BMJ Global Health

Factors influencing diagnosis and treatment initiation for multidrug-resistant/rifampicin-resistant tuberculosis in six sub-Saharan African countries: a mixed-methods systematic review

Charity Oga-Omenka ,[1,2,3] Azhee Tseja-Akinrin,[4] Paulami Sen,[3,5] Muriel Mac-Seing ,[1,2] Aderonke Agbaje,[6] Dick Menzies,[3,5] Christina Zarowsky[1,2,7]

To cite: Oga-Omenka C, Tseja-Akinrin A, Sen P, *et al*. Factors influencing diagnosis and treatment initiation for multidrug-resistant/rifampicin-resistant tuberculosis in six sub-Saharan African countries: a mixed-methods systematic review. *BMJ Global Health* 2020;**5**:e002280. doi:10.1136/bmjgh-2019-002280

Handling editor Alberto L Garcia-Basteiro

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2019-002280).

Received 6 January 2020
Revised 10 April 2020
Accepted 15 April 2020

For numbered affiliations see end of article.

Correspondence to
Ms Charity Oga-Omenka; omenkac@gmail.com

ABSTRACT

Background Drug-resistant tuberculosis burdens fragile health systems in sub-Saharan Africa (SSA), complicated by high prevalence of HIV. Several African countries reported large gaps between estimated incidence and diagnosed or treated cases. Our review aimed to identify barriers and facilitators influencing diagnosis and treatment for drug-resistant tuberculosis (DR-TB) in SSA, which is necessary to develop effective strategies to find the missing incident cases and improve quality of care.

Methods Using an integrative design, we reviewed and narratively synthesised qualitative, quantitative and mixed-methods studies from nine electronic databases: Medline, Global Health, CINAHL, EMBASE, Scopus, Web of Science, International Journal of Tuberculosis and Lung Disease, PubMed and Google Scholar (January 2006 to June 2019).

Results Of 3181 original studies identified, 55 full texts were screened, and 29 retained. The studies included were from 6 countries, mostly South Africa. Barriers and facilitators to DR-TB care were identified at the health system and patient levels. Predominant health system barriers were laboratory operational issues, provider knowledge and attitudes and information management. Facilitators included GeneXpert MTB/RIF (Xpert) diagnosis and decentralisation of services. At the patient level, predominant barriers were patients being lost to follow-up or dying due to lengthy diagnostic and treatment delays, negative public sector care perceptions, family, work or school commitments and using private sector care. Some patient-level facilitators were HIV positivity and having more symptoms.

Conclusion Case detection and treatment for DR -TB in SSA currently relies on individual patients presenting voluntarily to the hospital for care. Specific interventions targeting identified barriers may improve rates and timeliness of detection and treatment.

Summary box

What is already known?

- Globally, only 39% and 32% of the estimated drug-resistant tuberculosis (DR-TB) patients are diagnosed and started on appropriate treatment, respectively.
- Ten high burden countries in Africa contributed 12% of the estimated global incident cases in 2018, with 54% of these in only Nigeria and South Africa.
- For patients who are diagnosed and placed on treatment, delays in access to diagnosis and treatment were up to several months in some sub-Saharan African countries.

What are the new findings?

- Laboratory operational challenges as well as inadequate healthcare worker knowledge, attitude and skills were the predominant barriers noted at the health system level.
- Predominant patient-level barriers included loss to follow-up and death, as well as inability to pay care-related costs.
- Availability of newer diagnostic tools was the predominant health-level facilitator of quicker diagnosis and treatment; however, this did not always translate to significantly higher rates of diagnosis and treatment.

What do the new findings imply?

- Implementers and policymakers need to better understand and address various issues that impact DR-TB care at different levels, in order to maximise the impact of new care innovations.

INTRODUCTION

Drug-resistant tuberculosis (DR-TB) is a major threat to global health as it undermines gains in TB control, and is especially burdensome to health systems in resource-limited settings.[1] Defined as TB resistant to both isoniazid and rifampicin, it is the leading cause of deaths

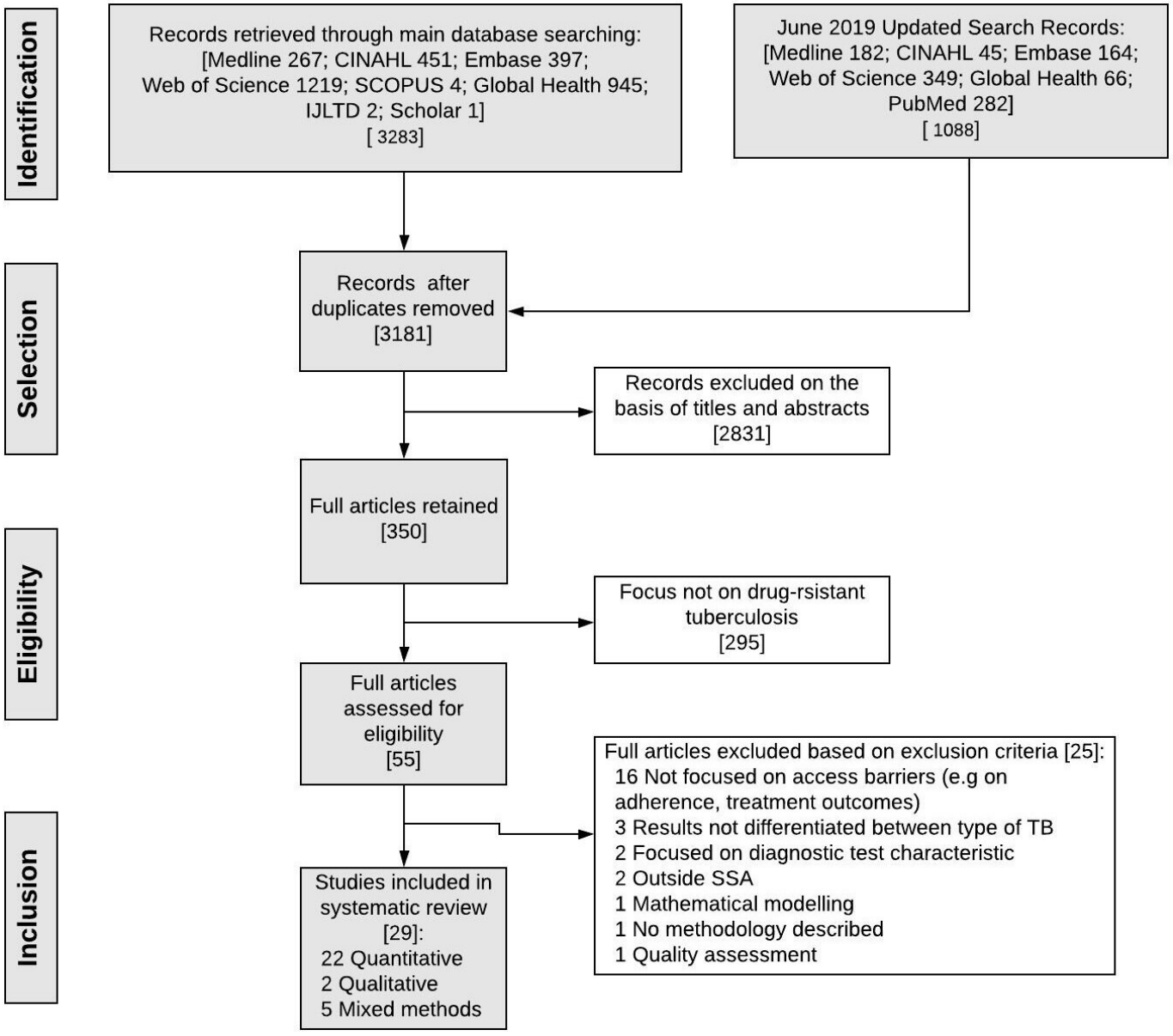

Figure 1 Study selection. SSA, sub-Saharan Africa; TB, tuberculosis.

due to antimicrobial resistance and took an estimated 214 000 lives in 2018.[2] The 2018 United Nations High-Level resolution to 'end TB including DR-TB' by accelerating access to affordable prevention and care, is in line with earlier goals including the Sustainable Development Goals (SDGs) and The End TB Strategy.[3–5] To meet these goals, it is essential to synthesise the growing evidence on barriers and facilitators to DR-TB care.

DR-TB is more difficult to diagnose and treat than drug-susceptible TB and is often associated with up to 5.5 times higher treatment costs, longer treatment courses and lower treatment success rates.[1 2 6] Globally, only 39% and 32% of the estimated patients diagnosed with DR-TB are started on appropriate treatment, respectively.[2] Ten high burden countries (HBCs) in sub-Saharan Africa (SSA) contributed 12% of the 484 000 estimated incident cases in 2018, mostly in Nigeria and South Africa. Nigeria and Mozambique were among 10 countries contributing 75% of the global treatment enrolment gap.[2]

Gaps in TB care were notedly higher in Africa, where the HIV-associated TB incidence is highest, as HIV further complicates TB care. Of 14 countries classified by WHO as HBCs for TB, DR-TB and HIV, 8 are in Africa.[2]

For patients with DR-TB who are diagnosed and treated, several studies have reported delays in access running into several months in several SSA countries.[7–10] These delays, occurring at patient and health system (provider) levels, contribute to increased morbidity, infection transmission, loss to follow-up and poorer treatment outcomes.[11 12] This review examines any synthesised qualitative and quantitative literature, with a view to inform policy and practice in SSA.

Table 1 Overview of selected studies

Study ID number	Study (year), country	Research design and methods Period	Populations (number)	Study objectives	Level of care (diagnosis/treatment)	Dimensions of access	Summary of findings	Assessment of study quality (score)
Qualitative studies								
1	Bieh (2017) Nigeria	Qualitative FGDs, IDIs and KIIs 2014	Patients (11) and health workers (4)	NA	Treatment	Structural and patient dimensions	Treatment delays due to stigma and discrimination, as well as a lack of required hospital tools.	B
2	Naidoo (2015) South Africa	Qualitative IDIs (part of a bigger study including a retrospective cohort 2010–2012	Patients (26)	NA	Diagnosis and treatment	Structural and patient dimensions	Patients beliefs and knowledge of TB symptoms, wrong perceptions of healthcare and family commitments, compounded by health systems missed opportunities and delays, impact access.	A
Quantitative studies								
3	Cox (2015) South Africa	Retrospective trend analysis2009– 2013	Patients (158)	Time to treatment initiation (TTI) before the decentralisation, during decentralisation and after decentralisation.	Diagnosis and treatment	Structural dimensions	Decentralisation and introducing Xpert were associated with significant reductions in TTI, after initial gains with the LPA.	B
4	Cox (2017) South Africa	Retrospective cohort study 2011–2013	Patients (2508 in 2011) (2528 in 2013)	Treatment initiation were assessed among laboratory-diagnosed patients before and after Xpert implementation.	Diagnosis and treatment	Structural and patient dimensions	Patients age and HIV status, as well as diagnostic timeliness delay access.	A
5	Dlamini-Mvelase (2014) South Africa	Retrospective cohort study 2011–2012	Patients (637)	Availability of confirmatory DST and TTI with Xpert compared with phenotypic and genotypic DST.	Diagnosis	Structural dimensions	Poor adherence to Xpert algorithmwas due to rollout of Xpert preceding training of clinicians	A
Quantitative studies								
6	Ebonwu (2013) South Africa	Cross-sectional study 2011	Patients (942)	Evaluation of treatment uptake, loss to follow-up and retention of newly diagnosed patients.	Treatment	Structural and patient dimensions	Referrals from hospitals, some health districts, being HIV negative and township place of residence were associated with treatment non-initiation.	A
7	Evans *et al* (2018) South Africa	Retrospective cohort study: First cohort: 2011–2012 (35% Xpert implementation) Second cohort: 20132014 (>90% implementation)	Patients: First cohort (594) Second cohort 713	Compared treatment initiation and TTI forlaboratory-confirmed patients with (first vs second cohort).	Diagnosis and treatment	Structural and patient dimensions	Xpert implementation increased diagnostic capacity and treatment rates.	A

