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Challenges and knowledge gaps in the management of non-tuberculous mycobacterial pulmonary disease in sub-Saharan African countries with a high tuberculosis burden: a scoping review

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ABSTRACT

Introduction In sub-Saharan African (SSA) countries endemic for tuberculosis (TB), previous TB is a significant risk factor for non-tuberculous mycobacterial pulmonary disease (NTM-PD). The deployment of GeneXpert MTB/RIF in pulmonary TB diagnostic work-up regularly identifies symptomatic patients with a positive smear microscopy but negative GeneXpert, indicative of NTM presence. This scoping review outlines recent evidence for NTM-PD diagnosis and management in SSA.

Objective The review's objective was to outline the risk factors, available diagnostics, management options and outcomes of NTM-PD in high-burden TB settings in SSA using the population-concept-context framework.

Design and data sources We searched existing literature from PubMed, Web of Science, African Journals Online, Google Scholar and grey literature. Studies published between January 2005 and December 2022 were retained. Data were extracted into Rayyan software and Mendeley and summarised using Excel.

Results We identified 785 potential articles, of which 105 were included in the full-text review, with 7 papers retained. Included articles used international criteria for diagnosing NTM-PD. Multiple papers were excluded due to non-application of the criteria, suggesting challenging application in the SSA setting. Identified risk factors include previous TB, smoking and mining. Most commonly, chest radiography and not CT was used for the radiological diagnosis of PD, which may miss early changes related to NTM-PD. Molecular methods for NTM species identification were employed in research settings, usually at referral centres, but were unavailable for routine care. Most studies did not report a standardised approach to treatment and they were not offered treatment for the specific disease, marking a lack of guidance in treatment decision-making. When treatment was provided, the outcome was often not reported due to the lack of implementation of standardised outcome definitions.

Conclusions These outlined challenges present a unique opportunity for researchers to undertake further studies in NTM-PD and proffer solutions more applicable to SSA.

STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ We used a systematic approach for the literature search and synthesis, ensuring that the review is reproducible.
⇒ An extensive search was conducted to identify all possible articles needed.
⇒ This review expanded on the knowledge gaps and areas where research is needed in SSA on non-tuberculous mycobacterial pulmonary disease.
⇒ Case reports were included to improve the establishment of existing knowledge on treatment options.
⇒ The identification of a few papers makes the generalisability of findings challenging.

INTRODUCTION

The epidemiology of non-tuberculous mycobacterial (NTM) infection and disease is increasingly being reported.[1] A recent systematic review by Dahl *et al* reports the global prevalence of NTM infection with a pooled estimate of 1.95 per 100 000 and NTM disease with 1.04 per 100 000 population.[2]

In tuberculosis-endemic regions of sub-Saharan Africa (SSA), tuberculosis (TB) diagnosis may overshadow NTM lung disease. Diagnosing TB is still largely dependent on sputum-smear microscopy (SSM), with GeneXpert MTB/RIF (Cepheid, USA; Xpert) being prioritised for patients who are failing first-line treatment regimens.[3] A positive SSM only indicates a mycobacterial infection without differentiating between TB

and NTM. As NTM pulmonary disease (NTM-PD) can present as SSM positive and Xpert negative, some studies have reported patients with NTM-PD being considered (and treated) as recurrent TB or as drug-resistant (DR) TB.[4] On the other hand, in patients who present for a TB retreatment, problems with the interpretation of investigation arise when the GeneXpert MTB/RIF assay does not confirm a positive SSM.[5]

The isolation of NTM from pulmonary samples is common since NTM, being environmental microorganisms, may transiently be present in airways.[6 7] NTM-PD, on the other hand, is diagnosed by fulfilling a set of microbiological, clinical and radiological criteria set forth by the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA)/European Society of Clinical Microbiology and Infectious Disease (ESCMID)/European Respiratory Society (ERS).[8] However, the clinical symptoms and radiological signs of NTM-PD may overlap with TB, with many patients presenting with cough, fever and weight loss.[8] Mycobacterial culture is increasingly available for treatment monitoring, especially in patients with DR-TB. The clinical interpretation of cultures positive for NTM or NTM in combination with *Mycobacterium tuberculosis* (MTB) poses challenges. The very stringent NTM-PD definition necessitating multiple isolates of the same NTM species over several weeks from the same patient does not match with routine clinical settings in SSA.

