Missed opportunities for diagnosis and treatment in patients with tuberculosis symptoms: a systematic review

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Research article

Keywords: tuberculosis, symptoms, identification, underdiagnosis

Posted Date: October 28th, 2020

DOI: <https://doi.org/10.21203/rs.2.22742/v4>

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Abstract

Background Identification of symptomatic patients followed by prompt on-site investigation form the foundation of facility-based tuberculosis (TB) screening and diagnosis. However, underdiagnosis is common, contributing to ongoing transmission and adverse health outcomes. We conducted this systematic review with the hypothesis that underdiagnosis is largely secondary to failure of the symptom-screen-based approach to efficiently identify patients at risk of TB.

Methods We searched (to 22 January 2019) MEDLINE, Embase, and Cinahl for studies investigating the pathway of care for patients (and standardised patients) presenting to health facilities or pharmacies with TB symptoms. We used QUADAS-2 to assess risk of bias. We reported the proportions of symptomatic patients at each stage of the diagnostic and care pathway from symptom screening to treatment initiation. We adhered to the PRISMA statement throughout this work.

Results After screening 3,184 titles and abstracts, we identified 14 eligible studies. None provided data addressing the full cascade of care from clinical presentation to treatment initiation in the same patient population. Symptom-screening, the critical entry point for diagnosis of TB, was not done for 40%, 50%, and 96% of symptomatic participants in the three studies that reported this outcome. The proportion of symptomatic attendees offered a diagnostic investigation (data available for 13 studies), was very low with a study level median of 38% (IQR: 22% to 45%, range 5% to 84%).

Conclusions Inefficiencies of the TB symptom screen-based patient pathway are a major contributor to underdiagnosis of TB in health facilities, and reflect inconsistent implementation of longstanding guidelines to ask all patients attending health facilities about respiratory symptoms and to offer diagnostic tests to all patients promptly once TB symptoms are identified. Screening tools and interventions with better diagnostic performance than symptoms, are urgently needed to improve the efficiency of TB care pathways in health facilities.

Background

Every year, the fate of 3 million of the 10 million people who develop active tuberculosis (TB) remains unclear.[1] This large case-notification gap is comprised of both patients who are diagnosed but unreported (especially in countries with large private sectors), and people with active but undiagnosed TB.[1] Underdiagnosis is most common in low-income settings, where geographical and financial barriers impede access to care.[1-3] These and other delays in the pathway to effective treatment[4] are major contributors to the high case fatality of TB[5] – with 1.5 million deaths estimated in 2018[1] – and to onward TB transmission.[2, 3, 6]

The diagnosis and care pathway for adult presumptive TB patients starts with presentation to healthcare services, followed by the need for healthcare workers to elicit symptoms, initiate and complete TB diagnostic investigations by interpreting results and communicating to patients, before commencing and supporting completion of effective anti-tuberculosis treatment.[7] Progress along this pathway can be analysed using a TB “cascade of care” model (Figure 1). Key indicators of cascade progress include: percentage of facility attenders in whom TB symptoms are elicited; percentage of TB symptomatic individuals who are offered and complete TB diagnostic testing; percentage of patients with TB disease (identified either by diagnostic test or clinical diagnosis) who initiate TB treatment; and percentage of patients who start treatment, are retained to treatment completion and achieve recurrence-free survival for at least a year.[4, 7]

The International Standards for Tuberculosis Care recommend that all patients attending a health facility with unexplained cough of two weeks or more should be investigated for TB.[8] However, symptoms of TB are often missed by healthcare workers,[9] leading to diagnostic and care delay.[10] The scale of missed TB symptoms is poorly defined, but thought to make a considerable contribution to TB underdiagnosis at the global level. International infection control guidelines recommend systematic enquiry for cough for all patients attending acute care services.[11] Since 2013 International TB guidelines have also recommended systematic enquiry of all patients in high TB burden countries for cough duration, and additional TB symptoms according to the national prevalence of TB and HIV, aiming to support early diagnosis.[12]

This systematic review aimed to collate evidence relating to how effectively TB symptoms are recognized and acted upon under routine programmatic conditions in the 48 countries that appear in the three lists of WHO-defined high-TB burden countries (HBCs) for general TB, TB/HIV and MDR TB. Specifically, we aimed to investigate proportions of patients who make it to each next stage of the pathway of care from the time they present with TB symptoms through to treatment initiation (Figure 1).

