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Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review

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SUMMARY

OBJECTIVE: To systematically review Indian literature on delays in tuberculosis (TB) diagnosis and treatment.

METHODS: We searched multiple sources for studies on delays in patients with pulmonary TB and those with chest symptoms. Studies were included if numeric data on any delay were reported. Patient delay was defined as the interval between onset of symptoms and the patient's first contact with a health care provider. Diagnostic delay was defined as the interval between the first consultation with a health care provider and diagnosis. Treatment delay was defined as the interval between diagnosis and initiation of anti-tuberculosis treatment. Total delay was defined as time interval from the onset of symptoms until treatment initiation.

RESULTS: Among 541 potential citations identified, 23 studies met the inclusion criteria. Included studies used a variety of definitions for onset of symptoms and delays. Median estimates of patient, diagnostic and treatment delay were respectively 18.4 (IQR 14.3–27.0), 31.0 (IQR 24.5–35.4) and 2.5 days (IQR 1.9–3.6) for patients with TB and those with chest symptoms combined. The median total delay was 55.3 days (IQR 46.5–61.5). About 48% of all patients first consulted private providers; an average of 2.7 health care providers were consulted before diagnosis. Number and type of provider first consulted were the most important risk factors for delay.

CONCLUSIONS: These findings underscore the need to develop novel strategies for reducing patient and diagnostic delays and engaging first-contact health care providers.

KEY WORDS: tuberculosis; delayed diagnosis; delivery of health care; care seeking behaviour; India

ALTHOUGH early case detection and treatment are critical for controlling tuberculosis (TB),[1] national TB programmes are heavily dependent on passive case finding. Studies suggest that the diagnosis of TB is often delayed,[2] and one major reason is repeated visits at the same health care level and non-specific antibiotic therapies.[3] Reasons for overall diagnostic delay have been attributed to both patients and the health system.[4] Delayed diagnosis of TB can enhance the transmission of infection, worsen the disease, increase the risk of death, and may be a reason why TB incidence has not substantially declined despite the global scale-up of the DOTS strategy.[5] Studies about health care-seeking behaviour and diagnostic delays therefore provide important information for programme managers.

India has the highest TB burden among the 22 high TB burden countries, with an estimated incidence of 2.2 million cases in 2011.[1] In 1997, India started implementing the DOTS strategy under the Revised National TB Control Programme (RNTCP), and had covered the entire country by 2006. Despite this scale-up, TB incidence remains high, indicating substantial ongoing transmission.

India has a complex and highly heterogeneous health care delivery system, with both public and private sector (both formal and informal) health care providers (HCPs). Private and informal HCPs are often the first source of care for any illness,[6–8] including TB.[9] There is evidence, albeit limited, that patients with TB symptoms often begin seeking advice in the informal private sector, from chemists and unqualified practitioners, then seek care from qualified practitioners, and eventually end up in the public sector for free treatment.[10] Patients thus move from one provider to another before they are finally diagnosed and started on anti-tuberculosis treatment.[10–12] Although two systematic reviews have been published on diagnostic delay,[2,3] they did not report the health care-seeking behaviour of patients with presumed TB, and thus included few studies from India.

CTS and ZZQ contributed equally to this study.

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METHODS

Objective

We aimed to systematically review the literature from India about health care-seeking behaviour, patient, diagnostic and treatment delays for pulmonary TB patients and those with chest symptoms as well as risk factors for delay.

Search strategy

With the assistance of a medical librarian, we searched PubMed, Embase and Web of Science for studies published between January 2000 and May 2013, without any language restrictions, using the following search terms, adapted from previous reviews:[2,3] 1) 'tuberculosis'[Mesh] OR 'mycobacterium tuberculosis' [Mesh] OR 'tuberculosis'[tiab]; 2) 'delayed diagnosis'[Mesh] OR (diagnosis*[tiab] AND delay* [tiab]) OR (treatment* [tiab] AND delay* [tiab]) OR (case [tiab] AND finding [tiab]); 3) 'patient acceptance of health care'[Mesh] OR ((health [tiab] OR health care [tiab]) AND seeking [tiab] AND (behaviour* [tiab] OR behaviour*)) OR (care [tiab] AND seeking [tiab]); 4) 'India'[Mesh] OR 'India*' [tiab]; 5) 2 OR 3; and 6) 1 AND 4 AND 5.

In addition, we carried out an electronic search of several Indian journals to increase the yield of relevant studies, especially from non-indexed journals: Indian Journal of Tuberculosis, Indian Journal of Public Health, Indian Journal of Community Medicine, National Medical Journal of India and Indian Journal of Medical Research. Additional studies were identified by contacting the authors of primary studies and experts in the field of TB, and by searching the reference lists of primary studies and previous systematic reviews. We requested unpublished data from organisations such as the Central TB Division of the Ministry of Health and Family Welfare, Government of India, the RNTCP and the International Union Against Tuberculosis and Lung Disease, South-East Asia Office.

Inclusion/exclusion criteria

With respect to study designs, we included cross-sectional surveys, prospective patient recruitment and retrospective analyses of medical records. Participants included patients with chest symptoms (individuals with cough $\geq$2 weeks and presumed to have TB), pulmonary TB (PTB) patients (smear-negative, new smear-positive or retreatment patients), pulmonary and extra-pulmonary TB (EPTB; if data were presented for PTB separately). Outcome measures included health-seeking behaviour, 'delays' such as patient delay, health system, diagnostic delay, treatment delay and total delay, risk factors for patient delay, and health system delay (defined below).

If there were duplicate publications of the same study, the most recent publication that reported full data was included. Studies reporting health care-seeking behaviour and 'delays' for only EPTB, those that did not report data separately for PTB and EPTB (if our attempt to obtain disaggregated data from the authors for PTB failed) and purely qualitative studies were excluded. Studies that reported only health care-seeking behaviour but not duration of delays were also excluded.