In 2017, a systematic review by Okoi *et al* summarised the data available on NTM pulmonary infection and NTM-PD in SSA, applying the ATS/IDSA/ESCMID/ERS criteria to differentiate NTM infection and disease. Out of 37 identified studies, only 7 qualified to classify the participants as having NTM-PD. Of these, three were from South Africa, two from Zambia and one each from Mali and Tanzania. Overall, organisms isolated from pulmonary specimens predominantly belonged to *M. avium* complex (MAC), yet most did not meet the criteria to be associated with disease. The predominant organism identified to cause NTM-PD was *M. kansasii*, accounting for 69.2% of cases, followed by *M. scrofulaceum* (13.9%) and MAC (13.5%), with *M. abscessus* complex accounting for 0.4%. The predominance of *M. kansasii* in NTM-PD was attributed to the high prevalence of silico-TB related to mining activities and urbanisation in southern Africa, where people are socioeconomically disenfranchised. Still, the reasons for geographically defined species predominance in NTM infection and NTM-PD remain to be better unravelled.

Okoi and colleagues presented the epidemiology and risk factors of NTM-PD.[9] The majority (87.1%) of study participants with NTM-PD had a history of pulmonary TB (PTB).[10] However, the review did not discuss management options or outcomes. The objective of the study was to outline the risk factors, available diagnostics, management options and outcomes of NTM-PD in high-burden TB settings in SSA, using data available after Okoi *et al*'s review.

REVIEW QUESTIONS

We aimed to answer the clinical question, 'What are the risk factors, available diagnostics, management options and outcomes of NTM-PD in high-burden TB settings in sub-Saharan Africa?', in this review.

INCLUSION CRITERIA

We used the population-concept-context framework to define our scope for this review. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for scoping review to present our results.[11] Studies evaluating adults and children with NTM-PD or NTM/TB coinfection in SSA with a high TB burden were eligible for inclusion. We used the population, concept and context strategy to define the inclusion of papers for this study.[12] The population were individuals with risk factors and diagnosed with NTM-PD but not extrapulmonary or disease such as *Mycobacterium ulcerans*, in the context of SSA countries with a high TB burden. The concepts assessed were risk factors, current management strategies and management outcomes. All studies that covered NTM and NTM-PD were eligible for assessment for inclusion into the study.

The publication date was restricted from January 2005 to December 2022. The year 2005 coincides with the introduction of the mycobacterial growth indicator tube for liquid culture by the WHO, making it more likely for NTM to be isolated from sputum samples.[13]

We used the ATS/IDSA/ESCMID/ERS criteria to determine if articles covered NTM-PD (online supplemental appendix I, ATS/IDSA/ESCMID/ERS criteria).[8] Articles comprising experimental and observational study designs, systematic reviews, controlled trials (randomised and non-randomised), cohort studies (prospective and retrospective), case-control studies, cross-sectional studies, case series and case reports and reviews were eligible for inclusion. Excluded were articles on extrapulmonary or disseminated NTM-related disease, preclinical studies, studies done outside SSA and studies lacking speciation of NTM.

METHODOLOGY

Search strategy

We searched the electronic databases PubMed, Web of Science, African Journals Online, Google Scholar and grey literature.

The search items included 'Persons', 'Person', 'Individual', 'adult', 'child', 'Pulmonary samples', 'Nontuberculous Mycobacteria', 'Mycobacteria other than tuberculosis', 'MOTT', 'Nontuberculous mycobacteri*', 'NTM', 'African South of the Sahara', 'sub-Saharan Africa' 'Low- and Middle-Income Country'. Boolean terms 'AND' and 'OR' were used to assist in the search for the final search results. All papers were restricted to humans (online supplemental appendix II, Concept

Search Strategy). The protocol for the review can be publicly located in Figshare.[14]

Data extraction

Two independent reviewers (ETA and LL) worked with Rayyan software to review all abstracts and titles for inclusion. Disagreements were resolved by consensus. All included papers were imported into Mendeley, where we performed full-text reviews for final inclusion. After the initial search, both reviewers set a reminder on PubMed, Web of Science and Google Scholar to be updated on new articles under non-tuberculous mycobacteria using the same search terms. These articles were also assessed for inclusion in the review. The draft data extraction document is provided in online supplemental appendix III.

