des recherches ont été menée dans les bases de données PubMed, EMBASE, Web of Science et China National Knowledge Infrastructure (CNKI) afin d'identifier les études pertinentes. La sélection des études, l'extraction de données et l'évaluation de la qualité des études ont été entreprises par deux chercheurs indépendants. Les médianes des longueurs de temps et l'écart interquartile (EI) des médianes des délais déclarés par les études primaires ont été résumés.

De plus, des estimations ont été faites pour le moyen des délais et la variation des délais au niveau des études individuelles. Cela a été fait en se basant sur des médianes connues, les tailles des échantillons, et les EI/intervalles pour chaque étude de cas. Ces résultats ont été employés pour mutualiser la durée des délais en utilisant un modèle à effets aléatoires. Finalement, afin de conduire une méta-analyse des comportements de la recherche des soins pour TB, un modèle à effets aléatoires a été employé en utilisant le test binomial exact (bilatéral). Les revues ont été conduites en se fiant à la déclaration et à la liste de contrôle PRISMA. Des analyses de sous-groupe ont été conduites à partir des données de différents niveaux d'urbanisation, régions et type de TB.

RÉSULTATS

94 études ont été inclues dans l'analyse finale. La médiane de la durée du délai tel que reporté par le patient était de 18 jours (EI = 10 à 23 jours) et la moyenne était de 18,4 jours (IC à 95% = 11,8 à 25 jours, I2 = 0). La médiane de la durée du délai diagnostic était de 11 jours (EI = 5 à 24 jours) avec une moyenne de 8,8 jours (IC à 95% = 3,6 à 13,9 jours, I2 = 19,8%). La médiane et la moyenne du délai total étaient de 55,5 jours (EI = 43,8 à 64,3 jours) et 52,5 jours (IC à 95% = -6,5 à 111,4 jours, I2 = 0). Il y avait une variation significative identifiée dans les modes de traitement à travers la Chine. Le délai total du patient dans l'ouest de la Chine (85,2 jours, IC à 95% = 23,8 à 146,7 jours) était significativement plus longue que dans la Chine de l'est (17,4 jours, IC à 95% = 10,4 à

24,4 jours) puisque les intervalles de confiance ne se croisent aucunement. Des 64 études qui ont observé le comportement de recherche de soins de TB, 23 ont indiqué que les cliniques de village ont été utilisées pour les consultations initiales et 36 ont indiqué que les hôpitaux généraux (au niveau du comté et au-dessus) étaient des points de contact initial. Plus important encore, 82,7% des patients qui ont d'abord cherché à se faire soigner dans des hôpitaux généraux ont été référés directement aux dispensaires de TB (IC à 95% = 51,2 à 95,6%) alors que la même statistique était seulement de 14,3% chez les patients qui avaient initialement sollicité des soins dans les cliniques de village (IC à 95% = 6,1 à 63,2%). En général, les personnes qui ont d'abord cherché à se faire soigner dans les cliniques de village avaient un chemin plus complexe à naviguer dans le système de santé : elles ont dû visiter un nombre plus grand de services de santé avant d'obtenir une référence pour un dispensaire de TB.

CONCLUSIONS

Les résultats mettent en évidence le délai vécu par les patients dans l'ouest de la Chine ainsi que les chemins complexes à naviguer dans le système de santé qui confrontent les patients de TB des régions rurales. De plus, l'étude présente s'agit d'une des premières méta-analyses des médianes de résultats dans cette région qui tient compte des estimations de la moyenne et des variations de moyenne. Ainsi, les résultats utilisant l'estimation de la moyenne et de la variation des moyennes fournissent un indicateur utile des points forts et des limites de cette nouvelle méthode d'approche. Ceci servira à identifier des domaines de recherche dans l'avenir.

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Chapter 1. Introduction

1.1. Epidemiology of Tuberculosis

Tuberculosis (TB) is one of the major communicable diseases. It is estimated that approximately 1 in 3 people worldwide is infected with *Mycobacterium tuberculosis* [2]. According to the latest global tuberculosis report, from the World Health Organization (WHO), 9 million new TB cases were reported in 2013 [2], compared with 2.1 million new HIV cases in the same year [3]. Additionally, there were 1.5 million deaths that were attributed to TB in 2013 [2]. The burden of TB is highest in developing nations, particularly in the countries of South Asia and East Asia. Of the estimated 9 million incident cases, in 2013, more than half (56%) were from South Asia (predominantly India) or the Western Pacific Region (predominantly China) [2].

Nevertheless, the incidence of TB has been declining in recent years, and it is estimated that 37 million lives were saved between 2000 and 2013 [2]. However, the decline in TB incidence is slow – an average rate of 1.5% per year from 2000 to 2013 and 0.6% from 2012 to 2013 [2]. Furthermore, although effective medicine exists to completely cure tuberculosis, the disease remains the second most deadly infectious disease in the world in terms of number of deaths [4]. Therefore, if the new World Health Organization "End TB Strategy" target, which sets out to reduce the incidence rate of the disease by 90% between 2015 and 2035 [5], is to be achieved, then new approaches will be required.

1.2. Tuberculosis Epidemiology in China

The People's Republic of China (China) is the country with the second highest TB disease burden, with incidence reported at a total of 847,176 new and relapsed TB cases in 2013, accounting for approximately 14% of the global burden in that same year [2]. China also suffers from a serious epidemic of drug-resistant tuberculosis (DR-TB), especially

multidrug-resistant tuberculosis (MDR-TB) [6]. In 2013, there were approximately 41,812 cases of rifampicin-resistant and MDR tuberculosis in China, accounting for 13.3% of the global burden. Moreover, the number of DR TB cases is high not only on the absolute scale, which is reflective of the large population in China, but also in relative terms. According to the latest national MDR-TB survey in China, 5.7% of new TB cases and 26% of retreated cases were MDR-TB [6]. In comparison, the global average is much lower. Worldwide, only 3.5% of new cases and 20.5% of the retreated cases were MDR [2].

Nevertheless, great progress has been made over recent decades in the control of the TB epidemic in China. Since the WHO-endorsed Directly Observed Treatment, Short-course (DOTS) programme was scaled up in the country, in the late 1990s [7], the prevalence of smear-positive TB has decreased dramatically. Whereas 170 cases per 100,000 population were identified in 1990, by 2010 the figure had fallen to 59 per 100,000 [8]. According to the WHO Global Tuberculosis Report, the prevalence of TB (all forms) has also decreased by more than 50% (Figure 1), surpassing the Stop TB Partnership's target of halving TB prevalence, compared to the 1990 baseline, by 2015 [2, 9].

The decline in TB prevalence concurred with the scale-up of the DOTS programme, which was implemented as part of public health system reform (details in section 1.4.1). After implementing the programme across half of the country, during the 1990s, the prevalence of smear-positive TB fell by 19%, and the case detection rate (the percentage of estimated TB cases that are diagnosed and notified) increased to roughly 35% [7]. DOTS programme was subsequently scaled up nationwide, and by 2005, the prevalence of smear-positive TB had fallen by 57% compared to 2000 [8]. The level of case detection has also increased dramatically to about 85% (Figure 1) [2].

Nevertheless, despite these advances, TB control programme in China still face several challenges. The incidence of MDR among pulmonary TB cases has failed to decrease over the past decade, and the number of cases that are resistant to first-line TB

drugs among newly diagnosed TB patients rose from 34.2% in 2007/2008 to 36.9% in 2010 [6]. Additionally, according to the latest national prevalence survey, there are significant regional disparities. TB prevalence in 2010 was highest in western regions (212 per 100,000 population) and lowest in Eastern regions (66 per 100,000 population) [8].

1.3. Delays in Tuberculosis Diagnosis and Treatment

One of the main impediments to effective TB control is any delay in timely and accurate diagnosis [10]. Approximately 3 million TB cases and almost 50% of the rifampicin–resistant TB and MDR-TB cases were estimated to be undiagnosed or not notified in 2013 [2]. Delayed diagnosis and treatment is particularly serious because it can facilitate the ongoing transmission of the infection, worsen the health of the undiagnosed sufferers themselves, increase mortality, and may therefore contribute to the low rate of decline in TB incidence.

Previous studies have demonstrated significant delays in TB diagnosis and treatment across low-income and middle-income countries. According to a systematic review of 39 studies, spanning 45 of these countries, led by Sreeramareddy, the median time interval between the onset of symptoms suggestive of PTB and the patient's first contact with a health care provider was 31.7 days (patient delay). The median time interval between the first health consultation and the date of diagnosis was 28.4 days (health system delay). The median time interval between the onset of PTB symptoms and the initiation of anti-tuberculosis therapy (ATT) was 67.8 days (total delay) [11]. A subsequent systematic review, that focused on 23 studies from different parts of India, identified that the medians of patient, diagnostic and total delay were 18.4 days (IQR 14.3 to 27 days), 30 days (IQR 24.5 to 35.4 days), and 55.3 days (IQR 46.5 to 61.5 days) respectively [12]. Formal definitions for the types of delay are as follows (Figure 2):

- *Patient delay (PD): the time interval between the onset of symptoms suggestive of PTB and the patient's first contact with a health care provider (HCP).*
- *Diagnostic delay (DxD): the time interval between the first consultation with an HCP and diagnosis of TB.*
- *Treatment delay (RxD): the time interval between the confirmation of diagnosis and the initiation of anti-tuberculosis therapy (ATT).*
- *Total delay (TD): the time interval between the onset of symptoms and ATT initiation.*

China has a unique socio-political and cultural context compared to other low and middle-income countries. Nevertheless, since it is one of the top ten countries contributing to the three million undiagnosed TB cases every year worldwide [2], it is particularly vital that we should fully understand the delays in TB diagnosis that take place there. In order to do this, it we must identify the pathways to care-seeking in China and identify weak links that contribute to prolonged delays in diagnosis. This will facilitate interventions to improve the effectiveness of China's TB control programme.

Although a few studies assessing diagnostic and treatment delays have been published in China, these studies are regional and do not summarize the totality of evidence from all parts of the country. Somewhat surprisingly, there is only one national level systematic review of delay in TB diagnosis and treatment in China, published by Li and colleagues in 2003. While this review summarized data on risk factors associated with various delays, it did not summarize numerical data on delay duration [13]. Therefore, our first objective is to provide a systematic review of the literature from China focused especially on the length of delays associated with TB diagnosis and treatment that are encountered across the country.

Similarly, there is no existing review of data on TB patients' pathways to care in China. Li's review identified that one of the key risk factors contributing to delays in diagnosis and treatment of TB in China is related to the type of health facilities initially

visited by TB patients [13]. There is also evidence suggesting that complicated pathways to reach health facilities can contribute to prolonged delay in TB diagnosis [13]. However, overall coverage of this area in the academic literature remains very limited. This is problematic because China has a highly unique TB control program, which inevitably results in distinctive patterns of patient behavior and care-seeking. With this in mind, we also aimed to systematically review the literature on care-seeking behavior and pathways.

1.4. TB Care Delivery in China

1.4.1. Public Health System (CDC System)

The system of tuberculosis care and control in China is managed by the Chinese Center for Disease Control and Prevention (China CDC), an arm of the public health system. In the 1990s, China CDC established the China Center for Tuberculosis Control and Prevention [14], which is equivalent to the National TB Program (NTP) that exists in most Asian countries. TB diagnosis (chest X-ray and smear microscopy) and anti-tuberculosis drugs (ATT) are provided free of charge to presumptive and confirmed TB patients at their first visit in the CDC system [15]. The Chinese NTP itself is comprised of a network of TB dispensaries, which are established at 4 administrative levels: national, provincial, prefectural and county [15, 16] .Figure 3 provides a schematic illustration of the Chinese system for TB control.

Before the release of the National TB Control and Prevention Guideline (2011-2015) [15], China's TB dispensaries were mandated to diagnose and treat TB cases and conduct active follow-up of referred presumptive cases. The requirement of active follow-up obliged the dispensaries to identify and make contact with presumptive TB patients who were referred from the hospital system but failed to arrive and report to them for treatment within 3 days [15]. However, the 2011-2015 National TB Control and Prevention

Guide changed the mandates of TB dispensaries, moving the aforementioned functions to TB-specific hospitals (details in Section 1.4.4).

1.4.2. Hospital System

The hospital system in China is composed mainly of general hospitals. These institutions are owned by the state, but the government contributes little by way of funding [17]. Therefore, Chinese general hospitals are mainly financed by their own profits [17, 18]. In this regard, the hospital system in China is similar to the private healthcare sector of most Asian countries. These general hospitals form the backbone of the healthcare system in China. A majority of healthcare in China is delivered through general hospitals, which are available across the country, including in remote regions (organized at township and village level) where TB dispensaries are absent.

It should be noted that there is no system of general practitioners in China, and patients can go directly to specialist health care providers; this is the key reason why general hospitals are the most common first point of consultation for TB patients and chest symptomatics [19]. However, general hospitals are prohibited from confirming TB diagnosis and prescribing TB treatment. As a result, after tuberculosis-related symptoms have been identified in a general hospital, through chest X-ray and/or sputum examination, patients are referred to TB dispensaries for further diagnosis (Figure 3).

According to "the hospital classification system", formally defined by the Ministry of Health, all general hospitals in China are classified as primary, secondary, or tertiary hospitals, based on the quality of healthcare and medical education that they provide, as well as their research capacity [20]. Secondary and tertiary hospitals are those general hospitals with comprehensive healthcare services; as such they operate at the county level or higher [20]. Primary hospitals operate at township and village levels, and this category includes community/township health centers and village clinics/doctors [20]. TB

dispensaries, which operate at the county level, represent the lowest tier of the public TB control system and are not available at township and village levels.

1.4.3. Collaboration between Public Health and Hospital Systems

Hospital – Public Health collaboration is an important way to detect TB cases in China. Upon identifying presumptive TB cases, general hospitals are mandated to report and refer these cases to the public health system using the Chinese Information System for Infectious Diseases Control and Prevention (CISDCP). This contains real-time epidemiological data on 39 notifiable infectious diseases [21]. Designated staff at the China CDC are then responsible for reviewing and verifying each patient's information, using the CISDCP, and conducting active follow-up/tracing of those who fail to report at TB dispensaries following referral. In 2005, the Electronic Tuberculosis Information Management System (TBIMS) was also phased in. TBIMS collects key information on TB cases notified within the public health system [22]. It was designed to include more details on reported TB cases, such as patients' characteristics, diagnostic test results, treatment prescribed, etc. [22].

The proportion of presumptive TB patients referred to the public health system out of all presumptive TB patients identified in the same health facility is defined as the *referral rate* [15]. Of those referred to the public health system, the proportion of patients that successfully arrive at TB dispensaries within 3 days is defined as *referral arrival rate* [15]. The proportion of presumptive TB patients actively followed up by TB dispensaries out of all those who failed to arrive at TB dispensaries within 3 days of referral is defined as the *rate of active follow-up*. Among those actively followed up, the proportion of presumptive TB patients who eventually arrived at TB dispensaries is defined as the *trace rate*. Detailed formulas are summarized below:

$$Referral\ rate = \frac{number\ of\ presumptive\ TB\ patients\ referred\ to\ the\ public\ health\ system\ in\ general\ hospitals}{total\ number\ of\ presumptive\ TB\ patinets\ identified\ in\ the\ same\ health\ facility}$$

$$Referral\ arrival\ rate = \frac{tnumber\ of\ referred\ presumptive\ \ TB\ patients\ who\ arrived\ in\ the\ public\ health\ system}{total\ number\ of presumptive\ TB\ patinets\ who\ were\ referred\ to\ the\ public\ health\ system}$$

$$Active\ follow\ up\ rate = \frac{number\ of\ presumptive\ TB\ cases\ actively\ \ followed\ up\ by\ TB\ dispensaries}{total\ number\ of\ referred\ presumptive\ TB\ patients\ who\ \ failed\ to\ arrived\ at\ the\ public\ health\ system}$$

$$Trace\ rate = \frac{number\ of\ presumptive\ TB\ patients\ who\ arrived\ at\ TB\ dispensaries\ after\ \ following\ up}{total\ number\ of\ \ presumptive\ TB\ patients\ who\ were\ actively\ \ followed\ by\ TB\ dispensaries}$$

1.4.4. Moving Towards Hospital-based TB Control

Management of TB care by the China CDC has proven challenging. The majority of TB patients initially seek care in the hospital system, instead of the public health system [23]. Additionally, only a small proportion of people, who initially seek care at general hospitals, are reported to the public health system. Even fewer of these individuals are then able to arrive successfully at the public health system for clinical treatment and management. As a result, many TB patients who are first seen in general hospitals are never properly diagnosed, nor do they receive treatment under DOTS. Furthermore, there are fewer qualified medical professionals within the public health system than there are within the general hospital system. This is due to the relatively poor levels of compensation for medical staff within the public health system [24].

Recognizing these challenges, the Ministry of Health released a guideline in 2011 which was intended to streamline TB services across China and move the task of tackling TB towards hospitals, both in terms of diagnosis and care [25]. At the center of hospital-based approach are TB-specific hospitals, where the clinical management of TB is provided [25]. Tuberculosis-specific hospitals are those hospitals and health facilities that are designated by the relevant local authority to carry out the diagnosis and treatment of tuberculosis. They include specialized tuberculosis hospitals, pulmonary hospitals, chest hospitals, infectious disease hospitals, designated tuberculosis hospitals, and general hospitals with tuberculosis departments [25, 26].

However, new challenges seem to be emerging as China shifts its TB diagnosis and treatment efforts back to hospitals. The dramatic progress in the past was achieved through the dispensary model, whereby TB patients received treatment from the public health system, which adopted standard DOTS. It is unclear whether the shift of clinical management of TB from the public health system to tuberculosis-specific hospitals has had any impact on reducing delay in TB diagnosis and treatment, and streamlining patients' pathway to care. This is because there is very little published data available for the period since the new policy was introduced in 2011. In this review, therefore, we concentrate on examining systematically the delays and pathways to care before the implementation of the hospital-based TB care model. This can serve as a baseline for future comparison. Due to the limited numbers of studies that have been published concerning diagnosis and treatment delays in the period after 2011, we did not examine delays and care-seeking pathways after the transition to hospital-based TB care.

Chapter 2. Study Objectives

2.1. Primary Objective:

To systematically review and summarize available quantitative data on the diagnostic delay in China between the onset of the TB symptoms and the initiation of anti-TB treatment for patients who are suffering from TB or chest symptomatics. The types of delay of interest are listed and defined in Section 1.3.

2.2. Secondary Objective:

To explore existing care-seeking behavior and pathways of TB patients and chest symptomatics in China. Key patient care-seeking behavior data includes the type of health facilities that were first visited by these patients and the average number of health care providers consulted before confirmation of any TB diagnosis. Data pertaining to care-seeking pathways includes the referral rate, referral arrival rate, active follow-up rate, and trace rate (as previously defined).

Chapter 3. Systematic Review Methods

Prior to conducting our systematic review and meta-analysis, we prepared a protocol using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27] and checklist [28]. The review followed the roadmap for systematic review and meta-analysis suggested by Pai et al. [1] (Appendix 1). Two reviewers (ZZQ and XJH) independently carried out study selection, quality assessment, and data extraction.

3.1. Search Strategy

We developed a search strategy (Appendix 3) for PubMed with the assistance of a medical librarian. This strategy was then adapted to search Embase and Web of Science. Since DOTS was scaled up in the late 1990s in China [7], we searched all databases for the period between January 1, 2000 and January 1, 2015. We also adapted and applied our search strategy to China National Knowledge Infrastructure (CNKI), a key Chinese biomedical database covering 8,200 Chinese journals published after 1994 [29]. In addition, we searched the bibliographies of all primary studies, as well as previously published systematic or narrative reviews on TB diagnostic delays [11-13, 30], for additional data. All relevant citations were compiled in an EndNote library and de-duplicated. The citations then underwent a first screen of titles and abstracts, undertaken independently, by two review authors (ZZQ and XJH). Those found relevant were retrieved and underwent a second screen (this time of the full-text) using the inclusion and exclusion criteria listed below. Disagreements between the two reviewers were resolved by consulting a third reviewer (MP) and by contacting primary study authors.

3.2. Selection Criteria

Studies were included if all of the following four criteria were met:

1. Participants — studies were included if study participants met one of the following criteria. Participants surveyed had to be:

    a. Newly diagnosed drug-sensitive pulmonary TB (PTB) patients (either smear-positive or negative).
    b. Retreated drug-sensitive PTB patients.
    c. Patients with chest symptoms (cough $\geqslant$2 weeks and presumed to have TB).

2. Outcomes measures — studies were included if they reported one of the following outcomes.

    a. An outcome relating to delay time intervals among known TB cases and those with TB symptoms ($\geqslant$2 weeks of cough). This could relate to: patient delay; diagnostic delay; treatment delay; or total delay.
    b. An outcome relating to care-seeking pathways among known TB cases and those with TB symptoms ($\geqslant$2 weeks of cough). This could relate to: the first point of medical consultation; the average, minimum, and maximum number of health care providers visited before diagnosis; referral rate to the public health system; the rate of ATT initiation prior to arriving at an institution within the public health system; or tracing rate by TB dispensaries.