Study selection

Citations identified by the search were independently assessed by two authors (CTS and ZZQ). In the next stage, full-text articles were retrieved to identify all eligible studies using the inclusion and exclusion criteria listed above. Disagreements between the reviewers were resolved by a third reviewer (MP).

Quality assessment

As tools such as QUADAS (quality assessment of diagnostic accuracy studies) are meant for diagnostic accuracy studies,[13] and as there are no quality assessment tools for studies on diagnostic delays, we used a few indicators to summarise quality of included studies:

1 Retrospective analysis of already collected data: Yes/No
2 A representative sample of TB patients was included: Yes/No
3 TB patients confirmed by either smear or culture: Yes/No
4 Diagnostic delays separately reported as patient and health system delays: Yes/No
5 Risk factors for diagnostic delays were reported: Yes/No

All included studies were assessed independently by two reviewers (CTS and ZZQ).

Data extraction and analysis

Two reviewers (CTS and ZZQ) extracted the data from the included studies using a data extraction form adapted from previous reviews. Disagreements were resolved either through discussion or by a third reviewer (MP). Data extracted included name of the first author, year of publication, year of study, study characteristics (design, location, urban/rural, setting, sample size) and patient characteristics (age, sex, education), type of participant (individuals with chest symptoms, newly diagnosed smear-positive/negative, retreatment PTB patients), delays, health care-seeking behaviour and risk factors for delays.

We adopted the conceptual framework used in our previous systematic review (Figure 1) for extracting data on delays. This was adapted from the terminology for delays used in a study by Yimer et al.[4] Patient delay (PD) was defined as the interval between the onset of symptoms suggestive of PTB and the patient's first contact with an HCP. Diagnostic delay

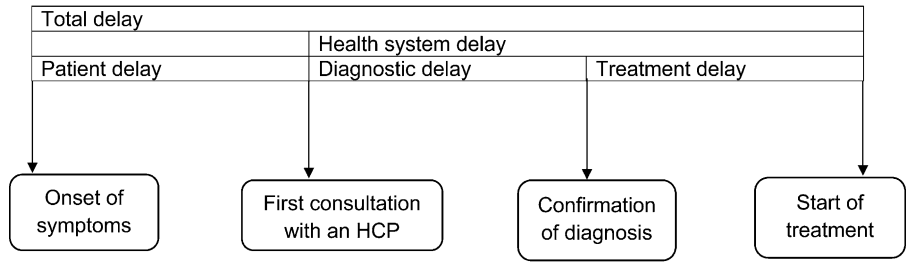

Figure 1 Conceptual framework on definitions of delays (NB: the size/length of components does not represent actual durations). Adapted from Yimer et al.[4] HCP = health care provider.

(DxD) was defined as the interval between the first consultation with an HCP and diagnosis. Treatment delay (RxD) was defined as the interval between diagnosis and initiation of anti-tuberculosis treatment. Total delay was defined as the interval from the onset of symptoms until treatment initiation. In this review, health system delay (HSD) includes DxD and RxD. This modification was made considering that both DxD and RxD are caused by the health system or HCPs consulted by the patients (Figure 1).

Of the six studies conducted among patients with chest symptoms, two studies reported DxD. One study defined DxD as the interval between first visit to HCP and collection of sputum, while the other did not define DxD. PD was reported in all six studies and was defined as for PTB patients. None of them reported RxD, as it was not applicable. We therefore do not provide separate definitions for various delays for studies conducted among individuals with chest symptoms.

Where necessary, authors were contacted for additional information. For the average duration of each delay, we extracted the average (median) reported in the included studies. We extracted mean estimates from studies that did not provide data on median delays. We only extracted the average total delays reported in the primary studies, and did not sum up various delays to get the total. Durations of delays reported in weeks or months were transformed into number of days. For health care-seeking behaviour, we extracted the percentage of patients who first consulted a private practitioner, and the average (median or mean) number of HCPs consulted before a diagnosis was made. Significant risk factors for longer PD and DxD were extracted if multivariate analyses were carried out and reported.

Data analysis

We generated a summary of the results in a table to describe the characteristics and results of each of the

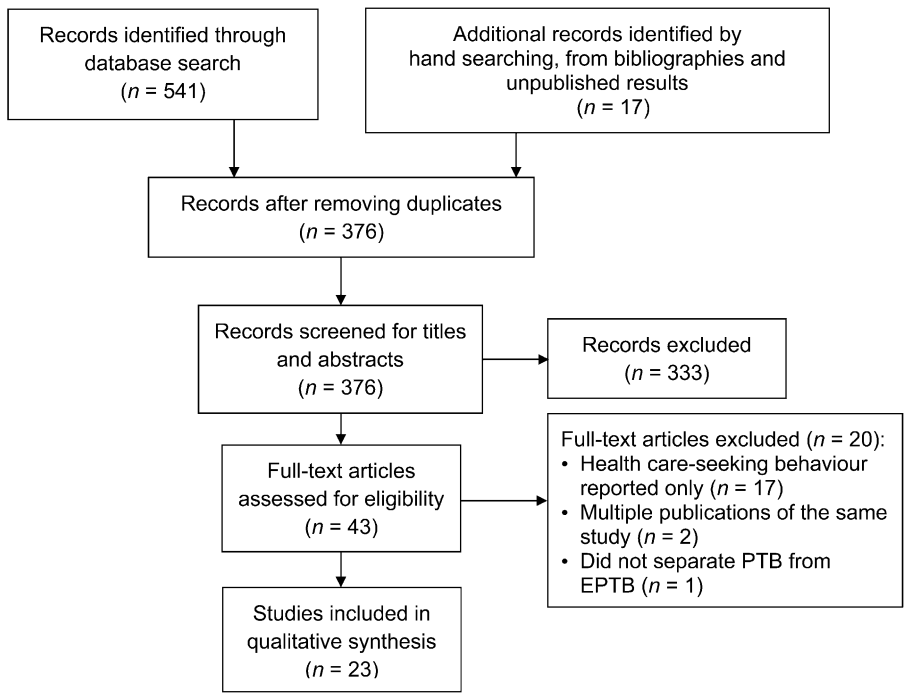

Figure 2 Study selection flow chart. PTB = pulmonary tuberculosis; EPTB = extra-pulmonary TB.