Data analysis

The identified papers were divided into primary research papers and case reports or reviews. For the papers classified as primary research, we extracted data on the author details, country of origin, study design and population, the prevalence of NTM-PD among presumptive patients with TB, sample size if applicable, enumerated risk factors, type of diagnostic method and diagnostic outcomes as well as speciation of NTM. Treatment strategies and outcomes, if available, were extracted. For the papers primarily presented as case reviews, we summarised them into author details, country of origin, study design and the main findings. All data were extracted into an Excel sheet, and the results were tabulated.

Patient and public involvement

None.

RESULTS

Search results

A summary of the data extraction is presented in figure 1. Our literature search identified 785 articles that were imported into the Rayyan software, of which 129 were removed after deduplication. We screened 656 abstracts and titles and excluded 552. Three additional papers from the set reminders on PubMed were included throughout the review period for full-text review. A total of 105 abstracts were included for full-text review. Following the complete evaluation of the articles, some were excluded as follows: 73 papers not applying the international criteria of NTM-PD, 15 articles without NTM speciation and 3 with no primary report on NTM. A further two articles were excluded because they were preclinical studies, three papers had their location outside SSA and two were duplicates. A summary of the sources excluded following full-text review is provided in online supplemental appendix IV.

Inclusion of sources of evidence

Following the full-text review, seven articles were deemed eligible to be included in the scoping review, two of which were covered by the Okoi *et al* paper (figure 1).

Data were summarised under themes according to the objectives of the study, which include the risk factors of NTM-PD, available diagnostic methods, NTM-PD treatment and challenges and gaps. Online supplemental appendix III summarises the included papers.

Review findings

Our review shows data from SSA on TB/NTM coinfection published after the systematic review of Okoi *et al* in 2017. The summary of the papers is presented in tables 1–3, outlining author details, study design, population, identified risk factors and diagnostics employed with the identified NTM species. Furthermore, the management strategy and its outcomes were summarised. Figure 2 summarises the geographic distribution of the studies included in the review. The included papers comprised three cohort studies, one cross-sectional study and three case reports on patients diagnosed with NTM-PD.

Patient population and risk factors

Patient populations were heterogeneous: one study reported on children and six on adults; original studies like Maiga *et al* and Lopez-Varela *et al* included presumptive TB cases, whereas Ouattara *et al* included recurrent TB diagnosis (figure 2).[4 15 16] The three case reports were on adults between the ages of 40 and 59 years (table 3). Presumed recurrent TB diagnosis, that is patients who remain symptomatic and often smear positive following one or several courses of TB treatment, was a risk factor for NTM-PD in most of the studies.

The study by Ouattara *et al* specifically looked at MAC disease. Of the 17 patients with MAC NTM-PD, two were HIV positive.[17] None of the four identified children in Mozambique was HIV positive, and one of the three case reports was on a patient who was HIV positive(tables 2 and 3).[18 19]

We identified other risk factors for NTM-PD as structural lung diseases such as silicosis, smoking, occupational exposure such as working in the mining industry or agricultural sector, and malnutrition (table 1).[18 20–22]

Available diagnostic strategies

All but one study in this review used chest radiography to assess NTM-PD. In high-resource, low-TB incidence settings, a high-resolution chest CT scan is employed to diagnose and monitor NTM-PD.[23–25]

Sputum samples, gastric aspirates or bronchoalveolar fluids were taken for culture in all the studies reviewed. Although many of these studies were carried out in presumed patients with TB, GeneXpert results were presented and negative in only one case report.[22]

All the studies had speciation of NTM done. This was done through molecular techniques such as line probe assay (LPA) using GenoType CM/AS (Bruker, Germany) and DNA hybridisation probes using 16S sequencing techniques (table 1).[17–19 21] All these diagnostics were employed in research settings and unavailable for routine healthcare delivery.