Continued

Table 1 Continued

Study ID number	Study (year), country	Research design and methods Period	Populations (number)	Study objectives	Level of care (diagnosis/treatment)	Dimensions of access	Summary of findings	Assessment of study quality (score)
8	Hanrahan *et al* (2012) South Afria	Observational cohort study: 2007– 2008 with MGIT phenotypic DST 2009– 2010 with LPA	Patients (n=1176 MGIT) and (n=1177 LPA)	Compared data on patients registration before and after an expanded DST algorithm.	Diagnosis and treatment	Structural and patient dimensions	Introducing the faster LPA DST testing cut down time to diagnosis and increased case detection without the expected impact on TTI due to other health system bottlenecks.	A
9	Hanrahan (2013) South Africa	Prospective cohort study Jul–Sep 2011	Patients (641)	Evaluated diagnostic follow-up and outcomes for a cohort of presumptive patients screened using a single point-of-care Xpert.	Diagnosis and treatment	Structural and patient dimensions	Point-of-care Xpert provided quicker treatment initiation, mostly same day treatment. This was 2 weeks faster than for those started empirically or based on suggestive chest X-ray, and 20 weeks faster than for culture diagnosis.	A
10	Iruedo (2017) South Africa	Retrospective cohort study Jan 2009–Dec 2014	Patients (342)	Analysed records of diagnosed patients, comparing diagnostic modalities to assess the Xpert effect on TTI.	Diagnosis and treatment	Structural and patient dimensions	Xpert significantly reduced the time to diagnosis and TTI. This was significantly shorter compared with LPA and culture/phenotypic DST.	A
11	Jacobson (2012) South Africa	Retrospective cohort study 2007–2011	Patients (197)	Compared records of patients tested using the MTBDRplus and with culture-based DST to determine if TTI from specimen collection was shortened.	Diagnosis and treatment	Structural and patient dimensions	The use of LPA for diagnosis dramatically improved TTI but laboratory and clinical operational delays remained a problem.	A
Quantitative studies								
12	Jacobson *et al* (2017) South Africa	Retrospective cohort in Western Cape: two samples at baseline— for Xpert; and for LPA plus DST 2011– 2013. Prospective cohort in three other provinces: one sample collected at baseline for Xpert; a subsequent one for LPA plus culture-based DST only with detection of RR-TB. 2012– 2013	Patients (1332) *Western Cape Province: (835) *Eastern Cape, Free State and Gauteng Province: (497)	Quantified the time to DST results and proportion of patients potentially placed on suboptimal therapy.	Diagnosis and treatment	Structural and patient dimensions	Incomplete and decreasing adherence to National requirements for DSTimpedes diagnosis rates. Long turnaround time for DST results following RR-TB diagnosis.	A

Continued

Table 1 Continued

Study ID number	Study (year), country	Research design and methods Period	Populations (number)	Study objectives	Level of care (diagnosis/treatment)	Dimensions of access	Summary of findings	Assessment of study quality (score)
13	Jokwiro *et al* (2018) Zimbabwe	Cross-sectional study. 2016– 2017 with two phases: Xpert only for presumptive DR-TB and HIV coinfection: 2016; Xpert recommended for all presumptive patients: 2017.	. Thirteen Xpert assays (13 137 total assays): *2016: (4556) *2017: (8581)	Compared the use of deploying Xpert only for presumptive DR-TB and HIV coinfection vs Xpert for all presumptive TB patients.	Diagnosis	Structural dimensions	Increased access to Xpert utilisation beyond high-risk groups slightly increased detection of drug susceptible TB, but not DR-TB strains. Persistent HS challenges impeded Xpert utilisation.	A
14	Kweza (2018) South Africa	Cross-sectional survey 2015	Patients (1255)	Estimated the proportion of patients missed by PHCs using surveys and testing.	Diagnosis	Structural and patient dimensions	HS missed most patients with TB attending PHCs for TB-related symptoms and for other reasons.	A
15	McLaren (2017) South Africa	Healthcare evaluation 2004–2011	26 million tests in 429 hospitals	Assessed quality of care in public health facilities by analysing National Health Laboratory Service database for TB tests .	Diagnosis	Structural and patient dimensions	Facilities not adhering to national standards for TB testing. However, DST rates improved steadily over time. Testing rates were transiently affected by policy and guideline changes.	B
Quantitative studies								
16	Metcalfe *et al* (2016) Zimbabwe	Prospective study: 2011– 2014	Patients (352)	Diagnostic accuracy and TTI for Xpert were compared with culture and DST.	Diagnosis and treatment	Structural and patient dimensions	Rapid diagnosis with Xpert was not, in itself, enough to remove health system delays to treatment initiation.	A
17	Mohr (2017) South Africa	Retrospective cohort study 2012– 2014	Patients (543)	Analysed records of diagnosed patients to assess proportion that could have been diagnosed earlier.	Diagnosis	Structural dimensions	Lack of guideline adherence led to patients not being diagnosed.	A
18	Moyo *et al* (2015) South Africa	Retrospective analysis study: 2008–2013	Adolescent patients (71)	Analysed data for adolescents patients to describe frequency of treatment success or failure, loss to follow-up and deaths.	Treatment	Structural and patient dimensions	Treatment refusal and loss to follow-up were the predominant reasons for non-initiation of treatment.	A
19	Naidoo (2014) South Africa	Observational analysis of 10 facilities 2008– 2012	Patients (541)	Study compared TTI in MDRTBPlus Line Probe Assay vs Xpert-based algorithms.	Diagnosis and treatment	Structural and patient dimensions	Xpert reduced TTI by reducing LTAT. However, patients were being delayed by other steps needed before treatment initiation.	A
20	Nkosi (2013) South Africa	Cross-sectional survey 2008	Patients (148)	Determined reasons for non-referral of DR-TB patients.	Treatment	Structural and patient dimensions	Poor HCW knowledge of the national DR-TB guidelines, and patients loss to follow-up contributed to non-referrals.	A

Continued

Table 1 Continued

Study ID number	Study (year), country	Research design and methods Period	Populations (number)	Study objectives	Level of care (diagnosis/treatment)	Dimensions of access	Summary of findings	Assessment of study quality (score)
21	Oga-Omenka *et al* (2019) Nigeria	Retrospective cohort study. 2015– 2017	Patients (996)	Examined treatment rates and TTI using 2015 the TB programme records.	Treatment	Structural and patient dimensions	Geographic location and level of healthcare influenced patient treatment initiation within the time recommended by the National guidelines.	A
Quantitative studies								
22	Oliwa *et al* (2018) Kenya	Cross-sectional study: 2015	Patients (82 313)	Analysed National TB programme data for case notification rates, and capacity to perform diagnostic tests.	Diagnosis	Structural and patient dimensions	Despite guideline specifications, Xpert use was suboptimal, negatively affecting diagnosis, especially in children and low risk groups.	A
23	Timire *et al* (2019) Zimbabwe	Cohort study 2017– 2018	Patients (133)	Determined the impact of the Hain technology (timeliness and proportion of DST tests).	Diagnosis and treatment	Structural and patient dimensions	While decentralisation and treatment access positively impacted TTI, distance from the NRL hindered timely collection and return of DST.	A
24	Van Den Handel (2015) South Africa	Prospective evaluation of different diagnostic approaches 2011– 2013	Patients (1449)	Determined the impact of Xpert and decentralisation on patient care in areas with poor access to laboratory services.	Diagnosis	Structural dimensions	Xpert introduction and decentralisation impacted treatment rates and timelines, but did not significantly increase rates of detection.	A
Mixed-methods studies								
25	Doulla *et al* (2019) Tanzania	Qualitative FGDs, IDIs: 2012 Quantitative cross-sectional sample analysis: 2011– 2013	Qualitative 45 HCW Quantitative 2759 samples	Evaluated the effectiveness and stakeholder perception of routine surveillance system for previously treated TB cases.	Diagnosis	Structural dimensions	Delayedspecimen transportation, lack of resources and other laboratory challenges (eg, miscommunication, inconsistent training, etc) delayed diagnosis.	A
26	Mpagama *et al* (2019) Tanzania	Retrospective cohort study and cross-sectional study: 2015	28 TB districts 399 patients	Identified healthcare barriers to implementation of molecular diagnostics and TB collaborative practices in HIV clinics.	Diagnosis and treatment	Structural and patient dimensions	Overall, underdiagnosesoccurred where drug resistance is expected to be prevalent. HCWs lacked the tools, expertise and knowledge to appropriately manage patients with TB.	B
Mixed-methods studies								

Continued

Table 1 Continued

Study ID number	Study (year), country	Research design and methods Period	Populations (number)	Study objectives	Level of care (diagnosis/treatment)	Dimensions of access	Summary of findings	Assessment of study quality (score)
27	Mnyambwa *et al* (2018) Tanzania	Retrospective cohort study: 2013– 2016 Qualitative: IDIs	Chart review: patients (782) Qualitative interviews: TB coordinators (27)	Assessed the effectiveness of the Xpert GxAlert platformon linkage of patients to care.	Diagnosis and treatment	Structural and patient dimensions	Although the GxAlert platform improved diagnosis, healthcare inconsistencies impaired correct management of patients.	B
28	Westhuizen *et al* (2017) South Africa	Cross-sectional study: 2015	Medical students (12)	Determined the frequency and impact of occupational TB disease in current medical students and recently graduated doctors.	Diagnosis and treatment	Structural and patient dimensions	Overall, medical students did not have adequate access to the support and services needed for all TB care, including DR-TB.	B
29	Zimri (2012) South Africa	Qualitative FGDs and quantitative case control 2011	10 FGD with parentsand providers; Case control: 50 patients each arm	Caregivers of children referred to a specialist paediatric MDR-TB clinic to determine why many child contacts were not brought for assessment.	Diagnosis	Structural and patient dimensions	HCW attitude, coloured ethnicity, the mother being the source case, having a smoker in the house, transport time, cost and number of transitions, and fear of infection were identified as barriers.	A

DR-TB, drug-resistant TB; DST, drug-sensitivity testing; FGDs, focus group discussions; HCW, healthcare worker; HS, health system; IDI, in-depth interviews; KIIs, key informant interviews; LPA, line probe assay; LTAT, Laboratory turn-around time; MDR, multidrug-resistant TB; MGIT, mycobacteria growth indicator tube; NA, not applicable; NRL, National or Central Reference Laboratory; PHC, Primary Health Clinics; RR-TB, rifampicin-resistant TB; TB, tuberculosis; TTI, time to treatment initiation; Xpert, GeneXpert MTB/RIF Assay.

Our review question was 'What are the patient or provider factors associated with delays in tuberculosis diagnosis and treatment in sub-Saharan Africa?'.

METHODS

We used a mixed-methods systematic review with an integrative approach[13] to analyse data from qualitative, quantitative and mixed-methods literature and assessed quality using the *COnsolidated criteria for REporting Qualitative research* for qualitative studies (COREQ), *Strengthening the Reporting of Observational Studies in Epidemiology* -Combined tool (STROBE) and *Mixed Methods Appraisal Tool* (MMAT) tools, respectively.[14–16]

We registered the systematic review protocol in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=106875).

Search strategy

Using a combination of key terms, we searched nine electronic databases: CINAHL, Medline, Embase, Global Health, Scopus, Web of Science, International Journal of Tuberculosis and Lung Disease, PubMed and Google Scholar between January 2006 and June 2017, updating the search in June 2019. The year 2006 was used as this was the date of the first WHO publication guiding the programmatic management of DR-TB.