3. Types of studies included: cross-sectional, case-control, and cohort studies.

4. Language restrictions: English and Chinese studies were included.

When the same publication was indexed in both English and Chinese databases, only the one in the original language was kept. Similarly for multiple publications of the same study, only the latest publication was included. We excluded qualitative studies without numerical data. Conference abstracts usually contain inadequate information to judge quality, and were therefore also excluded. We restricted the studies to those conducted after 2000, as the DOTS programme had not scaled up in China before this point.

3.3. Quality Assessment

Quality assessment is a key component of systematic reviews because the quality of evidence generated is largely contingent on the quality of the selected studies [31]. Study quality in this case refers to the internal validity of the methodologies of the primary studies (i.e. lack of bias) [31]. There are several validated and widely accepted tools to assess the quality and risk of bias of primary studies, such as the Cochrane risk of bias tool for randomized trials [32], the Newcastle-Ottawa Scale for case-control and cohort studies [33], and the QUADAS tool for quality of diagnostic accuracy studies [34]. However, there are no standardized instruments to assess the methodological quality of studies on diagnostic delays and health care-seeking behaviors. Furthermore, none of the above mentioned tools are designed for cross-sectional studies.

Therefore, we developed a quality assessment tool for our review. This was based on a critical appraisal tool that had been developed for cross-sectional studies [35], one previous review on TB diagnostic and treatment delays and pathways to care [12], and other recognized epidemiological principles [36]. We used a component approach to develop the quality assessment tool, instead of assigning numeric scores, because a study showed that using summary quality scores is problematic [37]. Each item in the assessment checklist is scored as having a “low” or “high risk of bias”. When there was a lack of relevant information, the category of “no description” was assigned instead of “high risk of bias”. Subgroup analysis was performed based on the checklist (details in section 3.7). We pilot tested our quality assessment tool on 10 randomly selected articles and revised it. The final quality assessment instrument is shown below (Box 1).

Box 1. Quality assessment tool for Objective 1: Delay intervals

1. Patient sampling:
    a. Consecutive / random sampling. (low risk of bias)
    b. No description of the sampling strategy. (no description)
2. Definition of onset of TB symptom:

a. Clearly stated whether day 1 of coughing was counted as onset of TB symptom or after 2 or 3 weeks of coughing. (low risk of bias)
b. No clear description on the onset of TB symptoms. (no description)

3. Definition of confirmation of TB diagnosis:
    a. Clearly stated that the diagnosis of PTB is confirmed by culture or smear microscopy. (low risk of bias)
    b. No description. (no description)
4. Measurement of outcome
    a. Cross-check with hospital records (or other methods to eliminate recall bias). (low risk of bias)
    b. Used self-reported data without any cross checking. (high risk of bias)
    c. No description. (no description)

For objective 1, patient sampling was considered as having a low risk of bias if the participants were sampled consecutively or randomly. Since the results of patient delay are contingent on what is defined as the onset of TB symptoms, if a study did not clearly state whether day 1 of coughing was considered as the onset of TB symptoms, or whether a point of time 2 or 3 weeks after coughing started was considered as the onset, then this may lead to bias due to misclassification. Therefore, only studies with a clear definition of the onset of TB symptoms were considered as having a low risk of bias. Likewise, the results for diagnostic delay depend on what is considered as a confirmed TB diagnosis. Only studies which clearly stated that the diagnosis of PTB is based on gold standard (culture) or smear microscopy were considered as having a low risk of bias. As for the measurement of outcome, it was considered that the use of self-reporting data (without any cross-checking against medical records) had a high risk of bias. This is because of possible problems resulting from poor patient recall or recall bias that potentially might be left unadjusted for.

Box 2. Quality assessment tool for Objective 2: Care-seeking pathways

1. Patient sampling:
    d. Consecutive / random sampling. (low risk of bias)
    e. No description of the sampling strategy. (no description)

2. Participant selection
    a. Participants were recruited from general hospitals' outpatient department who may or may not end up in TB dispensaries. (low risk of bias)
    b. Participants who were registered with CDC were recruited. (high risk of bias)
    c. Presence of selection bias. (high risk of bias)
    d. No description of the selection strategy. (no description)
3. Definition of referral rate
    a. The denominator of referral rate is the number of presumptive cases identified. (low risk of bias)
    b. The denominator of referral rate is the total number of cases reported. (high risk of bias)
    c. No description. (no description)
4. Measurement of outcome
    a. Cross-check with hospital record (or other methods eliminate recall bias). (low risk of bias)
    b. Used self-reported data without any cross checking (high risk of bias)
    c. No description. (no description)

Similar assessments were made of patient sampling and outcome measurement methodologies for studies that related to objective 2 (Box 2). In terms of participant selection, it was recognized that those selected only from patients who were actually registered with the China CDC were likely to have care-seeking pathways that may be different from those who did not eventually reach the public health system. For example, presumptive PTB cases who were lost to follow-up or were retained in general hospitals may have a very low referral rate and referral arrival rate compared to those who were eventually registered with TB dispensaries. Therefore, these studies were considered as having high risk of bias. In contrast, participants selected from outpatient departments in general hospitals may have similar care-seeking behaviors to the broader population, because general hospitals were the most common first point of consultation for TB patients and chest symptomatics [19]. Therefore, these studies were considered to have a low risk of bias. In addition, those studies with selection bias, such as those that only selected areas with high TB notification rates, were considered as having a high risk of bias. Also, bearing in mind our definition of referral rate, the studies that computed the

referral rate by dividing the number of the patients who were referred to TB dispensaries by the total number of presumptive PTB cases were considered as having low risk of bias. However, since not all presumptive cases were reported, studies that used the total number of reported presumptive PTB cases as the denominator for referral rate probably overestimated the actual referral rate, and were therefore considered as having high risk of bias.

3.4. Data Extraction

We developed an electronic data extraction form using Microsoft Access 2013 to reduce data entry errors (Appendix 4). Two review authors piloted and revised the draft form on 10 randomly selected articles. Data extracted included study population characteristics, data on primary and secondary outcomes, and study quality. Since seniors were defined differently in different primary studies, we collapsed some age groups and defined seniors as 50 years and older. If a paper included data on hospital-based TB care, we either excluded it entirely, or only extracted data from the control pair (under the dispensary-based model). Since delay time intervals are not normally distributed, we extracted the median from the primary studies. Additionally, because the sum of the medians of various delays does not equal to overall median, such calculation was not performed when the median figure for total delay was not reported, When the median was not reported in the primary studies, it was substituted by mean delay duration. All time intervals reported were transformed into days.

The type of health facilities first visited were reported in the following categories: (1) pharmacies; (2) village clinics/doctors; (3) township hospitals/health facilities; (4) county and above general hospitals; (5) TB dispensaries; (6) private clinics. To obtain the number of health care providers consulted before confirmation of TB diagnosis, we extracted the median number of visits (mean was extracted if median was not reported) from the reported data. Where possible, we mapped the type of health care providers

and the number of subsequent visits prior to the initiation of ATT in the public health system. If the relevant information was missing from the selected studies, the primary study authors were contacted up to three times to complete the missing data.

3.5. Data Analysis

We summarized the main results in two tables, describing characteristics and outcome relating to each objective. One table set out outcomes relating to delays and the other established outcomes in terms of health care-seeking behavior. In addition, a separate summary of socio-economic and demographic profiles across the selected studies was prepared in histogram form.

3.5.1. Analysis of delay interval

The fact that conventional meta-analytic models for means assume normality of effect sizes posed a challenge for our analysis; the effect sizes of interest in this study were not normally distributed. Based on some primary studies [38-41] and a previous systematic review from India [12], we found instead that the distribution of delay duration was right (positive) skewed. To be certain of the skewness, we calculated the Bowley skewness coefficient (quartile skewness coefficient), which is defined as follows [42, 43]:

$$\frac{(Q_3 - Q2) - (Q2 - Q1)}{Q_3 - Q_1} = \frac{Q_3 + Q_1 - 2Q_2}{Q_3 - Q_1}$$

where Q_1 is the first quartile, Q_3 is the third quartile, and Q_2 is the median. A positive Bowley skewness value indicates that the median is closer to the lower quantile, i.e. positive skewness; a negative value indicates a negative skewness; and a zero Bowley skewness value indicates a symmetrical distribution of the data [43, 44]. To summarize delay duration, we adopted two approaches in our meta-analysis.

Method 1: First, we calculated the median and interquartile range (IQR) of the median delay durations (in days) reported by individual primary studies and constructed box plots on their spread around the median. The Mann-Whitney-Wilcoxon Test [45] was used to compare the estimates in different subgroups.

Method 2: Second, we estimated sample mean and standard deviation of each individual study using sample size, median, IQR, and/or range according to methods suggested by Wan et al. [46]. Through simulation studies, Wan's method outperformed other existing methods [47-49] in estimating both normally distributed and skewed data [46]. In scenario 1, under Wan's method, where IQR ($q_1 = the\ first\ quartile, q_3 = the\ third\ quartile$) and sample size ($n$) and median ($m$) are available, the mean ($\bar{X}$) and standard deviation (S) can be estimated as follows [46]:

$$\bar{X} \approx \frac{(q_1 + m + q_3)}{3}$$

$$S \approx \frac{q_3 - q_1}{2\Phi^{-1}(\frac{0.75n - 0.125}{n + 0.2})}$$

where $\Phi^{-1}(z)$ is the upper zth percentile which can be calculated using the command "*qnorm(z)*" in R (R Foundation for Statistical Computing, Vienna, Austria). Alternatively, in scenario 2, where range ($a = the\ minimun\ value, b = maximun\ value$) and sample size ($n$) and median ($m$) are available, the mean ($\bar{X}$) and standard deviation (S) can be estimated as follows [46]:

$$\bar{X} \approx \frac{(a + 2m + b)}{4}$$

$$S \approx \frac{b - a}{2\Phi^{-1}(\frac{n - 0.375}{n + 0.2})}$$

As Wan and colleagues discussed in their paper, inclusion of extreme values may lead to worse and less reliable estimates [46]. Since we expected that the distribution of delay durations in each primary study to be positive skewed with a long tail on the right side, we anticipated that this might cause difficulties - the minimum and maximum of delays reported in each primary study are very likely to be extreme. For example, one of our included articles [38] reported the minimum patient delay was 0 days while the maximum was 2,530 days. Therefore, we applied the formulae in scenario 1 to estimate the mean and variance in a primary study whenever the study reported the IQRs of delays. It was only when IQRs were not reported that the formulae in scenario 2 were applied.

Once we had estimated the mean diagnostic delay and standard deviation from each study, we pooled the means across studies using a random effects model [50]. The random effects model was used because that we expected that the observed variations in delays between studies were caused by more than random chance. For example, patients in different geographical regions seemed to experience different delays (details in section 3.7). Therefore, we preferred the random effects model because it does not assume that the true effect size for all studies is fixed [51]. All the analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria); the random effects model was built using the *"metafor"* and *"meta"* package [52, 53]. Restricted maximum likelihood was used to build the random effects model as per the R package manuals [52, 53]. For illustration purpose, selected R code to build the random effects model for patient delay is showed in Appendix 5.

3.5.2. Analysis of care-seeking behavior

Because we expected different care-seeking behaviors in different subgroups (urban *vs.* rural populations, etc.), we also used a random effects model to conduct the meta-analysis when analyzing care-seeking behavior [51]. However, we recognized that the conventional random effects model (DerSimonian and Laird method [54]) can

potentially lead to biases when analyzing care-seeking behaviors because the relevant data is reported as proportions. Point of healthcare entry (health facilities first visited), referral rate, active follow rate, and trace rate are all measured by proportions. One of the reasons why the conventional model leads to biases when analyzing proportions is that it approximates the distribution of within-study variations as normal while it is actually binomial, and normal approximation is not reliable when the proportion is close to one and zero [55-58]. Furthermore, this method does not correct for the correlation between estimated percentage and its variance, which also leads to bias in the pooled proportions [55-59]. An alternative is to build a generalized linear mixed model (GLMM), and fit it by the exact binomial within-study likelihood instead of an approximated normal distribution [57]. According to simulation study, the exact binomial likelihood approach always performed better than the approximated normal approach, and estimated proportions calculated using the exact binomial likelihood were unbiased [57].

We then constructed the GLMM model according to methods proposed by Hamza and colleagues [57]. For illustration purpose, we show here an example of meta-analysis of the percentage of patients who first visited village clinics upon onset of TB symptoms. The logit of the percentage reported by each primary study ($\mathrm{p_i}$) follows a normal distribution:

$$p_i \sim \mathcal{N}(p, \tau^2)$$

where the parameter p is the pooled mean logit of the percentage across all the studies. The parameter τ^2 is the between-study variance [57]. Because the within-study variance follows a binomial distribution, the observed number of patients who first visited village clinics in each study ($\mathrm{x_i}$) can be summarized as follows:

$$x_i \sim Binomial\ (\pi_i, n_i)$$

where $\pi_i = \frac{1}{1+e^{p_i}}$ and n_i is total number of subjects in that study [57]. The GLMM was fitted using the *lme4* package in R [60]. The corresponding R code is shown in Appendix 6.

3.6. Assessment of Heterogeneity

Heterogeneity in systematic reviews refers to variability (inconsistency) in results across different studies. It can arise from variability between sample populations or in the time when studies were conducted, from alternative definitions of certain outcome measures, from the overall quality of primary studies, and there is also the potential for random variability [61]. To investigate heterogeneity, we used the I-squared statistic, developed by Higgins et al [61].

$$I^2 = 100\% * \frac{Q - df}{Q}$$

where the parameter Q is the weighted sum of squared differences between the effect size in each primary study and the pooled effect size in all the studies. The Q statistic has a distribution of χ^2 with degree of freedom (df) of $k - 1$, where k denotes the number of primary studies [62, 63]. The I-squared statistic measures the percentage of total variability in effect measure that is attributable to heterogeneity rather than random chance [61]. An I-squared value between 30% to 60% suggests moderate heterogeneity and an I-squared greater than 75% represents considerable heterogeneity [64].

3.7. Subgroup Analyses

Delay in TB diagnosis and treatment as well as variations between pathways to care are highly context-specific and are strongly linked to local socio-economic and cultural issues. For this reason, we anticipated heterogeneity in our main outcomes measures. To address this, we conducted subgroup analyses. We stratified the data, using region, level

of urbanization of patients, type of TB, and study quality as the main stratifying variables. The rationale is provided below:

- Region (Western, Central, and Eastern regions). People living in the western region are likely to experience a longer delay before diagnosis and treatment because there is a significant difference in the overall level of economic development between the western and eastern regions [65]. Although basic diagnosis and anti-TB drugs are free of cost to all TB patients, patients have to pay out-of-pocket for other services, such as liver protection drugs, CT scans, etc. [66]. Patients living in the underdeveloped western region might not be able afford such services. According to the Chinese government, geographic regions are defined as follows: the 12 Eastern provinces include Beijing, Shanghai, Liaoning, Shandong, Jiangsu, Hebei, Tianjin, Zhejiang, Fujian, Hainan, Guangxi and Guangdong; the Central provinces are Henan, Jilin, Inner Mongolia, Shanxi, Heilongjiang, Hubei, Jiangxi, Hunan and Anhui; the 10 Western provinces include Ningxia, Xinjiang, Tibet, Shaanxi, Gansu, Qinghai, Chongqing, Sichuan, Yunnan, and Guizhou.
- Urbanization (urban, rural, and migrant). Migrants work and live in crowded environment and have been found to be reluctant to seek healthcare when ill [7]. They are also a group that is particularly susceptible to TB and likely to have a prolonged and complicated pathway to healthcare. Other previous research [13] has shown that rural residence is a risk factor associated with long delays. On the contrary, well-established urban groups are more likely to achieve speedy access to good healthcare. We therefore stratify the data according to urbanization level to reduce confounding.
- Type of PTB: Since a negative smear result is a risk factor for increasing delay [30], we stratified participants based on their smear status. Additionally, newly diagnosed patients tend to be less knowledgeable and

well informed about TB than retreated patients; hence their care-seeking behaviors were also analyzed separately.

- Quality of data: since patient delay is contingent on what is defined as the onset of TB symptoms, a subgroup analysis on patient delay was performance in the studies that were deemed “low risk of bias”.

3.8. Publication bias:

Publication bias occurs when the likelihood of a study being published is associated with the particular outcome of its research rather than quality of its scholarship and overall significance of the work itself. It has been found, for instance, that in biomedical research, positive results are more likely to be published than negative ones [67]. Funnel plots [68] and statistical tests derived from them, such as Begg’s test [69], Egger’s test [70], and the Trim and Fill method [71], are commonly used to assess publication bias in randomized control trials (RCTs). However, several researchers have voiced their concern about problems associated with application of these tests to observational data [70, 72]. In our case, since all of the primary studies used are observational, and effect estimates are time delays, publication bias was not formally assessed in this review.

Chapter 4. Results

4.1. Study Selection

The study selection process is shown in Figure 4 as a flow chart. A total of 2,433 potentially eligible articles were identified through literature searches, including 11 publications identified by hand-searching and screening the bibliographies of previously published systematic reviews. After removing any duplicates, the two review independently screened the titles and abstracts of the remaining 1,834 articles and selected 122 publications for full-text screening. In the end, 83 articles were included in our final analysis. Some articles reported outcomes separately for different subgroups without pooling results. For example, one article reported delay duration among migrant and urban populations separately; this was counted as two separate studies. Hence, the final analysis included 94 studies. A list of excluded studies, with reasons for their exclusion, is provided in the Appendix 7.

4.2. Characteristics of the Included Studies

Table 1 and Table 2 provide summaries of all those studies that were included for delay and pathway to care outcomes respectively. Social and demographic profiles across the 94 studies are shown in Figure 5. All studies were conducted between 2000 and 2012, and they all, with 5 only exceptions, used a cross-sectional design. The sample sizes of those reports using operational data from TB dispensaries were large, as expected, ranging from 567 to 978,500 patients, with a mean of 144,800. However, if these reports were excluded, the sample size of the remaining epidemiological studies ranged from 46 to 43,830 patients, with a mean of 1,396.

Regional distribution: The majority of the studies were conducted in 6 provinces: Shandong (n=20); Hunan (n=12); Chongqing (n=11); Jiangsu (n=6); Shanghai (n=5); and

Zhejiang (n=4). Those remaining were carried out in a further 25 provinces, as shown in Table 3. In terms of region, more than half of the studies were conducted in the eastern part of China (n=53); a similar number of studies were conducted in the western provinces (n=22) and in central China (n=19). The total number of all provinces referenced here exceeds 94 because many studies were conducted at multiple sites.

Urban versus rural distribution: In terms of the level of urbanization, 7 studies [38, 73-78] were carried out among urban populations; 21 among rural populations [79-96]; and 16 among migrant populations [39, 73, 75-78, 89, 97-105]. Migrant populations are defined as comprising people who dwell in an administrative district without having Hukou registration within that district for more than a specific period of time, usually 3 months [106].

Data sources: A total of 66 studies were conducted among PTB patients registered at TBIMS (post-2005) or at local TB registries (pre-2005); 16 studies [73, 75-77, 85, 92, 107-109] were carried out among participants who attended an outpatient department in a general hospital; while 5 studies [41, 84, 96, 110, 111] were conducted among community members. Our review also included 8 reports [112-120] from local TB dispensaries that used operational data obtained directly through surveillance systems – i.e. no epidemiological study was conducted.

Type of TB: There were 29 studies that included both new and retreated PTB patients [38, 74, 79, 88, 89, 95, 98, 104, 105, 115, 116, 119-131]; 23 studies included chest symptomatics [73, 75-77, 84, 92, 94, 96, 107-111, 113, 118, 132-134]; 13 studies included only smear-positive new PTB cases [39, 80, 81, 86, 88, 91, 93, 102, 135-139]; 13 studies included new PTB patients regardless of smear status [40, 41, 82, 83, 92, 97, 101, 103, 140-144]; 11 studies sampled smear-positive PTB cases (new and retreated) [78, 87, 90, 99, 100, 145-148]; 3 studies sampled both known PTB cases and chest symptomatics [117, 119, 149]; 1 study sampled retreated drug-sensitive PTB [150]. Furthermore, some studies restricted their participant populations to specific subgroups: 4 studies, all set out

in 1 article, focused on the poor [79]; 3 studies only included seniors [86, 123, 148]; while 2 studies concentrated specifically on students [92] and the young [123].

4.3. Quality Assessment

Figure 6 shows the quality assessment results for each outcome across the included studies.

Of the studies (n=56) relating to delay duration, 80% did not clearly state whether day 1 of coughing was counted as the onset of TB symptoms, or whether onset was measured from a point 2 or 3 weeks after that. Since all studies defined patient delay as the time interval between the onset of TB symptoms and first health consultation, this failure to specify the starting point for patient delay may lead to bias due to misclassification. In terms of the actual measurement of delay, 78% of the selected studies used self-reporting data without cross-checking against medical records. Poor recall or recall bias in each study may be left unadjusted for in these cases.