Methods

Protocol registration and adherence to international standards

We registered the systematic review protocol with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42018106284). We prepared our study protocol, performed the systematic review and wrote the report following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[13]

Definitions

We aimed to provide summary estimates of: the proportion of patients seeking health care at different levels of the health system (community providers, primary health care, secondary health care, and specialist outpatients clinics) who had symptoms consistent with TB; the proportion of those who were offered TB symptom screening; the proportion who were offered and received diagnostic testing for TB (including patient receipt of results); and the proportion found to have microbiologically confirmed TB who were subsequently initiated on anti-tuberculosis treatment.

We defined “TB symptom screening” as any enquiry into symptoms consistent with TB. We defined “investigation for TB” as any screening/diagnostic test for tuberculosis defined by primary studies including (but not limited to) microbiologic (including, but not limited to smear of sputum or other body fluid, culture or Xpert), or radiological (including but not limited to chest x-ray or ultrasound), or referral to another health facility with the intent to diagnose TB. “Investigation” was defined as undergoing a TB investigation. “Receipt of result” was defined as receiving outcome after undergoing a TB investigation. We defined “initiation of TB therapy” as commencement of any course of therapy with intent to treat active TB. We defined “recruitment period” as the time during which a patient with symptoms consistent with TB attended any healthcare setting. For participant follow-up time, we adopted the definitions provided by individual studies.

Eligibility criteria

We included studies published in any language in or after 2000, that recruited adult participants from WHO’s Published List of 30 High TB Burden Countries, attending any healthcare setting for any reason with symptoms consistent with TB. To be eligible, a study needed to report data allowing extraction of at least one of the following proportions of the population of interest that enter into any step of the TB cascade of care: offered TB symptom screening; offered TB investigation for TB; received investigation for TB; and initiated TB therapy.

Eligible study designs were cross-sectional studies, standardised patient studies, exit interview studies, and cohort studies (prospective and retrospective). Standardised (simulated) patient were studies that involved a covert member of the research team (the standardised patient) who presented to a healthcare facility or pharmacy and, when questioned by health workers, would give a history of TB symptoms that should prompt further clinical questions, examinations and tests for TB. Exit interview studies are typically done at the point of clinic exit shown in Figure 1, where a sample of patients leaving the health facility are asked about the screening and diagnostic tests received during their clinic visit. We excluded studies that reported on clinical trials, register linkage studies, autopsy studies, prevalence surveys, and community-based studies because participants in these studies would not be representative of patients in routine care. Studies starting with diagnosed TB patients were excluded as being unable to provide unbiased numbers for stages earlier in the TB care cascade.

Information sources and data extraction

We systematically searched for studies meeting our eligibility criteria in Medline (Pubmed), Embase (OVID), and CINAHL (EBSCOHost) using the search strategies shown in Appendix 1. We included studies published between 01 Jan 2000 and 22 January 2019, when we ran the search.

Two reviewers (THD and JL) independently screened titles and abstracts of the articles identified through the electronic searches against the eligibility criteria. THD and JL independently assessed full texts of the included papers, extracted data from eligible studies using a standardised electronic form (Google Forms, Google, United States), and documented reasons for non-inclusion. A third reviewer, PM, resolved disagreements in eligibility.

We extracted the following data from the eligible articles: first author; year of publication; facility and country of data collection; dates of study; level of healthcare facility (primary care, hospital); study definitions of review outcomes (TB symptoms, TB symptom screening, TB investigation); management options available on site (e.g. smear, chest X-ray, Xpert, TB treatment); study design; study eligibility criteria; study population characteristics (HIV status, sex, age); number of patients recruited; number of patients with TB symptoms; number of patients symptom-screened; number of patients with symptoms tested for TB; number of patients with microbiologically confirmed TB; number of patients started on TB treatment; and factors associated with an individual being screened based on quantitative analysis. We excluded studies that did not report information on any of the study outcomes.

Assessment of methodological quality

For a meta-analysis of exit-interview and standardised patient studies, no accepted risk of bias tool exists. We therefore adapted the QUADAS-2 tool[14] to our specific question (see Appendix 2) to assess risk of bias, at the level of the study, across three domains: patient selection, classifying TB symptoms, and diagnosing TB. For each domain, we reported the level of risk or concern as being either high, low or unclear. TD and JL independently performed risk of bias assessment on all studies, and PM resolved discrepancies.

Statistical analysis

For each included study, we reported on the following proportions (and corresponding 95% exact binomial confidence intervals, either as reported in respective articles or, if not available, as calculated by us): a) patients attending a health care facility for any reason who were offered symptom screening for TB; b) patients with TB symptoms who were offered further investigation for TB; c) patients who were offered further investigation for TB who receive results of TB testing; d) patients who receive results of TB testing who were initiated on TB therapy; and e) missed TB: the proportion of patients with TB who were not initiated on TB therapy. We performed descriptive analysis producing forest plots of these proportions. Study level median and IQR were calculated rather than formal meta analysis because of heterogeneity. All statistical analysis was carried out in R V3.6.0 (R Foundation for Statistical Computing, Vienna).