The Population, Intervention, Comparator and Outcomes (PICO) framework[17] and key search terms used are summarised in online supplementary annex 1. The initial search terms were piloted and refined in CINAHL, and replicated in other databases, using appropriate strategies specific to each. The public health librarian at the University of Montreal School of Public Health validated this process.

Study selection and inclusion criteria

We selected studies (figure 1) based on our inclusion criteria and PICO framework (online supplementary annex 1). Search results were downloaded into EndNote X7.7 and deduplicated. Titles and abstracts were screened, and full texts reviewed to determine studies for inclusion, and reasons for exclusion. All discrepancies or uncertainties were discussed and resolved by consensus during the final review.

Data extraction

Descriptive and analytical data were extracted (table 1). Study findings and outcomes were grouped quantitatively and qualitatively (table 2). Paired access dimensions and recommendations for some identified barriers, drawn from the studies themselves, were presented in the context of the healthcare access model by Levesque *et al* (table 3).[18] Finally, a summary of access factors based on perceived importance and frequency of appearance[19] are presented in figure 2, online supplementary annex 3.

Quality assessment

We assessed the quality of studies through different critical quality appraisal tools based on study designs. Consensus was reached by discussion. For quantitative studies, we used the STROBE combined tool.[14] The COREQ[15] and the MMAT was used to appraise mixed-methods studies.[16] The quality assessment are provided in online supplementary annex 2.

The overall quality assessments of 'A' for high (>70%), 'B' (50%–69%) for medium or 'C' (<50%) for low were assigned based on independent evaluation by at least two reviewers for each study. The STROBE, COREQ and MMAT tools have been used in several systematic reviews as a basis for excluding low quality studies.[20–22]

Conceptual framework

We adapted a conceptual framework, mapping the TB care continuum from symptom onset to treatment initiation[23] to four corresponding dimensions of access at the provider and patient levels,[18 24] and aligned these to identified barriers and facilitators from our review (figure 3). We explained provider factors using the six health systems building blocks described by WHO.[25] Patient-level barriers and facilitators were described using the Andersen and Newman individual determinants of healthcare utilisation.[26]

Data analysis

We used an integrative approach[13] to develop a narrative analysis of key findings from qualitative, quantitative and mixed-methods studies, due to the high heterogeneity of selected studies. We repeatedly screened, coded and categorised data from each study in four ways: table 1 gives the selected study overview—first author (year) and country, research design, population, intervention (when applicable), summary of barriers and facilitators, the level of care (diagnosis or treatment) in which they occurred and the dimensions of care (provider or patient), the main findings and the quality assessment score.

In table 2, we separated quantitative and qualitative findings for each identified factor. We reported associations that were statistically significant or relevant to our analysis and included representative quotes where available.

In table 3, we used the healthcare access model by Levesque *et al*[18 24] to categorise data into four provider and patient paired dimensions: approachability/ability to perceive; acceptability/ability to seek; availability/ability to reach; affordability/ability to pay and finally appropriateness/ability to engage. The paired dimension of approachability and ability to perceive relates mostly to knowledge of providers and patients about services. Acceptability and the corresponding ability to seek focuses on cultural and social aspects that influence people's decisions to use health service and the personal autonomy and agency to make these decisions. Availability and the ability to reach refers to the physical existence of health systems and health workers, as well as the physical mobility and work flexibility of patients to reach available health resources. The dimensions of affordability and the corresponding ability to pay reflects the

Table 2 Quantitative and qualitative findings

	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
Factor	**Barrier**	**Facilitator**	**Barrier**	**Facilitator**
Healthcare system level barriers (based on the WHO Health Systems Framework)				
Leadership and governance				
Guidelines availability and inclusion of low-risk groups	▶ Patient referral hampered as most HCWs were unaware of the national guidelines.[42]	▶ Testing rates were transiently responsive to changes in clinical guidelines and with increased awareness[47] ▶ Implementingan expanded algorithm signficantly increased DST use and rates of diagnosis[51]		
Service delivery				
Infrastructure and equipment	▶ Xpert and chest X-ray were unevenly distributed.[44] ▶ Few districts had laboratory capacity[29] ▶ Non-functional Xpert machines reported, varying by region[67]	▶ The GxAlert notification system sending short texts messages to TB coordinators when a MDR-TB case was detected. The coordinators also communicated this info with the respective district coordinators[31]	▶ Lack of necessary infrastructure and tools[28 45] ▶ HCW blamed for lack of equipment and delays[45] ▶ *"… they take it out on the health workers because, they are the people they see. If there is any form of dissatisfaction with service, if … power outage, …they take it out on you and its very painful… "*[45] ▶ Unreliable equipment maintenance and electrical fluctuations[67]	
Decentralisation and integration	▶ Pre-treatment delays persist after Xpert implementation due to centralisation of clinical requirements like X-ray, liver function tests, and audiometry[19]	▶ significantly increased treatment rates.[35] ▶ Decentralisation and Xpert implementation reduced TTI and improved patient outcomes.[36] ▶ Decentralisation and treatment availability improved treatment rates[30] ▶ Decentralised Xpert reduced LTAT and improved rates of diagnosis.[37] ▶ Decentralisation reduced TTI;[38]	▶ A lack in integration resulted in shortage of materials[28] *"Our programme is vertical, …there is a shortage of [supplies]; they should integrate so that some of these things could also be budgeted for…"*[28]	▶ Available, decentralised DR-TB treatment a facilitator to early care[32]
Laboratory operational issues: sputum transportation, turn-around time, misdiagnosis, communication and linkage to care	▶ Reasons for DST not done were contamination, failure to grow /loss of viability[27] ▶ Laboratory operational issues resulted in only half of DST results, even though sputum was collected, and most of the samples reached the NRL. Only very few results got back to requesting facilities.[30] ▶ Only 32.4% of samples were received at the NRL in 3 years; 58% and 97% of culture and DST had LTAT longer than recommended[28] ▶ 25% of submitted specimens did not have results communicated back to the clinic [67] ▶ Only 32.3% of newly diagnosed patients were treated, due to incomplete records on the GxAlert database and miscommunication[31] ▶ Mean diagnostic delay of 8.1 weeks[29]		▶ Difficulty in packaging, contamination, batching and transporting samples resulting in prolonged delays in diagnosis.[28] *"In a parcel of specimens, you could find one specimen … 15 days old and another 3 days old.… I think they [recieve] but they don't send it on time. Instead they wait for them to be many before sending*[28] ▶ Specimens received at late hours or not in sufficient numbers affect laboratory operations[67] ▶ An initial negative test result delayed diagnostic process[32] ▶ Prolonged delay in receiving results from the laboratory[32]	▶ The use of the Expedited Mail Services for sample transportation helpful if sustained[28]

Continued

Table 2 Continued

	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
Factor	**Barrier**	**Facilitator**	**Barrier**	**Facilitator**
Clinic operational issues: patient tracking and follow-up, long waiting times	▶ High rates (76%) of loss to follow-up led to non-referrals [42] ▶ Referrals as per guidelines were not implemented due to not having contact information for treatment facility[42]		▶ Inadequate tracking of patients and unavailable results for follow-up appointments at hampered access[32] ▶ "*…The clinic phoned me [but] did not say why. I only went [two weeks later] and was informed…that I have MDR-TB. … I was very disturbed that the clinic (had) not told me [earlier]…of this very contagious disease…I think this was very irresponsible of the clinic…"*. Delays in communicating results of up to 3 months.[32] ▶ A lack of specimen referral mechanism noted as a challenge by 43% of HCWs [67] ▶ Long waiting times in public factilities,[32 45] resulting in patients seeking care in the private sector where TB care options were often not as efficient[45] .	
Level of care	▶ Patients referred from a hospital were 8 times more likely not to initiate treatment than clinic referrals[50] ▶ Patients accessing care in higher level facilities had slightly lower odds of getting tested compared with those in lower levels[44]	▶ The treatment rate was highest in TB hospitals, with PHC rates higher than for secondary or tertiary hospitals.[43] ▶ Accessibility of care at a PHC facilitated treatment access. Most adolescents started treatment at a PHC compared with other levels[36] ▶ In-patients were more likely than outpatients to experience timely treatment[33] ▶ Variable testing rates between clinics and hospitalsfor all three comparisons[47]		
Public vs private sector care	▶ Patients in private sector had significantly lower odds of getting tested compared with those in public sector[44]		▶ Private sector as entry-point,[32] poor perception of public sector care,[32] and low index of suspicion at private facilities[29] as barriers to care. ▶ *"I went back again and again to the pharmacy and got different medication every time. I must have gone there five times"*.[32]	▶ Public sector care identified as having more DR-TB care options[32] ▶ *"…. There are much better options at the (public) clinic than the private doctors…lots of test which can be taken…"*[32]

Continued

Table 2 Continued

	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
Factor	**Barrier**	**Facilitator**	**Barrier**	**Facilitator**
Location and coverage (rural/urban)	▶ Wide regional variations in staff training, sample collection,testing capacity, rates and monitoring[27 47 67] ▶ Geographic location of referral was not associated with treatment initiation time[48] ▶ Facilities >250 km away from NRL took longer to receive DST results compared with facilities <50 km[30]	▶ Significant regional differences in treatment rates and TTI across the nine South African provinces .[43] ▶ Western Cape patients were more likely to have second-line DST results than the remaining provinces, due to the specific provincial guidelines [27] ▶ Utilisation of Xpert increased between 2016 and 2017 (88% increase), and was significantly higher in provincial than in rural hospitals.[49] ▶ Facilities that were <50 km away from the NRL were more likely to have DSTs done compared with those >250 km away.[30]	▶ Transportation of samples more difficult in rural areas[28] ▶ *"the transportation …to the NRL is not a problem…. Actually, biggest problem is referring samples from peripheral laboratory to district laboratory where post services is not available".*[28]	
Health workforce				
Adherence to guidelines	▶ Despite complete rollout of Xpert testing, only 59% of new cases were diagnosed [43] ▶ Less than half of RR-TB patients had DST results, as recommended by the guidelines[27] ▶ Poor guideline adherence was among reasons for incorrect patient screening and Xpert under-utilisation [34 44]. ▶ Guidelines not implemented due to patient follow-up perceived as difficult [42] ▶ [44] ▶ Incomplete adherence to National guidelines (51% of patients had DST).[30]		▶ Health providers' failure to follow diagnostic algorithms delayed DR-TB testing and led to wrong (first-line) treatment regimens[32] ▶ *"When the results came back they told me I do not take my tablets. I told them 'but I take my pills every day'. They could not understand why my results were 3-plus positive… The treatment did not help…I started to give up hope" (Xpert-6—a high-risk patient with DR-TB experienced 5-month delay due to not having a test done and initiation on first-line treatment).*[32]	
Workload and staff numbers			▶ *Laboratory staff shortages contributing to delays*[28 45] ▶ *"NRL staff have been trying to perform their work but they are overloaded with many specimens from each side of the country. ".*[28] ▶ Shortage of trained laboratory staff to man the Xpert machines noted as a challenge by heads of laboratories[10]	