Of the studies (n=64) reporting care-seeking pathway, 75% of these were conducted among those who were registered with the CDC and whose care-seeking experience, therefore, may very likely differ from others who did not eventually reach the public health system, such as those who were retained in general hospitals. As a consequence, the reported care-seeking pathway from these studies may be biased and/or overestimated. In addition, almost 70% of the studies that reported referral rates did not provide a definition of referral rate. Of the remaining 30%, only half computed the referral rate by dividing by the total number of presumptive PTB cases. The other half used the total number of reported presumptive PTB cases as the denominator for referral rate. Since not all presumptive cases are reported, these studies probably overestimated the actual referral rate.

4.4. Patient Delay

Following the first method, as set out in Section 3.5.1, we calculated the median of all the median patient delays reported in the primary studies; the result was 18 days (IQR = 10 to 23 days) with a range of 3 to 107 days (Table 4). Although only 16 studies reported the IQR of patient delay, we calculated the Bowley skewness coefficients in those studies. All of the skewness coefficients were positive (range from 1.1 to 7.8), confirming our assumption of positive skewness.

In terms of the second method, we were able to estimate mean and standard deviation for 33 studies. The remaining primary studies only reported the median delay, but not IQR or range; hence, no estimation could be made in these cases. However, because the original distributions of delay in primary studies are right skewed and start from zero, fitting a normal distribution to the delay data will extend the distribution to the left of zero. We are aware that this method has flaws because it fits a normal distribution to non-normal data. These negative values are the intrinsic limitations of using this method because there can be no negative delay in real life. Additionally, since the original data is highly skewed (large Bowley skewness coefficients), the estimated within-study variation is very large which further leads to small I-squared values. In the case of patient delay, the I-squared using estimated means and variances was 0%. However, we are uncertain about whether or not the I-squared calculated using such method accurately reflects the degree of heterogeneity given the large estimated within-study variation. Therefore, in order to be certain, we performed a random effects meta-analysis using estimated mean and variance. We are aware the downside of using random effects model instead of fixed effects one is wide confidence intervals (CIs) of the pooled estimate. The overall pooled patient delay from the random effect model was 18.4 days (95% CI = 11.8 to 25 days), close to the median estimate of 18 days. Figure 8 displays the forest plot of patient delay from the 33 studies, stratified based on geographical region. The presence of negative lower limits of the pooled 95% CIs was the result of: (1) fitting a normal distribution to data that is right skewed and starts from zero; (2) large estimated variance

due to a high degree of skewness; and (3) random effects models give out larger CIs than fixed effects models [50].

Subgroup analyses were also conducted using both methods (Table 4). When using median and IQR to compare across subgroups, we employed the Mann-Whitney-Wilcoxon Test. The median patient delay among the migrant population was 18 days (IQR = 10 to 22.8 days) showing no significant difference (p=0.36) from that for the urban population (median = 16.5 days, IQR= 11.3 to 18 days). The median patient delay in the rural population was 11.3 days (IQR=8.8 to 27.8 days), also showing no difference with that of the urban population (p=1) and the migrant population (p=0.65). The median duration of reported patient delay in western China was 23 days (IQR = 18 to 31.9 days), 10 days (IQR = 10 to 19.3 days) in eastern China, and 14.7 days (IQR=8 to 27.8 days) in central China. None of the differences (p>0.05) between any two of the three subgroups were statistically significant.

We also meta-analyzed different subgroups using estimated means and variances (Table 4). The pooled mean patient delay was significantly larger for the migrant population than for the rural population when comparing both point estimates and the 95% confidence interval. Since only one study reported patient delay among the urban population, the data here could not be pooled. As is consistent with our results using the first method, the pooled mean patient delay was much larger in the western region (mean = 85.2 days, 95% CI = 23.8 to 146.7 days) than in the east (mean = 17.4 days, 95% CI = 10.4 to 24.4 days); the CIs almost do not overlap. The stratified results based on type of PTB using second method are similar to those using the first method.

When only limited to the studies that were deemed to have low risk of bias, only 6 studies [38, 41, 76, 107, 110] were selected (two of the studies were split one article). The median of all the 6 medians reported by individual studies were 15 days (IQR = 11.3 to 21 days), while the pooled mean patient delay was 20.9 days (95% CI = 0.1 to 41.8 days).

4.5. Diagnostic Delay

The median diagnostic delay was reported in 29 studies, 20 of which also reported IQR or range so that the mean and variance could be estimated (Table 5). According to the first method (see Section 3.5.1), the median length of the diagnostic delay reported was 11 days (IQR = 5 to 24 days), ranging from 3 to 107 days. All of the skewness coefficients from the 29 studies are positive (range from 1 to 13.7), indicating positive skewness. Therefore similar issues, as for patient delay (above), occurred when using the second method: negative delay values are shown in Figure 9 and there is a small I-squared figure (19.8%). For the same reasons as outlined in Section 4.4, we still used a random effects model to analyze diagnostic delay. The overall random-effects pooled diagnostic delay was 8.8 days with a 95% confidence interval spanning 3.6 to 13.9 days; this includes the median estimate (11 days).

Subgroup analyses were also conducted for diagnostic delay (Table 5). Urban populations had a median diagnostic delay of 6.5 days (IQR = 4.3 to 8.8 days), the median delay for migrant populations was 8 days (IQR = 7.3 to 14.3 days), while the median diagnostic delay for rural residents was 15.5 days (IQR = 5.8 to 24 days). According to the Mann-Whitney-Wilcoxon Test, none of the differences ($p>0.05$) between these subgroups are statistically significant.

Since only one study reported diagnostic delay in the urban population, the delay in this case was not pooled. However, the pooled mean diagnostic delay among the rural population was 21.6 days (95% CI = -13 to 56.1 days) while that among the migrant population was 11.5 days (95% CI = 6.8 to 16.2 days). The CIs between rural and migrant populations overlap; hence, the difference between these two subgroups was not statistically significant. Among the three geographic regions, the western part of China had a median diagnostic delay of 44.6 days (IQR = 20.8 to 60.3 days). This was in clear contrast to the eastern region, whose median diagnostic delay was 8 days (IQR = 4 to 18 days). The pooled average diagnostic delay in the west could not be calculated because

the relevant primary studies did not report any information that could be used to estimate the mean and variance. In terms of variation between type of PTB, diagnostic delay was longest among mixed new and retreated PTB and shortest among new smear positive PTB patients.

Since all studies that reported diagnostic delay were deemed to have low risk of bias (Figure 6), subgroup analysis based on quality assessment was not performed for diagnostic delay.

4.6. Treatment Delay

Only 9 studies reported treatment delay, and 5 of these studies included data that allowed us to estimate mean and variance. The median of the reported treatment delay was 1 day (IQR = 1 to 3 days), and the pooled treatment delay from the random effect model was 0 days (95% CI = 0 to 0 days).

Since there were only a very limited number of studies available in each subgroup, stratified analyses could not be performed using the pooled estimate method. The median length of reported treatment delay for each subgroup is shown in Table 6. The data indicates that ATT initiation was clearly quicker in the eastern region than in the center of China.

4.7. Total Delay

Only 4 studies reported total delay. The median total delay was 55.5 days (IQR = 43.8 to 64.3 days). Because there were only 1 study each for the west and the east and 2 studies for the center, we could not perform the Mann-Whitney-Wilcoxon Test to compare subgroups. The only study from western China reported a median total delay of 71 days; the one study from eastern China reported a median of 49 days; and the median of the

two total delays reported from central China was 45 days (IQR=36.5-53.5). The pooled mean total delay was close to the median estimate at 52.5 days (95% CI = -6.5 to 111.4 days). The reason for the low (and negative) lower limit of the CI is explained in Section 4.4. As only very limited numbers of studies were available that recorded total delay, there was insufficient information on subgroups to provide detailed analysis.

4.8. Initial Care-Seeking and Number of Health Consultations

Of the 64 studies included in our final pathway-to-care analysis, 37 reported the percentage of patients who first visited TB dispensaries, 36 studies reported the percentage of first visits to general hospitals at county or higher levels, 32 studies reported the percentage of visits to township hospitals, and 23 studies included data on visits to village clinics. Three studies reported the percentage of patients' first visiting township hospitals and village clinics collectively, describing these as primary healthcare facilities. First visit to private clinics was reported in 13 studies; however, only 1 of these yielded a definition for private clinics [126]. This was obtained after specific inquiry to the primary study author. The author defined private clinics as the type of health facilities whose property rights and earnings belong to private owners instead of the Chinese government. Only 11 studies included information on any visit to a pharmacy (Table 8).

Table 8 shows the pooled percentages of participants based on the types of healthcare facilities they first visited. Overall, the two most common points of healthcare entry (first contact) were village clinics (36.2%, 95% CI = 28.4 to 44.9%) and general hospitals at county and higher levels (34.7%, 95% CI = 30 to 40%). Significantly fewer people visited township hospitals first following the onset of TB symptoms (19.6%, 95% CI = 16.1 to 23.7%). The difference between number of first visits to both village clinics and county and larger hospitals, on the one hand, and to township hospitals, on the other, is significant, based on their non-overlapping CIs. The percentage of those who first visited TB dispensaries was also low – the pooled average was 7.8% (95% CI = 5.8 to

10.4%). However, based on non-overlapping CIs, the least common point of initial health consultation was the private clinic, with a pooled average of 0.1% (95% CI = 0.04 to 0.3%).

With regard to variation between different geographic regions, a high percentage (76.9%) of patients using self-medication (first visiting a pharmacy) was reported in a study conducted in the western region [77]. However the significance of this effect might be mitigated by the fact that the study was also conducted among the migrant population. As compared to those in central and eastern China, significantly fewer people in the western part of China first visited a village clinic (11.9%, 95% CI = 7 to 19.4%), while a higher proportion first visited a township hospital (34.7%, 95% CI = 24.6 to 46.5%).

4.9. Referral Rate

The general hospital referral rates reported from 9 studies were pooled and the results show that 78.9% (95% CI = 51 to 93.1%) of participants who were seen at general hospitals (county and above levels) were referred to TB dispensaries (Table 9). Of these 9 studies, 3 were conducted among outpatient visitors in general hospitals, and the pooled referral rate for this group was 69.5% (95% CI = 19.4 to 95.6%). The remaining 6 studies were conducted among the patients who were registered with TB dispensaries, and the referral rate was higher, at 82.7% (95% CI = 51.2 to 95.6%). This is expected since those patients who were not referred were also not registered with TB dispensaries. In the case of patients at township health facilities, the pooled referral rate was 52.3% (95% CI = 43.2 to 63.2%). Although the 95% CI in this case overlaps a little with that of the group within general hospitals at county and above levels (51.2 to 95.6%), the CI for township health facilities is generally outside (and lower) than that of the equivalent general hospital range. All 4 studies that reported referral rates of township hospitals were conducted among patient who registered with TB dispensaries. The referral rate of village clinics was the lowest, with a pooled estimate of 14.3% (95% CI = 6.1 to 30.1%). All 4

studies that reported village clinics' referral rate were carried out among people who were registered with TB dispensaries.

4.10. Referral Arrival Rate and Active Follow-Up Rate

As previously defined, the referral arrival rate is the proportion of patients referred to TB clinics who then actually successfully report to the clinics. Six studies, which were conducted among patients registered with the CDC, reported referral arrival rates with a pooled mean rate of 68.1% (95% CI = 44.8 to 85%). Seven of the eight reports from local TB dispensaries, which used operational data obtained directly through surveillance systems, reported referral arrival rate and the pool rate was 69.4% (95% CI = 41.8 to 87.8%) (Table 9). Two studies conducted among participants recruited at general hospital outpatient departments reported a mean referral arrival rate of 79.8% (95% CI = 74.6 to 84.1%). Since all these 95% CIs overlap, the differences between the subgroups are not statistically significant.

Three studies, based on data obtained from TB registries, report an active follow-up rate ranging from 93.5% to 99.84%.

4.11. Pathways for Access to TB Care

We traced the major pathways that TB patients took to reach TB dispensaries, based on 4 studies that reported the necessary detailed level of data [88, 91, 93, 104]. All 4 studies were conducted among registered PTB patients. The pathway flow chart that we derived (Figure 12) is consistent with some of the results reported above.

It appears that pathways to TB care were the most complicated for those patients who had first visited a village clinic or a village doctor. Of the 309 patients in this category, 261 were referred to one healthcare facility (168 to general hospital, 93 to township health

facilities) before reaching TB dispensaries, while 24 went through two health facilities. The remaining 48 went direct to TB dispensaries. Among the 67 patients who first visited a township hospitals, 33 were referred directly to TB dispensaries, while the other 34 were first referred to general hospitals before reaching TB dispensaries. We also summarized the average number of healthcare providers visited before reaching a diagnosis. According to 11 studies, the mean number of provider visits before TB diagnosis was 2.5 with a range from 1.1 to 4.

Chapter 5. Discussion

5.1. Main Findings

The overall median for reported patient delay was 18 days (IQR = 10 to 23 days) with a range of 3 to 107 days. The pooled overall mean patient delay based on estimated mean and variance was 18.4 days (95% CI = 11.8 to 25 days). Additionally, the overall median for reported diagnostic delay was 11 days (IQR = 5 to 24 days) and the pooled diagnostic delay was 8.8 days (95% CI = 3.6 to 13.9 days). The average patient delay in our review is significantly lower than the diagnostic delay when comparing the confidence interval. We find that the median figure for reported total delay was 55.5 days (IQR = 43.8 to 64.3 days) with a pooled mean effect of 52.5 days (95% CI = -6.5 to 111.4 days). A previous systematic review, based on 39 studies from 45 countries, reported a median patient delay, median diagnostic delay, and total delay of 31.7 days, 28.4 days, and 67.8 days respectively [11]. All of these median figures appear to be much higher than those that we have identified in China, especially that for diagnostic delay.

One key finding is that people living in western China took a longer time to reach effective TB care. The pooled median patient delay in the west of the country (85.2 days, 95% CI=23.8 to 146.7 days) was significantly higher than that in the east (17.4 days, 95% CI=10.4 to 24.4 days) given the non-overlapping confidence interval. This highlights the critical challenge in TB care and control that exists in the western part of China, which is less affluent than the wealthy eastern region. A national 10-year longitudinal survey, published in 2014, suggested that hospital infrastructure and resources were scarcer in western regions than in the east [151]. Together with our finding concerning the prolonged diagnostic delay in the west and higher prevalence of TB in this region [8], this indicates that there is an urgent need to enhance TB control in western China.

Although, based on Mann-Whitney-Wilcoxon Test, the differences in diagnostic delay among different subgroups were not significant at a 95% confidence level, the results in Section 4.11 nevertheless show that the people who initially sought care in village clinics had to follow the most complicated pathways to reach TB dispensaries.

When considering differences between pathways to TB care in China, we found that the healthcare providers that were most involved in providing initial health consultation to TB patients were village clinics and general hospitals at county and higher levels. On average, 36.3% (95% CI = 28.4 to 44.9%) and 34.7% (95% CI = 30 to 40%) of patients first visited village clinics/doctors or general hospitals at county and above levels respectively. In contrast, only a tiny proportion (0.1%) of people first visited private clinics. This is a direct contrast to the situation in other Asian countries. For instance, a previous systematic review, conducted in India, reported that 48% of (presumptive) PTB patients first visited a private practitioner [12]. Additionally, not surprisingly, (presumptive) PTB patients rarely go to TB dispensaries directly after the onset of TB-related symptoms. Only 7.8% (95% CI = 5.8 - 10.4%) of people visited dispensaries first.

A sizeable proportion of (presumptive) PTB patients who first visited a general hospital at county and level or above are referred to TB dispensaries (82.7%, 95% CI = 51.2 to 95.6%). However, at the most common point of healthcare entry, village clinics, the TB referral rate is very low at 14.3% (95% CI = 6.1 to 63.2%). Then, after referral, almost one third of all (presumptive) PTB patients fail to report to TB dispensaries, although, according to three selected TB dispensary reports, the active follow-up rate is very high, ranging from 93.5 to 99.8%.

5.2. Strengths and Limitations of the Review

Our review has several strengths. We developed a comprehensive search strategy and adapted it to several databases with the assistance of a medical librarian. Both English and Chinese biomedical databases were searched, which resulted in the inclusion of a

large number of studies. Additionally, two reviewers independently selected and extracted the data from all the selected studies, and also undertook independent quality assessment. If the required information was missing from the selected studies, the primary study authors were contacted up to three times to complete the missing data.

We also used two approaches to analyze delay duration. Since the effect size is very unlikely to be normally distributed, we reported the median figures for various reported delays. As this is the most common approach in current literature on the topic, we were able to compare the delays in China with other countries that have been the subject of previous systematic review. Additionally, we also estimated mean and variance as described by Wan et al. [46] and used a random effects model to pool the estimated delay duration. This is a novel way to analyze time-to-event outcome (delay duration). By using this method to calculate the pooled effect size, however, we were able to include more information that was could not be determined from the more standard methodology, such as sample size and within-study variation, etc. Additionally, using estimated mean and variance figures allowed us to conduct heterogeneity assessment and meta-analysis. This requires mean and variance data instead of information on median and IQR. Finally, measurements of initial care-seeking behavior and of rates related to referral were modeled and pooled using binomial exact likelihood instead of a normal approximate approach.

However, certain limitations must also be acknowledged. First, the method used to pool estimated mean delays is based on the assumption that these variables are normally distributed [46], whereas this is not the case. As demonstrated in Sections 4.4 and 4.5, the delay outcomes are in fact highly positive skewed. As a consequence, when we applied this estimation method, with its normality assumption, the original distribution was stretched to the left and the spread of the data also increased. Due to this increased spread, within-study variations were also elevated, which further resulted in small I-squared outcomes (0-20%). Additionally, since time-to-event outcomes are non-negative, the original distribution is positive skewed and has a lower bound at 0. When stretching

the left tail of the distribution, through the process of fitting it to a normal distribution, a new distribution was created that included negative values. Indeed, some of lower limits of 95% confidence intervals from the pooled estimates were negative, which clearly cannot reflect the situation in real life.

Overall, it is uncertain what influence the normality assumption associated with our estimation method had on the pooled estimates. There are a limited number of studies that meta-analyze median figures for time-to-event outcomes, and fewer using estimated means calculated from those medians. There one other paper, recently published [152], that meta-analyzes the median survival time difference between intervention and control groups. However, the method employed in that study could not apply to our research because of the necessary lack of any intervention or control group. It can be said, however, that this ours is one of the first few studies that tests meta-analysis results, using estimated mean from medians, and that it shows how most of the pooled delay data estimates are reassuringly close to the median of reported median delay duration.

A further potential limitation is the fact that most of the studies included in the review were conducted in the eastern region of China, whereas relatively few were conducted in the west, where the TB incidence is highest. As a consequence, there were insufficient studies to conduct subgroup analyses. Finally, as is the case with any systematic review, it is possible that some relevant studies were overlooked (or not published) and therefore omitted from the analysis.

5.3. Limitations of the primary studies

One of the main limitations of the primary studies used in our survey is that, in many cases, there was no clear definition given for patient delay. Almost none of the studies reported whether patient delay was measured from 2 weeks after the onset of a cough, or 3 weeks, or even from the first day of coughing symptoms. Instead, the definition was

usually vague: “from the onset of TB-related symptoms”. As a result, there may be bias due to potential misclassification. This problem was exacerbated by the fact that the process of contacting primary study authors to clarify such matters proved challenging; most Chinese studies indexed in CNKI do not provide email addresses of corresponding authors. With just a few exceptions, the only contact details provided by the publication were mailing addresses. Although we made efforts to discover relevant email contact details, using an author search on PubMed, we found that this process was also often unsuccessful. Many different authors, for example, were identified who share the same name, leaving us with no means of identifying the correct individuals to contact.

Additionally, there was always the risk that the findings of the primary studies could be undermined by the existence of poor recall, on the part of participants, or recall bias. Finally, the vast majority of the studies published only surveyed notified TB patients. However, this group is likely to experience less delay in diagnosis and treatment and to follow less a complex route to TB care compared to the TB patients who are lost to follow-up, or never seek treatment in the first place. Further studies to assess delay duration should recruit participants from outpatient departments in general hospitals and village clinics, which are the most common points of health care entry.

5.4. Conclusion and public health implications

Early diagnosis and treatment is important to effective global TB control. Our review demonstrated that PTB patients and presumptive cases experienced a relatively short diagnostic and treatment delay in China compared to that experienced in other high-burden countries [11, 12, 30]. While this is good news , there remains significant opportunities for improvement. Given that the most common points of entry to the healthcare system in China are general hospitals, instead of TB dispensaries, shifting to

a hospital-based TB control model could help to diagnose patients earlier, reduce diagnostic delay, and simplify the care-seeking pathway for millions of patients. Furthermore, since the referral rate at lower administrative levels is lower than that at county and above level, it is of little surprise that rural patients experience the longest median diagnostic delay compared to migrant and urban populations. This suggests that greater effort should be made to streamline the diagnostic pathway of TB patients in rural areas.

Our review also provides valuable information on regional differences within China. Compared to a nationwide average of slightly over one week diagnostic delay (11 days) across China, the inhabitants in western China experience a median diagnostic delay of 44.6 days. Additionally, there are still significant differences in terms of economic development and TB epidemics between the western and eastern parts of China. The less affluent west suffers a much heavier TB burden than the wealthier eastern area [8]. Therefore, we hope this finding will encourage the country's authorities to increase their efforts to combat TB and improve resource allocation in western China.