Results

Selection of studies

We identified 5,062 articles from the electronic searches, which reduced to 3,184 after removing duplicates (Figure 2) using Endnote X7, and to 26 after title and abstract screening against the study eligibility criteria. After full text review against eligibility criteria, 14 articles remained and were included in the systematic review. We excluded 12 articles: two because the data applicable to the review was already included in the authors' other included publication,[15, 16] two because data were not original to research manuscripts (one commentary and one systematic review),[7, 17] seven studies because they did not report data that could be mapped to our pre-defined patient categories, and one because it was a community-based study.[18-24]

Description of studies

The 14 eligible studies were published between 2000 and 2018 and reported data from India,[25-29] South Africa,[9, 30-32] Kenya,[33] Thailand,[34] China,[16] Vietnam[35] and Ghana[36] (Table 1). Nine studies employed the standardised patient design, three were exit interview studies, and the remaining two were cross-sectional studies. All studies included adults only; most studies defined TB symptoms as “having chronic cough”; and available TB tests included smear microscopy, chest X-ray, or referral to the next level of care. All three Exit Interview studies[9, 30, 32] were from South African primary health care settings. The two included cross-sectional studies were: a rural hospital study from Ghana,[36] and a hospital based study from India.[29] Four of the seven standardised patient studies were done at pharmacies in India,[27, 28] Thailand,[34] and Vietnam;[35] one was in a South African primary health care setting;[31] one involved facilities at various levels of care in Kenya;[33] and another two involved various levels of Indian health care system.[25, 26]

Table 1: Characteristics of the included studies (n=14)

Study	Country	Study design	Setting	Participants eligibility	TB symptom definition	TB test available at study site	Number (%) with TB symptoms ¹	Number (%) with TB symptoms screened ¹	Number (%) offered TB test ¹	Number (%) received TB test ¹	Number (%) received TB result ¹
Menuvegbegbe 2016[36]	Ghana	Cross-sectional	Two rural hospitals	Outpatient presentation during study period with cough of ≥2 weeks	≥2 weeks of cough	Smear	Not reported	Not reported	Not reported	230/932 (25%)	Not reported
Shihota 2015[30]	South Africa	Exit interview	PHC	≥ 18yrs exiting PHC	Any of cough ≥24hr or fever of night sweats or weight loss	Xpert	4098/8104 (51%)	2130/3604 (60%)	818/2130 (38%)	Not reported	Not reported
Laassens 2013[9] ²	South Africa	Exit interview	PHC	≥ 18yrs exiting PHC not on TB Rx or collecting TB results	Any cough, productive cough, haemoptysis, fever, night sweats, chest pain or weight loss.	Smear and culture	3564/4686 (71%)	16/423 (4%)	4/16 (25%)	2/4 (50%)	Not reported
Weza 2018[32] ³	South Africa	Exit interview	PHC	≥ 18yrs exiting PHC not on TB Rx	any duration of cough, loss of weight, fever or night sweats	Xpert	Not reported	622/1255 (50%)	134/622 (22%)	61/134 (46%)	Not reported
Christian 2018[31]	South Africa	Standardised patient	PHC	SP, presumptive TB	Cough ≥2/52	Sputum test and HIV test	143/143 (100%)	143/143 (100%)	119/143 (83%)	Not reported	Not reported
Maniatis 2017[33]	Kenya	Standardised patient	Various	SP, presumptive TB	2 to 3 weeks of cough and fever	Sputum testing	42/42 (100%)	42/42 (100%)	21/42 (50%)	Not reported	Not reported
Das 2015[25]	India	Standardised patient	Various	SP, presumptive TB	2 to 3 weeks of cough and fever	Sputum test, CXR or referral	150/150 (100%)	Not reported	22/150 (15%)	Not reported	Not reported
Shanwan 2018[26]	India	Standardised patient	Various	SP, presumptive TB	2 to 3 weeks of cough and fever	Sputum test, CXR or referral	1762/1762 (100%)	1762/1762 (100%)	807/1762 (46%)	Not reported	Not reported
Shiller 2017[27]	India	Standardised patient	Pharmacies	SP, presumptive TB	3 to 4 weeks of cough and fever	Refer	333/333 (100%)	333/333 (100%)	150/333 (45%)	Not reported	Not reported
Chaiyapibulstit 2007[34]	Thailand	Standardised patient	Pharmacies	SP, presumptive TB	1 month of cough and fever	Refer	70/70 (100%)	70/70 (100%)	3/70 (4%)	Not reported	Not reported
Chaitanyanarayana 2016[28]	India	Standardised patient	Pharmacies	SP, presumptive TB	2 to 3 weeks of cough and fever	Refer	599/599 (100%)	599/599 (100%)	96/599 (16%)	Not reported	Not reported
Li via 2017[16]	China	Standardised patient	Various (hospital, health centre)	SP, presumptive TB	2 to 3 weeks of cough and fever	Sputum test, CXR or refer	274/274 (100%)	274/274 (100%)	112/274 (41%)	Not reported	Not reported
Phu 2012[35]	Vietnam	Standardised patient	Pharmacies	SP, presumptive TB	4 weeks of cough and fever	Refer	138/138 (100%)	138/138 (100%)	59/138 (43%)	Not reported	Not reported