Continued

Table 2 Continued

	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
Factor	**Barrier**	**Facilitator**	**Barrier**	**Facilitator**
HCW knowledge, training, experience and supervision	▶ Poor adherence to Xpert algorithm attributed to Xpert rollout preceding training of clinicians; only half of patients tested received confirmatory results.[41] ▶ HCW knowledge, application and interpretation of molecular diagnostics below expected levels. [67] ▶ Frequency of untrained laboratory staff performing Xpert was common in all regions[67] ▶ Only 41.7% of initial diagnoses were correct and a patient was started empirically on a DS-TB regimen without culture, delayed diagnosis.[29]	▶ Most HCWs were more comfortable and knowledgeable using Xpert than other test types and it was the most common test used (72%)[67]	▶ HCW low index of suspicion for TB resulting in delayed diagnosis[32] ▶ *"I was at (the CHC) for 24 hours …they told me that I had infection in my lungs and gave me the drip and antibiotics…In the same month I didn't feel so well so I went back… and they gave me the same drip and antibiotics".*[32] ▶ *"I just feel some of the staff at the clinic is inexperienced."*[40] ▶ Poor supervision leading to demotivation[28]	▶ Provider scheduling early return visits for DR-TB test results identified as a facilitator[32] ▶ *Support to the districts by the National programme helpful if sustained*[28] ▶ *"there is a need to strengthen supervision, make it more fruitful not just a vehicle visiting. It needs to be supportive, get there, stay with the staff, for them to recognize and listen to their problems … then provide solution"*[28]
HCW motivation and attitude, including stigma and discrimination			▶ Pre-treatment assessment tests were often not performed as other HCWs distanced themselves from DR-TB services[45] ▶ Fear of infection leading to stigma and discrimination affecting both DR-TB HCWs and patients. Deliberate patients appointments cancellation noted[45] ▶ *"…some nurses and medical workers treated us like we are not fit to live. They keep a distance when they [talk] with us. If you come closer, they will shout go! go!! go!!! … I felt like the worst person on earth having MDR-TB"*[45] ▶ HCW blamed for lack of equipment and delays[45] ▶ A lack of HCW motivation noted as a challenge to care[67]	▶ HCW attitude and patient counselling expedited treatment acceptance and process[32] ▶ Provider responsiveness at first contact and communicating concern about patients' well-being facilitated early care[32] ▶ *"I … had mixed feelings(when I was told about MDR-TB). …. I thought it was the end of time for me, but when the treatment process was explained to me, I felt much better and looked forward to the treatment"*[32]
Health information systems				
Data management	▶ Only 68% of specimens received by the laboratory had retrievable request forms[34] ▶ 56% of patients with confirmatory samples were untraceable within 3 months of Xpert samples,[41] 21% not found at all[33] ▶ Data errors missing data and 21.2% of treated patients not linked to diagnostic register likely indicative of missing patients[33] ▶ Incomplete records likely contributed to why most patients (67%) of patients were untreated[31]		▶ Incorrectly filled laboratory requests forms leading to misplaced results[28] ▶ *"This is a long-standing problem laboratory request forms not filled in well, a lot of information is missing. We see forms coming with either one name or just initials and the rest of the information not filled in".*[28] ▶ Unreliable patient addresses a challenge for HCWs[67]	
Access to second-line diagnostics, medications and technologies				

Continued

Table 2 Continued

Factor	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
	Barrier	**Facilitator**	**Barrier**	**Facilitator**
Type of diagnostic test	▶ Median time to treatment reduced to 0 days for Xpert-positive patients, compared with 14 days for empiric TB and suggestive chest X-ray findings, and 144 for culture-positive, Xpert-negative patients[38] ▶ Use of LPA was associated with delays in diagnosis and treatment, mostly due to prolonged laboratory TAT[39]	▶ LPA introduction associated with reduced TTI (76 to 50 days). Xpert associated with a further reduction to 8 days .[7] ▶ LTAT reduced from 38 to 2 days for new patients; and to 1 day for patients diagnosed with Xpert, [43] ▶ LPA diagnosis vs liquid culture reduced laboratory TAT from 52 to 26 days, and TTI from 79 to 54 days; and from 89 to 73.5 days for smear positives and negatives, respectively[51] ▶ Compared with culture, patients diagnosed with LPA were 73.3% less likely to be initiated late on treatment[52] ▶ Patients diagnosed with Xpert were more likely to have an earlier TTI when compared with DST culture and were less likely to have late TTI (after 60 days)[53] ▶ TTI in the Xpert-based algorithm was 17 days, with a median laboratory TAT of 1 day. There was a decrease of 25 days in median MDR-TB TTI in the Xpert-based algorithm.[39]	▶ Older diagnostic tests prolonged diagnostic process[28] ▶ *"I would say the methods used to examine the specimens … I think it is a big challenge because we need to be able to get these results quicker, for instance, they could be examined by liquid culture and drug susceptibility testing is done using molecular methods these could give results quicker"*[28]	
Newer diagnostics impact on rates	▶ * Treatment rates remained unchanged with Xpert.[7 39 43] ▶ Case detection rates did not increase following the introduction of Xpert[37]	▶ The proportion of RR-TB cases diagnosed by Xpert increased from 43% to 61% with increased Xpert implementation. The proportion who initiated treatment increased from 43% to 60% also.[35]		
Access to testing products	▶ Unavailable diagnostic services in campus health facilities and students were referred to private or public hospitals.[29]	▶ Full implementation of Xpert resulted in increased diagnosis rates (20%) and timeliness (92%), treatment referral and initiation (15%), increased treatment timeliness (49%) and decreased deaths before treatment (66.9%)[35]	▶ Stock outs of Xpert cartridges and reagents reported as a challenge by HCWs[67]	
Health financing				
TB health financing			▶ Inadequate health financing resulted in a poor access to care or catastrophic costs for patients.[29] ▶ Funding for sample transportation[29] ▶ *"… Who will take the specimens to the stations and …pick [them] up … and who will pay the costs for sending …? …"*[29]	
Patient level (based on the Andersen and Newman health services utilisation model)				

Continued

Table 2 Continued

	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
Factor	**Barrier**	**Facilitator**	**Barrier**	**Facilitator**
Predisposing characteristics				
Sex	▶ Sex not associated with having a DST done,[27 30] nor with treatment initiation rates or timeliness[33 43 48 54] ▶ Females less likely to have TB screening on hospital presentation with TB-related symptoms, OR=0.6[46] ▶ LTAT was for females was 1.09 times longer.[27] ▶ The mother being the TB source case resulted in children being more likely to miss clinic appointments OR=3.78[40]	▶ Being male was associated with increased odds of getting and Xpert test in all age groups.[44] ▶ Females more likely to have timely diagnosis as males were 89.3% more likely to be diagnosed after 12 days compared with those diagnosed in 2 days or less, even when adjusted for the HIV status.[52]		
Age	▶ Patients aged ≥ 55 years a had lower treatment rates than those 45–54 years[43] ▶ Adults (aged 20–59 years) were less likely than children (aged 0–19 years) to be initiated on treatment[33] ▶ TTI was longer for children aged 0–15 years compared with those aged 16–24 years[43] ▶ Patients age ≤10 years were less likely to have a DST result[27] ▶ Few patients aged 0–14 years (5%) and ≥15 years (12.2%) had an Xpert test done[44] ▶ Age was not associated with time to diagnosis,[52] nor having a DST done,[30] nor with rates of treatment[36] or timeliness.[39]	▶ Adults aged 55 years and above were more likely to be screened for TB on hospital presentation for other reasons than those aged 18–24 years[46] ▶ Middle-aged adults 35–44 years had higher case notification rates, whereas it was the lowest for children aged 5–9 years[44]		
Pregnancy			▶ Being pregnant made it more difficult to access TB care, resulting in transmission to family members[32] ▶ *"I was coughing and having sharp pains …They said they could not help me because I am pregnant…It was a very bad pregnancy"*[32]	

Continued

Table 2 Continued

	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
Factor	**Barrier**	**Facilitator**	**Barrier**	**Facilitator**
HIV	▶ Inconclusive: HIV-negative (aOR=0.6)[50] or with unknown status[43] patients, and in orther cases HIV positive,[43] were less likely to start treatment[50] ▶ HIV status was not associated with having a DST done,[30] nor with treatment timeliness[48 53]	▶ Odds of receiving TB diagnosis higher if HIV-positive using Xpert than for ART-naïve[38] ▶ HIV-positive patients had nearly twice the odds of receiving an Xpert test.[44]	▶ Fear of an HIV diagnosis delayed care-seeking[32] ▶ *"My mother said I must go to the clinic for a TB test. She was worried that I may have TB because my (relative) also had TB. I did not want to go …too scared that if I go for a TB test, they will also test me for HIV"*[32]	▶ Some HIV-infected patient had an awareness of their increased risk of TB[32] ▶ *"I was coughing, my bones pained and I was losing weight…I thought I had TB …I went to the ARV doctor because I had an appointment … and told him how I feel. I asked him to send me for a TB test"*[32] ▶ *"I knew I was HIV positive, and that made me more worried when I felt sick. Even when my TB results were negative…I went again for a TB test"*[32]
Presenting symptoms and history	▶ Patients with smear-negative disease were less likely to have DST results [27] ▶ Patients from the Western Cape had more forms of resistance than patients from the other provinces; leading to increased likelihood of ineffective DR-TB treatment.[27] ▶ Patients with fever and any two symptom combination (cough, fever, weight loss, night sweats) were less likely to be screened for TB[46]	▶ Patients with any three or four symptom combination (cough, fever, weight loss, night sweats) were more likely to be screened for TB on hospital presentation[46] ▶ Retreatment cases (ie, failures, relapses/ recurrences, defaulters) had the highest odds of getting an Xpert[44] ▶ Being underweight, especially in children aged 0–14 years doubled the odds of receiving an Xpert test.[44]	▶ Half the patients had previously been treated for TB but that did not always translate to symptom recognition or timely health seeking *"I did not believe it could be TB again because I completed my treatment the first time".*[32]	▶ Half the patients were previously treated for TB and several recognised the symptoms as a recurrence, responding by quickly seeking help at a PHC facility *"I had all the symptoms that I had the last time when I had TB. So I wanted them to check (for TB)".*[32]
Self-denial and non-disclosure				
Lifestyle and ethnicity	▶ Patients had a higher likelihood of missing clinic appointments when cigarettes were smoked in the house[40] ▶ Coloured patients when compared with Xhosa were less likely to attend clinic appointments and more likely delayed diagnosis[40]			

Continued

Table 2 Continued

	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
Factor	**Barrier**	**Facilitator**	**Barrier**	**Facilitator**
Patient agency, perceptions, and attitudes	▶ Patients concerned about the risk of DR-TB infection at the clinic: OR=2.45 ; and those with perception of long waiting times not attending clinic OR=2.47[40]		▶ Failure to recognise TB symptoms or lack of awareness that TB can recur resulted in delayed care-seeking[32] ▶ *"I was having a terrible cough and I was sweating at night, but … I still thought this was just a fever and the change of season and that everything was going to be fine"*[32] ▶ Negative perceptions of the public sector (over-burdened; rights infringement; negative staff attitudes; lack of privacy)[32 45] ▶ *"I was expecting long queues and sitting for ages before getting help, but … there was no queue and I got helped within 10 min…t"*[32] ▶ Beliefs in superstitions [31] among patients, non-disclosure delayed proper care[45] *"An illness that will make doctors and nurses to run away, if you tell a non-medic, will they stay with you? . … …I cannot tell them. Not even my girlfriend"*[45]	▶ Earlier care-seeking was enabled by symptom recognition or an awareness of increased risk of TB among HIV patients[32] *"I knew I was HIV positive, and that made me more worried … Even when my TB results were negative…I went again for a TB test"*.[32] ▶ Perceptions of good quality service and familiarity with service[32 32] ▶ Patient's agency in specifically requesting TB screening services that were not offered facilitated early diagnosis[32] ▶ Patient patience in waiting for care[32] ▶ *"I waited for a long time …I just told myself that… I am sick already and I need help and in order for me to get help I must be patient"*.[32]
Enabling characteristics				
Family, school or work support/commitments	▶ Health seeking delay was 3.2 weeks (0–16 weeks, SD 4.6) due to fear of missing academic teaching and clinical duties[29]		▶ *Family/ work/ school commitments or dissatisfaction with the service preventing a return to facilities or interruptions to the diagnostic process.*[29 32 40] ▶ *"The day… I was told I have MDR-TB, my family phoned… that my sister passed away. Everything then went crazy. All I could think about then was the fastest way to get (home.) …not thinking about my MDR-TB treatment, maybe because my mind was very occupied with my family responsibilities …"*.[32]	▶ Family support enabled early care-seeking[32]
Loss to follow-up or death	▶ 31.2% of patients died before treatment initiation and 46.4% lost to follow-up[50] ▶ Main reason for patients' non-referral was LFTU[42] ▶ Several patients (19% vs 33% in hospital and PHC respectively) died before referral.[42] ▶ Only 32% new diagnosed patients were treated; 38% were untraceable and 26% died before treatment[31] ▶ Of six untreated patients, one outmigrated and one died before treatment.[36]		▶ Symptoms worsening and death before treatment'*…this patient …decided to contact RTLC for help. … but the patient died before [being] taken to KIDH'*.[31] ▶ Patients reluctant to disclose their correct addresses due to confidentiality concerns[29]	