5.5. Suggestion for future research

There are a few statistical tools currently available to meta-analyze medians of time-to-event outcomes. One recent meta-analysis study [152], for example, examined median survival time using hazard ratio, which is the ratio of risk of an event happening in an intervention group as opposed to in a control group. However, such a method could not be applied to our meta-analysis (assessing baseline time-to-event outcomes) because there is no intervention group. As a result, existing systematic reviews and meta-analysis relating to delay duration have only reported figures for the median and IQR of the median. Of course, this approach does not take into account within-study variation and sample size. There is a need therefore for a more comprehensive methodology to meta-analyze median time-to-event outcomes.

Our attempt to estimate mean figures, using reported median and IQR data, before performing a meta-analysis using a random effects model, demonstrates the uncertainty associated with the normality assumption used in the estimation.

Chapter 6. References

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Chapter 7. Tables

Table 1 Study Characteristics (the studies pertaining to delay of diagnosis and treatment of TB), n=56

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	PD (d)	DxD (d)	RxD (d)	TD (d)
Chest symptomatics											
[73]	CS	Hospital	2002	Chongqing	U	776	Males: 53.5%; Seniors: 50.8%; Insurance rate: 68.2%; Primary School: 37.1%	18			
[73]	CS	Hospital	2002	Chongqing	M	229	Males: 56.3%; Seniors: 9.6%; Insurance rate: 5.7%; Primary School: 44.3%	23			
[110]	CS	Community residents	2004	Jiangsu		171	Males: 57.89%; Seniors: 63.2%; Farmers: 51.5%; Insurance rate: 65.5%; Primary School: 74.3%	10			
[75]	CS	Hospital	2004	Chongqing	M	229	Insurance rate: 6%; Primary School: 44%	23			
[75]	CS	Hospital	2004	Chongqing	U	776	Insurance rate: 68.9%; Primary School: 37%	18			

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	PD (d)	DxD (d)	RxD (d)	TD (d)
[76]	CS	Hospital	2007	Chongqing	U	458	Mean age: 60; Males: 54.8%	15			
[76]	CS	Hospital	2007	Chongqing	M	132	Mean age: 36; Males: 56.8%	22.5			
[92]	CC	Hospital	2007	Shaanxi		180	Only among the students				
[77]	CS	Hospital	2007	Chongqing	M	229	Insurance rate: 5.68%; Junior High: 49.12%; Primary School: 44.3%	23			
[77]	CS	Hospital	2007	Chongqing	U	776	Seniors: 50.77%; Insurance rate: 68.17%; Junior High: 46.65%	18			
[107]	CS	Hospital	2002-2003	Jiangsu		550	Males: 59.8%; Seniors: 33.1%; Farmers: 56.8%; Insurance rate: 19.5%; Primary School: 49.1%	15			
New PTB											
[82]	CS	CDC	2002	Jiangsu	R	187	Males: 74.9%; Seniors: 29.9%; Farmers: 73.8%; Insurance rate: 4.8%; Primary School: 55.6%	3	18		
[140]		CDC	2007	Shandong		819	Mean age: 53; Males: 72.5%; Seniors: 43%; Farmers: 80%; Insurance rate: 9%; Junior High: 88.3%; Primary School: 61.1%	6			
[97]	CS	CDC	2008	East	M	323	Mean age: 30; Males: 63.8%; Insurance rate: 6.5%; Junior High: 46.1%; Primary School: 21.4%	10			
[143]	CS	CDC	2012	Beijing	M&U	159	Mean age: 36.7; Males: 65.4%; Insurance rate: 62.9%	35	11		

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	PD (d)	DxD (d)	RxD (d)	TD (d)
[103]	CS	CDC	2003-2004	Shanghai	M	116	Males: 64.7%; Insurance rate: 0.9%; Primary School: 21.5%	18	13	0	
[141]	CS	CDC	2003-2004	Shanghai	M	222	Males: 66.67%; Insurance rate: 0.9%; Primary School: 22.97%	21	8		
[153]	RC	CDC	2003-2005	Shanghai	M	146	Males: 65.07%	19	5		
[83]	CS	CDC	2004-2005	Zhejiang	R	557	Males: 72.7%; Seniors: 34.2%; Farmers: 61.3%; Insurance rate: 57.5%; Primary School: 64.4%		7		
[40]	CS	CDC	2007-2008	Zhejiang, Guangxi		100	Mean age: 52.57; Males: 62%; Farmers: 67.5%; Insurance rate: 94%		4	1	
[41]	PS	Community residents	2009-2011	Shanghai, Jiangsu, Guangdong, and Hunan		202	Males: 77.7%; Seniors: 40.1%	37.8	0		
PTB (mixed with new cases and retreated cases)											
[98]	CS	CDC	2004	Hong Kong		1249	Males: 68.4%; Seniors: 47.7%; Retreatment: 9.3%	20			49
[125]	CS	CDC	2007	Zhejiang & Guangxi		100	Mean age: 52.57; Males: 62%; Farmers: 67.5%; Insurance rate: 94%		35	12	
[121]	CS	CDC	2007	Shandong		819	Mean age: 53; Males: 72.5%; Seniors: 43%; Farmers: 80%; Insurance rate: 9%; Junior High: 88.3%; Primary School: 61.1%	6			

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	PD (d)	DxD (d)	RxD (d)	TD (d)
[126]	CS	CDC	2008	Shandong		246	Farmers: 30.49%; Retreatment: 10.98%; Junior High: 28.05%; Primary School: 26.02%	5	30		
[95]	CS	CDC	2010	Hubei	R	583	Males: 57.8%; Seniors: 10.63%; Junior High: 58.66%; Primary School: 24.01%	8.4	12.78		
[123]	CS	CDC	2004-2009	Shandong		400	Mean age: 25.67; Males: 57.3%; Junior High: 90.3%	16			
[123]	CS	CDC	2004-2009	Shandong		332	Mean age: 65.1; Males: 83.4%	27.5			
[119]	CS	CDC	2005-2010	Xinjiang		43832		106.5	80.1		
[74]	CS	CDC	2006-2007	Shanxi	U	70	Males: 57.14%				28
[88]	CS	CDC	2006-2007	Shandong	R	247	Mean age: 55; Males: 76%; Primary School: 69%	10			
[105]	CS	CDC	2007-2008	Shandong	M	314	Mean age: 31.78; Males: 63.38%; Retreatment: 5.41%; Insurance rate: 35.35%; Junior High: 40.13%; Primary School: 18.79%	10			
[104]	CS	CDC	2007-2008	Shandong	M	314	Mean age: 31.78; Males: 63.38%; Retreatment: 5.41%; Insurance rate: 35.35%; Junior High: 40.13%; Primary School: 18.79%	10	8	1	

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	PD (d)	DxD (d)	RxD (d)	TD (d)
[124]	CS	CDC	2008-2009	Chongqing	M&U	233	Males: 65.7%; Seniors: 17.2%; Farmers: 14.6%; Insurance rate: 76%; Junior High: 27%; Primary School: 32.6%	29.9			
[89]	CS	CDC	2008-2009	Shandong	M	333	Males: 68.47%; Seniors: 10.81%; Farmers: 48.65%; Retreatment: 6.01%	15	0		
[89]	CS	CDC	2008-2009	Shandong	R	595	Males: 69.92%; Seniors: 32.77%; Farmers: 75.97%; Retreatment: 9.24%	21	0		
[38]	CS	CDC	2009-2010	Guangdong	U	4677	Males: 64%; Seniors: 2.33%; Retreatment: 10.18%	10	2	0	
[122]	CS	CDC	2010-2011	Beijing		1126	Males: 66.7%; Farmers: 49.9%	7			
Retreated drug-sensitive PTB											
[150]	CS	CDC	2011	Hunan	M&U	188	Mean age: 41.24; Males: 69.7%; Retreatment: 100%; Insurance rate: 73.4%	6			
Sputum smear positive (new)											
[81]	CS	CDC	2001	Shandong	R	190	Mean age: 48.1; Males: 65.3%; Primary School: 62.6%	12.5	2		
[136]	CS	CDC	2001	Jilin				53	7.7		
[135]	CS	CDC	2005	Yunan		11232	Mean age: 38; Males: 65.5%; Seniors: 15.5%; Farmers: 85.2%; Junior high: 27.2%; Primary school: 61.1%	60			71

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	PD (d)	DxD (d)	RxD (d)	TD (d)
[93]	CS	CDC	2005	Shandong	R	247	Mean age: 55; Males: 76%; Primary School: 69%	7			
[137]	CS	CDC	2007	Hunan		217	Mean age: 40.88; Males: 71.89%; Farmers: 71.89%; Insurance rate: 68.66%	21	29	3	
[102]	CS	CDC	2010	Hebei	M	168	Mean age: 46.12; Males: 53%; Seniors: 26.79%; Insurance rate: 31.5%; Junior High: 49.4%; Primary School: 15.5%	43	35		
[86]	CS	CDC	2005-2008	Zhejiang	R	210	Males: 77.14%; Junior High: 9%; Primary School: 89.3%	54.6			
[88]	CS	CDC	2006-2007	Shandong	R	247	Mean age: 55; Males: 76%; Primary School: 69%	10	24		
[38]	CS	CDC	2007-2008	Shandong	M	314	Mean age: 31.8; Males: 63.4%; Insurance rate: 35.4%; Junior High: 40.1%; Primary School: 18.8%	10	8		
Sputum smear positive (mixed with new and retreated cases)											
[87]	CS	CDC	2002	Hunan	R	318	Mean age: 38.2; Males: 72%; Farmers: 84.6%	30	24		
[90]	CS	CDC	2002	Hunan	R	318	Mean age: 38.2; Males: 72.01%; Farmers: 84.6%; Retreatment: 18.9%; Insurance rate: 4.4%; Junior High: 44.6%; Primary School: 41.8%	30	24		
[99]	CS	CDC	2008	Shandong	M	314	Mean age: 31.8; Males: 63.4%; Insurance rate: 35.4%; Junior High: 40.1%; Primary School: 18.8%			1	

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	PD (d)	DxD (d)	RxD (d)	TD (d)
[100]	CS	CDC	2009	Shandong	M	314	Mean age: 31.8; Males: 63.4%; Insurance rate: 35.4%; Junior High: 40.1%; Primary School: 18.8%	10			
[147]	CS	CDC	2009	Hunan	M&U	229	Mean age: 41.32; Males: 70.31%	8	12	1	
[78]	CS	CDC	2009	Hunan	M	46		8	18		
[78]	CS	CDC	2009	Hunan	U	178		8	11		
[145]	CS	CDC	2008-2009	Chongqing		30845	Males: 73.53%; Seniors: 13.7%; Farmers: 68.42%	38	1		

CS: cross sectional; RC: retrospective cohort; PC: prospective cohort; CDC: studies conducted among PTB patients registered with TB dispensaries; Hospital: studies conducted among visitors in outpatient department in general hospitals; M: migrant; U: urban; R: rural; PD: patient delay; DxD: diagnostic delay; RxD: treatment delay; TB: total delay;

Table 2 Study Characteristics (the studies pertaining to care-seeking behavior and pathway to care), n=64

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
Chest symptomatics										
[77]	CS	Hospital	2007	Chongqing	M	229	Insurance rate: 5.68%; Junior High: 49.12%; Primary School: 44.3%	Pharmacy: 76.86%;		
[75]	CS	Hospital	2004	Chongqing	U	776	Insurance rate: 68.9%; Primary School: 37%	Dispensary: 0.4%		
[118]	CS	TB registry	2001	Guangdong		8035			Referral arrival; 98.1%	
[84]	CS	Community residents	2003	Inner Mongolia	R	614	Males: 51.14%; Seniors: 21.66%; Farmers: 100%	Village: 51%;		
[96]	CS	Community residents	203	North	R	2308	Males: 53.12%; Seniors: 37.95%; Farmers: 73.31%; Insurance rate: 12.87%; Primary School: 73.92%			
[85]	CS	Hospital	203	Jiangsu	R	291	Males: 55.33%; Seniors: 15.81%; Farmers: 33.68%; Insurance rate: 16.15%; Primary School: 43.99%	Village: 44.33%;		
[133]	CS	CDC	2004	Sichuan		160	Mean age: 29.61; Males: 53.75%; Farmers: 25%	County+: 43.8%; Dispensary: 14.4%		

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[134]	CS	CDC	2004	Sichuan		185	Mean age: 30.56; Males: 56.76%	County+: 53.4%; Dispensary: 12.4%		
[94]	CS	CDC	2006	Guizhou	R	150	Mean age: 44.5; Males: 58.57%; Farmers: 80.7%; Insurance rate: 91.3%; Junior High: 42%; Primary School: 55.3%	Village: 14%; Township: 44.7%; County+: 20%; Dispensary: 16.7%		1.79
[92]	CS	Hospital	2007	Shaanxi		180	Only among the students		County+: 42.78%; Referral arrival: 42.86%; Active follow up: 45.69%; Traced; 39.62%	
[111]	CS	Community residents	2010	Hunan	M&U	259	Mean age: 50.85; Males: 53.7%; Seniors: 34.75%; Insurance rate: 88.8%			
[111]	CS	TB registry	2010	Shanghai		1577			Referral arrival; 87.06%	
[108]	CS	Hospital	2003-2004	Jiangsu		268			County+: 16%; Referral arrival: 90%;	
[108]	CS	Hospital	2003-2004	Shandong		325			County+: 73.7%; Referral arrival: 78.02%;	

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
New PTB										
[83]	CS	CDC	2004-2005	Zhejiang	R	557	Males: 72.7%; Seniors: 34.2%; Farmers: 61.3%; Insurance rate: 57.5%; Primary School: 64.4%	Pharmacy: 1.62%; Village: 31.42%; Township: 30.16%; County+: 21.01%; Dispensary: 13.29%	Village: 21.7%; Township: 54.2%; County+: 73.5%; Referral arrival; 93.02%	
[82]	CS	CDC	2002	Jiangsu	R	187	Males: 74.9%; Seniors: 29.9%; Farmers: 73.8%; Insurance rate: 4.8%; Primary School: 55.6%	Pharmacy: 4.8%; Village: 35.8%; Dispensary: 2.1%		
[144]	CS	CDC	2007	Hunan	U&R	186	Mean age: 40.5; Males: 69.4%	Pharmacy: 11.3%; Village: 16.7%; Township: 9.7%; County+: 67.1%; Dispensary: 3.8%	Village: 6.4%; Township: 61.11%; County+: 66.18%;	
[140]	CS	CDC	2007	Shandong		819	Mean age: 53; Males: 72.5%; Seniors: 43%; Farmers: 80%; Insurance rate: 9%; Junior High: 88.3%; Primary School: 61.1%	Village: 33%; Township: 31%; County+: 17%; Dispensary: 13.1%		
[40]	CS	CDC	2007-2008	Zhejiang, Guangxi		100	Mean age: 52.57; Males: 62%; Farmers: 67.5%; Insurance rate: 94%	Primary care: 38%; County+: 52%; Dispensary: 10%	Primary care: 31.58%; County+: 100%	1.1

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[97]	CS	CDC	2008	East	M	323	Mean age: 30; Males: 63.8%; Insurance rate: 6.5%; Junior High: 46.1%; Primary School: 21.4%	Primary care: 27.2%; County+: 57.6%; Dispensary: 5.9%		
[143]	CS	CDC	2012	Beijing	M&U	159	Mean age: 36.7; Males: 65.4%; Insurance rate: 62.9%	Township: 15.72%; County+: 64.15%; Dispensary: 7.55%		
[142]	CS	CDC	2004	Sichuan		157		Dispensary: 14%		
[92]	CS	CDC	20092010	Shandong	R	1431	Males: 68.6%; Seniors: 29.6%; Farmers: 69.2%; Insurance rate: 91.26%; Junior High: 35.1%; Primary School: 42.9%	Village: 33.4%; Township: 14.54%; County+: 41.2%; Dispensary: 16.98%		
PTB (mixed with new and retreated cases)										
[88]	CS	CDC	20062007	Shandong	R	247	Mean age: 55; Males: 76%; Primary School: 69%	Pharmacy: 2%; Village: 58%; Township: 21%; County+: 21%; Dispensary: 0.8%		
[126]	CS	CDC		Shandong		246	Farmers: 30.49%; Retreatment: 10.98%; Junior High: 28.05%; Primary School: 26.02%	Pharmacy: 9.35%; Township: 11.8%; County+: 21.95%; Dispensary: 7.7%		

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[121]	CS	CDC	2007	Shandong		819	Mean age: 53; Males: 72.5%; Seniors: 43%; Farmers: 80%; Insurance rate: 9%; Junior High: 88.3%; Primary School: 61.1%	Village: 33%; Township: 31%; County+: 17%; Dispensary: 13.1%		
[95]	CS	CDC	2010	Hubei	R	583	Males: 57.8%; Seniors: 10.63%; Junior High: 58.66%; Primary School: 24.01%	Village: 17%; Township: 35.2%; County+: 21.6%; Dispensary: 9.8%		
[124]	CS	CDC	20082009	Chongqing	M&U	233	Males: 65.7%; Seniors: 17.2%; Farmers: 14.6%; Insurance rate: 76%; Junior High: 27%; Primary School: 32.6%	Township: 19.3%; County+: 42.9%; Dispensary: 8.6%		
[104]	CS	CDC	20072008	Shandong	M	314	Mean age: 31.78; Males: 63.38%; Retreatment: 5.41%; Insurance rate: 35.35%; Junior High: 40.13%; Primary School: 18.79%	Township: 41.7%; County+: 48.73%; Dispensary: 6.37%		2.44
[125]	CS	CDC	2007	Zhejiang & Guangxi		100	Mean age: 52.57; Males: 62%; Farmers: 67.5%; Insurance rate: 94%	Township: 20%; County+: 52%; Dispensary: 10%		2.6

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[127]	CS	CDC	2000	Fujian					County+: 29.2%; Referral arrival: 70.3%;	
[130]	CS	CDC	2002	Hebei		308			Referral arrival: 24.68%; Traced; 33.19%	
[79]	CS	CDC	2004	Fujian	R	217	Junior High: 16.59%; Primary School: 75.58%; Only the poor	Village: 54%; Township: 13%; County+: 24%; Dispensary: 9%		4
[79]	CS	CDC	2004	Henan	R	228	Junior High: 29.96%; Primary School: 55.95%; Only the poor	Village: 69%; Township: 10%; County+: 13%; Dispensary: 8%		4
[79]	CS	CDC	2004	Liaoning	R	223	Junior High: 44.84%; Primary School: 45.74%; Only the poor	Village: 29%; Township: 26%; County+: 27%; Dispensary: 13%		3
[79]	CS	CDC	2004	Xinjiang	R	221	Junior High: 32.42%; Primary School: 54.34%; Only the poor	Village: 18%; Township: 42%; County+: 29%; Dispensary: 11%		3
[131]	CS	CDC	2006	Ningxia		221			Referral arrival: 48.87%; Traced; 80.5%	

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[115]	CS	TB registry	2008	Shandong		19293			Active follow up: 99.84%; Traced; 76.37%	
[120]	CS	TB registry	2010	National		978477			Referral arrival: 45.6%; Traced; 73.4%	
[128]	CS	CDC	2012	Guizhou		243	Males: 60.9%; Seniors: 22.2%; Retreatment: 36.2%; Insurance rate: 96.7%; Junior High: 27.2%; Primary School: 58.8%	Village: 6.2%; Township: 23.9%; County+: 41.1%; Dispensary: 24.3%		
[116]	CS	TB registry	20072008	Guangdong		1837			Referral arrival: 26.8%; Traced; 57.1%	
[129]	CS	Hospital	20102011	Beijing	M&U	96	Males: 65.7%; Seniors: 17.2%; Farmers: 14.6%; Insurance rate: 76%; Junior High: 27%; Primary School: 32.6%	Township: 19.3%; County+: 42.9%; Dispensary: 8.6%	County+: 95.83%;	
PTB and chest symptomatics										

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[117]	CS	TB registry	2008	Guizhou		567			Referral arrival: 50.79%; Active follow up: 91.76%; Traced; 50%	
[119]	CS	TB registry	2009	Zhejiang		4120			Referral arrival: 46.8%; Active follow up: 95.2%; Traced; 86.4%	
[149]	CS	CDC	2011	Shanghai		395			Traced; 81.8%	
Retreated drug-sensitive PTB										
[150]	CS	CDC	2011	Hunan	M&U	188	Mean age: 41.24; Males: 69.7%; Retreatment: 100%; Insurance rate: 73.4%	Township: 19.7%; County+: 40.4%; Dispensary: 19.1%		
New sputum smear positive										
[91]	CS	CDC	2005-2006	Shandong	R	247	Mean age: 55; Males: 76%; Primary School: 69%	Pharmacy: 1.2%; Village: 58%; Township: 11%; County+: 24.24%; Dispensary: 0.81%		