Study	Country	Study design	Setting	Participants eligibility	TB symptom definition	TB test available at study site	Number (%) with TB symptoms ¹	Number (%) with TB symptoms screened ¹	Number (%) offered TB test ¹	Number (%) received TB test ¹	Number (%) received TB result ¹
Ingth 2014[29]	India	Cross-sectional	Hospital	cough more than 2 weeks or HIV pos and cough any duration	Cough ≥ 2 weeks or HIV+ and cough any duration	Smear or CXR or "serological test"	242/242 (100%)	Not reported	93/242 (39%)	Not reported	Not reported

Outcome (definitions): TB symptoms (as reported in studies); TB symptoms screen (any enquiry into symptoms consistent with TB); TB test (any screening/diagnostic test for tuberculosis or referral to another health facility for the same); receiving TB test (undergoing a TB investigation); receiving TB result (receiving outcome after undergoing a TB investigation)

Assessments 2013: collected spot sputum from 423 TB symptomatic participants individuals exiting a health facility regardless of reason for presentation to clinic management. 21 of the 406 (5%) with available smear and/or culture result were positive. None of the 21 presented because of their respiratory symptoms, none had TB symptoms screen, and none were offered TB test during their visit

Weza 2018: collected spot sputum from 779 TB symptomatic participants missed by clinic staff and performed Xpert/MTB/RIF and 39 (5%) tested positive,

HC = primary health care; SP = Simulated patient study; CXR = chest x-ray.

The TB diagnostic and care pathway

None of the included studies provided data addressing the full cascade of care from clinical presentation to treatment initiation in the same patient population. Exit interview studies reported proportion of participants systematically screened for symptoms, while the remainder of the studies mostly reported the proportion that were offered or received a diagnostic investigation.

The proportions of participants who reported having been screened for TB symptoms in the three exit interview studies were 0.60 (2130/3604),[30] 0.50 (622/1255),[15] and 0.04 (16/423)[9] respectively (Figure 3A). The proportion of symptomatic attendees offered a diagnostic investigation (data available for 13 studies), was highly variable, ranging from 0.05 to 0.84 (median 0.38 [IQR: 0.22 to 0.45]) (Figure 3B). Of note is that nine of these 13 studies were standardised patient studies[25-28, 31, 33-35, 37] in which, despite reporting classical TB symptoms to attending care givers, up to 0.96 of the participants were not offered a TB diagnostic investigation (Table 1). The three studies that assessed receipt of TB investigation reported the following proportions: 0.50 (2/4),[9] 0.46 (61/134),[32] and 0.24 (230/932).[36] One study[32] that collected sputum, at point of exit, from 779 individuals not tested by clinic staff, detected 39 cases (0.05). Out of the 39, twenty-four were symptom screened by clinic staff, but not offered a TB test.

Assessment of risk of bias

We evaluated the identified studies using the pre-adapted QUADAS 2 tool for assessment of risk of bias and found that all included studies conducted their patient selection and classification of TB symptoms according to the expectation of the systematic review question. In the five studies that involved diagnosing TB, one exhibited a high risk of bias because not all patients utilised the same diagnostic strategy (Table 2).[29]

Table 2: Assessment of the included studies for Risk of Bias using the QUADAs 2 tool

	Risk of Bias in each of the assessed domains		
Author and Year	Patient Selection	Classification of TB symptoms	Diagnosing TB
Amenuvegbe	High	High	High
Chihota 2015	Low	Low	Low
Claassens 2013	Low	Low	Low
Kweza 2018	Unclear	Low	High
Christian 2018	Low	Unclear	Not applicable
Daniels 2017	Low	Low	Not applicable
Das 2015	Low	Low	Not applicable
Kwan 2018	Low	Low	Not applicable
Miller 2017	Low	Low	Not applicable
Rojpibulstit 2007	Low	Low	Not applicable
Satyanarayana 2016	Low	Low	Not applicable
Sylvia 2017	Low	Low	Not applicable
Singh 2014	Low	High	High
Vu 2012	Low	Low	Not applicable