included studies, including health care-seeking behaviour and outcomes of delays. A separate summary of results was prepared for significant risk factors by multivariate analysis for prolonged delays. As duration is generally not normally distributed, we used median for our analysis. We summarised duration (in days) for each type of delay by constructing box plots to depict median, interquartile range (IQR), minimum and maximum. We compared each of the delays between two groups of study participants, namely patients with chest symptoms and PTB patients (any type), and conducted subgroup analyses (e.g., urban vs. rural) where appropriate.

RESULTS

Study selection

We identified 541 potentially eligible citations from the database searches, and 15 studies from hand searching and screening of bibliographies, including studies published before 2000. Two additional unpublished reports were obtained from the Central TB Division, RNTCP. We removed duplicates and screened the titles and abstracts of the remaining 376 records: 43 publications were selected for full-text screening, after which 23 articles were included in the final analysis (Figure 2). A list of excluded studies, with reasons for exclusion, is available from the authors upon request.

Characteristics of studies included

The studies included were published between 1998 and 2013, and the research was actually conducted between 1996 and 2012 (Table 1).[12,14–35] All except two studies had a cross-sectional design. The majority of the studies were conducted in three states: Tamil Nadu (n = 7),[14–20] Maharashtra (n = 5)[21–25] and Karnataka (n = 4).[12,26–28] The remaining studies were carried out in the states of Delhi,[29] West Bengal,[30,31] Andhra Pradesh,[30] Himachal Pradesh,[32] Haryana[33] and Sikkim,[34] or covered several regions.[35] Six studies were conducted in urban areas, five in rural areas, and 10 in both urban and rural areas. Five studies collected data using community surveys, while the remainder collected data by recruiting patients from the RNTCP (n = 15) and the National Tuberculosis Programme (NTP; n = 3), which preceded the RNTCP.

Study participants in the studies included were new PTB patients (n = 17), which included new smear-positive PTB patients (n = 11) and patients with chest symptoms (n = 6). One[14] of the 16 studies conducted among PTB patients excluded TB-HIV (human immunodeficiency virus) co-infected patients. The sample sizes of the studies conducted in new PTB patients ranged from 53 to 2027, and among patients with chest symptoms from 192 to 649.

Heterogeneity in definitions

Included studies used a variety of definitions for onset of symptoms and delay. The symptoms suggestive of PTB and various types of HCPs reported in the included studies are summarised in Table 2. Nine studies used onset of symptoms as any of the five cardinal TB manifestations, i.e., cough of ⩾2 or 3 weeks with/without chest pain, with or without fever, with or without weight loss, and with or without haemoptysis.[17,20,21,23,25,29,31–33] Five of these nine studies also included other symptoms of TB, such as breathlessness, loss of appetite and wheezing.[21,23,25,31,33] One study included symptoms that patients perceived as TB,[23] another study defined cough lasting for ⩾3 weeks as onset of symptoms,[34] and another defined it as cough of ⩾2 weeks.[18] Three studies defined cough as onset of symptoms without a specific duration.[15,16,28] Nine studies did not report any or a clear definition for onset of symptoms.[12,14,19,22,24,26,27,30,35]

The first contact of the patient with an HCP used for defining DxD also varied across the included studies. Six studies used a qualified allopathic practitioner for defining first contact with HCP.[14,16,18,31–33] However, three studies defined initial contact as a patient seeking care from a qualified or an unqualified HCP.[19,21,34] This included non-allopathic practitioners such as homeopathy, *ayurveda*, *unani*, *siddha* or acupuncture practitioner, faith healer, etc. Seven studies defined self-medication, or visiting pharmacies and chemists shops as the first contact with an HCP.[12,17,20,23,25,26,28] The remaining seven studies did not provide a clear definition of an HCP.[15,22,24,27,29,30,35]

Six studies defined health system delay (HSD) as the interval between the first contact with an HCP and the confirmation of TB diagnosis (i.e., DxD).[18,22–24,27,31] However, four studies defined the end point of HSD as the initiation of (correct) anti-tuberculosis treatment.[12,18,19,25] Six studies separately defined the interval between confirmation of diagnosis and initiation of anti-tuberculosis treatment as treatment delay.[21–24,27,31] Nine studies did not provide definitions for HSD, DxD or RxD.[14,15,17,20,29,30,32,33,35]

Because of this heterogeneity in definitions, a decision was made not to perform a meta-analysis, but instead to summarise the results as simple averages in tables and distribution plots. Even these numbers need to be interpreted with caution, because of the underlying heterogeneity. Notably, the study by Bawankule et al. included patients who were severely ill and hospitalised in a tertiary care hospital.[25] This study was identified as an outlier in the box plots when compared with studies that included ambulatory patients.