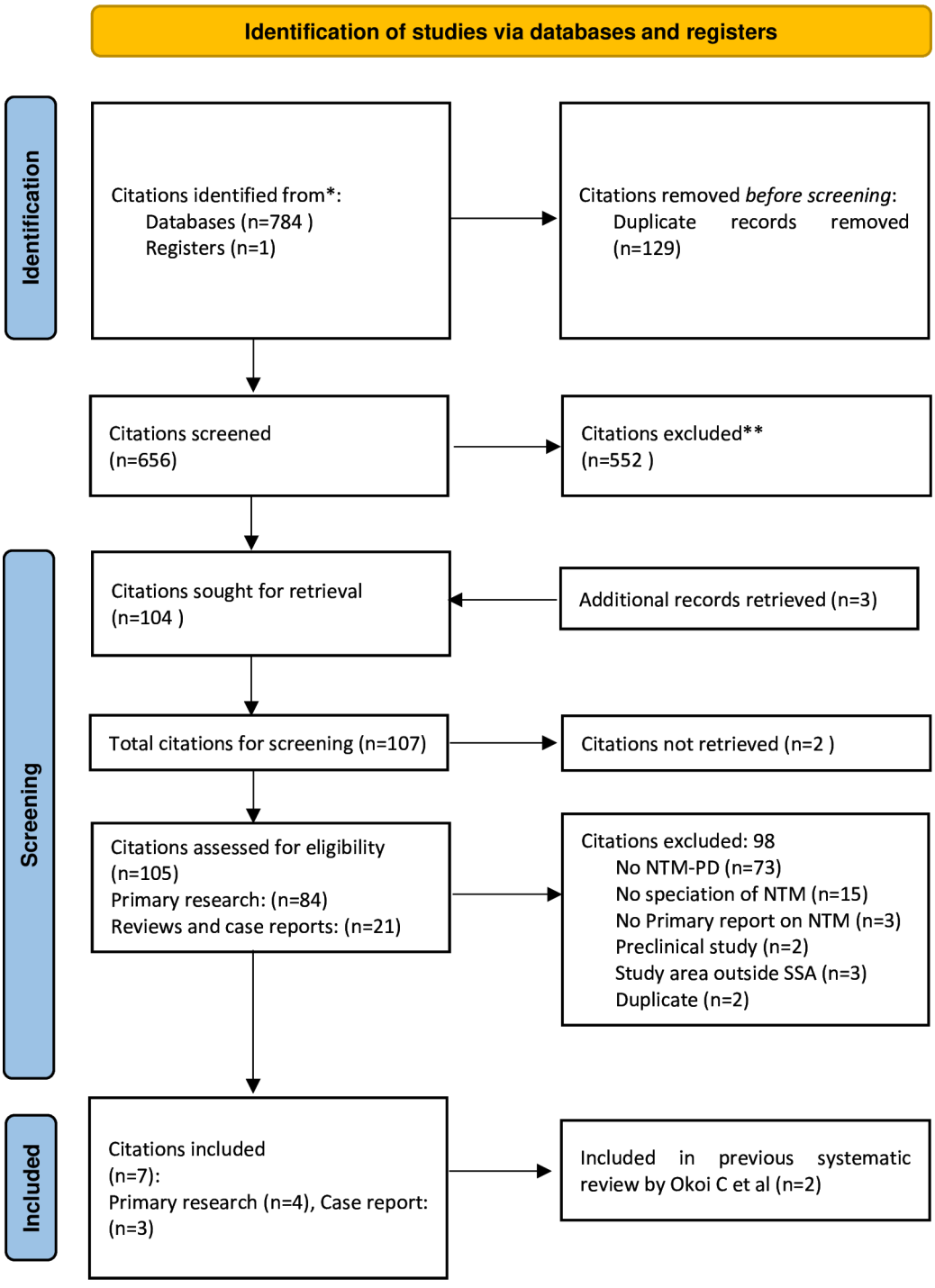

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for identification and inclusion of papers. NTM-PD, non-tuberculous mycobacterial pulmonary disease; SSA, sub-Saharan African.