Not applicable: risk of bias in the “diagnosing TB” domain for studies that involved standardised patients was reported as not applicable

Discussion

The main finding of this systematic review was that in 13 studies across high-TB burden countries, a study-level median of only 38% (IQR 22-45%) of patients with TB symptoms were offered a TB test. TB symptom-screening, the critical entry point for diagnosis of TB, was reportedly not done for 40% to 96% of symptomatic participants in the three studies that reported this outcome. There was substantial heterogeneity between studies largely driven by between-setting variations in implementation approach and level of adherence to TB screening protocols. Nevertheless, this review suggests that a failure to identify TB symptoms in those seeking health care and a failure to test those that present with TB symptoms may be a key driver of missed TB diagnosis in high TB settings. If so, this should be amenable to interventions that aim to reduce the TB diagnosis and treatment gap but also highlights existing gaps for screening and diagnostic tools that can be employed at the point of care.

Our results are consistent with long-standing concerns about the quality of TB care provided at primary care level facilities, with high levels of missed identification of symptoms and suboptimal management once symptoms are identified, and contributing to inefficiency in the TB diagnostic pathway.[38] Optimising facility-based management of self-presenting patients with TB symptoms should be a priority for national TB programmes because it addresses the targeting of the “missing millions,” infection control, and complements community-based active case finding.[6] Failure to promptly identify symptomatic patients will also reduce the likely patient and public health impact of new TB diagnostics because most of the target population would simply not be offered the testing they should receive.[39]

Better management of symptomatic self-presenting primary care-level patients is an urgent priority that all countries should be focused on. However, we also recognise the limitations of a symptom-based approach. The inherent subjectivity with symptom-screening leads to variations in the way questions are asked or responded to,[40] and different responses to the same question when asked at different times or by different individuals.[40] In population-level TB prevalence surveys, the sensitivity of cough[≥]2 weeks for active TB disease is only 35% (95% CI 24%; 46%) compared to microbiological reference standards.[41] This highlights the need for screening tools that are more accurate, less subjective and easier to monitor than symptom screening, while ideally staying as accessible and low-cost.

A key principle of TB screening is that it must be directed towards populations with higher prevalence of disease where individual benefits are likely to outweigh risks, and delivered with patient convenience as a key priority.[42] Amongst populations attending health centres, alternatives to symptom-based approaches for facility-based TB screening include TB triage tests such as digital chest radiography and computer-aided diagnosis or point-of care host biomarkers performed prior to confirmatory testing. Triage tests aim to rule-out TB, allowing health workers to prioritise patients with a higher prior probability of TB for more expensive, slower confirmatory tests such as Xpert or culture. [40]

Individual and public health consequences of inefficiencies in establishing a diagnosis and providing prompt and effective treatment of TB include premature death, as patients with undiagnosed TB have a high mortality rate especially if also living with HIV,[5] and more severe

post-tuberculous lung disease and other permanent sequelae of TB.[43] Increasingly severe illness tends to prompt multiple healthcare visits, with patients incurring pre-diagnosis “catastrophic costs” and repeated courses of non-specific treatments including broad-spectrum antibiotics until their TB is finally diagnosed.[38, 44, 45] Cost-savings from timely diagnosis of TB averting visits, from both health-system and patient-perspective need to be factored into economic decision-making when TB diagnostic investments are considered. Public health consequences of delayed diagnosis include onward transmission, including nosocomial transmission while attending health facilities for diagnosis, with patients potentially becoming more infectious as the severity of their underlying TB and symptoms progress.[46-48] Early diagnosis and treatment therefore are key tools if national TB programs are to arrest transmission.

The key programmatic implication of our findings is that front line health workers in the TB diagnostic pathway either are unaware of expectations of national programs or are unable to adhere to current TB case finding guidelines. Results from two included studies done in India[25, 26] suggest that TB diagnosis can be improved in that setting by having better qualified personnel at the entry point of the diagnostic pathway. On the other hand, Silvia et. al found that management at a higher level facility (hospital) was more likely to include TB diagnosis than health centre or village clinic management.[37] Finally, Singh et.al, who compared management of symptomatic patients in public and private facilities, found that public facilities performed better.[29] There are three likely underlying problems issues that need to be addressed. First is general health system weakness, which can be amenable to investments in health sector strengthening programs (particularly in universal health coverage)[49] and in public private partnerships.[50] Second is the lack of good screening tools beyond symptom-screening which – if faithfully adhered to – would overburden the already limited capacity for confirmatory testing. Third is the very lack of simple, quick and low-cost confirmatory diagnostic test with the ability to provide same-day, same-clinic results.