Patient delay

The reported average PD for PTB patients (n = 17 studies) and for all patients, including patients with chest symptoms (n = 6 studies), had the same range,

Table 1 Characteristics of included studies and key outcomes ($N = 23$)

Author, year, reference	Year of study	Location	Urban/ rural	Study setting	Sample size	Sample characteristics	PD days	DxD days	RxD days	TD days	Patients who first consulted a private HCP %	Average no. of HCPs visited before reaching a diagnosis
Studies on delays in PTB patients												
Ananthakrishnan, 2012[14]*	2007	Chennai, Tamil Nadu	Urban	10 TB units	219 PTB	Aged <55 years: 86.7% Males: 62% No or primary education: 44%	11.4	—	—	—	64.4	2.8
Bawankule, 2010[25]*	2007	Wardha, Maharashtra	Rural	Tertiary care hospital	53 PTB	Mean age: 28.2 years Males: 69.8% Up to primary education: 39.6%	95.0	47.0†		118.0	26.4	4.3
Dhanvij, 2009[21]*	2007	Wardha, Maharashtra	Rural	Tertiary care hospital	39 PTB	Mean age: 39.3 years Male: 71%	47.2	25.0	1.8	73.9	48.7	1.9
Dhingra, 2002[29]*	2001	New Delhi, Delhi	Urban	4 TB subcentres	301 PTB	Mean age: 33 years; Male: 53.1% Illiterate: 49.2%	18.8	—	—	—	56.8	—
Uplekar, 1998[24‡]	—	Pune & Mumbai, Maharastra	Both	Private and public health institutions	173 PTB	Aged >45 years: 20% Male: 65% Illiterate: 31%	21.2	36.7	3.4	—	86	—
Balasubramanian, 2004[16]*	1999	Tiruvallur, Tamil Nadu	Rural	TB patients registered under DOTS	566 new smear+	Male: 76.5%	14.0	31.0	—	45.0	53.0	—
Chakraborty, 2001[26]*	—	2 Districts, Karnataka		District TB centre, TB units	147 new smear+	Male: 74.8% Illiterate: 34.7%	267.7	39.4	—	—	10.9	12.3
Goel, 2012[27]*	2006–2007	Udupi District Karnataka	Both	Community survey	98 new smear+	Aged >45 years: 38.8% Male: 58% Illiterate: 63.2%	30.0	54.5	2.0	57.5	76.5	2.5
Jagadish, 2012[28]*	2009	Bangalore, Karnataka	Urban	TB units/ district medical centres	468 new smear+	Mean age: 38.5 years Male: 69.7% Up to primary school: 40.6%	24.0	18.0†		41.0	49.8	—
Pantoja, 2009[12]	2005	Bangalore, Karnataka	Urban	Under registry of RNTCP	658 PTB	Mean age: 36 years Aged >45 years: 30% of PTB patients Males: 65% Illiterate: 35%	7.0	35.0†		51.0	75.0	3.3

(*continued*)

Table 1 (*Continued*)

Author, year, reference	Year of study	Location	Urban/ rural	Study setting	Sample size	Sample characteristics	PD days	DxD days	RxD days	TD days	Patients who first consulted a private HCP %	Average no. of HCPs visited before reaching a diagnosis
Studies on delays in PTB patients (*continued*)												
Paul, 2012[30]*§	2010	Bardhaman, West Bengal, and Nalagonda, Andhra Pradesh	Rural		2027 new smear+	Mean age: 39 years Male: 79%	—	—	8.0	—	—	—
Pradhan, 2010[22]*	2005–2006	Mumbai, Maharastra	Urban	DOTS centres	266 new smear+	Mean age: 31 years Male: 59% Up to primary school: 37%	6.0	31.0	4.0	—	82.3	2.0
Rajeswari, 2002[18]*	1997–1998	Chennai, Madurai, Chingleput and Vellore Tamil Nadu	Both	Private and public health institutions	531 new smear+	Aged >45 years: 38% Male: 72% Illiterate: 30%	20.0	23.0	—	60.0	54.0	—
Selvam, 2007[19]*	2003	All districts of Tamil Nadu	Both	TB units	601 new smear+	Mean age: 43 years Male: 73% Illiterate: 39%	28.0	28.0†		62.0	43.0	—
Tamhane, 2012[23]*	2002	Mumbai, Maharashtra	Urban	DOTS centres 12 wards	150 new smear+	Median age: 30 years Male: 50% Illiterate: 25%	15.0	31.0	2.0	—	65.0	—
Thakur, 2013[31]*	2009–2010	Mandi District Hospital, Himachal Pradesh	Both	Patients under RNTCP	234 new smear+	Aged >35 years: 50.9% Male: 66.6% Illiterate: 25.6%	15.0	33.5	1.0	36.0	22.0	—
India Central TB Division 2013[35]*§	2011–2012	India Central TB Division's internal evaluation done across India	—	5 new smear+ patients from each of the 330 microscopy centres in 66 districts	1644 new smear+	Mean age: 37 years Male: 66% Female: 34%	15.0	4.0	3.0	—	48.0	2.2
Median delays for PTB patients (range)							19.4 (6.0–267.7)	31.0 (4.0–54.5)	2.5 (1.0–8.0)	57.5 (36.0–118.0)	51.4 (10.9–82.3)	2.5 (1.9–12.3)

(*continued*)

Table 1 (*Continued*)