Treatment decisions, options and outcomes

International NTM treatment guidelines were not adhered to in the reviewed articles, and treatment decisions were not presented. In the reviewed studies, Ouattara *et al* focused on MAC-PD. Patients were administered a combination therapy of rifampicin (R), isoniazid (H), ethambutol (E) and azithromycin. The criteria on which the treatment decision was based were not expatiated. Of the 17 patients—all of whom had cavitary lung disease following at least 2 unsuccessful antituberculous treatment courses—initiated on treatment, 6 died, and 10 were lost to follow-up. No TB/NTM coinfected patients were included (table 2).[17] The case by Twabi *et al* was given rifampicin, isoniazid, pyrazinamide, ethambutol and azithromycin. Neither treatment duration nor outcome was outlined (table 3).[22] Lopez-Varela *et al* did not treat any of the three symptomatic children with *M. intracellulare*; all children were alive 2 years later.[18] In the case report by Adekanmbi *et al*, the patient was administered azithromycin and rifampicin for 10 months, after

Table 1 Diagnosis, risk factors for NTM-PD and species

Author, year	Country	Study design	Study population	Number investigated	Type of diagnostic method	Number diagnosed with NTM-PD	Species identification	Risk factors for NTM-PD
Ouattara *et al*, 2019	Mali	Retrospective cohort study	Patients initially treated for recurrent TB (presumed MDR-TB) in whom MAC was isolated from sputum	96	Sputum smear (auramine-rhodamine staining), sputum culture (MGIT, 7H11), nucleic acid probes	17	*Mycobacterium avium* complex (MAC)	Male gender, occupational risk (agriculture), smoking, 'recurrent TB'
Lopez-Varela *et al*, 2017	Mozambique	Prospective cohort study	Children <3 years with presumed TB	775	ZN microscopy (LED microscopy), liquid and solid culture, genotype CM/AS	3	*M. intracellulare*	Malnutrition
Maiga *et al*, 2012	Mali	Prospective cohort study	Presumed patients with TB (treatment naïve and recurrent TB)	142	Sputum smear, culture (MGIT and Middlebrook 7H11 agar), gene sequencing	11	MAC (8), *M. simiae* (2), *M. palustre* (1)	'Recurrent TB'
Buitjels PCAM et al, 2010 [45]	Zambia	Cross-sectional study	Chronically ill presumed patients with TB	320	ZN staining, liquid culture (MGIT), 16S rRNA gene sequencing	5	*M. lentiflavum* (4), *M. intracellulare* (1)	HIV, previously TB

AS, additional Species; CM, common species; HIV, Human immunodeficiency virus; LED, light emitting diode; MAC, *Mycobacterium avium* complex; MDR-TB, multidrug-resistant TB; MGIT, mycobacterial growth indicator tube; NTM-PD, non-tuberculous mycobacterial pulmonary disease; TB, tuberculosis; ZN, Ziehl-Neelsen.

Table 2 Management of NTM-PD

Author, year	Country	Number diagnosed with NTM-PD	Management strategy	Outcome of management
Ouattara *et al*, 2019	Mali	17	Rifampicin (R)+isoniazid (H)+ethambutol (E)+azithromycin for 1 month, then RHE+clarithromycin for a total of 18 months	Six patients died at an average 10 months and 10 cases LTFU. One patient had undetectable sputum culture at month 5 and then positive at month 12 during treatment
Lopez-Varela *et al*, 2017	Mozambique	3	None were treated for NTM disease, and one received TB treatment	None reported
Maiga *et al*, 2012	Mali	11	MAC treatment for one patient. Drug regimen not specified	The patient treated for MAC returned 8 months later with MDR-TB
Buitjels PCAM *et al*, 2010[45]	Zambia	5	Antituberculous medicines (not specified)	Three died

E, ethambutol; H, isoniazid; LTFU, loss to follow-up; MAC, *Mycobacterium avium* complex; MDR-TB, multidrug-resistant TB; NTM, non-tuberculous mycobacteria; NTM-PD, non-tuberculous mycobacterial pulmonary disease; R, rifampicin; TB, tuberculosis; Z, pyrazinamide.

which the patient was culture negative. No outcome definition was applied to the patient.[20] *M. kansasii* isolated from a South African miner was treated for 15 months with antituberculous drugs (table 3).[21]

The paper by Maiga *et al* identified 11 patients with recurrent TB diagnosis who met the NTM-PD diagnostic criteria, 8 of whom had MAC-PD, 2 had *M. simiae* and 1 had *M. palustre*. Another six patients who had treatment-naïve TB with positive NTM isolates were coinfected with TB; given their TB treatment-naïve status, TB—and not NTM—treatment was prioritised. Only one of the patients diagnosed with MAC-PD received treatment, although the patient represented 8 months later and was diagnosed as having multidrug-resistant TB (MDR-TB). No outcomes were reported.[4]