Continued

Table 2 Continued

Factor	Quantitative findings 95% CI (study ID)		Qualitative findings (study ID)	
	Barrier	**Facilitator**	**Barrier**	**Facilitator**
Direct and indirect costs of care	▶ More than one minibus transfer to get to clinic was associated with children missing appointments[40] ▶ Patients incurred substantial healthcare costs and transport costs.[29]		▶ Lack of transportation cost to keep appointments[32] ▶ Participants reported substantial expenses, including specialist appointments, investigations, treatment costs[29]	
Geographic location	▶ Informal settlements, (aOR=0.4) suburb (0.3) and prison (0.1) less likely to start treatment compared with township residence[50] ▶ Late DR-TB treatment Initiation (after 60 days) was less likely in patients having a town address.[53] ▶ Variable treatment initiation patterns within regions and within states in the same region; and between semi-urban and urban locations.[33]	▶ City/town residence was more likely to initiate treatment compared with township residence[50] ▶ Patients living in semi-urban areas were more likely to experience timely initiation of treatment than those in urban areas.[33]		▶ Convenience of free, accessible local services enabled early care-seeking[32]
Need characteristics and health seeking practice				
Treatment refusal or symptom minimization	▶ Of six patients who were not placed on treatment, two were due to treatment refusals.[36]		▶ Symptom minimisation or denial,resulted in delayed care-seeking[32] *"But at all these times I was not sick. It was just a cough, sweat at night and I felt that I was also losing weight, nothing else, not a day I ever felt like I was sick".*[32]	
Alternative care	▶ Patients opt for traditional medicine and do not return for results[67]		▶ Cultural beliefs and seeking traditional healthcare[32] ▶ Patients opting for traditional medicine and not returning for results noted as a challenge to care by HCWs[67]	

#1—even though a study of patients already on treatment, some issues like discrimination have been shown in other studies to impact patient access to care.
#28—distinguishing between factors related to diagnosis/treatment access from impact of treatment.
aOR, adjusted OR; DR-TB, drug-resistant TB; DST, drug-sensitivity testing; HCW, healthcare worker; LPA, line probe assay; LTAT, Laboratory turnaround time; LTFU, lost to follow-up; NRL, National or Central TB Reference Laboratory; RR-TB, rifampicin-resistant TB; SE, SouthEast; SW, SouthWest; TB, tuberculosis; TTI, time to treatment initiation; Xpert, GeneXpert MTB/RIF Assay.

financial implications of health services and the capacity on the side of patients to bear these costs.[18]

To synthesise the factors identified across the variety of studies, we ranked each barrier and facilitator based on its importance within each study and the number of studies where it appeared (figure 2, online supplementary annex 3). A factor is assigned the maximum score of 3 if it affects >50% of participants or has an OR of <0.65 or >1.5 for quantitative studies; and deemed as being of high importance or repeatedly mentioned across participant types. Factors are assigned a 2 if they affect 25%–50% of participants, or OR 0.65–0.8 or 1.25–1.5 for quantitative studies; or were deemed of moderate importance or by default when mentioned but not rated in qualitative studies. Factors were assigned 1 if affecting few participants and a zero if not mentioned. These scores were added for each study where the factor appeared. A similar method for synthesising mixed-methods reviews has been previously described.[19]

Patient and public involvement

Patients or members of the public were not involved in this research.

RESULTS

After an initial search yield of 3181 unique studies, 55 full texts met screening criteria, and a final selection of 30 articles were retained (figure 1).

Study characteristics

The majority of the included studies were conducted in South Africa (n=20), with Zimbabwe (n=3), Tanzania (n=3), Nigeria (n=2), Kenya (n=1) and Gabon (n=1) making up the rest. These six countries represent 49.5% of the 77 000 estimated DR-TB incident cases in Africa in 2018.[2] There were 3 qualitative, 22 quantitative and 5 mixed-methods studies. Among the quantitative studies, there were 13 retrospective, 3 prospective and 1 mixed cohort studies, and 5 cross-sectional surveys. All of the three qualitative studies employed in-depth interviews, with one study including focus group discussions. Five studies examined access factors related to DR-TB treatment only, 9 on DR-TB diagnosis only and 16 focused on both diagnosis and treatment. Factors impacting access were identified at provider (n=30) and patient (n=24) levels. Sixteen studies explored the influence of diagnostic tools on laboratory turnaround time and on treatment initiation. Table 1 summarises the study characteristics for this review.

Quality appraisal

The results of our quality assessment are shown in online supplementary annex 2. Out of a total of 22 quantitative studies, 20 were classified as A, with 2 scoring B based on the STROBE criteria.[14] The two qualitative studies scored A and B using the COREQ tool,[15] with one study, graded a C, excluded. Using the MMAT tool,[16] four studies were graded A and one as B in mixed methodology.

Provider factors affecting DR-TB diagnosis and treatment

In all 29 retained studies, the most dominant factors affecting DR-TB care were provider-related (table 2, figure 3). Our study highlighted a wide range of specific problems reflecting nearly all aspects of service delivery and health workforce with a few issues related to leadership and governance, and management of health products and information.

Service delivery was, by far, the most predominant provider-related barrier. Laboratory[10 27–32] and clinic[10 28 31 33 34] operational challenges, as well as centralisation of services[7 28 30 32 35–39] and poor linkage between the public and private sector,[29 32] hampered care. Inadequate provider knowledge, skill and adherence to national guidelines were also recurring themes.[10 27–30 32 34 40–44] These are discussed in more detail in the context of the paired dimensions of access.

Patient-level factors influencing DR-TB diagnosis and treatment

Most patient-level barriers were related to predisposing characteristics including knowledge and perceptions,[29 39 40 45] HIV status,[7 38 43 44] presenting symptoms,[44 46] gender[44 46] and age[27 43 44 46]; and enabling characteristics including geographic location,[10 27 28 30 43 47–49] life commitments[29 32 40] and the ability to pay for transportation or services.[29 32 39 40] A few need and health-seeking characteristics were also identified relating to treatment refusal,[36] and choosing private sector care.[10 32]

Paired access dimensions

We have summarised access factors and recommendations from the reviewed studies into four paired dimensions (table 3).[18]

Approachability/ability to perceive

We found that provider and patient knowledge about DR-TB services[18] were hindered by inadequate leadership and governance, provider training, service delivery, patients' predisposing and need characteristics.[18 25 26] At the systems level, inadequate patient tracking, referrals and follow-up, poor provider knowledge about the service requirements and inadequate guideline availability and non-adherence were identified challenges.[10 28 31 32 34 35 40–43 46 50] Patients' ability to perceive the right services were hampered by health illiteracy, poor perceptions of services, distrust and unmet expectations.[31 39 40]

At the health systems level, the consequences of poor leadership and governance were reflected in patient non-referral, misdiagnosis and treatment with ineffective regimens.[32 42] Guidelines awareness, availability and expansion to include low-risk groups were shown to improve access.[32 42 47 51]

Provider knowledge, skills and attitude were repeatedly shown to influence access and was a predominant theme (figure 3). Delayed or inadequate training, inexperience and poor supervision of health workers influenced

Table 3 Paired access dimensions and recommendations

Structural access dimensions and barriers (study ID #)	Patients access dimensions and barriers (study ID #)	Recommendations (study ID #)
Approachability: ▶ Outreach—lack of patient tracking and follow-up[35 42 50] ▶ Referrals from clinics or private facilities to DRTB care centres not done[42 43 50] ▶ Poor HCW information or knowledge of TB, resistance, guidelines or algorithms[31 35 39–41 46 67] ▶ Lack of guideline knowledge and adherence[28 31 34 42]	Ability to perceive: ▶ Poor knowledge of disease and perceptions of service[31 32 40] ▶ Distrust and unmet expectations[31 32]	▶ Raise public awareness of symptoms and the need for early care[32 40] ▶ Improve HCW knowledge/training and supervision on TB surveillance, resistance monitoring, guidelines and algorithms.[27 29 31 39 41 42 44 46 47 53] ▶ Improve surveillance, data management, referral and screening, eg, intensified case finding, appointment of dedicated linkage officers in each district.[28 30 32 34 35 39 41 43 44 46 47 50 51] ▶ Increase access to newer, rapid diagnostics point-of-care Xpert and ensure proper deployment and use.[7 36 38 41 44 49 51–53 67] ▶ Use of home visits or alert systems to follow-up patients[35 40–42] ▶ Broad-based policies and strategies to improve screening[41 47 51]
Acceptability: ▶ Professional values, norms and attitude[45] ▶ Care attributes—infection control, long duration of hospitalisation/ treatment[40 45]	Ability to seek: ▶ Personal and social values[32 36] ▶ Disclosure and confidentiality[31 45] ▶ Culture and gender norms[32] ▶ Work and family commitments[32] ▶ Patient sociodemographic characteristic, treatment history and comorbidities[27 30 33 39 43 44 50 51] ▶ Choosing alternative care[32] ▶ Fear of infection, delays or side effects[29 32 40]	▶ Improve service delivery including integration and retention in care, eg, appointment of linkage officers in each district.[2 4 6 20] ▶ Reduce hospitalisation duration[45] ▶ - Strengthen infection control measures and occupational health services.[29 31 40 45] ▶ Increase home-based care of DR-TB[42 45] ▶ Improve visitation policies for hospitalised patients[45] ▶ More attention to patient-level barriers.[29 33]
Structural access dimensions and barriers (study ID #)	**Patients access dimensions and barriers (study ID #)**	**Recommendations (study ID #)**
Availability: coverage/centralisation of services[7 37] ▶ Bed spaces for hospitalisation phase[51] ▶ Health products: inadequate supplies of diagnostics and drugs[67] ▶ Personnel: shortages in HCW quantity and quality[45 47] ▶ Laboratory and clinic operational errors and delays[27 28 31 34 37 47 51 53 54] ▶ Inadequate access to or low utilisation of newer diagnostic instruments[7 27 32 35 38 49 52 54 67] ▶ Regional operational differences[27 33]	Ability to reach: ▶ Poor sputum specimen[27] ▶ Difficult transportation to facility[37 39 40 49] ▶ Lack of social support[45] ▶ Geographic located far from care[27 33 37 40 50 51] ▶ Outmigration or death[36 42]	▶ Decentralising, linking and integrating services[7 33 37 40 41 51] ▶ Improve social and psychosocial support[45] ▶ Increase HCW quantity and quality.[47] ▶ Enable same day treatment initiation after Xpert[37] ▶ Two sputum specimen at baseline[27] ▶ Increase capacity and quality of inpatient and community-based care[51] ▶ Ensuring continuous supply of health products.[49] ▶ Expanded and timely access to treatment regimens, facilities and strategies.[8 21 23]
Affordability: ▶ Programme structure[29 32 40] ▶ Lack of funding for sputum transportation and consumables[28]	Ability to pay: ▶ Inability to pay for transport or treatment requirements; opportunity costs[40]	▶ Increased government investment[28]

HCW, healthcare worker; TB, tuberculosis.