Author, year, reference	Year of study	Location	Urban/ rural	Study setting	Sample size	Sample characteristics	PD days	DxD days	RxD days	TD days	Patients who first consulted a private HCP %	Average no. of HCPs visited before reaching a diagnosis
Studies on delays in patients with chest symptoms												
Grover, 2003[33]*	1998–2000	2 Villages and Chandigarh City, Haryana	Both	Community survey	192	Aged 15–44 years: 45.5% Male: 58% Illiterate: 32.5%	56.6	—	—	—	34.3	—
Balasangameshwara, 1998[15§]	1996–1997	Dharmapuri, Tamil Nadu	Both	Private and public health institutions	673	Median age: 48 years urban & 42 years rural	18.0	35.0	—	53.0	42.3% rural 36.4% urban	—
Charles, 2010[17]*	2008	Chennai and Madurai, Tamil Nadu	Both	Community survey	444	Male: 51.2%	16.0	—	—	—	38.0	—
Sudha, 2003[20]*	1997	Chennai and Madurai, Tamil Nadu	Both	Community survey	649	Male: 45.9% Aged >45 years: 52.3% Up to primary school: 37%	10.0	—	—	—	37.7	—
Tobgay, 2006[34]*	2003	Eastern Sikkim	Rural	2 TB units and 4 microscopy centres	323	Median age: 30 years Male: 58.8% Up to primary school: 33.1%	21.0	7.0	—	—	26.0	—
Ghosh, 2010[32]*	2008	Patpur, Bankura West Bengal	Both	Community survey	64	Aged ⩾45 years: 18.7% Male: 68.7%	7.0	—	—	—	37.5	—
Median delays for both patients with PTB and those with chest symptoms (range)							18.4 (6.0–267.7)	31.0 (4.0–54.5)	2.5 (1.0–8.0)	55.3 (36.0–118.0)	48.0 (10.9–82.3)	2.7 (1.9–12.3)

Note: The average TDs were extracted from the primary studies (not by summing up PD, DxD and TD to get the total when it was not reported by the authors). Of the 16 records that reported HSD, five reported DxD, whereas one reported RxD only. Ten studies reported both delays; however, four studies did not separate DxD and RxD, but reported them together as HSD. In the box plot for HSD, we use HSD in these four studies as DxD, as it is much larger than RxD.

*Cross-sectional study.

†DxD and RxD reported together as HSD.

‡Prospective recruitment.

§Retrospective cohort.

PD = patient delay; DxD = diagnostic delay; RxD = treatment delay; TD = total delay; HCP = health care provider; PTB = pulmonary TB; TB = tuberculosis; + = positive; RNTCP = Revised National Tuberculosis Control Programme; HSD = health system delay.

Table 2 TB-related symptoms and first contact with health care providers/facilities used to define patient delay and diagnostic and health system delays

Symptoms
Five cardinal TB symptoms: cough of ⩾2 or ⩾3 weeks, chest pain, fever, loss of weight, haemoptysis
Symptoms relevant to TB: breathlessness, loss of appetite
Other symptoms/signs that patients attributed to TB
Health care provider
Traditional healers: faith healers, priests, etc.
Pharmacies or chemist shops
Non-allopathic practitioners: homeopathy, *ayurveda*, *unani*, *siddha*, acupuncture, etc.
Unqualified medical practitioners: non-licensed practitioners, village health guides, traditional midwives, etc.
Qualified allopathic health care providers from both public and private sectors, specialist such as internal medicine and chest medicine, etc.

TB = tuberculosis.

i.e., from 6.0 to 267.7 days, but medians were respectively 19.4 and 18.4 days. There was much variability across studies, as shown in Table 1.

Health system delay (diagnostic and treatment delays)

The reported DxD among PTB patients ranged from 4.0 to 54.5 days (median 31.0; Figure 3). The median and range were the same for all 16 studies that reported DxD (14 studies on PTB patients and two studies on patients with chest symptoms). The reported RxDs (in eight studies on PTB patients) ranged from 1 to 8 days (median 2.5). None of the studies conducted among patients with chest symptoms reported data on treatment delay (Table 1).

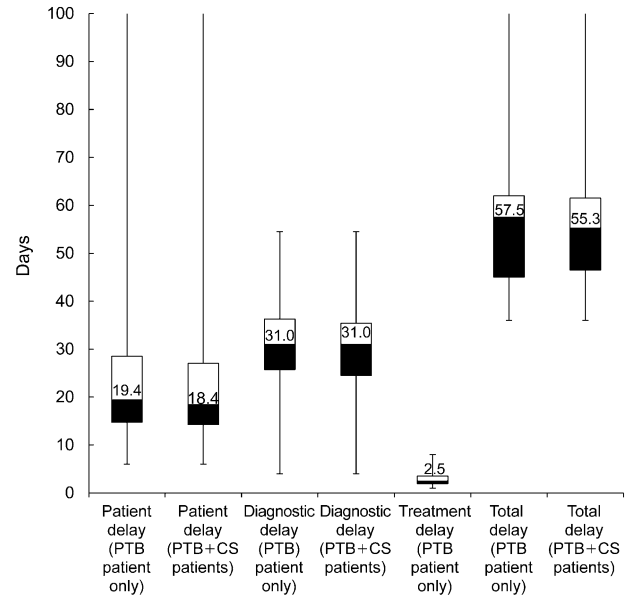

Figure 3 Distribution of patient delay, diagnostic delay, treatment delay and total delay among PTB patients and CS in India. Box plots depict the median (central line), interquartile range (box) and range (whiskers). PTB = pulmonary TB; CS = chest symptomatic.

Total delay

Data on total delay were reported in 10 studies (nine studies on PTB patients and one study on patients with chest symptoms). Total delay ranged from 36.0 to 118.0 days in studies on PTB patients (median delay 57.5 days; Figure 3). The median TD in all studies (including those with chest symptoms) was 55.3 days (range 36.0–118.0; Table 1).