Our review has several limitations. The first limitation is paucity of data; only 14 studies were identified with relevant data, and the number of participants per study also limited our analytical scope. Although unlikely, one potential explanation for paucity of data may be the fact that we limited our search to three major databases. Secondly, our focus on a single clinical episode, may have limited our ability to fully interrogate the TB diagnostic pathway, which often includes multiple clinical encounters. Thirdly, our case definitions for TB investigation which included referral for TB assessment, as well as more sensitive diagnostics such as Xpert/MTB/RIF in one category, may have limited specificity. Fourthly, we were unable to report disaggregate data for various forms of TB because the included studies did not distinguish between screening algorithms recommend for different patient subgroups.

Conclusions

In conclusion, this study demonstrates that the substantial gaps within the TB diagnosis and care pathway are likely making substantial contributions to the so-called “missing millions” of TB cases. Failure to complete TB symptom screening and offering TB tests to all those screening positive is a critical breakpoint in this cascade at which patients with TB may be missed. Acknowledging the limitations of symptom screening and the need for better tools, there is urgent need to identify and implement interventions and health systems strengthening approaches that recognise local TB epidemiology and can improve the quality of clinical encounters in favour of TB recognition, diagnosis and treatment.

Abbreviations

TB	Tuberculosis
PROSPERO	Prospective Register of Systematic Reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO	World Health Organisation
PHC	Primary Health Care
SP	Simulated patient study
CXR	Chest X-ray

Declarations

Ethics approval and consent to participate

This work did not involve direct contact with human subjects or participant identifiable data. Ethical approval was therefore not required.

Consent to publish

Not applicable.

Availability of data and materials

We have included all data and analysis code in Appendix 3.

Competing interests

The authors declare that they have no competing interests.

Funding

THD is funded by the Commonwealth Scholarship Commission and the Helse Nord RHF. PM and ELC are funded by Wellcome Fellowships in Clinical Science (WT206575 and WT200901, respectively). The funding agencies had no role in the systematic review, preparation or decision to submit this manuscript.

Acknowledgements

Not applicable.

Authors' Contributions

All authors substantially contributed to the conception and design of the study and reviewed all documents and materials. PM, SGS, and ELC designed the study. VL developed and implemented the search strategy. THD screened articles, extracted data, interpreted results, and developed the first draft of the manuscript. JL screened articles, extracted data, analysed data, interpreted results, and reviewed manuscript. PM screened articles, interpreted results, and reviewed manuscript. SGS, MAB, VL and ELC critically reviewed results, and manuscript. All authors read and approved the final manuscript. TD is the guarantor for this work.

Ethics approval and consent to participate

This work did not involve direct contact with human subjects or participant identifiable data. Ethical approval was therefore not required.

References

1. World Health Organization. Global tuberculosis report 2019. Geneva: World Health Organization; 2019.
2. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Social science & medicine*. 2009;68(12):2240-6.
3. Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex differences in tuberculosis burden and notifications in low-and middle-income countries: a systematic review and meta-analysis. *PLoS medicine*. 2016;13(9):e1002119.
4. MacPherson P, Houben RM, Glynn JR, Corbett EL, Kranzer K. Pre-treatment loss to follow-up in tuberculosis patients in low-and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *Bulletin of the World Health Organization*. 2013;92:126-38.
5. Nliwasa M, MacPherson P, Gupta-Wright A, Mwapasa M, Horton K, Odland JØ, et al. High HIV and active tuberculosis prevalence and increased mortality risk in adults with symptoms of TB: a systematic review and meta-analyses. *Journal of the International AIDS Society*. 2018;21(7):e25162.
6. Kranzer K, Afnan-Holmes H, Tomlin K, Golub JE, Shapiro A, Schaap A, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review [State of the art series. Case finding/screening. Number 2 in the series]. *The international journal of tuberculosis and lung disease*. 2013;17(4):432-46.
7. Subbaraman R, Nathavitharana RR, Satyanarayana S, Pai M, Thomas BE, Chadha VK, et al. The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. *PLoS Med*. 2016;13(10):e1002149.
8. Hopewell PC, Pai M, Maher D, Uplekar M, Raviglione MC. International standards for tuberculosis care. *The Lancet infectious diseases*. 2006;6(11):710-25.
9. Claassens MM, Jacobs E, Cyster E, Jennings K, James A, Dunbar R, et al. Tuberculosis cases missed in primary health care facilities: should we redefine case finding? *Int J Tuberc Lung Dis*. 2013;17(5):608-14.

10. Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, Pai M. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *The International Journal of Tuberculosis and Lung Disease*. 2014;18(3):255-66.
11. World Health Organization. Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level 2016 14 Nov 2019 [cited 2019 11 November]. Available from: <https://www.who.int/infection-prevention/publications/core-components/en/>.
12. World Health Organization. Systematic screening for active tuberculosis: principles and recommendations: World Health Organization; 2013.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ (Clinical research ed)*. 2009;339:b2535.
14. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine*. 2011;155(8):529-36.
15. Kweza PF, Abraham N, Claassens MM, Van Schalkwyk C, Medino-Marino A. Missed pulmonary TB screening opportunities at Primary Healthcare Facilities: An Exit Study, Eastern Cape Province, South Africa. *International Journal of Infectious Diseases*. 2016;45(SUPPL. 1):34.
16. Sylvia S, Xue H, Zhou C, Shi Y, Yi H, Zhou H, et al. Tuberculosis detection and the cost of integrated care in rural China: a cross-sectional standardised patient study. *The Lancet*. 2017;390:S60.
17. Miller R, Das J, Pai M. Quality of tuberculosis care by Indian pharmacies: mystery clients offer new insights. *J Clin Tuberc Other Mycobact Dis*. 2018.
18. Bailey SL, Roper MH, Huayta M, Trejos N, Lopez Alarcon V, Moore DA. Missed opportunities for tuberculosis diagnosis. *Int J Tuberc Lung Dis*. 2011;15(2):205-10, i.
19. Masini E, Hanson C, Ogoro J, Brown J, Ngari F, Mingkwan P, et al. Using Patient-Pathway Analysis to Inform a Differentiated Program Response to Tuberculosis: The Case of Kenya. *The Journal of infectious diseases*. 2017;216(suppl_7):S714-s23.
20. Meintjes G, Schoeman H, Morroni C, Wilson D, Maartens G. Patient and provider delay in tuberculosis suspects from communities with a high HIV prevalence in South Africa: a cross-sectional study. *BMC infectious diseases*. 2008;8:72.
21. Wesen A, Mitike G. Screening and case detection for tuberculosis among people living with HIV in Addis Ababa, Ethiopia. *Ethiopian medical journal*. 2009;47(2):109-15.
22. Xu B, Diwan VK, Bogg L. Access to tuberculosis care: what did chronic cough patients experience in the way of healthcare-seeking? *Scandinavian journal of public health*. 2007;35(4):396-402.
23. Ouyang H, Chepote F, Gilman RH, Moore DA. Failure to complete the TB diagnostic algorithm in urban Perú: a study of contributing factors. *Tropical doctor*. 2005;35(2):120-.
24. Roy M, Muyindike W, Vijayan T, Kanyesigye M, Bwana M, Wenger M, et al. Use of symptom screening and sputum microscopy testing for active tuberculosis case detection among HIV-infected patients in real-world clinical practice in Uganda. *Journal of acquired immune deficiency syndromes (1999)*. 2016;72(5):e86.
25. Das J, Kwan A, Daniels B, Satyanarayana S, Subbaraman R, Bergkvist S, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. *The Lancet Infectious diseases*. 2015;15(11):1305-13.
26. Kwan A, Daniels B, Saria V, Satyanarayana S, Subbaraman R, McDowell A, et al. Variations in the quality of tuberculosis care in urban India: A cross-sectional, standardized patient study in two cities. *PLoS medicine*. 2018;15(9):e1002653.
27. Miller R, Goodman C. Do chain pharmacies perform better than independent pharmacies? Evidence from a standardised patient study of the management of childhood diarrhoea and suspected tuberculosis in urban India. *BMJ global health*. 2017;2(3):e000457.
28. Satyanarayana S, Kwan A, Daniels B, Subbaraman R, McDowell A, Bergkvist S, et al. Use of standardised patients to assess antibiotic dispensing for tuberculosis by pharmacies in urban India: a cross-sectional study. *The Lancet Infectious diseases*. 2016;16(11):1261-8.
29. Singh AK, Salve H, Selvaraj K, Rai SK, Kant S. Quality of diagnostic and treatment practices of pulmonary tuberculosis management amongst health practitioners in Haryana, north India. *Rural and remote health*. 2014;14(4):2784.
30. Chihota VN, Ginindza S, McCarthy K, Grant AD, Churchyard G, Fielding K. Missed Opportunities for TB Investigation in Primary Care Clinics in South Africa: Experience from the XTEND Trial. *PLoS One*. 2015;10(9):e0138149.
31. Christian CS, Gerdtham UG, Hompashe D, Smith A, Burger R. Measuring Quality Gaps in TB Screening in South Africa Using Standardised Patient Analysis. *International journal of environmental research and public health*. 2018;15(4).
32. Kweza P, Van Schalkwyk C, Abraham N, Uys M, Claassens M, Medina-Marino A. Estimating the magnitude of pulmonary tuberculosis patients missed by primary health care clinics in South Africa. *The International Journal of Tuberculosis and Lung Disease*. 2018;22(3):264-72.