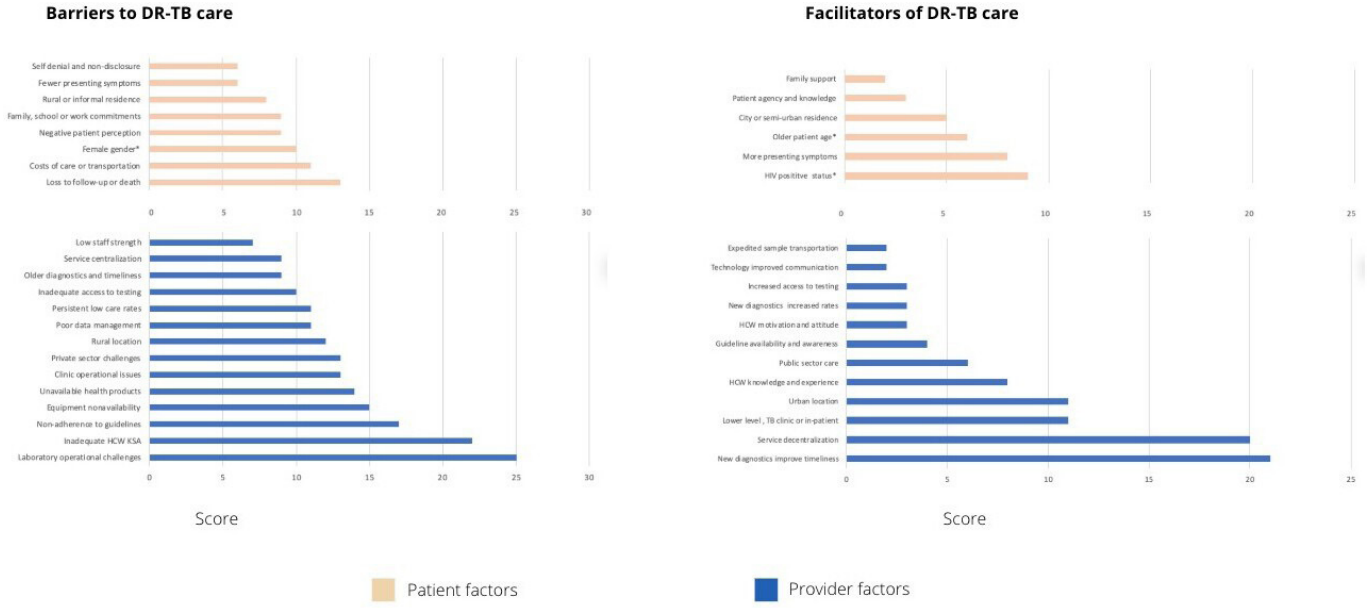

Figure 2 Summary of barriers and facilitators influencing drug-resistant tuberculosis (DR-TB) diagnosis and treatment in sub-Saharan Africa (SSA), ranked both on frequency of appearance and perceived importance.
HCW, healthcare worker; KSA, knowledge, skills and attitude. *Inconclusive results; see table 2.

product availability, diagnosis and treatment.[10 28 29 32 40 41] Poor adherence to DR-TB testing algorithm, treatment guidelines or referral procedures hampered diagnosis and treatment,[27 30 32 34 42–44] with patients often left undiagnosed, untreated, treated with ineffective drugs or only after serious complications.[32 42]

At the patient level, poor perception of the public sector (overburdened, long waiting times, negative staff attitudes, poor confidentiality, lack of privacy, risk of infection) were some reasons why patients were avoiding the public sector hospitals where DR-TB services could be accessed.[29 39 40 45]

Wrong disease attribution, symptom minimisation, non-disclosure, treatment refusal and choosing traditional care were also noted as delaying care-seeking.[10 32 36 45]

Patients seeking care first in the private sector (private hospitals, pharmacies, patent medicine vendors, traditional healers), where the index of suspicion was lower, instead of public sector, where services were available, had lower odds of getting tested.[44]

Acceptability/ability to seek

Our review found that although provider attitudes and practice were implicated, patients' predisposing characteristics were predominant in influencing their decisions to use health services.[18 25 26] Acceptability challenges were related to poor healthcare worker norms and attitude including confidentiality concerns, stigma and how the care patients received were influenced by their symptoms[7 43 44 46] or sociodemographic characteristics.[40 45] Patient's ability to seek were influenced by their sociodemographic characteristics, personal, cultural and social values, disclosure, work and family commitments, use of private sector alternatives and fear of poor infection control.[27 29–33 36 39 40 44 50 51]

At the provider level, stigma and discrimination towards providers from other hospital workers, and from provider to patients compromised access to and quality of care.[10 32 45]

At the patient level, living with HIV had conflicting results. Some studies found no association between HIV status and having a DST done, nor with time to treatment.[48 52] However, two studies found patients with HIV having overall higher odds of receiving a TB diagnosis.[38 44] However, HIV-positive patients had longer times to treatment or were less likely to initiate treatment,[7 43] except in one study where treatment initiation rates were higher than in HIV-negative patients.[50] In qualitative studies, the fear of an HIV diagnosis delayed health-seeking, and some patients with HIV were seen to have an increased awareness of TB risk.[32]

Patients presenting with more than any two of TB symptoms (cough, fever, weight loss, night sweats), retreatment cases and undernourished children were more likely to be screened for TB on hospital presentation for other reasons than those presenting with fewer symptoms, new cases and well-nourished children, respectively.[44 46] Smear-positive cases and more symptomatic patients were more likely to have a DST done.[27 47] Half of the time, previous TB led to faster symptom recognition and care-seeking.[32] In one study, being pregnant made accessing DR-TB care more difficult as providers refused to initiate any DR-TB-related care.[32]

Patient agency and persistence in demanding DR-TB testing where none was offered was noted as a facilitator to DR-TB healthcare, and this was linked to HIV positivity

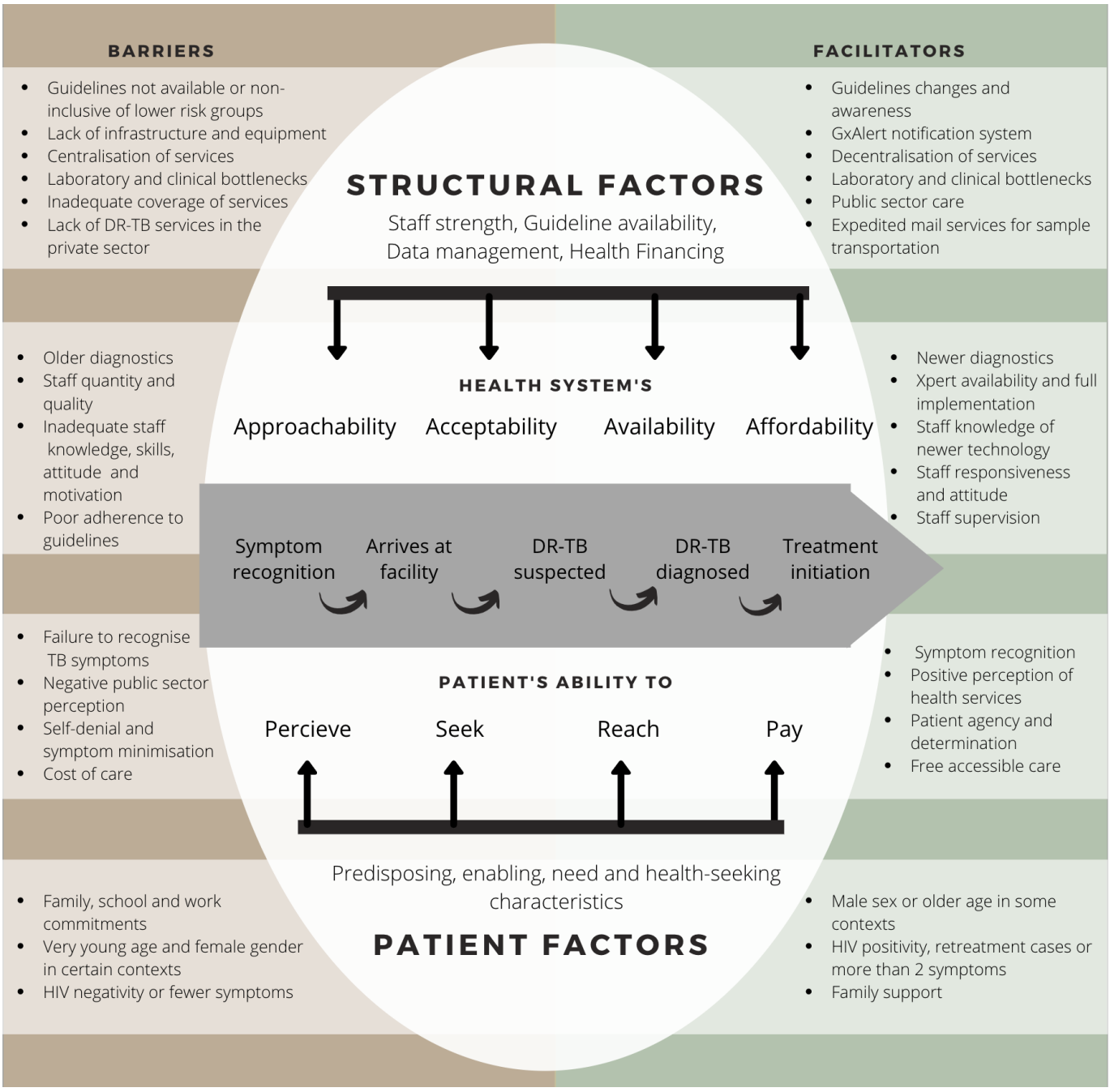

Figure 3 An adapted conceptual framework of identified barriers and facilitators to to DR-TB care.

or prior knowledge of the disease, either through an earlier TB infection or knowing another patient with DR-TB.[32]

Results linking access to patient gender and age were largely inconclusive. In several studies, neither patient gender nor age were found to be associated with diagnosis timeliness or rates,[27 30 52] nor with treatment initiation rates or timeliness.[36 39 43 48] There were some indications that females[44 46] or children whose mothers are the primary TB source,[40] or younger age[27 43 44 46] were less like to be diagnosed or treated (table 2). One study[33] found children to be more likely to initiate treatment than adults.