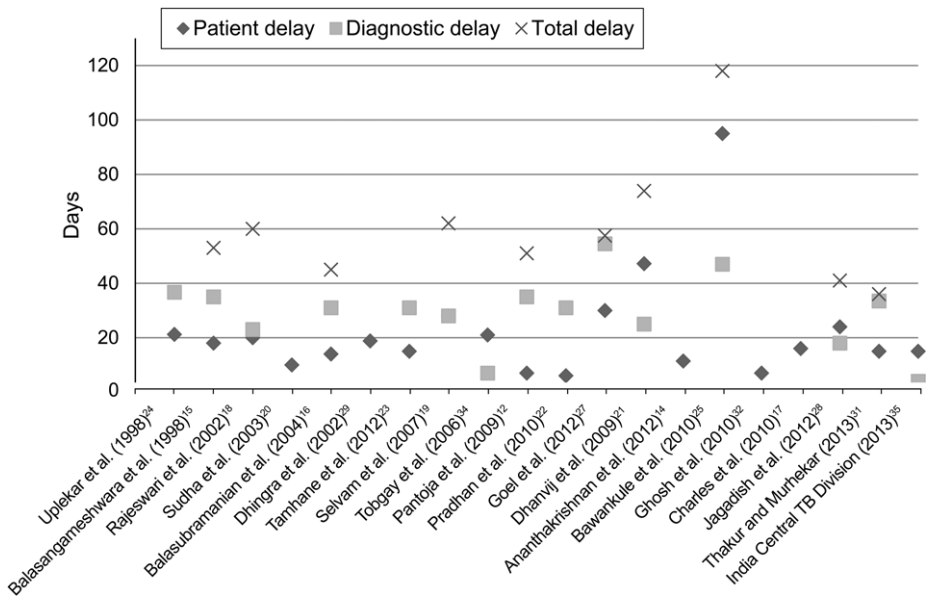

Figure 4 Patient delay, diagnostic delay and total delay among patients with pulmonary tuberculosis and those with chest symptoms, with studies ordered chronologically. The total delays were extracted from the primary studies (not by summing up patient delay, diagnostic delay and treatment delay to get the total when it was not reported by the authors).

Table 3 Rural vs. urban comparison of delays and health care-seeking behaviour of patients with pulmonary tuberculosis and those with chest symptoms

	Patient delay, days median [IQR]	Diagnostic delay, days median [IQR]	Treatment delay, days median [IQR]	Total delay, days median [IQR]	Private sector as first point of care median %	Average no. of HCPs consulted median
Urban (n = 6)	13.2 [6.75–20.1]	31.0 [18.8–31]	3.0 [2.5–3.5]	46.0 [43.5–48.5]	65	2.8
Rural (n = 5)	34.1 [17.5–58.0]	28.0 [20.5–35.0]	4.9 [3.3–6.4]	73.9 [59.5–96.0]	38	3.1
Total (N = 23)	18.4 [14.3–27.0]	31.0 [24.5–35.4]	2.5 [1.9–3.6]	55.3 [46.5–61.5]	48	2.7

IQR = interquartile range; HCP = health care provider.

Care seeking and number of providers seen

Although there was a lot of variation (range 11–82%), on average 48% (median) of TB patients (both PTB and patients with chest symptoms) first visited the private/informal sector. The median number of HCPs consulted before reaching a diagnosis (reported in eight studies) was 2.7 (range 1.9–12.3; Table 1).

Subgroup analysis by study period

Among 20 studies in which the time period of the research was clearly reported, four studies were conducted before the implementation of the DOTS strategy. All types of delay (except RxD) were plotted by year of study, but not according to year of publication (Figure 4). Treatment delays were not included in the graph due to the limited amount of data (only eight studies reported RxD). This plot shows no evidence that PD, DxD and TD have reduced over time. However, considerable heterogeneity is evident, and study populations and definitions are not consistent across studies. As mentioned earlier, the study by Bawankule et al. is the outlier (Figure 4).[25]

Subgroup analysis: rural vs. urban

We did a sub-group analysis on six studies conducted in urban settings and five in rural settings (Table 3). Of these 11 studies, 10 included PTB patients, while the study by Tobgay et al. (2006) was carried out among patients with chest symptoms.[34] The sample of patients studied in urban and rural settings ranged from respectively 150 to 468 and 53 to 2027.

The median PD, DxD and TD in urban areas were respectively 13.2, 31.0 and 46.0 days, whereas in rural areas these were respectively 34.1, 28.0 and 73.9 days. PD and TD were higher in rural areas; however, the DxD was nearly the same in both urban and rural areas. The percentage of private sector as first point of care was much higher in urban than in rural areas (65% vs. 38%; Table 3). RxDs were not compared due to the limited available data in these 11 studies.

Significant risk factors for delays

Risk factors for delay were not reported in all of the studies included: only five studies reported adjusted odd ratios (aORs) for delays from multivariable analysis. Tables 4 and 5 only included the risk factors positively associated with PD and HSD. Prolonged PD appeared to be strongly associated with type of HCP as the first contact, especially if first action after onset of symptoms was self-medication as well as the inability to pay HCP (aORs 7.8[31] and 2.9,[23] respectively). Two studies reported that first contact of patient with government HCP was a risk factor for prolonged PD (aORs 2.2[18] and 2.76[34]; Table 4).

In contrast, initially seeking care from a private HCP was clearly a significant risk factor for prolonged HSD (aORs 33.1,[34] 6.68[31] and 4.0[18]). Although the above-mentioned aORs vary, this still ranks as the factor most strongly associated with HSD. In addition, visiting a non-allopathic HCP first was also an important risk factor (aOR 12.3[23]). We also found that consulting multiple HCPs was associated with prolonged HSD (aOR 8.0[31]; Table 5).