33. Daniels B, Dolinger A, Bedoya G, Rogo K, Goicoechea A, Coarasa J, et al. Use of standardised patients to assess quality of healthcare in Nairobi, Kenya: a pilot, cross-sectional study with international comparisons. *BMJ global health*. 2017;2(2):e000333.
34. Rojpibulstit M, Chongsuvivatwong V. Drugstore personnel's management of a tuberculosis suspect: Consideration of actual and perceived management. *International Journal of Pharmacy Practice*. 2007;15(3):177-83.
35. Vu DH, van Rein N, Cobelens FG, Nguyen TT, Le VH, Brouwers JR. Suspected tuberculosis case detection and referral in private pharmacies in Viet Nam. *Int J Tuberc Lung Dis*. 2012;16(12):1625-9.
36. Amenuvegbe GK, Francis A, Fred B. Low tuberculosis case detection: a community and health facility based study of contributory factors in the Nkwanta South district of Ghana. *BMC research notes*. 2016;9:330.
37. Sylvia S, Xue H, Zhou C, Shi Y, Yi H, Zhou H, et al. Tuberculosis detection and the challenges of integrated care in rural China: A cross-sectional standardized patient study. *PLoS Med*. 2017;14(10):e1002405.
38. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC public health*. 2008;8(1):15.
39. McNerney R, Cunningham J, Hepple P, Zumla A. New tuberculosis diagnostics and rollout. *International journal of infectious diseases*. 2015;32:81-6.
40. Yoon C, Dowdy DW, Esmail H, MacPherson P, Schumacher SG. Screening for tuberculosis: time to move beyond symptoms. *The Lancet Respiratory Medicine*. 2019;7(3):202-4.
41. Van't Hoog A, Langendam M, Mitchell E, Cobelens F, Sinclair D, Leeflang M, et al. A systematic review of the sensitivity and specificity of symptom-and chest-radiography screening for active pulmonary tuberculosis in HIV-negative persons and persons with unknown HIV status. REPORT-Version March 2013. World Health Organization, Geneva, Switzerland: WHO. 2013.
42. Organization WH. Global tuberculosis report 2013. Geneva: World Health Organization; 2013.
43. Lee C-H, Lee M-C, Lin H-H, Shu C-C, Wang J-Y, Lee L-N, et al. Pulmonary tuberculosis and delay in anti-tuberculous treatment are important risk factors for chronic obstructive pulmonary disease. *PloS one*. 2012;7(5):e37978.
44. Barter DM, Agboola SO, Murray MB, Bärnighausen T. Tuberculosis and poverty: the contribution of patient costs in sub-Saharan Africa—a systematic review. *BMC public health*. 2012;12(1):980.
45. World Health Organization. Gear up to end TB: introducing the end TB strategy. World Health Organization; 2015.
46. Madebo T, Lindtjorn B. Delay in treatment of pulmonary tuberculosis: an analysis of symptom duration among Ethiopian patients. *MedGenMed: Medscape general medicine*. 1999:E6-E.
47. Mathema B, Andrews JR, Cohen T, Borgdorff MW, Behr M, Glynn JR, et al. Drivers of Tuberculosis Transmission. *The Journal of infectious diseases*. 2017;216(suppl_6):S644-S53.
48. Turner RD, Chiu C, Churchyard GJ, Esmail H, Lewinsohn DM, Gandhi NR, et al. Tuberculosis Infectiousness and Host Susceptibility. *The Journal of infectious diseases*. 2017;216(suppl_6):S636-S43.
49. Atun R, Weil DE, Eang MT, Mwakyusa D. Health-system strengthening and tuberculosis control. *The Lancet*. 2010;375(9732):2169-78.
50. Lei X, Liu Q, Escobar E, Philogene J, Zhu H, Wang Y, et al. Public–private mix for tuberculosis care and control: a systematic review. *International Journal of Infectious Diseases*. 2015;34:20-32.

Figures

Figure 1

The diagnostic and care pathway for tuberculosis at health facility level, outlining opportunities for tuberculosis diagnosis and treatment in a symptomatic individual.

Figure 2

Flowchart for the selection of studies on the diagnostic and care pathway for tuberculosis in high burden countries

Figure 3

(A) TB diagnostic and care cascade for exit interview studies showing proportion of symptomatic attendees in whom symptoms were elicited, who were offered a diagnostic test and who received test results and (B) proportion of symptomatic attendees who were offered a diagnostic test after being asked about symptoms in all included studies. In all cases exact binomial confidence intervals are shown

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