One study noted other contextual patient factors that were seen to influence DR-TB care. In South Africa, *ethnicity* and *cigarette smoking*—with children failing to attend clinic appointments more frequently from coloured ethnicity and homes with cigarette smokers. No particular reason was given for these differences, however, it was acknowledged that these were markers for other socioeconomic and cultural factors needing further research.[40]

Availability/ability to reach

These were mostly related to service delivery, access to health products and patient tracking on the provider

side and geographic access and life commitments on the patient side.[18 25 26] Specific health system barriers were related to coverage, bed spaces and centralisation of services; inadequate availability and coverage of health products—equipment and technology, advanced diagnostics and medications; shortages of health personnel; clinic and laboratory errors.[7 10 27 28 30–35 37–40 45 47 49 51–53] Patients were prevented from reaching health services when they lived in inaccessible locations or faraway distances, lack of social support and difficulty in transportation, poor sputum specimen, out-migration or death.[27 32 33 36 37 40 42 45 49–51]

Laboratory operational challenges were the most reoccurring barriers to care (figure 3). Specimen contamination, loss of viability, difficulty in packaging, batching, transportation and delivery of samples[10 27 28] delayed diagnosis. Not requesting tests, incomplete records, delayed results were other barriers preventing patients form accessing care.[10 28–32] Staff shortages, especially laboratory staff, contributed to diagnostic delays and patient waiting times.[10 28 45] There were significant geographical variations, mostly in laboratory operations, which impacted referral, diagnosis and treatment rates.[10 27 28 30 33 43 47–49] National programme support to health centres and using expedited mail service for sample transportation were helpful in reducing laboratory delays.[28]

Poor data management affected patient linkage to care and reporting. Errors including missing patient records in diagnosis or treatment registers, irretrievable request forms, incomplete data entry led to misplaced results, untraceable patients and poor linkage to care.[10 28 31 33 34]

Inadequate coverage and maintenance of diagnostic equipment, as well as power outages hampered diagnostic capacity[10 28 44 45] and staff motivation.[45] Where available, using the Xpert notification system improved team communication and facilitated diagnosis.[31]

Centralisation (in few specialised health centres) of GeneXpert MTB/RIF (Xpert) or other pretreatment requirements like X-rays, and a lack of integration, increased diagnosis time[28 39] and resulted in negative patient experiences.[45] Service decentralisation (widespread availability of services, and at the different healthcare levels) was, consequently shown to be a major facilitator of access (figure 3), reducing time to diagnosis and treatment and increasing diagnosis rates.[7 30 32 35–38] However, patients initiating care at higher facilities had lower odds of getting tested or initiating treatment.[36 44 50] Treatment initiation rate was highest among patients diagnosed directly through TB hospitals.[43] In one setting, timeliness of treatment was higher among patients initiated as inpatients compared with outpatients.[33]

The public sector had longer waiting times pushing patients to access care in the private sector, with poor linkages between the two.[29 32] Failure or delay in tracking patients, and unavailability of results at appointments prevented access.[10 32]

Access to newer diagnostics was the principal facilitator of access identified (figure 3). There was an overall consensus that the use of older diagnostic tests (eg, X-rays, drug susceptibility testing (DST) or line probe assay (LPA)), when compared with Xpert, was associated with longer times to diagnosis and treatment.[7 28 37–39 41 43 51–53] With the exception of one study,[35] Xpert implementation did not result in corresponding increases in diagnosis and treatment rates.[7 37 43 54] Also, the average time to DR-TB care remained significantly higher than the national targets in most settings.[33 39 41 43 52 53]

At the patient level, several studies noted high rates of patients being lost to follow-up or dying before treatment due to non-referrals, data errors, prolonged pretreatment processes and delayed care-seeking.[31 42 50]

Geographical location of patients was also identified as an access barrier. Patients in an urban/formal settlement accessed care more compared with those in rural, informal settlements or prison. Other variations were likely linked to the healthcare location, as noted above.[32 33 50 53] Significant variations in accessing diagnosis and treatment were due to geographical locations of the patients, with urban residence or proximity to care facility increasing likelihood of testing and treatment, as well as reducing time to results and treatment.[10 27 28 30 43 47–49]

Family, work or school commitments were seen to prevent or interrupt the care process, while the presence of family support enabled care-seeking.[29 32 40]

Affordability/ability to pay

The financial implications of services were mostly related to the enabling characteristics of patients to pay for care including transportation costs.[18 25 26] In our review, we found difficulties in paying for transport to health facilities, and high opportunity costs borne by patients.[32 40]

Ease of access and cost of health services were some reasons for choice of facility. A lack of money for transport, travel time and numerous bus transfers influenced whether they returned to the facility after initial visit.[29 39 40] Seeking care in the private sector was noted as contributing to the high costs of care for patients, as some go the public sector, where care was perceived as poor, only when they could no longer afford private care.[32] In another study where high costs of care was noted, majority of the patients sought care in the private sector.[29]

Discussion

Our review synthesises the diverse knowledge base about obstacles to DR-TB care in SSA to create a consolidated understanding to inform practice. It highlighted several health system and patient barriers.

Our key findings include the role of rapid diagnostics and laboratory operational issues play in facilitating or impeding access. Rapid diagnostic tools, particularly Xpert, play a central role in accessing DR-TB diagnosis and treatment, and their absence would constitute a significant barrier to receiving care.[28 38 39] The introduction of these tools has led to a significant reduction in times to care for DR-TB.[7 38 39 43 51–53] However, although

times were shortened, patients still experienced unnecessary delays in accessing care. The gains of rapid diagnostic technology have, so far, not translated into a commensurate increase in rates of detection and treatment.[7 37 39 43] These were likely due to the range of laboratory operational errors identified,[10 27–32] and which need to be targeted to improve case finding and treatment rates.

Our review data reveal several missed opportunities for screening and treatment initiation.[7 32 34 46] These contribute to the global 'missing cases', perpetuate transmission and highlight critical gaps in the care cascade. For example, the inadequate linkage between the private and the public sector occur before access to testing and are beyond the scope of rapid diagnostics. They contribute to the persistence of low diagnostic and treatment rates despite Xpert implementation.

Results for age and sex were found to be divergent, as many studies found both factors not significant in impacting care. In the studies where age was significant, younger age was mostly a barrier,[27 43 44 46] except in one study[33] where the programme prioritised children and other high-risk groups for Xpert diagnosis and inpatient care. Where most studies found sex not associated with DR-TB care, some found being female or a child or a female patient with DR-TB to be a barrier to care.[27 40 44 46] One study found females more likely to have earlier diagnosis, likely due to care-seeking behaviours.[52]

Several contextual factors like language, religion and culture were not identified by the studies included in this review. Geographic locations of the health centres and of the patients themselves were identified as influencing access to care, and this has been reported by other authors.[55 56] Ethnicity and lifestyle were identified in one study to influence access, likely due to socioeconomic and cultural implications.[40] The lack of qualitative data on the influence of sex and age on access makes it difficult to draw conclusions about whether the effects seen were due to contextual factors.

To improve patient-level barriers calls for a close examination of social determinants like poverty and geographic access as an addition to biomedical approaches, as recommended by the Commission on Social Determinants of Health (CSDH).[57–59] The burdens of infectious diseases like TB are disproportionately borne by patients with certain sociodemographic characteristics. For example, rural patients bear higher treatment costs and report more difficulty with transport to health centres for treatment.[60 61] Demographic characteristics such as gender, poverty or ethnicity often interact in complex ways, further increasing vulnerability and disadvantage.[62 63] Inadequate knowledge of DR-TB disease and health services was also identified as a major cause of poor health-seeking behaviour among patients. Raising public awareness of symptoms and available resources may contribute to reducing these delays.

The biomedical approach, which focuses more on the use of technology to manage diseases needs to be combined with efforts to tackle root causes and social determinants of DR-TB disease.[60 64]

Our findings indicate that, in order to overcome prevailing barriers to care, innovative diagnostic tools and treatment require functional, efficient and accessible health systems to reach and track patients who are, themselves, informed and motivated. The high susceptibility of individuals getting harmed from DR-TB, due to the complex interaction between risk factors and available resources, is manifested in their inability to manage risks or recover from the disease effectively.[63] This is corroborated by many of the reviewed studies in which diagnosed patients died before they could be initiated on life-saving treatment.[31 36 42 50] This highlights the fact that DR-TB continues to be characterised by avoidable morbidity and deaths, especially in SSA, and must be treated with urgency. The *raison d'être* of rapid diagnostic methods is to improve these outcomes by facilitating quicker diagnosis and treatment. Xpert implementation did not translate to universal increases in diagnosis and treatment rates, presenting a significant setback and missed opportunity in the control of DR-TB.

Gaps in the capacity of the health system to deliver care need to be closed. This would require significant investments at lower levels of care towards more decentralised and ambulatory models of care. In order to fund these efforts, SSA governments need to prioritise and increase health investments and mobilise resources to fund TB control.

Strengths and limitations

The strengths of this review include the adaptation of our conceptual framework to align factors influencing DR-TB care with other well-known frameworks in the field of healthcare access and systems strengthening,[18 25 26] using a mixed-methods approach.

This review has a few limitations. First, due to the heterogeneity of study methods and outcome variables, neither summary measures (eg, effect size) nor pooled analysis for specific interventions were determined, as the studies were not sufficiently comparable to each other. Another limitation is related to the location of the studies. Our search showed a dominance of studies from South Africa, with only two from Nigeria, and none from Angola, DR Congo, Ethiopia, Kenya, Mozambique, the other TB/DR-TB/HIV HBCs in the region. This may have affected the generalisability of our findings within the region, as there are likely other barriers in the different other settings that were not identified. However, the relatively higher HIV burden in South Africa, and the country's quick adoption of newer diagnostics and medications could serve as an example for these other countries as they scale-up services for DR-TB.

CONCLUSIONS

The implications of these findings are sobering; they suggest that despite significant progress in cutting down

time to diagnosis and treatment by using rapid diagnostics, this is not enough, in itself, to remove all delays to diagnosis, as other barriers persist in the health system.

WHO recognises that DR-TB is a social justice problem and as a threat to global health security, requiring universal access to the tools and services needed for rapid diagnosis, treatment and care.[65] Diagnosis and treatment for DR-TB is a complex and multifaceted socioeconomic problem that needs to be addressed using a multisectoral approach.[66] Provider-level and patient-level barriers need to be addressed to maximise the impact of advanced diagnostics. Most of the operational problems identified, such as the poor provider knowledge and implementation of DR-TB guidelines or inefficient screening or laboratory processes, are rectifiable, although with a substantial amount of effort and investment. We have identified this review as a call to action for all relevant players.

There is a need for more studies focusing on contextual access dimensions and care cascades from more HBCs in SSA, as this review has highlighted a dominance of studies from South Africa.

Author affiliations
[1]École de santé publique de l'Université de Montréal (ESPUM), Montréal, Quebec, Canada
[2]Centre de recherche en santé publique, Université de Montréal (CReSP), Montréal, Quebec, Canada
[3]McGill International TB Centre, Montreal, Quebec, Canada
[4]Azhee Akinrin Consulting, Lagos, Nigeria
[5]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada
[6]Institute of Human Virology, Abuja, Nigeria
[7]School of Public Health, University of the Western Cape, Cape Town, South Africa

Twitter Charity Oga-Omenka @omenkac and Muriel Mac-Seing @MMacSeing

Acknowledgements The authors would like to thank the University of Montreal librarian Sylvie Fontaine for her valuable assistance in conducting the search strategy.