Table 4 Significant risk factors for patient delay by multivariate analysis

Risk factor for patient delay	aOR (95%CI)	Author, year, reference
First contact		
Self-medication	2.28 (1.0–5.18)	Tobgay, 2006[34]
Self-medication/consulting drug store	7.8 (4.17–14.58)	Thakur, 2013[31]
Use of traditional healer	2.18 (1.03–4.61)	Tobgay, 2006[34]
Initial consultation with government HCP (compared with private provider)	2.2 (1.5–3.4)	Rajeswari, 2002[18]
Government HCP	2.76 (1.15–6.62)	Tobgay, 2006[34]
Monetary concerns		
Family income <3000 INR	2.5 (1.23–6.15)	Thakur, 2013[31]
Inability to pay the HCP	2.9 (1.1–7.1)	Tamhane, 2012[23]
Cost of treatment >400 INR	2.52 (1.17–5.38)	Tobgay, 2006[34]
Smoking/alcohol		
Alcohol use	1.6 (1–2.4)	Rajeswari, 2002[18]
Smoking	1.9 (1.3–2.6)	Selvam, 2007[19]
Accessibility of health care facilities		
Mode of transportation	2 (1.3–3.1)	Selvam, 2007[19]
Residing 2 km from a health facility	1.6 (1–2.4)	Rajeswari, 2002[18]
Stigma	1.81 (0.99–3.32)	Thakur, 2013[31]

aOR = adjusted odds ratio; CI = confidence interval; HCP = health care provider; INR = Indian rupee (1 USD = 60 INR approx. in 2013).

Table 5 Significant risk factors for health system delay by multivariate analysis

Risk factor for health system delay	aOR (95%CI)	Author, year, reference
First contact		
Private HCP	33.1 (13.44–81.5)	Tobgay, 2006[34]
Private HCP	6.68 (2.75–16.23)	Thakur, 2013[31]
Private HCP	4 (2.6–6.4)	Rajeswari, 2002[18]
Non-allopathic HCP	12.3 (1.4–104.9)	Tamhane, 2012[23]
Non-government sector	2 (1.5–2.7)	Selvam, 2007[19]
Number of HCPs visited		
>3 consultations with an HCP	5 (1.4–17.4)	Tamhane, 2012[23]
Multiple health seeking encounters with HCP	8 (4.0–16.2)	Thakur, 2013[31]
Monetary concerns		
Cost of treatment (>400 INR)	2.5 (1.22–5.13)	Tobgay, 2006[34]
Expenses (>median) incurred before initial diagnosis	2.58 (1.34–4.95)	Thakur, 2013[31]
Accessibility of health care facilities		
Longer distance of health care facility	1.8 (1.2–2.5)	Selvam, 2007[19]
Distance >2 km from residence to health facility	1.8 (1.1–28)	Rajeswari, 2002[18]
Alcohol use	1.6 (1–2.6)	Rajeswari, 2002[18]
Duration of cough		
Shorter duration	2.6 (1.6–4.3)	Rajeswari, 2002[18]
Longer duration	2.5 (1.8–3.6)	Selvam, 2007[19]

aOR = adjusted odds ratio; CI = confidence interval; HCP = health care provider; INR = Indian rupee (1 USD = 60 INR approx. in 2013).

DISCUSSION

Principal findings

Despite the widespread implementation of the DOTS strategy, TB incidence remains high in India.[1] Our review shows long PD and HSD, and this may partially explain the current epidemiology.[5,36] A sizeable fraction of persons with PTB or presumed PTB first visit informal and private sector providers, particularly in urban areas, and multiple visits to HCPs appears to be an important risk factor for total delay. Data on risk factors for delays are limited, and further work is necessary to better understand patient pathways to care in India, to understand why patients seek private sector care and why they move between providers.

The previous review included 39 studies from 45 low- and middle-income countries,[2] and estimated average PD, HSD and total delay at respectively 31.7, 28.4 and 67.8 days. PD in the present review was much lower, but DxD was slightly higher than that of the previous review, which included only three studies from India and did not include TD or consider treatment initiation as an end point for HSD.

The average PD (18.4 days) in our review is only slightly longer than the criterion generally used to screen for TB, i.e., cough of ⩾2 weeks' duration. However, the average PD was twice as long in rural areas where the majority of India's population lives, suggesting that PD may still be a substantial problem for many. In addition, DxD was high in both rural and urban areas. These results suggest that even when patients seek care in a timely manner, significant time can be lost after their first contact with the health care system. Incentivising first contact and informal providers to refer persons with TB symptoms to the RNTCP may be one approach to reduce such delay.

Total delay in our review was lower than that reported by Storla et al. (72 days),[3] which included studies from high-income countries and a single study from India. Storla et al. did not summarise PD and HSD separately, nor did they report TD. Any comparisons of our results with those of the previous reviews should therefore be interpreted with caution.

Factors such as type of health care provider, treatment cost, income and accessibility of health care facilities were significantly associated with delays in our review, similar to the summary results reported by Storla et al.[3] However, Storla et al. reported that factors such as HIV, female sex, negative sputum smear, income and education were also associated with delays, but these factors were not reported in our review, as only five of the 23 included studies had assessed the risk factors for delays.

Studies included in the review spanned the period from 1998 to 2013, and there is insufficient evidence to conclude that delays have reduced over the period. However, time trend data should be interpreted with caution, as representative data collected using the same definitions are not available over time.

Strengths and limitations of the review

Our search strategy was rigorous, and multiple sources were searched. Two reviewers independently selected the studies and extracted data, and authors were contacted up to three times to retrieve relevant data. Where possible, we analysed the data separately as PD, HSD and TD. We also conducted subgroup analyses to better understand the reasons for variations in delays reported across studies.

However, our review had limitations. There was considerable variation in how key terms were defined in the primary studies, such as PD, HSD, DxD, TD, HCP and symptoms. The start and end points of delay differ and therefore the duration of delay varied. Almost inevitably, there was an element of poor recall or recall bias in each study. Most studies included newly diagnosed smear-positive patients to minimise recall bias. DxD is likely to be higher for smear-negative TB patients, but most studies recruited only smear-positive patients. Furthermore, while some studies accounted for first-contact care from unqualified HCPs, others only took qualified HCPs into account.