DISCUSSION

Our review aimed to outline the challenges and gaps of NTM-PD in SSA. We identified the following: (1) primary

Table 3 Summary of the case reports included in the review

Author, year	Country	Study design	Study summary	Key finding
Adekanmbi *et al*, 2021	Nigeria	Case report	A man in his early 40s with a history of chronic bronchitis diagnosed with NTM-PD caused by *M. chelonae* subspecies abscessus and immunogenum	'Treated' with azithromycin and rifampin for 10 months
Twabi *et al*, 2021	Malawi	Case report	A man in his late 40s who is HIV positive with presumed TB (but afebrile) who had SSM (2+) and GeneXpert MTB/RIF negative. Culture and LPA revealed *M. avium* complex. The patient had been started on RHZE. After isolating *M. avium*, azithromycin 500 mg three times a week was added to this regimen.	The treatment duration and outcome were not reported
Oni *et al*, 2015	South Africa	Case report	A male South African miner between the ages 50 and 60 years old with a history of silicosis who presented with CT scan findings of cystic nodularity and cavities. Culture isolated MTB and *M. kansasii* and was treated with anti-TB drugs for 8 months. The patient had previously been given IPT with isoniazid for 12 months	*M. kansasii* and MTB for 8 months until culture negative. *M. kansasii* treatment lasted for 15 months

E, ethambutol; H, isoniazid; IPT, isoniazid preventive therapy; LPA, line probe assay; MTB, *Mycobacterium tuberculosis*; NTM-PD, non-tuberculous mycobacterial pulmonary disease; R, rifampicin; SSM, sputum-smear microscopy; TB, tuberculosis; Z, pyrazinamide.