Contributors CO-O, MM-S and CZ conceived the study, DM and CZ supervised the study. CO-O, AT-A and MM-S collected data. CO-O, AT-A, PS and AA analysed the data. All coauthors reviewed and provided feedback on the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Charity Oga-Omenka http://orcid.org/0000-0003-0779-570X
Muriel Mac-Seing http://orcid.org/0000-0001-5966-6702

REFERENCES

1 Gandhi NR, Nunn P, Dheda K, *et al*. Multidrug-Resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet* 2010;375:1830–43.
2 WHO. *Global tuberculosis report 2019*, 2019.
3 UN. *UN General Assembly High-Level Meeting on the fight against tuberculosis*. New York: United Nations, 2018.
4 Osborn D, Cutter A, Ullah F. *Universal sustainable development goals. in Understanding the transformational Challenge for Developed Countries. Report of Study by Stakeholder Forum*, 2015.
5 WHO. *Gear up to end TB: introducing the end TB strategy*. World Health Organization, 2015.
6 UN. *UN General Assembly, Seventy-third session, in 18th plenary meeting*. New York: United Nations, 2018.
7 Cox HS*et al*. Impact of decentralized care and the Xpert MTB/RIF test on rifampicin-resistant tuberculosis treatment initiation in Khayelitsha, South Africa. *Open Forum Infectious Diseases* 2015;2.
8 Heller T, Lessells RJ, Wallrauch CG, *et al*. Community-Based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa. *Int J Tuberc Lung Dis* 2010;14:420–6.
9 Schaaf HS, Shean K, Donald PR. Culture confirmed multidrug resistant tuberculosis: diagnostic delay, clinical features, and outcome. *Arch Dis Child* 2003;88:1106–11.
10 Mpagama SG, Heysell SK, Ndusilo ND, *et al*. Diagnosis and interim treatment outcomes from the first cohort of multidrug-resistant tuberculosis patients in Tanzania. *PLoS One* 2013;8:e62034.
11 Dharmadhikari AS, Mphahlele M, Venter K, *et al*. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2014;18:1019–25.
12 Boyd R, Ford N, Padgen P, *et al*. Time to treatment for rifampicin-resistant tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2017;21:1173–80.
13 Whittemore R, Knafl K. The integrative review: updated methodology. *J Adv Nurs* 2005;52:546–53.
14 STROBE Statement. STROBE Statement - Checklist of items that shouldbe included in reports of observational studies, 2007. Available: https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf [Accessed 15 Sep 2018].
15 Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;19:349–57.
16 Hong QN*et al*. The mixed methods appraisal tool (MMAT) version 2018 for information professionals and researchers. *Education for Information* 2018:1–7.
17 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
18 Levesque J-F, Harris MF, Russell G. Patient-Centred access to health care: conceptualising access at the interface of health systems and populations. *Int J Equity Health* 2013;12:18.
19 Clifford BK, Mizrahi D, Sandler CX, *et al*. Barriers and facilitators of exercise experienced by cancer survivors: a mixed methods systematic review. *Supportive Care in Cancer* 2018;26:685–700.
20 Abegaz TM, Shehab A, Gebreyohannes EA, *et al*. Nonadherence to antihypertensive drugs: a systematic review and meta-analysis. *Medicine* 2017;96:e5641.
21 Reeve E, To J, Hendrix I, *et al*. Patient barriers to and enablers of deprescribing: a systematic review. *Drugs Aging* 2013;30:793–807.
22 Pace R, Pluye P, Bartlett G, *et al*. Testing the reliability and efficiency of the pilot mixed methods appraisal tool (MMAT) for systematic mixed studies review. *Int J Nurs Stud* 2012;49:47–53.
23 Yang W-T, Gounder CR, Akande T, *et al*. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? *Tuberc Res Treat* 2014;2014:1–15.
24 Bailie J, Schierhout G, Laycock A, *et al*. Determinants of access to chronic illness care: a mixed-methods evaluation of a national multifaceted chronic disease package for Indigenous Australians. *BMJ Open* 2015;5:e008103.
25 WHO. *Everybody's business-strengthening health systems to improve health outcomes: who's framework for action*, 2007.
26 Andersen R, Newman JF. Societal and individual determinants of medical care utilization in the United States. *The Milbank Quarterly* 2005;83.
27 Jacobson KR, Barnard M, Kleinman MB, *et al*. Implications of failure to routinely diagnose resistance to second-line drugs in patients with rifampicin-resistant tuberculosis on Xpert MTB/RIF: a multisite observational study. *Clin Infect Dis* 2017;64:1502–8.
28 Doulla BE, Squire SB, MacPherson E, *et al*. Routine surveillance for the identification of drug resistant tuberculosis in Tanzania: a

cross-sectional study of stakeholders' perceptions. *PLoS One* 2019;14:e0212421.
29 Van der Westhuizen H-M, Dramowski A. When students become patients: TB disease among medical undergraduates in Cape town, South Africa. *S Afr Med J* 2017;107:475–9.
30 Timire C, Sandy C, Kumar AMV, *et al*. Access to second-line drug susceptibility testing results among patients with Rifampicin resistant tuberculosis after introduction of the Hain® Line Probe Assay in Southern provinces, Zimbabwe. *Int J Infect Dis* 2019;81:236–43.
31 Mnyambwa NP, Lekule I, Ngadaya ES, *et al*. Assessment of GeneXpert GxAlert platform for multi-drug resistant tuberculosis diagnosis and patients' linkage to care in Tanzania. *BMC Res Notes* 2018;11:121.
32 Naidoo P, van Niekerk M, du Toit E, *et al*. Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients' experiences in the era of rapid molecular diagnostic tests. *BMC Health Serv Res* 2015;15:488.
33 Oga-Omenka C, Zarowsky C, Agbaje A, *et al*. Rates and timeliness of treatment initiation among drug-resistant tuberculosis patients in Nigeria- a retrospective cohort study. *PLoS One* 2019;14:e0215542.
34 Mohr E, Daniels J, Muller O, *et al*. Missed opportunities for earlier diagnosis of rifampicin-resistant tuberculosis despite access to Xpert® MTB/RIF. *Int J Tuberc Lung Dis* 2017;21:1100–5.
35 Evans D, Sineke T, Schnippel K, *et al*. Impact of Xpert MTB/RIF and decentralized care on linkage to care and drug-resistant tuberculosis treatment outcomes in Johannesburg, South Africa. *BMC Health Serv Res* 2018;18:973.
36 Moyo S, J Furin J, Hughes J, *et al*. Outcomes in adolescents undergoing treatment for drug-resistant tuberculosis in Cape town, South Africa, 2008-2013. *Arch Pediatr Infect Dis* 2014;2.
37 Van Den Handel T, Hampton KH, Sanne I, *et al*. The impact of Xpert(®) MTB/RIF in sparsely populated rural settings. *Int J Tuberc Lung Dis* 2015;19:392–8.
38 Hanrahan CF, Selibas K, Deery CB, *et al*. Time to treatment and patient outcomes among TB suspects screened by a single point-of-care Xpert MTB/RIF at a primary care clinic in Johannesburg, South Africa. *PLoS One* 2013;8:e65421.
39 Naidoo P, du Toit E, Dunbar R, *et al*. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-Based algorithms in a routine operational setting in Cape town. *PLoS One* 2014;9:e103328.
40 Zimri K, Hesseling AC, Godfrey-Faussett P, *et al*. Why do child contacts of multidrug-resistant tuberculosis not come to the assessment clinic? *Public Health Action* 2012;2:71–5.
41 Dlamini-Mvelase NR, Werner L, Phili R, *et al*. Effects of introducing Xpert MTB/RIF test on multi-drug resistant tuberculosis diagnosis in KwaZulu-Natal South Africa. *BMC Infect Dis* 2014;14:442.
42 Nkosi D, Janssen S, Padanilam X, *et al*. Factors influencing specialist care referral of multidrug- and extensively drug-resistant tuberculosis patients in Gauteng/South Africa: a descriptive questionnaire-based study. *BMC Health Serv Res* 2013;13:268.
43 Cox H, Dickson-Hall L, Ndjeka N, *et al*. Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: a retrospective cohort study. *PLoS Med* 2017;14:e1002238–19.
44 Oliwa JN, Maina J, Ayieko P, *et al*. Variability in distribution and use of tuberculosis diagnostic tests in Kenya: a cross-sectional survey. *BMC Infect Dis* 2018;18:328.
45 Bieh KL, Weigel R, Smith H. Hospitalized care for MDR-TB in Port Harcourt, Nigeria: a qualitative study. *BMC Infect Dis* 2017;17:50.
46 Kweza PF, Van Schalkwyk C, Abraham N, *et al*. Estimating the magnitude of pulmonary tuberculosis patients missed by primary health care clinics in South Africa. *Int J Tuberc Lung Dis* 2018;22:264–72.
47 McLaren ZM, Sharp AR, Zhou J, *et al*. Assessing healthcare quality using routine data: evaluating the performance of the National tuberculosis programme in South Africa. *Trop Med Int Health* 2017;22:171–9.
48 Metcalfe JZ, Makumbirofa S, Makamure B, *et al*. Xpert(®) MTB/RIF detection of rifampin resistance and time to treatment initiation in Harare, Zimbabwe. *Int J Tuberc Lung Dis* 2016;20:882–9.
49 Jokwiro A, Timire C, Harries AD, *et al*. Has the utilisation of Xpert® MTB/RIF in Manicaland Province, Zimbabwe, improved with new guidance on whom to test? *Public Health Action* 2018;8:124–9.
50 Ebonwu JI, Tint KS, Ihekweazu C. Low treatment initiation rates among multidrug-resistant tuberculosis patients in Gauteng, South Africa, 2011. *Int J Tuberc Lung Dis* 2013;17:1043–8.
51 Hanrahan CF, Dorman SE, Erasmus L, *et al*. The impact of expanded testing for multidrug resistant tuberculosis using genotype [correction of geontype] MTBDRplus in South Africa: an observational cohort study. *PLoS One* 2012;7:e49898.
52 Iruedo J, O'Mahony D, Mabunda S, *et al*. The effect of the Xpert MTB/RIF test on the time to MDR-TB treatment initiation in a rural setting: a cohort study in South Africa's Eastern Cape Province. *BMC Infect Dis* 2017;17:1–9.
53 Jacobson KR, Theron D, Kendall EA, *et al*. Implementation of genotype MTBDRplus reduces time to multidrug-resistant tuberculosis therapy initiation in South Africa. *Clin Infect Dis* 2013;56:503–8.
54 Naidoo P, du Toit E, Dunbar R, *et al*. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape town. *PLoS One* 2014;9:e103328.
55 Sullivan BJ, Esmaili BE, Cunningham CK. Barriers to initiating tuberculosis treatment in sub-Saharan Africa: a systematic review focused on children and youth. *Glob Health Action* 2017;10:1290317.
56 van de Water BJ, Prvu Bettger J, Silva S, *et al*. Time to drug-resistant tuberculosis treatment in a prospective South African cohort. *Glob Pediatr Health* 2017;4:2333794X1774414.
57 Hargreaves JR, Boccia D, Evans CA, *et al*. The social determinants of tuberculosis: from evidence to action. *Am J Public Health* 2011;101:654–62.
58 Rasanathan K, Sivasankara Kurup A, Jaramillo E, *et al*. The social determinants of health: key to global tuberculosis control. *Int J Tuberc Lung Dis* 2011;15 Suppl 2:30–6.
59 CSDH. *Closing the gap in a generation: health equity through action on the social determinants of health. final report of the Commission on social determinants of health*. World Health Organization: Geneva, 2008: 256.
60 Farmer P. Social inequalities and emerging infectious diseases. *Emerg Infect Dis* 1996;2:259–69.
61 Bhutta ZA, Salam RA, Das JK, *et al*. Tackling the existing burden of infectious diseases in the developing world: existing gaps and the way forward. *Infect Dis Poverty* 2014;3:1.
62 Marmot M, Allen J, Bell R, *et al*. Who European review of social determinants of health and the health divide. *Lancet* 2012;380:1011–29.
63 Zarowsky C, Haddad S, Nguyen V-K. Beyond 'vulnerable groups': contexts and dynamics of vulnerability. *Glob Health Promot* 2013;20:3–9.
64 WHO. *Health in all policies: Helsinki statement. framework for country action*, 2014.
65 Organization, W.H. *Gear up to end TB: introducing the end TB strategy*. World Health Organization, 2015.
66 World Health Organization,. *Health in all policies: Helsinki statement. framework for country action*, 2014.
67 Mpagama SG, Mbelele PM, Chongolo AM, *et al*. Gridlock from diagnosis to treatment of multidrug-resistant tuberculosis in Tanzania: low accessibility of molecular diagnostic services and lack of healthcare worker empowerment in 28 districts of 5 high burden TB regions with mixed methods evaluation. *BMC Public Health* 2019;19:395.