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[93]	CS	CDC	2005	Shandong	R	247	Mean age: 55; Males: 76%; Primary School: 69%	Pharmacy: 2%; Village: 57.9%; Township: 10.9%; County+: 25.9%; Dispensary: 1.2%	Village: 5.6%; Township: 37%; County+: 76.2%;	2
[88]	CS	CDC	2006-2007	Shandong	R	247	Mean age: 55; Males: 76%; Primary School: 69%	Pharmacy: 2.02%; Village: 58%; Township: 11%; County+: 25.51%; Dispensary: 0.81%		2
[154]	CS	CDC	2007	Hunan	Urban & Rural	217	Mean age: 40.88; Males: 71.89%; Farmers: 71.89%; Insurance rate: 68.66%	Pharmacy: 9.68%; Village: 14.29%; Township: 8.29%; County+: 36.41%; Dispensary: 12.44%		1.71
[102]	CS	CDC	2010	Hebei	M	168	Mean age: 46.12; Males: 53%; Seniors: 26.79%; Insurance rate: 31.5%; Junior High: 49.4%; Primary School: 15.5%	Pharmacy: 73.2%; Township: 5.4%;		
[136]	CS	CDC	2001	Jilin					Referral arrival; 72.4%	

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[81]	CS	CDC	2001	Shandong	R	190	Mean age: 48.1; Males: 65.3%; Primary School: 62.6%	Village: 45.8%; Township: 20.5%; County+: 29%; Dispensary: 4.9%		
[39]	CS	CDC	2007-2008	Shandong	M	314	Mean age: 31.8; Males: 63.4%; Insurance rate: 35.4%; Junior High: 40.1%; Primary School: 18.8%	Township: 8.92%; County+: 58.28%;		
[139]	CS	CDC	2004	Shanxi		291			Referral arrival; 86.6%	
[80]	CS	CDC	2007	Guangxi	R	109	Males: 73.4%; Seniors: 61.5%; Farmers: 73.4%; Insurance rate: 16.5%; Primary School: 74.3%	Village: 52.23%; Township: 21.1%; County+: 20.18%; Dispensary: 6.4%	Village: 35.6%; Township: 64.44%; County+: 66.1%;	
[138]	CS	CDC	2003-2004	Zhejiang		174			Referral arrival; 61.6%	
[90]	CS	CDC	2002	Hunan	R	318	Mean age: 38.2; Males: 72.01%; Farmers: 84.6%; Retreatment: 18.9%; Insurance rate: 4.4%; Junior High: 44.6%; Primary School: 41.8%	Township: 33%; County+: 33.3%; Dispensary: 5.3%		2.46

ID	Study type	Data source	Year	Province	Residence	Size	Characteristics	Health care entry (%)	Referral and traced (%)	Mean HCP visit
[100]	CS	CDC	2009	Shandong	M	314	Mean age: 31.8; Males: 63.4%; Insurance rate: 35.4%; Junior High: 40.1%; Primary School: 18.8%	Primary care: 31.8%; County+: 40.8%		
Sputum smear positive (mixed with new and retreated cases)										
[147]	CS	CDC	2009	Hunan	M&U	229	Mean age: 41.32; Males: 70.31%	Township: 17.1%; County+: 48%; Dispensary: 15.7%		
[78]	CS	CDC	2009	Hunan	M&U	224	Mean age: 41.1; Males: 69.6%	Township: 17.4%; County+: 46.9%; Dispensary: 16.1%		
[146]	CS	CDC	2009	Hunan		229	Mean age: 41.32; Males: 70.31%	Township: 17.1%; County+: 48%; Dispensary: 15.7%		
[119]	CS	CDC	20022005	Chongqing		141	Males: 85.1%; Seniors: 100%	Township: 49.6%; County+: 25.5%; Dispensary: 18.4%		
[114]	CS	TB registry	2006			1471			Referral arrival: 76.6%; Traced; 63.5%	

HCP: healthcare provider; CS: cross sectional; RC: retrospective cohort; PC: prospective cohort; CDC: studies conducted among PTB patients registered with TB dispensaries; Hospital: studies conducted among visitors in outpatient department in general hospitals; TB registry: data from annual TB dispensary reports; M: migrant; U: urban; R: rural; PD: patient delay; DxD: diagnostic delay; RxD: treatment delay; TB: total delay;

Table 3 Number of studies conducted in different provinces and regions

West	N=22	Center	N=18	East	N=53*
Chongqing	11	Hunan	12	Shandong	20
Sichuan	3	Shanxi	2	Jiangsu	7
Guizhou	3	Jilin	1	Zhejiang	6
Xinjiang	2	Inner Mongolia	1	Shanghai	6
Shaanxi	1	Henan	1	Guangdong	4
Ningxia	1	Hubei	1	Guangxi	3
Yunnan	1	Jiangxi	0	Fujian	2
				Hebei	2
				Liaoning	1
				Beijing	1
				Hong Kong	1

* The reason why the sum of the numbers of studies in the three regions is less than 94 is that there are two studies which didn't report the provinces where the studies were carried out.

Table 4 Patient delay (days)

Patient delay	Median of reported median delays			Pooled estimates from random effects model using estimated means and variances		
	N	Median	IQR	N	Mean	95% CI
Overall	51	18	10-23	33	18.4	11.8-25
Residence						
Rural	10	11.3	8.8-27.8	5	11.5	-0.9-23.8
Migrant	15	18.0	10-22.8	14	21.5	11.1-32
Urban	6	16.5	11.3-18.0	1	-	-
Geographic region						
West *	12	23	18-31.9	4	85.2	23.8-146.7
Center	10	14.7	8-27.8	6	19.2	-1.5-39.95
East *	28	10	10-19.3	22	17.4	10.4-24.4
Type of PTB						
Chest symptomatics	10	18	15.8-22.9	4	19.9	-1.1-40.9
New & retreated PTB	15	10	20.5	11	33.1	14.5-51.7
Smear positive (new & retreated)	7	10	30	4	31.1	-8.5-70.7
New PTB	8	18.5	24.5	7	15.6	6.1-25.1
Smear positive (new)	10	21	50.5	6	15.6	1.1-30.3
Low risk of bias for the quality criteria "2. Definition of onset of TB symptom"						
Low risk of bias	6	15	11.3-21	6	20.9	0.1-41.8

* The difference of patient delay between western and eastern China was statistically significant due to non-overlapping confidence intervals.

Table 5 Diagnostic delay (days)

Diagnostic delay	Median of reported median delays			Pooled estimates from random effects model using estimated means and variances		
	N	Median	IQR	N	Mean	95% CI
Overall	29	11	5-24	20	8.8	3.6-13.9
Residence						
Rural	8	15.5	5.8-24	4	21.6	-13-56.1
Migrant	6	8	7.3-14.3	6	11.5	6.8-16.2
Urban	2	6.5	4.3-8.8	1	-	-
Geographic region						
West	2	44.6	20.8-60.3	0	-	-
Center	8	18	12-24	5	50.2	8.2-92.2
East	17	8	4-18	13	8.6	3.0-14.2
Type of PTB						
Chest symptomatics	0	-	-	0	-	-
New & retreated PTB	8	10.4	1.5-31.3	5	120.8	38.5-202.8
Smear positive (new & retreated)	7	15	11.3-22.5	4	47.3	5.1-89.6
New PTB	8	7.5	4.8-11.5	5	10.7	5.7-15.6
Smear positive (new)	7	24	7.9-29	4	3.4	-2.3 – 9.1

Table 6 Treatment delay (days)

Treatment delay	Median of reported median delays			Pooled estimates from random effects model using estimated means and variances		
	N	Median	IQR	N	Mean	95% CI
Overall	9	1	1-3	5	0	0-0
Geographic region						
West	0	-	-	0	-	-
Center	3	3	1-3	2	-	-
East	9	1	0.3-1	3	-	-
Type of PTB						
Chest symptomatics	0			0	-	-
New & retreated PTB	3	1	0.5-6.5	1	-	-
Smear positive (new & retreated)	2	1	1-1	1	-	-
New PTB	2	0.5	0.3-0.8	1	-	-
Smear positive (new)	2	3	3-3	2	-	-

Table 7 Total delay (days)

Total delay	Median of reported median delays			Pooled estimates from random effects model using estimated means and variances		
	N	Median	IQR	N	Mean	95% CI
Overall	4	55.5	43.8-64.3	3	52.5	-6.5-111.4
Geographic region						
West	1	71	-	1	-	-
Center	2	45	36.5-53.5	1	-	-
East	1	49	-	1	-	-

Table 8 Initial care seeking behavior of TB patients

Mean percentage (95% CI)	Pharmacy	Village clinic	Township hospital	Primary health facility	County and above general hospital	Private clinic	Dispensary
Overall	7.5% (2.5-20.1%) N=11	36.2% (28.4-44.9%) N=23	19.6% (16.1-23.7%) N=32	30.9% (26.9-35.2%) N=3	34.7% (30-40%) N=36	0.1% (0.04-0.3%) N=13	7.8% (5.8-10.4%) N=37
Geographical regions							
West	76.9% N=1	11.9% (7-19.4%), N=3	34.7% (24.6-46.5%) N=5	N=0	34% (28-44.8%) N=7	0.7% N=1	10.3% (5.2-19.2%) N=9
Center	10.4% (0.7-13.8%) N=2	30.4% (14.8-52.4%) N=5	17.2% (12.3-23.6%) N=9	N=0	38.1% (27.9-49.4%) N=9	0.08% (0.02-0.3%) N=10	10.8% (7.9-14.8%) N=9
East	4.4% (1.3-13.1%) N=8	44.9% (39.1-50.8%) N=15	17.6% (13.8-22.2%) N=18	30.9% (26.9-35.2) N=3	32.9% (26.6-39.9%) N=20	0.2% (0.02-1.4%) N=2	5.7% (3.8-8.7%) N=19

Table 9 Referral and Referral arrival rate

Referral rate		Data source		
		Registered PTB patients	Visitors to outpatient department in general hospitals	TB dispensary reports
	General hospitals (county level and above)#	82.7% (95% CI=51.2-95.6%) N=6	69.5% (95% CI=19.4-95.6%) N=3	N=0
	Township hospitals	52.3% (95% CI=43.2-63.2%) N=4	N=0	N=0
	Village clinics	14.3% (95% CI=6.1-63.2%) N=4	N=0	N=0
Referral arrival rate*		68.1% (95% CI=44.8-85%) N=6	79.8% (95% CI = 74.6-84.1%) N=2	69.4% (95% CI=41.8-87.8%) N=7

#The overall pooled referral rate at these general hospitals were 78.9% (95% CI=51-93.1%).

*The overall pooled referral arrival rate was 71.4% (95% CI=55.6-83.4%)

Chapter 8. Figures

Figure 1 Prevalence of TB (all forms) and case detection rate in China from 1990 to 2013

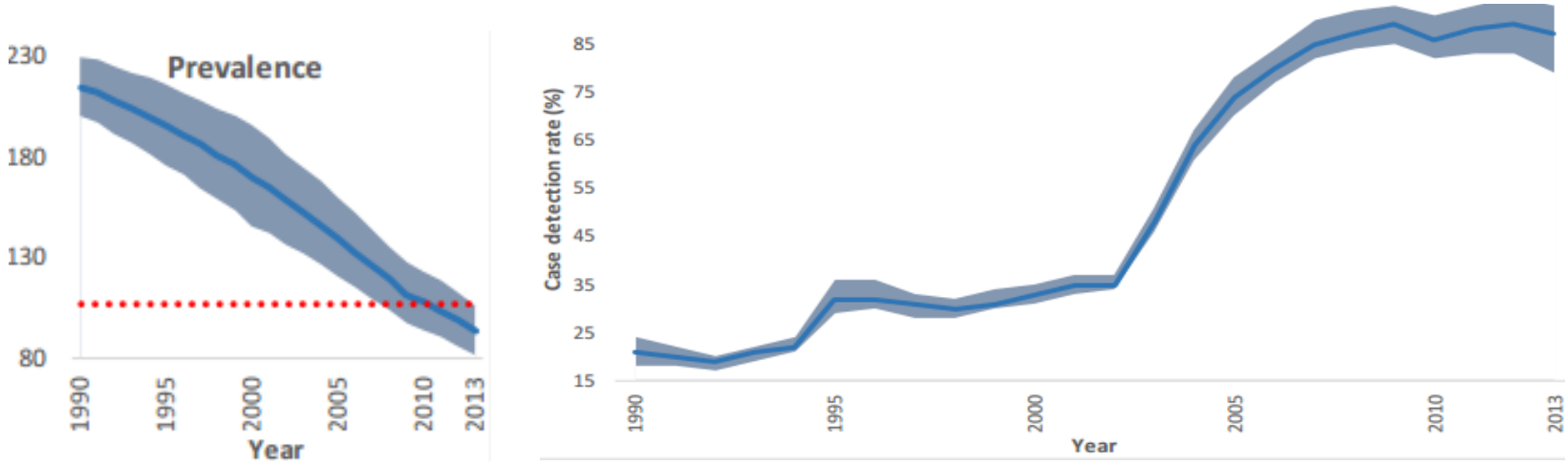
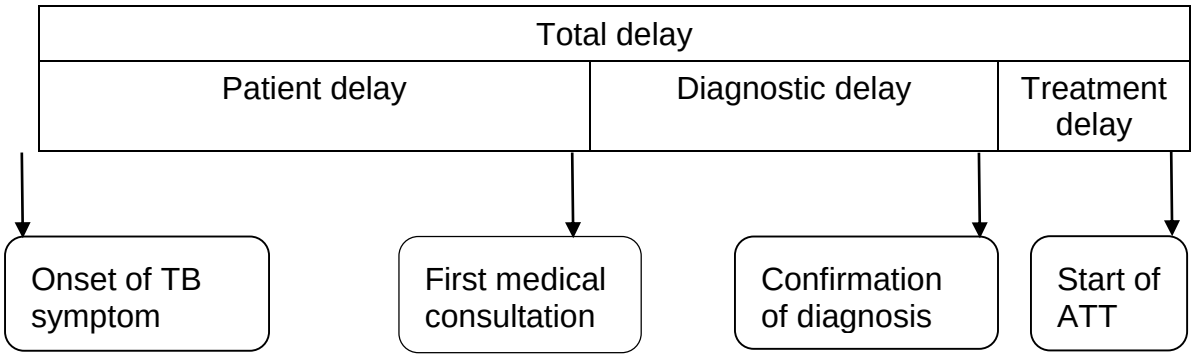


Figure source: WHO Global Tuberculosis Report [2]. Prevalence (left); Case detection rate (right)

Figure 2 Definitions of types of delay used in the review



The lengths of the table cells do not represent the actual time interval of each types of delay. ATT: anti-tuberculosis treatment.

From Sreeramareddy, C., et al. (2014). "Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review." The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease 18(3): 255-266. [12]

Figure 3 The collaboration between the public health and hospital systems for TB care in China

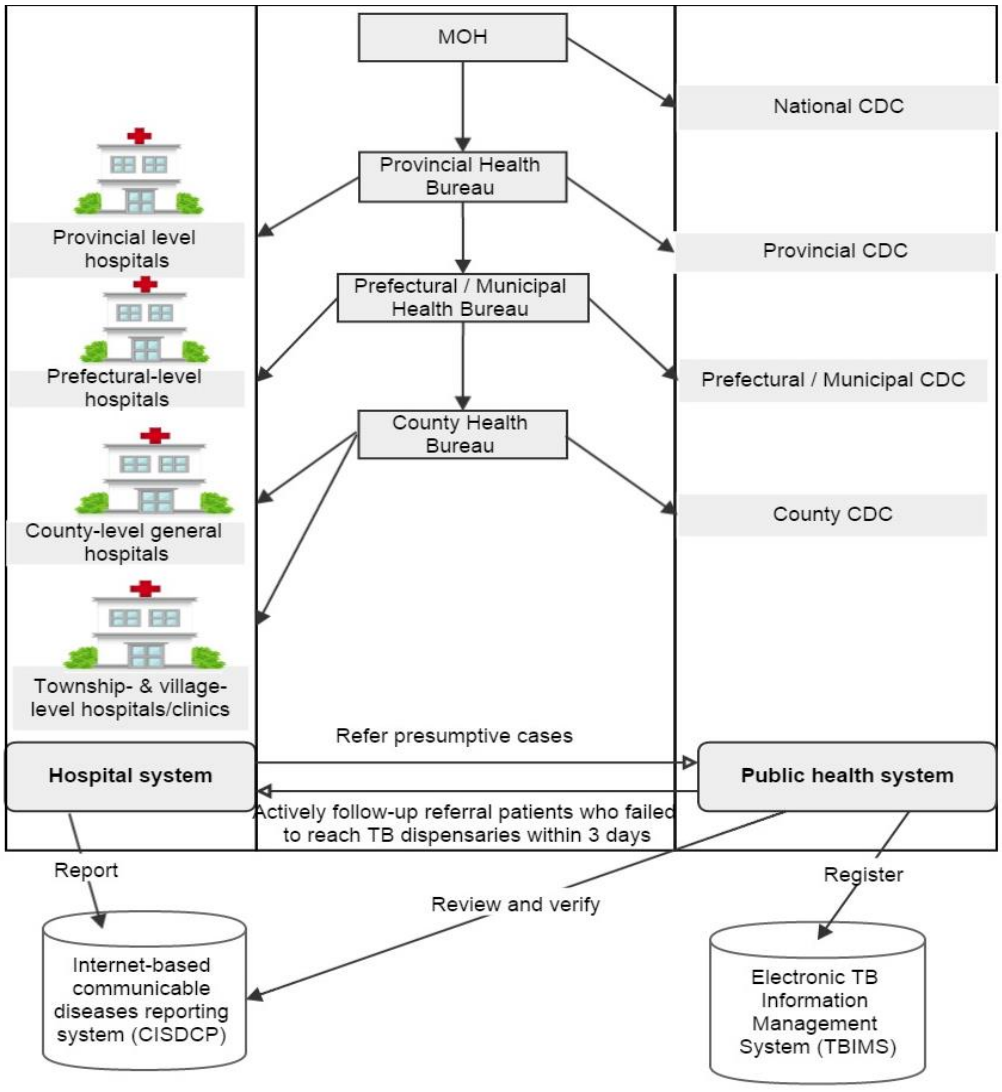


Figure 4 Study selection

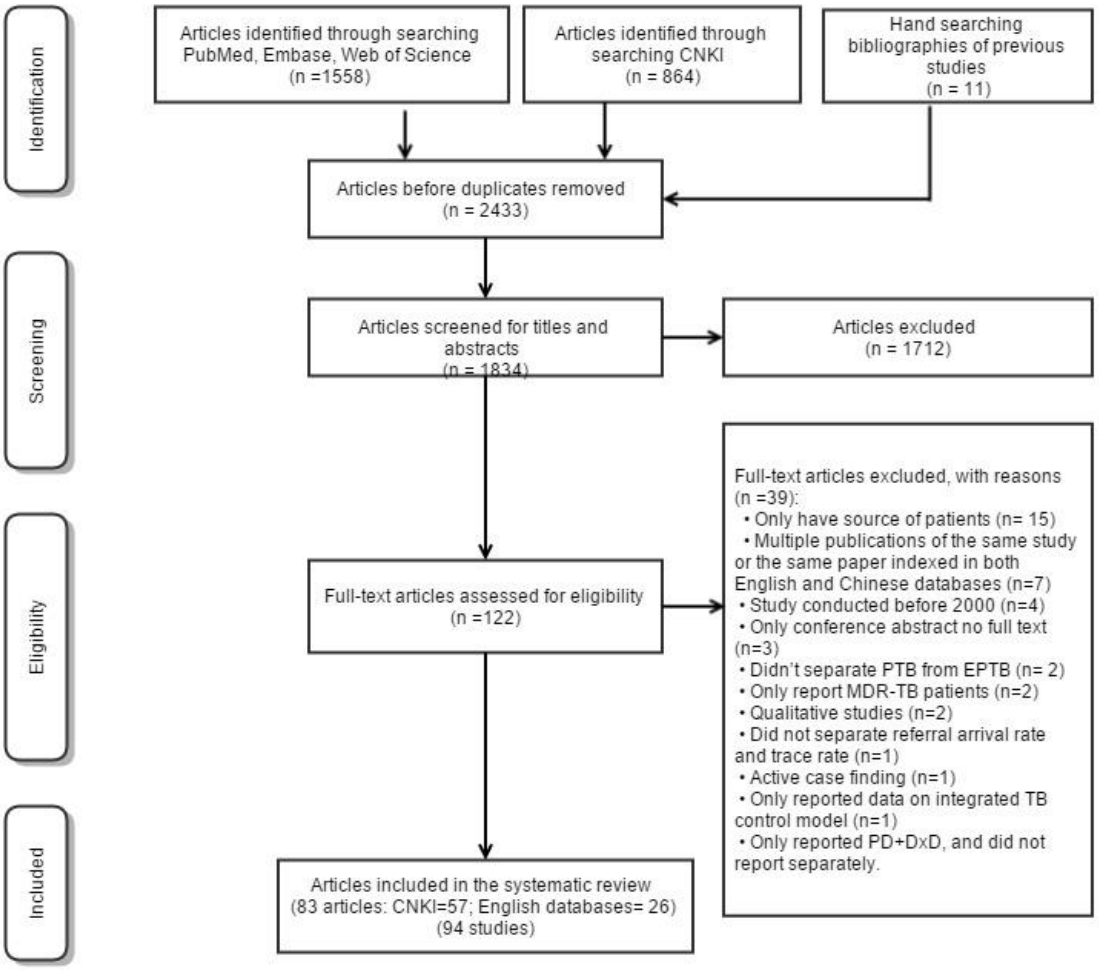


Figure 5 Summary of the social and demographic profiles of the 94 studies included