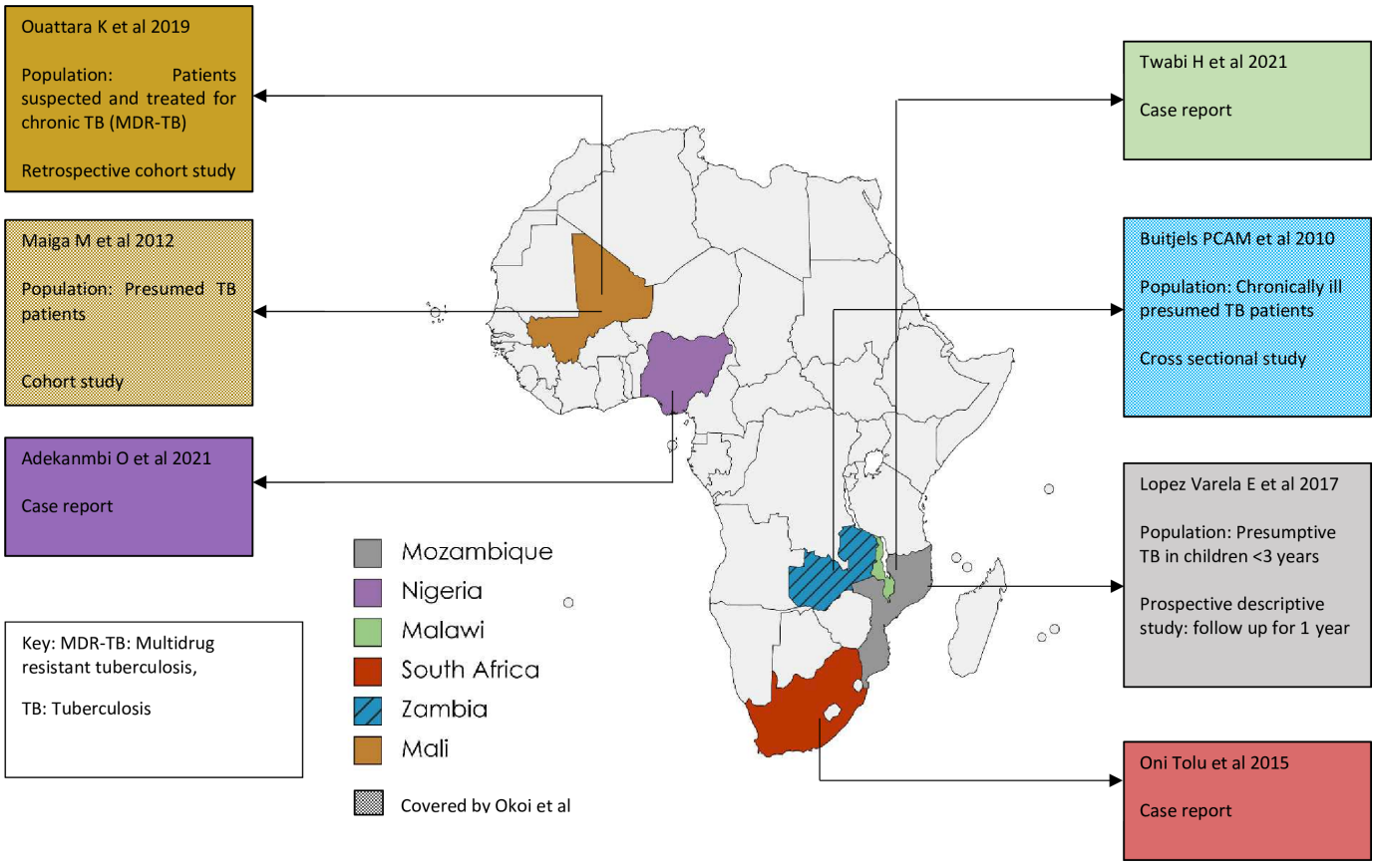

Figure 2 Geographic distribution of studies included in the review. MDR-TB, multidrug-resistant TB; TB, tuberculosis.

or recurrent TB diagnosis is an important risk group, (2) adhering to the widely accepted diagnostic criteria for NTM-PD is challenging beyond research settings in SSA settings, and (3) data on NTM management, let alone outcome, are scarce, and guidance adapted to a low resource setting (LRS) is lacking.

In TB-endemic regions, previous TB infection, particularly recurrent TB diagnosis, that is patients who remain symptomatic and often smear positive following one or several courses of TB treatment, was identified as a strong risk factor for NTM-PD.[26] We corroborate the findings in the review by Okoi *et al*, in which 87.1 % of the evaluated participants had a history of PTB.[10] In our review, all patients had presumptive TB or were managed as 'recurrent TB diagnosis' before being diagnosed as NTM-PD. In other regions, such as Europe and the USA, cystic fibrosis, bronchiectasis and chronic obstructive lung disease are well-known risk factors for NTM-PD.[27] Still, the disease can also occur in individuals (mainly women) seemingly without any predisposing lung or immunological abnormality.[1 28] Thus, in SSA, targeting symptomatic individuals with prior (or presumptive) TB seems a valuable option in NTM case identification in the future. Although HIV infection is a risk factor for disseminated NTM disease and TB[29 30], it is not associated with increased risk for NTM-PD. As HIV is common in SSA, its presence as a comorbidity in people with NTM-PD should be assessed. In our review, only 2 of 17 patients from Mali and 1 of the 3 case studies were HIV positive. The review by Okoi *et al* identified HIV coinfection in 50.2% of the population.[9]

A diagnosis of NTM-PD starts with suggestive symptoms and radiology.[31] Symptoms are non-specific and largely overlap with TB symptoms.[32] Chest radiography can be used; however, unlike CT, chest radiography risks identifying only advanced, often cavitary, disease and is unlikely to pick up more subtle radiological abnormalities such as nodular-bronchiectasis NTM lung disease.[8] This gap has to be bridged in low-resource settings. Rather than rolling out CT facilities, exploring the role of computer-aided detection (CAD4TB) in the radiological evaluation of presumed NTM-PD building on the experience in TB may be worthwhile.[33]

Because NTMs are widespread in the environment and do not obligate pathogens, the guidelines require repetitive isolation of the same species from the sputum and a suggestive clinical and radiological presentation for which no other explanation is found.[8 27 28] This requirement of appropriate and repetitive sampling established mycobacterial culture facilities, and an ability to speciate the NTM may be challenging to implement in LRS. First of all, the diagnostic criteria for NTM-PD are widely accepted though validation is limited, and ascertainment of its applicability in LRS is non-existent. In the review, one guideline identified in Nigeria seeks to direct clinicians managing TB when NTM is identified. This guideline presents the various clinical presentations

of NTM, including pulmonary disease, and advises clinicians on treatment options for various NTM species.[34] It, however, does not stipulate a diagnostic algorithm to aid in decision-making for clinicians. Despite these setbacks, this guideline is a first step in collecting regional evidence on NTM-PD.