Another limitation is the generalisability of the results, as most of the studies interviewed patients from

government health facilities and recruited participants mainly from hospitals and clinics (often TB centres), and there were few studies from poorer, highly populated and high TB burden states. Future studies should focus on patients from private health facilities and TB patients and individuals with chest symptoms identified during population-based surveys to obtain representative data and in high-burden states. As with any systematic review, it is possible that we missed some studies.

Policy implications and research directions

In India, patients with TB symptoms spend a considerable length of time consulting various HCPs before receiving a final diagnosis. A first consultation with a private/informal HCP was common, and a significant risk factor for prolonged HSD. These results underscore the importance of private sector engagement to shorten the care-seeking pathway. Recognising this reality, the RNTCP has announced a National Strategic Plan (2012–2017) with the goal of 'universal access to quality TB diagnosis and treatment for all TB patients in the community'. The plan envisions large-scale engagement of the private sector to reduce DxD and improve quality of care.[37] More accurate, rapid molecular tests, combined with information and communication technologies and innovative delivery approaches to engage the private sector could be used to reduce overall delay and improve case notification.[38]

From a research perspective, there is a need for the RNTCP to collect standardised data on DxD and TD as part of routine monitoring and evaluation. Ideally, such data should include patients in both the public and private sectors, and capture information on how many providers were seen before the TB diagnosis, how long the process took and what costs were incurred by the patients.

Our review also underscores the need to better understand the quantitative relationship between DxD and TB transmission, and determine the likely number of secondary cases generated during the long pathway to care. Here, there are several unknowns.[5,39,40] How large a reduction in DxD is necessary before a meaningful decline in TB incidence occurs? Do delays before diagnosis translate directly to duration of infectiousness, or do most transmission events cluster toward the beginning or end of the infectious period? Do symptoms correlate with infectiousness? Does the risk of transmission vary dramatically across individuals (e.g., a few individuals with long delays may account for much of the avertible secondary cases)? Our review does not address these issues, but may be helpful to mathematical modellers exploring these complex questions.

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RÉSUMÉ

OBJECTIF : Faire une revue systématique de la littérature indienne relative au retard de diagnostic et de traitement de la tuberculose (TB).

MÉTHODE : Nous avons recherché des études relatives au retard au diagnostic de la TB pulmonaire et des patients présentant des symptômes respiratoires dans des sources multiples. Seules les études comportant des données numériques relatives à ce retard ont été incluses. Le retard au diagnostic a été défini comme l'intervalle entre la première consultation et le diagnostic. Le retard au traitement a été défini comme le temps séparant le diagnostic et la mise en œuvre du traitement antituberculeux. Le retard total était le temps écoulé entre le début des symptômes et la mise en route du traitement.

RÉSULTATS : Sur 541 études identifiées, 23 répondaient à nos critères. Les études utilisaient toute une gamme de définitions pour le début de symptômes et le retard. L'estimation médiane du retard pour le patient, le diagnostic et le traitement était de 18,4 jours (IQR 14,3–27), 31 jours (IQR 24,5–35,4) et 2,5 jours (IQR 1,9–3,6), respectivement, pour tous les patients combinés, avec TB ou symptômes respiratoires. Le retard médian total était de 55,3 jours (46,5–61,5). Près de 45% des patients ont d'abord consulté un prestataire de soins privé et 2,7 prestataires en moyenne ont été consultés avant le diagnostic. Le nombre et le type de prestataires vus constituaient les facteurs de risque de retard les plus importants.

CONCLUSION : Ces résultats soulignent la nécessité d'élaborer de nouvelles stratégies de réduction des retards liés au patient et au diagnostic et de stimuler les prestataires de soins qui sont les premiers contacts des patients.

RESUMEN

OBJETIVO: Llevar a cabo un examen sistemático de las publicaciones científicas en la India sobre el retraso en el diagnóstico y el tratamiento de la tuberculosis (TB).

MÉTODOS: Se investigaron múltiples fuentes de estudios científicos sobre el retraso en los casos de TB pulmonar y los pacientes con síntomas respiratorios. Se incluyeron en el examen los estudios que comportaban datos numéricos sobre algún tipo de retraso. Se definió el retraso dependiente del paciente como el lapso entre el comienzo de los síntomas y el primer contacto del paciente con un profesional de salud. El retraso del diagnóstico consistió en el lapso entre la primera consulta con un profesional sanitario y el establecimiento del diagnóstico. Se definió el retraso en el tratamiento como el lapso entre el diagnóstico y el comienzo del tratamiento antituberculoso. El retraso total fue el lapso entre el comienzo de los síntomas y el inicio del tratamiento.

RESULTADOS: De las 541 posibles citas reconocidas, 23 estudios cumplieron con los criterios de inclusión. En los estudios incluidos se aplicó una diversidad de definiciones del comienzo de los síntomas y los retrasos. La mediana del cálculo del retraso dependiente del paciente fue 18,4 días (IQR de 14,3 a 27,0 días), el retraso diagnóstico fue 31,0 días (IQR de 24,5 a 35,4 días) y el retraso del tratamiento fue 2,5 días (IQR de 1,9 a 3,6 días) en los pacientes tuberculosos y en los pacientes con síntomas respiratorios combinados. La mediana del retraso total fue 55,3 días (IQR de 46,5 a 61,5 días). Cerca de 48% de todos los pacientes consultaron profesionales del sector privado en primera instancia y los pacientes consultaron en promedio 2,7 profesionales antes de obtener el diagnóstico. El número y la categoría de profesional de salud fueron los principales factores de riesgo de retraso.

CONCLUSIÓN: Estos resultados destacan la necesidad de elaborar estrategias encaminadas a disminuir los retrasos del paciente y del diagnóstico y a estimular un primer contacto con los profesionales de salud.