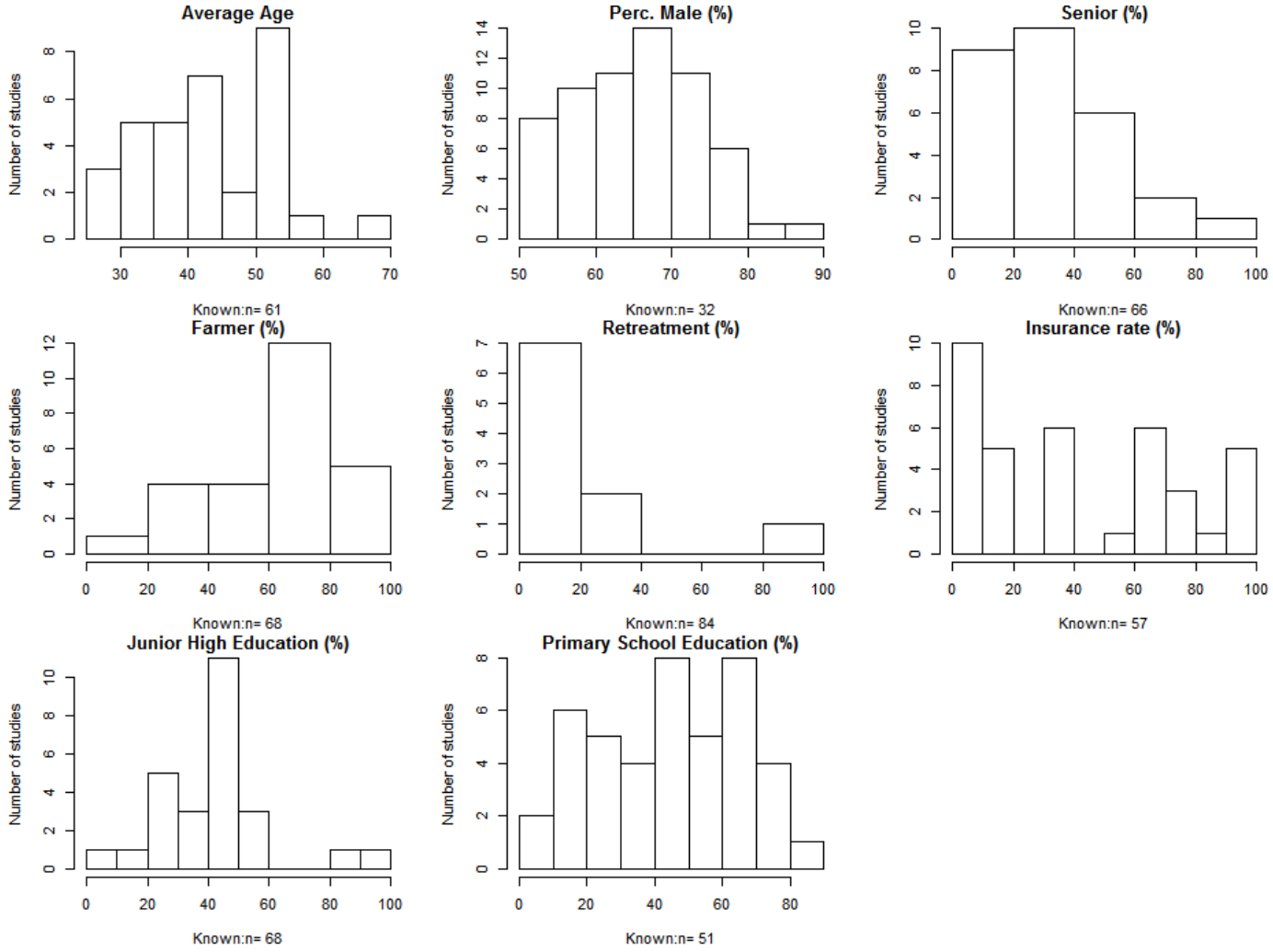


Figure 6 Quality assessment for each outcome objective across selected studies

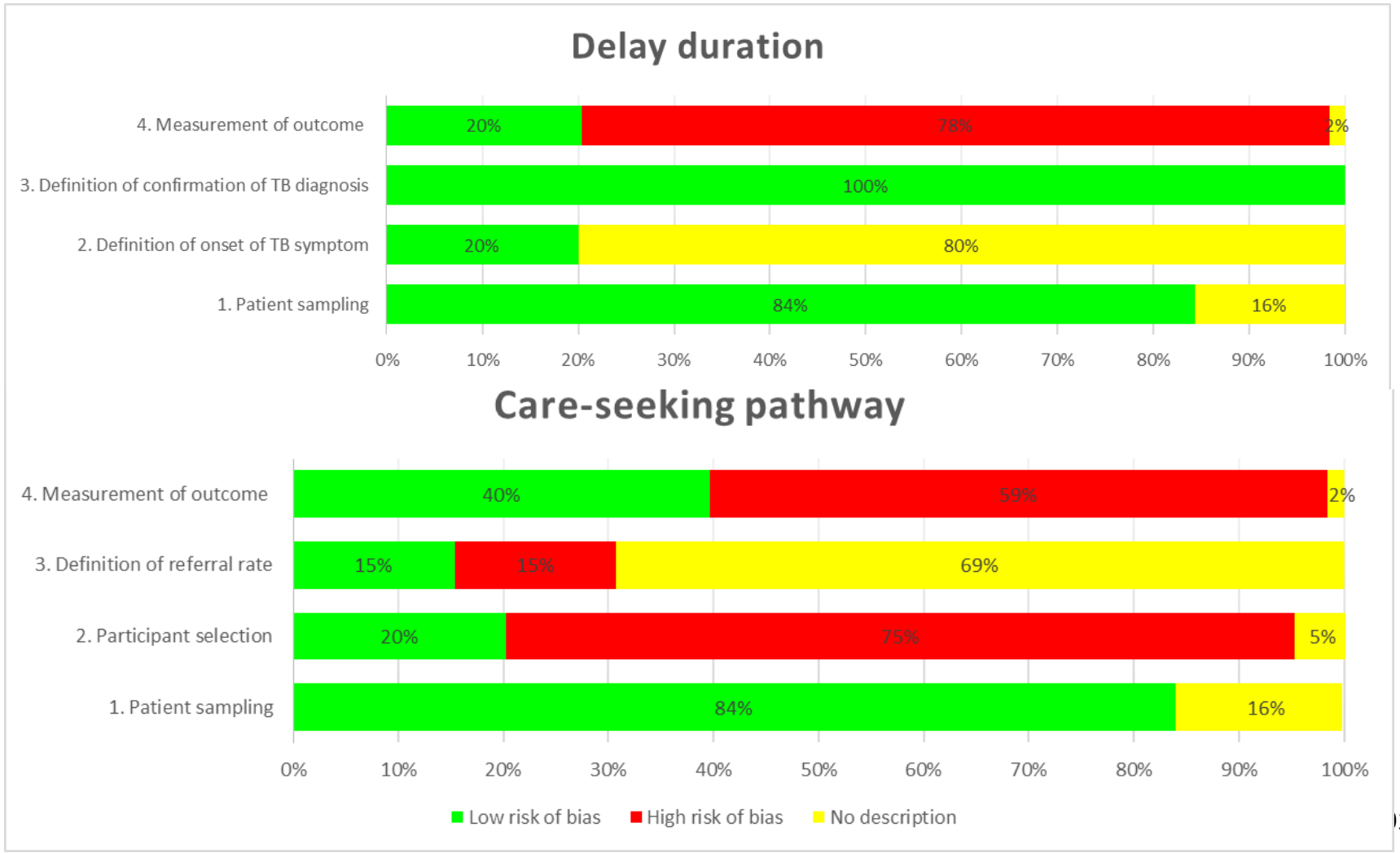
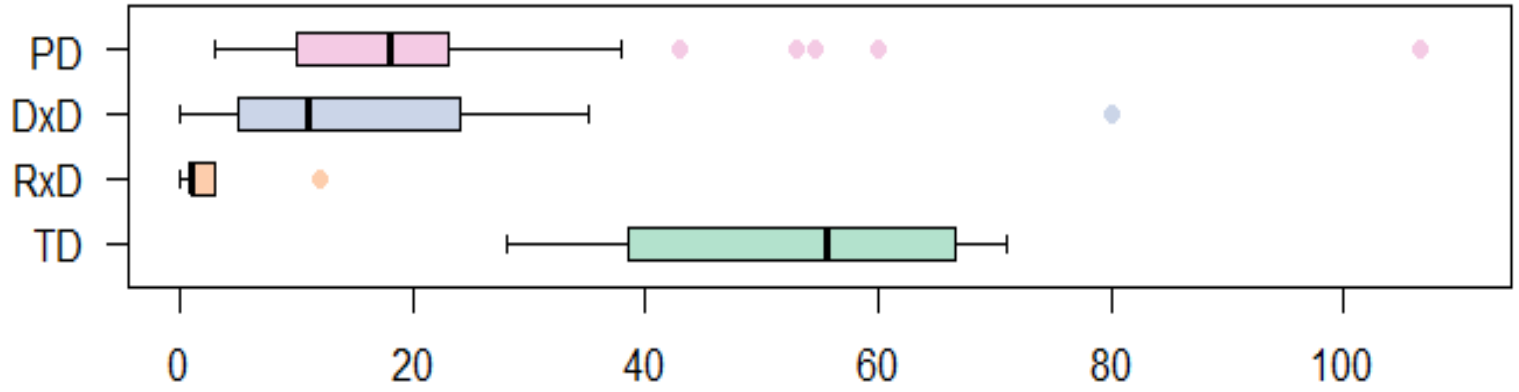
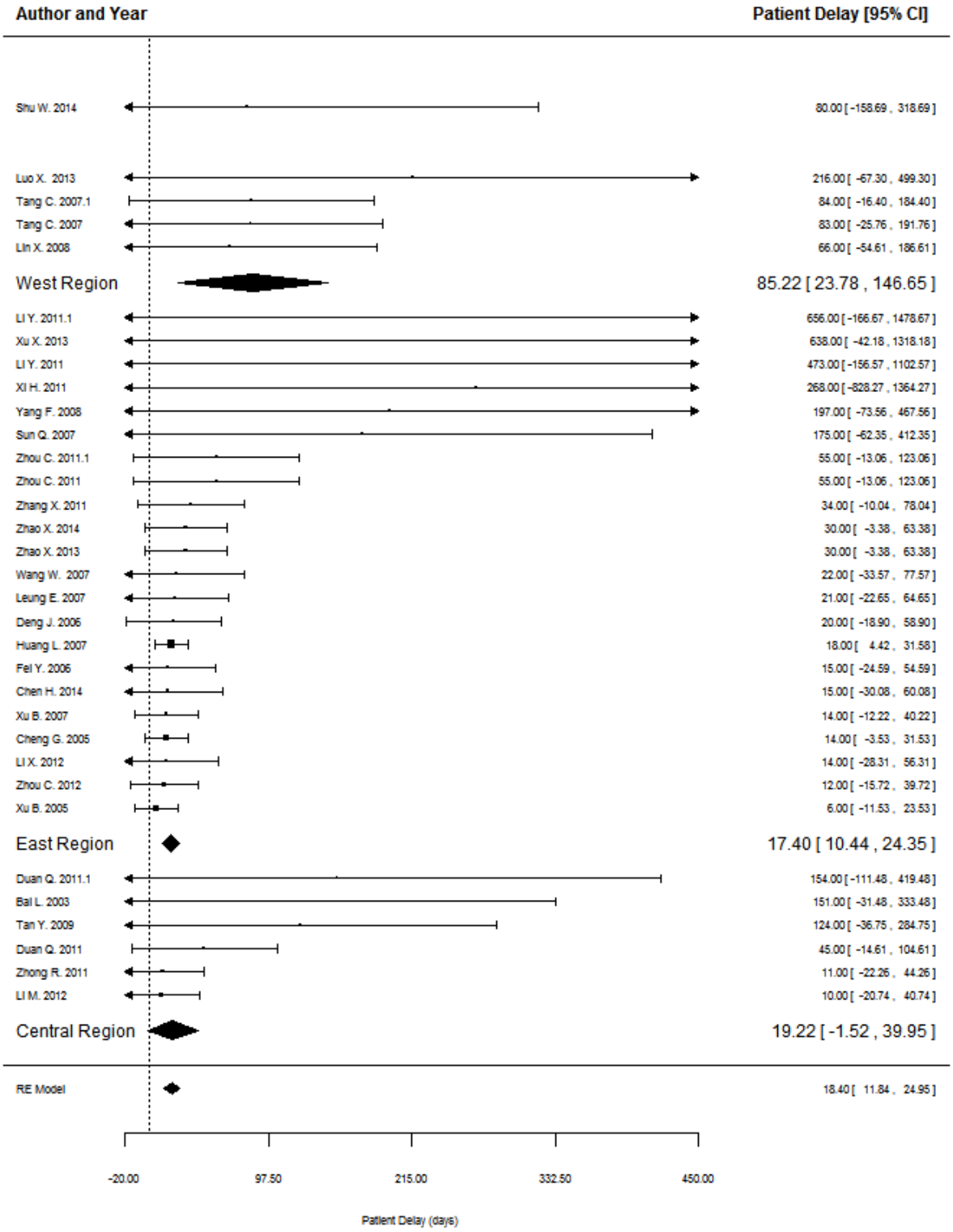


Figure 7 The reported median days of various delays



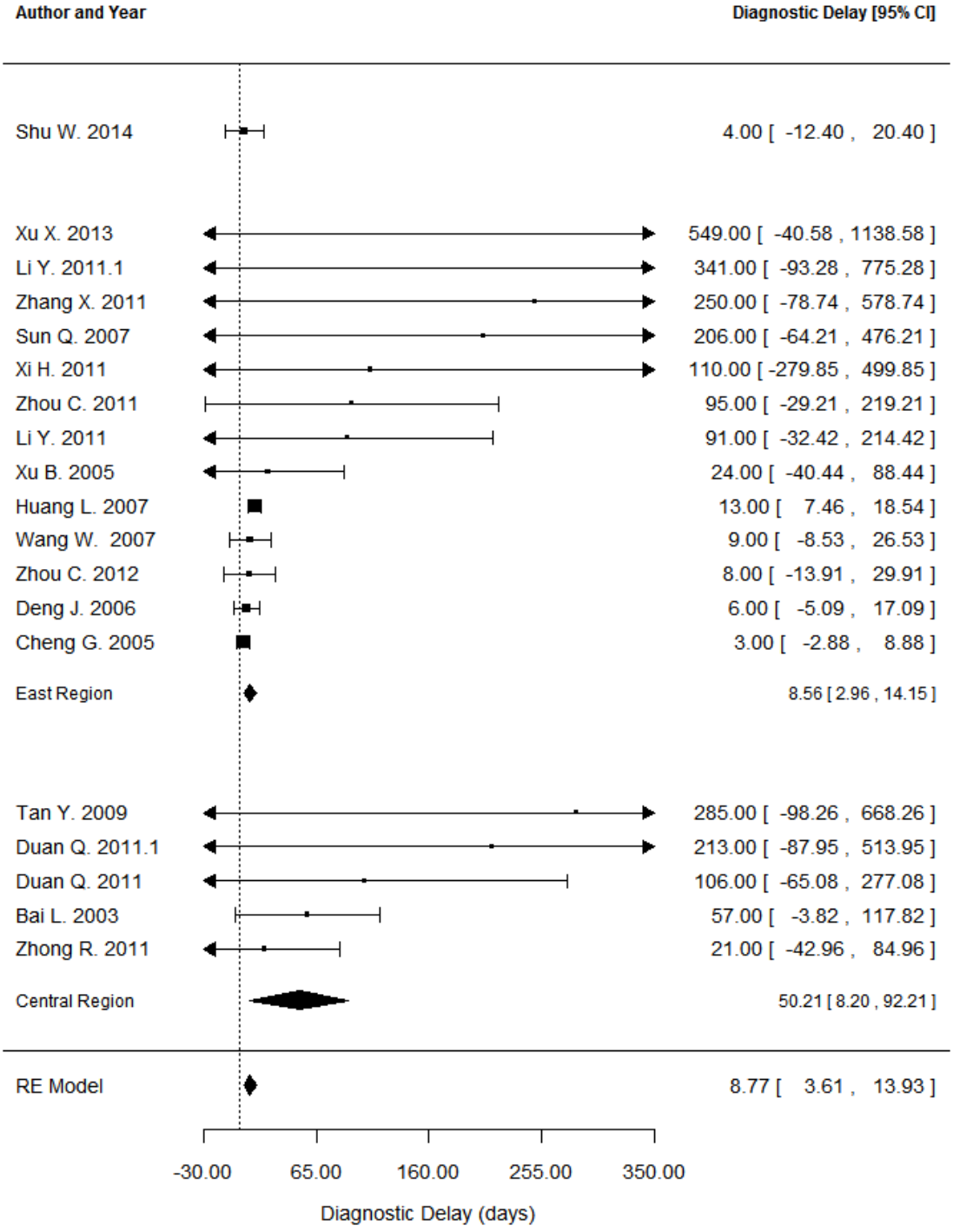
PD: patient delay, median =18 days, IQR=10 to 23 days, n=51
DxD: diagnostic delay, median =11 days, IQR=5 to 24 days, n=29
RxD: treatment delay, median =1 day, IQR=1 to 3 days, n=9
TD: total delay, median = 55.5 days, IQR=43.8 to 64.3 days, n=4

Figure 8 Forest plot of mean patient delay (days), n=33 studies



The estimated means patient delay from each primary study are shown as dark rectangles, whose sizes are proportionate to the sizes of the studies. The solid lines show the 95% confidence intervals of the estimated mean patient delay from each studies. The arrows show that the confidence intervals continue and pass the boundary of x-axis. The dark rhombuses are the pooled patient delays.

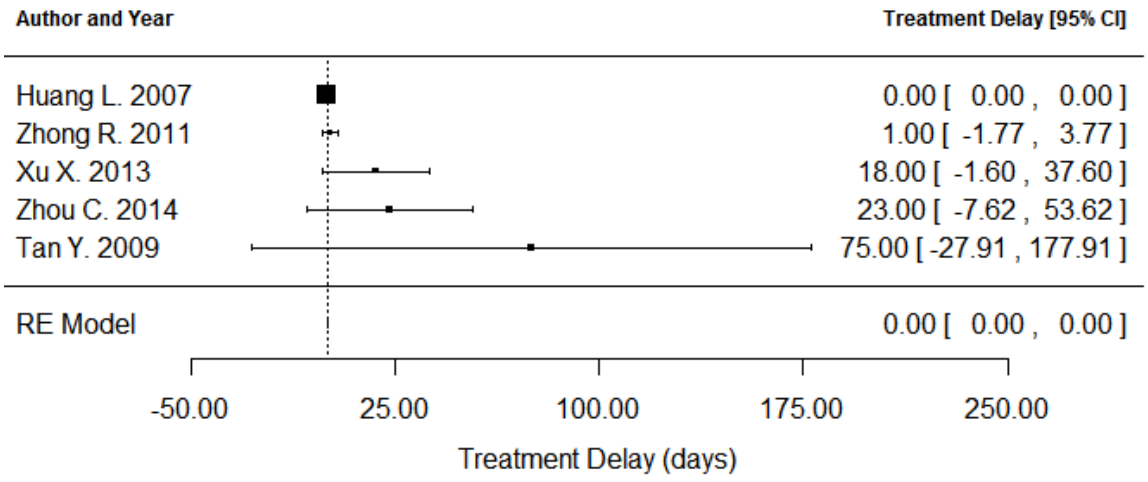
Figure 9 Forest plot of mean diagnostic delay (days), n=20 studies



The estimated means diagnostic delay from each primary study are shown as dark

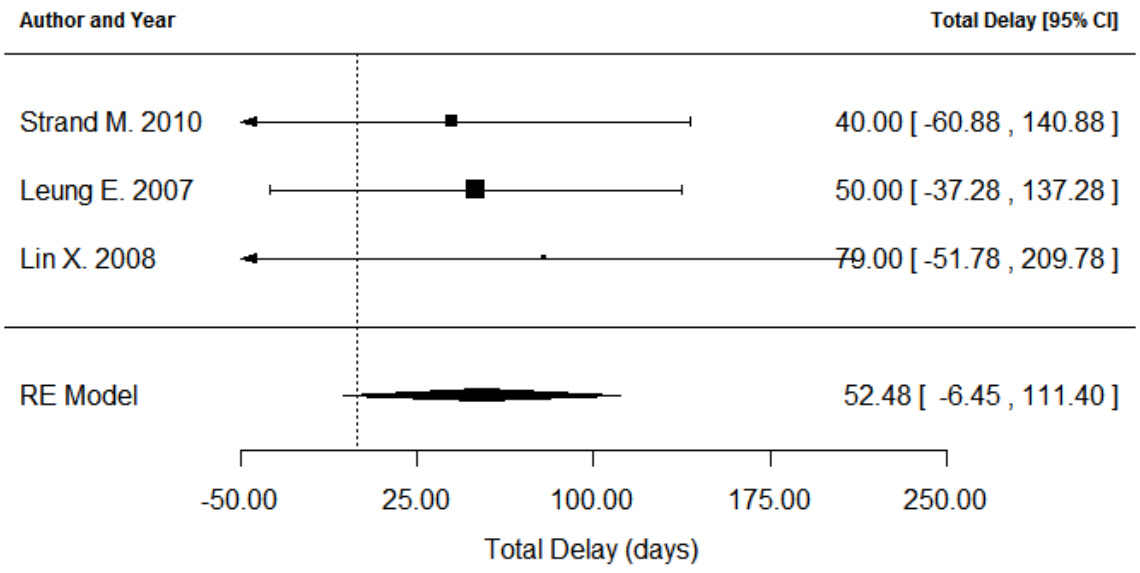
rectangles, whose sizes are proportionate to the sizes of the studies. The solid lines show the 95% confidence intervals of the estimated mean diagnostic delay from each studies. The arrows show that the confidence intervals continue and pass the boundary of x-axis. The dark rhombuses are the pooled diagnostic delays.