Advances in TB diagnostics using molecular platforms such as GeneXpert MTB/RIF have increased the identification of SSM-positive and Xpert-negative cases.[35–37] Although molecular techniques such as LPA offer a unique opportunity for NTM species identification, which is crucial for decision-making,[38 39] these methods are not widely available as they require a biosafety level-3 laboratory and skilled personnel and are costly.[40] All the molecular techniques employed in the review were deployed in a research setting, and none were accessible in routine care.[32 38 39] Ideally, a new test—preferably using widely available existing molecular platforms—that can identify the most common pathogenic NTM directly from appropriate samples will be preferred in an LRS setting. While awaiting these developments, national TB programmes could consider using molecular assays to identify NTM species in symptomatic individuals with culture-confirmed NTM-PD to bridge the gap in available diagnostics in SSA countries. Unfortunately, up to date, NTM-PD is not considered a public health threat and is consequently not embraced by most national authorities.[40]

NTMs are not obligate pathogens, and diagnosing NTM-PD does not necessarily imply treatment. On the other hand, NTM-PD, even the nodular-bronchiectatic form, can progress to cause substantial morbidity and mortality over time.[41] An initiation of treatment rather than watchful waiting is suggested in patients meeting the diagnostic criteria.[8] Nevertheless, a treatment decision is based on clinical presentation, the clinical relevance of the infecting species and patient preferences. It involves weighing of potential benefits versus harms of an antibiotic regimen and a thorough discussion with a patient. Current NTM treatment regimens are costly, long, associated with adverse effects, and suboptimally effective. Conversely, it may prevent unnecessary repetitive TB treatments, including that for MDR-TB.[40 42]

The treatment duration is also not as standard as for TB. Apart from *M. kansasii*, which is recommended to be treated for at least 12 months, the recommended duration of treatment of NTM-PD caused by other species is at least 12 months after sputum culture conversion,[8 43] hence the importance of sputum culture monitoring to guide the duration of therapy. This practice will be challenging in low-income and middle-income countries such as SSA. Apart from one, none of the reviewed papers strictly followed the guidelines for continuing antibiotics for at least 12 months after culture conversion. In 2018, the NTM-Network European Trials Group proposed some outcome definitions for patients undergoing treatment for NTM-PD. These outcomes include culture conversion, cure, treatment failure, recurrence, relapse, reinfection, death, unknown outcome and death due to NTM-PD.[44] Although challenging to apply, it is prudent for researchers to use these definitions to help classify outcomes of NTM-PD.

The field of NTM-PD and TB/NTM coinfection in SSA is under-researched. As a result, few papers were identified that fit this review's objectives, thus making the generalisability of these findings challenging. More studies are needed to contribute to the scientific evidence on the subject.

Conclusion and recommendations

To conclude, our scoping review provides insight into the main risk factors of NTM-PD in high TB-endemic settings and the challenges of diagnosing and managing this condition in SSA. NTM may confound TB diagnosis. The applicability of the widely accepted diagnostic criteria for NTM-PD, as does the management approach for this highly complex lung infection, deserves further exploration.

These challenges offer the chance for researchers in this area to pursue answers to questions arising from our review that is context specific and will improve the management of patients with NTM-PD.

Implications of the findings for research

This review shows the gaps in applying the international criteria in diagnosing NTM-PD in SSA. Future research should focus on applying these guidelines. In a setting where chest X-ray is widely used, it may be worth pursuing the use of CAD4TB to increase the sensitivity of radiological evaluation of NTM-PD. As there are existing molecular platforms, research should look into building a more accessible platform to routinely identify clinically significant NTMs for clinical decision-making. Lastly, research into NTM-PD treatment decisions and validation of proposed outcome definitions is encouraged. We propose the following next steps: to encourage research collaborators across SSA to document NTM isolates as NTM-PD diagnosis and management practice, foster regional collaboration on NTM identification and management decisions, and informed by international guidelines, which at present are poorly implemented further develop regional guidelines fitting the African context based on research.

Implications of the findings for practice

We have outlined the identified risk factors and available diagnostics that can currently be employed to identify patients with NTM-PD. This will be important for clinicians and public health officers who work in TB and identify patients not responding to routine TB medications.

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