Figure 10 Forest plot of mean treatment delay (days), n=5 studies



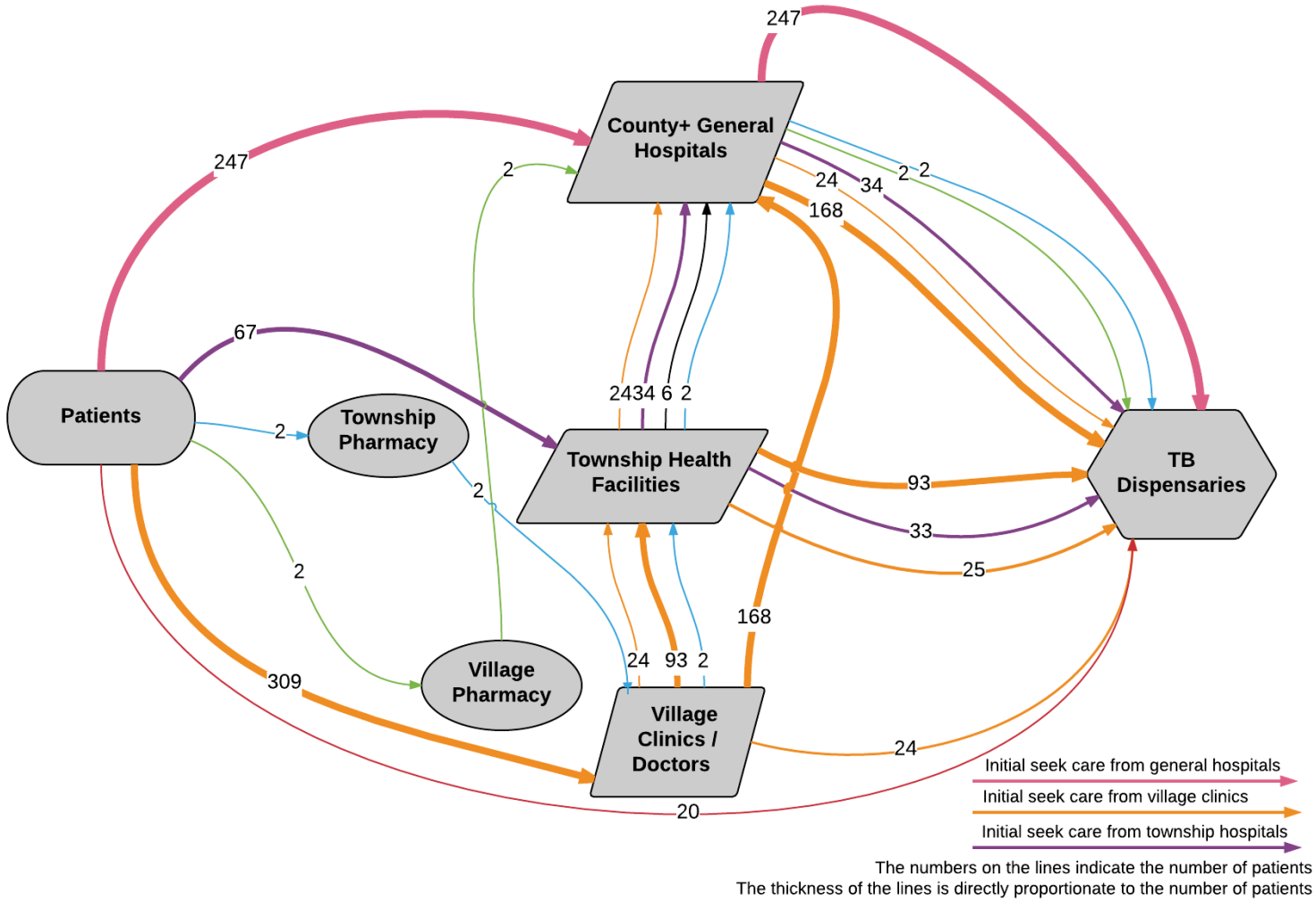
The estimated means treatment delay from each primary study are shown as dark rectangles, whose sizes are proportionate to the sizes of the studies. The solid lines show the 95% confidence intervals of the estimated mean treatment delay from each studies.

Figure 11 Forest plot of mean total delay (days), n=3 studies



The estimated means total delay from each primary study are shown as dark rectangles, whose sizes are proportionate to the sizes of the studies. The solid lines show the 95% confidence intervals of the estimated mean total delay from each studies. The arrows show that the confidence intervals continue and pass the boundary of x-axis. The dark rhombuses are the pooled total delays.

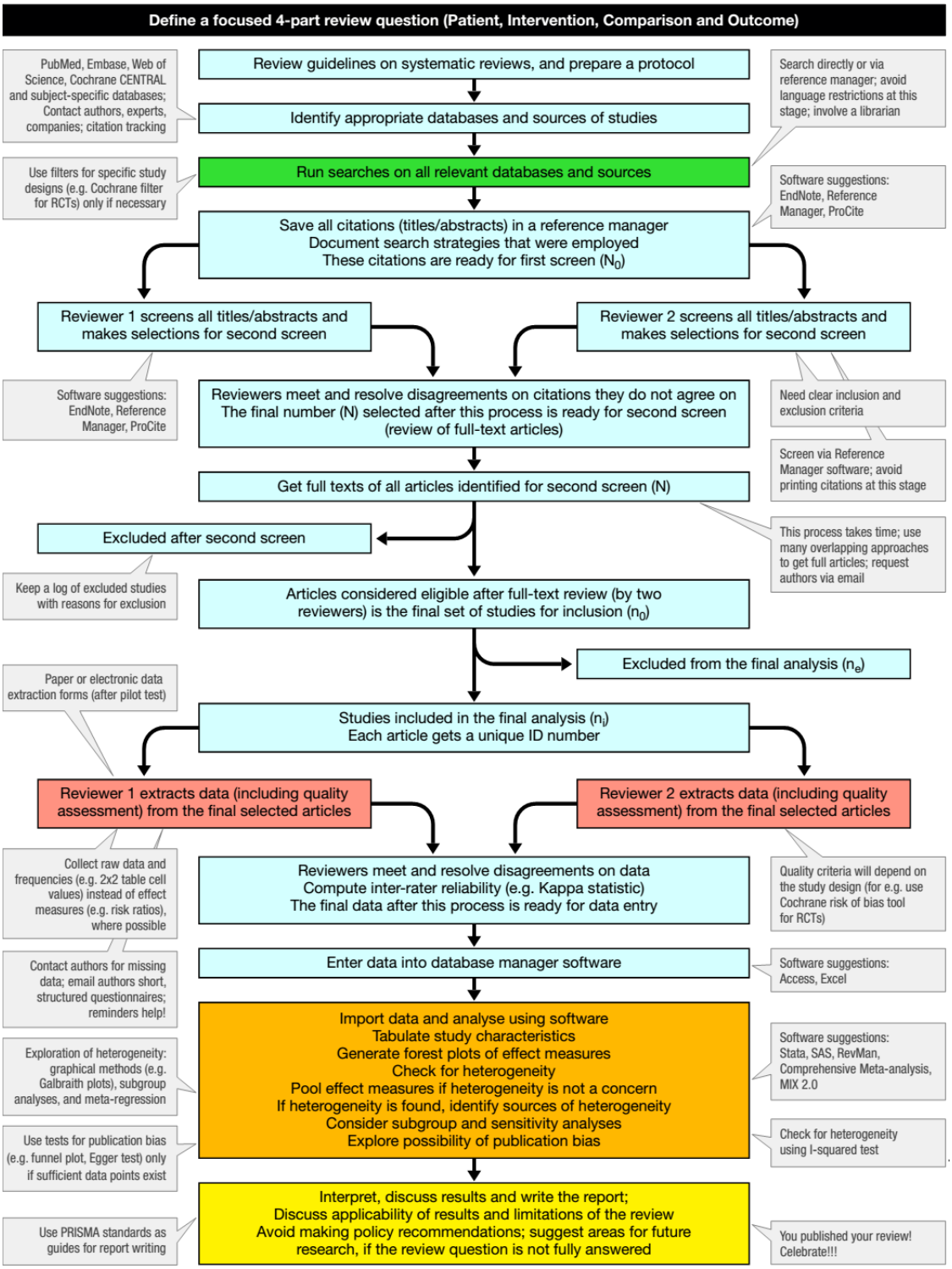
Figure 12 Pathways undertaken to reach TB dispensaries



Chapter 9. Appendices

Appendix 1 A roadmap for systematic review & meta-analysis

From: Pai, M., et al. (2004). "Systematic reviews of diagnostic test evaluations: what's behind the scenes?" Evidence Based Medicine 9(4): 101-103. [1]



Appendix 2 Protocol

Introduction

Epidemiology of tuberculosis

Tuberculosis (TB) is a one of the major communicable diseases. It is estimated that approximately 1 in 3 people is infected with *Mycobacterium tuberculosis* in the world. According to the latest global tuberculosis report from the World Health Organization (WHO), 9 million new TB cases were reported in 2013 [2], compared with 2.1 million new HIV cases in the same year [3]. The burden of TB is the highest in developing nations, particularly in countries in South Asia and East Asia.

Tuberculosis epidemics and control in China

The People's Republic of China (China), the country with the second highest disease burden, reported a total of 847,176 notified new and relapse TB cases in 2013, accounting for approximately 14% of the global burden in the same year [2]. China also suffers from a serious epidemic of drug-resistant tuberculosis (DR-TB), especially multi-drug resistant tuberculosis (MDR-TB) [6]. In 2013, there were approximately 41,812 cases of RR-/MDR-TB in China, accounting for 13.3% of the global burden. The number of DR-TB is high not only on the absolute scale, which may be contributed to the large population in the country, but also on the relative scale. According to the latest national MDR-TB survey in China, 5.7% of new TB cases and 26% of retreated cases were MDR-TB [6]. While the global average is much lower – only 3.5% of new cases and 20.5% of the retreated cases were MDR[2].

Nevertheless, great progress has been made in the past decades in the control of the TB epidemic in China. Since WHO-endorsed Directly Observed Treatment, Short-course (DOTS) was scaled up in the country in the late 1990s [7], the prevalence of smear-positive TB decreased from 170 per 100 000 population in 1990 to 59 per 100 000 population in 2010 [8]. This is a stunning 65% decrease in smear-positive TB prevalence, which surpasses the Stop TB Partnership's target of halving TB prevalence compared to the 1990 baseline by 2015 [2, 9].

However, the prevalence of all forms of TB only declined minimally from 466 in 2000 to 459 in 2010 [8]. Additionally, the incidence of MDR among PTB has not decreased in the past decades, and the number of cases resistant to first-line TB drugs among newly diagnosed TB patients rose from 34.2% in 2007/2008 to 36.9% in 2010 [6].

Delays in tuberculosis diagnosis and treatment

One of the main impediments to effective TB control is timely and accurate diagnosis, which is a key step in effective national TB control [10]. Approximately 3 million TB cases and almost 50% of the rifampicin – resistant TB and MDR-TB cases were estimated to be undiagnosed in 2013 [2]. Delayed diagnosis and

treatment can facilitate the ongoing transmission of the infection, exacerbate the disease condition, and may therefore contribute to the slow decrease of TB incidence.

Previous studies demonstrated significant delays in TB diagnosis and treatment in low-, middle- income countries — according to Sreeramareddy et colleagues, the median time interval between the onset of symptoms suggestive of PTB and the patient's first contact with a health care provider in low and middle income countries was 31.7 days (patient delay), and the median time interval between the first health consultation and the initiation of anti-tuberculosis treatment (ATT) was 28.4 days (health system delay) [11]. Additionally, another study identified that patient delay in India is shorter to the median delays in low and middle income countries, but it was the health system delay that was more problematic [12].

China has a unique socio-political and cultural context comparing to other low and middle-income countries. Since China is one of the top ten countries contributing to the three million undiagnosed TB cases [2], it is important to understanding the delays in TB diagnosis and the pathways of care-seeking in China in order to identify the weak links that contribute to prolonged delay in TB diagnosis and improve the effectiveness of China's TB control program. Although a few studies assessing diagnostic and treatment delays have been published in China, these studies were regional and not representative of the nation. The only national level systematic review from China provided the risk factors associated with various delays, and did not provide the numerical delay time [13]. Therefore, our first objective is to systematically review the literature from China on time interval of TB diagnostic and treatment delays.

Similarly, there is no review on TB patients' pathway to care from China. The only systematic review from China only identified that one of the key risk factors contributing to delay in diagnosis and treatment in TB in China is related to the type of health facilities initially visited by TB patients [13]. However, there is evidence suggesting that complicated pathways to reach health facilities can contribute to prolong delay in TB diagnosis [155]. Furthermore, China has a very distinct TB control program, which inevitably results in distinct patient behavior and care-seeking. Therefore, we will also aim to review literature on care-seeking behavior and pathways.

TB control in China

Tuberculosis care and control are managed by the Chinese Center for Disease Control and Prevention (China CDC) within the public health system. In around 1990s, China CDC established China Center for Tuberculosis Control and Prevention to curb the spread of TB [14]. Under the leadership of the newly founded institutes, the National TB program (NTP) was comprised of a network of TB control institutions, including TB dispensaries and some TB-specific hospitals.

According to the National TB Control and Prevention Guide (2011-2015) [15], the TB dispensaries are mandated to carry out case management, conduct follow-up and provide TB-related education. One of the main functions of TB dispensaries is to actively follow up with TB patients and with presumptive TB cases referred from the hospital system who fail to arrive at TB dispensaries within a day. There is a total of approximately 3490 dispensaries which are established at 4 administrative levels: national, provincial, prefectural and county [16].

TB-specific hospitals are the hospitals designated by local health authorities to provide TB care. This includes TB hospitals, chest/pulmonary hospitals, infectious disease hospitals, and general hospitals with TB departments/clinics [15].

The hospital system in China is composed mainly by general hospitals – publically owned privately financed physician compensation are tied to profit [18]. In this regard, the hospital system in China is similar to the private sector of most Asian countries. These general hospitals form the backbone of healthcare system in China – the majority of Chinese healthcare is delivered through general hospitals and their health services are available in remote regions where TB dispensaries are absent, namely township and village levels. As per "the hospital classification system" by the Ministry of Health of People's Republic of China, all general hospitals in China are classified as primary, secondary, and tertiary hospitals based on their quality of healthcare and medical education provided as well as research capacity [20]. Secondary and tertiary hospitals are those general hospitals with comprehensive healthcare services and operate at county and above levels. Primary hospitals operate at township and village levels and often referred as community health centers or township health centers. The TB dispensary at the county level is the endpoint of TB control and is not available at township and village levels.

There is no system of general practitioners, patients can go directly to health care providers; hence, general hospitals are the most comment first point of consultation for TB patients and chest symptomatics. However, general hospitals are prohibited from confirming TB diagnosis and prescribing TB treatment. After identified of having tuberculosis-related symptoms in the general hospitals through chest X-ray and/or sputum examination, these patients are obliged to be referred to TB dispensaries by physicians in general hospitals.

Hospital – Public Health collaboration is an important way to detect TB cases in China. Upon identifying presumptive TB cases, general hospitals are mandated to report and refer the cases to public health system through a Chinese Information System for Infectious Diseases Control and Prevention (CISDCP) which contains epidemiological data on 39 infectious diseases in real-time [19, 156]. Designated staff at China CDC are responsible for reviewing and verifying

patients' information on CISDCP and conducting active-follow up/tracing of patients who fail to arrive at TB dispensaries following referral.

The proportion of the presumptive TB patients referred to public health system among all the presumptive TB patients identified in the same health facility is defined as referral rate [15]. Of those referred to public health system, the proportion of patients successfully arrive at TB dispensaries within 3 days is defined as referral arrival rate [15] The proportion of presumptive TB patients actively followed up by TB dispensaries among all those failed to arrive at TB dispensaries within 3 days of referral is defined as the rate of active follow up. Among those actively followed up, the proportion of presumptive TB patients who eventually arrived at TB dispensaries is defined as trace rate. Detailed formulas are summarized below:

$$Referral\ rate = (the\ number\ of\ presumptive\ TB\ patients\ referred\ to\ the\ public\ health\ system\ in\ general\ hospitals)/(the\ total\ number\ of\ presumptive\ TB\ patinets\ identified\ in\ the\ same\ health\ facility)$$

$$Referral\ arrival\ rate = \frac{the\ number\ of\ referred\ presumptive\ TB\ patients\ who\ arrived\ in\ the\ public\ health\ system}{the\ total\ number\ of presumptive\ TB\ patinets\ who\ were\ referred\ to\ public\ health\ system}$$

$$Active\ follow\ up\ rate = \frac{the\ number\ of\ presumptive\ TB\ cases\ actively\ followed\ up\ by\ TB\ dispensaries}{the\ total\ number\ of\ referred\ presumptive\ TB\ patients\ who\ failed\ to\ arrived\ at\ public\ health\ system}$$

$$Trace\ rate = \frac{the\ nubmer\ of\ presumptive\ TB\ patients\ who\ arrived\ at\ TB\ dispensaries\ after\ following\ up}{the\ total\ number\ of\ presumptive\ TB\ patinets\ who\ were\ actively\ followed\ by\ TB\ dispeansaries}$$

However management of TB care in the public health system has proven challenging. The majority of TB patients seek care in the hospital system, instead of public health system [23]. Additionally, only a few people who initially sought care in the general hospitals were reported to the public health system, and less were able to successfully arrive at public health system for clinical treatment and management. As a result, many TB patients seen in the hospital system were never diagnosed nor received treatment under DOTS. Furthermore, there are few qualified medical professionals in public health system than in hospital system due to unsatisfying compensation [24]. Recognizing the challenges, the Chinese Ministry of Health released a guideline in 2011 which was intended to streamline TB services and move TB care towards hospital-based diagnosis and care [25]. At the center of hospital-based approach are TB-specific hospitals, where the clinical management of TB is provided [25]. Tuberculosis-specific hospitals are the hospitals and health facilities that are designated by local authority to carry out the diagnosis and treatment of tuberculosis, consisting of specialized tuberculosis hospitals, pulmonary hospitals, chest hospitals, infectious disease hospitals, designated tuberculosis hospitals, and general hospitals with tuberculosis departments [25, 26].

However, there may be new challenges emerging as China is shifting its TB diagnosis and treatment efforts back to hospitals. The dramatic progress in the past was achieved through the dispensary model whereby TB patients receiving treatment from the public health system, which adopted standard DOTS. It is unclear whether or not the shift of clinical management of TB from public health system to tuberculosis-specific hospitals has any impact on reducing delay in TB diagnosis and treatment and streamlining patients' pathway to care. Since the policy was introduced in 2011, little published data are available to assess the performance of hospital-based control model, therefore in this review, we systematically examined the delay and pathways to care before the implementation of hospital-based TB care, which can serve as a baseline for future comparison.

.

Study Objectives

Primary objective:

To systematically review the quantitative data describing the distinctive time intervals from onset of the TB symptoms to the initiation of anti-TB treatment of the patients suffering from TB or chest symptomatics in China. The time intervals include the following:

- Patient delay (PD): the time interval between the onset of symptoms suggestive of PTB and the patient's first contact with a health care provider.
- Diagnostic delay (DxD): the time interval between the first consultation with an HCP and diagnosis of TB.
- Treatment delay (RxD): the time interval between the confirmed of diagnosis and the initiation of ATT.
- Total delay (TD): the time interval between the onset of symptoms and ATT initiation.
- Health system delay (HSD): includes DxD and RxD.

Secondary objective:

To explore care-seeking behavior and care-seeking pathways of TB patients and chest symptomatics in China. The key patient care-seeking behavior data include the type of health facilities that were first visited by TB patients and chest symptomatics and the average number of health care providers consulted before the confirmation of TB diagnosis. Data pertaining to care-seeking pathways include the referral rate, referral arrival rate, active follow up rate, and trace rate.

Methods

Search strategy

With the assistance of a medical librarian, we will search PubMed, Embase and Web of Science up to January 1st, 2015 without any language restrictions using the following terms. Since DOTS was scaled up in the late 1990s in China [7], the studies published and conducted before January 1st, 2000 were excluded. We will

also adopt and apply the search strategy to China National Knowledge Infrastructure (CNKI), a key Chinese biomedical database covering 8,200 Chinese journals from 1994 [29]. We will search the bibliographies of primary studies and previously published reviews articles [11, 13, 30] for additional data.

1. *tuberculosis[Mesh] OR mycobacterium tuberculosis[Mesh] OR tuberculosis[tiab]*
2. *"community health services"[Mesh] OR "health behavior"[Mesh] OR patient acceptance of healthcare[Mesh] OR "Follow-Up Studies" [Mesh] OR "Referral and Consultation"[Mesh]*
3. *diagnos*[tiab] OR treat*[tiab]) AND (delay*[tiab] OR time*[tiab] OR late[tiab] OR latenc*[tiab] OR lateness[tiab] OR interval*[tiab] OR barrier*[tiab]*
4. *health[tiab] OR healthcare[tiab] OR care[tiab] OR treatment*[tiab]) AND (seek*[tiab] OR path[tiab] OR paths[tiab] OR pathway*[tiab] OR behavior*[tiab] OR behaviour*[tiab]*
5. *health facilities[tiab] OR "health facility"[tiab] OR refer[tiab] OR referral[tiab] OR referred[tiab]*
6. *#2 OR #3 OR #4 OR #5*
7. *china[Mesh] OR China[tiab] OR Chinese[tiab]*
8. *#1 AND #6 AND #7*

Selection criteria

- Participants — studies will be included if study participants met one of the following criteria:
    - Newly diagnosed drug-sensitive pulmonary TB (PTB) patients (smear-positive or negative patients).
    - Retreated drug-sensitive PTB.
    - Patients with chest symptoms (cough $\geqslant$2 weeks and presumed to have TB).
- Outcomes measures — studies will be included if they report one of the following outcomes.
    - Primary outcome on delay time intervals among known TB cases and those with TB symptoms (2 weeks of cough): patient delay, diagnostic delay, treatment delay or total delay.
    - Secondary outcomes on care-seeking pathways among known TB cases and those with TB symptoms (2 weeks of cough): the first point of medical consultation; the average, minimum, and the maximum of the number of health care providers visited before diagnosis is made; referral rate to the public health system; the rate of ATT initiation prior to arriving to an institution of the public health system; tracing rate by TB dispensaries.

- Types of studies included: cross-sectional, case-control, and cohort studies.

When the same publication is indexed in both English and Chinese databases, only the one in the original language will be kept. Similarly for multiple publications of the same study, only the latest publication will be included. We excluded qualitative studies without numerical data. Conference abstracts usually contain inadequate information, especially key demographic data will therefore be excluded. We also will restrict the studies to those conducted after 2000 as DOTS programme hadn't scaled up in China until 2000.

Quality assessment

There are several validated and wildly accepted tools to assess the quality and bias of primary studies, such as the Cochrane's tool for randomized trails [32], Newcastle-Ottawa Scale for case-control and cohort studies [33], and QUADAS for diagnostic accuracy studies [34]. However, there is no standardized instruments to assess the methodological quality for the studies on delays and health care-seeking behaviors. Additionally, it is not suitable to use the tools mentioned above because most of the selected studies are cross-sectional. Therefore we developed a quality assessment scale based on the guideline for quality assessment of cross-sectional studies adopted from Newcastle-Ottawa Scale [35], one previous review on delays and pathways to care [12], and other recognized epidemiological theories and principles [36]. Component approach will be used instead of assigning numeric store. The quality assessment score will be used for subgroup analysis. We will pilot tested the scaled on 10 randomly selected articles and revised it on inter-rater agreement. The tentative quality assessment is as following:

Objective 1: delay interval

1. Patient sampling:
    c. Consecutive / random sampling. (low risk of bias)
    d. No description of the sampling strategy. (no description)
2. Definition of onset of TB symptom:
    a. Clearly stated whether day 1 of coughing was counted as onset of TB symptom or after 2 or 3 weeks of coughing. (low risk of bias)
    b. No clear description on the onset of TB symptoms. (no description)
3. Definition of confirmation of TB diagnosis:
    a. Clearly stated that the diagnosis of PTB is confirmed by culture or smear microscopy. (low risk of bias)
    b. No description. (no description)
4. Measurement of outcome
    a. Cross-check with hospital record (or other methods eliminate recall bias). (low risk of bias)
    b. Used self-reported data without any cross checking. (high risk of bias)

c. No description. (no description)No description
Objective 2: care-seeking pathway studies 1. Patient sampling: a. Consecutive / random sampling. (low risk of bias) b. No description of the sampling strategy. (no description) 2. Participant selection a. Participants were recruited from general hospitals' outpatient department who may or may not end up in TB dispensaries. (low risk of bias) b. Participants who were registered with CDC were recruited. (high risk of bias) c. Presence of selection bias. (high risk of bias) d. No description of the selection strategy. (no description) 3. Definition of referral rate a. The denominator of referral rate is the number of presumptive cases identified. (low risk of bias) b. The denominator of referral rate is the total number of cases reported. (high risk of bias) c. No description. (no description) 4. Measurement of outcome a. Cross-check with hospital record (or other methods eliminate recall bias). (low risk of bias) b. Used self-reported data without any cross checking (high risk of bias) c. No description. (no description)

Data extraction

Titles and abstracts identified through database search will be independently assessed by two review authors (ZZQ and XJH). Full text articles will be retrieved and reviewed using the inclusion and exclusion criteria mentioned above. Disagreements between the two reviewers will be resolved by consulting a third reviewer (MP) and contacting primary study authors.

We will develop a data extraction form using Microsoft Access 2013 to reduce data entry errors. Two review authors will pilot and revised the draft form on 10 randomly selected articles. Data extracted include study population characteristics, primary and secondary outcomes. If a paper includes data on hospital-based TB care, we will either exclude it or only extract data from the control pair (under the dispensary-based model). Since the delay time intervals are not normally distributed, we will extract the median from the primary studies. Additionally, when the median of total delay was not reported, we did not calculate the total by summing up the median of various delays. However, when the median

is not reported in the primary studies, it will be substituted by mean delay duration. All time intervals reported will be transformed into days.

The type of health facilities first visited are in the following hierarchical order: (1) pharmacy and self-medication; (2) village clinics, township hospitals, and community health centers; (3) county and above general hospitals; (4) TB dispensaries; (5) no care seeking. For number of health care providers consulted before the confirmed of TB diagnosis, we will extract the average (median, or mean if median was not reported) of the reported data. Where possible, we will extract the data on the tests ordered by physician in hospital system, and we also map the type of health care providers and the sequent visits prior to the initiation of ATT in public health system.

Data Analysis

We will summarize the main results in two tables, describing the characteristics and outcome of each objective – one for outcome of delays and the other for the outcome of health care-seeking behavior. In addition, a separate summary of the socio-economic and demographic profiles across the selected studies will be prepared using histograms.

The fact that conventional meta-analytic models assume normality of effect sizes posed a challenge for our analysis; the effect sizes of interest in this study are not normally distributed. Based on some primary studies [38-41] and the previous systematic review from India [12], the distribution of delay duration is right (positive) skewed. To be certain of the skewness, we will calculate Bowley skewness coefficient (quartile skewness coefficient), which is defined as follows [42, 43]:

$$\frac{(Q_3 - Q2) - (Q2 - Q1)}{Q_3 - Q_1} = \frac{Q_3 + Q_1 - 2Q_2}{Q_3 - Q_1}$$

where Q_1 is the first quartile, Q_3 is the third quartile, and Q_2 is the median. A positive Bowley skewness value indicates that the median is closer to the lower quantile, i.e. positive skewness, a negative value indicate a negative skewness, and a zero Bowley skewness value indicates a symmetrical distribution of the data [43, 44]. To summarize delay duration, we will adopt two approaches to conduct the meta-analysis.

Method 1: First, we will calculate the median and interquartile range (IQR) of the median delay durations (in days) reported by individual primary studies and construct box plots on their spread around the median. Mann-Whitney-Wilcoxon Test will be used to compare the estimates in different subgroups.

Method 2: We will estimate sample mean and standard deviation of each individual study using sample size, median, IQR, and/or range according to methods suggested by Wan et al. [46]. Through simulation studies, Wan's method outperformed other existing methods [47-49] in estimating both normally

distributed and skewed data [46]. In scenario 1 where IQR ($q_1 = the\ first\ quartile, q_3 = the\ third\ quartile$) and sample size ($n$) and median ($m$) are available, the mean ($\bar{X}$) and standard deviation (S) can be estimated as follows [46]:

$$\bar{X} \approx \frac{(q_1 + m + q_3)}{3}$$

$$S \approx \frac{q_3 - q_1}{2\Phi^{-1}(\frac{0.75n - 0.125}{n + 0.2})}$$

where $\Phi^{-1}(z)$ is the upper zth percentile which can be calculated using the command "*qnorm(z)*" in R (R Foundation for Statistical Computing, Vienna, Austria). Alternatively, in scenario 2 where range ($a = the\ minimun\ value, b = maximun\ value$) and sample size ($n$) and median ($m$) are available, the mean ($\bar{X}$) and standard deviation (S) can be estimated as follows [46]:

$$\bar{X} \approx \frac{(a + 2m + b)}{4}$$

$$S \approx \frac{b - a}{2\Phi^{-1}(\frac{n - 0.375}{n + 0.2})}$$

As Wan and colleagues discussed in the paper, including extreme values may lead to worse and less reliable estimates [46]. Since we expect that the distribution of delay duration in each primary study to be positive skewed with a long tail on the right side, so the minimum and maximum of delays reported in each primary study are very likely to be extreme. For example, one [38] of our target articles reported the minimum patient delay was 0 day while the maximum was 2,530 days. Therefore, we will apply the formulae in scenario 1 to estimate the mean and variance in a primary study whenever the study reported the IQRs of delays. It was only when IQRs were not reported that the formulae in scenario 2 were applied.

Once we will estimate the mean and standard deviation from each study, we will pool the means across studies using a random effects model [50]. The random effects model will be used because that we expected that the observed variations in delays between studies is caused by more than random chance. For example, patients in different geographical regions may experience different delays (details in section 3.7). In order to incorporate between-study variations into the overall estimate of the effect sizes, we used the random effects model to pool the delay across studies [51]. All the analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria) and the random effects model was built using the *"metafor"* and *"meta"* package [52, 53].

Similarly, as we expect different care-seeking behaviors in different subgroups (urban vs rural populations, etc.), we will also use a random effects

model to conduct the meta-analysis in this case [51]. However, the conventional random effects model (DerSimonian and Laird method [54]) can potentially lead to biases when analyzing care-seeking behaviors because they were reported as proportions. The point of healthcare entry (health facilities first visited), referral rate, active follow rate, and trace rate were all measured by proportions. One of the reasons why the conventional model leads to biases when analyzing proportions is that this method approximates the distribution of within-study variations as normal while it is actually binomial, and normal approximation is not reliable when the proportion is close to one and zero [55-58]. Furthermore, this method does not correct the correlation between estimated percentage and its variance, which also leads to bias in the pooled proportions [55-59]. An alternative is to build a generalized linear mixed model (GLMM), and fit it by the exact binomial within-study likelihood instead of an approximated normal distribution [57]. According to simulation study, the exact binomial likelihood approach always performed better than the approximated normal approach, and the estimated proportions using the exact binomial likelihood were unbiased [57].

We therefore will construct the GLMM model according to methods proposed by Hamza and colleagues [57]. For illustration purpose, here it shows an example of meta-analyzing the percentage of patients who first visited village clinics upon onset of TB symptoms. The logit of the percentage reported by each primary study ($\mathrm{p_i}$) follows a normal distribution:

$$p_i \sim \mathcal{N}(p, \tau^2)$$

where the parameter p is the pooled mean logit of the percentage across all the studies. The parameter τ^2 is the between-study variance [57]. Because the within-study variance follows a binomial distribution, so the observed number of patients who first visited village clinics in each study ($\mathrm{x_i}$) can be summarized as follows:

$$x_i \sim Binomial\ (\pi_i, n_i)$$

where $\pi_i = \frac{1}{1+e^{p_i}}$ and $\mathrm{n_i}$ is total number of subjects in that study [57]. The GLMM will be fitted using *lme4* package in R [60].

Assessment of Heterogeneity

Heterogeneity in systematic reviews refers to variability (inconsistency) in results across studies[61]. To investigate heterogeneity, we will use the I-squared statistic, developed by Higgins et al [61].

$$I^2 = 100\% * \frac{Q - df}{Q}$$

where the parameter Q is the weighted sum of squared differences between the effect size in each primary study and the pooled effect size in all the studies. The Q statistic has a distribution of χ^2 with degree of freedom (df) of $k-1$, where k denotes the number of primary studies [62, 63]. The I-squared statistic measures the percentage of total variability in effect measure that is attributable to

heterogeneity rather than random chance [61]. An I-squared value higher than 40-50% suggests a high degree of heterogeneity[64].

Subgroup Analyses

Delay in TB diagnosis and treatment as well as pathways to care are highly context-specific and are strongly linked to local socio-economic and cultural issues. Hence, we anticipate heterogeneity in the main outcomes measures. To address this, we will conduct subgroup analyses. We will stratify the data using region, urbanization, and type of TB as the main stratifying variables. The rationale is provided below.

Region (western, central, and eastern regions). People living in the western region are likely to experience a longer delay in diagnosis and treatment because there is significant difference in the economic development between the western and eastern regions [65]. Although basic diagnosis and anti-TB drugs are free of charge to all TB patients, patients have to pay out-of-pocket for other services, such as liver protection drugs, CT scan, etc. [66]. Patients living in the underdeveloped western region might not be able afford such services. According to the Chinese government, the geographic regions are defined as follows: the 12 Eastern provinces includes: Beijing, Shanghai, Liaoning, Shandong, Jiangsu, Hebei, Tianjin, Zhejiang, Fujian, Hainan, Guangxi and Guangdong. Henan, Jilin, Inner Mongolia, Shanxi, Heilongjiang, Hubei, Jiangxi, Hunan and Anhui are in Central China. The Western region includes the following 10 provinces: Ningxia, Xinjiang, Tibet, Shaanxi, Gansu, Qinghai, Chongqing, Sichuan, Yunnan, and Guizhou.

Urbanization (urban, rural, and migrant). Urban migrants work and live in crowded environment and are reluctant to seek healthcare when ill [7]. They are a particularly vulnerable group of TB and likely to have prolonged and complicated pathway to healthcare. Additionally previous research [13] has shown that rural residence is a risk factor of delay. We therefore stratify the data according to urbanization level to reduce confounding.

Type of PTB: Since negative smear result is a risk factor for increasing delay [30], we stratified the participants based on their smear status. Additionally, newly diagnosed patients tend to be less knowledgeable and informed about TB than retreated patients, hence their care-seeking behaviors were analyzed separately.

Publication bias:

Publication bias occurs when the likelihood of being published is associated with the results of a study rather than the quality of the study. Frequently in biomedical research, positive results are more likely to be published than negatives one [67]. Funnel plots [68] and statistical tests that are based on it, such as Begg's test [69], Egger's test [70] and Trim and fill method [71], are commonly used to assess publication bias in randomized control trials (RCTs). However, several researchers have voiced their concern of applying these tests to observational data [70, 72].

Since all of the included studies are observational studies, therefore, publication bias will not be assessed in this review.

Appendix 3 Search strategy used in PubMed

1. tuberculosis[Mesh] OR mycobacterium tuberculosis[Mesh] OR tuberculosis[tiab]
2. "community health services"[Mesh] OR "health behavior"[Mesh] OR patient acceptance of healthcare[Mesh] OR "Follow-Up Studies" [Mesh] OR "Referral and Consultation"[Mesh]
3. diagnos*[tiab] OR treat*[tiab]) AND (delay*[tiab] OR time*[tiab] OR late[tiab] OR latenc*[tiab] OR lateness[tiab] OR interval*[tiab] OR barrier*[tiab]
4. health[tiab] OR healthcare[tiab] OR care[tiab] OR treatment*[tiab]) AND (seek*[tiab] OR path[tiab] OR paths[tiab] OR pathway*[tiab] OR behavior*[tiab] OR behavior*[tiab]
5. health facilities[tiab] OR "health facility"[tiab] OR refer[tiab] OR referral[tiab] OR referred[tiab]
6. #2 OR #3 OR #4 OR #5
7. china[Mesh] OR China[tiab] OR Chinese[tiab]
8. #1 AND #6 AND #7

Appendix 4 Data Extraction Form

Study ID: ☐ Reference ID: ☐

Reviewer: _____ Date of review: _____

Reference information

Study Type	
First Author	
Journal	
Year of Pub	
Vol.	
Issue	

Title	
Corresponding Author	
Corresponding Author Email:	

Study information (general)

Year of Study	
Study Type	(cohort, CS, etc)
Smear pos. / All PTB	

Province	
Sample size	
Rural/Urban/ Migrant	

Population characteristics

Average age:	
% Farmer:	
New/re-treat	
% Low / no edu	

% Senior (55+):	
% Male	
% On Insurance	
% High school +	

Time Delay Information

(/days)	Median or mean	Range	IQR
Patient delay (PD) Median, Median, Range, IQR			
Delay initiating diagnosis (DxD) Median, Median, Range, IQR			
Delay initiating treatment (RxD) Median, Median, Range, IQR			
Health system delay (HSD) Median, Median, Range, IQR			
Total diagnostic delay (TD) Median, Median, Range, IQR			

Pathway of health care seeking

	First point of medical consultation %	Referral rate %
Pharmacy		
Village and township health facilities		
Village health clinics		
Township hospitals		
County or above hospitals		
Dispensaries or TB-specific hospitals		
No care seeking		

TB dispensaries active follow up rate (%): _____

Dispensaries traced rate (%): _____

% ATT initiation prior to arrival at TB dispensaries: _____

Number of health care providers visited:

Average: _____

Max: _____

Min: _____

Appendix 5 Selected code to meta-analyze patient delay

```
library(nlme)
library(lme4)

setwd("C:/Users//zhizhenq//Dropbox//EPI//thesis//Results")
# Load the dataset
df  <- read.table(file = "result_7apr.csv", sep=",", header=TRUE)

# Create a subset with the percentage of patients who first visited village
clinics upon onset of TB symptoms excluding NA.
village <- subset(df, is.na(df$village)==F)
village$xi <- village$Study_size*village$Village/100 # created xi variable for
observed # success.
village$x2<-round(village$xi,0)
names(village)[11] <- "mi" # create a var for study size.

# This is how to run the model
m2<-glmer(cbind(x2,mi-x2)~ 1 + (1 | Record_ID), data = village, family
=binomial)
se <- sqrt(diag(vcov(m2)))
# table of estimates with 95% CI

tab <- cbind(Est = fixef(m2), LL = fixef(m2) - 1.96 * se, UL = fixef(m2) + 1.96
*se)

# Exponentiate the beta to get the pooled rate
invlogit <- function(x){
exp(x)/(1+exp(x))
}

invlogit(tab)
```

Appendix 6 Selected code to meta-analyze care-seeking pathway outcome

```
library(nlme)
library(lme4)

setwd("C:/Users//zhizhenq//Dropbox//EPI//thesis//Results")
# Load the dataset
df  <- read.table(file = "result_7apr.csv", sep=",", header=TRUE)

# Create a subset with the percentage of patients who first visited village
clinics upon onset of TB symptoms excluding NA.
village <- subset(df, is.na(df$village)==F)
village$xi <- village$Study_size*village$village/100 # created xi variable for
observed # success.
village$x2<-round(village$xi,0)
names(village)[11] <- "mi" # create a var for study size.

# This is how to run the model
m2<-glmer(cbind(x2,mi-x2)~ 1 + (1 | Record_ID), data = village, family
=binomial)
se <- sqrt(diag(vcov(m2)))
# table of estimates with 95% CI

tab <- cbind(Est = fixef(m2), LL = fixef(m2) - 1.96 * se, UL = fixef(m2) + 1.96
*se)

# Exponentiate the beta to get the pooled rate
invlogit <- function(x){
exp(x)/(1+exp(x))
}

invlogit(tab)
```

Appendix 7 List of excluded studies and reasons for exclusion

Reason for exclusion	**Excluded studies**
Not referral rate but sources of patients who registered with China CDC (n= 15)	[157-170]
Multiple publications of the same study or the same paper indexed in both English and Chinese databases (n=7)	[154, 171-176]
Only conference abstract no full text (n=3)	[177-179]
Study conducted before 2000 (n=4)	[180-183]
Didn't separate PTB from EPTB (n= 2)	[184, 185]
Only report MDR-TB patients (n=2)	[186, 187]
Qualitative studies (n=2)	[188, 189]
Did not separate referral arrival rate and trace rate (n=1)	[190]
Active case finding (n=1)	[185]
Only reported data on integrated TB control model (n=1)	[191]
Only reported PD+DxD, and did not report separately (n=1)	[192]

China CDC: China Center for disease control and prevention; PTB: pulmonary tuberculosis; EPTB: extra-pulmonary tuberculosis; MDR-TB: multi-drug resistant tuberculosis; PD: patient delay; DxD: diagnostic delay